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# Electronic cigarettes and nicotine clinical pharmacology

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Received 2 December 2013  
Accepted 11 February 2014

## ABSTRACT

**Objective** To review the available literature evaluating electronic cigarette (e-cigarette) nicotine clinical pharmacology in order to understand the potential impact of e-cigarettes on individual users, nicotine dependence and public health.

**Methods** Literature searches were conducted between 1 October 2012 and 30 September 2013 using key terms in five electronic databases. Studies were included in the review if they were in English and publicly available; non-clinical studies, conference abstracts and studies exclusively measuring nicotine content in e-cigarette cartridges were excluded from the review.

**Results** Nicotine yields from automated smoking machines suggest that e-cigarettes deliver less nicotine per puff than traditional cigarettes, and clinical studies indicate that e-cigarettes deliver only modest nicotine concentrations to the inexperienced e-cigarette user. However, current e-cigarette smokers are able to achieve systemic nicotine and/or cotinine concentrations similar to those produced from traditional cigarettes. Therefore, user experience is critically important for nicotine exposure, and may contribute to the products' ability to support and maintain nicotine dependence.

**Conclusions** Knowledge about e-cigarette nicotine pharmacology remains limited. Because a user's e-cigarette experience may significantly impact nicotine delivery, future nicotine pharmacokinetic and pharmacodynamic studies should be conducted in experienced users to accurately assess the products' impact on public health.

## INTRODUCTION

Electronic cigarettes (e-cigarettes) are relatively new to the market, but already encompass a wide variety of product types and brands. Many e-cigarettes contain nicotine, the primary addictive chemical in tobacco.<sup>1</sup> Nicotine content varies widely among products, typically ranging between 0 and 34 mg/mL, but recent studies have found discrepancies between labelled and measured nicotine content.<sup>2</sup>

Traditionally, tobacco product nicotine exposure and pharmacokinetics largely depend on the delivery system, tobacco pH and smoke pH (for combusted products). E-cigarettes purportedly do not produce a combusted smoke; rather, they deliver an aerosol containing nicotine and other tobacco-related compounds. The temperature at which the e-liquid is aerosolised has a direct effect on nicotine yield; higher temperatures are associated with greater nicotine aerosolisation.<sup>3</sup> E-cigarette design is evolving (rechargeable, disposable, tank systems, variable voltage, etc) which may also affect nicotine yield.

E-cigarettes may provide a mechanism for flexible nicotine delivery, as do traditional cigarettes. Several online surveys with current e-cigarette users indicate that e-cigarettes may be effective in reducing traditional cigarette use or for complete smoking cessation,<sup>4, 5</sup> although many products do not make a smoking cessation claim and no e-cigarette has been approved by the Food and Drug Administration (FDA) as a cessation aid. Nevertheless, these data suggest that e-cigarettes may deliver nicotine at levels that are sufficient to substitute, at least partially, for cigarettes.

Nicotine dependence and abuse liability are, in part, influenced by nicotine bioavailability, rate of absorption and exposure.<sup>6</sup> When delivered through the pulmonary route (as with tobacco smoke inhalation), nicotine is rapidly absorbed into the circulation and reaches the brain within seconds.<sup>7</sup> Buccal and dermal nicotine absorption (as with nicotine replacement therapies (NRT)) is slower and subject to first-pass metabolism; therefore, these products may pose less abuse liability. Thus, nicotine pharmacokinetic studies may provide insight into whether or not e-cigarettes (alone or in combination with other tobacco products) can initiate or maintain nicotine dependence.

Because e-cigarettes are new, diverse, different than traditional tobacco products, and likely addictive, it is necessary to evaluate product-specific nicotine clinical pharmacology to understand their potential impact on individual users and the public health.

## METHODS

Systematic literature searches were conducted between October 2012 and September 2013 to identify research related to nicotine pharmacology and dependence associated with e-cigarettes. 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') AND ('nicotine' OR 'cotinine' OR 'addiction' OR 'dependence'). The search date range was unrestricted.

To be considered for inclusion, the article 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 e-cigarette nicotine pharmacology. Publicly available FDA memos were also included if relevant. Studies that exclusively reported or measured e-cigarette nicotine content



To cite: Schroeder MJ, Hoffman AC. *Tob Control* 2014;**23**:ii30–ii35.

were excluded. The reference lists of applicable studies were also manually searched to identify additional relevant publications.

Sixteen e-cigarette studies were deemed relevant for this review; articles selected for inclusion were published between 2009 and 2013. All clinical studies were conducted in male and female adults aged 18 years and older. The validity and strength of each study were determined based on a qualitative assessment of risk of bias and experimental methods, including sample characteristics, product variability and other experimental details. Meaningful study limitations are noted in the analysis.

## RESULTS

### Nicotine yield

Because only a portion of the nicotine in an e-cigarette's liquid cartridge (e-liquid) becomes aerosolised, nicotine yield in aerosol is critical to nicotine pharmacokinetics. A memo from the FDA Division of Pharmaceutical Analysis measured nicotine yield from 18 NJOY and Smoking Everywhere e-cigarettes with 'no,' 'medium,' or 'high' nicotine concentrations (based on the author's description) and several flavours.<sup>8</sup> Nicotine yield was measured from 100 mL puffs. Among Smoking Everywhere products, nicotine yield ranged from 0.35 µg/100 mL puff in an apple-flavored 'no' nicotine product to 31.5 µg/100 mL puff in a 'high' nicotine product. Among NJOY products, a menthol 'medium' nicotine product delivered 10.6 µg nicotine/100 mL puff, while the menthol 'high' nicotine products ranged from 26.8 to 43.2 µg nicotine/100 mL puff.

In an editorial, Cobb and Byron reported nicotine yield in 35 mL puffs from an NJOY e-cigarette (measured 4.1 mg nicotine/cartridge).<sup>9</sup> Based on International Organisation for Standardisation (ISO) smoking conditions (commonly used for assessing traditional cigarette smoke yields; a 2 s puff duration, 35 mL puff volume, one puff per minute), puffs 1–10 contained 1 µg nicotine/puff, while puffs 11–50 contained less than 0.3 µg nicotine/puff. Because this study used the ISO smoking method, which fails to activate some e-cigarette models<sup>10</sup> and may not mimic smoking behaviours in e-cigarette users, the nicotine yields reported here may not be indicative of yields associated with actual use.

Trehy and colleagues measured nicotine yield in 100 mL puffs from eight NJOY, Smoking Everywhere and CIXI products.<sup>3</sup> Labelled nicotine content ranged from 11 to 24 mg/cartridge. Nicotine yield was highly variable, ranging from 0 to 43.2 µg nicotine/100 mL puff. For comparison, a Marlboro cigarette yielded 152–193 µg nicotine/100 mL puff with the same experimental method.

In a study by McAuley *et al*<sup>11</sup> that assessed indoor air quality with e-cigarette aerosol, nicotine yields were measured from four different e-cigarettes (24–26 mg nicotine/mL) with 50 puffs of 50 mL each. Nicotine concentration varied significantly (538–8770 ng/L), but remained below the concentrations measured in 35 mL puffs from traditional cigarettes.

A study by Pellegrino and colleagues evaluated nicotine content and yield from two e-cigarettes (Aria), one with nicotine (0.25% by weight) and one without (<0.001%).<sup>12</sup> To analyse the aerosol, a modified smoking method of 16 simulated puffs, a 3 s puff duration, 8 s interpuff interval, and 0.166 L/s flow rate was used. Nicotine yield from the nicotine e-cigarette was 6.21 mg/m<sup>3</sup>; the zero-nicotine e-cigarette yielded less than 0.01 mg/m<sup>3</sup>.

Goniewicz and colleagues used an altered smoking machine method to simulate experienced e-cigarette user puff topography (n=10, use for ≥1 month): a 1.8 s puff duration, 10 s interpuff interval, 70 mL puff volume, and 5 min between every

15 puffs.<sup>2</sup> Each cartridge was used for 300 puffs (approximate puff count in a cigarette pack). Among the 16 brands of e-cigarettes studied, measured nicotine content ranged from 1.6 to 19 mg/cartridge. Three hundred puffs of e-cigarette aerosol were found to contain between 21% and 85% of the cartridge's total nicotine content, or between 0.5 (from a 1.6 mg nicotine cartridge) and 15.4 mg nicotine (from an 18 mg nicotine cartridge). The authors concluded that 15 puffs on an e-cigarette (approximately equivalent to smoking one cigarette) yielded 0.025–0.77 mg nicotine. Although direct comparisons cannot be made with other e-cigarette nicotine yields, posthoc calculations suggest that Goniewicz *et al* reported an average of 82.8 µg nicotine/100 mL aerosol with 18 mg nicotine cartridge e-cigarettes.

Farsalinos *et al*<sup>13</sup> estimated nicotine delivery from a 9 mg nicotine/mL e-cigarette based on e-liquid volume consumed by experienced e-cigarette users. Calculated nicotine delivery was 0.46 mg after 5 min of ad libitum use (to approximate the time to smoke a traditional cigarette). The authors determined that the e-cigarette delivered 54% lower nicotine than a traditional cigarette, which yields approximately 1 mg. Because puff volume was not measured, comparisons to nicotine yield studies are limited. Furthermore, this study should be interpreted with caution, because nicotine concentrations were not measured but rather calculated based on e-liquid volume consumed during use.

While machine-smoked e-cigarette nicotine yields are not directly comparable with those from traditional cigarettes due to differences in smoking machine methods and product nicotine content, the average ISO nicotine yield for a single traditional cigarette ranges from 0.5 to 1.5 mg/cigarette.<sup>14–16</sup> Several studies attempted to modify smoking methods to account for smoking behaviours in e-cigarette users, but others did not. Nevertheless, these studies indicate that e-cigarettes deliver less nicotine than traditional cigarettes and highlight variable nicotine delivery among e-cigarette brands and smoking methods.

### Nicotine exposure

Clinical studies investigating nicotine exposure have increased in recent years and can be divided into two groups based on the recruited population. Older studies evaluated nicotine exposure from e-cigarette use in current cigarette smokers who were naive to e-cigarettes, while more recent studies have studied exposure in current users and emphasise the importance of actual use behaviours to nicotine exposure.

#### Inexperienced users

Five studies measured nicotine or cotinine exposure in participants with no e-cigarette experience (table 1).

Bullen and colleagues investigated the relationship between tobacco product type, nicotine delivery rate and peak nicotine concentration.<sup>17</sup> In a cross-over study, eight nicotine-dependent participants used an e-cigarette (Ruyan V8, 16 mg nicotine), a nicotine inhaler (Nicorette, 10 mg nicotine; n=9), and smoked an own brand cigarette (n=9). Significant increases in nicotine concentration occurred only with own brand cigarettes. On average, peak venous plasma nicotine levels were achieved at 19.6 min following the initial e-cigarette puff, slower than with the own brand cigarette but more rapid than with the nicotine inhaler. This nicotine kinetic profile is also more rapid than smokeless tobacco products.<sup>18</sup> Given the slower nicotine absorption profile, the authors suggest that e-cigarette aerosol may deliver nicotine through the buccal membranes (as with nicotine

**Table 1** Nicotine exposure in inexperienced e-cigarette users

Reference	Study characteristics				Results		
	Study product	Labelled nicotine content	Sample size	Use duration	Biomarkers of exposure	Relevant comparisons	Other physiological measures
Bullen <i>et al</i> <sup>17</sup>	Ruyan V8	16 mg	8	e-cigarette: 5 min; inhaler: 10 min; cigarette: 5 min	plasma nicotine (venous): Cmax 1.3 ng/mL, Tmax 19.6 min	Nicorette inhaler (10 mg nicotine): Cmax 2.1 ng/mL, Tmax 32 min; own brand cigarette: Cmax 13.4 ng/mL; Tmax 14.3 min	
Eissenberg <sup>19</sup>	NJOY or Crown 7	16 mg	16	2 bouts of 10 puffs, 30 s interpuff interval, 1 hr between bouts	plasma nicotine: after 5 min, 2.5 ng/mL (NJOY), 3.5 ng/mL (Crown 7)	own brand cigarette: 16.8 ng/mL	no increases in HR
Vansickel <i>et al</i> <sup>20</sup>	NJOY or Crown 7	18 mg, 16 mg	32	2 bouts of 10 puffs, 30 s interpuff interval, 1 h between bouts	no significant changes to plasma nicotine	own brand cigarette: within 5 min, 2.1–18.8 ng/mL	no increases in HR
Vansickel <i>et al</i> <sup>21</sup>	Vapor King	18 mg/mL	20	6 bouts of 10 puffs, 20 s interpuff interval, 30 min between bouts	plasma nicotine: 5 min after final bout, 2.2–7.4 ng/mL		5 min after first bout, HR increased from 67.5 to 75 bpm
Flouris <i>et al</i> <sup>22</sup>	Giant	11 mg/mL	15	Equivalent puffs to approximate nicotine delivery with two own brand cigarettes, based on 1.5 cigarette/e-cigarette nicotine absorption ratio	serum cotinine: significant increases immediately following and 1 h after use	2 own brand cigarettes: no difference between e-cigarette and cigarette use	

HR, heart rate; bpm, beats per minute; Cmax, maximum drug concentration; Tmax, time at which maximum drug concentration is observed.

inhalers and smokeless tobacco) and the respiratory tract (similar to traditional cigarettes).

Eissenberg described preliminary findings from a cross-over study in which 16 smokers smoked their own brand cigarette, two brands of 16 mg nicotine e-cigarettes (NJOY and Crown 7), and puffed on an unlit own brand cigarette in a control condition.<sup>19</sup> E-cigarette flavour (menthol or regular) was matched to the participant's preferred cigarette flavour category. In a controlled puff setting, both e-cigarette brands failed to increase plasma nicotine concentrations, whereas own brand cigarettes increased nicotine levels.

Results of the full study were reported by Vansickel *et al*.<sup>20</sup> This cross-over study with 32 cigarette smokers compared the nicotine delivery profile of an e-cigarette (NJOY, 16 mg nicotine/cartridge or Crown 7, 18 mg nicotine/cartridge), the smoker's own brand cigarette (Federal Trade Commission (FTC)

measured average 1.06 mg nicotine yield/cigarette) and a control condition. In a puff-controlled setting that approximated ad libitum cigarette smoking, own brand cigarettes significantly increased plasma nicotine levels, while levels remained unchanged with both e-cigarettes.

In another study, Vansickel *et al*<sup>21</sup> measured plasma nicotine concentrations after multiple puffs on an 18 mg nicotine/mL e-cigarette (Vapor King) in 20 cigarette smokers. Although no participants were also current e-cigarette users, some had sampled them in the past. Plasma nicotine concentrations increased significantly after the fourth 10-puff bout. After the sixth (and final) bout, mean plasma nicotine concentrations increased from 2.2 to 7.4 ng/mL, yet remained below reported values for traditional cigarettes.

A recent study by Flouris *et al*<sup>22</sup> measured serum cotinine (the primary nicotine metabolite) levels after 15 cigarette

**Table 2** Nicotine exposure in experienced e-cigarette users

Reference	Study characteristics			Results		
	Study product	Labelled nicotine content	Sample size	Use duration	Biomarkers of exposure	Other physiological measures
Etter and Bullen <sup>23</sup>	preferred e-cigarette: flavour, nicotine concentration	ave. 18 mg/mL	30	ad libitum	salivary cotinine: 322 ng/mL	
Vansickel and Eissenberg <sup>25</sup>	preferred e-cigarette: flavour, nicotine concentration	9–24 mg/mL	8	10 puffs, 30 s interpuff interval 1 h ad libitum	plasma nicotine: after 5 min, 2–10.3 ng nicotine/mL plasma nicotine: 16.3 ng/mL	within 5 min of bout, HR increased HR remained increased
Dawkins and Corcoran <sup>26</sup>	SKYCI	18 mg/mL	14	10 puffs within 5 min 1 h ad libitum	plasma nicotine: after 10 min, 0.74–6.77 ng/mL plasma nicotine: 13.91 ng/mL (range: 4.35 ng/mL–25.6 ng/mL)	
Caponnetto <i>et al</i> <sup>28</sup>	Categoria	7.2 mg for 12 weeks 7.2 mg for 6 weeks, 5.4 mg for another 6 weeks	NR	12 weeks 12 weeks	salivary cotinine: 6 weeks, 42.5 ng/mL; 12 weeks, 91 ng/mL salivary cotinine: 6 weeks, 67.8 ng/mL; 12 weeks, 69.8 ng/mL	

HR, heart rate.

smokers smoked their own brand cigarette or an e-cigarette (Giant, 11 mg nicotine/mL). Cigarette smokers who reported using e-cigarettes in the past were specifically excluded from this study. To ensure similar nicotine delivery between the cigarette and e-cigarette conditions, a pilot study surveyed 141 current e-cigarette users about their e-cigarette and former cigarette use behaviours, and determined that the traditional cigarette/e-cigarette nicotine absorption ratio was 1.5, confirming earlier findings that e-cigarettes deliver lower amounts of nicotine than traditional cigarettes.<sup>3–11</sup> Participants were instructed to smoke two own brand cigarettes or, in the e-cigarette group, puff behaviours were individually tailored to approximate nicotine delivery from their own brand cigarette. Immediately and 1 h following both product use sessions, serum cotinine levels were significantly higher than baseline. Because this study attempted to normalise nicotine delivery between the two products, these results suggest that e-cigarettes are capable of delivering similar amounts of nicotine as traditional cigarettes.

These studies suggest that e-cigarettes deliver modest amounts of nicotine to the inexperienced user. However, Bullen and colleagues reported that e-cigarettes were rated less desirable compared to own brand cigarettes,<sup>17</sup> and it is likely that different (and unaccustomed) use behaviours account for some differences between e-cigarette and own brand cigarette nicotine exposure.

#### Experienced e-cigarette users

Four clinical studies have been conducted in current e-cigarette users and suggest that e-cigarette experience may significantly impact smoking behaviour and nicotine exposure (table 2).

Published as a letter to the editor, Etter and Bullen<sup>23</sup> studied 31 current, experienced e-cigarette users (average length of use 94 days) who provided saliva samples for cotinine measurements. Users' average e-cigarette cartridges were labelled as 18 mg nicotine/mL. In the 30 e-cigarette users who reported no tobacco or NRT use in the previous 48 h, median salivary cotinine levels were 322 ng/mL. The single participant who did not previously use traditional cigarettes had 141 ng cotinine/mL, and the single participant who reported only using an e-cigarette 2 days a week had 13 ng cotinine/mL. These salivary cotinine levels approximate levels previously observed in cigarette smokers (66.9–283.7 ng/mL),<sup>24</sup> suggesting that daily e-cigarette users are exposed to substantial amounts of nicotine.

Vansickel and Eissenberg<sup>25</sup> measured plasma nicotine concentrations in experienced e-cigarette users (n=8, average length of use 11.5 months) who formerly used cigarettes. Study participants used their preferred e-cigarette for a 10-puff bout (to approximate a single cigarette) and a 1 h ad libitum period. Five minutes after the bout, plasma nicotine concentrations were significantly increased; after 1 h of ad libitum use (4–76 puffs), peak plasma levels measured 16.3 ng/mL, suggesting that e-cigarettes are capable of reliable and significant nicotine delivery.

In an industry-funded study, Dawkins and Corcoran recruited 14 current e-cigarette users to use an 18 mg nicotine/mL SKYCIG product (average length of use 4.7 months).<sup>26</sup> Approximately half the participants were concurrent cigarette smokers. Plasma nicotine concentrations were measured after a single bout and a 1 h ad libitum session. Ten minutes after the 10-puff bout, plasma nicotine concentrations significantly increased to 6.77 ng/mL. Although direct comparisons to traditional cigarettes cannot be made, plasma nicotine concentrations following a single cigarette average 15–20 ng/mL.<sup>27</sup> By the end of the ad libitum session, nicotine levels averaged 13.91 ng/

mL (similar to levels found by Vansickel and Eissenberg<sup>25</sup>). Puff number and plasma nicotine concentration were not significantly correlated, suggesting that other factors (eg, time between puffs, puff volume, puff duration) may be critical determinants of nicotine exposure.

A recent Italian clinical study monitored decreases in cigarette smoking associated with concurrent e-cigarette (Categoria, 7.2 and/or 5.4 mg nicotine cartridges) use.<sup>28</sup> The study did not specify whether participants had prior e-cigarette experience. Products were used for more than 12 weeks, and use behaviours may have changed during the study. Participants were randomised into three groups: one group received 7.2 mg nicotine/cartridge e-cigarettes for 12 weeks; another group used the 7.2 mg nicotine/cartridge e-cigarette for 6 weeks and the 5.4 mg nicotine/cartridge for the following 6 weeks; and a control group used e-cigarettes with a zero nicotine cartridge. Exhaled carbon monoxide (CO) measurements verified cigarette abstinence. Salivary cotinine levels were used to assess nicotine exposure, yet extent of e-cigarette use during each study period is unknown. At 12 weeks, median salivary cotinine concentrations were 91 and 69.8 ng/mL for the 7.2 and 5.4 mg nicotine cartridges, respectively. Participants using a zero nicotine cartridge did not have detectible levels of cotinine. This study suggests that e-cigarettes alone are able to produce salivary cotinine levels similar to traditional cigarette smokers, as previously reported.<sup>23</sup>

These studies in experienced and current e-cigarette users highlight the role of experience and use behaviour in nicotine exposure, and suggest that experienced e-cigarette users may achieve systemic nicotine concentrations akin to traditional cigarettes.

#### Pharmacodynamics

Nicotine affects the peripheral and central nervous systems, and has been shown to increase heart rate (HR) and blood pressure while constricting cutaneous and coronary blood vessels.<sup>29</sup> Indeed, clinical studies have shown that e-cigarette aerosol may deliver sufficient nicotine for physiological responses.

Three studies have investigated the effect of e-cigarette use on cardiovascular endpoints in inexperienced e-cigarette users. Two studies observed no changes in HR following two 10-puff bouts on a 16 or 18 mg nicotine/cartridge e-cigarette (n=32; n=16), although neither study observed increases in nicotine exposure.<sup>19–20</sup> Significant increases in HR were reported with own brand cigarettes. A third study (n=20) that reported significant increases in plasma nicotine concentration after four bouts found that HR increased over baseline levels 5 min after a 10-puff bout with an 18 mg nicotine/mL e-cigarette.<sup>21</sup> However, the increase was not sustained throughout the six-bout protocol and was smaller than previously reported for cigarettes.

Vansickel and Eissenberg<sup>25</sup> measured HR in experienced e-cigarette users who used their own brand e-cigarettes for a 10-puff bout and an ad libitum period. Five minutes after the bout, HR increased by an average of 5.8 bpm and remained elevated throughout the ad libitum period.

Interpreting these study results is challenging because most studies were conducted in inexperienced e-cigarette users with low nicotine exposure. Given the differences in nicotine exposure between inexperienced and experienced e-cigarette users, all potential pharmacodynamic biomarkers should be studied in experienced e-cigarette users. Nevertheless, these data suggest that e-cigarettes are able to deliver sufficient nicotine for physiological effects.

## Impact on dependence

The 1988 Surgeon General's report on tobacco was dedicated to nicotine addiction, and concluded that the nicotine in tobacco causes addiction.<sup>1</sup> Numerous studies have determined that traditional cigarettes and other tobacco products cause nicotine dependence. However, no dependence questionnaire has been specifically developed to evaluate e-cigarettes, and development of a systematic test may be critical for properly assessing nicotine dependence in e-cigarette users.<sup>30</sup>

Nicotine dependence and abuse liability are closely related to rapid nicotine absorption rates and exposure.<sup>6</sup> In cigarette smokers, Bullen *et al*<sup>17</sup> compared the nicotine absorption kinetics and exposure of an e-cigarette, traditional cigarette and a nicotine inhaler. When using the 16 mg nicotine e-cigarette for 5 min, nicotine absorption was slower and associated with lower nicotine exposure (Tmax 19.6 min, Cmax 1.3 ng/mL) than 5 min of cigarette smoking (Tmax 14.3 min, Cmax 13.4 ng/mL), but more rapid than 20 min of inhaler use (Tmax 32.0 min, Cmax 2.1 ng/mL). These data may suggest e-cigarettes deliver nicotine through the pulmonary and buccal routes in inexperienced e-cigarette users. Although such data may appear to imply that e-cigarettes have decreased abuse potential, it may be misleading to make direct comparisons between favoured (own brand cigarettes) and novel products (e-cigarettes) when assessing nicotine pharmacokinetics and abuse liability.

Nevertheless, current literature suggests that experienced e-cigarette users are able to achieve nicotine exposures similar to cigarette smokers.<sup>23 25 26 28</sup> These studies suggest that e-cigarettes may support dependence behaviours in the experienced user.

## DISCUSSION

This review aimed to evaluate the current literature related to e-cigarette nicotine pharmacology and dependence. Smoking machine studies suggest that a single e-cigarette puff yields less nicotine than a single cigarette puff, yet only one study directly compared yields between e-cigarettes and traditional cigarettes using the same methods.<sup>3</sup> Interestingly, two studies showed that e-cigarettes can deliver similar amounts of nicotine as traditional cigarettes using methods that may better represent current e-cigarette use behaviour.<sup>10 13</sup>

Several studies investigated nicotine exposure associated with e-cigarettes, demonstrating that exposure may depend on experience and use behaviours. For example, early studies showed that e-cigarettes did not significantly increase nicotine levels in inexperienced users,<sup>17 19 21</sup> but recent studies suggest that current users are able to achieve nicotine levels similar to cigarette smokers.<sup>23 25 26 28</sup> These studies also highlight use behaviour as an important factor for nicotine exposure. Indeed, although smoking machine yields report lower nicotine delivery from e-cigarettes, experienced users may adapt their use behaviours to achieve similar nicotine exposures as from traditional cigarettes.

The site of nicotine absorption (lung or buccal membranes), aerosol particle size and nicotine exposure are critical factors in determining whether or not these products may support or maintain nicotine dependence. Although more studies are required to understand nicotine dependence in experienced e-cigarette users, existing data suggest that dependence severity in current e-cigarette users may be akin to traditional cigarette dependence.

While nicotine is the primary addictive constituent in tobacco, non-nicotine tobacco constituents, including anabasine,

nornicotine, and acetaldehyde, may also impact tobacco addiction.<sup>31</sup> In an FDA analysis, anabasine was detected at low levels in several types of e-cigarettes.<sup>8</sup> Furthermore, Etter *et al* measured nicotine-related alkaloids, including nornicotine and anabasine, in the e-liquid from 20 different e-cigarette models. Although expressed as a percentage of nicotine content, anabasine was measured in several samples, and ranged from 0.04% to 0.45% nicotine content. Nornicotine was measured at 0.02% to 0.10% nicotine content.<sup>32</sup> In a sample of 12 e-cigarettes, acetaldehyde yield varied from 0.11–1.36 µg/15 puffs, nearly 450 times lower than yields from traditional cigarettes.<sup>10</sup> The extent to which these tobacco constituents may contribute to e-cigarette use and dependence is unknown.

Complicating a thorough understanding of e-cigarette clinical pharmacology and e-cigarettes' impact on nicotine dependence is the wide variety of e-cigarette products. Indeed, differences in study products' nicotine content and design features (which may impact nicotine delivery and pharmacology) impede meaningful comparisons across products. Furthermore, due to the vast and rapidly developing e-cigarette market, the study products reviewed here represent a small percentage of currently marketed products; others<sup>20</sup> may no longer be available.

These studies highlight several important research areas, including: (1) measuring effective pH and other characteristics of e-cigarette aerosol that influence nicotine absorption, (2) development of a standardised e-cigarette smoking regimen based on experienced e-cigarette use behaviours and standard reporting units, (3) clinical nicotine pharmacokinetic and pharmacodynamic studies conducted in current and experienced e-cigarette users and (4) evaluating differences in e-cigarette effects between populations (eg, gender, former and current cigarette smokers, and daily vs non-daily e-cigarette users).

### What this paper adds

- ▶ This is the first review to systematically evaluate studies of e-cigarette clinical nicotine pharmacology and the relationships with nicotine dependence.
- ▶ The review found that e-cigarette nicotine exposure depends on product experience and use behaviours. Experienced e-cigarette users are able to achieve nicotine concentrations similar to cigarette smokers, while e-cigarette use in inexperienced users does not significantly affect nicotine concentrations.
- ▶ Although more studies are required to understand nicotine dependence among current e-cigarette users, existing data suggest that e-cigarette nicotine delivery is sufficient to maintain nicotine dependence.

**Contributors** MJS performed the literature review. MJS and ACH wrote the paper. MJS is the guarantor.

**Competing interests** None.

**Provenance and peer review** Not commissioned; externally peer reviewed.

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