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REVIEW ARTICLE

E-cigarettes: Impact of E-liquid Components and Device Characteristics on Nicotine Exposure

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Abstract: ***Background***: Electronic cigarette (e-cigarette) use has increased substantially in recent years. While e-cigarettes have been proposed as a potentially effective smoking cessation tool, dual-use in smokers is common and e-cigarettes are widely used by non-smokers, including youth and young-adult non-smokers. Nicotine, the primary addictive component in cigarettes, is present at varying levels in many e-liquids. E-cigarettes may lead to initiation of nicotine use in adult and youth non-smokers, re-initiation of nicotine dependence in ex-smokers or increased severity of nicotine dependence in dual-users of cigarettes and e-cigarettes. As such, there are important clinical and policy implications to understanding factors impacting nicotine exposure from e-cigarettes. However, the broad and rapidly changing range of e-liquid constituents and e-cigarette hardware which could impact nicotine exposure presents a challenge. Recent changes in regulatory oversight of e-cigarettes underscore the importance of synthesizing current knowledge on common factors which may impact nicotine exposure.

Methods: This review focuses on factors which may impact nicotine exposure by changing e-cigarette use behavior, puff topography, altering the nicotine yield (amount of nicotine exiting the e-cigarette mouth piece including nicotine exhaled as vapor) or more directly by altering nicotine absorption and bioavailability.

Results: Topics reviewed include e-liquid components or characteristics including flavor additives (*e.g*., menthol), base e-liquid ingredients (propylene glycol, vegetable glycerin), components commonly used to dissolve flavorants (*e.g*., ethanol), and resulting properties of the e-liquid (*e.g*., pH), e-cigarette device characteristics (*e.g*., wattage, temperature, model) and user behavior (*e.g*., puff topography) which may impact nicotine exposure.

Conclusion: E-liquid characteristics and components, e-cigarette hardware and settings, and user behavior can all contribute substantially to nicotine exposure from e-cigarettes.

Keywords: E-cigarette, electronic cigarette, nicotine, vaping, flavor, e-liquid.

1. INTRODUCTION

Nicotine is the primary addictive component of tobacco cigarettes [1]. Nicotine absorption rates and overall nicotine exposure impact nicotine dependence and abuse liability [2]. In addition to its addictive potential, nicotine also has negative health impacts (*e.g.*, [3-5]).

Electronic cigarettes (e-cigarettes) are a rapidly developing technology which has become widely used within the past decade as a means of nicotine delivery (*e.g.*, [6]). The impact of e-cigarettes from a public health and clinical perspective remains uncertain. How best to approach or regulate this technology remains an important discussion point, given the need to balance potential adverse health effects of the product with the potential for harm-reduction if they are found to be effective, for example, to aid in cessation of combustible cigarette smoking [7-27].

Since nicotine is the primary addictive component of combustible cigarettes and has known health consequences, it is important to characterize factors that influence nicotine delivery from e-cigarettes, to inform regulation and considerations of health impacts of this nicotine-delivery device. The goal of this article is to review factors which may contribute to variability in nicotine delivery from e-cigarettes. Based on factors known to influence nicotine delivery from other nicotine-containing products, as well as research directly on e-cigarettes, we review e-liquid, e-cigarette hardware characteristics, and user behaviors that have been shown to, or may be expected to, impact nicotine delivery from e-cigarettes. We first briefly note the variability in the literature regarding level of nicotine delivered by e-

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cigarettes. We then review factors which likely contribute to this variability including: nicotine levels in e-liquids, other non-nicotine components and characteristics of e-liquids (*e.g.*, flavorants such as menthol and sweeteners, vegetable glycerin and propylene glycol, pH, alcohol, minor alkaloids), e-cigarette hardware characteristics (*e.g.*, generations/models, heat/power settings, activation mechanism such as airflow versus button-activated) and user behavior (*e.g.*, topography, user experience).

2. OVERVIEW OF NICOTINE IN E-CIGARETTE AEROSOL AND NICOTINE DELIVERY

Nicotine exposure from e-liquids could occur through several routes: from inhalation of the aerosolized e-liquid directly to the user, to non-users through secondhand aerosol exposure, through third-hand exposure to emissions which have settled onto surfaces, and from direct interaction with the nicotine-containing e-liquid (*e.g.*, handling, misuse). Approaches to studying these various routes of administration have tested levels of nicotine or nicotine metabolites in e-cigarette users following laboratory self-administration paradigms or more naturalistic use patterns, have assessed aerosol composition or other measures of air quality, or measured settled e-liquid constituents on surfaces or investigated possible nicotine exposure through other means of e-liquid use. We briefly review this literature below.

2.1. Nicotine Delivery from E-Cigarettes to the User

A number of human laboratory studies have measured the nicotine delivery from e-cigarettes, under directed-puffing or ad libitum conditions. Although some studies found low nicotine delivery from the e-cigarettes, relative to the levels generally obtained from combustible cigarettes, it is now well-established that under certain circumstances, e-cigarettes can deliver nicotine levels equivalent to or exceeding the levels commonly delivered by combustible cigarettes [3, 28-45].

Several longitudinal studies have tracked nicotine exposure in e-cigarette users or combustible cigarette smokers switching to e-cigarette use. Within the context of trials where combustible cigarette smokers are given access to e-cigarettes or asked to switch to e-cigarettes during take-home trials, many show a reduction in combustible cigarette use during the trial (*e.g.*, [43]). The degree to which a switch to dual use or e-cigarette only use affects nicotine exposure has differed across trials. Several studies have shown maintenance in indicators of nicotine exposure, despite reduction in in combustible cigarette use, suggesting that substitution of combustible cigarettes with e-cigarettes can maintain levels of nicotine intake at cigarette-smoking levels in some individuals [46, 47] and that e-cigarette use patterns may be adjusted to maintain nicotine intake across different e-liquid nicotine concentrations [48]. Other studies have shown a reduction in nicotine intake when combustible cigarette smokers incorporate or shift to e-cigarette use [49, 50]. The likelihood of individuals shifting to dual or e-cigarette only use and ability to abstain from combustible cigarette use may also differ based on patterns of use at study baseline [51, 52].

Several cross-sectional studies have measured biomarkers of nicotine exposure across groups of e-cigarette users and/or combustible cigarette smokers. Comparable levels of biomarkers of nicotine exposure were found in combustible cigarette smokers and e-cigarette users [53-55], although some studies find lower nicotine exposure indicators in e-cigarette users [56-58].

2.2. Nicotine Levels in E-cigarette Aerosol

Using human laboratory studies with controlled or ad libitum puffing or smoke-machine-generated aerosol, nicotine in aerosol has been found to vary widely. Some studies have found less nicotine in the aerosol from e-cigarettes relative to combustible cigarettes [59, 60]. Other studies have found the nicotine levels in e-cigarettes aerosol under certain conditions to be equivalent to or more than that from a combustible cigarette [61, 62]. The nicotine concentration of the e-liquid appears to affect the particle dose of the aerosol [63-66]. The other non-nicotine components of e-cigarette aerosol, including potentially toxic components, are beyond the scope of this review. Briefly, e-cigarette aerosol contains nicotine and other potentially toxic compounds (carbonyls, metals, particulate matter ≤2.5 μm in diameter (PM2.5)) [14] and substantial levels of propylene glycol and glycerin are retained from e-cigarettes [67].

2.3. Other Means of Exposure to Nicotine from E-Liquids

Second-hand exposure to nicotine from e-cigarettes is possible [34]. Third-hand exposure (*e.g.*, transdermal absorption) has been demonstrated [68-70]. Nicotine levels on surfaces following e-cigarette use are measurable [71, 72]. Accidental or deliberate self-administration of nicotine-containing e-liquids has been reported [73-75].

2.4. Summary of Nicotine in E-Cigarette Aerosol and Nicotine Delivery

Nicotine in the aerosol and nicotine delivery to the user can reach or exceed levels from combustible cigarette smoking. Non-users may experience second or third hand exposure to nicotine from e-cigarettes.

3. E-LIQUID COMPONENTS AND CHARACTERISTICS

In addition to the nicotine concentration in the e-liquid itself, there are other components and characteristics of e-liquids or the e-cigarette which may impact nicotine exposure, by changing the patterns of e-cigarette use behavior in general, making nicotine more palatable, or enhancing nicotine delivery or bioavailability. For example, a study of vapor produced from 27 e-cigarette products, using 15 puffs from a smoke machine, observed that the correlation between nicotine mass fraction in the aerosol and nicotine concentration in the e-liquid was moderate (28%), and that other characteristics of the e-liquid (*e.g.*, base propylene glycol (PG)/vegetable glycerin (VG) ratio, flavor) and e-cigarette (type, brand, electrical power) also contributed significantly to variance in nicotine yield in the aerosol [61]. Furthermore, aerosol generated by 15 puffs from a smoke-machine under a range of conditions (puff duration=2, 4, 8-sec; puff velocity 17, 33ml/s; voltage 3.3-5.2V or wattage 3.0-7.5 W; e-liquid nicotine concentration 18-36mg/ml) with type of e-cigarette held constant (V4L CoolCart), found a greater than 50-fold variation in nicotine yield generated across conditions [76]. As such, it is also important to consider characteristics of the aerosol that influence nicotine absorption (*e.g.*, pH, aerosol particle size), how vaping behavior influences nicotine delivery (*e.g.*, experienced vs. inexperienced users differential use patterns) and pharmacokinetic and pharmacodynamic studies of e-cigarettes (including site of absorption: *e.g.*, buccal vs. pulmonary), in order to better understand the nicotine delivery profile of e-cigarettes [3]. The level of nicotine in the e-liquid is also a factor in determining nicotine delivery. Therefore, it is also important to consider the accuracy of nicotine labeling and perception of nicotine as a motivating factor for use, to understand how informed users are regarding the nicotine in their chosen products. A listing of various factors and how they might influence e-cigarette use behaviors and nicotine yield is provided in Table **1**.

3.1. Flavors

There is currently an extensive range of flavors available on the current market. Some flavors are designed to mimic the flavors found in combustible cigarettes (*e.g.*, tobacco, menthol-tobacco), cigars (sweet, fruit), while others mimic palatable foods (fruit, desserts, candy) or drinks (coffee, alcoholic drinks) and others contain names that provide little information about the flavor category (*e.g.*, unicorn blood, truth serum, snake oil, *etc*.). The sheer number of flavor products and fact that many products do not disclose their constituents on labels pose a research challenge. As such, the literature systematically assessing how specific flavor additives may directly impact nicotine delivery remains limited. Below we review the converging evidence that flavors may impact patterns of use by increasing the likelihood that individuals will try e-cigarette products or continue to use them and by facilitating nicotine use in e-cigarettes by masking nicotine's aversive properties; and the more limited literature suggesting that flavor additives may alter the properties of the aerosol to facilitate nicotine delivery.

The palatability of flavors and the range of available flavors have been cited as motivators for initiation or persistence of e-cigarette use, particularly among youth and young adult smokers. Experimentation with e-cigarettes among youth may be motivated in part by flavors. Focus group and survey data from adolescents and young adults found flavors to be one of the top reasons cited for motivating e-cigarette use [77]. Taste was the most commonly reported reason (39.4%) that ever users of tobacco and e-cigarettes (N=2430; aged ≥15) reported for choosing their preferred brand of e-cigarettes [78]. In an online sample of adult smokers (N=1200), a discrete choice experiment performed to measure hypothetical choice and price elasticity of e-cigarettes,

Table 1. Overview of potential mechanisms influencing nicotine delivery from E-cigarettes.

Topics			Facilitate Initiation or Continued Use			Enhance Nicotine Delivery			Central Nicotine Effects		Other
Domain	**Factor**	**Paper Section**	**Appeal**	**Perceived Harm**	**Nicotine Dependence**	**Aerosol Volume/ Nicotine in Aerosol**	**Respiration/ Topography**	**Nicotine Absorption/ Bioavailability**	**Nicotine Metabolism**	**Act on nAChRs?**	**Impact Toxicity**
E-Liquid	Flavors (general)	3.1	X	X		~					X
	Menthol	3.1.1	X	X	X		X	X	X	X	
	Sweeteners	3.1.2	X								X
	pH	3.2						X			
	PG/VG base	3.3	X			X		X			X
	Alcohol	3.4			~			X		X	
	Nicotyrine	3.5						X	X		
	Nicotine concentration	3.6	X		X	X			X	X	
Hardware	E-cigarette generations/models/types	4.1	X			X					X
	Activation mechanism (airflow, button)	4.2				X	X				
	Power/Heat	4.3	X			X					X
User Behavior	Puff topography and level of user experience	5.1				X	X	X			X

X=data presented to support this mechanism; ~=preliminary data/hypothesized mechanism.

cigarettes and nicotine replacement therapy, observed that when flavors were unrestricted, younger adults (age 18-24) chose e-cigarettes 3.7% more than older smokers (age ≥25). In the sample overall (age ≥18), hypothetically restricting flavors to only tobacco and menthol reduced choice for e-cigarettes 2.1%, relative to the condition when all flavors were available (*i.e.*, unrestricted flavor condition), an effect that, while limited, was nearly twice as large as the effect of the FDA proposed health warning (1.1%) on hypothetical choice [79]. Adolescents reported higher interest in trying menthol, candy or fruit-flavored e-cigarettes over tobacco-flavored e-cigarettes [80], and perceived fruit-flavored e-cigarettes as less harmful than tobacco-flavored [80]. Furthermore, the perceived harm of e-cigarettes in general and flavors more specifically differs between adolescent ever/current users and non-users of e-cigarettes. Youth who have used e-cigarettes were more likely than non-users to report that e-cigarettes were not harmful or addictive and to report that flavored e-cigarettes were less harmful than non-flavored e-cigarettes [81]. An online survey of Canadian non-smoking youth and young adults (n=279); smoking youth and young adults (n=264) and smoking adults (n=372) assessed the impacts of flavors, nicotine levels and health warnings on perceptions of harm, efficacy as a cessation aid, intentions to try, and choice preference using a discrete choice task. When comparing the overall impact of different attributes (*i.e*., flavors, nicotine level, health warnings), flavors were as influential as health warnings in determining 'perceived harm' of the product (flavors reduced perceived harm, health warnings increased perceived harm), and flavors were more influential than nicotine level at determining perceived harm. Across the different subgroups, different flavors were associated with reduced perceived harm: adult smoking men (tobacco-flavored), adult smoking women (menthol), younger non-smokers (coffee -flavored), younger smokers (cherry-flavored). Intentions to try different e-cigarette flavors followed a similar pattern across subgroups and flavor was only second to health warnings as a predictor of intention to try a given option. Flavors (*e.g.*, menthol, coffee) also increased perceived efficacy of e-cigarettes as cessation aids in the sample overall, while the exact flavors differed across subgroups [82]. Within a sample of adult e-cigarette users, the most common reported reasons for using flavors were increased satisfaction/enjoyment and better feel/taste than cigarettes (including statements indicating that users perceived flavors as increasing palatability by seeming to mask aversive effects of nicotine or other aversive tastes associated with cigarettes), while other common responses included Variety/Customization and Food Craving Suppression [83].

Laboratory self-administration studies with e-cigarettes have also shown that flavors can increase palatability and facilitate self-administration. In a study of e-cigarette users who sampled and rated e-liquids (12mg/mL nicotine) differing in flavors, higher ratings of perceived sweetness and perceived cooling were positively associated with liking the product, while perceived harshness and bitterness were negatively associated with liking. Although nicotine was consistent across e-liquids, so a direct effect of nicotine could not be tested, nicotine is known to increase ratings of harshness and bitterness [84-86]. Therefore, flavors that are perceived as sweet or to have cooling properties or that counteract nicotine's aversive subjective effects may make e-cigarettes more palatable [87]. In a three-part laboratory study, young adult cigarette smokers who were exposed to multiple flavors (unflavored, fruit (green apple), dessert (chocolate)) e-cigarettes, containing nicotine levels that were personalized for each subject based on usual cigarette smoking rates, rated the flavored liquids as more rewarding, more relatively reinforcing (*i.e.* subjects were willing to work harder to receive puffs) and self-administered twice as much of the flavored e-liquid, as the unflavored e-liquid [88]. Adult non-treatment-seeking smokers who had familiarized themselves with the e-cigarette and flavor (*i.e*., take home for one week each and use in place of cigarettes) performed separate 5-minute ad libitum self-administration sessions for each e-cigarette (tobacco or tobacco+menthol) wherein serum nicotine levels were measured prior to and after (+ 5, 10, 15, 20 and 30 minutes) the onset of each *ad libitum* session. A sex by preference interaction indicated that women self-administered more nicotine from the preferred-flavor e-cigarette (tobacco or tobacco+menthol) relative to the non-preferred-flavor e-cigarette. This suggests women's e-cigarette use (and nicotine self-administration) may be more sensitive to flavors than men's [89]. In another study, cigarette smokers with low intention to quit rated their preference for 5 e-liquid flavors at a set nicotine level (18mg/mL) in a laboratory paradigm, then were randomly assigned to a take-home e-liquid condition varying by nicotine (0, 18mg/mL) and flavor (preferred flavor or tobacco-flavor) and asked to use the e-cigarette in place of cigarettes for 6 weeks. Interestingly, those randomized to receive their preferred cherry flavor or tobacco flavor vaped the most over the trial, while those who received their preferred menthol flavor vaped lower levels but also showed greatest reduction in their combustible cigarette use, suggesting that flavors may have differential impact on both e-cigarette use but also the degree to which e-cigarette use replaces cigarette use [90].

The perception of reduced harm in products containing flavorings in general, or certain flavors is problematic not only because it may facilitate use (initiation of, continuation of or increase in use) and exposure to other known risks related to e-cigarettes (general risks of inhalation, exposure to nicotine, *etc*.) but also because some flavor constituents may increase harm. For example, an *in vitro* study which exposed human bronchial epithelial cells to e-cigarette vapor generated from a smoking machine found that indicators of toxicity (metabolic activity, cell viability and release of cytokines) differed significantly across e-liquids matched for nicotine levels, base (PG only) and delivery device settings, but which varied in flavor (*e.g.*, exposure to this particular strawberry e-liquid produced more indicators of toxicity than exposure to some other flavors tested, such as pina colada), suggesting that certain flavor additives contribute to variability in inhalation toxicity of the vapor [91]. An analysis of the flavor chemicals included in a variety of e-liquids found that many were aldehydes, which are known to irritate the mucosal tissue in the respiratory tract, and the levels of total flavor chemicals detected within these samples were often high enough (*e.g.*, 10-40mg/mL) to potentially be of toxicological relevance when inhaling [92]. A subset of tobacco-flavored e-liquids use extracts from cured tobacco leaves as one of the flavor components (*i.e.*, Natural Extract of Tobacco (NET) liquids). While samples of NET had similar nicotine level (and similar inconsistencies of nicotine-labeling) as standard e-liquids, they contained more nitrates and less acetaldehyde, indicating that the method used to flavor e-liquids can impact its toxicity and composition [93]. Flavors could influence nicotine delivery by enhancing the palatability of the e-liquids. As such, additional research and accompanying public education on flavor additives with potential irritant or harmful effects may indirectly influence nicotine delivery from e-cigarettes by altering the perception that some flavors decrease the harmfulness of the product and by extension possibly changing user behavior.

Some preliminary evidence suggests that flavors may impact the total aerosol volume or nicotine delivery, but this has not been systematically studied across flavor constituents. Aerosols from eight e-cigarettes at different nicotine levels and flavors did not find an effect of flavor on concentration of deposited particles in a human lung model [64]. Furthermore, another study tested the amount of smoke-machine-generated aerosol from three e-liquid flavors (strawberry, tobacco, unflavored), across a range of hardware settings (e-cigarettes types, replacement atomizers, power), while holding other e-liquid characteristics constant (50PG/50VG; 18mg/mL nicotine), and observed no significant overall effect of flavor on the amount of e-liquid aerosolized (of note, there was a trend towards less aerosolized strawberry e-liquid, relative to either tobacco or unflavored) [94]. However, a laboratory study in cigarette smokers assessed nicotine delivery from e-cigarettes (~75PG/20VG; unflavored or menthol flavored; 2% nicotine; rechargeable cig-a-like) and found a difference in maximum plasma nicotine concentration by flavor, wherein Cmax for the unflavored 2% nicotine e-liquid (Cmax=3.64) was higher than for flavored 2% nicotine (Cmax menthol flavored=2.5) [40].

The sheer number of flavors commercially available makes it difficult to conduct comprehensive testing to definitively disprove any effect of flavor on aerosol concentration or characteristics. However, one approach might be to focus on common flavor compounds found in e-liquids, rather than testing the range of commercial flavors themselves. Although the variety of flavors on the market poses a research challenge, testing of convenience samples of e-liquids has shown that many of the same chemicals are widely used across flavored e-liquids (*e.g.* vanillin, ethyl vanillin, menthol, 'fruity esters' in fruit-flavored e-liquids, *etc.*) [92, 95]. Furthermore, certain chemicals or additives are known to create the perception of certain flavors in the context of other tobacco products [96], so these chemicals could be assessed for impact on nicotine delivery from e-cigarettes, in addition to focusing directly on commercial flavors.

3.1.1. Menthol

Menthol is a common component of e-cigarettes, as it is with combustible cigarettes. Menthol levels (3,700-12,000 μg/g) found in 36 commercial e-liquids are similar to those often found in commercial combustible cigarettes; and as is the case with combustible cigarettes, low levels of menthol were also observed in a substantial subset (40%) of the 'tobacco flavored, non-menthol' e-liquids assessed [97] and found in e-liquid products not labelled as 'mint' [98]. Review of internal tobacco industry documents regarding their rationale for using menthol in combustible cigarettes as well as extensive clinical and preclinical research on menthol in the context of combustible tobacco products have revealed multiple mechanisms through which menthol impacts smoking behavior and facilitates nicotine delivery, particularly among younger smokers (*e.g.*, [99-107]), it will be only briefly summarized here.

Internal tobacco industry documents indicate that menthol was used and marketed to increase the palatability and appeal of cigarettes and facilitate initiation and continued use in certain subgroups of smokers (*e.g.*, youth, African Americans, women). Menthol was known to enhance the impact of nicotine or provide its own reinforcing impact. By highlighting menthol's cooling and soothing properties (*e.g.*, anesthetic properties which reduced perceived harshness and irritation of tobacco smoke), the tobacco industry promoted the perception that menthol decreased the harm of smoking, which could discourage cessation in those concerned about cigarettes' health risks [102]. Furthermore, menthol, even at low levels (insufficient levels to create a characterizing menthol flavor), was known to decrease harshness and increase palatability if included at appropriate doses relative to nicotine [104]. While at smoking initiation menthol may be preferred to reduce nicotine's harshness (*e.g.*, 'throat hit'), a subset of menthol smokers (primarily black males) transition to cigarettes with higher levels of menthol where the taste and sensory properties of the menthol itself are reported as driving the behavior [103]. Internal tobacco industry documents also indicate that higher levels of menthol could produce its own characteristic 'throat hit', and therefore function to increase the impact of low nicotine combustible cigarettes [104].

Menthol appears to have a clinical impact. Menthol may facilitate dependence or worsen cessation outcomes in some groups of smokers. For example, a review of cessation trials in menthol and non-menthol smokers found mixed results. Five out of the ten studies found worse cessation outcomes in menthol vs. non-menthol smokers, while the remaining five did not show a significant menthol effect. The associations between menthol and worse cessation outcomes were stronger in younger and ethnic/racial minority populations and in studies carried out in the 1990s or later, leading the authors to suggest that the relationship is more pronounced when economic or other constraints force a reduction on cigarettes per day and that menthol may facilitate more efficient nicotine delivery (*via* changes in smoking topography or other factors) with fewer cigarettes [105]. In a separate review of the literature from 2002 to 2010, menthol was associated with increased nicotine dependence in cigarette smokers (*e.g.*, shorter time to first cigarette upon waking), the menthol cigarette smokers displayed lower quit rates and higher relapse rates relative to non-menthol smokers [106].

Numerous mechanisms have been proposed to contribute to menthol's effects on tobacco product use and outcomes (for review: [99, 101]), including but not limited to the following: a) sensory impact, which undermines the aversive sensory effects of nicotine and irritants; b) role as a primary or conditioned reinforcer, c) respiratory effects, d) slowing of nicotine metabolism, thereby increasing bioavailability; e) central modulation of nicotinic acetylcholine receptors (nAChRs) function; e) increasing of transdermal and transbuccal absorption of drugs (*e.g.*, nicotine).

Menthol has sensory impacts of its own and affects the sensory impact of nicotine and irritants (*e.g.*, in combustible cigarette smoke or e-cigarette aerosol) (for review: [99, 101]). Menthol acts on TRP (transient receptor potential) channels, and its action as a nonselective agonist of TRPM8 (transient receptor potential melastatin 8) is responsible for its cooling effects and possibly its analgesic effects and counterirritant properties [108]. In a human e-cigarette self-administration paradigm, higher dose menthol (3.5%), delivered by e-cigarettes induced subjective irritation and harshness in the presence of low nicotine but lowers the subjective reporting of harshness and irritation from high nicotine (24mg/mL) and coolness from menthol was reported to be enhanced with nicotine [86]. Furthermore, youth e-cigarette users rate e-liquids containing a higher (12mg/ml) nicotine level as higher "like/wanting" in the presence of 3.5% menthol, relative to no menthol, but the menthol effect on subjective ratings was not significant at the lower (6mg/ml) nicotine level; while both lower (0.5%) and higher (3.5%) menthol levels increased taste and coolness ratings of e-cigarettes, relative to no menthol [109]. These findings indicate that even very low (*i.e.*, sub-characterizing) concentrations of menthol increase appeal of e-cigarettes and that commercially available higher (*i.e.*, 'characterizing') levels of menthol increase the palatability of higher doses of nicotine.

Menthol can act as a primary or secondary reinforcer [101, 106]. The flavor and cooling sensation of menthol can be reinforcing, pairing menthol with nicotine can increase nicotine's impact thereby increasing the primary reinforcing qualities of nicotine, and repeatedly pairing menthol with nicotine can transfer reinforcing properties to menthol not only as a conditioned cue but also because nicotine is thought to enhance the reinforcing value of paired cues [110]. In mice, chronic menthol plus nicotine administration increased conditioned place preference, upregulated α4α6β2* nAChRs, and increased firing frequency of midbrain dopamine neurons more than nicotine alone [111]. In rats, nicotine self-administration was increased when contingently-paired with menthol or another agent which induced cooling by activating TRPM8, but not by non-contingently-paired menthol [112]. These data indicated that menthol, likely by inducing a cooling sensation, becomes a potent conditioned reinforcer when it is contingently delivered with nicotine. Together, these results provide a key behavioral mechanism by which menthol promotes the use of tobacco products or electronic cigarettes. A review of the combustible cigarette literature from 2002 to 2010 found menthol smokers reported that the taste and sensory effects of menthol were a motivating factor for use, supporting its role as a reinforcer of smoking behavior [106].

Menthol may increase nicotine delivery through its effects on respiration (for review [99, 100, 113]). Garten [100] proposed a mechanism for this effect wherein menthol inhibits respiration *via* its action on cold receptors in the upper airway (activation of cold receptors by cold air also inhibits respiration); resulting in increased breath hold times which he proposed could increase transfer of inhaled constituents-including nicotine and particulate matter in cigarette smoke by increasing the time that the smoke/vapor is held in the lungs but also because breath holding decreases the volume of the lungs thereby increasing pressure in the lungs which facilities transfer of the constituents to the blood stream. However, the size of this effect on nicotine delivery from e-cigarettes is unknown, and may be limited, given rapid absorption of nicotine from the lungs from combustible cigarette smoke.

Menthol has been shown to inhibit nicotine metabolism in an *in vitro* study [114] and in a human laboratory study using a crossover design, in smokers, which found that one week of mentholated combustible cigarette smoking reduced nicotine metabolism relative to one week of non-mentholated combustible cigarette smoking [115]. In young adult daily smokers, menthol smokers have lower nicotine metabolite ratios (NMR= 0.19; indicating slower nicotine metabolism) than non-menthol smokers (NMR= 0.24), after adjusting for important factors associated with NMR (race/ethnicity, gender, body mass index (BMI), (cigarettes/day) [116]. Within Caucasian daily smokers, menthol smokers (compared to non-menthol smokers) had higher cotinine concentration relative to their reported cigarettes per day, consistent with slower metabolism of nicotine and cotinine in menthol smokers [116]. Slower nicotine metabolism would be expected to increase the exposure to nicotine (*i.e.*, remains in system for longer period after intake).

Menthol may also act centrally on nAChR subtypes (α7, α4β2*, α4β6*), in the ventral tegmental area (VTA), therefore impacting nicotine's acute effects and reinforcing properties centrally [101].

Menthol may also increase drug absorption, including nicotine absorption, through multiple routes. As a terpene, menthol has been demonstrated to increase the permeability of drugs through both transdermal and transbuccal routes. Menthol increases salivary flow, which further facilitates transbuccal absorption. Given its impact on other absorption mechanisms, it is possible it also increases pulmonary absorption [99].

3.1.2. Sweeteners

Many commercially available products are marketed as sweet (*e.g.*, 'dessert' flavors), or give the perception of sweetness and may contain sweeteners. For example, assessment of a convenience sample of 37 e-liquid samples of different flavors and manufacturers, detected sucrose in all samples, with substantial variations in levels (range 0.76 to 72.93 μg/g) and no clear associations with different flavor labels or manufacturers. The source of the sucrose in the products was not clear (*e.g.*, from the process of extraction from tobacco leaves or added as part of flavoring) and the authors note that the presence of sucrose could pose a toxicity concern since sucrose could produce aldehydes if heated to sufficient temperatures [117].

Sweet flavors may also increase appeal. Young adult regular e-cigarette users, self-administered then rated e-liquids which authors categorized as 'sweet' (peach, watermelon, blackberry, cotton candy, cola, sweet lemon tea) or 'non-sweet' (mint, tobacco and menthol). The flavors categorized as sweet were rated as more sweet and more appealing than 'non-sweet' flavors, while nicotine-containing (6mg/mL) e-liquids were rating as having more throat hit than e-liquids without nicotine. Perceived sweetness, but not throat hit, was associated with higher appeal ratings (intent to use, willingness to pay, liking), after controlling for nicotine and flavor [118].

Some chemicals used to produce sweet flavors may increase risk. Chemical analysis of 'sweet' flavored e-liquids found the chemicals diacetyl and acetyl propionyl to be present in the majority of e-liquids tested [119]. The authors note that these chemicals could pose health risks: diacetyl is used to create a buttery flavory but has known associations with the respiratory disease known as "popcorn lung" [120-122], and acetyl propionyl is used as a replacement for diacetyl due to the known risks of diacetyl, but preclinical data suggests it may also come with respiratory risks [123].

3.2. pH

The bioavailability of nicotine is dependent upon pH. When nicotine is at a higher pH, a larger proportion of it is in its unionized (aka, "bioavailable", "unprotonated ", "free nicotine", "free-base" nicotine) form, which is more easily and rapidly absorbed through biological membranes. The dissociation constant (pKa) for nicotine is 8.02, meaning that at a pH of 8.02, half of the nicotine is in the unionized free base (more rapidly absorbable) form. Buffering nicotine solutions to make them more alkaline increases the rate of absorption. Buffering agents can be added to the nicotine-containing product itself or influenced by the preparation of the tobacco products. For example, flue-cured cigarette smoke has a lower pH (resulting in less buccal absorption) than air-cured tobacco smoke. Buffering can also occur as a result of biological characteristics of the absorption area. For example, saliva in the mouth, especially when it is at a high flow rate, buffers nicotine solutions (*via* the presence of the bicarbonate, which acts as a natural buffering agent). Furthermore, dissolution of inhaled nicotine-containing smoke into the fluid of the lungs (which has a pH of 7.4) enables absorption (for review of pH and nicotine absorption from smokeless or combustible tobacco: [124, 125]).

Preclinical research indicated that the physiological response to nicotine doses, rate of absorption, and to a lesser degree, total levels of nicotine absorbed are dependent on pH [124]. Absorption of nicotine across mucosa or skin increases exponentially with pH. The tobacco industry appears to manipulate pH levels to alter nicotine delivery across different products. For example, the pH of smokeless tobacco products is associated with the target marketing audiences: with higher pH products generally marketed to more experienced users [124].

The pH of e-liquids has been shown to vary substantially across different e-liquids and has been verified to relate to proportion of nicotine in its bioavailable state. One study, which tested several e-liquid flavors from different brands, found that pH varied substantially (4.78 - 9.60). Non-nicotine e-liquids tend to have lower pH (neutral or slightly acidic), while over half of the nicotine-containing e-liquids had pH higher than 9. Menthol-containing e-liquid also tended to have higher pH. In addition, pH also varied across brands of e-liquids with the same nicotine level, indicating that other constituents, beyond nicotine itself, likely contribute to this variability. Therefore, e-liquids of the same listed nicotine level, which differ on pH, would be expected to differ in nicotine delivery to the user [126]. Similarly, in a second study which tested 36 commercial e-liquid samples, pH ranged from 5.1 to 9.1. Total nicotine concentration of the e-liquids correlated positively with pH. Non-nicotine-containing e-liquids had lower pH in general (weakly acidic: pH = 5.1–6.4). To test whether the alkalinity of nicotine itself was driving the association between nicotine and pH, in-house liquids were made (containing 50PG/50VG base and nicotine concentrations of 6 mg/ml, 11 mg/ml, 18 mg/ml and 24 mg/ml) and tested for pH. The correlation between nicotine and pH was even stronger in the in-house liquids (R2 = 0.965), than in the commercial e-liquids (R2 = 0.827), supporting the hypothesis that nicotine is contributing to pH but also illustrating that other constituents in the commercial e-liquids are likely contributing to pH determination. Using the Henderson-Hasselbalch equation to calculate free-base (*i.e*., more absorbable form) nicotine from the total nicotine and pH, the commercial e-liquids were found to have 60-90% of their nicotine in free-base (bioavailable) form, with a trend towards a higher percentage of the nicotine found in unprotonated form in e-liquids with higher nicotine concentrations (as expected due to the relationship between higher pH and higher total nicotine) [97]. In a sample of commercially available e-liquids which differed in flavor, nicotine content, brand and PG/VG ratio, pH ranged from 5.35 to 9.26 (mean=8.51, SD=0.75). Using pH with the Henderson–Hasselbalch equation to calculate freebase (*i.e*., more absorbable) form of nicotine, there was as strong correlation between the estimated freebase nicotine and directly experimentally measured freebase nicotine (69% shared variance), reinforcing the notion that pH is useful in roughly estimate the percentage of nicotine partitioned into its freebase form. Furthermore, a multiple regression analysis, assessing which characteristics of these e-liquids and e-cigarettes related to nicotine levels in the vapor produced from a smoking machine, found that higher pH had a small but significant association with higher nicotine levels in the aerosol [61]. As such, like with combustible or smokeless tobacco products, manipulation of pH in e-liquids would be expected to influence nicotine absorption [127].

3.3. E-liquid Base Constituents: Propylene Glycol (PG) and Vegetable Glycerin (VG)

E-liquids consist of a base, which is usually comprised mainly of propylene glycol (PG) and vegetable glycerin (VG), and nicotine and flavorants can be added to this PG/VG base. The ratio of PG/VG may influence nicotine delivery as well as toxicity of the aerosol.

In two studies, a higher proportion of PG in the base was associated with more nicotine in the generated vapor or more nicotine delivery to users. In one study, a multiple regression analysis, assessing which characteristics of e-liquids and e-cigarettes related to nicotine levels in the vapor produced from a smoking machine, found that higher percent PG in the base was associated with higher nicotine levels in the vapor [61]. In a separate study, self-administration (30 minutes structured + 1 hour ad libitum) of various e-liquids, found higher plasma nicotine levels achieved from e-liquids containing PG and VG, compared to VG only [128].

Associations between PG/VG ratio and toxic components in the vapor have also been demonstrated. An *in vitro* study that exposed human bronchial epithelial cells to vapor generated from a smoking machine using consistent e-cigarettes, nicotine levels, voltage settings, unflavored e-liquids and varying only the base constituents (PG only, VG only, 50PG/50VG), observed differential effects of PG and VG on two different indicators of toxicity (*i.e.*, reduced metabolic activity, cytokine release): reduced metabolic activity was observed following exposure to vapors from 50PG/50VG and VG only, but not PG only, while cytokine release was increased following exposure to PG only [91]. In a separate study, assessment of vapors emitted from an e-cigarette (*via* smoking machine) from 10 commercial e-liquids, and three control e-liquids where e-liquids varied in the PG/VG ratio of their base solutions VG, PG or 50PG/50VG) found higher carbonyl (formaldehyde, acetaldehyde, acetone) levels in vapor from PG-based e-liquids, relative to VG-based solutions. Since carbonyl levels have toxic properties and been hypothesized to cause mouth and throat irritation, the ratio of PG/VG in the base solution may impact the palatability of products as well as the adverse health risks [129]. However, in a third study, no associations between PG/VG and carbonyls in aerosol were observed [61]. Using a third-generation 'Mod' device containing pure PG or VG (80%VG/20% water) to assess carbonyl emissions at a range of power settings (5-25W), with an increase in power, PG emissions contained more acetaldehyde, VG emissions contained more acrolein, while both PG and VG emissions contained increasing levels of formaldehyde at increasing power settings [130].

PG and VG differ in characteristics (*e.g.*, boiling point (PG=186.6 °C, VG=286.9 °C); molecular weight (PG=76, VG=92)) which could impact their rate of aerosolization at different temperatures, the droplet size or overall volume of aerosol generated from each [131]. Deposition of particles from e-cigarettes was estimated using a human respiratory tract model at two theoretical levels of work effort (reference: nose breathing at ventilation of $1.2m^3$/hr. or heavy work: mouth breathing at $1.688m^3$/hr. under single puff) and observed particle size and concentration in smoking machine-generated aerosols from e-liquid with 16mg/ml nicotine in either a PG or VG base, under single-puff or steady-state puff conditions. Particle size was much smaller from a single puff paradigm relative to a steady-state puffing paradigm. The total volume of particles was higher from the PG e-liquid relative to the VG e-liquid under single puff (30%) and steady-stead (17%) conditions. The distribution of the size of aerosol particles differed by PG/VG, with peak particle counts being larger for VG (180nm) compared to PG (120nm). The model estimated 9-17% of total volume of aerosol would deposit in regions associated with venous absorption (head and airways) and 9-18% in regions associated with arterial absorption (alveoli), with heavy worker models predicting more arterial and reference work model predicting more venous absorption [131]. Taken together this shows that PG/VG may interact with puffing behavior and other conditions to influence aerosol characteristics and absorption.

3.4. Alcohol

Variable ethanol levels have been detected in e-liquids, even in cases when it is not listed as a component [98, 132]. In one study, the maximum ethanol levels detected in a sampling of cartridges or refill liquids was 7.7-fold higher than the limit (0.5%) for pharmaceutical products [133]. Alcohol may be added as a solvent (*e.g.*, to dissolve flavor components such as menthol crystals) or be present due to other stages of production.

It is not known how much alcohol is delivered by e-cigarettes, but there is some evidence that it can be delivered *via* e-cigarettes in sufficient levels to impact behavior. Young adult smokers self-administered e-cigarettes containing nicotine and either high (23.5%) or trace (0.4%) alcohol levels. Although alcohol level did not impact subjective e-cigarette effects, performance on a task of motor control (grooved pegboard) improved with repeated testing in the trace alcohol but not in the high alcohol e-cigarette condition. Furthermore, a subset of participants went from having no detectable ethyl glucuronide (an alcohol metabolite detectible after even low levels of alcohol intake) at baseline to detectable ethyl glucuronide in urine following the high alcohol condition [134]. These findings suggest that e-cigarettes may deliver sufficient alcohol to acutely impact psychomotor function, without detectable subjective effects.

Alcohol and tobacco use is the most common form of polysubstance use and remains a significant clinical challenge [135]. For example, within a large, representative survey of adults in the U.S., higher levels of cigarette smoking and nicotine dependence were found in those who drank more alcohol or met criteria for an alcohol use disorder [136]. Similarly, e-cigarette users report more problematic alcohol use than non-e-cigarette users [137].

There appear to be no published studies directly assessing the impact of ethanol, delivered *via* e-cigarette, on nicotine self-administration. However, the combustible cigarette literature has demonstrated an acute impact of oral alcohol consumption on smoking behavior. In human laboratory studies, alcohol administration has shown to increase urges to smoke, smoking behavior and positive subjective ratings of smoking experience. In smokers, a moderate dose of alcohol, relative to placebo, increased urges to smoke and enhanced cigarette-cue-induced urges to smoke [138]. Smokers (20-30 cigarettes/day) who drank moderate levels of alcohol (4-10 units/week) smoked more during the first hour of ad libitum sessions following higher alcohol doses relative to ad libitum sessions following placebo (*i.e.*, no alcohol) or low alcohol doses [139]. Smokers (5-20 cigarettes/day) who drank alcohol (>5 units/week) but had no history of alcohol use disorder, smoked longer (took more puffs, burnt more tobacco), rated higher urges to smoke, more positive smoking expectancies and rated smoking as more enjoyable (cigarette effects and taste) after ingesting alcoholic drinks, relative to placebo (no alcohol) drinks [140]. Similarly, individuals with alcohol use disorder smoked more cigarettes after drinking an alcohol-containing relative to an alcohol-free drink, including when alcohol doses were blinded [141].

Extensive preclinical and clinical research show interactions between alcohol and nicotine (for review [142]). For example, concurrent delivery of alcohol and nicotine had additive effects on dopamine release in the nucleus accumbens, relative to either administered alone [143, 144]; and impact on the cholinergic system [145, 146]. Preclinical studies, using operant behavior paradigms, provide evidence that nicotine can promote the acquisition, maintenance or reinstatement of alcohol self-administration [147]. Although the neural mechanisms underlying these behavioral effects are unclear, they have been proposed to arise from modulation of the function of neural substrates acted on by both nicotine and alcohol (*e.g.*, mesolimbic dopamine system; 'stress hormone' systems) (for review [147-149]). Furthermore, preclinical research suggests that alcohol's stimulation of the mesolimbic dopaminergic system and locomotor stimulatory and reinforcing effects may be modulated by a direct or indirect (*e.g.*, *via* cholinergic systems) effect of alcohol on certain nAChR subtypes (for review: [150, 151]).

Clinical and preclinical research also suggest chronic alcohol use may speed nicotine metabolism and this effect may be reversible with prolonged abstinence from alcohol. Faster nicotine metabolism is strongly impacted by higher CYP2A6 activity and has been associated with more nicotine dependence [125] (*e.g.*, higher subjective reward from nicotine [152]). The mouse orthologue of CYP2A6 (*i.e.*, CYP2A5 in mice) is induced by chronic alcohol consumption [153, 154], which would be expected to speed nicotine metabolism. In a large sample (N=1,672; 65% Caucasian, 35% African American) of smokers (>/=10cigs/day) who drink fewer than 25 alcoholic drinks per week, more self-reported average alcoholic drinks per week was associated with higher nicotine metabolite ratio (NMR; *i.e.*, faster nicotine metabolism) [155]. However, an association between NMR and alcoholic drinks per month was not found in a mixed sample of smokers and non-smokers, who were all of Black-African descent (N=190) [156]. Within Caucasian males (N=22) undergoing treatment for alcohol use disorder, NMR reduced on average 50% from alcohol-detoxification week 1 through the 7th week of treatment, despite indications that smoking rates had not changed (as indicated by no significant changes in total nicotine equivalents (TNE) in the urine) [157]. Taken together, these findings suggest that alcohol in e-cigarettes may influence nicotine effects and, if delivered chronically in sufficient levels, may influence nicotine metabolism.

3.5. Nicotyrine

A hypothesis has been put forth by Abramovitz, suggesting that nicotine delivery and withdrawal-suppressing effects of e-cigarettes are optimized in the presence of nicotyrine, which may increase aerosolized nicotine absorption through the airways and slow the process of nicotine clearance (by the liver) leading to higher and more sustained nicotine levels [158].

Nicotyrine, a minor tobacco alkaloid, has been proposed as a possible candidate for the component in combustible cigarette smoke which inhibits nicotine metabolism [125, 159, 160], perhaps accounting for slower rate of nicotine metabolism in cigarette smokers, relative to non-smokers [161]. Nicotyrine inhibits CYP2A enzymes, known to be central to the metabolism of nicotine into cotinine and trans 3-hydroxycotinine [159, 162].

The levels of nicotyrine in e-liquids could be influenced by several factors in the preparation, ingredients and storage of e-liquids. Nicotyrine has been detected in some e-liquids [15, 163]. Nicotyrine is one byproduct of the gradual oxidation of nicotine. Oxidation of e-liquids is possible when they are exposed to air as tanks are refilled, or if they are pre-loaded in non-air-tight e-cigarettes. The relationship between nicotine and minor alkaloids in e-liquids is inconsistent, which the authors noted could be due to impurities in the original nicotine used for the e-liquids or could be due to oxidation, which is difficult to estimate since the manufacture date of commercial e-liquids is often unknown [97]. Nicotyrine levels (relative to nicotine levels), measured in commercial e-liquids and their aerosol, increased across e-liquid storage time (days 11-65). The slope of nicotyrine increase was similar regardless of type of storage container and temperature, although nicotine (relative to nicotine) increased more in the aerosol than in the e-liquid. Puff topography also influenced the relative nicotyrine levels in the aerosol: the quantity of nicotyrine produced relative to the quantity of nicotine was 26% with short heating pulses, but only 4% when the atomizer was heated for longer periods (3 seconds). Furthermore, a higher ratio of nicotyrine to nicotine levels were detected in aerosol of e-liquids with PG only base, compared to the aerosol produced from e-liquids with a PG/VG base [164].

3.6. User Awareness of Nicotine Levels

3.6.1. Accuracy of E-Liquid and E-Cigarette Nicotine Labels

Inconsistencies between the labelled and experimentally confirmed nicotine concentrations in e-liquids have been widely reported [165-168] including e-liquids that were labelled as containing nicotine and did not contain detectable levels, but also some e-liquids labelled as 'no nicotine' which did contain measurable nicotine levels [169, 170] or which had higher or lower nicotine levels than labeled [98, 165-171]. The degree of deviation from the labelled levels not only varied across manufacturers, but also -within manufacturers- it varied across flavors [97] and varied across different batches of the same brand and type of e-liquid [28]. Two studies found that the majority of tested samples varied by more than 10% from the label [172, 173]. In contrast, some studies have found labels to be mostly consistent with measured nicotine concentrations [95, 174, 175].

Other aspects of labeling which may impact nicotine delivery have also shown some inconsistencies. For example, the total amount of nicotine in an e-cigarette or cartridge and may not provide a reliable indication of how much is likely to be delivered to the user. For example, nicotine levels were measured in the cartridges from six brands/types of e-cigarette prior to and following 300 smoke-machine-generated puffs (1.8 second puff duration, 70ml puff volume, 10 second inter-puff interval, 15 puffs/bout, 20 bouts, 5 min between each bout) to estimate the amount of nicotine released from the cartridge by puffing. The estimated nicotine released from the cartridge ranged from 10 to 81% of the nicotine originally in the cartridge, and the estimated amount of nicotine released (2-15mg of nicotine released) did not correlate with the nicotine concentration of the e-liquid [28]. Furthermore, five brands of disposable e-cigarettes were tested using a smoke machine for all puffs until the e-cigarette was depleted (*i.e*., no longer produced a puff- for example, due to low battery or insufficient e-liquid). The number of puffs was 28-60% lower than claimed on the packaging across all devices and only 14.4-57.5% of the nicotine measured in the e-cigarette was aerosolized before the e-cigarette was depleted [176]. Even if all the nicotine in the e-cigarette were aerosolized, the nicotine may vary in its degree of bioavailability and rate of absorption. Nicotine delivery is dependent not only on the total nicotine, but also the partitioning between freebase (more bioavailable) and protonated forms, however nicotine levels are frequently report total nicotine, without consideration of this factor. Analysis of e-liquids and aerosolized e-liquids found that the majority of the nicotine was in the free base form and aerosols contained a higher proportion of freebase (relative to protonated nicotine) than the liquids [165].

Taken together these findings underscore the importance of confirming nicotine levels, rather than relying on labeling, when conducting e-cigarette research. Although e-liquid nicotine level is only one of many factors (*e.g.*, e-cigarette device design and settings, puff topography, *etc.*) that influences nicotine delivery from e-cigarettes, inaccurate e-liquid nicotine level labelling could have important clinical implications. For example, individuals opting to avoid nicotine or lower their nicotine exposure by choosing nicotine e-liquids incorrectly labeled as containing no or low nicotine (despite containing higher levels) may be inadvertently exposed to more nicotine than intended, while individuals using e-cigarettes as a nicotine delivery device (*e.g.*, to aid in cessation of other tobacco product use) may be unknowingly obtaining insufficient nicotine to address craving/withdrawal symptoms if using e-liquids incorrectly labeled as containing medium to high nicotine (despite containing lower levels).

3.6.2. Nicotine as a Motivating Factor for use

Nicotine is known to be the primary addictive component of cigarettes, and is therefore important for reinforcing continued use. Higher nicotine delivery from e-cigarettes may facilitate dependence, but may also improve the efficacy (or perceived efficacy) of e-cigarettes as smoking cessation aids. Nicotine levels in e-liquids is one of many factors which influence nicotine delivery from e-cigarettes. However, e-cigarette users vary on the degree to which they report being aware of nicotine levels in their chosen e-liquids, and on the degree to which they report nicotine as a motivating factor contributing to e-cigarette use.

Subsets of users may not be aware of nicotine levels or choose to use e-liquids that they believe do not contain nicotine. For example, among adolescent e-cigarette users, 37.4% reported using nicotine-containing e-liquids, 28.5% reported using nicotine-free e-liquids, but 34.1% reported not knowing the nicotine concentration of the e-liquids they used. Consistent with the addictive characteristics of nicotine, and/or the potential aversiveness of nicotine to nicotine-naïve individuals, those who reported using nicotine-containing e-liquids were more likely to be smokers and heavier e-cigarette users than those preferring no nicotine or not reporting awareness of nicotine levels in preferred e-liquids [177].

Beliefs about nicotine, even in the absence of nicotine, can influence e-cigarette use behavior. Participants were exposed to two e-cigarette self-administration sessions and although both e-cigarettes were nicotine-free, in one of the sessions they were told the e-cigarette contained nicotine. Regardless of reported subjective importance of nicotine, subjects reported greater reduction in urge to smoke to relieve withdrawal symptoms and intention to smoke following the "nicotine" e-cigarette session relative to non-nicotine, and women who reported strong a-priori beliefs that nicotine would alleviate craving had shorter latencies to self-administer the "nicotine" e-cigarette [178].

Substantial proportions of e-cigarette users report nicotine as a motivating factor for use, or one that impacts their perceived efficacy of e-cigarettes as a cessation device. Amount of nicotine was the third most commonly reported reason (27.3%; following taste and price) that ever users of tobacco and e-cigarettes (N = 2430) reported for choosing their preferred brand of e-cigarette [78]. An internet survey of e-cigarette users who visited websites related to e-cigarettes and smoking cessation found that higher ratings of throat hit was reported by those who used higher nicotine content (17.3mg/mL) and throat hit was associated with e-cigarettes perceived as being more effective at alleviating craving to smoke cigarettes and aid in smoking cessation, but was also associated with higher levels of dependence on e-cigarettes [179]. Within individuals who reported having successfully quit combustible cigarette use with the aid of e-cigarettes, a majority (74%) began e-cigarette use with high nicotine levels (>15mg/ml nicotine e-liquids) and none reported reducing their nicotine concentration prior to successful cessation (while 16.2% reported increasing the nicotine concentration of the e-liquid prior to successful smoking cessation). However, a majority (64.9%) reduced the nicotine concentration they used after successful smoking cessation with longer duration of smoking abstinence associated with a greater reduction in preferred e-liquid nicotine concentration [180].

3.7. Summary of E-Liquid Components and Characteristics

Several characteristics and components of e-liquids may influence nicotine delivery. Higher nicotine concentration of the e-liquid will result in greater nicotine delivery, if all other factors are held constant. Flavors may increase exposure to nicotine by motivating users to initiate or maintain use of nicotine-containing e-cigarettes and facilitate use by masking or counteracting the aversive characteristics of nicotine (*e.g.*, bitterness, harshness). Alcohol may interact with nicotine's effects acutely and chronic alcohol exposure may slow nicotine clearance rates. Nicotyrine, a minor tobacco alkaloid, may increase exposure to nicotine by slowing nicotine clearance rates. The relative ratio of PG and VG in the base liquid can affect nicotine delivery.

4. E-CIGARETTE HARDWARE CHARACTERISTICS AND SETTINGS

4.1. E-Cigarette Generations, Models/Types

A large range of e-cigarette hardware products are available on the market. There is extensive evidence that the nicotine (and other constituents) generated by different devices varies substantially. There are a number of design characteristics which appear to contribute to this variability, including power settings, method of activation (airflow versus button-activated), and the method by which the e-liquid is brought in contact with the heating element and how it is heated. Here we review the evidence that different types or brands of e-cigarettes differ in their nicotine delivery and discuss some of the possible design characteristics and settings that appear to contribute to that variability. One challenge to this line of research is that many brands/models differ on multiple characteristics, making it difficult to identify a singular design feature contributing to the variance. In cases where a single feature was highlighted or directly manipulated by the authors, that is noted and otherwise the differences are discussed more generally across brands/models/types.

Most e-cigarettes contain an aerosol generator (*e.g.*, atomizer), flow sensor (if air-flow activated), battery, and storage area for the e-liquid (*e.g.*, cartridge). In some cases the atomizer and cartridge are integrated ('cartomizer'). Rechargeable e-cigarettes have a rechargeable battery and allow for refilling the e-liquid holder, while disposables usually do not have either of those features. The components are made of metals, ceramics, plastics, rubber, fibers and foams- some of which may be aerosolized. First generation cigarettes generally work as follows: Inhalation by the user creates and air flow, which is detected by the airflow sensor, which triggers the flow of power to the heating element, and e-liquids (saturating the wick, *via* capillary action) is aerosolized by the heating element and the aerosol is inhaled into the mouth/lungs. More advanced generation devices enable the user to change settings (*e.g.*, heating coil temperature, air flow rate, *etc*.) and have other hardware differences. The sensor used to determine when to initiate power to the heating element can vary by mode of input (*e.g.*, acoustic) or may be replaced with a button press which initiates the power. The e-liquid can be delivered either by saturation of a wick, like with first generation devices, or with a pump, nozzle or diaphragm. Some advanced generation e-cigarettes contain an adjustable screen with openings so that airflow can be adjusted. Models also differ in the strength of the battery and default power settings, with advanced-generation devices often allowing the user to adjust power settings. Increasing power to the heating element (which vaporizes the e-liquid) can increase the temperature of the aerosol. Since warmer air can hold more e-liquid mass per unit of air volume, heating to higher temperatures can increase vapor generation and may alter the composition of the aerosol (for review of common device characteristics of devices available between years 2004-2013 [181]).

4.1.1. Effects of Generation/Model/Type on Aerosol and Nicotine Delivery

Generally, advanced generation devices produce more aerosol with a higher nicotine yield and deliver more aerosol to the user. For example, nicotine yield in smoke-machine-generated aerosol from 15 puffs differed significantly across type of e-cigarette, with prefilled (rechargeable) and tank-type e-cigarettes generally generating more nicotine in the aerosol than disposable e-cigarettes (disposable= 0.74 ± 0.33 mg; prefilled= 1.06 ± 0.45 mg; tank-system=1.39 ± 0.7 mg) [61]. In a separate study, smoke-machine generated nicotine in aerosol was tested from a selection of e-cigarettes with cartomizers (first-generation, cig-a-like, rechargeable) or tank-type with atomizers (advanced-generation) and combustible cigarettes. The amount of aerosolized nicotine (20 puffs, 4-sec puffs, 30 sec interpuff interval; 45PG/45VG, 2% nicotine) was higher from e-cigarettes with tanks (2.72-10.61 mg/20 puffs) versus cartomizers (1.01-3.01 mg/20 puffs). The amount of nicotine delivered per puff from e-cigarettes with cartomizers was lower than from combustible cigarettes, but some tank e-cigarettes exceeded combustible cigarette levels. The variability across devices were higher with cartomizer-containing e-cigarettes (intersample relative standard deviation (RSD)= 6.9–37.8%; intrasample RSD=5.5-12.5%) relative to tank-containing e-cigarettes (intersample RSD=6.4–9.3%; intrasample RSD=6.4–9.3%). Therefore, advanced-generation tank e-cigarettes provided higher and more consistent levels of nicotine compared with first-generation cartomizer e-cigarettes [182]. Experienced e-cigarette users (N=3; experience with first- and second-generation e-cigarettes; currently using tank systems daily), performed 2-hour ad libitum sessions with a disposable first-generation device or a second-generation tank-system device (on separate test days). Nicotine concentration in the air and nicotine accumulation on surfaces in the testing room were both approximately twice as high following the tank-system session, relative to the disposable device session [72]. Experienced e-cigarette users, who were former heavy cigarette smokers, self-administered a first-generation (V2 standard with cartomizer) and new-generation (EVIC with EVOD atomizer; power set at 9 watts) e-cigarettes containing the same 18mg/mL nicotine e-liquid for one hour (ad libitum) each on separate testing days in a randomized cross-over design. Plasma nicotine levels were higher from the new-generation device at all timepoints (starting 5 minutes into ad libitum; every 15 minutes throughout) with new-generation nicotine levels 70% higher than first-generation at 20 minutes into the sessions and 50% higher by the end of the session. Ratings of satisfaction and craving reduction were also higher for the new-generation versus first-generation device. Plasma nicotine levels reached by the new-generation device by 35 minutes (18.52 ng/mL) were equivalent to those from a combustible cigarette (5 minutes smoking; data from [32]) but the first-generation device did not achieve equivalent levels as a combustible cigarette (at 35 min=7.88ng/mL; at 65 min=15.75ng/mL; peak was 19% less a combustible cigarette) [183]. These findings show that even though new-generation devices only reach 1/3-1/4 the nicotine levels of a tobacco cigarette within the same time frame (*i.e.*, 5 minutes of self-administration), the new-generation device can reach levels of plasma nicotine delivered by a tobacco cigarette with sufficient self-administration period (*e.g.*, 35min *vs*. 5 min with tobacco cigarette) [183]. Dual e-cigarette and cigarette users (N=11; 91% male) self-administered (5 minutes each) their own brand cigarette and e-cigarette as well as 8 popular e-cigarette brands/types (6 first-generation cig-a-likes including 5 from major tobacco companies; 1 second-generation and 1 third-generation) on separate test days, each following overnight abstinence. Despite taking more puffs of e-cigarettes than cigarettes, cigarettes delivered more nicotine than e-cigarettes. Of the e-cigarettes, a first-generation device (Vuse) with very high nicotine concentration (48ng/ml; other e-cigarettes ranged from 16-24ng/mL) delivered the most nicotine, followed by the third-generation, then the second-generation device. Within the cig-a-likes, nicotine concentration in the e-liquids (ranging from 16-24ng/mL; excluding the high 48ng/ml) did not significant relate to nicotine delivery and delivered less than the advanced generation devices (Cmax 8.5 *vs*. 11.7; AUC 158 vs. 238). However, e-cigarette devices did not differ in time to peak nicotine (Tmax 6 *vs*. 6min), which represented a slower delivery than traditional cigarettes, interpreted by the authors as indicating that nicotine was being delivered largely by buccal rather than pulmonary absorption [184]. E-cigarette brands/types available for sale in New Zealand in 2013 were compared with those available for sale and tested in 2008. The newer brands delivered more nicotine and less toxicants to the aerosol than older brands (which were tested at the earlier date) [185].

A cross-sectional study assessed nicotine delivery and other factors from users self-administering their own preferred brand and type of e-cigarette or combustible cigarette. Exclusive cigarette smokers (N=10), second-generation e-cigarette users (defined as tank-style systems; N=9) and third-generation e-cigarette users (defined as mechanical mods, rebuildable drip tanks, rebuildable atomizers, advanced personal vaporizers; N=11) performed a guided then ad libitum self-administration paradigm using their own preferred products (and preferred e-liquids), following overnight abstinence. Voltage did not differ between second and third generation devices (4.1 *vs*. 4.1 volts) but third generation devices had higher power (8.6 *vs*. 71.6 watts), due to higher resistance of the atomizer (0.2 *vs*. 0.4 ohms), and number of atomizer coils did not differ. At baseline, urinary cotinine levels did not differ between groups (smokers *vs*. second-generation vs. third-generation e-cigarette users), but urinary markers of a carcinogenic tobacco-specific nitrosamine (NNAL levels) were higher in smokers than e-cigarette users. During the ad libitum testing period, third-generation users consumed more e-liquid (4.7mg) than second-generation (0.5mg) but third-generation used lower nicotine concentrations on average (4.1mg/mL *vs*. 22.3mg/mL) so taken together, the e-cigarette groups did not significantly differ in the amount of estimated nicotine mass aerosolized (second-generation=9.0mg, third-generation=12.0mg). Plasma nicotine levels were higher for third- *vs*. second-generation e-cigarettes within the first hour of the ad libitum session, but then levels converged at 20-24ng/mL and remained comparable across e-cigarette generation groups within the second ad libitum hour. Reduction in craving was similar across e-cigarette generation groups [186].

E-cigarette types/models also differ in the consistency with which they aerosolize nicotine and the number of puffs generated from a cartridge or percent of e-liquid aerosolized from the device. One study found that the variability of nicotine in aerosol within a single manufacturer and cartridge was similarly consistent as conventional cigarettes within brand/type, but the amount of nicotine aerosolized from different cartridges made by the same e-cigarette manufacturer was more variable compared to conventional cigarettes, and even greater variability was found across cartridges made by different e-cigarette manufacturers [169]. Furthermore, between e-cigarette brands/models there was variability in the number of puffs generated from a cartridge before it was depleted [187]. In a separate study, e-cigarette devices (N=16), chosen based on high popularity in Polish, U.K. and U.S. markets, were tested with smoking machine paradigms to test the amount of nicotine in the vapor (relative to in the cartridge) across bouts of 15 puffs, up to 300 total puffs. There was wide variation across e-cigarettes in terms of the effectiveness of the product in vaporizing nicotine: after 300 puffs products ranged widely in the percent of the nicotine in the cartridge that was vaporized (range 21-85%; on average 50-60%) with e-cigarettes labelled as ‘high’ nicotine delivering from 0.5-15.4mg and those labelled as ‘low’ nicotine delivering from 0.5-3.1mg. Furthermore, most of the nicotine was vaporized within the first 150-180 puffs, indicating that the usage history/fullness of the cartridge could also impact nicotine delivery per puff [188].

The type of e-cigarette may also impact the levels of toxic components delivered to the aerosol. For example, variation in e-cigarette brand has been found to be related to variation in carbonyl levels. [61]. In addition, a laboratory self-administration study with different types of e-cigarettes (at separate sessions) found that while (air plus surface) levels of particles <2.5 microns (PM2.5) were higher using a tank-style e-cigarette, relative to a disposable first-generation device, levels of ultrafine particles (<100nm) were higher after the disposable relative to the tank session [72].

4.1.2. User Perception of Model/Type Effects on Smoking Cessation and Alleviation of Smoking Urges

Some studies indicate that more advanced generation devices deliver a more satisfying ‘hit’ to the user and are perceived as more effective cessation aids. Within individuals who reported having successfully quit combustible cigarette use with the aid of e-cigarettes, all reported using second or third-generation devices at the time of successful smoking cessation, with 31.5% reporting initiating e-cigarette use with a first-generation device which reportedly aided in smoking-reduction, but shifting to second-generation prior to successful smoking cessation [180]. An internet survey in experienced e-cigarette users (N=4,421; predominantly white, male; 18% current dual users of combustible cigarettes) found users of advanced generation devices (as defined as larger than a cigarette and button-activated), relative to first generation devices (size of a cigarette and air-flow activated) reported longer duration of e-cigarette use, more frequent daily use, higher levels of e-cigarette dependence despite use of e-liquids with lower nicotine concentrations, were less likely to be current dual users of combustible cigarettes and rated variety of flavors as more important to their use. While respondents were more likely to report initiating e-cigarette use with a first-generation device, transitions from first-generation device to advanced-generation device were more likely than vice versa and 77% of advanced generation devices report switching to their current device because it had a more satisfying 'hit' [189]. Daily combustible cigarette smokers (>1/day for past year) with no current e-cigarette use, were asked to hypothetically choose between a first-generation (cig-a-like, rechargeable, cartomizer) or second-generation (vape-pen, rechargeable). Rates of choice for each generation did not differ (49%, 51%), but the primary stated reason differed (first-generation: 87% because it resembled a cigarette; second-generation: 45% because it did not resemble a cigarette, 45% because it looked stylish). When randomly assigned to self-administer a disposable first-generation device or the second-generation device (10 puffs, 3-sec puffs; 30sec inter-puff interval; 18mg/mL nicotine concentration, tobacco-flavored), after overnight abstinence, the degree of alleviation of withdrawal symptoms and smoking urges did not differ between generations, but the second-generation device was rated as more 'satisfying' and more likely to be used in a cessation attempt [190].

Some studies have shown greater reduction in craving with advanced-generation devices. For example, overnight-abstinent cigarette smokers with limited e-cigarette experience (<5 puffs in lifetime), self-administered first-generation (rechargeable cig-a-like, Blu, 3.7 volts) vs. second-generation (tank-style, JoyeTech E-go C®, 3.2 volts) e-cigarettes both containing tobacco-flavored e-liquid (16 mg/mL nicotine), following overnight abstinence. Five minutes of ad libitum self-administration with either e-cigarette reduced overnight-abstinence-related withdrawal symptoms, but the reduction in withdrawal symptoms was greater with the second-generation device relative to the first-generation device [191]. Furthermore, an internet survey of e-cigarette users who had quit smoking combustible cigarettes in the past two months (recruited from websites related to e-cigarettes and smoking cessation), assessed which factors were related to user report of e-cigarettes' abilities to reduce craving. Respondents who reported greater reduction in smoking urges following use of e-cigarettes also reported more intensive e-cigarette use, greater dependence on and satisfaction from e-cigarette use, and use of e-cigarettes with higher nicotine concentrations, higher voltage batteries and modular systems (as opposed to unmodified e-cigarette devices) [192].

4.2. Airflow and Activation Method (Button-activated vs. Airflow-activated)

E-cigarette devices vary in the method of power activation. Earlier generation models were generally airflow activated, wherein the puff itself triggered a puff sensor which activated the device to begin the heating of the element. Advanced-generation devices often contain a button which, when pressed, activates the device and begins sending power to heat the element. With button-activated devices, airflow (*i.e.*, a puff) is still required to generate aerosol (therefore, puff duration still impacts aerosol generation), but airflow is not the factor that initiates the power. Some button-activated devices also enable the user to set the amount of time that the element is heated after each button press, whereas with air-flow activated devices, the airflow itself (puff duration, of sufficient velocity to trigger the sensor) would be the major factor determining the duration that the element is heated.

Button-activated and air-flow devices differ on the air flow (puff velocity) required to generate aerosol, pressure drop and characteristics of the aerosol generated. For example, within disposable e-cigarettes tested, button flow activated devices required lower air flow to activate, had lower pressure drop across puffs (during a smoke-out procedure wherein a cartridge was puffed to depletion) and generated fewer puffs before the battery died, but also generated less aerosol at the initial puffs (with vapor production peaking at around puff 50), compared to air-flow activated devices [193]. Machine-generated mainstream aerosol with a standardized puffing paradigm generated more aerosol from a button-activated device with an atomizer and a 280mAh battery compared with an air-flow-activated device with a cartomizer and 180mAh battery [62].

Within device types, there is also substantial variability in airflow required to create aerosol, and it is higher for e-cigarettes relative to combustible cigarettes. For example, using a smoke machine (2.2sec puffs, 1 puff/min) the vacuum required to create cigarette smoke or e-cigarette aerosol was tested in a range of commercial combustible cigarettes and e-cigarettes. Within combustible cigarettes, light brands required stronger vacuum to generate smoke; and e-cigarettes required stronger vacuum than combustible cigarettes. The required vacuum and subsequent density of the smoke or aerosol was consistent within each combustible cigarette brand/type and within e-cigarettes for the first 10 puffs, but then both factors (required vacuum and aerosol density) became more variable through the remainder of the e-cigarette smoke-out procedure (of remainder of the cartridge) [194]. In a separate study, using two different smoking machine puff protocols (10 puff; smoke-out protocol), 12 brands of second-generation cartomizer style e-cigarettes were tested for airflow rate, pressure drop and aerosol absorbance. Pressure drop refers to the leakiness of air from the device and higher pressure drop requires more air flow to produce vapor. Most brands had consistent pressure drop across continued use but pressure drop varied significantly across brands, despite similar e-cigarette styles, but were mostly within the range of tobacco cigarettes (in contrast to reports on first-generation e-cigarettes having higher pressure drops than tobacco cigarettes [187, 194]) but all e-cigarettes tested required higher air flow rates than conventional cigarettes. Air flow rates necessary to produce vapor varied widely across cartomizer e-cigarettes (4–21 mL/s). Aerosol absorbance, a measure of vapor density, was variable across and within cartomizer e-cigarettes (except for those made by major tobacco companies, which were more consistent and had higher densities) [195]. The size of ventilation holes may influence pressure drop (and related required airflow required to produce aerosol) in some models. For example, while lower pressure drop was associated with larger air hole area in 4 out of 8 brand/models tested, it was not associated with airhole size in the remaining models [187].

4.3. Power/Heat

Aerosol is created by e-cigarettes by sending power to the heating element, which then aerosolizes the e-liquid as it heats sufficiently[1]. Different types/models of e-cigarettes have different power defaults or ranges. Advanced-generation devices often allow the user to adjust the power setting themselves, while earlier generation devices come with a set unadjustable power setting. For example, one study assessing a range of devices found power ranged significantly across types of e-cigarettes (range: 2.18-6.96 watts; tank type=6.41± 0.59; disposable= 4.54 ± 1.23; pre-filled cartridges=4.80 ± 0.78) [61].

Increasing power has been shown to increase the amount of nicotine aerosolized. For example, higher electrical power was modestly associated with higher nicotine levels in the vapor generated from a smoke-machine and was also associated with higher total particulate matter in the vapor [61]. A study testing three e-liquids across 3 e-cigarette brands which ranged in power, observed that a 40-fold increase in nicotine in the aerosol was detected at the highest power (35W) relative to the lowest power (5W) device [95]. Furthermore, aerosol generated by 15 puffs from a smoke-machine under a range of conditions (puff duration=2, 4, 8 secs; velocity 17, 33ml/s; voltage 3.3-5.2V or 3.0-7.5W; e-liquid nicotine concentration 18-36mg/ml) with type of e-cigarette held constant (V4L CoolCart), found a greater than 50-fold variation in nicotine yield generated across conditions. Higher power resulted in higher nicotine yield in the aerosol as well as higher total particulate matter (TPM). This study also found that longer puffs were associated with greater nicotine yield and nicotine flux and the authors suggested this effect of puff duration may be attributable to the higher heat achieved with longer puffs (since the heating element is activated during the puff) [76].

Higher power and heat also increases the total volume of aerosol, as well as the composition of the aerosol. A study testing smoke-machine-generated aerosol across a range of conditions (*e.g.*, flavor, e-cigarette types, hardware settings) found that, within different e-cigarette types, increased voltage had a positive linear relationship with the amount of e-liquid aerosolized [94]. In a separate study using two e-cigarette types (EGO and AERO at 3.8V), temperature increased rapidly within the first 20 puffs (5-10 min), then reached a steady state (approximately 34 and 30 degrees centigrade, respectively) with repeated puffs, and emissions were slightly higher during the steady state (when coil and vapor temperatures were highest) [196]. Increasing voltage increased the amount of e-liquid aerosolized and the composition (amount of emissions) in the aerosol. More specifically, increasing voltage between 3.3-4.3 V primarily had the effect of increasing amount of e-liquid aerosolized, while increasing to higher voltages (*e.g.*, 4.8 V) had only modest additional effects on increasing vapor but increased emissions. When increasing power from 3.3 to 4.8 V, the average mass of e-liquid aerosolized per-puff more than doubled (3.7 to 7.5 mg), while the amount of total volatile aldehyde emissions tripled [196]. Several additional studies have linked higher power with more toxins in the aerosol. Electrical power was strongly associated with carbonyls (including formaldehyde) in the aerosol, which range from 3.72 to 48.85 µg/15 puffs [61]. Toxicant emissions (*e.g.*, acetaldehyde, acrolein, and formaldehyde) increased with higher voltage (substantial increase at or above 5 volts) across several e-cigarette types [94]. Using a third-generation 'Mod' device with tobacco-flavored e-liquid (0.9% nicotine; 40PG/50VG), smoke-machine-generated carbonyl (formaldehyde, acetaldehyde) emissions increased with increasing power (5-25 W) [130]. An assessment of aerosols emitted from an e-cigarette (eGo-3; *via* smoking machine) found that increasing the power from 3.2 to 4.8V resulted in a 4-200-fold increase in carbonyl levels (formaldehyde, acetaldehyde, acetone) in the aerosol, with formaldehyde levels reaching the range found in combustible tobacco smoke [129]. In addition, an *in vitro* study exposed human bronchial epithelial cells to aerosol generated from a smoking machine, using consistent e-cigarettes and e-liquids, but varying battery output voltage setting (3.3, 4.0, 4.8 V), found markers of toxicity (metabolic activity, cell viability and release of cytokines) at higher voltages that were not present at the lowest voltages (*i.e.*, no different than air) [91]. However, it is not clear how widespread the use of advanced generation devices at high power settings is amongst e-cigarette users.

4.4. Summary of E-Cigarette Hardware Characteristics and Settings

There is a wide range of hardware available and advanced generation devices allow for user manipulation of settings which can have a substantial impact on nicotine delivery. All other factors being held constant, advanced generation devices operating at higher power/heat will deliver more nicotine than first generation cig-a-like devices or devices operated at low power or heat settings.

5. E-CIGARETTE USE PATTERNS

5.1. Puff Topography and Level of E-Cigarette Experience

Combustible cigarette smokers often compensate for lower nicotine levels or other characteristics (*e.g.*, pressure drop) in combustible cigarettes by changing smoking topography (*e.g.*, increasing puff volume) [197]. Aspects of puff topography have also been shown to significantly impact nicotine delivery from e-cigarettes. Not only does average topography differ between e-cigarettes and combustible cigarettes, but the elements of puff topography that relate to nicotine delivery also differ. Importantly, the validity of nicotine delivery measures does not appear to be undermined by the presence of a topography-measuring device

[1] Power (Watts (W)) is determined by the voltage (Volts (V)) and the resistance (Ohms (Ω)) (Power=Voltage^2/Resistance), where the voltage output is determined by the battery setting and resistance is provided by the heating element from which e-liquids are aerosolized (*e.g.*, atomizer).

on the e-cigarette, although it may affect user's subjective experience. Experienced e-cigarette users, using their preferred device and e-liquid with or without a topography-measuring equipment attached, reported more difficulty of use and lower 'taste good' subjective ratings with the topography-measuring attachment, but achieved equivalent increases in blood nicotine levels and withdrawal suppression [198, 199].

Extensive evidence from human laboratory studies show that puff duration is longer in e-cigarettes than combustible cigarettes and that duration of puff is positively associated with nicotine delivery. For example, cigarette smokers (N=28) were randomized to one of 5 e-cigarettes brand/types (all of which contained 18mg/ml nicotine e-liquid) for 9 days of take-home use. After this take-home experience with e-cigarettes, topography differed between smoking and vaping, with e-cigarette sessions having longer puffs (20% longer) and shorter interpuff intervals (25sec vs. 11sec). There were no effects of brand on topography [49]. A topography study with two e-cigarette types (Blue, V2) found substantial individual differences in puffing topography, but on average more puffs (32 (8)) and longer puffs (2.65 (0.98) seconds) for e-cigarettes relative to typical combustible cigarette topography with more puffs and longer puffs for Blue vs. V2, and no significant difference in puff topography between e-cigarette only users and dual users of e-cigarettes and combustible cigarettes. The estimated nicotine intake (Blue=1.2 (0.5); V2=1.4 (0.7) mg) was comparable to combustible cigarettes. Together these findings suggested that e-cigarette users adjust topography to compensate for lower efficiency devices, to achieve sufficient nicotine levels [200]. Cigarette smokers with no past-month use of e-cigarettes self-administered own brand cigarettes or e-cigarettes and found reduced craving in response to own brand cigarettes but not e-cigarettes. While they increased puff volume and puff velocity for e-cigarettes relative to own brand combustible cigarette, the puff duration was equivalent across both and they took more puffs of the combustible cigarette, so received more nicotine from the combustible relative to the e-cigarette session [201]. These findings are consistent with the notion that puff duration and puff number are greater determinants of nicotine delivery from e-cigarettes than puff volume or velocity (both of which are important determinants of nicotine delivery from combustible cigarettes). In experienced e-cigarette users self-administering e-cigarettes containing 8, 16, and 20 mg/g nicotine (67%PG/30%VG base), nicotine concentration in mainstream aerosol correlated positively with puff duration [202].

Studies with smoke-machine-generated aerosol support the human laboratory studies and find an important impact of puff duration, but not puff velocity. For example, nicotine yield (as measured by nicotine accumulation in a filter attached to the e-cigarette mouthpiece) was increased with longer puff duration, but was not affected by puff velocity in smoke machine-generated aerosols, generated under different puff duration and velocity conditions that were based on hypothetical topographies from combustible cigarette (2sec duration; 33ml/s velocity) or e-cigarette users (4 or 8 sec duration; 17ml/s or 33 ml/s velocity) [76]. Similarly, within smoke-machine-generated aerosol, tested across a range of controlled conditions (*e.g.*, flavor, power, e-cigarette types), puff velocity (*i.e.*, flow rate) did not appear to influence the amount of e-liquid aerosolized [94]. Using a smoke-machine protocol with either a 30-second or 0-second inter-puff-interval, nicotine delivery was substantially increased when there was no pause between puffs, an effect proposed to arise from the consistent heating of the element enabling greater aerosolization of the nicotine [169].

Preliminary data from a small study with experienced e-cigarette users (N=3), found that nicotine retention was approximately 86% after breath-hold only (in mouth), and nicotine retention was higher (approximately 99%) after breath-hold plus inhalation (into lungs), consistent with nicotine absorption from e-cigarettes through buccal and pulmonary routes. Duration of breath-hold was not significantly associated with amount of nicotine retention in the breath-hold only condition [202].

"Direct dripping" refers to a method of e-cigarette use wherein small amounts of the e-liquid are dripped onto the heating element of the atomizer every few puffs. Using a protocol where e-liquid (PG-based, 18mg/mL nicotine) was 'dripped' onto the heating element every 2, 3, or 4 puffs found higher nicotine yields with more frequent dripping (every 2 puffs= 1.03mg; every 3 puffs =0.91mg; every 4 puffs= 0.74mg). In contrast, levels of volatile aldehydes (*e.g.*, formaldehyde) were higher with less frequent dripping: volatile aldehyde release increased at the third and fourth puff after a drip (*i.e.*, as the heating element was hotter (350°C at post-drip puff 4 *vs.* 130°C at post-drip puff 1) with less e-liquid on it) [203].

Level of experience with e-cigarette use impacts nicotine delivery. Many studies with e-cigarette naïve participants use combustible cigarette smokers so their patterns of use may be more optimized for combustible cigarette use. As reviewed above, factors such as the required vacuum to generate aerosol or the average puff duration and velocity differ between combustible cigarettes and e-cigarettes. Therefore, adaptive topography is likely one, but not necessarily the only, factor influencing the effect of experience on nicotine delivery.

Cross-sectional studies comparing individuals with different levels of e-cigarette use show greater nicotine delivery from e-cigarettes in experienced users. Using an advanced generation device (EVIC, 9 Watts, 18mg/ml nicotine e-liquid), experienced e-cigarette users, relative to e-cigarette-naïve combustible cigarette smokers, achieved 46% higher plasma nicotine levels after 5 minutes (10 directed puffs; but still lower than an average combustible cigarette) and maintained this approximate margin of higher nicotine levels throughout a 60-min ad libitum session. During the ad libitum session, the experienced and naïve groups did not differ in the number of puffs they self-administered, but experienced users took longer puffs on average (3.5 vs. 2.3 seconds) and the change in plasma nicotine levels across the session was significantly positively correlated (r=0.37) with puff duration [204, 205]. Furthermore, in two linked studies, cigarette smokers (=/>10/day) who were familiar with but not regular users of e-cigarettes (N=24) reached lower nicotine peaks following 5 minutes (10 puffs/ 30 second interpuff interval) from an e-cigarette (Cmax 2.5ng/mL) relative to a combustible cigarette (Cmax 13.4ng/mL); while in the related study, regular e-cigarette users who smoked cigarettes occasionally (1-5/week) achieved equivalent peak nicotine levels after a 5-minute ad libitum bout of e-cigarette (Cmax for modular system= 7.8ng/mL; for first-generation rechargeable= 4.7ng/mL) or combustible cigarette (Cmax 7.2ng/mL)[206].

Longitudinal studies that recruited individuals without e-cigarette experience and provided them an opportunity to use and familiarize themselves with the product prior to retesting, showed increased nicotine delivery with more experience, which was related to changes in topography (*e.g.*, puff duration). For example, combustible cigarette smokers (N=11) with no prior e-cigarette experience were given take-home e-cigarettes (M201 type, 11mg/mL nicotine) for two weeks and asked to use e-cigarettes and abstain from combustible cigarettes during the two weeks. During ad libitum e-cigarette self-administration sessions, following overnight abstinence, at day 7 and 14 of e-cigarette use, puff duration increased by approximately 40% and puff flow-rate decreased by approximately 20%, relative to e-cigarette-naïve baseline [207]. In a separate study, combustible cigarette smokers (N=6; average 25 cigarettes/day (range 10-60)), with interest in smoking-cessation, participated in two e-cigarette self-administration sessions following overnight abstinence. After the baseline session, participants were given the e-cigarettes (first-generation, rechargeable, cig-a-like with tobacco-flavored e-liquid containing 2.4% nicotine) to take home for 4 weeks (all reported using at home), then returned for a second session after 4 weeks. Nicotine intake from e-cigarette self-administration in the laboratory (5 min, ad libitum) increased at the 4-week session relative to baseline (average peak: Cmax=5.7 vs. 4.6 ng/ml; average overall nicotine: AUC= 206 vs. 115 ng*min/ml), with 4 out of the 6 participants showing the increase in nicotine intake [208].

5.2. Summary of E-Cigarette Use Patterns

E-cigarette users tend to take longer puffs and have longer use bouts than combustible cigarette users. All other factors held constant, longer puff duration increases nicotine delivery from e-cigarettes.

CONCLUSION

E-cigarettes can deliver high levels of nicotine under certain circumstances. E-liquids with higher nicotine levels, advanced-generation devices used at higher power, and longer puffs increase nicotine delivery. Other characteristics, such as flavors, may exert their effect on nicotine exposure more through influencing user behavior (*e.g.*, increased palatability and appeal). Other components/characteristics of the e-liquid, such as pH, alcohol, sweeteners and nicotine minor alkaloids are also important to consider. Given the large range of factors that can impact nicotine delivery, not only within the e-liquids but also in the hardware and user behavior, any regulatory framework intended to moderate nicotine exposure in users may not achieve its intended aim if it is solely limited to a regulation of the nicotine concentration of the e-liquid.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

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