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Review

The Role of Nicotine and Flavor in the Abuse Potential and Appeal of Electronic Cigarettes for Adult Current and Former Cigarette and Electronic Cigarette Users: A Systematic Review

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Abstract

Introduction: Many adult cigarette smokers use electronic cigarettes (e-cigarettes) to cut down on or quit smoking cigarettes. E-cigarettes with higher abuse potential and appeal might facilitate complete switching. E-liquid nicotine concentration and flavor are two of the characteristics that may affect the abuse potential and appeal of e-cigarettes. The objective of this systematic review was to compile results from survey, animal, human laboratory, and clinical studies to understand the possible effects of nicotine concentration and flavor on abuse potential and appeal of e-cigarettes in adult current and former cigarette and e-cigarette users.

Aims and Methods: A comprehensive literature search was conducted in Ovid Medline and PsycINFO followed by citation tracking in Web of Science Core Collection. Peer-reviewed studies published in English between 2007 and August 2020 were selected that analyzed differences between e-liquid nicotine concentration and/or flavors, had outcome measures related to abuse potential and/or appeal, and included adult humans (18+) or animals. A total of 1624 studies were identified and screened. A qualitative synthesis of results was performed.

Results: Results from 104 studies included in this review suggest that higher nicotine concentration and access to a variety of flavors are likely to be associated with higher abuse potential and appeal of e-cigarettes for adult current and former cigarette and e-cigarette users.

Conclusions: Higher nicotine concentrations and the availability of a variety of flavors in e-cigarettes might facilitate complete substitution for cigarettes. Future e-cigarette regulations should take into account their impact on smokers, for whom e-cigarettes may be a cessation tool or reduced-harm alternative.

Implications: E-cigarettes may provide a reduced-harm alternative to cigarettes for smokers unwilling/unable to quit or serve as a path for quitting all nicotine products. Higher nicotine concentrations and flavor variety are associated with higher abuse potential and appeal of e-cigarettes. Higher abuse potential and appeal products may help facilitate complete switching from cigarettes to e-cigarettes. Regulation of nicotine concentration and flavors aimed at decreasing naïve uptake may inadvertently decrease uptake and complete switching among smokers, reducing the harm reduction potential of e-cigarettes. Evidence-based effects of regulating nicotine concentration and flavors must be considered for the population as a whole, including smokers.

Introduction

Electronic cigarettes (e-cigarettes) are a potential "disruptive technology" in the landscape of current tobacco products. They are associated with lower levels of known tobacco-related toxicants compared with cigarettes,[1,2] making them a potentially less-harmful substitute for combustible tobacco use.[3] However, the rising popularity of e-cigarettes has been controversial for several reasons: the high uptake among youth, unknown long-term health consequences, and the potential gateway to and re-normalization of cigarette smoking.[4]

Despite the controversy, there is "moderate-certainty evidence that [e-cigarettes] with nicotine increase quit rates compared to [nicotine replacement therapies]."[5] According to the CDC, there are 34.1 million smokers in the United States, and 68% of them want to quit smoking. Many current and former cigarette smokers report using e-cigarettes to cut down or quit smoking.[6] However, concurrent use of e-cigarette and combustible tobacco products (dual use) is a predominant pattern of use, and co-exposure to e-cigarette aerosol and cigarette smoke, as it occurs in dual users, may result in higher nicotine intake and increased exposure to

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tobacco-related toxicants compared to e-cigarette or cigarette use alone.[2] Therefore, for cigarette smokers to achieve any potential health benefits of e-cigarettes, they must completely substitute e-cigarettes for their cigarettes.[2] To achieve complete switching, smokers may need to have access to e-cigarettes that compete with the abuse potential and appeal of their cigarettes. Abuse potential is the "likelihood that [intentional, nontherapeutic use to achieve a desired psychological or physiological effect] will occur with a particular drug or substance with CNS activity"[7]; appeal is also referred to as consumer appeal, product appeal, or product attractiveness.[8] Both abuse potential and appeal measures are related to nicotine product uptake and continued use.[9–11] Measurements of abuse potential and appeal can therefore point to which product characteristics and under which circumstances e-cigarettes can substitute for combustible cigarettes.

The overarching goal of this systematic review is to characterize the contributions of e-liquid nicotine concentration and flavor on the potential to substitute for cigarettes in an adult population. Nicotine, as the primary addictive drug in tobacco products and a common treatment such as in nicotine replacement therapies, can impact abuse potential of e-cigarettes through affecting the central nervous system and providing sensory effects (eg, harshness, throat hit). Flavor has historically been linked with appeal and even abuse potential in other tobacco products, as exemplified when the 2009 Family Smoking and Prevention Act banned flavored cigarettes (except menthol) and cigarette sales decreased while other flavored tobacco sales increased.[12]

This systematic review will describe how these factors relate to the abuse potential and appeal of e-cigarettes in surveys and human controlled trials for adult current and former cigarette and e-cigarette users,[8,13] as well as in experimental adult animal studies, with the premise that higher abuse potential and appeal of e-cigarettes leads to greater substitution for cigarettes.

The specific question this systematic review aims to answer is: How does nicotine concentration and/or flavor affect measures of abuse potential and appeal of e-cigarettes for adult current and former cigarette and e-cigarette users? Our review is novel in many ways. First, it expands on previous reviews by including research through 2020. Our review includes both tobacco and menthol flavors that are now the only US options for pod-based e-cigarettes on the market, whereas many previous reviews do not include these classic tobacco flavors. It also includes animal research, which is often excluded or ignored in other abuse potential reviews on e-cigarettes despite the fact that it not only provides additional insight (eg, neuroplasticity) but also is often used in abuse liability assessments and FDA policy decisions, particularly with medications.[7] Previous systematic reviews, especially those on e-cigarette flavors, have focused on decreasing youth uptake through banning flavors. In contrast, this review focuses on measures related to abuse liability assessment and appeal within the framework of harm reduction for individuals already addicted to nicotine, in this case focused on adults because they are past the stage of naïve e-cigarette acquisition and are the targets for harm reduction. Finally, we include a section dedicated to nicotine and flavor interactions, which can be informative and includes recent research not included in previous reviews.

Methods

Eligibility Criteria

Studies were eligible if they met all the following criteria:

1. Were a peer reviewed study (all study designs were included) published in English between 2007 and August 2020. This date range was selected based on the emergence of vaping products and research conducted on this topic starting in 2007.
2. Analyzed differences between e-liquid nicotine concentrations, between e-liquid flavors, and interactions between e-liquid nicotine concentrations and flavors.
3. Had an outcome measure related to abuse potential and/or appeal, including dependence, pharmacokinetics, pharmacodynamics, preference/choice, self-administration, intracranial self-stimulation (ICSS), subjective responses, and sensory ratings.
4. Included adult current or former cigarette and/or e-cigarette users (18 and older) or adult animals. If data included youth, adult data needed to be able to be disentangled from youth data.

Information Sources and Search

To build a comprehensive set of relevant studies, a Social Sciences Librarian (AR) designed a search strategy for Ovid Medline. The search strategy was then translated to PsycINFO via Ovid. The search terms and subject headings included *electronic cigarettes*, *e-cig, electronic nicotine delivery system, vaporizer cigarette*, *vape pen*, *vapes*, and *vaping* regarding the product. Additionally terms were used to reflect factors for abuse potential and appeal such as *nicotine concentration*, *nicotine delivery*, *nicotine dose*, *nicotine pharmacokinetic*, *nicotine pharmacodynamic*, *taste perception,* and *flavor*. Database filters were used to eliminate sources published prior to 2007. Searches were conducted originally in September 2019 and updated August 2020. A full search strategy for the primary database, Ovid Medline, is viewable in Appendix A. The database searching produced 1359 items, and EndNote identified 266 duplicates that were removed prior to title and abstract screening. Additionally forward and backward citation tracking in Web of Science was performed on the studies that met eligibility wherein additional studies were discovered. Figure 1 features a PRISMA Flow Diagram with the total number of studies during each phase.[14]

Study Selection and Data Collection

After deduplication of records, two of the authors (MSG and AA) independently screened the title and abstract of each record for inclusion. Discrepancies were resolved by discussion. Irrelevant records were removed from the pool, and potentially relevant records were each individually reviewed in their full text form by the same authors (MSG and AA). Discrepancies were again resolved by discussion. One author (MSG) screened all forward and backward cited records, with 25% of citations checked for reliability by AA. Once selected, one author (MSG) extracted data from each study using a formatted spreadsheet. Rayyan cloud-based software was used to manage the coding process.[15]

Data Items

Data items included in the tables of this review are:

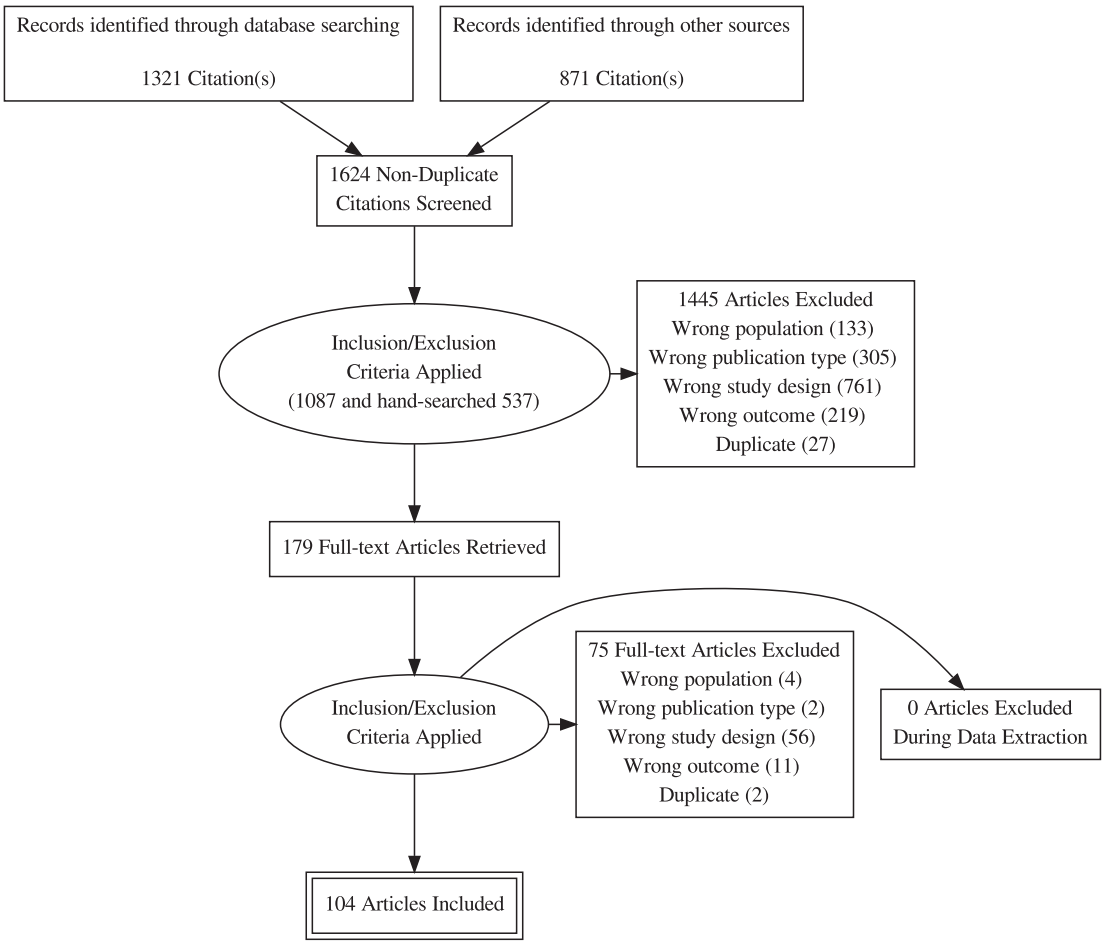

Figure 1. PRISMA flow diagram of article identification, screening, and selection.

- Citation
- Study design (Experimental Animal, Clinical Trial, Human Control Trial [eg, human experimental study], Cross-Sectional, Cohort)
- Sample size, demographics, nicotine use
- Nicotine concentrations and/or flavors
- Abuse potential/appeal measures used
- Summary of results

Risk of Bias in Individual Studies

Risk of bias was assessed using the OHAT Risk of Bias Tool for Human and Animal Studies.[16] Studies were scored on a 4-point scale from 1 (Definitely Low Risk) to 4 (Definitely High Risk). While scores were not used for inclusion or exclusion of studies, this assessment provides a general assessment of the quality of included studies. Two authors (AA and MSG) assessed the same 10 articles then compared results, resolving discrepancies through discussion. Once mutual standards were agreed upon, the remaining articles were split between the two authors to assess on their own.[17] Risk of bias assessment outcomes can be found in Supplementary Table 1.

Results

Study Selection

The search and subsequent forward and backward citation tracking identified 1624 records. Following the screening process, 179 records were reviewed in their full text form; 104 articles were included in the final review. Study characteristics and results of individual studies can be found in Supplementary Tables 2 (Nicotine), 3 (Flavor), and 4 (Interactions). Although risk of bias scores were not used for inclusion/exclusion, they provide a broad view of the general quality of included studies. The majority of included studies showed low-to-probably-low risk of bias (mean score 1.64; standard deviation 0.31; range 1.14–2.63).

Nicotine

Epidemiology/Survey Studies

Twelve epidemiology and survey studies focused on nicotine concentrations used by e-cigarette users and correlates of those concentrations (Supplementary Table 2).

E-cigarette dependence was related to reported e-liquid nicotine concentrations used by daily e-cigarette users. Specifically, increased e-cigarette dependence was associated with increased self-reported nicotine e-liquid concentration, indicating a positive relationship between e-cigarette abuse potential and nicotine concentration.[18] Another study found that e-cigarette dependence was greater specifically among those who reported using more than 13 mg/mL nicotine compared to users who reported using 0–12 mg/mL.[19]

Research on daily e-cigarette users also showed that 74% of e-cigarette users who have recently completely switched from cigarettes report using e-liquid nicotine concentrations greater than 15 mg/mL at the time of cigarette cessation, and

16.9% reported needing to increase their initial nicotine concentrations to achieve complete smoking abstinence. Many (64.9%) substantially decreased their nicotine concentrations following complete smoking abstinence.[20] Findings related to preferred nicotine concentrations were similar for both current and former smokers who are current e-cigarette users; that is, they preferred 15 mg/mL followed by 15+ mg/mL nicotine e-liquid concentrations.[21] In other studies, former smokers reported initiating and continuing to use higher nicotine concentrations compared with current smokers or never smokers.[22,23] In another study of e-cigarette users that had recently quit smoking, higher nicotine concentrations were related to stronger perceived cigarette craving reduction and higher e-cigarette satisfaction.[24] Higher nicotine concentrations may be associated with increased satisfaction and craving relief through providing a stronger throat hit.[25]

Demographic subpopulations of e-cigarette users may be using different nicotine concentrations. For example, among pregnant dual users, most participants (54.1%) reported using low nicotine concentrations (1–6 mg/mL).[26] Furthermore, young adult dual and exclusive e-cigarette users reported using a variety of nicotine concentrations, with the most popular tied between 6, 12, and 18 mg/mL.[27] Among American Indian (Cherokee) dual users, 39% reported using 1–12 mg/mL, 18% reported using 13–17 mg/mL, and 23% reported using 18 mg/mL or more nicotine.[28] Among active-duty military members, participants using an e-cigarette with nicotine reported using an e-cigarette for longer than those using an e-cigarette without nicotine.[29] These studies suggest that higher concentrations of nicotine are associated with greater abuse potential (eg, dependence, duration of use) and associated with complete switching.

Experimental Animal Studies

Experimental animal studies have explored the effects of a range of nicotine doses in e-liquids through self-administration, demand elasticity, intracranial self-stimulation (ICSS), forced choice, and dependence indicators. Since previous reviews have discussed dose response curves and reinforcement thresholds for nicotine in general (eg, Sofuoglu and LeSage, 2012[30]), this section focuses on nicotine in e-liquid or aerosol.

Five animal studies examined the effects of e-cigarette liquid nicotine concentrations on the abuse potential measures listed above (Supplementary Table 2). In general, findings show that higher doses of nicotine are more reinforcing and have higher abuse potential, except at very high doses which become aversive. Adult male rats intravenously self-administered e-liquid aerosol solutions containing nicotine more than vehicle control, denoting higher abuse potential for nicotine containing e-liquid solutions.[31] Male adult rats had greater decreases in ICSS thresholds with higher nicotine concentrations compared to lower concentrations if given either e-cigarette liquid or nicotine-alone; lower thresholds indicate that higher nicotine concentrations are more rewarding than lower concentrations.[32,33] Interestingly, while administration of high nicotine doses increased the ICSS threshold, denoting aversion to the drug dose, this increase was attenuated with nicotine e-liquid compared to nicotine alone.[32] Nicotine-free e-liquids had no affect on ICSS thresholds, supporting a direct effect of nicotine.[32]

Two studies used whole-cage aerosol exposure, finding that higher levels of nicotine in aerosol were associated with higher plasma nicotine and plasma cotinine in rats,[34] and that higher nicotine was associated with more behavioral sensitization—a physiological sign of stimulant dependence in rodents—where more sensitization is related to higher abuse potential.[35] Additionally, after 10 days of aerosol exposure, higher nicotine concentrations were associated with higher withdrawal scores than lower nicotine.[34]

Experiments and Clinical Trials

The fifteen human control experiments and nine clinical trials on the abuse potential and appeal of nicotine in e-cigarettes focused on physiological, psychological, and behavioral effects of different nicotine concentrations in e-liquids (Supplementary Table 2). Physiologically, plasma nicotine was related to liquid nicotine concentrations in both e-cigarette-experienced and e-cigarette-naïve individuals, with higher nicotine concentrations translating to higher plasma nicotine, which according to traditional abuse liability assessments[7] translates to higher abuse potential.[36–40] Specific pharmacokinetic measures, such as Cmax (peak plasma nicotine) and area under the curve (AUC), were positively related to nicotine concentrations, with the highest nicotine concentration (40 mg/mL salt-based nicotine) not being significantly different than combustible cigarette measures.[41,42]

Compared to placebo e-cigarettes, nicotine-containing e-cigarettes relieved withdrawal and craving symptoms in smokers.[43] Higher nicotine concentrations (2.4 vs. 1.6%, 8 vs. 3 mg/mL, and 18 vs. 6 mg/mL) were associated with decreased urge to use cigarettes or e-cigarettes and nicotine withdrawal symptoms compared to lower concentrations following use in e-cigarette naïve cigarette smokers[36] and experienced e-cigarette users (a majority of whom are former cigarette smokers).[38,44] One study found that this was only true if participants were told they were receiving e-liquid containing nicotine.[45] In aggregated cigarette smokers and e-cigarette users, higher nicotine concentrations (8 vs. 3 mg/mL and 36 vs. 8 or 0 mg/mL) were associated with more suppression of nicotine abstinence symptoms and reduced nicotine craving.[37,41] In cigarette smokers, higher nicotine concentrations in e-liquid (40 vs. 16 mg/mL and nicotine containing vs nicotine-free) were associated with reduced desire to smoke in clinical trials,[42,46] and higher nicotine Cmax was associated with increased perceived smoking urge relief in a laboratory study.[47] Higher nicotine concentration (1–24+ mg/mL) was associated with greater nicotine dependence and cigarette dependence in dual users.[48] On the other hand, cigarette smokers that were asked to switch to an e-cigarette (8 vs. 0 mg/mL and 24 vs. 16 mg/mL) showed lower levels of cigarette nicotine dependence in clinical trials if the e-cigarette contained nicotine or higher nicotine.[49,50] One study found that desire to smoke and withdrawal symptoms were equally lower for nicotine-free and nicotine-containing e-cigarettes compared with just holding an e-cigarette, and another study found that nicotine dose did not affect cigarette craving.[51,52]

Liking and choice of e-cigarette doses do not seem to be related to higher nicotine concentrations. Laboratory studies found that greater positive subjective responses and liking of e-cigarettes was associated with lower levels of nicotine for cigarette smokers (0 vs. 18 mg/mL)[53] and e-cigarette users (3 vs. 8 mg/mL).[38] Another clinical trial found no differences in liking ratings based on nicotine concentration of e-liquid for cigarette smokers with medical/psychiatric comorbidities.[54] Gender and anticipation of nicotine also contribute to the psychological response to nicotine in e-liquid. For example,

daily female e-cigarette-only and dual users reported higher psychological reward for nicotine-containing e-cigarettes only if they were told they contained nicotine.[55] This effect was not found for the male participants. Female participants had higher aversion to e-cigarettes containing nicotine regardless of whether they were told it had nicotine or no nicotine in it. Furthermore, in a discrete choice experiment among dual users, choice did not depend on nicotine concentration.[56]

Higher nicotine dose may be related to greater intensity of use. Higher nicotine concentrations were associated with higher puff number and shorter puffs on an e-cigarette, as well as higher e-liquid consumption and nicotine intake for experienced e-cigarette users (18 vs. 6 mg/mL)[44] and e-cigarette naïve cigarette smokers (0–36 mg/mL).[39] One study found that higher nicotine was associated with longer puffs for e-cigarette users.[38]

Higher doses of nicotine may also serve as a better substitute for smoking. In clinical trials where cigarette smokers were asked to use or switch to an e-cigarette, nicotine-containing e-cigarettes (8–45 mg/mL), especially those with higher nicotine concentration, were related to fewer cigarettes smoked per day and lower exhaled carbon monoxide compared with cigarette control or nicotine-free e-cigarettes.[49,57,58] Another clinical trial found that e-cigarette naïve cigarette smokers given nicotine patches and an e-cigarette with 18 mg/mL e-liquid were more likely to have CO-verified cigarette abstinence six months later compared to 0 mg/mL e-liquid or nicotine patch alone.[59] Motivation to quit smoking for cigarette smokers with comorbid medical/psychiatric conditions increased more from baseline to follow-up for participants who used a higher nicotine concentration (24 mg/mL vs. 12 mg/mL).[54]

Conclusions

In general, included studies suggest that higher nicotine concentrations are related to higher abuse potential and appeal, but that nicotine can become aversive at very high concentrations. Epidemiology and survey studies suggest that higher nicotine concentrations are more likely to be used by individuals interested in or who have recently quit smoking. Experimental animal studies added to this finding by showing that nicotine in e-liquid relates to its reinforcing effects, which would be important for individuals who may need a more rewarding experience to switch from cigarettes. Measures of abuse potential and appeal in experimental and clinical studies supported these findings, suggesting that higher nicotine concentration is associated with higher plasma nicotine levels, greater relief of craving and withdrawal, greater dependence, increased use, and a better substitution for cigarettes. Further studies are necessary to include newer e-cigarette devices, larger populations, a wider variety of nicotine concentrations, and control over factors that affect nicotine delivery (eg, power, e-liquid solvent composition).[60] Overall, current research on e-liquid nicotine concentrations and abuse potential and appeal suggest that higher nicotine concentrations (12+ mg/mL) are experienced more favorably and used more for quitting than lower or no nicotine in e-liquid but also that access to a variety of nicotine concentrations is likely the most helpful for cigarette smokers trying to quit smoking.

Flavor

Epidemiology/Survey Studies

Thirty-one epidemiology and survey studies examined the relation between flavor and abuse potential or appeal measures such as preference/use, intention to use, value/importance, and smoking reduction/cessation outcomes (Supplementary Table 3). Between 2012 and 2013, market share of nonflavored and menthol/mint flavored e-liquids decreased, while fruit and "other" flavors increased.[61] Research since then has shown an increase in the number of e-cigarette users whose first product and current product is flavored.[62–65] This is supported by surveys of adult e-cigarette users, which show that over time, flavor preferences have changed, migrating from traditional tobacco flavors (tobacco and menthol/mint) toward sweets and candy flavors.[66] One survey found that between 2011 and 2016, tobacco as an initial flavor decreased from 46% to 24% of e-cigarette users, while fruit as a first flavor increased from 17.8% to 33.5%, followed closely by dessert/pastry and candy/chocolate/sweets flavors.[67] This change may be the result of an increased availability of flavors or a real change in flavor preference.

In general, the most preferred/used flavors were fruit, mint/menthol, and candy/dessert flavors.[21,27,62,64,68–75] For cigarette smokers who recently bought a JUUL e-cigarette online, mint and mango were the most commonly used flavors.[76] Mint and fruit flavors were also the most preferred JUUL flavors for college student and adult JUUL ever-users.[77,78] These preferences replicate in subpopulations such as pregnant or racial and ethnic minority e-cigarette users (eg, Asian American/Pacific Islander or Maori).[26,79–81] Users of these flavors rate their e-cigarettes higher on satisfaction and lower on perceived addiction risk compared with tobacco flavored or unflavored e-liquid users.[63]

Compared to former smokers or cigarette-naive e-cigarette users, dual use and/or increasing age were associated with higher tobacco flavor preference, although fruit and/or menthol/mint flavors were still generally more preferred than tobacco even in these populations.[21,27,62,69] Dual users were more likely to begin e-cigarette use with tobacco flavor compared with former smokers.[62]

Availability of a variety of flavors and the ability to switch between flavors was a valued aspect of e-cigarettes, and was often cited as a main reason for use—behind health and smoking cessation.[26,29,65,72] Flavor was also associated with increased intention to use, ever trying, and current use of e-cigarettes in college students.[82] However, another study of adult e-cigarette users found that neither preference for specific flavors nor total number of preferred flavors were significantly associated with e-cigarette use.[83] These findings may mean that dual users, smokers who have tried and rejected e-cigarettes, switchers, and nicotine quitters have different flavor preferences (eg, tobacco related flavors were associated with dual users while fruit flavors were associated with switchers[84]).

The focus of many studies has been the effect of flavored e-cigarette use on cigarette use and cigarette/nicotine dependence among cigarette smokers and dual users, as greater uptake of e-cigarettes would suggest higher abuse potential and appeal and possibly greater substitution for cigarettes. These studies show varying results. Compared with using tobacco or unflavored e-liquids alone, cigarette smokers who used one or multiple nontobacco flavored e-liquids were more likely to have reduced or quit smoking.[76,85–87] Another study also found that flavored e-cigarette use was associated with fewer cigarettes smoked per day; however, it found no change in number of days smoked per month or nicotine dependence compared with unflavored and tobacco flavored e-liquids.[88]

The number of flavors used may also be important, as one study found that the number of flavors used was associated with increased cigarette smoking cessation for dual users.[72] In sum, the epidemiological studies suggest that nontobacco flavors are highly valued and increase the abuse potential and appeal of e-cigarettes.

Experimental Animal Studies

Five animal studies examined the impact of flavor on abuse potential and appeal (Supplementary Table 3). Wickham et al. (2018)[89] found that oral sweeteners increased dopamine release in the nucleus accumbens in rats, an area of the brain associated with reward and addiction. This study also found that oral sweeteners increased intravenous nicotine self-administration. Last, they found that oral menthol flavor attenuated nicotine aversion. Avelar et al. (2019)[90] examined farnesol, a flavorant used in fruit-flavored e-liquids. They found that intraperitoneal (i.p.)-injected farnesol increased dopamine neuron firing rates and reward-related behavior for male but not female mice. Additionally, farnesol increased locomotor sensitization and upregulated alpha-6 containing nicotinic acetylcholine receptors. Wong et al. (2020)[91] described higher consumption and preference for fruit-flavored nicotine-containing e-liquids compared with nicotine alone for 75, 100, and 200 μg/mL concentrations for adult male mice in a two-bottle choice task. However, conditioned place preference, place aversion, and serum nicotine/cotinine at 10, 20, 30, or 50 min did not differ across flavors (tobacco, fruit, and unflavored) compared with nicotine alone following intraperitoneal injections.

Menthol flavoring added to a bottle of nicotine liquid increased nicotine intake and nicotine preference for male but not female rats.[92] Menthol injections dose-dependently decreased nicotine clearance, resulting in increased nicotine AUC and prolonged nicotine effects (eg, antinociception) in adult male mice.[93] The results from these various studies suggest that sweetness and cooling flavors elicit reward-related behaviors and neuroplasticity on their own, as well as increase the rewarding properties of nicotine.

Experiments and Clinical Trials

Sixteen laboratory experiments and four clinical trials focused on the role of flavor in e-cigarette abuse potential and appeal (Supplementary Table 3). One laboratory study found that young adult e-cigarette users found fruit flavors more appealing than tobacco flavor; female participants additionally found menthol more appealing than tobacco flavor while male participants did not, even after controlling for menthol smoking.[94] However, in another laboratory study users found their usual flavor—which varied—more likeable and satisfying compared with strawberry or tobacco flavors sampled in a study, suggesting less emphasis on specific flavors and more emphasis on access to flavors preferred by the individual.[95]

Liking an e-liquid flavor correlated with increased sweetness and coolness and decreased harshness and bitterness for dual users.[96] Supporting this, another study found that for young adult e-cigarette users and adult cigarette smokers, ratings of sweetness positively correlated with liking, willingness to use again, and perceived monetary value of e-cigarettes.[53,97] Furthermore, sweet and fruit flavors shown in e-cigarette ads elicited greater fMRI nucleus accumbens activity compared with tobacco flavors for nonsmoking young adults who had tried an e-cigarette before and were deemed susceptible for future e-cigarette use.[98]

Cherry and menthol flavor were rated more highly on perceived pleasantness, taste, and physical sensation compared with unflavored and tobacco flavors by e-cigarette naive cigarette smokers.[99] Young adult cigarette smokers rated fruit and dessert flavors significantly more rewarding and satisfying than unflavored e-liquid, and preferred fruit flavor over dessert flavor.[100] Cigarette smokers in one clinical trial rated menthol flavor as more likeable than tobacco flavor.[54] One study found that while there was no difference in demand elasticity for tobacco versus menthol flavored e-liquids, cherry had a higher crossover point and less demand elasticity than unflavored e-liquid, indicating that participants found cherry more valuable than unflavored e-liquid.[101]

St. Helen et al. (2017)[95] found that nicotine $AUC_{0\rightarrow180}$ and Cmax were higher with strawberry flavor than tobacco flavor. The study also found that puff duration was longer with strawberry than tobacco, and even longer for their usual brand e-liquid, which varied in flavor.[102] One clinical trial found that for daily smokers, cherry flavor had the highest Cmax and AUC over the first 10 min, while vanilla had the lowest of these measures; menthol flavor had the highest AUC over 2 h, and tobacco had the lowest.[103] However, another clinical trial found that for cigarette smokers, there was no main effect of preferred flavor (menthol or tobacco) on nicotine delivery.[104] Young adult cigarette smokers worked harder for flavored compared with unflavored puffs on an e-cigarette, and took more puffs on flavored compared with unflavored e-liquid during *ad-libitum* use.[100]

Discrete choice tasks in e-cigarette literature parse out which product features relate to consumer choice, and many have included flavor. Increased flavor availability was related to increased e-cigarette selection for younger but not older adult smokers, and for e-cigarette-naïve but not for individuals who had used e-cigarettes before.[105] However, another study found that fruit/candy/sweet/other flavors and menthol flavors decreased probability of dual users choosing e-cigarettes over cigarettes compared with tobacco flavor, although menthol smokers specifically preferred menthol flavored e-cigarettes.[56] This may be due to smoking status, as current adult smokers chose tobacco flavors, e-cigarette users who had recently quit smoking chose fruit/sweet flavors.[106] Supporting this finding, young adult nicotine users who preferred smoking to e-cigarettes preferred tobacco flavor; while participants who preferred e-cigarettes to smoking preferred fruit and candy flavors.[107]

Cigarette smokers reduced cigarettes per day more in a clinical trial when asked to use a menthol flavored e-cigarette compared to other flavors, and reduced the fewest cigarettes per day with chocolate and cherry flavors compared to other flavors.[108] The same study found that the highest e-cigarette uptake was for tobacco and cherry flavors and lowest for chocolate flavors. However, two other clinical trials found no differences between flavors in cigarette withdrawal symptoms or smoking/e-cigarette craving for daily cigarette smokers[103] or e-cigarette users.[36] In general, the results from the experimental and clinical trial studies are concordant with the other type of studies: sweet and cooling flavors had higher appeal and abuse potential compared to tobacco-flavor, with some variability based on age and smoking history.

Conclusions

Overall, the included studies suggest that flavors, especially fruit, candy, and menthol/mint, increase the abuse potential and appeal of e-cigarettes through increasing sweetness or coolness and decreasing bitterness and harshness of the product. This in turn leads to higher use and choice of that product. Individuals overwhelmingly favored fruit flavors, followed closely by menthol/mint and candy/dessert flavors. Tobacco flavors, however, were appealing among nonmenthol cigarette smokers and dual users. Animal studies similarly found preferences and reward-related behaviors associated with fruit flavors and sweeteners; flavors alone can also serve as a reward. Interestingly, in human studies there were differences in appeal, choice, and nicotine delivery of flavored products based on smoking status and age. In general, young adults and exclusive e-cigarette users who are either cigarette-naive or recent quitters were more likely to use nontobacco/menthol flavors, while increasing age, dual use, and cigarette-only use were more likely to choose tobacco or menthol flavors. Overall, these results suggest that flavors affect the abuse potential of e-cigarettes through increasing product appeal, especially through the availability of a variety of flavors to account for individual preference.

Nicotine and Flavor Interactions

Fifteen studies discussed how the statistical interaction between nicotine and flavor affects e-cigarette abuse potential and appeal measures (Supplementary Table 4).

E-liquid Nicotine Concentration and Flavor Interactions

In a discrete choice experiment with cigarette users and nonusers, interest in trying an e-cigarette was positively related to cherry and menthol flavors with "low" nicotine levels, and negatively related to tobacco flavor with "medium" nicotine levels.[109] The same study found that perceived cigarette quit efficacy was associated with menthol and coffee flavors with low nicotine content, and negatively associated with tobacco and cherry flavor with nicotine-free or medium nicotine content. Another study found that for young adult cigarette smokers, "high" nicotine dose plus tobacco/menthol flavor was associated with a significant decrease in cigarette smoking urges.[110] Interestingly, tobacco/menthol flavor was associated with increased nicotine/drug effects even in nicotine-free e-liquid, and the nicotine-free e-liquids containing cream and fruit flavors were rated the most pleasant and led to more interest in using again compared with any other nicotine/flavor combinations.[110] Menthol and fruit flavors interacted with nicotine concentration (0 vs. 24 mg/mL) in another study, with menthol being more disliked than fruit in nicotine-free e-liquid, but less disliked than fruit in nicotine-containing e-liquid.[111]

Effects of Sweet and Cooling Flavors on Nicotine's Harshness

The majority of research on interaction effects focused on the ability of flavors to attenuate the harshness or appeal reduction of higher nicotine concentrations. Results from this research were inconsistent. While some studies found this attenuation for fruit and menthol/mint flavors for young adult vapers and adult cigarette smokers[112–116] other studies found no such association with fruit, menthol, or sweet flavors for young adult exclusive e-cigarette users or young adult menthol cigarette smokers.[97,117,118] One animal study also failed to show this association, with no affect of arctic blast flavor on responding for nicotine injection or aerosolized e-liquid.[119] However, another animal study showed that i.p. menthol injections led to more lever presses for lower nicotine and fewer for higher nicotine, as well as a higher nicotine breakpoint, than without menthol.[120] Similarly, another study showed that i.p. menthol injection increased nicotine conditioned placed preference more than nicotine or menthol alone and enhanced nicotine-related neuroplasticity.[121]

This discrepancy in the research on whether flavors have attenuating effects for higher doses of nicotine may be due to flavors chosen, or due to the smoking history of the e-cigarette users, as one study found that flavors attenuated harshness only for e-cigarette users who were not current/former cigarette smokers.[112] Another study found that fruit and menthol attenuated nicotine appeal-reducing effects for young adult users who did not vape to quit smoking, but not for those who did vape to quit smoking.[114] Attenuating effects may also be due to the sweetness level of an e-liquid, as one study found that enhancing the sweetness of nicotine-containing flavored e-liquid increased wanting and liking ratings compared with nonsweetness-enhanced nicotine e-liquids or sweet nonnicotine e-liquids, and that sweetness enhancement led to increased nucleus accumbens activation suggesting higher reward.[122]

Conclusions

Overall, the included articles suggest that nicotine and flavor may interact to affect the abuse potential and appeal of e-cigarettes. While the evidence presented on how these factors interact is conflicting, it is likely that sweet or cooling flavors (eg, fruit or menthol/mint) attenuate the harshness and bitterness of higher nicotine concentrations, or increase the pleasantness and liking of nonnicotine e-liquids. It is important to note that smoking history and using an e-cigarette to quit smoking may play a role in how nicotine concentrations and flavors interact.

Discussion

Summary of Evidence

There were several important findings of this review. In general, increased nicotine concentrations in e-liquid were associated with higher abuse potential and appeal in animals and for adult cigarette, e-cigarette, and dual users. Medium to high levels of nicotine (12–18 mg/mL on average) were the most preferred/used nicotine concentrations, especially for individuals trying to or who had recently succeeded in quitting smoking (eg, Farsalinos et al., 2013[20]). Higher nicotine concentrations were also related to higher levels of plasma nicotine, greater decreases in withdrawal symptoms and higher dependence, indicating greater central nervous system activation (eg, D'Ruiz et al., 2015[36]). This is supported by animal studies, which showed increased reward-related behaviors with increasing nicotine doses, although nicotine became aversive at very high levels (eg, Harris et al., 2018[31]).

Another major finding was that flavors, especially nontobacco flavors, were related to increased abuse potential, especially through increasing the appeal of e-cigarettes. Fruit, menthol/mint, and candy/dessert flavors were the most preferred/used across all e-cigarette user groups, although dual

users rated tobacco flavor highly as well (eg, Berg, 2016[27]). In animal studies, flavors themselves elicited reward-related behaviors (eg, Avelar et al., 2019[90]). Use of nontobacco and nonmenthol flavors were associated with quit rates in cigarette smokers, suggesting flavors, especially access to a variety of flavors, are an important aspect of the e-cigarette experience and may make up for an e-cigarettes lower nicotine delivery abilities (eg, Chen, 2018[85]). However, no study to date has done a head-to-head comparison of cigarette cessation between different flavors (eg, flavored vs. tobacco/menthol or tobacco vs. menthol).

While nicotine and flavor have their own rewarding effects, their interaction may further increase the abuse potential and appeal of an e-cigarette through decreasing negative sensory experiences and increasing positive ones (eg, Leventhal et al., 2019[113]). These results, however, are not consistent, likely due to differences in nicotine concentrations or flavors used in studies, as well as the fact that many studies used convenience samples or did not include all types of e-cigarette users (eg, dual users vs. e-cigarette-only).

Implications

This study's findings may provide guidance on the prospective effectiveness of regulations such as nicotine caps or flavor bans on overall public health. Promoting complete switching to e-cigarettes among smokers unwilling or unable to quit nicotine is predicated on the evidence that e-cigarettes reduce harm compared to cigarettes.[1,2] Current evidence indicates substantial reduction in exposures to tobacco-related toxicants in cigarette users who completely switch to e-cigarettes; however, long-term health consequences are unknown.[4] Abuse potential and appeal is important to measure as it relates to product uptake and persistent use, and may provide insight into an e-cigarette's potential to act as a complete substitute for cigarettes. The US Food and Drug Administration (FDA) aims to regulate e-cigarettes to decrease youth uptake and addiction. However, the FDA also recognizes that e-cigarettes may be used as a harm reduction device for cigarette smokers, leading to possible health benefits for these individuals.[123] Therefore, thoughtful consideration needs to be given on how to balance the risks and benefits to youth and to adult smokers.

Results from this review point to the potential unintended consequences of capping nicotine concentrations too low in e-liquids, as higher e-liquid nicotine concentrations (>12 mg/mL) were associated with cigarette smokers completely switching to e-cigarettes. Indeed, young adult dual users report that if e-cigarettes were offered only nicotine-free, they would decrease or stop using their e-cigarette and maintain or increase their combusted cigarette use.[124] The United Kingdom and European Union have issued a cap on nicotine concentration to 20 mg/mL, which is likely sufficient for cigarette smokers interested in quitting, especially since higher nicotine concentrations are associated with harshness and bitterness (Tobacco Products Directive, 2017). However, recent studies show that smokers who use higher doses of nicotine e-liquid (5% nicotine salt by weight or 36 mg/mL) had higher rates of cessation success or smoked fewer cigarettes per day than smokers using lower doses (2% nicotine salt by weight or 0–8 mg/mL).[125,126]

While randomized control trials did not examine whether certain flavors are necessary for switching to e-cigarettes, results from this review highlight a majority preference for nontobacco flavored e-liquids in the United States that has grown over time. However, these results were not consistent on whether and which flavors might be associated with e-cigarette uptake and switching from cigarettes, instead emphasizing the appeal of access to a variety of flavors. Importantly, young adult dual users report that if e-cigarettes were offered in only tobacco and menthol flavors, they would decrease e-cigarette use but maintain or increase their cigarette use, raising concerns about the possible harm of a flavor ban.[124] This is important, as in 2020 the US FDA banned flavors for pod and cartridge devices, except for menthol and tobacco, as youth populations have been using these devices with nonmenthol/tobacco flavors the most.[127] While other types of e-cigarettes (eg, tank systems) currently have many available flavors, discussions on banning flavors for these devices should take into account that banning flavors might turn e-cigarette-only and dual users towards combustible cigarettes and do not promote cessation attempts among cigarette smokers.

Limitations and Future Directions

This study included research with a wide variety of study designs, populations, and outcome measures. However, there are a few limitations to the review and the studies involved. First, while a systematic search was created and used, this search may have missed important studies on how nicotine or flavor affects the abuse potential and appeal of e-cigarettes. For example, Cooper et al. (2021) found that menthol or green apple flavoring increased nicotine vapor self-administration in male mice.[128] We were also unable to perform a meta-analysis or include effect sizes for studies due to the heterogeneity of the included research. Additionally, although young adults are an important population, we did not focus on age group differences in this paper since only some included studies divided the population into age groups, and the variability in definitions of these age groups differed substantially (eg, young adults ages 18–25 vs. 21–34). However, this heterogeneity also allowed the review to include important studies and increase the wealth of information contained within our results.

Another limitation is that many of these studies suffered from small sample sizes that limited their power and generalizability. Further research is necessary with larger populations to increase power for these studies to analyze interaction effects or multiple outcome variables. Additionally, many populations in these studies were convenience samples or limited by recruitment strategies. For example, recruitment through online vaping forums likely resulted in a positive bias of vaping. One population that was rarely included was individuals who tried vaping and then stopped, who would add valuable data on negative perceptions to balance the current research.

While outcome measures within this review encompassed many aspects of abuse potential and appeal, measures in each study largely stood alone. Integrating perception, physiology, and behavior within results of the same study would give better insight into how these different variables interact to create "abuse potential and appeal."

Finally, randomized control trials will be needed to answer specific questions about which nicotine concentrations and flavors promote cigarette smokers to switch completely to e-cigarettes.

Conclusions

While there is still much to learn about how flavor and nicotine concentration in e-liquids affect the abuse potential and appeal of these products for adults, current research suggests that medium and high nicotine concentrations and sweet or cooling flavors such as fruit and mint are more preferred and used, especially for those who have recently switched completely to an e-cigarette from cigarettes. This may suggest that availability of flavors is related to increased e-cigarette use. This preference for flavors warrants further research exploring whether the availability of flavors increases the potential of e-cigarettes to serve as a viable substitute for cigarettes. The high value of medium-to-high levels of nicotine and fruit and sweet flavors in e-liquids suggests that nicotine caps and flavor bans would likely affect adult e-cigarette users, including those using e-cigarettes to quit cigarette use. Other regulatory strategies such as restrictions on marketing or access and sales of e-cigarettes to youth might be considered over flavor bans and caps on nicotine concentrations in e-liquids to attenuate adolescent uptake while allowing adults to use this nicotine product as a harm reduction tool for cigarette smokers.

Supplementary Material

A Contributorship Form detailing each author's specific involvement with this content, as well as any supplementary data, are available online at https://academic.oup.com/ntr.

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Declaration of Interests

None declared.

Data Availability

No new data were generated or analyzed in support of this research.

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