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Review

Addiction-Related Outcomes of Nicotine and Alcohol Co-use: New Insights Following the Rise in Vaping

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Abstract

Purpose: Nicotine and alcohol-containing products are some of the most commonly used substances of abuse and are both leading causes of preventable death. These substances also have significant interactions that have additive and, in some cases, multiplicative effects on the health consequences of their use. Thus, to reduce these negative consequences, it is important to understand the abuse liability of nicotine and alcohol in combination, especially in the most relevant use cases among those who are most vulnerable. Specifically, as tobacco cigarette use is continually decreasing, vaping is quickly replacing cigarettes as the primary mode of nicotine use. This pattern is especially true in adolescent populations in which vaping has grown considerably. Particularly concerning is that adolescents are more vulnerable than adults to the negative consequences of substance use. It is therefore imperative to revisit the literature as it relates to the rising state of co-use of vaping products with alcohol. Here, we review the clinical outcomes of nicotine and alcohol co-use as they relate to the abuse liability of each individually. Special attention is paid to adolescent findings, where available, as well as investigations that use nontobacco nicotine products as these may more accurately reflect the more recent trends of co-use.

Implications: Though nicotine alone has previously been considered a proxy for tobacco and tobacco cigarette use, combustible routes of administration have been decreasing. They are, instead, being replaced by e-cigarettes that do not involve other tobacco constituents and contain additional nonnicotine constituents of their own. Unfortunately, the literature remains limited with regard to e-cigarettes and their interactions with other substances, especially their prevalent co-use with alcohol. This review attempts to discuss the current literature on nicotine and alcohol co-use in the context of the vaping epidemic, predominantly focusing on addiction-related outcomes and why e-cigarette use may be unique.

Introduction

Tobacco and alcohol are the leading and third leading causes of preventable death in the United States, respectively, representing an exceedingly large economic burden and loss of human life.[1,2] Use disorders of these substances are also highly comorbid, with 80%–90% of patients with alcohol use disorder being smokers.[3] While each substance has their own associated risks, combined use may have additive effects on substance dependence, as well as negative physical and mental health outcomes including increased prevalence of certain cancers and psychiatric comorbidities.[4] It is therefore vital to understand the interactions between these substances such that the consequences of their use can be minimized both individually and in combination.

To understand this relationship, research must match the dynamic nature of substance use, adapting quickly to the changing landscape—particularly that of nicotine. Cigarette use has been steadily declining, while new forms of nicotine use have been growing at alarming rates, especially among vulnerable populations.[5,6] Past 30-day e-cigarette use among middle and high school students has grown from 0.6% and 1.5% to 4.7% and 19.6%, respectively, between 2011 and 2020.[7,8] Although adolescent alcohol use has been steadily decreasing during this period, its use remains high with adolescents reporting past 30-day use at 29.2% in 2019.[9] Nicotine and alcohol are also some of the most commonly co-used substances among adolescents, with nearly one in four adolescents reporting past 30-day use of both substances.[10] Despite these facts, there is very little research investigating the interactions specific to e-cigarette and alcohol co-use (for summaries of reported findings, see Supplementary Table 1), and investigations in adolescents is even more limited.

Excellent previous reviews have extensively evaluated the genetic,[11,12] pharmacological,[3,4,11,13–16] metabolic,[17,18] and behavioral,[4,11,15,19,20] mechanisms of interactions between nicotine and alcohol in great detail. Here, we have reviewed and updated the current state of knowledge in the field based on the clinical addiction-related outcomes of these interactions, and where available, the impact of sex and gender. Finally, we add our contention that further research must be carefully designed within the specific context of vaping, and how it might differ from previous investigations on the topic. As nicotine vaping and alcohol co-use is the focus, we attempt to give special attention to studies that use nontobacco nicotine routes of administration, though much of the research interchanges tobacco, particularly cigarettes, and nicotine. Throughout, we highlight adolescent

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co-use, where available, as this population is especially vulnerable to the consequences of substance use and is also where the most growth in vaping has been concentrated.[21–23]

Addiction-Related Outcomes of Co-use

Reported Reward

Several studies have found interactions between the subjective experiences associated with alcohol and nicotine. The potentiation of the rewarding effects of nicotine by alcohol and vice versa has been linked to a shared reward pathway, with both substances increasing the perceived rewarding effects of the other via mesolimbic dopamine pathway stimulation (for review, see ref. [16]).

Nicotine Effects on Alcohol Reward

The effects of alcohol are biphasic; that is, while blood alcohol levels are low and rising, alcohol acts as a stimulant; when they are high and decreasing, alcohol acts as a depressant.[24] Nicotine may increase the positive subjective experience of alcohol by either potentiating the stimulant or attenuating the depressant phases of the blood alcohol curve.[17] Several laboratory studies have investigated the subjective effects of nicotine on alcohol; however, these findings have been somewhat inconsistent and highly methodologically dependent.

When investigating the effects of nicotine without nonnicotine tobacco constituents, pretreatment via transdermal nicotine patches has been found to increase feelings of euphoria and feelings of intoxication 3 hours after acute alcohol consumption in moderate- to heavy drinking daily smokers.[25] Likewise, when light-smoking social drinkers were pretreated with a transdermal patch, ratings of alcohol-induced sedation were potentiated.[26] A similar study, however, found the opposite with transdermal nicotine patch pretreatment leading to a decrease in the reported subjective feeling of alcohol's effects 6 hours later as measured using the Alcohol Effects Scale—an average of five reported subjective effects (high, like, rush, feel-good, intoxicated).[27] Similarly, nicotine administered by nasal spray reduced feelings of intoxication in a group of moderate drinking smokers.[28] It is important to note that in each of those studies, participants had been deprived of nicotine for several hours prior to experiments; thus, the subjective interactions of nicotine and alcohol may have been confounded by withdrawal and/or craving. When social drinking nonsmokers were administered nicotine and alcohol intravenously, nicotine significantly attenuated feelings of alcohol intoxication.[29] Further, if nonsmokers were administered the nonspecific nicotinic acetylcholine receptor antagonist, mecamylamine, the reports of stimulant and euphoric effects of alcohol were attenuated, consistent with the findings that nicotine increases the euphoric feelings associated with alcohol administration.[30]

Ecological momentary assessments of smokers, in which participants are frequently assessed while in their natural environments, show a clearer picture, with smoking evoking a small but significant increase in pleasure following the last drink.[31] Of particular interest, smoking was only associated with enhanced alcohol buzz and excitement when estimated blood alcohol levels were high and descending, suggesting that interactions between alcohol and nicotine on subjective experience are influenced by the biphasic nature of alcohol, possibly explaining some of the contradictions seen in human laboratory findings.[32]

Alcohol Effects on Nicotine Reward

Many studies examine the effects of alcohol on tobacco cigarette reward, but none have used pure nicotine, exposing a gap in the literature. Studies investigating these effects provide overwhelming evidence for potentiated subjective hedonic experiences when smoking followed alcohol. In an *ad-lib* smoking session, previous exposure to a priming dose of alcohol (0.5 g/kg) significantly increased reports of stimulant and calming tobacco effects as well as enhanced smoking satisfaction.[33] Alcohol pretreatment also results in higher ratings of enjoyable taste,[34] satisfaction,[33,35] liking,[33,36] calming,[33] pleasantness,[37] and greater positive and lower negative affect[36] in response to smoking. Like adults, young adult smokers and experimenters (<100 lifetime cigarettes) report greater pleasure for cigarettes when drinking.[38] Further, in heavy drinking young adults who were experimenting with tobacco, both alcohol and taste-masked placebo increased smoking satisfaction, calm, and taste, suggesting that expectancy of alcohol consumption partially mediates tobacco-potentiated reward.[39] The same study determined that alcohol but not alcohol expectancy resulted in decreased nausea associated with *ad-lib* cigarette smoking; thus, some of alcohol's reward-potentiating effects on tobacco may be due to the attenuation of negative smoking affect.

Only two ecological momentary assessments have been conducted on alcohol and cigarette co-use that evaluated subjective feelings associated with tobacco reward. Alcohol use was associated with more frequent reports of good tobacco taste, rush/buzz, and increased smoking satisfaction and pleasantness when drinking in the preceding hour.[40] The authors suggested that alcohol may extend the euphoria associated with cigarette smoking, thus increasing the chances of the rush/buzz still being present when self-reports were conducted. Interestingly, another ecological momentary assessment found no effect of alcohol on smoking satisfaction, although there was a trend when alcohol preceded smoking by 15 minutes.[41] This may suggest that, like nicotine's effect on alcohol reward, alcohol's effect on cigarette, and possibly nicotine, reward may be contingent on the timing of the biphasic subjective alcohol experience.

Conclusions

Alcohol and nicotine can potentiate the rewarding properties of each other, and nicotine may attenuate the intoxicating and sedating properties of alcohol, although this effect is less straightforward. There is also evidence for increased addiction liability for each substance when used together, as the positive subjective properties of a drug are involved in the initial motivation for repeated exposures, and the formation of associated cues required for impulsive drug taking.[42] Though no clinical laboratory studies have investigated adolescents to our knowledge, reports from young adults were consistent with findings in older adults.[38,39] Unfortunately, the studies that used nontobacco nicotine produced mixed findings[25–29]; thus, more studies investigating alcohol and nicotine reward that use nontobacco nicotine exposures (vaping, transdermal patch, intravenous infusion, etc.) are required.

Reinforcement

Laboratory studies have shown variable effects of nicotine on alcohol reinforcement, whereas alcohol consistently increases nicotine reinforcement. Further, there is evidence that alcohol

consumption predicts nicotine use more strongly than the reverse relationship.[43]

Nicotine Effects on Alcohol Reinforcement

Nicotine alone and nicotine from cigarettes increases alcohol reinforcement. Using a progressive ratio task in which participants were required to work harder for subsequent reinforcers, nicotinized cigarette self-administration increased alcohol consumption, compared with denicotinized cigarettes, as well as increased breakpoints in male occasional smokers.[44] Similarly, users of cigarettes with very low nicotine content showed lower alcohol use compared with moderate and normal nicotine cigarettes.[45] Further, there is no evidence of compensatory drinking or binge drinking in response to nicotine reduction, suggesting that reduced nicotine cigarettes could have positive consequences for public health.[45]

Many studies, however, show mixed results in male and female participants. Responding for alcohol after daylong *ad-lib* smoking was significantly greater than after smoking abstinence in men, but not in women.[46] Furthermore, whilst comparing 7 or 14 mg of transdermal nicotine or a placebo on the effects of alcohol self-administration, men (14 mg nicotine) increased alcohol consumption, whereas in women (14 mg nicotine) decreased alcohol consumption, in response to a priming drink (0.2 g/kg).[26] In comparison, in heavy drinking daily smokers it was also found that both men and women participants who were administered 21 mg/day of transdermal nicotine, took longer to start drinking after a priming drink and consumed fewer drinks compared with a placebo patch.[47] It is of note that neither of these studies chose doses of nicotine considering body weight differences, however the former found that neither body weight nor body mass index were correlated with nicotine-induced nausea or with mood changes after nicotine administration,[26] and in the latter study comparisons between genders were underpowered.[47]

Importantly, when comparing the use of e-cigarettes to that of combustible tobacco cigarettes, similar results have been found. Self-reported data show that the use of e-cigarettes increases alcohol reinforcement and leads to problematic alcohol use,[48] and heavy drinking.[49] E-cigarette users had increased risk of harmful alcohol use including hazardous drinking, alcohol use disorder, and binge drinking, compared with e-cigarette nonusers.[50] Additionally, combined e-cigarette and tobacco cigarette use was associated with an additive risk of harmful alcohol use, especially in nondaily users. Furthermore, e-cigarette users drink more alcohol than nonusers, but less than tobacco cigarette or dual e-cigarette/cigarette users.[51] In the same study, dual e-cigarette/cigarette users reported a higher number of drinks consumed in the past month than e-cigarette users alone, and they were more likely to meet hazardous drinking criteria at follow up. Both tobacco cigarette users and dual e-cigarette/cigarette users, however, showed higher total drinks in the past month compared with e-cigarette users, and there were no significant differences between cigarette and dual-cigarette users.[51] In contrast, while no differences in alcohol drinking were observed among tobacco cigarette, e-cigarette, or dual users, all three groups had higher rates of heavy drinking than nonnicotine users.[49]

In adolescents, there is a bidirectional association, and sex difference, between e-cigarette use and alcohol use.[52] Adolescents who reported e-cigarette use had 3.5 times the odds of initiating alcohol use 6 months later, compared with those who have never used e-cigarettes. This association was found to be stronger in boys than in girls. Further, alcohol users had 3.2 times the odds of initiating subsequent e-cigarette use 6 months later.[52]

Overall, these studies provide evidence that depending on dose and type of nicotine-containing product, nicotine appears to increase alcohol reinforcement in men but not women. There is a lack of experimental studies of e-cigarette use and further research is required to examine these effects in adolescents.

Alcohol Effects on Nicotine Reinforcement

Alcohol dependency is positively correlated with the number of combustible cigarettes smoked per session.[53,54] Differing doses of alcohol significantly increased cigarette smoking in participants with alcohol dependency compared with those without; however, in nonalcohol-dependent participants, differing alcohol doses had no significant effect on smoking behavior.[54] There were, however, individual differences in the non-dependent group, such that smoking decreased in two participants, increased in two participants, and remained unchanged in a fifth.[54] In comparison, in men with opioid use disorder, drinking alcohol significantly increased the amount and rate of smoking in most, but not in all participants,[55] further demonstrating individual differences in those with other co-occurring substance use disorders.

In moderate-to-heavy smokers who drank alcohol regularly, participants smoked more tobacco cigarettes in the first hour after 0.4 or 0.8 mg/kg alcohol than participants who consumed 0.2 mg/kg alcohol or placebo.[56] Similarly, low doses of alcohol increased cigarette use in daily smokers who were heavy drinkers. After consuming a priming alcoholic drink, participants were less able to resist a first cigarette, initiated smoking sooner, and smoked more cigarettes compared with a placebo beverage.[57]

Sex differences also emerge in the effect of alcohol on cigarette smoking. Alcohol increased men's smoking behaviors compared with placebo, including number of puffs, number of cigarettes, and duration of smoking; however, women's behavior did not differ between alcohol and placebo conditions.[34] Thus, further consideration for sex differences is required in studying the cross-tolerance of nicotine and alcohol reinforcement.

Conclusions

Although studies generally find that nicotine in both combustible tobacco cigarettes and e-cigarettes increases alcohol reinforcement, and to a lesser extent the converse, further research is required to examine sex differences, adolescent use, and e-cigarette use in controlled laboratory settings, with special consideration for the effects of alcohol on nicotine reinforcement in nontobacco products.

Relapse

Commonly, patients that have both nicotine and alcohol use disorders have worse treatment outcomes when compared with those with only one.[11] This is likely due to the interactions between alcohol and nicotine cues that contribute to relapse of either, known as the cross-substance cue reactivity theory.[58] These interactions fall into two main overlapping categories: (1) increased craving of one substance following

the consumption of the other[19]; and (2) nonpharmacological alcohol cross-cue provoked urge to use nicotine and vice versa.[20]

Nicotine Effects on Alcohol Relapse

Laboratory studies investigating nicotine's (alone and from tobacco containing cigarettes) effects on alcohol craving have been mixed. In participants who drink alcohol and smoke cigarettes with a broad range of use patterns, alcohol craving increased significantly after smoking a cigarette in heavier drinkers but decreased in light drinkers; though the combination of both low-dose (men: 0.3 g/kg; women: 0.27 g/kg) alcohol and cigarette smoking resulted in greater cravings for alcohol than either alone regardless of drinking patterns.[36] Among a group of occasional smokers, no effect of cigarette smoking was observed on alcohol craving, suggesting that consistent co-use may be required for sufficient cue conditioning.[44] Similarly, cigarette smoking did not evoke a desire to drink in young male and female daily smokers who drank moderate amounts of alcohol.[46] Especially relevant to this review, *ad-lib* vaping has been found to increase craving for alcohol in light drinkers who vape.[59]

Of course, visual smoking cues are also an important factor for relapse, and there is strong evidence that cross-cue conditioning occurs in dual users—though most research to date has focused on the effects of alcohol cues on smoking behavior. Smokers with alcohol use disorder display strong cravings for alcohol when exposed to smoking-related images.[60] Additionally, nicotine withdrawal may increase alcohol craving in response to smoking cues, though results are inconsistent. This effect was only seen in a group of daily smoking hazardous drinkers (those that scored 8 or above on the Alcohol Use Disorders Identification Test) following 6 hours of nicotine deprivation[61] but not in either alcohol-dependent heavy smokers[62] or moderate-to-heavy smoking young adult drinkers[63] at 34 or 5 hours of nicotine deprivation, respectively.[62,63]

Pretreatment with a transdermal patch containing nicotine alone (21 mg nicotine) increased craving to drink among socially drinking daily smoking men.[25] This finding is important as it divorces visual smoking cues as a factor influencing alcohol craving; thus, nicotine's subjective effects alone may be enough to act as a conditioned cue for alcohol craving.[64] Interestingly, the same dose of nicotine in women showed no effect on alcohol craving,[65] again highlighting the need to examine sex differences as they relate to dosing regimens and metabolism as well as age.

Alcohol Effects on Nicotine Relapse

Alcohol consumption is strongly associated with smoking relapse.[66] There is extensive laboratory evidence that alcohol increases craving for cigarettes across a variety of use patterns. Following fixed doses of alcohol in laboratory settings, increased urge to smoke has been observed in heavy social drinking light smokers,[67,68] heavy social drinking daily smokers,[57] heavy drinking heavy smokers,[25,69] young adult heavy social drinking light smokers,[34] occasional drinking daily smokers,[70] nicotine-dependent and non-dependent smokers,[71] and moderate drinking daily and nondaily smokers.[72] No effect of alcohol on the urge to smoke in heavy drinking heavy smokers was found; however, it is suggested that this may be due to subjects being 15 hours smoking abstinent, and therefore, a ceiling effect on cigarette craving was responsible for the finding.[73] Notably, increased craving for cigarettes in heavy drinking light smokers was also found following intravenous alcohol administration; thus, alcohol's subjective effects may increase craving for cigarettes without any drinking-related cue.[74] An ecological momentary assessment study of daily smokers found that alcohol use predicted smoking and was associated with more frequent reporting of urge to smoke.[40]

Unlike with reward, there does not appear to be a relationship between craving and the biphasic effects of alcohol, as cigarette craving evoked by alcohol is maintained throughout the blood alcohol curve.[67,68,74,75] There may also be an effect of gender, with women reporting stronger smoking cravings following alcohol consumption than men,[34,75] and women, but not men, having increased urges to smoke following a placebo drink, suggesting that women participants' urge to smoke may be more cue driven than men.[73] However, there are again inconsistent reports, with both men and women showing increased craving following a placebo beverage.[39,71] Notably, alcohol cues have been consistently shown to increase urge to smoke. Among daily smoking alcohol-dependent men, the smell of alcohol promoted the urge to smoke.[58,76] Both alcohol- and nonalcohol-dependent daily smokers exhibited substantial increases in urge to smoke following presentations of alcohol-related images, with alcohol-dependent smokers showing equivalent alcohol cue potentiated cravings to those elicited by smoking-related cues.[60]

Conclusions

Both alcohol and nicotine consumption, and exposure to their associated cues, increase cravings for each other, though this effect is especially pronounced for alcohol consumption and alcohol cue exposure on urge to smoke. Although, to our knowledge, no studies have evaluated these effects on e-cigarette relapse or vaping's effect on alcohol relapse, most studies investigating smoking's effect on alcohol relapse used denicotinized cigarettes as controls. Thus, the primary differences seen were likely mediated by nicotine, though there could be a nicotine and nonnicotine tobacco constituent interaction as well. Overall findings are consistent with epidemiological observations that the use of e-cigarettes is associated with problematic alcohol use in adult,[48,51,77] young adult,[49,78] and adolescent populations.[79] For summaries of all vaping and alcohol co-use findings, see Supplementary Table 1.

What Makes E-cigarettes Different: An Ever-Changing Landscape

It is difficult to categorize e-cigarettes in existing nicotine use classifications as not only do they differ greatly from current nicotine replacement therapies and tobacco products, but they are also a remarkably broad category of products themselves, making it challenging to establish any consistent conclusions regarding their properties. E-cigarettes vary in many ways, including flavor, nicotine concentration, nicotine type (ie, salt or base), device voltage, primary vehicle constituents and their ratios, and form factor. This variation results in a mixed literature that often neglects to differentiate amongst, or even explicitly state, these properties. Here, we discuss why many of these properties make e-cigarettes a unique category of nicotine products that requires further studies to understand how they affect behavior alone, and in combination with other drugs

of abuse, including alcohol. We also point out areas that may overlap (summarized in Figure 1) such that some inferences may be made from previously conducted research on alcohol and nicotine co-use.

Nicotine Type and Concentration

Nicotine's ability to enter the body depends highly on pH, with higher pH increasing absorption across tissues and being required for efficient absorption through buccal and dermal membranes.[80] For inhalation, however, lower pH results in increased palatability allowing for easier initiation of use and the potential for higher nicotine concentrations; thus, there exists a balancing act for "ideal" ratios of nicotine salt (low pH form) to nicotine base (high pH form) that has created a long history of tobacco companies searching for the perfect combination to evoke the greatest level of consumption.[81] The first generation of e-cigarette liquids (e-liquids) were almost entirely nicotine base, like that of nicotine replacement therapies such as nicotine patches, gums, lozenges, inhalers, and nasal sprays; however, recent e-liquids that are commonly used in pod and disposable devices are now primarily salt based, with a ratio of base to salt of ~0.1, the same ratio used in most cigarettes.[80,81]

Newer e-liquids also have significantly higher nicotine concentrations, as the more physiological pH of nicotine salt reduces alkaline activated pulmonary protective mechanisms resulting in increased palatability.[82] This is likely why the most popular nicotine base e-liquid concentration is 18 mg/mL, whereas nicotine salt e-liquid is most commonly 59 mg/mL.[83] Thus, there are two separate populations that have often been placed under the umbrella of "e-cigarette users" that are using very different products. These products differ significantly in their pharmacokinetics, with nicotine salt-based e-liquids having near identical pharmacokinetics to that of tobacco cigarettes and nicotine base having a lower blood plasma maximum concentration (C_{max}) and time to maximum concentration (T_{max}) compared with both.[83] It should be noted, however, that these results were found in adults, which corresponds well with findings showing consistent salivary cotinine, a primary metabolite of nicotine, levels in adults who use JUUL e-cigarettes or smoke tobacco cigarettes[84]; but, it is not consistent with adolescent urinary cotinine levels that suggest that adolescents who use nicotine salt-based products are being exposed to significantly more nicotine than their tobacco cigarette-smoking counterparts; thus, adolescents are a unique population whose e-cigarette

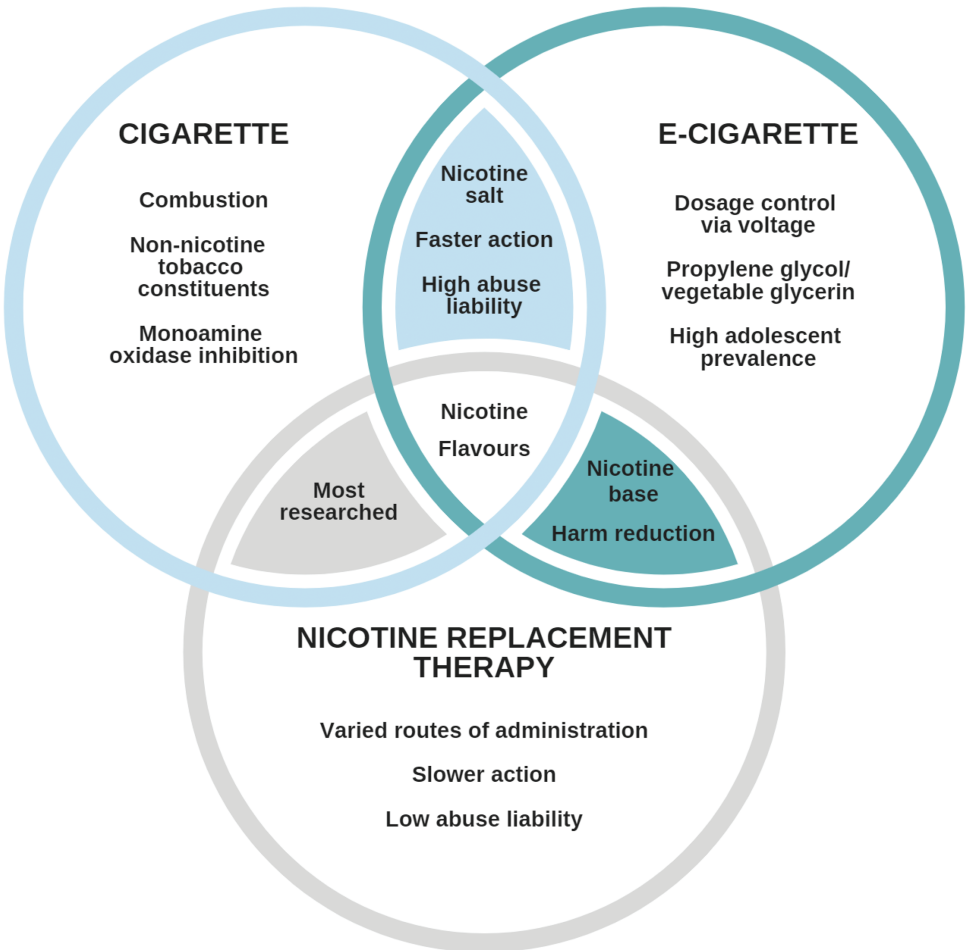

Figure 1. Properties of tobacco cigarettes, e-cigarettes, NRTs, and their overlapping relationships. For the purposes of this review, e-cigarettes are not considered a NRT. Though the FDA is working to ban menthol in cigarettes, mentholated cigarettes are still currently available; thus, for now all nicotine products have flavors in common. Depending on whether e-cigarettes contain nicotine salt or base, they may be more likely to overlap with cigarettes or NRTs. There is significant overlap between each nicotine product allowing for some understanding of e-cigarette properties to be gleaned from past literature. Past findings, therefore, have validity for directing future clinical and preclinical studies observing the effects of e-cigarettes directly.

use should be studied independently.[85,86] Overall, there is very little consistency across e-cigarettes product to product. Even when simply considering e-cigarettes that primarily use nicotine base, studies cannot agree as to whether they result in greater, equal, or lower nicotine plasma in the blood compared with tobacco cigarettes, likely owing to the differential e-cigarette puff topography by concentration and device voltage.[87] Compared with e-cigarettes and tobacco cigarettes, nicotine replacement therapies, which were designed to be smoking cessation aids, have much slower absorption rates and produce more gradual increases in blood nicotine resulting in lower abuse liability.[88]

Nonnicotine Constituents

There are many unique factors apart from nicotine chemistry that differentiate e-cigarettes from tobacco products and nicotine replacement therapies. Though the FDA has banned most flavored cartridge-based e-cigarettes, flavored e-liquids that can be used to refill these devices, as well as menthol cartridges, are still available.[89] There are over 15 000 flavorants available for use in e-liquids, many of which have known pharmacological interactions with nicotine and nicotinic acetylcholine receptors (for review, see ref. [90]); and, given alcohol's interaction at nicotinic acetylcholine receptors, it is not unlikely that there are additional complex relationships among alcohol, nicotine, and these flavorants.[16] Flavors such as menthol also alter nicotine metabolism and act as a highly reinforcing sensory cue to smoke (for review, see ref. [91]), leading the FDA to recently announce a ban on menthol in cigarettes.[92] Therefore, except for limited flavorants in nicotine gum and lozenges, the reinforcement potential of flavors and the novelty of trying new flavors is now exclusive to e-cigarettes.

Like flavors, e-liquids uniquely contain propylene glycol and/or vegetable glycerin that, when vaporized, carry nicotine and flavorants to the mouth, throat, and lungs. The ratio of these constituents in an e-liquid has been shown to affect puff topography and nicotine delivery in experienced users.[93] Because both propylene glycol and alcohol are primarily metabolized by alcohol dehydrogenase in the liver (which becomes saturated at low alcohol concentrations), there are likely metabolic interactions between these substances.[94] For instance, ethanol is known to competitively inhibit propylene glycol metabolism.[95] Additionally, a recent paper validating a rat model of nicotine self-administration found similar responding for nicotine and vehicle vapor (50:50 propylene glycol/vegetable glycerin); the authors suggested that the vehicle itself may have some rewarding properties.[96] This finding could additionally explain why many individuals regularly vape nicotine-free e-liquid.[97]

Tobacco cigarettes, too, are distinct in terms of nonnicotine constituents. Cigarettes have over 7000 nonnicotine constituents, most of which have not been studied, and several of which have been shown to have potentiating effects on nicotine reinforcement—some even being reinforcing themselves.[98,99] Further, cigarettes contain monoamine oxidase inhibitor constituents, which may also potentiate nicotine reinforcement.[100]

Conclusions

Because it is difficult to find consistency in the properties of e-cigarettes, and many properties of other nicotine routes are not shared with e-cigarettes, inferences made from other forms of nicotine exposure (ie, tobacco, nicotine replacement therapies) will only be applicable to a subsection of the properties of a particular type of device/e-liquid. Thus, not only is there need for studies investigating the effects of e-cigarettes on co-use with alcohol, but there is need for studies on each type of e-cigarette/liquid on alcohol co-use to fully understand the addiction-related outcomes of nicotine and alcohol interactions. There is also a need for preclinical research to disambiguate the causal mechanistic underpinnings of nicotine and nonnicotine constituents in their role in co-use. By revisiting this clinical literature using the lens of emerging routes of nicotine administration and its rapid growth amongst more vulnerable populations, preclinical research can then be guided by the existing gaps in knowledge in human studies.

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.

Authors' Contribution

JAF, CJN, JEM, and JYK conceptualized the paper. JAF and CJN wrote initial drafts. JEM and JYK provided manuscript revisions and finalized the manuscript for submission; all authors have given feedback on the final manuscript and approved its submission.

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