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Curr Addict Rep. 2017 June ; 4(2): 200–208. doi:10.1007/s40429-017-0148-9.**“Essentially, All Models are Wrong, but Some Are Useful”*: A Preliminary Conceptual Model Of Co-Occurring E-Cig and Alcohol Use****Alexandra Hershberger, M.S.^a and Melissa A. Cyders, Ph.D.**

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Abstract

Purpose of review—As prevalence rates of electronic cigarette (e-cig) use increase, researchers and clinicians should not only be paying careful attention to the direct health effects of e-cigs, but also the potential impact e-cigs may have on alcohol use behaviors. We review the current state of the literature and propose a conceptual model for the relationship between e-cig and alcohol use, including important consequences, mechanisms, and moderators of this relationship.

Recent findings—The model is based in emerging literature examining the direct relationship between e-cig and alcohol use, as well as indirect evidence concerning potential mechanisms from research on cigarette and alcohol use. Overall, research indicates a robust relationship between e-cig and alcohol use.

Summary—We suggest that a relationship between e-cig use and alcohol use could be particularly problematic, especially for adolescents and for those with or at risk for alcohol use disorders. We hope the presented conceptual model can stimulate research in this area. We make research recommendations, including the need for more methodological rigor, including improved measurement of e-cig use, and expanding research to longitudinal and experimental designs.

Keywords

electronic-cigarettes; alcohol; substance use; co-occurring

Introduction

Electronic-cigarettes (e-cigs), an alternative form of nicotine delivery, have gained significant popularity, and as such, increasing research has examined the potential health benefits and consequences of e-cig use. The majority of research has focused on the efficacy of e-cigs for smoking cessation [1] and the direct health impact of e-cigs on lung and

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Compliance with Ethics Guidelines**Conflict of Interest**

Ms. Alexandra Hershberger reports grants from NIAAA (F31 AA024682), during the conduct of the study. Dr. Melissa Cyders declares that she has no conflicts of interest.

Human and Animal Rights and Informed Consent

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cardiovascular function [2–4]. However, a growing area of research examines an under-recognized health risk of e-cig use: e-cig use may impart risk for sustained or increased alcohol use [5]. This work is based on the large body of research indicating that cigarette use and alcohol use are related, providing viability of a relationship between e-cig and alcohol use, and some initial direct evidence is emerging. Given the similarities between e-cigs and cigarettes in drug content and user experience, e-cig use likely has a similar relationship with alcohol use.

In the present paper we review the current state of the literature concerning e-cig and alcohol use and propose a model (see Figure 1) to describe 1) risk factors by which e-cig use and alcohol use may come to co-occur and current evidence on their co-occurrence, 2) why this relationship may be especially problematic, and 3) how co-use may lead to the perpetuation of both e-cig and alcohol use. This model is not exhaustive and is, at best, preliminary. As Box & Draper (1987) [6] note: “All models are wrong, but some are useful.” The present model attempts to provide a parsimonious depiction of this relationship and is likely an oversimplification of the relationship between e-cig use and alcohol use. However, the current state of the empirical literature in this area is quite preliminary; thus, we expect that future research will lead to the addition or removal of different aspects and pathways in our model. We believe that this model, although likely “wrong” in this sense, is useful for stimulating discussion and important research in this field. First, using the Acquired Preparedness Model [7–8] as a framework and illustrative example, we propose that impulsive personality leads to the development of positive expectancies of e-cig and alcohol use, which are ultimately predictive of both e-cig and alcohol use. Second, we describe the potential negative health effects that follow e-cig use and the potential negative health effects of combined e-cig and alcohol use. Third, we propose two candidate mechanisms by which e-cig use and alcohol use may reinforce use of the other substance.

Shared risk for e-cig and alcohol use

There are likely multiple common risk factors underlying e-cig and alcohol use. Given emerging data suggesting e-cig use is related to impulsive personality [9–10] and a substantial body of literature indicating impulsive personality is related to alcohol use [11], we have chosen to use impulsive personality as one example of a common risk factor for both e-cig and alcohol use (see Figure 1, box A). Research indicates that impulsive personality developmentally precedes and contributes to alcohol use [12–13]. The Acquired Preparedness Model [7–8] suggests that impulsive personality affects learning, which then subsequently affects behavior. For example, impulsive personality makes it more likely for one to attend to and remember the positive aspects of alcohol use, thus forming positive expectancies of alcohol use (e.g. “If I drink, I will feel happy”; see Figure 1, box B), which further drive and perpetuate alcohol use [14]. It is important to note that the development of these positive expectancies can occur prior to any drug experimentation (e.g., through social learning via observing behaviors in the media or family, for instance) and such positive expectancies are further reinforced and solidified through use [7].

There is emerging evidence that e-cig use is related to impulsive personality traits [9–10]. Impulsive personality is likely composed of multiple separate, though related, traits [15]:

sensation seeking (the tendency to seek out new and exciting experiences), lack of planning (the tendency to not think before acting), lack of perseverance (the tendency to not finish what one starts), negative urgency (the tendency to act rashly in response to negative emotions), and positive urgency (the tendency to act rashly in response to positive emotions). Recent research has begun to suggest how these separate traits are associated with e-cig use, although this work is quite preliminary. Sensation seeking is related to past 30-day e-cig use [9], whereas the remaining traits are related to current e-cig use [10]. Clearly, more work needs to be done in this area to better understand how these separate impulsive personality traits relate to e-cig use.

E-cig users have positive expectancies of e-cig use [16], which could be one way through which impulsive personality is related to e-cig use. Research with cigarettes indicates that sensation seeking and negative urgency are related to cigarette use initiation in part through reinforcement expectancies of cigarette use [17], leading us to hypothesize that this might also occur with e-cigs. Preliminary work suggests that these impulsive personality traits are related to e-cig use through more positive attitudes towards e-cigs [10], although this work has been done in cross-sectional samples, thereby preventing the examination of prospective trajectories. Taken together, we suggest impulsive personality is a viable risk factor for both e-cig and alcohol use through the development of positive expectancies of e-cig use [9–10, 16] and alcohol use [14] (see Figure 1, box A and B). Due to the preliminary nature of this work, we do not make specific claims concerning which impulsive personality traits predispose one to developing such positive e-cig expectancies and subsequent use, although the cigarette research literature suggests viability of sensation seeking and negative urgency as prime initial candidates [14].

Co-occurrence of e-cig and alcohol use

A growing body of research indicates that e-cig and alcohol use do co-occur (see Figure 1, box C). Cross-sectional literature indicates that both current (past 30 day) and lifetime use of e-cigs is positively related to ever-use of alcohol [18–20] and current alcohol use (i.e. past 30 day use) [9, 20–23]. Further, current and lifetime use of e-cigs is related to problematic alcohol use, including binge drinking [22–27], and scores on measures of alcohol use disorders [5, 27–28]. Importantly, these patterns appear to be quite robust in adolescent samples, but less robust in adult samples. For current e-cig using adolescents, past 30-day e-cig use is strongly associated with ever-use of alcohol [23] and binge drinking [23, 26]. Interestingly, current e-cig use in adults has shown only a small relationship with scores on measures of alcohol use disorders [5, 27], but a larger relationship with binge drinking [24, 29]. Although prevalence rates of co-occurring e-cig use and alcohol use increase with age in high-school students [26], the strength of the relationship between e-cig and alcohol use is less robust as age increases [26]. The moderating effect of age on the relationship between e-cig and alcohol use is not well studied, but appears to be a viable target of future research (see Figure 1, box D).

Overall, findings appear to be robust, with the majority of evidence pointing towards a strong positive relationship between e-cig and alcohol use. At the same time, most literature to date has examined the relationship between e-cig and alcohol use cross-sectionally,

making it impossible to conclude any direction of this effect. However, three, non-mutually exclusive, options exist: 1) e-cig use contributes to alcohol use, 2) alcohol use contributes to e-cig use, and 3) e-cig and alcohol use are related due to a shared third factor. The current state of the literature suggests viability to all three of these options and, as such, all are included in our model (see Figure 1). We do believe, however, that current findings provide sufficient premise for longitudinal and laboratory examinations of the relationship between e-cig and alcohol use to better determine the most likely nature of this relationship.

Negative outcomes of combined e-cig and alcohol use

Current adult e-cig use (“every day” or “some days”) rates have increased from 0.3% in 2010 to 6.8% in 2013 [30]. Rates of e-cig use for adolescents are also increasing, surpassing rates of cigarette use, with recent data indicating approximately 13% of eighth through twelfth graders report past month e-cig use, compared to 7% reporting past month cigarette use [31]. From a harm reduction perspective, if increased rates of e-cig use are related to decreases in cigarette use, this could have potential health benefits. Research has examined e-cigs for smoking cessation benefits, although results are inconclusive and increased methodical rigor is required to determine effectiveness [1]. At this point, there are mixed findings concerning the health risks and benefits of e-cigs. We include three prime negative outcomes in our model (see Figure 1, box E): negative health effects, more problematic use, and poor treatment outcomes.

Data indicate that e-cig refill liquid and vapor contain potentially harmful substances [2–4, 32]. Recent research using animal models has demonstrated that e-cig liquid, independent of the effects of nicotine, resulted in decreased lung endothelial barrier function and increased inflammation [2], which may lead to high blood pressure and cardiovascular disease [33]. Additionally, e-cig vapor exposure in mice has resulted in impaired anti-bacterial and anti-viral defenses in the lungs [3]. Research using human lung fibroblasts (i.e., cells of connective tissues) exposed to e-cig liquid has demonstrated the release Interleuken-8 (IL-8) [4], a pro-inflammatory protein that contributes to chronic inflammation in the lungs [34]. Also, many commercial e-cig liquids contain ethyl alcohol, with recent research finding detectible levels of urine ethyl glucuronide in individuals exposed to such e-liquids, which was associated with impaired psychomotor performance following e-cig exposure [35]. Taken together, it appears that e-cigs have direct negative health effects that, although are arguably less harmful than traditional cigarettes, should not be dismissed.

Further problematic, the co-occurrence of e-cig and alcohol use raises a number of potential concerns. First, e-cig use rates are increasing among adolescents [31], which could be met with corresponding increases in alcohol use. Regardless of the directionality of this effect (i.e., whether e-cig use influences alcohol use, vice versa, or both), both nicotine and alcohol are mutually reinforcing [36], which could potentiate both e-cig and alcohol use beginning in adolescence. Further, recent evidence indicates that e-cigs serve as a cue to cigarette use [37] and adolescent e-cig use increases subsequent cigarette use [38].

E-cig use could sustain or even increase alcohol use, extending into adulthood. The impact of cigarette prohibitions on alcohol use helps illustrate this point. Following the institution of

cigarette prohibitions in public places in the United States, there were significant decreases in alcohol use among adults [39–40], likely as a result of decreased pairings of alcohol and cigarettes in time and place (i.e. extinction of cigarette and alcohol pairing). However, recent data indicate that in areas where cigarette use is prohibited, but not e-cig use, there are higher rates of both e-cig and alcohol use [28]. Thus, it is possible that the ability to pair e-cigs with alcohol could be undoing the positive impact cigarette prohibitions had on alcohol use.

Additionally problematic, approximately 30% of individuals in substance use treatment report current use of e-cigs [41]. Research indicates that targeting both smoking cessation and alcohol use in treatment results in better substance use outcomes [42] likely as a result of the mutually reinforcing properties of alcohol use and nicotine. Thus, it is possible that e-cig use could hamper benefits of smoking cessation on alcohol use in treatment.

Co-occurrence of e-cig and alcohol use: Potential mechanisms

Overall, research has strongly supported a relationship between cigarette use and alcohol use: individuals who smoke cigarettes are more likely to drink alcohol and individuals who drink alcohol are more likely to smoke cigarettes [43]. Just as alcohol use and smoking go hand-in-hand, the same is likely true of e-cigs and alcohol use. Multiple mechanisms likely explain the co-occurrence of e-cig and alcohol use (see Figure 1, box C) and here we focus on two likely related processes: 1) classically conditioned cues and 2) dopaminergic sensitization to cues. First, research has examined classical conditioning processes that strengthen the relationship between cigarette and alcohol use. For example, Rohsenow and colleagues [36] propose a “priming hypothesis,” in which cigarette use serves as a conditioned stimulus for alcohol consumption and vice versa. Evidence supports this model, as exposure to typical alcohol cues (e.g., odor) increases cigarette craving [36] and likely consumption as well. Thus, classical conditioning processes likely result in increases of both cigarette and alcohol use. Although this has not yet been examined in the e-cig and alcohol use relationship, it is viable that e-cig use may serve as a conditioned stimulus for alcohol consumption and vice versa. In line with the priming hypothesis [36], through the continued pairing of alcohol and e-cig use, classical conditioning processes likely result in increases of both e-cig and alcohol use.

At the same time, there is likely sensitization of dopaminergic pathways to these bi-directional cues [44–45]. In line with Incentive Sensitization Theory [44–45], the mesolimbic dopamine system, which is responsible for the reinforcing effects of substances of abuse [46] and motivation to seek both alcohol and nicotine, becomes sensitized to cues for reward (i.e. the substance). Although not yet examined in e-cig and alcohol use, it is possible that e-cig and alcohol use become mutually rewarding cues for one-another, with dopaminergic processes leading e-cigs to cue alcohol use and vice versa. Research has found nicotine and alcohol to have mutually rewarding properties; for example, blocking nicotinic receptors of the dopamine reward system has shown to lessen alcohol consumption [47] and blocking nicotine receptors during alcohol consumption eliminates alcohol-induced dopamine release [46, 48–49].

Other factors related to the co-occurrence of e-cig and alcohol use

The present model of proposed risk factors and mechanisms underlying the e-cig and alcohol use relationship is one theory, and by no means an exhaustive account of the e-cig and alcohol use relationship. There are likely other predictors of the co-occurrence of e-cigs and alcohol use. For example, research indicates children with alcoholic fathers are more likely to use e-cigs, and further, co-use e-cigs and alcohol [18], thus genetics may be a third factor predicting both e-cig and alcohol use. Additionally, other factors, such as mutual e-cig and alcohol craving, reinforcement value of co-use (e.g. “If I use an e-cig while I drink, I will become more relaxed”), and motives for co-use (e.g. to cope with emotions), likely interact with and serve as mechanisms explaining how impulsive personality traits, expectancies, dopaminergic sensitization, and classical conditioning processes perpetuate co-use. No research to-date has examined the complex role of these constructs in the e-cig and alcohol use relationship.

Summary and critique of the conceptual model, reviewed literature, and methodological recommendations

The public debate on e-cigs often centers on the direct health impact of e-cigs, particularly on lung and cardiovascular function, and the use of e-cigs for smoking cessation. What have been largely neglected are the potential secondary effects of e-cigs on heavier alcohol use. We have proposed a conceptual model concerning the relationship between e-cig and alcohol use, supported by a combination of direct e-cig evidence and indirect evidence based on the relationship between cigarettes and alcohol use (see Figure 1). It is our hope that this proposed model will stimulate future research concerning mechanisms, moderators, and consequences of the relationship between e-cig and alcohol use. We particularly highlight the important role of age in this relationship, as data suggests the relationship between e-cig and alcohol use might be more robust for adolescents than adults. We suggest the potential for worse outcomes when alcohol and e-cigs are paired together, including negative health effects, problematic use, and poorer treatment outcomes. We also propose two potential mechanisms explaining any causal relationship between e-cig and alcohol use: classical conditioning and dopaminergic sensitization. Because much of the data concerning the relationship between e-cig and alcohol use is cross-sectional in nature, three, not mutually exclusive, options for the nature of this relationship remain viable: 1) e-cig use influences alcohol use, 2) alcohol use influences e-cig use, and 3) e-cig and alcohol use are related due to the presence of shared risk factors (e.g., impulsivity).

Research concerning the relationship between cigarettes and alcohol use informed the current theory and model; however, this comparison may not be completely valid, as there are important differences between how e-cig use and cigarette use relate to alcohol use. First, there are some aspects of the proposed model relating to nicotine effects (e.g., dopaminergic sensitization and classical conditioning) that would likely apply to both e-cig and cigarette use. On the other hand, the drug content of cigarettes and e-cigs differs quite markedly, which might lead to differential effects in some cases. For example, one unique pattern can be found in e-cig liquids that contain alcohol, which might not affect subjective

drug effects, but can affect psychomotor performance [35]. Second, processes linking impulsive personality traits to the development of positive drug expectancies (see Figure 1, box A and B) and motives, as well as how these beliefs influence subsequent use, may generalize between cigarette and e-cig use, as expectancy processes apply to a wide range of behaviors [17, 50–51]. However, the specific content of such expectancies would differ between cigarettes and e-cigs. For example, e-cig users often endorse using e-cigs for pleasure [52] and to quit smoking [53], whereas cigarette users often endorse smoking with the goal of positive or negative reinforcement [54].

Other aspects of the model would likely be unique to e-cigs. First, e-cigs are easier to purchase for adolescents, which might be one reason why age is a stronger moderator for relationship between e-cig and alcohol use (see Figure 1, box D) than for the relationship between cigarette and alcohol use [26, 55]. Second, e-cigs are considered more socially acceptable and less hazardous to one's health than cigarettes [56], whereas the social acceptability of cigarettes had dropped significantly over the last 50 years [57]. E-cig use is in fact increasing, particularly in adolescents, and surpassing cigarette use rates [31]. These differences might increase the likelihood of one learning positive ideas about e-cig use, even without prior use of e-cigs. We see this as particularly important: if e-cigs are viewed as safer, less risky, and more socially acceptable than cigarettes, impulsivity traits might play less of a role in e-cig use rather than cigarette use (see Figure 1, box A). If this is true, the strength of the relationship between these traits and e-cig use might be weaker than the relationship between these traits and cigarette use, or, at the very least, the specific impulsive personality traits implicated in e-cig use might differ from those implicated in cigarette use. Third, since many public places have now banned cigarettes, but relatively fewer places have banned e-cigs, the strength of the relationship between cigarettes and alcohol use is decreasing [58], whereas the strength of the relationship between e-cig and alcohol use might continue to increase over time (see Figure 1, box C). Finally, the experience of the drug “high” when using e-cigs is likely very different than when using cigarettes. Although research indicates e-cigs alleviate tobacco withdrawal symptoms [59], subjective effects of e-cigs versus cigarettes are not well documented, but likely play an important role in conditioning effects of e-cig use on alcohol use (see Figure 1, box C). Although it's not clear how this could affect the generalizability of the model across cigarette and e-cig use, this could be examined empirically. Overall, these differences between cigarette and e-cig use likely results in limited generalizability in parts of the current model.

We want to note that the model we propose is not comprehensive and is based in initial research that is limited to mostly self-report, cross-sectional data and prior indirect evidence based on the relationship between cigarettes and alcohol use. We know that there are likely many shared risk factors, mechanisms, and moderators that we have left out of this model, including risks related to genetics, gender, and other factors that have yet to be considered. Current research examining e-cig and alcohol use is in need of a methodological shift to more fully understand the relationship between e-cig and alcohol use. In defense of the current research, this relationship was left virtually unexamined until recently; thus, initial data and basic cross-sectional research was needed to warrant time and funding to conduct future complex research. At the same time, the quality of the literature can be improved and

researchers should consider new methodologies for examining the relationship between e-cig and alcohol use.

First, improvement in the measurement of e-cig use is needed. There are no gold standards of measuring e-cig use. E-cig use is often measured as current use [5], past 30-day use [29] and lifetime use [21]. While these are straightforward measures, they are dichotomous and limit the field's understanding of variability in e-cig use. At the same time, e-cig use does not lend itself well to being measured continuously and there are unique challenges in assessing e-cig use behaviors [60]. Whereas individuals can report how many cigarettes they smoke in a day, quantifying e-cig use to generalize across individuals is not as straightforward. Variability in e-cig devices and refill liquid, including e-cig nicotine liquid volume, nicotine concentration of the e-cig liquid, and the amount of e-cig liquid used in a day, complicate operationalizing e-cig use. Further, e-cig refill liquids vary considerably between products, and even within products, with refills containing various additives and flavorings, and often unconfirmed amounts of nicotine, all of which make the assessment of nicotine exposure difficult. Qualitative findings have demonstrated that, due to the heterogeneity associated with e-cig use behavior, it is difficult to identify a single means of measuring quantity and frequency of e-cig use, and further, e-cig users demonstrate difficulty in recording their e-cig use behavior [61]. Second, individual behaviors of e-cig use, such as puff velocity, also present a challenge in measuring e-cig use. Quantitative analyses of e-cig use puff-topography, including the mean puff volume and flow rate per e-cig use session, has shown significant variability between users, further complicating the measurement of e-cig use [62].

Another important consideration in assessing e-cig use is accounting for the co-use of other nicotine products (often referred to as “dual use”), which complicate measurement of nicotine exposure. There is emerging literature suggesting that dual users may be a unique population of e-cig users, leading to questions concerning whether or not e-cig use models generalize to dual users. For example, recent evidence indicates that dual e-cig users score higher than non-users on a measure of alcohol use disorder symptomology, while e-cig only and non-users scored similarly on this measure [5]. It is possible that dual users could be a high-risk group for which different models would need to be developed. In order to extend this research, measures should be developed to identify dual users (e.g., dichotomous dual use/no dual use) and better characterize patterns of dual use (e.g., does the individual switch to e-cigs only when cigarettes are banned or is there more frequent switching between e-cigs and cigarettes?).

E-cig use should be assessed using more continuous measures of nicotine dependence [63] and simple measures of frequency of use (e.g. days per week), rather than dichotomous measures of whether the person has used or currently uses e-cigs. More detailed characterization, including dual use and the setting in which e-cigs are used, will increase our understanding of how e-cig use patterns relate to alcohol use. A recent potentially helpful development is an e-cig mouthpiece that can be used to assess user puff topography, which could be harnessed to quantify e-cig use in future studies [64], but more complete self-report measures should also be developed for when lab research is not possible. Continuous measures of alcohol use (e.g. quantity, frequency, alcohol use disorder, alcohol

use problems, binge drinking) are well established and much research suggests different risks and outcomes across various drinking patterns [65]. The current research on e-cig and alcohol use did tend to examine varying alcohol use outcomes, including binge drinking, problematic use, and ever-use of alcohol; however, these outcomes were often dichotomized, potentially losing important variability and nuances in the e-cig and alcohol relationship. In order to fully understand the relationship between e-cig and alcohol use, researchers should aim to fully characterize both e-cig and alcohol use patterns.

Second, longitudinal data is needed to examine the direction of the e-cig and alcohol use relationship. Although combined use, regardless of the causal direction, is likely mutually reinforcing for both e-cig and alcohol use, thereby increasing use of both substances, understanding this relationship from a developmental perspective would aid in targeting behaviors in adolescents. For example, if e-cig use precedes alcohol use on average, e-cig use could serve as a red flag to clinicians as a risk for future alcohol use, requiring interventions on both e-cig use and psychoeducation on the relationship with alcohol use. In addition, longitudinal designs should be used to examine e-cig and alcohol use trajectories, starting in adolescence and extending into adulthood. There is likely a complex relationship between cigarette use, e-cig use, dual use of both products, and alcohol use, relationships that cannot be ascertained without longitudinal studies. Some research indicates that adult former smokers that transition to e-cigs, report higher rates of alcohol use than those that do not transition to e-cigs [66], suggesting that e-cig use might perpetuate alcohol use among former smokers. However, these findings are cross-sectional, and thus, this should be explored longitudinally.

Third, there is a wealth of avenues for investigating mechanisms involved in the relationship between e-cig use and alcohol use. Overall, it is likely classically conditioned cues and dopaminergic processes could serve as mechanisms in the e-cig and alcohol use relationship, given their likely roles in co-occurring cigarette and alcohol use [36, 44–48]. Significant research is required to elucidate other potential mechanisms, including well-designed laboratory studies and field-based studies, such as those utilizing daily diary and ecological momentary assessment methodologies, in order to improve understanding concerning the nature of these relationships.

Conclusion

Emerging literature points to a relationship between e-cig use and alcohol use. We propose a conceptual model concerning the relationship between e-cig and alcohol use (see Figure 1). It is our hope that this proposed model will stimulate future research concerning mechanisms, moderators, and consequences of the relationship between e-cig and alcohol use. We make research recommendations, including the need for more methodological rigor, including improved measurement of e-cig use and expanding research to longitudinal and experimental designs, as well as research exploring potential mechanisms, moderators, and consequences of the relationship between e-cig and alcohol use. As prevalence rates of e-cig use increase, researchers and clinicians should not only be paying careful attention to the direct health effects of e-cigs, but also the potential impact e-cigs may have on alcohol use behaviors.

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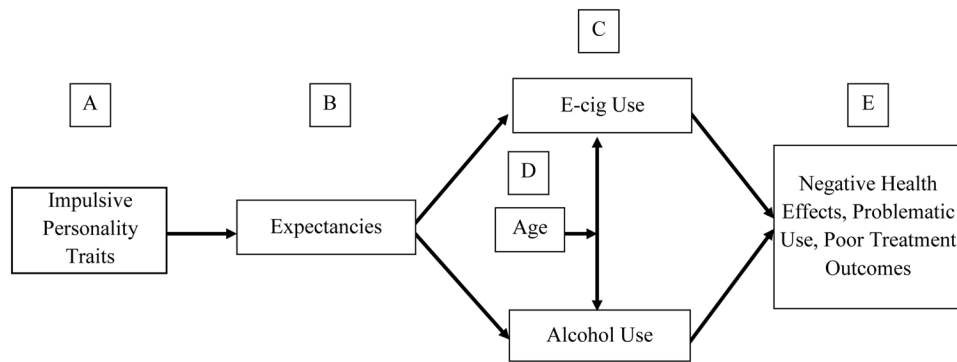


Figure 1.

A) Impulsive personality is one risk factor for both e-cig and alcohol use; B) Impulsive personality likely imparts risk for both e-cig and alcohol use through positive expectancies of use; C) Once initiated, the co-use of e-cigs and alcohol perpetuates use of each substance, such as through dopaminergic sensitization and classical conditioning processes; D) The strength of the relationship between e-cig and alcohol use likely varies by age, with younger individuals demonstrating a stronger relationship; E) The co-occurrence of e-cig and alcohol use then potentially lead to negative outcomes, including negative health effects, problematic levels of use (e.g. substance use disorder criteria), and poor substance use treatment outcomes.