HHS Public Access

Author manuscript

Am J Drug Alcohol Abuse. Author manuscript; available in PMC 2018 March 01.

Published in final edited form as:

Am J Drug Alcohol Abuse. 2017 March ; 43(2): 186–196. doi:10.1080/00952990.2016.1189927.

An overview of alcohol and tobacco/nicotine interactions in the human laboratory

Terril L. Verplaetse, PhD and **Sherry A. McKee, PhD**

Department of Psychiatry, Yale School of Medicine, New Haven, CT, USA

Abstract

Alcohol use disorders and tobacco use contribute significant risk to the global burden of disease, and each are major public health concerns. Together, alcohol and tobacco use are highly comorbid and have multiplicative health risks when used concurrently, underscoring the importance of examining alcohol-tobacco interactions in the human laboratory. The aims of this review were to summarize the state of research examining alcohol-tobacco interactions in the human laboratory, including 1) craving in drinkers and smokers exposed to smoking or drinking cues, 2) fixed-dosing of alcohol or nicotine in smokers and drinkers, and 3) smoking and alcohol influences on self-administration behaviors. The interactive effects of tobacco/nicotine with other drugs of abuse are also briefly discussed. Overall, results identified that alcohol and tobacco have reciprocal influences on potentiating craving, subjective responses to fixed-dose alcohol or nicotine administration, and self-administration. The literature identified that alcohol increases craving to smoke, decreases time to initiate smoking, and increases smoking self-administration. Similarly, tobacco and nicotine increase alcohol craving, decrease subjective effects of alcohol, and increase alcohol consumption. Future studies should continue to focus on alcohol and tobacco/nicotine interactions in individuals with a wide scope of drinking and smoking histories, different states of alcohol and nicotine deprivation, and influences of either drug on craving, subjective responses, and consumption over the course of the blood alcohol curve. This work could have important implications for the impact of alcohol-tobacco interactions on guiding clinical practice, as well as in the changing landscape of addiction.

Keywords

Alcohol; tobacco; nicotine; self-administration; human laboratory; craving

Introduction

Alcohol use disorders affect as many as 32 million Americans, and prevalence rates for 12-month and lifetime alcohol use disorders in the United States are 13.9% and 29.1%, respectively (1). Alcohol use has been found to increase risk for developing hypertensive

CONTACT Sherry A. McKee, PhD, sherry.mckee@yale.edu Department of Psychiatry, Yale School of Medicine, 2 Church St South, Suite 109, New Haven, CT 06519, USA.

Declaration of Interest

SAM has consulting to Cerecor and Embera, has received research support for investigator-initiated studies from Pfizer, Inc., and has ownership in Lumme, Inc.

disease, cancer, cirrhosis of the liver, cardiovascular disease, hemorrhagic stroke, and various other medical conditions (2). In addition to detrimental health risks, excessive alcohol consumption imposes an economic cost of $249 billion dollars in the United States due to lost productivity, increased healthcare, criminal justice expenses, and motor vehicular crashes (3). This figure has increased by $25.5 billion dollars in the United States in the last four years (4). Despite the extensive medical and financial consequences of alcohol use disorders, only 19.8% of those with lifetime alcohol use disorders ever receive treatment (1).

Cigarette smoking affects as many as 42 million Americans (5), and tobacco use remains the leading cause of morbidity and mortality in the United States, with over 556,000 deaths attributable to smoking-related causes per year (6). Looking at the global picture, tobacco use is responsible for more than 6 million annual deaths around the world (7). The effects of smoking on health has been well-documented, including increased risk for lung, oropharynx, liver, and bladder cancers, chronic obstructive pulmonary disease (COPD), heart disease, and cardiovascular disease amongst many others (8). Smoking imposes an economic burden of $289 billion dollars in medical expenses and lost productivity annually in the United States (9). Similar to alcohol use, smokers often fail to maintain long-term abstinence and relapse to tobacco use remains high.

Though excessive alcohol consumption and cigarette smoking are each risk factors for the global burden of disease and remain significant public health concerns, alcohol and tobacco use are highly co-morbid and the consequences of concurrent use are multiplicative. Epidemiological data suggest that daily smokers are more likely to meet criteria for hazardous drinking and other alcohol-related diagnoses by three-fold, and this risk increases by five-fold and 16-fold in non-daily smoking adults and non-daily smoking young adults, respectively (10, 11). For example, in the general population, the likelihood of meeting criteria for hazardous drinking was 26%, but non-daily smoking increased the risk for hazardous drinking to 56% (10). Similarly, the rate of hazardous drinking among past-year drinkers was 39.9%, whereas the rate of hazardous drinking in drinkers who were also smokers was 58% (10). Non-daily and daily smokers were also at higher risk for greater alcohol use patterns, including greater consumption and higher binge-like alcohol intake (10, 12, 13). Forty-seven percent of non-smokers reported engaging in binge-drinking in the past 12 months, whereas 76% and 69% of non-daily and daily smokers reported binge-drinking, respectively (11). The presence of an alcohol use disorder also increased the odds for non-daily, daily, and former smoking, and women meeting criteria for an alcohol use disorder were 5 times more likely to be non-daily smokers than never smokers (11).

The detrimental health risks and mortality rates seen with singular abuse of alcohol or tobacco also increase substantially as a result of their co-use (14). For example, alcohol or tobacco, when used alone, is associated with 6 to 7 times increased risk for developing oral cancers, whereas concurrent use of both alcohol and tobacco increases this risk by 300 times (15). The supra-multiplicative health risks associated with co-use also extend to increased cardiovascular risks and increased risk for cirrhosis, head and neck cancers, pancreatitis, and psychiatric co-morbidity (15–18). Thus, examining alcohol-tobacco interactions in the human laboratory may have implications for reducing the odds of co-use, reducing health risks, and guiding treatment strategies for concurrent alcohol and tobacco use.

Human laboratory paradigms have been utilized extensively to provide insight into the reciprocal relationship between alcohol and tobacco use. These models can be used to evaluate primary aspects of tobacco/nicotine effects on alcohol-motivated behavior and alcohol-induced smoking behavior, such as the urge to drink or smoke, the ability to resist drinking or smoking, and subsequent alcohol or smoking self-administration (19). For example, cue reactivity and controlled alcohol or tobacco/nicotine administration are often used to elucidate the interactive effects of these two drugs on craving, subjective responses of stimulation or sedation, and alcohol and smoking consumption. The following sections will review the state of the literature on human laboratory models of 1) cue-provoked craving, 2) subjective responses to fixed-dosed alcohol or tobacco/nicotine administration, and 3) alcohol or smoking influences on subsequent smoking or alcohol self-administration, respectively. Guidance for future work on alcohol-tobacco interactions and the changing landscape of addiction will be discussed.

Craving in the Human Laboratory

Effect of Alcohol Cues on Cue-Provoked Tobacco Craving

The frequent concurrent use of alcohol and smoking may elicit cue-provoked craving and urge to drink or smoke through a process called cue conditioning (20). Cues previously paired with drug-taking behavior may come to elicit craving or urge to use for that drug. For co-users of alcohol and tobacco, cues associated with one drug may elicit craving for the other. For example, the sight of cigarettes and an ashtray may provoke craving for alcohol, and the smell of an alcoholic beverage may increase the urge to smoke. Indeed, cross-cue reactivity (alcohol and smoking picture primes) has demonstrated delayed response latencies to both alcohol- and smoking-related words (21). It is established that cue-induced alcohol craving or craving to smoke may provoke increased drug use and promote relapse to drinking or smoking. Thus, the examination of cross-cue reactivity on drug craving in the human laboratory may elucidate mechanisms by which drug-associated cues influence alcohol and tobacco use.

Laboratory studies assessing the effects of alcohol cues on the urge to smoke demonstrate that alcohol cues elicit cravings to smoke and increase intention to smoke in alcohol-dependent and non-dependent daily smokers (22–25). Alcohol-dependent daily smokers demonstrated the strongest cravings to smoke when presented with alcohol-related picture cues, although non-alcohol dependent daily smokers also exhibited increased urge to smoke in response to alcohol cues (22). Nicotine-dependent and non-dependent occasional drinkers also exhibit increased intention to smoke cigarettes following alcohol-related image cues (25). Similar findings demonstrate that the sight and smell of alcohol elicit heightened urges to smoke in alcohol-dependent men who were also daily smokers in a treatment facility (23, 24), and that greater alcohol dependence predicted smoking cravings during alcohol treatment (24).

Overall, alcohol cues elicited greater urge to smoke in both alcohol-dependent and non-dependent daily smokers, in alcohol-dependent individuals admitted for detoxification in alcohol treatment centers, and in nicotine-dependent and non-dependent social drinkers. Given the high rates of smoking in the presence of alcohol regardless of drinking status, it is

not surprising that alcohol cues increase craving to smoke in both alcohol-dependent and non-dependent samples. It is also plausible that alcohol-dependent daily smokers may be particularly vulnerable to cue-provoked smoking cravings, as these individuals demonstrated the strongest self-reported urge to smoke.

Effect of Nicotine Deprivation and Smoking Cues on Cue-Provoked Alcohol Craving

Laboratory studies assessing the effects of nicotine deprivation and smoking-related cues have been conducted to the same extent, and demonstrate that both a nicotine deprivation period and smoking cues heighten the urge to drink alcohol in alcohol-dependent and non-dependent daily smokers (22, 26, 27). Palfai et al. (26) demonstrated that six hours of nicotine deprivation increased the urge to drink alcohol in hazardous drinkers who were also daily smokers. In contrast, Colby et al. (27) found that five hours of nicotine deprivation had no effect on urge to drink in social drinking daily smokers, but increased urge to smoke.

Research on the effects of smoking cues on alcohol craving have also been mixed. Smoking cues (lighter, ashtray, and cigarette) elicited cue-induced alcohol craving only after a six hour deprivation period in hazardous drinking daily smokers, and this effect was not specific to smoking cues (26). Neutral cues (pencils) also increased rating of urge to drink. However, Drobes (22) demonstrated that smoking-related picture cues increased the urge to drink in alcohol-dependent daily smokers.

Overall, studies have found mixed results regarding the effects of nicotine deprivation and smoking cues on the urge to drink alcohol. One explanation could be varying lengths of nicotine deprivation. Longer deprivation periods may elicit stronger urges to drink, whereas the craving for alcohol may be less apparent with shorter periods of nicotine deprivation. Stronger nicotine withdrawal symptoms associated with longer nicotine deprivation may elicit craving for negative reinforcement of both drugs in dual users of alcohol and tobacco/nicotine. Although, this may be unlikely because both laboratory studies used brief deprivation periods that only differed by one hour. Another possible explanation for the mixed findings on the effects of nicotine deprivation and smoking-related cues on alcohol craving could be differences in drinking patterns and drinking history of the individuals examined. For example, nicotine deprivation and smoking cues increased urge to drink in hazardous and alcohol-dependent drinkers, whereas social drinkers were unaffected by nicotine deprivation. Thus, individuals with heavier drinking patterns may be more susceptible to the effects of smoking cues on alcohol craving.

Future work may want to consider examining differing nicotine deprivation lengths on craving, possibly elucidating the role of nicotine deprivation on craving for positive and negative reinforcement. The studies reviewed above primarily focused on cue-provoked craving in alcohol-dependent daily smokers. The role of drinking and smoking patterns across the spectrum (e.g., binge drinkers, light smokers, etc.) may be helpful in elucidating the role of drug cues on craving in individuals with different histories of alcohol and tobacco/nicotine use. Finally, cross-cue reactivity may influence clinical treatment outcomes in dual users. For example, dual users receiving treatment for smoking cessation may be more likely to relapse to smoking if they are repeatedly exposed to alcohol cues. Clinical

treatment strategies promoting the abstinence of both alcohol and tobacco use may be important for treatment outcomes in dual alcohol and tobacco/nicotine users.

Dosing in the Human Laboratory

Fixed-Dose Alcohol in Smokers

Fixed-dose alcohol allows for standardized control of alcohol administration, and laboratory studies utilize fixed-dose alcohol administration to examine the effects of alcohol on subjective reactivity and primed self-administration behavior. For the purposes of this review, the effects of fixed-dose alcohol on subjective smoking responses will be examined, including urge to smoke and subjective stimulation and sedation. In human laboratory studies, fixed-dose alcohol administration has been found to increase craving to smoke for positive and negative reinforcement (28–37), potentiate the rewarding effects of nicotine (38), and decrease latency to start smoking (31, 32, 34). In an early study, alcohol administration (0.5 g/kg) increased time spent smoking, number of puffs on each cigarette, and amount of tobacco burnt, and increased smoking satisfaction (39). Subsequently, King and Epstein (28) and Epstein et al. (29) demonstrated that low (0.4 g/kg)- and high (0.8 g/kg)-dose priming drinks of alcohol dose-dependently increased cigarette craving on the ascending (28, 29) and descending (28) limbs of the blood alcohol curve in light smoking social drinkers after three hours of nicotine deprivation. The urge to smoke was particularly strong for the positive reinforcing effects of nicotine, but desire to smoke was also increased for negative reinforcement following alcohol administration (28). The effects of alcohol on cigarette craving for positive reinforcement were more strongly associated with subjective stimulation, rather than sedation (29). In agreement, a moderate-dose alcohol priming drink (0.6 g/kg) increased cigarette craving in female versus male non-daily smokers (35). Intravenous (IV) alcohol administration in heavy drinking light smokers also demonstrated a positive association between breath alcohol concentration and cigarette craving, indicating that the pharmacological effects of alcohol alone can induce smoking urge (36).

More recently, Kahler et al. (31) demonstrated that acute alcohol administration (0.4 and 0.8 g/kg) dose-dependently reduced the ability to resist smoking in heavy drinkers who were also moderate-to-heavy daily smokers. Individuals started smoking more quickly following alcohol consumption, exhibited greater urge to smoke, and increased the number of cigarettes smoked compared to a taste-masked placebo beverage. Greater increases in the urge to smoke following alcohol administration also predicted shorter latencies to start smoking, but the dose-dependent effects of alcohol on urge to smoke were not mediated by subjective ratings of stimulation and sedation (31). In contrast, alcohol administration (0.4 g/kg) did not demonstrate effects on latency to start smoking and urge to smoke compared with a taste-masked placebo beverage in heavy drinkers who were also moderate-to-heavy daily smokers (32). It should be noted that these two studies used nicotine deprivation periods of three and fifteen hours, respectively, before fixed-dose alcohol administration. Although, alcohol administration (0.4 g/kg) versus a non-alcoholic control beverage increased smoking urge after twelve hours of deprivation in a study of social drinkers who were also light smokers (40). In an attempt to clarify the effects of smoking deprivation on alcohol-induced smoking urges, Day et al. (41) demonstrated that alcohol administration

after three hours of nicotine deprivation increased subjective craving to smoke in heavy drinkers who were moderate-to-heavy daily smokers. The authors suggest that long, overnight nicotine deprivation may have led to higher baseline smoking cravings, potentially masking the effect of alcohol on craving to smoke (32, 41).

Alcohol expectancy may also play a role on the influence of fixed-dose alcohol administration on smoking behavior. Kahler et al. (32) demonstrated that women who expected to drink an alcoholic beverage were more likely to initiate smoking and rate satisfaction from smoking as higher compared with women expecting a placebo beverage. It is plausible that men are more likely to increase smoking behavior following alcohol consumption due to the pharmacologic effects of alcohol, whereas women may be more likely to exhibit increased smoke behavior due to expectancy effects. Indeed, the authors suggest that women may be more likely to smoke when using alcohol due to the expectation that alcohol may enhance the positive reinforcing effects of nicotine (32). However, few studies have examined gender differences in relation to the effects of fixed-dose alcohol administration on smoking-related outcomes.

Overall, low- and high-dose alcohol administration increased the urge to smoke, quickened time to initiate smoking, and increased subsequent smoking, and that moderate dosing may elicit cigarette craving to a greater degree in females versus males. It seems likely that fixed-dose alcohol administration may affect light or non-daily smokers differently than heavy daily smokers. Alcohol may act as a more potent cue for light smokers than regular smokers since light smokers may only smoke when drinking alcohol. Daily smokers most likely use cigarettes in a variety of contexts, including during drinking episodes, possibly accounting for the mixed results in light smokers versus heavy smokers. Findings also demonstrate that urge to smoke was greater during the ascending limb of the blood alcohol curve following alcohol administration. This result may suggest that alcohol and nicotine potentiate the reinforcing effects of one another during the ascending limb of the blood alcohol curve, possibly leading to greater use. It is possible that nicotine then counteracts the sedating properties of alcohol on the descending limb of the blood alcohol curve, allowing individuals to prolong a drinking episode.

Fixed-Dose Nicotine in Drinkers

Fixed-dose nicotine administration allows for standardized control of nicotine inhalation or absorption. In human laboratory studies examining alcohol-tobacco interactions, fixed-dose nicotine has been investigated for its effects on subjective responding to alcohol and alcohol self-administration. Laboratory studies assessing nicotine administration on alcohol-related outcomes demonstrate increased craving to drink (33, 42), and decreased subjective effects of alcohol (43, 44), including attenuated changes in stimulation (43) and sedation (43, 44). Fixed-dose nicotine administered via nasal spray (20 μg/kg/presentation) resulted in an attenuation of the intoxicating and sedating effects of alcohol in daily smokers who were moderate drinkers. In that study, nicotine administration was preceded by a moderate, fixed-dose of alcohol (0.5 g/kg), and the combination of nicotine and alcohol had additive effects on attenuated subjective responses to alcohol and nicotine alone, but enhanced effects in women only (43). More recently, fixed-dose administration of IV nicotine demonstrated an

attenuation of the sedative-like effects of IV alcohol administration in healthy, social drinkers (44). In contrast, nicotine lozenge (4 mg) demonstrated no effect on alcohol cue-reactivity (25) in dependent and non-dependent smokers who were also social drinkers.

Research on the effects of fixed-dose nicotine administration on drinking behavior has demonstrated mixed results regarding the subjective intoxicating effects of alcohol. As mentioned above, nicotine administered nasally attenuated the intoxicating effects of alcohol in moderate drinkers (43). This is consistent with a twin study indicating that nicotine decreases subjective alcohol intoxication in male and female drinkers (45). In contrast, transdermal nicotine (21 mg) increased subjective intoxication following acute alcohol administration in social drinking daily smokers (33).

Overall, fixed-dose nicotine interacts with alcohol to produce interactive effects on alcohol craving and subjective stimulation and sedation due to alcohol. The decrease in the intoxicating and sedating subjective effects of alcohol followed by nicotine administration may increase the likelihood of heavier drinking episodes. That is, individuals may not feel as ‘drunk’ while using both tobacco and alcohol concurrently, possibly perpetuating drinking. The mixed results on the effects of fixed-dose nicotine on subjective reactivity may be due to different lengths of nicotine deprivation or different drinking patterns. However, this is unlikely since overnight nicotine deprivation both decreased and increased subjective intoxication (33, 43), and moderate and social drinking samples were examined in all studies reviewed above. Nicotine dose and route of administration may account for differences seen in self-reported alcohol intoxication and craving ratings. Only higher-dose transdermal nicotine (21 mg) was associated with increased subjective intoxication (33).

Self-Administration in the Human Laboratory

Nicotine/Smoking Influences on Alcohol Self-Administration

Human laboratory studies demonstrate that nicotine deprivation and nicotine administration have mixed effects on subjective responses to alcohol and alcohol consumption. Palfair et al. (26) demonstrated that six hours of nicotine deprivation increased alcohol consumption in hazardous drinking daily smokers, and nicotine deprivation increased response times on an alcohol expectancy task, indicating that nicotine-deprived individuals had greater accessibility to alcohol expectancies. In contrast, five hours of nicotine deprivation did not increase alcohol self-administration in young social drinkers who were also daily smokers (27).

Two studies examined the effects of transdermal nicotine on alcohol self-administration. McKee et al. (46) demonstrated that transdermal nicotine (21 mg/day) altered reactivity to a low-dose priming alcohol (0.03 g/dl) drink and subsequent alcohol self-administration in non-dependent heavy drinkers who were also daily smokers (46). In that study, transdermal nicotine administration demonstrated longer latencies to start drinking alcohol and fewer drinks consumed versus placebo patch. Acheson et al. (47) used transdermal nicotine at lower doses (7 and 14 mg/day) to examine the effects of nicotine on reactivity to a low-dose priming drink (0.2 g/kg) and subsequent alcohol self-administration in social drinking light smokers. In that study, transdermal nicotine (14 mg) increased alcohol intake in men during

a two-hour self-administration period, but decreased alcohol consumption in women. It is important to note that, in the former study, individuals who received a placebo nicotine patch were nicotine deprived for six hours before the start of the alcohol self-administration period (46). Individuals in the latter study receiving placebo nicotine patch were only nicotine deprived for approximately three hours (47), possibly accounting for differences in self-administration behavior. It is likely that individuals on placebo used alcohol to medicate for nicotine withdrawal following a longer nicotine deprivation period, masking the effect of nicotine on alcohol self-administration behavior.

Laboratory studies assessing the pharmacologic effects of controlled, smoked nicotine on alcohol consumption also demonstrate increased drinking behavior. Barrett et al. (48) used a progressive ratio task to examine the effects of nicotinized versus denicotinized cigarettes on responding for alcohol in male, light smokers deprived of nicotine for twelve hours. Progressive ratio tasks involve working progressively harder for alcohol on each successive trial. In that study, nicotinized cigarettes increased alcohol self-administration and increased PR breakpoints for alcohol compared to denicotinized cigarettes. Relatedly, smoking reduced nicotine content cigarettes versus normal nicotine content cigarettes reduced alcohol use in daily smokers who were also current drinkers in a recent double-blind, randomized clinical trial (49).

Overall, findings suggest that nicotine increases alcohol-motivated behaviors. However, findings are mixed regarding the effects of nicotine deprivation and nicotine patch administration on subsequent alcohol self-administration. Nicotine content of cigarettes may also impact on alcohol consumption, such that reduced nicotine content cigarettes may also reduce alcohol use as a result of decreased nicotine exposure and subsequent reduced cross-cue reactivity (49, 50). Finally, few studies examined the role of gender on smoking-related drinking behavior. Nicotine patch increased alcohol intake in men, but decreased alcohol consumption in women (47). This is consistent with work demonstrating that responding for alcohol after ad-libitum smoking was greater following an alcohol prime in men compared to women (51). These findings suggest that men may be more sensitive to the effects of nicotine on increased alcohol responding and alcohol self-administration compared to women.

Alcohol Influences on Smoking Self-Administration

Alcohol is a known precipitant of smoking, and the effects of alcohol on smoking topography and smoking self-administration in the human laboratory may have serious implications for individuals attempting to quit smoking. Acute alcohol administration has been shown to decrease time to initiate smoking (19, 52) and increase smoking self-administration behavior (19, 30, 52, 53). In a smoking lapse model developed by McKee et al. (19), the effects of alcohol on smoking lapse behavior (i.e., time to initiate smoking after a quit attempt or period of nicotine deprivation) demonstrate that an alcohol priming drink (0.03 g/dl) quickened latency to initiate smoking consumption and increased smoking self-administration in heavy social drinking daily smokers. In that study, subjects were more likely to end the delay period to start smoking during the ascending limb of the blood alcohol curve. This study indicates that alcohol may reduce the ability to resist smoking in

dependent smokers, especially within the first hour of alcohol consumption. This is consistent with work indicating that the urge to smoke and smoking self-administration behaviors are greater post-alcohol consumption, during the ascending limb of the blood alcohol curve (30, 33, 52).

King et al. (30) examined the effects of alcohol on smoking behavior for nicotinized and denicotinized cigarettes in non-dependent heavy social drinking light smokers. Three hours of nicotine deprivation followed by an alcohol priming drink (0.8 g/kg) demonstrated increased smoking behavior, including greater number of cigarettes smoked and increased puff count, volume, and duration regardless of cigarette type in males only. McKee et al. (53) demonstrated that the expectation of drinking alcohol increased subjective positive effects of smoking (i.e., satisfaction, calm) rather than actual alcohol consumption, but only alcohol consumption decreased subjective negative effects of smoking (i.e., nausea). Alcohol administration (0.08 g/dl) also increased smoking self-administration compared to the placebo and mixer beverages, but smoking topography measures were not different between beverage conditions (53). These results are consistent with the former findings by King et al. (30) demonstrating that, following two standardized cigarette puffs, alcohol and a taste-masked placebo increased the urge to smoke and increased the positive, stimulating effects of smoking. Further, it is interesting to note that the expectation of alcohol intake increased the positive subjective effects of smoking (53). These results are supported by finding that women will increase smoking behavior due to the expectation that alcohol will enhance the positive effects of smoking (32), and that both an alcohol beverage and a taste-masked placebo beverage increase craving for cigarettes in light smokers (54). As discussed previously, the expectation of drinking alcohol may function as a cue for smoking initiation in dual users of alcohol and tobacco/nicotine.

More recently, Barrett et al. (55) examined the effects of alcohol on nicotinized versus denicotinized cigarettes smoking behavior in dependent daily smokers and non-dependent nondaily smokers who were also moderate drinkers. Alcohol increased the self-administration of both nicotinized and denicotinized cigarettes in non-dependent nondaily smokers. Alcohol also increased nicotinized cigarette smoking, but decreased denicotinized cigarette self-administration behavior in dependent daily smokers. The authors suggest that nicotine may be critical for the smoking-drinking relationship in dependent daily smokers, and that nicotine may not play as important a role in non-dependent smokers who increase smoking behavior following alcohol.

Taken together, findings across multiple smoking self-administration paradigms indicate that alcohol plays an intricate role in increasing tobacco-motivated behaviors. A range of alcohol doses influence smoking cravings, subjective effects of smoking, and smoking self-administration. Alcohol consumption decreases the ability to resist smoking and increases subsequent smoking self-administration, and the mere expectation of consuming alcohol increases the positive subjective effects of tobacco. Findings suggest that alcohol may exert maximal effects on smoking behavior during the ascending limb of the blood alcohol curve. As mentioned above, it is also likely that alcohol and nicotine potentiate the positive reinforcing effects of each other during the ascending limb of the blood alcohol curve, leading to greater self-administration behaviors.

Nicotine and Other Drugs of Abuse

There are fewer studies examining the interactive effects of nicotine with other drugs of abuse in the human laboratory. Tobacco/nicotine use is positively associated with cocaine use (56), and cigarette smoking in cocaine users is almost 3.5 times greater than in the general population (57). Similarly, ecological momentary assessment (EMA) studies indicate that smoking increases during periods of cocaine use and cocaine craving (56). In human laboratory studies, cocaine administration demonstrated increased rates of cigarette smoking (58, 59), and acute nicotine dosing by transdermal nicotine patch (22 mg) increased cue-induced cocaine craving in individuals with a history of cocaine use (60). Mixed findings also demonstrate a decrease or no change in subjective effects of cocaine following pretreatment with nicotine patch in occasional and heavy cocaine users, respectively (61, 62). More recently, a human laboratory study demonstrated that cocaine users exhibit an orienting, but not attentional, bias towards cigarette cues versus non-cocaine users, and that cocaine users demonstrate increased urge to smoke cigarettes for negative reinforcement versus non-users (63). Correspondingly, abstinence from smoking is also associated with decreased cocaine use in cocaine-dependent individuals (64). Overall, human laboratory studies suggest that tobacco/nicotine use and nicotine cues may facilitate higher cocaine use and craving, and that decreased cigarette use or abstinence may improve cocaine use outcomes.

Similarly, tobacco/nicotine use is also associated with greater heroin and marijuana use (65), although human laboratory paradigms assessing the interactive effects of tobacco/nicotine and heroin or marijuana are limited. An EMA study found that cigarette smoking frequencies were greater during episodes of heroin use and craving (56). Human laboratory findings are consistent with EMA findings demonstrating that cigarette smoking increased during IV heroin self-administration versus heroin-absent and methadone detoxification groups (66). More recent studies have examined smoking rates in individuals undergoing opioid treatment and found that cigarette smoking was heavier among individuals in opioid replacement therapy (ORT) versus non-ORT (67), but that buprenorphine detoxification reduced cigarette smoking (68). With regard to marijuana use, human laboratory data suggest that current cigarette smokers who were also daily marijuana smokers were more likely to relapse to marijuana use than non-smokers (69). However, in that study, short-term tobacco cessation did not improve marijuana relapse rates. This is consistent with epidemiological data indicating that 90% of marijuana users are also tobacco smokers (70), and that marijuana users who smoke cigarettes are more likely to relapse to marijuana use than non-smokers (for a recent review see Rabin and George, 2015)(71, 72). To summarize, the co-use of heroin or marijuana with tobacco/nicotine is highly prevalent, such that heroin and marijuana administration increases cigarette smoking. However, the paucity of human laboratory studies evaluating the reciprocal effects of tobacco/nicotine and other drugs of abuse on cue-induced craving, fixed-dose responding, and self-administration remains a concern. Future research is needed to further elucidate the interactive effects of tobacco/nicotine and other drugs of abuse in the human laboratory.

Conclusions and Implications

Alcohol and tobacco/nicotine have interactive effects on cross-cue reactivity to alcohol and tobacco craving, subjective feelings of stimulation and sedation, and alcohol and smoking self-administration. Social and heavy drinkers may experience tobacco as more reinforcing while using both drugs concurrently. Likewise, tobacco users may experience alcohol as more reinforcing while co-using. This is likely due to a potentiated reinforcement effect when both alcohol and tobacco are used simultaneously. The mechanisms by which alcohol potentiates smoking behavior and vice versa may be due to common reward pathways involving the mesolimbic dopamine and the nicotinic acetylcholine receptor (nAchR) systems. Both alcohol and tobacco directly mediate the release of dopamine in the nucleus accumbens (NA) and the ventral tegmental area (VTA) (73, 74), brain regions associated with the rewarding properties of drugs of abuse (75). It is thought that the increase in dopamine by alcohol and nicotine seen in the mesolimbic dopamine system may be mediated by the activation of the nAchR system and subsequent release of acetylcholine, possibly potentiating alcohol and nicotine reward (76, 77). Another possibility is that alcohol may influence the rate of metabolism of nicotine leading to increased use. However, this is unlikely since it has been demonstrated that alcohol does not influence the metabolic clearance of nicotine (18).

Additional work regarding alcohol and tobacco/nicotine interactions should examine differential effects of nicotine versus tobacco interactions with alcohol. To our knowledge, alcohol/tobacco interactions versus alcohol/nicotine interactions have not been examined in the human laboratory. Additionally, there are no studies examining the direct effects of smoked tobacco on precipitating alcohol self-administration. Correspondingly, few studies have examined the effects of nicotinized versus denicotinized cigarettes on drinking behavior or the effects of alcohol administration on nicotinized versus denicotinized cigarette smoking (30, 48, 55), but findings demonstrate a reciprocal influence. Finally, only two studies examined the effects of IV alcohol and nicotine on subsequent craving and self-administration behavior (44). IV administration of either drug controls for individual variability of the time course of brain exposure to alcohol or nicotine across subjects seen with traditional administration paradigms (78). Future human laboratory work examining the interactive effects of alcohol and tobacco/nicotine could clarify the role of concurrent drug use on alcohol- and tobacco-motivated behaviors.

These findings also have implications for treatment strategies in dual users of alcohol and tobacco. Heavy drinking smokers enrolled in smoking cessation treatment with brief alcohol intervention demonstrated increased risk to relapse to smoking when drinking alcohol, and moderate drinking days were associated with a four times increased risk of smoking lapse (79). Perhaps, treatment strategies that target common neurobiological pathways of alcohol and tobacco would reduce both drinking and smoking behavior. Indeed, human laboratory studies examining varenicline, a partial agonist at $\alpha 4\beta 2$ nAchRs and FDA-approved smoking cessation aid, for alcohol and tobacco use disorders show promise in promoting reduced alcohol and smoking consumption. Varenicline is well-tolerated in smokers and has demonstrated efficacy in reducing smoking (80–82). Varenicline has been shown to reduce alcohol craving and alcohol consumption in heavy drinking smokers and in alcohol-

dependent smokers and non-smokers (83–85), and decreases the subjective reinforcing effects of alcohol following a priming drink (83). Further, in a clinical trial examining the efficacy of varenicline for the treatment of alcohol dependence, improved drinking outcomes were associated with reductions in smoking (85).

The changing landscape of addiction also has new implications regarding e-cigarette use. The impact of e-cigarettes, as a nicotine delivery device, on drinking-behavior is unknown, and future work should elucidate how e-cigarettes impact on alcohol-motivated behaviors in the human laboratory. Vaping is allowed in most drinking establishments, circumventing the effects of smoke-free legislation on reduced alcohol consumption. Young-Wolff et al. (86) demonstrated that smoke-free laws reduced drinking behavior and rates of alcohol-related diagnoses, particularly in smokers. Importantly, human laboratory investigations of e-cigarette and alcohol interactions may help inform whether smoke-free legislation should extend to e-cigarette use.

The use of human laboratory paradigms to examine alcohol and tobacco/nicotine interactions does have limitations. There has been relatively little work extending human laboratory findings to real-world assessments of drinking and smoking behavior. For example, measures of subjective reactivity and self-administration behavior are assessed in a laboratory setting, typically void of peer or social influences or a realistic drinking or smoking context. Few laboratory studies have attempted to address this gap by creating a social drinking or social smoking laboratory setting. This work has found that men tend to match the alcohol consumption of their social drinking partner regardless of light or heavy use (87), and that non-daily smokers tended to match their smoking behavior to that of their smoking partner (88). Future work should further address the existing gaps between human laboratory findings and real-world co-morbid alcohol and tobacco/nicotine use. In addition, a limitation to this overview of alcohol and tobacco/nicotine interactions in the human laboratory is the possibility of missing literature, as this was not a systematic review.

Alcohol and tobacco use are highly co-morbid and have interactive effects on alcohol- and tobacco-motivated behaviors, with interactive effects of tobacco/nicotine extending to other drugs of abuse. Human laboratory studies have contributed important findings to understanding alcohol and tobacco/nicotine interactions, with implications for etiology of both alcohol and tobacco dependence and the maintenance and treatment of their co-use. Utilizing knowledge of alcohol and tobacco interactions may reduce the multiplicative effects of dual use and the associated impact on the global burden of disease.

Acknowledgments

Funding

This work was supported by NIH Grant Numbers T32DA007238 (TLV), P50DA033945 (SAM), and R01AA022285 (SAM).

References

1. Grant BF, Goldstein RB, Saha TD, Chou SP, Jung J, Zhang H, et al. Epidemiology of DSM-5 alcohol use disorder: results from the National Epidemiologic Survey on Alcohol and Related Conditions III. JAMA psychiatry. 2015; 72(8):757–66. [PubMed: 26039070]
2. Rehm J, Mathers C, Popova S, Thavorncharoensap M, Teerawattananon Y, Patra J. Global burden of disease and injury and economic cost attributable to alcohol use and alcohol-use disorders. The Lancet. 2009; 373(9682):2223–33.
3. Sacks JJ, Gonzales KR, Bouchery EE, Tomedi LE, Brewer RD. 2010 national and state costs of excessive alcohol consumption. American journal of preventive medicine. 2015; 49(5):e73–e9. [PubMed: 26477807]
4. Bouchery EE, Harwood HJ, Sacks JJ, Simon CJ, Brewer RD. Economic costs of excessive alcohol consumption in the US, 2006. American journal of preventive medicine. 2011; 41(5):516–24. [PubMed: 22011424]
5. Agaku IT, King BA, Dube SR. Current cigarette smoking among adults - United States, 2005–2012. MMWR Morbidity and mortality weekly report. 2014; 63(2):29–34. Epub 2014/01/17. [PubMed: 24430098]
6. Carter BD, Abnet CC, Feskanich D, Freedman ND, Hartge P, Lewis CE, et al. Smoking and mortality—beyond established causes. New England journal of medicine. 2015; 372(7):631–40. [PubMed: 25671255]
7. World Health Organization (WHO). WHO global report on trends in prevalence of tobacco smoking. 2015; 2015 [cited 2016 January 26]. Available from: http://apps.who.int/iris/bitstream/10665/156262/1/9789241564922_eng.pdf?ua=1.
8. Centers for Disease Control and Prevention (CDC). Smoking-attributable mortality, years of potential life lost, and productivity losses--United States, 2000–2004. MMWR Morbidity and mortality weekly report. 2008; 57(45):1226–8. Epub 2008/11/15. [PubMed: 19008791]
9. Health UDo, Human Services. The health consequences of smoking—50 years of progress: a report of the Surgeon General. Atlanta, GA: US Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health; 2014. p. 17
10. McKee SA, Falba T, O'Malley SS, Sindelar J, O'Connor PG. Smoking status as a clinical indicator for alcohol misuse in US adults. Archives of Internal Medicine. 2007; 167(7):716–21. [PubMed: 17420431]
11. Husky MM, Paliwal P, Mazure CM, McKee SA. Gender differences in association with substance use diagnoses and smoking. Journal of addiction medicine. 2007; 1(3):161–4. [PubMed: 21768952]
12. Harrison EL, Desai RA, McKee SA. Nondaily smoking and alcohol use, hazardous drinking, and alcohol diagnoses among young adults: findings from the NESARC. Alcoholism: Clinical and Experimental Research. 2008; 32(12):2081–7.
13. Grant BF. Age at smoking onset and its association with alcohol consumption and DSM-IV alcohol abuse and dependence: results from the National Longitudinal Alcohol Epidemiologic Survey. Journal of substance abuse. 1998; 10(1):59–73. [PubMed: 9720007]
14. ROSENGREN A, WILHELMSEN L, WEDEL H. Separate and Combined Effects of Smoking and Alcohol Abuse in Middle-aged Men. Acta Medica Scandinavica. 1988; 223(2):111–8. [PubMed: 3348108]
15. Zheng, T., Boyle, P., Zhang, B., Zhang, Y., Owens, PH., Lan, Q. Tobacco use and risk of oral cancer. Tobacco: Science, Policy and Public Health; 2004. p. 399-432.
16. Pelucchi C, Gallus S, Garavello W, Bosetti C, La Vecchia C. Cancer risk associated with alcohol and tobacco use: focus on upper aero-digestive tract and liver. Alcohol Research & Health. 2006; 29(3):193–9. [PubMed: 17373408]
17. Le Strat Y, Ramoz N, Gorwood P. In alcohol-dependent drinkers, what does the presence of nicotine dependence tell us about psychiatric and addictive disorders comorbidity? Alcohol and alcoholism. 2010; 45(2):167–72. [PubMed: 20089545]

18. Benowitz NL, Jones RT, Jacob P 3rd. Additive cardiovascular effects of nicotine and ethanol. Clinical pharmacology and therapeutics. 1986; 40(4):420–4. Epub 1986/10/01. [PubMed: 3757405]
19. McKee SA, Krishnan-Sarin S, Shi J, Mase T, O'Malley SS. Modeling the effect of alcohol on smoking lapse behavior. Psychopharmacology. 2006; 189(2):201–10. [PubMed: 17013640]
20. Drobes DJ. Concurrent alcohol and tobacco dependence: mechanisms and treatment. Alcohol Research and Health. 2002; 26(2):136–42.
21. Oliver JA, Drobes DJ. Cognitive manifestations of drinking-smoking associations: preliminary findings with a cross-primed Stroop task. Drug and alcohol dependence. 2015; 147:81–8. Epub 2015/01/07. DOI: 10.1016/j.drugalcdep.2014.12.010 [PubMed: 25561386]
22. Drobes DJ. Cue reactivity in alcohol and tobacco dependence. Alcoholism: Clinical and Experimental Research. 2002
23. Rohsenow DJ, Monti PM, Colby SM, Gulliver SB, Sirota AD, Niaura RS, et al. Effects of alcohol cues on smoking urges and topography among alcoholic men. Alcoholism: Clinical and Experimental Research. 1997; 21(1):101–7.
24. Gulliver SB, Rohsenow DJ, Colby SM, Dey AN, Abrams DB, Niaura RS, et al. Interrelationship of smoking and alcohol dependence, use and urges to use. Journal of studies on alcohol. 1995; 56(2): 202–6. [PubMed: 7760567]
25. McGrath DS, Peloquin MP, Ferdinand JC, Barrett SP. Acute effects of nicotine on alcohol cue-reactivity in nondependent and dependent smokers. Exp Clin Psychopharmacol. 2015; 23(1):29–36. Epub 2015/02/03. DOI: 10.1037/a0038606. [PubMed: 25643027]
26. Palfai TP, Monti PM, Ostafin B, Hutchison K. Effects of nicotine deprivation on alcohol-related information processing and drinking behavior. Journal of abnormal psychology. 2000; 109(1):96. [PubMed: 10740940]
27. Colby SM, Rohsenow DJ, Monti PM, Gwaltney CJ, Gulliver SB, Abrams DB, et al. Effects of tobacco deprivation on alcohol cue reactivity and drinking among young adults. Addictive behaviors. 2004; 29(5):879–92. [PubMed: 15219332]
28. King AC, Epstein AM. Alcohol dose–dependent increases in smoking urge in light smokers. Alcoholism: Clinical and Experimental Research. 2005; 29(4):547–52.
29. Epstein AM, Sher TG, Young MA, King AC. Tobacco chippers show robust increases in smoking urge after alcohol consumption. Psychopharmacology. 2007; 190(3):321–9. [PubMed: 16804691]
30. King A, McNamara P, Conrad M, Cao D. Alcohol-induced increases in smoking behavior for nicotinized and denicotinized cigarettes in men and women. Psychopharmacology. 2009; 207(1): 107–17. Epub 2009/09/17. DOI: 10.1007/s00213-009-1638-9 [PubMed: 19756530]
31. Kahler CW, Metrik J, Spillane NS, Day A, Leventhal AM, McKee SA, et al. Acute effects of low and high dose alcohol on smoking lapse behavior in a laboratory analogue task. Psychopharmacology. 2014; 231(24):4649–57. [PubMed: 24858377]
32. Kahler CW, Metrik J, Spillane NS, Leventhal AM, McKee SA, Tidey JW, et al. Sex differences in stimulus expectancy and pharmacologic effects of a moderate dose of alcohol on smoking lapse risk in a laboratory analogue study. Psychopharmacology. 2012; 222(1):71–80. [PubMed: 22227611]
33. Kouri EM, McCarthy EM, Faust AH, Lukas SE. Pretreatment with transdermal nicotine enhances some of ethanol's acute effects in men. Drug and alcohol dependence. 2004; 75(1):55–65. [PubMed: 15225889]
34. Peloquin MP, Hecimovic K, Sardinha J, Stewart SH, Barrett SP. The effect of snus on alcohol-related cigarette administration in dependent and non-dependent smokers. Pharmacology Biochemistry and Behavior. 2013; 114:97–102.
35. Peloquin MP, McGrath DS, Telbis D, Barrett SP. Alcohol and tobacco cue effects on craving in non-daily smokers. Experimental and clinical psychopharmacology. 2014; 22(6):502. [PubMed: 25436842]
36. Ray LA, Miranda R Jr, Kahler CW, Leventhal AM, Monti PM, Swift R, et al. Pharmacological effects of naltrexone and intravenous alcohol on craving for cigarettes among light smokers: a pilot study. Psychopharmacology. 2007; 193(4):449–56. [PubMed: 17484067]

37. Burton SM, Tiffany ST. The effect of alcohol consumption on craving to smoke. Addiction (Abingdon, England). 1997; 92(1):15–26. Epub 1997/01/01.
38. Rose JE, Brauer LH, Behm FM, Cramblett M, Calkins K, Lawhon D. Potentiation of nicotine reward by alcohol. Alcoholism: Clinical and Experimental Research. 2002
39. Glautier S, Clements K, White J, Taylor C, Stolerman I. Alcohol and the reward value of cigarette smoking. Behavioural pharmacology. 1996; 7(2):144–54. [PubMed: 11224406]
40. Attwood AS, Penton-Voak IS, Goodwin C, Munafo MR. Effects of acute nicotine and alcohol on the rating of attractiveness in social smokers and alcohol drinkers. Drug and alcohol dependence. 2012; 125(1–2):43–8. Epub 2012/04/13. DOI: 10.1016/j.drugalcdep.2012.03.014. [PubMed: 22494879]
41. Day AM, Kahler CW, Spillane NS, Metrik J, Rohsenow DJ. Length of smoking deprivation moderates the effects of alcohol administration on urge to smoke. Addictive behaviors. 2014; 39(5):976–9. [PubMed: 24556154]
42. Oliver JA, Blank MD, Van Rensburg KJ, MacQueen DA, Brandon TH, Drobes DJ. Nicotine interactions with low-dose alcohol: pharmacological influences on smoking and drinking motivation. Journal of abnormal psychology. 2013; 122(4):1154. [PubMed: 24364618]
43. Perkins K, Sexton J, DiMarco A, Grobe J, Scierka A, Stiller R. Subjective and cardiovascular responses to nicotine combined with alcohol in male and female smokers. Psychopharmacology. 1995; 119(2):205–12. [PubMed: 7659768]
44. Ralevski E, Perry EB, D'Souza DC, Bufis V, Elander J, Limoncelli D, et al. Preliminary findings on the interactive effects of IV ethanol and IV nicotine on human behavior and cognition: A laboratory study. Nicotine & Tobacco Research. 2011:ntr258.
45. Madden PA, Heath A, Starmer G, Whitfield J, Martin N. Alcohol sensitivity and smoking history in men and women. Alcoholism: Clinical and experimental research. 1995; 19(5):1111–20.
46. McKee SA, O'Malley SS, Shi J, Mase T, Krishnan-Sarin S. Effect of transdermal nicotine replacement on alcohol responses and alcohol self-administration. Psychopharmacology. 2008; 196(2):189–200. [PubMed: 17912500]
47. Acheson A, Mahler SV, Chi H, de Wit H. Differential effects of nicotine on alcohol consumption in men and women. Psychopharmacology. 2006; 186(1):54–63. Epub 2006/03/28. DOI: 10.1007/s00213-006-0338-y. [PubMed: 16565827]
48. Barrett SP, Tichauer M, Leyton M, Pihl RO. Nicotine increases alcohol self-administration in non-dependent male smokers. Drug and alcohol dependence. 2006; 81(2):197–204. [PubMed: 16054779]
49. Dermody SS, Tidey JW, Denlinger RL, Pacek LR, al'Absi M, Drobes DJ, et al. The Impact of Smoking Very Low Nicotine Content Cigarettes on Alcohol Use. Alcohol Clin Exp Res. 2016; 40(3):606–15. Epub 2016/02/27. DOI: 10.1111/acer.12980. [PubMed: 26916879]
50. Dermody SS, Donny EC. The predicted impact of reducing the nicotine content in cigarettes on alcohol use. Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco. 2014; 16(8):1033–44. Epub 2014/03/22. DOI: 10.1093/ntr/ntu037
51. Perkins K, Fonte C, Grobe J. Sex differences in the acute effects of cigarette smoking on the reinforcing value of alcohol. Behavioural pharmacology. 2000; 11(1):63–70. [PubMed: 10821210]
52. Mitchell S, De Wit H, Zacny J. Effects of varying ethanol dose on cigarette consumption in healthy normal volunteers. Behavioural pharmacology. 1995
53. McKee SA, Harrison EL, Shi J. Alcohol expectancy increases positive responses to cigarettes in young, escalating smokers. Psychopharmacology. 2010; 210(3):355–64. [PubMed: 20352411]
54. Sayette MA, Martin CS, Wertz JM, Perrott MA, Peters AR. The effects of alcohol on cigarette craving in heavy smokers and tobacco chippers. Psychology of Addictive Behaviors. 2005; 19(3): 263. [PubMed: 16187804]
55. Barrett SP, Campbell ML, Roach S, Stewart SH, Darredeau C. The Effects of Alcohol on Responses to Nicotine-Containing and Denicotinized Cigarettes in Dependent and Nondaily Smokers. Alcoholism: Clinical and Experimental Research. 2013; 37(8):1402–9.
56. Epstein DH, Marrone GF, Heishman SJ, Schmittner J, Preston KL. Tobacco, cocaine, and heroin: craving and use during daily life. Addictive behaviors. 2010; 35(4):318–24. [PubMed: 19939575]

57. Budney AJ, Higgins ST, Hughes JR, Bickel WK. Nicotine and caffeine use in cocaine-dependent individuals. Journal of Substance Abuse. 1993; 5(2):117–30. [PubMed: 8400835]
58. Nemeth-Coslett, R.Henningfield, J.Katz, J., Goldberg, S., editors. Pharmacology Biochemistry and Behavior. PERGAMON-ELSEVIER SCIENCE LTD; THE BOULEVARD, LANGFORD LANE, KIDLINGTON, OXFORD, ENGLAND OX5 1GB: 1986. Effect of cocaine on rate of cigarette-smoking.
59. Roll JM, Higgins ST, Tidey J. Cocaine use can increase cigarette smoking: evidence from laboratory and naturalistic settings. Experimental and clinical psychopharmacology. 1997; 5(3): 263. [PubMed: 9260074]
60. Reid MS, Mickalian JD, Delucchi KL, Hall SM, Berger SP. An acute dose of nicotine enhances cue-induced cocaine craving. Drug and alcohol dependence. 1998; 49(2):95–104. [PubMed: 9543646]
61. Kouri EM, Stull M, Lukas SE. Nicotine alters some of cocaine's subjective effects in the absence of physiological or pharmacokinetic changes. Pharmacology Biochemistry and Behavior. 2001; 69(1):209–17.
62. Sobel B-FX, Sigmon SC, Griffiths RR. Transdermal nicotine maintenance attenuates the subjective and reinforcing effects of intravenous nicotine, but not cocaine or caffeine, in cigarette-smoking stimulant abusers. Neuropsychopharmacology. 2004; 29(5):991–1003. [PubMed: 15010695]
63. Marks KR, Alcorn JL 3rd, Stoops WW, Rush CR. Cigarette Cue Attentional Bias in Cocaine-Smoking and Non-Cocaine-Using Cigarette Smokers. Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco. 2016; Epub 2016/02/28. doi: 10.1093/ntr/ntw026.
64. Winhusen TM, Kropp F, Theobald J, Lewis DF. Achieving smoking abstinence is associated with decreased cocaine use in cocaine-dependent patients receiving smoking-cessation treatment. Drug and alcohol dependence. 2014; 134:391–5. doi:10.1016/j.drugalcdep.2013.09.019. PubMed PMID: WOS:000332425500055. [PubMed: 24128381]
65. Harrell P, Trenz R, Scherer M, Pacek L, Latimer W. Cigarette smoking, illicit drug use, and routes of administration among heroin and cocaine users. Addictive behaviors. 2012; 37(5):678–81. [PubMed: 22305644]
66. Mello NK, Mendelson JH, Sellers ML, Kuehnle JC. Effects of heroin self-administration on cigarette smoking. Psychopharmacology. 1980; 67(1):45–52. [PubMed: 6768078]
67. McClure EA, Acquavita SP, Dunn KE, Stoller KB, Stitzer ML. Characterizing smoking, cessation services, and quit interest across outpatient substance abuse treatment modalities. Journal of substance abuse treatment. 2014; 46(2):194–201. [PubMed: 23988192]
68. Patrick ME, Dunn KE, Badger GJ, Heil SH, Higgins ST, Sigmon SC. Spontaneous reductions in smoking during double-blind buprenorphine detoxification. Addictive behaviors. 2014; 39(9): 1353–6. [PubMed: 24845165]
69. Haney M, Bedi G, Cooper ZD, Glass A, Vosburg SK, Comer SD, et al. Predictors of marijuana relapse in the human laboratory: robust impact of tobacco cigarette smoking status. Biological psychiatry. 2013; 73(3):242–8. [PubMed: 22939992]
70. Rabin RA, George TP. A review of co-morbid tobacco and cannabis use disorders: Possible mechanisms to explain high rates of co-use. The American Journal on Addictions. 2015; 24(2): 105–16. [PubMed: 25662704]
71. de Dios MA, Vaughan EL, Stanton CA, Niaura R. Adolescent tobacco use and substance abuse treatment outcomes. Journal of substance abuse treatment. 2009; 37(1):17–24. [PubMed: 19004603]
72. Moore BA, Budney AJ. Tobacco smoking in marijuana-dependent outpatients. Journal of Substance Abuse. 2001; 13(4):583–96. [PubMed: 11775084]
73. Corrigall WA, Franklin KB, Coen KM, Clarke PB. The mesolimbic dopaminergic system is implicated in the reinforcing effects of nicotine. Psychopharmacology. 1992; 107(2–3):285–9. [PubMed: 1615127]
74. Gonzales RA, Weiss F. Suppression of ethanol-reinforced behavior by naltrexone is associated with attenuation of the ethanol-induced increase in dialysate dopamine levels in the nucleus accumbens. The Journal of neuroscience. 1998; 18(24):10663–71. [PubMed: 9852601]

75. Koob GF, Bloom FE. Cellular and molecular mechanisms of drug dependence. Science. 1988; 242(4879):715–23. [PubMed: 2903550]
76. McKee SA, Weinberger AH. How can we use our knowledge of alcohol-tobacco interactions to reduce alcohol use? Annual review of clinical psychology. 2013; 9:649–74. Epub 2012/11/20. DOI: 10.1146/annurev-clinpsy-050212-185549
77. Larsson A, Engel JA. Neurochemical and behavioral studies on ethanol and nicotine interactions. Neuroscience & Biobehavioral Reviews. 2004; 27(8):713–20. [PubMed: 15019421]
78. Zimmermann, US., O'Connor, S., Ramchandani, VA. Behavioral Neurobiology of Alcohol Addiction. Springer; 2013. Modeling alcohol self-administration in the human laboratory; p. 315-53.
79. Kahler CW, Spillane NS, Metrik J. Alcohol use and initial smoking lapses among heavy drinkers in smoking cessation treatment. Nicotine & Tobacco Research. 2010:ntq083.
80. McKee SA, Weinberger AH, Shi J, Tetrault J, Coppola S. Developing and validating a human laboratory model to screen medications for smoking cessation. Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco. 2012; 14(11):1362–71. Epub 2012/04/12. DOI: 10.1093/ntr/nts090 [PubMed: 22492085]
81. Cahill K, Stead LF, Lancaster T, Polonio IB. Nicotine receptor partial agonists for smoking cessation. Sao Paulo Medical Journal. 2012; 130(5):346–7.
82. Garrison GD, Dugan SE. Varenicline: a first-line treatment option for smoking cessation. Clinical therapeutics. 2009; 31(3):463–91. [PubMed: 19393839]
83. McKee SA, Harrison EL, O'Malley SS, Krishnan-Sarin S, Shi J, Tetrault JM, et al. Varenicline reduces alcohol self-administration in heavy-drinking smokers. Biological psychiatry. 2009; 66(2): 185–90. [PubMed: 19249750]
84. Plebani JG, Lynch KG, Rennert L, Pettinati HM, O'Brien CP, Kampman KM. Results from a pilot clinical trial of varenicline for the treatment of alcohol dependence. Drug and alcohol dependence. 2013; 133(2):754–8. [PubMed: 23916324]
85. Litten RZ, Ryan ML, Fertig JB, Falk DE, Johnson B, Dunn KE, et al. A double-blind, placebo-controlled trial assessing the efficacy of varenicline tartrate for alcohol dependence. Journal of addiction medicine. 2013; 7(4):277. [PubMed: 23728065]
86. Young-Wolff KC, Hyland AJ, Desai R, Sindelar J, Pilver CE, McKee SA. Smoke-free policies in drinking venues predict transitions in alcohol use disorders in a longitudinal US sample. Drug and alcohol dependence. 2013; 128(3):214–21. [PubMed: 22999418]
87. Collins RL, Parks GA, Marlatt GA. Social determinants of alcohol consumption: the effects of social interaction and model status on the self-administration of alcohol. Journal of consulting and clinical psychology. 1985; 53(2):189. [PubMed: 3998247]
88. Reymarova E, Schlagintweit HE, Barrett SP. The impact of social context on cigarette self-administration in nondependent smokers. Behavioural pharmacology. 2015; 26:627–30. (7-Special Issue Pharmacological Approaches To The Study Of Social Behaviour-Part 2: Social Modul). [PubMed: 26086725]