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Critical Review

A Critical Review of the Effects of Nicotine and Alcohol Coadministration in Human Laboratory Studies

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Simultaneous use of cigarettes and alcohol is common and may be driven by nicotine increasing alcohol self-administration or vice versa. To better evaluate the causal nature of this relationship, we systematically reviewed human experimental laboratory studies that coadministered nicotine and alcohol with control conditions. Searches of PubMed/MEDLINE and PsycINFO databases and study bibliographies identified 30 studies that met our inclusion criteria. Research methodologies were critically reviewed. Effects of coadministration on drug self-administration and related factors such as craving, subjective response, motivation, and heart rate are reported. Results most strongly supported that alcohol increases nicotine and cigarette self-administration, whereas, depending on the context, nicotine increased, decreased, or had no effect on alcohol self-administration. Craving and subjective drug effects were also impacted by coadministration. Interaction effects of nicotine and alcohol on self-administration and subjective responses were reported infrequently. The effects may be moderated by a number of factors, including dose of administered drug and sex. Recommendations are made for future research, and clinical and policy implications of findings are discussed.

Key Words: Alcohol, Nicotine, Self-Administration, Tobacco, Human Laboratory, Review.

CIGARETTE AND ALCOHOL use are leading preventable causes of death in the United States, contributing annually to at least 480,000 deaths (US Department of Health Human Services, 2014) and 88,000 deaths (Stahre et al., 2014), respectively. Cigarettes and alcohol are also commonly co-used (McKee and Weinberger, 2013) by nearly 1 in 5 adults (Falk et al., 2006). Co-use, relative to using each substance alone, has been associated with increased use, dependence, and negative health outcomes such as certain cancers, cirrhosis, and pancreatitis (Hashibe et al., 2007; McKee and Weinberger, 2013).

To reduce nicotine and alcohol co-use and associated negative outcomes, it is critical to understand the extent to which smoking affects drinking, and vice versa, when both drugs are used simultaneously. Ecological momentary assessment studies have demonstrated that smoking and drinking are closely interrelated at the event level. Specifically, when individuals self-administer nicotine or alcohol, they are more likely to use the other substance during the same episode (Piasecki et al., 2011, 2012; Shiffman et al., 2002, 2007). Event-level co-use, subsequently referred to as *simultaneous use*, may reflect causal effects of nicotine on alcohol use and/or vice versa.

Potential causal associations have not been clarified with respect to the directionality of effects or the behavioral, subjective, and physiological outcomes that might contribute to these effects. Specifically, many studies examining alcohol and nicotine interactions are observational, precluding causal inferences. Prior selective reviews have included both experimental and observational studies to evaluate the effect of nicotine on alcohol administration only (Dermody and Donny, 2014; McKee and Weinberger, 2013) or bidirectional effects (Shiffman and Balabanis, 1995; Verplaetse and McKee, 2016; Zacny, 1990). While these reviews have demonstrated that smoking and drinking are correlated, the conclusions of these studies differed with respect to the extent to which a bidirectional causal relationship exists.

Human laboratory paradigms have evaluated causal relations by manipulating drug exposure to examine the independent effects of nicotine or alcohol on self-administration (and/or effects of) of the other drug, as well as potential additive and interactive effects. Therefore, human laboratory paradigms can experimentally test the main effects of each substance on the self-administration of the other, as well as additive and interactive effects on concurrent changes in craving and other subjective responses that may correspond

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with changes in self-administration. To further inform the causal nature of relationships between nicotine and alcohol, we systematically review human laboratory research relevant to this area, describing experimental paradigms, discussing experimental evidence of processes leading to nicotine and alcohol co-use, and providing recommendations for future research.

MATERIALS AND METHODS

Human laboratory studies that administered nicotine and alcohol were identified using (i) PubMed/MEDLINE and PsycINFO databases and (ii) bibliographic searches. The Boolean terms included keywords and their variants relating to alcohol (alcohol, ethanol), nicotine (nicotine, cigarette, tobacco), and experimental methods (administration, intravenous (IV), transdermal, pretreatment, subjective, laboratory, experiment, randomized, placebo). The search was limited to peer-reviewed studies published in English through June 2016, with human participants.

Abstracts were independently reviewed by SSD and CSH to determine whether they appeared to meet inclusion criteria. After full review, studies were retained if they (i) reported experimental methods (utilized random assignment); (ii) administered both nicotine and alcohol in the laboratory; (iii) included a control condition (e.g., placebo or very low nicotine content cigarette) for the manipulated substance(s); and (iv) reported effects of the manipulated substance on response to the intake of (or behavioral, physiological, and/or subjective response to) the other substance.

RESULTS

Study Selection

Initially, 363 unique records were identified (Fig. 1). Articles that clearly did not meet inclusion criteria were discarded, and disagreement was resolved through discussion. Following full-text review of 55 studies, 26 met inclusion criteria. Reliability (kappa) between the researchers for screening these studies was 0.92. Four additional qualifying studies were identified through bibliography searches, resulting in 30 qualifying studies. A meta-analysis was ruled out due to considerable heterogeneity in experimental paradigms and outcomes.

Summary of Experimental Paradigms. Study methodologies are summarized in Table 1. Alcohol manipulations included oral priming dose (blood alcohol concentration [BAC] <30 mg%), moderate (BAC > 30 mg%) doses, and IV administration. A nonalcohol placebo or control group (BAC = 0.00) was reported in nearly all studies. Self-administration outcomes included drinks consumed, latency to drink, BAC, and motivation to drink via progressive ratio (PR) and alcohol purchase tasks. Nicotine administration included cigarette smoking, nicotine-containing transdermal patch, nasal spray, snus, gum, smokeless tobacco, or IV nicotine), usually compared against nicotine-free placebos. Some studies used cigarette control conditions involving cigarettes with substantially reduced nicotine content or nonsmoking conditions. Nicotine self-administration outcomes included cigarette puff topography, number of cigarettes smoked, carbon monoxide (CO), and latency to smoke. Other outcomes reviewed included alcohol/cigarette craving, several domains of subjective drug responses (see Table 1), and heart rate increase, a potential index of drug reward.

Below, we first review the effect of nicotine on alcohol responses. Only significant effects are interpreted for studies

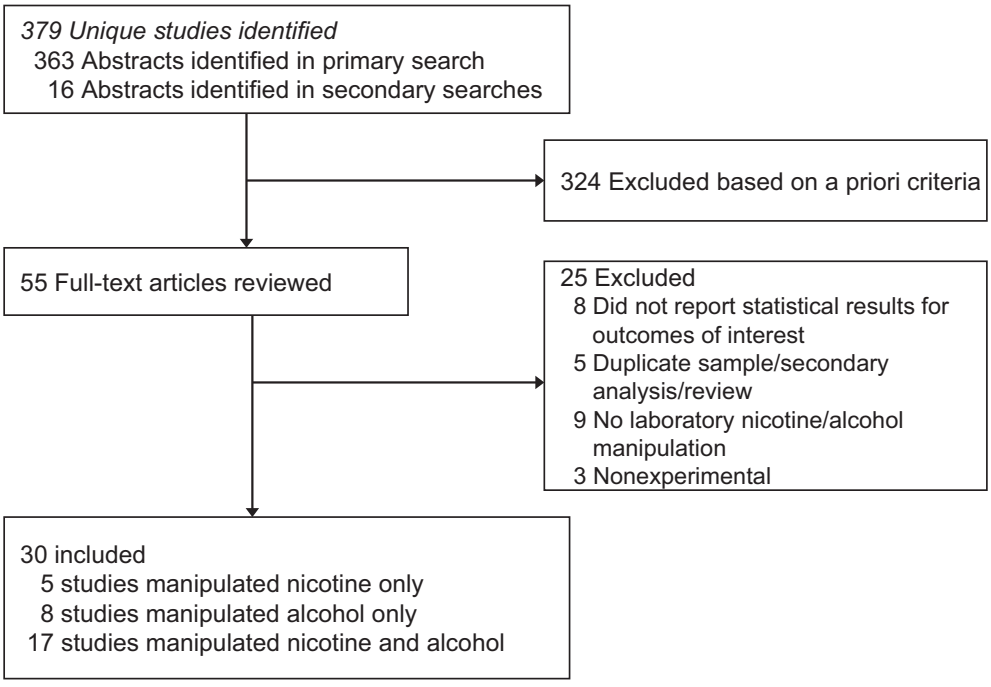

Fig. 1. Flow diagram of study selection for critical review.

Table 1. Studies of Alcohol and Nicotine Coadministration in Relation to Drug Self-Administration and Related Outcomes

First author, year (place)	*N*	% Male	Mean age (SD)	Drug use Hx[a]	Drug manipulation	Drug outcome paradigm	Outcome measure	Significant effects
Studies that manipulated nicotine only								
Acheson, 2006 (USA)	34	65	26 (NR)	2 CPD 11 DPW	Nicotine transdermal patch (0, 7, 14 mg)	Priming oral alcohol dose and then alcohol purchase task	Priming dose: BAC Sedative Stimulant Affect Heart rate Self-administration: No. drinks	 None Increase (14 mg only) None None None M: Increase (14 mg only); F: Decrease
Barrett, 2006 (Canada)	15	100	22 (2)	2 CPD FTND 0 12 DPW	4 cigarettes (0.05, 1.2 mg)	Priming oral alcohol dose and then alcohol PR task	No. drinks Motivation—alcohol	Increase Increase
McKee, 2008 (USA)	19	58	27 (9)	19 CPD 24 DPW	Nicotine transdermal patch (0, 21 mg)	Priming oral alcohol dose and then 2-hour alcohol self-administration period	Priming dose: BAC Craving—alcohol Subjective—alcohol Stimulant/sedative Heart rate Self-administration: Abstinence Latency to drink No. drinks BAC Craving—alcohol Subjective—alcohol Stimulant Sedative Heart rate	 None None Decrease None None None Increase Decrease Decrease None None Increase None None
Perkins, 2000 (USA)	25	44	24 (1)	20 CPD FTND 5 13 DPW	Ad lib smoking versus abstinence	Priming oral alcohol dose and then alcohol PR task with fixed alcohol exposure	BAC Craving—alcohol Intoxication Stimulant Sedative Motivation—alcohol	None None None None Decreased Increased
Udo, 2013 (USA)	22	77	37 (10)	21 CPD FTND 4 38 DPW AUDIT 7	Nicotine nasal spray (0, 1 mg)	Priming alcohol dose (0.3 g/kg) and then two 1-hour alcohol self-administration periods	Priming dose: BAC Craving—alcohol Subjective—alcohol Stimulant/sedative Heart rate Self-administration: No. drinks BAC Subjective—alcohol Stimulant/sedative Craving—alcohol Heart rate	 None None None None None None None Increase None Decrease None

Continued.

Table 1. (Continued)

First author, year (place)	*N*	% Male	Mean age (SD)	Drug use Hx[a]	Drug manipulation	Drug outcome paradigm	Outcome measure	Significant effects
Studies that manipulated alcohol only								
Glautier, 1996 (UK)	16	73	28 (1)	12 CPD FTND 2 28 DPW	Oral alcohol (0, 0.5 g/kg)	Fixed exposure (2 cigarettes)	CO Time smoking No. puffs Puff frequency Craving—cigarette Cigarette choice Satisfaction—cigarette Alertness Positive affect	None None Increase None Increase None Increase Decrease None
Kahler, 2012 (USA)	96	56	39 (11)	17 CPD FTND 5 21 DPW	Oral alcohol (0, 0.4 g/kg)	Lapse with usual brand cigarette	Latency to smoke Craving—cigarette Taste/liking	None None None
Kahler, 2014 (USA)	100	57	39 (10)	16 CPD FTND 5 23 DPW	Oral alcohol (0, 0.4, 0.8 g/kg)	Lapse with usual brand cigarette	Latency to smoke No. smoked Craving—cigarette	None/decrease[b] Increase Increase
McKee, 2006 (USA)	16	63	28 (8)	20 CPD FTND 5 24 DPW AUDIT 11	Priming alcohol dose (0, 0.03 g/dl)	Lapse with usual brand cigarette	Latency to smoke No. smoked Puff topography Craving—cigarette	Decrease Increase None Increase
McKee, 2010 (USA)	19	53	22 (1)	0.6 CPD FTND 0 17 DPW AUDIT 11	Oral alcohol (0, 0.08 g/dl)	Fixed exposure (1 usual brand cigarette) then 60-minute cigarette self-administration	Fixed exposure: Topography Nausea Other subjective Craving—cigarette Self-administration: No. smoked Topography	 None Decrease None Increase Increase None
Mintz, 1985 (USA)	14	100	41 (NR)	24 CPD Social drinkers	Oral alcohol (0, 0.6 g/kg)	Self-administer up to 3 usual brand cigarettes	No. smoked Puff volume/frequency	Increase Increase
Mitchell, 1995 (USA)	7	57	29 (5)	25 CPD 7 DPW	Oral alcohol (0, 0.2, 0.4, 0.8 g/kg)	Fixed exposure (1 usual brand cigarette) and then three 1-hour cigarette self-administration periods	Fixed exposure: Latency Self-administration: Latency No. smoked Intercigarette interval CO	 None Decrease Increase None Increase
Nil, 1984 (Switzerland)	20	0	31 (8)	20 CPD 4.5 DDPW	Oral alcohol (0, 0.5, 0.7 g/kg)	Fixed exposure (1 usual brand cigarette)	CO Puff topography Heart rate	None/increase[b] None None
Studies that manipulated alcohol and nicotine exposure to examine interactive effects[c]								
Attwood, 2012 (UK)	96	50	22 (3)	<2 CPD FTND 0 AUDIT 14	Oral alcohol (0, 0.4 g/kg) Cigarette (0.05, 0.6 mg)	None	Intoxication Craving—alcohol Craving—cigarette Positive affect Negative affect	None None None Antagonistic None
Barrett, 2013 (Canada)	40	53	25 (7)	13 CPD/FTND 5 or 1 CPD /FTND 0; 18 DPW SMAST<3	Oral alcohol (0, 0.08 BAC) Cigarette (0.01, 0.6 mg)	Cigarette PR task	No. puffs Latency to smoke Subjective effects Craving reduction—cigarette Motivation—cigarette	Synergistic Reduced by alcohol None Antagonistic Synergistic

Continued.

Table 1. (Continued)

First author, year (place)	*N*	% Male	Mean age (SD)	Drug use Hx[a]	Drug manipulation	Drug outcome paradigm	Outcome measure	Significant effects
Barrett, 2015 (Canada)	16	69	35 (12)	12 CPD 13 DPW	Oral alcohol dose (0, 0.08 BAC) Cigarette (0.05, 0.6 mg)	None	Craving—alcohol Craving—cigarette Intoxication Stimulant/sedative Affect Heart rate	None None None None None Additive
Braun, 2012 (USA)	147	70	32 (9)	18 CPD 15 DPW	Oral alcohol (0, 0.8 g/kg) Cigarette (0.05, 1.1 mg)	None	Negative affect	Antagonistic
Greenstein, 2010 (USA)	127	67	31 (9)	18 CPD FTND 5 15 DPW SMAST<8	Oral alcohol (0, 0.8 g/kg) Cigarette (0.06, 1.14 mg)	None	BAC Intoxication Cigarette ratings	None None None
King, 2009 (USA)	42	52	25 (1)	2 CPD 3 DDPW	Oral alcohol (0, 0.8 g/kg) and cigarette (0.05, 0.6 mg)	Cigarette (0.05, 0.6 mg)	No. cigarettes Puff topography Craving—cigarette Head rush Enjoy taste	M: Increased by alc; F: none M: Increased by alc; F: none Increased by alcohol None Additive
Kouri, 2004 (USA)	12	100	21 to 35	10 to 20 CPD 10 to 20 DPW	Oral alcohol (0.4, 0.7 mg/kg) Nicotine patch (0, 21 mg)	None	Craving—alcohol Craving—cigarette Drunkenness Alcohol effects Stimulant/sedative Affect Heart rate Pharmacokinetic—alcohol	None None None None None None Increased by nicotine Additive or none
Mintz, 1991 (USA)	72	68	31 (8)	20 to 40 CPD Social drinkers	Oral alcohol (0, 1.5 g/kg) Nicotine gum (0, 2 mg)	None	Craving—cigarette	Antagonistic
Michel, 1989 (Switzerland)	20	0	18 to 30	19 CPD NR DPW	Oral alcohol (0, 0.7 g/kg) Cigarette (lit, unlit)	None	Puff topography	None
Oliver, 2013 (USA)	87	67	29 (9)	15 CPD FTND 4 17 DPW ADS 4	Oral alcohol (0, 0.3 g/kg) Cigarette (0.05, 0.6 mg)	None	Craving—alcohol Craving reduction—cigarette Drug liking—alcohol Drug liking—cigarette Positive affect Negative affect BAC	Increased by nicotine Antagonistic Additive None Additive None Subtractive
Peloquin, 2013 (Canada)	35	54	NR	17 CPD FTND 5 or 2 CPD FTND 0; SMAST<2	Oral alcohol (0, 0.05 BAC) Snus (0, 4 mg)	Cigarette PR task	Latency to smoke No. puffs Affect Craving—cigarettes Sedative/stimulant Motivation—cigarette Heart rate BAC	None None None Increased by alcohol None None Additive None
Penetar, 2009 (USA)	20	0	23 (2)	15 CPD FTND 4 10 DPW	Oral alcohol (0, 0.4 g/kg) Nicotine patch (0, 21 mg)	None	Craving—alcohol Craving—cigarette Affect Stimulant/sedative Heart rate	None None None None Additive

Continued.

Table 1. (Continued)

First author, year (place)	*N*	% Male	Mean age (SD)	Drug use Hx[a]	Drug manipulation	Drug outcome paradigm	Outcome measure	Significant effects
Perkins, 1995 (USA)	18	50	22 (1)	18 CPD FTND 5 10 DPW	Oral alcohol (0, 0.5 g/kg) Nicotine nasal spray (0, 20 μg/kg)	None	Craving—cigarettes Intoxicated Arousal Fatigue Affect Head rush, jittery, dizzy Heart rate BAC Plasma nicotine	None Antagonistic ($p < 0.10$) Antagonistic ($p < 0.10$) Antagonistic None Additive Additive Subtractive None
Perkins, 2005 (USA)	12	33	22 (0.5)	16 CPD FTND 4 12 DPW	Oral alcohol (0, 0.4, 0.8 g/kg) Nicotine nasal spray (0, 20 μg/kg)	Nicotine nasal spray (2.5 μg/kg per spray)	No. nicotine sprays Nicotine discrimination Plasma nicotine Craving—cigarette Intoxicated Stimulant/sedative Fatigue Head rush Affect BAC Heart rate	None None None None None None Synergistic Synergistic None None Additive
Ralevski, 2012 (USA)	15	46.7	25 (6)	0 CPD 5 DDPW	Intravenous alcohol (0, 40, 80 mg%) and nicotine (0, 1 mg)	None	Intoxication Stimulant Sedative	Subtractive None Subtractive
Rose, 2004 (USA)	48	42	33 (9)	22 CPD FTND 6; 12 DPW	Oral alcohol (0, 0.5 g/kg) Cigarettes (0.1 mg, usual brand)	2-hour cigarette self-administration period (0.1 mg vs. usual brand)	Heart rate Withdrawal—cigarette Satisfaction—cigarette Liking—cigarette Calming—cigarette Stimulant—cigarettes Other subjective—cigarette Subjective effects—alcohol Negative affect No. cigarettes smoked CO boost BAC	None None Synergistic Synergistic ($p = 0.07$) Synergistic Additive None None None None None Subtractive
Tong, 1974 (Canada)	8	100	22 to 26 (NR)	15 to 30 CPD NR DPW	Oral alcohol (0, 0.02, 0.09 BAC) Cigarettes (0, 2)	None	Heart rate	Additive

SD, standard deviation; Hx, history; NR, not reported; CPD, cigarettes per day; DPW, drinks per week; DDPW, drinking days per week; BAC, blood alcohol concentration; PR, progressive ratio; FTND, Fagerstrom Test for Nicotine Dependence; AUDIT, Alcohol Use Disorders Identification Test; SMAST, Short Michigan Alcohol Screening Test; ADS, 9-Item Alcohol Dependence Scale; CO, carbon monoxide; alc, alcohol; M, male; F, female.

g/kg for alcohol was reported if available.

[a]Mean levels of baseline cigarette (CPD) and alcohol use (DPW) were reported. If available, mean scores were reported for dependence measures such as the FTND (range: 0 to 10), AUDIT (range: 0 to 40), SMAST (range: 0 to 13), and ADS (range: 0 to 9) (Heatherton et al., 1991; Kahler et al., 2003; Saunders et al., 1993; Selzer et al., 1975). In cases where means of use and dependence levels were unavailable, ranges were reported or qualitative information was included as a substitute.

[b]Different results are reported for multiple doses (for instance, low-dose result/high-dose result).

[c]The prioritized significant effects reported for studies that manipulated both nicotine and alcohol were higher-order interactive effects (synergistic, antagonistic). If the higher-order interactive effects were nonsignificant, then any additive or subtractive main effects were reported (for instance, an additive effect would be reported if alcohol and nicotine both increased the outcome). If none of these effects occurred, then if alcohol was shown to have a main effect on a nicotine-related outcome, or vice versa, this was reported.

that did not detect any higher-order interactions with alcohol, including nicotine-by-time interactions or effects of nicotine on change in alcohol outcomes. The same approach is used for reviewing the effects of alcohol on nicotine responses. Then, any nicotine-by-alcohol interactions are described. Last, results from studies that reported moderation analyses are summarized in Table 2.

Effect of Manipulating Nicotine on Alcohol Outcomes

Study Descriptions. Five studies manipulated nicotine/cigarette exposure only; 17 studies manipulated both alcohol and nicotine/cigarette exposure. Studies primarily examined adult daily smokers who were social or heavy drinkers, but nondaily smokers were also examined (see Table 1 for sample characteristics). Most studies used placebo-controlled, within-subjects designs. Five studies included between-subjects manipulations (Attwood et al., 2012; Braun et al., 2012; Greenstein et al., 2010; King et al., 2009b; Rose et al., 2004), and 2 were not placebo-controlled (Perkins et al., 2000; Tong et al., 1974). All but 4 studies administered alcohol prior to nicotine (Acheson et al., 2006; Kouri et al., 2004; McKee et al., 2008; Penetar et al., 2009), and one administered cigarettes during alcohol administration (Barrett et al., 2006).

Effects of Nicotine on Alcohol Self-Administration. Among 4 studies, nicotine exposure increased (Acheson et al., 2006; Barrett et al., 2006), decreased (Acheson et al., 2006; McKee et al., 2008), or had no effect (Udo et al., 2013) on alcohol self-administration. Nicotine increased alcohol consumption among nondependent male smokers who drank a priming dose of alcohol and then smoked 4 cigarettes (1.2 or 0.05 mg nicotine) during a 2-hour PR task to earn alcohol (Barrett et al., 2006). Similarly, for light daily smokers, 14 mg nicotine transdermal patch pretreatment increased men's alcohol self-administration 3 hours later relative to placebo (Acheson et al., 2006); however, for women, 7 or 14 mg nicotine transdermal patch decreased alcohol administration. Among male and female dependent smokers who drink heavily, nicotine transdermal patch pretreatment reduced alcohol self-administration over a 2-hour ad lib alcohol self-administration period during which participants received payment for drinks not consumed (McKee et al., 2008). Relative to placebo, nicotine transdermal patch (21 mg) increased latency to drink and reduced alcohol consumption and BAC. In contrast, among heavy-drinking smokers who first wore a 21 mg nicotine transdermal patch for 6 hours, nicotine nasal spray (0 vs. 1 mg) did not impact subsequent drinking during two 1-hour ad lib alcohol self-administration periods following a priming dose of alcohol (Udo et al., 2013). Notably, nasal spray did not significantly increase nicotine serum levels, which may account for the null findings. Overall, while some findings suggest that nicotine impacts alcohol self-administration, the nature of the effect varied across studies.

Effects of Nicotine on Alcohol Craving. Seven studies tested the effect of nicotine on alcohol craving, with 6 studies finding no effect and 1 study detecting a positive association.

Table 2. Summary of Studies Testing Moderators of Response to Alcohol and Nicotine Coadministration

Moderator tested	Studies reporting significant moderation effect	Studies reporting null effect
Sex	• Nicotine increased alcohol self-administration for men and decreased self-administration for women (Acheson et al., 2006). • For men only, craving to smoke was reduced after coadministration (Barrett et al., 2013). • For men only, alcohol increased cigarette administration (King et al., 2009b). • For women only, craving to drink was higher when alcohol and nicotine were coadministered (Oliver et al., 2013). • Coadministration tended to enhance subjective effects more for women (e.g., relaxed and dizziness) than men (Perkins et al., 1995).	Attwood and colleagues (2012), Braun and colleagues (2012), Greenstein and colleagues (2010), Kahler and colleagues (2012, 2014), McKee and colleagues (2006, 2008, 2010), Peloquin and colleagues (2013), Perkins and colleagues (2000, 2005), Udo and colleagues (2013)
Nicotine dependence	• For daily but not nondaily smokers, alcohol increased responding specifically for nicotinized cigarettes (Barrett et al., 2013). • Nondaily smokers, but not daily smokers, started smoking more quickly in the alcohol condition versus placebo (Peloquin et al., 2013).	Oliver and colleagues (2013)
Alcohol dependence		Oliver and colleagues (2013)
Cigarette use level	• Alcohol reduced postdrug craving to smoke among heavier versus lighter smokers (Oliver et al., 2013).	
Alcohol use level	• Coadministration versus double placebo led to greater increase in alcohol craving for heavier than lighter drinkers (Oliver et al., 2013).	
Mecamylamine	• With mecamylamine, alcohol enhanced craving reduction from nicotine-containing but not denicotinized cigarettes (Rose et al., 2004).	
Progesterone	• Greater heart rate changes from nicotine with alcohol in low- versus high-progesterone women (Penetar et al., 2009).	

Nicotine transdermal patch pretreatment (21 mg) versus placebo, 3 hours prior to a fixed oral alcohol dose (0.4 or 0.7 mg/kg), did not impact alcohol craving when assessed every 30 minutes after alcohol use for male daily smokers (Kouri et al., 2004). Likewise, in an analogous design but with female daily smokers and an oral alcohol dose of 0.4 g/kg, there was no effect of 21 mg nicotine transdermal patch on alcohol craving (Penetar et al., 2009). Smoking 2 nicotine-containing cigarettes versus none prior to and during drinking a fixed dose of alcohol (raised BAC to 0.01%) also did not affect the change in desire to drink alcohol from baseline to postdrink (Perkins et al., 2000). Nicotine also inconsistently impacted alcohol craving when administered after alcohol. Among nondaily smokers who drank 0.4 g/kg alcohol or placebo beverage and then smoked a nicotine or placebo cigarette (0.01 vs. 0.6 mg), nicotine did not impact alcohol craving (Attwood et al., 2012). Using similar drug manipulations but among daily smokers, Barrett and colleagues (2015) also found no effect of nicotinized (0.6 mg) versus placebo cigarettes on alcohol craving when smoked immediately after drinking a placebo or alcoholic (0.08 g%) beverages. One study supported an effect of nicotine on alcohol craving (Oliver et al., 2013). Specifically, daily smokers drank 0.3 g/kg alcohol or placebo and then immediately smoked nicotinized or denicotinized cigarettes (0.05 or 0.6 mg) on a fixed-pace puffing regimen designed to standardize nicotine delivery. Craving to drink was elevated when both alcohol and nicotine or nicotine alone was administered, relative to the double-placebo condition. In summary, most studies have not detected an effect of nicotine on alcohol craving.

Effects of Nicotine on Other Subjective Effects of Alcohol. Two studies supported a negative association between nicotine and subjective alcohol intoxication (Ralevski et al., 2012) or overall subjective response to alcohol (McKee et al., 2008), while 5 studies found no significant associations with subjective responses (Attwood et al., 2012; Barrett et al., 2015; Greenstein et al., 2010; Kouri et al., 2004; Perkins et al., 2000). Specifically, when examining overall subjective response to a priming alcohol dose (for instance, total score on high, like, rush, feel good, and intoxicated), nicotine transdermal patch or nasal spray has reduced (McKee et al., 2008) or had no effect (Kouri et al., 2004) on these aggregated ratings. When focusing specifically on subjective intoxication/drunkenness, a nicotine transdermal patch pretreatment did not impact subsequent ratings of drunkenness (Kouri et al., 2004). Additional studies that measured effects of nicotine on changes in intoxication/drunkenness after a fixed alcohol dose found no effects (Attwood et al., 2012; Barrett et al., 2015; Perkins et al., 2000). Likewise, when examining interactive effects of nicotine and alcohol, differential reports of intoxication among daily smokers who drank alcohol (0.8 g/kg) or placebo then smoked nicotinized (1.14 mg) or denicotinized cigarettes were not supported (Greenstein et al., 2010). Only 1 study supported nicotine effects on subjective intoxication (Ralevski et al., 2012). During each of 3 IV alcohol/saline sessions (0, 40, vs. 80 mg%), nonsmokers received placebo and then nicotine equivalent to 1 cigarette (0 or 70 minutes into alcohol IV administration, respectively). Nicotine reduced subjective alcohol intoxication at both levels of alcohol exposure.

Of 9 studies examining stimulant or sedative effects of alcohol, one supported increased stimulation due to nicotine (McKee et al., 2008), while 2 found decreased sedation (Perkins et al., 2000; Ralevski et al., 2012) and one supported increased sedation (Acheson et al., 2006). Transdermal patch pretreatment did not affect stimulant effects associated with a fixed dose of alcohol consumed approximately 3 (Acheson et al., 2006; Kouri et al., 2004; Penetar et al., 2009) or 6 hours later (McKee et al., 2008). Likewise, ad lib smoking versus not smoking did not impact stimulant effects following a fixed alcohol dose (Perkins et al., 2000). However, in 1 study, nicotine transdermal patch pretreatment increased stimulant effects in response to alcohol self-administration (McKee et al., 2008). Nicotine administered by cigarettes or snus immediately after a fixed dose of alcohol (Barrett et al., 2015; Penetar et al., 2009) or during IV alcohol administration (Ralevski et al., 2012) also had no effect on stimulation. Most of these studies have similarly found no effects for subjective sedation, with the following exceptions. Smoking after a priming oral dose (Perkins et al., 2000) and nicotine delivered during IV alcohol administration (Ralevski et al., 2012) decreased sedative effects in response to alcohol. In contrast, 14 mg nicotine transdermal patch, but not 7 mg, increased sedation in response to a priming alcohol dose (Acheson et al., 2006).

When examining self-reported positive and negative affect after drinking, 6 studies found no differences between nicotine and placebo (Acheson et al., 2006; Kouri et al., 2004; Peloquin et al., 2013; Penetar et al., 2009; Perkins et al., 1995, 2000), but 1 study found that smoking and alcohol increased positive affect additively (Oliver et al., 2013). Nicotine also increased liking of alcoholic beverages. Taken together, nicotine may primarily influence the sedative effects of alcohol, although isolated effects on pleasurable/hedonic alcohol responses have also been reported.

Effects of Nicotine on Alcohol Motivation. In 2 studies, smoking nicotine-containing cigarettes relative to denicotinized cigarettes (Barrett et al., 2006) or not smoking (Perkins et al., 2000) significantly increased responding on a PR task to earn alcohol-containing beverages. The effect was seen only after consuming a priming dose of alcohol (Perkins et al., 2000), suggesting that smoking after drinking increases motivation to continue drinking.

Effects of Nicotine on Physiological Effects of Alcohol and BAC. Six of 8 studies supported combined effects of nicotine and alcohol on heart rate. Of previously described studies, nicotinized cigarettes (Barrett et al., 2015) or nasal spray (Perkins et al., 2005) during the ascending BAC limb

additively increase heart rate. Similar effects were observed with oral doses of alcohol administered after a nicotine transdermal patch (Kouri et al., 2004; Penetar et al., 2009), but not with priming alcohol doses. Among daily smokers who drank an oral dose of alcohol (0.5 g/kg) or placebo and then administered 4 nasal sprays of nicotine (totaling 20 μg/kg nicotine) or placebo, there was an additive increase in heart rate when both drugs were administered (Perkins et al., 1995). Additive effects of nicotine and alcohol on heart rate were also observed when daily smokers drank alcohol (raising BAC to 0.02 g% or 0.09 g%, vs. placebo) and then smoked 2 cigarettes (Tong et al., 1974).

Regarding BAC, BAC following a priming oral dose of alcohol did not change due to nicotine transdermal patch or nasal spray pretreatments (Acheson et al., 2006; Kouri et al., 2004; McKee et al., 2008), nicotinized cigarettes smoked concurrently (Perkins et al., 2000), or nicotine via cigarette, snus, or nasal spray administered postdrink (Greenstein et al., 2010; Peloquin et al., 2013; Perkins et al., 2005). Some studies have found that after a fixed dose of alcohol, nicotine from nasal spray (Perkins et al., 1995) or cigarettes (Oliver et al., 2013; Rose et al., 2004) lowered BAC relative to placebo. Similarly, nicotine transdermal patch pretreatment reduced latency to peak BAC (but not peak BAC) after consuming 0.4 but not 0.7 g/kg alcohol (Kouri et al., 2004). Thus, there is inconsistent support that nicotine impacts BAC.

Effect of Manipulating Alcohol on Nicotine Outcomes

Study Descriptions. Eight studies manipulated alcohol exposure and examined effects on nicotine outcomes (Table 1). Studies primarily examined adult daily smokers with varied drinking levels (7 to 28 drinks per week; see Table 1 participant drug-use histories). One study included nondaily smokers (McKee et al., 2010). Generally, studies first administered oral alcohol (or placebo) then had participants smoke cigarettes using a lapse or ad lib self-administration paradigm. One study utilized a priming alcohol dose (McKee et al., 2006). Only 1 study used a between-subjects design (Kahler et al., 2012).

Effects of Alcohol on Nicotine Self-Administration. Of 7 studies examining effects of alcohol on nicotine self-administration, alcohol has increased (Barrett et al., 2013; King et al., 2009b; McKee et al., 2010; Mitchell et al., 1995) or had no effect (Peloquin et al., 2013; Perkins et al., 2005; Rose et al., 2004) on nicotine self-administration. Young adult nondaily smokers who drink heavily consumed alcohol (0.08 g/dl), smoked a cigarette, and then 45 minutes after alcohol consumption were allowed to smoke freely for 1 hour (McKee et al., 2010). Alcohol, relative to placebo, increased the number of cigarettes smoked. Using a similar design, but with heavy-drinking daily smokers who were not required to smoke at least 1 cigarette in the session, increasing alcohol dose (0, 0.2, 0.4, or 0.8 g/kg), increased number of cigarettes smoked and CO immediately after drinking, and reduced latency to smoke (Mitchell et al., 1995). Similar findings were supported in a study by King and colleagues (2009b) for nondaily smoking men, but not women. Specifically, 1 hour after drinking 0.8 g/kg alcohol versus placebo, men increased their smoking of both nicotinized and denicotinized cigarettes (number of cigarettes and puffs, puff volume, and duration) during a 3-hour period. Studies that have not supported a relationship have had daily or nondaily smokers drink alcohol and subsequently self-administer nicotine nasal spray (Perkins et al., 2005) or cigarettes 30 minutes later (Peloquin et al., 2013; Rose et al., 2004). Specifically, when daily smokers drank 1 of 3 alcohol doses (0, 0.4, or 0.8 g/kg, with "topping doses" to maintain BAC) and then self-administered 8 sprays of nicotine-containing (2.5 μg/kg) or placebo nasal spray using any combination of the 2 bottles (Perkins et al., 2005), alcohol administration did not impact nicotine self-administration. Furthermore, Peloquin and colleagues (2013) provided daily-dependent or nondependent smokers an oral alcohol dose (0.5 g/kg) or placebo and then immediately administered nicotine-containing snus (4 mg) or placebo prior to completing a PR task to earn cigarette puffs. There was no effect of alcohol on number of cigarette puffs earned. Likewise, daily smokers who administered oral alcohol dose (0.5 g/kg) versus placebo and one usual brand or denicotinized (0.1 mg) cigarette did not differentially self-administer these cigarettes during a 2-hour ad lib period (Rose et al., 2004). One interpretation of the null effect with nicotine nasal spray is that the effect of alcohol on nicotine self-administration is specific to cigarettes.

Three of five studies have supported effects of alcohol on puff topography and/or CO in response to a fixed number of cigarettes. For instance, social-drinking daily smokers drank alcohol (0.5 g/kg) or placebo, and then approximately 15 minutes later, they smoked 2 nicotine-containing cigarettes (Glautier et al., 1996). Consuming alcohol increased the number of puffs smoked, but not CO, time spent smoking, or puff frequency. Among daily smoking males in a methadone maintenance program, alcohol (0.6 vs. 0 g/kg) increased amount smoked, puff volume, rate, and frequency when smoking up to 3 cigarettes ad lib (15 minutes postdrink) (Mintz et al., 1985). In contrast, in female daily smokers, oral alcohol (0.7 g/kg) relative to placebo did not change puff topography 15 minutes postdrink (Michel and Bättig, 1989). Also among female daily smokers, alcohol condition (0, 0.5, or 0.7 g/kg) did not impact puff topography of 1 cigarette smoked 45 minutes postdrink; however, the highest alcohol dose increased CO relative to placebo (Nil et al., 1984). Similarly, in an aforementioned study of nondaily smokers (McKee et al., 2010), 0.08 g/dl oral alcohol relative to placebo did not affect puff topography of 1 cigarette 35 minutes after they began drinking. Thus, while alcohol may increase nicotine self-administration by altering puff topography, this may be specific to daily smoking men that smoked shortly after drinking.

Among daily smokers, alcohol increased susceptibility to smoking lapse in 2 studies (Kahler et al., 2014; McKee et al., 2006), but not another (Kahler et al., 2012). Specifically, the effect of alcohol (0 vs. 0.4 g/kg) was examined on participant's ability to delay smoking in exchange for payment per 5-minute delay (Kahler et al., 2012). Alcohol did not affect time to initiate smoking 50 minutes after drinking began. In contrast, a similar subsequent study by the same group, utilizing a within-subjects design and including an additional alcohol dose (0.8 g/kg), found that the highest alcohol dose reduced latency to smoke and increased the number of cigarettes smoked (Kahler et al., 2014). The lower dose had no effect on latency but increased cigarettes smoked. Similar results were obtained in a sample of daily smokers who were heavy drinkers (McKee et al., 2006). A priming dose of alcohol (0.03 g/dl) relative to placebo decreased latency to smoke and increased the number of cigarettes smoked on a lapse task that began 5 minutes after initiating drinking and that continued for 60 minutes postlapse. Taken together, alcohol increased smoking lapse behaviors, particularly in studies where smoking occurred shortly after drinking or higher doses of alcohol were consumed.

Effects of Alcohol on Cigarette Craving. Six of 7 studies have shown that alcohol increases cigarette craving prior to smoking. For instance, alcohol relative to placebo increased baseline cigarette craving among daily smokers (Glautier et al., 1996; Kahler et al., 2014; McKee et al., 2006) and nondaily smokers (King et al., 2009b; McKee et al., 2010; Peloquin et al., 2013). One study found no effect of alcohol on cigarette craving with nondaily smokers (Attwood et al., 2012). In another, alcohol increased desire to smoke for positive reinforcement only (McKee et al., 2010). In contrast, studies that examined the effect of alcohol on smoking-induced changes in cigarette craving have not found an effect of alcohol (Barrett et al., 2015; Kouri et al., 2004; Peloquin et al., 2013; Penetar et al., 2009; Perkins et al., 1995, 2005), although interactive effects have been detected and are described below. Notably, with the exception of Barrett and colleagues (2015), none of these studies administered nicotine via cigarettes. Overall, alcohol appears to increase baseline cigarette craving among smokers.

Effects of Alcohol on Other Subjective Effects of Smoking. Ten studies tested whether alcohol influenced subjective effects of nicotine from pre- to postnicotine exposure (Glautier et al., 1996; Greenstein et al., 2010; Kahler et al., 2012; McKee et al., 2010; Perkins et al., 1995) or comparing postnicotine scores (King et al., 2009b; Oliver et al., 2013; Peloquin et al., 2013; Perkins et al., 2005; Rose et al., 2004) between the alcohol and placebo groups, with 4 studies identifying significant effects. Alcohol pretreatment versus placebo has increased (Perkins et al., 2005) or had no effect (King et al., 2009b; McKee et al., 2010) on head rush or dizziness following smoking. Alcohol increased (Glautier et al., 1996; King et al., 2009b) or had no effect (Greenstein et al., 2010; Kahler et al., 2012; Rose et al., 2004) on the rated strength or estimated nicotine delivery of cigarettes and decreased alertness from smoking (Glautier et al., 1996). With respect to hedonic effects, alcohol has generally had no effect on liking of cigarettes (Greenstein et al., 2010; Kahler et al., 2012; Oliver et al., 2013) or enjoyment of airway sensations (McKee et al., 2010; Rose et al., 2004), with the exception of Glautier and colleagues (1996), in which alcohol increased ratings of enjoyment from cigarettes smoked. Alcohol has increased ratings of the taste of cigarettes relative to placebo (Glautier et al., 1996; King et al., 2009b) or had no effect on taste (Kahler et al., 2012; McKee et al., 2010) or harshness (Greenstein et al., 2010). When examining affect in response to nicotine from nasal spray, cigarettes, or snus, studies have found no differences between alcohol and placebo conditions (Peloquin et al., 2013), with the exception of 1 study in which alcohol and nicotine additively increased positive affect (Oliver et al., 2013). Thus, while inconsistently supported, alcohol tended to enhance some of the effects and ratings of cigarettes.

Effects of Alcohol on Motivation to Smoke. In 2 studies of this effect, alcohol increased motivation to smoke (Barrett et al., 2013) or had no significant effect (Peloquin et al., 2013). Barrett and colleagues (2013) had nondaily and daily smokers drink alcohol (raising BAC to 0.08 g%) or placebo, smoke an assigned nicotinized (0.6 mg) or denicotinized (0.01 mg) cigarette, and then complete a 60-minute PR task to earn puffs of the same cigarette type. Drinking alcohol reduced latency to start the PR task. Furthermore, in nondaily smokers, alcohol increased responding for cigarettes regardless of nicotine content, while in daily smokers, alcohol increased responding specifically for nicotinized cigarettes. In a similar design involving a lower BAC (0.06 g%) and no cigarette prior to the PR task, alcohol did not influence responding in daily and nondaily smokers; however, nondaily smokers trended toward smoking more quickly in the alcohol condition (Peloquin et al., 2013). Thus, alcohol may increase motivation to smoke, but this effect may be sensitive to nicotine dependence level and alcohol dose.

Effects of Alcohol on Physiological Effects of Smoking and Nicotine Pharmacokinetics. One study examined the effects of alcohol on heart rate changes associated with smoking and found no effect (Nil et al., 1984). As previously described, however, a number of studies that manipulated nicotine and alcohol have supported additive effects on heart rate. Two studies found no effect of alcohol on plasma nicotine levels after a fixed dose of nicotine via nasal spray (Perkins et al., 1995, 2005).

Interactions Between Alcohol and Nicotine on Self-Administration and Subjective Outcomes

Sixteen of the previously described studies manipulated both alcohol and nicotine exposure, evaluating interactive

effects on various outcomes. Notably, more than half of these studies ($n = 9$) did not identify interactive effects (Barrett et al., 2015; Greenstein et al., 2010; King et al., 2009b; Kouri et al., 2004; Michel and Bättig, 1989; Peloquin et al., 2013; Penetar et al., 2009; Ralevski et al., 2012; Tong et al., 1974).

One study identified a synergistic effect of alcohol and cigarette smoking on subsequent smoking behavior such that alcohol and nicotinized cigarettes synergistically increased motivation to smoke and subsequent number of cigarette puffs administered (Barrett et al., 2013). These findings are in line with the previously described studies in which alcohol increased nicotine administration, but further suggest that these effects are enhanced when both nicotine and alcohol have been used.

In 3 studies, synergistic effects of alcohol and nicotine were seen for cigarette craving. Two of these studies, previously described, administered an oral dose of alcohol or placebo and then had participants use nicotine-containing cigarettes (Barrett et al., 2013; Oliver et al., 2013). A third study had participants consume 1.5 g/kg alcohol or placebo and then immediately chew nicotinized (2 mg) or placebo gum (Mintz et al., 1991). These studies found that alcohol suppressed craving reduction from nicotine. This suppression of the craving-reducing effects of nicotine could, in part, account for increased cigarette administration due to alcohol seen in other studies.

When examining interactive effects on other subjective outcomes, nicotine has mitigated sedative and intoxicating effects of alcohol (Perkins et al., 1995) and reversed decreases in positive affect associated with alcohol consumption over time (Attwood et al., 2012). Similar results were seen in a study of daily smokers who drank an assigned beverage (placebo or 0.8 g/kg alcohol) and then smoked 2 assigned cigarettes (0.01 vs. 0.6 mg) using a controlled puff procedure. Specifically, nicotine reversed increases in negative affect related to drinking during an anxiety-provoking task (Braun et al., 2012). Alcohol also has potentiated effects of nicotine on ratings of satisfaction from smoking, liking cigarettes, and calming effects (Rose et al., 2004). Taken together, interactive effects are the exception rather than the norm in these studies. However, the direction of these isolated interaction effects are in line with many of the previously reviewed main effects (e.g., nicotine attenuating sedative effects and subjective intoxication of alcohol) and generally consistent with coadministration being a potential risk factor for greater use of either drug.

DISCUSSION

The aim of this investigation was to critically review human laboratory research of the effects of nicotine and alcohol coadministration. Overall, the effects of nicotine on alcohol administration were more tenuous than the effects of alcohol on nicotine administration and associated outcomes. Specifically, while nicotine-containing patch or cigarettes may increase behavioral indices of motivation to drink (Barrett et al., 2006; Perkins et al., 2000), nicotine has increased, decreased, or had no effect on alcohol self-administration. Furthermore, nicotine generally did not impact alcohol craving; however, nicotine may reduce other effects of alcohol (McKee et al., 2008), including alcohol intoxication (Ralevski et al., 2012) and sedation (Perkins et al., 2000; Ralevski et al., 2012), and may increase positive affect and liking of alcohol (Oliver et al., 2013). Nicotine also additively increased heart rate following alcohol use, which may relate to alcohol reward and decreased sedative effects.

Inconsistent effects of nicotine on alcohol-related outcomes may reflect variable participant characteristics (dependence levels, sex) and methods (e.g., abstinence prior to sessions, sample size, timing, and route of administration) across studies. Few investigations have evaluated these factors as moderators. Nicotine may increase alcohol self-administration primarily for men (Table 2); however, other participant characteristics have not been widely tested or supported as moderators. Similarly, only 1 study tested multiple nicotine doses, finding more robust effects of nicotine on alcohol with a larger dose (Acheson et al., 2006). Other methodological differences (e.g., abstinence duration and timing of nicotine administration) have not been tested and could moderate effects given the potential importance of nicotine withdrawal and the bioavailability of nicotine (Dermody and Donny, 2014). Similarly, whether or not nicotine is administered alongside other tobacco constituents could affect outcomes. Finally, that nicotine affected some aspects of alcohol motivation and response without affecting self-administration could reflect limited sensitivity of the self-administration paradigms utilized in these studies.

In contrast, alcohol generally increased nicotine self-administration and risk for smoking lapse. This relationship was strongest with increasing alcohol dose (Kahler et al., 2014; Mitchell et al., 1995; Nil et al., 1984) and when alcohol was administered shortly before smoking. While the effect of the timing of coadministration has not been tested, patterns of findings may suggest differential effects during the ascending and descending BAC limb. Few moderators were tested or supported (Table 2). Nondaily and daily smokers generally demonstrated similar effects of alcohol on smoking, although for daily smokers the effects were specific to patterns of nicotinized cigarettes (Barrett et al., 2013). With the exception of 1 study (King et al., 2009b), there were no sex effects and alcohol has increased cigarette self-administration in all-male (Mintz et al., 1991) and all-female (Nil et al., 1984) samples; however, alcohol may not alter women's puff topography (Michel and Bättig, 1989; Nil et al., 1984). Taken together, alcohol, particularly higher doses, increased smoking.

Consistent with these findings, alcohol increased craving for cigarettes for daily (Glautier et al., 1996; Kahler et al., 2014; McKee et al., 2006) and nondaily smokers (McKee et al., 2010). Moreover, alcohol pretreatment suppressed craving reduction from nicotine (Barrett et al., 2013; Mintz

et al., 1991; Oliver et al., 2013), which could increase nicotine administration to compensate. Furthermore, the 1 study to test mediation, Kahler and colleagues (2014), found that changes in craving to smoke statistically mediated the effect of alcohol on latency to smoke. The effects of alcohol on other subjective effects of nicotine and smoking were less consistently supported. For instance, alcohol tended to enhance cigarette strength and nicotine ratings but not ratings of enjoyment/liking. Also, changes in stimulation and sedation did not mediate the effects of alcohol on latency to smoke (Kahler et al., 2014), implying that mediation effects are specific to craving. The role of motivation and pharmacokinetic interactions are not clear given the dearth of studies examining these pathways, but they warrant future study.

This review brought to the forefront several limitations in this research literature, many of which may account for nonreplicable findings. The methodologies used to coadminister alcohol and nicotine varied widely between studies. While one way to overcome this limitation in future research would be to standardize alcohol/nicotine coadministration paradigms, a preferable approach may be to experimentally manipulate these methodological factors (dose, timing, length abstinence, route of administration) to determine to what extent they impact outcomes. The results of this review suggest that higher doses and shorter delays between drug administrations could maximize effects. Relatedly, BAC and nicotine plasma levels were often not reported, and alcohol limb effects were not investigated. Moreover, most cigarette manipulations allowed participants to smoke freely; however, significant between-person variability in puffing patterns impacts nicotine exposure (Hammond et al., 2005; Patterson et al., 2003). These limitations can be remedied by reporting BACs when administering nicotine and conducting other assessments, as well as adopting more controlled methods of nicotine administration (e.g., controlled puffing regimens or IV administration). Finally, given the sample sizes reported, it is possible that many of the studies were underpowered to detect interactions between nicotine and alcohol. As studies generally did not report a priori power analyses, it is unclear to what extent studies had sufficient statistical power to detect interaction effects, by extension limiting confidence in the null effects summarized here.

Future experimental research is warranted to address the aforementioned limitations and to further clarify alcohol and nicotine interactions. First, only 5 human laboratory studies examined the effects of nicotine on alcohol self-administration, and none have examined effects on alcohol lapse. Additional investigations taking into account the aforementioned methodological issues may clarify this relationship. Second, while laboratory studies are necessarily limited in external validity (for instance, due to nonecologically valid routes of administration), additional laboratory research that maximizes ecological validity is warranted. For example, allowing participants to freely coadminister cigarettes with alcohol could provide important insight into typical self-administration patterns. Third, future research focusing on dose–response relationships is warranted. This is now possible with improved precision given the advances in the available tools for laboratory nicotine/alcohol administration (e.g., cigarettes with varying nicotine and IV nicotine/alcohol).

Despite these limitations, this review found evidence that nicotine and alcohol can have augmentative effects that may promote coadministration. In particular, alcohol appears to reliably promote nicotine craving and self-administration, a finding generally consistent with ecological momentary assessment studies showing that simultaneous use increases reward for both substances and that alcohol may potentiate smoking reward more so than smoking potentiates alcohol reward (Piasecki et al., 2011, 2012). As reviewed elsewhere (Dermody and Donny, 2014; McKee and Weinberger, 2013), the nicotinic acetylcholine receptor (nAChR) system plays a role in nicotine (Buisson and Bertrand, 2002) and alcohol (Chi and de Wit, 2003 reinforcement. Consistent with this pathway, mecamylamine, a nAChR antagonist, alters subjective response to alcohol (Blomqvist et al., 2002; Chi and de Wit, 2003) and may moderate response to coadministration (Rose et al., 2004). Similarly, varenicline, a nAChR partial agonist and smoking cessation treatment, also reduces alcohol self-administration among heavy-drinking smokers (McKee et al., 2009). Furthermore, these effects on drug reward may be attributed to nicotine indirectly potentiating alcohol reward through the mesolimbic dopamine system (for review, see McKee and Weinberger, 2013). As nicotine did not consistently increase alcohol self-administration, this pathway is likely moderated by other processes (e.g., expectancies, drug-use history, and withdrawal). Taken together, these pathways have important clinical implications as they suggest that coordinating smoking and drinking intervention efforts, including pharmacological interventions such as varenicline or naltrexone (King et al., 2006, 2009a) that target shared pathways, could maximize health benefits.

In short, human laboratory studies provide important insight into alcohol and nicotine interactions that perpetuate simultaneous use. The present findings suggest that simultaneous alcohol and nicotine use is partly driven by the acute effects of alcohol on nicotine self-administration and also, but to a lesser extent, the effects of nicotine on subjective alcohol effects. The effects may be moderated by a number of factors that warrant additional research. As has been shown in prior research (Dermody and Donny, 2014; McKee and Weinberger, 2013), these acute effects of nicotine and alcohol coadministration have important clinical and policy implications as changing use of either substance can have cascading effects on use of the other. In light of these findings, there is a need to develop ways to target simultaneous use and reduce its impact on public health.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest to report.

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