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HOW CAN WE USE OUR KNOWLEDGE OF ALCOHOL-TOBACCO INTERACTIONS TO REDUCE ALCOHOL USE?

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Abstract

Currently, 8.5% of the US population meets criteria for alcohol use disorders, with a total cost to the US economy estimated at $234 billion per year. Alcohol and tobacco use share a high degree of co-morbidity and interact across many levels of analysis. This review begins by highlighting alcohol and tobacco co-morbidity and presenting evidence that tobacco increases the risk for alcohol misuse and likely has a causal role in this relationship. We then discuss how knowledge of alcohol and tobacco interactions can be used to reduce alcohol use focusing on whether; 1) smoking status can be used as a clinical indicator for alcohol misuse; 2) tobacco policies reduce alcohol use; and 3) nAChR medications can be used to treat alcohol use disorders.

Keywords

nicotine; screening; smoke-free policies; nAChR; varenicline; mecamylamine

Introduction

Excessive alcohol use is the third leading cause of death (CDC 2004), and the associated yearly economic burden is estimated at $234 billion (Rehm et al. 2009). Excessive consumption of alcohol is related to adverse consequences such as hypertension, gastrointestinal bleeding, sleep disorders, major depression, hemorrhagic stroke, cirrhosis of the liver, several cancers, unintentional injuries, and violence (CDC 2004; USDHHS 2005). Each death which is attributable to an alcohol-related cause is associated with 30 years of lost life. Forty-six percent of these deaths are associated with chronic health events, while the other 54% of deaths result from acute events, such as motor vehicle crashes (CDC 2004). Estimates find that 8.5% of the population meets criteria for a current alcohol abuse or dependence (Grant et al. 2004), which translates to 18 million US adults.

As will be reviewed in the following sections, alcohol and tobacco use share a high degree of co-morbidity and interact across many levels of analysis including cross-tolerance, cross-cue reactivity, pharmacological, neurochemical, electrophysiological, molecular, genetic,

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and environmental levels (Dani & Harris 2005; Davis & de Fiebre 2007; Larsson & Engel 2004; Schlaepfer et al. 2008; Söderpalm et al. 2000). While alcohol and tobacco interactions are complex and typically demonstrate reciprocal effects across these levels of analysis, for this review we will be primarily concerned with the effect of tobacco and nicotine on alcohol use. We contend that potentiated reinforcement is at the core of alcohol and tobacco interactions and it is possible to use this knowledge to reduce alcohol use. In the first section, we will review alcohol and tobacco co-morbidity and present evidence documenting that tobacco use increases the risk for alcohol misuse and likely has a causal role in this relationship. In the second section, we will discuss how knowledge of alcohol and tobacco interactions can be used to reduce alcohol use.

Part I: Alcohol and Tobacco Co-Use

Prevalence of alcohol and tobacco use and associated health risk

Alcohol consumption and tobacco use are highly correlated across levels of use and diagnostic categories in the general population (Dawson 2000; Grant et al. 2004; McKee et al. 2007). Epidemiological data has shown that daily and nondaily smokers are more likely to consume alcohol; to consume alcohol on a daily basis; to consume greater quantities of alcohol; and to meet criteria for binge drinking, hazardous drinking, and alcohol use disorder diagnoses (Grant 1998; Dawson 2000; Husky et al. 2007; McKee et al. 2007; Harrison et al. 2008; Harrison & McKee 2011). Current smoking is associated with greater numbers of alcohol drinks per day and alcohol consumption days per month, greater severity of alcohol dependence, and greater alcohol withdrawal symptoms (Daeppen et al. 2000; Mason & Lehert 2009). Smoking is also highly correlated with drinking in individuals who do not meet criteria for alcohol use disorders, particularly among those who are heavy drinkers (Henningfield et al. 1984). Further, smokers are slower to mature out of heavy drinking patterns (Karlamangla et al. 2006). The relationship between smoking and alcohol is so well-known that tobacco companies have researched and exploited this relationship as part of their marketing strategies targeting both drinkers and drinking venues (Jiang & Ling 2011).

We examined Wave I data (2000–2001) from the National Epidemiological Survey of Alcohol and Related Conditions (NESARC; Grant et al. 2003) and demonstrated that among past year drinkers (n=27,935), 29%were cigarette smokers compared to 15% among past year alcohol abstainers (n=14,620; McKee 2010). Conversely, among past year drinkers, 51% never progressed beyond 100 cigarettes in their lifetime compared to 66% among past year alcohol abstainers. While it is evident that the co-use of both substances is highly co-morbid, so is the non-use of both substances.

With regard to alcohol dependence, Wave I data from the NESARC demonstrates that approximately 50% of adults with a current (past 12-month) DSM-IV alcohol dependence disorder also smoke cigarettes. Even though rates of alcohol use disorders are substantially greater among smokers (16.8% daily smokers vs. 5.4% never smokers), non-smokers comprise a greater percentage of the population (75% non-smokers vs. 21% daily smokers). Thus, among those with alcohol dependence, smokers and non-smokers are evenly divided (i.e., 49.5% vs. 50.5%; McKee et al. 2007). Rates of co-morbid smoking and alcohol dependence among epidemiological samples are substantially lower than rates reported in treatment populations, which are typically reported to be upwards of 90% (Batel et al. 1995).

One reason for the growing concern regarding the co-use of alcohol and tobacco is that diseases related to tobacco use are the leading cause of morbidity and mortality in alcoholics (Hurt et al. 1996) and the relative risk of mortality increases with the combined versus singular abuse of alcohol and tobacco (Rosengren et al. 1988). In particular, the concurrent

use of alcohol and tobacco increases the incidence of head and neck cancers, cirrhosis, and pancreatitis (Marrero et al. 2005; Pelucchi et al. 2006). In some cases the health risk of alcohol and tobacco use is supra-multiplicative. For example, the singular use of alcohol or tobacco is associated with 6 to 7 times increased risk for oral cancers, whereas their co-use increases the risk by 300 times (Zheng et al. 2004). In addition to health risk, the co-use of alcohol and tobacco is also associated with greater psychiatric co-morbidity. Adults with both alcohol and nicotine dependence are more likely than adults with alcohol dependence alone to report comorbid anxiety, mood, and other addictive disorders (Le Strat et al. 2010).

Does tobacco use increase the risk for alcohol misuse?

Epidemiological investigations, human laboratory studies, and naturalistic observations all document that tobacco and nicotine can increase alcohol use and increase the risk for meeting criteria for hazardous drinking and alcohol use disorders. The National Institute of Alcohol Abuse and Alcoholism (NIAAA) defines hazardous drinking as exceeding gender-specific weekly limits (males – more than 14 drinks per week; females- more than 7 drinks per week) or daily drinking limits (males – more than 5 drinks per day; females – more than 4 drinks per day at least once in the past year; USDHHS 2005). Epidemiological investigations have demonstrated that this pattern of consumption is associated with increased risk for experiencing alcohol-related consequences (e.g., cirrohosis, driving while intoxicated, Dawson et al., 2000). In an epidemiological investigation using the NESARC data, we have found that daily smoking increased the risk of meeting criteria for hazardous drinking and alcohol use disorders by three-fold (McKee et al. 2007). Importantly, we were the first to document that non-daily smoking conferred the greatest risk associated with hazardous drinking and alcohol-related diagnoses, increasing the risk by five-fold. In the general population, the rate of hazardous drinking was 26%; however, non-daily smokers had a 56% probability of meeting criteria for hazardous drinking. Non-daily smokers represented 17% of current smokers, which is consistent with other population studies that have reported rates of non-daily smoking at 18%–24% of current smokers (e.g., Hassmiller et al. 2003).

While tobacco use is clearly associated with increased risk for meeting criteria for problematic alcohol use, this relationship is more pronounced among young adults (Jackson et al. 2002; Jackson et al. 2005; Harrison et al 2008; Harrison & McKee 2011). Longitudinal evidence suggests that the co-occurrence of alcohol and tobacco use escalates during adolescence and reaches an asymptote by age 25 (Jackson et al. 2002). After reaching its peak in young adults, the prevalence rates for alcohol-tobacco comorbidity decrease with increasing age (Falk et al. 2006). In young adults (ages 18–25), we have found that smoking increases the risk of meeting NIAAA criteria for hazardous drinking by seven-fold for daily smokers and by sixteen-fold for nondaily smokers, and increases the risk of meeting criteria for an alcohol use disorder by fourfold for daily smokers and by five-fold for nondaily smokers (Harrison et al. 2008). It should be noted that the odds of meeting criteria for hazardous drinking in young adults (Odds Ratio [O.R] = 16) was substantially greater than the odds found for the full adult age range (O.R. = 5; McKee et al. 2007). In a longitudinal investigation using both waves of the NESARC data (Wave 1, 2001–2001; Wave 2, 2004–2005; n=4,468), we examined whether smoking status at the Wave 1 was predictive of hazardous drinking and alcohol use diagnoses at Wave 2, while controlling for Wave 1 drinking (Harrison & McKee 2011). Both daily and non-daily smoking was predictive of hazardous drinking, and alcohol abuse and dependence across the three year time span.

How might tobacco use be increasing the risk for alcohol misuse?—Research has documented that tobacco users are more likely to engage in binge drinking, are able to consume alcohol for longer periods of time, and experience alcohol as more reinforcing. It's

likely a combination of these factors which mediate the increased risk for hazardous drinking and alcohol use diagnoses that is documented in tobacco users. For example, research examining young adult 'low-level' smokers has documented that non-daily smoking is most likely to occur in the context of alcohol use (Nichter et al. 2006). We have found that non-dependent smokers report that 74% of all smoking episodes occurred while under the influence of alcohol (McKee et al. 2004). Interviews conducted with these smokers find that they are cognizant of the reasons why they co-use alcohol and tobacco. They report that tobacco enhances the effect of alcohol or "brings on the buzz", and that alcohol and cigarettes go together like "drinking milk with cookies" or "eating peanut butter with jelly" (Nichter et al. 2006; Stromberg et al. 2007). We examined expectations of smoking while drinking in non-dependent smokers and found expectations that smoking enhanced reinforcement from alcohol (e.g., "enjoy drinking more"; McKee et al. 2004).

We have also found that tobacco use is associated with the duration of a drinking episode (McKee 2010). In this study we had young adult (age 21–25 years) participants report, hour by hour, the use of alcohol and cigarettes during their most recent drinking episode. By the fourth hour of a drinking episode, 58% of daily smokers and 66% of non-daily smokers were still consuming alcohol, whereas only 33% of non-smokers were still engaged in alcohol consumption. Laboratory based investigations have shown that nicotine decreases subjective intoxication and attenuates the sedating properties of alcohol, potentially allowing for larger quantities of alcohol to be consumed (Perkins et al. 1995).

Binge drinking is a consumption pattern defined as consuming 5 or more drinks per episode for males, and 4 or more drinks per episode for females (USDHHS 2005) that is associated with serious adverse consequences including the development of alcohol use disorders, unintentional injuries, property damage, assault, car crashes, unprotected sex, alcohol poisoning, and death (e.g., Wechsler et al. 1994; Wechsler et al. 2002). Both non-daily and daily smokers were 4 times more likely than non-smokers to report binge drinking (Schorling et al. 1994), and 44% of current smokers engaged in binge drinking at least once per month (Weitzman 2005). Using the NESARC data, we found that 27% of all young adults (21–25 years) engaged in binge drinking at least once per month, and that this rate increased to 51% among non-daily smokers. Across additional samples of young adults, we have found that 36% of daily smokers, 33% of non-daily smokers, and 16% of never smokers engaged in binge drinking at least once per week (McKee et al. 2004, Harrison et al. 2009).

Thus, tobacco users experience alcohol as more reinforcing and are able to consume alcohol for longer periods of time. It is these two effects which likely contribute to the increased occurrence of binge drinking among tobacco users. Binge drinking is a criteria for hazardous drinking status, and also increases risk for alcohol use disorders. It is known that negative alcohol-related consequences (e.g., alcohol-related aggression, driving while intoxicated) are more likely to occur at higher blood alcohol concentrations (BACs; Dawson et al. 2005), which then increases the risk for meeting criteria for alcohol abuse. Frequent binge drinking is also associated with the development of alcohol dependence (Dawson et al. 2008). In the next section, we will review how the nicotinic acetylcholine system may be mediating this risk.

How might the nicotinic acetylcholine receptor system (nAChR) increase alcohol use?

Description of nAChR system: Nicotine exerts its actions through activation and desensitization of nAChRs in the central nervous system and autonomic ganglia (Picciotto et al. 1998). Nicotinic receptors are composed five subunits, and consist of either simple combinations of α and β subunits (e.g., α4β2), more complex subunits (e.g., α3β2β4*,

where * denotes the possibility of additional subunits), or single α units (e.g., α7, α9). It appears that α4β2 and α7 predominate in the central nervous system (Coe et al. 2005). The α4β2 receptor appears to plays a key role in nicotine dependence. Mice lacking the β2 subunit fail to self-administer nicotine (Picciotto et al. 1998), and the α4subunit is involved in nicotine reinforcement, tolerance, and sensitization (Tapper et al. 2004). It seems likely that nAChRs play a primarily neuromodulatory role in the CNS rather than mediating direct synaptic transmission. Nicotine can potentiate release of acetylcholine, dopamine, gamma-aminobutyric acid (GABA), glutamate, norepinephrine, and serotonin from presynaptic terminals in several brain areas (Giorguieff-Chesselet et al. 1979; Wonnacott et al. 1980). One pathway in which nicotine's ability to potentiate neurotransmitter release has been linked to addiction-related behaviors is in the mesolimbic dopamine system. The rewarding and sensitizing effects of nicotine are thought to be mediated through dopamine release in the nucleus accumbens (NA) and the ventral tegmental area (VTA; Corrigall et al. 1992).

nAChR effects in alcohol reinforcement: The reinforcing effects of alcohol are thought to also be mediated, in part, by dopamine release in the NA and VTA (Gonzales & Weiss 1998), although it is recognized that other neurotransmitters are involved in alcohol reinforcement (e.g., GABA, glutamate, serotonin, and opioid peptides). The VTA is important for the rewarding properties of drugs of abuse (Koob & Bloom 1988). It is known that the VTA receives cholinergic innervation, which regulates mesolimbic dopamine function, likely through multiple nAChRs. It has been hypothesized that ethanol may produce mesolimbic activation, at least in part by its effects on central nAChRs (Blomqvist et al. 1993; Blomqvist et al. 1996; Söderpalm et al. 2009). Alcohol administration increases acetylcholine levels in the VTA, and dopamine levels in the NA (Larsson et al. 2005). In addition to acetylcholine, nAChR effects on increased dopamine may also occur through the inhibition of GABA as well as the activation of glutamate, which then activates n-methyl-d-aspartic acid (NMDA) receptors in dopaminergic neurons (Schlapfer et al. 2008). It is through these actions that alcohol may interact with the nAChR system to potentiate alcohol reward.

Studies utilizing microdialysis techniques have documented that mecamylamine (a noncompetitive, non-specific nicotinic antagonist) administered directly into the VTA blocked ethanol-induced increases in dopamine release in the NA (Tizabi et al. 2002). Further, while alcohol and nicotine additively increase dopamine response in the NA, mecamylamine blocked this increase (Tizabi et al. 2007). When administered systemically, mecamylamine blocked ethanol-induced dopamine overflow in the NA (Larsson et al. 2002). Additionally, ethanol intake and preference for alcohol is attenuated when mecamylamine is either directly administered into the VTA (Ericson et al. 1998)or administered systemically (Blomqvist et al. 1996; Lê et al. 2000).

nAChR effects in alcohol use: There is much additional evidence supporting a role for central nAChR effects in alcohol use. Chronic alcohol exposure increases nicotine receptor binding (Yoshida et al. 1982), enhanced nicotine-induced upregulation (Dohrman & Reiter 2003), as well as altered the electrophysiological properties of several nAChR subtypes (Cardoso et al. 1999). Studies examining specific nAChR subtypes, either cloned and expressed into frog eggs (*Xenopus oocytes*) (de Fiebre et al. 2005) or isolated from rat brain (Narahashi et al. 1999), find that alcohol enhances the function of α4β2 receptors, and inhibits the function of α7 receptors. As mentioned previously, the α4β2 receptor is involved in alcohol-related reinforcement, and both the α4β2 and α7 subtypes have been implicated in modulating alcohol withdrawal effects and have protective effects against alcohol-related neurotoxicity (Butt 2004; Tizabi et al. 2004; de Fiebre et al. 2005).

In addition to the neurochemical and pharmacological studies cited above, further evidence supporting a role for central nAChRs in alcohol use comes from behavioral, genetic, and electrophysiological investigations. Studies examining behavioral effects of alcohol following acute and chronic administration of nicotine (and visa-versa) have found evidence of cross-tolerance (Collins et al. 1988; Blomqvist et al. 1992; de Fiebre & Collins 1992; de Fiebre & Collins 1993). Further, genetically determined effects of alcohol may be influenced by nAChR polymorphisms (Davis & de Fiebre 2007). A study of long- and short-sleep mice (genetically bred for differences in sleep time following ethanol) identified a polymorphism in the nAChR α4 subunit (Stitzel et al. 2001). This α4 polymorphism has been shown to affect alcohol-induced suppression of acoustic startle (Owens et al. 2003), alcohol withdrawal-related hyperexcitability (Butt et al. 2004), as well as alcohol intake and alcohol-related locomotor effects (Tritto et al. 2001). Other investigations of knock-out mice have found that α7 nAChRs are involved in alcohol effects on aversive learning (Wehner et al. 2004), locomotor activity, hypothermia, and sleep time (Bowers et al. 2005). Recent SNP studies in adolescents demonstrated that neuronal nicotinic receptor subunit genes CHRNA5/A3/B4 and CHRNA4/B2 are involved in early initiation and initial subjective responses to alcohol (Ehringer et al. 2007; Schlaepfer et al. 2008). In a national sample of adults, *CHRNA6/B3* was associated with alcohol consumption (Hoft et al. 2009).

Nicotine effects on alcohol reactivity and consumption: Pre-clinical studies have found that nicotine both increases and decreases alcohol self-administration. Acute administration of nicotine decreases alcohol self-administration behavior (Nadel et al. 1998; Hendrickson et al. 2011). However, in alcohol-experienced rats, chronic administration of nicotine increases alcohol intake (Blomqvist et al. 1996; Smith et al. 1999; Clark et al. 2001). Nicotine has also been shown to facilitate the acquisition of alcohol self-administration behavior in rats (Smith et al. 1999), and to reinstate alcohol-seeking behavior that had been previously extinguished (Lê et al. 2003).

While a number of naturalistic and human laboratory paradigms document that alcohol potentiates nicotine reward (Rose et al. 2002), increases cravings to smoke (King & Epstein 2005), increases smoking behavior (e.g., Shiffman et al. 1994; King et al. 2009), and reduces the ability to resist smoking (McKee et al., 2006), relatively fewer studies have examined the impact of nicotine on alcohol self-administration. Human laboratory studies have examined the effect of smoked tobacco on alcohol use (Madden et al. 1995; Barrett et al. 2006); the effect of nicotine on subjective alcohol responses (Perkins et al. 1995; Kouri et al. 2004) and alcohol self-administration behavior (Acheson et al. 2006; McKee et al. 2008); and the effect of nicotine deprivation on the reinforcing value of alcohol (Palfai et al. 2000; Perkins et al. 2000; Colby et al. 2004), with conflicting results.

In fixed-dose alcohol studies, nicotine has been found to attenuate the subjective effects of alcohol (Perkins et al. 1995; Ralevski et al. 2012), and alcohol-induced changes in arousal (Perkins et al. 1995) and sedation (Perkins et al. 1995; Ralevski et al. 2012; although see also Kouri et al. 2004). Research on the effects of nicotine on alcohol-related subjective intoxication have been mixed, with some studies documenting attenuated intoxication (Madden et al. 1995; Perkins et al. 1995), and other studies finding increased intoxication (Kouri et al. 2004).

Two studies have examined the effect of transdermal nicotine patch (TNP) on alcohol self-administration behavior while one study has examined the effect of cigarettes on alcohol responding. We (McKee et al. 2008) have demonstrated that TNP (21 mg/day), compared to 6 hours of nicotine deprivation (i.e., placebo patch), reduced alcohol self-administration behavior, attenuated craving responses, and reduced subjective alcohol intoxication in non-treatment seeking heavy drinkers who were daily cigarette smokers. The second study

(Acheson et al. 2006) examined the effect of TNP (0,7,14 mg/day) on reactivity to an initial priming drink (0.2 g/kg) and subsequent alcohol self-administration behavior in light smoking social drinkers (2–3 cigarettes per day; 1–2 drinks per day). The priming drink increased ratings of desire for additional alcohol regardless of nicotine condition. However, during the self-administration phase, TNP increased drinking behavior in men, but decreased drinking behavior in women. Barrett et al. (2006) examined the influence of nicotinized versus denicotinized cigarettes on progressive ratio (PR) responding for alcohol in male smokers. Subjects smoked four cigarettes, each spaced 30 minutes apart, while PR responding for up to 10 units of alcohol (equivalent to six drinks) or water. Results demonstrated that there was a trend towards increased responding for alcohol compared to water during the nicotinized cigarette condition.

Given the high co-occurrence of drinking and smoking behavior, it follows that alcohol and tobacco use can act as a conditioned cue for the other substance (see Tiffany 1995 for a review). There is evidence for cross-substance craving from both clinical and non-clinical samples (Drobes et al. 2000; Kouri et al. 2004). Cross-cue reactivity has also been demonstrated in ‘light smokers’ or ‘chippers’ (King & Epstein 2005; Epstein et al. 2007). Epstein et al. (2007) examined the effect of alcohol (0, 0.4, 0.8 g/kg) on the time course of tobacco craving in chippers. There was a dose-dependent effect of alcohol on tobacco craving, with craving being greatest in the 0.8 g/kg condition and increasing over the ascending limb of the BAC. Craving was found to be partially mediated by alcohol stimulation. The authors suggest that tobacco chippers “may crave cigarettes during heavy drinking episodes to enhance the reinforcing stimulating properties of alcohol” (pg. 328).

Research has begun to use ecological momentary assessment (EMA) devices (e.g., electronic diaries) to investigate the relationship of smoking and alcohol in real-world settings. EMA methods allow investigators to take research questions outside of the laboratory and to capture experiences during daily activities in real world settings (see Shiffman et al. 2008 for review). Cooney et al. (2007) examined electronic diary reports of 102 adults after they completed a trial of concurrent alcohol and tobacco use treatment. Participants reported, through the electronic diary assessments, that they had an increase in urges to consume alcohol after smoking cigarettes and alcohol relapses were predicted, in part, by a high urge to smoke cigarettes. In a second study, Piasecki and associates (2011) used electronic diaries to examine the relationship of alcohol and smoking in real world environments in 259 current cigarettes smokers who reported consuming alcohol at least once a week. Cigarette smoking and alcohol consumption were significantly associated with each other. Use of alcohol and cigarettes together synergistically affected ratings of feeling “buzzed” and “dizzy” and led to higher levels of cravings for both alcohol and cigarettes.

Part I: Summary

In this first section, we have demonstrated that alcohol and tobacco are highly co-morbid behaviors. Tobacco use is associated with frequent binge drinking, increased length of drinking episodes, and potentiates the experience of alcohol-related reinforcement. It is likely a combination of these factors which mediates the effect of tobacco use on increasing the risk of meeting criteria for hazardous drinking and alcohol use disorders. Overall, there is clear evidence that the central nAChR system is involved in neurochemical, pharmacological, electrophysiological, behavioral, and genetic effects of alcohol. Importantly, the nAChR system potentiates alcohol-reward likely through cholinergic excitatory input into the mesolimbic dopamine system. While there is some conflicting evidence regarding the effect of nicotine on alcohol reactivity and consumption, most findings support that nicotine and tobacco increase alcohol craving and consumption. Given all that we know about how alcohol and tobacco interact, it is important to understand how we can use our knowledge of these interactions to reduce alcohol use. For the second part of

this review, we will consider whether; 1) smoking status can be used as a clinical indicator for alcohol misuse; 2) tobacco policies reduce alcohol use; and 3) nAChR medications can be used to treat alcohol use disorders.

Part II: How can knowledge of alcohol-tobacco interactions be utilized to reduce alcohol use?

Can smoking status be used as a clinical indicator for alcohol misuse?

The U.S. Preventative Services Task Force recommends providing screening and brief interventions for hazardous drinking and alcohol use disorders in primary care settings (USPSTF 2004). Based on the available evidence concerning the efficacy of screening, they have assigned a Grade B recommendation for screening and brief inventions for hazardous alcohol consumption in primary care settings. This viewpoint is also consistent with the NIAAA Clinician's Guide, Helping Patients Who Drink Too Much (USDHHS 2005), which recommends screening for alcohol use disorders as well as for less severe 'at-risk' or hazardous drinking. Overall, evidence demonstrates that it is feasible and effective to administer screenings and interventions in acute hospital and primary care settings (Wilk et al. 1997; Fiellin et al. 2000; D'Onofrio et al. 2012). In a meta-analysis of randomized clinical trials of brief alcohol interventions provided in outpatient settings, heavy drinkers who received a brief intervention were twice as likely to reduce their drinking up to one year later compared to heavy drinkers who did not receive an intervention (Wilk et al. 1997).

While screening and brief interventions to reduce alcohol use demonstrate efficacy and are cost effective to deliver in outpatient settings, clinicians evidence low rates of adherence to the guidelines for screening for alcohol misuse (Spandorfer et al. 1999). Data from a national sample finds that only 30% of individuals who had a primary care visit reported being screened for an alcohol or drug use problem (Edlund et al. 2004). This is in contrast to the evaluation of smoking status, where physicians are much more likely to assess for and provide a brief intervention for smoking. Upwards of 80% of patients report that smoking status was evaluated and addressed during medical visits (Taira et al. 1997; McBride et al. 1997; Aira et al. 2004). Given the importance of assessing smoking status during medical visits, this assessment has been elevated to that of a routine vital sign (Fiore 1991).

As described earlier, a large literature has shown that smoking status is strongly associated with hazardous drinking and alcohol use diagnoses. Smoking status may therefore be a useful tool for identifying primary care patients at higher risk for alcohol misuse. Following NIAAA clinical care guidelines for the assessment of drinking behavior, we used data from Wave I of the NESARC to evaluate current drinking status, hazardous drinking status, and alcohol use diagnoses (McKee et al. 2007). We then evaluated whether smoking status (current daily smokers, current non-daily smokers, former smoker, and never smoker) was an effective clinical indicator for alcohol misuse using standard test statistics to evaluate medical screening tools. We found that current smoking (daily + non-daily smokers combined) demonstrated moderate sensitivity (i.e., rate of true positives) for predicting hazardous drinking (43%) and alcohol use disorder diagnoses (52%). Further, current smoking status evidenced high specificity (i.e., rate of true negatives) for predicting hazardous drinking (82%) and alcohol use disorder diagnoses (78%). In other words, if an individual is a smoker (daily or non-daily) then they are at heightened risk for alcohol misuse but the presence of alcohol misuse is not guaranteed as the sensitivity was only moderate. Among the entire sample 26.1% met criteria for hazardous drinking and 8.5% met criteria for an alcohol diagnosis. Among current smokers these rates increased to 45.3% for hazardous drinking and 17.8% for an alcohol diagnosis. While smoking status adds

important information regarding the presence of alcohol misuse, there is clearly not a 1:1 correspondence.

We suggest that smoking status be used as a "red flag" to help identify primary care patients at higher risk for alcohol misuse and as a helpful mnemonic for alcohol screening in general. Our data highlight the importance of physicians adopting standard alcohol screening questions into their practice, particularly as methods for office based alcohol-interventions, including medication management approaches (Pettinati 2004; Anton et al. 2006), continue to show promise.

Can tobacco policies reduce alcohol use?

Smoke-free policies and tobacco taxation are two of the most effective means of reducing tobacco consumption, as summarized in the World Health Organization MPower report on the global tobacco epidemic (WHO 2008). Given the degree of association between alcohol and tobacco use, it is possible that the public health benefits of smoke-free policies may extend beyond smoking-related outcomes to alcohol use. There are other examples in the economics literature on spillover impacts of substance abuse policies on other areas (e.g., on zero tolerance alcohol laws on crime and risky sexual behavior; Carpenter 2005; Carpenter 2008), but very little on the spillover from tobacco policy to alcohol consumption. As reviewed below, the research to date has been promising and may represent a new and innovative policy approach to decrease morbidity and mortality associated with alcohol consumption.

Smoke-free legislation—Evidence supporting the public health significance of smoke-free policies is clear. Smoke-free legislation prohibiting smoking in indoor public venues, including bars and pubs, reduces exposure of non-smokers to passive smoke and the risk of respiratory symptoms (Eisner et al. 1998; Farrelly et al. 2005; Menzies et al. 2006). Recent evidence suggests that smoke-free policies reduce the rate of coronary heart disease in the population (Sargent et al. 2004). Moreover, such policies can reduce overall levels of smoking (Fitchenberg & Glantz 2002), including smoking levels among addiction treatment facility staff and patients (Guydish et al. 2012), and motivate smokers to make their homes smoke-free (Borland et al. 2006). Fichtenberg and Glantz (2002) reviewed the literature in this area and concluded that smoke-free legislation reduced the smoking prevalence by 3.8% and those who continued to smoke consumed an average of three fewer cigarettes per day. Bauer et al. (2005) report even larger effects on cessation and consumption with the longer duration of a smoke-free policy suggesting that the effects may grow over time. Smoke-free legislation increased the odds of quitting by 2.3 times, and decreased daily cigarette consumption by four cigarettes. In addition to the smoking-related benefits accrued by smoke-free policies, there may be additional public health benefits associated with possible concomitant reductions in drinking behavior.

Few studies to date have examined the impact of smoke-free policies on alcohol consumption. One study (Picone et al. 2004) examined longitudinal data from the US Health and Retirement Survey (1992–2002) and found that smoking restrictions were associated with a reduction in alcohol consumption in older adult females. However, this was a generalized population effect that did not consider when specific state policies were enacted, nor did it evaluate reductions in alcohol consumption as a function of smoking status or of heavy drinking status. A second study examined the effect of smoking bans on economic indicators of alcohol consumption in the US from 1982 to 1998 (Gallet & Eastman 2007). Smoking bans were associated with a reduction in the demand for beer and spirits and this effect was more pronounced when bans were specific to bars or restaurants. As a limitation

to their findings, they note that they were not able to examine effects for specific populations of interest (e.g., heavy alcohol users).

We have now conducted three investigations examining the effect of smoke-free legislation on indices of alcohol use including consumption and rates of alcohol misuse (McKee et al 2009; Kasza et al. in press; Young-Wolff et al. in press). In the first study, we conducted a longitudinal examination of the impact of the Scottish smoke-free policy on drinking behavior in smokers and non-smokers. We compared drinking behavior in Scotland, at baseline and 1-year following the enactment of the ban, to the rest of the United Kingdom which did not have a comprehensive smoke-free policy during the study period. Telephone interviews (n=1,059) were conducted to evaluate smoking behavior, drinking behavior, and pub attendance. Among heavy drinkers, we found that drinking behavior in pubs decreased among Scottish smokers, compared to smokers in the rest of the UK, one year following the enactment of the smoke-free legislation in Scotland, representing a 48% decrease in consumption. Importantly, drinking behavior did not increase in other settings such as the home. Consistent with these findings, we observed decreases in self-reported pub patronage among Scottish smokers who consumed alcohol compared with smokers in the rest of the United Kingdom. However, Scottish nonsmokers reported more pub patronage after the smoke-free law, which supports other reports showing no overall change in the frequency of pub patronage but some increases among nonsmokers and some decreases among smokers (Hyland et al. 2008).

In a subsequent study, we conducted a longitudinal evaluation examining changes in drinking behavior as a function changes in of smoke-free legislation (Kasza et al. in press). Data were collected in the U.S., Canada, Australia, and the United Kingdom and included n=5,786 participants collected across three waves (2005, 2007, 2008). We assessed community-level smoke-free legislation in bars through participant query. The impact of smoke-free legislation on alcohol consumption across the four countries was consistent with our results from Scotland. There was a reduction in the quantity of alcohol typically consumed among hazardous drinkers and a reduction in the frequency of consumption among individuals who both smoked heavily and were hazardous drinkers. Taken together, these two studies suggest that associations between smoke-free legislation on alcohol consumption appear to be most pronounced in heavier drinkers and indicate that physically disaggregating drinking and smoking behavior in bars may reduce drinking behavior.

For our third investigation in this line of research, we evaluated whether smoke-free polices in drinking venues may correspondingly be associated with reductions in the rates of alcohol use disorders. We conducted a longitudinal evaluation using two waves of the NESARC data (Wave 1, 2001–2002, Wave 2, 2004–2005) to evaluate whether statewide changes in smoke-free bar and restaurant policies influenced remission, onset, and recurrence of DSM-IV alcohol use disorders over time in a representative sample of U.S. drinkers (Young-Wolff et al. in press). The analysis was confined to those who reported consuming alcohol in public venues (N=5,930). Results demonstrated that among all drinkers, enactment of a smoke-free ban in bars or restaurants was significantly associated with increased remission of alcohol use disorders. Among drinkers who did not experience a ban across the two waves, there was a 50% remission rate for alcohol use disorders, compared to 61% among drinkers who lived in a state which enacted a ban. There was also a significant effect on new cases of alcohol use disorders during the study period. Among drinkers who did not experience a ban across the two waves, 11% had a new onset of an alcohol use disorder, compared to 7% among drinkers who lived in a state which enacted a ban. There were no associations between the ban and recurrence of an alcohol use disorder. In general, these effects were more pronounced among smokers, males, and young adults. Given that the prevalence of alcohol-tobacco comorbidity is greatest in young adults (Falk et al. 2006),

these findings are particularly important from a prevention perspective and suggest that statewide smoking bans may offer a broad approach to prevent onset of alcohol use disorders among individuals in the highest risk age group.

Across studies, our results to date suggest that smoke-free legislation has added public health benefits by reducing alcohol consumption and alcohol use disorders among segments of the population (i.e., heavy drinkers, smokers) most at risk to experience adverse alcohol-related consequences.

Tobacco tax—A large body of evidence finds that increases in tobacco taxes lead to reductions in cigarette consumption, with the resulting outcomes of decreased initiation, increased quit behavior, and reductions in premature death (e.g., Chaloupka 2000). Using 1996 estimates, Chaloupka (1998) found that a $1.50 increase in cigarette taxes maintained in real price (i.e., controlling for inflation) would decrease overall cigarette consumption by 30%. Others estimate that a 10% increase in taxes equates to a 3–5% decrease in cigarette consumption in adults (Evans & Farrelly 1998). Cigarette taxation has been identified as one of the most significant policy instruments to reduce smoking rates and extensive resources have been allocated to understanding the direct effect of taxes on reducing tobacco use. However, very little attention has been allocated to the effect of tobacco taxation on other associated health behaviors, such as alcohol use. A number of economic investigations have found that the cross-price elasticity between alcohol and tobacco is negative suggesting that the two behaviors function as complements (Lee 2007; Aristei & Pieroni 2010). In other words, increasing the tax on cigarettes will result in reductions in consumption of both alcohol and cigarettes.

In an adult sample, Jimenez and Labeaga (1994) found that tobacco use decreased as a function of increasing alcohol taxation and in an adolescent sample, Dee (1999) demonstrated that higher cigarette taxes were (non-significantly) associated with reductions in rates of drinking. Both investigations support that alcohol and tobacco function as complements. We are currently investigating the effect of tobacco tax and price on alcohol drinking outcomes in large, nationally representative samples. We predict that increased tobacco taxation (and price) will decrease alcohol consumption, and rates of hazardous drinking and alcohol use disorders.

Can nAChR based medications be used to treat alcohol use disorders?

Current clinical care guidelines for the treatment of alcohol use disorders recommend that behavioral interventions be combined with adjunctive pharmacotherapy (USDHHS 2005). There are currently three medications approved by the FDA for the treatment of alcohol use disorders; disulfiram, naltrexone, and acamprosate. Disulfiram is an aversive agent that alters the metabolism of alcohol and produces hypotension, flushing, and vomiting when alcohol is consumed. While it has been used for the management of alcohol use disorders for over 50 years, clinical investigations do not clearly support the efficacy of disulfiram for the treatment of alcoholism (Fuller et al. 1986; Garbutt et al. 1999). However, this agent may still have a role in the treatment of individuals with co-morbid disorders such as cocaine dependence (Petrakis et al. 2000; Carroll et al. 2004)and post traumatic stress disorder (Petrakis et al. 2006). Naltrexone, a mu-opioid receptor antagonist, has demonstrated clinical efficacy (Anton et al. 2006), however negative studies have also been reported (Kranzler et al. 2000; Krystal et al. 2001). A Cochrane review (Cahill et al. 2007) finds that naltrexone decreases the likelihood of relapse by 36%, and supports its use as a short-term adjunctive treatment for alcoholism. Acamprosate is a structural analogue of GABA, and while European trials have found this medication efficacious (Mann et al. 2004), two large US trials found that acamprosate did not improve outcomes relative to placebo (Anton et al.

2006; Mason et al. 2006). Overall, the evidence suggests that the efficacy of currently available medications is modest at best. Estimated effect sizes for percent days abstinent for both acamprosate (effect size = 0.04) and naltrexone (effect size = 0.22) are small to moderate (Anton et al. 2006), suggesting that there is much room for improvement. Additionally, it is unlikely that a single medication will be effective for all subpopulations of drinkers, underscoring the need to identify additional agents focused on novel neurobiological targets.

As described above, alcohol and nicotine use are highly co-morbid behaviors, demonstrate cross-tolerance and cross-cue reactivity, and interact at molecular and genetic levels. There is strong evidence from electrophysiological, pharmacological, and neurochemical studies suggesting that nAChRs are involved in alcohol effects and self-administration behavior (See Söderpalm et al. 2000; Larsson & Engel 2004; Dani & Harris 2005; Davis & de Fiebre 2007; Li et al. 2007 for reviews). To date there has been limited work investigating nAChRs as a viable target for medications development for alcohol use disorders, primarily due to the lack of suitable and specific agents available for human administration. There are currently two agents, mecamylamine and varenicline, which have been studied as potential medications to treat alcohol use disorders.

Mecamylamine—Mecamylamine is a non-competitive and non-selective nAChR antagonist, originally marketed as Inversine for the treatment of hypertension. Overall, mecamylamine has demonstrated limited efficacy as a smoking cessation medication (Frishman et al. 2006). With regard to alcohol use, preclinical investigations find that ethanol intake and preference for alcohol was attenuated when mecamylamine was either administered into the VTA (Ericson et al. 1998)or systemically (Blomqvist et al. 1996; Lê et al. 2000; Hendrickson et al. 2009). Perfusion of mecamylamine in to the VTA has been shown to reduce dopamine release in the NA in response to an ethanol-associated conditioned stimulus in rats (Löf et al. 2007). Additionally, mecamylamine has been shown to block the acquisition of a condition place preference to alcohol (Bhutada et al. 2012).

In humans, mecamylamine has been found to attenuate the stimulating effects of alcohol, cravings for alcohol, and alcohol-related withdrawal symptoms (Blomqvist et al. 2002; Chi & de Wit 2003; Houtsmuller et al. 2005; Bhutada et al. 2010). However, the impact of mecamylamine on reduced drinking in humans has yet to be demonstrated. To date, there has only been a single investigation examining the effects of mecamylamine on alcohol consumption in social drinkers (n=24; Young et al. 2005). While mecamylamine reduced self-reported stimulation after consumption of alcohol, there was no reduction in participant choice for alcohol (versus money). Currently, there are ongoing trials evaluating mecamylamine as a treatment for alcohol dependence but results are not yet available.

Varenicline—Varenicline (Chantix ™) is a partial nicotinic agonist that binds with higher affinity at α4β2 nAChRs, than at other nAChR subtypes (e.g., α3β2, α3β4, α6) and a full agonist of α7 nAChRs (Coe et al. 2005; Mihalak et al. 2006). Partial agonists with high binding affinity act as agonists with smaller maximal effects than a full agonist at full receptor occupancy, and as antagonists when the full agonist is co-administered (Rollema et al. 2007). For human α4β2 nAChRs, electrophysiological studies have determined that varenicline had 45% to 68% of the agonist activity of nicotine, and when co-administered with nicotine, reduced the efficacy of nicotine by 34% (Coe et al. 2005, Rollema et al. 2007). Similar findings were produced when varenicline was injected systemically in rats. In rat brain slices, varenicline had 40–60% efficacy in stimulating dopamine release (Rollema et al. 2007), and microdialysis investigations found that varenicline produced 60% of the dopamine release as compared to nicotine in the rat NA (Coe et al. 2005). Mecamylamine was found to block dopamine release stimulated by varenicline (Rollema et al. 2007). With

regard to acetylcholine response, varenicline is a full agonist of α7 nAChRs, producing 93% of the nicotine response (Mihalak et al. 2006). Behavioral investigations of varenicline suggest that it can mimic the subjective effects of nicotine.

Consistent with its partial agonist effects, varenicline is hypothesized to reduce smoking behavior in two ways: 1) by acting as an agonist at α4β2 receptors stimulating adequate levels of dopamine release to prevent tobacco craving, and 2) by acting as an antagonist preventing nicotine-related reinforcement should smoking occur during a quit attempt (Rollema et al. 2007). These hypothesized mechanisms are supported by both preclinical and clinical literature. Animal studies have documented that varenicline reduces nicotine self-administration, lowers progressive ratio break points, and substitutes for nicotine in drug discriminations studies(Rollema et al. 2007). In human studies, varenicline has been found to reduce tobacco craving, withdrawal symptoms, and reinforcing effects of smoking (Gonzales et al. 2006; Jorenby et al. 2006; McKee et al. 2012). Varenicline improves smoking cessation rates 2-fold over bupropion, and almost 4-fold when compared to placebo, and is well tolerated (Gonzales et al. 2006; Jorenby et al. 2006). For example, rates of prolonged abstinence (last 4 weeks of treatment) for varenicline, bupropion, and placebo were 43.9%, 29.8%, and 17.6% respectively (Jorenby et al. 2006). Although there has been concern that varenicline is associated with neuropsychiatric side effects, reports examining varenicline for smoking cessation in smokers with and without psychiatric conditions (including alcohol problems) found that varenicline was safe, well tolerated, and did not exacerbate mental illness (Stapleton et al. 2007; Kasliwal et al. 2009; Gunnell et al. 2009; Tonstad et al. 2010).

Varenicline's actions occur at nAChR subtypes (e.g., α4β2, α7) which have been identified as having a role in alcohol effects (e.g., reinforcement, self-administration, withdrawal), suggesting that varenicline may be a promising candidate to modify alcohol reactivity and self-administration behavior. Preclinical investigations have demonstrated that varenicline reduces ethanol seeking (Steensland et al. 2007), ethanol self-administration (Steensland et al. 2007; Hendrickson et al. 2010; Kamens et al. 2010; Bito-Onon et al. 2011), and reinstatement of responding to an alcohol cue (Steensland et al. 2008, Wouda et al. 2011). In a micro-dialysis study, varenicline attenuated the extracellular dopamine response in the NA, in response to alcohol and nicotine co-administration (Ericson et al. 2009). Using a knock-out model with adult male C57BL/6J mice, Hendrickson and colleagues (2011) demonstrated that the α4 nAChR subunit is necessary and sufficient to produce a decrease in ethanol consumption following administration of varenicline.

We (McKee et al. 2009) were the first to demonstrate that varenicline, when administered to steady state (2mg/day vs. placebo), significantly reduced alcohol cravings and positive subjective alcohol effects (i.e., *high, like, rush, feel good, intoxicated*) in response to a low fixed dose of alcohol (0.3 g/kg). During the subsequent two-hour self-administration period, where subjects could consume up to eight additional drinks (each 0.015 g/kg) or receive monetary compensation, varenicline robustly reduced drinking behavior. Importantly, reductions in cravings during the low fixed-dose of alcohol were strongly associated with reductions in drinking. Based on these results, and consistent with the Ericson et al. (2009) findings described above, it is possible that varenicline may facilitate sufficient levels of dopamine release in the NA, while blocking the effect of alcohol consumption to further augment dopamine levels. This may serve to attenuate alcohol craving, while inhibiting alcohol-related reinforcement thereby reducing self-administration behavior.

Others have since found that varenicline reduced craving and had a tendency towards reducing heavy drinking among heavy drinking smokers taking varenicline for smoking cessation (Fucito et al. 2011). In a sample of social drinkers taking varenicline for smoking

cessation, Mitchell et al (in press) found that varenicline, compared to placebo, reduced alcohol consumption across the twelve week trial. In both of these studies, there was no effect of varenicline on smoking behavior. In a laboratory study of social drinkers, varenicline versus placebo increased negative affect following alcohol consumption and tended to reduce ratings of alcohol liking (Childs et al. 2012).

We have completed a longitudinal epidemiological investigation examining the effect of smoking cessation medications on changes in alcohol consumption (McKee et al. in press). Using the International Tobacco Control – Four Country Data (US, Canada, United Kingdom, Australia) we evaluated drinking behavior, smoking behavior, smoking cessation medication use (varenicline, nicotine replacement therapy, no medication use) across two waves of data (2007, 2008; n=4,995). While controlling for baseline drinking, smokers taking varenicline versus nicotine replacement therapy for smoking cessation significantly reduced the likelihood of any drinking (O.R. = 0.56) and drinking once a month or more (O.R. = 0.43). Additionally, smokers taking varenicline versus no medication reduced the likelihood of drinking once a month or more (O.R. = 0.62). Importantly, these effects on drinking were not associated with changes in smoking behavior (e.g. smoking cessation) and suggest that varenicline may have independent effects on alcohol consumption.

These initial studies in humans suggest that varenicline significantly reduces drinking during laboratory self-administration sessions in heavy drinkers, and in social and heavy drinking smokers using varenicline for smoking cessation. Given that varenicline was found to be well tolerated, alone and in combination with alcohol, clinical trials examining varenicline as a primary treatment for alcohol use disorders and as a potential treatment for co-morbid alcohol and tobacco use disorders are promising routes to pursue. To our knowledge, there are several ongoing studies and two completed studies examining the efficacy of varenicline for the treatment of alcohol usedisorders. However, there are no published reports to date.

Summary and Conclusions

Alcohol and tobacco interactions are complex, but at their core, involve potentiated reinforcement. In the second part of this review, we have considered how we may use our knowledge of alcohol and tobacco interactions to reduce alcohol use. Given the high rates of co-morbidity between alcohol and tobacco use, we suggest that tobacco use can be used in medical settings as an effective screen for hazardous drinking and alcohol use disorders (McKee et al. 2007). We found that current smoking, which includes daily and non-daily smoking, produced the best test statistics (i.e., moderate sensitivity and high specificity) when evaluating tobacco use as a clinical indicator for alcohol misuse. Based on our results, it would be important to carefully assess for both daily and non-daily smoking status, as non-daily smokers do not typically identify themselves as ‘smokers’. This line of investigation has now been extended to other populations, such as smokers calling in to a quitline. Toll et al (in press), found that 56% of 88,479 smokers calling the New York Quitline were drinkers and that 41% of the drinkers met criteria for hazardous drinking. These results suggest that quitlines may be one previously neglected yet important venue to identify alcohol misuse and to potentially provide brief interventions designed to reduce alcohol consumption. Future work should evaluate the efficacy of using tobacco use as a screening tool for alcohol misuse and the effectiveness of providing brief alcohol interventions to populations of drinkers identified through smoking status.

We have found that smoke-free policies, which demonstrate efficacy in reducing smoking and smoking-related disease, were associated with reduced alcohol consumption among heavy drinkers and smokers (McKee et al. 2009, Kasza et al. in press). Importantly, smoke-free polices were associated with reduced occurrence and increased remission of alcohol use

disorders (Young-Wolff et al. in press). Overall, these results suggest that smoke-free policies may represent a new and innovative policy approach to decrease morbidity and mortality associated with alcohol consumption. It will be important to continue to evaluate the impact of smoke-free legislation on alcohol outcomes over time. The effect of smoke-free policies on smoking outcomes continue to grow over time (Bauer et al. 2005), and it will be important to evaluate whether this effect is mirrored with alcohol outcomes.

Tobacco legislation has broad population reach and has the potential to reduce alcohol consumption and its adverse health impacts. As the next step in this line of work, we plan to focus on the effects of tobacco taxes on alcohol consumption and rates of alcohol use disorders. Additionally, we plan to expand the scope of our outcomes to include psychosocial consequences of heavy drinking (e.g., fights in bars), drunk driving, and alcohol-related morbidity or mortality. Tobacco-related products came under FDA regulation in 2009 through the Family Smoking Prevention and Tobacco Control Act. It will be important to evaluate possible concomitant reductions in drinking and alcohol-related diagnoses as the FDA enacts policies designed to reduce the harm and addictive potential of tobacco products, including cigarettes.

From a practical standpoint, documenting that tobacco legislation has beneficial alcohol-related outcomes has the potential to bring additional partners into policy debates. As of January 2012, only 29 states had enacted 100% smoke-free legislation for bars; however, debates over the policy continue in the remaining states (ANRF 2012). Resistance to such policies is based on concern over adverse economic consequences to the local hospitality industry. Research has demonstrated that no such adverse economic consequences attributable to the smoke-free policies have been observed in places that have gone smoke-free (Scollo et al. 2003). Given that smoke-free policies are associated with more favorable alcohol-related outcomes, this information should be brought to the debates to more fully capture the public health benefits of implementing such policies. A careful and complete economic analysis would include the full set of effects of a policy. If the spillover effects to alcohol and alcohol-related costs are ignored in economic evaluations of tobacco-related policies, then the evaluation will systematically underestimate the true effect.

With regard to medication development, the nAChR system demonstrates promise for the treatment of alcohol use disorders given the complexity of this system's involvement in alcohol-related effects and consumption. While it appears that α4β2 and α7 receptors have been most consistently involved in alcohol effects in preclinical models, the involvement of other subtypes has been identified (e.g., α3β2, α3β4, α6; Larsson & Engel 2004). Importantly, these receptor subtypes nicely overlap with the bindings sites for varenicline. Studies by us (McKee et al. 2009) and others (Mitchell et al. in press) suggest that varenicline may effectively reduce alcohol consumption among social and heavy drinkers. However, whether these findings will translate to a clinical setting evaluating varenicline for the treatment of alcohol dependence is currently unknown. If varenicline is found effective, it will be important to identify which nAChR subtypes are responsible for varenicline's effect on reduced drinking. Preclinical investigations have found evidence for α4 (Hendrickson et al. 2010) and α3β2 (Chatterjee et al. 2010), but not α7 or β2 (Kamen et al. 2010) which typically combines with α4. Varenicline is also a partial agonist of α6, which is highly involved in nicotine-evoked dopamine release (Drenan et al. 2010). Understanding which nAChR receptors mediate effects of varenicline on alcohol consumption would lead to the identification or development of additional nAChR agents which may have greater therapeutic potential. A number of other nicotinic partial agonists have shown promise in reducing alcohol preference and self-administration in preclinical research including cytisine (Bell et al. 2009; Hendrickson et al. 2009; Sajja & Rahman 2011), lobeline (Bell et al. 2009; Farook et al. 2009; Sajja & Rahman 2011), and sazetidine-A (Rezvani et al. 2010), and there

are additional α4β2 and α7 agents available for Phase II testing with humans (http://www.ncats.nih.gov/research/reengineering/rescue-repurpose/therapeutic-uses/directory.html.)

Utilizing knowledge of alcohol and tobacco interactions may represent an innovative approach to reduce the public health burden associated with alcohol use. The evidence suggests that smoking status can be used as a clinical indicator for alcohol misuse, that tobacco policies are associated with reductions in alcohol use, and that nAChR agents show promise for the treatment of alcohol use disorders. Targeting the interactions of alcohol with tobacco through multiple domains; including clinical settings, public health policies, and treatment development; will be critical steps in the comprehensive effort to reduce the enormous personal and societal consequences associated with hazardous drinking and alcohol use disorders.

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SUMMARY POINTS

1. Alcohol and tobacco use share a high degree of co-morbidity across levels of use and diagnostic categories in the general population.
2. The use of tobacco and nicotine can increase alcohol use and increase the risk for meeting criteria for hazardous drinking and alcohol use disorders.
3. The central nAChR system, the system through which nicotine exerts its effects, is involved in neurochemical, pharmacological, electrophysiological, behavioral, and genetic effects of alcohol.
4. The nAChR system potentiates alcohol-reward through cholinergic excitatory input into the mesolimbic dopamine system
5. Given the high rates of co-morbidity between alcohol and tobacco use, tobacco use can be used in medical settings as an effective screen for hazardous drinking and alcohol use disorders.
6. Smoke-free policies, in addition to reducing smoking and smoking-related disease, also reduce alcohol consumption, decrease the new occurrence of alcohol use disorders, and increase remission from alcohol use disorders among both heavy drinkers and smokers.
7. Varenicline, a partial agonist of nAChRs, reduces alcohol consumption among social and heavy drinkers.
8. Targeting the interactions of alcohol with tobacco through multiple domains; including clinical settings, public health policies, and treatment development; will be critical steps in the comprehensive effort to reduce the enormous personal and societal consequences associated with hazardous drinking and alcohol use disorders.

FUTURE ISSUES

1. What is the effectiveness of providing brief alcohol interventions to populations of drinkers identified by their smoking status?
2. How does smoke-free legislation impact alcohol outcomes over long periods of time?
3. What effects do tobacco taxes have on alcohol consumption and rates of alcohol use disorders?
4. What are the impacts of tobacco taxes and other smoke-free legislation on the psychosocial consequences of heavy drinking, drunk driving, and alcohol-related morbidity or mortality?
5. In what ways will the policies that the FDA enacts to reduce the harm of tobacco products as part of the Family Smoking Prevention and Tobacco Control Act be associated with changes in drinking and alcohol use disorders?
6. Which nAChR subtypes are responsible for varenicline's effects on reduced drinking?
7. What is the efficacy of varenicline for treating alcohol use disorders in clinical settings?