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ALCOHOL (RF LEEMAN, SECTION EDITOR)

Current Insights into the Mechanisms and Development of Treatments for Heavy-Drinking Cigarette Smokers

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Abstract There is a strong association between cigarette smoking and alcohol use at the epidemiological, behavioral, and molecular levels, and this co-use creates substantial impediments to smoking cessation among smokers who are also heavy drinkers. Compared with individuals who only smoke, those who both drink and smoke heavily experience more severe health consequences and have greater difficulty in quitting smoking. During smoking abstinence, greater alcohol use is associated with decreased odds of smoking cessation, and smokers are substantially more likely to experience a smoking lapse during drinking episodes. As heavy-drinking smokers are less responsive to the currently available pharmacological treatments, this subgroup of high-risk substance users possesses a unique clinical profile and treatment needs. Thus, treatment development for heavy-drinking smokers represents a significant and understudied research area within the field of smoking cessation. This review will briefly describe findings from epidemiological, behavioral, and molecular studies illustrating alcohol and tobacco co-use and identify how the behavioral and neurobiological mechanisms underlying the interaction of alcohol and nicotine may inform the development of targeted treatments for this unique population of smokers.

This article is part of the Topical Collection on *Alcohol*

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Introduction

Tobacco and alcohol use are among the top three leading causes of preventable disease and contribute to nearly seven million deaths each year worldwide [1, 2]. A strong link exists between cigarette smoking and alcohol use [3–5]. Co-use of these substances is associated with various negative health consequences including cancer, impaired brain structure and function, and pulmonary and cardiovascular disease [6–9]. Furthermore, beyond the risks associated with the use of each substance individually, regular alcohol and cigarette co-use synergistically increases esophageal, laryngeal, and oral cancer mortality rates [6, 8, 9]. In fact, more people with alcohol use disorder (AUD) die from tobacco-related than alcohol-related disease [10].

Despite the sizeable number of people who concurrently smoke and drink and the health risks that coincide with the regular co-use of these drugs, there are currently no treatments approved to reduce both alcohol consumption and cigarette consumption for this high-risk group of substance users. To reduce the health burden and prevalence of comorbid AUD and tobacco use disorder (TUD), there is a critical need to further examine existing as well as novel pharmacological agents and behavioral interventions aimed at co-use. This review will summarize findings from epidemiological, behavioral, and molecular studies on alcohol-nicotine co-use and discuss how understanding their behavioral and neurobiological mechanisms may enable further refinement of treatments for this often treatment-resistant subgroup of smokers. This approach is consistent with the precision medicine initiative

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calling for treatments that are personalized to patient's unique risk profiles [11, 12]. Furthermore, it is important to note that the majority of treatment development studies in heavy-drinking smokers have been performed in the context of smoking cessation interventions with the exception of a retrospective analysis of alcohol treatment from the COMBINE Study [13•]. This may be due to research showing that treatment for alcohol and tobacco use may produce better outcomes when delivered separately rather than simultaneously [14]. Additionally, smoking cessation is often not a priority in the treatment of AUD given the immediate health and personal consequences attributed to alcohol as opposed to the longer term consequences caused by tobacco use. Thus, while the ultimate treatment goal for heavy-drinking smokers is a reduction in both alcohol and tobacco use, this manuscript will predominantly focus on smoking cessation as the primary intervention in this subgroup. Finally, several priority areas for future clinical research on alcohol-nicotine interactions will also be discussed.

Evidence and Mechanisms of the Co-use of Alcohol and Tobacco

Epidemiological Findings

Alcohol and tobacco are two of the most widely abused substances and are often used in combination [15, 16]. According to the National Survey on Drug Use and Health, in 2013, the rates of heavy drinking [five or more drinks on the same occasion (four or more for women) on each of five or more days in the past 30 days] and binge drinking (four drinks for women and five drinks for men in one occasion) among those aged 12 years and older in the USA were 6.3 and 22.9 %, respectively, and 7.0 % of those 18 years and older met the criteria for AUD [17]. In this same survey, almost a quarter (22.5 %) of people aged 12 years and older reported currently using tobacco products.

Alcohol drinking levels are often higher in smokers than nonsmokers, and conversely, smoking levels are higher in heavy drinkers compared to nondrinkers [18]. Almost 20 % of smokers engage in heavy drinking compared to about 6.5 % of nonsmokers [18, 19], and more than 50 % of heavy drinkers aged 12 years and older reported smoking cigarettes within the past month compared with only 15.5 % of people who did not consume alcohol within the past month [17]. Co-use of these substances within the same occasion is relatively common [15, 20], and alcohol consumption during such bouts is often of a longer duration as compared with drinking occasions without smoking [21]. Epidemiological data shows that individuals with TUD are more likely to have AUD [22], and individuals with AUD are more likely to be smokers [23], compared with the general population. The National Institute on Alcohol Abuse and Alcoholism's (NIAAA's) 2001–2002 National Epidemiologic Survey on Alcohol and Related Conditions report that more than six million adults meet the criteria for comorbid AUD and TUD [24].

As there are myriad terms for the comorbidity of AUD and TUD, we will hereto use the term "heavy-drinking smokers" to describe this subgroup. Additionally, it is important to note that in studies examining heavy-drinking smokers, the level of cigarette smoking (e.g., cigarettes per day) has varied substantially depending on the research questions and experimental methods employed. Laboratory studies in this area have examined a wide range of smokers, ranging from light and nondaily smokers to heavy, daily smokers, while the majority of smoking cessation trials in co-users have examined heavier and daily smokers, as they are more often targeted in cessation treatment. The relatively high prevalence of heavy-drinking smokers at the population level, as well as the high comorbidity of AUD and TUD, may be explained by the manner in which these drugs act synergistically to alter drug-seeking behavior.

Behavioral Findings from Studies in Humans

Evidence for the behavioral mechanisms underlying the relationship between alcohol and tobacco co-use has been derived from controlled human laboratory experiments as well as studies of heavy-drinking smokers in their natural environment. Results from the majority of these studies suggest that the underlying motivation for coadministration of these substances is driven in part by three core psychological concepts: cue-induced craving (i.e., Pavlovian conditioning), positive reinforcement, and negative reinforcement [25–27].

In heavy-drinking smokers, consumption of one substance can become a conditioned cue and subsequently induce craving for the other substance. Alcohol consumption has been consistently found to increase craving for cigarettes in the laboratory as well as in the natural environment [15, 16, 28–32]. Increases in smoking urges after consumption of an intoxicating dose of alcohol appear to be mediated by concomitant increases in alcohol-induced subjective stimulation but not sedation [33]. This finding may be particularly relevant for understanding the reciprocal relationship between alcohol and cigarette use in heavy-drinking smokers, as heavy drinkers reliably report more alcohol-induced stimulation than light drinkers [34, 35]. This may suggest that smoking during a drinking episode may have less to do with offsetting the sedating effects of alcohol than it is with potentiating the stimulating effects.

Though less studied, data from real-life ecological momentary assessments (EMA) suggest that cigarette smoking may also increase alcohol craving [16, 36], and the coadministration of alcohol and nicotine can produce cumulatively heightened craving for both substances in the laboratory and natural

environment [16, 31, 37]. Importantly, this substance cross-reactivity has behavioral consequences: in some, but not all, laboratory studies [38], alcohol consumption [39, 40] and cigarette smoking or nicotine administration [41–43] independently increases the motivation to use, or decreases the ability to resist using, the other substance.

Alcohol consumption produces both rewarding (e.g., stimulation, tension reduction) and aversive (e.g., sedation) subjective effects [34, 44]. Importantly, the magnitude and direction of alcohol's subjective effects are directly associated with motivation to consume alcohol, as greater alcohol-induced stimulation and reward is associated with increased alcohol preference and subsequent consumption [45, 46], whereas heightened sedative and aversive effects, or attenuated reward, are associated with decreased consumption and preference [47, 48]. Nicotine also produces stimulatory subjective effects [49, 50], and individuals may coadminister alcohol and cigarettes to either amplify the rewarding effects of each drug (i.e., positive reinforcement) or alleviate the aversive effects of alcohol (i.e., negative reinforcement; [27]), which may lead to increased situational use of each substance [21].

There is laboratory evidence that cigarette and alcohol co-use may reciprocally potentiate the rewarding subjective effects of the other drug. Nicotine administration has been shown to enhance alcohol's stimulant, relaxing, euphoric, and intoxicating effects [31, 49]. Additionally, alcohol increases self-reported enjoyment and satisfaction from smoking and augments the stimulating and calming effects of cigarettes [51–53]. Conversely, nicotine administration or cigarette smoking attenuates alcohol's sedating and intoxicating effects, particularly during the declining portion of the breath alcohol curve [41, 49, 53–55]. Nicotine also reduces alcohol's impairing effects on attention, cognition, and motor function [51, 56, 57]. Taken as a whole, these results suggest that alcohol and nicotine act synergistically to reinforce co-use behavior by potentiating the rewarding effects of each drug and by blunting alcohol's sedating and impairing effects. The coreinforcement from these drugs contributes to increased cigarette and alcohol use both within a drinking session and frequency of overall use [21, 58, 59]. We speculate that this continued coreinforcement over time, as well as the development of cross-tolerance to these drugs [60], underlies the development of comorbid AUD and TUD and is partly facilitated by the neurobiological overlap between these substances.

Molecular and Neurobiological Findings

The profile of alcohol and nicotine's additive behavioral effects suggests that the frequent co-use of these substances may be related to the overlapping pharmacological action of both drugs at the molecular level. This is supported by neuroimaging research in heavy-drinking smokers showing that alcohol acutely increases activation in mesolimbic brain areas, including the ventral striatum, in response to smoking cues [61]. The preponderance of evidence suggests that the main pharmacological convergence between these substances occurs through the acetylcholine and endogenous opioid systems [62, 63]. Alcohol and nicotine affect acetylcholine activity through direct effects on nicotinic acetylcholine receptors (nAChRs) and indirectly modulate opioid transmission through both shared (i.e., nAChR activation) and independent pharmacological mechanisms. In turn, the endogenous acetylcholine and opioid systems modulate the neurocircuitry underlying addiction, including tobacco- and alcohol-related problems [62, 64–66] and the multitude of cognitive processes that can become dysfunctional in addiction, such as inhibitory control [67], working memory [68], decision-making [69], and cognitive flexibility [70].

A large amount of evidence suggests that alcohol and nicotine administration both activate nAChRs on dopamine neurons in the ventral tegmental area (VTA), thereby triggering the mesolimbic dopamine system, which is instrumental in the operant and Pavlovian learning and motivated behavior that are essential to the development of addiction [71–73]. Nicotine's direct activation of nAChRs in the VTA, particularly those containing α4 and β2 subunits in combination with α6, is thought to be most responsible for the reinforcing effects of nicotine and development of TUD [74, 75]. Furthermore, one of alcohol's primary targets is the nAChR [63], and nAChRs that contain α3, α4, α6, β2, and/or β3 subunits may contribute to its reinforcing effects [66, 76–79]. It has been suggested that alcohol either directly potentiates nAChRs on VTA dopamine neurons or increases the activation of cholinergic projections to these neurons [66]. Although contingent upon the order of administration, duration of exposure, and dosage [80, 81], coapplication of ethanol and nicotine has been shown to increase VTA dopamine neuron firing rates to a greater extent than either drug alone [82], suggesting a synergistic pharmacological interaction that parallels the behaviorally reinforcing effects of their co-use described above.

In addition to cholinergic mechanisms, the neurobiological literature has recognized a role for the endogenous opioid system in modulating responses to alcohol and nicotine [62, 83]. Endogenous opioids, particularly endorphins and enkephalins, are thought to mediate the acute, rewarding effects (i.e., "liking" and other pleasurable effects) of drugs, including alcohol and nicotine [63, 83, 84]. Alcohol increases endorphin transmission in the nucleus accumbens and VTA, and this signaling induces dopamine release to the nucleus accumbens through independent mechanisms [85, 86]. Multiple lines of evidence implicate the opioid system in both the hedonically rewarding and motivationally salient effects of alcohol [63, 87]. For example, blocking alcohol-induced dopamine release and endogenous opioid action in the nucleus accumbens with opioid receptor antagonists or via μ-opioid receptor knockout reduces alcohol self-administration and preference [88, 89].

Although relatively less understood, nicotine administration may also acutely increase endorphin and enkephalin release in the striatum and throughout the brain [90–92]. It has been shown that μ-opioid receptor activity modulates nicotine's stimulation of VTA dopamine neurons [93], and μ receptor antagonists can block nicotine's induction of the mesolimbic dopamine system [94]. Furthermore, in animal models, activation of μ-opioid receptors mediates the rewarding effects of nicotine and incentive salience to nicotine-conditioned cues [95–97] but, in contrast to alcohol, does not appear to be involved with nicotine self-administration [98, 99].

In sum, the behavioral effects of alcohol and nicotine coadministration are in part due to shared pharmacological targets in the endogenous opioid and acetylcholine systems. Our increasing knowledge of the neurocircuitry and behavioral pharmacology of alcohol and nicotine's effects suggests that nAChRs and μ-opioid receptors may be promising molecular targets for the development of treatments for heavy-drinking smokers. It should also be noted that chronic alcohol and nicotine exposure results in the upregulation of endogenous dynorphin activity, which contributes to withdrawal, negative affect, and relapse for both drugs [62, 100, 101]. Although the kappa-opioid system is a promising treatment target [102], there are currently no medications available clinically that are specific to kappa-opioid receptors. As such, we will focus on what is known regarding opioid system targets for treating heavy-drinking smokers that focus on the μ-opioid receptor.

Treatments for AUD and TUD: Current Developments and Future Directions

Challenges in Treating Alcohol and Tobacco Co-use

The treatment of heavy-drinking smokers is of high clinical importance, as greater alcohol use is associated with decreased odds of smoking cessation, with smokers four times more likely to have a smoking lapse during drinking episodes than nondrinking episodes [103–106]. In early smoking abstinence, one of the greatest predictors of relapse is the occurrence of a single smoking lapse, which is generally defined as smoking at least a puff of a cigarette [107, 108]. Because as many as 95 % of smokers who experience a lapse will progress to relapse [108, 109], the first lapse has been theorized to represent the transition from abstinence to regular smoking [110, 111]. Alcohol consumption has been identified as a major risk factor for precipitating a smoking lapse: approximately 25 % of smokers participating in smoking cessation trials report consuming alcohol immediately prior to a smoking lapse and identify alcohol as the predominant reason for choosing to smoke [112, 113].

Given these treatment challenges and the previously discussed health concerns associated with alcohol and tobacco co-use, it has been argued that heavy-drinking smokers represent a distinct and underserved subpopulation of smokers based on their unique clinical profile and treatment disparities [3, 114]. Although the Clinical Practice Guidelines recommend that smokers be advised to reduce or avoid drinking during a quit attempt [115], there is a paucity of support for behavioral or pharmacological treatments that have been shown to be efficacious for heavy-drinking smokers [3, 114]. In fact, smokers with current or past AUD have often been excluded from smoking cessation trials, thereby limiting the understanding of how to best treat this comorbid population [116]. While AUD treatment studies have not excluded smokers, the reporting of sample smoking rates, as well as cigarette quantity and frequency, as secondary outcomes has largely been ignored. Thus, treatment development for heavy-drinking smokers continues to represent a highly significant and relatively understudied research area within the larger field of smoking cessation. The behavioral and molecular findings on the combined effects of alcohol and nicotine summarized earlier in this review ("Behavioral Findings from Studies in Humans" and "Molecular and Neurobiological Findings" sections) have provided mechanisms to target in treatment development. As cue-induced craving, positive reinforcement, and negative reinforcement may be driving a significant component of alcohol and tobacco co-use, theoretically, a medication that blocks the additive rewarding effects of both substances (i.e., blocking positive and negative reinforcement), potentiates the aversive properties of either drug (i.e., blocking negative reinforcement and blunting positive reinforcement), and/or reduces reactivity to drug-conditioned cues may be particularly effective treatments for heavy-drinking smokers. For example, because alcohol use commonly precedes a smoking lapse [112, 113] and given that heavy-drinking smokers (1) engage in a pervasive pattern of drinking behavior [34] and (2) display a heightened stimulatory response to alcohol that may be predictive of increased cigarette craving [33], heavy-drinking smokers have a greater risk of experiencing a lapse, and ultimately full relapse, than lighter and nondrinking smokers [104, 117, 118••]. Therefore, behavioral skills or a medication that helps patients reduce or abstain from drinking could conceivably aid in heavy-drinking smokers' smoking quit attempts by preventing alcohol-related smoking lapses. Further, due to pharmacological evidence that alcohol and nicotine both affect nAChRs and opioid receptors, a medication targeting one or both of these systems may be ideal pharmacotherapy candidates.

Promising Behavioral Treatments

The few studies that have examined the effects of cognitive behavioral interventions without pharmacotherapy to reduce alcohol and cigarette co-use have shown modest results. In one randomized clinical trial, heavy-drinking smokers receiving a combined brief intervention for smoking cessation and

alcohol reduction showed better short-term outcomes than those receiving smoking cessation therapy, but these gains were not maintained 4 months after treatment [105]. Another recent pilot study showed that adding a personalized component to standard alcohol brief intervention, i.e., including feedback from a separate laboratory session demonstrating alcohol's positive effects and smoking urge increases, produced greater reductions in binge drinking frequency and alcohol-smoking co-use frequency than the standard alcohol brief intervention alone or a general health feedback attention control condition [119••]. Finally, adding a population-based motivational counseling to standard smoking telephone quit lines to address limiting both alcohol and cigarette consumption produced greater rates of smoking abstinence than did the standard care smoking quit line [118••]. These findings across a variety of behavioral treatments show initial promise on the efficacy and feasibility of such approaches for alcohol and tobacco co-use. More studies in this area are needed to expand this work in larger samples and also to develop additional novel cognitive-behavioral approaches.

Additional approaches that specifically target the behavioral mechanisms underlying alcohol and tobacco co-use may be another promising direction. As stated previously, newer approaches to include feedback on alcohol responses, including elicitation of smoking urges, may be incorporated into existing brief interventions in young adult co-users, and adding alcohol psychoeducation in tobacco quit lines may augment outcomes in co-users attempting to quit smoking. Furthermore, recent work has shown that a cognitive bias modification (CBM) technique consisting of training to alter automatic approach behaviors to drug cues produces better treatment outcomes in individuals with AUD [120]. This training may be useful in changing alcohol and tobacco approach biases in heavy-drinking smokers, although no studies have been conducted to date. Overall, the Clinical Practice Guidelines for smoking cessation suggest that pharmacological treatments be combined with psychotherapy or behavioral therapy [121], and accordingly, most clinical trials of medications in heavy-drinking smokers, but not smaller laboratory studies, have employed a combined therapy approach. We also recommend that combined behavioral and pharmacological therapies be employed in future clinical trials for heavy-drinking smokers. In the next section, we specifically review research investigating various pharmacotherapies in heavy-drinking smokers.

Promising Pharmacological Treatments

Varenicline

Recent research has focused on three promising pharmacotherapies for heavy-drinking smokers, which include varenicline (VAR), naltrexone (NTX), and the combination of VAR and low-dose NTX. Varenicline tartrate is an approved treatment for TUD, and a number of recent studies have also highlighted its potential role in the treatment of AUD. As multiple clinical trials have shown that VAR is more effective than bupropion and nicotine replacement therapy as a smoking cessation agent [122–125], VAR has been advanced as a first line treatment for TUD [121]. Varenicline is a partial agonist at nAChRs containing α4β2, α3β4, α3β2, and α6 subunits and a full agonist at those containing α7 [126, 127]. Varenicline has the highest affinity for the α4β2, producing ~45–70 % of the agonist activity and stimulating ~40–60 % of VTA dopamine release of nicotine [127, 128]. As previously discussed, the α4β2 and α6 subunits appear to primarily mediate smoking reward, withdrawal symptoms, nicotine-induced neuroplasticity, conditioning, and the development of TUD [75, 129–132]. Relatedly, the primary mechanisms of action of VAR are thought to stem from two primary effects. First, VAR stimulates the release of basal dopamine through activation of α4β2 nAChRs in the VTA, which is thought to reduce tonic nicotine craving and negative affect associated with nicotine withdrawal [16, 128, 133, 134]. Secondly, VAR acts as a functional nAChR antagonist by attenuating nicotine cue-induced craving and, if a smoking lapse occurs during a quit attempt, by blocking nicotine's reinforcing effects and conditioning to novel drug-related stimuli [134–136]. In support of this latter mechanism, VAR has been shown to be effective in reducing smoking lapse behavior in the laboratory [137] and disrupting the transition from smoking lapse to relapse in a smoking cessation trial [138]. Additional mechanisms of action may relate to improvements in working memory [139], attention [140], and inhibitory control [67]. While VAR is the most successful currently available treatment for tobacco use, abstinence rates with patients taking this medication are about 43 % at 12 weeks and 25 % at 1-year follow-up [141]. Thus, even among general smokers, the majority of persons taking VAR are not successful in quitting smoking long-term.

A recent line of research has yielded results in support of VAR as a potential treatment for AUD. It is currently unclear which nAChR receptor type is responsible for alcohol's pharmacological and behavioral effects [76, 78, 79, 142, 143], but most evidence does not support the involvement of the α4β2 nAChR despite this subtype being responsible for much of nicotine's acute and chronic effects and VAR's smoking treatment efficacy [144–148]. However, neurobiological evidence suggests that a nAChR containing the α4 subunit is necessary and sufficient for VAR's anti-alcohol effects, potentially implicating the relatively understudied striatal α4α6β2β3 nAChR in both alcohol's acute effects and as a novel treatment target for AUD [78, 142, 149].

Despite the uncertainty about the precise molecular mechanism of action, VAR is thought to produce similar neurobiological and behavioral changes as is observed with nicotine: the nAChR partial agonist effects stimulate VTA dopamine

neurons to reduce basal craving and negative mood, while the functional receptor antagonist effects block alcohol reward or alcohol cue-induced craving. In support, VAR has been shown to reduce alcohol self-administration [150], self-reported alcohol craving [151, 152, 153••, 154], and alcohol and cigarette consumption among general smokers, heavy-drinking smokers, and persons with AUD [151, 152, 153••, 155•]. Interestingly, one study found that varenicline increased dysphoria and tended to reduce alcohol liking ratings following a controlled alcohol administration in the laboratory, suggesting that varenicline may potentiate the aversive effects of alcohol [156]. Additionally, VAR may improve alcohol's impairment in attention [156] and reduce expectancy for alcohol's positive effects [157]. However, not all studies have found that VAR reduces alcohol consumption or self-administration [154, 157, 158]. Of note, there is also interest in studying other medications for AUD because of their effects on nAChRs. Mecamylamine, a general nAChR antagonist, blocks the rewarding effects of alcohol in rodents [159] and humans [160], but the results from the first clinical trial testing its effects on alcohol consumption have not been reported (NCT00342563).

Together, these findings suggest that varenicline is an effective treatment for TUD and may have therapeutic effects on alcohol use as well. Therefore, VAR may be a particularly promising pharmacotherapy for heavy-drinking smokers, as VAR's ability to blunt alcohol's positively reinforcing effects, potentiate alcohol's aversive effects, and attenuate basal alcohol craving may produce an overall reduction in alcohol consumption. Such beneficial changes in alcohol consumption and cue reactivity may promote smoking abstinence in heavy-drinking smokers [161•], potentially by reducing the incidence of alcohol-induced smoking lapses. However, the Food and Drug Administration has issued a warning that VAR may affect the manner in which individuals respond to alcohol, including increased intoxication and a rare risk for seizures, and recommends that patients taking VAR decrease alcohol consumption. This warning was not based on findings from controlled VAR clinical or registration trials; instead, it was due to post-marketing reports from patients using VAR who described increased intoxicating effects of alcohol and, in some cases, unusual and aggressive behavior while drinking that was often accompanied by "amnesia" for such events. As this warning was released in 2015, it is presently unclear how this will affect patient and provider receptivity to VAR as a treatment in heavy-drinking smokers, and this potential issue should be closely monitored going forward.

Naltrexone

Naltrexone hydrochloride is a competitive opioid receptor antagonist with the highest affinity for μ-opioid receptors and, accordingly, has been posited to block the hedonically rewarding effects of alcohol and nicotine [63, 83, 87]. Naltrexone is approved for the treatment of alcohol and opioid use disorders. In alcoholism treatment, its primary efficacy is in reducing relapse to heavy drinking [162] by preventing the transition from a lapse into a full-blown relapse [163, 164]. A number of additional studies have found that NTX may also have moderate efficacy in increasing time to first relapse [163, 165, 166] and in reducing relapse rates [167, 168], number of drinking days [167], and the number of drinks per drinking episode [166, 169].

As the endogenous opioid system also contributes to the behavioral effects of nicotine, NTX has been examined as a smoking cessation aid but results have been mixed [170–174]. The 50- or 100-mg dose of NTX shows better treatment outcomes than the 25-mg dose [171–174], which may be attributed to the relatively higher proportion of opioid receptor blockade [175]. The largest trial to date examining 50-mg NTX for smoking cessation recently reported that NTX (plus nicotine patch) improved quit rates over 12 weeks of treatment and lessened the amount of weight gain [171], with the latter finding extending in women through 1 year after the quit date [176]. As recently shown with VAR [177], these results suggest that smoking outcomes are better for NTX when used in conjunction with nicotine patch to alleviate tobacco withdrawal [171, 173, 178].

Although current evidence does not support NTX as an effective stand-alone treatment for smoking cessation [179], it is possible that NTX may be a useful adjunct in smoking cessation for heavy-drinking smokers. In this subgroup, naltrexone has been shown to reduce alcohol- and cigarette-induced smoking urge, the stimulatory effects of cigarettes, and smoking behavior [180–182]. A reanalysis of the COMBINE study found that naltrexone was more effective for the treatment of AUD among alcoholics who were also daily smokers than in nonsmokers [13•]. Furthermore, secondary analyses of three smoking cessation trials with NTX have indicated that heavy-drinking smokers were preferentially responsive to NTX, with NTX producing a twofold higher smoking quit rate in this group compared with placebo [183•] while also reducing alcohol consumption [183•, 184, 185]. Naltrexone's effect on heavy-drinking smokers' quit rates was mediated by its effect on reducing smoking urge but not by its reduction in drinking [183•], which may suggest independent mechanisms of action for NTX on reducing smoking and drinking in heavy-drinking smokers, but further studies are needed to elucidate this possibility.

Combined Varenicline and Naltrexone Therapy

It has become increasingly apparent that alcohol and tobacco co-use is a complex biobehavioral problem that requires novel and multifocal treatment approaches. The existing monotherapies for TUD and AUD have shown moderate efficacies at best [141, 162]. Therefore, a combination of

pharmacotherapies may be more effective at addressing the complex nature of heavy-drinking smokers. The selection of treatment combinations requires careful evaluation and ideally consists of two pharmacotherapies with compatible and synergistic behavioral and pharmacological mechanisms of action [186]. The combination of NTX and VAR represents one such potential combination.

A recent human laboratory study has shown that short-term treatment with the combination of VAR and low-dose NTX (25 mg) was superior to both monotherapies and placebo in reducing alcohol-induced cigarette craving and better than placebo at attenuating smoking intensity [187•] and subsequent craving while smoking the first cigarette of the day [187•, 188••, 189]. These results are consistent with the notion that VAR reduces cigarette craving and attenuates the positive reinforcing effects of smoking through the blockade of $\alpha4\beta2$ nAChRs [75, 127, 128, 135]. Additionally, the combination of VAR + NTX was superior to placebo, and at times monotherapies, in attenuating alcohol and cigarette "high" during the experiment, as well as reducing drinks and cigarettes per drinking day during the 9-day medication titration period before the experimental session. Finally, a subset of participants from this study also completed a neuroimaging session, which found that the combination of VAR + NTX was associated with reduced activation of the anterior cingulate cortex in response to cigarette cues compared with placebo and NTX [189]. While these laboratory studies suggest that the combination of VAR + NTX may be an effective smoking cessation strategy to improve quit rates and reduce alcohol use in heavy-drinking smokers, clinical studies of this combination are needed and are currently underway in order to determine whether combining VAR + NTX yields better clinical outcomes than VAR monotherapy.

Conclusions

This manuscript sought to review the evidence for the behavioral and molecular mechanisms subserving the co-use of tobacco and alcohol and the treatment implications of these mechanisms. Specifically, we focused on heavy-drinking smokers, as they are a sizeable subgroup of daily smokers for whom alcohol use may pose a unique obstacle to successful smoking cessation [11, 12]. Evidence from experimental studies in humans has suggested that alcohol and nicotine act synergistically to reinforce co-use behavior by inducing craving for the other substance, potentiating the rewarding effects of each drug, and blunting alcohol's sedating and impairing effects. This coreinforcement and cue cross-reactivity contributes to increased cigarette and alcohol use within an episode and overtime and likely to the development of comorbid AUD and TUD as well. As we reviewed the molecular underpinning of the co-use of nicotine and alcohol, we argued that the behavioral effects of coadministration are, in part, due to shared pharmacological targets in the acetylcholine and endogenous opioid systems. In translating these findings to pharmacological treatments, we contend that nAChRs and μ-opioid receptors may be promising molecular targets for the development of treatments for heavy-drinking smokers.

Based on the recognition of nAChRs and μ-opioid receptors as plausible targets for pharmacological treatments of heavy-drinking smokers, the evidence for NTX, VAR, and their combination was reviewed suggesting that there may be benefits for each medication alone and also potentially for the combination of these medications as dual therapy. While initial controlled experimental and neuroimaging studies have supported the combination of VAR + NTX over placebo and monotherapy, until additional research is completed, these findings are not yet applicable to clinical populations. Finally, more studies are needed to determine whether behavioral and psychosocial interventions can effectively reduce alcohol and tobacco co-use, either as stand-alone treatment or in conjunction with pharmacotherapy. Development of optimal strategies may be hampered by reduced enthusiasm at granting agencies to conduct research on established or repurposed medications for alcohol addiction, i.e., NIAAA's NOT-AA-14-009, as this also includes clinical studies of such treatments in heavy-drinking smokers. Thus, this particularly high-risk co-using subgroup could be further marginalized in standard treatment programs or physician's offices as there are no guidelines and evidence-based treatments for providers to utilize. Heavy-drinking smokers then will continue to incur health disparities compared with non- and light-drinking smokers in terms of cancer and other early mortality risks.

In conclusion, there is ample evidence from a host of experimental, molecular, and clinical studies that heavy-drinking smokers comprise a unique group of substance users. Elucidating the behavioral and underlying molecular mechanisms subserving alcohol and tobacco co-use has the potential to inform personalized treatments for this subgroup of smokers. This review demonstrated that knowledge deriving from epidemiological data on co-use, behavioral findings from laboratory and in vivo studies, basic bench science, and clinical trials can be better understood and integrated to inform treatment development based on patients' unique vulnerabilities. While much work remains to be done before more effective guidelines of care can be offered to heavy-drinking smokers, this approach holds promise as a road map for implementing precision medicine efforts applying to both AUD and TUD.

Compliance with Ethical Standards

Conflict of Interest Daniel Roche, Megan Yardley, and Andrea King declare that they have no conflict of interest.

Lara Ray has received medication from Pfizer and Medicinova and has consulted for GSK.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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