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Journal
CNS Drugs, 29(10)

ISSN
1172-7047

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Publication Date
2015-10-01

DOI
10.1007/s40263-015-0284-5

Peer reviewed

HHS Public Access

Author manuscript

CNS Drugs. Author manuscript; available in PMC 2016 October 01.

Published in final edited form as:

CNS Drugs. 2015 October ; 29(10): 833–845. doi:10.1007/s40263-015-0284-5.

Pharmacological Options for Smoking Cessation in Heavy Drinking Smokers

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Abstract

There is a high prevalence of comorbid tobacco and alcohol use disorder (AUD), affecting more than 6 million people in the United States. Globally, tobacco and alcohol use rank fourth and fifth, respectively, for disability adjusted life years lost. Levels of alcohol use are higher in smokers than non-smokers, and the prevalence of smoking is higher in heavy drinkers compared to non-drinkers. This relationship is driven by many different factors including genetics, neurobiological mechanisms, conditioning processes, and psychosocial influences. Although this unique population tends to experience more negative health consequences, more severe AUD and poorer response to treatment than those with either AUD or tobacco use disorder alone, there are currently no available treatment protocols tailored to this comorbid condition. Here, we provide a comprehensive review of ongoing clinical research into smoking cessation options for heavy drinking smokers (HDS) through an evaluation of the effect of promising novel pharmacotherapies as well as combination therapies including: varenicline, naltrexone, the combination of varenicline and naltrexone, and the combination of naltrexone and nicotine replacement therapy (NRT). These treatments are considered in light of the standard of care for smoking cessation and seek to improve upon the available guidelines for this sizable subgroup of smokers, namely those smokers who drink heavily.

1. INTRODUCTION

There is a strong positive association between cigarette smoking and alcohol use both at the epidemiologic (1) and neuropharmacological (2) levels, with the former being the focus of this manuscript. In the National Institute of Alcohol Abuse and Alcoholism's (NIAAA) 2001–2002 National Epidemiologic Survey on Alcohol and Related Conditions, more than 6 million Americans reported suffering from comorbid nicotine and alcohol dependence, with over 46 million reporting using alcohol and tobacco within the past year (3). Globally, tobacco and alcohol use rank fourth and fifth, respectively, for disability adjusted life years

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COMPLIANCE WITH ETHICAL STANDINGS

Conflicts of interest: LAR has consulted for GSK and has received study medication from Pfizer and from Medicinova. MMY and MMM have no conflicts of interest to disclose.

lost (1). Of all substances used in combination, alcohol and tobacco are the most frequently paired (4). Levels of alcohol use are higher in smokers than non-smokers, and the prevalence of smoking is higher in heavy drinkers compared to non-drinkers (5–7). In fact, between 50–90% of alcoholics are also dependent on nicotine (8). Almost 20% of current smokers engage in hazardous drinking, consuming 5 or more drinks on one occasion (4 or more for females) at least once per month (7, 9), compared to about 6.5% of nonsmokers (7). Moreover, just over 55% of those with an alcohol use disorder (AUD) smoke compared to 22.5% of lifetime alcohol abstainers (7). A recent study found that 56% of tobacco quitline callers reported drinking and 23% reported hazardous drinking using NIAAA guidelines (10). Importantly, greater alcohol use is associated with decreased odds of smoking cessation (10–12) and it is estimated that smokers are four times more likely to experience a smoking lapse during drinking episodes (12).

The manuscript will focus on pharmacological treatments for smoking cessation in heavy drinking smokers (HDS), with heavy drinking defined as 5 or more drinks on the same occasion on 5 or more days in the past 30 days (13). It is important to highlight that heavy drinking alone hinders smoking cessation, and tailored treatments should start at the heavy drinking mark, as opposed to an AUD. HDS experience more negative health consequences, such as impairments in brain morphology and function (14) and greater risks for cardiovascular disease and various cancers (15). There is also evidence suggesting that nicotine dependent individuals tend to experience more severe alcohol dependence (16) and poorer response to alcohol treatment (17). Given the co-occurrence of smoking and drinking, it has been convincingly argued that HDS constitute a distinct sub-population of smokers with a unique clinical profile and specific treatment needs (2, 18). Despite these epidemiological findings suggesting that HDS constitute a sizable and treatment-resistant subgroup, there are no available pharmacological treatments tailored to these patients. Given that alcohol and smoking use have a relatively high co-occurrence rate and represent a distinct population with unique treatment requirements, we will begin with a review of the mechanisms of interaction between alcohol and nicotine, discuss general pharmacological guidelines for smoking cessation and then introduce suggested pharmacological treatment options for HDS.

2. MECHANISMS OF INTERACTION BETWEEN ALCOHOL AND NICOTINE

The link between heavy drinking and smoking is thought to be driven by many factors including genetics, neurobiological mechanisms, conditioning processes, and psychosocial influences (19). It is widely recognized that both tobacco use disorder (TUD) and AUD have a shared genetic etiology based on the numerous family, twin and adoption studies that have been conducted, with each having a heritability of approximately 60% (20–22). Although there are known genetic regions independently linked to alcohol and smoking use, several studies suggest there are also shared genetics across the two, providing support for a genetic component to this comorbid phenotype (22–24).

The potential overlap in alcohol and nicotine neurobiology likely contributes to the high frequency of these substances being paired. Nicotine and alcohol share numerous neural targets within the mesolimbic dopamine (DA) pathway including γ-aminobutyric acid

receptors (GABARs), glutamate receptors, 5-hydroxytryptamine receptors (5-HTRs), nicotinic acetylcholine receptors (nAChRs), the endocannabinoid system and the μ-opioid system [for review see (25)]. Animal self-administration studies demonstrating that both nicotine and alcohol, among other drugs of abuse, have reinforcing properties and lead to an increase in DA release in the nucleus accumbens (NAc), support the role of the DA system in both disorders. This neurobiological overlap likely facilitates the cross-tolerance and cross-reinforcement that occur [for review see (26)] (27, 28).

While the exact neurobiological mechanisms that promote the co-use between alcohol and nicotine use are still being explored, there are two probable means that have become the focus of investigation [for review see (26)]. The first possibility is via negative reinforcement: one drug decreases the negative effects associated with the other. There have been multiple studies supporting the negative reinforcement theory conducted in both cerebellar granule cells obtained from Sprague Dawley rat embryos and a rat model of binge drinking (29, 30). In the first study, Tizabi and colleagues found that pretreatment of the cells with nicotine resulted in a dose-dependent neuroprotective effect against the ethanol-induced toxicity and that these protective effects could be blocked by nicotinic antagonists (30). In the second study, Penland and colleagues demonstrated that nicotine was able to reduce alcohol-induced neurotoxic effects in the olfactory bulb in rats after a 4-day ethanol binge treatment (29). Numerous clinical studies have looked at the effects of the combined use of alcohol and tobacco and although the results are somewhat mixed (31, 32), there is evidence that nicotine may have protective effects in regards to cognitive deficits (33), motor incoordination (34), sedation and intoxicating effects associated with alcohol use [for review see (35–38)]. However, a study conducted by Piasecki and colleagues evaluating subjective effects related to the co-use of alcohol and tobacco provided little support for the negative reinforcement theory (39).

The second possibility that has garnered attention is the positive reinforcement model, whereby one drug increases the positive reinforcing effects associated with the other [for review see (26)]. Although the Piasecki study described above did not find support for the negative reinforcement theory, their results do support that the frequent co-use of alcohol and tobacco is, in part, driven by positive reinforcement (39). They reported that when alcohol and tobacco were used concomitantly, alcohol produced a modest increase in the self-reported pleasure from smoking and tobacco produced a relatively smaller increase in the pleasure from consuming alcohol. Similarly, a study conducted by Rose and colleagues found that alcohol enhanced certain subjective rewarding effects of nicotine including satisfaction, liking and calming effects (38). Tizabi and colleagues demonstrated that co-administration of alcohol and nicotine in rats increased dopamine (DA) release in the nucleus accumbens shell, oftentimes used as a quantitative measure of the rewarding effects of a drug, compared to either drug alone (40). These findings suggest that the co-use of alcohol and tobacco produces an additive effect in regards to DA release and could result in increased rewarding effects compared to either drug alone. For both the positive and negative reinforcement theory, it is important to note that there is evidence suggesting the effect of nicotine on alcohol differs by sex such that one study found a trend suggesting nicotine increased alcohol consumption in men but decreased alcohol consumption in women (41).

Alcohol and smoking-related cues can elicit conditioned responses such as increased urge to drink or smoke, respectively [for review see (19, 42)]. Interestingly, in a laboratory study by Gulliver and colleagues, exposure to alcohol cues increased the participants' urge to smoke (43). Conditioning mechanisms related to addiction, including environmental, visual and sensory cues appear to play an important role in the high incidence of tobacco and alcohol co-use [for review see (19)]. Not surprisingly, alcohol consumption has also been shown to increase urge to smoke (44). In a laboratory study conducted by King and colleagues, alcohol consumption, compared to placebo, increased urge to smoke in both men and women heavy social drinking smokers, however, alcohol increased smoking behavior (i.e., puff count, volume and duration) in men only suggesting that the interactions between alcohol and smoking may differ between sexes.

The high prevalence in the co-use of alcohol and tobacco can also be, in part, facilitated by psychosocial mechanisms [for review see (19)]. One possible reason why the co-use remains relatively high is that these are both legal substances and are easily accessible (45). As reviewed by Flay and colleagues, psychosocial factors that influence both alcohol and tobacco use include, but are not limited to, personality, social and academic aptitude, and sense of self. These characteristics play an important role in the development of many addictions [for review see (46)]. Additional psychosocial factors to consider include family and social environment as individuals exposed to alcohol and tobacco use are more likely to engage in these behaviors [for review see (19)].

3. MANAGEMENT OF NICOTINE DEPENDENCE

Treating TUD remains extremely challenging for clinicians, as only about one-fifth of people with this disorder express a willingness to quit, and approximately half of those who seek treatment do not receive all required doses or complete all scheduled counseling sessions (47). Further, 95% of smoking cessation attempts that do not involve evidence-based therapies ultimately fail (47). However, great strides have been made in the field, as evidenced by the numerous treatment options available that have been shown to improve smoking cessation outcomes. These include psychosocial treatments such as intensive counseling and cognitive behavioral interventions, and pharmacotherapies including nicotine replacement therapy (NRT), bupropion and varenicline [for review see (48)]. For the purposes of this paper, we will focus solely on the pharmaceutical interventions that are available and approved by the Food and Drug Administration (FDA) to aid in smoking cessation.

3.1. Nicotine Replacement Therapy

Nicotine replacement therapies have been available for more than 30 years and are approved for many routes of administration including transdermal patch, gum, inhaler, lozenge and intranasal spray (47). Each form of NRT appears to be equally effective for increasing the odds of smoking cessation, such that the choice should be based on patient preference (49). The principle of NRT is to offer agonist treatment in sufficient doses over an extended period of time, combined with psychosocial and behavioral treatments, and taper doses gradually to avoid withdrawal symptoms. In 2013, a meta-analysis conducted by Cahill and colleagues found that NRT increased odds of smoking cessation compared to placebo over a

6-month period (49). However, despite these seemingly promising results, it appears that similar to other smoking cessation treatments, less than a quarter of individuals treated with NRT remain abstinent after one year (50). Failure of NRT usually results from use of insufficient nicotine doses, treatment duration and/or infrequent dosing administration, as the half-life of nicotine is 60–90 minutes. Importantly, although the efficacy of each form of NRT is comparable, the use of multiple routes of NRT administration simultaneously (specifically, long- and short-acting forms combined) has been shown to improve smoking cessation outcomes at 6 months compared to use of a single form of NRT (49).

3.2. Bupropion

Bupropion represents the first non-nicotine medication approved for the treatment of TUD. Although the exact mechanism of action of bupropion as a smoking cessation agent remains unknown, preclinical and clinical studies point to several possible mechanisms, including inhibition of the DA transporter (DAT), inhibition of norepinephrine transporters, and competitive antagonism of nicotine at nAChRs (51). These mechanisms serve to increase both dopaminergic and noradrenergic neurotransmission in the midbrain and frontal cortex, while putatively blunting the effects of nicotine. Numerous studies indicate that treatment with bupropion leads to improved treatment outcomes compared to placebo (49, 52). Although there is some evidence to suggest that bupropion (sustained release; SR) can be used effectively in conjunction with NRT in specific populations (48, 53), the majority of studies do not indicate improved smoking cessation outcomes with the combination of bupropion and nicotine gum (54), bupropion and nicotine patch (55, 56) or bupropion and various single forms of NRT (57). There are two FDA black box warnings for bupropion including a risk of adverse neuropsychiatric events (e.g., behavioral changes, hostility, agitation, depression, etc.) and suicidal ideation or suicidal behaviors in children, adolescents or young adults with major depressive disorder; however, the meta-analysis described above found no evidence of increased neuropsychiatric events with use of bupropion compared to placebo (49).

3.3. Varenicline

More recently (in 2006), varenicline was approved for the treatment of TUD. Varenicline is a partial agonist at multiple heteromeric nAChRs including $\alpha_4\beta_2$ (58), $\alpha_3\beta_4$ (59) and $\alpha_6\beta_2$ nAChRs (60) and a full agonist at α_7 nAChRs (61). Varenicline prevents nicotine from binding to nAChRs and, as such, decreases the associated rewarding effects, while its action as a partial $\alpha_4\beta_2$ agonist appears to attenuate withdrawal symptoms and reduce cravings (58). In the meta-analysis described above conducted by Cahill and colleagues, varenicline was found to be superior to both single forms of NRT and bupropion in achieving smoking cessation over a 6-month period (49). Varenicline and combination NRT appear to have similar efficacy, which has led some researchers to conclude that either varenicline or combination NRT should be used as first-line pharmacotherapies for the treatment of TUD (49, 62). Concomitant use of NRT with varenicline, however, has been associated with increased side effects, and is currently not recommended (48).

3.4. Summary

A number of pharmacological treatments have been developed for nicotine dependence. NRT appears to be modestly effective, presumably by decreasing withdrawal (63). Bupropion is another medication with moderate effectiveness. Lastly, varenicline has been approved for the treatment of TUD and a number of clinical trials found that it is more effective than bupropion (64), superior to NRT (65), and significantly more effective than placebo (64, 66–69) as a smoking cessation agent. In view of the current available data, varenicline is the most efficacious pharmacologic treatment for long-term outcomes in TUD, with combination NRT being a suitable first-line alternative. Although there is some support suggesting varenicline has enhanced effectiveness when combined with NRT [for review see (70)], further studies are needed to fully understand this effect and special considerations need to be given to individuals with certain comorbid conditions. However, it should be noted that abstinence rates with varenicline after 12 weeks and 1 year are approximately 43% and 25%, respectively (71). Thus, even though varenicline is superior to other treatments, there is a clear opportunity to improve upon these clinical outcomes, particularly among subgroups such as HDS that are difficult to treat. Although beyond the scope of this manuscript, it is important to note that clinical guidelines suggest that smoking cessation interventions should employ both pharmacotherapy and psychosocial treatment (72). Psychosocial or behavioral interventions can range from individual behavioral counseling which can include motivational interviewing to group behavior therapy to the use of self-help materials to telephone counseling (e.g., 1-800-QUIT-NOW) and the use of new technologies such as text messaging services (e.g., txt2stop and txt2quit).

4. TREATMENT OPTIONS FOR HEAVY DRINKING SMOKERS

Despite the high prevalence and known health consequences associated with co-occurring tobacco use and heavy drinking, there are no available treatments tailored to this subgroup of smokers that have been approved by the FDA. Current clinical guidelines recommend treating both TUD and AUD simultaneously, highlighting the need for effective treatments for this population (48). Recent clinical trials have investigated the use of several medications in HDS, including varenicline, naltrexone, the combination of naltrexone and NRT, and the combination of varenicline and naltrexone. Next, we review the evidence for each medication and the relevant combination therapies for the treatment of HDS given that heavy drinking alone hinders smoking cessation, and tailored treatments should start at the heavy drinking mark, as opposed to an AUD. Table 1 has been developed to summarize key positive findings from animal studies, behavioral pharmacology studies and clinical trials supporting the use of these pharmacotherapies as novels treatments for HDS.

4.1. Varenicline

Based on preclinical studies indicating varenicline reduces ethanol intake in rodents (73), there is now growing evidence suggesting that varenicline, already FDA-approved for smoking cessation, is effective in treating HDS (74–76). Studies have suggested that alcohol produces mesolimbic activation through its effects on nAChRs (77–79). Therefore, there is considerable enthusiasm for varenicline as a possible treatment for AUD as well as the co-abuse of alcohol and nicotine (2). Preclinical studies have found that varenicline decreases

ethanol self-administration in rats (73, 80). Recent human studies of varenicline for alcohol use found that, compared to placebo, varenicline reduced alcohol self-administration in the human laboratory (76), as well as alcohol craving (74) and alcohol consumption (74, 75) in smoking cessation trials. 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 (81).

Although varenicline carries a FDA black box warning for increased risks of serious neuropsychiatric events in individuals with or without pre-existing psychiatric illnesses, recent meta-analyses have demonstrated no statistically significant increase in neuropsychiatric events (49, 82, 83). In March 2015, the FDA issued labeling changes for varenicline following post-marketing surveillance reports from the manufacturer. These reports indicated varenicline may lower alcohol tolerance, leading to increased drunkenness, unusual or aggressive behaviors and/or amnesia to such events with exposure to alcohol, and may cause a rare risk of seizures (less than 1%) in individuals who have no prior history of seizures, or had a seizure disorder that was remote or had been well-controlled prior to use of varenicline (84). The risk of seizures was greatest in the first month of treatment with varenicline, and presently the FDA recommends that individuals decrease their alcohol consumption while initiating varenicline to determine if the medication has any effect on their tolerance. This is an important consideration in the context of varenicline treatment of HDS. Together, these studies suggest that varenicline is an effective treatment for smoking cessation and that it may have beneficial effects on alcohol use as well.

4.2. Naltrexone

Naltrexone is an opioid receptor antagonist with established efficacy, albeit moderate, for the treatment of AUD. Shortly after two initial trials suggested that naltrexone resulted in significantly fewer drinking days and lower rates of relapse after three months of treatment (85, 86), naltrexone was regarded as one of the more promising pharmacological interventions for AUD (87). These initial results have been largely supported by more recent trials of naltrexone that generally demonstrate beneficial effects on heavy drinking rates, particularly among those who are compliant with the medication (88–91). Studies have found that naltrexone reduces the occurrence of heavy drinking days (89, 92, 93), increases time to first relapse (91, 94, 95), yields lower relapse rates (85, 96, 97), reduces the number of drinking days (85, 86), the number of drinks per drinking episode (86, 88, 90, 94), and the latency to first and second drink among social drinkers (98). However, the support for naltrexone is not uniform. A few trials found no significant outcome differences between naltrexone and placebo treated-patients (99, 100). Most recently, in 2006, naltrexone was tested in the large, multi-site, COMBINE Study and was superior to placebo when delivered in combination with medical management (101), which advanced naltrexone as a first-line of treatment for AUD.

The neurobiological literature has recognized a role for the endogenous opioid system in modulating responses not only to alcohol, but to nicotine as well [for review see (102)]. As such, naltrexone has been evaluated as a stand-alone as well as an adjunctive treatment to

smoking cessation. A randomized controlled trial conducted by O'Malley and colleagues found that naltrexone (25 and 50 mg/day) combined with open-label transdermal nicotine patch reduces drinking even among heavy drinking smokers who are not seeking treatment for alcohol problems compared to placebo combined with a nicotine patch (103). Similar results were found in a clinical trial by King and colleagues who reported that naltrexone, compared to placebo, reduced number of cigarettes smoked, smoking urge and number of alcoholic drinks consumed (104). Two laboratory studies suggest naltrexone reduces urge to smoke during alcohol exposure in HDS (105) and attenuates smoking behavior (106) in chronic smokers. Similarly, a double-blind, placebo-controlled, randomized study found that naltrexone improved smoking quit rates (107). An exploratory study conducted by King and colleagues found that not only did naltrexone reduce weekly heavy drinking rates but also that naltrexone may preferentially improve smoking quit rates in HDS (108). Providing support to this assumption, re-analysis of the COMBINE Study found that naltrexone is more effective for the treatment of alcoholism in daily smokers than non-smokers (17). However, when naltrexone was used as an adjunct to smoking cessation, along with counseling and nicotine patches, naltrexone produced significantly higher quit rates than placebo but only at higher levels of depressive symptoms (109) or among females (110, 111).

Although naltrexone appears to be more effective as an adjunct pharmacotherapy for a subgroup of smokers, particularly HDS, this combination is only recently beginning to be investigated as a treatment option for this population. While several studies indicate no benefit of naltrexone plus NRT compared to placebo plus NRT for smoking cessation (49, 110, 112–114), others demonstrate this combination produces significant reductions in smoking rates (111, 115, 116). Remarkably, subgroup analyses in one of the negative studies (110) and one of the positive studies (111) found preferential efficacy of combination treatment for smoking cessation in women compared to men. Given the paucity of data and mixed results, we cannot conclude that the combination of naltrexone with NRT is an effective treatment for HDS, although varenicline plus naltrexone with NRT augmentation may be a robust treatment option for future research.

4.3. Combination of varenicline and naltrexone

It has been increasingly recognized that complex biobehavioral problems such as co-morbid alcohol and tobacco use require novel and multifocal treatment approaches. The rationale for adding naltrexone to varenicline for smoking cessation in HDS is based on the recognition that HDS are more prone to a smoking lapse during drinking episodes (12); hence a medication that helps patients reduce drinking may help them maintain smoking abstinence by preventing alcohol-related smoking lapses. The existing monotherapies for smoking, including varenicline, have shown moderate efficacy at best (71, 117). Therefore, a combination of pharmacotherapies may be more effective at addressing the complex nature of TUD, particularly among this treatment-resistant group of HDS. Specifically, effective treatment combinations may be composed of two pharmacotherapies with compatible neuropharmacological mechanisms of action as well as compatible influences on behavior.

Based on the known pharmacological and behavioral effects of both naltrexone and varenicline, the combined use of these medications has been of particular interest as a possible treatment option for this high-risk group comprised of heavy drinking daily smokers. In recent studies, the combination of varenicline (1 mg b.i.d.) and low dose naltrexone (25 mg daily) has been shown to decrease both alcohol consumption and cigarette use in HDS compared to placebo (118). This dose was based on a dose-response study of naltrexone as an adjunct to smoking cessation that found benefits on drinking behavior at 25 mg daily, which in turn has a more favorable side-effect profile (103). In this double-blind, placebo-controlled, randomized study HDS (n=130) were given either varenicline, low dose naltrexone, a combination of varenicline and low dose naltrexone or placebo and tested after a 9-day titration period (118). Experimental sessions commenced following 12 hours of nicotine abstinence, administration of a standard dose of alcohol and smoking the first cigarette of the day. Craving for cigarettes, changes in mood, alcohol and cigarette high, alcohol and cigarette use during the 9-day titration period and adverse events were assessed during the experimental session. Interestingly, the combination of varenicline and low dose naltrexone was more effective than either medication alone and placebo for reducing post-alcohol craving for cigarettes and post-alcohol alcohol high feeling (*p*s< 0.05) in HDS. Specifically, the combination of varenicline and low dose naltrexone decreased post-alcohol craving for cigarettes by 15%, 13.2% and 12.7% more than varenicline, low dose naltrexone and placebo, respectively. Similarly, this combination decreased post-alcohol high feeling by 23.1%, 22.7% and 22% compared to varenicline, low dose naltrexone and placebo, respectively. The combination treatment decreased post-cigarette cigarette craving 6.6% more than placebo ($p<0.05$) and post-cigarette cigarette high feeling 33.0% more than low dose naltrexone ($p<0.05$) and 34.7% more than placebo ($p<0.01$). Finally, the combination of varenicline and low dose naltrexone decreased drinks per drinking day compared to placebo ($p<0.05$) and cigarettes per day compared to naltrexone alone and placebo (*p*s<0.05) during the 9-day titration period, all by approximately 25%.

In additional to clinical studies and laboratory paradigms, brain-imaging studies have provided additional insight into the efficacy of novel pharmacotherapies for HDS. A neuroimaging analysis of a subset of patients in the laboratory study by Ray and colleagues, found that the combination of varenicline and low dose naltrexone was associated with reduced activation of the bilateral anterior cingulate cortex during the presentation of visual cigarette cues when compared to placebo or naltrexone alone, suggesting that the combination of varenicline and low dose naltrexone may be effective in attenuating craving for cigarettes in this population of smokers (119). The combination therapy did not provide any additional benefit over monotherapy in terms of NAc activation during cigarette cues as compared to placebo, suggesting that both medications, used either alone or in combination, reduce neural signals associated with appetitive drives. Lastly, analysis evaluating the effect of the combination of naltrexone and varenicline on smoking topography in the same sample who completed the laboratory study, found this combination modulates smoking topography via attenuation of puffing behavior in HDS (120). Though there are only a few studies on the combination of varenicline and naltrexone, and they mostly consist of analyses of the same sample of HDS, the current evidence suggests promise for this combination as an effective treatment for HDS. Combining pharmacotherapies appears to offer significant advantages

over monotherapies, such as permitting the use of lower doses of each component to achieve a given level of efficacy (121). Importantly, combined treatments may facilitate tailoring of pharmacotherapies to the needs of individual patients, such as treatment augmentation in non-responders or patients with special needs (e.g., heavy drinkers, patients with psychiatric conditions, cancer patients) thereby addressing one of the challenges outlined by Lerman and colleagues (117).

4.5. Summary

Though there are currently no FDA-approved treatments for HDS, recent studies have focused on evaluating the effect of several medications and combinations of medications to treat this population of smokers. Human laboratory studies testing the effect of medication on alcohol and smoking use in HDS have demonstrated positive results for the combination of varenicline plus low dose naltrexone and the combination of NRT plus naltrexone, although the combination of varenicline and naltrexone appears to be the most promising. In particular, the evidence suggests that varenicline alone may reduce drinking (122) and that naltrexone may promote smoking cessation, but only among those smokers who are also heavy drinkers (108). Thus, triangulating these lines of evidence suggests that the combination of varenicline and naltrexone may be especially helpful to those smokers who drink heavily, and in fact, this is supported by human laboratory (118, 120) and neuroimaging findings (119). Ultimately, clinical trials of treatment-seeking HDS are needed to determine whether the combination is superior to monotherapy, particularly varenicline, the field standard for smoking cessation, at promoting abstinence from smoking and reducing drinking in this population. As with other smoking cessation trials, NRT augmentation or utilization may also boost overall outcomes across the varenicline only and the varenicline plus naltrexone groups. A more liberal approach towards NRT, even in the context of combination pharmacotherapy, is generally supported by the literature as a way to improve overall outcomes across conditions. Currently, there are no studies demonstrating the synergistic effects of varenicline or naltrexone with NRT in HDS. Similar to smoking cessation interventions, clinical guidelines support the concurrent use of pharmacotherapy and behavioral interventions for smoking cessation in HDS (72).

5. REMAINING QUESTIONS

While the current research regarding treatment development for HDS is growing, there are certain concerns that remain in the quest for successful treatment regimen for this unique, hard to treat population. First, one of the more promising medications to treat this population, varenicline, appears to potentiate the aversive effects of alcohol and has been associated with a risk of seizures, which could lead to an increase in severe adverse events in individuals who experience complicated alcohol withdrawal (81). Furthermore, surveillance reports from the manufacturer indicate that varenicline may lower alcohol tolerance leading to increased drunkenness, unusual or aggressive behaviors, and/or amnesia to such events with exposure to alcohol (84, 123). More research needs to be conducted to determine the risk factors associated with these adverse events such as number of heavy drinking days, drinks per drinking day, genetic determinants, etc. Furthermore, as current clinical guidelines recommend treating both TUD and AUD simultaneously (48), it is important to

extend this research to individuals seeking treatment for AUD. Likewise, treatments that simultaneously target smoking cessation and drinking outcomes are sorely needed. Given the documented sex differences regarding the interactions between alcohol and nicotine (44), and different response to smoking cessation treatments (124), more research is needed to understand these differences and subsequent effect on smoking cessation medications. Taken together, successful medication development for HDS represents a critical challenge, especially considering only about one fifth of smokers from the general population are able to remain abstinent for one year with the use of an available FDA-approved smoking cessation medication (125). Emerging research in this area suggests that the combination of varenicline and naltrexone may be especially useful given that heavy drinking constitutes a significant obstacle to smoking cessation and the fact that both naltrexone and varenicline, have each shown promise for reducing drinking. Additional studies examining this combination in the context of a treatment that targets both smoking cessation and drinking reduction are underway and will ultimately inform whether the mechanistic findings (from the laboratory and neuroimaging) can be translated into improved clinical care for this hard-to-treat and sizeable subgroup of smokers.

6. CONCLUSION

There is a high prevalence of co-use of alcohol and tobacco and it is well established that nicotine dependent patients tend to experience more severe alcohol dependence and poorer response to alcohol treatment. As such, HDS constitute a distinct sub-population of smokers with a unique clinical profile and specific treatment needs. Currently, there are three FDA-approved medications for smoking cessation: NRT, bupropion, and varenicline. Though there are no available tailored treatments for HDS, this article discusses four promising options that are being investigated as possible treatments for HDS: varenicline, naltrexone, the combination of varenicline plus naltrexone, and the combination of naltrexone plus NRT, with the combination of varenicline plus naltrexone representing the most promising treatment option for HDS based on recent human laboratory and neuroimaging analyses. While this review was centered around pharmacological treatments, it should be noted that ongoing efforts to target HDS through behavioral interventions are also underway given the recognition that this subgroup has special treatment needs and that some level of drinking reduction may be necessary for successful and long-lasting smoking cessation (126, 127).

In this vein, additional studies are warranted to evaluate smoking cessation treatments in treatment-seeking HDS, particularly clinical trials of the combination of varenicline plus naltrexone, which may be superior to the field standard of varenicline, for this subgroup of smokers. In conclusion, this review highlights the need to consider HDS as a subgroup with unique treatment needs. This is important as it moves the field beyond the requirement that HDS have an AUD diagnosis by highlighting that heavy drinking alone hinders smoking cessation, and tailored treatments should start at the heavy drinking mark, as opposed to an AUD. This review also discusses opportunities for medication development for this subgroup of smokers, with a promising approach comprising of the combination of varenicline and naltrexone, along with the liberal use of NRT products. This recommendation, while promising, awaits support from clinical trials and is currently based entirely on experimental studies. As the field of smoking cessation continues to mature,

understanding subgroups, particularly those who are resistant to standard treatments, will ultimately lead to more effective and tailored treatments that can effectively target unique mechanisms of risk in broader populations.

Acknowledgments

Funding: This work was supported by the following grants: F32 AA023449 (MMY), R01 AA021744 (LAR), R21 AA022214 (LAR) and R21 AA022752 (LAR).

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Key Points

- There is a strong positive association between cigarette smoking and alcohol use both at the epidemiologic and neuropharmacological levels
- Greater alcohol use is associated with a decreased odds of achieving smoking cessation
- The combination of varenicline plus naltrexone represents the most promising option for achieving smoking cessation in heavy drinking smokers, based on recent human laboratory and neuroimaging analyses

Table 1

Summary of key positive findings on medications for heavy drinking smokers (HDS) across levels of analyses.

	Preclinical	Laboratory	Clinical
Varenicline (VAR)	• Attenuated the additive dopamine increase observed with the co-administration of alcohol and nicotine (128) • Decreased alcohol seeking in an operant conditioning paradigm and alcohol consumption in animals chronically exposed to alcohol (73)	• Decreased alcohol craving, heavy drinking days and number of cigarettes smoked over 8 week study (extended pretreatment only) (74) • Decreased cigarettes smoked during breaks and number of drinks consumed; Increased likelihood of remaining abstinent during self-administration period (76)	• Decreased cumulative cigarette and alcohol consumption over 16-week study (75)
Naltrexone (NTX)	• Decreased conditioned stimulus-reinstated responding on the active lever in reinstatement and extinction tests (129)	• Decreased progression of craving for cigarettes at higher levels of BrAC (105) • Reduced weekly heavy drinking rates and preferentially improved smoking quit rates in HDS (108) • Reduced the reinforcing effects of nicotine compared to placebo (130)	• Decreased number of cigarettes smokes, smoking urge and number of alcoholic drinks consumed (104) • Improved smoking quit rates and urge to smoke during 12 week study (107)
NTX + NRT		• Increased continuous smoking abstinence rates and reduced desire to smoke (116)	• Improved continuous smoking abstinence rates among completers (115)
VAR + NTX		• Decreased cigarette craving, cigarette and alcohol high, and consumption of cigarette and alcohol during 9-day titration period 4 (118) • Reduced activation of the bilateral anterior cingulate cortex during presentation of visual cigarette cues (119) • Blunted puff duration and velocity trajectories compared to placebo; Decreased mean puff volume vs. placebo and monotherapies (120)	

brAC – breath alcohol concentration; NRT – nicotine replacement therapy.