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ALCOHOL (RF LEEMAN, SECTION EDITOR)

"Killing Two Birds with One Stone": Alcohol Use Reduction Interventions with Potential Efficacy at Enhancing Self-control

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Abstract We review interventions with empirical support for reducing alcohol use and enhancing self-control. Although any intervention that reduces drinking could improve self-control, we focus here on interventions with evidence of direct benefit for both indications. Although no intervention yet has strong evidence for dual efficacy, multiple interventions have strong evidence for one indication and solid or suggestive evidence for the other. Among pharmacotherapy, opioid antagonists currently have the best evidence of efficacy at reducing alcohol use and enhancing self-control. Nicotinic partial agonist varenicline also seems to be efficacious for alcohol use and self-control. Many psychosocial and behavioral interventions (e.g. cognitive behavioral therapy, contingency management, mindfulness training) may have efficacy for both indications, on the basis of purported mechanisms of action and empirical evidence. Cognitive bias modification and neurophysiological interventions have promise for alcohol use and self-control, and warrant further research. We offer several other suggestions for future research.

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Introduction

Self-control has been defined as restraint exercised over one's own impulses, emotions, or desires [1], and encompasses several domains. Impulsivity, arguably the best studied of all self-control difficulties, is a multifaceted construct [2, 3•] entailing "a predisposition toward rapid, unplanned reactions to internal or external stimuli with diminished regard to the negative consequences of these reactions to the impulsive individual or others" [4, 5]. Impulsive behaviors are often theorized to result from an imbalance between competing tendencies: responding to salient internal or external stimuli (sometimes referred to as "activation"[6]), and inhibiting prepotent responses (sometimes referred to as "inhibition"[6]). According to these dual process theories, impulsive behaviors may reflect an excessive tendency to respond and/or inability to inhibit responses adaptively [7•, 8, 9]. Ability to focus attention optimally, even in the face of distraction, is believed to be essential to inhibiting prepotent responses [10, 11]. Attention is also highly relevant to alcohol misuse: frequent heavy drinkers often have a bias toward attending to alcohol-related stimuli in their environment [12], and several studies have reported that attentional bias to alcohol cues prospectively predicts alcohol-related outcomes (e.g. [13, 14]).

Executive functions also have an important effect on ability to inhibit prepotent responses. Like the term "impulsivity," "executive function" is an umbrella term that encompasses several cognitive operations involving the coordination of sub-processes to facilitate complex cognitive processes [15]. Working memory, which enables both short-term retention of information and active manipulation of this information [16], is an aspect of executive function with strong relevance to impulsivity and substance use [17]. For instance, people with better working memory capacity may be better able to inhibit attentional focus on substance-related cues in the environment [18], which could have implications for impulsive behavior and likelihood of substance use.

In addition to impulsive responses, individuals make impulsive decisions or choices when they favor immediate and certain outcomes over distant and less certain ones to an inordinate degree. Excessive preference for immediate outcomes is often referred to as delay discounting, whereas excessive preference for certain outcomes is often referred to as probability discounting [19, 20•].

Difficulties with self-control and addictive behaviors are closely related in several respects (see [21, 22] in this section). Difficulties with self-control longitudinally predict alcohol involvement. Impulsive adolescents are at greater risk of subsequent heavy alcohol and/or drug use, which, in turn, is associated with greater likelihood of an alcohol use disorder (AUD) [23]. Relationships between alcohol use and impulsivity and/or related constructs are likely to be reciprocal. Impulsivity predisposes individuals to alcohol misuse and related problems, and heavy alcohol use is associated with subsequent increases in impulsivity among college students ([24•], though see [25•]). Alcohol use probably also affects self-control over the longer term. Alcohol-dependent older adults have frontal-lobe volume losses [26], suggesting possible compromised executive functioning and poorer self-control as a result. Acute alcohol use can also lead to more impulsive action: in particular, greater difficulties inhibiting automatic, prepotent responses (see [27•]).

Neurobiological and genetic evidence also support close relationships between alcohol involvement and difficulties with self-control. Problem alcohol use and difficulties with self-control are associated with atypical function in similar brain regions (e.g. prefrontal cortex (PFC), ventral striatum; [28]) and in common neurotransmitter and peptide systems, for example dopamine, serotonin, and endogenous opioids [29, 30]). Genetic studies have found common risk factors for self-control difficulties including conduct disorder and substance-use disorders [31] (see also [22], this section). Conduct disorder is a psychological condition diagnosed in childhood or adolescence, and is characterized by a pattern of repetitive and persistent behavior in which basic rights of others or age-appropriate norms are violated. Conduct disorder is often regarded as a precursor to antisocial personality disorder [32].

Given the strength of the relationship between alcohol use and difficulties with self-control, those who successfully reduce their alcohol use in treatment are likely to have greater subsequent self-control. It is also advantageous to target self-control enhancement directly. Although clearly related to alcohol misuse, self-control difficulties tend to predate alcohol use [33]. Furthermore, impulsive individuals are at greater risk of relapse after alcohol treatment [34].

Although any intervention that reduces alcohol use could lead to parallel enhancement of self-control, we have focused on alcohol reduction interventions for which there is evidence suggesting a direct benefit of enhancing self-control. Interventions could enhance self-control by targeting any of the cognitive operations and patterns of impulsive behavior discussed above, including difficulty inhibiting prepotent responses, delay discounting, and working memory. Given the focus on alcohol, we report evidence from alcohol studies wherever possible; however, when no alcohol findings are available we discuss findings on other addictive behaviors or forms of psychopathology. We summarize the evidence for three primary types of intervention: pharmacotherapy, psychosocial and/or behavioral interventions, and neurophysiological interventions (see Table 1 for an overview of evidence supporting each type of intervention).

The objective of this review is to suggest several treatment options; it is not intended to be an exhaustive review of interventions for alcohol use reduction and self-control enhancement. Currently, there is no intervention with strong evidence of efficacy for both alcohol use reduction and self-control enhancement. However, multiple interventions have strong evidence for one indication and solid or suggestive evidence for the other. In this review, we report only on interventions with at least some evidence for both indications. Although some interventions are well-supported empirically for one indication and have proposed mechanisms of action supporting potential benefit for the other (e.g. the catechol-O-methyltransferase [COMT] inhibitor tolcapone [35, 36]), we regarded such interventions as too speculative at this stage and thus opted not to include them in this review. With each intervention, we began by presenting evidence of its efficacy for alcohol use reduction and related potential mechanisms of action, followed by evidence and mechanisms related to enhanced self-control. In all cases, we first discuss the clearest, strongest evidence, followed by relevant equivocal or negative results.

Pharmacotherapy

Opioid Antagonists

Naltrexone and other opioid antagonists are the class of pharmacotherapy with the strongest empirical support for alcohol

Table 1 Overview of interventions with possible efficacy for reducing alcohol use and enhancing self-control

Pharmacotherapy			
Intervention	Description and/or examples	Evidence for alcohol use reduction	Evidence for self-control enhancement
Opioid antagonists	Medications including naltrexone and nalmefene believed to block effects of opioid release stimulated by alcohol consumption, resulting in fewer rewarding effects of alcohol	Significant advantage over placebo in multiple clinical trials: FDA approved for alcohol dependence	Efficacy in clinical trials for kleptomania (an impulse control disorder) and gambling, mixed results in basic research and human laboratory findings
Varenciline	Highly selective partial agonist of the alpha-4 and beta-2, and full agonist of the alpha-7, nicotinic acetylocholine receptors. Decreases rewarding effects of alcohol and nicotine that are believed to be partially mediated by activity at nicotinic acetylcholine receptors	Reduced alcohol self-administration in basic and human laboratory studies. Clinical trial results show advantage over placebo for reducing alcohol use by both smokers and non-smokers	Beneficial effects on concentration, working memory and attention in human research with smokers
Glutamatergic medications	Medications believed to regulate glutamatergic activity and, as a result, modulate substance-related reward-seeking activity. Examples are: memantine, an NMDA-type glutamate receptor antagonist; and N-acetyl cysteine (NAC), a glutamatergic nutriceutical	Multiple basic science findings reveal that memantine can reduce alcohol self-administration. Human laboratory studies show that memantine decreases alcohol-cue-induced craving, although clinical trial findings have been negative	Human studies suggest a function for glutamatergic medications in improving impulse control disorder symptoms; however, basic science findings regarding memantine have been largely negative in terms of benefit for self-control difficulties
Modafinil	A wakefulness agent that is FDA approved for treating narcolepsy, but has also been used more broadly as a cognitive enhancer	Limited results pertaining only to certain clinical outcomes. Tended to be beneficial only for participants with poor response inhibition	Enhanced cognitive task performance among alcohol-dependent patients and healthy controls, although strongest evidence for alcohol-dependent individuals who perform poorly on tasks initially
Psychosocial and/or behavioral interventions			
Intervention	Description and/or examples	Evidence for alcohol use reduction	Evidence for self-control enhancement
Cognitive behavioral therapy (CBT)	Designed to teach tangible strategies to prevent substance use. Maladaptive cognitions are identified and challenged, and strategies are provided to change such cognitions	Evidence for efficacy at treating AUD	Probable that skills taught in CBT could lead to enhanced self-control. Neuroimaging findings related to other addictions support beneficial effects of CBT related to self-control enhancement, but found no such results for AUD patients.
Contingency management (CM)	Objective is to decrease substance use through provision of alternate reinforcers	Evidence for efficacy at treating AUD	A focus on alternate reinforcers may help to enhance self-control. CM has been associated with decreases in psychiatric symptoms relevant to self-control in cocaine dependent patients, but no parallel evidence for alcohol, as far as we are aware
Mindfulness training	Involves attending to immediate experience with an attitude of acceptance	Early evidence supports decreased probability of relapse among AUD patients, also associated with reduced attentional bias to alcohol-related cues	Associated with improvements in executive function
Cognitive bias modification	Procedures derived from computer-based cognitive tasks in which attention is repeatedly oriented away from salient substance-related cues or participants are	Evidence that cognitive biases can be diminished with training; in some cases, retraining has been related to decreased alcohol use and better clinical outcomes	Diminished cognitive biases toward substance cues likely to more broadly enhance self-control; but found no evidence of relationships between retraining and general

Table 1 (continued)

	trained to approach non-substance-related stimuli		decrease in impulsive response or choice or other general enhancement to self-control
Neurophysiological interventions			
Repetitive transcranial magnetic stimulation (rTMS), transcranial direct current stimulation (tDCS), and deep brain stimulation (DBS)	Non-invasive (rTMS and tDCS) and invasive (DBS) procedures are believed to modulate frontal circuits engaged in decision-making processes, effectively increasing cognitive control	Decreased subjective craving with rTMS and tDCS, but depends on location of stimulation and frequency of application. Case reports support DBS effect of reducing alcohol use and craving	Enhanced performance on cognitive tasks indicating less impulsive choices, but again depends on location of stimulation and frequency of application

use reduction and self-control enhancement. Naltrexone is FDA-approved for treating alcohol dependence, and has efficacy at reducing alcohol consumption [37], although there have been negative trials (e.g. [38]). Nalmefene is another opioid antagonist that reduces alcohol intake, with a recent placebo-controlled clinical trial supporting "as needed" use in anticipation-of-drinking situations [39•]. Mechanisms of action underlying reduction of alcohol use by opioid antagonists are not fully understood, but seem to include dampening of rewarding and stimulating effects and increasing sedative effects [40, 41], resulting in a slower pace of drinking [42, 43].

On the basis of aforementioned dual process theories [7•, 8, 9], dampened reward and a slowing effect on drinking would theoretically facilitate adaptive response inhibition, thereby reducing impulsive behavior. The efficacy of opioid antagonists for treating kleptomania (an impulse control disorder) and gambling disorder (previously classified as an impulse control disorder [44]; now classified as a behavioral addiction in DSM-5 [45]) supports their use for self-control enhancement. Impulsivity and risk-taking are a inherent parts of these conditions [46, 47]; thus, a reduction in symptoms necessarily entails enhancement of self-control. Clinical trials of naltrexone [48, 49] and nalmefene [50] support the efficacy of these medications for treating gambling disorder. Naltrexone also had positive results on kleptomania symptoms in a small clinical trial [51].

Animal and human laboratory data provide some support for opioid antagonist efficacy in reducing impulsive behavior, but also some equivocal results. Naltrexone reduced morphine-induced preference for small immediate rewards over larger delayed rewards in rats [52], but not in mice [53]. A later rat study found that the opioid antagonist naloxone reduced impulsive responding on the five-choice serial reaction time task, but did not ameliorate impulsive choice in a delayed reward task [54]. Human laboratory studies of delay-discounting show beneficial effects of naltrexone for abstinent alcoholics [55] and for people with a positive family history of alcoholism who had consumed a moderate dose of alcohol [56]; however, these effects were modified by a personality factor: locus of control (LOC) [57]. LOC is a personality measure reflecting one's perception of individual control over life events. An internal attribution style predicted more impulsive choices on naltrexone, whereas for those with an external attribution style impulsive choices were reduced by naltrexone [55, 56]. Naltrexone may alter impulsive choice by altering the level of dopamine signaling in the frontal cortex [58–60], on the basis of the following evidence: LOC scores reflect tonic frontal dopamine transmission [61]; impulsive choice varies with measures of tonic frontal dopamine, by a U-shaped function [62, 63]; and the effect of acute changes in dopamine signaling on impulsive choice depends on tonic frontal dopamine [64]. Family history dependence of this effect could reflect family-history-based differences in naltrexone-induced cortisol release [65] or in endogenous opioid signaling [66].

Brief Summary of Opioid Antagonist Findings

Evidence shows beneficial effects of opioid antagonists for reducing alcohol use. Regarding enhancement of self-control, the strongest evidence comes from clinical trials on gambling disorder and kleptomania. Animal studies have observed reduced impulsive response and choice; however, there have also been negative results. Human laboratory findings suggest naltrexone has beneficial effects, but also indicate that these effects may be moderated by pre-existing traits. On balance, the evidence suggests a beneficial effect of opioid antagonists on self-control enhancement, but further research is needed to clarify the relationship between their effects on impulsive responding and on alcohol use, particularly in humans, and to identify mechanisms that explain why effects of naltrexone may be moderated by personality traits.

Varenicline

Although less well studied than opioid antagonists, there is solid evidence that varenicline, an FDA-approved pharmacotherapy for nicotine dependence, can also reduce alcohol use

and enhance self-control. Varenicline is a highly selective partial agonist of the alpha-4 and beta-2, and full agonist of the alpha-7, nicotinic acetylocholine receptors. Rewarding effects of both alcohol and nicotine are believed to be partially mediated by activity at nicotinic acetylcholine receptors [67, 68], suggesting potential efficacy for reducing alcohol and nicotine intake. Varenicline has been shown to reduce alcohol seeking and self-administration in rats [69] and mice [70]. Findings from human laboratory research [71] and small clinical trials [72, 73] similarly support varenicline's efficacy at reducing alcohol use among smokers who drink heavily. Most recently, findings from a multi-site clinical trial indicated that varenicline reduces alcohol intake among both smokers and non-smokers [74•]. Varenicline has been associated with weaker rewarding effects [71] and greater sedating effects of alcohol [70, 72].

Evidence suggests varenicline may have direct effects on executive functioning. First, a recent smoking-cessation clinical trial revealed beneficial effects of varenicline on concentration [75]. Second, varenicline improved working memory and attentional deficits during nicotine withdrawal in a short-term study [76]. Finally, a recent monkey neurophysiology study revealed an integral function for the alpha-7 nicotine acetylcholine receptor, a varenicline target, in the persistent activity in the dorsolateral prefrontal cortex underlying working memory [77]. This last result suggests a possible mechanism underlying varenicline's beneficial effect on working memory, and potentially on other executive functions.

In addition to evidence that varenicline may benefit executive function, varenicline's attenuation of alcohol-related reward [71] and potentiation of alcohol-related sedation [72, 78] may have ramifications for impulse control. Again on the basis of dual-process theories [7•, 8, 9], greater self-control is probable when reward is less salient and a "slowing" effect occurs. Studies are needed to directly relate varenicline's effects of reducing alcohol-related reward and enhancing sedation to performance on impulsive response and choice tasks in humans.

In summary, solid evidence supports varenicline's efficacy at reducing alcohol use. Initial results suggest it has the additional benefit of enhancing cognitive operations associated with executive function. Studies on humans are needed to directly relate varenicline's effects on alcohol-related reward and sedation to its effects on impulsive response and choice tasks.

Other Possible Pharmacotherapy

Glutamatergic Medications

Glutamate is the brain's primary excitatory neurotransmitter and, as such, mediates both general reward seeking and reward seeking pertaining to substance use [4, 79, 80]. Imbalanced glutamate homeostasis induces changes in neuroplasticity that adversely affect communications between the PFC and nucleus accumbens, potentially leading to excessive reward-seeking [79]. Animal models also support a function for glutamatergic signaling in mediating reward seeking in substance use disorders [81]. For example, memantine, an NMDA-type glutamate receptor antagonist, reduces alcohol self-administration (e.g. [53]). Moreover, human laboratory studies show that memantine reduces alcohol-cue-induced craving [82], although clinical trial findings to date are negative (e.g. [83]). However, clinical trial data do suggest a function for glutamatergic medications in improving impulse control. N-acetyl cysteine (NAC)—a glutamatergic nutriceutical believed to restore substance-abuse-induced glutamatergic dysregulation in the ventral striatum and to regulate extracellular glutamate concentration—reduced problem gambling severity in an open-label study with a double-blind discontinuation phase [84]. Furthermore, memantine improved the performance of gamblers on the intradimensional/extradimensional set-shifting task, a measure of cognitive flexibility (i.e. avoidance of perseveration) [85•]. In contrast with these human findings, basic science findings with memantine have been largely negative in terms of benefit to impulsivity [53] and other self-control deficits (e.g. overactivity [86]),

In summary, animal studies and human laboratory research suggest medications regulating glutamatergic activity may reduce alcohol consumption, although limited human-clinical-trial findings have been negative. In contrast, human findings are somewhat stronger in terms of self-control benefits when compared with evidence from animals. Although these findings suggest promise for gluatmatergic medications for both indications, further research is needed, particularly given these contrasting results.

Modafinil

Modafinil is a wakefulness agent that is FDA approved for narcolepsy and also used as a cognitive enhancer [87]. Although there is solid evidence for the cognitive-enhancing effects of modafinil, current evidence regarding alcohol use is limited. In a recent study, modafinil outperformed placebo on some alcohol outcomes, including time to relapse; however, the medication did not have beneficial effects overall. Also, the benefits of modafinil for alcohol use were limited to participants who had weaker response inhibition initially [88].

Modafinil weakly inhibits the dopamine transporter, with additional effects on GABA and glutamate transmission [89]. Cognitive-enhancing effects of modafinil may be attributable to its actions at the dopamine transporter [90]. Notably, the benefits of modafinil regarding preventing executive dysfunction caused by sleep deprivation were moderated by the

COMT genotype. COMT catalyzes breakdown of dopamine, supporting a relationship between modafinil's cognitive-enhancing effects and dopamine activity [91]. Modafinil administration has also been linked to increased activity in the anterior cingulate cortex and the ventrolateral PFC [92], brain regions implicated in executive functions.

Recent evidence suggests modafinil can improve self-control among alcohol-dependent patients. In both alcohol-dependent patients and healthy controls, modafinil improved performance on a Stroop task, which requires inhibition of prepotent responses and, specifically, avoidance of cognitive interference [93]. Among alcohol-dependent participants only, modulation of activity in the default mode network (a brain network underlying internally-focused thought, which optimally is subsumed during demanding external tasks) may have partly mediated modafinil's effects [93]. In another investigation, the same group found that modafinil enhanced performance on a different task requiring inhibition of prepotent responses; however, this effect was only observed for alcohol-dependent participants who initially performed poorly on the task. Modafinil was associated with declining performance for alcohol-dependent individuals with better initial performance [93]. These results are reminiscent of the "inverted-U" model of dopamine's effect on cognitive function [94], and thus provide further evidence for attributing modafinil's effects to its effect on dopaminergic signaling.

In summary, the benefit of modafinil for reducing alcohol use remains uncertain, although data suggest beneficial effects for those with response inhibition difficulties. Modafinil has promise for enhancing self-control among those with alcohol dependence, with mediating neurological effects. These effects are more pronounced among those with greater initial self-control difficulties. Further research is needed to determine whether modafinil can directly reduce alcohol use; its most promising indication may be for cognitive enhancement in conjunction with other interventions directly targeting alcohol use.

Summary of Pharmacotherapy Results

Few medications are currently approved for treating AUD, and the mechanisms underlying their therapeutic benefit remain unclear. However, converging evidence suggests that at least some of their clinical benefit may derive from increasing cognitive control, particularly for those with more severe cognitive control deficits. This suggests there may be a benefit to investigating other medications that have been shown to improve cognitive control, particularly for patients characterized by high trait impulsivity, for possible use in treating AUD.

Psychosocial and/or Behavioral Intervention

Cognitive Behavioral Therapy

Cognitive behavioral therapy (CBT) is a psychotherapy modality designed to teach tangible strategies to prevent substance use. An important assumption of CBT is that maladaptive behaviors are acquired through learning. Distorted thoughts (e.g. the only way to have fun is to drink) and poor coping responses to feelings also have a fundamental effect on behavior. Accordingly, CBT sessions are often focused on challenging such cognitions and learning how to cope with thoughts and feelings without substance use. A recent meta-analysis showed an overall beneficial effect of CBT for AUD [95].

CBT could enhance self-control more broadly, in addition to its associations with alcohol use reduction. CBT typically includes building skills to recognize and avoid high-risk contexts and to cope effectively with these situations [96]. It is probable that gains in these areas would translate to enhanced self-control. In a sample of primarily cocaine-dependent individuals, CBT reduced the fMRI BOLD signal, associated with cognitive interference during the Stroop task, in frontal cortical regions previously implicated in impulse control [97•]. This result suggests the possibility of minimized cognitive interference after CBT, which could promote less impulsive responding and decision-making. In another study, nicotine-dependent participants using CBT-compatible cognitive strategies had enhanced activity in frontal cortical regions and reduced activity in subcortical regions compared with trials when they used CBT-incompatible strategies. These patterns of frontal cortical and subcortical activity are associated with effective impulse control and emotion regulation [98•]. We found no published results in which CBT for AUD was also associated with enhanced self-control, although these results in other addictions are promising.

In summary, CBT reduces alcohol use and findings suggest that it can enhance self-control among those with other addictions. At present, data regarding self-control effects of CBT for heavy drinkers and/or individuals with AUD are lacking.

Contingency Management

The objective of contingency management (CM) is to reduce substance use through provision of alternative reinforcers, often vouchers exchanged for prizes or direct cash payments. CM requires two primary components: 1) a target behavior that can be detected reliably and frequently; and 2) provision of tangible reinforcers immediately after confirming the target behavior [99]. CM has efficacy for treating AUD [100, 101]. By substituting alternate reinforcers, CM intends to weaken powerful automatic, associative learning underlying addiction.

In addition to benefits regarding substance use, this shift away from substance-related reinforcement toward other types of reinforcement may benefit self-control generally. Weakening automatic associations linking substance use with reward may facilitate both inhibition of prepotent responses and choices to delay gratification. Supporting evidence regarding CM and self-control comes from a combined analysis of three clinical trials on cocaine use disorder [102]. These findings showed greater reductions in other psychiatric symptoms among those in the CM group compared with control group participants. Several of the psychiatric symptoms that improved under treatment with CM have relevance to self-control, including hostility. In future research, it would be valuable to assess the extent to which these types of gain apply to AUD treatment.

Mindfulness Training

Mindfulness-based training interventions involve attending to immediate experience with an attitude of acceptance [103•]. As such, much of the benefit of mindfulness training relates to enhanced ability to focus and maintain attention optimally. The ability to focus and maintain attention optimally is highly relevant to avoiding substance use and to self-control generally. Alcohol-related attentional bias decreased among adults with AUD after mindfulness training [104], suggesting that mindfulness training may have a clinical benefit. Bowen et al. [105] compared a mindfulness training aftercare program to treatment as usual, and found that those in the mindfulness group reported significantly less alcohol and drug use.

Experienced meditators can more broadly reduce mental engagement with distracting stimuli, as verified by neurophysiological data showing reduced amplitude in the P3a event-related potential in response to distractors [106]. On a related note, mindfulness has been linked to enhanced performance on the Stroop task, indicating stronger cognitive control and less interference from salient distractor stimuli [107]. Mindfulness has also been associated with other executive function enhancements, including sustained attention and working memory [108–111].

In summary, early evidence supports the use of mindfulness training for AUD and for enhancing multiple aspects of cognitive control, including attention, resistance to distraction, and other executive functions. Thus, this intervention has promise as a dual intervention to reduce alcohol use and to enhance self-control.

Other Cognitive Control Training Procedures

Other training procedures have shown promise for reducing alcohol and other substance use, and for enhancing cognitive functions relevant to self-control. Given the relevance of these approaches to this review, we believed it important to include them, but, given outstanding recent review articles on the topic of cognitive control training (e.g. [112•]), we only mention them briefly. These procedures are grouped into two categories: cognitive bias modification, and strategies targeting general cognitive abilities pertinent to addictions.

There is strong evidence that perpetuation of addictive behaviors is mediated in part by cognitive biases favoring continued substance use. The most well-articulated form of cognitive bias is the tendency for substance users to attend disproportionately to cues associated with that substance, referred to as attentional bias [112•, 113]. Many substance users also have a tendency to seek out and approach cues associated with that substance, referred to as automatic approach tendency [7•, 112•]. Cognitive bias modification procedures have been developed to ameliorate both attentional bias toward alcohol cues [12] and automatic approach tendencies toward alcohol [7•]. These procedures have shown efficacy at reducing cognitive biases toward alcohol cues and, in some cases, have been associated with reductions in alcohol self-administration in the laboratory [12] and with more favorable clinical outcomes [114•, 115, 116]. Evidence for reduced attention allocated to alcohol cues and reduced approach tendencies toward alcohol cues suggest benefit to self-control generally. However, we are aware of no findings in which reduced cognitive bias toward alcohol cues was associated with improved performance on cognitive tasks related to impulsivity, including response-inhibition or delay-discounting tasks.

Several interventions that target general cognitive abilities have shown efficacy in reducing alcohol and other substance use. For example, working memory training has solid supporting evidence. A training procedure enhanced working memory among problem drinkers, which was associated with reduced alcohol use—but only among those with strong automatic positive associations to alcohol [117]. Although working memory training has promise, the question of which subjects may be most likely to benefit should be addressed further in future studies.

Neurophysiological Interventions

The advent and growing use of tools enabling direct electrical intervention into the neurophysiology of the human brain has made possible the newest class of potential AUD treatments. These include the non-invasive repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS), and the highly invasive deep brain stimulation (DBS). Of these, rTMS has been most frequently investigated [118]. These interventions theoretically act by modulating frontal circuits engaged during decision-making processes, effectively altering cognitive control [119]. Results of rTMS depend to a great extent upon the target, stimulation frequency, and number of sessions. In a study of detoxified alcohol-dependent female patients, 10 days of high-frequency rTMS to the right dorsolateral PFC significantly reduced subjective craving [120]. In

contrast, 10 days of high-frequency rTMS to the left dorsolateral PFC increased attentional bias toward alcohol cues [121]. For nicotine addiction, 10 daily rTMS sessions over the left dorsolateral PFC, followed by less frequent rTMS sessions, significantly reduced cigarette use, nicotine dependence, and cue-induced craving [122]. However, although a single application of high-frequency rTMS to the left dorsolateral PFC reduced delay discounting among non-treatment-seeking smokers, it had no effect on cigarette use [123]. These findings show that rTMS has potential as a treatment, with direct benefit for alcohol use and other addictive behaviors, and potential benefit for enhancing self-control. However, further research is needed to identify precisely which settings are associated with particular beneficial effects. Seizure risk associated with rTMS is also an important consideration.

Another noninvasive method for modulating neural circuit function, with a lower seizure risk, is tDCS. Initial use for alcoholism showed that tDCS treatment to the right or left dorsolateral PFC reduced alcohol craving [124]. A more recent study of tDCS to the left dorsolateral PFC replicated the effect on alcohol craving, with a trend toward increased executive function; however, tDCS was also associated with increased relapse probability [125]. Again, the precise procedure may be critical, because repeated tDCS to the dorsolateral PFC reduces both smoking-cue-induced cigarette craving and actual cigarette use [126]. As with the pharmacological interventions discussed above, these neurophysiological interventions may be best suited to those AUD patients with the greatest cognitive control deficits, although direct testing in this area is needed.

Because it requires surgery, DBS is a treatment of last resort for AUD. However, DBS has been used for several neurobehavioral disorders, and, on the basis of its ability to modulate dysregulated brain networks, it is of growing interest for treating addiction [127]. Alleviation of comorbid AUD was reported in the initial case study of DBS to the nucleus accumbens to treat severe anxiety and depression [128]. A more recent report on DBS to the nucleus accumbens specifically to treat AUD also reported reduced alcohol intake and craving [129]. Pertinent to this review, the latter study also found general improvements in cognitive control associated with DBS treatment. Although results are preliminary, DBS to the nucleus accumbens holds promise for treating severe intractable AUD, and may prove particularly helpful for populations with severe cognitive control deficits.

Conclusion

Overall, evidence for concurrent direct benefit of one intervention for both alcohol use reduction and self-control enhancement is limited. However, several interventions have strong evidence for one indication and at least suggestive evidence for the other. Opioid antagonists have the strongest evidence for both alcohol use reduction and self-control enhancement. Varenicline also has solid evidence in terms of both alcohol use and self-control. However, even for these medications, there are some negative findings regarding self-control enhancement. Regarding psychosocial and behavioral interventions, both empirical evidence and the mechanisms believed to underlie the effects of CBT, CM, and mindfulness training suggest possible use for alcohol use reduction and self-control enhancement. Cognitive bias modification has evidence to support its efficacy for reducing alcohol use and for ameliorating attentional bias and approach biases toward alcohol cues. Reduced cognitive bias is likely to have a broader positive effect on self-control. However, we found no results linking reduced cognitive bias for substance cues with enhanced performance on tasks indicative of reduced impulsivity or more broadly relevant cognitive functions. Neurophysiological interventions have promise both for alcohol use reduction and self-control enhancement; however, they have considerable side effects, and DBS is an invasive procedure.

We have offered several suggestions for future topics of study. In terms of self-control enhancement, the proposed mechanisms of some treatments suggest that, in many cases, there may be a potential benefit of more broadly reducing self-control; however, more empirical evidence is needed. Cognitive bias modification is one example of such a treatment; another is CBT, which has the benefit of enhancing the self-control of AUD patients. More research on possible moderator effects and their clinical implications is warranted, because self-control enhancement may apply only to subsets of participants. In the absence of overwhelming evidence supporting the efficacy of individual interventions for both alcohol use reduction and self-control enhancement, further studies are needed to test combined interventions.

Compliance with Ethics Guidelines

Conflict of Interest Robert F. Leeman, Devorah Bogart, Lisa M. Fucito, and Charlotte A. Boettiger declare that they have no conflict of interest.

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

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