Published in final edited form as:
Curr Addict Reports. 2014 March ; 1(1): 41–52. doi:10.1007/s40429-013-0008-1.

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

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Abstract

We review interventions with empirical support for reducing alcohol use and enhancing self-control. While any intervention that decreases drinking could improve self-control, we focus here on interventions with evidence of direct benefit for both indications. Although no intervention yet shows strong evidence for dual efficacy, multiple interventions have strong evidence for one indication and solid or suggestive evidence for the other. Among pharmacotherapies, opioid antagonists currently have the best evidence for reducing alcohol use and enhancing self-control. Nicotinic partial agonist varenicline also appears 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 based on purported mechanisms of action and empirical evidence. Cognitive bias modification and neurophysiological interventions have promise for alcohol use and self-control as well and warrant further research. We offer several other suggestions for future research directions.

Keywords

naltrexone; nalmefene; naloxone; varenicline; opioid antagonist; glutamate; GABA; cognitive behavioral therapy; contingency management; mindfulness; cognitive bias modification;

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Compliance with Ethics Guidelines

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This article does not contain any unpublished studies with human or animal subjects performed by any of the authors.

Conflict of Interest

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

neurophysiological interventions; impulsivity; alcohol use disorders; delay discounting; memantine; dopamine; repetitive transcranial magnetic stimulation; transcranial direct current stimulation; deep brain stimulation; attentional bias; approach bias; response inhibition; executive function; animal model

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 most well studied among all difficulties with self-control, is a multifaceted construct [2, 3], which entails “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 as resulting from an imbalance between competing tendencies to respond to salient internal or external stimuli (sometimes referred to as “activation”[6]) and to inhibit prepotent responses (sometimes referred to as “inhibition”[6]). According to these dual process theories, impulsive behaviors may reflect excessive tendencies to respond and/or inability to inhibit these responses adaptively [7–9]. Ability to focus attention optimally, even in the face of distraction, is considered essential to inhibiting prepotent responses [10, 11]. Attention is also highly relevant to alcohol misuse in that frequent heavy drinkers often demonstrate a bias to attend 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 play a key role in the ability to inhibit prepotent responses. Not unlike the term “impulsivity,” “executive function” is an umbrella term that encompasses a number of cognitive operations involving the coordination of sub-processes in order 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 distal 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 predict alcohol involvement longitudinally. 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/related constructs are likely to be reciprocal. Impulsivity predisposes individuals to alcohol misuse and related problems,

and heavy alcohol is associated with subsequent increases in impulsivity among college students ([24], though see [25]). Alcohol use is likely to affect self-control over the longer term as well. Alcohol dependent older adults exhibit frontal lobe volume losses [26], suggesting possible compromised executive functioning and poorer self-control as a result. Acutely, alcohol use can also lead to more impulsive action: in particular, greater difficulties inhibiting automatic, prepotent responses (see [27]).

Neurobiological and genetic evidence also supports close relationships between alcohol involvement and difficulties with self-control. Problem alcohol use and difficulties with selfcontrol are associated with atypical function in similar brain regions (e.g., prefrontal cortex (PFC), ventral striatum; [28]) and in common neurotransmitter and peptide systems, such as dopamine, serotonin and endogenous opioids [29, 30]). Genetic studies have found common risk factors among self-control difficulties such as conduct disorder and substance-use disorders [31] (see also [22], this section). Conduct disorder is a psychological condition diagnosed in childhood or adolescence 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 viewed 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 exhibit greater self-control subsequently. However, it is also advantageous to target self-control enhancement directly. Though clearly related to alcohol misuse, self-control difficulties tend to predate alcohol use [33]. Further, impulsive individuals are at greater risk of relapse following alcohol treatment [34].

While any intervention that decreases alcohol use could lead to parallel enhancement of self-control, we have focused on alcohol reduction interventions for which there is evidence suggesting direct benefit in 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, for cases in which 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 interventions: pharmacotherapy, psychosocial/behavioral interventions and neurophysiological interventions (see Table 1 for an overview of evidence supporting each type of intervention).

The present review aims merely to suggest a number of treatment options and 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 demonstrated evidence for both indications. While 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 viewed such

interventions as too speculative at this stage and thus opted not to include them in the present 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 pharmacotherapies with the strongest empirical support for alcohol use reduction and self-control enhancement. Naltrexone is FDA-approved for the treatment of alcohol dependence and has demonstrated efficacy in reducing alcohol consumption [37], although there have been negative trials (e.g., [38]). Nalmefene is another opioid antagonist that is efficacious for reducing alcohol intake, including a recent placebo-controlled clinical trial supporting “as needed” use in anticipation of drinking situations [39]. Mechanisms of action underlying reduction of alcohol use with opioid antagonists are not fully understood, but appear to include dampening of rewarding and stimulating effects, along with increasing sedative effects [40, 41], resulting in a slower pace of drinking [42, 43].

Based on aforementioned dual process theories [7–9], 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 utility for self-control enhancement. Impulsivity and risk-taking are inherently part of these conditions [46, 47]; thus, a decrease in symptoms necessarily entails enhancement of self-control. Clinical trials of naltrexone [48, 49] and nalmefene [50] support the efficacy of these medications for the treatment of gambling disorder. Naltrexone also had positive results for kleptomania symptoms in a small clinical trial [51].

Animal and human laboratory data offer 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 among abstinent alcoholics [55] and people with a positive family history of alcoholism following 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, while impulsive choices were reduced by naltrexone among those with an external attribution style [55, 56]. Naltrexone may alter impulsive choice by altering the level of dopamine signaling in the frontal cortex [58–60], based on the following evidence. LOC scores reflect tonic frontal dopamine transmission [61]; impulsive choice varies with measures of tonic frontal

dopamine according to 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 in reducing alcohol use. Regarding enhancement of self-control, the strongest evidence comes from clinical trials for gambling disorder and kleptomania. Animal studies have yielded findings of reduced impulsive response and choice; however there have also been negative results. Human laboratory findings suggest beneficial effects of naltrexone but that these effects are moderated by pre-existing traits. On balance, the evidence suggests a beneficial effect of opioid antagonists in self-control enhancement, however 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 also solid evidence that varenicline, an FDA-approved pharmacotherapy for nicotine dependence, can reduce alcohol use and enhance self-control. Varenicline is a highly selective partial agonist of the alpha-4, 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 as well as 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 demonstrate varenicline's efficacy in reducing alcohol use among smokers who drink heavily. Most recently, findings from a multi-site clinical trial indicate 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 demonstrated beneficial effects of varenicline on concentration [75]. Second, varenicline has also been shown to improve working memory and attentional deficits during nicotine withdrawal in a short-term study [76]. Finally, a recent monkey neurophysiology study demonstrated an integral role for the alpha-7 nicotine acetylcholine receptor, a varenicline target, in the persistent activity in the dorsolateral prefrontal cortex underlying working memory [77]. This latter result suggests a possible mechanism underlying varenicline's beneficial effect on working memory and potentially other executive functions.

In addition to evidence that varenicline may benefit executive function, varenicline's attenuation of alcohol-related reward [78] and potentiation of alcohol-related sedation [79, 80] may have ramifications for impulse control. Again based on dual-process theories [7, 9, 81], greater self-control is probable when reward is less salient and a "slowing" effect

occurs. Studies are needed to relate varenicline's effects in reducing alcohol-related reward and enhancing sedation to performance on impulsive response and choice tasks in humans directly.

In summary, solid evidence supports varenicline's efficacy in reducing alcohol use. Initial results suggest benefits in enhancing cognitive operations associated with executive function. Studies in 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 Pharmacotherapies

Glutamatergic medications—Glutamate is the brain's primary excitatory neurotransmitter and, as such, mediates reward-seeking both generally and pertaining to substance use [4, 82, 83]. Imbalance in glutamate homeostasis triggers changes in neuroplasticity that adversely affect communications between the PFC and nucleus accumbens, potentially leading to excessive reward-seeking [82]. Animal models also support a role for glutamatergic signaling in mediating reward-seeking in substance use disorders [84]. For example, memantine, an NMDA-type glutamate receptor antagonist, reduces alcohol self-administration (e.g., [53]). Moreover, human laboratory studies show that memantine decreases alcohol cue-induced craving [85], though clinical trial findings to date are negative (e.g., [86]). However, clinical trial data do suggest a role for glutamatergic medications in improving impulse control. N-acetyl cysteine (NAC) —a glutamatergic nutriceutical thought to restore substance-abuse-induced glutamatergic dysregulation in the ventral striatum and to regulate extracellular glutamate concentration—showed efficacy in reducing problem gambling severity in an open-label study with double-blind discontinuation phase [87]. Further, memantine improved performance among gamblers on the intradimensional/extradimensional set-shifting task, a measure of cognitive flexibility (i.e., avoidance of perseveration) [88]. In contrast to 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; [89]),

In summary, animal studies and human laboratory research suggest potential efficacy for medications regulating glutamatergic activity in reducing alcohol consumption though 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. While these findings suggest promise for gluatmatergic medications for both indications, further research is needed, particularly due to these contrasting results.

Modafinil—Modafinil is a wakefulness agent that is FDA approved for narcolepsy and also shows utility as a cognitive enhancer [90]. Though there is solid evidence for cognitive enhancing effects of modafinil, current evidence regarding alcohol use is limited. In a recent study, modafinil outperformed placebo on certain alcohol outcomes such as time to relapse, however the medication did not have beneficial effects overall. Also, the benefits of modafinil on alcohol were limited to participants who showed weaker response inhibition initially [91].

Modafinil weakly inhibits the dopamine transporter with additional effects on GABA and glutamate transmission [92]. Cognitive enhancing effects of modafinil may be attributable to its actions at the dopamine transporter [93]. Notably, the benefits of modafinil in preventing executive dysfunction due to sleep deprivation were moderated by COMT genotype. COMT catalyzes the breakdown of dopamine, supporting a relationship between modafinil's cognitive enhancing effects and dopamine activity [94]. Modafinil administration has also been linked to enhanced activation in the anterior cingulate cortex and ventrolateral PFC [95], 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 [96]. 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 [96]. In another investigation, the same group found benefits of modafinil in enhancing performance on a different task requiring inhibition of prepotent responses, however only among alcohol dependent participants who initially performed poorly on the task. Modafinil was associated with declining performance among alcohol dependent individuals with better initial performance [96]. These results are reminiscent of the "inverted-U" model of dopamine's effect on cognitive function [97] and thus provide further evidence to attribute modafinil's effects to its impact on dopaminergic signaling.

In summary, modafinil's benefit in reducing alcohol use remains uncertain although data suggest beneficial effects among those with response inhibition difficulties. Modafinil shows promise for enhancing self-control among those with alcohol dependence with demonstrated mediating neurological effects. These effects are more pronounced among those with greater initial self-control difficulties. Further research is needed to determine whether modafinil has a direct effect in reducing alcohol use though 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 among those with more severe cognitive control deficits. This points to the idea of pursuing further medications for AUD that have been shown to improve cognitive control, particularly in patients characterized by high trait impulsivity.

Psychosocial/Behavioral Interventions

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. Further, distorted thoughts (e.g., the only way to

have fun is to drink) and poor coping responses to feelings play a fundamental role in 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 [98].

CBT could enhance self-control more broadly, in addition to its associations with alcohol use reduction. CBT typically includes skill-building to recognize and avoid high-risk contexts and to cope effectively with these situations [99]. It is likely that gains in these areas would translate to enhanced self-control. In a sample of primarily cocaine dependent individuals, CBT decreased fMRI BOLD signal associated with cognitive interference during the Stroop task in frontal cortical regions previously implicated in impulse control [100]. This result suggests the possibility of minimized cognitive interference following CBT, which could promote less impulsive responding and decision-making. Moreover, in another study, when nicotine dependent participants used CBT-compatible cognitive strategies, they showed enhanced activity in frontal cortical regions and decreased activity in subcortical regions compared to trials when they used CBT-incompatible strategies. These patterns of frontal cortical and subcortical activity are associated with effective impulse control and emotion regulation [101]. 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 among heavy drinkers/individuals with AUD are lacking.

Contingency management

The objective of contingency management (CM) is to decrease substance use through provision of alternate 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 goal behavior [102]. CM has demonstrated efficacy in the treatment of AUD [103, 104]. By substituting alternate reinforcers, CM essentially aims to weaken powerful automatic, associative learning underlying addiction.

In addition to benefits regarding substance use, this shift in orientation 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 inhibition of prepotent responses and choices to delay gratification. Suggestive evidence regarding CM and self-control comes from a pooled analysis of three clinical trials for cocaine use disorder [105]. These findings showed greater decreases in other psychiatric symptoms among those in CM conditions compared to control condition participants. Several of the psychiatric symptoms that showed improvement 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 gains apply to AUD treatment as well.

Mindfulness training

Mindfulness-based training interventions involve attending to immediate experience with an attitude of acceptance [106]. 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 both to avoiding substance use and to self-control generally. Alcohol-related attentional bias decreased following mindfulness training among adults with AUD [107], suggesting that mindfulness training may have clinical benefit. Along these lines, Bowen et al. [108] compared a mindfulness training aftercare program to treatment as usual and found that those in the mindfulness condition reported significantly less alcohol and drug use.

Experienced meditators can decrease mental engagement by distracting stimuli more broadly, which has been verified by neurophysiologic data showing reduced amplitude in the P3a event-related potential in response to distractors [109]. On a related note, mindfulness has been linked to enhanced performance on the Stroop task, indicating stronger cognitive control and less interference by salient distractor stimuli [110]. Mindfulness has also been associated with other executive function enhancements, including sustained attention and working memory [111–114].

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

Other cognitive control training procedures

Other training procedures have shown promise in reducing alcohol and other substance use, and in enhancing cognitive functions relevant to self-control. Given the relevance of these approaches to the present review, we considered it important to include them, albeit briefly given outstanding recent review articles on the topic of cognitive control training (e.g., [115]). 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 inordinately to cues associated with that substance, referred to as attentional bias [115, 116]. Many substance users also show a tendency to seek out and approach cues associated with that substance, referred to as automatic approach tendencies [7, 115]. 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 in reducing cognitive biases toward alcohol cues and, in some cases, have been associated with reductions in alcohol self-administration in the laboratory [12] and more favorable clinical outcomes [117–119]. 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, such as response inhibition or delay discounting tasks.

A number of 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 to date. A training procedure showed effects in enhancing working memory among problem drinkers, which related to reduced alcohol use, but only among those with strong automatic positive associations to alcohol [120]. While working memory training holds promise, the issue 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 allowing direct electrical interventions into the neurophysiology of the human brain has ushered in the newest class of potential AUD treatments. These include 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 the most frequently investigated [121]. These interventions theoretically act by modulating frontal circuits engaged during decision-making processes, effectively altering cognitive control [122]. 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 [123]. In contrast, 10 days of high frequency rTMS to the left dorsolateral PFC increased attentional bias toward alcohol cues [124]. In the case of 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 [125]. However, while 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 [126]. These findings show that rTMS has potential as a treatment with direct benefit to alcohol use and other addictive behaviors and potential benefit in enhancing self-control. However, further research is needed to identify precisely which parameters are associated with particular beneficial effects. Seizure risk associated with rTMS is also an important consideration.

Another noninvasive method for modulating neural circuit function, which poses less seizure risk, is tDCS. The initial application to alcoholism showed that tDCS treatment to right or left dorsolateral PFC reduced alcohol craving [127]. A more recent study of tDCS to the left dorsolateral PFC replicated the effect on alcohol craving, along with a trend toward increased executive function; however, tDCS treatment was also associated with increased relapse likelihood [128]. Again, the precise protocol may be critical, as repeated tDCS to the dorsolateral PFC reduces both smoking-cue induced cigarette craving and actual cigarette use [129]. As with the pharmacological interventions discussed above, these neurophysiological interventions may be best suited to AUD patients with the greatest cognitive control deficits, although direct testing in this area is needed.

Due to its requirement of surgery, DBS is a treatment of last resort for AUDs. However, DBS has been applied to several neurobehavioral disorders and based on its utility in modulating dysregulated brain networks, it is of growing interest in the addictions [130]. Alleviation of comorbid AUD was also reported in the initial case report of DBS in the nucleus accumbens to treat severe anxiety and depression [131]. A more recent report of DBS in the nucleus accumbens specifically to treat AUD also showed reduced alcohol intake and craving [132]. Pertinent to this review, the latter study also found general improvements in cognitive control with DBS treatment. While preliminary, DBS in the nucleus accumbens holds promise for treating severe intractable AUD, and may prove particularly helpful in populations with severe cognitive control deficits.

Conclusion

Overall, evidence for concurrent direct benefit to both alcohol use reduction and to self-control enhancement is limited, however a number of interventions show 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 with these medications, there are some negative findings in terms of self-control enhancement. Regarding psychosocial and behavioral interventions, both mechanisms believed to underlie effects of CBT, CM and mindfulness training, along with empirical evidence, suggest their utility for alcohol use reduction and self-control enhancement. Cognitive bias modification has evidence to support its efficacy in reducing alcohol use and in ameliorating attentional bias and approach biases toward alcohol cues. Decreased cognitive bias is likely to have a positive effect on self-control more broadly. However, we found no results linking decreased cognitive bias for substance cues with enhanced performance on tasks indicative of decreased impulsivity or other relevant cognitive functions more broadly. 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 areas of study. In terms of self-control enhancement, proposed mechanisms support benefit in reducing self-control more broadly in multiple cases, however more empirical evidence is needed. Cognitive bias modification is an example, along with benefits of CBT for self-control enhancement among AUD patients specifically. Also, more research on possible moderator effects and their clinical implications should be explored since self-control enhancement may only apply to subsets of participants. In the absence of overwhelming evidence supporting efficacy of individual interventions for both alcohol use reduction and self-control enhancement, further studies are needed to test combined interventions.

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Table 1

Overview of interventions with possible efficacy in reducing alcohol use and enhancing self-control

Pharmacotherapy			
Intervention	Description/examples	Evidence for alcohol use reduction	Evidence for self-control enhancement
Opioid antagonists	Medications such as 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, 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 in reducing alcohol use both in 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 demonstrate that memantine can reduce alcohol self-administration. Human laboratory studies show that memantine decreases alcohol cue-induced craving, though clinical trial findings have been negative	Human studies suggest a role for glutamatergic medications in improving impulse control disorder symptoms, however basic science findings with memantine have been largely negative in terms of benefit to self-control difficulties
Modafinil	A wakefulness agent that is FDA approved for the treatment of narcolepsy, but has also been utilized more broadly as a cognitive enhancer	Limited results pertaining only to certain clinical outcomes. Tended to be beneficial only among participants with poor response inhibition	Enhanced cognitive task performance among alcohol dependent patients and healthy controls though strongest evidence among alcohol dependent individuals who perform poorly on tasks initially
Psychosocial/behavioral interventions			
Intervention	Description/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, challenged and strategies are provided to change such cognitions	Evidence for efficacy in treating AUDs	Likely that skills taught in CBT could lead to enhanced self-control. Neuroimaging findings from other addictions support beneficial effects of CBT related to self-control enhancement, but found no such findings among AUD patients.
Contingency management (CM)	Objective is to decrease substance use through provision of alternate reinforcers	Evidence for efficacy in treating AUDs	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, to our knowledge
Mindfulness training	Involves attending to immediate experience with an attitude of acceptance	Early evidence supports decrease in likelihood of relapse among AUD patients, also associated with decreases in attentional bias to alcohol-related cues	Associated with improvements in executive function
Cognitive bias modification	Procedures derived from computer-based cognitive tasks in	Evidence that cognitive biases can be diminished	Diminished cognitive biases toward substance cues likely to enhance self-

	which attention is repeatedly oriented away from salient substance-related cues or participants are trained to approach non-substance-related stimuli	with training and in some cases, retraining has been related to decreased alcohol use and better clinical outcomes	control more broadly, but found no evidence of relationships between retraining and general 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 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 applications, case reports support DBS effect in reducing alcohol use and craving	Enhanced performance on cognitive tasks indicating less impulsive choices, but again depends on location of stimulation and frequency of applications