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Cognitive Enhancement as a Treatment for Drug Addictions

Mehmet Sofuoglu[1], **Elise E. DeVito**[1], **Andrew J. Waters**[2], and **Kathleen M. Carroll**[1]

[1]Yale University, School of Medicine, Department of Psychiatry and VA Connecticut Healthcare System, West Haven, CT

[2]Department of Medical and Clinical Psychology, Uniformed Services University of the Health Science, Bethesda, MD

Abstract

Drug addiction continues to be an important public health problem, with an estimated 22.6 million current illicit drug users in the United States alone. For many addictions, including cocaine, methamphetamine, and marijuana addiction, there are no approved pharmacological treatments. Behavioral treatments are effective but effects vary widely across individuals. Treatments that are effective across multiple addictions are greatly needed, and accumulating evidence suggests that one such approach may be pharmacological or behavioral interventions that enhance executive inhibitory control in addicts. Current evidence indicates that most forms of chronic drug use may be associated with significant cognitive impairments, especially in attention, working memory, and response inhibition functions. In some studies, these impairments predict poor treatment retention and outcome. A number of cognitive enhancing agents, including galantamine, modafinil, atomoxetine, methylphenidate, and guanfacine, have shown promising findings in human studies. Specific behavioral interventions, including cognitive remediation, also show promise. However, whether improvement of selective cognitive functions reduces drug use behavior remains to be determined. Cognitive enhancement to improve treatment outcomes is a novel strategy worthy of future research, as are related questions such as whether these approaches may be broadly beneficial to most addicts or best reserved for substance users with specific demonstrated cognitive impairments.

1. Introduction

Drug addiction continues to be an important public health problem, with an estimated 22.6 million current illicit drug users in the United States (SAMHSA, 2011). Effective medications are available for the treatment of nicotine, alcohol, and opioid addictions (Potenza et al., 2011; Sofuoglu and Kosten, 2004). Unfortunately, no medications have been proven to be effective for cocaine addiction despite a large number of medications screened in randomized clinical trials (Sofuoglu and Kosten, 2006). Similarly, no medications have been approved for the treatment of methamphetamine (Hill and Sofuoglu, 2007) or cannabis addiction (Sofuoglu et al., 2010b), although fewer clinical trials have been conducted for those addictions.

*Mehmet Sofuoglu, Yale University, Department of Psychiatry, VA Connecticut Healthcare System, 950 Campbell Ave., Bldg. 36/116A4, West Haven, CT 06516, Phone: (203) 937-4809.

A number of effective behavioral treatments have been developed for addictive behaviors (Carroll and Onken, 2005; Dutra et al., 2008; Miller and Wilbourne, 2002). Among those with the strongest level of empirical support from randomized clinical trials are contingency management (CM, where abstinence or other targeted outcomes are reinforced with incentives)(Higgins et al., 1991; Petry, 2006), motivational interviewing (MI, where a specific, nonjudgmental interviewing style is used to enhance motivation and harness the individuals capacity for change)(Hettema et al., 2005; Miller, 1985), and cognitive behavioral therapy (CBT, which teaches specific strategies and skills to reduce substance use) (Carroll et al., 1994; Marlatt and George, 1984). In contrast to the specificity of effects of most medications for drugs of abuse (e.g., methadone or buprenorphine have demonstrated efficacy for opioid dependence with little effect on concomitant cocaine use), empirically validated behavioral therapies tend to be effective across the range of substance use disorders. For example, CBT, CM, and MI have been found to be effective across alcohol, cannabis, and cocaine use disorders (Burke et al., 2003; Dutra et al., 2008; Lussier et al., 2006; Marijuana Treatment Project Research Group, 2004; Miller and Wilbourne, 2002). This effectiveness of behavioral treatments across addictions is also consistent with many common features of addictive disorders, including continued substance use despite consequences, impaired control over behavior, repeated unsuccessful attempts to reduce use, narrowing of activities in favor of drug use, and diminished control over use (Edwards and Gross, 1976). Effect sizes remain modest for most behavioral therapies and outcomes vary widely across individuals (Dutra et al., 2008). Therefore, focusing on individual variables associated with poorer outcomes, including impaired cognition, may be an important strategy to enhance the effectiveness of behavioral treatments.

Disruptions to inhibitory or executive control have been identified as defining features of many theories of addictions, as they address the maintenance of drug use behavior and the difficulty many individuals have in resisting habitual drug use once established (Everitt et al., 2007; Goldstein and Volkow, 2011; Li and Sinha, 2008; Porrino et al., 2007). The inhibitory and executive control functions, concentrated primarily in the prefrontal and parietal cortices, are especially important when the individual needs to override a prepotent response, such as drug-taking behavior in response to drug cues (Sarter et al., 2006). Thus, addressing these critical aspects of cognitive function may be may be a successful strategy for increasing treatment efficacy across addictive disorders (Sofuoglu, 2010).

The goal of this review is to provide an overview of the rationale for targeting cognitive-enhancement strategies for the treatment of drug addiction and to outline some existing pharmacological and behavioral approaches which show promise in achieving cognitive enhancement in drug addicted populations. We first present a summary of studies documenting cognitive impairments associated with addictions and discuss the relevance of these cognitive deficits as predictors of treatment outcome in addiction. We then review potential mechanisms linking cognitive deficits to drug use and conclude with examples of candidate medications and behavioral interventions which show potential as cognitive-enhancing agents and may serve as stand-alone or adjunct treatments for drug dependence. While intended as a broad overview of cognitive enhancement as a treatment strategy across the addictions, it should be noted that most of the empirical work on this topic has focused on cocaine and methamphetamine addictions. This review complements the recent reviews on this topic that focused on individual drugs of abuse (Sofuoglu, 2010; Sofuoglu et al., 2010b) or covered pharmacological treatments (Brady et al., 2011). Cognitive consequences of chronic alcohol use have been reviewed recently and will not be included in this manuscript (Stavro et al., 2012).

2. Cognitive deficits in addicted individuals

Multiple studies have reported that chronic drug use, especially cocaine, methamphetamine, cannabis use, and cigarette smoking are associated with deficits in cognitive functioning, including in decision-making, response inhibition, planning, working memory, and attention (Durazzo et al., 2010; Fernandez-Serrano et al., 2012; Jovanovski et al., 2005; Nordahl et al., 2003; Price et al., 2011; Simon et al., 2002; Stavro et al., 2012). While many studies report the results of statistical significance testing, effect size analyses better describe the magnitude of differences between drug users and controls (Zakzanis, 2001). A meta-analysis by Jovanoski et al. (2005) comparing cocaine users (n=481) with healthy controls (n=586) reported large effect sizes for attentional function (Cohen's $d \geq 0.8$), moderate effect sizes for visual and working memory ($0.8 > d \geq 0.5$) and small effect sizes for language and sensory-perceptual functions ($0.5 > d \geq 0.2$) (Cohen 1988). A separate meta-analysis comparing methamphetamine users (N=487) with healthy controls (N=464) observed moderate effect sizes for learning, executive function, memory, and speed of information processing domains and small effect sizes for motor skills, attention, working memory, visuo-construction, and language domains (Scott et al., 2007). In a recent study, cigarette smokers performed worse than non-smokers on several domains of cognitive function with large effect sizes for performance on auditory–verbal and visuospatial learning, visuospatial memory, cognitive efficiency, executive skills, general intelligence, and processing speed (Durazzo et al., 2012). These findings are consistent with several previous studies with cigarette smokers and matched controls (Nooyens et al., 2008; Paul et al., 2006; Sabia et al., 2008). However, comparing drug users and healthy controls on cognitive function requires careful consideration of many potential confounds. As discussed in a recent review by Hart et al. (2012), studies examining the neurocognitive effects of chronic methamphetamine use often do not control for differences between drug users and controls in education, IQ, and other psychiatric comorbidities or length of abstinence within substance users; may employ suboptimal cognitive assessment tools; and are often limited by small sample sizes. Thus, findings from these studies should be interpreted with such possible limitations in mind (Hart et al., 2012).

Studies on the influence of chronic cannabis use on cognitive function have found mixed results. Some studies reported that chronic heavy marijuana use is associated with impairments in verbal learning and memory, sustained attention, and executive functioning (Bolla et al., 2002; Pope et al., 1995; Pope and Yurgelun-Todd, 1996; Solowij, 1995; Solowij et al., 1995; Solowij et al., 2002). In contrast, other studies reported minimal (Grant et al., 2003) or no lasting effects of chronic cannabis use on overall IQ, attention, working memory, and abstract reasoning (Fried et al., 2005; Jager et al., 2006). Cannabis-induced cognitive impairments may depend on age of onset; with those beginning cannabis use before age 17 demonstrating greater impairment (Kempel et al., 2003; Pope et al., 2003). Thus, age of onset and other baseline variables, particularly IQ (Bolla et al., 2002), may explain the conflicting findings regarding long-term cannabis use on cognitive function.

Functional neuroimaging studies have examined the neural substrates of these deficits. A resting state positron emission tomography (PET) study demonstrated low glucose metabolism in the anterior cingulate cortex (ACC) and high glucose metabolism in the lateral orbitofrontal area, middle and posterior cingulate, amygdala, ventral striatum, and cerebellum of recently abstinent methamphetamine abusers (London et al., 2004). Methamphetamine (Nestor et al., 2011) and chronic cocaine (Bolla et al., 2004) users demonstrate prefrontal cortical (PFC) hypoactivation during Stroop task performance, a measure of cognitive control and response inhibition. Similarly, long-term cannabis users show hypoactivity in the ACC and the left lateral PFC during the Stroop task (Eldreth et al.,

2004; Gruber and Yurgelun-Todd, 2005). These and many other studies provide evidence for PFC dysfunction in chronic drug users.

Despite evidence of a strong association of cognitive deficits in substance dependent populations, particularly in their most severe form, the clinical implications of these findings has received limited attention, perhaps due to the subtle nature of many of these deficits, variability across individuals, and observations that that at least some of these deficits may be reversible following cessation of drug use. However, several studies suggest that these cognitive deficits are not reversible after short-term abstinence. For example, methamphetamine dependent individuals failed to demonstrate significant improvement in cognitive performance following one month of abstinence (Simon et al., 2010). Similarly, in a PET study, abstinent individuals who were previously methamphetamine-dependent, displayed persistent neurocognitive deficits despite nearly full recovery of dopamine transporter (DAT) deficiency (Volkow et al., 2001). Furthermore, some cognitive impairments associated with cannabis use do not appear reversible with short-term abstinence, further emphasizing that some impairments are not entirely accounted for by the acute effects of the drugs (Medina et al., 2007).

Another consideration is the extent to which cognitive impairments are caused by chronic drug use. While chronic drug use may cause cognitive impairment, individuals with cognitive deficits may also be more vulnerable to initiating drug use and/or becoming drug-dependent (Wagner et al., 2012). Furthermore, drug use is often associated with psychiatric co-morbidity (e.g., depression, attention deficit hyperactivity disorder) and cognitive impairments may be primarily accounted for by these co-morbid disorders. Some evidence suggests that especially smokers may have preexisting mild cognitive impairments (Wagner et al., 2012; Yakir et al., 2007). A recent study reported that smokers (n=1002) were more likely than non-smokers (n=1161) to have impairments in visual attention and impulsivity (Wagner et al., 2012). However these impairments were also present in smokers with low levels of cigarette consumption and lifetime cigarette consumption was not correlated with cognitive function. As these findings suggest, cognitive impairments may predate the initiation of drug use, rendering individuals more vulnerable for drug addiction (Wagner et al., 2012). Carefully controlled longitudinal studies are needed to disentangle the associations between cognitive impairments and drug use. If cognition influences substance use outcomes and general functioning, cognitive enhancement will serve as an important treatment target, regardless of whether cognitive impairments in addicted populations reflect persistent brain dysfunction arising secondary to chronic substance use; acute drug effects; short-term withdrawal effects; pre-existing vulnerability factors for addiction; or, perhaps most plausibly, a combination of several of such factors.

3. Cognitive Impairments as Predictors of Relapse and Treatment Outcomes

While the clinical literature linking cognitive functioning to treatment outcome has shown mixed results, cognitive impairments are generally associated with poorer treatment retention in most substance-using samples. For example, Aharonovich and colleagues reported that cognitive impairments in cocaine or cannabis users are associated with poorer response to behavioral treatment (Aharonovich et al., 2008; Aharonovich et al., 2006; Aharonovich et al., 2003). Among cocaine users offered CBT (n=56), treatment non-completers performed significantly worse on laboratory measures of attention, memory, spatial ability, speed, accuracy, global functioning, and cognitive proficiency compared with treatment completers (Aharonovich et al., 2006). Similarly, cannabis dependent treatment non-completers performed significantly worse than treatment completers on measures of abstract reasoning and processing accuracy (Aharonovich et al., 2008). However, these

measures of cognitive function were not related to rates of abstinence during the treatment trial in these cocaine and cannabis using samples (Aharonovich et al., 2008; Aharonovich et al., 2006; Aharonovich et al., 2003). While self-reported baseline drug use did not differ between treatment completers and non-completers, these studies did not directly investigate whether cognitive function is a predictor of treatment outcomes independently of drug use severity. A more recent study by Carroll et al extended the Aharonovich study by including both treatment as usual (TAU) and computerized CBT treatment for cocaine addiction (n=77) (Carroll et al., 2011). Baseline performance on a subset of the cognitive measures assessed (i.e. BART, a task of risk-taking; CPT, a sustained attention task) differentially predicted retention (e.g. days in treatment), treatment engagement (e.g. CBT modules and homework completed) and treatment outcomes (e.g. drug-positive urines) in the CBT arm but were less predictive of outcome in the TAU arm. However, composite score of overall cognitive performance at baseline was not significantly predictive of treatment response in either treatment condition (Carroll et al., 2011). Furthermore, an association between IQ at pre-treatment and drug-positive urines during post-treatment follow-up was mediated by the quality of coping skills demonstrated at the end of treatment in the CBT arm (after controlling for baseline coping skills), but this relationship did not hold within the TAU arm (Kiluk et al., 2011) These findings highlight the importance of carefully assessing differential relationships between cognitive domains and aspects of the clinical course (e.g. vulnerability to initiate use or transition to dependence; ability to understand or engage in certain treatments; drug use outcomes). In methamphetamine dependent individuals (N=60), measures of cognitive function predicted treatment outcome and study retention less robustly than an indicator of baseline methamphetamine use (urine drug screening) (Dean et al., 2009). This study raised questions about the independent contribution of cognitive function as a treatment outcome predictor. More recently, in 131 cocaine-dependent individuals, baseline executive function predicted treatment retention (Verdejo-Garcia et al., 2012). Of note, baseline demographics and cognitive function explained 14 % of the variation in treatment outcome. These findings are consistent with other studies suggesting that impairments in cognitive functioning and inhibitory control tend to be associated with higher drop-out rates (Brewer et al., 2008; Streeter et al., 2008; Turner et al., 2009). However, the effect sizes in these studies seem to be modest and questions remain for the independent contribution of cognitive function as a predictor of treatment outcome.

4. Mechanisms Linking Cognitive Impairments to Drug Use

Both executive and implicit/automatic cognitive processes play a role in controlling drug use. We review these processes as they relate to addiction (for a broader review, see (Field and Cox, 2008; Miller and Cohen, 2001; Wiers and Stacy, 2006).

4.1 Executive Control

Many contemporary theories of addiction emphasize a disrupted inhibitory or executive control in compulsive drug use (Everitt et al., 2007; Goldstein and Volkow, 2011; Li and Sinha, 2008; Porrino et al., 2007). The executive control is coordinated by two parallel networks of the PFC: the dorsolateral “executive” and the orbitofrontal “limbic” network primarily contained in the orbito frontal cortex (OFC) (Abernathy et al., 2010). While the dorsolateral PFC is the primary regulator of goal-directed behavior, the ACC is critical in conflict resolution. The “limbic” OFC is connected with many sensory cortical areas and limbic regions including hippocampus and determines the salience of information about environmental contingencies. PFC control over executive function is a result of the coordination between the “executive” and “limbic” networks as well as the top-down control over the ascending neuromodulators which include monoamines (dopamine, serotonin, norepinephrine), orexin, and acetylcholine (Robbins and Arnsten, 2009). These

neuromodulators have powerful influences over PFC functions (Robbins and Arnsten, 2009).

Executive control, rather than being a unitary function, can best be characterized as a collection of related but separable functions (Friedman et al., 2008) including response inhibition, working memory, attention, problem solving, decision making, set shifting, and other functions. Among executive functions, response inhibition, working memory, and sustained attention are particularly relevant for addictive disorders (de Wit, 2009; Eagle et al., 2008; Gregoire et al., 2012). These functions have been operationalized by separate tasks and may serve as potential treatment targets for cognitive-enhancement approaches.

4.1.1 Response Inhibition—Response inhibition refers to the ability to voluntarily inhibit a dominant, automatic, or pre-potent response (Friedman et al., 2008) and is often assessed via tasks such as the Stop-Signal Task (SST) or Go/No-Go (Eagle et al., 2008). The SST is a speeded choice response task (e.g. press right button as quickly as possible for a right-pointing arrow and left button for a left-pointing arrow). Similarly, the Go/No-Go task presents a majority of ‘go’ trials, but intermixes a small proportion of ‘stop’ trials. In both tasks the motor response is correct in the majority of trials, therefore it becomes pre-potent as the task is learned and this response must be actively inhibited in the minority of ‘stop’ or ‘no-go’ trials.

Reduced response inhibition function, as determined by the SST or Go-No/Go task, have been repeatedly demonstrated in cocaine (e.g. Fernandez-Serrano et al., 2012; Li et al., 2006; Fillmore et al 2007) and methamphetamine dependent individuals (Monterosso et al., 2005), compared to non-addicted controls.

The norepinephrine (NE) system is thought to play a key role for response inhibition function (Aston-Jones et al., 2009). For example, norepinephrine transporter (NET) inhibitor atomoxetine improves response inhibition function in healthy controls as well as in patients with ADHD (Chamberlain et al., 2006). Atomoxetine increases dopamine (DA) and NE levels in the PFC; however, increases in NE likely mediate the improvement in response inhibition function (Bari et al., 2011).

4.1.2 Working Memory—Working memory refers to the ability to keep in mind an event that had just been experienced or retrieve information from long-term memory storage and use this information to regulate behavior (Arnsten, 2011). Classic measures of working memory include auditory or visuo-spatial span tasks, which require information to be held ‘on line’ while it is actively updated or manipulated.

As mentioned above, meta-analyses found impaired working memory function in cocaine (Jovanovski et al., 2005) and methamphetamine users, with medium to small effect sizes (Scott et al., 2007). Many studies have suggested that working memory function is linked to inhibitory control in that high working memory demand or reduced working memory function may facilitate drug craving or relapse (Chambers et al., 2009). For example, under high working demand, cocaine users have reduced response inhibition, measured by a Go-No/Go task, compared to healthy controls (Hester and Garavan, 2004). In abstinent smokers, poorer working memory function is predictive of relapse (Patterson et al., 2010).

The ascending DA and NE pathways are the main neuromodulators for working memory function. Monoamine transporter inhibitors atomoxetine, modafinil, and methyphenidate, as well as the alpha2-adrenergic agonist, guanfacine, may improve working memory function (Marquand et al., 2011; Minzenberg and Carter, 2008; Swartz et al., 2008b).

4.1.3 Sustained Attention—Sustained attention is controlled by both bottom-up and top-down processes (Posner and Rothbart, 1998). Bottom-up processing, also known as exogenous or stimulus-driven attention, refers to an automatic process driven by external stimuli (e.g. visual drug cues). Top-down processing, also known as the endogenous or executive attention, is controlled via engagement of PFC and basal ganglia neural circuitry and is closely linked to working memory and response inhibition functions (Rueda et al., 2005). Sustained attention is often measured by continuous performance tasks, such as Rapid Visual Information Processing task (RVIP;(Turner et al., 2005)) where subjects are asked to attend to rapidly presented visual stimuli and respond to specific stimuli which are presented infrequently.

Individuals addicted to methamphetamine, cocaine, cannabis, or nicotine have shown impairments in sustained attention function (Bolla et al., 2002; Durazzo et al., 2012; Jovanovski et al., 2005; Simon et al., 2010; Scott et al., 2007), with effect sizes ranging from large in cocaine users (Jovanovski et al., 2005) to small in methamphetamine users (Scott et al., 2007). Sustained attention has a bidirectional interaction with drug craving. For example, craving for drugs demands attentional resources and takes attention away from non-drug stimuli resulting in impaired performance in sustained attention tasks (Sayette et al., 2010). Lapses in attention during early abstinence have been linked to relapse, possibly by reducing behavioral inhibition (de Wit, 2009), leading to apparent ‘hijacking’ of the brain by drug cues.

Sustained attention function is modulated by acetylcholine (ACh), NE, DA, glutamate, and gamma-aminobutyric acid (GABA) (Levin et al., 2011). Mounting evidence supports the role of Ach release in the PFC is an essential step in mediating attentional processes (Kozak et al. 2006; Sarter et al. 2006; Sarter et al. 2009). Medications enhancing DA, NE and ACh transmission have been shown to improve sustained attention (Levin et al., 2011).

4.2 Automatic/Implicit Cognitive Processes

Recently, addiction researchers have highlighted the role of automatic/implicit cognitive processes in drug addiction (Wiers and Stacy, 2006). Automatic/implicit cognitive processes are fast, parallel, effortless, and may not engage conscious awareness. These processes are often measured with modified Stroop tasks, where subjects are shown words written in colored ink and are asked to identify the ink color (Wiers and Stacy, 2006). Attentional bias is indicated by the degree to which performance slows or diminishes in accuracy for drug-related words relative to neutral words. Other common tasks of attentional bias (e.g. dot probe task) measure the relative speed at which subjects visually attend to a neutral stimulus (e.g. dot) when it is presented in the same location as a drug-related visual cue as compared to when it is presented in the neutral-cue location.

Meta-analyses have confirmed that measures of automatic/implicit cognition are associated with craving (small-to-medium effect size of r=.19 from 68 datasets; (Field et al., 2009)) and substance use (medium effect size of r=.31 from 89 datasets; (Rooke et al., 2008)). Measures of automatic/implicit cognition are also associated with relapse (Carpenter et al., 2006; Cox et al., 2002; Cox et al., 2007; Janes et al., 2010; Powell et al., 2010; Waters et al., 2003). One widely studied automatic process is “attentional bias”. In addiction, attentional bias refers to exaggerated attention to drug cues, an important cognitive mechanism in drug addiction (Field and Cox, 2008; Franken, 2003; Ryan, 2002). An individual with high attentional bias for a specific drug will be more likely than an individual with low attentional bias to attend to drug cues, which in turn may provoke drug craving. Another important automatic/implicit process is approach bias (Wiers et al., 2010). An individual with a large approach bias to drug cues will be more likely than an individual with a small approach bias to automatically approach drug cues when exposed to those cues. Therefore, attentional bias

increases exposure to drug cues, and approach bias increases approach behavior to those cues. The neuropharmacology of automatic/implicit processes has not been well characterized. However, one study reported that attentional bias was attenuated by a DA antagonist (Franken et al., 2004)

5. Cognitive-Enhancement Treatments

5.1 Pharmacological Treatments

Table 1 summaries some of the promising cognitive enhancing pharmacotherapies for addictions.

5.1.1 Cholinergic Medications

5.1.1.1 Galantamine: Galantamine, in addition to its acetylcholinesterase inhibitor effects, is also an allosteric potentiator of the nicotinic acetylcholine receptor (nAChR), especially α_7 and $\alpha_4\beta_2$ subtypes (Schilstrom et al., 2007). In a series of studies, we examined the potential use of galantamine as a cognitive-enhancing treatment for drug addiction. In a recent double-blind, placebo-controlled study, ten days of galantamine treatment (8 mg/day) improved sustained attention and working memory functions in abstinent cocaine users (N=28), as assessed by the Rapid Visual Information Processing (RVIP) test (Sofuoglu et al., 2011). In a separate 8-week, double-blind study in opioid and cocaine dependent individuals (N=14), those receiving galantamine (16 mg/day) submitted fewer cocaine-positive urine specimens and reported less cocaine use than those assigned to placebo, and the medication was well-tolerated (Sofuoglu and Carroll, 2011). Together, these results indicate the feasibility, safety, and promise of galantamine as a potential cognitive enhancer for the treatment of cocaine addiction. Randomized clinical trials are underway to test the efficacy of galantamine for the treatment of cocaine addiction.

Furthermore, in a placebo-controlled study in abstinent cigarette smokers, galantamine (8 mg/day) improved sustained attention and response inhibition as assessed by Go/No-Go (Sofuoglu et al., 2012). Galantamine also attenuated the subjective effects of nicotine administered intravenously, consistent with galantamine's enhancement of cholinergic transmission. These findings support the potential utility of galantamine for the treatment of nicotine addiction.

5.1.1.2 Varenicline: Varenicline, a partial agonist of $\alpha_4\beta_2$ and full agonist for the α_7 nAChR subtypes, is used for smoking cessation. In a recent study of cigarette smokers, 10 days of varenicline treatment improved working memory and attention impairments induced by nicotine withdrawal (Patterson et al., 2009). In a functional MRI study using a visual working memory task, abstinent smokers receiving varenicline treatment, compared to placebo, showed greater activation of many PFC regions which was associated with improved task performance in highly dependent smokers (Loughead et al., 2010). Medications targeting $\alpha_4\beta_2$ and α_7 nAChR are under investigation as cognitive-enhancing treatments (Dunbar et al., 2007; Wallace and Porter, 2011).

5.1.2 Monoamine Transporter Inhibitors

5.1.2.1 Modafinil: Modafinil is a wakefulness-promoting agent, approved for the treatment of narcolepsy, sleep apnea, and shift work-induced sleep disorder. Modafinil, is a weak inhibitor of DAT and NET and has additional effects on the brain GABA, glutamate, and orexin (Minzenberg and Carter, 2008). Modafinil's cognitive enhancing effects have been well-recognized in individuals with neuropsychiatric disorders, including those with addictions (Minzenberg and Carter, 2008). In a series of studies, the cognitive-enhancing effects of modafinil were examined in methamphetamine dependent individuals. In a small

inpatient study, 7 days of modafinil treatment improved immediate verbal memory function (Hester et al., 2010). In another study a single 200 mg oral dose of modafinil improved sustained attention (Dean et al., 2011). Furthermore, treatment with 400 mg/day of modafinil for 3 days improved working memory function in methamphetamine dependent individuals who had impaired working memory function at baseline (Kalechstein et al., 2010). Consistent with these findings, a single 200 mg dose of modafinil enhanced activation in the ventrolateral PFC and ACC (Ghahremani et al., 2011), brain regions associated with executive functions. Modafinil has also shown promise in randomized clinical trials for the treatment of methamphetamine addiction (Heinzerling et al., 2010; Shearer et al., 2009).

5.1.2.2 Methylphenidate: Methylphenidate is a stimulant drug similar to amphetamines. It is marketed for the treatment of attention-deficit hyperactivity disorder (ADHD) and has been repeatedly shown to improve response inhibition in individuals with ADHD (e.g. (DeVito et al., 2009)). Methylphenidate, similar to cocaine, inhibits DAT and NET (Challman and Lipsky, 2000). In a functional MRI study with cocaine users, a single 20 mg oral methylphenidate treatment ameliorated ACC hypoactivation and improved behavioral measures of response inhibition (Goldstein et al., 2010). In another study with cocaine dependent individuals, intravenous methylphenidate, compared to placebo, improved response inhibition, as assessed with the SST (Li et al., 2010). Methylphenidate also showed promise in reducing cocaine use in individuals with co-morbid ADHD and cocaine addiction (Levin et al., 2007).

5.1.2.3 Atomoxetine: Atomoxetine is used for the treatment of ADHD. It is a selective NET inhibitor that increases synaptic NE levels in the PFC (Bymaster et al., 2002; Swanson et al., 2006). Atomoxetine also increases dopamine levels in the PFC, but not in the nucleus accumbens or other striatal regions (Bymaster et al., 2002; Swanson et al., 2006). This discrepancy has been attributed to sparse distribution of dopamine transporters in the PFC, indicating that NET significantly contributes to clearance of extracellular dopamine in the PFC (Carboni et al., 1990). In contrast, amphetamines increase both DA and NE levels in the nucleus accumbens and in the PFC (Kuczenski and Segal, 1997), which may contribute to the differences between the pharmacological effects of atomoxetine and amphetamines, including the lower abuse liability of atomoxetine (Heil et al., 2002; Wee and Woolverton, 2004).

In healthy controls and patients with ADHD, atomoxetine improved response inhibition, measured with the SST (Chamberlain et al., 2007) or Stroop (Faraone et al., 2005), (see also (Nandam et al., 2011). As both methamphetamine and cocaine users have been reported to have poorer response inhibition than healthy controls, as indicated by slower SST reaction times (Li et al., 2006; Monterosso et al., 2005), it would be of interest to examine atomoxetine's ability to improve performance on this task in stimulant users. Atomoxetine remains to be evaluated in clinical trials for stimulant addiction.

5.1.3 Alpha$_2$-adrenergic Agonist

5.1.3.1 Guanfacine: Guanfacine, an alpha$_2$-adrenergic agonist, is used for the treatment of hypertension and ADHD. Guanfacine reduces NE activity by stimulating presynaptic alpha$_2$-adrenergic receptors. Stimulation of post-synaptic alpha$_2$ adrenergic receptors may mediate the beneficial effects of guanfacine on working memory and attention (Ramos and Arnsten, 2007). Guanfacine has been demonstrated to improve working memory performance in healthy volunteers (Jakala et al., 1999; Swartz et al., 2008a) and sustained attention in individuals with schizophrenia (Friedman et al., 2001) or ADHD (Scahill et al.,

2001). Guanfacine's effects on cognitive function in addictive individuals remain to be determined.

5.1.4 Glutamatergic Medications—Several medications targeting the glutamate system are also under investigation as cognitive-enhancing treatments.

5.1.4.1 Memantine: Memantine, a non-competitive NMDA antagonist is marketed as a cognitive enhancer for Alzheimer's disease. Memantine may also have antidepressant properties (Hashimoto, 2009). Memantine's efficacy as a cognitive enhancer has not been examined in addicted individuals. However, clinical trials with memantine have been negative for alcohol (Evans et al., 2007) or cocaine dependence (Bisaga et al., 2010).

5.1.4.2 D-cycloserine: D-cycloserine (DCS) is a partial agonist at the glycine site of the NMDA-type glutamate receptors. DCS enhances the effectiveness of behavioral treatments for phobias and other anxiety disorders (McNally, 2007; Ressler et al., 2004; Wilhelm et al., 2008), without demonstrated therapeutic effects as a monotherapy for these disorders. In a pilot study, DCS attenuated smoking urges and physiological reactivity to smoking cues in cigarette smokers (Santa Ana et al., 2009). In another study, DSC improved declarative memory function in healthy controls (Onur et al., 2010), although DSC's cognitive-enhancing effects in addicted individuals remain to be examined.

5.1.4.3 Minocycline: Minocycline, an antibiotic which is used to treat acne, is also under investigation for the treatment of neurodegenerative and neuropsychiatric disorders. Minocycline has significant inhibitory effects on dopamine and glutamate transmission, although the exact mechanism of action is unknown. Minocycline improved methamphetamine-induced recognition memory impairments (Mizoguchi et al., 2008) and neurotoxicity in mice (Zhang et al., 2006). In healthy controls, 4 days of minocycline (200mg/day) improved response inhibition function as measured by Go/No-Go (Sofuoglu et al., 2010a). The effects of minocycline in addicted individuals remain to be determined.

To summarize, although several cognitive-enhancing medications are available for clinical use, it remains to be determined whether these medications can reduce drug use through improvement of selective cognitive functions. Many of these cognitive-enhancing medications may have mood-elevating and antidepressant effects as well (e.g., atomoxetine, memantine, or modafinil) (Dell'Osso et al., 2011; Hashimoto, 2009). Given the close association between depression and drug use (Davis et al., 2008), mood elevation may potentially contribute to the proposed efficacy of cognitive-enhancers for drug addiction (Mitchell and Phillips, 2007). To probe these possibilities, future research should address both whether cognitive-enhancing medications improve drug use outcomes and whether these effects are mediated by improvement in selective cognitive functions or mood states.

5.2 Behavioral Treatments

The accumulating data on cognitive deficits among substance users has also led to articulation of how behavioral approaches might be developed or modified to address these issues in clinical samples.

5.2.1 Cognitive Behavioral Therapy—While Cognitive Behavioral Therapy (CBT) for drug abuse is often thought of as teaching specific coping strategies, many of the putative 'active ingredients' of CBT may exert their effects via strengthening aspects of executive control over behavior, as there is some evidence that acquisition of these types of skills in CBT mediates long term-outcomes (Kiluk et al., 2010).

For example, a promising explanation for CBT's durability is its focus on conveying *generalizable* strategies to (1) exert cognitive control over over-learned patterns of substance use via functional analysis of behavior (e.g., understanding episodes of substance use in terms of antecedents and consequences), (2) reduce impulsive responding in response to drug cues via implementing strategies to control craving (regulation of craving and negative affect), (3) improve general decision-making and problem-solving skills, (4) and recognize, challenge, and exert control over cognitions associated with drug use.

CBT requires a comparatively high cognitive workload. The learning, practicing, and implementation of new cognitive skills is complex and requires that patients be able to attend to and understand the therapist's instructions, then remember and execute these new skills in difficult situations. As such, several investigators have hypothesized that CBT would be a sub-optimal treatment for patients with greater cognitive impairment (Kadden et al., 2001). The Aharonovich studies which linking poorer CBT retention to higher levels of cognitive impairment may be consistent with these expectations (Aharonovich et al., 2008; Aharonovich et al., 2006; Aharonovich et al., 2003). Rather than avoid using CBT with cognitively impaired drug users who might most benefit from strengthening of executive control, our group has sought to develop modified versions of CBT that are suitable for use by individuals with a broad range of cognitive abilities. For example, we have delivered a computerized version of CBT that can be tailored for individuals with mild cognitive impairments. This modification of CBT capitalizes on the multimedia capabilities of computer-based learning to present information in formats compatible with a range of learning styles. Computer-based CBT also allows users to pace the presentation of information, repeat material as often as required, be presented with multiple examples of effective skill implementation through videotaped demonstrations, and thus have multiple opportunities for clarification, evaluation and consolidation of learning (Carroll et al., 2008). A recent study showing little evidence of relationships between level of cognitive function and treatment retention or outcome suggests that this computer-based CBT may 'level the playing field' amongst cognitively impaired patients (Carroll et al., 2010). Nevertheless, there was some evidence that cognitive capacity was negatively associated with acquisition of CBT skills, highlighting the challenges of learning cognitively complex skills amongst many drug using individuals (Kiluk et al., 2011).

5.2.2. General Cognitive Training—Another behavioral strategy that may prove useful as an adjunct to, or preparation for, addiction treatment is cognitive rehabilitation training. Cognitive rehabilitation typically involves repeated practice of cognitive tasks involving memory, problem-solving, response inhibition, visuo-construction and perception, visual tracking, and discrimination skills for several hours per week over the course of several months. In general, these approaches have been associated with improvements among individuals with traumatic brain injury, and more recently, schizophrenia (Bell et al., 2005; Lynch, 2002). Neuroimaging data from these studies suggests that cognitive rehabilitation may normalize regional brain activation in the PFC (Wexler et al., 2000). Recent technological advances in computer-delivered cognitive rehabilitation allow for a high level of individualization of the program to account for patients patterns of cognitive strengths and deficits. In a recent trial, Bickel demonstrated that focused training on computerized memory tasks resulted in significant reductions in an aspect of impulsivity, delay discounting (i.e. preference for immediate versus delayed rewards), among stimulant users (Bickel et al., 2011). Adherence to the computerized memory training was facilitated by integrating the computerized cognitive rehabilitation with contingency management.

5.2.3 Attentional Retraining and Cognitive Bias Modification—Recently, novel behavioral Interventions have been developed to specifically target automatic/implicit processes as described earlier, such as attentional bias (Schoenmakers et al., 2010) and

approach bias (Wiers et al., 2010). This Cognitive Bias Modification (CBM) strategy has shown promise in the treatment of addiction (Wiers et al., 2011) and other psychopathologies (Hakamata et al., 2010). For example, in a meta-analysis of 12 attentional retraining studies in individuals with anxiety disorders, attentional retraining yielded significantly greater reductions in anxiety than control training, with a medium-to-large effect size (d =.61). In a randomized trial involving 43 alcoholic patients, 5 sessions of attentional retraining (delivered over 21 days) reduced attentional bias and reduced the time to discharge from treatment (Schoenmakers et al., 2010). In a randomized trial with alcohol-dependent individuals (N=214) (Wiers et al., 2011), 4 brief sessions of training to automatically avoid alcohol cues, improved treatment outcomes at a 1-year follow-up (OR = 2.14) (Wiers et al., 2011). Thus, CBM may useful as an adjunctive treatment for addiction.

5.2.4 Combined Approaches—The bulk of the literature on treatments for addictive disorders suggests that combinations of behavioral therapies and pharmacotherapies may be more effective than single approaches (Carroll, 2001). For example, combining ‘bottom up’ anti-craving medications with ‘top down’ approaches like contingency management or CBT may improve outcome. For instance, reduction of the drive to use drugs via medication may make it easier for patients to deploy cognitive control in the early phases of treatment while these skills are still developing. Combining existing pharmacologic and behavioral addiction treatments with cognitive enhancement treatments could similarly improve treatment outcomes. For example, we are currently conducting a randomized placebo-controlled trial of galantamine with and without computerized CBT, hypothesizing that improved capacity for memory and attention via galantamine may facilitate learning of cognitive skills and strategies via the computerized CBT program. Similarly, we would also predict that combining CBM with cognitive enhancers would be beneficial, because CBM targets automatic/implicit processes and cognitive enhancers target executive control.

6. Conclusions

Long-term drug use is associated with a wide-range of cognitive impairments. These cognitive impairments seem to be predictive of poorer treatment retention and outcome. Among the many executive-control functions, response inhibition, working memory, and sustained attention are potential targets for the treatment of addictive disorder. Medications, (e.g., cholinesterase inhibitors, nicotinic agonists and monoamine transporter inhibitors (modafinil, atomoxetine, methylphenidate)) and behavioral approaches (e.g., CBT and CBM) which target these cognitive functions may have utility for the treatment of addictions. However, there is a dearth of research directly assessing the capacity for cognitive enhancing treatments to improve substance use outcomes via their modulation of cognition and this this gap in our knowledge presents a clinically important topic for future research. If the efficacy of these approaches bears out in clinical trials, future research could further refine this area by addressing issues of specific subgroups of substance users who might show particular benefit from these approaches (e.g., mild versus moderate cognitive impairment) or when in the course of treatment cognitive enhancers should be implemented (e.g., as preparation for treatment or after an initial period of abstinence has been established).

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- Long-term drug use is associated with a wide-range of cognitive impairments.
- Cognitive impairments are potential targets for the treatment of addictive disorders.
- These impairments can be targeted by both medications and behavioral approaches.
- Cognitive enhancement to improve treatment outcomes is a novel strategy.

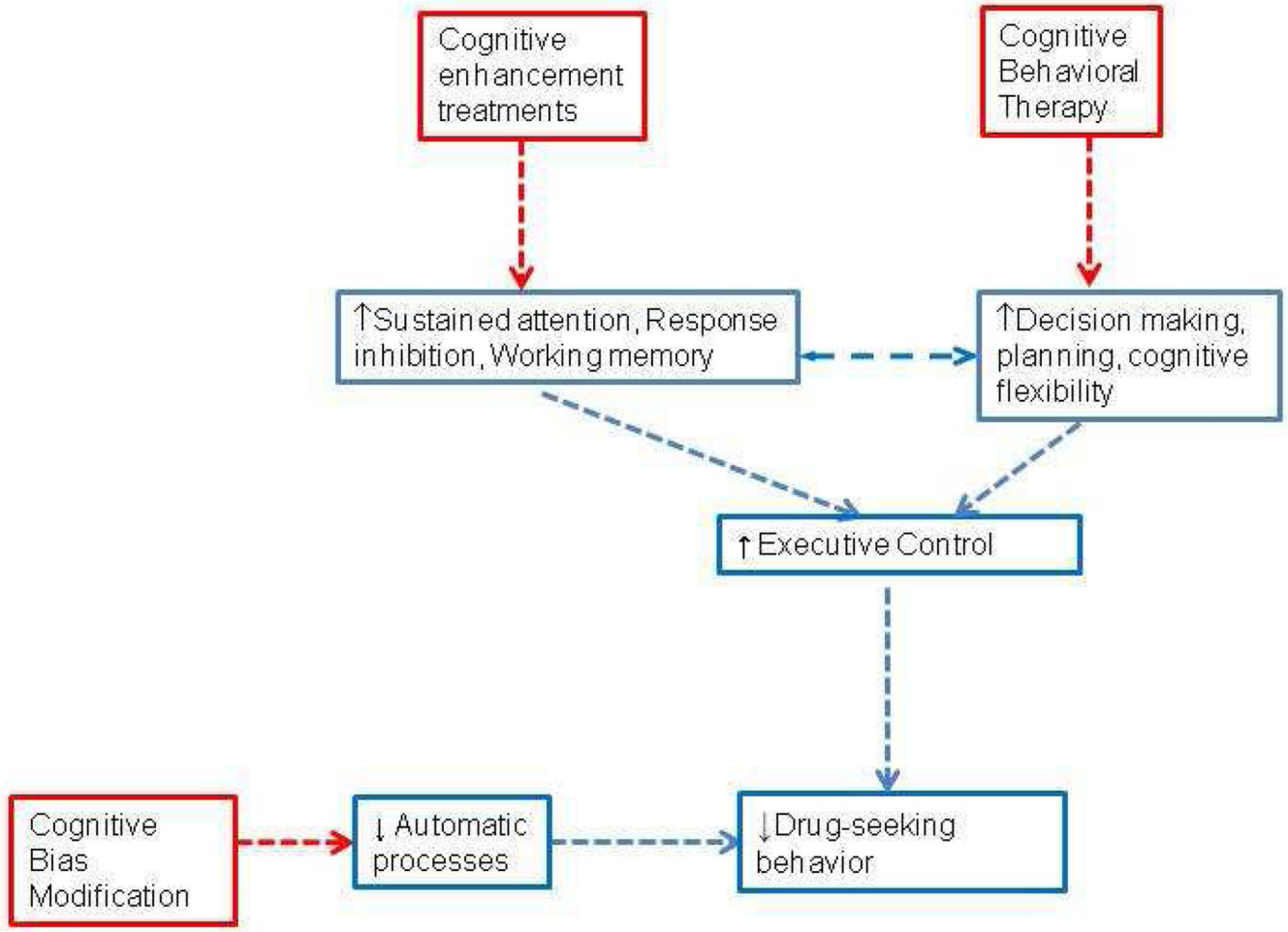

Figure 1.
This figure illustrates the potential therapeutic mechanisms for behavioral and pharmacological cognitive-enhancing treatments for addictions. See text for details.

Table 1

Medications that may be used as cognitive enhancers in addicted individuals

Target	Medication	Dose/Design	Improved Cognitive Domain	Cognitive Measure (E.S.)	Participants in relevant analyses	Caveats/Limitations
Acetylcholine	Galantamine (Sofuoglu et al., 2011)	8 mg/day for 10 days. Between-subject.	Sustained attention	RVIP A' (d=0.91)	26 abstinent CD (13 placebo, 13 galantamine)	Small sample, no substance use outcomes were included.
	Varenicline (Patterson et al., 2009)	1 mg/twice daily for 21 days. Between-subject	Sustained attention Working memory	CPT # True Positives (d=0.5) N-Back Correct RT (d=0.41)	67 treatment-seeking abstinent cigarette smokers	Seven days of smoking abstinence as the main outcome. No long-term smoking cessation outcomes.
Monoamine transporters	Modafinil (Dean et al., 2011)	200 mg, single dose. Within-subject	Sustained attention	CPT reaction time variability (MA d= 0.59; HC d= 0.82)	24 short-term abstinent MA; 17 HC	Small sample. MA and HC groups not matched for cigarette smoking or IQ. Heavier MA use was associated with greater cognitive improvement on modafinil.
	Modafinil (Hester et al., 2010)	200 mg/day for 6 days. Between-subject.	Immediate verbal memory	RAVLT Recall B (MA d=1.2)	14 one week abstinent MA (residential withdrawal unit)	Small sample
	Methylphenidate (Li et al., 2010)	0.5 mg/kg intravenous. Within-subject.	Response inhibition	Stop Signal Reaction Time (d=1.49)	10 non-treatment seeking, ≥5 days abstinent CD	Small sample. IV administration may limit generalizibility.
	Atomoxetine Chamberlain et al., 2007)	60 mg, single dose. Within-subject	Response inhibition	Stop Signal Reaction Time (d=0.8)	20 adult ADHD	Non- addicted sample. Mixed medication status at study entry.
Adrenergic receptors	Guanfacine Swartz et al., 2008b	2–3 mg, single dose. Within-subject	Visual memory	Delayed match to sample accuracy (HC d= 0.74)	10 HC, 14 frontal lobe epilepsy (FLE), 13 temporal lobe epilepsy (TLE)	Non-addicted sample. Tested before and after guanfacine without placebo-control
	Guanfacine (Scahill et al., 2001)	1 mg 3 times/day for 8 weeks. Between subject.	Motor impulsivity Sustained attention	CPT commission errors (d=0.9) CPT omission errors (d=0.8)	34 children with ADHD combined type and tic disorder (17 guanfacine; 17 placebo)	Non-addicted sample of children (mean age 10.4).
Glutamate and others	D-cycloserine (Onur et al., 2010)	250 mg single dose. Between-subject.	Declarative memory	Item category association task response accuracy (d=0.89)	40 HC	Non-addicted sample.

Target	Medication	Dose/Design	Improved Cognitive Domain	Cognitive Measure (E.S.)	Participants in relevant analyses	Caveats/Limitations
	Minocycline (Sofuoglu et al., 2010a)	200 mg/day for 5 days. Within-subject	Attention/ psychomotor speed	"Go" reaction time on Go/No-Go task (d=1.0)	10 HC	Small sample size. Non-addicted sample.

Participant Groups (MA: methamphetamine dependent; CD: cocaine dependent; HC: healthy control; ADHD: attention-deficit hyperactivity)
Cognitive Measures (RAVLT: Rey Auditory Verbal Learning test; RVIP A': Rapid Visual Information Processing, signal detection measure; CPT: continuous performance task)
E.S.=Effect size.