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Review

Cognitive enhancers in the treatment of substance use disorders: Clinical evidence

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ABSTRACT

Attenuation of drug reward has been the major focus of medication development in the addiction area to date. With the growth of research in the area of cognitive neuroscience, the importance of executive function and inhibitory cognitive control in addictive disorders is becoming increasingly apparent. An emerging strategy in the pharmacotherapy of addictions and other psychiatric disorders involves the use of medications that improve cognitive function.

In particular, agents that facilitate inhibitory and attentional control, improve abstraction, planning and mental flexibility could be beneficial in the treatment of substance use disorders. Because there are multiple neurotransmitter systems involved in the regulation of cognitive function, agents from a number of drug classes have been tested. In particular, agents acting through the cholinergic, adrenergic and glutamatergic systems have shown potential for improving cognitive function in a number of psychiatric and neurologic disorders, but most of these agents have not been tested in the treatment of individuals with substance use disorders. This manuscript provides a review of clinical data supporting the use of the major classes of cognitive enhancing agents in substance use disorders. Agents that have shown promise in cognitive enhancement in other disorders, and have a theoretical or mechanistic rationale for application to substance use disorders are also highlighted.

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1. Introduction

Substance use disorders are a problem of considerable public health concern. A great deal of progress has been made in identifying the underlying neurobiology (Kalivas and Volkow, 2005) and a number of pharmacotherapeutic agents have been tested over the past 10 years. New treatments have been approved for alcohol, opiate and nicotine dependence (O'Brien et al., 2006). Unfortunately, no medications have proven efficacious for the treatment of stimulant (cocaine and methamphetamine) or marijuana dependence in spite of multiple clinical trials focused in these areas (Sofuoglu, 2009; Sofuoglu et al., 2010). Even in those areas where medication development has been successful, there remains room for improvement in treatment outcomes. As such, it is important to broaden our medication development strategies and identify new targets in the treatment of addictions.

Attenuation of drug reward has been the major focus of medication development in the addiction area to date. With the growth of cognitive neuroscience research, the importance of executive function and inhibitory cognitive control in addictive disorders is becoming increasingly apparent. Disruption in inhibitory control is a critical element of most theories of addiction (Kalivas and Volkow, 2005) and is closely linked to a number of prefrontal cortex functions, including attention and working memory. Medications that enhance PFC function are of interest in a number of disease states (schizophrenia, Alzheimer's disease) in which disruption in PFC function is critical to key features of the pathophysiology.

In this manuscript, rationale for the use of cognitive enhancing agents in the treatment of addictive disorders will be reviewed. There will be a review of clinical data, identified through database searches, citations in prior reviews, and examination of recent volumes of relevant journals, supporting the use of the major classes of cognitive enhancing agents in substance use disorders, and suggested areas for future development will be elucidated. It must be noted that there are no pharmacotherapeutic trials in which the impact of an agent on both cognitive function and substance use outcomes is evaluated in a manner that permits direct evaluation of the relationship between the two. In addition to pharmacotherapeutic approaches to cognitive enhancement, a number of cognitive training approaches have shown considerable promise. While this manuscript focuses on pharmacotherapeutic strategies, an excellent recent review includes studies investigating cognitive training in individuals with substance use disorders (Vocci, 2008).

2. Cognitive function and addiction

Several studies suggest that a substantial number of substance-dependent individuals in treatment have significant cognitive deficits. In one study of patients entering treatment at the Veterans Affairs Medical Center, 37% had memory problems and 21% had problems with abstract reasoning (Schrimsher et al., 2007). In a recent meta-analysis, cocaine-dependent individuals in treatment were found to have greater impairment in attention, visual memory and working memory when compared to a control group (Jovanovski et al., 2005). A number of studies have demonstrated that chronic use of methamphetamine is associated with deficits in cognitive function including information processing speed, attention, working memory, and executive functions such as response inhibition, decision-making, and problem solving (London et al., 2005; Salo et al., 2005; Scott et al., 2007). Chronic exposure to marijuana is associated with dose-related cognitive impairments including problems with attention, working memory, verbal learning and memory functions (Solowij and Battisti, 2008). Neurocognitive deficits with chronic alcohol use are also well documented and include impairments in memory, visual–spatial processing, problem solving and executive function (Glass et al., 2009).

As mentioned above, disruptions in inhibitory control are central to many theories of addiction (Kalivas and Volkow, 2005; Porrino et al., 2007). The inhibitory activities of the PFC are particularly important when an individual needs to over-ride a reflexive response, such as a craving response to drug-related cues. There are a number of brain regions within the PFC involved in inhibitory control including the orbitofrontal and anterior cingulate cortices, dorsolateral and dorsomedial PFC (Swick et al., 2008). Importantly, the neural circuitry within the PFC is more sensitive to changes in neurochemical environment than other brain regions (Brennan and Arnsten, 2008). This makes the PFC susceptible to the influence of environmental factors, such as stress, but also makes the circuitry within the PFC a good target for therapeutic intervention.

Inhibitory control involves a number of closely linked PFC functions. Both working memory and attentional control are necessary for optimum inhibitory control. Working memory is the term used to describe the ability to maintain task-appropriate information to guide decision-making while ignoring irrelevant or distracting information (Goldman-Rakic, 1995). Attentional control, abstraction, planning, and mental flexibility are all processes involved in working memory. Deficits in attention and vigilance have been reported in individuals with substance use disorders including inability to ignore distracting information on a task-switching test (Salo et al., 2005) and impaired vigilance on a continuous performance monitoring task (London et al., 2005). Attentional bias to drug-related cues occurs when an individual preferentially responds to stimuli associated with drugs. A number of studies have demonstrated that attentional bias to drug-related cues is related to quantity and frequency of use and predictive of relapse to drugs of abuse (Field and Cox, 2008). As such, improvement in working memory and attentional bias are potential therapeutic targets.

3. Cognitive function and treatment outcome

Successful cognitive and behavioral treatment of substance use disorders is dependent on an individual's ability to assimilate and integrate new information into a plan for behavior change that can lead to sobriety and the ability to maintain focus on long-term goals (Sofuoglu et al., 2010). This requires intact cognitive skills and executive function. Therefore, it is not surprising that individuals in treatment with compromised cognitive function have higher dropout rates and poorer treatment outcomes (Aharonovich et al., 2006, 2008; Fox et al., 2009). To the extent that cognitive deficits impede effective treatment engagement, interventions that improve cognitive functioning represent an important therapeutic strategy for individuals suffering with addictive disorders (Vocci, 2008; Sofuoglu et al., 2010). Adjunctive, computer-assisted, cognitive rehabilitation interventions, which involve exercises designed to enhance skills such as problem solving, attention, memory and abstract reasoning, have shown promise in preliminary trials in improving cognitive performance

and treatment outcomes in substance-dependent individuals in treatment (Kiluk et al., 2010; Carroll et al., 2011; Bickel et al., 2011).

4. Cholinergic medications

The neurotransmitter acetylcholine, via interactions with the dopaminergic reward system in the nucleus accumbens, prefrontal cortex, and ventral tegmental area, plays a key role in cognitive and behavioral processes relevant to substance use disorders (Sofuoglu and Mooney, 2009). Addicted individuals display altered cholinergic responses in areas relevant to craving, learning, and memory, suggesting that the cholinergic system may be a promising pharmacological treatment target (Adinoff et al., 2010).

4.1. Cholinesterase inhibitors

The cholinesterase inhibitors donepezil, galantamine, and rivastigmine increase levels of synaptic acetylcholine via inhibition of hydrolysis by the enzyme cholinesterase (Sofuoglu and Mooney, 2009). These medications have been studied extensively and FDA-approved for the treatment of Alzheimer's disease, owing to their effects on dementia-associated cognitive and functional impairments (Farlow, 2002). Recent efforts have sought to determine whether these medications might provide cognitive enhancement among individuals without dementia (Repantis et al., 2010). In light of known cognitive impairments underlying addiction, with likely involvement of acetylcholine, substance-dependent individuals appear to be particularly relevant candidates for this research. Encouraging preclinical work with donepezil, galantamine, and rivastigmine has led to preliminary human laboratory and clinical investigations.

4.1.1. Donepezil

Donepezil has been investigated in two published human trials in cocaine-dependent individuals. In a 10-week randomized, controlled pilot trial of donepezil (goal dose 10 mg) added to weekly cognitive-behavioral therapy for treatment of cocaine dependence, participants taking donepezil (n = 17) did not exhibit reduction in cocaine use, relative to those taking placebo (n = 17) (Winhusen et al., 2005). Of note, this study was underpowered due to small sample size making it difficult to draw any definitive conclusions. A subsequent laboratory study in cocaine-dependent subjects (n = 12) investigated the effect of pre-dosing of donepezil 5 mg, versus placebo, on response to intravenous cocaine (Grasing et al., 2010). Relative to placebo, donepezil was associated with an increase in positive responses to low-dose cocaine. It did not significantly alter positive or negative response to high-dose cocaine.

4.1.2. Galantamine

In a randomized, controlled 12-week trial, galantamine did not reduce relapse in recently detoxified alcohol-dependent individuals (n = 149), but those who relapsed while taking galantamine drank fewer drinks per drinking day (86.0 ± 80.4 g/day) than those taking placebo (112.5 ± 83.8 g/day; Cohen's *d* 0.32) (Mann et al., 2006). Galantamine-randomized participants who smoked cigarettes (n = 56), relative to those randomized to placebo (n = 58), demonstrated a modest reduction in cigarette smoking (59.13 ± 30.52 versus 69.13 ± 25.09 smoking days; Cohen's *d* 0.36) despite no specific psychosocial treatment targeting cigarette smoking (Diehl et al., 2006).

The high rate of cigarette smoking in schizophrenia has led to speculation that smoking may be a form of self-medication to address cognitive difficulties associated with the illness (Simosky et al., 2002). Galantamine was thus investigated in a 12-week randomized, controlled clinical trial as a treatment for smoking in individuals with schizophrenia (n = 43) (Kelly et al., 2008). Results indicated that, relative to placebo, galantamine was not associated with smoking reduction, but was instead associated with worsening of self-ratings of nicotine dependence.

The effects of galantamine on the cognitive deficits associated with other drugs of abuse are less studied. A recent double-blind, randomized trial of galantamine treatment for 10 days in recently abstinent chronic cocaine abusers (n = 34) has demonstrated selective improvement in measures of sustained attention using the Rapid Visual Information Processing task (Sofuoglu et al., 2011). Improved reaction times on the cocaine – Stroop task were also evident in galantamine – treated subjects relative to placebo. Other cognitive and mood outcomes were unaffected in this sample, and substance use outcomes were not assessed (Sofuoglu et al., 2011). Future studies of galantamine in cocaine-dependent subjects that evaluate drug use outcomes and improvement in cognitive function in the context of cognitive behavioral treatment are of interest.

4.1.3. Rivastigmine

In a human laboratory study of intravenous methamphetamine self-administration in 22 individuals with methamphetamine dependence, pretreatment with rivastigmine, relative to placebo, did not alter total choices for methamphetamine (De La Garza et al., 2008). However, participants taking rivastigmine exhibited reduced positive subjective effects of methamphetamine administration. In a recent clinical trial, alcohol- and nicotine-dependent individuals were randomized to 12-weeks of rivastigmine (n = 14) or placebo (n = 12) (Diehl et al., 2009). Those taking rivastigmine exhibited 18% reduction in cigarette craving and 30% reduction in cigarette smoking, while those taking placebo exhibited no significant reductions.

4.2. Nicotinic agonists

Acetylcholine exerts its effects via muscarinic and nicotinic receptors. Nicotine, most commonly delivered in tobacco smoke, occupies nicotinic receptors and interacts with dopaminergic reward pathways. This interaction is thought to be the basis for the reinforcing and addictive properties of nicotine (Balfour and Fagerstrom, 1996; Wise, 1996).

4.2.1. Nicotine

Nicotine replacement therapy, in the context of tobacco withdrawal, has been associated with improvement in cognitive and psychomotor task performance, suggesting a potential role of nicotinic receptor modulation in cognitive enhancement (Atzori et al., 2008; Hughes et al., 1984; Snyder et al., 1989). A recent meta-analysis indicated that nicotine provides cognitive performance enhancement in nonsmokers and in smokers during non-deprived states (Heishman et al., 2010). However, the addictive potential of nicotine is cause for caution regarding the use of nicotine as a cognitive enhancer, particularly among individuals with substance use disorders.

4.2.2. Varenicline

Varenicline is an $\alpha_4\beta_2$ nicotinic acetylcholine receptor partial agonist that is FDA-approved as a smoking cessation treatment. Given its reported lack of abuse potential, varenicline may represent an avenue of exploration for nicotinic receptor-facilitated cognitive enhancement. Studies exploring the effect of varenicline on cognition, and its potential role in non-nicotine substance use disorders, are in early stages.

In a crossover human laboratory study (n = 12), pre-treatment with varenicline for four days reduced the positive subjective effects of intravenous nicotine administration as compared to placebo, but exerted mixed effects on cognition (Sofuoglu et al., 2009a). In another crossover study, smokers (n = 67) exhibited improved sustained attention (Cohen's *d* 0.33) and working memory (Cohen's *d* 0.21) during abstinence after 21 days of varenicline as compared to placebo (Patterson et al., 2009). In a third crossover study incorporating functional magnetic resonance

imaging, highly dependent smokers (n = 7) demonstrated improvement in memory-related complex task performance during a 13-day course of varenicline as compared to placebo (Cohen's *d* 0.37) (Loughead et al., 2010). These improvements were not seen in less dependent smokers (n = 15). For the highly dependent smokers, the improvement in task performance correlated with blood oxygenation level-dependent response. A recent open-label study (n = 14) explored varenicline for smoking cessation in individuals with schizophrenia (Smith et al., 2009). Improvements in verbal learning and memory, as well as smoking reduction, were observed.

Treatment with varenicline, relative to placebo, was associated with reduced alcohol craving, drinking, and reinforcing effects during a self-administration laboratory study (n = 20) among heavy drinking smokers, suggesting that varenicline may also have potential as a treatment agent in non-nicotine substance use disorders (McKee et al., 2009). A recent pilot trial (n = 10) demonstrated the safety of co-administering varenicline and intravenous methamphetamine, opening the potential for further studies of varenicline in methamphetamine-dependent individuals (Zorick et al., 2009).

5. Catecholaminergic agents

The role of the catecholamine neurotransmitters, norepinephrine and dopamine, in cognition, motivation, and reward has been recognized for decades (Berridge et al., 2003; Robbins, 1984; Wise, 1978, 2004). A large body of evidence indicates that mesolimbic dopamine neurons projecting from the ventral tegmental area to the nucleus accumbens are necessary for the acquisition of drug self-administration, an essential step in the progression of addiction (Everitt and Robbins, 2005; Kalivas and O'Brien, 2008). However, medications development strategies aimed at blocking the rewarding effects of addictive drugs through effects on mesolimbic dopamine transmission have had limited success (Vocci and Ling, 2005). This is especially true in the case of addiction to cocaine and methamphetamine, which both act directly on presynaptic dopaminergic and noradrenergic neurons (Fleckenstein et al., 2000; Johanson and Fischman, 1989). As discussed above, recent studies have begun to target improvement in cognitive deficits as one treatment avenue for stimulant dependence (Sofuoglu, 2009; Vocci, 2008) and catecholaminergic agents have been prioritized in much of the this research (Sofuoglu and Sewell, 2009).

Brainstem noradrenergic neurons project widely throughout the brain and mediate diverse functions including general arousal and wakefulness, attention, vigilance, memory consolidation and retrieval, and mood (Berridge et al., 2003). Ascending noradrenergic afferent projections from the locus coeruleus (LC) to the prefrontal cortex (PFC) are thought to exert a modulatory role on attention and working memory by facilitating functional connectivity between frontal cortex and other brain regions rather than by specific local effects in any one region (Sara, 2009). In this framework, reciprocal LC–PFC interactions serve a gating function between frontoparietal cortical circuits that mediate attentional states depending on environmental context. Activity in the LC can shift between high-tonic patterns associated with task-independent (inattentive/exploratory) contexts to high-phasic patterns during task-dependent (stimulus detection) contexts that also correspond to increased PFC activation (Aston-Jones and Cohen, 2005). As such, the LC–PFC system may comprise a critical link between dorsal and ventral frontoparietal attentional circuits that orient goal-driven versus stimulus-driven attention, respectively (Corbetta et al., 2008).

5.1. Stimulant medications

Given the clinical similarities between cognitive impairments observed in chronic stimulant abusers and those seen in individuals with ADHD (Scott et al., 2007), as well as the rate of co-morbid ADHD in the stimulant-dependent population, it is not surprising that stimulants such as amphetamine and methylphenidate have been evaluated extensively as substitution agents (Castells et al., 2007; Herin et al., 2010). Whereas methylphenidate is a selective inhibitor of the norepinephrine and dopamine transporters, amphetamine acts as both an inhibitor and substrate of norepinephrine, dopamine, and serotonin transporters and also promotes presynaptic release of all three neurotransmitters through its inhibition of the vesicular transporter responsible for concentrating monoamines in presynaptic vesicles (Kuczenski and Segal, 1997). Approved for use in children and adults with ADHD, both methylphenidate and amphetamine increase sustained attention, improve inhibitory control, and reduce impulsivity in ADHD, effects attributed to actions on norepinephrine and dopamine neurons projecting to the PFC (Arnsten, 2007; Pliszka, 2005).

However, data concerning the potential for stimulant replacement therapy in the treatment of cocaine and methamphetamine dependence is mixed. A recent meta-analysis of 16 randomized controlled clinical trials (total n = 1345) found no effect of stimulant treatment on treatment retention or cocaine use as assessed by urine drug screens (Castells et al., 2007). However, this analysis included studies of the non-amphetamine drugs modafinil and bupropion, neither of which are FDA-approved treatments of adult or pediatric ADHD. Further, though participants with co-occurring alcohol and cocaine dependence were excluded, roughly 50% of the subjects in the included studies had comorbid opioid dependence. Secondary analyses of individual drug treatments found evidence for reduced cocaine use in subjects treated with dexamphetamine compared to placebo, and those studies that evaluated subjects with comorbid cocaine and heroin dependence found significant improvement in sustained heroin abstinence in psychostimulant-treated patients (Castells et al., 2007). Other studies have reported positive results with stimulant replacement in cocaine dependence. In a double-blind controlled trial of methylphenidate in treatment-seeking cocaine-dependent subjects with co-morbid ADHD, no significant treatment effect was observed in the overall sample, but subjects whose ADHD symptoms improved with methylphenidate reduced cocaine use significantly relative to placebo-treated subjects (Levin et al., 2007). More recently, Mooney et al. (2009) reported significantly greater reduction of cocaine use in subjects treated with methamphetamine as compared to placebo (n = 82). In addition, two trials have shown efficacy of stimulant replacement in reducing use of amphetamine/methamphetamine in dependent subjects. Tiihonen and colleagues reported superiority of high-dose methylphenidate over placebo in a cohort of heavy amphetamine users whose primary route of administration was intravenous injection (Tiihonen et al., 2007). Interestingly, this trial was halted early due to significant clinical decline in a comparison group treated with aripiprazole. Finally, a recent randomized, controlled trial conducted in methamphetamine dependent subjects (n = 80) found significantly improved retention, lower level of dependence, and a trend toward greater reduction in methamphetamine use in subjects treated with dexamphetamine as compared to those receiving placebo (Longo et al., 2010). Unfortunately, none of these studies systematically evaluated the effects of stimulant treatment on cognitive functioning or ability to engage in cognitive behavioral therapy, so the role of improvement in cognitive function in any positive studies is unclear.

5.2. Modafinil

The non-amphetamine stimulant modafinil has received considerable attention as a potential psychotropic agent in several psychiatric disorders, including schizophrenia, ADHD, and more recently, cocaine and methamphetamine dependence (Ballon and Feifel, 2006; Minzenberg and Carter, 2008). Currently approved for the treatment of narcolepsy and shift-work sleep disorder, modafinil exerts complex pharmacologic effects on multiple neurotransmitter systems that

are clearly distinct from those of psychostimulant drugs such as methylphenidate or amphetamine, yet its definitive mechanism(s) of action remain unknown. Modafinil increases activity of noradrenergic, dopaminergic, serotonergic, glutamatergic, and hypocretin (orexin) neurotransmitter systems, and decreases γ-aminobutyric acid (GABA) activity, in multiple discrete brain regions. Recent neuroimaging studies, however, suggest that the actions of modafinil on catecholamine neurons may contribute significantly to its effects on wakefulness and cognition. Findings from PET studies in nonhuman primates demonstrate significant binding occupancy of norepinephrine and dopamine transporters by modafinil in vivo (Madras et al., 2006). Similarly, modafinil displaces [^{11}C]-cocaine binding from the dopamine transporter and elevates extracellular dopamine levels in caudate, putamen, and nucleus accumbens of human volunteers at clinically relevant doses (Volkow et al., 2009). Modafinil also shifts activity in the human locus coeruleus, a pontine noradrenergic nucleus with afferent projections to the PFC, from tonic to task-dependent phasic patterns that correlate with enhanced functional prefrontal connectivity and improved cognitive task performance (Minzenberg et al., 2008).

Modafinil has been shown to improve cognitive performance in several domains in both animals and humans, though findings have not been uniformly positive (Minzenberg and Carter, 2008). Improvement in response accuracy and reaction times in tests of sustained attention have been reported in healthy adult volunteers with and without sleep deprivation (Hart et al., 2006a, b; Randall et al., 2005a; Turner et al., 2003), but effects in healthy subjects without sleep deprivation may be limited to those with lower cognitive functioning at baseline (Randall et al., 2005b). Similarly, though negative results have been reported in small samples of subjects with ADHD (Taylor and Russo, 2000), modafinil has been shown to significantly improve digit span performance, visual recognition memory, and response inhibition in adults with ADHD (Turner et al., 2004).

The rationale for evaluation of modafinil as a treatment for stimulant dependence is based on several lines of research. Modafinil exerts minimal stimulant-like subjective effects (Rush et al., 2002a) and does not serve as a cocaine-like discriminative stimulus (Rush et al., 2002b) in experienced cocaine users. Co-administration of modafinil does not adversely interact with cocaine (Dackis et al., 2003; Donovan et al., 2005; Malcolm et al., 2006) or methamphetamine (De La Garza et al., 2010), even when these drugs are administered intravenously. In fact, daily pretreatment with modafinil for 1 week reduced peak plasma concentration of cocaine achieved after intravenous infusion (Donovan et al., 2005) and attenuated subjective effects of cocaine in cocaine-dependent subjects in the laboratory (Hart et al., 2008; Malcolm et al., 2006). Modafinil pretreatment has been reported to similarly reduce self-rated euphoria after intravenous methamphetamine infusion, though this effect did not reach statistical significance (De La Garza et al., 2010). Perhaps most encouraging, modafinil has been shown to reduce smoked cocaine self-administration in a human laboratory paradigm (Hart et al., 2008), and appears to have minimal abuse liability in stimulant users (Vosburg et al., 2010) despite its ability to block dopamine uptake in human volunteers (Volkow et al., 2009). Finally, modafinil has been shown to normalize sleep disruptions in chronic cocaine users by reducing nighttime sleep latency, increasing slow-wave sleep, and reducing subjective daytime somnolence during early abstinence (Morgan et al., 2010).

Despite the encouraging evidence discussed above, translation of human laboratory findings to randomized, placebo-controlled clinical trials of modafinil for cocaine and methamphetamine dependence has been mixed. In a single-center, double-blind, placebo-controlled trial of fixed dose (400 mg/day) modafinil conducted over 8 weeks in 62 cocaine-dependent outpatients, Dackis et al. (2005) found no effect of modafinil on study retention or CBT attendance but reported a significantly higher proportion of benzoylecgonine-negative urine drug screens in modafinil-treated subjects as compared to the placebo-treated group (Dackis et al., 2005). In this study, modafinil treatment also resulted in a larger percentage of subjects who were able to attain sustained abstinence (≥3 consecutive weeks with negative urines) than placebo (Dackis et al., 2005). However, modafinil-treated subjects tended to have lower baseline use of cocaine, a factor that is predictive of treatment outcomes. A larger multicenter trial of 210 treatment-seeking cocaine-dependent patients randomized to placebo or one of two doses (200 or 400 mg/day) of modafinil found no significant effect of modafinil on study retention, counseling attendance, or cocaine use in the full sample over the 12-week study period (Anderson et al., 2009). However, post hoc exploratory analyses suggested that alcohol dependence influenced the efficacy of modafinil in reducing cocaine use. In cocaine-dependent subjects with no history of alcohol dependence, modafinil treatment at either dose resulted in fewer cocaine using days and more consecutive abstinent days as compared to placebo (Anderson et al., 2009). Even so, the differences in non-using days in each modafinil group were only 8–9% higher than in placebo-treated subjects, suggesting that the effect size of modafinil treatment is modest even in cocaine-dependent subjects without alcohol dependence. Unfortunately, there was no report of cognitive testing in any of the trials of modafinil in cocaine-dependent individuals.

Efficacy of modafinil in two recent double-blind, placebo-controlled trials for methamphetamine dependence has been less encouraging. In each study, modafinil at daily doses of 200 mg (Shearer et al., 2009) and 400 mg (Heinzerling et al., 2010) failed to improve retention or reduce methamphetamine use in full sample analyses. Secondary analyses in the study by Shearer et al. (2009) found a trend toward improved abstinence in subjects with high medication compliance, but this did not differ across treatment groups (Shearer et al., 2009). Similarly, there was no advantage of modafinil in increasing participation in psychosocial counseling sessions (Shearer et al., 2009). Post hoc analyses in one study suggested a trend toward reduced methamphetamine use in modafinil-treated subjects with high methamphetamine use frequency and/or low CBT attendance, but differences between treatment groups in these subsets of participants did not reach significance (Heinzerling et al., 2010).

Studies of cognitive outcomes in methamphetamine-dependent patients treated with modafinil are scarce. In a recent double-blind, placebo-controlled, crossover study of 400 mg/day modafinil in nontreatment-seeking subjects with methamphetamine dependence tested sequentially at baseline and after each treatment condition, modafinil improved scores on a working memory task, but only in subjects with low baseline performance (Kalechstein et al., 2010). No effect of treatment on either a simple reaction time task or a verbal learning and memory task was evident. Though suggestive, this study employed a very small sample (n = 11) of nontreatment-seeking subjects in a crossover design and thus the impact of any cognitive improvement on treatment engagement, retention or substance use-related outcomes is unknown. Future studies of cognitive enhancement in treatment-seeking individuals undergoing concurrent psychosocial treatment will be required to address this fundamental question.

6. Noradrenergic medications

6.1. Nonstimulant noradrenergic agents

Two medications approved for the treatment of ADHD selectively modulate noradrenergic transmission without amphetamine-type stimulant properties (Pliszka, 2005). Atomoxetine is a selective inhibitor of the norepinephrine transporter and increases extracellular norepinephrine levels in the PFC (Bymaster et al., 2002). Effective in improving attention in both children and adults with ADHD (Michelson et al., 2002, 2003), atomoxetine also selectively improved response inhibition without affecting probabilistic learning in healthy volunteers (Chamberlain et al., 2006). In studies conducted by independent research

groups, atomoxetine exerted minimal stimulant-like subjective effects or abuse liability in human laboratory volunteers (Heil et al., 2002; Jasinski et al., 2008) and attenuated the euphoric subjective effects of dextroamphetamine (Sofuoglu and Sewell, 2009), though none of these studies included stimulant-dependent subjects. In a small sample of cocaine-dependent subjects, atomoxetine did not influence the subjective effects of intranasal cocaine administration in a human laboratory setting (Stoops et al., 2008). Results from studies of the effect of atomoxetine on cognition in substance-dependent individuals have been mixed. Alcohol dependent adults with ADHD treated with atomoxetine for 12 weeks exhibited significant improvement in ADHD symptoms and reduced cumulative heavy drinking days compared with placebo (Wilens et al., 2008). In contrast, no effect of the drug on cognitive outcomes was found in abstinent nicotine-dependent subjects without ADHD despite reduced subjective craving and withdrawal (Ray et al., 2009).

Guanfacine, a selective agonist of the α-2A adrenergic receptor found in high density in the PFC, is another noradrenergic medication approved for treatment of ADHD in children (Ramos and Arnsten, 2007). Localized on both presynaptic and postsynaptic noradrenergic terminals neurons of the PFC, the α-2A adrenergic receptor binds synaptic norepinephrine with higher affinity than other adrenoceptors and thus mediates preferential (presynaptic) inhibition of neurotransmitter release at low agonist concentrations. Though the cognitive effects of guanfacine in substance-dependent individuals is currently unknown, its ability to improve working memory in healthy controls (Jakala et al., 1999), as well as enhancing attentional performance in subjects with schizophrenia (Friedman et al., 2001) suggests that guanfacine or related medications may warrant further study as cognitive enhancers in individuals with addictions.

7. Glutamatergic medications

Glutamate, the most common excitatory neurotransmitter in the CNS, is critical to synaptic plasticity, and, therefore learning and memory (Antzoulatos and Byrne, 2004). A large body of evidence suggests that activity at the glutamatergic N-methyl-D-aspartate (NMDA) receptor is involved in the acquisition and retention of conditioned or emotional learning as well as the extinction of response to conditioned cues (Davis and Myers, 2002). This has led to a number of studies exploring the use of glutamate-modulating medications as potential pharmacotherapy to enhance response to extinction-based psychosocial treatments in a variety of disorders (Myers et al., 2011). In addition, animal studies using the reinstatement model of relapse have demonstrated that glutamatergic projections to the nucleus accumbens are critical for both stress and cocaine-primed reinstatement (McFarland et al., 2003; Park et al., 2002) and human imaging studies implicate glutamatergic pathways in the response to cocaine and cocaine cues (Garavan et al., 2000). As such, glutamatergic agents could have utility in the treatment of substance use disorders by accelerating extinction of response to drug-related environmental cues or through targeting glutamatergic pathways directly involved in drug craving and withdrawal (Gass and Olive, 2008).

7.1. D-Cycloserine

Acute treatment with D-cycloserine (DCS), a partial glutamate NMDA receptor agonist active at the glycine binding site, enhances learning processes underlying the acquisition of the extinction of conditioned fear responding in animal models as well as in clinical populations of individuals with anxiety disorders (D'Souza et al., 1995; Norberg et al., 2008). Animal studies demonstrated that DCS facilitated extinction of cocaine conditioned place preference and impaired reacquisition of COC self-administration (Paolone et al., 2009), indicating a potential role for DCS in the treatment of addiction. This has led to exploration of the potential of DCS to facilitate extinction of reactivity to drug-related cues in addiction. A recent controlled study demonstrated that DCS, coupled with an exposure-based psychosocial treatment, facilitated reduction in smoking-related cue reactivity among non-treatment seeking smokers (n = 25) (Santa Ana et al., 2009). Participants in the DCS group exhibited a lower mean expired carbon monoxide level ($F[1, 18] = 8.3$, $p = 0.01$; Cohen's $d = 1.1$) at one-week follow-up compared to participants in the placebo group. In a preliminary analysis (n = 10) of an ongoing trial of DCS in cocaine users, the medication increased acute reactivity to cocaine cues, relative to placebo, but facilitated trend-level reductions in drug craving at follow-up (Price et al., 2009). DCS has demonstrated improvements in visuospatial cognitive task performance among healthy individuals (Bailey et al., 2007), but broad cognitive effects have not yet been investigated in substance dependent individuals.

7.2. Memantine

The noncompetitive NMDA receptor antagonist memantine is approved for treatment of Alzheimer's disease, and has been investigated as a potential cognitive enhancer in broader populations, yielding mixed but generally encouraging results (for review, Repantis et al., 2010). Given the role of glutamate in addiction, human laboratory and pilot clinical research studies have been conducted to explore the potential of memantine as a pharmacotherapy for substance use disorders, although studies to date have not explored the impact of memantine on cognitive function in individuals with substance use disorders.

Initial laboratory studies (n = 18 and 38) revealed that memantine, relative to placebo, reduced craving for alcohol and reactivity to alcohol-related cues (Bisaga and Evans, 2004; Krupitsky et al., 2007). However, when co-administered with alcohol, memantine increased the dissociative effects of alcohol, but did not alter overall intoxicating effects (Bisaga and Evans, 2004). A subsequent 16-week pilot randomized, controlled trial of memantine in treatment-seeking alcohol-dependent individuals (n = 44) revealed that participants receiving placebo, compared with those receiving memantine, demonstrated improved alcohol reduction and abstinence outcomes (Evans et al., 2007). Difficulty with tolerability led 26% of participants taking memantine to decrease dosing or discontinue the medication. These findings do not support the use of memantine as a treatment among active drinkers.

In an 8-week inpatient trial, detoxified heroin-dependent individuals (n = 8) pre-treated with memantine as compared to placebo demonstrated reduced subjective, but not reinforcing, effects of laboratory-administered intranasal heroin (Comer and Sullivan, 2007). A recent human laboratory study (n = 60) investigated the effects of memantine (and the nicotinic-receptor antagonist mecamylamine) on smoking-induced improvement in sustained attention and smoking-related subjective effects (Jackson et al., 2009). Memantine reduced the smoking-induced "buzzed" feeling, but did not alter other effects.

7.3. N-Acetylcysteine

Based on encouraging cognitive-enhancing studies in animals, the antioxidant N-Acetylcysteine has been investigated as a potential treatment in humans targeting cognitive decline in dementia (McCaddon and Hudson, 2010), demonstrating reduced mitochondria-related oxidative stress in fibroblasts of patients with Alzheimer's disease (Moreira et al., 2007). N-Acetylcysteine has also recently garnered attention in addiction-related research. In animal models, N-Acetylcysteine has demonstrated glutamate modulation in the nucleus accumbens, via activation of the cystine–glutamate exchanger, leading to changes in drug seeking and self-administration (Zhou, 2010). Preliminary investigations in cocaine-dependent humans have revealed that N-Acetylcysteine, relative to placebo, is well tolerated and may reduce cocaine withdrawal, craving, and cue reactivity (LaRowe et al., 2006, 2007). A subsequent 4-week

open-label clinical trial revealed adequate tolerability and reduced cocaine use among cocaine-dependent individuals (n = 23) taking N-Acetylcysteine (LaRowe et al., 2007). These findings have led to encouraging pilot clinical investigations of N-Acetylcysteine in other substance using populations. N-Acetylcysteine, relative to placebo, treatment led to cigarette smoking reduction in nicotine-dependent individuals. An open-label pilot study in cannabis-dependent youth (n = 24) demonstrated adequate tolerability and reductions in cannabis craving and use during treatment with N-Acetylcysteine (Gray et al., 2010). To date, no studies have investigated the impact of N-Acetylcysteine on cognitive function in individuals with substance use disorders.

8. Other medications

8.1. Tiagabine

The anticonvulsant tiagabine has garnered interest in addictions research due to its inhibition of presynaptic reuptake of gamma-aminobutyric acid (GABA), a neurotransmitter that interacts with dopaminergic reward systems (Adkins and Noble, 1998; Cousins et al., 2002). In a crossover human laboratory study of acutely abstinent smokers (n = 12), tiagabine reduced craving for cigarettes and attenuated subjective positive effects of IV nicotine administration (Sofuoglu et al., 2005). Participants in this study also demonstrated enhanced performance on a Stroop cognitive task while taking tiagabine, relative to placebo. In a 10-week randomized, controlled clinical trial for cocaine dependence (n = 17 in tiagabine and in placebo groups), a trend toward reduced urine cocaine metabolites was seen in the tiagabine group ($p = 0.1$) (Winhusen et al., 2005).

8.2. Minocycline

The antibiotic minocycline exerts general anti-inflammatory and neuroprotective effects (Yrjanheikki et al., 1999). In animal models, minocycline has been shown to attenuate cognitive and behavioral disturbances resulting from NMDA antagonist administration, presumably by modulating glutamate transmission (Fujita et al., 2008; Zhang et al., 2007). These animal studies, coupled with encouraging preliminary human studies, led to a controlled trial of minocycline targeting cognition and negative symptoms in schizophrenia (Levkovitz et al., 2010). Cognitive effects were significant, including improvement in cognitive planning and reduced errors in working memory and cognitive shifting.

Minocycline reduces nitric oxide (NO) production by inhibiting the neuronal NO synthase enzyme (Du et al., 2001). NO, in turn, has been shown to modulate interactions between nicotine and the dopaminergic reward system, suggesting NO modulation as a potential target for the development of pharmacotherapies targeting nicotine dependence (Vleeming et al., 2002). In a controlled crossover study of minocycline pre-treatment effects on intravenous nicotine administration in cigarette smokers (n = 12), minocycline did not reduce nicotine selection, self-administration, or subjective effects, but did reduce subsequent craving for cigarettes (Sofuoglu et al., 2009b).

9. Future directions

The exploration of cognitive enhancement in the treatment of substance use disorders is in its infancy. While it is clear that chronic use of most substances of abuse is associated with cognitive deficits, the relationship of these cognitive deficits to substance use treatment outcomes is not clear. The idea that deficits in information processing, working memory, response inhibition, decision-making, and problem solving would interfere with an individual's recovery and ability to benefit from psychosocial treatment has much intuitive appeal, but few studies have actually demonstrated this. It will be important to get a better understanding of the relationship between specific cognitive impairments and treatment outcomes so that targeted treatments can be designed. For example, are there certain cognitive deficits that are associated with greater difficulty in treatment? A related and critical issue is whether improvement in cognitive deficits is related to improvement in substance abuse treatment outcomes.

None of the pharmacotherapeutic studies to date have comprehensively evaluated the impact of medications on cognitive function and substance use outcomes in a manner that allows for direct examination of the relationship between the two. In fact, most of the studies reviewed solely investigated the impact of an agent on cognitive function or substance use outcomes, making it impossible to even draw preliminary conclusions about the relationship between the two. In addition, if the potential for an agent to work through cognitive enhancement is to be examined, studies investigating the agent in the context of a learning paradigm might be most relevant. The only examples in the reviewed literature were studies investigating D-cycloserine administered in the context of an extinction-learning paradigm. Further human laboratory studies examining the impact of cognitive-enhancing agents in the context of learning opportunities that might be relevant to recovery as well as basic cognitive function would be useful. Future clinical trials in which both substance use and cognitive outcomes are measured, focused on combining cognitive-enhancing agents with psychosocial therapies involving specific aspects of cognitive function to investigate potential synergistic effects, would be of great interest. For example, certain agents such as D-cycloserine may act by facilitating extinction learning, and would thus be best paired with treatments focused on the extinction of response to drug-related cues. On the other hand, agents that work to improve informational processing, problem solving and decision-making might work best in combination with cognitive-behavioral therapy. Finally, because there could be differences in medication effects and cognitive function based on gender, ethnicity and level and type of substance use, future studies should measure and report on these variables.

10. Conclusions

With the growth of cognitive neuroscience research, the importance of executive function and inhibitory cognitive control in addictive disorders is becoming increasingly apparent. In many therapeutic areas, explorations of medications that can improve cognitive function are promising. These explorations have just begun in the area of addictions, but some preliminary findings are promising. In particular, exploration of cholinergic, noradrenergic and glutamatergic agents is encouraging. However, no studies to date comprehensively measure both cognitive function and substance use outcomes, so exploration of the relationship between the two cannot be addressed with existing data. Furthermore, there is little investigation of these agents in the context of specific learning paradigms. Future studies should focus on agents that have shown promise in cognitive enhancement in other disorders, and have a theoretical or mechanistic rationale for application to substance use disorders. In addition, the interaction of cognitive enhancing agents with psychosocial treatments that involve specific aspects of cognitive function and examination of the relationship between improvement in cognitive function and substance use outcomes are areas that warrant further investigation.

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