Addiction

REVIEW

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Cognitive enhancement as a pharmacotherapy target for stimulant addiction

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ABSTRACT

Background No medications have been proven to be effective for cocaine and methamphetamine addiction. Attenuation of drug reward has been the main strategy for medications development, but this approach has not led to effective treatments. Thus, there is a need to identify novel treatment targets in addition to the brain reward system. **Aim** To propose a novel treatment strategy for stimulant addiction that will focus on medications enhancing cognitive function and attenuating drug reward. **Methods** Pre-clinical and clinical literature on potential use of cognitive enhancers for stimulant addiction pharmacotherapy was reviewed. **Results and conclusions** Cocaine and methamphetamine users show significant cognitive impairments, especially in attention, working memory and response inhibition functions. The cognitive impairments seem to be predictive of poor treatment retention and outcome. Medications targeting acetylcholine and norepinephrine are particularly well suited for enhancing cognitive function in stimulant users. Many cholinergic and noradrenergic medications are on the market and have a good safety profile and low abuse potential. These include galantamine, donepezil and rivastigmine (cholinesterase inhibitors), varenicline (partial nicotine agonist), guanfacine (alpha$_2$-adrenergic agonist) and atomoxetine (norepinephrine transporter inhibitor). Future clinical studies designed optimally to measure cognitive function as well as drug use behavior would be needed to test the efficacy of these cognitive enhancers for stimulant addiction.

Keywords Cognition, cognitive enhancers, pharmacotherapy, stimulants.

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INTRODUCTION

Stimulant addiction, most notably cocaine and methamphetamine, continues to be an important public health problem, with an estimated 36 million current users world-wide [1]. Unfortunately, no medications have been proven to be effective for cocaine and methamphetamine addiction in spite of the large number of compounds screened in randomized clinical trials [2–5]. For stimulant addiction, the traditional medications development strategy has been to identify medications that attenuate drug reward [5], which is mediated by the dopaminergic pathway from the ventral tegmental area (VTA) to the nucleus accumbens (subcortical structures in the brain). This strategy, however, has not resulted in effective medication development. Thus, there is a clear need to examine critically our medication development strategies and identify new treatment targets for stimulant addiction.

A new strategy proposed in this review is to develop new science-based treatment targets that will broaden our screening methods for potential medications for addictions. Converging evidence, especially from human neuroimaging and cognitive neuroscience studies, indicates that cognitive functions, particularly inhibitory cognitive control, are linked closely to addictive behaviors [6–9]. These cognitive functions, which are attributed to the prefrontal cortex (PFC), can also be improved by selective medications known as cognitive enhancers. In this review, cognitive function in stimulant addiction will be overviewed, followed by examples of cognitive enhancers that may be used for the treatment of stimulant addicted individuals. An ideal cognitive enhancer for addiction pharmacotherapy should enhance cognitive function and attenuate drug reward. Although such medications remain to be identified, promising candidates for addiction pharmacotherapy will be reviewed and future

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research directions will be discussed. This will be a selective review of potential use of cognitive enhancers for stimulant addiction, with a focus upon medications development. Systematic reviews of medications under investigation for stimulant addiction can be found elsewhere [2–5]. For a broader perspective of cognitive remediation in stimulant addiction, the reader is referred to an excellent review by Vocci [9].

COGNITIVE FUNCTION AND ADDICTION

Many studies have demonstrated that chronic use of cocaine and methamphetamine is associated with deficits in cognitive functioning, including decision-making, response inhibition, planning, working memory and attention [10–15]. In a recent meta-analysis [12], cocaine users ($n = 481$) showed greater impairment in attention, visual memory, design reproduction and working memory compared to healthy controls ($n = 586$). These deficits seem to be correlated with the severity of cocaine use, suggesting a dose-related effect of drug use [13]. Similarly, methamphetamine-dependent individuals showed deficits in memory, attention, set-shifting, response inhibition and decision-making abilities [16–20]. The severity of impairments in verbal memory and psychomotor function for methamphetamine users were correlated with loss of dopamine transporters in the striatum and nucleus accumbens [21,22]. The neural substrates of these deficits have been examined in functional imaging studies. A recent PET study demonstrated low glucose metabolism in the anterior cingulate and high glucose metabolism in the lateral orbitofrontal area, middle and posterior cingulate, amygdala, ventral striatum and cerebellum of recently abstinent methamphetamine abusers [23]. These and many other studies point to a dysfunction in the PFC in stimulant users [24]. The PFC serves many functions that are highly relevant for addiction, including attention, working memory, response inhibition and decision-making [8,25].

Among PFC functions, disruptions in inhibitory control of the PFC have been the centerpiece in many theories of addiction [6–8]. The inhibitory function of the PFC is especially important when the individual needs to override a reflexive pre-potent response, such as drug-taking behavior in response to drug cues. In fact, compulsive drug use, the hallmark of drug addiction, is characterized by behavioral inflexibility and more specifically a decreased ability to inhibit responses to drug-related cues, also commonly called impulsivity [26].

From a treatment perspective, the inhibitory control function of the PFC has two unique features. First, inhibitory control and other cognitive functions of the PFC are influenced greatly by the neurochemical environment of the PFC to a greater degree than other brain regions [27]. This quality renders PFC functions very susceptible to genetic and environmental influences, including stress. However, this sensitivity also renders PFC cognitive functions amenable to treatment with selective cognitive enhancers. Secondly, inhibitory control is not a circumscribed function of the PFC. Rather, many PFC areas contribute to inhibitory function including the orbitofrontal cortex, anterior cingulate cortex, dorsolateral PFC, dorsomedial PFC and inferior frontal gyrus [28,29]. Moreover, inhibitory control is linked closely to other PFC functions, most notably to attention and working memory. For example, lapses in attention during early abstinence have been linked to relapse, possibly by reducing behavioral inhibition [30]. Similarly, working memory function is essential for optimum inhibitory control. Under high working demand, cocaine users have reduced inhibitory control measured by impaired suppression of pre-potent responses compared to healthy controls [31]. As these examples suggest, optimum inhibitory control function depends on other PFC functions including attention and working memory. One possible, as yet untested, treatment implication of these findings is that in stimulant users, medications improving attention and working memory may lead to better inhibitory control.

COGNITIVE DEFICITS AND TREATMENT OUTCOME

Despite evidence supporting the presence of cognitive deficits in drug users including decision-making, response inhibition, planning, working memory and attention, the clinical implications of these findings have received limited attention, due perhaps to the subtle nature of these deficits and observations that at least some may be reversible following cessation of drug use. However, former amphetamine users have shown cognitive impairments similar to current users, suggesting that these cognitive impairments were not reversible after short-term abstinence [32]. Similarly, in a longitudinal study of methamphetamine-dependent individuals participating in an out-patient treatment program [33], the group continuing to use methamphetamine performed best in cognitive tests, followed by the recent relapse group, and the abstinent group (6 months) performed the poorest overall. In addition, recent cocaine use seems to mask underlying cognitive deficits in cocaine users [34], further indicating a possible decrease in cognitive functioning during early abstinence from stimulant use.

Several lines of evidence link cognitive function to treatment outcome in stimulant users. In a series of studies, Aharonovich and colleagues have demonstrated that cognitive impairment renders cocaine users less able

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to benefit from behavioral treatment [35,36]. That is, cocaine users who dropped out of treatment had significantly lower performance on attention, memory, spatial ability, speed, accuracy, global functioning and cognitive proficiency tests. Similarly, in a study with treatment-seeking cocaine users, performance in the Stroop color–word interference task, a reliable measure of inhibitory control function at treatment entry was predictive of treatment retention [37]. Further, impulsivity or poor response inhibition as a personality trait, measured with the Barratt Impulsiveness Scale (BIS-11), was a predictor of poor treatment retention in cocaine users [38,39]. In previous studies with users of other substances, deficits in cognitive functioning and inhibitory control also predicted higher dropout rates and poor treatment response [40–42]. These findings emphasize the importance of addressing cognitive functioning in drug users early in treatment to alleviate cognitive deficits that may impact treatment adherence and outcome.

MEDICATIONS TARGETING COGNITIVE FUNCTION AND ADDICTION

Cognitive functioning in the PFC is modulated by many neurotransmitters, including glutamate, gamma aminobutyric acid (GABA), serotonin, acetylcholine (ACh), dopamine (DA) and norepinephrine (NE) [43]. Medications enhancing dopaminergic transmission, including methylphenidate and amphetamine derivatives, are used most commonly, especially for the treatment of attention deficit hyperactivity disorder (ADHD). These dopaminergic enhancers have also shown promise in short-term clinical trials for the treatment of cocaine and amphetamine addiction [44–46]. However, these medications have significant abuse potential, and the safety and feasibility of their long-term use in addicted populations remains to be determined [47]. Another cognitive enhancer is modafinil, which has mixed neurotransmitter actions, including GABA, glutamate and dopaminergic transmitters. Modafinil has been evaluated for cocaine and methamphetamine addiction, with some promising findings [48]. However, modafinil may also have abuse potential, which may limit its utility in stimulant addicted individuals [49].

As will be summarized below, based on our recent review of the literature [50,51], medications targeting ACh and NE share several features that make them potential treatments to improve inhibitory control function in stimulant-addicted individuals. First, both ACh and NE have well-established effects on PFC cognitive functions that are impaired in drug users, including response inhibition, attention and working memory. Secondly, both ACh and NE are emerging treatment targets for addiction pharmacotherapies. Thirdly, several cholinergic and noradrenergic medications are on the market, have a good safety profile and have low abuse potential.

Cholinergic system

Acetylcholine participates in many central nervous system (CNS) functions, including sensory and motor processing, sleep, nociception, mood, stress response, attention, arousal, memory, motivation and reward [52–54]. These diverse functions are mediated by nicotinic and muscarinic cholinergic receptors. Cholinergic neurons are either projection neurons, terminating diffusely in the brain (including in the PFC), or interneurons, which are located mainly in the striatum and nucleus accumbens [55]. While cholinergic projection neurons are critical in cognitive function, cholinergic interneurons integrate cortical and subcortical information related to reward [56,57].

Cognition

ACh plays an important role in mediating PFC cognitive functions, including attention and declarative and working memory, which are mediated possibly through nicotinic cholinergic receptors [54,58]. Recent studies also suggest that reduction in ACh release in the PFC may be critical in mediating attentional deficits associated with chronic amphetamine exposure in rats [59,60]. The reduction in ACh release in response to cognitive tasks (called ACh 'freezing') may be alleviated by medications increasing ACh release, such as cholinesterase inhibitors.

Reward

ACh also interacts with the dopaminergic reward system, especially in the nucleus accumbens. Lesioning of these neurons by a cholinergic immune toxin results in greater sensitivity and preference to cocaine in mice [61]. In contrast, enhancement of cholinergic transmission by treatment with the cholinesterase inhibitor physostigmine decreased cocaine self-administration in monkeys [62]. Similarly, donepezil reduced locomotor sensitivity and preference to cocaine in mice [63].

Cholinergic medications

Two classes of medications targeting the cholinergic system may potentially be useful for stimulant addiction: cholinesterase inhibitors and partial nicotine agonists.

Cholinesterase inhibitors

Cholinesterase inhibitors increase the synaptic concentrations of ACh, which results in increased stimulation of both nicotinic and muscarinic ACh receptors. A number of cholinesterase inhibitors, including tacrine, rivastig-

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mine, donepezil and galantamine, are available for clinical use for the treatment of dementia [64–66]. Cholinesterase inhibitors have also been evaluated for other disorders characterized by cognitive impairment, including Parkinson's disease, traumatic brain injury and schizophrenia [67–69]. The pharmacological and side-effect profiles of cholinesterase inhibitors differ. Tacrine has limited use due to hepatotoxicity and a short half-life [67–69]. Galantamine also binds to nicotinic receptors, especially α_7 and $\alpha_4\beta_2$ subtypes, and enhances responses to acetylcholine [70]. Donepezil and rivastigmine are more potent cholinesterase inhibitors compared to galantamine [71].

There have been few human studies examining cholinesterase inhibitors as potential treatments for amphetamine addiction. Janowsky *et al.* [72] reported that physostigmine cholinesterase inhibitors attenuate the subjective effects of methylphenidate, a stimulant medication, in bipolar and schizophrenic patients. Recently, De La Garza *et al.* examined the effects of a cholinesterase inhibitor, rivastigmine (1.5 or 3 mg/day), on intravenous methamphetamine responses (30 mg/day) in 23 methamphetamine-dependent humans [73]. In that study, 3 mg rivastigmine attenuated some of methamphetamine's subjective effects, including 'desire' and 'anxiety'. These findings are promising, and warrant further studies evaluating cholinesterase inhibitors as potential treatments for stimulant addiction.

In a clinical trial, 10 mg/day donepezil, a cholinesterase inhibitor, was well tolerated but did not reduce cocaine use behavior [74]. The sample size of the study was small (only 17 subjects assigned to donepezil), providing inadequate statistical power to test the study hypothesis. Further, only one dose of donepezil was evaluated. In spite of these limitations, those treated with donepezil showed significant reductions in craving and other indexes of addiction severity to cocaine and other drugs.

In a recent study, our group examined the cognitive effect of galantamine treatment in 28 abstinent cocaine users (Sofuoglu *et al.*, unpublished). Preliminary analysis indicates that galantamine administered at 8 mg/day for 10 days improved sustained attention more effectively than placebo, as measured by the Rapid Visual Information Processing (RVIP) subtest of the Cambridge Neuropsychological Test Automated Battery (CANTAB). Most notably, galantamine treatment, compared to placebo, was associated with shorter mean latency score for the RVIP task. These results indicate the feasibility, safety and promise of galantamine as a cognitive enhancer among cocaine users.

Partial nicotine agonists

Varenicline, a partial agonist of $\alpha_4\beta_2$ nicotinic receptors, has been marketed recently for smoking cessation. Several other partial nicotinic agonists, including dianicline and ispronicline, are undergoing human studies for smoking cessation and treatment of dementia [76]. In pre-clinical studies, varenicline has been shown to alleviate learning deficits in mice induced by alcohol administration [76] or nicotine withdrawal [77]. In a recent study of cigarette smokers, 10 days of varenicline treatment improved working memory and attention deficits induced by nicotine withdrawal [78]. Another similarly acting partial nicotine agonist, AZD3480, enhanced attention and episodic memory functions in healthy volunteers [75].

Partial nicotinic agonists may also have value for stimulant addiction pharmacotherapy, given the role of nicotinic receptors in stimulant effects. For example, nicotine treatment reduced methamphetamine-seeking behavior in rodents [79]. In humans, nicotine may change typical subjective and physiological responses to stimulants. In one study, a 14-mg nicotine patch attenuated cocaine-induced 'high' and 'stimulation' and increased the latency of detection of cocaine effects compared to placebo, without affecting physiological responses or the pharmacokinetics of cocaine [80]. Rapid desensitization to nicotine's effects has limited the use of nicotinic agonists. Varenicline and other partial nicotine agonists do not seem to cause rapid desensitization in nicotinic receptors [81] and may be useful to examine the contribution of nicotinic receptors in stimulant responses. Varenicline and other partial nicotinic agonists remain to be evaluated for stimulant addiction.

Noradrenergic system

The noradrenergic system uses norepinephrine (NE) as its main chemical messenger and serves multiple brain functions, including arousal, attention, mood, learning, memory and stress response [82,83]. Noradrenergic neurons are localized in brainstem nuclei such as the locus ceruleus, and noradrenergic axons project diffusely to almost every part of the brain [84]. NE's effects are mediated by three families of adrenergic receptors: α_1, α_2 and β [85].

Cognition

Increasing evidence from pre-clinical and clinical studies indicate that NE is critical in many PFC cognitive functions, including sustained attention, working memory and response inhibition [86,87]. The beneficial effect of NE on PFC cognitive functioning is thought to be mediated by the stimulation of postsynaptic alpha$_2$-adrenergic receptors in the PFC [88]. Alpha$_2$-adrenergic receptors are targeted by several medications, including alpha$_2$-adrenergic agonists (clonidine, lofexidine and guanfa-

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cine) and norepinephrine transporter inhibitors (reboxetine and atomoxetine).

Reward

NE is also connected closely to the dopaminergic reward system. For example, lesioning of noradrenergic neurons in the locus ceruleus decreases DA release in the nucleus accumbens [89] and, conversely, activation of locus ceruleus noradrenergic neurons increases the activity of dopaminergic neurons in the VTA [90]. This regulation is mediated by the α_1-adrenergic receptor subtype [91].

Noradrenergic medications

Two classes of medications targeting NE may potentially be useful for stimulant addiction: norepinephrine transporter inhibitors and alpha$_2$-adrenergic agonists.

Norepinephrine transporter inhibitors

Recently, two highly selective norepinephrine transporter (NET) inhibitors were developed for clinical use: reboxetine and atomoxetine. Some tricyclic antidepressants, including desipramine, also have NET inhibitor effects. However, these medications also interact with adrenergic and non-adrenergic receptors, making the precise role of NET inhibition difficult to elucidate [92]. Reboxetine, an antidepressant medication, was evaluated in a 12-week open-label study in 26 cocaine users. In that study, reboxetine was well tolerated and reduced cocaine use, suggesting its potential efficacy [93]. However, reboxetine was not approved by the Food and Drug Administration (FDA) for marketing in the US.

Atomoxetine, a medication used for the treatment of ADHD, is a selective norepinephrine transporter (NET) inhibitor that increases synaptic NE levels in the PFC [94,95] and may increase cognitive functioning by stimulating postsynaptic alpha$_2$-adrenergic receptors. Atomoxetine also increases dopamine levels in the PFC, but not in the striatum or in the nucleus accumbens [94,95]. This discrepancy was attributed to sparse distribution of dopamine transporters in prefrontal cortex, indicating that NET contributes significantly to clearing of extracellular dopamine in this region [96]. In contrast, amphetamines increase both DA and NE levels in the nucleus accumbens and in the PFC [97]. These differential neurochemical effects probably contribute to the high and low abuse liability of amphetamines and atomoxetine, respectively [98,99].

In pre-clinical studies, atomoxetine improved performance in various forms of impulsivity [100] and attention in rats [101] as well as reversal learning in rats and monkeys [102]. Atomoxetine also improved attentional set-shifting deficits associated with PFC deafferentation in rats [103]. In humans, atomoxetine improved response inhibition, measured with the Stop Signal test in healthy controls and patients with ADHD [104]. In ADHD patients, atomoxetine also improved Stroop performance [105]. As both methamphetamine and cocaine users have been reported to have slower Stop Signal Reaction times than controls [106,107], it would be of interest to examine atomoxetine's ability to improve performance on this task in stimulant users.

Recently, atomoxetine's effects on the acute physiological and subjective responses to dextroamphetamine were examined in healthy volunteers [108]. Four days of atomoxetine (40 mg/day, orally) treatment attenuated some of the subjective effects of dextroamphetamine, including ratings of 'stimulated', 'high' and 'good drug effects'. As the rating of 'good drug effects' and 'high' are predictive of reinforcing effects from amphetamines [109], their attenuation by atomoxetine supports its potential use as a treatment for stimulant addiction. Atomoxetine remains to be evaluated in clinical trials for stimulant addiction.

Alpha$_2$-adrenergic agonists

Guanfacine is an alpha$_2$-adrenergic agonist similar to clonidine and lofexidine. Guanfacine is used for the treatment of hypertension, ADHD and opioid withdrawal. Guanfacine decreases noradrenergic activity by stimulating presynaptic alpha$_2$-adrenergic receptors. Compared to clonidine, guanfacine is less sedating and has more selectivity for the alpha$_2$ adrenergic receptors found in the PFC, alpha$_{2A}$ subtype [110–112]. The alpha$_{2A}$-adrenergic receptors may mediate the beneficial effects of guanfacine on cognitive function [88]. Guanfacine has been used to improve cognitive functioning in many disorders, including schizophrenia, epilepsy and ADHD [113–117].

In pre-clinical studies, guanfacine improved attention and working memory in rats [111,118] and visuomotor [119] and working memory in monkeys [111,120]. In humans, guanfacine improved working memory performance in healthy volunteers [116,121] and sustained attention in schizophrenics [113] and those with ADHD [122]. In pre-clinical studies, clonidine and lofexidine attenuated the stress-induced reinstatement of cocaine seeking in rats [123,124], a pre-clinical model for relapse. Given the more beneficial effects of guanfacine on cognitive functioning, it will be of interest to evaluate its effects for stimulant addiction.

FUTURE DIRECTIONS

The main theme of this review is that medications enhancing inhibitory control and attenuating drug

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Table 1 Proposed cognitive enhancers for stimulant addiction.

Medication	*Target*	*Effects on cognitive function*	*Effects in stimulant addiction*
Galantamine, rivastigmine, donepezil	Cholinergic system Nicotinic and muscarinic receptors	Improve sustained attention in cocaine users (Sofuoglu *et al.*, unpublished)	Physostigmine [72] or rivastigmine [73] attenuate subjective effects of amphetamines
Varenicline	Cholinergic system Nicotinic receptors	Improve attention and working memory in cigarette smokers [78]	Not examined
Atomoxetine	Noradrenergic system Norepinephrine transporter	Improve response inhibition in those with ADHD [104]	Attenuate subjective effects of amphetamine [108], did not change the subjective effects of cocaine [133]
Guanfacine	Noradrenergic system Alpha$_2$-adrenergic receptors	Improve sustained attention in ADHD [122]	Not examined

ADHD: attention deficit hyperactivity disorder.

reward may lead to development of effective treatments for stimulant addiction. Table 1 summarizes the relevant studies with these medications. Many questions remain to be addressed about this proposed strategy to use cognitive enhancers targeting Ach and NE for stimulant addiction:

1 Does improving cognition with medications also improve treatment outcome? As summarized above, cognitive deficits in stimulant users, including decision-making, response inhibition, planning, working memory and attention functions have been well documented. Studies also indicate that these deficits predict higher dropout rates and poor treatment response. The medications reviewed improve cognitive function in substance abusers or in other clinical conditions. None the less, this promising chain of evidence fails to make the crucial next step of demonstrating a clinically significant impact on treatment outcome.
2 What types of treatment will be optimized by use of cognitive enhancing medications in stimulant users? It is possible that cognitive enhancers may be effective for the pharmacotherapy of stimulant addiction in combination with psychosocial treatment. Alternatively, cognitive enhancers could be used to augment response to behavioral treatments for stimulant addiction such as cognitive behavioral therapy (CBT). Although proven to be efficacious, CBT helps only a minority of patients with stimulant addiction [125,126]. Adequate cognitive function is most crucial for behavioral treatments, particularly those such as CBT that emphasize cognitive retraining and learning of new behavioral skills, as demonstrated by Aharonovich [35,36]. However, inhibitory function and the ability to maintain awareness of long-term goals are key elements of even the most behavioral of treatments such as contingency management. There are examples of augmentation of behavioral treatment with the cognitive enhancer cycloserine for the treatment of phobias and other anxiety disorders [126–128] [129]. Such augmentation strategies remain to be evaluated for the treatment of stimulant addiction.

Cognitive-enhancing medications may also optimize the efficacy of other types of medications, especially early in treatment when cognitive function is likely to decline with abstinence from stimulant use. For example, during early phases of cocaine vaccine administration, a promising medication for cocaine addiction [130], antibody titers are insufficient to block large doses of cocaine, and the ability to maintain sobriety during this time may be crucial. Cognitive-enhancing agents may improve outcomes through enhancing patients' ability to comply with medication regimens. These possibilities need to be evaluated in future controlled studies.
3 What aspects of improved cognitive function are related most strongly to improved treatment outcome? Although response inhibition is associated commonly with addictive behavior, optimum inhibitory control function depends upon other PFC functions, including attention and working memory. The independent contribution of these functions to treatment outcomes needs to be examined in future studies. Further, for each cognitive function of interest, there are many tests to choose from. For example, to evaluate response inhibition in drug users, researchers have used the Stop Signal Test, the Go–No Go test and the Stroop test [25,31,37,131,132]. This variation across studies makes cross-study comparisons difficult to conduct. Selecting validated cognitive tests with good psychometric properties that are sensitive to pharmacological interventions will be a crucial step. Future clinical studies designed optimally to measure cognitive function as well as drug use behavior are necessary to address these questions.

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