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Invited review

Cognitive enhancement as a treatment for drug addictions

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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.

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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.

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

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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 pre-potent 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 Jovanovski 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, 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