Published in final edited form as:
Am J Addict. 2014 ; 23(2): 189–193. doi:10.1111/j.1521-0391.2013.12086.x.

The Self-Medication Hypothesis and Psychostimulant Treatment of Cocaine Dependence: An Update

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Abstract

Background—Stimulant medications have shown promise as a treatment for cocaine dependence (CD) for several decades, yet these treatments have not been widely studied and substantial barriers to clinical implementation remain. The “Self-Medication Hypothesis,” posits that an individual's choice to use a particular substance is to some degree based on the substance's effect on subjective painful affects or unpleasant emotional states which may or may not be associated with a psychiatric disorder.

Objectives—The Self-Medication Hypothesis remains relevant, particularly when considering the scenario of cocaine dependence, both with and without and co-occurring attention-deficit/hyperactivity disorder (ADHD).

Methods—Two case studies (N = 2) and a review of the relevant literature are provided in this clinical update on psychostimulant treatment of cocaine dependence.

Results—Two case studies are presented in which psychostimulant treatment of cocaine dependence was associated with a good clinical outcome.

Discussion—While the use of psychostimulant medication for the treatment of cocaine dependence is controversial, emerging evidence suggests potential utility for this approach.

Conclusions—Cocaine use in individuals with CD may represent self-medication, and prescribed psychostimulants may have benefit in restoring dopaminergic function.

Scientific Significance—Psychostimulant treatment of cocaine dependence is consistent with the Self-Meidcation Hypothesis and is deserving of further study.

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INTRODUCTION

Although effective pharmacologic treatments have been developed and widely employed for opioid, nicotine, and alcohol dependence there are no FDA-approved pharmaco-therapies for cocaine dependence. Cocaine dependence (CD) remains one of the most debilitating and lethal addictions and remains widely prevalent in society; there are approximately 1.6 million current users of cocaine in the US,[1] and the past-year prevalence of CD is estimated to be 1.1%.[2] Standard psychosocial treatments for CD are only moderately effective, with an average abstinence rate of approximately 30%.[3] The need for effective pharmacotherapy for CD remains.

In 1983, one of us (EJK) reported on a case in which there was marked improvement of an extreme case of IV CD treated with methylphenidate (MP).[4] The patient suffered with comorbid attention deficit disorder. The patient has been followed now for 30 years and has experience no relapse to cocaine. In a subsequent publication we reported on two additional cases of individuals who suffered with CD who also responded favorably to psychostimulant treatment.[5] For reasons not exactly clear these promising outcomes were essentiality ignored for over a decade as far as follow-up clinical trials or controlled studies testing the efficacy of psychostimulant treatment for cocaine dependency, although recent studies are promising.[6] As we will elaborate subsequently, in our experience we believe that such patients can respond favorably to psychostimulant substitution because they are self-medicating painful subjective states and feelings due to the dopaminergic dysregulation associated with cocaine dependence.

The main effects of cocaine are due to the inhibition of catecholamine reuptake, particularly dopamine, by binding to the dopamine transporter.[7] Substitution pharmacotherapy is effective for opioid[8] and nicotine[9] dependence, and is a plausible strategy for treating cocaine dependence. However, cocaine interactions with neurotransmitter systems are more complex and indirect than nicotine and opioid agonist actions. Psychostimulants, including amphetamine, methamphetamine, methylphenidate, bupropion, and modafinil, have been studied as substitution treatments for cocaine dependence, both in patients with[10,11] and without[6,12–20] co-occurring attention-deficit/hyperactivity disorder (ADHD). The results of these studies have been mixed with regard to effects on cocaine use, with the most consistent therapeutic effects reported for dextroamphetamine[21,22] and methamphet-amine.[18] Amphetamine and cocaine have similar pharmacological and clinical characteristics; they differ mainly in onset of action and half-life. The mechanism of action of amphetamine is to both block dopamine reuptake and promote dopamine release.

Animal studies evaluating the potential of psychostimulants as treatments for CD have been promising. Rats have been shown to have dose-dependent decreases in cocaine-reinforced responding with dextroamphetamine administration.[23] Dextro-amphetamine has also been shown to reduce cocaine self-administration in rhesus monkeys,[24] and that this effect diminishes after discontinuation of dextroamphetamine, suggesting that prolonged treatment may be necessary to produce a sustained reduction in the reinforcing effects of cocaine.[25] Generally, these preclinical data support the hypothesis that psychostimulants are potentially

efficacious treatments for CD deserving of further study, although animal models of addiction can only be suggestive of potential clinical utility.

The results of brain imaging studies have provided additional support for the potential utility of psychostimulant treatment of cocaine dependence. Findings with the positron emission tomography (PET) raclopride displacement procedure have shown that deficient dopamine transmission is associated with failure to respond to behavioral treatment.[26] Stimulant medication may correct this deficit, and by enhancing dopamine release, may improve the salience of competing reinforcers to cocaine. Using PET and 2-deoxy-2-fluoro-D-glucose (FDG) to measure brain glucose metabolism as a marker of brain function, MP administration was associated with blunting of regional brain responses to cocaine cues.[27] These brain imaging findings can be interpreted as supporing the hypothesis that psychostimulant administration has the potential to "normalize" brain function for individuals with cocaine dependence.

Human laboratory experiments have also yielded results supporting the potential value of psychostimulant treatment of cocaine dependence. Cocaine use during dextroamphetamine maintenance has been reported to be safe and tolerable at moderate doses.[28] Dextroamphetamine administration has been found to reduce cocaine self-administration, most likely by altering the reinforcing effects of cocaine.[29] These carefully controlled experiments point to the feasibility of using psychostimulants to treat individuals actively using cocaine. Controlled trial experience with using psychostimulants to treat CD has been mixed. A recently conducted metanalysis,[21] pooled the results of 16 clinical trials that investigated bupropion, dextroamphetamine, methylphenidate, modafinil, mazindol, methamphetamine, and selegiline. Psychostimulants were not associated with improvements in cocaine use, retention in treatment, or sustained abstinence, although sustained abstinence did differ by type of drug used, and was higher with bupropion and dextroamphetamine. We believe the approach of looking at all dopamine agonists as having equal potential is flawed. In our view, the existing evidence, as well as our clinical experience, suggests that more potent classical stimulants (eg, amphetamines and methylphenidate) have the highest potential to be effective. Cocaine is a powerful stimulant medication; a pharmacotherapy that substantially modifies the reinforcing effects of cocaine needs to compete with its pharmacodynamic actions.

In a significant number of these cases dating back to the first published cases in the early 1980s and up to the present, the responses to MP treatment have been dramatic and sustained. In this report we report on an additional recent case example of marked improvement with sustained released MP, the rationale for such treatment, preliminary studies of stimulant treatment of non-ADHD cocaine dependent patients, and explore the basis for further study of this potentially promising treatment.

THE CASE OF BOBBY AND THE "MIRACLE CURE"

The patient reported here was treated in the summer of 2011 for the first time with sustained release MP and in his own words described his response as a "miracle." Bobby is a 49-year-old married handyman who is currently separated from his wife, mainly as a result of

Bobby's many relapses to his drug of choice, cocaine—in its crack form. He has also been subject to heavy periodic alcohol use and dependence. Bobby has been followed by one of us (EJK) for 6 years. He has a moderately severe learning disability that has rendered him borderline illiterate. Furthermore he describes attentional problems, restlessness, and hyperactivity growing up as a child.

He has responded to mood stabilizer, antidepressants, and disulfiram which have provided some degree of relief from persistent feelings of depression, anxiety, agitation, and impulses to resort to alcohol. The periodic use of cocaine has been the most unrelenting clinical problem. MP treatment was recently reconsidered because of marked deterioration in his condition from the drug use including suicidal depressive feelings. After consulting with a colleague (JM) doing research with stimulant drug substitution for stimulant dependent patients, sustained release MP was prescribed 36 mg (Concerta®), a long acting form of MP, subsequently adjusted to 27 mg per day. Within 24 hours of commencing the MP the patient left a voice message describing the effects of the treatment as a “miracle” exuding gratitude for the relief the medication had afforded him.

Bobby maintained contact by phone almost daily until his scheduled appointment a week later continuing to be elated about his improved mood and expressing appreciation for his new-found sense of well-being. When seen in person he again excitedly proclaimed that it was a miracle how much better he felt and emphasized that he now had a choice about using cocaine, much like the patient first treated with MP indicated in the early 1980s. He bragged that he was 8 days abstinent. Not insignificantly, two mornings before his visit he described how he was not sure if he had taken his medication (when it turned out he had) and mistakenly took a second dose. Loudly and animatedly he said, “I didn't like it at all, it was too much.”

Four weeks after commencing the MP in a context of developing severe back pain he reverted to using some illicitly obtained oxycodone which in turn led to a “limited” amount of cocaine. He quickly reassured his psychiatrist that he felt he did not have to continue the cocaine, uncharacteristic for him prior to being treated with the MP. Despite his back pain he indicated he has become much better organized, has been catching up with chores and tasks at home that he had been ignoring. Despite his back pain he has remained buoyant and more optimistic in his outlook. At the time of writing this paper Bobby has been abstinent from cocaine use for 8 months.

MIXED-AMPHETAMINE SALTS TREATMENT OF COCAINE DEPENDENC

A 32-year-old man with CD presented for treatment with one of the authors (JJM). He had a history of opioid dependence successfully treated with buprenorphine, but over the past year, developed a pattern of nightly cocaine use. The patient would stay up late every night using cocaine and compulsively tinkering with old computers. This pattern caused problems with work attendance and financial difficulties due to the cost of the cocaine. The patient would experience progressively more intense cocaine cravings while at work and then buy cocaine immediately arriving home each evening. Motivational and cognitive-based interventions were ineffective in changing the pattern of cocaine use. Extended-release

mixed-amphetamine salts were started at a dose of 20 mg per day and gradually titrated to a dose of 30 mg every morning and 20 mg at 1 PM. Very soon after initiation of amphetamine treatment the patient's cocaine use ceased. The patient also reported elimination of cocaine craving and a cessation of the compulsive computer tinkering each evening. The patient has achieved 6 months of abstinence from cocaine. The plan is to continue amphetamine treatment for a total of 1 year and then gradually taper off.

Interestingly, these positive findings have been difficult to replicate in clinical trials with cocaine-dependent trials. Our group has carried out several trials assessing MP with cocaine abusing adults. Unfortunately, the primary outcomes did not demonstrate a significant difference between those receiving MP and those receiving placebo. However, in these studies older sustained-release MP preparations were used, resulting in less consistent absorption and perhaps diminished efficacy of the medication. Importantly, our studies, as well as additional ones conducted by other experienced groups, have found little evidence of medication misuse/abuse. This should not be interpreted to mean that abuse of prescribed stimulants is not possible. The risks and benefits of prescribing stimulants should be thoughtfully considered with the patient and an appropriate decision should be made.

METHYLPHENIDATE TREATMENT OF COCAINE DEPENDENCE—A SELF-MEDICATION PERSPECTIVE

There is six time greater risk for developing substance use disorders (SUDs) among patients with ADHD compared to people who do not have the disorder[30] and such patients experience earlier onset and more severe SUDs.[31] There is an older clinical literature describing the enormous distress and dysfunction associated with ADHD, previously designated as minimal brain dysfunction (MBD), characterized by lack of emotional control, attentional and learning disabilities, depressive affect, marked irritability, low self-esteem, anergia, and restlessness.[32,33] The recent literature on ADHD documents a disproportionately high co-occurrence of bipolar, depression, and anxiety disorders.34–36 In objectively cataloging and classifying the symptoms associated with each diagnostic category what is often lost is the enormous subjective psychological suffering experienced with psychiatric disorders, including ADHD. The emphasis on painful feeling and emotional states is central to the self-medication hypothesis (SMH). Namely, it is not so much a psychiatric diagnosis or conditions that an individual self-medicates, rather the hypothesis underscores the psychological suffering associated with SUDs.

The observations about the SMH were derived from the clinical work of psychodynamic investigators dating to the early 1970s. Terms such as “drug-of-choice,” “preferential use of drugs,” and “self-selection” were coined to describe how individuals found certain drugs appealing, contributing to the articulation of the SMH.[37] The two main aspects of the SMH are: (a) individuals use addictive drugs to relieve their suffering and distress and, (b) that there is a considerable degree of psychopharmacologic specificity in an individual's drug preference.[37,38] Although the SMH derives from a psychodynamic perspective emphasizing deficits in affect defense and psychological pain associated with regulating self-esteem, relationships, and self-care, it is also consistent with the fact that individuals self-medicate the pain and suffering associated with psychiatric disorders.[39] The concept of self-

medication has been applied to a variety of substance-symptom pairings such as cannabis use and aggression,[40] nicotine use and schizophrenia,[41] and alcohol consumption and mood.[42] However, the empiric evidence base is inconsistent, and some reports have not supported self-medication mechanisms of substance use disorders.[43–45]

From a self-medication perspective, it is important to consider what affects or painful co-occurring psychiatric symptoms might be targeted to alleviate the distress that individuals wittingly and unwittingly attempt to relieve with their drug-of-choice. We have reviewed elsewhere in more detail the action of the classes of abused drugs.[37] For the purposes here, we described how stimulants act as augmentors for hypomanic, high-energy individuals as well as persons with atypical bipolar disorder. They also appeal to people who are de-energized and bored, and to those who suffer from depression, often of a subclinical variety. In addition, stimulants, including cocaine, can act paradoxically to calm and counteract hyperactivity, emotional lability, and inattention in persons with ADHD.

For the purposes of this report, we focus on the actions of illicit psychostimulants in considering treatment with prescribed psychostimulants. When considering treatment of CD with or without co-occurring with ADHD, it is important to explore and identify the painful feeling states or affects that patients are trying to relieve with their drug-of-choice. Such distress might or might not be associated with diagnosable psychiatric disorders. In the case of successful treatment of ADHD, it is arguable whether improvement is the result of "curing" the disorder, or whether improvement is the result of alleviating the painful affects and dysphoria that patients experience with the disorder. It is our clinical experience that the sense of well-being patients express with treatment is likely the result of relieving the gnawing depressive affect, anhedonia, and dysphoria associated with the pain and dysfunction of dopaminergic dysregulation. The SMH suggests that it is not so much euphoria but the relief of dysphoria that individuals experience when they respond to addictive drugs. As we indicated in a previous publication,[5] it is likely that craving or desire for drugs is rooted in the corrections and relief from suffering patients experience with their drug use. In the first case reported here, and in the reported case in 1983,[4] the substitution of the more long acting stabilizing form of MP (compared to the short acting destabilizing action of snorted, IV, and free base cocaine) corrects the predisposing and resultant chemical and emotional instability associated with CD. In doing so, it is our experience that the desire or craving for cocaine is reduced or eliminated.

In the case of non-ADHD patients with CD, explorations of what painful affects and psychiatric conditions such individuals are self-medicating are useful and can guide treatment choices and be therapeutically beneficial. The SMH is rooted in a seemingly simple question, namely asking patients, "What did the drug do for you when you first used it?"[37] As we have indicated some patients describe how stimulants heighten expansive, hypomanic, high-energy states, or modes of relating. In other instances individuals discover that stimulants counteract states of anergia and related depressive symptoms if not frank co-existing depression. In other cases depressive reactions are accompanied by agitation or irritability. Psychostimulants might be used as augmenting agents when antidepressants alone produce only partial remission. When irritability, anger, or agitation complicates depression or subclinical bipolar or mixed states, mood regulators may be combined with

stimulants or antidepressants. In our experience it is likely that mood regulators are useful because they act effectively as affect modulators and make painful/intense feeling more manageable and tolerable. In effect, the SMH suggests that a patient's self-medication provides an important clue in predicting which psychopharmacological approach might best relieve the patient's psychiatric symptoms.

BARRIERS TO ACCEPTANCE OF PSYCHOSTIMULANT TREATMENT

The use of psychostimulants to treat CD is controversial for several reasons. First, psychostimulants are controlled substances with well-recognized risks for misuse, diversion, and compulsive use. Second, cardiovascular risks are associated with the therapeutic use of psychostimulants, and there is concern that these risks would be additive. Finally, the tradition of substance use disorder treatment in the United States is heavily influenced by 12-step approaches, which tend to de-emphasize medication treatments, particularly substitution pharmacotherapy. Clinicians would be well advised to prepare and instruct patients to be discreet when in 12-step meetings in discussing their treatment with psychostimulants. If and when it does come up they might explain it as treatment for an underlying psychiatric condition(s).

However, the field must follow where the evidence leads us, regardless of our preconceived preferences for therapies for substance use disorders to be benign, non-abusable medications. A similar dynamic has existed in the treatment for opioid dependence, where the evidence supporting the use of agonist replacement treatment (eg, methadone and buprenorphine) is as strong as for any therapies in any field of medicine, yet many clinicians and institutions have strong reservations about their use. This is not to gloss over the safety limitations of psychostimulant treatment of cocaine dependence, and these risks will need to be managed as treatment models have emerged, perhaps using methadone and buprenorphine treatment as a model.

The main risks of psychostimulant treatment of CD are cardiovascular. In some cases, where cardiac disease risk factors are present, obtaining a baseline electrocardiogram would be indicated. As with all psychostimulant treatment, baseline and intermittent monitoring of pulse and blood pressure should be performed. However, normal readings do not preclude the risk of elevated pulse and blood pressure if prescription stimulants and cocaine are used simultaneously. Some medical conditions, such as a history of myocardial infarction, stroke, and poorly controlled hypertension, would be contraindications for psychostimulant treatment of cocaine dependence.

Acknowledgments

This research was supported by NIDA grant K24 029647 (Levin). The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

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