HHS Public Access

Author manuscript

Addict Biol. Author manuscript; available in PMC 2024 January 01.

Published in final edited form as:

Addict Biol. 2023 ; 28(4): e13271. doi:10.1111/adb.13271.

Prescription Psychostimulants for cocaine use disorder: a review from molecular basis to clinical approach

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Abstract

Cocaine use is a public health concern in many countries worldwide, particularly in the Americas and Oceania. Overdose deaths involving stimulants, such as cocaine, have been increasing markedly in North America, especially with concurrent opioid involvement. To date, no pharmacological treatment is available to treat stimulant (including cocaine) use disorders. Prescription psychostimulants (PPs) could be useful to treat cocaine use disorder (CUD) as they share the pharmacological effects with cocaine, as evidenced by a recent meta-analysis that assessed 38 randomized clinical trials (RCTs). PPs were found to promote sustained abstinence and reduce drug use in patients with CUD. The aim of this paper is to provide a narrative review of the clinical pharmacology of PPs and comment on the current stage of evidence supporting PPs to treat CUD. We also propose a model of care that integrates PPs with evidence-based psychosocial interventions (such as cognitive-behavioral therapy[CBT] and Contingency Management [CM]), a harm reduction approach, and case management with social support.

Graphical Abstract

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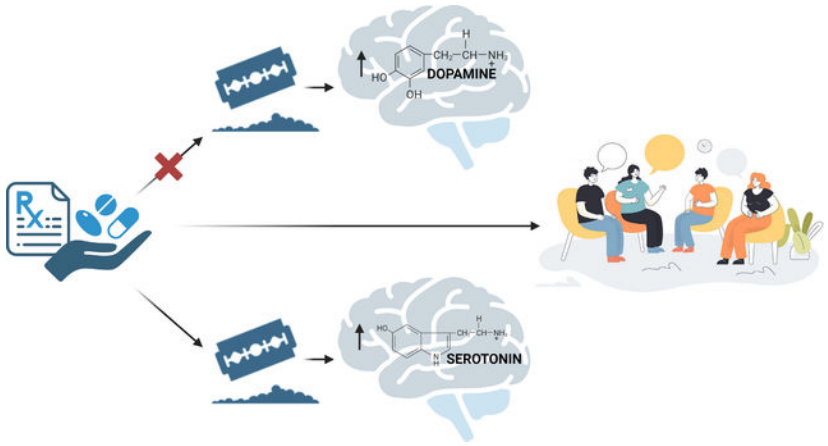
Author Contributions

Conceptualization: All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

The authors declare no conflict of interest.



Keywords

stimulants; dopaminergic agonists; cocaine; prescription amphetamines; cocaine use disorder

1. Introduction

Cocaine use is prevalent worldwide, with 0.4% of the world population having used cocaine in the past year [1]. Cocaine use also is endemic in the Americas and Oceania and has recently become more available in Europe [1]. The use of crack-cocaine is still a major concern in the Americas, particularly in the US[2] and Brazil[3]. Overdose deaths involving stimulants are also an increasing threat worldwide [4–6], particularly when used concurrently with opioids [7].. Yet, no pharmacological treatment is currently approved by the United States FDA to treat cocaine use disorder (CUD) [8,9], which also applies to crack-cocaine[10]. Historically, medications such as antidepressants [11], antipsychotics [12], opioid antagonists [9], and topiramate [13] have been tested for CUD with no compelling results.

Prescription psychostimulants (PPs), such as prescription amphetamines, methylphenidate, and modafinil, are dopaminergic agonists that share pharmacological effects with non-prescribed stimulants [14]. A recent meta-analysis with 38 randomized clinical trials (RCTs) found that PPs could effectively promote abstinence and reduce drug use in patients with CUD [15]. Here, we review the pharmacological properties of PPs and discuss the current evidence supporting their clinical use for the treatment of CUD. Moreover, we discuss future directions of a model of care integrating PPs with psychosocial interventions, harm reduction measures, and case management.

2. Pharmacological aspects of the treatment of CUD with PPs

The main targets for both cocaine and PPs in the brain are monoamine transporters, transmembrane proteins located in the plasma membranes of monoaminergic neurons [16,17]. Cocaine and PPs interfere with monoamine transporter function, enhancing monoaminergic signaling. However, some differences exist between the pharmacology of cocaine and PPs regarding their activity at monoamine transporters. For instance, cocaine and PPs have different affinities for the dopamine (DAT), serotonin (SERT), and norepinephrine (NET)

transporters. While cocaine has a similar affinity for the three monoamine transporters, PPs have a lower affinity for SERT compared to DAT/NET [18]. Cocaine and PPs also differ in their specific actions at the monoamine transporters [19]. Cocaine acts exclusively as a reuptake inhibitor, interfering with transport function by prohibiting the inward transport of released neurotransmitters [20]. In addition to being reuptake inhibitors, most PPs also act as substrate-type releasers, being transported into the nerve terminal and directly increasing extracellular monoamine levels by reversing the process of transporter-mediated exchange and interfering with vesicular storage [21]. Because of these differences, substrate-type releasers (e.g., PPs) induce more robust increases in extracellular monoamine levels compared to exclusive reuptake inhibitors (e.g., cocaine) [22]. Of note, modafinil is a particular outlier when it comes to its mechanisms of action in comparison to other PPs, having a much higher DAT affinity and exclusively acting as a reuptake inhibitor, and not as a releaser[23].

Therefore, cocaine and PPs have similar mechanisms of action, which supports the hypothesis that PPs might be useful as an agonist replacement therapy for CUD. Importantly, accumulating evidence suggests that DAT is the main molecular target that mediates the abuse-related effects of cocaine, particularly at the nucleus accumbens [24–26]. Evidence also indicates that the therapeutic effects of amphetamine may be due to interactions with the DAT that result in changes in cocaine potency and dopamine neurotransmission [27]. In fact, nonhuman primate studies show that selective DAT inhibitors reduce the abuse-related behavioral effects of cocaine, but only at high levels of DAT occupancy [17].

Chronic (maintenance) treatment with PPs has been shown to mitigate the dysregulation of dopamine neurochemistry and behavior induced by chronic cocaine use. Studies in rhesus monkeys and human post-mortem studies showed that long-term exposure to cocaine led to increased striatal DAT density [28–30]. In rodents, the effects of chronic cocaine exposure on behavior and DAT density vary depending on the schedule of cocaine access, with long-term access being associated with tolerance and intermittent access being associated with sensitization to cocaine-induced inhibition of dopamine uptake at the DAT [31,32]. While those are opposing effects that may occur following chronic cocaine exposure, treatment with d-amphetamine has been shown to block tolerance and sensitization by preventing or restoring cocaine-induced changes at the DAT [27,31,32]. Therefore, d-amphetamine treatment during cocaine self-administration may reduce subsequent cocaine self-administration by interacting with the DAT to prevent tolerance- and/or sensitization-related changes in cocaine potency and dopamine-mediated signaling.

While dopamine neurotransmission dysregulation has been proposed as the primary mechanism underlying CUD, chronic cocaine exposure also increases SERT density in nonhuman primates [33,34] and humans [35,36]. These data implicate a potential role for serotonin in CUD and PP-induced decreases in cocaine use. Selective SERT inhibitors also decrease cocaine intake in animal models [37–41]. However, pre-clinical studies with monoamine releasers show that decreasing pharmacological selectivity for DAT/NET vs. SERT is associated with a shift in the therapeutic window, in which decreased cocaine intake is accompanied by the emergence of undesirable side effects [17].

Notably, even though PPs have relatively lower affinity for SERT than DAT/NET, a study has shown a prominent role for serotonin in the therapeutic effects of PPs – specifically, amphetamine – for the treatment of CUD. Johnson and colleagues (2018) showed that amphetamine maintenance differentially modulated the neurochemical effects of cocaine and methamphetamine on nucleus accumbens dopamine and serotonin levels. These effects predicted whether amphetamine had a therapeutic impact in their cocaine or methamphetamine use disorder models. Particularly, the authors found that amphetamine maintenance attenuated the abuse-related behavioral effects of cocaine and cocaine-induced increases in dopamine, but not serotonin, levels in the nucleus accumbens [42]. On the other hand, chronic treatment with amphetamine did not alter methamphetamine-induced changes in dopamine or serotonin levels and, consequently, did not block its abuse-related effects [42]. Finally, amphetamine maintenance did not alter the behavioral effects of the selective dopamine reuptake inhibitor 3,4-methylenedioxypyrovalerone (MDPV), despite blocking MDPV-induced increases in extracellular dopamine levels [42].

Together, these preclinical findings suggest that amphetamine maintenance attenuates the abuse-related behavioral effects of cocaine by reducing the effects of cocaine on nucleus accumbens dopamine levels, possibly via interactions with DAT [27,31,32], while conserving its effects on nucleus accumbens serotonin levels [42]. These findings also indicate that PPs seem to be useful therapeutic tools for the treatment of CUD, but not methamphetamine use disorder. This selective effectiveness to treat CUD may reflect the specific pharmacological effects of PPs on monoamine transporters in individuals with CUD.

3. The current state of evidence for clinical use of PPs for the treatment of CUD

Agonist-based treatments have been previously employed for the treatment of substance use disorders, and are first-line treatment for opioid [43] and tobacco use disorder [44]. The agonist-based therapy relies on the administration of a medication with similar pharmacological and subjective properties as the primary non-prescribed drug, with the goal of relieving symptoms such as craving and withdrawal. Addressing those symptoms can have a significant impact on craving leading to better results in outcomes such as drug use, abstinence, and improvement of functioning [45], in addition to reducing overdose risk [46]. Darke and Farrell (2016) have defined eight requirements for a suitable agonist replacement medication: agonist properties similar to the target drug; pharmacological stability (longer half-life than the non-prescribed drug); escalating dose (increasing drug tolerance); clinical, psychiatric, and cognitive non-toxicity; craving-reducing properties; and limited salience [45].

A suitable agonist replacement medication should meet as many of those criteria as possible. An agonist-based treatment can increase adherence by offering mildly positive effects and usually have an acceptable safety profile if administered correctly [15,45]. The use of extended-release formulations and medications with a longer half-life is important to guarantee the success of an agonist replacement therapy. It is well-known that reward processing, timing, and decision-making processes are heavily interconnected, with drugs with more immediate and short-lived action showing increased reinforcing effects (and,

consequently, increased abuse potential) compared to longer-acting drugs that do not show a rapid increase in dopamine release and reward peak [47,48]. In fact, amphetamine maintenance attenuates cocaine abuse behaviors by reducing its effects on nucleus accumbens dopamine levels and preventing cocaine-induced rewarding and reinforcing effects [27]. Furthermore, by normalizing dopamine function in patients with CUD, long-acting stimulants also would be expected to prevent drug-seeking behavior prompted by the presentation to drug-conditioned cues and to facilitate the extinction of conditioned behavior [47].

Importantly, a major concern over the use of PPs for the treatment of CUD is the potential for a misuse of the prescribed medication. However, many years of experience using agonist and partial agonist medication for treatment of opioid use disorder has shown that when medication intake is properly supervised, these medications are effective and safe with low risk for misuse [49]. In fact, recent post-pandemic studies have shown that less rigorous rules about take-home methadone doses (due to necessary isolation and social distancing) for opioid use disorder treatment was not only effective, but also increased adherence to treatment without compromising safety [50], suggesting that the agonist-based approach is flexible and adaptable even for high-risk medications such as methadone.

Agonist-based treatment of a stimulant use disorder has been debated for decades. The first case report of a woman with CUD incidentally treated with methylphenidate was published in 1983 [51]. This was followed by case reports and single-arm studies assessing immediate-release methylphenidate formulations, with conflicting results [52,53]. Early RCTs initially used low doses of methylphenidate for CUD [54,55]. With time, researchers started using different PPs such as modafinil and prescription amphetamines, in addition to extended-release methylphenidate. Results from different trials were contradictory, as researchers employed different doses and formulations of PPs and assessed different outcomes. While safety has historically been a concern from prescribers, a Cochrane meta-analyses shows that, in comparison with placebo, PPs do not have a higher incidence of adverse events, including cardiovascular adverse events and serious adverse events[56]. Yet, further studies are needed to assess potential mild and long-term adverse effects of using PPs for the treatment of CUD.

The evidence supporting the efficacy of PPs for the treatment of CUD has been gradually emerging. A Cochrane review published about PPs in the treatment of and CUD [56] in 2016 brought inconclusive results with regards to their efficacy, with very low-quality evidence on promoting abstinence but not treatment retention. However, more recent RCTs with prescription amphetamines for the treatment of CUD brought compelling results and endorsed the efficacy of an agonist-based approach when employing more appropriate methods, such as higher doses, extended-release formulations, and low attrition. Examples of this were the study by Nuijten and colleagues (2016) and Levin and colleagues (2020), which used slow-release amphetamine salts with doses as high as 60mg [57,58], though it is noteworthy that the former was conducted among individuals receiving injectable heroin-assisted treatment and the latter had concurrent administration of topiramate, which might impact on the generalizability of their results. The most recent comprehensive meta-analysis on the topic was conducted in 2020 and assessed several efficacy outcomes (e.g., substance use throughout study, sustained abstinence, and retention to treatment) on 38 RCTs of

PPs for either cocaine or amphetamine use disorder [15]. The main finding was that PPs, particularly prescription amphetamines, were effective in promoting sustained abstinence and reducing drug use among patients with CUD. Secondary analyses also showed that higher doses of PPs were more effective to promote abstinence as compared to lower doses. The same study found that PPs were not effective to treat methamphetamine use disorder, which is in line with pre-clinical studies described previously [42]. However, it should be noted that none of the included RCTs assessed a prescription amphetamine to treat methamphetamine use disorder. Those studies used modafinil and methylphenidate, which also did not yield compelling results for the treatment of CUD.

Although studies using modafinil and methylphenidate yielded no positive results for MUD, Longo and colleagues (2010) found that patients given dexamphetamine up to 110mg/day (mean dose: 80mg/day) remained in treatment longer and showed lower dependence levels after a two-month follow-up, even though there were no differences in methamphetamine use across the two groups. [59]. Galloway and colleagues (2011) also found that patients with methamphetamine use disorder treated with dexamphetamine experienced less withdrawal and craving compared to individuals receiving placebo [60]. The primary outcome (methamphetamine-negative scores), however, was negative in this study. Pilot studies have shown that lisdexamfetamine is feasible and tolerated in the treatment of CUD in doses up to 140mg/day [61] and methamphetamine use disorder up to 250mg/day [62]. Because lisdexamfetamine has not been extensively tested as a treatment for stimulant use disorder and considering its lesser abuse potential compared to other prescription amphetamines [63], this can be a promising direction for future clinical studies. Moreover, the association of pharmacotherapy with PPs and evidence-based psychosocial approaches should be explored in future trials [9,64]. Similar to many treatment trials in substance use disorders, most of the trials using PPs for cocaine use disorder excluded individuals with significant psychiatric comorbidities, which compromises the generalizability of those findings to community treatment settings. Moreover, excluding those individuals prevents further knowledge about the precipitation of psychiatric side effects by PPs in those patients, such as psychosis, although rare in clinical practice.

4. A (not so) new care-model proposal

For many years, the focus of stimulant use disorders' treatment has been on psychosocial programs. Community-based outpatient programs commonly offer a variety of psychosocial interventions for individuals with substance use disorders, including those struggling with stimulants. Treatment usually includes a form of group-based drug counselling and supportive therapy, which can be intensive. However, meta-analyses comparing their efficacy to other psychosocial interventions have shown that those modalities are less effective than Contingency Management (CM) interventions for patient-important outcomes such as reduction in drug use [65,66]. Despite being undeniably effective[67], one issue of CM is its short-term efficacy, as the positive effects may not be sustained after the suspension of the intervention. Other interventions, such as self-help groups that use the 12-step facilitation, are not particularly effective for cocaine use disorder[66], which discourages further investment on these strategies. Although psychosocial interventions such as CM remain as the most effective interventions for CUD to date, these interventions usually do

not reach patients in more vulnerable situations. With these limitations, the psychosocial model of treatment has failed to increase patients' adherence and to address each patient needs, as the interventions tend to be highly standardized [64,68–75].

Residential programs are another treatment model that also faces several obstacles. Usually, they are not associated with general health care facilities and often do not have adequate medical support, which may leave patients with severe health conditions caused by stimulants use and withdrawal untreated (75). Also, as psychiatric comorbidities are frequent among this population, the lack of psychiatric evaluation and treatment may worsen prognosis, favoring relapses and increasing suffering (78–80). It is also worth mentioning that many of these residential treatments are involuntary and compulsory and fail to adhere to human rights guidelines, thus failing to follow the United Nations and the World Health Organization recommendations. Previous studies have suggested that this treatment modality might be acceptable when integrated into a broader treatment plan that includes other interventions [68,71–73, 75, 76].

Drawing a comprehensive treatment plan that cohesively integrates several interventions is the current treatment model for opioid use disorder, which relies on treatment with medication, including the opioid antagonist naltrexone, the opioid partial agonist buprenorphine, or the full opioid agonist methadone. Methadone has been successfully used as an agonist treatment for opioid use disorders for the past 50 years. Although it is highly effective and has saved countless lives throughout the years, its use remains with a primary critique that a replacement therapy should not be recognized as a treatment strategy. Fortunately, its efficacy rose above the controversy, and methadone clinics are found in most urban areas in the United States. Importantly, methadone has a major advantage over buprenorphine and naltrexone, as it does not require patients to go through a period of opioid withdrawal prior to treatment onset, which also would be expected with the use of PPs for CUD. Agonist treatment of OUD has proven to be the an effective approach to address the patient's health and social needs, engaging them in treatment and increasing positive outcomes, with treatment success often going beyond just abstinence. Furthermore, models such as the Office-Based Opioid Treatment (OBOT) and the One-Stop-Shop emphasize an integrative approach to treatment. In both, medication is part of the treatment, but other strategies also improve treatment outcome in those initiatives. In the OBOT model, for instance, a trained primary care physician is responsible for the patient, usually with the support of a nurse or social worker. On the One-Stop-Shop, in the same setting, the patient can find integrated care for OUD, HIV and hepatitis C infection, mental and primary health care, and harm reduction strategies, such as syringe exchange, crack pipes (for polydrug users) and condoms. Usually, a single person is responsible for coordinating each patient's care, assuring all professionals involved in the case work aligned [43,77–81].

Developing such a model for stimulant use disorders might be an answer to this public health issue. Previous studies found that people who use cocaine and/or amphetamines do not seek treatment for many reasons, including low confidence in available treatment options, concerns regarding the effectiveness of treatment services, and that the available services do not provide specific care for stimulants[82,83]. Combining different approaches, from primary health care and essential social support to CM and CBT, could increase

patients' adherence to treatment. Also, housing first, supervised consumption sites, needle-exchange programs, and a safe supply of non-adulterated stimulants are some examples of harm reduction strategies that could be included and disseminated among this population. A One-Stop-Shop model explicitly designed for stimulant users, with trained professionals from different backgrounds, is another strategy that should be carefully evaluated. As for agonist treatment of OUD, as discussed throughout this review, high-dose extended-release formulations of PPs seems to be the best fit for the treatment of CUD and other stimulant use disorders, preferably taken under a health professional supervision [68,69,73,75,84–88]. Finally, treatment goals should focus not only on abstinence rates, but also on improving quality of life and functionality [89].

Conclusion

The scarcity of evidence-based treatment options to treat CUD warrants the consideration of PPs as a therapeutic option in community-based treatment settings, especially in remote areas and LMICs, where psychosocial models are limited by implementation issues. Prescription should be mindful of the medication risks and patients should be monitored closely. A medication-centered approach could successfully attract patients to a treatment setting where the pharmacological treatment would be integrated to psychosocial approaches, harm reduction strategies, social, and housing support, promoting access to a holistic and humanized model of care.

Acknowledgments

Dr. Berro's work is supported by the National Institutes of Health (DA049886). Dr. Bisaga's work has been supported by the statutory activity of the New York State Psychiatric Institute. He has received research grant funding from Alkermes.

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