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Novel Medications to Treat Addictive Disorders

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Abstract

Recent discoveries about the effects of drugs of abuse on the brain and the mechanisms of their addictions; new chemical compounds, including immunotherapies; and new actions of available medications are offering many opportunities for the discovery and development of novel medications to treat addictive disorders. Furthermore, advancements in the understanding of the genetic and epigenetic basis of drug addiction and the pharmacogenetics of the safety and/or efficacy of the medications are providing opportunities for more individualized pharmacotherapy approaches. Although multiple medications have been investigated for treating addictions, only a handful have shown acceptable safety and efficacy and are approved by the US Food and Drug Administration. This article reviews the current medications that are medically safe and have shown promising results for treating opioid, cocaine, methamphetamine, and cannabis addictions.

Introduction

The development of safe, effective treatments for addictive disorders is a high public health priority because addictive disorders represent a significant burden to the individual who suffers from them and to society. Addiction is a chronic condition characterized by the compulsive use of a drug in spite of the psychosocial and physical consequences of its use. It is accompanied by brain changes, which may be associated with the onset, duration, and amount of drug use. Interrupting use of the drug is often associated with craving and withdrawal symptoms, which may be alleviated by using the drug again. Its etiology is associated with genetic and environment interactions. It can be prevented and treated, and its treatment may be associated with drug use relapses.

Multiple medications have been investigated for the treatment of addictions, but only a few are approved by the US Food and Drug Administration (FDA). In recent years, various factors have facilitated progress in the development of medications to treat addictions. New research findings are shedding light on the effects of drugs of abuse on the brain and are offering novel pharmacologic approaches to treat addictive disorders. Concomitantly, advances in the development of new compounds, including immunotherapies, and the discovery of new actions of available medications are allowing the evaluation of new pharmacotherapies for these disorders. In addition, the recent advancements in the understanding of the genetic and epigenetic basis of drug addiction and the pharmacogenetics of the safety and/or efficacy of the medications used for their treatment may allow the development of more individualized pharmacotherapy approaches.

This article does not intend to be an exhaustive review of the medications that have been evaluated for treating drug addictions. Instead, the emphasis is on the novel pharmacotherapies

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that are more advanced in the medication development process, have shown some preliminary efficacy, and/or are being clinically evaluated for the treatment of opioid, cocaine, methamphetamine (MA), and cannabis addiction with some “promising” results. The data for this review come not only from published literature but also from open-access, Internet-based research databases such as <http://www.clinicaltrials.gov> (which are cited with the NCT numbers) and the Computer Retrieval of Information on Scientific Projects (<http://crisp.cit.nih.gov>).

Opioid Addiction

Opioid agonists such as methadone and buprenorphine and antagonists such as naloxone and naltrexone are FDA approved for treating opioid addiction. Their main indications are abstinence initiation, opioid withdrawal treatment, and relapse prevention. These medications are being investigated further to determine their safety and/or efficacy in specific populations, such as pregnant women, adolescents, and people in the criminal justice system. In addition, new formulations of these medications have shown promising results and are being investigated (Table 1).

New formulations of buprenorphine intended to provide long-term delivery are being investigated to determine their safety and efficacy for treating opioid dependence [1,2]. One of them, Probuphine (Titan Pharmaceuticals, South San Francisco, CA), a subcutaneous implant reported to provide 6 months of stable buprenorphine blood levels, is currently being tested in humans (NCT00630201 and NCT00447564).

Given naltrexone's opioid antagonist effects, this medication would be, in theory, an excellent option for preventing relapse among formerly opioid-dependent individuals. However, its clinical effectiveness has been disappointing because of adherence problems, given that most patients stop taking the medication early in the treatment. The recent development of sustained-release formulations of naltrexone is offering new alternatives to naltrexone that are expected to be more effective [3•]. However, not enough evidence regarding the safety and efficacy of depot naltrexone exists to request approval from the FDA for treating opioid dependence. A study comparing oral versus depot naltrexone in a 6-month trial is being conducted to evaluate their efficacy in maintaining opioid abstinence, medication compliance, and treatment retention (NCT00577408).

A naltrexone implant formulation with longer duration of action is also being investigated for treating opioid addiction. A study being conducted in Russia involves opioid detoxification followed by treatment with oral naltrexone or a naltrexone implant manufactured and approved for use in that country. This implant is said to provide opioid blockade for 8 to 10 weeks (NCT00218426). Also, a series of studies evaluating a naltrexone implant is being conducted in Norway (NCT00204243).

α -2 adrenergic agonists such as lofexidine and clonidine have been investigated for treating opioid withdrawal but are not currently FDA approved for this indication. They may assist during the opioid detoxification without the risk of opioid diversion or perpetuating opioid dependence. One of the advantages of lofexidine is that it appears to produce less hypotension than clonidine [4]. Lofexidine is currently being clinically investigated alone and in combination with naltrexone for treating opioid withdrawal in individuals undergoing opioid detoxification (NCT00235729 and NCT00142909). Tramadol is a marketed analgesic with moderate μ -agonist opioid action. It may be useful for treating opioid withdrawal while producing low levels of opioid physical dependence [5]. A recent report suggests that tramadol, 200 and 400 mg, initially produced significant dose-related uncomfortable effects but then suppressed opioid withdrawal. In contrast, the positive drug effects were not significant, suggesting that the risk of dependence may be low [6]. Research is being conducted to

determine tramadol's ability to produce opioid dependence and its efficacy for treating opioid withdrawal (NCT00301210).

Antagonists at the *N*-methyl-D-aspartate (NMDA) receptor, such as memantine, ketamine, dextromethorphan, and phencyclidine, appear to prevent the development of tolerance to and dependence on the analgesic effects of morphine in rodents [7]. A recent report suggests that memantine may be moderately useful for treating opioid craving and reinforcing effects of heroin in humans, thus supporting the evidence that NMDA antagonists may be useful as an adjunct to other medications for treating opioid addiction [8]. Further research is needed to determine the role of NMDA antagonists in treating opioid addiction.

It has been reported that corticotropin-releasing hormone (CRH) antagonists can attenuate opiate withdrawal, block conditioned aversion responses, and prevent stress-related reinstatement in preclinical models. CRH controls the hypothalamic-pituitary-adrenal axis at the basal state and in response to stress; it is also a central nervous system (CNS) modulator. Given the aversive nature of drug withdrawal syndromes, it has been suggested that CRH may be involved in the pathophysiology of these syndromes. Several nonpeptidic, selective CRH-R1 receptor antagonists with clinical potential have been synthesized and are being investigated as a potential treatment for mental disorders such as anxiety and depression and for substance abuse. They may offer a therapeutic opportunity, particularly for treating opioid drug withdrawal [9].

Cocaine Addiction

Most review articles about cocaine pharmacotherapies agree that no medication has established efficacy for treating cocaine dependence or addiction. Currently, more than 60 medications have been investigated for treating cocaine use disorders or addiction [10•]. It has been suggested that cocaine addiction is associated with multiple neurobiologic mechanisms. Some of them have been the target of pharmacologic studies. Initially, it was hypothesized that the brain dysfunction associated with cocaine addiction was an imbalance in the mesocorticolimbic dopaminergic system, but new findings are demonstrating that this is a more complex neurobiologic disorder. Serotonin, norepinephrine, glutamate, γ -aminobutyric acid (GABA), endocannabinoid, and CRH are also affected by chronic cocaine use [11•]. More recently, cocaine use has been associated with changes in cellular events and signaling cascades that underlie synaptic plasticity processes of learning and memory [12].

The main pharmacotherapy approaches for cocaine dependence have been the following: 1) medications with effects on the dopamine system, with some specifically targeting subtypes of the dopamine receptors; 2) medications that affect other neurotransmitter systems associated with cocaine addiction, such as norepinephrine, serotonin, acetylcholine, GABA, glutamate, opioids, endocannabinoids, and CRH; 3) medications with effects on general brain processes, such as anticonvulsants, calcium channel blockers, antithrombotics, cyclooxygenase-2 inhibitors, and nootropics; and 4) medications that alter the pharmacokinetics of cocaine and reduce the concentrations that can reach the brain, such as the immunotherapies. This review focuses on the medications that are considered “promising” or have shown a signal of efficacy and are being further investigated for the treatment of cocaine addiction. They include modafinil, baclofen, topiramate, ondansetron, topiramate, baclofen, N-acetylcysteine (NAC), opioid agonists and antagonists, CRH antagonists, and immunotherapies (Table 2).

Modafinil is a glutamate enhancer with an alerting effect. It increases energy, attention, wakefulness, and locomotion; improves mood; and reduces appetite. The clinical effects of modafinil appear to be the opposite of the symptoms of cocaine withdrawal, which often include anergia, somnolence, hypokinesia, anhedonia, hyperphagia, poor concentration, and dysphoria. It has been hypothesized that modafinil may be useful to treat cocaine withdrawal

and thus break the cycle of cocaine addiction. Additionally, modafinil appears to blunt cocaine euphoria, reduce cocaine priming, and enhance inhibition of prepotent responses in normal volunteers. Clinical studies have shown that cocaine-dependent patients treated with modafinil reported less cocaine use than those treated with placebo [13,14,15]. Currently, three clinical trials evaluating the safety and efficacy of modafinil for treating cocaine dependence are near completion or have been completed recently (NCT00218387, NCT00129285, and NCT00033046). Their final results are not yet available. We hope that the results from these and other studies will provide data to further advance the development of the medication for this indication.

Ondansetron is a 5-HT₃ receptor antagonist marketed for treating nausea and vomiting. Given its mechanism of action, it has been hypothesized that ondansetron may be able to indirectly inhibit corticomesolimbic dopamine release and thus reduce cocaine's reinforcing effects. A pilot, randomized, double-blind, outpatient study comparing ondansetron, 0.25 mg, 1.0 mg, or 4.0 mg twice daily, versus placebo showed that the group that received 4.0 mg had the lowest dropout rate of all treatment groups and a significantly greater proportion of participants with a cocaine-free week as compared with placebo [16]. Given the high prevalence of HIV infection among cocaine users, ondansetron may be a good alternative for treating not only their cocaine addiction but also the nausea and vomiting associated with their HIV infection or its therapy. More research is needed to determine ondansetron's efficacy for treating cocaine use and withdrawal. Currently, ondansetron is being evaluated for the treatment of cocaine-dependent, HIV-infected individuals (NCT00599573).

Topiramate is an anticonvulsant medication with GABA-enhancing effects and antagonist properties at the ionotropic glutamate receptor. A pilot, double-blind, placebo-controlled study conducted in cocaine-dependent patients with low cocaine withdrawal scores showed that those treated with topiramate, 200 mg/d, had higher cocaine abstinence rates than the placebo group (59% vs 26%). A post hoc analysis showed that topiramate also helped those who had stopped using cocaine to remain abstinent, which makes this medication a potential cocaine relapse prevention pharmacotherapy [17]. Currently, clinical trials are recruiting participants to evaluate the subjective, behavioral, and physiologic effects of topiramate in individuals addicted to cocaine (NCT00223626 and NCT00249691).

Recent research has identified changes associated with chronic cocaine use in specific proteins located in selective areas of the brain that regulate glutamate and/or GABA transmission. It has been suggested that NAC may help to restore the cystine–glutamate exchange. NAC is metabolized by the body to form cysteine, an active compound that normalizes glutamate levels that may normalize a cocaine-induced imbalance without affecting behavioral response for biologic rewards [18]. A randomized, double-blind, placebo-controlled study comparing NAC with placebo for the treatment of cocaine dependence is currently being conducted (NCT00218491), as is a human laboratory study (NCT00136825).

Atomoxetine blocks the norepinephrine reuptake transporter and increases extracellular dopamine levels in the prefrontal cortex. It is approved for treating adult attention-deficit/hyperactivity disorder (ADHD). Given that its pharmacologic effects are similar to those of cocaine use, this medication may have potential as a substitution therapy for treating cocaine withdrawal. A recently reported human laboratory study showed that cocaine is well tolerated during atomoxetine maintenance [19]. Furthermore, given the high prevalence of comorbid cocaine addiction and ADHD, it has been suggested that atomoxetine could be a good pharmacologic option for individuals with this comorbidity. It is possible that reducing ADHD symptoms in cocaine abusers with ADHD will help to decrease their need for cocaine. Atomoxetine's effectiveness in reducing cocaine use in people with ADHD who abuse cocaine is being evaluated in a pilot clinical trial (NCT00218543).

Buprenorphine, a μ -opioid agonist and κ antagonist approved by the FDA for treating opioid dependence, has been investigated for the treatment of cocaine dependence comorbid with opioid dependence. It has been suggested that the effect of buprenorphine on the treatment of cocaine dependence may be due to the opioid receptor antagonism and/or its ability to act as an opioid receptor-like 1 receptor agonist [20]. Results of a clinical trial directly targeting cocaine and heroin dependence suggest that buprenorphine, 16 mg/d, is safe and may be efficacious in reducing heroin and cocaine use [21]. Further research is needed to determine the efficacy of buprenorphine for treating cocaine addiction in the presence of opioid addiction.

Several classes of κ -opioid ligands are being explored for the treatment of cocaine addiction [22]. It has been reported that the κ -opioid receptors may contribute to the dysregulation of behavior that characterizes addiction and the individual differences in the pharmacologic actions of cocaine and alcohol. The κ -opioid receptor is involved, via indirect effects, in synaptic dopamine levels. Repeated administration of cocaine and alcohol seems to upregulate the κ -opioid receptor system, and medications that target this system may be helpful for treating their addictive disorders [23].

Immunotherapy is a relatively new approach to treating addictions, in particular cocaine addiction. TA-CD (Celtic Pharma, Hamilton, Bermuda) is a cocaine derivative (succinyl norcocaine) coupled to recombinant cholera toxin B that when injected can bind to the circulating cocaine and produce cocaine-specific antibodies. Cocaine is a small molecule that enters the brain, where it elicits its pleasurable effects and addictive properties. The cocaine-antibody complex is a large molecule that does not enter the brain and thus impedes cocaine's access to the brain. In rats, the anticocaine antibodies produce extinction of cocaine self-administration [24]. Studies in humans have shown that TA-CD has good immunogenicity for cocaine, is medically safe, and may be beneficial for treating cocaine dependence [25,26]. Planning of clinical trials with TA-CD is under way in Europe and the United States to further evaluate its immunogenicity, medical safety, and efficacy for treating cocaine dependence.

Methamphetamine Addiction

In recent years, MA use has significantly increased worldwide. Preclinical and clinical studies have demonstrated that its use can produce irreversible neuronal damage and serious neuropsychiatric consequences. The acute use of large amounts can induce a severe psychotic syndrome known as the MA psychosis. Presently, there are no FDA-approved treatments for MA addiction or MA-induced psychosis. Several medications are being investigated for both disorders [10•]. Medication development for MA addiction is a relatively new area of research. Presently, there are some “promising” medications to treat this disorder (Table 2), including bupropion, rivastigmine, modafinil, and lobeline [27,28•].

Bupropion is a dopamine reuptake inhibitor that is FDA approved to treat depression and nicotine dependence. Chronic MA use may result in low dopaminergic tone [29]. Therefore, by increasing the dopamine concentration in the synaptic cleft, bupropion may help to restore the dopamine system's homeostasis. In rats, bupropion has reduced the neurotoxic effects produced by a single large dose of MA. A recent double-blind, placebo-controlled trial comparing bupropion, 300 mg/d, with placebo showed that bupropion was more effective in increasing the number of weeks of abstinence in male patients with low to moderate MA dependence [30]. A similar clinical trial is currently being conducted (NCT00572234).

Modafinil is another medication of interest for treating MA addiction. It has an antidepressant effect that may help to treat the dysphoria associated with MA withdrawal. It also appears to decrease craving and MA seeking and may improve the cognitive functions of MA users and the response to cognitive-behavioral therapies. A recent inpatient pilot study showed that modafinil, 400 mg/d, and mirtazapine, 60 mg/d, for the treatment of MA withdrawal were well

tolerated, and the group of patients treated with modafinil had a milder withdrawal syndrome [31]. Modafinil is currently being evaluated for the treatment of MA dependence in several clinical trials (NCT00469508, NCT00538655, NCT00630097, NCT00569374, and NCT00520286).

The acetylcholinesterase inhibitor rivastigmine is being evaluated for the treatment of MA addiction because acetylcholine has been implicated in the reinforcing and locomotor-activating effects of MA. In human laboratory studies, rivastigmine attenuated MA-induced increases in diastolic blood pressure and self-reports of feeling anxious and drug desire [32] and may reduce the positive subjective effects produced by the self-administration of MA [33].

Lobeline, a tobacco plant derivative that inhibits uptake of dopamine into synaptic vesicles, interacts with the vesicular monoamine transporter and the cell surface dopamine transporter, two key sites of action for MA. Lobeline may be able to inhibit the amphetamine-induced release of dopamine in vitro and amphetamine-induced hyperactivity, drug discrimination, and self-administration [34–36].

Marijuana Addiction

Marijuana is the most commonly used illicit drug in the United States, with particularly heavy use occurring in adolescents. There is enough evidence that chronic cannabis use can produce physical and psychological consequences. Chronic cannabis users may experience difficulty in stopping or controlling drug use, develop tolerance to the subjective and cardiovascular effects, and eventually present with withdrawal symptoms after sudden discontinuation of use.

The pharmacologic profile of cannabis effects in humans is very well characterized. The best known active ingredient of marijuana is the δ -9-tetrahydrocannabinol (THC). This and other cannabinoid analogues have been shown to bind to two different types of cannabinoid receptors, termed the *CB1* and *CB2 receptors*. The CB1 receptors are located primarily in presynaptic neurons of the CNS and are responsible for the psychomimetic effects of marijuana and possibly the development of dependence and expression of withdrawal [37•]. The CB2 receptors are located in the periphery and modulate immune function and inflammatory response.

The mechanism of cannabis dependence may be associated with interactions of the cannabinoid system with the dopaminergic and opioid systems. Additionally, cannabinoid agonists, such as THC, act as inhibitors of neurotransmission, including acetylcholine, GABAergic, and glutamatergic pathways. Chronic administration of cannabinoids leads to downregulation of the receptor and receptor function desensitization. It has been proposed that endocannabinoids, such as anandamide, are biosynthesized postsynaptically, are released by a variety of stimuli upon demand, travel retrogradely across the synaptic cleft, and then activate the cannabinoid receptor. A membrane transporter actively takes anandamide into the cell. Anandamide is then broken down by the fatty acid amide hydrolase into arachidonic acid. In 2004, the National Institute on Drug Abuse launched a research program to develop medications for treating cannabis use disorders (CUDs) to respond to the public health need and the new scientific opportunities for developing pharmacotherapies for these disorders. Medications affecting the cannabinoid system are being actively investigated at the preclinical and clinical level. They include CB1 receptor agonists such as dronabinol, CB1 receptor antagonists, fatty acid amide hydrolase inhibitors, and anandamide inhibitors. Currently, the only ones that have been evaluated in humans for treating cannabis dependence are CB1 agonists and CB1 antagonists.

CB1 agonists such as dronabinol and oral THC have been investigated for treating marijuana withdrawal. In human laboratory studies, dronabinol appears to be superior to placebo in

reducing withdrawal symptoms without producing significant subjective effects [38]. A recent report of two clinical cases suggested that dronabinol may help to reduce marijuana use among marijuana-dependent individuals seeking treatment [39]. Another study showed that the combination of lofexidine and oral THC may have a synergistic effect for treating marijuana withdrawal [40••]. Outpatient clinical trials are being conducted to evaluate the safety and efficacy of dronabinol for treating marijuana withdrawal and use (NCT00217971 and NCT00480441).

CB1 antagonists such as rimonabant could be evaluated for the treatment of marijuana intoxication and as tools for cannabis use relapse prevention. For cannabis intoxication, rimonabant has decreased the marijuana effect in a dose-dependent fashion. A 90-mg dose of rimonabant produced a mean reduction of 40% in positive, subjective marijuana effects and a mean reduction in heart rate of 50% [41–43]. Rimonabant has been investigated for treating obesity and nicotine dependence but has not received FDA approval due to possible medication-related adverse events. No studies have evaluated rimonabant for the treatment of cannabis dependence. New CB1 antagonists are being developed with what investigators hope is a better safety profile.

A growing number of medications with effects at the “signal translation” are being investigated for treating CUDs. Detailed reviews of the study results can be consulted elsewhere [44,45••, 46••].

Conclusions

The development of medications to treat addiction is a very active area of research. The stage of development and degree of success of novel medications vary depending on the type of addictive disorder. Pharmacotherapies for opioid addiction are available, but new formulations of naltrexone and buprenorphine and new pharmacologic approaches beyond the opioid receptor soon may be offering new alternatives for their treatment. Medications for cocaine addiction have been investigated exhaustively in the past 20 years, but none have been approved by the FDA for this indication. Medications such as modafinil, ondansetron, topiramate, NAC, opioid agonists and antagonists, atomoxetine, and immunotherapies may provide an acceptable signal of efficacy for treating cocaine addiction alone or in combination with other psychiatric disorders. The development of pharmacotherapies for MA and cannabis addiction is in its early stages, but recent discoveries about their mechanism of action and development of addiction are offering new opportunities to find safe, effective medications for their treatment. For MA addiction, medications such as bupropion, modafinil, rivastigmine, and lobeline may be promising for treating MA withdrawal or dependence. Finally, given the great advances in understanding the endocannabinoid system and the effects of cannabis on the CNS in recent years, there has been increasing interest in evaluating pharmacotherapies for cannabis addiction and/or withdrawal and testing cannabinoids for the treatment of other addictive disorders. The cannabinoid agonists and antagonists and medications with actions on different neurotransmitter systems are being evaluated. With the recent advances in the knowledge of the neurobiology of addictions and the development of new pharmacotherapies for these disorders, it is hoped that more medication options will be available for the treatment of addictive disorders in the not-too-distant future.

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18161012]This article not only demonstrates the potential efficacy of cannabinoid agonists for the treatment of cocaine withdrawal but also introduces the idea that lofexidine may potentiate that effect and may be a useful pharmacotherapy tool. More research is needed with this combination of medications for this indication.

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Table 1**Medications for treating opioid addiction**

Study medication	Mechanism of action	Clinical target	Dose studied/route	FDA phase completed
Probuphine	Long-acting opioid agonist–antagonist	Prevents and treats opioid withdrawal	58 mg/SC implant	Phase 1
Naltrexone	Long-acting opioid antagonist	Prevents opioid effect, discourages opioid use, and prevents relapse	380 mg/SC or IM	Phase 2
Lofexidine	α -2 agonist	Treats the noradrenergic symptoms of opioid withdrawal	Up to 3.2 mg daily/oral	Phase 3 (recently published)
Tramadol	Moderate μ agonist	Treats opioid withdrawal	Up to 400 mg/oral	Phase 1
Memantine	NMDA antagonist	Reduces opioid craving and reinforcing effects	Up to 60 mg/oral	Phase 1

FDA—US Food and Drug Administration; IM—intramuscular; NMDA—*N*-methyl-D-aspartate; SC—subcutaneous.

Table 2
Medications for treating stimulant (cocaine or methamphetamine) addiction

Study medication	Mechanism of action	Clinical target	Dose studied/route	FDA phase completed
Modafinil	Glutamate enhancer	Reduces cocaine withdrawal symptoms and blunts cocaine euphoria	400 mg daily/oral	Phase 2
Ondansetron	5-HT ₃ antagonist	Reduces cocaine-reinforcing effects	Up to 8 mg daily/oral	Phase 2
Topiramate	GABA-enhancing and glutamate antagonist	Reduces cocaine withdrawal and prevents cocaine relapse	200 mg daily/oral	Phase 2
N-acetylcysteine	Balances glutamate levels	Reduces cocaine craving	Up to 2400 mg daily/oral	Phase 2
Atomoxetine	Norepinephrine reuptake blocker	Reduces cocaine withdrawal	Up to 20 mg daily/oral	Phase 1
Buprenorphine	Partial opioid receptor agonist and ORL-1 agonist	Reduces cocaine use	16 mg daily/sublingual	Phase 2
Cocaine vaccine	Pharmacokinetic antagonism	Extinction of cocaine addiction	400 µg/intramuscular	Phase 2
Bupropion	Dopamine reuptake inhibitor	Reduces MA withdrawal and prevents MA neurotoxic effect	300 mg/oral	Phase 2
Modafinil	Glutamate enhancer	Treats dysphoria due to MA withdrawal	400 mg/oral	Phase 2
Rivastigmine	AchE inhibitor	Reduces subjective effects of MA	Up to 3 mg/oral	Phase 1

AchE—acetylcholinesterase; FDA—US Food and Drug Administration; GABA—gamma-aminobutyric acid; MA—methamphetamine; ORL-1—opioid receptor-like 1.