UpToDate® Official reprint from UpToDate®
www.uptodate.com © 2023 UpToDate, Inc. and/or its affiliates. All Rights Reserved.

Wolters Kluwer

Stimulant use disorder: Treatment overview

AUTHOR: Kyle Kampman, MD
SECTION EDITOR: Andrew J Saxon, MD
DEPUTY EDITOR: Michael Friedman, MD

All topics are updated as new evidence becomes available and our peer review process is complete.

Literature review current through: **Oct 2023.**
This topic last updated: **Jul 05, 2023.**

INTRODUCTION

Cocaine, methamphetamine, and other stimulant use disorders are significant public health problems [1]. Users of cocaine and methamphetamine have elevated rates of medical morbidity and utilization of health care resources [2].

Initial management decisions and pharmacologic options for the treatment of stimulant use disorder is discussed in this topic and is summarized in an algorithm (algorithm 1). Psychosocial interventions for stimulant use disorders are discussed separately. The epidemiology, clinical manifestations, course, consequences, assessment, and diagnosis of cocaine use disorder and methamphetamine use disorder are also described separately.

- (See "Cocaine use disorder: Epidemiology, clinical features, and diagnosis".)
- (See "Methamphetamine use disorder: Epidemiology, clinical features, and diagnosis".)
- (See "Stimulant use disorder: Psychosocial management".)

PRINCIPLES OF TREATMENT

Cocaine, methamphetamine, and diverted pharmaceutical stimulants have similar mechanisms of action and similar manifestations of addiction. This suggests that a treatment with evidence for efficacy in one disorder may be effective in the treatment of another [3]. (See "Cocaine use disorder: Epidemiology, clinical features, and diagnosis" and "Methamphetamine use disorder:

Epidemiology, clinical features, and diagnosis" and "Acute amphetamine and synthetic cathinone ("bath salt") intoxication".)

Continuing care principles — We base the treatment of individuals with stimulant use disorder on the principles of the continuing care model as described below. Continuing care principles are described in detail separately. (See "Continuing care for addiction: Components and efficacy" and "Continuing care for addiction: Implementation" and "Stimulant use disorder: Psychosocial management".)

- We recognize that substance use disorders are often chronically recurring conditions that benefit from continuing care at varying levels of intensity rather than short-term treatment limited to periods of acute exacerbation.
- We base the intensity and number of psychosocial interventions used to treat a patient with stimulant use disorder on the patient's clinical status, stimulant use disorder severity, and response to prior treatment.
- We address continued treatment resistance by increasing the intensity of treatment. This could involve additional modalities, more hours per week, and/or more structure or restriction.
- Selection among treatment components is subject to patient preference, geographic variation in the availability of treatments/levels of care, and what payers will allow.

Setting goals — While we encourage complete sustained abstinence from stimulants in all individuals we treat for stimulant use disorder, we use shared decision making in establishing achievable treatment goals that lead to harm reduction and improvement in quality of life. Abstinence may be the most desirable outcome; however, it is often difficult to achieve. Furthermore, patients may find significant improvement in their lives with only a reduction of use.

PSYCHOSOCIAL INTERVENTION AS INITIAL TREATMENT

Only psychosocial interventions have demonstrated efficacy in reducing stimulant use in patients with stimulant use disorder [4-6]. Psychosocial interventions for stimulant use disorder include individual or group drug counseling including standard outpatient counseling and intensive outpatient therapy (IOT), cognitive-behavioral therapy (CBT), contingency management, and motivational interviewing. However, psychosocial treatments alone are

insufficient for many patients, prompting research into the neurobiology of stimulant use disorder and trials of several augmenting medications.

Psychosocial interventions for stimulant use disorder are discussed elsewhere. (See "Stimulant use disorder: Psychosocial management".)

Choosing a psychosocial intervention — Our initial treatment for stimulant use disorder is psychosocial intervention. Among psychosocial interventions, our choice is based on the severity of the disorder. Severity of the disorder is defined by the number of symptoms of the disorder that are present [7]. For example, using the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision (DSM-5-TR) criteria for stimulant use disorder, mild stimulant use disorder is characterized by the presence of two to three criteria, moderate stimulant use disorder is characterized by the presence of four to five criteria, and severe is characterized by the presence of six or more criteria (algorithm 1).

Mild stimulant use disorder — For individuals with mild stimulant use disorder, we suggest first-line treatment with individual or group drug counseling. We monitor for response for three weeks. If the patient experiences only a partial response or no response to drug counseling, we suggest a transition to IOT combined with contingency management. If contingency management is unavailable, we encourage treatment with IOT and CBT. Motivational interviewing can be used at any time if needed. These therapies are described separately. (See "Stimulant use disorder: Psychosocial management", section on 'Interventions'.)

Moderate or severe stimulant use disorder — For patients with moderate or severe stimulant use disorder, we suggest first-line treatment with IOT combined with contingency management. When contingency management is unavailable, we encourage treatment with IOT and CBT. Motivational interviewing can be used at any time if needed (See "Stimulant use disorder: Psychosocial management", section on 'Intensive outpatient therapy'.)

In clinical trials, both contingency management and CBT have been found to be effective for stimulant use disorder [4,6,8,9]. While evidence for motivational interviewing, drug counseling and IOT is equivocal, in our clinical experience, they sometimes can help patients with stimulant use disorder to maintain abstinence [5,10-13]. Further discussion of choices of psychotherapy and their effectiveness can be found elsewhere. (See "Stimulant use disorder: Psychosocial management", section on 'Interventions'.)

SUBSEQUENT TREATMENT

Assessing response — We assess treatment response in a variety of ways including whether goals were met, changes in quality of life, and patient satisfaction. Other useful measurements include the Addiction Severity Index and intermittent urine drug tests. (See 'Setting goals' above.)

Continuing care for treatment responders — For individuals who respond to psychosocial treatment, we continue treatment using the continuing care model for up to one year. We encourage the individual to return to treatment for recurrence of symptoms or return to use. (See 'Continuing care principles' above.)

Combined treatment for suboptimal response — For individuals who have suboptimal response after 8 to 12 weeks of the most intensive psychosocial treatments (eg, counseling, intensive outpatient therapy, contingency management or cognitive-behavioral therapy [CBT], motivational interviewing), we use pharmacologic augmentation. While limited and inconsistent evidence supports the use of pharmacologic treatment of stimulant use disorder [14-26], some studies suggest that the combination of medication (desipramine, bupropion, or citalopram) and psychosocial interventions (contingency management or CBT) for stimulant use disorder may be more efficacious than either modality alone [27-29]. (See 'Pharmacologic management' below.)

As an example, in a randomized trial, 160 individuals with cocaine and opioid use disorder (maintained on buprenorphine) were assigned to receive desipramine or placebo in conjunction with either contingency management or a noncontingent voucher control over 12 weeks of treatment [27]. Cocaine-free and combined cocaine and opiate-free urine specimens increased more rapidly over time in patients assigned to receive desipramine or contingency management compared with controls. Patients assigned to receive both desipramine and contingency management had a higher percentage of drug free specimens over the course of the treatment as compared with those assigned to desipramine plus noncontingency management, placebo plus contingency management, or placebo plus noncontingency management (50 versus 29 versus 25 versus 29 percent, respectively).

PHARMACOLOGIC MANAGEMENT

We use pharmacologic management combined with psychosocial treatments for suboptimal response to psychosocial treatment alone. Our choice of pharmacologic management is based on the stimulant being misused. However, when the individual is using more than one stimulant and the primary stimulant cannot be established, we use shared decision making to identify the substance most likely to be more problematic. There are no safety concerns in using any of the

following treatments for either cocaine use disorder or methamphetamine use disorder (algorithm 1).

Cocaine use disorder — We typically try medications for cocaine use disorder sequentially in the order listed below. Evidence supporting the usefulness of any of the medications listed is mixed. Our recommendations are based on limited data.

Topiramate as first choice — We use topiramate, a GABAergic medication as augmentation in individuals refractory to psychosocial treatments who do not have a contraindication to its use (eg, kidney stones, glaucoma).

GABA is the primary inhibitory neurotransmitter in the central nervous system. Activation of GABAergic neurons leads to decreased activation in the dopaminergic reward system [30-35]. These effects may help to prevent relapse either by blocking cocaine-induced euphoria, or by reducing craving caused by exposure to conditioned reminders of prior cocaine use.

Topiramate may be used to augment standard psychosocial treatment or may be used when psychosocial treatments fail or when efficacious treatments are not available. We begin topiramate at 25 mg daily. We increase by 25 to 50 mg weekly to a target dose of 150 to 300 mg per day in divided dose. If tolerated, we typically monitor over three months for efficacy. If ineffective, we taper topiramate slowly (eg, 50 mg/week) when discontinuing. If effective topiramate can be continued as long as a patient needs it. There is no established duration of treatment for any pharmacotherapy for substance use disorders.

Topiramate appears to be effective in the treatment of cocaine use disorder [24,25,36]. However, further studies are warranted. As examples, treatment with topiramate led to greater likelihood of abstinence and improved outcome versus placebo in the following trials:

- In a 13-week trial, 40 patients with cocaine use disorder were randomly assigned to treatment with topiramate (200 mg daily) or placebo [36]. Subjects assigned to receive topiramate were more likely to be abstinent during the last five weeks of the trial. In a secondary analysis among patients who returned for at least one visit after receiving medications, patients in the topiramate group were more likely to achieve at least three weeks of continuous abstinence from cocaine compared with patients in the placebo group (59 versus 26 percent). Topiramate patients were more likely than placebo patients to be rated “very much improved” at their last visit (71 versus 32 percent).

- In a 12-week trial, 142 patients with cocaine use disorder who were treated with CBT were randomly assigned to treatment with topiramate or placebo. Individuals in the topiramate

treatment group had a greater weekly proportion of cocaine nonuse days compared with those in the placebo group (13.3 versus 5.3 percent) [25].

Additionally, topiramate may be effective in individuals with comorbid alcohol use disorder:

- In a 13-week trial, 170 patients with cocaine use disorder and the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) alcohol dependence who were in weekly individual psychotherapy were randomly assigned augmentation with topiramate (300 mg daily) or placebo [24]. While differences prevention of relapse were not noted, subjects receiving topiramate were more likely to achieve three weeks of continuous abstinence from cocaine during the trial compared with the placebo group (20 versus 6 percent).

Long-acting amphetamines — We prefer to use long-acting amphetamines as the next agent for individuals who do not respond to treatment with topiramate. These agents block the same monoamine transporters as cocaine, but their relatively slower uptake and longer duration of action make them less likely to be misused [37]. This is analogous to the use of methadone in the treatment of opioid use disorder.

The use of long-acting stimulants for the treatment of cocaine use disorder should be done after a discussion of the risks (eg, misuse) and benefits with the patient. When prescribing long-acting stimulants to individuals with stimulant use disorder, we provide limited amount of medication and monitor for misuse or diversion at frequent intervals throughout the treatment.

We typically titrate long-acting amphetamines at the same titration rate and dose used in the treatment of attention deficit hyperactivity disorder in adults. For example, if using long-acting dextroamphetamine/amphetamine mixed salts, we would begin at 20 mg daily and increase by 10 mg at weekly intervals to a maximum dose of 60 mg per day. If ineffective (eg, after three months), we taper the medication over several weeks. (See "Attention deficit hyperactivity disorder in adults: Treatment overview", section on 'Stimulants as preferred pharmacologic treatment'.)

Limited data support the use of stimulants in the treatment of cocaine use disorder. Additionally, in some trials, treatment retention has been poor [15-17]. As examples:

- In a 12-week trial, 73 patients with treatment-refractory heroin and cocaine dependence were randomly assigned to treatment with oral dexamphetamine-SR 60 mg/day or placebo [14]. Both groups received methadone and diacetylmorphine (heroin-assisted treatment). Subjects treated with dexamphetamine-SR had fewer days of cocaine use as

compared with individuals treated with placebo (mean 44.9 versus 60.6 days). Secondary outcomes (eg, consecutive days reported abstinence, days abstinent in final four weeks of study) favored the dexamphetamine group over the placebo group. Eighty-nine percent of participants completed the trial. No serious adverse events occurred in dexamphetamine-treated patients.

- In an eight-week trial, 82 patients with cocaine use disorder were randomly assigned to treatment with sustained methamphetamine, immediate-release methamphetamine, or placebo [17]. Patients in the sustained-release methamphetamine group submitted fewer cocaine-positive urine drug screens during the trial compared with the immediate-release and placebo groups (29 versus 66 and 60 percent). Only 32 percent of patients completed the trial.

Combination of topiramate and long-acting amphetamine — For individuals with inadequate response to the above treatments, we use a combination of topiramate and long-acting amphetamine as the next choice. The combination of topiramate and long-acting amphetamine in the form of long-acting mixed amphetamine salts (MAS-ER) has shown efficacy for the treatment of cocaine use disorder [38-40].

For example, in a randomized trial, 81 individuals with cocaine use disorder were assigned to 12 weeks of treatment with either a combination of MAS-ER plus topiramate or double placebo [39]. MAS-ER was titrated to maximum dose of 60 mg/day over 2 weeks, topiramate was titrated to maximum dose of 300 mg/day over 6 weeks. More patients in the topiramate plus MAS-ER group achieved three consecutive weeks of abstinence during the trial as compared with the placebo group (33.3 versus 16.7 percent, respectively). The combination treatment was most effective for participants with a high baseline frequency of cocaine use. This was replicated in another trial in which 127 adults with cocaine use disorder were randomly assigned to 12 weeks treatment with the combination of topiramate (maximum dose 200 mg/day) and MAS-ER (maximum 60mg/day) or placebo [40]. The proportion of participants achieving three abstinent weeks at the end of the trial was greater in patients treated with topiramate and MAS-ER compared with the placebo group (14 versus 0 percent, respectively). Further trials are warranted.

Other agents with limited supporting data — We use the following agents only after the above agents have been ineffective.

- **Modafinil** – Modafinil, a stimulant used to treat narcolepsy and shift-work sleep disorder, has been studied as an agent to increase abstinence and reduce cocaine withdrawal symptoms in individuals with cocaine use disorder [18,20,21,41-46].

Clinical trials of modafinil in the treatment of cocaine use disorder have shown mixed results with some results finding evidence of benefit [18,21,45] and others not showing benefit [20].

- **Disulfiram** – Disulfiram is thought to effect cocaine use by decreasing the reinforcing properties of cocaine or by making cocaine use aversive [47-49]. It is also only indicated for patients committed to total abstinence from alcohol since it will provoke a disulfiram-alcohol reaction in the presence of alcohol. Limited data support its use in the treatment of cocaine use disorder and further studies are warranted. [22,23,50-52]. (See "Alcohol use disorder: Pharmacologic management", section on 'Disulfiram'.)

- **Antidepressants** – Little to no evidence supports the use of antidepressants in the treatment of cocaine use disorder [27,53-58]. In a small randomized trial, fluoxetine appeared to improve treatment retention in the outpatient treatment of primary crack cocaine dependence although similar finding in terms of cocaine use and craving were reported in this [53] and other studies [54]. In a single trial, citalopram 40 mg but not citalopram 20 mg appeared to improve duration of abstinence and likelihood of cocaine negative urine drug screen [59]. Small trials examining treatment with desipramine have shown mixed results for sustained abstinence as compared with placebo; however, interpretation is limited due to heterogeneity of methods and small sample sizes [55-57].

  We reserve the use of citalopram for individuals with cocaine use disorder only after the above treatments have been ineffective.

Methamphetamine use disorder — As with cocaine use disorder, we use medication management only after psychosocial treatment has been ineffective. Trials investigating bupropion, mirtazapine, methylphenidate, and a combination of bupropion and naltrexone have shown conflicting results with some showing some benefit; however, further trials with greater number of subjects are warranted [60-67]. (See 'Psychosocial intervention as initial treatment' above.)

Bupropion with naltrexone — Among medication treatments our first choice is combination of bupropion and naltrexone.

In clinical trials, treatment with combination injectable extended-release naltrexone 380 mg monthly with 450 mg bupropion daily appears to be effective in the treatment of methamphetamine use disorder [60,68]. In a clinical trial, 403 subjects with methamphetamine use disorder were randomly assigned to receive either a combination of injectable extended-release naltrexone with oral extended-release bupropion or placebo [60]. In this study, the naltrexone was given by injection at 380 mg every 3 weeks rather than at the approved

frequency of every 4 weeks. Bupropion was begun at 150 mg extended release and increased to 450 mg over the course of three days. At 12 weeks, overall weighted response rates (three out of four methamphetamine negative urine samples) were low in both groups but higher in the treatment group than in the placebo group (14 versus 3 percent). Secondary outcomes such as percentage of participants with negative urine samples and methamphetamine craving scores favored the treatment group.

Mirtazapine — If bupropion and naltrexone are ineffective our next choice is typically monotherapy with mirtazapine. Our target dose with mirtazapine is 30 mg nightly.

Two clinical trials and a subsequent meta-analysis suggest that mirtazapine may be efficacious in the treatment of methamphetamine use disorder [61-63]. In one trial including 120 individuals with methamphetamine use disorder, individuals receiving mirtazapine had fewer positive urine tests at 24 weeks (63 percent versus 74 percent; relative risk 0.75, 95% CI 0.56-1.00) and 36 weeks (71 versus 88 percent; relative risk 0.73, 95% CI 0.57-0.96) than those in placebo group [62]. Both mirtazapine trials were conducted in a special population of adult patients (cisgender men, transgender men, and transgender women who had sex with men) with stimulant use disorder who were sexually active.

Methylphenidate — Systematic reviews and meta-analyses show limited support for the use of methylphenidate in the treatment of methamphetamine use disorder. For example, in a meta-analysis of five trials including 642 participants no effect of treatment with psychostimulants for end-of-study abstinence (odds ratio 0.97, 95% CI 0.65-1.45) [66]. Additionally, the pooled estimate from 14 studies including 1184 participants showed no effect of psychostimulants for treatment retention (odds ratio 1.2, 95% CI 0.91-1.58).

In another meta-analysis, there was low-strength evidence from two randomized trials that methylphenidate reduced methamphetamine/amphetamine (MA/A) use: 6.5 versus 2.8 percent MA/A negative urine drug screens in one study (n = 34, p = 0.008) and 23 versus 16 percent in another study (n = 54, p = 0.047) [67].

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Stimulant use disorder and withdrawal" and "Society guideline links: Cocaine use and cocaine use disorder".)

SUMMARY AND RECOMMENDATIONS

- **Continuing care principles** – We use continuing care principles in the treatment of individuals with stimulant use disorder. Continuing care principles suggest that for individuals with substance use disorder who do not achieve abstinence or relapse following initial interventions, the intensity of the patient's treatment should be increased. This could involve additional modalities, more hours per week, and/or more structure or restriction. (See 'Continuing care principles' above.)

- **Psychosocial intervention** – Our initial treatment for stimulant use disorder is a psychosocial intervention. Among psychosocial interventions, our choice is based on the severity of the disorder. An algorithm describes the management of stimulant use disorder (algorithm 1).

  - **Mild stimulant use disorder** – For patients with mild stimulant use disorder, we suggest first line treatment with individual or group drug counseling, rather than other treatments (**Grade 2C**). (See 'Choosing a psychosocial intervention' above.)

    For patients with mild stimulant use disorder who do not achieve abstinence after three weeks of individual or group drug counseling we suggest transition to intensive outpatient therapy (IOT) combined with contingency management (if available) (**Grade 2C**). Motivational interviewing can be used at any time if needed.

  - **Moderate or severe stimulant use disorder** – For patients with moderate or severe stimulant use disorder, we suggest first-line treatment with IOT combined with contingency management (if available) along with motivational interviewing (**Grade 2C**). (See 'Choosing a psychosocial intervention' above.)

- **Subsequent treatment** – For individuals with stimulant use disorder who respond to psychosocial treatment we continue treatment using the continuing care model for up to one year. We encourage the individual to return to treatment for recurrence of symptoms or return to use. (See 'Subsequent treatment' above.)

  For individuals who have suboptimal response after 8 to 12 weeks of the most intensive psychosocial treatments (eg, counseling, IOT, contingency management or cognitive-behavioral therapy, motivational interviewing), we use pharmacologic augmentation. (See 'Combined treatment for suboptimal response' above.)

- **Pharmacologic management** – We use pharmacologic management combined with psychosocial treatments for suboptimal response to psychosocial treatment alone. Our choice of pharmacologic management is based on the stimulant being misused (algorithm 1).

- **Cocaine use disorder** – We suggest topiramate as the first choice for pharmacologic augmentation (**Grade 2C**). If this is ineffective our next choice is long-acting amphetamines, then combining topiramate with a long-acting amphetamine. (See 'Cocaine use disorder' above.)

- **Methamphetamine use disorder** – We suggest the combination of naltrexone and bupropion as the first choice in the pharmacologic augmentation of methamphetamine use disorder (**Grade 2C**). Mirtazapine and methylphenidate are other treatment options. (See 'Methamphetamine use disorder' above.)

ACKNOWLEDGMENT

The UpToDate editorial staff acknowledges David A Gorelick, MD, PhD, who contributed to an earlier version of this topic review.

Use of UpToDate is subject to the Terms of Use.

Topic 106878 Version 30.0

→