



HHS Public Access

Author manuscript

Med Clin North Am. Author manuscript; available in PMC 2023 January 01.

Published in final edited form as:

Med Clin North Am. 2022 January ; 106(1): 81–97. doi:10.1016/j.mcna.2021.08.010.

Understanding Stimulant Use and Use Disorders in a New Era

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Abstract

Extending from the ‘triple wave epidemic’ of opioid-related overdose deaths, a ‘fourth wave’ of high mortality involving methamphetamine and cocaine use has been gathering force. This paper provides a review of the published literature on stimulants including epidemiology, pharmacology, neurobiology, medical and psychiatric consequences, withdrawal management, and medical and behavioral treatments

Keywords

cocaine; methamphetamine; fentanyl; mortality; overdose; epidemiology; pharmacology; neurobiology; medical consequences; psychiatric consequences; medical treatment; behavioral treatment

Epidemiology

The US is in an era of unprecedented levels of drug-related mortality, evidenced by an exponential increase in deaths over a recent 38-year period.¹ The recent drivers of overdose deaths are illicit opioids; mortality from which has been described as a triple wave phenomenon.^{2–4} Most recently, illicit stimulant (including psychostimulants, predominantly methamphetamine, as well as cocaine) use and medical consequences, including overdose, are rising. This paper provides a review of the published literature on stimulants including epidemiology, pharmacology, neurobiology, medical and psychiatric consequences, withdrawal management, medical and behavioral treatments.

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Disclosures:

Dr Ciccarone reports consultant fees from Celero Systems and expert testimony fees from Motley Rice LLP.

National surveys reveal increased methamphetamine use prevalence 2016–19,⁵ but with considerable regional and demographic variation.⁶ The national prevalence of past-year cocaine use in 2019 is estimated at 5.5 million, increasing since 2011.⁵ Illicit supplies are growing as well as shifting. Seizures of methamphetamine, a proxy for supply, have risen in all US census regions including those in which supply was historically low.⁷ Correspondingly, for example, methamphetamine use is rising in Massachusetts, a state where its use was uncommon in the past.⁸ According to US DEA data, cocaine production estimates and US border seizures are at 10-year high levels as of 2019.⁹

Extending from the ‘triple wave epidemic’ of opioid-related overdose deaths, a ‘fourth wave’ of high mortality involving methamphetamine and cocaine use has been gathering force.¹⁰ From 2012–18 psychostimulant-related mortality has risen five-fold (from 0.8 to 3.9/100,000) and cocaine-related mortality 3-fold (from 1.4 to 4.5/100,000 pop.).¹¹ Rates for methamphetamine-involved deaths are higher among men and non-Hispanic American Indian or Alaska Native and non-Hispanic White individuals.¹²

The current rise in stimulant-related deaths, while poorly understood, appears entwined with the ongoing opioid epidemic.^{6,13–16} Polydrug use, e.g. the co-use of stimulants and opioids, may partially explain the rise in stimulant-related deaths; this is increasingly common,⁶ e.g., the 3-fold increase nationally, 2015–17, in methamphetamine use among those reporting past-month heroin use.¹⁷ Nationally, in 2019, 76% of cocaine-related overdose deaths also involved an opioid; for psychostimulant-related deaths 54% also involved an opioid; with co-involvement increasing over time¹⁶. Co-use of stimulants with high-potency synthetic opioids, e.g. fentanyl and fentanyl analogs, is particularly concerning. Synthetic opioids are involved in deaths attributable to psychostimulants (14%) and cocaine (40%).¹⁴ The reasons for co-use of stimulants, particularly methamphetamine, with synthetic opioids requires exploration.

In addition to the above illicit stimulants there are rising numbers of novel psychoactive substances (NPS) - including novel stimulants such as substituted cathinones. Eutylone and N-ethylpentylone are among the two most common NPS stimulants according to recent US DEA seizure data,⁹ toxicological surveillance¹⁸ and wastewater analyses.¹⁹

Prevalence of use data is scarce and a recent estimate using multiple sources indicated that under 3% of US adults have used any NPS in the past 12 months; estimates for younger persons were higher.²⁰ An estimated 5.8 percent of young adults aged 18 to 25, reported past year misuse of prescription stimulants in 2019; declining from 7.3 percent in 2015.⁵

Pharmacology

Methamphetamine supply, purity and potency have increased nationally to historically high levels following shifts in source and chemical production.⁹ Methamphetamine purity and potency now exceed 90% following several changes: decline in US domestic production and rise in Mexico-based production;²¹ historic shift from ephedrine-based to several variants of phenyl-2-propanone (P2P)-based chemical production;²² and increases in *d*-isomer to *l*-isomer ratio (i.e. potency is defined by the proportion of *d*-isomer).²² Methamphetamine

typically exists in a racemic mixture of these two stereo- isomers which have some known physiological differences: *l-methamphetamine* has strong peripheral *a*-adrenergic activity, while *d-methamphetamine* has 3 to 5 times the central nervous system activity (e.g. increased euphoria as well as mental health problems and addiction liability).²³ The broad clinical implications of increasing availability and use of potent d-methamphetamine need explication.

Illicit or street methamphetamine comes in liquid (rarely used on the street), powder, crystalline and pill (sometimes prescription mimics) forms.⁹ Powder methamphetamine (e.g. Meth; Speed; Crank) is the HCL salt of racemic methamphetamine; crystal methamphetamine (e.g. Crystal, Ice, Tina) tends to be a purer form of d-methamphetamine and is more smokable as such.^{23,24} Intake can be through oral ingestion, nasal insufflation (IN) (i.e. snorting), vapor inhalation (i.e. smoking, including “hot railing”), insertion per rectum (i.e. “booty bumping”), and injecting (IV) (i.e. “slamming”).²⁵ The plasma half-life following intake is 9 – 11 hours depending on route. Intravenous and intra-nasal routes lead to peak effects within 15 minutes; while smoking and oral routes take longer. Bioavailability is 100% for IV and 60–80% for other routes. Following use, approximately 70% of a dose is excreted in the urine within 24 hours.²⁶

Cocaine (benzoylecgonine) is a naturally occurring alkaloid extracted from the leaves of the *Erythroxylon coca* plant, indigenous to the Andean region of South America. The powder form of cocaine (e.g. Coke, Blow, Snow, etc.) is the hydrochloride salt, which is water soluble and consumable by IN and IV routes. The basic or bicarbonate form is well known as “crack”; this is typically smoked/inhaled unless converted by acidification to a more soluble, and thus injectable, form. Cocaine HCL is typically not smoked as its vaporization temp is too high.²³ Inhaled (smoked) cocaine has the fastest onset of action (3–5 seconds) followed by IV (1–3 minutes) and IN (>10 minutes). Inhaled cocaine leads to rapid cycling of use given its immediate effect and short duration of action. Half-life is 0.7 to 1.5 hours with rapid metabolism by the liver and excretion in the urine.^{27,28}

Cocaine is often consumed along with heroin, a combination known as a “speedball”.²³ The expected effects are to boost the euphoria from heroin; this is more common once physical dependence to heroin sets in. The combination of methamphetamine and strong opioids, e.g. heroin or fentanyl, is known as a “goofball.” This was historically less common than the cocaine and heroin speedball but appears to be getting more common.^{6,29} The combinations of stimulants and synthetic opioids appears to be driving the recent mortality wave.¹⁶

Synthetic cathinones are a class of NPS structurally similar to cathinone, a naturally occurring chemical derived from the khat plant (*Catha edulis*), native to East Africa and the Arabian Peninsula. Cathinones are the chemical analogues of amphetamine and were once marketed as “bath salts” or “legal highs” to avoid regulation, and often sold as counterfeit MDMA (aka Ecstasy). Synthetic cathinones are usually consumed in pill or capsule form, but smoking and insufflation, and more rarely injection, routes are options. There is a range of dosing (1–300 mg), onset of action (2–120 minutes), and duration of effect (.25–6 hours) depending on the substance; many have unknown pharmacokinetics. Regulation, beginning

in 2011 in the US, led to a decline in some of the initial products, however a diversity of cathinones has sprung up since.³⁰

Neurobiology

The neurobiology of methamphetamine has been well described in several excellent reviews.^{31,32} In brief, methamphetamine is a potent indirect agonist at noradrenaline, dopamine and serotonin receptors and thus stimulates releases of these monoamines in the central and peripheral nervous system. Mechanisms which combine to enhance neurotransmitter release include: redistribution from neuron synapse storage vesicles to the cytosol; increased (reversed) transport from cytosol to synapse; blockade as well as decreased expression of membrane transporters; inhibition of monoamine oxidase (metabolism); and increasing the activity of tyrosine hydroxylase (increasing dopamine production).³³ Methamphetamine is twice as potent at releasing noradrenaline than dopamine and 60-fold more effective at releasing serotonin.²⁶

Methamphetamine acts on the major CNS dopaminergic, noradrenergic and serotonergic pathways.³⁴ Dopaminergic circuits, mediating reward and reinforcement processes, include mesolimbic, mesocortical circuit and nigrostriatal pathways. Noradrenergic regions include the prefrontal cortex (cognitive processes), hippocampus (memory consolidation) and medial basal forebrain (arousal). The serotonergic system is diffuse and includes regulation of diverse functions e.g. those involving pain perception, reward, satiety and impulsivity, among others. The opioidergic pathways are also affected; with intertwined effects on drug reinforcement and craving.³⁴

CNS effects of acute methamphetamine use include arousal, euphoria, positive mood, improvements in cognitive function, as well as anxiety. Use over time leads to down regulation of receptors and depletion of monoamine stores. It is increasingly evident that chronic methamphetamine use is involved in neuroinflammation and degeneration processes. Three molecular cascades are being investigated: oxidative stress, neurotoxic and neuroinflammation. These neurobiological cascades are associated with altered brain metabolism and parallels in chronic dysfunction similar to other degenerative CNS diseases.³³

Cocaine also boosts postsynaptic monoamine levels, not through the mechanisms outlined above for methamphetamine leading to greater release of neurotransmitters, but through presynaptic reuptake blockade.²⁷ In addition to boosting the dopaminergic reward pathways, repeated cocaine exposure leads to significant neuroadaptations in the excitatory neurotransmitter glutamate³⁵ as well as brain pathways that respond to stress. Cocaine use disorders frequently co-occur with stress-related disorders and stress can contribute to recurrence of use.³⁶

Similar to methamphetamine and cocaine, synthetic cathinones are psychomotor stimulants that exert their effects by impairing monoamine transporter function. Ring-substituted cathinones, e.g. mephedrone, promote neurotransmitter release (like methamphetamine)

while pyrrolidine-containing cathinones (e.g. 3,4- methylenedioxypropylamphetamine (MDPV)) act through reuptake blockage (like cocaine).³⁰

Medical and Psychiatric Complications

The medical complications of stimulant use are diverse and occur in many organ systems (Table 1). Major mechanisms of organ injury include ischemia, excess central and peripheral nervous system stimulation and direct toxicity²³. Etiology of methamphetamine-related mortality is multifaceted including e.g. cardiovascular (common), pulmonary, CNS and renal systems; in addition, intentional and unintentional fatal injuries stemming from use, are common.²⁶

The most serious medical complications, leading to the most mortality, are cardiovascular and cerebrovascular.³³ Psychostimulants cause harm in these systems through excessive sympathetic nervous system stimulation; cocaine has an additional pro-thrombotic effect.³⁷ In the acute setting, chest pain is a more common presentation from cocaine than methamphetamine use. Chest pain is the most common complaint of persons using cocaine presenting to the emergency department,³⁸ however only a minority of patients have evidence of ischemia (10%) or acute myocardial infarction (6%).³⁹ Acute coronary syndrome is more likely due to vasospasm over plaque rupture.^{40,41} Myocardial infarction due to plaque rupture is seen in a minority of cases and more likely stemming from cocaine use due to its prothrombotic effect. Hypertension can be acute or chronic.³⁷ Cardiac arrhythmias can develop in persons using high dose psychostimulants. Long term use leads to chronic HTN, cardiomegaly, congestive heart failure and myocardial ischemia. Myocarditis is considered a precursor to the development of dilated cardiomyopathy, a significant clinical problem among persons using psychostimulants.^{42,43} Hypertensive, or hypertrophic, cardiomyopathy is less common; this resulting from profound chronic hypertension.³⁷ Injury to the cerebrovascular system also occurs due to persistent hypertension. Stroke, particularly hemorrhagic stroke, is found at higher rates among psychostimulant users.^{44,45}

There is mounting evidence that chronic methamphetamine use leads to neurodegeneration, cognitive impairment, psychiatric and psychomotor syndromes.³³ Cognitive impairment stemming from methamphetamine use is across multiple domains including executive function, memory, learning and processing speed, and motor and language skills.⁴⁶ Cocaine use is associated with milder or more transient deficits.⁴⁵ Premorbid impairments may account for some of these findings. Psychotic symptoms are common stemming from occasional use and become more frequent with regular, high-dose, or high-potency (e.g. *d-methamphetamine*) use. Psychotic symptom expression among persons who use methamphetamine may indicate an underlying vulnerability to schizophrenia,⁴⁵ although there are important differences: persons with methamphetamine induced psychotic symptoms had less “negative” symptoms (i.e. blunted affect, disorganization, social withdrawal) and similar levels of “positive” symptoms (i.e., grandiosity, hallucinations, paranoia) compared with individuals with schizophrenia.³² Co-morbid mood disorders are also common among those meeting criteria for methamphetamine use disorder.⁴⁷ Abnormal psychomotor symptoms include tremors, dyskinesia, akathisia, etc., as well as repetitive and compulsive behaviors e.g. “tweaking” (due to tactile hallucinations i.e. formication).²³

Neurodegeneration of dopaminergic CNS pathways, secondary to chronic methamphetamine use, may lead to premature development of Parkinson's disease and parkinsonism.⁴⁵ It is important to recognize that premorbid conditions, e.g. genetics, family history, childhood trauma or isolation, can lead to both substance use disorders and psychiatric syndromes.^{33,45}

Nationwide, HIV diagnoses are edging up among persons who inject drugs (PWID); this increase is more profound among White PWID.^{48,49} Recent outbreaks of HIV discovered among PWID in several US states accentuate this trend along with rising viral hepatitis infection rates.^{50–53} Injection stimulant use, both of cocaine and methamphetamine, has been associated with HIV seroconversion, whether through injection practices or high risk sexual behavior, often in patterns of polydrug use.^{6,54–56} Methamphetamine also incurs increased physiological risk of HIV acquisition⁵⁷ and is associated with lower rates of viral suppression among people living with HIV and therefore enhanced risk of transmission.⁵⁸

Long-term use of stimulants is frequently preformed in cycles of bingeing and abstinence.²³ Cohort studies estimate that following initiation of cocaine use 7% meet criteria for cocaine use disorder at 1-year; with a 15% cumulative probability of cocaine use disorder after 10 years.⁵⁹ Stimulant use disorder is a chronic relapsing condition. Criteria for meeting the diagnosis come from the Diagnostic and Statistical Manual, Fifth Edition (DSM-5) published by the American Psychiatric Association.⁶⁰ Eleven criteria are detailed including for example: craving; failure to satisfy important school, home, or work obligations; consistent desire to control use; and continued use despite psychological or physical difficulties. Three levels of severity of illness are diagnosed based on number of criteria met within a 12-month period: mild disorder (2–3 criteria); moderate disorder (4–5 criteria); or severe disorder (6 or more). Development of stimulant use disorder is strongly influenced by early childhood adversity. A recent national study found a statistically significant relationship between the number of self-reported adverse childhood experiences (ACEs) and stimulant use and use disorders among adult respondents.⁶¹

Management of Stimulant Withdrawal Symptoms

Abstinence following prolonged use can produce withdrawal symptoms defined by DSM-5 that include trouble sleeping, trouble concentrating, tiredness/fatigue, irritability, agitation, anxiety, sadness, depression and inability to do normal activities.⁶⁰

In the inpatient and emergency department settings, patients with stimulant-related agitation are usually managed with antipsychotics⁶² though these medications show no efficacy for sustaining abstinence after discharge. In outpatient settings, withdrawal symptoms are usually mild-to-moderate in severity; most are short-lived⁶³ and mostly absent after five weeks. On the other hand, craving for stimulants, diminishes slowly contributing to continued use or recurrence of use in the first weeks and months of abstinence.⁶³ Longer-term abstinence from stimulants leads some to attribute decreases in cognitive abilities, especially in settings of continued episodic use, as protracted withdrawal.⁶⁴ As no medications show consistent effects in treating stimulant withdrawal,⁶⁵ treatments are largely behavioral (e.g., cognitive-behavioral therapies, behavioral activation, 12-step facilitation and contingency management) – all of which require patients to allot cognitive

resources to sustain abstinence -- resources that may be diminished from direct effects of the stimulants themselves and of the effects of stimulant withdrawal symptoms. In addition, patients who experience repeated use and recurrence of use as a consequence of failures of treatments to successfully resolve withdrawal can lose motivation to remain in treatment. There are some innovations, however. One new approach that enhances cognitive reserve is repetitive transcranial magnetic stimulation. A pilot study showed superiority in reducing methamphetamine withdrawal symptoms compared to a sham condition in a small study of men acutely abstinent from methamphetamine use disorder.⁶⁶

Medication Treatments for Stimulant Use Disorder

Evidence-based treatments, whether pharmacological or behavioral, can be considered for use to the extent they show superiority over placebo or other comparisons along defined targets (Table 2). While there are no FDA-approved medications for cocaine or methamphetamine use disorders, clinical research shows some medications show statistically significant and clinically relevant outcomes over placebo. A small number of medications have data in placebo-controlled trials showing measurable reductions in stimulant use. The point worth remembering is that this benefit is due to a medication or medications, a benefit to patients that occurs directly related to the medication – and a benefit that accrues to the patient without needing to allot psychological energy or motivational resources regarding their stimulant use (or non-use).

One rule to evaluate the strength of findings reported by studies on stimulant pharmacotherapy outcomes involves whether positive outcomes are observed from two or more trials of a medication and/or whether there is one single well-powered study. With this in mind, there are four medications or classes of medications that show consistent signals of efficacy for improving cocaine use outcomes. Dopamine agonists show the most consistent findings for efficacy.⁶⁷ Significant cocaine abstinence outcomes are seen for *d-amphetamine* over placebo at doses between 30–60 mg flexible dose and 60 mg fixed dose in patients with cocaine dependence^{68,69}. A finding also seen for cocaine abstinence outcomes at 60 mg for people with cocaine and opioid use disorders.⁷⁰ Showing cocaine abstinence outcomes are improved at higher agonist doses, one trial evaluated extended release mixed amphetamine salts and showed dose-dependent effects (60mg, 80mg) over placebo for reducing cocaine use among participants with both cocaine use disorder and attention deficit hyperactivity disorder.⁷¹ A second medication involves repeated trials showing significant improvements in cocaine abstinence outcomes for topiramate over placebo,^{72,73} with cocaine use outcomes also reduced for one trial in a subset of participants with cocaine and alcohol use disorder.⁷⁴ Despite this consistency, a frequent side effect for topiramate involves cognitive dysfunction that can interfere with daily functioning. This side effect can be minimized by titrating dose to steady state in weekly increases, with abstinence outcomes observed at steady state. A combination pharmacotherapy that combines extended release mixed amphetamine salts and topiramate produced two trials showing strong, replication findings in reducing cocaine use, especially among participants who had greater frequency of cocaine use at baseline.^{75,76} An honorable mention in the list of medications for cocaine use disorder is disulfiram. Multiple trials have been conducted on the medication. Two systematic reviews that evaluated the complex set of trial findings regarding use of disulfiram for cocaine use disorder concluded,

however, that if there is a signal for disulfiram,⁷⁷ it is not replicable and there is a signal that disulfiram actually reduces retention in trials compared to placebo.⁷⁸

These findings underscore the importance of replicating findings from single trials, especially when trials are small and/or have conflicting findings. There does appear, however, to be sufficient evidence to consider an agonist approach, or the combination topiramate and extended release mixed amphetamine salts strategy, when developing a treatment plan for patients with cocaine use disorder. It is worth re-stating that none of these medications have been evaluated for use as a treatment for cocaine use disorder by the FDA.

Using the same metric for considering medications to improve drug use outcomes for methamphetamine use disorder, one medication and one combination pharmacotherapy deserve consideration. The single pharmacotherapy involves mirtazapine (30mg/day). In a small, 12-week randomized placebo-controlled trial⁷⁹ and a larger, 36-week replication study⁸⁰, nearly identical superior signals in methamphetamine use over placebo were observed for mirtazapine for reducing methamphetamine use. It is worth noting that both trials were conducted in San Francisco and both trials were conducted among men who have sex with men and transgender women. It is also worth noting that the majority of methamphetamine reduction occurred in the first 12 weeks, with the mirtazapine group maintaining their abstinence gains to the end of the study. A recent multisite, fully-powered 12-week trial of combination pharmacotherapy of extended release naltrexone (XR-NTX) and oral daily bupropion (450 mg) showed significant reduction in methamphetamine use.⁸¹ The trial was the largest methamphetamine clinical trial ever (n=403). It is worth noting that the XR-NTX was administered every three weeks with the high dose bupropion condition to address the tendency of pharmacotherapy trials to evaluate sub-optimal study doses. The number needed to treat using the combination is 9, which compares favorably to other medications used for substance use disorder. It remains unclear if the combination pharmacotherapy can be used with patients with methamphetamine use disorder who have moderate or severe opioid use disorder. Still, the consistency of the findings from these two studies with clear signals of efficacy provide rationale for considering their use in clinical settings.

Behavioral Treatments for Stimulant Use Disorder

There is a mature evidence base describing outcomes for behavioral treatments for cocaine and methamphetamine use disorders. Behavioral treatments with efficacy for cocaine also show efficacy for methamphetamine. Taking advantage of the number of completed trials, systematic reviews and meta-analyses will describe signals of efficacy for behavioral treatments of cocaine and stimulant use disorders. It is worth noting that ability to respond to behavioral therapies for stimulant use disorders are linked to availability of dopamine D2, D3 receptors^{82,83} and the cognitive ability to avoid making decisions of risk in the setting of recent loss.^{84,85} As all behavior reflects brain activity, it is encouraging to note that behavioral therapies have neural and cognitive correlates that predict treatment outcome and signal key neurocognitive mechanisms in recovery from stimulant use disorder.

Contingency Management.

Contingency management is the behavioral therapy with greatest efficacy for producing sustained abstinence from cocaine and methamphetamine use. The therapy works by providing incentives of increasing value for successive biomarkers documenting stimulant abstinence. It is based on the principles of operant behavior.⁸⁶ The operant principles of contingency management were first applied to determining who qualified for take-home medications in methadone treatment clinics.⁸⁷ The principles were adapted for use in treating cocaine use disorder in the 1990s.⁸⁸ The original method of providing vouchers in exchange for urine samples documenting stimulant abstinence was adapted further by using a “fish-bowl” method that provided increasing numbers of draws for prizes from the fish-bowl with consecutive samples documenting stimulant abstinence.⁸⁹ Four meta-analyses of clinical trials measuring the signal for contingency management report an effect size (“d”) between 0.4 to 0.6.^{90–93} The size of this signal is such that if contingency management were a medication, it would be the standard of care. A frequent complaint about contingency management is that the therapy works by paying people to make healthy choices that they should do without incentives. Yet, there are limits to the contingency management: it works only when participants have some intention to change their stimulant use behaviors.⁹⁴ Another concern expressed notes that until recently, contingency management was only available in research clinics and a limited number of public health treatment settings. Notably the Veterans Administration Healthcare System now provides contingency management treatment of cocaine use disorder.⁹⁵ Scale-up of contingency management and addressing sticky issues in providing resources for the contingency management schedules in insurance markets, both privately and publicly funded, is currently underway.

Cognitive Behavioral Therapy.

Cognitive behavioral therapy involves teaching a set of common principles to patients in order to facilitate remission, to return to abstinence following use and recurrence of use, and to prevent recurrence of use. Cognitive behavioral therapies are didactic and taught over a series of weeks in individual or group formats. Manuals are available online to deliver cognitive behavioral therapy^{96,97} and the therapy is now available to engage on-line (www.CBT4CBT.com). Cognitive behavioral therapies show weaker and less consistent signals of efficacy compared to contingency management.^{98,99} The effects noted above on direct stimulant effects and withdrawal symptoms in eroding cognitive capacity can interfere with some patients being able to engage the learning process in the short term. Yet there are data showing that even with the relatively weaker signal for cognitive behavioral therapy over contingency management during early recovery, data do show significant improvements in abstinence outcomes at distal follow-up evaluations. One explanation for this observation is that some believe that skills for recurrence of use prevention are best learned in real time by applying the skills to return to abstinence during recurrence of use of stimulants. In individual trials, there is a consistent “sleeper effect” for cognitive behavioral therapy, where abstinence outcomes improve over time as patients apply the skills necessary to sustain abstinence and importantly, to return to abstinence following recurrence of use.¹⁰⁰ Still, principles of cognitive behavioral therapy are omnibus, with uptake of these concepts used in most intervention settings, including peer and social recovery and harm reduction. Their wide-scale use is the basis for cognitive behavioral therapies as having comparatively

weaker efficacy to contingency management, but greater effectiveness in reducing suffering across the community of people in treatment for stimulant use disorders.

Behavioral therapies and strategies with less consistent evidence of efficacy.

There are several behavioral therapies that have trials showing initial signals of comparative efficacy for patients trying to establish and sustain abstinence from stimulants. These include motivational interviewing¹⁰¹ and 12-step facilitation approaches.¹⁰² As with pharmacotherapies, there appears to be some additional benefit to abstinence outcomes when combining behavioral therapies, with especially strong signal observed for the few trials that combine contingency management and cognitive behavioral therapy.^{91,101} This strategy, of combining behavioral therapies, underscores that notion that stimulant use disorder is difficult to treat, with best outcomes seen when interventions that address multiple targets are outlined in the treatment plan (Table 2). In spite of this replicated boost in efficacy for the combination, few programs incorporate contingency management. Similarly, there is increasing interest in incorporating behavioral therapies with the few medications showing signals of efficacy for stimulant use disorder to boost outcomes, particularly in those patients with severe stimulant use disorders. There are some indications that incorporating agonist medications with contingency management can boost achieving remission, with the medications reinforcing incentive salience.¹⁰³ Use of behavioral therapies for stimulant use disorders is complex for clinicians who work in primary care, emergency departments and other settings that do not have access to behavioral health. This is an area ripe for development in the field, with a notable example of the “bridge to recovery” movement for increasing access to medications for opioid use disorder. A parallel focus that involves increasing access to medications for stimulant use disorders is an important research direction for the near future.

In summary, for the first time there is a consistent signal of efficacy supporting use of agonists for cocaine use disorder and mirtazapine for methamphetamine use disorder as single medications in outpatient settings. A similar report on the strength and consistency of signal for combination pharmacotherapies for cocaine use disorder (mixed amphetamine salts, extended release plus topiramate) and for methamphetamine use disorder (extended release naltrexone plus high dose bupropion) in outpatient settings can now be made. Moreover, there is now sufficient evidence to support consideration of a medication approach as a foundation for outpatient treatment for stimulant use disorders. A single approach, however, will likely be insufficient to overcome the pernicious and difficult challenges to achieving and maintaining remission from stimulants. Integrating medications with behavioral therapies (contingency management, cognitive behavioral) and social/peer support approaches (12-step groups, 12-step facilitation) represent opportunity for helping patients to make significant reductions in stimulant use and in reaching their substance use goals.

Funding:

The authors acknowledge funding from National Institutes of Health, National Institute of Drug Abuse, grant R01DA037820; U01DA036267; UG1DA020024; P30MH058107

References

1. Jalal H, Buchanich JM, Roberts MS, Balmert LC, Zhang K, Burke DS. Changing dynamics of the drug overdose epidemic in the United States from 1979 through 2016. *Science*. 2018;361(6408):eaau1184. [PubMed: 30237320]
2. Ciccarone D The triple wave epidemic: supply and demand drivers of the US opioid overdose crisis. *Int J Drug Policy*. 2019;71:183–188. [PubMed: 30718120]
3. Ciccarone D Fentanyl in the US heroin supply: A rapidly changing risk environment. *International Journal of Drug Policy*. 2017;46:107–111. [PubMed: 28735776]
4. Centers for Disease Control and Prevention. 2019 Annual Surveillance Report of Drug-Related Risks and Outcomes — United States Surveillance Special Report. 2019.
5. Substance Abuse and Mental Health Services Administration. Key substance use and mental health indicators in the United States: Results from the 2019 National Survey on Drug Use and Health. Rockville, MD: Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration;2020.
6. Glick SN, Burt R, Kummer K, Tinsley J, Banta-Green CJ, Golden MR. Increasing methamphetamine injection among non-MSM who inject drugs in King County, Washington. *Drug and Alcohol Dependence*. 2018;182:86–92. [PubMed: 29175463]
7. Artigiani EE, Hsu MH, Hauser W, Al-Nassir M, Dhatt Z, Wish ED. U.S. Law Enforcement Seizures of Methamphetamine Widespread and Increasing College Park, MD: National Drug Early Warning System.2020.
8. Wakeman S, Flood J, Ciccarone D. Rise in Presence of Methamphetamine in Oral Fluid Toxicology Tests Among Outpatients in a Large Healthcare Setting in the Northeast. *J Addict Med*. 2021;15(1):85–87. [PubMed: 32732682]
9. US Drug Enforcement Administration. National Drug Threat Assessment. Department of Justice. In:2021.
10. Ciccarone D The Rise of Illicit Fentanyls, Stimulants and the Fourth Wave of the Opioid Overdose Crisis. *Curr Opin Psychiatry*. 2021 7 1;34(4):344–350. doi: 10.1097/YCO.0000000000000717. [PubMed: 33965972]
11. Hedegaard HMA, Warner M. Drug overdose deaths in the United States, 1999–2018. Hyattsville, MD2020.
12. Han B, Cotto J, Etz K, Einstein EB, Compton WM, Volkow ND. Methamphetamine Overdose Deaths in the US by Sex and Race and Ethnicity. *JAMA Psychiatry*. 2021.
13. Gladden RM, O'Donnell J, Mattson CL, Seth P. Changes in Opioid-Involved Overdose Deaths by Opioid Type and Presence of Benzodiazepines, Cocaine, and Methamphetamine - 25 States, July-December 2017 to January-June 2018. *MMWR Morb Mortal Wkly Rep*. 2019;68(34):737–744.
14. Jones CM, Einstein EB, Compton WM. Changes in synthetic opioid involvement in drug overdose deaths in the united states, 2010–2016. *JAMA*. 2018;319(17):1819–1821. [PubMed: 29715347]
15. Al-Tayyib A, Koester S, Langegger S, Raville L. Heroin and methamphetamine injection: an emerging drug use pattern. *Substance use & misuse*. 2017;52(8):1051–1058. [PubMed: 28323507]
16. Hedegaard H, Minino AM, Warner M. Co-involvement of Opioids in Drug Overdose Deaths Involving Cocaine and Psychostimulants. *NCHS Data Brief*. 2021(406):1–8.
17. Strickland JC, Havens JR, Stoops WW. A nationally representative analysis of “twin epidemics”: Rising rates of methamphetamine use among persons who use opioids. *Drug and alcohol dependence*. 2019;204:107592. [PubMed: 31586804]
18. NPS Stimulants & Hallucinogens in the United States: Trend Report Q1:2021. https://www.npsdiscovery.org/wpcontent/uploads/2021/04/2021-Q1_NPS-Stimulants-and-Hallucinogens_Trend-Report.pdf. Accessed May 3, 2021.
19. Bade R, White JM, Chen J, et al. International snapshot of new psychoactive substance use: Case study of eight countries over the 2019/2020 new year period. *Water Res*. 2021;193:116891. [PubMed: 33582495]

20. Peacock A, Bruno R, Gisev N, et al. New psychoactive substances: challenges for drug surveillance, control, and public health responses. *Lancet* (London, England). 2019;394(10209):1668–1684.
21. United Nations Office on Drug and Crime. *World Drug Report 2020: Booklet 3, Drug Supply*. Vienna: United Nations;2020. E.20.XI.6.
22. Drug Enforcement Administration. *National Drug Threat Assessment*. Department of Justice;2019.
23. Ciccarone D Stimulant abuse: pharmacology, cocaine, methamphetamine, treatment, attempts at pharmacotherapy. *Prim Care*. 2011;38(1):41–58, v-vi. [PubMed: 21356420]
24. Erowid. https://www.erowid.org/chemicals/meth/meth_basics.shtml. Accessed April 30, 2021.
25. Tweaker.org. <https://tweaker.org/crystal-meth/ways-guys-dometh/>. Accessed April 30, 2021.
26. Cruickshank CC, Dyer KR. A review of the clinical pharmacology of methamphetamine. *Addiction* (Abingdon, England). 2009;104(7):1085–1099.
27. Zimmerman JL. Cocaine intoxication. *Crit Care Clin*. 2012;28(4):517–526. [PubMed: 22998988]
28. Volkow ND, Wang GJ, Fischman MW, et al. Effects of route of administration on cocaine induced dopamine transporter blockade in the human brain. *Life Sci*. 2000;67(12):1507–1515. [PubMed: 10983846]
29. Ellis MS, Kasper ZA, Cicero TJ. Twin epidemics: The surging rise of methamphetamine use in chronic opioid users. *Drug and Alcohol Dependence*. 2018;193:14–20. [PubMed: 30326396]
30. Goncalves JL, Alves VL, Aguiar J, Teixeira HM, Camara JS. Synthetic cathinones: an evolving class of new psychoactive substances. *Crit Rev Toxicol*. 2019;49(7):549–566. [PubMed: 31747318]
31. Fleckenstein AE, Volz TJ, Riddle EL, Gibb JW, Hanson GR. New insights into the mechanism of action of amphetamines. *Annu Rev Pharmacol Toxicol*. 2007;47:681–698. [PubMed: 17209801]
32. Panenka WJ, Procyshyn RM, Lecomte T, et al. Methamphetamine use: a comprehensive review of molecular, preclinical and clinical findings. *Drug and alcohol dependence*. 2013;129(3):167–179. [PubMed: 23273775]
33. Paulus MP, Stewart JL. Neurobiology, Clinical Presentation, and Treatment of Methamphetamine Use Disorder: A Review. *JAMA psychiatry*. 2020;77(9):959–966. [PubMed: 32267484]
34. Courtney KE, Ray LA. Methamphetamine: an update on epidemiology, pharmacology, clinical phenomenology, and treatment literature. *Drug and alcohol dependence*. 2014;143:11–21. [PubMed: 25176528]
35. Schmidt HD, Pierce RC. Cocaine-induced neuroadaptations in glutamate transmission: potential therapeutic targets for craving and addiction. *Annals of the New York Academy of Sciences*. 2010;1187:35–75. [PubMed: 20201846]
36. Mantsch JR, Vranjkovic O, Twining RC, Gasser PJ, McReynolds JR, Blacktop JM. Neurobiological mechanisms that contribute to stress-related cocaine use. *Neuropharmacology*. 2014;76 Pt B:383–394. [PubMed: 24447715]
37. Dufloy J Psychostimulant use disorder and the heart. *Addiction*. 2020;115(1):175–183. [PubMed: 31321853]
38. Brody SL, Slovis CM, Wrenn KD. Cocaine-related medical problems: consecutive series of 233 patients. *The American journal of medicine*. 1990;88(4):325–331. [PubMed: 2327419]
39. Weber JE, Chudnofsky CR, Boczar M, Boyer EW, Wilkerson MD, Hollander JE. Cocaine-associated chest pain: how common is myocardial infarction? *Academic emergency medicine : official journal of the Society for Academic Emergency Medicine*. 2000;7(8):873–877. [PubMed: 10958126]
40. Paratz ED, Cunningham NJ, MacIsaac AI. The Cardiac Complications of Methamphetamines. *Heart Lung Circ*. 2016;25(4):325–332. [PubMed: 26706652]
41. Chen JP. Methamphetamine-associated acute myocardial infarction and cardiogenic shock with normal coronary arteries: refractory global coronary microvascular spasm. *J Invasive Cardiol*. 2007;19(4):E89–92. [PubMed: 17404411]
42. Neeki MM, Kulczycki M, Toy J, et al. Frequency of Methamphetamine Use as a Major Contributor Toward the Severity of Cardiomyopathy in Adults 50Years. *The American journal of cardiology*. 2016;118(4):585–589. [PubMed: 27374605]

43. Virmani R, Robinowitz M, Smialek JE, Smyth DF. Cardiovascular effects of cocaine: an autopsy study of 40 patients. *Am Heart J.* 1988;115(5):1068–1076. [PubMed: 3364339]
44. Darke S, Duflou J, Kaye S, Farrell M, Lappin J. Psychostimulant Use and Fatal Stroke in Young Adults. *Journal of forensic sciences.* 2019;64(5):1421–1426. [PubMed: 30941776]
45. Lappin JM, Sara GE. Psychostimulant use and the brain. *Addiction (Abingdon, England).* 2019;114(11):2065–2077.
46. Scott JC, Woods SP, Matt GE, et al. Neurocognitive effects of methamphetamine: a critical review and meta-analysis. *Neuropsychol Rev.* 2007;17(3):275–297. [PubMed: 17694436]
47. Akindipe T, Wilson D, Stein DJ. Psychiatric disorders in individuals with methamphetamine dependence: prevalence and risk factors. *Metab Brain Dis.* 2014;29(2):351–357. [PubMed: 24532047]
48. Centers for Disease Control and Prevention. HIV Surveillance Report, 2018 (Preliminary). 2019.
49. AtlasPlus. <https://gis.cdc.gov/grasp/nchhstpatlas/charts.html>. Accessed April 29, 2021.
50. Peters PJ, Pontones P, Hoover KW, et al. HIV Infection Linked to Injection Use of Oxymorphone in Indiana, 2014–2015. *N Engl J Med.* 2016;375(3):229–239. [PubMed: 27468059]
51. Evans ME LS, Hogan V, Agnew-Brune C, Armstrong J, Karuppiah ABP, et al. Notes from the Field: HIV Infection Investigation in a Rural Area — West Virginia, 2017. *Morb Mortal Wkly Rep* 2018;67:257–258.
52. Wheeling-Ohio West Virginia Health Department. HIV Cluster Identified in Ohio County. 2018; <http://www.ohiocountyhealth.com/news/hiv-cluster-identified-in-ohiocounty/>.
53. Centers for Disease Control and Prevention. Epi-2: Preliminary Epi-Aid Report: Undetermined Risk Factors and Mode of Transmission for HIV Infection Among Persons Who Inject Drugs — Massachusetts, 2018. Atlanta, GA. 7 17, 2018 2018.
54. Tyndall MW, Currie S, Spittal P, et al. Intensive injection cocaine use as the primary risk factor in the Vancouver HIV-1 epidemic. *Aids.* 2003;17(6):887–893. [PubMed: 12660536]
55. Patterson TL, Semple SJ, Zians JK, Strathdee SA. Methamphetamine-using HIV-positive men who have sex with men: Correlates of polydrug use. *Journal of urban health : bulletin of the New York Academy of Medicine.* 2005;82(Suppl 1):i120–i126. [PubMed: 15738313]
56. Spindler HH, Scheer S, Chen SY, et al. Viagra, methamphetamine, and HIV risk: results from a probability sample of MSM, San Francisco. *Sex Transm Dis.* 2007;34(8):586–591. [PubMed: 17334264]
57. Fulcher JA, Shoptaw S, Makgoeng SB, et al. Brief Report: Recent Methamphetamine Use Is Associated With Increased Rectal Mucosal Inflammatory Cytokines, Regardless of HIV-1 Serostatus. *Journal of acquired immune deficiency syndromes (1999).* 2018;78(1):119–123. [PubMed: 29419567]
58. Fairbairn N, Kerr T, Milloy M-J, Zhang R, Montaner J, Wood E. Crystal methamphetamine injection predicts slower HIV RNA suppression among injection drug users. *Addict Behav.* 2011;36(7):762–763. [PubMed: 21396784]
59. Lopez-Quintero C, Perez de los Cobos J, Hasin DS, et al. Probability and predictors of transition from first use to dependence on nicotine, alcohol, cannabis, and cocaine: results of the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC). *Drug and alcohol dependence.* 2011;115(1–2):120–130. [PubMed: 21145178]
60. American Psychiatric Association FE, DSM-5. *Diagnostic and Statistical Manual of Mental Disorders.* Washington DC: American Psychiatric Publishing; 2013.
61. Tang S, Jones CM, Wisdom A, Lin H-C, Bacon S, Houry D. Adverse childhood experiences and stimulant use disorders among adults in the United States. *Psychiatry research.* 2021;299:113870. [PubMed: 33780857]
62. Richards JR, Hawkins JA, Acevedo EW, Laurin EG. The care of patients using methamphetamine in the emergency department: Perception of nurses, residents, and faculty. *Subst Abus.* 2019;40(1):95–101. [PubMed: 29595368]
63. Zorick T, Nestor L, Miotto K, et al. Withdrawal symptoms in abstinent methamphetamine-dependent subjects. *Addiction.* 2010;105(10):1809–1818. [PubMed: 20840201]

64. Amato L, Minozzi S, Davoli M, Vecchi S, Ferri MM, Mayet S. Psychosocial and pharmacological treatments versus pharmacological treatments for opioid detoxification. *Cochrane Database Syst Rev.* 2008(3):CD005031–CD005031.
65. Shoptaw SJ, Kao U, Heinzerling K, Ling W. Treatment for amphetamine withdrawal. *Cochrane Database Syst Rev.* 2009;2009(2):Cd003021.
66. Liang Y, Wang L, Yuan TF. Targeting Withdrawal Symptoms in Men Addicted to Methamphetamine With Transcranial Magnetic Stimulation: A Randomized Clinical Trial. *JAMA Psychiatry.* 2018;75(11):1199–1201. [PubMed: 30208372]
67. Brandt L, Chao T, Comer SD, Levin FR. Pharmacotherapeutic strategies for treating cocaine use disorder-what do we have to offer? *Addiction.* 2020.
68. Grabowski J, Rhoades H, Schmitz J, et al. Dextroamphetamine for cocaine-dependence treatment: a double-blind randomized clinical trial. *J Clin Psychopharmacol.* 2001;21(5):522–526. [PubMed: 11593078]
69. Schmitz JM, Rathnayaka N, Green CE, Moeller FG, Dougherty AE, Grabowski J. Combination of Modafinil and d-amphetamine for the Treatment of Cocaine Dependence: A Preliminary Investigation. *Frontiers in psychiatry.* 2012;3:77. [PubMed: 22969732]
70. Nuijten M, Blanken P, van de Wetering B, Nuijen B, van den Brink W, Hendriks VM. Sustained-release dexamfetamine in the treatment of chronic cocaine-dependent patients on heroin- assisted treatment: a randomised, double-blind, placebo-controlled trial. *Lancet.* 2016;387(10034):2226–2234. [PubMed: 27015909]
71. Levin FR, Mariani JJ, Specker S, Mooney M, Mahony A, Brooks DJ, Babb D, Bai Y, Eberly LE, Nunes EV, Grabowski J. Extended-Release Mixed Amphetamine Salts vs Placebo for Comorbid Adult Attention-Deficit/Hyperactivity Disorder and Cocaine Use Disorder: A Randomized Clinical Trial. *JAMA Psychiatry.* 2015;72(6):593–602. [PubMed: 25887096]
72. Kampman KM, Pettinati H, Lynch KG, et al. A pilot trial of topiramate for the treatment of cocaine dependence. *Drug Alcohol Depend.* 2004;75(3):233–240. [PubMed: 15283944]
73. Johnson BA, Ait-Daoud N, Wang XQ, et al. Topiramate for the treatment of cocaine addiction: a randomized clinical trial. *JAMA Psychiatry.* 2013;70(12):1338–1346. [PubMed: 24132249]
74. Kampman KM, Pettinati HM, Lynch KG, Spratt K, Wierzbicki MR, O'Brien CP. A double-blind, placebo-controlled trial of topiramate for the treatment of comorbid cocaine and alcohol dependence. *Drug Alcohol Depend.* 2013;133(1):94–99. [PubMed: 23810644]
75. Levin FR, Mariani JJ, Pavlicova M, et al. Extended release mixed amphetamine salts and topiramate for cocaine dependence: A randomized clinical replication trial with frequent users. *Drug Alcohol Depend.* 2020;206:107700. [PubMed: 31753736]
76. Mariani JJ, Pavlicova M, Bisaga A, Nunes EV, Brooks DJ, Levin FR. Extended-release mixed amphetamine salts and topiramate for cocaine dependence: a randomized controlled trial. *Biol Psychiatry.* 2012;72(11):950–956. [PubMed: 22795453]
77. Pani PP, Trogu E, Vacca R, Amato L, Vecchi S, Davoli M. Disulfiram for the treatment of cocaine dependence. *Cochrane Database Syst Rev.* 2010(1):Cd007024. [PubMed: 20091613]
78. Chan B, Freeman M, Ayers C, et al. A systematic review and meta-analysis of medications for stimulant use disorders in patients with co-occurring opioid use disorders. *Drug Alcohol Depend.* 2020;216:108193. [PubMed: 32861136]
79. Colfax GN, Santos G-M, Das M, et al. Mirtazapine to reduce methamphetamine use: A randomized controlled trial. *Archives of General Psychiatry.* 2011;68(11):1168–1175. [PubMed: 22065532]
80. Coffin PO, Santos GM, Hern J, et al. Effects of Mirtazapine for Methamphetamine Use Disorder Among Cisgender Men and Transgender Women Who Have Sex With Men: A Placebo-Controlled Randomized Clinical Trial. *JAMA Psychiatry.* 2020;77(3):246–255. [PubMed: 31825466]
81. Trivedi MH, Walker R, Ling W, et al. Bupropion and Naltrexone in Methamphetamine Use Disorder. *New England Journal of Medicine.* 2021;384(2):140–153.
82. Wang GJ, Smith L, Volkow ND, et al. Decreased dopamine activity predicts relapse in methamphetamine abusers. *Molecular Psychiatry.* 2011;17:918. [PubMed: 21747399]
83. Martinez D, Carpenter KM, Liu F, Slifstein M, Broft A, Calvo Friedman A, Kumar D, Van Heertum R, Kleber HD, Nunes E. Imaging dopamine transmission in cocaine dependence:

Link between neurochemistry and response to treatment. *American Journal of Psychiatry*. 2011;138(634–641).

84. Gowin JLS JL, May AC, Ball TM, Wittman M, Tapert SF, Paulus MP Altered cingulate and insular cortex activation during risk-taking in methamphetamine dependence: losses lose impact. *Addiction*. 2013;109:237–247. [PubMed: 24033715]
85. Lake MT, Shoptaw S, Ipser JC, et al. Decision-Making by Patients With Methamphetamine Use Disorder Receiving Contingency Management Treatment: Magnitude and Frequency Effects. *Frontiers in psychiatry*. 2020;11:22. [PubMed: 32180733]
86. Skinner BF. *The Behaviour of organisms: An experimental analysis*. . New York: Appleton-Century; 1938.
87. Stitzer M, Bigelow G, Lawrence C, Cohen J, D’Lugoff B, Hawthorne J. Medication take-home as a reinforcer in a methadone maintenance program. *Addict Behav*. 1977;2(1):9–14. [PubMed: 848377]
88. Higgins ST, Budney AJ, Bickel WK, Hughes JR, Foerg F, Badger G. Achieving cocaine abstinence with a behavioral approach. *The American journal of psychiatry*. 1993;150(5):763–769. [PubMed: 8480823]
89. Petry NM, Bohn MJ. Fishbowls and candy bars: using low-cost incentives to increase treatment retention. *Sci Pract Perspect*. 2003;2(1):55–61. [PubMed: 18552724]
90. Benishek LA, Dugosh KL, Kirby KC, et al. Prize-based contingency management for the treatment of substance abusers: a meta-analysis. *Addiction (Abingdon, England)*. 2014;109(9):1426–1436.
91. Dutra L, Stathopoulou G, Basden SL, Leyro TM, Powers MB, Otto MW . A meta-analytic review of psychosocial interventions for substance use disorders. *American Journal of Psychiatry*. 2008;165(2):179–187.
92. Griffith JD, Rowan-Szal GA, Roark RR, Simpson DD. Contingency management in outpatient methadone treatment: a meta-analysis. *Drug Alcohol Depend*. 2000;58(1–2):55–66. [PubMed: 10669055]
93. Prendergast M, Podus D, Finney J, Greenwell L, Roll J . Contingency management for treatment of substance use disorders: a meta-analysis. *Addiction*. 2006.
94. Menza TW, Jameson DR, Hughes JP, Colfax GN, Shoptaw S, Golden MR Contingency management to reduce methamphetamine use and sexual risk among men who have sex with men: a randomized controlled trial. *BMC Public Health*. 2010;10:774. [PubMed: 21172026]
95. DePhilippis D, Petry NM, Bonn-Miller MO, Rosenbach SB, McKay JR. The national implementation of Contingency Management (CM) in the Department of Veterans Affairs: Attendance at CM sessions and substance use outcomes. *Drug and alcohol dependence*. 2018;185:367–373. [PubMed: 29524874]
96. Treatment CfSA. *Counselor’s Treatment Manual: Matrix Intensive Outpatient Treatment for People With Stimulant Use Disorders*. . In. Rockville, MD: Substance Abuse and Mental Health Services Administration; 2006.
97. Carroll K A *Cognitive Behavioral Approach: Treating Cocaine Addiction*. In. Rockville MD: National Institute on Drug Abuse; 1998.
98. De Crescenzo F, Ciabattini M, D’Alò GL, et al. Comparative efficacy and acceptability of psychosocial interventions for individuals with cocaine and amphetamine addiction: A systematic review and network meta-analysis. *PLoS Med*. 2018;15(12):e1002715. [PubMed: 30586362]
99. Harada T, Tsutomi H, Mori R, Wilson DB. Cognitive-behavioural treatment for amphetamine- type stimulants (ATS)-use disorders. *Cochrane Database Syst Rev*. 2018;12(12):Cd011315. [PubMed: 30577083]
100. Carroll KM, Ball SA, Martino S, Nich C, Babuscio TA, Rounsaville BJ. Enduring effects of a computer-assisted training program for cognitive behavioral therapy: a 6-month follow-up of CBT4CBT. *Drug and alcohol dependence*. 2009;100(1–2):178–181. [PubMed: 19041197]
101. De Crescenzo F, Ciabattini M, D’Alò GL, et al. Comparative efficacy and acceptability of psychosocial interventions for individuals with cocaine and amphetamine addiction: A systematic review and network meta-analysis. *PLoS Med*. 2018;15(12):e1002715–e1002715. [PubMed: 30586362]

102. Donovan DM, Wells EA. 'Tweaking 12-Step': the potential role of 12-Step self-help group involvement in methamphetamine recovery. *Addiction*. 2007;102 Suppl 1:121–129. [PubMed: 17493061]
103. Schmitz JM, Lindsay JA, Stotts AL, Green CE, Moeller FG Contingency management and levodopa-carbidopa for cocaine treatment: a comparison of three behavioral targets. *Experimental and Clinical Psychopharmacology*. 2010;18(3):238–244. [PubMed: 20545388]
104. Pasha AK, Chowdhury A, Sadiq S, Fairbanks J, Sinha S. Substance use disorders: diagnosis and management for hospitalists. *J Community Hosp Intern Med Perspect*. 2020;10(2):117–126. [PubMed: 32850046]

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Table 1

Medical complications of stimulant use

Organ system	Acute	Chronic
Nervous system	Agitation	Psychotic symptoms, mood disorders
	Hallucinations, esp. tactile	Cerebrovascular disease/stroke
	Dyskinesia	Cognitive impairment
	Cognitive impairment	Movement disorders, e.g., dystonic reactions, akathisia, choreoathetosis, tardive dyskinesia
Cardiovascular system	Tachycardia	Malignant hypertension
	Hypertension	Myocarditis
	Coronary artery vasospasm	Cardiomyopathy
	Myocardial infarction	Pulmonary hypertension
	Arrhythmias	Accelerated atherosclerosis
	Thoracic aortic dissection	Acute coronary syndrome
Pulmonary	Cough, shortness of breath	Interstitial pneumonitis
	Reactive airways disease	Bronchiolitis obliterans
	Pulmonary edema, hemorrhage	Pulmonary hypertension
	Pneumothorax	
Renal	Acute renal failure	Renal ischemia
		Glomerulonephritis
		Chronic renal failure
Gastrointestinal	Reduced gastric motility GI bleeding	Gastric ulceration and perforation
		Intestinal infarction
		Ischemic colitis
Liver		Viral hepatitis and HIV
Endocrine	Reduced prolactin	Inc, normal or dec. prolactin
	Increased epinephrine, CRH, ACTH, cortisol and LH	Normal testosterone, cortisol, LH, thyroid hormones
Musculoskeletal	Movement disorders (see CNS)	Rhabdomyolysis
Head and neck	Rhinitis	Rhinitis, sinusitis
		Perforated nasal septum
		Nasal and gingival ulceration
		Dental decay and periodontal disease
		Xerostomia
		Corneal ulcers
		Vasculitis syndromes
Immune system		Erectile dysfunction
		Irregular menses
Sexual function		FDA category C
		Placenta previa
		Low birth weight
Reproductive	Vaginal bleeding	Skin and soft tissue infections
	Abruption placenta	
	Premature rupture of membranes	
Dermatologic		Weight loss
General/other	Dehydration	

Organ system	Acute	Chronic
	Hyperthermia	Nutritional deficits

References: 23,27,32,37,45,104

Abbreviations: CRH, corticotropin-releasing hormone; ACTH, adrenocorticotropic hormone; LH, luteinizing hormone

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Table 2

What would effective medication and behavioral treatments for stimulant use disorder do?^a

Pharmacologic Targets	Behavioral Targets
Full agonist	Achieve remission
Block stimulant effect (antagonists)	Prevention of recurrence of use
Relieve drug-related symptoms (cravings)	Improve mood, cognition, and motivation
Alter biological mechanisms of stimulant use disorder	Decrease cravings

^aAddiction is a chronic, relapsing disorder. Multiple treatments are usually required before remission is achieved.

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