

## Stimulant Use Disorder Presentation and Pharmacotherapies

**Stimulants are a class of drugs that enhance activity in the central and peripheral sympathetic nervous systems.**

Most stimulants are variants of the basic phenethylamine structure, which is shared by endogenous neurotransmitters (norepinephrine and dopamine). Stimulants exert their effects by inhibiting presynaptic reuptake of norepinephrine, dopamine, and serotonin. Increased extracellular neurotransmitter concentrations then amplify neuron-to-neuron transmission.

Examples of stimulants

- Plant alkaloids (e.g., cocaine, ephedra, and khat [*Catha edulis* plant])
- Synthetic compounds (e.g., amphetamine, methamphetamine, methylphenidate, synthetic cathinones, modafinil)

### Stimulant Use Disorder Diagnostic Criteria (DSM 5-TR)

A pattern of amphetamine-type substance, cocaine, or other stimulant use leading to clinically significant impairment or distress, as manifested by at least two of the following, occurring within a 12-month period.

- Loss of Control: Using more or for longer than intended
- Inability to Quit: Persistent desire or failed attempts to cut down
- Time Commitment: Spending excessive time getting, using or recovering from stimulants
- Cravings: Intense urges or desires to use
- Role Neglect: Use causes failure to meet work, school or home duties
- Social Conflict: Continued use despite related interpersonal/social problems
- Loss of Interest: Giving up important social, work or hobbies
- Hazardous Use: Use in physically dangerous situations
- Physical/Psychological Risk: Use despite knowing it causes/worsens health or mental issues
- Tolerance: Needing more for the same effect, or getting less effect from the same amount
- Withdrawal: Presence of withdrawal symptoms or use to avoid them; withdrawal develops within a few hours to several days after cessation of (or marked reduction in) prolonged (often high dose) stimulant use

Note: The tolerance or withdrawal criterion is not considered to be met for those taking stimulant medications solely under appropriate medical supervision, such as medications for attention-deficit/hyperactivity disorder or narcolepsy.

## Signs of Stimulant Intoxication and Withdrawal

Note: Mild = 2-3 symptoms; Moderate = 4-5 symptoms; Severe =  $\geq$  6 symptoms

	Stimulant Intoxication	Stimulant Intoxication
Physical Effects	Restlessness, sinus tachycardia, hyperventilation, mydriasis, bruxism (teeth grinding), headache, diaphoresis, tremor; at higher doses or repeated use – more serious medical events (ischemic colitis, acute coronary syndrome – unstable angina, myocardial infarction), tachyarrhythmia, hypertension, seizures, stroke, hyperthermia, rhabdomyolysis).	Headache, nonspecific musculoskeletal pain, dental pain, tremor, and chills (usually self-limiting and do not require medical treatment). Myocardial ischemia has been observed during the first week of cocaine withdrawal.
Disulfiram	250-500 mg daily for 1-2 weeks, then 250 mg daily maintenance	250-500 mg daily for 1-2 weeks, then 250 mg daily maintenance
Psychological and Behavioral Effects	Increased energy and alertness, increased sociability, elation, euphoria, decreased fatigue, decreased appetite, panic reactions, decreased need for sleep;  With high or repeated stimulant dosing – anxiety, irritability, interpersonal sensitivity, hypervigilance, suspiciousness, grandiosity, impaired judgment, stereotyped behaviors*, psychosis (hallucinations, paranoia) *, very severe stimulant intoxication may present with symptoms of delirium.	Withdrawal syndrome consisting of depression, irritability, fatigue, difficulty concentrating, anhedonia*, increased drug cravings, increased appetite, hypersomnolence; withdrawal symptoms typically peak in 2-3 days and resolve within 1-2 weeks without treatment; some patients experience a protracted withdrawal $\geq$ 1 month that includes mild depression and cognitive impairment.
Footnotes	*1. Patients intoxicated on stimulants may closely resemble acute schizophrenia and be misdiagnosed. Stimulant-induced hallucinations may be auditory, visual, or somatosensory. Tactile hallucinations are typical of stimulant-induced psychosis (e.g., sensation of something crawling on skin). *2. Stereotyped behaviors - repetitive behaviors (e.g., repeated dismantling of objects, cleaning, doodling, looking for imaginary objects)	*1. Anhedonia is the inability to feel pleasure

## Pharmacotherapy Interventions for Stimulant Use Disorder

No pharmacotherapies have been approved by the U.S. Food and Drug Administration (FDA) for stimulant use disorder. Overall, the evidence for treating stimulant use disorder with medications is of relatively low quality. In some individual cases, the treatments below may be preferable to no treatment at all.

### Non-psychostimulants

Medication	Data Findings
Bupropion	FDA-approved for the treatment of major depressive disorders (MDD), seasonal affective disorder, and smoking cessation. A small amount of evidence suggests that bupropion may facilitate abstinence from cocaine and amphetamine-type stimulants (ATS). May be a reasonable consideration for patients with co-occurring depressive disorders and tobacco use disorder. Bupropion and naltrexone in combination shows more promise for ATS. Research into this combination was conducted using higher bupropion extended-release doses (e.g., 450 mg) and long-acting injectable naltrexone dosed at 380 mg IM every 4 weeks. Naltrexone is FDA-approved for the treatment of alcohol use disorder (AUD) and opioid use disorder (OUD).
Mirtazapine	FDA-approved for treatment of MDD; two studies demonstrated a small reduction in ATS use and risky sexual behaviors, and a positive effect on sleep compared to placebo; consider using in patients with co-occurring depressive disorders.
Topiramate	FDA-approved for treatment of epilepsy and migraines. Study results are mixed, but topiramate demonstrated a higher rate of stimulant abstinence and reduction in stimulant use; topiramate has been shown to reduce alcohol use; consider in patients with co-occurring AUD.

### Psychostimulants

Many studies performed on psychostimulant medications were conducted with close physician oversight and frequent monitoring. Generally, avoid using in patients with a history of stimulant-induced mood disorders; A thorough risk-benefit analysis should be conducted, preferably by a specialist in addiction medicine or addiction psychiatry.

Medication	Data Findings
Amphetamine salts (extended-release)	FDA-approved for attention deficit hyperactivity disorder (ADHD) and narcolepsy; meta-analysis showed positive effects for achieving a period of cocaine abstinence when taken in combination with topiramate; consider in patients with co-occurring AUD and/or ADHD.
Methylphenidate (long-acting formulation)	FDA-approved for treatment of ADHD and narcolepsy; higher doses associated with short-term methamphetamine abstinence; reduced use of and cravings for methamphetamine; may be more effective for patients with a moderate or higher frequency of ATS use before treatment; consider in patients with co-occurring ADHD.
Modafinil	FDA-approved for treatment of narcolepsy, obstructive sleep apnea, and shift work-related sleep disorder; mixed evidence regarding effectiveness in reducing cocaine use (although poor medication adherence rates in studies); some promise in patients with co-occurring AUD and high treatment adherence.

## Psychosocial Interventions for Stimulant Use Disorder

### Contingency management (CM)

CM involves rewarding patients with tangible awards (e.g., vouchers, prizes) to reinforce positive behaviors related to treatment engagement and outcomes.

- CM has demonstrated the best effectiveness for treating stimulant use disorder compared to other interventions and is the current standard of care.
- Extensive research supports that CM reinforces behaviors including abstinence from substances, treatment attendance, and medication adherence.
- CM may also be combined with other interventions such as cognitive behavior therapy (CBT).

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