Treating methamphetamine abuse disorder

As prevalence of methamphetamine abuse mushrooms, practitioners face the challenge of treating the disorder, its withdrawal symptoms, and stimulant-induced psychosis.

Effects and manifestations of methamphetamine use

Different routes of administration produce different consequences, in terms of medical comorbidity and propensity to induce addiction. Smoked or injected, methamphetamine enters the brain in seconds; snorted or taken by mouth, the drug produces its effects in several minutes and a half hour, respectively.

Rapid uptake and effects of methamphetamine result from its ability to cross the blood–brain barrier. Its primary effects are caused by inhibition of dopamine storage and release of intracellular dopamine.

Methamphetamine stimulates the CNS and the cardiovascular sys-
Methamphetamine abuse

Clinical Point
In severe cases of intoxication, a benzodiazepine, an antipsychotic, or both, might be indicated beyond calming reassurance.

Box

Worldwide, abuse of amphetamine-type stimulants rises; need for treatment grows

The highest prevalence of amphetamine-type stimulant (ATS) abuse is in North America, Western and Central Europe, and South-East and East Asia. The United Nations estimates that up to 52.5 million people age 15 to 64 had used an ATS in the past year. Over the past decade, growing abuse of ATS has meant a rise in the incidence of related disorders requiring treatment. The percentage of people who need treatment for ATS use disorder (among all those who require treatment for substance abuse) is now 10% in Europe; 12% in North America; 20% in Australia and New Zealand; 21% in Asia; and 36% in East Asia and Southeast Asia. Abuse of ATS accounts for more than 50% of treatment demand in Japan, South Korea, Thailand, Cambodia, the Philippines, and Saudi Arabia and other regions of the Near and Middle East. An increase in ATS use has been reported recently in West Africa, Central Asia, and the South Caucasus region.

As in the rest of the world, methamphetamine has been the primary ATS used in the United States, although the rate of methamphetamine use disorder varies by state, with resulting variations in the levels of treatment need and treatment participation. Relatively few methamphetamine treatment admissions are found in the Northeast, whereas methamphetamine use is rampant in the Southwest. In California, 46.6% of young adults (age 18 to 25) in drug treatment had abused methamphetamine.

Therapy for methamphetamine abuse

Treatment of methamphetamine abuse—with the goal of stopping drug use—is a complicated matter on 2 counts:

1. Methamphetamine intoxication and withdrawal
   At initial clinical contact with a person who abuses methamphetamine, practitioners may face several acute consequences requiring attention. Prominent among presenting conditions, especially during acute intoxication, are agitation, anxiety, and psychotic symptoms, which may improve by providing the patient with calming reassurance in a quiet space. In more severe cases, a benzodiazepine, antipsychotic, or both might be indicated (Table 1, page 40).

   Methamphetamine withdrawal is characterized by anxiety, depression, and insomnia. These symptoms generally resolve in a matter of days after the start of withdrawal without pharmacotherapy. In some cases, depression or psychosis becomes chronic, as a result of methamphetamine use itself or as an emergent concomitant psychiatric condition.

   A sedative-hypnotic medication or an anxiolytic can be used as necessary to ameliorate insomnia or anxiety, respectively. Prolonged depression can be treated with an antidepressant. An antipsychotic might be indicated for long-term management of patients who have persistent psychosis.

2. Treatment of methamphetamine abuse
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• No medications are FDA-approved for treating methamphetamine addiction.
• There are no accepted substitution medications (ie, stimulants that can be used in place of methamphetamine, as is available for opioid addiction).

**Pharmacotherapeutic possibilities.** The rationale for considering replacement pharmacotherapy is that psychostimulants can counter the cravings, dysphoria, and fatigue produced by methamphetamine withdrawal and can alleviate methamphetamine-related cognitive impairment. Although dextroamphetamine and other psychostimulants have been evaluated in small trials as replacement medication, most countries are reluctant to consider their use, because of the potential for abuse and accompanying liability.

After decades of medication research, several drugs have shown promise for reducing methamphetamine abuse, although results have not been robust (Table 2):

- **Bupropion** has shown benefit in reducing methamphetamine use among users with less severe addiction.\(^7\)\(^8\)
- **Methylphenidate**, a psychostimulant FDA-approved for attention-deficit/hyperactivity disorder, was found to reduce methamphetamine use compared with placebo in a European sample of amphetamine injectors who had attained abstinence in a residential program.\(^9\) Those results were not replicated in a recent study by Miles et al, however.\(^10\) A study with a more clinically realistic approach (ie, not requiring daily clinic attendance, as in the Miles trial) vs placebo for methamphetamine abuse was recently published, with promising results that require confirmation in further study.\(^11\)
  - **Mirtazapine**, an antidepressant, has demonstrated efficacy in reducing methamphetamine use compared with placebo.\(^12\)
  - **Modafinil**, another medication with stimulant properties, reduced methamphetamine use in a subgroup analysis of heavy users, compared with placebo.\(^13\)
  - **Dextroamphetamine**, 60 mg/d, showed no difference in reducing methamphetamine compared with placebo, but did diminish cravings and withdrawal symptoms.\(^14\)

A trial of the phosphodiesterase inhibitor ibudilast (not available in the United States) for methamphetamine abuse is underway. Ibudilast has anti-inflammatory activity in the peripheral immune system and the central nervous system, including modulating the activity of glial cells.\(^15\)

Many medications have yielded negligible results in studies: selegiline, baclofen, sertraline, topiramate, gabapentin, rivastigmine, risperidone, and ondansetron.\(^16\) Recent evaluation of disulfiram, vigabatrin, and lobeline also has yielded inconsistent findings.\(^17\)

No drug has proved effective for preventing relapse; research continues, focusing on several types of compounds that target various mechanisms: the dopamine system, the opioid system (by way of the \(\gamma\)-aminobutyric acid inhibitory system), and cortico-limbic reward circuitry.

Once-monthly injectable naltrexone has potential for ameliorating craving and
relapse by modulating the opioid receptor system. However, the drug has not been adequately explored in generalizable settings of methamphetamine users.

Trials of oral naltrexone in Sweden have shown encouraging results, including reduced subjective effects and amphetamine use in open-label trials\textsuperscript{18,19}; results were replicated in a subsequent placebo-controlled trial.\textsuperscript{20} In an unpublished study, however, no differences in amphetamine use were found among users randomized to depot naltrexone or placebo.\textsuperscript{21}

Depot naltrexone with assured dosing might have a role in treating methamphetamine abuse, however; a combination of depot naltrexone and oral bupropion is being examined in a National Institute on Drug Abuse Clinical Trials Networks study that commenced in 2013. Pairing medications that have different mechanistic targets might work toward promoting cessation of methamphetamine abuse and reducing relapse once patients are abstinent.

In an early phase of research, but showing promise based on their ability to target different systems, are:

- N-acetylcysteine, modulator of the glutamate system
- D3 antagonists and partial agonists\textsuperscript{22}
- Varenicline.\textsuperscript{23}

Potential “vaccines” against methamphetamine are in preclinical development, including use of a protein carrier or other immune-stimulating molecule to create antibodies that bind methamphetamine in the bloodstream and block its psychoactive effects.\textsuperscript{24,25}

Sigma receptor effects are being studied in rodents as potential targets to mitigate effects of methamphetamine. The ligand AZ66, a sigma receptor antagonist, has demonstrated efficacy in reducing methamphetamine-induced cognitive impairment—suggesting that the sigma receptor has a potential role in ameliorating methamphetamine-related neurotoxicity.\textsuperscript{26}

**Psychosocial and behavioral interventions.** Among the non-drug treatments that have demonstrated efficacy for treating methamphetamine abuse, cognitive-behavioral therapy (CBT) and contingency management (CM) have been most widely studied and applied in treatment settings.

CBT involves individual or group counseling that focuses on relapse prevention skills, including identification of relapse triggers, strategies to diminish cravings, and engagement in alternative non-drug activities (Table 3).

CM, which is based on positive reinforcement, offers tangible reinforcers, or rewards, for behaviors (eg, clinic attendance, providing a drug-free urine sample) according to guidelines set by the practitioner. CM-based interventions are the most reliably documented approaches for treating methamphetamine abuse,\textsuperscript{29,30} but their utility might prove to be most
Methamphetamine abuse

Clinical Point

Patients who abuse methamphetamine can benefit from residential treatment in a drug-free setting for 30 days or longer.

Related Resources


Drug Brand Names

- Baclofen • Lioresal
- Bupropion • Wellbutrin
- D-amphetamine • Seconal
- Adderall
- Disulfiram • Antabuse
- Gabapentin • Neurontin
- Mirtazapine • Remeron
- Modafinil • Provigil
- N-acetylcysteine • Mucomyst
- Naltrexone (depot) • Vivitol
- Naltrexone (oral) • ReVia
- Ondansetron • Zofran
- Risperidone • Risperdal
- Rivastigmine • Exelon
- Selegiline • EMSAM
- Sertraline • Zoloft
- Topiramate • Topamax
- Varenicline • Chantix
- Vigabatrin • Sabril

Bottom Line

Practitioners who work in emergency, inpatient, and outpatient settings will be called on more and more to treat acute stimulant intoxication and withdrawal, stimulant-induced psychosis, and methamphetamine abuse. Few evidence-based treatments and no FDA-approved medications are available to treat this addiction; many drugs and a few psychotherapeutic techniques have shown promise. Ongoing research promises to deliver medical and behavioral interventions to help patients quit using methamphetamine.

tances combined with group and individual counseling reaches an inevitable end: discharge into the community. Then the patient’s battle to avoid relapse begins.

Because cognitive impairment is common among patients who abuse methamphetamine, even after they stop using,35 researchers have examined the potential for increasing participation in psychosocial interventions such as CBT by using medications that might have potential to increase cognitive function, such as modafinil.36 Increased attention and concentration afforded by medication could enhance efficacy of CBT. Results of trials and new drug development have been mixed37; no clear candidate for preventing relapse through any of the putative mechanisms of action has emerged.

Relapse is a problematic target for treatment

Ending methamphetamine abuse and sustaining abstinence from stimulants require a change in the cognitive associations that have been laid down in a drug user’s memory. Relapse occurs because of recalled memories that can be cued, or triggered, by internal or external stimuli. Eliminating drug memories, perhaps assisted by medications such as d-cycloserine (an antagonist of the N-methyl-D-aspartate receptor), could be useful for suppressing the inclination to relapse.

Last, alternative, non-drug forms of cognitive amendment have shown efficacy in preventing relapse: for example, incorporating mindfulness meditation, which has shown promise in managing craving for continued on page 44
methylphenidate and decreasing reactivity to environmental cues for drug use.38

References