

'Met

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'Moving the frontal lobe back to the front' allows for improved executive functioning, decreased impulsivity, and increased motivation to remain drug-free



Meeting of the Minds

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h' recovery

3 steps to successful chronic management

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Clinicians could become discouraged when confronting methamphetamine-dependent patients' wide-ranging psychiatric symptoms.

These patients often present with:

- overlapping primary psychiatric syndromes and secondary substance abuse
- complex histories fraught with psychological trauma, limited social supports, and court involvement.

Treatment can be successful, however, and patients can change their addictive behaviors with a chronic disease management approach that targets the drug's cognitive sequelae and psychiatric effects. Medications show limited benefit (*Box 1, page 30*),¹⁻⁸ but behavioral treatments—including cognitive behavioral therapy (CBT) and motivational incentives—have proven efficacy in treating methamphetamine addiction.

This article discusses how to counteract methamphetamine's negative cognitive effects and enable patients to engage in psychosocial treatment. Our discussion is informed by an extensive literature search and clinical experience from treating patients in the Midwest—at the geographic heart of the “meth” epidemic.

CASE REPORT

Overwhelmed and suicidal

Ms. D, age 27, presents to the emergency department with anxiety, dysphoria, and a plan to commit suicide



'Meth' recovery

Clinical Point

Improved executive functioning (a frontal lobe task) becomes possible as the brain recovers from methamphetamine's effects

Box 1

Medications for 'meth' dependence? Little empiric support

No medications are FDA-approved for treating methamphetamine dependence, and evidence supporting medication use in methamphetamine dependence is extremely limited. Research efforts are aimed at finding medications that might be neuroprotective, decrease craving, block reinforcement mechanisms, or affect other factors behind methamphetamine addiction and relapse.¹ Most trials have been conducted in animal models or controlled laboratory evaluations of drug effects on methamphetamine-induced states.

Bupropion has shown slight treatment efficacy, possibly by decreasing neuronal damage and blocking reinforcement.²⁻⁴ Modafinil⁵ and baclofen⁶ may have potential, but evidence is lacking.

Some results have been unexpectedly negative. Sertraline might be contraindicated in methamphetamine dependence treatment, according to results of a randomized, placebo-controlled trial⁷ of sertraline and contingency management (Table 1). In a human laboratory study,⁸ topiramate accentuated—rather than diminished—subjective response to methamphetamine (Table 2, page 32).

by overdose. She feels overwhelmed by her 4-hour-a-day customer service job—a prerequisite for staying at the halfway house where she has lived for 2 months. She has a 13-year history of polysubstance dependence and is under court order to complete chemical dependence treatment or go to jail.

Methamphetamine has been Ms. D's primary drug of abuse for 5 years, with some intervals of treatment and sobriety. She has not used methamphetamine in 3 months, after a severe relapse when she used methamphetamine daily for 6 months.

Ms. D began using drugs at age 14 and has 3 convictions for driving under the influence of alcohol. An average student, she dropped out of high school but obtained a GED certificate. She first had psychiatric contact at age 16 and has been diagnosed at various times with

attention deficit/hyperactivity disorder, bipolar disorder, and anxiety disorder. She also has been violently sexually assaulted while engaging in prostitution to support her drug habit.

Ms. D has been hospitalized multiple times—voluntarily and involuntarily—in dual diagnosis treatment centers. Her 5-year-old son no longer lives with her, and she has limited social supports beyond her parents, who live in a neighboring state.

3-step approach

For patients such as Ms. D, clinical evidence supports a 3-step approach to treating methamphetamine dependence:

- step 1: institute acute management and stabilization
- step 2: eliminate or decrease methamphetamine use to “move the frontal lobe back to the front”
- step 3: identify and target psychiatric and psychosocial comorbidities.

We discussed step 1 and the methamphetamine epidemic in the November 2006 CURRENT PSYCHIATRY.⁹ For Ms. D, step 1 means inpatient psychiatric care to protect her from suicidal intent and manage dysphoria and anxiety. In step 2, we aim to:

- help her eliminate or decrease methamphetamine use to allow neuronal systems to recover
- target maladaptive behaviors that hinder sobriety while providing motivational incentives to help her maintain a methamphetamine-free life.

Improved executive functioning, a frontal lobe task, becomes possible as the brain recovers from methamphetamine's effects. Patients then are able to use healthier coping strategies to live drug-free. We call this step “moving the frontal lobe back to the front” because its goal is to restore the normal relationship between the frontal lobe and limbic system.

How 'meth' affects cognition

Methamphetamine use has been associated with cognitive dysfunction at initial abstinence and even years later in some patients.¹⁰ Ms. D's cognitive limitations in

a fast-paced customer service job—even though hours are limited—lead to anxiety, dysphoria, and loss of self-esteem when she can't manage patrons' requests.

Methamphetamine has profound acute and chronic effects on the sympathetic nervous system, and dopaminergic, serotonergic, and noradrenergic neuronal networks. Most evidence of chronic neuronal effects comes from animal research and reflects toxic damage to dopaminergic and serotonergic neuronal systems.

Postmortem human studies of direct neurotoxicity from chronic methamphetamine exposure show:

- decreased dopamine and tyrosine hydroxylase levels
- reduced concentrations of dopamine transporters.¹¹

Methamphetamine selectively affects dopamine in the nigrostriatal system, causing substantial dopamine depletion in the ventral tegmental reward system but relatively sparing motor regions. This may explain the lack of parkinsonism with methamphetamine dependence.¹² In a study comparing serotonergic system damage caused by methamphetamine or 3,4-methylenedioxymethamphetamine (MDMA ["Ecstasy"]),¹³ methamphetamine had greater toxicity in the fore-brain, including the septum, anterior cingulate, caudate nucleus, and nucleus accumbens.

In chronic methamphetamine abusers, functional magnetic resonance imaging, proton magnetic resonance spectroscopy, and positron emission tomography show:

- changes in neurotransmitter, protein, brain metabolism, and transporter levels
- damage in multiple brain areas including the frontal region, basal ganglia, grey matter, corpus callosum, and striatum; smaller hippocampi; and cerebral vasculature changes.¹⁴⁻¹⁶

Imaging studies typically have enrolled abstinent users, which emphasizes

Table 1
Antidepressant trials for treating methamphetamine dependence

Drug	Investigation	Comments
Bupropion ²⁻⁴	Laboratory	Safety of bupropion with MAP
	Laboratory	Reduced subjective effects and cue-induced craving
	Clinical trial	Trend toward reduced MAP use compared with placebo
Sertraline ⁷	Clinical trial	Sertraline-treated subjects showed higher use of MAP compared with those receiving placebo and were less likely to complete treatment

MAP: methamphetamine

methamphetamine's long-lasting effects. For practical purposes, the extent of brain damage is fairly dependably associated with the length and intensity of methamphetamine abuse. Because these changes may last for years and can be permanent,¹⁷ how does this play out clinically?

CASE CONTINUED

Does she understand?

After Ms. D is stabilized, her case manager expresses concern about her ability to follow through with treatment planning. He says, "I just don't think she understands some of the things we discuss." She then is referred for neuropsychological testing, which shows clear cognitive impairment. Specifically, she has a slowed rate of thinking, general cognitive inefficiency, deficits in learning and memory retention, and mild impulsivity.

Patients with a history of extensive methamphetamine abuse are ruled by the limbic system and may have higher cortical damage that complicates initiating, maintaining, and fully participating in treatment. Patients' deficits in memory, executive functioning, attention, and cognitive speed may require you to simplify, repeat, and otherwise modify your treatment plan. You will need to provide clear instructions and consistent support—individually and psychosocially—and to recognize and reinforce patients' treatment gains.

Clinical Point

The extent of brain damage is fairly dependably associated with the length and intensity of 'meth' abuse

continued



'Meth' recovery

Clinical Point

CM uses vouchers, privileges, or small amounts of money linked to healthy behaviors as incentives for negative urine tests

Table 2

Other agents studied in methamphetamine dependence trials

Drug	Investigation	Comment
Baclofen ⁶ (GABAergic)	Clinical trial	No statistically significant effect compared with placebo; post hoc analysis showed 'small' treatment effects vs placebo
Gabapentin ⁶ (GABAergic)	Clinical trial	No statistically significant effect compared with placebo; post hoc analysis showed no treatment effects vs placebo
Topiramate ⁹ (anticonvulsant)	Laboratory	Accentuated (rather than diminished) subjective effects of MAP
Aripiprazole ¹⁹ (SGA)	Laboratory	Decreased subjective effects of amphetamine
Modafinil ⁵ (wakefulness agent)	Clinical trial	Successful trial in cocaine dependence; potential option for MAP

MAP: methamphetamine; SGA: second-generation antipsychotic

Even before using methamphetamine, patients may have had academic problems or learning disabilities that will compromise their ability to participate in treatment. Infection with HIV, syphilis, or hepatitis C can further hamper cognitive function.¹⁸

Screen methamphetamine abusers—particularly those such as Ms. D with a history of high-risk behavior—for sexually transmitted diseases. Also provide care address to common medical complications of methamphetamine abuse, including cardiac damage, dental disease, and skin lesions. Centers for Disease Control and Prevention guidelines recommend vaccinating methamphetamine-abusing patients against hepatitis A and B viruses (see *Related Resources*, page 40).

What treatments are effective?

Medications. Evidence is extremely limited, and no medications are approved to treat methamphetamine-addicted patients. Bupropion has shown some efficacy (*Table 1*, page 31),^{2-4,7} but other drugs such as sertraline and topiramate may aggravate rather than diminish methamphetamine dependence (*Table 2*).^{5,6,8,19}

Behavioral treatments supply the evidence basis for methamphetamine dependence treatment. Cognitive behavioral therapy (CBT),²⁰ contingency management (CM),^{21,22} and a manualized structured

treatment—the Matrix Model²³—all have proven efficacy.

CBT involves functional analysis and skills training. Patients are guided through analyzing their drug use and associated cognitions, emotions, and expectations and in identifying situations that trigger methamphetamine use or relapse. Skills training involves identifying, reinforcing, and practicing coping skills to help the patient avoid drug use and reinforce the ability to refuse use.

CM is based on operant conditioning—the use of consequences to modify behavior. It involves establishing a “contingent” relationship between a desired behavior/outcome (such as methamphetamine-free urinalysis) and delivering a positive reinforcing event to promote abstinence:

- Vouchers, privileges, or small amounts of money linked to healthy behaviors serve as incentives for negative urine testing.
- Rewards increase as periods of confirmed abstinence lengthen and are reset to smaller rewards if relapse occurs.

The precise reward structure that provides optimal treatment value is under study.²⁴

CM does not require extensive staff training and has been described as relatively simple to implement. CM also has been used successfully in urban gay and bisexual men with methamphetamine dependence (*Box 2*, page 37).^{18,25-29}

continued on page 37

Although CM's efficacy is well-supported by clinical trials, we have encountered some resistance to the idea of "paying individuals to not use drugs" when training medical students, allied health staff, and residents. The National Institute on Drug Abuse (NIDA) supports the use of motivational incentives in treating substance abuse and offers support materials, resources, and training on this approach (see *Related Resources, page 40*).

Multiple studies show that CBT and CM are equally effective for treating chronic methamphetamine abuse at a 1-year follow-up, although CM may be more effective than CBT for acute treatment.

The Matrix model is a 4-month intensive, manualized treatment program that uses CBT, education on drug effects, positive reinforcement for intended behavioral change, and a 12-step approach.

Methamphetamine dependence outcomes based on the Matrix treatment model were compared with community treatment as usual in a project sponsored by The Center for Substance Abuse Treatment of the Substance Abuse and Mental Health Services Administration, U.S. Department of Health and Human Services.³⁰ End-point outcomes were similar, but the Matrix treatment was more effective in early treatment, including decreased urinalyses positive for methamphetamine and increased abstinence.

Recommendations. Select a psychosocial treatment approach with your patient's strengths, social setting, and community resources in mind. Twelve-step approaches may play an important role.

In patients such as Ms. D, the structure of court-ordered treatment can provide accountability, enforced abstinence, and mandated treatment resources. This, in

Box 2

Methamphetamine abuse increases risk of HIV infection

Methamphetamine use is estimated to be 5 to 10 times more prevalent in U.S. urban gay and bisexual groups than in the general population²⁵ and likely is contributing to rising human immunodeficiency virus (HIV) infection rates in men having sex with men (MSM).

Used to enhance sexual performance, libido, and mood, methamphetamine is associated with increased rates of unprotected anal sex and multiple partners in MSM.²⁶ An HIV infection rate of 61% was reported in methamphetamine-dependent MSM seeking treatment in a Los Angeles clinical trial.²⁷ Methamphetamine also results in high-risk sexual practices and multiple partners among heterosexual men and women.²⁸

Although seroconverted men report using methamphetamine to alleviate HIV-associated depression, the combination of HIV infection and methamphetamine use may have powerful negative effects. Methamphetamine use is associated with HIV treatment nonadherence and also may suppress immune function.²⁹ Cognitive impairments associated with HIV and methamphetamine use are additive and are further exacerbated by hepatitis C infection.¹⁸

Recommendation. Screen for methamphetamine use in MSM populations, and educate these patients about risks associated with methamphetamine use. In all patient groups who report using methamphetamine, provide counseling on high-risk sexual behavior, screen for sexually transmitted diseases, and ensure that patients are vaccinated against hepatitis A and B infection (see *Related Resources, page 40*). Most important, refer for medical treatment when indicated.

turn, may give your patient a better chance to engage a recovering and better functioning frontal lobe to inhibit urges for methamphetamine use and manage stress.

CASE CONTINUED

Racing thoughts and psychosis

Before hospital admission, Ms. D was being treated with gabapentin, 300 mg bid, and sustained-release bupropion, 150 mg/d, for anxiety and dysphoria. Previously, she has received multiple antidepressants and mood stabilizers with reportedly little effect.

continued

Clinical Point

Screen for sexually transmitted diseases and address medical complications such as cardiac damage, dental disease, and skin lesions



'Meth' recovery

Clinical Point

Some patients may need low-dose antipsychotics as maintenance treatment to manage residual post-acute psychotic symptoms

Box 3

2 priorities in managing psychiatric symptoms of 'meth' abuse

Methamphetamine abuse can cause and exacerbate psychiatric symptoms. Keep in mind 2 priorities as you approach these symptoms:

Aim for abstinence. Methamphetamine abuse produces a remarkable array of adverse effects. It causes dysphoria, anxiety, and psychosis during active use and in the interval after initial abstinence. Many of methamphetamine's use and withdrawal symptoms resolve with time, however, and may not require pharmacologic treatment.³¹ Therefore, achieving abstinence and keeping patients in treatment is high priority.

Use behavioral approaches whenever feasible. Balance the need to use benzodiazepines for ongoing treatment of severe anxiety or agitation with the high risk of addiction or diversion in this group. Anxiety may resolve over time in association with sustained abstinence. Similarly, receiving treatment for methamphetamine dependence and maintaining abstinence appears to ease depressive symptoms, as shown by sustained improvements in Beck Depression Inventory scores at 1 year.³²

Manage stress. Stress can worsen psychiatric symptoms, trigger methamphetamine abuse relapse and psychosis, and acutely and chronically augment methamphetamine's toxic effects.³³ You can help patients manage stress by:

- providing case management and CBT training
- advising them about proper sleep, nutrition, and medical care.

She describes racing thoughts and profound anxiety, but her presentation is remarkable for latency in response, apathy, and amotivation. She intermittently refuses to take medication, and collateral history shows adherence problems with medication and psychosocial treatment in her group home. She refuses to take bupropion, saying it makes her symptoms worse, but agrees to

take quetiapine to address her complaints of anxiety and "being manic."

Initially guarded, she at first denies psychotic symptoms but acknowledges their extent several days later. She describes periods of 6 months or more when she feels "lost." The treatment team titrates quetiapine up to 200 mg/d and restarts duloxetine, 30 mg/d, for depressive symptoms, based on her past positive response to this antidepressant.

Targeting psychiatric symptoms

Step 3 in the chronic disease management approach to methamphetamine dependence is to identify and target psychiatric and psychosocial comorbidities. When approaching psychiatric symptoms, high priorities are to aim for abstinence and manage the patient's stress (*Box 3*).³¹⁻³³

Psychotic symptoms may present acutely, continue as residual symptoms, or reappear at stressful times long after an individual no longer abuses methamphetamine. Acute psychotic symptom intensity appears to be methamphetamine dose-related.³⁴

In clinical practice, we find it difficult to diagnostically categorize and treat methamphetamine-abusing patients who show residual post-acute psychotic symptoms. Some appear to have no risk factors for primary psychotic illness, and their symptoms show an association with the severity of their past methamphetamine abuse.

Other patient presentations can be difficult to separate from family histories of psychotic illness. Research suggests that genetic risk factors may be associated with methamphetamine psychosis in some vulnerable patients.³⁵

Unfortunately, no data exist to guide the use of antipsychotics to maintain symptom control. Some patients may need low-dose antipsychotics for maintenance treatment, and second-generation antipsychotics may have a theoretical advantage over first-generation antipsychotics. Use your clinical judgment in determining dosing and treatment duration, and in weighing risks and benefits of continued treatment.

Residual violent behavior. Violence, aggression, and poor impulse control are synonymous with methamphetamine abuse and have devastating individual, societal, and public health effects. Even abstinent methamphetamine abusers show long-standing elevated baseline aggression, compared with controls.

Using imaging, researchers found aggression severity to be directly correlated with past total methamphetamine use and globally decreased serotonin transporter density.³⁶ Serotonin transporter densities were 30% lower in methamphetamine users vs controls after >1 year of abstinence.

CASE CONTINUED

Discharge plans

Because of the severity of her psychiatric symptoms, Ms. D is unable to return to the halfway house after discharge. As her treatment team works to coordinate discharge placement, Ms. D continues to improve. Her psychotic and dysphoria symptoms resolve, and she shows increased spontaneity. These changes—attributed to supports during hospitalization, decreased stressors, and quetiapine treatment—continue until her

discharge to a combined mental illness and chemical dependence program.

Ms. D's report of "racing thoughts" is clarified; rather than mania, they represent recurrent thoughts and ruminations about past sexual abuse. Her psychotic symptoms resolve quickly with quetiapine, but she struggles with morning sedation. The team reduces the dosage, and she tolerates quetiapine, 25 mg hs, with trazodone, 100 mg hs, for sleep, anxiety, and psychotic symptoms. She is discharged on this regimen plus duloxetine, 60 mg/d, with plans to continue psychosocial treatment for methamphetamine dependence and posttraumatic stress.

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continued

Clinical Point

Abstinent 'meth' abusers show long-standing elevated baseline aggression, compared with controls

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'Meth' recovery: 3 steps to successful chronic management



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'Meth' recovery

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Many 'meth' abuse and withdrawal symptoms resolve with time and may not require pharmacologic treatment

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Related Resources

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- National Institute on Drug Abuse Blending Initiative. Promoting Awareness of Motivational Incentives (PAMI). www.drugabuse.gov/blending/PAMI.html.

Drug Brand Names

Aripiprazole • Abilify	Modafinil • Provigil
Baclofen • various	Quetiapine • Seroquel
Bupropion • Wellbutrin	Sertraline • Zoloft
Duloxetine • Cymbalta	Topiramate • Topamax
Gabapentin • Neurontin	Trazodone • Desyrel

Disclosure

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Bottom Line

After acute methamphetamine addiction has been stabilized, provide or refer the patient for substance dependence treatment. Evidence supports motivational incentives, 12-step programs, and cognitive-behavioral therapy. Test for HIV infection, and address medical comorbidities. Treat psychosocial and psychiatric comorbidities as needed; many will resolve as abstinence is maintained.