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Neurobiology, Clinical Presentation, and Treatment of Methamphetamine Use Disorder
A Review

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IMPORTANCE The prevalence of and mortality associated with methamphetamine use has doubled during the past 10 years. There is evidence suggesting that methamphetamine use disorder could be the next substance use crisis in the United States and possibly worldwide.

OBSERVATION The neurobiology of methamphetamine use disorder extends beyond the acute effect of the drug as a monoaminergic modulator and includes intracellular pathways focused on oxidative stress, neurotoxic and excitotoxic effects, and neuroinflammation. Similarly, the clinical picture extends beyond the acute psychostimulatory symptoms to include complex cardiovascular and cerebrovascular signs and symptoms that need to be identified by the clinician. Although there are no pharmacologic treatments for methamphetamine use disorder, cognitive behavioral therapy, behavioral activation, and contingency management show modest effectiveness.

CONCLUSIONS AND RELEVANCE There is a need to better understand the complex neurobiology of methamphetamine use disorder and to develop interventions aimed at novel biological targets. Parsing the disorder into different processes (eg, craving or mood-associated alterations) and targeting the neural systems and biological pathways underlying these processes may lead to greater success in identifying disease-modifying interventions. Finally, mental health professionals need to be trained in recognizing early cardiovascular and cerebrovascular warning signs to mitigate the mortality associated with methamphetamine use disorder.

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Supplemental content

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In the wake of the opioid crisis, methamphetamine has re-emerged as a challenge to mental health clinicians and researchers alike. Methamphetamine is now available in different forms such as ice, powder, and pills, with different pharmacokinetic characteristics that make them popular among certain types of individuals.[1] Recent seizure data suggest that methamphetamine production and trafficking are spreading into new areas of the globe.[2] According to the Automation of Reports and Consolidated Orders System, methamphetamine consumption increased 4-fold between 2015 and 2016 and total stimulant use doubled in the last decade.[3] From 2011 through 2016, the age-adjusted rate of drug overdose deaths involving methamphetamine more than tripled.[4] Moreover, drug overdose deaths involving cocaine, amphetamines, or both substances combined increased 42.4% from 12 122 in 2015 to 17 258 in 2016.[5] Based on the most recent data from the National Survey on Drug Use and Health,[6] the 12-month prevalence of individuals aged 12 years or older reporting methamphetamine use has increased by 195% from its low in 2010 to 2018 (**Figure 1**), and it is estimated that 1.86 million Americans used methamphetamine in 2018. These numbers underline the importance of paying attention to the possibility of the next substance use crisis. However, whereas opioid use disorder can be treated pharmacologically[7] and behaviorally,[8] there are significant challenges for the treatment of methamphetamine use disorder (MUD). This review focuses on 3 specific aspects of MUD. First, the neurobiology of methamphetamine is more complex than the traditional view of it as a monoaminergic modulator. Second, the clinical presentation is not limited to the symptoms associated with use disorder but extend to medical presentations, most notably the cardiovascular and cerebrovascular systems. Third, pharmacologic interventions focused on modulating the monoaminergic pathways have largely failed, and new pharmacologic approaches are necessary to focus on novel treatment targets. In the final section, several suggestions will be proposed for both clinicians and researchers to advance the understanding of MUD.

Biological Pathways, Neural Basis, and Cognition

Methamphetamine has been conceptualized primarily as a releaser of dopamine, serotonin, noradrenaline, and adrenaline from nerve terminals in the central and peripheral nervous system,[9] which occurs via several different mechanisms, including (1) redistributing catecholamines from synaptic vesicles to the cytosol, (2) reversing the plasma membrane transport of neurotransmitters, (3) blocking the activity of monoamine transporters, (4) decreasing the expression of dopamine transporters at the cell surface, (5) inhibiting monoamine oxidase activity, and (6) increasing the activity and

Figure 1. Summary Statistics of Articles Published Mentioning Methamphetamine and Past-Year Methamphetamine Use From 2009 to 2019

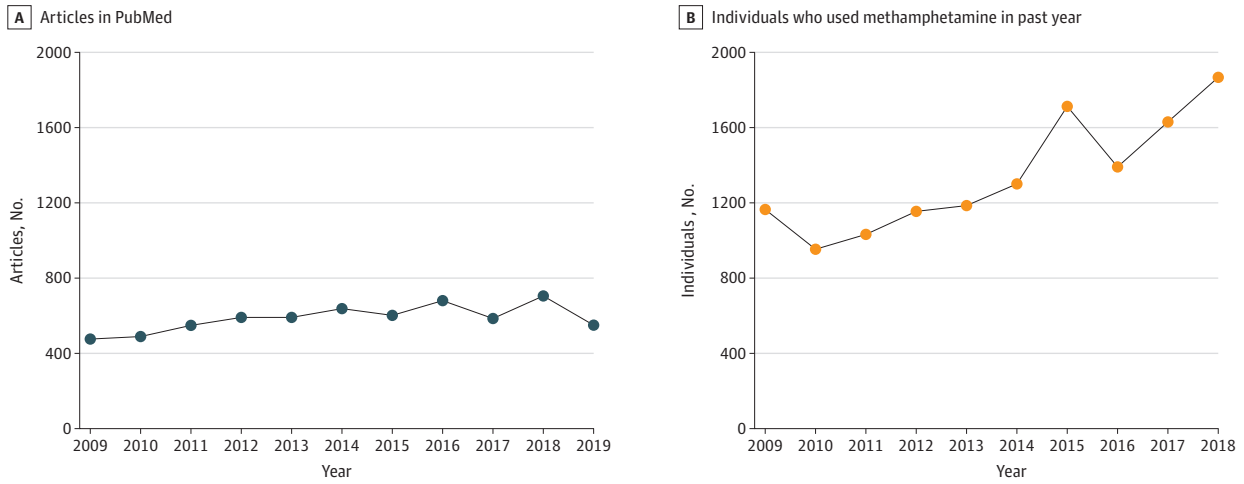
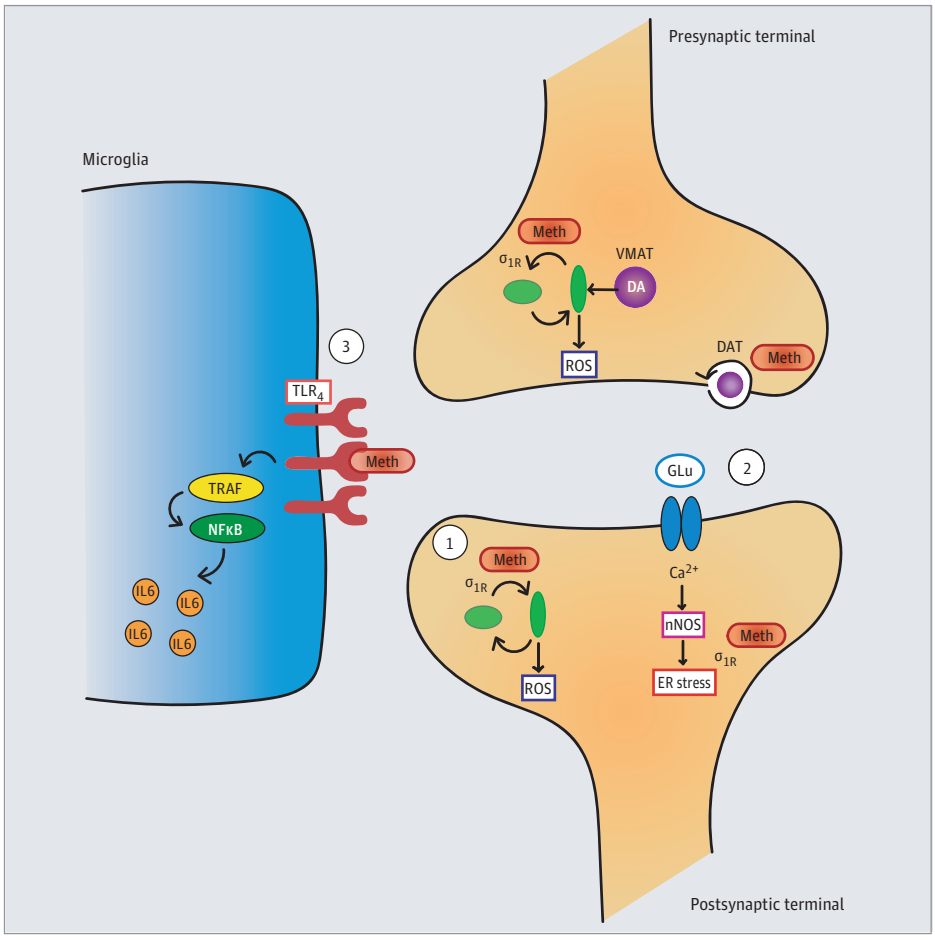


Figure 2. Methamphetamine-Induced Changes in Synaptic and Intracellular Pathways



Methamphetamine (Meth) increases dopamine in the synaptic cleft via its effect on the cell surface dopamine (DA) transporter (DAT) and increases DA in the cell via its effect on the vesicular monoamine transporter (VMAT). Methamphetamine (1) directly alters mitochondrial fusion and fission via sigma-1 receptor (σ_{1R}) binding, leading to an increase in reactive oxygen species (ROS); (2) increases glutamatergic (GLu) transmission, which via increased intracellular calcium (Ca^{2+}) and nitric oxide synthase (nNOS) leads to endoplasmic reticulum (ER) stress; and (3) binds to the toll-like 4 (TLR_4) receptor to activate inflammatory pathways via nuclear factor κ-light-chain enhancer of activated B cells (NFκB) and tumor necrosis factor receptor–associated factors (TRAF) to produce proinflammatory cytokines (interleukin 6 [IL-6]).

expression of tyrosine hydroxylase, the critical enzyme for synthesizing dopamine.[10] However, there has been a substantial expansion of methamphetamine-associated neurobiological targets during the past decade. Methamphetamine modulates at least 3 different molecular cascades, which have been described as oxidative stress, neurotoxic and excitotoxic effects, and neuroinflammation[11] (**Figure 2**).

For example, mitochondria are theprimary sites of oxidative metabolism and are organized in a tubular, dynamic network that undergoes continuous remodeling via fusion or fission.[12] Metham-

phetamine induces changes in morphologic characteristics of mitochondria in neurons and microglia, which disturbs the mitochondrial homeostasis, morphologic characteristics, and oxidative stress metabolism toward an increase in oxidative burden conducive to neurodegeneration.[13] Methamphetamine also causes single-strand and double-strand breaks in DNA owing to reactive oxygen species, leading to persisting alterations at the chromosomal level at blood concentrations that are observed in individuals taking methamphetamine.[14] Methamphetamine-induced neuroinflammation is partially mediated by direct binding to the toll-like receptor 4 transmembrane protein within the ventral tegmental area, which has the downstream effect of elevating dopamine levels in the nucleus accumbens shell.[15] The inflammatory changes in the brain occur largely in microglia (ie, the primary cells of active immune defense in the central nervous system). The inflammasome is a molecular system that consists of the sensing molecule NLRP3, the adaptor apoptosis-associated speck–like protein, and the executive enzyme caspase-1. Methamphetamine upregulates caspase-1 and apoptosis-associated speck-like protein aggregation, which promotes inflammasome-mediated interleukin 1β maturation and secretion, mediating microglia-induced neurotoxic effects.[16] This process also occurs in several conditions ranging from neurodevelopmental disorders to neurodegenerative disorders.[17]

More important, the methamphetamine-induced cellular dysregulation in neurons and microglia may be associated with neural processing,[18] altered reward motivation due to sickness behavior,[19] and reduced prefrontal control[20] that, together, may be associated with the development and maintenance of drug-taking behavior.[21] Methamphetamine-induced neurotoxic effects have been hypothesized to be the result of interdependent mechanisms, including (1) excessive dopamine, resulting in an increased production of reactive oxygen species, such as peroxides, that can damage cell structures; (2) ubiquitin-proteasome system dysfunction, activating intracellular degradation systems leading to autophagy; (3) protein nitration, leading to an increase in radical nitric oxide with subsequent cytotoxic effects; (4) endoplasmic reticulum stress, leading to increased apoptosis; (5) increased tumor protein p53 expression in the striatum, altering DNA repair, arresting cell cycles, and dysregulating the expression of stress response genes; (6) inflammatory cytokines, leading to inflammatory activation in the brain; (7) activation of the dopamine D3 receptor, resulting in hyperthermia; and (8) microtubule deacetylation, disrupting the blood-brain barrier.[22]

Together, these neurobiological cascades of oxidative stress, neurotoxic and excitotoxic effects, and neuroinflammation are associated with a unique metabolic state of the brain that has been termed the *Warburg effect* (ie, when cells favor metabolism via glycolysis rather than the much more efficient oxidative phosphorylation).[23] Thus, methamphetamine use acutely, and possibly chronically, places the brain in a different metabolic state characterized by (1) a quicker but less efficient availability of energy, (2) an increased rate of biosynthesis, (3) acidification of the microenvironment, and (4) altered cell signaling via reactive oxygen species, which promotes an oncogenic and degenerative cell environment. In summary, MUD does not reflect just dopamine dysregulation but represents an altered brain state that is consistent with those observed in degenerative central nervous system diseases. These complex molecular dysregulations provide an opportunity to identify modifiable drug targets to develop novel pharmacologic interventions for MUD.

Others have proposed that compulsive drug taking is associated with an imbalance between an orbitofrontal cortex–dorsomedial striatal "go" circuit and an opposing dorsolateral frontal–striatal "stop" circuit.[24] Numerous studies have focused on examining evidence of structural and functional alterations within these circuits. For example, individuals taking methamphetamine show widespread gray and white matter alterations, particularly affecting the frontostriatal system,[25] as well as prominent reductions in the left superior temporal gyrus and the right inferior parietal lobe that provide contextual information to the dorsolateral frontal circuits.[26] Moreover, abnormalities include deficits in markers of dopaminergic and serotonergic neurotransmitter systems, differences in glucose metabolism, and deficits in gray matter.[27] Individuals taking methamphetamine on a long-term basis show aberrant patterns of brain connectivity and function within both the orbitofrontal-striatal and dorsolateral frontal–striatal systems when engaged in cognitive tasks and at rest.[28] Functional neuroimaging studies have shown that individuals taking methamphetamine show changes in the orbitofrontal cortex during empathic processing,[29] in salience and dorsolateral frontal functioning areas during decision making,[30,31] and in both the dorsolateral and inferior frontal areas during inhibitory processing.[32] Lower corticostriatal connectivity as measured by resting-state functional magnetic resonance imaging has been associated with a higher concentration of peripherally measured cytokines,[33] which may provide evidence for the link between neuroinflammation and brain processing changes in MUD. Although functional brain activation differences during various behavioral tasks among individuals with MUD have been used to assess relapse,[34-36] none of these measures have thus far been clinically useful[37] (ie, none have been able to aid in the diagnosis, prognosis, or treatment of the disorder.[38])

The association of methamphetamine with cognition has been heavily debated,[39] and a dearth of longitudinal studies makes it difficult to assess whether the observed cognitive dysfunctions are preexisting, a consequence of the exposure, or a consequence of behaviors that are associated with substance use disorders in general. Nevertheless, several recent studies provide a more cohesive picture of the cognitive problems that exist both shortly after cessation of use and, to some extent, after longer periods of abstinence. For example, individuals with MUD in early abstinence but after the acute withdrawal period show poorer performance on tasks examining motor and processing speed, verbal fluency, and attention.[40] Even after prolonged abstinence, individuals with MUD perform more poorly than matched comparison individuals on learning efficiency, visual-spatial processing, comprehension knowledge, retrieval fluency, processing speed, and psychomotor speed.[41] In addition, dysfunctions of impulsivity have been associated with a greater severity of methamphetamine use[42] and an earlier age at onset of methamphetamine use.[43] Global assessments of cognitive function support the idea that more than two-thirds of individuals with MUD show cognitive impairment,[44] the extent of which is associated with older age, longer duration of use, and higher frequency of use. Aside from providing an objective assessment of the outcomes of methamphetamine use, a neuropsychological assessment can also be used as a prognostic indicator. For example, cognitive measures, such as problems with sustained attention, may be

associated with reduced treatment motivation,[45] and different forms of impulsivity may be associated with poorer 6-week outcomes in treatment.[46] Taken together, methamphetamine use is associated with moderate dysfunction of several cognitive processes, limiting the degree to which individuals with MUD are able to focus attention on goal-directed activity away from methamphetamine use in early abstinence. Given that neuropsychological function may be used to assess treatment retention and success, more work needs to be done to determine whether any of these cognitive dysfunctions can be remediated by targeted interventions.

Clinical Presentation

The acute behavioral outcomes of methamphetamine use include increased energy and alertness, decreased need for sleep, euphoria, increased sexuality, excessive talking, weight loss, sweating, tightened jaw muscles, grinding teeth, and loss of appetite.[47] The symptoms exacerbated by methamphetamine use can be divided into the following 3 factors: (1) positive psychotic symptoms such as suspiciousness, unusual thought content, hallucinations, and bizarre behavior; (2) affective symptoms including depression, suicidality, guilt, hostility, somatic concern, and self-neglect; and (3) psychomotor symptoms such as tension, excitement, distractibility, and motor hyperactivity.[48] The clinical picture can be complex and mimics many psychiatric disorders. The transition from casual to compulsive methamphetamine use can be rapid, and some have reported that it takes a mean of approximately 50 days from the onset of use to the first drug craving, 60 days to regular use, and 85 days to compulsive use.[49] Although most methamphetamine-associated psychoses are brief, lasting hours to days, in some cases, psychotic episodes may persist for longer than 6 months and can reoccur during periods of abstinence from the drug.[50] A mean of 36.5% of individuals using methamphetamine, regardless of age or sex, report psychotic symptoms, but when lifetime symptoms are taken into account, this percentage increases to 42.7%.[51] Some have suggested that self-reported psychotic illness is more prevalent among individuals using crystal methamphetamine than among those using other forms of methamphetamine,[52] which may be associated with the purity of crystal methamphetamine and the self-selection of individuals who use this form of the drug. The psychiatric comorbidity of MUD is complex[53] because there is evidence for both preexisting factors that increase the risk for psychiatric disorders (eg, a 44% prevalence of moderate to severe childhood abuse or neglect).[54] Moreover, early lifetime adversity, such as emotional or sexual trauma, may also increase the likelihood of MUD owing to the fact that some individuals use methamphetamine as a coping method.[55] In addition, other psychiatric disorders, such as mood disorders (16.0%), psychotic disorders (13.0%), and anxiety disorders (7.0%), coexist with MUD.[56] Both early-life trauma and psychiatric comorbidity can be adversely associated with both age at first use of methamphetamine[57] and treatment success.[58]

The path to methamphetamine use involves at least 2 trajectories. First, younger individuals use methamphetamines primarily for recreational and performance enhancement purposes, whereas those initiating at a later age may use methamphetamines to "self-medicate" (eg, to cope with stressful life events).[59] This finding is consistent with the observation that the rate of methamphetamine use among women, who are much more likely than men to report using methamphetamines for weight-related issues, is higher among adolescents relative to adults.[60] Second, there is emerging evidence of individuals using methamphetamine as an opioid substitute to obtain a synergistic high or to balance the effects of opioids.[61] Recent longitudinal evidence suggests that the increase of cannabis use among adolescents may increase the probability that they will initiate the use of other illicit drugs, such as methamphetamine, via both biological and social processes,[62] providing some evidence for the "gateway hypothesis."[63] Similar to many other substance use disorders, the course of MUD is often characterized by repeated periods of intense use with intermittent periods of sobriety and relapse.[64,65] Those who do not undergo treatment show 5-year remission rates of up to 30%,[66] and of those who do undergo treatment, 61% relapse within the first 12 months and another 14% relapse during years 2 to 5.[65] These findings underscore the fact that MUD is a chronic, relapsing, and possibly degenerative condition, which is consistent with the profound molecular changes induced by methamphetamine use.

The most severe medical problems and the leading causes of death associated with MUD are cardiovascular disease and cerebrovascular disease.[67] Methamphetamine-associated strokes[68] have been increasing, most often among young men, and are primarily hemorrhagic in nature. Methamphetamine use is associated with vasoconstriction, pulmonary hypertension, atherosclerotic plaque formation, cardiac arrhythmia, and cardiomyopathy.[69] Methamphetamine-associated cardiomyopathy[70] is characterized by left ventricular dilatation and impaired left ventricular ejection fraction as well as elevated tissue markers of inflammation and fibrosis.[71] On electrocardiograms, these individuals frequently show tachyarrhythmia, right axis deviation, left ventricular hypertrophy, a P pulmonale pattern, inferior Q waves, lateral T-wave inversion, and a longer QTc interval.[72] The symptoms preceding death due to the toxic effects of methamphetamine include collapse, breathing difficulty, and hyperthermia, which may be a consequence of acute abnormal enlargement of the heart.[73] Methamphetamine was also present in 63% of individuals who died of opioids.[74] For individuals who present with acute intoxication with methamphetamine, symptoms of dyspnea, angina, palpitations, cough, and hemoptysis should prompt the clinician to closely monitor the medical status to prevent mortality.

Interventions

There are very limited pharmacologic options to treat MUD for which there are sufficient data.[75] The **Table** summarizes all of the intervention trials registered at ClinicialTrials.gov that contained the term *methamphetamine*. Of the 159 registered studies, 65 represented randomized clinical trials; of those, 25 reported results, of which 14 resulted in publications with identifiable PMIDs (PubMed reference numbers). Examining these publications, 8 reported no effect, 3 reported some effect, and 3 reported effects that did not speak to the efficacy of the intervention. Moreover, the studies submitted to ClinicalTrials.gov were mostly unclear with respect to efficacy or reported null results (eTable in the Supplement). This short summary is consistent with the conclusions of systematic reviews and meta-analyses. Specifically, in a systematic review examining

49 studies investigating 20 potential pharmacotherapies, 35 studies were associated with 33 phase 2 randomized clinical trials (ie, efficacy studies).[76] For the 5 medications that were included in multiple randomized clinical trials, 4 of these—methylphenidate, bupropion, modafinil, and naltrexone—demonstrated some limited evidence of benefit for reducing methamphetamine use. The authors concluded that none of these drugs showed sufficient or consistent evidence of effectiveness to support its use in routine treatment. This assessment is similar to that in 2 other studies, one of which concluded that no agent demonstrated a broad or strong enough effect of achieving methamphetamine abstinence in phase 2 trials[77] and the other concluding that there was no sufficient evidence available for dopamine analogue treatment after the initial withdrawal period.[78] Studies of anticonvulsants, antipsychotics, opioid antagonists, varenicline, and atomoxetine provided either low-strength evidence or insufficient evidence of no association with the outcomes of interest (ie, abstinence, defined as ≥3 consecutive weeks with negative urine drug test results).[79] Immunotherapy has been suggested as an alternative form of treatment for drug abuse; however, none of the antidrug immunotherapies have reached phase 3 clinical trials so far, to our knowledge.[80] Although some have reported that the combination of pharmacologic treatments aimed at treating psychiatric target symptoms and brief cognitive behavioral treatments in a research setting outperformed control conditions,[81] there is no sufficient evidence that pharmacologic interventions by themselves are useful for the treatment of MUD.

Results from studies using behavioral interventions to treat MUD are more encouraging. In a recent network meta-analysis, compared with treatment as usual, only contingency management (ie, a procedure that aims to alter drug use by systematically arranging consequences that are designed to weaken drug use and strengthen abstinence) plus community reinforcement (ie, adjusting an individual's environment such that abstinence is more rewarding than using the drug) increased the number of abstinent patients with MUD at the end of treatment.[82] Others reported that brief cognitive behavioral therapy resulted in significant reductions in the frequency of methamphetamine use, MUD severity, and number of days of methamphetamine use at weeks 4 and 12,[83] findings consistent with those in a systematic review that found weak evidence for an increased percentage of abstinent days (during a 90-day period) and reduced MUD symptoms.[84] Similarly, behavioral activation, which aims to maximize activities that are not drug-related but are positively valued by the individual, was associated with abstinence of alcohol, tobacco, opioid, and methamphetamine use in 7 of the 8 reviewed studies and with improved depression over time in 6 studies.[85] Finally, several studies demonstrated a beneficial association of exercise with reducing MUD symptoms. For example, an aerobic exercise program was associated with reducing cravings for methamphetamine and with improved inhibitory control in individuals with MUD.[86] Moreover, compared with a health education control group, exercise by individuals taking methamphetamine was associated with reduced levels of depression and anxiety during an 8-week period.[87] Taken together, there is some evidence that contingency management, cognitive behavioral therapy, behavioral activation, and exercise help to maintain abstinence. There is also encouraging evidence for computer-delivered interventions[88] and app-based approaches.[89] Nevertheless, there are 2 significant shortcomings. First, intervention programs for methamphetamine use have high discontinuation rates. For example, in 1 large program, 51% of individuals dropped out within the first 2 weeks, and the mean number of days that individuals stayed in the program was only 60 days.[90] Second, there is little understanding as to how these behavioral interventions affect the underlying neurobiology of MUD and whether these interventions improve neural processing and cognitive dysfunctions in these individuals.

Table. Data on Intervention Trials[a]

Trials	Studies, No. (%)	
	All (n = 159)	RCTs (n = 65)
Trials with a randomized intervention model		
With some results reported	25 (15.7)	25 (38.5)
Published	14 (8.8)	14 (21.5)
Studies with PMIDs		
No effect	8 (5.0)	8 (12.3)
Some effect	3 (1.9)	3 (4.6)
Unclear	3 (1.9)	3 (4.6)
Other studies		
No effect	5 (3.1)	5 (7.7)
Some effect	0	0
Unclear	6 (3.8)	6 (9.2)

Abbreviations: PMID, PubMed reference number; RCTs, randomized clinical trials.

[a] Registered at ClinicalTrials.gov that contained the term *methamphetamine*.

Conclusions

Methamphetamine use disorder is reemerging as a significant public health burden, a challenge for clinicians, and a difficult problem to solve for researchers. First, MUD can develop rapidly, has a complex course characterized by episodes of intense use and intermittent abstinence, has profound medical consequences, is difficult to treat, and is associated with significant long-term cognitive and neurologic deficits. Second, clinicians faced with the presentation of an individual with acute methamphetamine intoxication should examine the patient for evidence of cardiovascular and cerebrovascular signs and symptoms, which are the primary causes of death due to methamphetamine use. Third, there are several steps to consider for a pragmatically focused program of research. Modifiable biological targets should be examined in individuals with MUD that focus on dysregulation of oxidative stress, neurotoxic and excitotoxic effects, and neuroinflammation. Neuromodulatory approaches appear promising in ameliorating impairments associated with MUD. For example, electroencephalography neurofeedback targeting the beta frequency band has increased, among other outcomes, periods of abstinence in individuals taking methamphetamine.[91] Moreover, repetitive transcranial magnetic stimulation targeting the frontal regions has resulted in decreased methamphetamine craving and/or increased cognitive-emotional function.[92] Real-time functional magnetic resonance imaging neurofeedback, which demonstrates the beneficial effect of reducing depressive symptoms,[93] may also be helpful in reducing dysphoria

present in individuals taking methamphetamine. Understanding the neurobiology of exercise-induced reduction in craving methamphetamine[94] may help to delineate novel disease-relevant targets. Fourth, preventive behavioral interventions focused on factors such as childhood trauma and dysregulated negative affect processing that increase the likelihood of initiating or continuing methamphetamine use may help to reduce future use.[95] Fifth, the neurobiology of this disorder is derived almost entirely from cross-sectional studies, which provide very little mechanistic insights. Thus, longitudinal assessments of brain-associated changes are necessary to determine what brain-based treatment targets are modifiable and what brain processes put individuals at high risk for relapse. Taken together and given the limited evidence-based intervention options, it will be critically important to develop an implementation framework such that behavioral interventions can be delivered with high fidelity to maximize treatment effects and help individuals overcome MUD.

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