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Methamphetamine Toxicities and Clinical Management

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Abstract

Methamphetamine use has increased over the past 15 years, with corresponding increases in associated morbidity and mortality. Toxicities from methamphetamine use largely consist of vascular and neuropsychiatric disorders, and are more likely to be due to long-term rather than acute exposure. The approach to managing methamphetamine use in clinical care settings has advanced recently, with universal diagnostic criteria for substance use disorders, promising data for several off-label pharmacotherapies, novel ideas for preventing and treating vascular and neuropsychiatric toxicities, and systematic prevention and screening for associated infectious and medical disorders among people who use substances. Here we review morbidity and mortality associated with methamphetamine use and discuss prevention and treatment strategies.

Introduction

Discovered in 1893, methamphetamine is a psychostimulant that increases the release and blocks the uptake of norepinephrine, serotonin, and dopamine. Methamphetamine, a psychostimulant alongside methylphenidate and other amphetamine-type medications, was listed as a Schedule II controlled substance by the United States Drug Enforcement Administration (DEA) in 1970 and is approved by the Food and Drug Administration (FDA) for the treatment of attention-deficit disorder and obesity, albeit with cautionary notes.[1] Methamphetamine manufactured outside of the medical system is often distributed as powder or crystals and can consist of multiple related or unrelated substances. Following the regulation of direct to consumer sales of ephedrine and pseudoephedrine, precursors of the chemical synthesis of methamphetamine, in 2005, non-medical methamphetamine production transitioned to use phenyl-2-propanone, resulting in a product with a higher concentration of d-methamphetamine thought to produce greater euphoria and more psychiatric toxicities.[2]

Methamphetamine use and mortality has been slowly increasing since 2009, and is now referred to as part of the “fourth wave” of the overdose crisis in the U.S. (after the first three waves of prescription opioids, heroin, and fentanyl).[3] US emergency department visits for methamphetamine use rose from 22 to 129 visits per 10,000 population from 2008–

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2018,[4] while psychiatric hospitalizations involving methamphetamine rose from 31 to 53 per 10,000 population from 2015–2019.[5] United States drug overdose deaths involving methamphetamine rose from 547 in 1999 to 32,537 in 2021.[6] Historically more present in the western United States, methamphetamine use has become more prevalent across the country.[7]

Here we review toxicities specific to methamphetamine and approaches to prevent or manage methamphetamine use disorder, as well as associated acute and chronic toxicities. Methamphetamine use is associated with many other medical disorders, including transmission of blood-borne viruses; bloodstream, bone/joint, or endovascular infections; and disorders specific to route of administration (i.e., injection or smoking). Those diseases present and can be managed similarly to when they arise as a result of other illicit drug use (e.g., opioids) and are reviewed in detail elsewhere.[8,9] While there are no therapies approved by the Food and Drug Administration (FDA) for methamphetamine use disorder, there are several behavioral and off-label pharmacologic therapies with compelling evidence.

Clinical manifestations of methamphetamine toxicity

Methamphetamine use leads to increased dopamine levels in the brain by binding to dopamine receptors to increase extracellular dopamine availability, as well as altering dopamine reuptake through the transporter.[10,11] This excess of dopamine induces a heightened sense of euphoria, explaining the significant addictive nature of methamphetamine. Prolonged and habitual methamphetamine use exposes the brain to excessive dopamine over an extended period, triggering a state of prolonged neuroinflammation, oxidative stress, and methamphetamine-induced neurotoxicity and apoptosis.[12] This chronic inflammatory state contributes to the development and exacerbation of various medical comorbidities.

Toxicities from methamphetamine use are dominated by vascular and neuropsychiatric pathologies; clinical management to-date has been markedly limited. Like most psychoactive substances, methamphetamine can affect multiple organ systems, from neurologic to renal, and many of these toxicities are associated with route of administration. However, in contrast to opioids, which generally result in acute toxicity and death through suppression of the respiratory drive, acute toxicity due to methamphetamine is more varied and less understood (Figure 1).

Vascular Methamphetamine Toxicities

Cardiac complaints account for 23% of emergency department visits for methamphetamine, with “chest pain” the most common chief complaint, accounting for 10.4% of all such visits nationally.[4] Cardiac complications of methamphetamine use include systemic hypertension, dilated cardiomyopathy, atherosclerosis, arrythmias, and aortic dissection. Additional vascular complications include cerebrovascular disease (e.g., cerebrovascular hypertension, intracerebral hemorrhage), and related phenomena such as pulmonary and renovascular hypertension or intestinal ischemia. Chronic methamphetamine exposure leading to dilated cardiomyopathy and heart failure with reduced ejection fraction is another increasingly recognized complication. Despite being younger than patients with other

types of cardiomyopathies, patients with methamphetamine-associated cardiomyopathy have higher rates of hospitalizations, morbidity, and mortality.[13]

The pathophysiology by which acute methamphetamine toxicity results in death is difficult to characterize. Most deaths attributed to acute methamphetamine toxicity not involving opioids have no additional cause of death listed. However, among decedents with additional causes of death listed in one large dataset, 20% had a cardiac cause of death and 55% had a cerebrovascular cause; an additional 27% had cardiac significant contributing conditions listed on the death certificate.[14] Other causes of death were far less common, including neurologic, infectious, traumatic, and complications of overdose. Among the roughly three-quarters of deaths due to methamphetamine with no additional cause of death listed, a fatal cardiac arrhythmia was among the most likely etiologies. A cardiac arrhythmia would not necessarily be detectable, nor suspected in the absence of data supporting an underlying cardiac disease from medical records or autopsy findings.

Neuropsychiatric Methamphetamine Toxicities

Neuropsychiatric toxicities can be profound for people who use methamphetamine. Among those reporting past-year methamphetamine use, 55% have a methamphetamine use disorder.[15] Moreover, about 27% of people who report heavy methamphetamine use have experienced at least one psychotic episode related to their use, and over 30% of drug-induced psychotic episodes are expected to transition to schizophrenia.[16] While methamphetamine use may lead to earlier onset or worse symptoms of psychosis in those with genetic vulnerability or pre-existing disease, respectively,[17] psychosis remains three times more likely to occur among people who use methamphetamine even in the absence of such risks.[18] Psychiatric complaints account for 50% of ED visits for methamphetamine toxicity in the United States, including concerns such as agitated delirium or psychosis.[4] Nearly half (47%) of patients visiting emergency psychiatric services in San Francisco were intoxicated on methamphetamine; visits involving methamphetamine had adjusted odds of 3.2 for resulting in chemical restraint.[19] The cause of psychosis is likely related to methamphetamine dose, duration of use, and pre-existing vulnerability to psychosis, although sleep deprivation has also been theorized to contribute.[20]

Even in the absence of psychosis, the neuropsychiatric and behavioral effects of methamphetamine may result in adverse outcomes. Methamphetamine has well-established detrimental effects on several domains of cognitive functioning, including learning, executive function, concentration, and memory.[16] Risk for Parkinson’s disease is increased 1.5 to 3-fold.[16] Moreover, methamphetamine use has been associated with risky and impulsive behavior,[21] including sexual risk for acquisition and transmission of HIV.[22] People who use amphetamines are overrepresented worldwide in traumatic deaths, including suicides (standardized mortality rate [SMR]=12.20, 95%CI 4.89–30.87) and homicides (SMR=11.90, 95%CI 7.82–18.12).[23] Some of these deaths may be indirectly attributable to neuropsychiatric effects of methamphetamine use. Unfortunately, these data are not captured in our current approach to surveillance for methamphetamine toxicity.

Experience with prescribed psychostimulants is of limited utility in understanding the long-term effects of methamphetamine use. Studies of the impact of prescribed stimulants

on cardiovascular health, while generally finding minimal harm, have been limited to under two years of follow-up; long-term effects and the effects of cumulative exposure remain unknown, even through systematic reviews and meta-analyses.[24] Similarly, the neuropsychiatric effects of prescribed psychostimulants overall suggest an increased risk of psychosis that abates with discontinuation of the medication, as well as an increase in tic disorders, but long-term follow-up that would correspond to the length of time people may be exposed to non-prescribed methamphetamine is limited.[25]

Management

The approach to managing methamphetamine use in clinical practice can be divided into four domains: general approach, reducing use, addressing toxicities, and preventive strategies (Figure 2).

General approach

As with any substance use, the first step in management is to ensure that the patient's medical and mental health concerns are addressed without worsening stigma. This requires the use of motivational interviewing techniques, akin to smoking cessation counseling.[26] Clinicians might first ask the patient what benefits they get from methamphetamine use, then what harms they perceive, prior to reviewing the known medical risks. Clinicians should then undertake careful assessment of the patient's goals regarding their methamphetamine use. While methamphetamine cessation is recommended to reduce health consequences, abstinence may not always be feasible or prioritized as the patient's immediate goal due to competing demands, such as social and economic stressors, employment, or lack of housing. In instances where methamphetamine cessation is not the patient's goal despite discussion of risks and benefits, treatment should focus on reducing the harms associated with use. This practice acknowledges the structural realities of patients' lives and prioritizes the ongoing patient-clinician relationship.

Diagnosis of methamphetamine use disorder follows the same rubric as other substance use disorders (SUDs) defined by the Diagnostic and Statistical Manual-V (DSM-V; Figure 3). Methamphetamine use alone is insufficient for formal diagnosis; patients must meet two or more DSM-V criteria for uncontrolled or chaotic methamphetamine use patterns with negative social or health consequences. While the risk of toxicities should be discussed with all patients who use methamphetamine, regardless of the presence of a use disorder, confirming the diagnosis helps to guide the intensity of the intervention. Given that over half of persons reporting past year methamphetamine use have a methamphetamine use disorder,[15] diagnosis is a critical first step.

Reducing use

Cessation of methamphetamine use is the most effective way to reduce associated toxicities, and any reduction in use would also be expected to produce benefits. Cessation of methamphetamine use may result in withdrawal, defined by the DSM-V as dysphoric mood with two or more of the following symptoms causing significant distress or impaired function and not attributed to other causes: 1) fatigue, 2) vivid dreams, 3) disruptions

in rapid eye movement sleep cycles presenting as insomnia or hypersomnia, 4) increased appetite, and 5) psychomotor retardation or agitation. Withdrawal symptoms can occur within several hours of last methamphetamine use and can last 5–14 days, with the most severe symptoms in the first 72 hours.[27,28] Cravings to use methamphetamine are high during this time. Because methamphetamine withdrawal is a diagnosis of exclusion, management in hospital settings involves ruling out other toxic-metabolic causes of hypersomnolence (often perceived as sedation) and agitation. Once other causes have been ruled out, management is focused on supportive care. Measures include offering adjunctive medications to treat symptoms like insomnia, agitation, and anxiety; ensuring ready access to food to manage increased appetite; avoiding unnecessary interruptions to sleep; and creating quiet, peaceful spaces using trauma-informed practices to avoid triggering further agitation. Certain medications shown to reduce methamphetamine use, such as mirtazapine or bupropion, may also help to alleviate withdrawal symptoms.[29,30]

Data are limited for non-pharmacologic therapies: cognitive behavioral therapy (CBT), the Matrix Model (incorporating individual counseling, group CBT, family education and social support groups, and encouragement for mutual support group participation), residential rehabilitation (often incorporating community-based rehabilitation, individual and group therapy, skill development, and employment training), and repetitive transcranial magnetic stimulation have some evidence for increased abstinence, reduced methamphetamine use, and reduced craving.[31] By far the strongest data for achieving these outcomes supports contingency management, a behavioral therapy that reinforces desired behaviors through incentivization.[31] Contingency management has also been shown to improve other clinical outcomes, such as antiretroviral medication adherence for patients living with HIV.[32] Notwithstanding extensive evidence of the benefits of contingency management, this approach has rarely been utilized outside of research settings. However, the Center for Medicare Services recently approved pilot contingency management projects in California, which may lead to more widespread utilization.[33]

Absent FDA-approved pharmacotherapies for methamphetamine use disorder, promising medications include mirtazapine, bupropion, oral naltrexone, bupropion with injectable naltrexone, and amphetamine-type stimulants; these agents are often used off-label in clinical settings (see Table 1). There are multiple other agents under study, or which may be worthy of a therapeutic trial in the appropriate patient. Of note, gold standard medication trials for methamphetamine use disorder to-date have been designed to detect methamphetamine abstinence through qualitative urine assays and lacked the ability to quantitatively measure reductions in use. Therefore, medications that have not been shown to reduce methamphetamine use in clinical trials may still have a benefit for some patients.

Mirtazapine 30mg daily has been tested in two placebo-controlled phase 2 trials among sexual/gender minorities and found to result in a lower relative risk of methamphetamine use of 0.57–0.67 over 12 weeks,[34,35] and 0.75 at 24 weeks,[35] with persistence of the benefit for 12 weeks off treatment in the second study.[35] Both trials also found mirtazapine to be associated with reduced sexual risk behaviors for HIV transmission. There were no serious adverse events associated with the study drug, and expected adverse events, such as fatigue

and weight gain, were minimal. An earlier pilot trial among persons using amphetamines also showed benefit.[36]

Bupropion has had mixed results, with poor medication adherence and intent-to-treat analyses showing negative results.[37-40] Studies of craving and drug effect suggested there would be a benefit[30] and some post-hoc analyses have suggested a benefit,[37] thus it remains in use clinically. Furthermore, as nicotine dependence is often a comorbid condition with methamphetamine use disorder, bupropion can be used to target both tobacco and methamphetamine cessation. Naltrexone has also shown mixed results, with one study finding a reduction in methamphetamine use with oral naltrexone[41] but two trials finding no evidence of benefit for injectable naltrexone.[42,43] The combination of injectable naltrexone administered every 3 weeks (instead of the standard 4 weeks) and high-dose bupropion (450mg daily) with cash-incentivized video directly-observed treatment significantly reduced methamphetamine use in a cohort with heavy methamphetamine use and moderate-to-severe methamphetamine use disorder.[44] A strength of this trial was that it achieved high-level adherence to bupropion (69%) and suggested that successful medication therapies for methamphetamine use disorder may require intensive adherence support.

Amphetamine-type stimulants have long been thought to help some people with methamphetamine use disorder. A recent observational study of 13,965 persons with amphetamine or methamphetamine use disorder in Sweden found receipt of lisdexamphetamine (45–65mg oral per day) to be associated with a lower rate of all-cause mortality (adjusted hazard ratio [aHR] 0.43; 95% CI 0.24–0.77), any hospitalization or death (aHR 0.86, 95% CI 0.78–0.95), and hospitalization due to substance use disorder (SUD; aHR 0.82, 95% CI 0.72–0.94).[47] Further, multiple studies of dextroamphetamine, methylphenidate, and modafinil have found reduced self-reported methamphetamine use, reduced craving, or reduced depressive symptoms. However, none have shown a reduction in methamphetamine use by an objective measure, the accepted standard, with the exception of one small trial of methylphenidate with methodological concerns (i.e., only 39% of participants completed the trial and the analysis was conducted using the ‘last observation carried forward’).[48] Overall, amphetamine-type stimulants show most promise for patients with cocaine use disorder, potentially in combination with topiramate[49] (topiramate by itself has very weak data for methamphetamine use disorder, with a negative phase IIb trial[46] and a pilot placebo-controlled trial with methodologic concerns, for which results were reported as positive based on fewer methamphetamine-positive urine results in the topiramate arm at only one mid-study assessment point[45]). Although data on sustained-release methylphenidate are mixed,[50,51] draft recommendations from the American Society of Addiction Medicine include this medication, along with mirtazapine, bupropion, naltrexone, and topiramate, as options for methamphetamine use disorder.[52]

Of these agents, both bupropion and amphetamine-type stimulants are contraindicated in the setting of cardiovascular disease, including hypertension or congestive heart failure. Bupropion is also contraindicated in patients with seizure disorders due to lowering of the seizure threshold. Naltrexone requires abstinence from opioids and would not be appropriate for a patient continuing to use opioids. Clinicians should also be aware that some medications, including bupropion and several other antidepressants, can result in

false-positive amphetamine results on immunoassays, thus positive results that occur when a patient reports abstinence should be sent for confirmatory testing.[53,54] In addition, while some clinicians utilize amphetamine-type stimulants explicitly for methamphetamine use disorder, others limit this therapy to patients with comorbid attention-deficit disorder due in part to potential concerns around using controlled substances long-term in the treatment of substance use disorders. US federal legislation specifically prohibits the use of "narcotic drugs" (defined as opioids or cocaine and their derivatives) in the treatment of substance use disorders except when specifically authorized; amphetamine-type stimulants are not included in the definition of narcotic drugs.[55]

Numerous other agents are under study for the treatment of methamphetamine use disorder, such as cannabidiol, psilocybin, levo-tetrahydropalmatine, oxytocin, injectable extended-release buprenorphine, monoclonal antibodies, and vaccines. Achieving substantial benefit will likely require combining multiple pharmacologic agents, alongside non-pharmacologic strategies.

Addressing acute methamphetamine toxicities

Acute toxicity from methamphetamine use generally presents with agitation, delirium, or cardiac symptoms such as chest pain, palpitations, or hypertensive crisis, as well as hyperthermia. Several trials and other studies have confirmed the benefits of benzodiazepines and antipsychotics in acutely managing these symptoms, although tachycardia and hypertension may not be mitigated with these therapies.

While any antipsychotic may be used for psychiatric symptoms, aripiprazole is commonly selected as it has the least effect on QTc interval, while olanzapine has the fewest drug-drug interactions; risperidone may be more effective at reducing positive symptoms of psychosis.[56] The only randomized trial addressing benzodiazepines compared lorazepam to droperidol in treating agitation due to methamphetamine use, finding the latter to achieve more rapid sedation with less need for repeated administrations.[57] Potential adverse effects of these agents include extrapyramidal signs, QTc prolongation (antipsychotics), and sedation, respiratory depression, or paradoxical agitation (benzodiazepines). Alternative agents for agitation include dexmedetomidine, ketamine, and propofol.[56]

A novel approach to addressing the acute psychiatric toxicities of methamphetamine use is to provide patients with a few tablets of olanzapine 5mg, to be taken when the patient perceives excessive psychiatric stimulation from methamphetamine use. Such a program has been initiated at the Psychiatric Emergency Services of San Francisco General Hospital, although data on the impact of the program are not yet available.

Beta blockers are important therapies to manage the hyperadrenergic effects of acute methamphetamine toxicity, such as hypertensive emergency or tachyarrhythmias. Concerns about "unopposed alpha stimulation" from stimulants have been repeatedly debunked through detailed review of case reports and several larger studies, although there are no randomized trials. These concerns initially arose for cocaine, with the most recent meta-analysis again showing no adverse outcomes from treating cocaine-associated chest pain with beta blockers compared to avoiding beta blockers.[58] Multiple trials have shown

the benefits of beta blockers, with most focused on atenolol, as well as carvedilol and labetalol.[56] There are more limited data for calcium channel blockers, alpha blockers, and alpha-2 agonists, with beneficial effects on blood pressure generally offset by increased heart rate.[56] Nitric oxide-mediated vasodilators have shown benefit in resolving cocaine-associated chest pain, but without ameliorating tachycardia.[56]

Addressing chronic methamphetamine toxicities

Ample data demonstrate that morbidity is associated with the intensity, frequency, and potentially binge use patterns of methamphetamine use,[59-61] thus any reduction in cumulative exposure to methamphetamine would be expected to reduce or delay adverse outcomes. This may mean reduced frequency of use or reduced quantity used each time, which may be missed with qualitative urine drug screening. Cessation of use has been repeatedly associated with reduced toxicities, although in some cases benefits may be due to improved adherence to medical therapies.[62] Unfortunately, many people who use methamphetamine are unable to significantly reduce use or achieve abstinence. In this setting, much like when a person with diabetes has a persistently elevated hemoglobin A1c, the clinician may focus on other strategies to minimize the harms of persistent use.

Preventing or treating cardiovascular disease should be a top priority for a clinician caring for a patient who uses methamphetamine. Stimulant use is not included as a cardiovascular risk factor in any guidelines, thus preventive tools are not routinely offered for this population. Although studies have not yet specifically assessed if prevention strategies, such as aspirin or 3-Hydroxy-3-methylglutaryl-CoA reductase inhibitors (statins), effectively prevent the development of cardiovascular disease due to methamphetamine, which is believed to be mediated by inflammation, a patient-centered discussion would allow patients to decide if hypothetical benefits outweigh risks. Analogy might be made to a randomized trial of pitavastatin 4mg daily among 7,769 people living with HIV without indications for statin use that was ended early due to a 35% reduction in major cardiovascular events and a 21% reduction in major cardiovascular events plus all-cause mortality. Laboratory and animal research suggests potential benefits of statins for people who use methamphetamine, particularly atorvastatin which has potent blood-brain barrier penetration, in reducing both cardiac and cerebral toxicities, including neurodegeneration.[63-65] Dapaglifozin, a sodium-glucose contransporter-2 (SGLT-2) inhibitor, has also been shown to reduce methamphetamine-induced cardiomyopathy in a mouse model.[65]

Management of cardiovascular diseases associated with methamphetamine use should follow standard clinical guidelines.[66] Treatment for hypertension should not be withheld pending cessation of drug use. Cardiomyopathy associated with methamphetamine use leading to reduced ejection fraction should be treated using guideline-directed medical therapy (GDMT), which includes beta blockers, inhibitors of the renin-angiotensin-aldosterone system including angiotensin receptor-neprilysin inhibitors, mineralocorticoid receptor antagonists like spironolactone, and SGLT-2 inhibitors.[67] Some patients will have cardiomyopathy meeting standard criteria for an implantable cardioverter-defibrillator (ICD) and should be referred to an electrophysiologist for consideration; electrophysiologists should determine if a high output device is required, as some

patients with methamphetamine-associated cardiomyopathy may have a higher defibrillation threshold.[66,68] Pulmonary hypertension associated with methamphetamine use is managed according to standard care (e.g., endothelin-receptor antagonist and phosphodiesterase-5 inhibitor, with addition of a prostacyclin pathway agent if needed in an adherent patient), although injectable prostacyclin agents are generally reserved for patients who have achieved abstinence from methamphetamine due to risks associated with that therapy.[62]

Development of neurocognitive deficits or psychiatric disease associated with methamphetamine is believed to predict a worse prognosis for treatment of methamphetamine use disorder, thus there is a dire need to prevent such outcomes. Cessation of use, any reduction in use, and perhaps improved sleep patterns, may help to prevent or at least delay the onset of these conditions. N-acetylcysteine, which can be accessed in vitamin shops, has a hypothetical neuroprotective benefit in the setting of methamphetamine use,[69] as do statins,[63-65] although there are no human trials. Modafinil has demonstrated some improvement in executive function and working memory among people who used methamphetamine, although the data do not indicate a reduction in use of methamphetamine.[70,71] Methamphetamine-associated psychosis often resolves after cessation of methamphetamine use, although this may take up to 6 months, and remains persistent in some patients. Persistent psychosis is generally responsive to atypical anti-psychotics, such as risperidone, aripiprazole, or olanzapine. Table 2 reviews interventions to be considered in the management of acute and chronic methamphetamine toxicities.

General Prevention

As with all substance use, clinicians should ensure that patients have received appropriate ancillary care. Screening for infectious diseases, including HIV, viral hepatitis, sexually-transmitted infections (STIs), and tuberculosis should be conducted at regular intervals (e.g., annually). Given the high prevalence of methamphetamine use among cisgender men and transgender women who have sex with men (MSM/TGWSM),[72,73] screening and prevention for HIV and STIs should be more frequent in these populations (e.g., quarterly). Vaccinations to prioritize include hepatitis A, hepatitis B, human papillomavirus, tetanus-diphtheria-pertussis, pneumococcus, meningococcus, influenza, and COVID-19. All patients should receive take-home naloxone and education in responding to an opioid overdose, regardless of opioid use, given the possibility of unintentional fentanyl exposure.[74] Use of fentanyl test strips may aid patients in testing drugs for fentanyl contamination, although performance characteristics of test strips may lead to frequent false positive results.[75] Pre-exposure prophylaxis for HIV (tenofovir-emtricitabine or cabotegravir)[76,77] and post-exposure prophylaxis for sexually-transmitted infections (doxycycline)[78] should be offered. Other substance use disorders should be addressed, including tobacco cessation, which may also help to mitigate the cardiovascular toxicities of ongoing methamphetamine use. Standard preventive care, treatment of comorbid psychiatric disorders, counseling on safer drug use practices, and support for housing, insurance, and food should be offered as well.

Conclusion

Methamphetamine use is highly prevalent and use disorders occur in approximately half of those who use regularly. Most toxicities are cardio- and cerebrovascular or neuropsychiatric in nature, with emergency presentations and death often resulting from long-term, cumulative exposure rather than acute “overdose”. Strategies to prevent or delay these toxicities include reduction in or cessation of methamphetamine use, aggressive management of cardiovascular risk factors, and smoking cessation; unproven approaches may include efforts to improve sleep architecture, as well as use of aspirin, statins, or SGLT-2 inhibitors for cardiovascular protection, statins or n-acetylcysteine for neurologic protection, and provision of olanzapine for self-management of psychotic episodes. Management of acute toxicity includes beta blockers, benzodiazepines, anti-psychotics, or droperidol depending on signs and symptoms. Management of chronic toxicities involves GDMT for cardiomyopathy, including beta blockers when indicated, and atypical anti-psychotics for psychotic disorders; psychostimulants may at least temporarily ameliorate some neurocognitive deficits. Therapies to help with use reduction or cessation for methamphetamine use disorder include contingency management, cognitive behavioral therapy, and rehabilitation, as well as off-label use of medications such as mirtazapine, bupropion, oral or extended-release naltrexone, sustained release methylphenidate, or possibly topiramate. All patients should receive appropriate infectious disease screenings and vaccinations, take-home naloxone, consideration for pre/post-exposure prophylaxis for HIV and STIs, and support for social needs.

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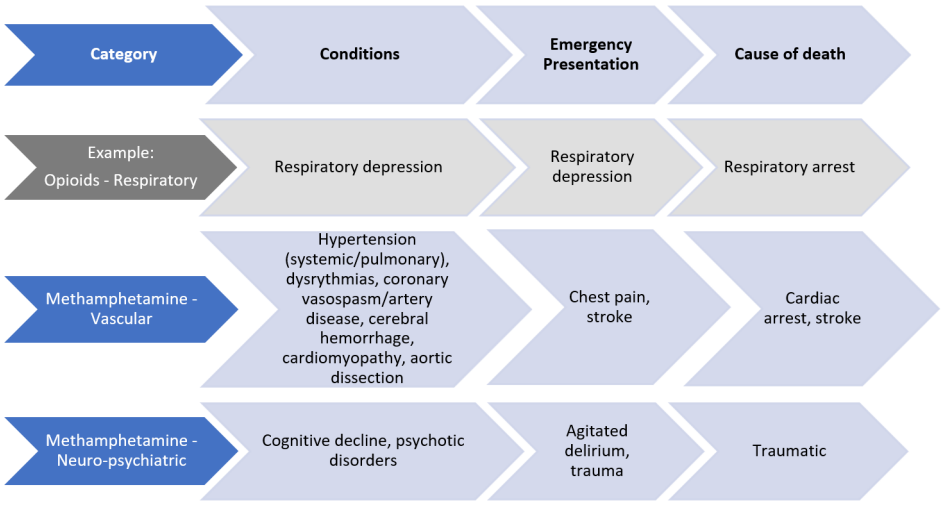

Figure 1: Construct for Major Toxicities Produced by Methamphetamine Use

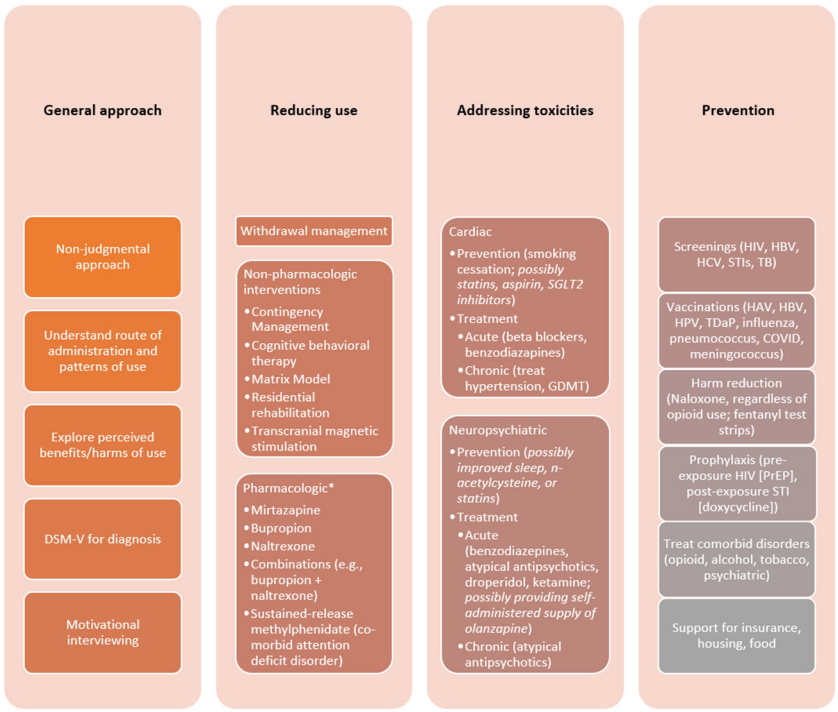

Figure 2: Addressing Methamphetamine Use in Clinical Care

Recommendations in italics remain hypothetical, with limited human or animal data

*no FDA-approved medications for methamphetamine use disorder; all options are off-label

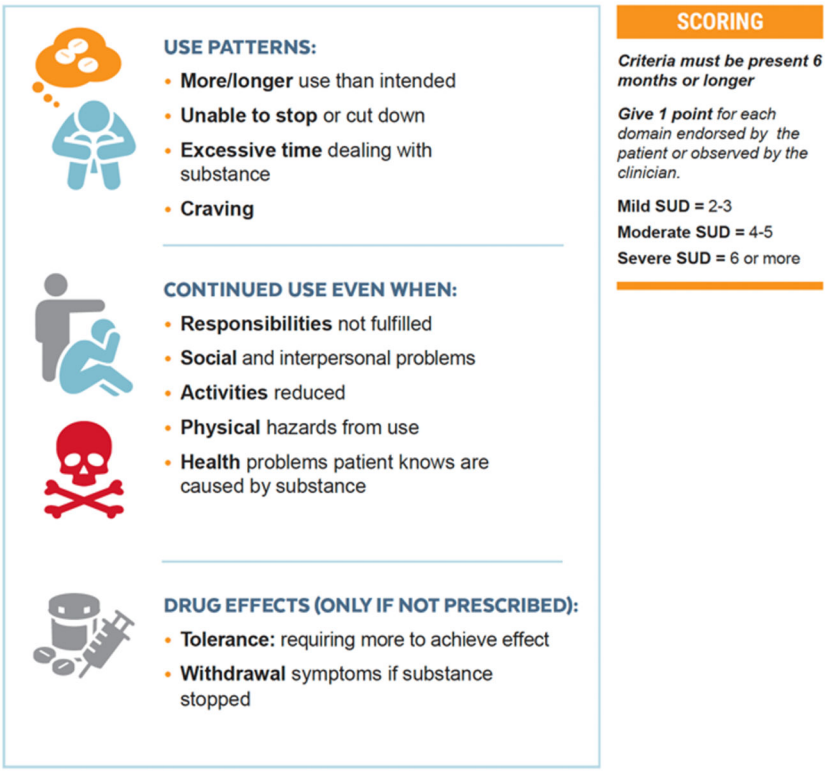

Figure 3: Diagnostic and Statistical Manual-V Criteria for Substance Use Disorder (SUD)

Table 1:

Off-Label Pharmacotherapies for Methamphetamine Use Disorder

Regimen	Initiation of therapy	Selected contraindications	Comments
mirtazapine 30mg oral daily at bedtime	Start at 15mg; increase to 30mg after one week.	Concomitant use of monoamine oxidase inhibitors Use with caution in patients with hepatic or renal dysfunction.	May help with sleep disruptions in a dose dependent manner. ; most data among sexual/ gender minorities[34-36]; 45mg dose associated with substantial weight gain; adherence concerns with daily dosing
bupropion sustained release (SR) 300 to 450 mg daily	Start at 150mg SR daily; increase in 150mg increments every 3 days	Concomitant use of monoamine oxidase inhibitors, seizure disorder, hypertension or related cardiovascular disease, eating disorder, prolonged QTc interval; Use caution in patients with hepatic impairment as extensively metabolized in the liver	Data are mixed[37-40]; adrenergic properties may function like “agonist” therapy; consider to treat comorbid tobacco use disorder; confirm QTc within normal range if increasing to 450mg; adherence concerns with daily dosing
naltrexone 50mg oral daily	Starting at 25mg may reduce initial nausea; increase to 50mg after 3–5 days	Active opioid use disorder (typically requires 7–10 days opioid free prior to use of naltrexone) or medical need for opioids; acute hepatitis or hepatic failure; Use caution with creatinine clearance <50 mL/min	Data are limited for oral therapy[41] and less promising for monotherapy with the intramuscular formulation[42,43]; monitor liver enzymes, may cause dose related increases in LFTs; consider “as needed” therapy for persons with sporadic use; can be used in combination with other agents; possible benefit if comorbid alcohol use disorder or if alcohol use is a trigger for methamphetamine use
bupropion extended release 450mg oral daily plus naltrexone extended release 380mg intramuscular every 3 weeks	Start bupropion at 150mg and increase by 150mg every 3 days	*bupropion*: concomitant use of monoamine oxidase inhibitors, seizure disorder, hypertension or other significant cardiovascular disease, eating disorder, prolonged QTc interval Use caution in patients with hepatic impairment *naltrexone* Active opioid use or medical need for opioids; acute hepatitis or hepatic failure Use caution with creatinine clearance <50 mL/min as naltrexone and metabolite are primarily renally cleared	Phase III trial demonstrated benefit in very heavy use when adherence to oral therapy supported by payment for successful video directly-observed therapy[44]; monitor QTc, renal and liver enzymes; Insurance coverage for intramuscular naltrexone in the treatment of methamphetamine use disorders may be challenging based on the off-label indication and more frequent dosing than is recommended in package labeling for the management of alcohol or opioid use disorder
methylphenidate sustained release at or near maximum approved dose of 60mg total per day dosed twice daily	Start at 15–20mg divided twice daily; increase total dose by 15–20mg weekly	Concomitant use of monoamine oxidase inhibitors; cardiovascular disease; coronary artery disease; anxiety disorder; glaucoma	Data are mixed; may be most effective with comorbid attention-deficit disorder.
topiramate 200mg oral daily	Start at 50mg; increase by 50mg each week in 1 to 2 divided doses based on chosen formulation; reduce dose by 50% if CrCl <70 mL/minute/1.73m^2	hypersensitivity to topiramate	Data are mixed and weak[45,46]; hypothetical benefit with comorbid alcohol use disorder; concerning adverse events include cognitive slowing, paresthesia, and appetite suppression; may cause fetal harm in pregnant patients; significant drug-drug interactions

Table 2:

Interventions to consider for prevention and management of toxicities related to methamphetamine use

Toxicity	Intervention	Potential use	Comments
Cardiovascular	use reduction	Prevention / management of chronic toxicity	Any reduction in cumulative exposure and possibly reduction in binge use patterns may be beneficial
	improved sleep hygiene	Prevention	Nightly sleep, avoidance of “runs” lasting multiple days
	tobacco smoking cessation (counseling, bupropion 300mg daily, varenicline 0.5–1.0mg daily, nicotine replacement therapies)	Prevention / management of chronic toxicity	Smoking cessation is rarely a priority, but may be easier to achieve than methamphetamine use reduction for some patients
	statins (for prevention of cardiotoxcity: pitivastatin 4mg oral daily[61]; pre-clinical data for atorvastatin, rosuvastatin)	Prevention / management of chronic toxicity	Compelling data for preventing cardiac events among people living with HIV and lacking primary indications for a statin; animal model data for methamphetamine-induced cardiomyopathy
	dapagliflozin 10mg oral daily	Prevention / management of chronic toxicity	Animal model data only; mechanism unknown
	benzodiazepines (e.g., lorazepam 0.5–2mg increments oral, IM, or IV)	Management of acute toxicity	Often in combination with cardiovascular agents
	beta blockers Acute toxicity: labetalol 5–20mg IV or carvedilol 25–50mg oral; Chronic toxicity: standard selections such as metoprolol or carvedilol)	Management of acute / chronic toxicity	Concerns about “unopposed alpha-stimulation” markedly rare, unrelated on detailed review of cases[56], not relevant for alpha/beta agents such as labetalol and carvedilol, and even less relevant for chronic disease; diltiazem may be helpful in acute toxicity; avoid dihydropyridine-class calcium channel blockers, alpha blockers, and alpha-2 agonists
	Goal-directed medical therapy	Management of chronic toxicity (methamphetamine-associated cardiomyopathy)	Should be managed similar to other etiologies of cardiomyopathy, although may require a higher implantable defibrillation threshold
Neuropsychiatric	use reduction	Prevention / management of chronic toxicity	Any reduction in cumulative exposure and possibly reduction in binge use may be beneficial
	improved sleep hygiene	Prevention	Nightly sleep, avoidance of “runs” lasting multiple days
	n-acetylcysteine 2,400mg oral daily	Prevention	Studies fail to demonstrate reduced methamphetamine use or psychotic symptoms, but animal models suggest neuroprotective benefit; caution in patients at high risk of gastrointestinal hemorrhage
	atorvastatin (undefined dose)	Prevention	Animal model data only; pitivastatin has poor blood-brain barrier penetration
	Benzodiazepines (e.g., lorazepam 0.5–5mg sublingual, IM, or IV)	Management of acute toxicity	May require repeat dosing; more effective for agitation than psychosis
	droperidol 2.5–5mg IV	Management of acute toxicity	More rapid sedation than with lorazepam; contraindicated with QTc prolongation; anticholinergic effects
	ketamine 0.5–1.0mg/kg IV initial dose	Management of acute toxicity	If repeat dosing required in first 60 minutes, consider infusion of 1–1.5mg/kg/hour with target of calm patient able to respond to verbal commands; can cause hypertension and requires ongoing monitoring
	Self-administered olanzapine 5mg sublingual as needed	Management of acute toxicity	Provided as 5 doses to patients with episodes of methamphetamine-induced psychosis but no indication for ongoing antipsychotic therapy
	Atypical antipsychotics (e.g., aripiprazole 5–10mg oral daily,	Management of acute / chronic toxicity	Aripiprazole/olanzapine have the least effect on QTc interval; olanzapine has the fewest drug-drug

Toxicity	Intervention	Potential use	Comments
	olanzapine 5–20mg oral daily, risperidone 4mg oral daily)		interactions; risperidone may be more effective for positive psychotic symptoms