REVIEW ARTICLE

Primary Care Recognition and Treatment of Methamphetamine Use Disorder

Richard Terry, DO, MBA[1,2]; Leslie Dally, DO, PGY-2[1]; Constantino Lambroussis, DO, MS[2]

[1]ArnotHealth, Elmira, NY
[2]Lake Erie College of Osteopathic Medicine, Erie, PA

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ABSTRACT: Methamphetamine addiction remains one of the most common substance use disorders encountered by physicians and is often unrecognized in the current opioid epidemic. Methamphetamine remains widely available in the United States despite laws designed to limit illicit production. Physical signs of methamphetamine abuse are not always recognized in the primary care setting. The utilization of the Drug Abuse Screening Test (DAST) has helped in identification of drug abusers in this setting. The mainstay of treatment remains cognitive behavioral therapy. Though various medications have been tried, none have gained FDA approval because of lack of proven efficacy. The most promising treatment modality on the horizon appears to be immunotherapy. Treatment, while not necessarily efficacious in the long term, is widely available today.

Methamphetamine is the most sought-after psychostimulant drug worldwide and most common illicit drug abused, aside from cannabis.[1,2] Methamphetamine abuse is at epidemic proportions and is now considered a major global health crisis. In the United States, methamphetamine abuse initially grew out of the overuse and overprescribing of amphetamines for depression and weight loss, especially from 1945-1971. In 1971 amphetamine products were made Schedule II by the Bureau of Narcotics and Dangerous Drugs, forerunner to the Drug Enforcement Administration.[3] In the 1970s, methamphetamine started to be mass-produced as an illicit drug from methylamine. Manufacture from pseudoephedrine and ephedrine using the Birch Reduction Method can also be done.[2] The ability to manufacture methamphetamine cheaply and efficiently has led to unprecedented availability of this drug on an international basis, predominately in the United States, South Africa, and Australia.[2] Of the drugs seized by United States law enforcement agencies in 2017, methamphetamine was the most common to be identified through laboratory testing.[4]

CORRESPONDENCE:
Constantino Lambroussis DO, MS | clambroussis@lecom.edu

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The listing of amphetamines as Schedule II led to limitations on legal production by pharmaceutical companies.[3] In 1971 the legal production limit was set at 15000kg, which is approximately 3 billion 10mg amphetamine sulfate tablets and 1 billion 10mg methamphetamine hydrochloride tablets. For 1972 the legal production limit was changed to one fifth of that in 1971, approximately 3000kg.[3] Local production of methamphetamine has decreased due to laws in the United States that mandate logging of pseudoephedrine and ephedrine purchases.[2,3] Unfortunately international methamphetamine production has increased dramatically and drug arrests at the southwestern border of the United States have increased by 157% since 2016.[5]

Methamphetamine has the common street names of: Meth, Crystal Meth, Crystal, Speed, Crank, Ice, Glass, Chalk, Redneck Cocaine, Yellow Powder, Yellow Barn, Tina, Tick-Tick, Spoosh, Scootie, Tweak, Uppers, Christina, Go Fast, Cookies, Cotton Candy, Dunk, Gak, Go-Go Juice, No Doze, White Cross, Pookie, Rocket Fuel, Scooby Snax, Wash, Trash, and Garbage.[6,7] Smokable methamphetamine also has several unique street names: Hot Ice, Super Ice, L.A. Glass, L.A. ICE, Quartz, Batu, Hanyak, and Hiropon.[6] Knowledge of street names pertaining to drugs aides in identifying drug use, however these names frequently change.[7]

The clandestine manufacturing of methamphetamine can result in explosions from the highly volatile chemicals used in production. Volatile materials in the production process can include acetone,

ethyl alcohol, red phosphorus, hypophosphorous acid, and lithium metal.8 Hospitalizations for methamphetamine toxicity within the United States have increased dramatically over the past decade and accounted for $2.17 billion in hospital costs in 2015.[9] Materials utilized in the manufacture of methamphetamine pose their own unique health hazards. Exposure can lead to pulmonary edema, chemical pneumonitis, disorientation, burns, and death.[8]

The challenge primary care physicians face is that many of the physical and psychological manifestations of methamphetamine abuse are not always specific. These can include headaches, mood swings, and sleeplessness.[10] As a result, users are often unrecognized, misdiagnosed, and mismanaged. Primary care physicians have failed to diagnose substance use disorder in approximately 43% of patients.[10] Methamphetamine can be taken orally, snorted, smoked, injected, or placed in the rectum. Smoking is the most common form of administration by users.[11]

The high methamphetamine users experience is caused by dopamine, norepinephrine, and serotonin release. Effects include a sense of euphoria, increased alertness, increased energy, increased libido, as well as increased sexual pleasure.[11] Advertisements for amphetamines in the past claimed to restore cheerfulness, mental alertness, optimism, and manage obesity.[3] Due to many of the effects, methamphetamine use can be associated with high-risk sexual behaviors.[11] *Table 1* lists additional reactions associated to methamphetamine use.[12]

TABLE 1:

Reactions to methamphetamine[12]

Psychosis	**Headache**
Mania	**Weight Loss**
Aggressive Behavior	**Emotional Lability**
Myocardial Infarction Stroke	**Dizziness**
Hypertension	**Diarrhea**
Cardiomegaly	**Tachycardia**
Seizures	**Constipation**
Priapism	**Libido Changes**
Peripheral Vasculopathy	**Motor Tic Exacerbation**
Raynaud Phenomenon	**Phonic Tic Exacerbation**
Growth Suppression	**Impotence**
Rhabdomyolysis	**Palpitations**
Anorexia	**Visual Disturbance**
Xerostomia	**Restlessness**
Insomnia	**Stroke**

PHYSICAL AND PSYCHOLOGICAL MANIFESTATIONS

The physical manifestations of acute methamphetamine can include tachycardia, elevated blood pressure, elevated respiratory rate, mydriasis, perspiration, hyperthermia, muscle fatigue, muscle cramping, as well as nausea and vomiting.[13] Oral examination of methamphetamine addicted patients is characterized by what is called "Meth Mouth" which consists of a combination of xerostomia, dental caries, discoloration of dentition, decay of dentition, missing dentition, as well as gum disease.[14] Less common but more serious symptoms include seizures, myocardial infarction, and even a psychosis-like state which mimics schizophrenia.[15] Chronic methamphetamine use changes the dopamine system of the brain and leads to cognitive decline, elevated anxiety, depression, irritability, aggressiveness, auditory hallucinations, motor skill impairment, confusion, as well as paranoia.[13]

The long-term psychological sequelae of methamphetamine abuse can lead to chronic anxiety, depression, schizophrenia, and bipolar disorder.[16] Methamphetamine abusers can also present with comorbid psychiatric illness.[17] The prolonged use of higher doses of methamphetamine, greater than 50mg, can lead to psychosis and has been associated with Parkinson's disease.[16] Neurotoxicity and neurocognitive effects occur from actions involving dopamine, norepinephrine, and serotonin. Mechanisms responsible for this may include excessive dopamine levels at the synaptic cleft as well as cytsol, pro-apoptotic changes, oxidative stresses, and neuroinflammation.[13] Even after cessation, neurologic symptoms can persist for several months to years.[16] Some of these symptoms improve following prolonged cessation from methamphetamine.[13]

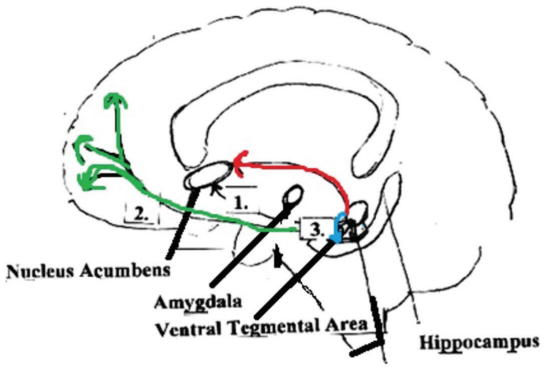
PHARMACOLOGY

Methamphetamine is an indirect agonist to the receptors for dopamine, norepinephrine, and serotonin.[16] As methamphetamine is structurally similar to monoamines, it is able to bind with the dopamine transporter (DAT), norepinephrine transporter (NET), serotonin transporter (SERT), and vesicular monoamine transpoert-2 (VMAT-2).[13] This results in a release of dopamine, norepinephrine, and serotonin into synapses, while methamphetamine can also inhibit monoamine oxidase.[16] The dopaminergic pathways affected include the mesolimbic, mesocortical, and nigrostriatal pathways of the central nervous system.[16] Additionally memory impairment can result from effects at the hippocampus, which is the site of memory formation.[16,18] Increased dopamine and norepinephrine affects cognition, executive function, decision making, as well as reward processing.[19]

Chronic repeated use of methamphetamine can lead to addiction. Chronic users and addicts may have difficulty achieving pleasure outside of consuming methamphetamine, which fuels further abuse of methamphetamine.[20] Sex, food, and other normal life activities fail to come close to methamphetamine's euphoria.[15,21] Intranasal administration takes approximately 5 minutes to reach euphoric peak, while oral administration takes approximately 20 minutes. The euphoric effects which also include elevated mental acuity, elevated mood, as well as social and sexual disinhibition, last for approximately 8-12 hours.[13]

FIGURE 1:

Mesolimbic and mesocortical pathways affected by methamphetamine[22]



1. Projections from the Ventral Tegmental Area to Nucleus Acumbens produce pleasure (Mesolimbic System).
2. Projections also extend from the Ventral Tegmental Area to the Prefrontal Cortex (Mesocortical System).
3. Projections from the Ventral Tegmental Area to the hippocampus are involved in the brain's formation of memory. When these get activated by the dopamine surge from methamphetamine, the memory of the intense pleasure is formed.

SCREENING

The utilization of the Drug Abuse Screening Test (DAST) has helped in identification of drug abusers in the primary care setting. The DAST consists of ten items and helps screen for drug use disorders. The ten items from a DAST will result in a score of zero to ten. A score above two indicates a positive screening test.[23] The DAST was designed for clinical screening as well as for research purposes.[24] Questions are answered in the yes/no format, and are as follows:[25]

1. Have you used drugs other than those required for medical reasons?
2. Do you abuse more than one drug at a time?
3. Are you unable to stop abusing drugs when you want to?
4. Have you ever had blackouts or flashbacks as a result of drug use?
5. Do you feel bad or guilty about your drug use?
6. Does your spouse (or parents) ever complain about your involvement with drugs?
7. Have you neglected your family because of your use of drugs?
8. Have you engaged in illegal activities in order to obtain drugs?
9. Have you ever experienced withdrawal symptoms (felt sick) when you stopped taking drugs?
10. Have you had medical problems as a result of your drug use (e.g. memory loss, hepatitis, convulsions, bleeding)?

The DAST takes approximately five minutes or less to be answered and can be scored rapidly.[26] Sensitivity range is 65-90%, while specificity range is 68-98%. Negative predictive value ranges from 93-99%, while positive predictive value ranges from 35-90%.[26]

TREATMENT

Even when abuse is recognized, there are a limited number of treatment options available. Cognitive Behavioral Therapy (CBT) remains the mainstay of therapy as there are currently no approved medications for methamphetamine abuse.[27,28] Combining psychosocial intervention, such as CBT, with suitable pharmacotherapy will likely result in improved patient outcomes.[27] Many medications have been used off label, such as Gabapentin, Anti-psychotics, Tri-cyclics, SSRI's, and SNRI's, but none have demonstrated any efficacy in the reduction of use or cravings.[29] Stimulant medications such as Adderall and Ritalin have been studied as well, but results are inconclusive and do not demonstrate a reduction in relapse rate, but do show a reduction in cravings in two studies.[21,29] One small study reported that N-acetylcysteamine demonstrated a reduction in cravings, but had no effect on relapse.[30] Modafinil (Provigil) weakly binds to DAT (presynaptic dopamine transporter), modulates hypocretin, histamine, GABA, and glutamate receptors and may play a role in medical treatment of methamphetamine addiction.[31] Most pharmaceutical studies that have been conducted to date have very small numbers and lack the power to be conclusive in their findings.

CBT has shown efficacy when utilized as a monotherapy as well as in combination therapy.[32] CBT as a psychosocial intervention has proven effective in reducing stimulant use by patients.[29] CBT utilizes multiple strategies that include: motivational interventions, contingency management, as well as relapse prevention.[32] When initiating CBT, it is important to consider the patient's motivation for seeking treatment as well as the probability that the patient will adhere to the recommended treatment regimen. Regarding contingency management, this is utilized in an effort to thwart the reinforcing properties of illicit drug use.[32,33] Contingency management achieves this by non-drug reinforcers, essentially rewards/prizes, for confirmed prolonged periods of abstinence from substance abuse.[32] Contingency management was first used with alcohol-abuse disorders, but is now utilized with all sorts of substance abuse disorders.[33] As abstinence duration increases, level of reward may also increase. The limitation to contingency management is however the limitation of available funding at programs that utilize it as part of their CBT.[32] Relapse prevention focuses on what has triggered the utilization of drugs in the past, and how to help the patient refrain from relapse when encountering these triggers. Identification of triggers, which may include the company of other drug users, alcohol, or settings where the patient has previously used, is a key element of relapse prevention.[32] Support groups can also be used as a form of supplemental treatment to prevent relapse of drug use. These groups do not typically have a formal curriculum, and topics of discussion are determined by the group members.[34]

One study in particular has evaluated CBT vs contingency management alone vs CBT with Contingency Management.[35] Each

group started with approximately 60 patients, with approximately 75% completing treatment in each group. Post-treatment stimulant use was assessed by utilization of urine samples and self-reported stimulant use during follow up at 17 weeks, 26 weeks, as well as 52 weeks after treatment completion. Results indicated that all three groups showed 67-79% stimulant free urine samples at these time points.[35] Self-reported stimulant use results indicated that pre-treatment mean days of use for each group was 9-10 days, and post-treatment 2-5 days at the same follow up time points.[35] The self-reported stimulant use by the patients in this study was for use within the 30 days prior to each follow up.[35]

The National Institute of Drug Abuse has identified research in methamphetamine abuse as a priority. Currently research is underway to determine the efficacy of stimulating monoclonal antibodies to methamphetamine in order to create a complex that cannot easily cross the blood brain barrier.[36] Concentrations of methamphetamine are typically greater in the brain as compared to serum concentrations, however with monoclonal antibodies the serum concentration is greater. If concentrations are greater outside the brain, this leads to a reduction in noticeable effects of methamphetamine.[36] Monoclonal antibodies with the ability to rapidly reverse methamphetamine effects could prove useful for overdose treatment. Monoclonal antibodies mAb4G9 and mAb7F9 have both shown ability towards rapid reduction in methamphetamine effects.[36]

Another drug undergoing studies for methamphetamine abuse is Ibudilast, a non-selective phosphodiesterase (PDE) inhibitor and modulator of central nervous system glial cell activation.[27] Ibudilast targets macrophage inhibitory factor (MIF), PDE-4, PDE-10, as well as having some activity with PDE-3, and PDE-11.[27] Glial cells may be involved in the rewarding properties of methamphetamine and other drugs of abuse, however glial cells also secrete pro-inflammatory cytokines which can be associated with cognitive dysfunction as well as other symptoms of neurotoxicity and neurodegenerative diseases.[27] Suppression of methamphetamine glial cell activation, and the associated pro-inflammatory cytokines, presents a treatment option for methamphetamine abuse.[27] Ibudilast has been shown to inhibit methamphetamine seeking in rats, and has already been in use for treatment of asthma, allergies, and post stroke dizziness in Asia since 1989. There has been an adequate safety record at doses of 30mg or less per day.[27] Phase 1 and phase 2a clinical trials, at doses above 30mg/day, have been conducted in the United States and Australia without significant adverse event[27]

CONCLUSION

In 2017 there were 70,237 drug overdose deaths in the Unites States, with 23,139 of these deaths involving psychostimulants.[4] Deaths attributable to psychostimulant abuse are increasing because of the availability of methamphetamine. Of the drug products seized by law enforcement in 2017, methamphetamine was the most commonly identified through laboratory testing.[4] Unfortunately, there are no currently approved medications for treatment of methamphetamine abuse.[27,28] Although medications, such as Gabapentin, Anti-psychotics, Tri-cyclics, SSRI's, and SNRI's, have been used off label, none have demonstrated efficacy in reduction of use or cravings.[29] Research with neuro-immune modulators, Provigil, and monoclonal antibodies to methamphetamine may show some promise.[27,31,36] CBT as a monotherapy as well as in combination therapy has shown efficacy in treatment of methamphetamine abuse.[32] Combining psychosocial intervention, such as CBT, with suitable pharmacotherapy will likely result in improved patient outcomes.[27] *Table 2* provides several additional resources for clinicians and patients to help obtain information as well as assistance with addiction.[7,28,37,38,39,40]

TABLE 2:[7,28,37,38,39,40]

Places for methamphetamine addicted individuals to seek help

samhsa.gov	Online treatment locator, searchable by zip code.
asam.org	"find a doctor" in resources section, also searchable by country.
na.org	Narcotics Anonymous Website, worldwide meeting finder available on site. Also available as phone app for iOS and Android.
luxury.rehabs.com	Treatment center website, many resources for assistance with addictions. 24/7 Phone# 1-866-308-1949.
drugabuse.gov	Patient & Families section with many resources for public use. Other resources for educators, researchers, & health professionals
americanaddictioncenters.org	American Addiction Centers website, many resources for assistance with addictions. 24/7 Phone# 1-888-987-1784.

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