Abstract
The following paper will discuss the pharmacology and pathophysiologic effects that methamphetamine use has on the body; providing a basis of understanding for how healthcare providers can support a patient recovering from methamphetamine addiction and its withdrawal effects.

Case Summary:
41 y.o. male with past history of methamphetamine (intranasal) abuse and mental/emotional irritability and anxiety has been treated for mood stabilization with naturopathic medicine. Patient has been clean from methamphetamine use for the last 6-7 months. He takes CatecholaCalm (Designs for Health) or Deproloft (Thorne) for mood support and fish oil for general health. Patient has also been given Nux vomica 200C which has been helping to decreased his irritability and anxiety. He has no concerning signs or symptoms on physical exams that warrant further workup.

Overview of Methamphetamine and Pharmacology
Methamphetamine (MA), often shortened to “Meth”, is derived from the parent drug amphetamine and is part of a class of psychostimulants known as phenylethylamines.\(^1,2\) It is classified as a Schedule II stimulant which is defined by the Drug Enforcement Association (DEA) as a substance “with a high potential for abuse, … with use potentially leading to severe psychological or physical dependence. These drugs are also considered dangerous.”\(^3\) Schedule II drugs are allowed to be prescribed for the treatment of medical conditions which, for methamphetamines and amphetamine analogs include: attention deficit hyperactivity disorder (ADHD),\(^4\) narcolepsy,\(^2,5\) short-term weight loss,\(^4\) and as a second-line treatment for depression.\(^2,4\)

Methamphetamine is a highly addictive stimulant and various clandestine “meth labs” or “super labs” have been created throughout the United States, predominately in the Midwest, and Mexico, to accommodate this addiction.\(^2\) Methamphetamine goes by a lot of different street names like, Speed, Crank, Crystal, Ice, Chalk, Tina, Yellow barn, and many others.\(^2\) MA comes in a variety of “forms and can be smoked, inhaled (snorted), injected, or orally ingested”\(^1\) but smoking it is the most common way of using it.\(^1\)

Before the adverse health effects started to become known, methamphetamine was used to treat numerous conditions because of the various physiological effects it had which include: increased energy and wakefulness, talkativeness, decreased appetite, pleasurable sense of wellbeing/euphoria, and increased sympathetic tone.\(^1,2\) Its effects on the body are far-reaching, affecting multiple organ systems including the nervous system, cardiovascular system, gastrointestinal, integumentary system, and musculoskeletal system (rhabdomyolysis,\(^2\) “meth mouth”) to name a few.\(^1,2\) Early on in its discovery in the early 20th century, methamphetamine was used in nasal decongestants and bronchial inhalers,\(^1\) but as its addictive nature started to come to the
forefront, abuse of these medications lead to regulations that limited their availability and use.

Even though methamphetamine is a stimulant derived from amphetamine, its effects on the body are much greater because of its increased lipid solubility allowing it to cross the blood-brain barrier more readily. This property causes methamphetamine to have more rapid effects on the central nervous system compared to peripheral nervous system. The half-life of methamphetamine is around 12 hours and roughly 45% of the methamphetamine is metabolized into amphetamine in the body before they are both excreted through the kidneys.\(^1,3,6-9\)

**Acute Effects of Methamphetamine Use**

Short-term effects of methamphetamine include increased attention, decreased fatigue and increased activity and wakefulness, decreased appetite, euphoria, increased blood pressure, tachycardia, arrhythmias, stroke, vasospasms, pulmonary hypertension, myocardial infarction, aortic dissection, sudden cardiac death, tachypnea, and hyperthermia.\(^1,7\) Acute use of methamphetamine results in increased levels of extracellular neurotransmitter dopamine (DA), predominately, but also affects 5-hydroxytryptamine (5-HT\(^3\); serotonin), norepinephrine (NE), and glutamate.\(^2,5\) Some of these effects are not exclusive to acute exposure and can be seen with chronic use.

**Effects of Chronic Methamphetamine Use**

Due to the highly addictive nature of methamphetamine, chronic use and effects are widely inevitable. Curiously, while acute use of methamphetamine causes an increase in dopamine, chronic use has been supported to cause decreased levels of dopamine.\(^2\) Berger and Roth state that long-term effects of MA use can include\(^4\): psychosis (paranoia, hallucinations, repetitive motor activity), which can last for months or years after cessation, altered brain structure and function, decreased ability to think and decreased motor skills, memory loss, aggressive or violent behavior, mood changes, easily distracted, severe dental problems and weight loss.\(^1\)

A review of the *Neuropsychological Effects of Chronic Methamphetamine Use on Neurotransmitters and Cognition* indicate that an “abrupt cessation of long-term use produces withdrawal, which can last for days and may be accompanied by dysphoria, irritability, and agitation.”\(^6\) While a great deal of the effects come from the nervous system, the central nervous system in particular, MA can also effect non-neuronal cells and tissues. MA increases and activates microglia and astrocytes producing inflammation.\(^8\) Beyond the nervous system, MA exerts its effects strongly on cardiac myocytes.\(^1\)

It is the NE and DA inducing effects that is thought to be the primary mechanism for why MA is cardiotoxic.\(^7\) While there are a number of factors that are involved in how and why MA is damaging to the cardiovascular system some of the discoveries are
noteworthy in understanding its action at the histopathological cellular level. A study using isolated murine cardiomyocytes revealed that MA depressed cardiac contractile function and adrenergic response, and induced intracellular $Ca^{2+}$ dysregulation. Additionally, myocyte degeneration, necrosis, and fibrosis, along with hypertrophy, and mitochondrial degeneration has been shown in various other studies, in cardiomyocytes exposed to MA.$^{(p34),9}$ Viewing the cardiovascular system in a global manner, a study out of the American Journal of Medicine, suggests that patients with cardiomyopathy who have a history of MA use have a significantly lower left ventricular ejection fraction compared with cardiomyopathy patients who have no history of MA use. “This finding [further] suggests that young patients who use methamphetamines are not only at a higher risk of developing cardiomyopathy but also of developing a more severe form of cardiomyopathy.”$^7$ Besides cardiovascular complications, there are immunological, liver, musculoskeletal and dermatologic issues that also arise as a consequence of chronic MA use. MA has been shown to cause dysregulation of the immune system, particularly with regard to hepatitis. It suppresses endogenous INF-alpha expression from hepatocytes, enhances HCV replication, and suppresses gene expression that regulates INF.$^{10}$

MA also affects the musculoskeletal system, particularly decaying dentition, which has become affectionately known as "meth mouth." This is most likely due to poor nutrition and lack of oral hygiene habits during binging periods, combined with the added affect of the drug which includes dry mouth and bruxism.$^{1,2}$ Vearrier et al reports of osteomyelitis of the frontal bone (Pott's puffy tumor) from intranasal MA use.$^2$ Additionally, MA has been associated with rhabdomyolysis$^2$ which causes the release of high levels of myoglobin into the blood which can then lead to renal damage.$^{11}$ This is likely due to MA’s immune dysregulation effects as well as increases HIV replication/production.$^{1,12}$ In non-IV drug users, the risk appears to be due to altered “judgment and inhibition” leading “people to engage in unsafe behaviors like unprotected sex.”$^1$ With regard to dermatologic issues, these occur because of a couple factors. Either they are skin infections from use of nonsterile needles and/or they are from MA-induced delusions of parasitosis$^2$ causing individuals to pick at their skin.

**Treatment Options**

Behavioral therapies such as cognitive-behavioral therapy and contingency-management interventions have been shown to be the most effective in treating MA addiction. An example of such a program is called the Matrix Model, which is a comprehensive, 16-week behavioral program.$^1$ “Dopamine receptor antagonists or synthesis inhibitors attenuate methamphetamine-induced deficits in DA neuronal activity, suggesting that the dopamine transporter (DAT) is critical to the mediation of neurotoxicity.”$^{13}$ A rat study put this theory into research and looked at dopamine agonists (terguride & ropinirole) and acetyl-l-carnitine effects during the withdrawal phase from MA. The conclusion was that all the test drugs “may represent potential therapeutic strategies for the treatment of methamphetamine addiction during the
withdrawal phase.”\textsuperscript{14} Another drug agent known as PG01037 (a D\textsubscript{3} antagonist) has been studied (rat model) for MA addiction and has shown support for inhibiting “methamphetamine-associated cue-triggered reinstatement of drug-seeking behavior and methamphetamine-enhanced brain stimulation reward.”\textsuperscript{15}

Rogers JL, De Santis S, See RE. Fig. 5. In: Medical University of South Carolina. Psychopharmacology. Charleston, SC: 2008.

Using this knowledge and understanding, it can be inferred that treatments, therapies, and screening labs that identify and counteract the negative effects on physiology previously discussed, may prove useful. Patients recovering from a methamphetamine addiction should be carefully monitored for neurological and cardiovascular issues\textsuperscript{*} using lab work and physical exams. Naturopathic medicine should support and focus on cardiovascular and neurological systems. Additionally, Naturopathic medicine should also refer patient for behavioral therapies and interventions as these have been supported to be the most effective treatments.\textsuperscript{1(p234)}

\textsuperscript{*} 1,2,4,6,7,10,11,13,15,16.
References:


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