

Methamphetamine Abuse and Consequences
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Introduction

Methamphetamine is a sympathomimetic, an indirect CNS stimulator that was originally produced from the ma houn plant in 1918 in Japan^{1,2,3}. Amphetamine, its precursor was developed in 1893 in Germany. Since their introduction, amphetamine and methamphetamine have been experimented for their CNS properties. During WWII, bomber pilots were given methamphetamine to increase in endurance, performance, aggression, and decrease in apathy; however, this practice was terminated secondary to agitation and hostility among the subjects^{1,4}. Japan also supposedly gave its Kamikaze pilots methamphetamine prior to their missions^{1,2,3,4}. It is believed, Adolph Hitler's personal physician also prescribed Pervitin or methamphetamine for the treatment of depression and "listlessness"⁵. The first methamphetamine epidemic occurred in Japan after WWII with the "dumping" of the military supplies among the mass markets^{2,3}. Methamphetamine abuse remains a serious problem in Japan and its surrounding countries like Taiwan and the Philippines to this day^{3,4}.

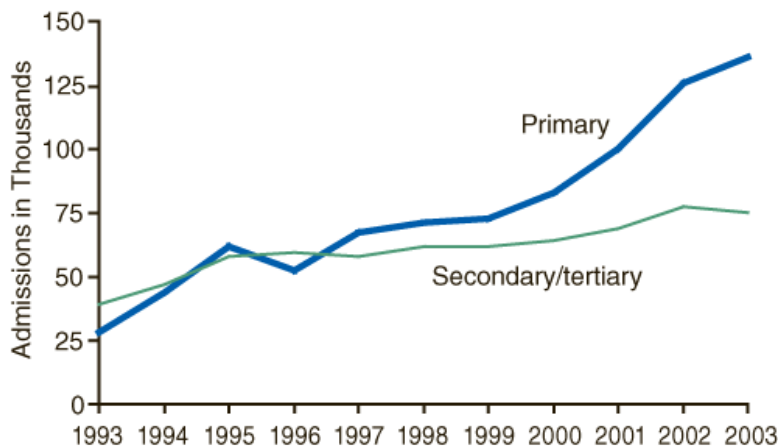
In the US, therapeutic investigations into amphetamine and methamphetamine for medical treatments began and vigorously pursued by the pharmaceutical companies in the 1920's¹. It was experimented for the treatment of various conditions such as radiation sickness, nicotine addiction, hypotension, and persistent hiccups among others¹. Until 1938, amphetamine and methamphetamine were actually available over the counter. Doctors began to use stimulants actively for the treatment of obesity and sinusitis in the 1950's and advertisements among the popular press during this time^{1,4}. In San Francisco, doctors gave amphetamine injections to heroin addicts to aid in their recovery¹. With the recognition of its addictive and dangerous potential, prescription methamphetamine itself was banned completely in 1962¹. It is also during this time also when home made labs began to appear especially in the West^{1,4}. In 1973, methamphetamine was finally included in the Controlled Substances Act in 1973⁶. This enactment recognized methamphetamine as a category II substance, allowing for regulation and prosecution for recreational use. In the 1990's, congress passes the Comprehensive Methamphetamine Control Act which allowed government to monitor suspicious behavior and pseudoephedrine buying behavior of a consumer⁶. More recently, over the counter cold medicine has come under state and federal regulations^{6,7}.

Epidemiology

The WHO reports methamphetamine is the second most popular drug in the world after cannabis⁷. In the US, The National Institute of Drug Abuse reports in 2006, 12 million or 1.3% of the US population had tried methamphetamine in their lifetime⁸. 1.4 million people have reported past year use of methamphetamine⁸. There were 700,000 new

users and 512,000 chronic users in the US. This represents almost a 50% rise when compared to 1996⁸. In addition, the potential for stimulant abuse is far more reaching, considering its current use for the treatment of attention deficit hyperactivity disorder or ADHD. Currently, there are 2.5 million children and 1.5 million adults taking stimulants on a daily basis⁹. In a recent survey, 12% of ADHD children reported being approached for abuse of their prescriptions of stimulants¹⁰. Heightened recognition and diagnosis of adult onset ADHD likely will only increase the number of stimulant users. Herbal supplements like ephedra and ma huang also pose an additional threat.

Methamphetamine related admissions to emergency rooms are also increasing across the United States^{11,12}. In 1993, there were 20,000 methamphetamine related ER visits reported by the SAMHSA; however, this increased by more than 50% ten years later with 40,000 admissions in 2003^{12,13}. Interestingly, the major increase of admission occurred in primary hospitals, suggestive of methamphetamine's increase of abuse in the rural and suburban regions¹⁴.



<http://www.oas.samhsa.gov/2k6/methTX/methTX.htm>

Data from 2002 show an alarming increase of all hospital admission. For example, in 1992, Iowa's admission rate ranged at 9.2 per 100,000¹⁵. Ten years later, this increased to 198 per 100,000. Although smaller, the East Coast also shows a similar trend with the highest increase in New Hampshire from 0.3 per 100,000 to 7.0 per 100,000 in a span of ten years¹⁵. This increasing trend is also seen in methamphetamine related drug rehabilitation admissions. Between the years 1992 to 2004, admissions increased from 21,000 to 150,000^{13,16}. This represents 8% of all drug rehabilitation admissions^{13,16}.

Historically, methamphetamine abuse has been problem concentrated in the West and the South^{7,11,12,15,16}. High rate of abuse has been especially challenging for Hawaii and California¹⁷. However, this landscape is changing as the problem migrates eastward. During the 1990's, the Midwest saw a dramatic rise in methamphetamine use, and many predict it will only be a matter of time before this epidemic hits the East coast^{6,11,13,15,16}. Hospital admissions both ER and drug treatment have confirmed this momentum. In a span of ten years, Newark and New York City saw an increase of 600% and 81% in all

methamphetamine related ER visits¹³. The absolute number however continues to be small when compared to the West or the Midwest.

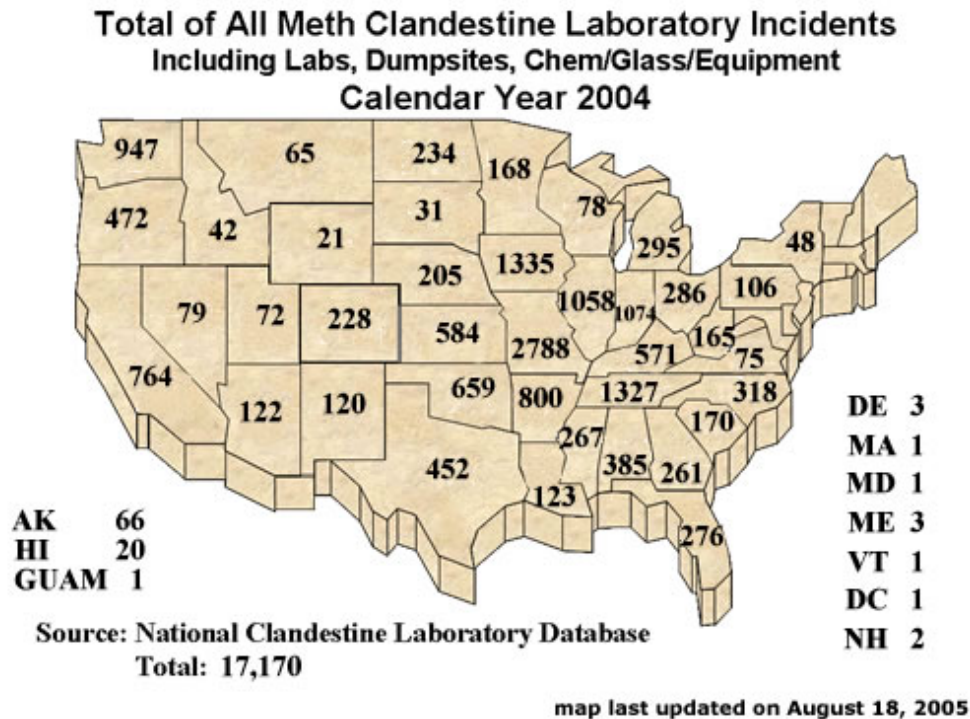
In Maryland, methamphetamine still is rarely produced or used when compared to the National data. It ranks last among most frequently abused drugs, with only 3.4 % of 10th to 12th graders ever trying methamphetamine compared to that of marijuana at 35.2% in 2006¹⁸. Only 0.3% of drug treatment admissions are related to methamphetamine while the national averages at 8%¹⁸. One death each was attributable to methamphetamine for 2004, 2005, 2006¹⁸. 36 ER visits were secondary to methamphetamine in 2002¹⁸. Primarily, methamphetamine use is concentrated in the western, eastern, southern parts of the state with western Maryland with highest lifetime rate at 5.1%. In Baltimore, DAWN reports ED visits at 8 per 100,000 in 2002 which is a 500% increase from 1 per 100,000 in 1994¹³. In 2004, there were 8 methamphetamine labs seized in the state of Maryland with 5 lab discoveries in 2005¹⁸. On the whole, methamphetamine use actually has been on decline in Maryland from 2002 to 2006. However, data from surrounding regions such as Virginia, Washington D.C., and Pennsylvania show increases in production, arrests, hospital visits which create a dangerous network for the citizens of Maryland¹⁸.

There are more male methamphetamine abusers than females at 51% and 39% respectively^{8,11,13,16}. They are typically between the ages 18-35. They tend to be less educated and live in smaller cities. The highest number of admissions was observed in small metropolitan areas¹⁶. However, as noted, abuse is becoming more wide spread with increase in the female populations across the entire country. The DAWN report states from 1995 to 2002 female admissions increased from 9434 to 15,482¹³. Among patients ages 6 to 17, an increase of 88% were seen from 2438 visits to 4394 visits while an increase of 50% were seen with patients older than 35 from 6199 to 12,746 visits⁸. Native Hawaiians and other Pacific Islanders have the highest percent of use among its population at rate of 2.2% when compared to only whites at 0.7% in 2004^{8,11,17}. In fact, in Hawaii, hospital admissions rate for methamphetamine use is at 217 per 100,000 in 2002¹⁷.

Currently, the largest supplier of methamphetamine to the U.S. is Mexico⁶. In 2004, over 4.5 tons of methamphetamine was smuggled in from Mexico to US. Mexico imported 230 tons of pseudoephedrine in US, primarily from Asia. It is estimated that Mexico only needs about 70 tons for legitimate use¹⁹. The second largest supplier of methamphetamine is actually the US itself and its self-producing “super labs”. The number of home grown methamphetamine has actually decreased in recent years likely from intensified law enforcement and limited availability of OTC cough medicines containing pseudoephedrine. However, our neighbors, Mexico and Canada do not regulate OTC cough medicines which likely is the source for “mom and pop” labs. The DEA reports that during the last 10 years, methamphetamine related cases, both filed and defended, have quadrupled. In 2006, 3.8 tons of methamphetamine was seized in the US, double the amount seized in 1996^{6,19}.

Methamphetamine is also known as “speed”, “crank”, “ice”, “stove top” among other names^{11,17}. It takes about a hundred dollars to produce a gram of methamphetamine,

typical dose of a methamphetamine hit, with a street value of 300 dollars^{6,19}. Methamphetamine is relatively easy to make using household items and OTC cough medicines. The “recipes” for methamphetamine is not easy to find. It is widely available through the world wide web. A Google search revealed multiple sites with step by step directions as to how to create methamphetamine. The creation of these “super labs” are dangerous as they pose explosion, fire hazards with increasing incidences of methamphetamine related property damages. In 2004, the National Clandestine Laboratory Database reported 17,033 methamphetamine related lab incidents across the United States with Indiana with the highest number of incidents at 2788 cases.

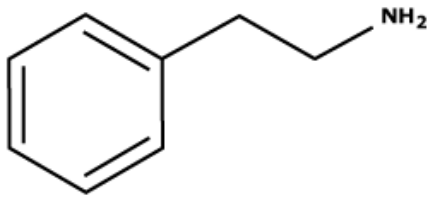


www.dea.org²⁰

In addition, these “super labs” create hazardous environments. The by products from methamphetamine production also create environmentally toxic waste products. It is estimated that for every pound of methamphetamine produced, there is six lbs of waste product, including methane and phosphine which are known to be dangerous to the environment^{15,17}.

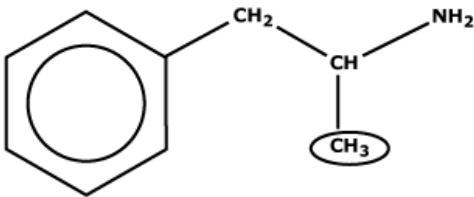
Pharmacokinetics

Methamphetamine is a indirect CNS stimulant, a derivative of the phenethylamine group, the backbone of all neurotransmitters²¹.

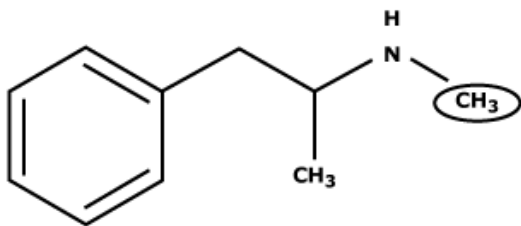


Phen - ethyl - amine = structural backbone of catecholamine substances

Various substitution on the basic phenethylamine structure ring determines pharmacokinetic properties including CNS penetration, lipophilicity, and receptor binding affinity.



AlphaMethylPhenethylamine = amphetamine



Methamphetamine

The addition of N-methyl group to amphetamine increases the potency methamphetamine by three times. The d-isomer of methamphetamine has the strongest potency and is the form produced for street consumption²¹.

Methamphetamine incorporates in to the presynaptic neurons as cytoplasmic vesicles where it displaces epinephrine, norepinephrine, dopamine, and serotonin to the cytosol. This leads to a rapid and complete release of these neurotransmitters where each can bind to its respective receptors leading a surge of adrenergic stimulation. In addition, methamphetamine inactivates MAO, thereby, inhibiting neurotransmitter reuptake in to presynaptic neurons which can lengthen the stimulation. It does not affect the slower, COMT neurotransmitter reuptake pathway²¹. The overwhelming and rapid release of neurotransmitters leads to activation of alpha and beta adrenergic stimulation which lead to hypertension, tachycardia, and vasospasm. Serotonergic activation leads to alteration in mood, increase in thirst, and decrease in hunger. Serotonin also leads to pulmonary vasoconstriction. Dopamine activation is associated with drug craving and seeking behavior, psychiatric symptoms of euphoria and possibly hallucinations^{15,17,21}.

Methamphetamine is readily absorbed via oral, pulmonary, nasal, intramuscular, intravenous, rectal and vaginal routes. It is highly lipophilic which makes crossing the

blood-brain barrier easy. Onset of effects differs between the various forms of methamphetamine; smoking has fastest onset within 1-2 seconds of intake.

	IV	Smoked	Snorted	Ingested
Time to effect	15-30 s	1-2 s	3-5 min	15-20 min
Peak	2-4 hrs	2-4 hrs	2-4 hrs	2-4 hrs
Half life	10-12 hrs	10-12 hrs	10-12 hrs	10-12 hrs

Adapted from Linberry et al.

Currently, the most popular method of methamphetamine consumption is via smoking, followed by injection. Its peak effect occurs within 2-4 hours of administration with a half life of ten to twelve hours. It is both renally and hepatically cleared. Both urine and serum toxicology tests are available although false negatives can result if the drug has not been metabolized through the kidney. False positive may also result from other medications such as selegiline. The l-isomer of methamphetamine used in cough medicine like Vicks also yields positive results; however, the l- isomer does not have neurological or cardiovascular toxicities^{15,17,21}.

Typical users experience a “rush” or feelings of euphoria, enhanced energy and increased libido after methamphetamine use. They can also exhibit paranoia, agitation, psychosis, and anxiety. Agitation, sometimes violent leading to homicides and self-injury is also common. Delusions include experiencing methamphetamine-induced parasitosis known as seeing “meth bugs” and this often leads to constant picking at imaginary bugs which ultimately lead to skin excoriations^{15,17,21}. After the initial rush, users often experience what is known as “tweaking” or restlessness, fatigue, irritability as they withdraw from the initial high. To alleviate these “tweaking” periods, they often use again which leads to sometimes days of meth or ‘binge’ by a “crash” period. They can sleep for days to compensate for the “meth high”^{15,17,21}.

The euphoria and symptoms of intoxication are similar between cocaine and methamphetamine. However, there are some properties that are different. Secondary to its pharmacokinetics, methamphetamine’s produces a longer high when compared to cocaine. The half life of cocaine is also shorter at 1 hour when compared to 12 hours with methamphetamine which allows a larger percentage to be not metabolized and allows it to stay in the brain longer^{8,11}. In addition, the mechanism by cocaine interacts on the CNS level is largely through its inhibition of dopamine reuptake. Methamphetamine also has this property but more importantly, it increases the release of dopamine leading to much higher concentration in the synapses.

Systemic effects

Establishing a direct, causal relationship between methamphetamine use and cardiovascular consequences has its limitations. First, the number of studies looking at this particular association is small. Second, the number of patients involved in the studies is small. In addition, given the nature of the subject, i.e. methamphetamine, it is difficult if not impossible to design a large, prospective study. Therefore, data primarily exist as

case reports and retrospective studies which further limit interpretation. Nevertheless, the association between methamphetamine on the body does exist. The consequences of methamphetamine, both acute intoxication and chronic abuse, are far ranging and all encompassing; it affects every system of the body. Briefly, some of the major systemic effects of methamphetamine intoxication will be reviewed with the main focus on the cardiovascular effects.

Acute Intoxication

Patients with acute methamphetamine intoxication commonly present with tachycardia, hypertension, and diaphoresis; the degree of intoxication is not related to the severity of these three presentations. Mildly intoxicated patients may also exhibit hypervigilance while moderate to severely intoxicated patients show hostility and severe agitation. In cases of life threatening intoxication, patients can have hyperthermia, delirium, rhabdomyolysis, acute renal failure, and metabolic acidosis^{15,17,21}. Cerebral vascular accidents, both hemorrhagic and ischemic have been reported. Rupture of Berry aneurysm has been linked to death in some cases. Seizures can also occur, typically within 24 hours of use^{15,17,21}. They may also present with acute myocardial ischemia and infarctions as well as seizures and hemorrhagic and ischemic strokes. Pulmonary edema, pulmonary hemorrhage and thermal injury are some of the pulmonary symptoms. Patients may complain of vomiting and diarrhea. Abdominal pain may result from vasoconstriction and subsequent small bowel ischemia is an urgent situation that requires immediate intervention^{15,17,21}. Bowel perforation from “body packing” or ingestion of large amounts of substance in contained condoms, paper bags and “booty bumping” or direct rectal incorporation and retention may also be the cause of abdominal pain^{15,17,21,22}. Deaths have been reported with this particular practice. Severe burns can result from lab related explosions and fires.

Chronic abuse

Chronic users can develop Parkinsonian like symptoms likely from dopaminergic depletion, memory loss, and vascular dementia likely from repeated vasoconstriction and small infarcts. Addicts may also develop permanent schizophrenic like behaviors with psychotic episodes. Skin excoriations and subsequent cellulites and abscess may result from “picking” at “meth bugs”^{15,17,21}. Chronic use is also linked to hypertension²³. In recent years, a surge of what is known as “meth mouth” has come to be a new problem in the dental community as more meth users present with extensive tooth decay that requires complete removal and replacement of teeth^{15,17,21}. “Meth mouth” results from poor overall dental hygiene of users as well as decreased saliva production and bruxism typically seen with methamphetamine intoxication. Mucosal burns, oropharyngeal burns, and gingival hypertrophy have been observed. Aphthous ulcers may result from vitamin deficiency^{15,17,21}.

Cardiovascular

Hypertension and ACS

In acute methamphetamine intoxication, tachycardia, palpitations, and hypertension are the most common physical findings secondary to adrenergic stimulation^{8,23}. Animal studies and human studies have also demonstrated these findings²³.

Chest pain, ischemia, and acute myocardial infarctions have been reported in the literature as case reports since the 1980's when the detrimental consequences of methamphetamine first began to be recognized^{24,25,26,27,28}. Richards et al reported chest pain as the initial presentation in 8% of acute methamphetamine intoxication in the ER²⁹. A retrospective study by Turnipseed et al showed that 25% of patients complaining of chest pain in the ER with methamphetamine intoxication had evidence of ACS³⁰. 8% of these patients in addition developed life threatening complications, including STEMI and ventricular arrhythmia. Mean age of patients was 41 years old and 78% of patients had no previous diagnosis of CAD, suggestive of methamphetamine itself as the cause of the acute infarcts.

A review of 20 case reports available in the literature by Kaye and et al concerning methamphetamine and acute infarctions demonstrate mean age of 32.1 of users with overwhelmingly negative history of CAD²³. The youngest patient reported is only 13 years old who had intentionally taken 6 tablets Adderall prescribed to a sibling in an attempt to get high²⁷. The patient presented with chest pain, nausea vomiting, shortness of breath, severe hypertension with blood pressure of 214/70 but without chest pain. EKG showed ST depressions in leads V1-V4 and positive cardiac enzymes. Subsequently, patient became unstable, developed acute pulmonary edema and needed to be intubated. Angiogram were only performed in 14/20 cases and 64% had normal angiograms despite having enzyme positive infarcts²³. 36% had abnormal angiograms with acute thrombus, stenosis, and infarcts although it is interesting to note that these patients were in their twenties and thirties with no previous diagnosis of CAD and risk factor significant for cigarette smoking in only one of the patients²³.

A study by Jacobs with postmortem examinations of six methamphetamine sudden death subjects demonstrated histological and pathological evidence of myocardial infarction, necrosis, neutrophilic influx to areas of necrosis without significant atherosclerosis in random distribution³¹. Again, subjects were healthy with ages ranging from 22 to 34. Interestingly, one patient did carry the diagnosis of "idiopathic cardiomyopathy" diagnosed only 2 years prior to death and authors speculated that possibly this diagnosis was actually related to his heavy methamphetamine use. Other autopsy studies have also confirmed these findings^{32,33}.

Although the majority of case reports in which a cardiac angiogram is performed reveal normal coronaries, stenosis and thrombus have also been seen which suggest that methamphetamine may a direct role in these processes as well^{24,34,35,36}. Furthermore, chronic users of methamphetamine appear to be at higher risk for development of atherosclerosis^{30,37}. A retrospective study by Karch et al examining 413 methamphetamine related deaths revealed CAD in 19% of methamphetamine users while only 5% in age matched controls³². They also noted increase in heart weight in the abusers than to controls. Histological examinations showed contraction band necrosis

and myocyte fibrosis. Other autopsy based studies have shown similar histological findings³⁸.

Catecholamine surge and activation is likely the mechanism of methamphetamines induced hypertension and tachycardia as demonstrated by in vitro and in vivo studies^{39, 40}. Smith et al gave animals and human increasing doses of methamphetamine and demonstrated a direct relationship between dose and hypertension and tachycardia⁴¹. High levels of catecholamine are known to increase vasoconstriction and its consequent effects³⁷. The mechanism by which methamphetamine causes CAD, ischemia, and infarct has not been completely elucidated. It is most likely an indirect effect via catecholamine surge and a direct effect of methamphetamine on the myocytes and vasculature itself^{23,37}. Coronary spasms, endothelial injury, increased shear forces, plaque rupture, platelet aggregation and resulting thrombus formation likely all contribute the process^{23,37}. In vivo and animal studies have shown catecholamine can cause necrosis, fibrosis, and hypertrophy of the heart^{23,37,39}. Similar pathological and histological changes have been observed with methamphetamine and cocaine. The interplay of catecholamines and its subsequent increase in oxygen demand in the setting of atherosclerosis, tachycardia, and coronary vasospasm from methamphetamine abuse with resulting decrease in oxygen supply likely leads to the myocardial ischemia, infarction or necrosis.

Arrhythmia

Arrhythmia also occurs with methamphetamine intoxication. Ventricular fibrillation and resulting arrest, supraventricular tachycardia, AV nodal dysjunction, Bundle Branch Blocks, T wave inversions, and complete heart block have been described in case reports^{25,27,29,30,31}. Watts and McCollester reported a 23 y.o. male with methamphetamine intoxication with STE and complete heart block requiring pacemaker placement²⁵. Ventricular fibrillation requiring resuscitation has also been described^{28,42}. EKG examinations of methamphetamine abusers reveal increased QTc intervals and widened QRS complexes^{43,44}. A retrospective study of 158 chronic users by Haning and Goebert revealed increased QRS by >440 ms in 26% of the population. Nonspecific T wave inversions and axis deviations were also found. QRS widening by >100ms have also been observed⁴³. These specific changes all may lead to lethal arrhythmia. In addition it can be surmised in cases of methamphetamine related sudden death related to methamphetamine when no direct causal process can be identified arrhythmia may be the contributing factor.

Cardiomyopathy/pulmonary HTN

Long term methamphetamine use can also lead to the development of cardiomyopathy, specifically dilated cardiomyopathy. Case reports and retrospective studies have shown this association^{23,45,46,47,48,49}. In their study, Wijetunga et al reported methamphetamine association in 18% of patients with dilated cardiomyopathy⁴⁵. These 21 patients had a mean average of 40.8 years, with mean EF of less than 25%. None of the patients had positive viral serologies and did not have previous history of CAD. Six patients underwent coronary catheterization and one had evidence of CAD. Patients in this study did have risk factors for CAD including diabetes, hypertension, and dyslipidemia which

may have been confounding variables. A case-control study by Yeo et al demonstrated methamphetamine users had an increased odds ratio of 3.7 to developing cardiomyopathy when compared to the control⁴⁹. The patients in the methamphetamine group tended to be younger with a mean average age of 35 years old and an average EF of 31%. Interestingly, 40% of patients who had used methamphetamine had cardiomyopathy in this particular study population. Unfortunately, these studies were based in Hawaii, a state in which methamphetamine abuse is particularly high and this likely led to overestimation of the incidences of methamphetamine related cardiomyopathy. Nevertheless, the association does exist. There are multiple case studies in which the absence of risk factors and heart disease are clearly established that also show this association. A case report by Hong et al described a 34 y.o. female with no history of cigarette use or any known medical conditions who had been using methamphetamine on a daily basis for weight control⁴⁸. She presented to the ER with dyspnea and peripheral edema and subsequently an echocardiogram showed an EF of 24%. Coronary angiography revealed normal coronaries. Review of methamphetamine associated cardiomyopathy case reports reveals overwhelmingly that patients are younger with mean average of 30 and without history of CAD. Although cardiomyopathy is generally a chronic disease, there have been case reports where function normalized after discontinuation of methamphetamine and medical management. Hypertrophic cardiomyopathy has been reported in one case⁵⁰.

There is also interesting reports of “Tako-Tsubo” cardiomyopathy or transient apical ballooning syndrome associated with acute methamphetamine use⁴⁶. The 30 y.o. female had smoked methamphetamine 24 hour prior to presentation and the echocardiogram revealed EF of 35% with basal akinesia and dilatation. Complete recovery of function was observed within 6 weeks. Currently, the mechanisms thought to cause apical ballooning syndrome involves massive adrenergic stimulation via stress, physical or emotional, and the observation of methamphetamine induced “Tako-Tsubo” may support this theory as it also causes catecholamine surge.

Sympathomimetic amines have been long associated with the development of pulmonary hypertension^{51,52,53,54}. For example, propylhexdrine, a related compound to amphetamine, has a strong causal relationship with pulmonary hypertension⁵³. Aminorex fumarate, an appetite suppressant introduced in Switzerland, Austria, and Germany in 1967 was withdrawn in 1972 from the market secondary to an “epidemic” of pulmonary hypertension⁵³. Shockingly, 77% of patients diagnosed in these countries between the 1967 and 1973 had used aminorex fumarate⁵³. There is also evidence that methamphetamine may also cause chronic pulmonary hypertension and subsequently heart failure⁵¹. Chin et observed stimulant use (amphetamine, methamphetamine, or cocaine) was found in 28% of patients with idiopathic hypertension compared to 4.3% of cardiothromboembolic pulmonary hypertension⁵². 3.8% of familial or collagen vascular related pulmonary hypertension patients had used methamphetamine. In addition, Idiopathic hypertension patients were also 8 times and 10 times more likely have used stimulants than that of thromboembolic and familial and collagen vascular pulmonary hypertension patients⁵². It is important to note that although cocaine use was included as a stimulant in this study, the actual patients who used cocaine alone or with

methamphetamine only consisted of two patients. Other studies have also demonstrated this possible association as well^{51,52,53,54}. Fenfluramine, a prescription diet supplement that was banned in the late 1990's secondary to elevated risk factors for developing hypertension, has been reported to increase the odds ratio by 7.5 times⁵⁴. Other anorexigen such as dexfenfluramine, phenteramine have odds ratio of 6.3 in the development of pulmonary hypertension⁵⁴.

How methamphetamine abuse leads to pulmonary hypertension is unclear, but it likely involves serotonin and norepinephrine, neurotransmitters that are released upon methamphetamine intake. In vitro and in vivo studies have shown both neurotransmitters lead to vasoconstriction in the pulmonary vasculature^{52,55}. Serotonin specifically promotes pulmonary smooth muscle cell proliferation which is a critical step to pulmonary vasculature remodeling and thickening seen in pulmonary hypertension. In fact, studies have shown elevated levels of serotonin in patients with pulmonary hypertension. In animal models, inhibition of serotonin receptors and serotonin transporter (SERT) can stop the development of pulmonary hypertension⁵⁶. SERT is also over expressed in pulmonary hypertension. This over expression of SERT in a setting of elevated levels of serotonin may be an important step in the pathogenesis⁵⁶. Inhibition of serotonin receptors also have shown to inhibit pulmonary vasoconstriction which further supports the importance of serotonin in the pathogenesis of pulmonary hypertension.

Acute aortic dissection

Aortic dissections result from a tear in the intima and its subsequent dissection of blood leading to reentry intimal tear or advential tear or tear through both. Acute aortic dissections can be disastrous with significant morbidity and mortality, sometimes requiring emergent surgical manipulation. The most common risk factor for aortic dissection is hypertension either chronic or acute. Although limited, case reports and postmortem studies have demonstrated this relationship^{57,58,59}. When Christopher et al examined 84 cases of deaths from aortic dissections, methamphetamine use could be identified in 20% of the subjects⁵⁹. In fact, they contributed methamphetamine use as the second most common factor in the study. More recently, Wako et al reported on methamphetamine related dissections at the University of Washington in 2 year period of time⁵⁷. These cases represented 5.5 % of all aortic dissection cases during the same period and 20% of patients with aortic dissection under the age of 50. Collectively, their mean age was 39.5 and all male. Also, 4/6 patients had preexisting diagnosis of hypertension and therefore, it is difficult to conclude methamphetamine as a direct cause of the dissection. Nevertheless, methamphetamine can and does cause profound hypertensive states which may precipitate the initial tear and propagation of the dissection.

Treatment

Acute

Treatment for acute intoxication is largely supportive^{15,17,21}. First, treatment should involve chemical sedation of the agitated patient. Benzodiazepines, ativan or valium, is typically used parenterally. The less severely intoxicated patient may just require

placement in a quite, darkened room; however, more intoxicated patients are typically who are typically very agitated to a point of requiring mechanical restraints, need urgent chemical sedation^{15,17,21}. Physical restraints are contraindicated as it often leads to isometric muscular contractions by the intoxicated as he or she tries to resist the restraints. Isometric muscular contraction leads to rhabdomyolysis, lactic acidosis, and hyperthermia which often precipitate cardiac collapse and death. Atypical antipsychotic including ziprasidone and haldol in combinations with benzodiazepines have also been used. This may potentiate the sedation effect and subside delirium^{15,17,21}. Haldol or butyphenones are less commonly used as it may interfere with heat dissipation, lower seizure threshold, and prolong the QTc interval.

Hypertension should be treated immediately with orals and IV infusions if needed. Typically, nipride, phentolamine, or labetalol drips are used. Similar to cocaine induced hypertension, beta 1 selective blockers should be avoided^{15,17,21}. Hyperthermia should be addressed immediately by cooling blankets and ice water baths. Paralysis of body using nondepolarizing agents such as vecuronium or rocuronium may be required in severe cases. This paralysis eliminates excessive muscle activity and thereby decreases the risk of the muscular contraction that leads to hyperthermia. Antipyretics have no effect as the pathophysiology of hyperthermia has no relation to autoregulation by the hypothalamus. Patients should also be put under seizure precautions. If a seizure is observed, benzodiazepines can once again be utilized^{15,17,21}. Airway protection and intubation may also be required in some cases.

If ingestion can be established to have occurred 1-2 hours of presentation, activated charcoal may be used for GI decontamination. This obviously should not be employed in the sedated or neurologically compromised patients. Polyethylene glycol may be used for whole bowel irrigation if a large single dose ingestion, body packing can be documented. If patient complains of abdominal pain, immediate laparotomy is indicated as this is often linked to bowel ischemia or perforation. Gastric lavage is not used as it is not helpful^{15,17,21}.

Chronic

The only established treatment plan show to be beneficial for methamphetamine addiction is drug rehab and ongoing treatment. The matrix model using the 12 step program and whole body approach has been the most successful^{15,17}. Unfortunately, there is no current pharmaceutical treatment that has been proven to beneficial for sobriety. In one study, participants were given Prozac 40mg daily which showed decrease in short term craving but no increase adherence rate by abusers^{15,17}. Imipramine has been show possibly lead to increase in adherence but this has not been conclusively proven. The latest drug therapy involves using Bupropion; however, studies are inconclusive¹⁵.

Conclusion

Since its creation in the 1930's, it has been abused for its euphoric effects. In fact, it is the second most popular recreational drug in the world. The rate of abuse is rising in the

United States as more and more people try and become addicted to this dangerous substance. The methamphetamine epidemic is no longer a problem of the South and South West. The landscape is changing as it migrates eastward and many experts have predicted that it will be only a matter of time before it also impacts the East Coast. Methamphetamine intoxication both acute and chronic has devastating, far reaching, and all encompassing consequences to every system. Its psychiatric and neurological effects have been well known; however, methamphetamine affects all systems and can be catastrophic including acute myocardial infarctions, aortic dissections, and cardiogenic shock. Treatment begins with the recognition of its presence in our communities and asking patients the specific question of methamphetamine involvement.

¹ Mendoza D. History of Methamphetamine. Available online at www.pcoa.org/uploads/HistoryofMeth.ppt. (Accessed on 12/3/08)

² Matsumoto T, Kamijo A, Miyakawa T, et al. Methamphetamine in Japan: the consequences of methamphetamine abuse as a function of route of administration. *Addiction*. 2002;97:809-817

³ Suwaki H, Fukui S, Kunuma K. Methamphetamine abuse in Japan: its 45 year history and the current situations. In: Klee H, ed. *Amphetamine Misuse: International Perspectives on Current Trends*. Amsterdam, Netherlands: Harwood Academic Publishers; 1997

⁴ Lineberry TW and Bostwick JM. Methamphetamine abuse: a perfect storm of complications. *Mayo Clinic Proceedings*. 2006;81(1):77-84

⁵ Doyle D. Adolf Hitler's medical care. *Journal of Royal College Physicians of Edinburgh*. 2005;35:75-82.

⁶ DEA Report. www.usdoj.gov/dea/pubs/pressrel/pr110807a.html

⁷ 2006 World Drug Report, Volume 1: Analysis. United Nations Office on Drugs and Crime. Available online at: www.unodc.org/pdf/WDR_2006/wdr_2006_volume1.pdf (Accessed on 1/11/08)

⁸ 2006 National Survey on Drug Use and Health (NSDUH), Substance Abuse and Mental Health Services Administration (SAMHSA). Available online at www.drugabusestatistics.samhsa.gov/nsduh/2k6nsduh/2k6Results.pdf (Accessed 1/15/08)

⁹ Nissen SE. ADHD Drugs and Cardiovascular Risk. *The New England Journal of Medicine*. 2006;354(14):1445-1448

¹⁰ Poulin C. From attention-deficit/hyperactivity disorder to medical stimulant use to the diversion of prescribed stimulants to non-medical stimulant use: connecting the dots. *Addiction*. 2007;102(5):740-751

¹¹ Methamphetamine Use, Abuse, and Dependence:2002, 2003, and 2004. The NSDUH Report. Available online at: www.drugabusestatistics.samhsa.gov/2k5/meth/meth.html (Accessed 1/11/08)

¹² Methamphetamine Abuse and Addiction. National Institute on Drug Abuse Research Report Series. Available online at: www.nida.org. (Accessed 1/11/08)

¹³ Amphetamine and methamphetamine Emergency Department Visits, 1995-20002. The Drug Abuse Warning Network (DAWN) Report 2004. Available online at www.oas.samhsa.gov/dawn.html (Accessed on 1/11/08)

¹⁴ Methamphetamine ER admission Trends. Office of Applied Statistics. Available at <http://www.oas.samhsa.gov/2k6/methTX/methTX.htm>. (Accessed on 1/15/08)

¹⁵ Lineberry TW and Bostwick JM. Methamphetamine Abuse: A Perfect Storm of Complications. *Mayo Clinic Proceedings*. 2006;81(1):77-84

¹⁶ Methamphetamine/Amphetamine Treatment Admissions in Urban and Rural Areas:2004. The Drug and Alcohol Services Information System (DASIS) Report 2006. Available online at www.oas.samhsa.gov/dasis.htm. (Accessed online at 1/11/08).

¹⁷ Winslow BT, Voorhees KI, Pehl KA. Methamphetamine Abuse. *American Family Physician*. 2007;76(8):1169-1174

¹⁸ Methamphetamine in Maryland 2007. Center for Substance Abuse Research (CESAR) Briefing 2007. Available only at www.cesar.umd.edu. (Accessed 2/2/08)

¹⁹ Fact Sheet:The Department of Justice's Efforts to Combat Methamphetamine. Available online at www.usdoj.gov/dea/pubs/pressrel/pr061606.html. (Accessed 2/2/08)

-
- ²⁰ Maps of methamphetamine lab incidents. Available online at www.usdoj.gov/dea/concern/map_lab_seizures.html. (Accessed 2/08/08)
- ²¹ Methamphetamine intoxication. Up-to-date. Available online at www.uptodate.com. (Accessed on 11/28/08)
- ²² Takekawa K, Ohmori T, Kido A, Oya M. Methamphetamine Body Packer: Acute Poisoning Death Due to Massive Leaking of Methamphetamine, Case report. *American Academy of Forensic Sciences*. 2007;52(5):1219-1222
- ²³ Kaye S, McKetin R, Duflou J, Darke S. Methamphetamine and Cardiovascular pathology: a review of the evidence. *Addiction*. 2007;102:1204-1211
- ²⁴ Furst SR, Fallon SP, Reznik GN, Shah PK. Myocardial Infarction after Inhalation of Methamphetamine. *New England Journal of Medicine*. 1993;323:1147-1148
- ²⁵ Watts DJ, McColleston L. Methamphetamine-induced myocardial infarction with elevated troponin I. *American Journal of Emergency Medicine*. 2006;24:132-4
- ²⁶ Chen JP. Methamphetamine-Associated Acute Myocardial Infarction and Cardiogenic Shock with Normal Coronary Arteries. *Journal of Invasive Cardiology*. 2007;19(4):E89-92
- ²⁷ Sztajnkrzyca MD, Hariharan S, Bond R. Cardiac Irritability and myocardial infarction in a 13-year-old girl following recreational amphetamine overdose. *Pediatric Emergency Care*. 2002;18:E11-E15
- ²⁸ Jacobs W. Fatal Amphetamine-Associated Cardiotoxicity and its Medicolegal Implications. *The American Journal of Forensic Medicine and Pathology*. 2006;27:156-160
- ²⁹ Richards JR, Bretz SW, Johnson EB, Turnipseed SD, Brofeldt BT, Derlet RW. Methamphetamine abuse and emergency department utilization. *Western Journal of Medicine*. 1999;170:198-202
- ³⁰ Turnipseed SD, Richards JR, Kirk JD, Diercks DB, Amsterdam EZ. Frequency of acute coronary syndrome in patients presenting to the emergency department with chest pain after methamphetamine use. *Journal of Emergency Medicine*. 2002;24 (4):369-373
- ³¹ Jacobs W. Fatal amphetamine-associated cardiotoxicity and its medicolegal implications. *The American Journal of Forensic Medicine and Pathology*. 2006;27(2):156-160
- ³² Karch SB, Stephens BG, Ho CH. Methamphetamine-related deaths in San Francisco: demographic, pathologic, and toxicological profiles. *Journal of Forensic Sciences*. 1999;44:359-368
- ³³ Zhu BL, Oritani S, Shimotouge K, Ishida K, Quan L, Fujita M, et al. Methamphetamine-related fatalities in forensic autopsy during 5 years in the southern half of Osaka city and surrounding areas. *Forensic Sciences International*. 2000;113:443-447
- ³⁴ Hung MJ, Kuo LT, Cherng WJ. Amphetamine-related acute myocardial infarction due to coronary artery spasm. *International Journal of Clinical Practice*. 2003;57:62-64
- ³⁵ Bashour TT. Acute myocardial infarction resulting from amphetamine abuse: a spasm-thrombus interplay? *American Heart Journal*. 1994;128:1237-1239
- ³⁶ Brennan K, Shurmur S, Elhendy A. Coronary artery rupture associated with amphetamine abuse. *Cardiology Review*. 2004;12:282-283
- ³⁷ Wijetunga M, Bhan R, Lindsay J, Karch S. Acute Coronary syndrome and crystal methamphetamine use: a case series. *Hawaii Medical Journal*. 2004;63:8-13
- ³⁸ Shaw KP. Human methamphetamine-related fatalities in Taiwan during 1991-1996. *Journal of Forensic Sciences*. 1999;44:27-31
- ³⁹ He SY, Matoba R, Fujitani N, Sodesaki K, Onishi S. Cardiac muscle lesions associated with chronic administration of methamphetamine in rats. *American Journal of Forensic Medical Pathology*. 1996;17:155-162
- ⁴⁰ Islam MN, Kuroki H, Hongcheng B, Ogura Y, Kawaguchi N, Onishi S, et al. Cardiac lesions and their reversibility after long term administration of methamphetamine. *Forensic Sciences International*. 1995;75:29-43.
- ⁴¹ Smith HJ, Roche AH, Jagusch MF, Herdson PB. Cardiomyopathy associated with amphetamine administration. *American Heart Journal*. 1976;91:792-797
- ⁴² Waksman J, Taylor R, Bodor GS, Daly FFS, Jolliff HA, Dart RC. Acute myocardial infarction associated with methamphetamine use. *Mayo Clinic Proceedings*. 2001;76:323-326
- ⁴³ Ling LH, Marchant C, Buckley NA, Irvine RJ. Poisoning with the recreational drug paramethoxyamphetamine ("death"). *Medical Journal of Australia*. 2001;174(9):453-455
- ⁴⁴ Haning W, Goebert D. Electrocardiographic abnormalities in methamphetamine abusers. *Addiction*. 2007;102(1):70-75

-
- ⁴⁵ Wijetunga M, Todd S, Lindsay J, Schatz I. Crystal methamphetamine-associated cardiomyopathy: tip of the iceberg? *Clinical Toxicology*. 2003;41(7):981-986
- ⁴⁶ Reuss CS, Lester S, Hurst T, et al. Isolated left ventricular basal ballooning phenotype of transient cardiomyopathy in young women. *American Journal of Cardiology*. 2007;99:1451-1453
- ⁴⁷ Crean AJ, Pohl JEF. "Ally McBeal Heart?" drug induced cardiomyopathy in a young woman. *British Journal of Clinical Pharmacology*. 2004;58:558-559
- ⁴⁸ Hong R, Matsuyama E, Nur K. Cardiomyopathy associated with the smoking of crystal methamphetamine. *JAMA*. 1991;265(9):1152-1154
- ⁴⁹ Yeo KK, Wijetunga M, Ito H, et al. The association of methamphetamine use and cardiomyopathy in young patients. *The American Journal of Medicine*. 2007;120:165-171
- ⁵⁰ Tanaka T, Nishi T, Chin M, Nagao M, Nishio T, Hashida E, et al. A case of hypertrophic cardiomyopathy associated with chronic administration of methamphetamine in rats. *American Journal of Forensic Medical Pathology*. 1996;17:155-162
- ⁵¹ Schaiberger PH, Kennedy TC, Miller FC, Gal J, Petty TL. Pulmonary hypertension associated with long term inhalation of "crank" methamphetamine. *Chest*. 1993;104:614-616
- ⁵² Chin KM, Channick RN, Rubin LJ. Is methamphetamine use associated with idiopathic pulmonary artery hypertension? *Chest*. 2006;130:1657-1663
- ⁵³ Rich S, Rubin L, Walker AM, Schneeweiss S, Abenhaim L. Anorexigens and pulmonary hypertension in the United States: Results from the surveillance of North American Pulmonary hypertension. *Chest*. 2000;117:870-874
- ⁵⁴ Abenhaim L, Moride Y, Brenot F, et al. Appetite-suppressant drugs and the risk of primary pulmonary hypertension. *New England Journal of Medicine*. 1996;335:609-616
- ⁵⁵ MacLean MR. Pulmonary hypertension and the serotonin hypothesis: where are we now? *International Journal of Clinical Practice*. 2007;61:27-31
- ⁵⁶ de Castecker M. Serotonin Signaling in pulmonary hypertension. *Circulation Research*. 2006;98:1229-1231
- ⁵⁷ Wako E, Ledoux D, Mitsumori L, Aldea GS. The emerging epidemic of methamphetamine-induced aortic dissections. *Journal of Cardiac Surgery*. 2007;22:390-393
- ⁵⁸ Davis GG, Swalwell CI. Acute aortic dissections and ruptured berry aneurysms associated with methamphetamine abuse. *Journal of Forensic Sciences*. 1994;39:1481-1485
- ⁵⁹ Swalwell CI, Davis GG. Methamphetamine as a risk factor for acute aortic dissection. *Journal of Forensic Sciences*. 1999;44:23-26