# Articles

## Methamphetamine and the Expanding Complications of Amphetamines

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**During the past 10 years, the use of methamphetamine has increased rapidly in the West and throughout the United States. Because of this increase, our attention has focused on methamphetamine's toxicity. Methamphetamine and related compounds generate many of the same toxic effects as cocaine. Because of methamphetamine's widespread use, clinicians should be familiar with its medical effects and toxicity and with treatment options for acute and long-term effects of methamphetamine abuse.**

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The use of methamphetamine hydrochloride (MAP) has increased markedly over the past 25 years. In San Diego County, California, MAP intoxication played a role in 40% of drug-related homicides in 1987, and 40% of drug rehabilitation referrals were related to MAP.[1] Maternal deaths associated with the use of MAP have also been reported.[2,3] A study of 29,494 women giving birth in California found that MAPs were the third most common illicit drugs found on toxicology screens (0.60%).[4] In San Bernardino County, twice as many more coroners' cases involved MAP than involved cocaine from 1980 to 1988.[5] Initially, MAP use was concentrated on the West Coast and in Hawaii, but later spread throughout the country.[5,6] A 1996 Drug Enforcement Administration report found large increases in MAP use in the West: For example, Phoenix reported a 570% increase in deaths related to MAP between 1992 and 1994.[7] Increases in use were also reported in the Southeast and Midwest. The increasing morbidity and mortality associated with MAP abuse are of great concern.[8,9]

Both oral and intravenous uses of MAP are well documented; but, until recently, the use of smokable MAP has received little attention in medical literature. Patients who inhale the smokable form of MAP ("ice") experience an immediate euphoria similar to that seen with "crack" cocaine, but the effects may last much longer than those seen with cocaine.[10] The immediate high that MAP provides, coupled with the drug's availability and low cost, may explain its popularity among adolescents.[11] A 1994 drug abuse survey found that the groups with the highest use of MAP were males aged 18 to 25 and females aged 12 to 17.[12]

Methamphetamine hydrochloride is relatively easy to synthesize; illicit production occurs in home kitchens, trailers, recreational vehicles, and rural cabins.[13] Once converted to its water-soluble form, MAP salt is sold on the street as "speed," "crank," "go," "crystal," or methamphetamine. Smoking MAP powder, crystals, or "ice" is done by placing the substance in a bowl-shaped piece of metal foil, a molded glass pipe, or a modified light bulb and heating it over the flame of a cigarette lighter or torch. The volatile MAP fumes are inhaled through a straw or pipe.

Street MAP may be mixed with many drugs including cocaine. Eight percent to 20% of street-available stimulants contain both MAP and cocaine.[14] In a report on cocaine intoxication, 7% of patients sought medical help resulting from the concurrent use of cocaine and amphetamines.[15]

Deaths related to amphetamines have been associated with assaults, suicides, homicides, accidents, driving impairment, and maternal-fetal and infant exposures.[1,2,16–19] In a recent study of drug abuse and alcohol consumption related to motor vehicle accidents in Belgium, MAP was the most commonly found drug other than alcohol.[20]

Causes of maternal deaths associated with amphetamine use include intracerebral hemorrhage, cardiovascular collapse, seizures, and amniotic fluid embolism.[3]

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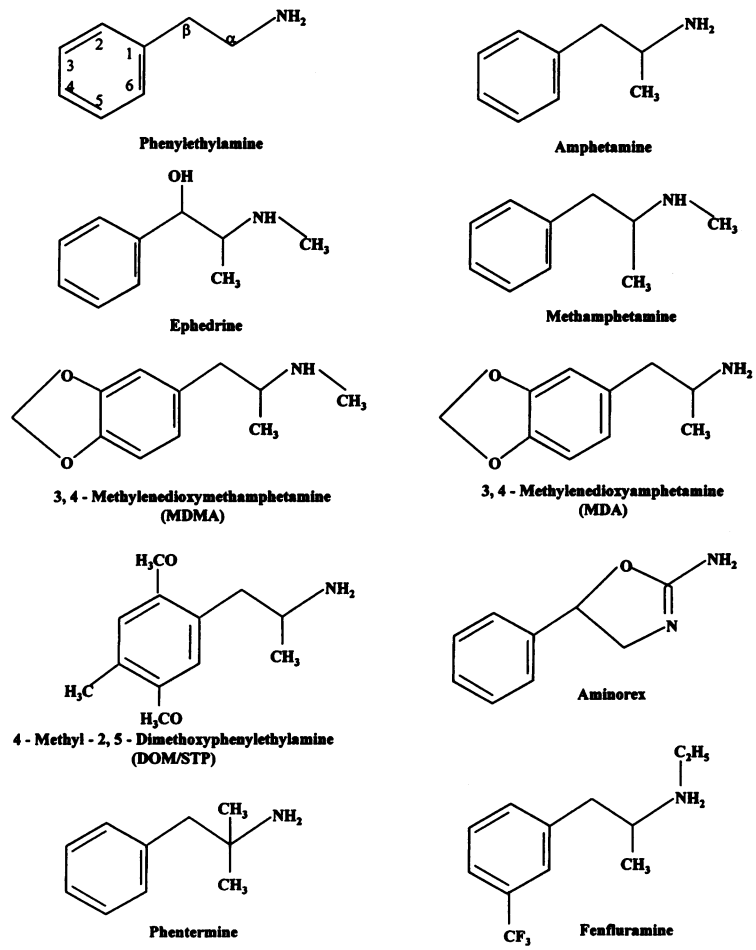


**Figure 1.**—The chemical structures of several amphetamine-like compounds are shown. The basic phenylethylamine structure is labeled. Both α and β side chain positions and the phenyl ring itself can be modified to alter the pharmacologic effects of these related compounds.

Increased risk for fetal and infant death is associated with maternal use of amphetamines.[2]

## Clinical Pharmacology of Amphetamines

Amphetamines cause central nervous system (CNS) stimulation that may induce euphoria, increase alertness, intensify emotions, increase aggression, alter self-esteem, and allegedly increase sexuality.[21] Presynaptic reuptake of catecholamines—including dopamine, norepinephrine, and serotonin—is blocked, causing hyperstimulation at selected postsynaptic neuron receptors.[21–25] Indirectly, these hyperstimulated neurons can stimulate various other noncatecholamine CNS and peripheral pathways. Changes in mood, excitation level, motor movement, and appetite appear to be more directly mediated by central dopaminergic alterations.[22] Serotonin alterations may also contribute to the amphetamine-related mood changes, psychotic behavior, and aggressiveness.[21,22,25]

The half-life of amphetamines in humans ranges from 10 to 30 hours depending on the drug, urine pH, and dosage.[26,27] Methamphetamine hydrochloride has greater CNS effects compared to D-amphetamine, presumably because of prolonged half-life and increased CNS penetration.[28] A portion of MAP is metabolized to form amphetamine. The amphetamines are weak bases with $pK_a$ values ranging from 8.8 to 10.4, and they are easily absorbed through the gut, airway, nasopharynx, muscle, placenta, and vagina.[25,29] Peak plasma levels are seen about 30 minutes after intravenous or intramuscular injection routes and about 2 to 3 hours after oral ingestion. Metabolism of amphetamines usually includes aromatic hydroxylation, aliphatic hydroxylation, and n-dealkylation, which give rise to both inactive and active metabolites such as the potent hallucinogen, p-hydroxyamphetamine [25](Fig. 1).

When MAP is used with ethanol, increased psychological and cardiac effects are seen.[30] Similarly,

TABLE 1.—*Major Signs and Symptoms of Amphetamine Toxicity*

| | |
|---|---|
| *Cardiac* | |
| Chest Pain | +++ |
| Myocardial infarction | + |
| Palpitations | ++ |
| Arrhythmia | ++ |
| Cardiomyopathy | + |
| Myocarditis | + |
| Hypertension | ++ |
| Sudden death | + |
| Valve thickening | +++ |
| *Neurologic* | |
| Headache | + |
| Seizure | ++ |
| Cerebral infarcts/stroke | ++ |
| Cerebral vasculitis | ++ |
| Cerebral edema | + |
| Mydriasis | ++ |
| Cerebral hemorrhage | ++ |
| Subarachnoid | ++ |
| Intraventricular | +++ |
| Intracerebral | ++ |
| *Psychiatric* | |
| Anxiety | +++ |
| Depression | ++ |
| Paranoia | ++ |
| Delirium/hallucination | +++ |
| Psychosis | +++ |
| Suicide | ++ |
| Aggressive behavior | ++ |
| Euphoria/hyperactivity | ++ |
| Irritability | ++ |
| *Respiratory* | |
| Pulmonary edema | + |
| Dyspnea | ++ |
| Bronchitis | + |
| Pulmonary hypertension | +++ |
| Hemoptysis | + |
| Pleuritic chest pain | ++ |
| Asthma exacerbation | + |
| Pulmonary granuloma | + |
| *Other* | |
| Ulcers | ++ |
| Hyperpyrexia | ++ |
| Renal failure | + |
| Ischemic colitis | + |
| Obstetric complications | ++ |
| Anorexia/weight loss | +++ |
| Rhabdomyolysis | ++ |
| Nausea/vomiting | + |
| Disseminated vasculitis | + |

Estimated frequency of events: +, reported rare cases; ++, commonly reported; +++, frequently seen or reported with chronic use or overdose.

simultaneous use of opioids and amphetamines, so-called "speedballing," increases toxicity.[29]

Because of the variability in quality and concentration of illicitly purchased MAP, the clinical observation of toxic effects is usually more relevant than an estimate of total ingested dose. Fatalities have been reported after ingestions as low as 105 mg per kg of MAP.[31] Blood levels of amphetamine in fatal cases have ranged from 0.5–41 mg/liter with an average of 8.6 mg/liter in a summary of 11 cases.[29] In addition, tachyphylaxis occurs with acute MAP use. Long-term users of amphetamine appear to tolerate higher doses (eg, averaging up to or greater than 1000 mg/d) with fewer symptoms.[28]

## Clinical Toxicity

The acute and chronic toxic manifestations of MAP mimic those of all amphetamine-related compounds. Table 1 outlines the major signs and symptoms of MAP toxicity.

### *Cardiovascular System*

Cardiovascular symptoms, including chest pain, palpitations, and dyspnea, are common.[32–34] The concern that thrombus formation may play a role in MAP-related myocardial infarctions has generated at least one case report of the use of a thorombolytic agent in addition to the use of nitrates and analgesics in treating these patients.[34] Significant hypotension with bradycardia and a metabolic acidosis has been seen in massive amphetamine overdoses.

Acute and chronic cardiomyopathy from MAP abuse is thought to be secondary to both direct amphetamine cardiac toxicity and indirect amphetamine-induced hypertension, necrosis, and ischemia.[35–38] Most reports of cardiomyopathy have been with oral and intravenous amphetamines, but cardiomyopathy has also been seen after smoking MAP.[39] Necrotizing angiitis with arterial aneurysms and sacculations has been seen in the kidney, liver, pancreas, and small bowel in MAP drug abusers.[40] Similarly, acute aortic dissections and arterial aneurysms have been associated with MAP abuse.[41]

### *Central Nervous System*

In toxic doses, MAP induces unpleasant CNS symptoms such as agitation, anxiety, hallucinations, delirium, psychosis, seizures, and death.[31,42–44] Many patients who have used MAP present unconscious to an emergency department. In some of these persons, lack of responsiveness may be due in part to the use of other drugs such as opioids. Other patients may be unresponsive because of the direct effects of intravenous MAP use or the secondary effects of amphetamine induced seizures.[45] Other CNS disorders induced by amphetamines include cerebrovascular accidents due to hemorrhage or vasospasm, cerebral edema, and cerebral vasculitis.[46,47]

The initial feeling of physically and mentally enhanced powers following MAP use can quickly deteriorate with high doses or chronic use, resulting in

emotional lability, confusion, paranoia, and hallucinations.[48] In addition to the acute paranoid delusional psychosis associated with high-dose amphetamine use, a lasting psychosis similar to schizophrenia may be simply a persistent drug-induced psychosis or may represent the emergence of an underlying psychiatric disorder.[49]

Acute and chronic amphetamine exposures have also been associated with choreoathetoid movement disorders independent of Huntington's disease.[50,51] Amphetamine-induced seizures have been seen as isolated events or associated with hyperthermia, coma, muscle hyperactivity, metabolic acidosis, secondary rhabdomyolysis, renal failure, or shock.[6,45,52–54] Cerebral hemorrhage with arteriovenous malformations and with amphetamine-induced cerebral vasculitis has been reported in patients using amphetamines.[44,47,55–57] Cerebral artery spasm and occlusion leading to ischemic strokes and transient cortical blindness have been noted after MAP use.[58,59]

*Infectious Diseases*

Infectious disease is a risk associated with intravenous MAP use. An association has been seen between MAP use and the risk of endocarditis, viral hepatitis, and human immunodeficiency virus (HIV) disease.[11,60–62] High-risk sexual activity, including survival sex and homosexual/bisexual lifestyles, is associated with MAP use in adults and "street" youths.[11,62] In related findings, both increases and decreases in sexual desire and activity have been reported with amphetamine use, although increases are more common than decreases.[63]

*Respiratory System*

Like cocaine abusers, many amphetamine abuse patients present to emergency departments with respiratory symptoms.[6,64] Although the exact incidence and prevalence of amphetamine-induced pulmonary symptoms have not been reported, the variability of symptoms appears to depend on the amphetamine compound used, the dosage, and the route. Acute noncardiogenic pulmonary edema has been related to MAP use.

Pulmonary hypertension has long been reported in amphetamine users. In the late 1960s, users of intravenous, nasal inhalant, or oral street amphetamines were reported to have pulmonary artery muscular hypertrophy with foreign body granulomas consistent with significant pulmonary hypertension.[65–67] Contaminants have also been suggested as the cause of pulmonary hypertension associated with inhalation of MAP, although a direct role of MAP inhalation has not been eliminated.[68]

*Systemic and Dermatologic Toxicity*

Reports of amphetamines and amphetamine-related agents producing severe systemic toxicity are common. Presentation of systemic toxicity varies but may include pulmonary and cardiovascular manifestations in addition to fulminant hyperthermia, convulsions, rhabdomyolysis, acute renal failure, hepatocellular damage, disseminated intravascular coagulation, and refractory hypotension.[54,69] Renal failure associated with amphetamines has been related to hyperexia, rhabdomyolysis, and cardiovascular shock leading to acute tubular necrosis and necrotizing angiitis.[69–74] The renal necrotizing angiitis noted in some cases of renal failure has been seen in the presence of hepatitis B serum antigen, usually in intravenous abusers of amphetamines.[74] Amphetamine-induced acute interstitial nephritis was thought to be the cause of renal failure in one case report.[74]

Hepatocellular damage has been reported after both acute and chronic amphetamine abuse.[52,75,76] Direct toxic effects, hypotension, hepatotoxic contaminants, hepatic vasoconstriction, lipid peroxidation, occult viral causes, and necrotizing angiitis have been postulated as mechanisms for the amphetamine-induced hepatocellular toxicity.[76] Abuse of MAP has also been associated with the formation of giant gastrointestinal ulcers and ischemic colitis.[76,77] Of note, the presenting complaint of abdominal pain was seen in 4% of amphetamine toxic patients in one emergency department series.[6]

Although not formally studied, the most common dermatological manifestations in patients abusing amphetamine-related compounds are probably induced by trauma (including self-inflicted), intravenous needles, or burns.[79] A case of lichenoid drug eruption has been reported with the use of MAP.[80]

## Treatment Approaches to Amphetamine Toxicity

Most cases of MAP toxicity can be managed supportively. Like all severe overdoses, MAP overdose requires immediate supportive care including airway control, oxygenation and ventilation support, and appropriate monitoring. In one study, as few as 10% of the patients presenting to emergency departments with amphetamine-related complaints required admission, and those who were admitted to the hospital were generally discharged within two days.[6] In severe overdoses, termination of amphetamine-induced seizure activity and arrhythmia is of immediate importance. Correction of hypertension, hypotension, hyperthermia, and metabolic and electrolyte abnormalities along with control of severe psychiatric agitation are indicated. Health maintenance activities, such as testing for hepatitis and HIV disease, should be considered.

Despite the ability of MAP to cause significant CNS and psychiatric activation, relatively few patients who present to emergency departments for acute intoxication require pharmacologic intervention.[6] In many emergency departments, patients can be treated for mild agitation with decreased stimuli alone unless they are thought to be a harm to themselves. The more severely hyperactive or agitated persons can be treated with an antipsychotic drug or a benzodiazepine.

Antipsychotic drugs that may specifically antagonize the central behavioral effects of MAP are haloperidol

and droperidol. Several clinical reports describe the efficacy of droperidol and haloperidol in acute amphetamine toxicity.[6,81] In a recent study of 146 patients presenting to the emergency department in an agitated, violent, or psychotic state from MAP, droperidol produced more rapid and profound sedation than lorazepam.[82] Haloperidol may quickly improve symptoms of patients with acute choreoathetoid syndrome associated with amphetamines. Benzodiazepines, such as diazepam (Valium), are used to terminate amphetamine-induced seizures.[82]

If sedation fails, several antihypertensive agents including β-blockers are effective in reversing MAP-induced cardiovascular symptoms. Earlier recommendations to acidify the urine to increase clearance were based on a single case report and are not recommended based on the risk for systemic acidification and exacerbation of potential rhabdomyolysis.[83] Rhabdomyolysis should be suspected and ruled out by drawing initial creatinine phosphokinase levels in any patient who presents to the emergency department in a severe, agitated state from amphetamines. Patients with rhabdomyolysis should be aggressively treated with fluids and admitted to the hospital. Renal function and vital signs, as well as fluid intake and output, should be monitored closely. Early and aggressive treatment of potential rhabdomyolysis is felt to improve the clinical outcome and decrease potential nephrotoxicity. Although we have focused on acute care, significant social and psychiatric intervention is needed to reduce the chance of long-term dependence on amphetamines.

## Summary

Methamphetamine hydrochloride is an amphetamine with a high potential for abuse. Like other amphetamines, MAP can induce symptoms similar to euphoria. As a drug of abuse, MAP vies with cocaine in its appeal for long-term or recreational users wanting a rapid high through inhalation. The half-life of MAP may produce exceptionally long-lasting toxic effects. The possibility of amphetamine use or abuse should be considered in any patient presenting with psychosis, violence, seizures, rhabdomyolysis, trauma, or cardiovascular abnormalities.

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