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EDITORIAL COMMENT

# Crystal Methamphetamine

## A Drug and Cardiovascular Epidemic*

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The past year has focused public attention on the opioid epidemic in the United States, with its mounting death toll, many from fentanyl overdose (1). Unfortunately, other substances of abuse also continue to exact a significant toll. Among these is methamphetamine, usually consumed in the United States as crystal methamphetamine. In the 2014 National Survey on Drug Abuse and Health, 4.9% of Americans aged 12 and older reported having used methamphetamine in their lifetimes, with 1.2 million reporting use in the preceding year (2). Worldwide, upwards of 33 million people are methamphetamine abusers according to the United Nations Office on Drugs and Crime (3). Certain groups, such as gay men, as well as certain geographies such as the Western and Midwest United States, Australia, New Zealand, Southeast and East Asia, as well as the Czech and Slovak Republics, are disproportionately affected.

First synthesized in 1893 by the Japanese chemist Nagai Nagayoshi (4), methamphetamine is a more potent version of amphetamine, first synthesized in Germany in 1887. During World War II, the Axis and Allied forces used methamphetamine and amphetamine to extend wakefulness, and in the postwar period both agents were used as diet pills, before their destructive and addictive nature were fully understood.

Methamphetamine is available in various forms including liquid, powder, and as a crystalline substance (first synthesized in Japan by Akira Ogata in 1919) (4), which can be smoked. Both when injected intravenously as well as when smoked, high levels of the drug are rapidly achieved in the circulation. The main effects are neurocognitive—both a euphoric and energized state as well as psychosis, depression, and other neuropsychiatric and cognitive sequelae. Methamphetamine abusers typically go on "meth binges" lasting hours to days.

Most of the research regarding methamphetamine pharmacology has centered on its central nervous system effects (4). Methamphetamine increases brain monoamine levels (predominantly dopamine) via several mechanisms, including reducing monoamine reuptake into the presynaptic terminals, reducing the breakdown of monoamines by inhibiting monoamine oxidase, and increasing the release of monoamines into the synapses (4). The euphoric effects of methamphetamine are believed to be the result of increases in dopamine levels in the brain's mesolimbocortical pathway.

The mechanism of methamphetamine's cardiovascular effects remains incompletely understood and may vary by route of administration. Acute and chronic effects may likewise involve different mechanisms. The most obvious pathway affecting cardiovascular function involves the release of catecholaminergic neurotransmitters in the peripheral nervous system, analogous to the better documented central nervous system effects. The resultant vasoconstriction, hypertension, and tachycardia may explain increased coronary risk and cardiomyopathy.

Methamphetamine is vaporized at temperatures of approximately 200°C; this is usually achieved by heating methamphetamine crystals on aluminum foil or in a glass pipe over an open flame and then inhaling the vapors. Several pyrolysis products have been identified, partially depending on the temperature used, including transphenylpropene (5), which is

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converted in the liver to transphenylpropylene oxide, which is toxic to glial cells and is also thought to lead to glutathione depletion and thus to mitochondrial injury (6). Because this toxic byproduct is not produced when methamphetamine is used either intranasally or intravenously, this byproduct may explain potential differences in the cardiac toxicity between the different routes of abuse.

Methamphetamine is also directly toxic to cells. This phenomenon has been most extensively studied in neural cells, where methamphetamine leads to a series of reactions resulting in the accumulation of reactive oxygen species and glutamate release eventually leading to cell death. High doses of methamphetamine injected intraperitoneally into rats can also produce cardiomyopathies with a disarray of cardiomyocytes, intracellular and extracellular edema and intramyocytic vacuoles, abnormally shaped nuclei and mitochondria, dilated T-tubules, myocyte degeneration and necrosis, contraction bands, degeneration of the cardiac mitochondria, and loss of myofilament (7).

In contrast, injecting methamphetamine exposes the pulmonary arterial circulation to a direct effect of methamphetamine as well as accompanying injected chemicals and particles, but not to the byproducts produced by smoking methamphetamine.

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In this issue of *JACC: Heart Failure*, Zhao et al. (8) extend our understanding of the cardiovascular complications of methamphetamine. Using a retrospective chart review of patients with positive urine toxicology for methamphetamine and/or known methamphetamine abuse (MA) seen at Santa Clara Valley Hospital in San Jose, California, the authors identified 2 cohorts with cardiovascular pathology—those with pulmonary arterial hypertension (PAH) and those with persistent cardiomyopathy (CM), and compared them with MA patients without overt cardiac pathology. Altogether they identified 364 patients with MA-induced CM (MA-CM) and 60 with MA-induced PAH (MA-PAH), thereby constituting one of the largest case series on these patients. After excluding patients with improved ejection fraction on follow-up as well as those with other causes for PAH (such as cirrhosis or human immunodeficiency virus) the 2 groups included 296 and 50 patients, respectively, who were then compared with 356 control MA patients without cardiovascular disease and followed for a mean of 20 months. The authors' main findings were: 1) both MA-CM and MA-PAH were associated with significantly increased mortality, above and beyond the increased mortality seen in MA; and 2) male sex, alcoholism, and hypertension were associated with MA-CM, whereas female sex was associated with PAH.

The exact incidence of cardiovascular disease among the MA population remains unknown. In the present study, approximately one-half of the patients with MA (n = 4,622) were excluded for lack of an echocardiogram. An additional 75% of those with echocardiograms were excluded due to the presence of coronary disease, valvular disease, mild left ventricular dysfunction, or other comorbidities that were not defined. Moreover, for the MA-CM, cohort the authors further excluded patients whose left ventricular function showed improvement on follow-up and for the MA-PAH cohort subjects with human immunodeficiency virus and hepatitis C cirrhosis as well as pulmonary embolism and interstitial lung disease. The findings in this study, therefore, apply to a select group of methamphetamine abusers. The mode of abuse, particularly smoking versus intravenous use, and its influence on disease presentation was not routinely documented in the medical record and no stratification by route of administration is presented by the authors in the manuscript.

The study by Zhao et al. (8) addressed the issue of heart disease among methamphetamine abusers. The complementary epidemiological issue of the incidence of methamphetamine among heart failure patients was recently addressed by a group from the San Diego Veteran's Administration Medical Center. (9) Among 9,588 veterans with heart failure treated at the San Diego Veteran's Administration Medical Center over a 10-year period, methamphetamine was responsible for 5% of the cases, with the incidence increasing from 1.7% in 2005 to 8% in 2015. Similar data were recently reported in an emergency department study that documented high rates of elevated B-type natriuretic peptide among MA patients (10).

Zhao et al. (8) have focused much-needed attention on the importance of MA in cardiovascular disease. Unfortunately, there are currently no approved pharmacologic therapies for MA and relapse rates after cognitive therapy as high as 88% have been documented. Many important questions for future research remain, including:

1. What is the mechanism underlying the cardiovascular complications of MA?
2. What are the best therapies for methamphetamine-induced PAH and CM?
3. Is there a genetic predisposition to cardiovascular complications of MA?
4. What is the role of concomitant human immunodeficiency virus, hepatitis B and C infection, and other drugs in the cardiovascular complications?

5. Can high-risk patients for cardiovascular complications be identified?
6. Why do some cardiomyopathies rapidly resolve whereas others persist?

The opioid epidemic has contributed to a documented decline in life expectancy in the United States in 2016 (11). Although less immediate in its effect on mortality, the cardiovascular effects of methamphetamine may have an appreciable effect on the life expectancy and quality of life of abusers of the drug. MA research and treatment should be a priority, not just of addiction medicine, but of cardiovascular medicine as well.

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