

## General

# Methamphetamine Use: A Narrative Review of Adverse Effects and Related Toxicities

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Methamphetamine has been labeled “America’s most dangerous drug” and has received significant public health attention. Stimulant addiction and tolerance are heavily documented in the literature; increasingly larger doses maintain euphoria in short time periods to withstand stimulant tolerance. Stimulant deaths are high in the United States and abroad. Between 2013 and 2019, deaths related to methamphetamine use quadrupled from 3,616 to 16,127. Methamphetamine use increased four-fold from 2015 to 2016. Due to this increase in methamphetamine use and its associated medical complications, the mortality rate associated with methamphetamine use has doubled over the past ten years. Cardiopulmonary symptoms include chest pain, palpitations, and shortness of breath. Methamphetamine-related myocardial infarction can also occur. Central nervous system symptoms include agitation, anxiety, delusions, hallucinations, and seizures. Methamphetamine-induced psychosis may unmask underlying psychiatric disorders. It can also cause cerebral vasculitis, which elicits cortical blindness and ischemic strokes. Methamphetamine-induced neurotoxicity in serotonergic systems is more diffuse, involving the striatum, hippocampus, septum, amygdala, and hypothalamus leading to mood changes, psychosis, and memory impairment. This narrative review will aim to highlight the adverse effects as well as the toxicity that can occur with methamphetamine use.

## INTRODUCTION

Methamphetamine has been labeled as “America’s most dangerous drug” and has received significant public health attention. The substance was first synthesized at the University of Berlin in 1887, and soldiers utilized the drug during World War II for stimulation and appetite suppression.<sup>1</sup> Methamphetamine received campaign recognition and inclusion in the Comprehensive Drug Abuse Prevention and Control Act of 1970. Stimulant addiction and tolerance are

heavily documented in the literature; increasingly larger doses maintain euphoria in short time periods to withstand stimulant tolerance.<sup>1</sup> Between 2013 and 2019, deaths related to methamphetamine use quadrupled from 3,616 to 16,127.<sup>2</sup> The deaths commonly had opioid involvement, as synthetic opioids are mixed with methamphetamine to deliver a balanced euphoria.<sup>2</sup> Methamphetamine deaths are highest in the Western United States compared to the Eastern United States and affect all age groups, with shifting paradigms of younger populations being affected.<sup>3</sup> Ready

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availability and low cost coupled with immediate onset of action are drivers of methamphetamine's popularity.

Methamphetamine induces multiple symptoms and side effects. Cardiopulmonary symptoms including chest pain, palpitations, and shortness of breath are common, and methamphetamine-related myocardial infarction may correlate with thrombus formation by direct and indirect mechanisms.<sup>4</sup> Cardiomyopathy has also been reported with methamphetamine use. Central nervous system (CNS) symptoms include agitation, anxiety, delusions, hallucinations, and seizures.<sup>4</sup> Methamphetamine-induced psychosis may unmask underlying psychiatric disorders.<sup>4</sup> It can also cause cerebral vasculitis, which elicits cortical blindness and ischemic strokes. Endocarditis, HIV, and viral hepatitis are associated with methamphetamine use primarily through the intravenous use of the drug, and pulmonary hypertension has been reported in methamphetamine use.<sup>4</sup> Systemic complications include hyperthermia, rhabdomyolysis, and acute liver and/or renal failure.<sup>4</sup>

Approximately 24 million people use methamphetamine worldwide. However, less than one-third of methamphetamine users receive treatment, and rural areas are disproportionately affected by methamphetamine use.<sup>5</sup> There is little known regarding the medical treatment of methamphetamine addiction at this time. Using intravenous amphetamines causes high rates of infectious disease in rural communities.<sup>5</sup> This narrative review will aim to highlight the adverse effects as well as the toxicity that can occur with methamphetamine use.

## EPIDEMIOLOGY

Stimulants, including methamphetamine, cocaine, ecstasy, and prescription stimulants, are the second most used substances in the United States.<sup>6</sup> Stimulant use disorder (SUD) is prevalent in the United States, Australia, South-East, and South-West Asia, with more than 35 million people worldwide using methamphetamine.<sup>7</sup> Methamphetamine use increased fourfold from 2015 to 2016.<sup>8</sup> Due to this increase in methamphetamine use and its associated medical complications, the mortality rate associated with methamphetamine use has doubled over the past ten years.<sup>8</sup>

People who use methamphetamine include individuals of all genders, adolescents of high school age, young professionals, and older adults.<sup>7</sup> Women who use methamphetamine have an observed death rate 26 times that of women who do not use methamphetamine.<sup>6</sup> Studies have found that younger users are more likely to take methamphetamine for recreational purposes and performance enhancement, while older individuals use methamphetamine to gain relief from stressful life events.<sup>8,9</sup>

## NEUROPHYSIOLOGY OF METHAMPHETAMINE USE

Crystal methamphetamine is the most commonly used form, and it is predominantly either smoked or injected.<sup>7</sup> When methamphetamine users ingest, inhale, or inject the drug, it enters the bloodstream, rapidly crosses the blood-brain barrier, and penetrates the brain due to its lipophilic nature.<sup>7,10-12</sup> The half-life of methamphetamine depends

on how it is absorbed but usually ranges from five to thirty hours.<sup>7</sup>

Methamphetamine causes this excess release by emptying synaptic vesicles within the cytosol, blocking the transport of endogenous neurotransmitters, inhibiting synaptic reuptake, and decreasing the expression of transporters at the cell surface.<sup>7,10,12</sup> When dopaminergic neurons take up methamphetamine, it inhibits the type 2 vesicular monoamine transporter (VMAT2), an intracellular transporter on the surface of synaptic vesicles responsible for taking up dopamine.<sup>10,11</sup> Similar to the inhibition of VMAT2, methamphetamine also reverses the transmembrane dopamine transporter (DAT).<sup>10,11</sup> Amphetamines promote phosphorylation of the N-terminal of DAT and VMAT2 by protein kinase C or calcium-calmodulin dependent kinase, which leads to their inhibition.<sup>11</sup> Methamphetamine also activates presynaptic scaffolding proteins via protein kinase C, increasing the internalization of DAT.<sup>11</sup>

The inhibition of VMAT2 and DAT transporters leads to a surplus of dopamine released directly into the mesolimbic, neocortical, and nigrostriatal pathways.<sup>6-8</sup> This excess dopamine release activates the brain's reward system and creates a sense of euphoria, enhanced mental acuity, positive mood, and social and sexual disinhibition, leading to substance addiction.<sup>10,11</sup> This supraphysiologic dopamine release leads to neuronal changes in the reward system that lead to tolerance and drug-seeking behavior.

## ADVERSE EFFECTS OF METHAMPHETAMINE

Women with SUD have high rates of pregnancy complications due to the socioeconomic uses associated with methamphetamine use and the adverse effects of the use itself. The two highest complications of methamphetamine use in pregnancy were placental abruption, high rates of operative deliveries, and preterm birth.<sup>13</sup> The use of concomitant substances leads to increased mortality.<sup>13</sup> Gorman et al. reported high rates of hypertensive disorders of pregnancy, and intrauterine fetal demise and neonatal demise were elevated.<sup>14</sup> Methamphetamine is a strong vasoconstrictor.<sup>15</sup> This vasoconstriction is a probable explanation for the high rates of hypertensive disorders. Vasoconstriction can also be an explanation for the increased rates of fetal demise.

Psychiatric manifestations are also common in methamphetamine use. Psychiatric symptoms may include agitation, anxiety, delusions, and psychosis.<sup>16</sup> Additionally, methamphetamine use correlates with higher underlying psychiatric disorders and health services use.<sup>17</sup> There are also multiple functional, molecular, and structural neuroimaging changes in those who use methamphetamine. The majority of these changes are located in cortical and striatal pathways.<sup>17</sup> These pathways contribute to cognitive and behavioral changes promoting compulsive drug use. Methamphetamine use also correlates with smaller cortical gray matter volume than larger striatal gray matter volume.<sup>18</sup> Deficits in gray matter volume are seen in several areas, including the anterior cingulate cortex, dorsolateral

prefrontal cortex, orbitofrontal cortex, superior temporal cortex, and hippocampus.<sup>13</sup> Cortical gray matter deficiencies may eventually reverse after cessation of methamphetamine use.<sup>19</sup>

Further, white matter volume abnormalities are also linked to methamphetamine use.<sup>20</sup> Those who use methamphetamine have lower amounts of diffusion across several brain areas, including prefrontal white matter, corpus callosum, superior corona radiata, and the perforant path.<sup>21</sup> Hypertrophy from methamphetamine use followed by abstinence may lead to altered gliosis and myelination.<sup>21</sup>

Effects on memory and cognition are another common adverse effect. Many students, both college and medical, may believe that the use of prescription stimulants may improve their academic performance. However, in a recent narrative review, it was highlighted that the actual effect on academic performance wasn't an improvement in academic performance at all, as evidenced by grade point averages, and there is a possible decrease in executive function in students who misuse stimulant medications than those without misuse.<sup>22</sup> The misuse of stimulant medications may not seem like an issue when we view it as a medication. However, it is important to note that the illicit methamphetamine used illicitly is a metabolite of amphetamine, found in stimulant medications such as Adderall.<sup>22</sup> When methamphetamine is used illicitly, larger amounts are used. However, the long-term effects of the misuse of the smaller medication doses of amphetamine are not well known at the time.

Long-term methamphetamine use in animal models demonstrated cardiac myocyte atrophy and necrosis, and the effects were partially reversible with abstinence.<sup>23</sup> Methamphetamine leads to hypertension due to potent vasoconstriction and hypertensive cardiomyopathy.<sup>24</sup> Case series have demonstrated associated left ventricular dysfunction and ejection fraction reduction with chronic use.<sup>25</sup> Methamphetamine use may prolong the QTc interval leading to various arrhythmias.<sup>26</sup> Myocardial infarction and methamphetamine use are correlated with spasms of coronary vessels and coronary stenosis.<sup>25</sup> Most strokes in amphetamine users are hemorrhagic, and the increase in hemorrhagic strokes as compared to the general population may be linked to arterial hypertension provoked by methamphetamine.<sup>25</sup> Rhabdomyolysis is also correlated with methamphetamine use.<sup>26</sup> Symptoms associated with rhabdomyolysis include elevated troponin, blood urea nitrogen, creatinine concentration, and male gender.<sup>26</sup> Rhabdomyolysis should be considered in patients with histories concerning methamphetamine use.<sup>26</sup> The complications of rhabdomyolysis can be liver damage and renal failure.

## METHAMPHETAMINE TOXICITY

### MECHANISMS OF METHAMPHETAMINE NEUROTOXICITY

Methamphetamine misuse can cause various neurological complications resulting in significant morbidity and mortality.<sup>7</sup> Methamphetamine can significantly alter microglial neuroimmune function, elicit neuroinflammation, and cause dopaminergic neurotoxicity.<sup>7,8,12,27</sup> Methampheta-

mine-induced neurotoxicity depends on multiple mechanisms, including increased dopamine conversion into reactive oxygen species (ROS), ubiquitin-proteasome system dysfunction, increased p53 expression which increases inflammatory cytokines leading to altering DNA repair, and disrupting the blood-brain barrier.<sup>8,11,12</sup>

The conversion of the excess dopamine into ROS is one of the leading theories behind methamphetamine-induced neurotoxicity.<sup>10</sup> Methamphetamine is associated with increased astrocytosis and microglial activation, producing ROS.<sup>7,28</sup> Uncontrollable ROS within the neuron damages its integrity.<sup>10</sup> This phenomenon occurs because positively charged methamphetamine alters the mitochondria by disrupting the transmembrane potential and pH gradient.<sup>11,29</sup> This inhibits the electron transport chain shifting the brain from an oxidative state into a glycolytic metabolic state.<sup>8</sup> This leaves the brain with less efficient energy, an acidic microenvironment, and altered cell signaling similar to the brain state involved in neurodegenerative CNS diseases.<sup>8</sup>

Further contributing to neurotoxicity, methamphetamine upregulates pro-apoptotic proteins such as Bax, Bad, and Bid and downregulates anti-apoptotic proteins such as Bcl-2 and Bcl-X. This leads to the release of cytochrome C from the mitochondria and subsequent neuronal death.<sup>11</sup> Methamphetamine also increased the expression of p53, a tumor suppressor gene.<sup>11</sup> P53 can increase the transcription of pro-apoptotic factors or enter the mitochondria and facilitate apoptosis by releasing cytochrome C.<sup>11</sup> Furthermore, methamphetamine use contributes to neuroinflammation by inducing microglial activation via increased expression of pro-inflammatory cytokines such as TNF $\alpha$ , interleukin-1B, and interleukin-6.<sup>11</sup>

The neurotoxicity of methamphetamine use may be directly related to some of the symptoms and behavior patterns exhibited by those who chronically use it. Through neuroimaging post-mortem brains, methamphetamine use is associated with widespread gray and white matter alterations in the frontostriatal system, the left temporal gyrus, and the right inferior parietal lobe.<sup>8</sup> With these alterations, the damaged orbitofrontal cortex-dorsomedial striata may be telling the methamphetamine user to "go," yet the damaged dorsolateral frontal striatal cannot balance that stimulus with "stop".<sup>8</sup> This imbalance can affect decision-making and inhibitory processing during the recovery stage.<sup>8</sup> Methamphetamine-induced neurotoxicity in serotonergic systems is more diffuse, involving the striatum, hippocampus, septum, amygdala, and hypothalamus leading to mood changes, psychosis, and memory impairment.<sup>8</sup>

### MEDICAL COMPLICATIONS OF METHAMPHETAMINE USE

With the enhanced release of catecholamines like norepinephrine and dopamine from the synaptic cleft, methamphetamine use causes an increase in blood pressure, increasing the risk of stroke and ocular abnormalities.<sup>7,28</sup> Hemorrhagic strokes are the most common methamphetamine-related strokes.<sup>7,8</sup> Methamphetamine is also associated with vasoconstriction, pulmonary hypertension, atherosclerotic plaque formation, cardiac arrhythmias, myocardial infarction, and cardiomyopathy.<sup>6,8</sup> Metham-

phetamines and cocaine can affect the expression and activation of multiple ion channels, resulting in arrhythmias.<sup>30</sup> Preexisting conditions surrounding heart rhythms can decrease the threshold for such drug-induced arrhythmias.<sup>30</sup> Methamphetamine toxicity can easily lead to death due to circulatory collapse, breathing difficulty, and hyperthermia.<sup>8,31</sup> A recent retrospective chart review looked at the onset of cardiovascular disease in those who chronically used methamphetamine. This study illustrated that the age of onset of cardiovascular disorder in the study population was eight years earlier in those who used methamphetamine compared to the age of cardiovascular disease in the control population.<sup>32</sup> The authors also found a 12-fold increase in premature cardiovascular in the population with methamphetamine use.<sup>32</sup> Premature age of onset was defined as being <30 years old. Hypertension was the most common cardiovascular disease found in the study population.<sup>32</sup>

Chronic methamphetamine misuse has been associated with decreased levels of dopamine within the striatum, which is particularly more pronounced in the caudate nucleus compared to the putamen.<sup>11,12</sup> Prolonged methamphetamine use leads to intracellular inclusions in the nucleus and cytoplasm of striatal and substantia nigra neurons.<sup>12</sup> The dopaminergic damage in the striatum caused by chronic methamphetamine use is similar to the dopaminergic damage caused by Parkinson's disease leading to an increased risk of Parkinson's disease in methamphetamine users.<sup>11</sup> Due to the location of the damage in the caudate nucleus compared to the putamen, SUD with a methamphetamine subtype has more cognitive psychomotor sequelae than gross motor impairment.<sup>11</sup>

## STUDIES IN THE LITERATURE

The toxicity and effects of methamphetamine have been widely studied, and multiple studies have been published looking at both the short- and long-term effects of methamphetamine. The kidney is one of the organs most commonly affected by methamphetamine use, and its effects are well documented. Isoardi et al. in 2020 performed a prospective observational series looking at patients with self-reported recent methamphetamine use or who had both a positive urine drug screen for methamphetamine and elevated creatinine. These patients then had urinary neutrophil gelatinase-associated lipocalin (NGAL), repeat serum creatinine, creatine kinase, and cystatin c concentrations measured to assess if the patient had developed an acute kidney injury (AKI). Of 595 patients presenting to the emergency department, 73 had elevated creatinine with a median concentration of 125  $\mu\text{mol/L}$ , with 90% of the cases meeting diagnostic criteria for AKI. It was also noted that concurrent rhabdomyolysis was seen in 44% of cases with a median creatine kinase level of 2695, and NGAL levels were elevated in 10% of cases. None of the patients in this study required dialysis as a result of their AKI, and a majority of the patients had resolution of their AKI with crystalloid therapy and were discharged within 19 hours of admission.<sup>33</sup>

In 2021 Maheshwari and Athiraman published a case study involving a 27-year-old male who presented after ingesting four "M30" pills he had purchased from the internet. This patient's urine drug screen was positive for methamphetamine, cannabinoid, fentanyl, and ethanol. He presented with acute confusion, hypotension, tachycardia, hyperthermia, and hypoxia. He was also found to have severely elevated transaminases, white blood cell count, cardiac enzymes, and CK levels. Due to this patient's acute condition, he was admitted for observation and monitoring. He developed acute tubular necrosis (ATN) due to elevated CK levels and rhabdomyolysis and eventually required hemodialysis while in the hospital. At discharge, the patient required dialysis three times a week for fulminant kidney failure and was awaiting a kidney transplant due to irreversible kidney damage.<sup>34</sup> Long-term methamphetamine use is likely linked with chronic kidney disease. However, more studies are required to assess the degree to which they are linked.<sup>33,34</sup>

Methamphetamine overdose commonly causes renal dysfunction and can cause multisystem organ failure and lead to death when taken in high enough doses. Pillai et al. wrote a case report in 2019 of a 27-year-old male who reportedly ingested approximately 1.5 grams of methamphetamine. On arrival at the ED, he was noted to have a Glasgow coma scale (GCS) score of 3T and was noted to have a heart rate of 200/min showing sinus tachycardia on cardiac monitoring, respirations at 40/min, and was hypotensive with systolic blood pressure in the 60s. His muscles were found to be rigid, and he had a core body temperature of 42.2 °C (108 °F). Initial laboratory assessment of the patient showed respiratory acidosis, hyperkalemia, AKI, and elevated CK levels. The patient's urine drug screen was positive only for methamphetamine. Aggressive measures were taken to correct the patient's acidosis, hypotension, and hyperthermia through an infusion of sodium bicarbonate, fluid resuscitation, and active cooling. The patient was transferred to the intensive care unit (ICU) after an improvement of core temp to 37 °C, and repeat arterial blood gas (ABG) showed increased blood pH. Four hours after transfer to the ICU, the patient began to cough up blood through his endotracheal (ET) tube, at which time labs drawn showed decreased platelet count, elevated prothrombin time, elevated international normalized ratio (INR), decreased fibrinogen, and elevated fibrin split products consistent with disseminated intravascular coagulation (DIC). After many hours of aggressive critical care through transfusion of several units of fresh frozen plasma and leukocyte-reduced red blood cells, the patient went into cardiac arrest with asystole and could not be resuscitated.<sup>35</sup> It is theorized that the prevention of rhabdomyolysis and AKI with aggressive fluid resuscitation and early detection of DIC in patients with methamphetamine overdose can improve outcomes.<sup>33-35</sup>

The cardiovascular system effects of methamphetamine have been studied. Darke et al. conducted a study analyzing 894 autopsy reports of methamphetamine-related deaths looking at the effects of long-term methamphetamine use on the cardiovascular system. The mean age of patients was

37.9 years, with 78.5% being males. They found that a quarter of patients had enlarged hearts, and 18.9% of cases were diagnosed with left ventricular hypertrophy. It was also noted that 19.0% of cases had severe coronary artery disease at the time of death. The left coronary artery was the most commonly stenosed vessel, which was seen in 16.6% of cases. Signs of previous ischemic events evident by replacement fibrosis of the myocardium were seen in 19.8% of cases, and the criteria for diagnosis of cardiomyopathy was met in 5.5% of cases. A significant number of cases (32.7%) showed histological evidence of hypertension, which was seen with changes to all vascular layers, including fibrosis of the perivascular adipose tissue, particularly affecting the muscular arteries greater than other blood vessels. A trend was seen that a majority of patients whose cause of death was not attributed to cardiovascular disease were noted to still have clinically significant levels of cardiovascular disease in the form of cardiomegaly, left ventricular hypertrophy, severe coronary artery disease, replacement fibrosis, and cardiomyopathy. It was also shown that cardiovascular disease was more commonly seen in males, particularly those older than 35. Despite the overall young age of the patients seen in the study, the rates of cardiovascular disease were high and significantly elevated compared to the general population.<sup>36</sup>

Huang et al. also conducted a long-term study that followed 1,315 inpatients treated for methamphetamine use in Taiwan between January 1, 1997, and December 31, 2000. Patients were matched with a proxy comparison group, and patients were monitored for any complications until December 31, 2010. This study also saw a male patient population, approximately half younger than 30. The methamphetamine cohort had higher incidences of cardiovascular disease and stroke events when compared to the control cohort. They also noted an increased risk of cardiovascular disease and stroke complications, particularly arrhythmia and hemorrhagic stroke. The increased risk of cardiovascular disease was more significant in the patients under 30 years old, whereas the risk of cerebrovascular accidents was more common among the patients over 30 years old.<sup>37</sup> With the increase in methamphetamine use, it is most likely that the rates of cardiovascular disease and stroke will increase, especially in the younger methamphetamine users under the age of 30.<sup>36,37</sup> Additionally, those with pre-existing heart conditions may experience exacerbations caused by methamphetamine use, leading to worse outcomes and more hospitalizations than those with pre-existing heart conditions who do not use illicit substances.<sup>37</sup>

Methamphetamine use has also been linked to complications and worse outcomes in intracerebral hemorrhage cases. Zhu et al. 2020 conducted a study looking at the differences in clinical presentations and outcomes in spontaneous intracerebral hemorrhage (ICH) cases in methamphetamine users (Meth-ICH) vs. Non-Meth-ICH. The study looked at patients with ICH between January 2011 and December 2017. The groups were defined by a history of methamphetamine use and a positive urine drug screen for methamphetamine at the time of admission. Among the 677 patients, 61 were identified as Meth-ICH and 350

as Non-Meth-ICH. The Meth-ICH group was more often younger and had a stronger history of tobacco smoking.

In contrast, the Non-Meth-ICH group was likelier to have a history of uncontrolled hypertension and anti-thrombotic use. There was no significant difference in hospital length of stay, clinical severity, rate of functional independence upon discharge, or mortality between the two groups. Since ICH is preventable with proper preventative health care and since the Meth-ICH group was younger, this study shows that methamphetamine use is correlated with worse quality of life compared to non-methamphetamine use.<sup>38</sup> While in this study, the Non-Meth-ICH group was found to have higher rates of uncontrolled hypertension, the vascular changes noted in methamphetamine users might play a role in causing cerebrovascular events.<sup>36,38</sup>

While most of the complications of methamphetamine use appear to result in immediate cardiovascular, renal, and neurological complications, methamphetamine use might also be linked to long-term complications due to neuronal damage. Recent clinical studies have found that methamphetamine use puts individuals at an increased risk of developing Parkinson's disease, likely through the formation of the toxic metabolite 6-hydroxy-dopamine and its associated oxidative stress. He et al. in 2022 set out to find the cause of methamphetamine-mediated dopaminergic neuronal damage. This study was conducted using an animal model of mice treated with four days of methamphetamine or a D1 receptor agonist known as SKF38393. This was done on two groups of mice, one with no gene knockouts and the other with a D1 receptor gene knockout. After treatment, cellular indices of autophagy such as LC2, P52, Beclin-1, tyrosine hydroxylase, and the AMPK/FOXO3A pathway were analyzed in the striatal tissue of treated mice.

They also analyzed PC12 cells in vitro to determine if there was D1 receptor-mediated activation of autophagy. Researchers found that repeated treatment with high-dose methamphetamine induces dopaminergic neurons and autophagy activation in the striatum of the non-knockout mice, increasing expression of LC3 and P62 signaling activation of autophagy pathways in the striatum. In knockout mice, treatment did not induce either loss of dopaminergic neurons or activation of autophagy pathways. The PC12 cells in vitro confirmed that D1 receptor activation via SKF38393 could lead to activation of autophagy through the AMPK/FOXO3A pathway. It is presumed that the over-activation of D1 receptors plays an important role in dopaminergic neuronal damage and neurotoxicity in patients with long-term methamphetamine use.<sup>39</sup> Many other studies have documented that methamphetamine can dysregulate and deplete the brain of dopamine, but few have shown clear neurocognitive or other function sequelae of these neurochemical changes. One such study demonstrates a clear association in mice between dopamine loss and impairment in tasks of associative learning and declarative memory. In a preclinical study, mice were exposed to dosing regimens of 3,4-methylenedioxymethamphetamine (MDMA), methamphetamine, or parachloroamphetamine (PCA) and the authors looked at deficits in learning and memory via passive avoidance behavior and changes

in the tissue content of monoamine neurotransmitters and their metabolites in the striatum, frontal cortex, cingulate, hippocampus, and amygdala.<sup>40</sup> The authors found that exposure to methamphetamine and PCA had impaired performance in the passive avoidance behavior tests and significant depletions of dopamine, serotonin, and their metabolites in several brain regions.<sup>40</sup> Previous research has also linked the Sigma 1 receptor as a major mediator of methamphetamine-induced persistent dopamine dysregulation, as well as having a role in acute toxic effects of methamphetamine – inducing its capacity to induce convulsions, seizures, and mortality.

Methamphetamine has also been linked to gastrointestinal mucosa damage. Yang et al. in 2021 set out to find if there were any alterations in the gut microbiome of chronic methamphetamine use. They collected fecal samples from 16 patients treated for SUD at Wuhan Mental Health Center in China. The samples were then analyzed via polymerase chain reaction (PCR), and researchers used a statistical Shannon index to determine the diversity of the gut microbiome. They noted a decreased Shannon index in those with chronic methamphetamine use, indicating a lower bacterial diversity when compared to age-matched controls. They also noted an increased concentration of Fusobacteria correlated to the duration of methamphetamine use and found higher concentrations of Bacteroides and Faecalibacterium, which have been correlated to persons with psychotic syndromes including schizophrenia and depression.<sup>41</sup>

Zhao et al. in 2019 aimed to find the cause of the mucosal inflammatory damage seen with methamphetamine use. Researchers theorized that the mechanism of inflammatory injury was due to Nod-like receptor protein 3 (NLRP3) inflammasome overexpression. To support this, they conducted an animal study in which two groups of mice cells were treated with methamphetamine (5 mg/kg) alone or methamphetamine plus MCC950, an NLRP3 inflammasome inhibitor, and apoptotic and proinflammatory factors were measured to determine the extent of mucosal damage in the mice. In the methamphetamine-only group, more apoptosis occurred, as evidenced by decreased transepithelial electrical resistance and higher levels of proinflammatory cytokines such as IL-6, INF-gamma, TNF-alpha, and NF-kB. In the methamphetamine plus inhibitor group, lower levels of IL-6, INF-gamma, and TNF-alpha were seen, but both groups had similar levels of NF-kB.<sup>42</sup> Alterations in the gut microbiome and intestinal mucosal damage are linked to higher rates of gastrointestinal infection and worse outcomes. It is likely from these studies that higher rates of methamphetamine use will lead to higher rates of hospital-acquired Clostridioides difficile infections as well as more complications of sepsis and death due to these infections.<sup>41,42</sup> More studies would be needed to see if this linkage exists. [Table 1](#) summarizes the studies discussed in this section.

## CONCLUSION

SUD is a public health hazard with a myriad of adverse effects on the human body. Methamphetamine is associated with varying organ system complications from hemorrhagic stroke to myocardial infarction. Symptoms may include agitation, anxiety, delusions, hallucinations, and seizures to even neuronal damage that can lead to changes in cognition. Chronic methamphetamine use elicits permanent substantia nigra dopaminergic neuron damage, leading to brain parkinsonian-like effects.

These effects are more pronounced in the younger population. This burden of cardiovascular disease, stroke, and other neurological complications is great, as this has been found in patients younger than 30 years old. More studies need to be done to further look after other adverse effects in the human population regarding changes in possible changes in the gut microbiome as that can lead to GI complications such as infections and more serious complications such as the possibility of toxic megacolon. More research should be done to help guide clinical, and public health discussion as the world continues to battle this substance and its use continues to increase.

**Table 1. Summary of studies**

Authors	Title of Study	Summary of findings
Isoardi et al.	Methamphetamine intoxication and acute kidney injury: A prospective observational case series	Patients presenting with methamphetamine intoxication will commonly have elevated creatinine concentrations suggestive of acute kidney injury. The AKI is often mild and resolves with crystalloid therapy.
Maheshwari and Athiraman	"Speedballing" to Severe Rhabdomyolysis and Hemodialysis in a 27-Year-Old Male	Patient presented to ED after ingestion of "M30" pills purchased on the internet. Patient required regular hemodialysis secondary to rhabdomyolysis and fulminant kidney failure and is awaiting a transplant.
Pillai et al.	Hypotension, Severe Hyperthermia (42°C), Rhabdomyolysis, and Disseminated Intravascular Coagulation Induced by Lethal Dose of Methamphetamine	Patient presented to the ED after ingestion of 1.5 grams of methamphetamine. Patient presented with hypotension, hyperthermia, and rhabdomyolysis, eventually progressing to disseminated intravascular coagulation and multiorgan failure. The patient died in the ICU after hours of supportive care.
Darke et al.	Prevalence and nature of cardiovascular disease in methamphetamine-related death: A national study	Analysis of 894 autopsy reports for methamphetamine-related deaths showed increased rates of cardiovascular disease, more commonly seen in males and adults older than 35 with significant methamphetamine use.
Huang et al.	Risk of Cardiovascular Diseases and Stroke Events in Methamphetamine Users: A 10-Year Follow-Up Study	A 10-year follow-up study of 1,315 inpatients treated for methamphetamine use was shown to have higher rates of cardiovascular disease and cerebrovascular accidents and higher rates of complications of these diseases due to methamphetamine use.
Zhu et al.	Clinical characteristics and outcomes of methamphetamine-associated versus non-methamphetamine intracerebral hemorrhage	A 6-year study examined the clinical characteristics and outcome of intracerebral hemorrhage in methamphetamine users vs. non-methamphetamine users. It was shown that despite demographical differences between the two groups, methamphetamine was not an independent predictor of poor outcomes.
He et al.	Dopamine D1 receptors mediate methamphetamine-induced dopaminergic damage: involvement of autophagy regulation via the AMPK/FOXO3A pathway	In an animal study, two groups of mice (Non-D1-Receptor Knockout and D1 Receptor Knockout) were given 4 days of high-dose methamphetamine or a D1 agonist. Results showed that methamphetamine groups showed loss of dopaminergic neurons and activation of autophagy pathways in non-knockout mice but no loss in the D1 receptor knockout mice group.
Yang et al.	Altered fecal microbiota composition in individuals who misuse methamphetamine	Analyzed fecal samples from 16 patients treated for methamphetamine use disorder. They found decreased diversity in the gut microbiome in methamphetamine users and higher concentrations of Bacteroides and Faecalibacterium correlated to persons with psychotic syndromes.
Zhao et al.	Methamphetamine Induces Intestinal Inflammatory Injury via Nod-Like Receptor 3 Protein (NLRP3) Inflammasome Overexpression <i>In Vitro</i> and <i>In Vivo</i>	An animal study in mice analyzed the cause of intestinal mucosal damage. Increased expression of NLRP3 and high expression of proinflammatory factors correlated with higher rates of inflammatory injury. When a NLRP3 inhibitor was added, lower rates of proinflammatory factors were noted.



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