

PART IX

Toxicology

Chapters 22–24

Acute Toxicity

The organ-level emergencies of methamphetamine poisoning — and how they connect into a single, potentially lethal cascade.

Chapter 15 described the clinical management of methamphetamine overdose; this chapter examines the underlying toxicology of the acute emergencies themselves — how each arises mechanistically, and how they interlock. The unifying theme is that the acute toxic effects of methamphetamine are not independent events but a connected physiological cascade, in which hyperthermia, muscle breakdown, and organ failure feed one another. Understanding the mechanism explains why time-critical intervention matters so much.

Hyperthermia

Hyperthermia is the most dangerous acute complication and, in many fatal cases, the engine that drives the others. It arises from the convergence of several mechanisms: dysregulation of central thermoregulation, greatly increased metabolic heat production, peripheral vasoconstriction that impairs the body's ability to shed heat, and the intense motor activity of agitation — all of which can be amplified by a hot, crowded environment or physical exertion. At the cellular level, oxidative and calcium-mediated stress promotes mitochondrial uncoupling, diverting energy from ATP synthesis into heat. The result can be a rise in core temperature above 40 °C, with reported cases reaching 42–43 °C.¹ Because this is a disorder of heat generation and dissipation rather than a fever, antipyretics are useless; as Chapter 15 emphasized, emergent physical cooling is the treatment, and its speed is often decisive for survival.

Stroke

Acute cerebrovascular catastrophe is a second major emergency. As detailed in Chapter 14, methamphetamine is an important cause of stroke in young adults, with hemorrhagic stroke — intracerebral and subarachnoid hemorrhage — being

the more common form.³ The acute mechanism is a sudden hypertensive surge superimposed on vascular changes such as vasospasm, endothelial injury, and, where present, aneurysms, which can rupture under the pressure. Methamphetamine-induced seizures compound the risk, which is why neuroimaging is indicated whenever they occur (Chapter 15). Ischemic stroke also occurs acutely, via vasoconstriction and cardioembolism.

Cardiac complications

The acute cardiac emergencies follow from the drug's profound sympathomimetic drive. Severe hypertension can precipitate a hypertensive emergency or aortic dissection; the sympathetic surge can trigger tachyarrhythmias and, through coronary vasospasm or thrombosis, an acute coronary syndrome or myocardial infarction even in a young person with normal coronary arteries.⁴ In the most severe presentations the cardiovascular system can collapse outright, contributing to the multiorgan failure discussed below. These acute events sit on a continuum with the chronic methamphetamine-associated cardiomyopathy of the next chapter.

Kidney injury

Acute kidney injury is a frequent and dangerous complication, and it is most often mediated by rhabdomyolysis — the breakdown of skeletal muscle. Methamphetamine drives rhabdomyolysis through several converging routes: hyperthermia, prolonged and violent muscular agitation, dehydration and electrolyte disturbance, and ischemia from vasoconstriction, all compounding to injure myocytes and release myoglobin, creatine kinase, and electrolytes into the circulation.^{1,2} The released myoglobin is directly toxic to the renal tubules, and acute kidney injury develops in a substantial fraction of rhabdomyolysis cases — by some estimates up to half.² Direct nephrotoxicity, renal vasoconstriction, and hypertensive injury contribute independently. Acute kidney injury may resolve with prompt fluid resuscitation but can progress to chronic kidney disease or dialysis dependence in severe cases.²

The lethal cascade

In the most severe poisonings these mechanisms converge: hyperthermia drives rhabdomyolysis, which drives acute kidney injury; hyperthermia and shock can trigger disseminated intravascular coagulation; and the sum is multiorgan failure. Case reports of fatal methamphetamine toxicity describe exactly this sequence — extreme hyperthermia, rigidity, rhabdomyolysis, acute renal failure, disseminated intravascular coagulation, and death.¹ Recognizing the cascade is what makes early, aggressive supportive care (Chapter 15) potentially life-saving. Consistent with Chapter 10, no single "toxic dose" defines this risk: tolerance and individual variability mean the threshold differs enormously between people.

Acute emergency	Principal mechanism(s)
Hyperthermia	Thermoregulatory dysregulation, metabolic heat, vasoconstriction, agitation, mitochondrial uncoupling
Stroke (hemorrhagic > ischemic)	Hypertensive surge, vasospasm, endothelial injury, aneurysm rupture; cardioembolism
Cardiac (arrhythmia, MI, dissection)	Sympathetic surge, coronary vasospasm/thrombosis, severe hypertension
Acute kidney injury	Rhabdomyolysis/myoglobinuria, direct nephrotoxicity, vasoconstriction, dehydration

Chronic Toxicity

The accumulating harms of sustained use — to the mind, the heart, the teeth, and the skin — with methamphetamine-associated psychosis as the defining neuropsychiatric complication.

Where acute toxicity is a crisis, chronic toxicity is an accretion — the slow accumulation of damage across organ systems over months and years of use. As noted in Chapter 15, many methamphetamine-related emergencies and deaths reflect this cumulative burden as much as any single overdose. This chapter surveys the principal chronic harms, several of which were introduced in Chapter 14 and are developed here, with particular depth on psychosis.

Cognitive decline

Chronic methamphetamine use is associated with measurable cognitive impairment across attention, executive function, and memory, as detailed in Part V.⁵ These deficits track with the reductions in dopamine transporter density and the structural brain changes documented on imaging, and — importantly — they show partial recovery with sustained abstinence, even as some deficits persist. Cognitive decline is not merely an abstract finding: it impairs daily functioning and predicts worse treatment outcomes, which is why cognitive rehabilitation (Chapter 12) has become a focus of care.

Psychosis

Methamphetamine-associated psychosis (MAP) is the signature neuropsychiatric complication of chronic use, and it is common: a meta-analysis estimated the prevalence of methamphetamine-induced psychotic disorder at roughly 36 percent across studies.⁶ Clinically it is dominated by persecutory and paranoid delusions, ideas of reference, and hallucinations that are characteristically auditory but, distinctively, frequently visual and tactile as well — the formication of Chapter 14 being a hallmark.⁶ The symptom picture so closely resembles acute paranoid

schizophrenia that the two can be difficult to tell apart, and this creates real diagnostic complexity, especially in emergency and forensic settings.

Several features nonetheless distinguish MAP from primary schizophrenia. MAP symptoms are typically more transient and co-occur with methamphetamine use, there is generally less of a residual negative-symptom syndrome, and visual and tactile hallucinations are comparatively more prominent, whereas pronounced thought disorder and certain cognitive deficits point more toward schizophrenia.⁶ By convention, the DSM-5 treats psychotic symptoms persisting beyond about a month past intoxication and withdrawal as indicating a primary psychotic disorder. The relationship between the two conditions is not merely one of resemblance: a meaningful proportion of people with an initial episode of stimulant-induced psychosis go on to transition to a persistent primary psychotic disorder, with estimates for amphetamine-type stimulants commonly cited in the range of roughly one-fifth to one-third.⁶ Shared vulnerability underlies this overlap — a family history of schizophrenia markedly raises the risk (first-degree relatives of people with MAP being substantially more likely to have schizophrenia), and dopamine-system genes and overlapping structural brain changes are implicated in both.⁶

A crucial and clinically consequential feature is *sensitization*: as introduced in Chapter 10, repeated use can leave a person primed such that psychosis recurs on re-exposure to even a small amount of the drug, or under stress, long after the original episode — a form of reverse tolerance that helps explain relapsing psychotic illness in this population. Risk rises with the dose, frequency, and duration of use, with dependence severity, with early age of onset, and with concurrent alcohol and cannabis use.⁶ Treatment relies on antipsychotic medication, which alleviates symptoms, together with abstinence; for transient episodes, sedation is often sufficient, and evidence suggests that the persistent form of MAP may respond to lower antipsychotic doses than schizophrenia does.⁶

Cardiomyopathy

Methamphetamine-associated cardiomyopathy, introduced in Chapter 14, is among the most serious chronic physical harms: a dilated cardiomyopathy with reduced ejection fraction that can progress to heart failure and, in severe cases,

require transplantation, and that carries a substantial risk of intraventricular thrombus and consequent cardioembolic stroke.⁴ Its partial reversibility with sustained abstinence is one of the more hopeful facts in the drug's toxicology and a concrete argument for cessation even after cardiac damage has occurred.

Dental disease

The severe dental disease of "meth mouth," examined mechanistically in Chapter 14, is a defining chronic stigma of methamphetamine use — a multifactorial process of xerostomia, bruxism, prolonged intoxication, high-sugar intake, and neglected oral hygiene producing rampant caries and tooth loss.⁷ Its recognition as multifactorial, rather than as simple chemical corrosion, points toward genuine preventive and restorative dental intervention.

Skin complications

The dermatologic complications of chronic use are both physically and psychiatrically revealing. The formication that accompanies stimulant use — often accompanied by delusions of parasitosis, the fixed belief that insects infest the skin — drives compulsive picking and scratching that produce excoriations, the lesions colloquially called "speed bumps," and, over time, prurigo nodularis.⁷ These wounds, compounded by poor healing, malnutrition, and (with injection) direct inoculation, are prone to infection. The skin thus becomes a visible record of both the drug's peripheral effects and its psychiatric ones.

Chronic harm	Key features
Cognitive decline	Attention/executive/memory deficits; partial recovery with abstinence (Part V)
Psychosis (MAP)	~36% prevalence; paranoid + visual/tactile hallucinations; ~1/5–1/3 transition to persistent disorder; sensitization/recurrence
Cardiomyopathy	Dilated, reduced EF; thrombus/embolic stroke; partially reversible with abstinence

Dental disease	"Meth mouth": multifactorial rampant caries and tooth loss
Skin complications	Formication, delusions of parasitosis, excoriations/"speed bumps," prurigo nodularis, infection

Drug Interactions

From the merely risky to the outright lethal — the combinations that turn a dangerous drug into a deadly one, and the single contraindication no clinician should forget.

Methamphetamine's interactions with other substances range from the additive to the catastrophic. Three mechanisms recur: additive sympathomimetic and cardiovascular toxicity, serotonergic excess culminating in serotonin syndrome, and the deceptive masking that occurs when a stimulant is combined with a depressant. These dangers are magnified by the reality of the illicit market, in which a person rarely knows the true identity or purity of what they have taken, and in which contamination — above all with fentanyl (Chapters 6 and 16) — is now common.

Monoamine oxidase inhibitors (MAOIs)

The interaction between methamphetamine and monoamine oxidase inhibitors is the most dangerous, and it is the reason the pharmaceutical product is absolutely contraindicated with MAOIs or their use within the preceding fourteen days (Chapter 13).⁸ Monoamine oxidase is the enzyme that degrades monoamines; when it is inhibited and methamphetamine then floods the system with released catecholamines, the result can be a catastrophic accumulation producing hypertensive crisis, cerebral hemorrhage, and life-threatening hyperpyrexia — outcomes documented in historical case reports of amphetamine–MAOI combinations.⁸ The same combination independently risks serotonin syndrome. The contraindication extends to less obvious MAO inhibitors, including the antibiotic linezolid, methylene blue, and selegiline. This is the single interaction every prescriber and clinician must keep in mind.

Antidepressants

Because methamphetamine releases serotonin, combining it with serotonergic antidepressants — selective serotonin reuptake inhibitors and serotonin–nor-

epinephrine reuptake inhibitors — can precipitate **serotonin syndrome**, a potentially life-threatening state of agitation, hyperreflexia, clonus, tremor, hyperthermia, and autonomic instability.⁹ Its management mirrors the principles of Chapter 15: immediate discontinuation of serotonergic agents, benzodiazepines, aggressive cooling (antipyretics again being ineffective), and the serotonin antagonist cyproheptadine in refractory cases.⁹ Bupropion warrants separate mention: it lowers the seizure threshold, which is additive with methamphetamine's own proconvulsant effect, even as it is, at controlled doses and in combination with naltrexone, among the more promising investigational treatments for methamphetamine use disorder (Chapter 21). Tricyclic antidepressants add cardiovascular and serotonergic risk.

Opioids

The combination of methamphetamine with opioids — the "goofball" of methamphetamine plus heroin or fentanyl — defines the fourth-wave polysubstance pattern of Part VII. The stimulant and the depressant exert opposing effects, but they do not cancel: the opioid's capacity to suppress breathing remains, and the lethal danger of the combination is opioid-induced respiratory depression, which naloxone reverses (naloxone having no effect on the methamphetamine itself).⁹ A further hazard is that several opioids — tramadol, meperidine (pethidine), methadone, and dextromethorphan among them — are themselves serotonergic and can contribute to serotonin syndrome when combined with methamphetamine.⁹

Alcohol

Alcohol is a central nervous system depressant, and its combination with methamphetamine is dangerous partly because each masks the other: the stimulant blunts the sedation that would ordinarily signal heavy drinking, while alcohol dampens some stimulant cues, encouraging greater consumption of both. The pairing imposes combined strain on the cardiovascular system, and alcohol can alter methamphetamine's disposition. The disinhibition and impaired judgment that result compound the behavioral risks.

Benzodiazepines

Benzodiazepines occupy an instructive dual position. Clinically, as Chapter 15 described, they are the *first-line* treatment for methamphetamine-induced agitation and hyperadrenergic toxicity — a therapeutic use. Outside that setting, non-medical co-use — often taken to "come down" from stimulation — pits a sedative against a stimulant, producing confusion, memory impairment, and heightened potential for dependence, and any stacking of benzodiazepines with other depressants such as alcohol or opioids carries its own overdose risk.

ADHD medications

Combining methamphetamine with other prescription stimulants — amphetamine or methylphenidate products used for ADHD — produces additive stimulant toxicity, compounding cardiovascular and psychiatric risk. This interaction also frames a clinical caution: prescribing stimulants to a person with stimulant use disorder requires careful judgment, which is one reason methamphetamine's own approved stimulant indication (Chapter 13) is hedged with such caution.

Combination	Principal danger
MAOIs (incl. linezolid, methylene blue, selegiline)	Hypertensive crisis, cerebral hemorrhage, hyperpyrexia, serotonin syndrome — absolute contraindication
SSRIs / SNRIs / TCAs	Serotonin syndrome; TCAs add cardiovascular risk
Bupropion	Additive seizure risk (yet investigational treatment at controlled dose)
Opioids ("goofball," fentanyl)	Respiratory depression (naloxone-reversible); serotonergic opioids add serotonin-syndrome risk
Alcohol	Mutual masking, cardiovascular strain, disinhibition
Benzodiazepines	First-line therapeutically; non-medical co-use → confusion, dependence, depressant stacking

Other stimulants (ADHD meds)	Additive sympathomimetic/psychiatric toxicity
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References — Part IX

Listed in order of first citation within Part IX. Numbering restarts each installment; the apparatus is to be consolidated on final assembly. Sources current as of 2026.

1. Methamphetamine acute toxicity and the hyperthermia-driven cascade: sympathomimetic toxidrome; severe hyperthermia (cases 42–43 °C), rhabdomyolysis, acute renal failure, disseminated intravascular coagulation, and multiorgan failure. (Cureus / PubMed 31565643; PMC6759040.) Mitochondrial-uncoupling mechanism of hyperthermic muscle injury (analogous amphetamine literature, PMC12904165).
2. Methamphetamine-induced rhabdomyolysis — multifactorial mechanism (hyperthermia, agitation, dehydration, ischemia) with myoglobin release; acute kidney injury in a substantial fraction (up to ~50%) of rhabdomyolysis cases, with risk of chronic kidney disease/dialysis. (Clinical toxicology reviews; rhabdomyolysis–AKI pathophysiology, PMC9603683.)
3. Methamphetamine and stroke in young adults — hemorrhagic (intracerebral/subarachnoid) more common than ischemic; hypertensive surge, vasospasm, aneurysm rupture. (PMC11076881; see Part VI.)
4. Richards JR, et al. Methamphetamine-associated cardiomyopathy — dilated cardiomyopathy, reduced ejection fraction, intraventricular thrombus/cardioembolic stroke, partial recovery with abstinence. *J Am Heart Assoc.* (see Part VI references.)
5. Cognitive impairment in methamphetamine use disorder (attention, executive function, memory), correlation with dopamine-transporter loss, and partial recovery with abstinence. (Potvin S, et al., meta-analysis; Volkow ND, et al.; see Part V.)
6. Methamphetamine-associated psychosis: meta-analytic prevalence of methamphetamine-induced psychotic disorder (~36.5%); clinical features and distinction from schizophrenia (transient course, fewer negative symptoms, prominent visual/tactile hallucinations); DSM-5 one-month threshold; transition to persistent psychotic disorder (~ $\frac{1}{5}$ – $\frac{1}{3}$ for amphetamine-type stimulants); familial schizophrenia risk (first-degree relatives OR $\approx$ 5.4); sensitization and spontaneous recurrence; antipsychotic treatment and lower dosing in persistent MAP. (PMC3280383; PMC6232294 [n=1,430]; Wearne TA & Cornish JL; PsychScene Hub review; ScienceDirect Topics.)
7. "Meth mouth" as multifactorial dental disease (American Dental Association; see Chapter 14) and dermatologic complications — formication, delusions of parasitosis, excoriations/"speed bumps," prurigo nodularis, and infection. (Methamphetamine Toxicity, StatPearls, NBK430895.)
8. Stimulant–MAOI interaction: hypertensive crisis and cerebral hemorrhage / hyperpyrexia from amphetamine–MAOI combinations; serotonin-syndrome risk; Desoxyn FDA labeling contraindicating MAOIs within 14 days. (Combining stimulants and MAOIs — literature review, PMC4805402.)
9. Serotonin syndrome — mechanisms, high-risk combinations (MAOIs with SSRIs/SNRIs/TCAs; MAOIs with serotonin-releasing agents including amphetamines/MDMA; serotonergic opioids: tramadol, meperidine, methadone, dextromethorphan), and management (discontinue serotonergic agents; benzodiazepines; cooling; cyproheptadine;

antipyretics ineffective). Opioid co-use and respiratory depression (naloxone-reversible). (Psychopharmacology Institute; *Serotonin syndrome* overview; Alcohol and Drug Foundation; harm-reduction/clinical sources on alcohol, benzodiazepine, and stimulant co-use.)

End of Part IX — Toxicology (Chapters 22–24)

*Part X — Forensic Science (Chapters 25–27: Drug Testing; Crime Laboratories;
Waste and Environmental Impact)
continues the volume.*