

PART IV

Pharmacology

Chapters 8–10

Pharmacodynamics

What methamphetamine does to the brain's chemical messaging — the mechanism that connects a small molecule to its enormous physiological and behavioral effects.

Pharmacodynamics is the study of what a drug does to the body. For methamphetamine, the answer is unusually unified: nearly all of its acute effects, therapeutic and harmful alike, flow from a single core action — a large, sustained increase in the synaptic concentration of the monoamine neurotransmitters, achieved by hijacking the very transport machinery that normally regulates them. Methamphetamine is, in pharmacological shorthand, an *indirect monoamine agonist*: it does not principally activate neurotransmitter receptors itself, but rather floods the synapse with the body's own dopamine, norepinephrine, and serotonin.

The monoamine systems

Dopamine is the central player. The mesolimbic dopamine pathway mediates reward, motivation, and reinforcement, and the surge of dopamine that methamphetamine produces in this circuit underlies its euphoric and powerfully reinforcing effects, while dopamine's roles in motor control and in the prefrontal cortex account for other features of intoxication. **Norepinephrine** drives much of the drug's sympathomimetic action — increased heart rate and blood pressure, pupil dilation, bronchodilation — together with heightened arousal, alertness, and suppression of fatigue. **Serotonin** is affected less potently than the catecholamines, but its involvement is relevant to effects on mood and, importantly, to thermoregulation and to the mechanisms of neurotoxicity examined in Part V. The clinical picture of methamphetamine intoxication is essentially the superimposed consequence of excess signaling in all three systems at once.

The transporters: DAT, NET, and SERT

Under normal physiology, after a neurotransmitter is released it is cleared from the synapse by reuptake through a dedicated plasma-membrane transporter: the dopamine transporter (DAT), the norepinephrine transporter (NET), and the serotonin transporter (SERT). Methamphetamine subverts these transporters in a way that distinguishes it sharply from cocaine. Cocaine is a *blocker* — it occupies the transporter and prevents reuptake, so that normally released neurotransmitter simply lingers. Methamphetamine, like the amphetamines generally, is instead a *substrate*: it is itself carried into the neuron by the transporter, and once inside it reverses the transporter's direction, so that the carrier begins pumping neurotransmitter *out* of the cell rather than in.^{1,4} This "reverse transport" or non-exocytotic efflux means methamphetamine actively drives neurotransmitter release rather than merely preventing its removal — a key reason its effects are so pronounced and so prolonged. Its potency is greatest at the dopamine and norepinephrine transporters and weaker at the serotonin transporter.

VMAT2 and the vesicular reservoir

The reverse-transport mechanism requires a supply of neurotransmitter in the cytoplasm, and methamphetamine generates that supply by raiding the neuron's internal vesicular stores. Within the presynaptic terminal, the vesicular monoamine transporter 2 (VMAT2) normally pumps monoamines into synaptic vesicles, a process powered by the vesicles' acidic interior (VMAT2 operates as a proton antiporter). Methamphetamine, being lipophilic, enters the terminal both through DAT and by direct diffusion across the membrane, and it disrupts the vesicular pH gradient, causing stored dopamine to leak out of the vesicles into the cytoplasm.^{1,3} There it becomes available for efflux through DAT. Notably, methamphetamine's direct binding affinity for VMAT2 is low; its effect on the vesicles is better understood as a functional collapse of the pH gradient that sequesters neurotransmitter, redistributing the vesicular reservoir into the cytoplasm.³ The combined action — vesicular depletion feeding transporter-mediated efflux — is what produces the characteristically massive rise in extracellular dopamine.

TAAR1 and MAO

Two further targets refine the picture. Methamphetamine is a potent agonist at the **trace amine-associated receptor 1 (TAAR1)**, a presynaptic receptor that modulates monoaminergic tone; through TAAR1, methamphetamine influences transporter function and trafficking, inhibiting uptake and promoting efflux, so that TAAR1 signaling is now understood to modulate the drug's neurochemical and behavioral effects rather than being incidental to them.² Methamphetamine also interacts with **monoamine oxidase (MAO)**, the mitochondrial enzyme that degrades cytoplasmic monoamines; by interfering with MAO, the drug further raises the pool of cytoplasmic neurotransmitter available for release.¹ The convergence of these mechanisms — substrate-driven efflux at the transporter, vesicular depletion via VMAT2, receptor-level modulation via TAAR1, and reduced enzymatic breakdown via MAO — explains why methamphetamine elevates synaptic monoamines so much more profoundly and durably than a simple reuptake blocker.

Target	Methamphetamine's action	Net effect
DAT / NET / SERT	Substrate; reverses transport (efflux)	Active release of dopamine, norepinephrine, serotonin
VMAT2	Disrupts vesicular pH gradient	Vesicular monoamines redistributed to cytoplasm
TAAR1	Potent agonist	Modulates transporter uptake/efflux and trafficking
MAO	Interaction / inhibition	Less breakdown of cytoplasmic monoamines
<i>Contrast: cocaine</i>	<i>Reuptake blocker (not a substrate)</i>	<i>Prevents clearance; depends on exocytotic release</i>

This same flood of cytoplasmic and synaptic dopamine — and the reactive oxygen species generated when excess dopamine auto-oxidizes — is also the starting point for the long-term neurotoxicity discussed in Part V. The mechanism that produces the drug's acute effects and the mechanism that produces its lasting harms are, at root, the same.

Pharmacokinetics

What the body does to methamphetamine — its absorption, distribution, metabolism, and elimination, and why these determine the long duration that shapes patterns of use.

If pharmacodynamics is what the drug does to the body, pharmacokinetics is the reverse: what the body does to the drug. The pharmacokinetics of methamphetamine explain several of its most consequential features — above all its long duration of action, which distinguishes it from shorter-acting stimulants and shapes the binge patterns described in later chapters.

Absorption

Methamphetamine is absorbed by every route through which it is taken, but the rate and completeness of absorption differ by route, and this has pharmacological consequences. Following oral administration, peak plasma concentrations are reached relatively slowly, at roughly 2.6 to 3.6 hours.⁵ Absorption is more rapid and the rise in plasma concentration more abrupt by inhalational and intravenous routes than by mouth, where the ascent to peak concentration is comparatively gradual; because the speed of onset is one determinant of a stimulant's reinforcing power, this difference in absorption kinetics is directly relevant to the differing abuse liability of different routes, a theme developed in Part VIII. The molecule's high lipophilicity ensures efficient crossing of the blood–brain barrier regardless of route.

Distribution

Once absorbed, methamphetamine distributes widely. Its lipophilicity gives it a large volume of distribution and ready access to the central nervous system, and it crosses both the blood–brain barrier and the placenta — the latter with implications detailed in the chapter on pregnancy (Chapter 18). As a weak base, the drug is subject to pH-dependent partitioning ("ion trapping"), accumulating in relative-

ly acidic compartments, and its plasma-protein binding is modest. The result is a drug that reaches its central site of action quickly and thoroughly.

Metabolism and the CYP enzymes

Methamphetamine is metabolized chiefly in the liver, and the principal enzyme is the polymorphic cytochrome P450 isoform **CYP2D6**.^{5,6} Two metabolic routes dominate. *N*-demethylation removes the nitrogen methyl group to yield **amphetamine**, which is itself pharmacologically active — so that a person who takes methamphetamine is, in effect, also dosed with amphetamine as the drug is metabolized. Aromatic hydroxylation yields **4-hydroxymethamphetamine**, likewise active.⁶ Additional enzymes, including flavin-containing monooxygenase 3 and others, contribute to a family of further metabolites, several of which (4-hydroxyamphetamine, 4-hydroxynorephedrine, norephedrine) retain sympathomimetic activity.⁵ Methamphetamine itself behaves as both a weak substrate and a competitive inhibitor of CYP2D6.⁷

Because CYP2D6 is genetically polymorphic, one might expect large differences between rapid and poor metabolizers, and this is a real source of interindividual variability. The clinical magnitude, however, is more muted than in-vitro studies alone would predict: the fraction of methamphetamine's clearance actually governed by CYP2D6 is lower than expected, because other enzymes and a substantial component of direct renal excretion also contribute.^{7,8} Drug interactions follow the same logic — CYP2D6 inhibitors can slow elimination and inducers accelerate it — and one interaction deserves particular emphasis: combining methamphetamine with a monoamine oxidase inhibitor can precipitate a dangerous hypertensive and serotonergic crisis, a clinically critical contraindication revisited in Chapter 24.

Elimination and half-life

Methamphetamine is eliminated largely by the kidneys, and a defining feature of its renal handling is a strong dependence on **urinary pH**. Because the drug is a weak base, acidic urine promotes its ionization and excretion (shortening the half-life), whereas alkaline urine favors reabsorption (prolonging it).^{5,6} After an oral

dose, roughly 30 to 54 percent is excreted unchanged as methamphetamine and 10 to 23 percent as amphetamine; after intravenous dosing the figures are about 45 percent and 7 percent respectively.⁶ Controlled-administration studies indicate a renal clearance on the order of 175 mL/min and provide evidence for an active renal secretion mechanism rather than passive filtration alone.⁸

The elimination half-life averages roughly 9 to 12 hours, with reported ranges spanning from about 5 to 30 hours and substantial variation between individuals; importantly, the half-life does *not* vary materially by route of administration.⁵ The active amphetamine metabolite peaks around 12 hours and extends the overall duration of effect.⁵ This long half-life — several times that of cocaine — is pharmacologically central: it means a single exposure produces effects lasting many hours, it shapes the prolonged binge-and-crash cycles described in Parts VIII and IX, and it produces detection windows in urine of roughly three to five days for methamphetamine.⁶

Parameter	Typical value
Time to peak (oral)	≈ 2.6–3.6 hours
Elimination half-life	≈ 9–12 hours average (reported range 5–30 h); route-independent; highly variable between individuals
Primary metabolic enzyme	CYP2D6 (polymorphic); FMO3 and others contribute
Major active metabolites	Amphetamine; 4-hydroxymethamphetamine
Excretion	Renal; strongly urinary-pH dependent; ~30–54% unchanged (oral)
Renal clearance	≈ 175 mL/min; evidence of active secretion
Urine detection window	≈ 3–5 days (methamphetamine)

Dose–Response Relationships

Why the relationship between dose and effect is real but far from simple — and why tolerance, individual variability, and context make a single "dangerous dose" impossible to state.

In classical pharmacology, increasing the dose of a drug produces a graded increase in effect up to a maximum. Methamphetamine follows this logic in broad outline, but three complications — tolerance, individual variability, and the modifying role of context — make its dose–response relationship considerably more intricate than a simple ascending curve, and they are the reason this book does not, and responsibly cannot, specify a universal threshold at which the drug becomes dangerous.

Therapeutic doses

The pharmaceutical context provides the clearest dose–response anchor. In the United States, the approved product Desoxyn (dextromethamphetamine hydrochloride) is FDA-approved for attention-deficit/hyperactivity disorder, with guidance recommending a low starting dose — on the order of 5 milligrams once or twice daily — titrated upward in small weekly increments to a usual effective range of roughly 20 to 25 milligrams per day, the dose individualized to clinical response and tolerability.⁹ It is also used off-label in narrowly defined circumstances such as narcolepsy and short-term weight management.⁹ The FDA itself frames these uses as ones in which limited therapeutic usefulness must be weighed against the drug's risks. These figures describe supervised clinical dosing of an enantiopure, known-strength pharmaceutical, and they bear little relationship to the unknown-purity, unknown-quantity exposures of the illicit context — one reason clinical dosing data cannot be read across to that context.

Toxicity

The relationship between dose and toxicity is genuine but not cleanly quantifiable, for reasons that recur throughout toxicology. Tolerance means that a habituated individual may sustain exposures that would seriously harm a naive one, so that blood or postmortem concentrations associated with toxicity in some people overlap with concentrations tolerated by others — a fact that makes the forensic interpretation of methamphetamine concentrations notoriously difficult and that defeats any attempt to name a single toxic or lethal dose. Toxicity is further shaped by route, by the presence of other substances (the methamphetamine–opioid combinations discussed in Part II being especially lethal), and by environmental factors such as ambient heat and physical exertion, which compound the drug's hyperthermic effects. The organ-by-organ clinical toxicology — cardiovascular, neurological, renal, hyperthermic, and psychiatric — is the subject of Part IX (Chapters 22–24); the point here is structural: dose matters, but it is only one variable among several, and never a sufficient predictor of harm in an individual case.

Individual variability

The same dose produces different effects in different people, for several compounding reasons. Pharmacogenetic differences in CYP2D6 and other enzymes alter metabolism, though, as Chapter 9 noted, their clinical impact is tempered by alternative clearance pathways.⁷ Urinary pH alters elimination and therefore the duration and intensity of exposure. Body composition, sex, age, baseline cardiovascular and psychiatric health, the state of tolerance, and concurrent medications all shift the response. A person with underlying cardiac disease or a predisposition to psychosis may experience serious harm at an exposure another individual tolerates — which is why clinical guidance emphasizes evaluating cardiovascular and psychiatric status before any therapeutic use.^{9,10}

Tolerance

Repeated use changes the dose–response relationship itself, and it does so in two opposing directions simultaneously — a duality that is central to understanding methamphetamine's harms. **Tolerance** develops to several of the drug's effects,

including the euphoric and appetite-suppressing effects, so that escalating doses are required to reproduce an earlier response; a degree of acute tolerance, or tachyphylaxis, also develops within a single episode of use, contributing to the repeated re-dosing that defines a binge. At the same time, and in the opposite direction, **sensitization** (sometimes called reverse tolerance) can develop to other effects — most significantly to psychotomimetic and certain motor effects — so that susceptibility to paranoia and psychosis may *increase* with continued use even in the absence of any dose increase. This combination — diminishing reward driving dose escalation, alongside rising vulnerability to psychosis — helps explain why methamphetamine use disorder so often follows a trajectory of increasing dose and increasing harm together, and it connects directly to the addiction science of Part VIII and the stimulant psychosis of Chapter 23. Cross-tolerance with other stimulants further shapes these patterns.

References — Part IV

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

1. Reviews of amphetamine/methamphetamine molecular mechanism: direct action on the dopamine transporter (DAT) producing reverse transport; vesicular release via VMAT2 with disruption of the vesicular pH gradient; interaction with monoamine oxidase. (Sulzer D, et al.; Fleckenstein AE, et al.; and "Modification of Monoaminergic Activity by MAO Inhibitors Influences Methamphetamine Actions," PMC3155216.)
2. Trace amine-associated receptor 1 (TAAR1) as a potent methamphetamine target modulating transporter function, efflux, and behavior. (Xie Z, Miller GM, "A Receptor Mechanism for Methamphetamine Action...", PMC2700171; "The trace amine-associated receptor 1 modulates methamphetamine's neurochemical and behavioral effects," *Frontiers in Neuroscience*, 2015.)
3. VMAT2 as a target enabling amphetamine-induced dopamine release; reverse transport requires both VMAT2 action and DAT efflux; methamphetamine's low direct VMAT2 binding affinity. ("VMAT2: a dynamic regulator of brain monoaminergic neuronal function...", PMC4183197; preclinical VMAT2-inhibitor binding data, PMC4934384.)
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5. Methamphetamine pharmacokinetics: oral $T_{\max}$ 2.6–3.6 h; mean elimination half-life ≈ 10 h (route-independent; wide interindividual range); amphetamine metabolite peak ≈ 12 h; CYP2D6 metabolism; pH-dependent renal excretion; urine detection windows. (Clinical pharmacokinetics summaries; consolidated reference data.)
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8. Schepers RJF, Huestis MA, et al. Urinary pharmacokinetics of methamphetamine and amphetamine following controlled oral administration: terminal half-lives, renal clearance (~ 175 mL/min), and evidence of an active renal excretion mechanism. (PubMed 15570192.)
9. Desoxyn (methamphetamine hydrochloride) FDA prescribing information — ADHD indication and dosing (initial ~ 5 mg, titrated to ~ 20 – 25 mg/day usual effective dose); off-label narcolepsy and short-term obesity; cardiovascular/psychiatric evaluation before use.
10. Yasaei R, Saadabadi A. *Methamphetamine*. StatPearls (NCBI Bookshelf NBK535356) — clinical pharmacology, tolerance, and pre-treatment cardiac/psychiatric assessment.

End of Part IV — Pharmacology (Chapters 8–10)

*Part V — Neuroscience (Chapters 11–12: The Brain on Meth; Long-Term Brain
Changes)
continues the volume.*