

PART VIII

Addiction Science

Chapters 19–21

Why Addiction Happens

Addiction is neither a moral failure nor a simple choice but the convergence of genetic vulnerability, early adversity, environment, and a drug's particular grip on the brain.

Why does one person who tries methamphetamine walk away while another descends into compulsive use? The honest answer is that addiction is multiply determined, arising from the interaction of factors no single one of which is sufficient on its own. The biopsychosocial model that frames modern addiction science holds that genetic predisposition, life history, social environment, and neurobiology each contribute, and that they act together rather than in isolation. Understanding this is not an academic nicety: it is the foundation for replacing blame with the kind of comprehension that makes effective, compassionate treatment possible.

Genetics

Vulnerability to addiction is substantially heritable. Twin and family studies generally estimate the heritability of substance use disorders in the range of roughly 40 to 70 percent, indicating that a large share of the variation in who develops dependence is attributable to genetic differences.¹ This inheritance is polygenic — distributed across many genes of small individual effect rather than any single "addiction gene" — and it operates through interaction with the environment rather than as destiny. The observation that growing up in a household where substances are used nearly doubles the risk of later dependence reflects both this heritability and the direct modeling of behavior, the two being difficult to disentangle.^{1,2} Genetic vulnerability raises the odds; it does not seal a fate.

Trauma

Among the most robust findings in all of addiction epidemiology is the link between adverse childhood experiences and later substance use disorder. The foun-

dational research established a graded, dose-response relationship: individuals who experienced five or more adverse childhood experiences — abuse, neglect, and household dysfunction — were on the order of seven to ten times more likely to report illicit drug use and addiction, and for each additional category of childhood adversity the odds of developing dependence rose substantially.² Reviews spanning a quarter-century of research consistently confirm this graded association, and some analyses suggest that adverse childhood experiences may account for a large fraction — by some estimates up to two-thirds — of substance use disorder cases.² The mechanisms are increasingly understood to involve dysregulation of the body's stress systems (the hypothalamic–pituitary–adrenal axis), effects on the developing brain, insecure attachment, and partial mediation through mood and anxiety disorders, consistent with a self-medication pathway in which the drug temporarily relieves the distress that adversity created. For methamphetamine specifically, adverse childhood experiences are associated not only with greater severity of use disorder but with heightened risk of methamphetamine-associated psychosis.³

Environment

Environment supplies both the opportunity and much of the pressure. Drug availability, peer and community norms, poverty, chronic stress, trauma exposure in adulthood, and the absence of opportunity or social support all shape the likelihood that vulnerability becomes use and that use becomes dependence. These are the same social determinants that ran through the epidemiology of Part VII, where methamphetamine use clustered tightly with poverty, housing instability, and marginalization. Environment also interacts with genetics and history: the same genetic predisposition or childhood adversity may or may not express itself depending on whether a person grows up amid availability and stress or stability and support.

Neurobiology

Finally, the drug acts on a brain that addiction progressively reshapes, as detailed in Part V. Methamphetamine's potent, sustained dopamine release and long dura-

tion of action give it high addictive liability, and repeated use drives the reward-system down-regulation and incentive-sensitization described earlier — the blunting of response to ordinary rewards alongside the sensitized motivational pull toward the drug and its cues. Addiction neuroscience frames this as a recurring cycle with three stages: binge and intoxication, withdrawal and negative affect, and preoccupation and anticipation, each engaging distinct neural circuits and each deepening with repetition.⁴ Across these cycles, use shifts from impulsive (driven by anticipated reward) to compulsive (driven by relief of a negative state and by entrenched habit), as control migrates away from deliberative prefrontal systems. This neurobiological trajectory is why addiction is classified as a chronic, relapsing condition rather than a series of free choices.

The convergence

No single factor explains addiction. A genetically vulnerable person, marked by early adversity, living amid availability and stress, who encounters a drug as neurobiologically potent as methamphetamine, sits at the intersection of every risk axis at once. Recognizing this convergence reframes addiction as a health condition with identifiable, modifiable contributors — the premise on which the treatment of Chapter 21 rests.

Withdrawal

Not physically dangerous in the way alcohol withdrawal is, but among the most psychologically severe withdrawal syndromes in medicine — and the period when the risk of relapse, and of self-harm, is highest.

Methamphetamine withdrawal differs fundamentally from the withdrawal syndromes of alcohol, benzodiazepines, or opioids. It is generally not life-threatening through a physical mechanism — there is no equivalent of the seizures or delirium of alcohol withdrawal — yet clinicians regard it as one of the most psychologically punishing withdrawal experiences encountered, precisely because its danger is affective rather than autonomic. The syndrome is driven by the depletion of dopamine and serotonin that follows sustained release, compounded by the receptor down-regulation and neurotoxic changes of Part V, leaving the brain transiently unable to generate ordinary pleasure or motivation.

Symptoms

The hallmark of withdrawal is the "crash": profound fatigue, hypersomnia (often preceded by a period of insomnia), markedly increased appetite, dysphoria, and — most characteristically — anhedonia, the loss of the capacity to feel pleasure. Vivid and unpleasant dreams, cognitive fog, irritability, and craving accompany these. The single most important clinical feature is the risk of depression severe enough to produce suicidal ideation: the dopamine-depleted state of early withdrawal can generate genuinely dangerous despair, and monitoring for suicide risk is an essential part of safe care during this period.⁵

Timeline

Withdrawal unfolds in three overlapping phases. The **acute crash** begins within hours of the last use and is most intense over roughly the first five to ten days; the acute depressive symptoms and any stimulant psychosis largely resolve by the end of the first week or so.⁵ A **subacute phase** then follows over several weeks,

dominated by persistent anhedonia, low energy, and cognitive sluggishness; notably, craving does not necessarily fall in the first days and has been observed not to decline significantly until around the second week, continuing at reduced intensity through at least the fifth week of abstinence.⁵ Finally, a **protracted phase** — post-acute withdrawal syndrome (PAWS) — can persist for two to six months and sometimes up to a year, with lingering anhedonia, low motivation, mood instability, and intermittent craving.⁵

One insight from this timeline carries disproportionate clinical weight: the primary driver of relapse is generally *not* craving for euphoria but flight from the anhedonia and dysphoria of a depleted brain. This means the highest-risk window is not the acute crash itself but the weeks of bleak, low-grade emptiness that follow it, when a person may conclude they will never feel normal again. That conclusion is, importantly, mistaken: the long-term picture is encouraging, with most people returning to a normal emotional range over roughly six to twelve months, though recovery is gradual and non-linear rather than steady.⁵ Communicating this trajectory is itself a therapeutic act, because it reframes a temporary neurochemical state as something that will pass.

Phase	Approximate timing	Dominant features
Acute "crash"	Hours after last use; peaks days ~5–10	Fatigue, hypersomnia, hyperphagia, dysphoria, depression (suicide risk), craving
Subacute	~2–6 weeks	Anhedonia, low energy, cognitive fog; craving persists/peaks ~week 2
Protracted (PAWS)	~2–6 months, some- times to a year	Lingering anhedonia, low motivation, mood instability, episodic craving

Management

There is no medication approved specifically for methamphetamine withdrawal, so management is supportive. The essentials are a safe, low-stimulus environment; rest, rehydration, and nutrition to repair the physiological toll; psychological support; and, above all, monitoring for and responding to suicide risk during the acute phase.⁵ Symptomatic medications are commonly used off-label — agents such as

trazodone or mirtazapine to support sleep, and antidepressants including bupropion to address mood and craving — though none is curative.⁵ Severity and duration are shaped by the duration and intensity of use, the dose, the route (smoking and injection tend to produce more severe withdrawal), polysubstance use, and co-occurring mental and physical health conditions. Because withdrawal is the gateway to treatment, it is also the moment to engage the person with the recovery supports of the next chapter while motivation and contact are present.

Recovery

Recovery from methamphetamine use disorder is genuinely difficult — there is still no approved medication — but it is achievable, and the evidence points clearly to what helps.

Methamphetamine use disorder is one of the harder addictions to treat: unlike opioid use disorder, it has no equivalent of methadone or buprenorphine, no agonist medication with an established place in care. Yet "difficult" is not "hopeless." A substantial evidence base identifies what works, the long-term trajectory for people who reach sustained abstinence is favorable, and an active research effort is steadily expanding the options. This chapter surveys the established and emerging components of recovery.

Behavioral therapies

In the absence of an approved medication, psychosocial treatment is the foundation of care. Cognitive behavioral therapy helps people identify and manage the cues and thought patterns that drive use; the Matrix Model — an intensive outpatient program developed specifically for stimulant use disorders — integrates cognitive behavioral techniques, family education, relapse prevention, and mutual-aid involvement into a structured multi-month protocol; the community reinforcement approach and motivational interviewing round out the established behavioral toolkit. These therapies share a logic suited to the neurobiology of Part V: they work to rebuild deliberative control and to reshape the cue-driven learning that sustains compulsive use.

Contingency management

One behavioral intervention stands apart for the strength of its evidence. Contingency management — which provides tangible incentives, typically vouchers or prizes, contingent on verified drug-negative urine tests — is the treatment strategy with the best demonstrated effectiveness for methamphetamine use disorder,

supported by dozens of controlled studies.⁶ It works by supplying an immediate, reliable alternative reward to a reward system that the drug has blunted, directly countering the hypodopaminergic state described earlier. Its limitations are practical rather than scientific: concerns about cost, the durability of gains after incentives stop, and regulatory and funding barriers have constrained its scale-up, though it remains the single most effective intervention available and is increasingly recognized as a standard of care.⁶

Peer support

Mutual-aid and peer support provide community, accountability, and lived-experience guidance that complement formal treatment. Programs such as Crystal Meth Anonymous offer a twelve-step framework tailored to stimulant use, while alternatives such as SMART Recovery provide a secular, skills-based model; peer recovery support specialists — people in recovery themselves — increasingly work within treatment and harm-reduction settings. For many people, the connection and belonging these supports provide are decisive, particularly given the social isolation that so often accompanies methamphetamine use.

Emerging treatments

The search for a pharmacotherapy is active, and while no medication is yet FDA-approved for methamphetamine use disorder, several show promise.^{7,8} The most significant recent result comes from the ADAPT-2 trial, a multisite, placebo-controlled study of extended-release injectable naltrexone combined with oral extended-release bupropion: participants receiving the combination achieved a meaningfully higher rate of methamphetamine-negative urine tests than those on placebo (an increase of roughly 27 percent versus about 11 percent), a modest but genuine effect that was notable because each drug alone had shown little benefit.⁷ Mirtazapine has reduced methamphetamine use in controlled trials, particularly among men who have sex with men receiving counseling, and other agents — modafinil, topiramate, and stimulant agonist-replacement approaches — have shown promising but small effects.⁸ Further trials, including extended studies of the naltrexone–bupropion combination, are ongoing.^{7,8} Beyond small molecules,

immunotherapies — an anti-methamphetamine monoclonal antibody and vaccine candidates — are under investigation and are discussed in Part XIII. The consistent recommendation across this literature is that pharmacotherapy works best in combination with behavioral treatment such as contingency management rather than as a stand-alone fix.⁷

Relapse prevention

Because methamphetamine use disorder is a chronic, relapsing condition, sustaining recovery is its own discipline. Effective relapse prevention combines several elements: identifying and managing the drug cues and triggers that the sensitized motivational system has wired in (Part V); anticipating and weathering the protracted anhedonia window that is the chief relapse driver (Chapter 20); building structure, routine, and supportive relationships; using physical activity, which the evidence suggests aids both mood and cognitive recovery (Part V); and treating co-occurring mental illness, which is common and which destabilizes recovery when neglected. Harm-reduction services (Part VII) function as a crucial bridge throughout, keeping people alive and connected during the periods between, or before, episodes of formal treatment. A realistic understanding is essential: lapses are common and are best treated as setbacks to learn from rather than as failures that erase progress. With the combination of behavioral treatment, emerging pharmacotherapy, peer support, and harm reduction — and with time — recovery is a reasonable and attainable goal.

Approach	Evidence / status
Contingency management	Best-evidenced treatment (dozens of trials); cost/scalability limits uptake
CBT / Matrix Model / CRA / MI	Established behavioral standard of care
Naltrexone + bupropion (ADAPT-2)	Modest but significant benefit; not FDA-approved; trials ongoing
Mirtazapine; modafinil; topiramate; agonist replacement	Promising but small effects; investigational

Immunotherapy (monoclonal anti-body, vaccines)	Investigational (see Part XIII)
Peer support (CMA, SMART Recovery)	Valuable complement to formal treatment

References — Part VIII

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

1. Heritability of substance use disorders from twin and family studies (broadly ~40–70%, polygenic, gene–environment interacting); household substance use approximately doubles risk of dependence. (Gelernter J, Kranzler HR; Kendler KS, et al.; see also PM-C2763992.)
2. Felitti VJ, Anda RF, et al. Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults (the Adverse Childhood Experiences Study). *Am J Prev Med.* 1998;14:245–258. Dube SR, et al. Childhood abuse, neglect, and household dysfunction and the risk of illicit drug use. *Pediatrics.* 2003;111:564–572. (≥5 ACEs associated with 7–10× greater likelihood of illicit drug use/addiction; dose-response; each additional ACE category roughly doubles odds.) Umbrella review: PMC9675346. Estimate that ACEs may account for up to two-thirds of SUD cases: PMC2763992; NCT06236100.
3. Adverse childhood experiences, depression, and addiction severity among people with methamphetamine use disorder; ACEs associated with greater MUD severity and increased risk of methamphetamine-associated psychosis (dose-response). (PM-C11130423.)
4. Koob GF, Volkow ND. Neurobiology of addiction: a neurocircuitry analysis — the three-stage cycle (binge/intoxication; withdrawal/negative affect; preoccupation/anticipation); incentive-sensitization and reward-deficiency frameworks. (See also Part V references.)
5. Methamphetamine withdrawal — phases and course: acute crash peaking days ~5–10 with depression and suicide risk; subacute anhedonia; protracted withdrawal (PAWS) lasting months; craving trajectory (Zorick T, et al., PMC3071736); supportive management and absence of approved pharmacotherapy. (SAMHSA treatment guidance; StatPearls/NBK576550; clinical reviews.)
6. Contingency management as the best-evidenced treatment for methamphetamine use disorder (dozens of controlled trials), with cost, durability, and scalability limitations. (PMC10433563; AshaPrethika / SAMHSA reviews.)
7. Trivedi MH, et al. Bupropion and naltrexone in methamphetamine use disorder (ADAPT-2). *N Engl J Med.* 2021;384:140–153. Extended observation: Li MJ, et al. *Addiction.* 2024 (~27% vs. ~11% methamphetamine-negative urine tests). NIH news release, 2025. No FDA-approved medication for MUD; combination with behavioral treatment recommended. Ongoing: REBOOT 2.0; NIDA XR-NTX/BUP-XL trial (ClinicalTrials.gov NCT06233799, 2026).
8. Emerging pharmacotherapy review — mirtazapine (reduced use, especially among men who have sex with men with counseling; Colfax/Coffin trials), modafinil, topiramate, and agonist-replacement approaches showing promising but small effects; no FDA-approved option. (PMC10433563; CSUH/NIDA CTN study summaries.)
9. Behavioral treatments for stimulant use disorder: the Matrix Model (Rawson RA, et al.), cognitive behavioral therapy, community reinforcement approach, and motivational interviewing. Mutual-aid resources: Crystal Meth Anonymous; SMART Recovery.

10. Immunotherapy for methamphetamine (anti-methamphetamine monoclonal antibody IXT-m200; vaccine candidates), ClinicalTrials.gov NCT04715230 — investigational; see Part XIII.

End of Part VIII — Addiction Science (Chapters 19–21)

Part IX — Toxicology (Chapters 22–24: Acute Toxicity; Chronic Toxicity; Drug Interactions)
continues the volume.