

PART XIII

Research Frontiers

Chapters 33–35

New Treatments

The absence of an approved medication has spurred a genuinely active research pipeline — immunotherapies, novel drugs, and brain stimulation — all still investigational, none yet proven.

A note on investigational status

Everything in this chapter is under investigation. None of the approaches described is an FDA-approved treatment for methamphetamine use disorder, and promising early results routinely fail to survive larger trials. The findings below are reported as active research directions, not as available or validated therapies, and the reader should read every "promising" and "may" as the genuine uncertainty it denotes.

As Parts VIII and XII established, there is no medication approved for methamphetamine use disorder, and behavioral treatment — above all contingency management — remains the evidence-based foundation of care. This gap has motivated an unusually broad search for new options, spanning immunological, pharmacological, and device-based strategies.

Monoclonal antibodies

Passive immunotherapy is among the most novel approaches. The strategy is to administer a laboratory-produced antibody that binds methamphetamine in the bloodstream, sequestering the drug and slowing or reducing its entry into the brain, thereby blunting its central effects.¹ An anti-methamphetamine monoclonal antibody (IXT-m200) has entered clinical trials, investigated both as a potential treatment for acute overdose — where its rapid binding could be valuable given the absence of any antidote (Chapter 15) — and as a relapse-prevention aid.¹ A practical appeal of a long-acting antibody is that it does not depend on a patient's remembering to take a daily medication.

Vaccines

Active immunotherapy pursues the same goal by a different route: a conjugate (hapten) vaccine that trains the person's own immune system to generate antibodies against methamphetamine.¹ The central scientific challenge has been eliciting antibody levels high enough, and sustained enough, to meaningfully affect the drug's action — a problem that has limited stimulant vaccines generally. Both passive and active immunotherapy remain promising but unproven pharmacologic strategies for the disorder.¹

Novel medications

A range of small-molecule medications is being evaluated, mostly by repurposing drugs approved for other conditions. The most significant result to date remains the combination of extended-release naltrexone and bupropion from the ADAPT-2 trial (Chapter 21), which produced a modest but genuine benefit.² Beyond it, agents under study include oxytocin, the alpha-blocker doxazosin, lobeline, disulfiram, acamprosate, atomoxetine, entacapone, topiramate, mirtazapine, and modafinil, among others.² The recurring pattern across this literature is of small and inconsistent effects, which is precisely why none has yet reached approval — and why the consistent recommendation is to pair any pharmacotherapy with behavioral treatment rather than expect a medication to work alone.²

Neuromodulation

Device-based brain stimulation targets the neural circuits described in Part V directly. The most studied approach is **repetitive transcranial magnetic stimulation (rTMS)**, which uses magnetic fields to modulate activity in the frontal-striatal circuits of addiction — typically the dorsolateral prefrontal cortex (associated with executive control) and the medial prefrontal cortex (associated with the limbic craving circuit).³ A meta-analysis of double-blind randomized trials found that rTMS may reduce craving in methamphetamine use disorder, with intermittent theta-burst stimulation possibly outperforming conventional 10-Hz protocols, and the treatment is generally well tolerated, with mild and short-lived side effects such as headache.³ The evidence base is now expanding through larger, rigorous

trials — including the multi-site, sham-controlled STIMULUS study sponsored by the U.S. National Drug Abuse Treatment Clinical Trials Network, evaluating rTMS over the left dorsolateral prefrontal cortex for moderate-to-severe cocaine and methamphetamine use disorder — alongside numerous trials refining stimulation targets and protocols.^{3,4} Deep brain stimulation is being explored for severe, treatment-refractory addiction, though it remains highly experimental. The unifying idea is to help rebuild the top-down control that chronic use erodes.

Approach	Mechanism / status
Monoclonal antibody (IXT-m200)	Passive immunotherapy; binds meth in blood; trials for overdose and relapse prevention
Conjugate vaccine	Active immunotherapy; challenge is sustained antibody titers; in development
Novel/repurposed drugs	Naltrexone+bupropion (modest); oxytocin, doxazosin, topiramate, mirtazapine, etc.; small effects
rTMS	Modulates dlPFC/mPFC circuits; reduces craving (meta-analysis); STIMULUS and other trials ongoing

Artificial Intelligence

Machine learning is being applied across the methamphetamine problem — from sewers to bedsides — with real promise and a set of ethical hazards unusually acute for this condition.

Artificial intelligence and machine learning are increasingly applied to substance use, and methamphetamine is no exception. The applications span scales, from monitoring whole populations to informing decisions about individual patients. The promise is real, but so are the hazards, which for substance use are sharper than for most medical applications of AI, and this chapter gives the ethical questions the weight they deserve.

Predictive epidemiology

Machine-learning models can forecast trends and detect emerging problems earlier than traditional methods. Trained on real-world data from electronic health records, insurance claims, digital devices, and social media, such models have been developed to predict overdose risk, and they have proven more accurate at identifying high-risk individuals than conventional risk-factor measures — an important gain, given that traditional approaches miss an estimated 70 to 80 percent of people who go on to overdose or develop a use disorder.⁵ The aim is earlier, better-targeted intervention.

Public health surveillance

At the population level, one of the most valuable and least ethically fraught applications is wastewater-based epidemiology: analyzing municipal wastewater for drug metabolites — including methamphetamine alongside fentanyl and cocaine — and normalizing the results against population biomarkers to produce near-real-time trend data for a community.⁶ Because it measures a population rather than individuals, wastewater surveillance provides drug-use trends and can flag emerging spikes without the consent and stigma problems that attach to individ-

ual-level monitoring.⁶ Combined with mining of social media and other digital signals, AI-enabled surveillance offers a faster picture of a fast-changing drug supply.

Clinical decision support

At the level of the individual patient, machine-learning-driven clinical decision support tools — integrated into electronic health record systems — can flag patients at elevated risk, help predict treatment outcomes and relapse, and support more personalized care.⁵ AI methods are also being used in research to analyze complex treatment-response data, such as the neuroimaging changes associated with the neuromodulation trials of Chapter 33. Across these uses, "explainable AI" — models whose reasoning clinicians can inspect and trust — is widely regarded as essential to responsible clinical implementation.⁵

Ethical considerations

For substance use, the ethical stakes of AI are distinctive and severe, and they should temper enthusiasm at every step. Several principles emerge from the literature. First, **identification is pointless, and arguably unethical, without treatment capacity to match**: flagging at-risk people without ensuring they can access care simply labels them.⁵ Second, and unlike most clinical AI, **substance-use predictions can trigger discrimination, criminal-justice involvement, and denial of care**; a false positive is not a harmless error but one that stigma actively amplifies, which means that for these tools *specificity matters more than sensitivity*.⁵ Third, **privacy** is a central concern for individual-level surveillance (and a key reason population-level wastewater methods are preferable where they suffice). Fourth, **algorithmic bias and equity** demand scrutiny, because a biased model can deepen the very disparities documented in Part VII, in which methamphetamine harm already falls disproportionately on some communities. The responsible path is to deploy these powerful tools deliberately, with transparency, consent where applicable, and constant attention to whether they help people or merely surveil them.

Future Directions

Three convergent directions — precision medicine, biomarkers, and digital therapeutics — that could reshape prevention and treatment, presented as grounded aspirations rather than accomplished facts.

This final chapter of the science looks forward. The directions below are genuine and active, but they are aspirations supported by early evidence, not realized capabilities. Their unifying theme is a shift away from one-size-fits-all responses toward care that is personalized, objectively measured, and deliverable at scale.

Precision medicine

Precision medicine aims to tailor treatment to the individual rather than the average patient. For methamphetamine, its most concrete handle is pharmacogenomics — using genetic information, such as a person's CYP2D6 metabolizer status (Chapter 9), to anticipate how they will process the drug and related medications. An honest account must note the caveat established earlier: the clinical impact of CYP2D6 variation is more muted than in-vitro data suggest, because other pathways and renal excretion also contribute.⁸ The broader precision-medicine aspiration is to match each patient to the pharmacological or behavioral intervention most likely to help them — a goal still largely ahead of us, but one that better biological and clinical characterization could bring closer.

Biomarkers

Biomarkers are objective, measurable indicators that could sharpen prevention and treatment. Neuroimaging already provides several — the dopamine-transporter and D2-receptor measures and the functional-connectivity changes used as outcomes in the neuromodulation trials of Chapter 33, together with the structural changes of Part V — and researchers are pursuing peripheral markers of oxidative stress and neurotoxicity as well.⁹ The aspiration is a set of validated biomarkers that could identify who is at greatest risk of developing a use disorder,

track the brain injury of chronic use and its recovery, and predict who will respond to a given treatment, with artificial intelligence increasingly assisting in discovering such markers from complex data.⁹ As with precision medicine, the promise is real and the validation still in progress.

Digital therapeutics

Perhaps the nearest-term of these directions is the delivery of treatment through software. The field's landmark product, reSET (developed by Pear Therapeutics), became the first prescription digital therapeutic authorized by the FDA in 2017, indicated for stimulant and other substance use disorders and delivering cognitive behavioral therapy together with contingency management via an app.¹⁰ For methamphetamine specifically, smartphone-delivered programs — such as those studied under the Affect Therapeutics platform and other application-based interventions combining cognitive behavioral therapy, approach-bias modification, cognitive training, contingency management, remote drug testing, and telemedicine counseling — have shown feasibility and preliminary efficacy in reducing use.¹⁰ The strategic significance is large: because digital delivery can extend treatment to people who cannot easily attend a clinic (owing to distance, work, or caregiving) and can *scale contingency management*, it directly addresses the scalability barrier that has limited that intervention (Chapter 32).¹⁰ A sobering caveat tempers the optimism, however: the bankruptcy of Pear Therapeutics in 2023 left patients without access to its FDA-cleared products, a reminder that the sustainability of digital therapeutics — commercial, regulatory, and reimbursement-related — is not yet solved.¹⁰

Taken together, the frontiers of this chapter and the last describe a field in motion. None of these directions has yet transformed care, and this book has been careful throughout to distinguish what is established from what is hoped for. But the trajectory — toward personalized, measurable, scalable, and more humane treatment, layered atop the behavioral and harm-reduction foundations that already save lives — is a genuinely hopeful one, and it is grounded in real science rather than wishful thinking.

Direction	Aim / status
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Precision medicine	Tailor treatment via pharmacogenomics (e.g., CYP2D6) and phenotype; largely aspirational
Biomarkers	Objective markers of risk, neurotoxicity, and treatment response; validation in progress
Digital therapeutics	App-delivered CBT + contingency management; scales access; sustainability unsolved

References — Part XIII

Listed in order of first citation within Part XIII. Numbering restarts each installment; the apparatus is to be consolidated on final assembly. All treatments described are investigational. Sources current as of 2026.

1. Immunotherapy for methamphetamine use disorder — passive (anti-methamphetamine monoclonal antibody IXT-m200; ClinicalTrials.gov NCT04715230) and active (conjugate/hapten vaccines) strategies. "Current and Emerging Treatments for Methamphetamine Use Disorder" (PMC9185770); see also Part VI.
2. Novel and repurposed pharmacotherapies under investigation — extended-release naltrexone plus bupropion (ADAPT-2, most promising to date; see Part VIII); oxytocin, doxazosin, lobeline, disulfiram, acamprosate, atomoxetine, entacapone, topiramate, mirtazapine, modafinil; contingency management producing the strongest non-pharmacological effect. (PMC9185770.)
3. Efficacy of rTMS in methamphetamine use disorder — systematic review and meta-analysis of double-blind randomized controlled trials (through March 2022): association with craving reduction; intermittent theta-burst stimulation possibly superior to 10-Hz; targets in the dorsolateral and medial prefrontal cortex; generally well tolerated. (PMC9197111.)
4. STIMULUS trial — repetitive transcranial magnetic stimulation for stimulant use disorders: multi-site, double-blind, sham-controlled trial (NIDA Clinical Trials Network; 10-Hz over left dorsolateral prefrontal cortex; ~160 participants with moderate-to-severe cocaine or methamphetamine use disorder). *Addiction Science & Clinical Practice* (2025), PMC12060337. Additional rTMS trials: Shanghai Mental Health Center (NCT03736317, NCT03827785, NCT06457230).
5. Artificial intelligence for substance use and overdose prevention — machine-learning overdose-risk prediction outperforming traditional risk measures (which miss ~70–80% of cases; Lo-Ciganic et al.); ML-driven clinical decision support integrated into electronic health records (PMC11488086); and the ethical framework (identification requiring matched treatment capacity; risk of discrimination/criminal-justice involvement/treatment denial; specificity over sensitivity; privacy; bias/equity; explainable AI). (Public Health AI Handbook, "AI for Substance Use and Overdose Prevention," 2025; medical-AI ethics literature, PMC11473215.)
6. Wastewater-based epidemiology for population-level drug monitoring — analysis of methamphetamine, fentanyl, and cocaine metabolites normalized by population biomarkers, providing near-real-time trend data and spike detection without individual consent/stigma concerns. (Public Health AI Handbook; wastewater-based epidemiology literature.)
7. Broader AI applications and cautions in medicine (drug discovery, decision support, imaging/biomarkers, natural language processing) and their ethical/transparency challenges. (PMC10539991; PMC10549955; PMC11473215.)
8. Pharmacogenomics and precision medicine — CYP2D6 metabolizer status and the muted clinical impact of its variation owing to alternative clearance pathways (de la Torre R, Peiró AM, et al., PMC3495276; see Part IV).

9. Biomarkers — neuroimaging (dopamine transporter and D2-receptor measures; functional connectivity as neuromodulation-trial outcomes; structural MRI, Part V) and peripheral markers of oxidative stress/neurotoxicity; AI-assisted biomarker discovery. (See Part V; AI in pharmacological research, PMC10539991.)
10. Digital therapeutics — reSET (Pear Therapeutics), the first FDA-authorized prescription digital therapeutic (2017) for stimulant/cocaine/cannabis/alcohol substance use disorders, delivering cognitive behavioral therapy and contingency management (based on the Therapeutic Education System); Pear Therapeutics bankruptcy (2023) illustrating sustainability challenges; methamphetamine-specific app programs — Affect Therapeutics field study (49 adults; 55% completion; greater likelihood of methamphetamine-negative tests week 1→8, OR 1.57; PMC10373299) and a smartphone application combining internet-based CBT, approach-bias modification, cognitive training, and contingency management (randomized study, PMC9627209); telehealth and remote monitoring scaling contingency management (PMC11406110; PMC9352538).

End of Part XIII — Research Frontiers (Chapters 33–35)

*Part XIV — Reference (Chapters 36–40: Glossary; FAQ; Timeline; Statistics Atlas;
Comprehensive Index)
and Appendices A–H conclude the volume.*