

Opioid Use Disorder Education and Treatment ECHO Series

Session 13 – Opioid Use Disorder and Stimulants

May 17, 2022

Heather Bell, MD and Kurt DeVine, MD

Some slides adapted from Lisa Lindquist, MD, Wilson Compton



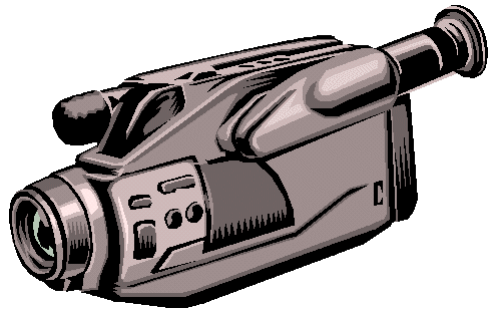
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STRONG MEDICINE FOR MINNESOTA

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Announcements

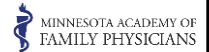


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SESSIONS ARE RECORDED

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YES, THERE'S *FREE* CME

This activity has been planned and implemented in accordance with the accreditation requirements and policies of the Minnesota Medical Association (MMA) through the joint providership of Stratis Health and the Minnesota Academy of Family Physicians. **Stratis Health is accredited by the MMA to provide continuing medical education for physicians.**

Stratis Health designates this educational activity for a maximum of **1 AMA PRA Category 1 Credits™**.

Physicians should claim credit commensurate with the extent of their participation in the activity.

Continuing Education Credits and Contact Hours for Other Health Professionals

The OUD Education and Treatment ECHO Series may meet continuing education requirements for your focus. It is the responsibility of the individual to determine if this activity fulfills that requirement.



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Attendance

- Please chat us the names of people on ECHO if there are multiple people in your room!
- “Re-name” your self so we know who’s here!
- Please turn your video on!
 - Human connection!
 - And we do NOT care if you are eating!



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Case Presentations!

The ECHO model is based on case-based learning!
The case presentation form is available on the MAFP website
(<https://bit.ly/OUDCase>) and in the announcements email!
BUT feel free to present in any de-identified format!

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Upcoming Tuesday ECHO Sessions

- **Tuesday, June 7, 2022:** OUD and Pregnancy
- **Tuesday, June 21, 2022:** OUD and Neonatal Opioid Withdrawal Syndrome (NOWS)
- **Tuesday, July 19:** Perioperative Management
- **Tuesday, August 2:** Community Collaboration Engagement
- **Tuesday, August 16:** Motivational Interviewing (MI) Lapse/Relapse

Upcoming Wednesday ECHO Sessions

- **Wednesday, May 18, 2022**
Understanding East African Clients, with Yussuf Shafie, MSW, LICSW, CEO, Alliance Wellness Center
- **Wednesday, May 25, 2022**
The Opioid Epidemic From The Perspective of an Emergency Physician and Toxicologist at a Safety-Net Hospital, with Jon Cole, MD, Hennepin Healthcare

“The Addiction Connection Podcast”

Weekly addiction
topics- Tuesday
release day!

www.buzzsprout.com/954034

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Email us questions:

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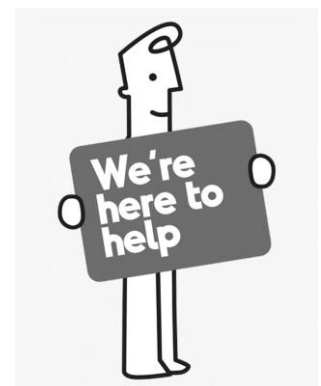
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TECHNICAL ASSISTANCE

- **We are ALWAYS here for you!**
 - Program implementation
 - Inductions
 - Difficult cases
 - Trouble-shooting
 - Anything!
- **Call us anytime:**
 - Erin Foss, RN, Program Manager/Nurse Specialist
efoss@stratishealth.org, Cell: 320-282-6553
 - Heather Bell: 320-630-5607
 - Kurt DeVine: 320-630-2507



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Objectives

- Describe the basic pharmacology of stimulants including methamphetamines and cocaine
- Associate symptomatology of intoxication and withdrawal
- Explain treatments for stimulant use
- Understand methamphetamine induced psychosis

Stimulants

Categories and Examples

- Stimulants: (Norepinephrine (Norepi), Dopamine, 5HT agonists)
 - Cocaine
 - Meth/amphetamines
 - Synthetic cathinones (bath salts)
- Empathogens: (5HT and Norepi, Dopamine agonists)
 - MDMA, PMA, etc.
- Hallucinogens: (5HT and Norepi, Dopamine agonists)
 - LSD
 - Psilocybin
 - DMT
 - Mescaline



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Monoamine Spectrum

Stimulant:
Dopaminergic
Adrenergic
Addictive
CV/SZ/SI risks



Hallucinogen:
Serotonergic
Mild N.epi
Nonaddictive
Psychiatric risk

Empathogen:
Balanced effects
Addictive?
Harmful?

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Hallucinogens

- 2 chemical ‘types’:
 - Indole alkalamines:
 - LSD, psilocybin
 - Similar structure to serotonin
 - Phenethylamine:
 - Inc. mescaline, MDMA
 - Structurally like norepinephrine
- Most ingested orally



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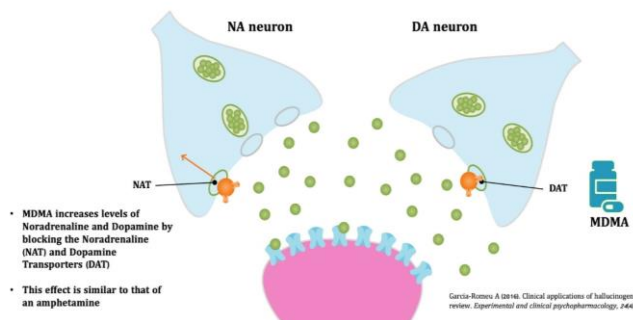
Hallucinogens

- Effects:
 - Euphoria, “spiritual insight”, alterations in space and time
 - Depression, anxiety, terror, delusions, and hallucinations
- Metabolism:
 - Most in the liver
- Mechanism of action:
 - Psychedelics have agonist or partial agonist activity at brain serotonin 5-HT_{2A} receptors



Methylenedioxy-Methamphetamine (MDMA)

Mechanism of Action



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Cocaine

- Alkaloid with a structure very similar to scopolamine
- Occurs in the leaves of the coca bush
- Use:
 - Base turns to vapor (inhaled) at 98° NOT soluble in water
 - Reaches brain in 6-8 seconds
 - Peak effect in 4-7 minutes
 - Cocaine salt dissolves in water and is easily injected
- Effect:
 - Increased energy, alertness, elation, euphoria
 - Intense pleasure - “full-body orgasm”



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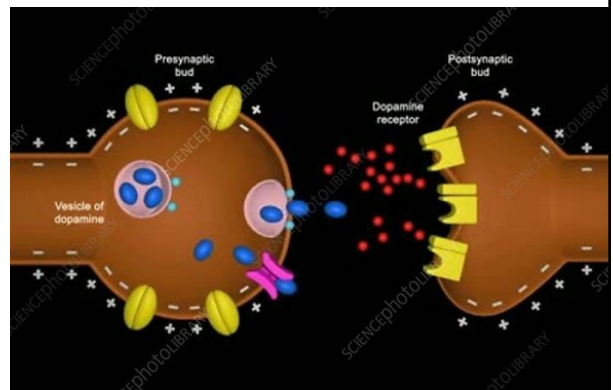
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Cocaine

- Metabolized to benzoylecgonine- excreted in the urine
 - The chemical tested in the urine drug screen
- Mechanism of action:
 - Blocks catecholamine and serotonin transporters and increases extra-cellular dopamine by binding with a dopamine transporter



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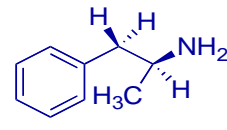
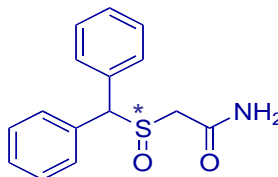
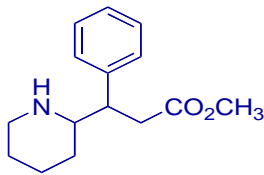
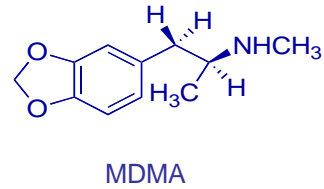
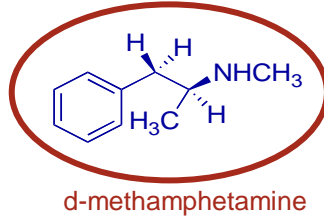
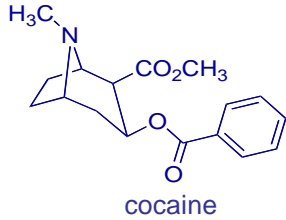
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Methamphetamine

**More common than opioids, so we
will spend a bit of time on this...**

Psychostimulant Drugs



Graphics created by NIDA

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Meth Basics

- Common names:
 - Meth
 - Crank
 - Speed
 - Blue
 - Ice
 - Crystal
 - Redneck cocaine
 - LA glass
 - Soap Dope
- Man-made potent stimulant
- Most commonly: white, odorless, crystalline powder



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Meth Basics

- 2017 U.S. Data:
 - 1.6 million people (0.5%) used meth
 - Involved in 15% of all OD deaths
 - 964,000 people had meth use disorder
 - 0.5% high schoolers used meth
 - Highest in western and midwestern USA
 - Primarily produced in Mexico
 - Pure, potent, cheap
 - Limited domestic production due to restrictions on ephedrine and pseudoephedrine



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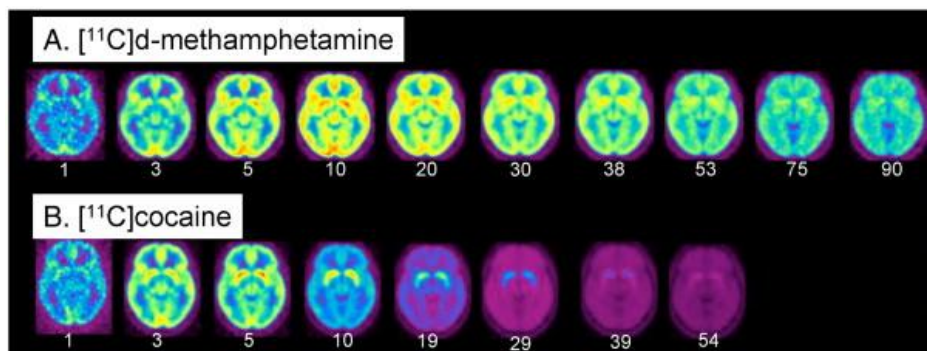
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Comparison of Meth and Cocaine Pharmacokinetics in Striatum

Meth clears slowly from the striatum relative to cocaine, which clears rapidly



JS Fowler, et al. NeuroImage. (2008) 43(4):756-763

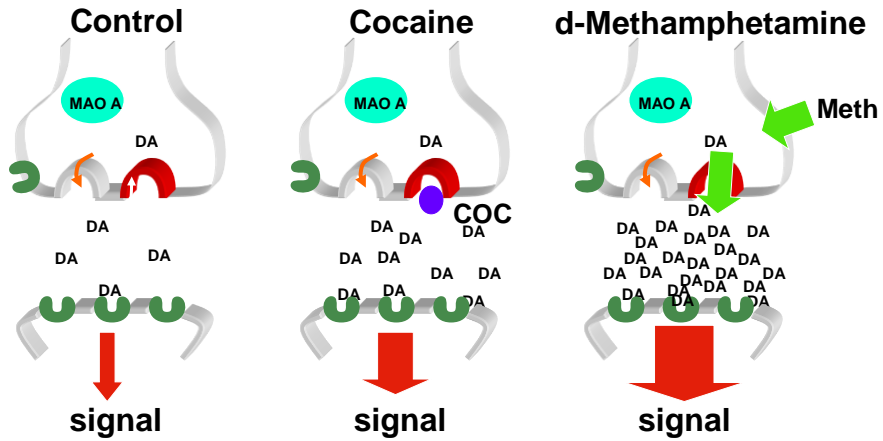
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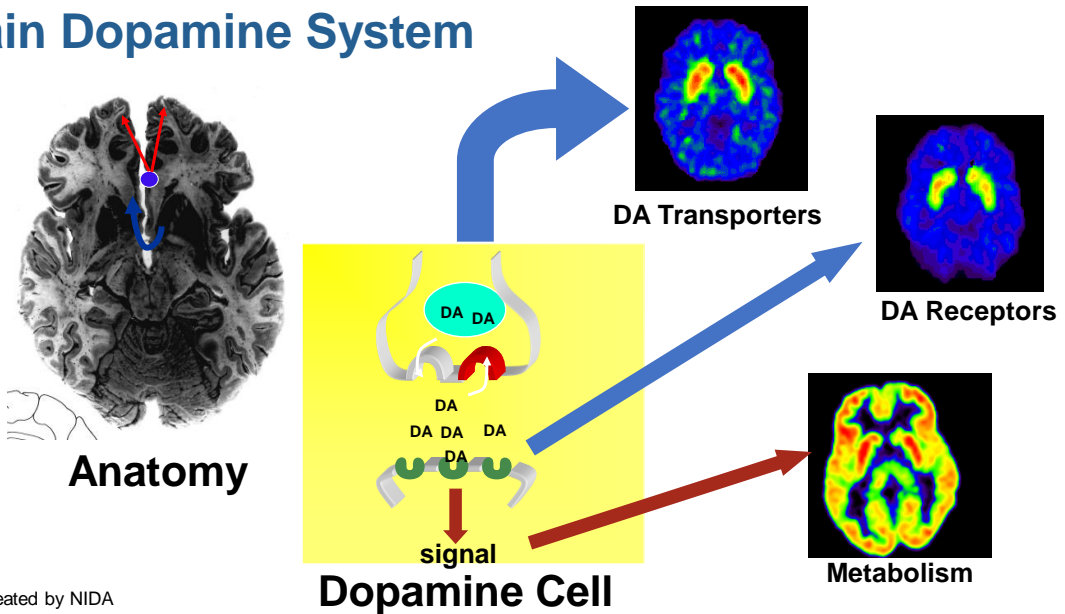
Cocaine blocks dopamine reuptake; Meth blocks dopamine reuptake and releases it from vesicles.



Graphics created by NIDA



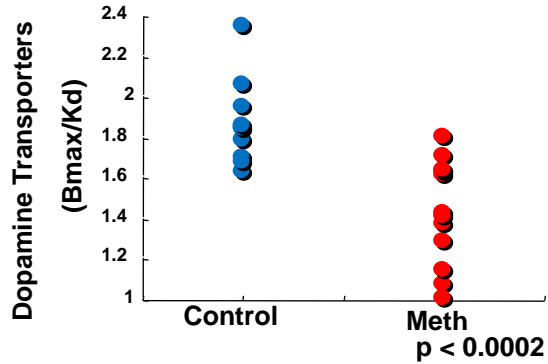
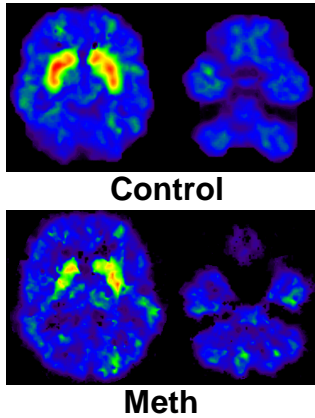
Brain Dopamine System



Graphics created by NIDA



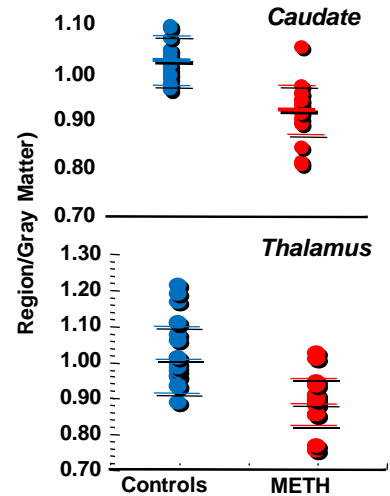
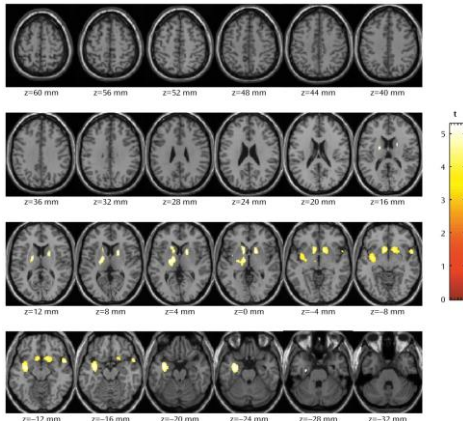
Meth Users Have Significant Reductions in Dopamine Transporters



ND Volkow, et al. Journal of Neuroscience. (2001) 21(23):9414-9418

ND Volkow, et al. Am J of Psych. (2001) 158:383-389

Decreased Metabolism in Methamphetamine Users

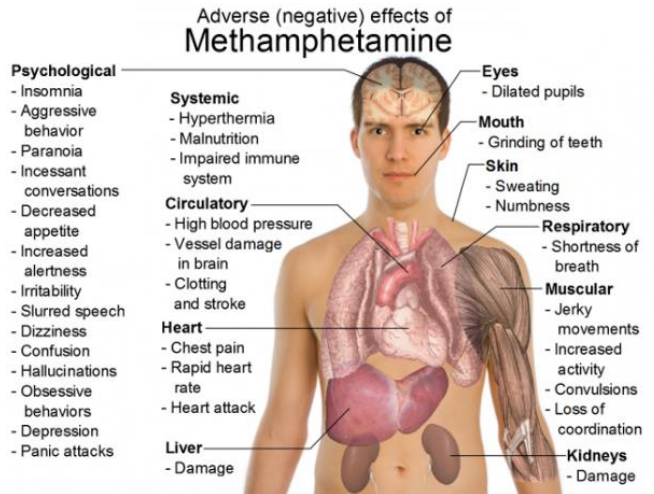


G-J Wang et al. Am J Psychiatry. (2004) 161(2):242-248.

ND Volkow, et al. Am J of Psych. (2001) 158:383-389

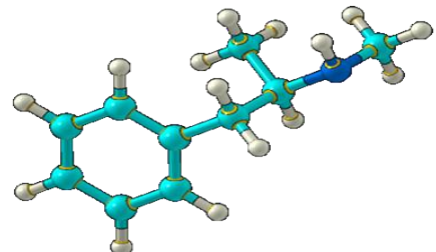
Concerns with Methamphetamine

- Neurotoxic and damaging to multiple organs in the body
- Euphorigenic effects wear off before drug out of the CNS, accumulates in CNS
- Low dose use: damage to serotonergic pathways of frontal cortex, hippocampus
- High dose use: damage to striatum, parietal cortex
 - Decreases density of D2 receptors
 - Decreases serotonin, dopamine, norepi with chronic use



Concerns with Methamphetamine cont.

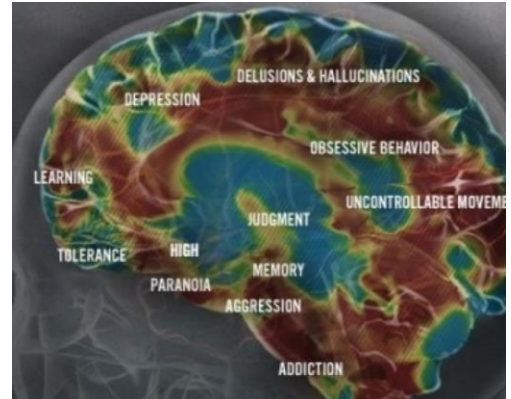
- Intoxication associated with impulsive risky behaviors including those that increase risk of HIV and HCV
- Can be easily manufactured in small clandestine laboratories
- NO medications available to help in its treatment
- and...



METH is Highly Addictive, Toxic, Hard to Treat

- Acute Effects

- Increased alertness/energy
- Aggression/violence
- Psychosis
- Decreased appetite
- Rhabdomyolysis
- Hyperthermia
- Suicidality/homicidality with binge use
- HTN, cardiac complications, strokes
- Seizures



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METH is Highly Addictive, Toxic, Hard to Treat

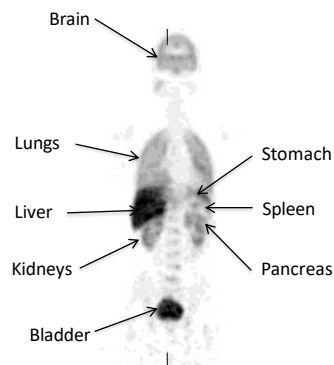
- Impairment:

- Episodic memory
- Executive functioning
- Processing speed
- Motor skills
- Language
- Visuoconstructional abilities

- Chronic Effects

- Difficulty feeling any pleasure other than from Meth, fueling further use
- Psychosis, violent behaviors, depression can persist long after last use

Distribution of
Methamphetamine in Body



ND Volkow, et al. PLoS ONE. (2010) 5(12):e15269

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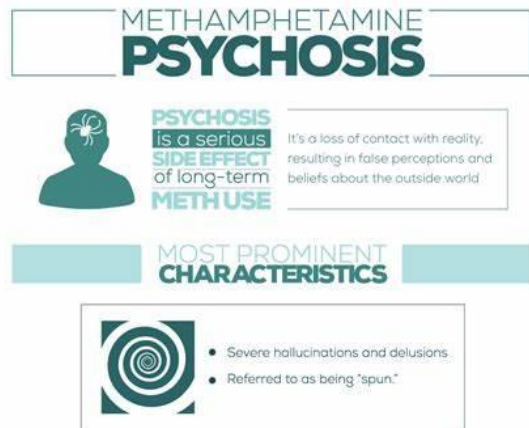
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Meth is Highly Addictive, Toxic, Hard to Treat

- Transient psychotic symptoms occur in up to 40% of those who use:
 - Auditory hallucinations
 - Visual hallucinations
 - Tactile hallucinations
 - Paranoia
 - Persecutory delusions
 - Ideas of reference



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Withdrawal and Abstinence Syndrome

- May develop in hours, peaks at ~48 hours, lasts up to 2 weeks
- Acute withdrawal or "crash"
 - Dysphoria
 - Irritability
 - Anhedonia
 - Fatigue
 - Hypersomnia or insomnia
 - Drug craving
 - Increased appetite and hyperphagia
- Post-acute withdrawal syndrome may persist for 1+ months
 - Sleep disturbance
 - Appetite changes
 - Depressed mood

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Methamphetamine Psychosis

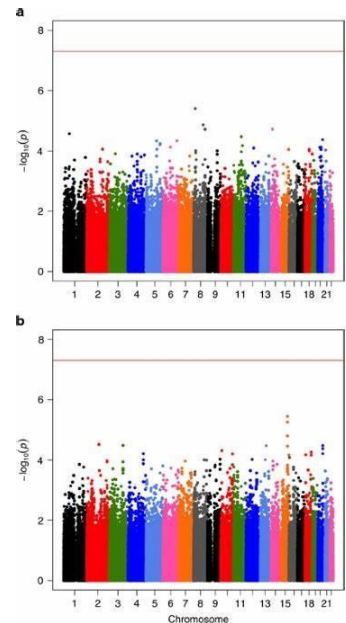
- Prevalence rate ~44% in those with methamphetamine use disorder
- Recreational users 2-3x more likely to develop psychotic symptoms vs. general population
- Regular users 11x more likely vs. general population
- Average time between first use and psychotic symptoms is:
 - 1.7 years when smoking
 - 4.4 years when injecting

Methamphetamine Psychosis cont.

- Significant variability in duration of psychotic symptoms after use
 - Days to months
 - Years of lifetime use
 - **Type A: <1 month of psychotic sx associated with <5 years of use**
 - **Type B: 1+ months of symptoms associated with 5+ years of use**
 - Role of chronic amphetamine effects on dopaminergic and serotonergic activity and neurotoxicity
 - 30% have sx for >6 months following abstinence
 - Dose-response relationship between methamphetamine use and psychotic symptoms
 - Binge use associated with psychosis
- High rates of recurrence with decreased periods of latency

Methamphetamine Psychosis cont.

- May be a genetic vulnerability to persistent psychosis
- Family members of persons with meth induced psychosis are 5x more likely to develop schizophrenia
- 7 candidate genes associated with susceptibility to meth psychosis and confer poorer clinical course
- Overlap between genetic markers for methamphetamine psychosis and schizophrenia
- In study of >1000 methamphetamine users in Thailand who experienced 1+ episodes of psychosis, within 6 years, 40% had been diagnosed with schizophrenia



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Methamphetamine Psychosis cont.

- Can exacerbate psychosis in patients with underlying psychotic disorder
- Other risk factors:
 - Poly drug use
 - Affective disorders
 - Antisocial personality disorder
 - Family psychiatric history
 - Childhood and adolescence use
 - Method of administration: higher in smoking vs injecting
- Meth psychosis Vs. schizophrenia: Meth has:
 - Higher prevalence of visual and tactile hallucinations
 - Fewer negative symptoms (withdrawal, blunted affect, poverty of speech)
 - Less disorganized
 - Presence of movement disorders (orofacial dyskinesia, choreoathetoid movements)

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Methamphetamine Psychosis cont.

- Treatment:
 - Acute:
 - Benzos:
 - Acute agitation, insomnia
 - Blunt hyperadrenergic effects of methamphetamine
 - Avoid physical restraints
 - Risk of isometric muscle contractions associated with lactic acidosis, hyperthermia etc.
 - Minimize environmental stimulus

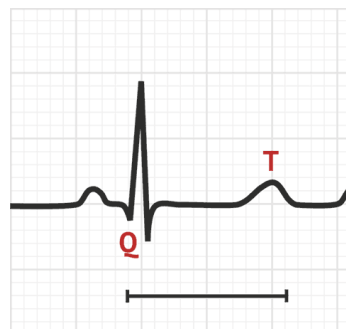


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Methamphetamine Psychosis cont.

- Treatment continued:
 - Neuroleptics?
 - Potential interaction between meth and Haldol:
 - » Resulting in GABAergic cell death
 - » Increasing risk of seizure and movement disorders
 - Risk of QT prolongation
 - Most patients have resolution of sx in ~1 week without any pharm intervention
 - Antipsychotic blockade may:
 - » Increase anhedonia
 - » Increase vulnerability to relapse
 - Psychosocial interventions



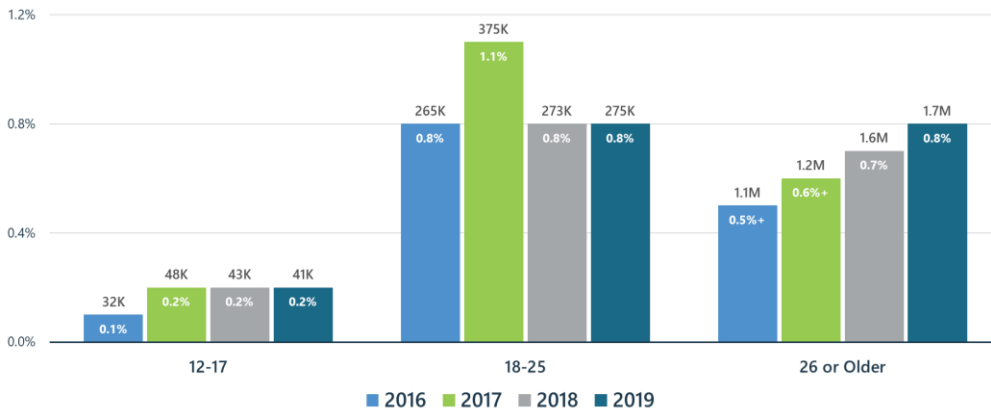
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Methamphetamine Psychosis cont.

- Treatment:
 - Chronic:
 - Antipsychotic medication:
 - Should it be discontinued?
 - When?
 - May persist up to 6-12 months
 - Comprehensive care management
 - Relapse prevention
 - Vocational rehabilitation
 - Psychotherapy
 - Family interventions

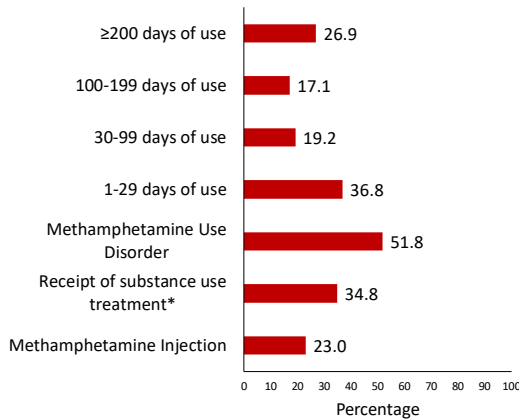
Past Year Methamphetamine Use, 2016-2019 NSDUH - Persons Ages 12 and Older



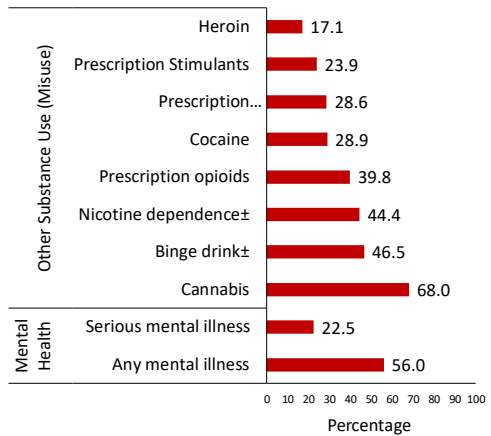
+ Difference between this estimate and the 2019 estimate is statistically significant at the .05 level.

Methamphetamine: Use Behaviors, Other Substance use and Mental Illness among Past-Year Users, 2015-2017

Methamphetamine Use Behaviors



Other Substance Use and Mental Illness



* Among those with methamphetamine use disorder

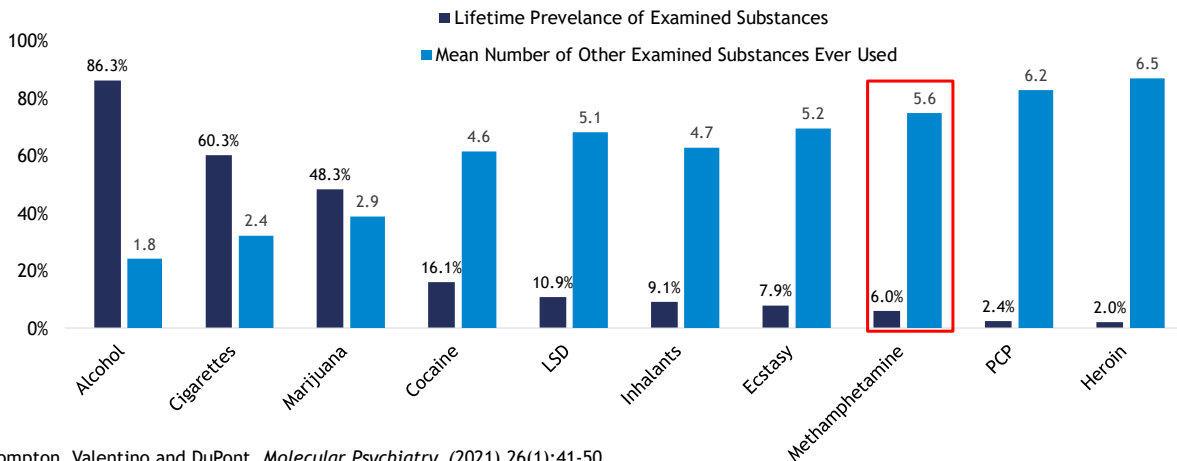
CM Jones, WM Compton, D Mustaquim. MMWR. (2020) 69(12):317-323

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Lifetime Prevalence and Mean Number of Other Substances Used among Age 18+ in the U.S. (NSDUH, 2018)



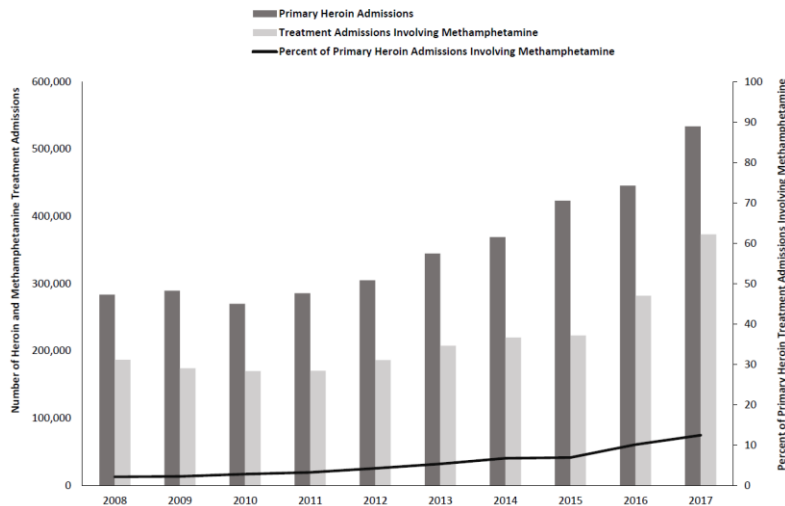
Compton, Valentino and DuPont. *Molecular Psychiatry*. (2021) 26(1):41-50

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Primary Heroin Treatment Admissions Reporting Methamphetamine Use



- Methamphetamine use among primary heroin treatment admissions went from 1 in 50 admissions in 2008 to 1 in 12 admission in 2017
- Increases were seen among males and females, all age groups, all race/ethnicity groups, and all U.S. census regions

CM Jones, N Underwood, WM Compton. *Addiction*. (2019) 2:347-353



Motivations for Co-Use of Opioids and Methamphetamine

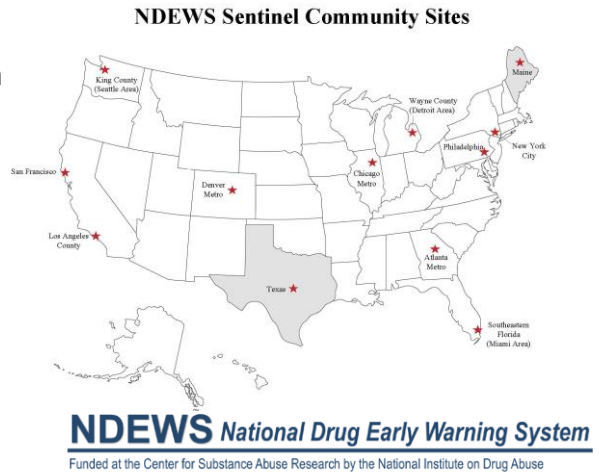
Coded responses	N (%)	Representative quotes
High-seeking	74 (51.0)	(1) <i>The high was like a roller coaster</i> (2) <i>I enjoyed the synergetic effect</i> (3) <i>I was told that it was a fabulous high, so I tried it and loved it</i>
Balance of effect	56 (38.6)	(1) <i>I could function on them together</i> (2) <i>I used meth to give me the rush & to have energy. I used heroin to numb myself or to get the high from the opioids. If i used too much meth id use heroin to calm down;</i> (3) <i>Cause I was trying to get allot of work done energy with no pain make you be able to get stuff done</i> (4) <i>Use meth sometimes to counter the drowsiness from opioids</i>
Available as Opioid Substitute	22 (15.2)	(1) <i>So when i couldn't use opioids because of money or availability, i used methamphetamine</i> (2) <i>I would use meth when I had ran out.</i> (3) <i>When I was really sick from the withdrawal and I couldn't find opioids, I would use methamphetamine</i>
Escape from life/ Numbness	14 (9.7)	(1) <i>Just feel numb n not worry about my problems</i> (2) <i>Because I hated to be fully aware and have to percieve my surroundings, situations and life. When I was high it was like walking around in a dream state. I was numbed</i> (3) <i>Escape from the reality of life</i>
Addiction	13 (9.0)	(1) <i>Because I'm a drug addict and would do anything I could to avoid being sober. I would use any excuse I could to justify use of different drugs</i> (2) <i>Because I'm a addict and it didn't matter how I got high just that I did.</i>
Social Setting	9 (6.2)	(1) <i>Initially it was just to party with socially then became addicted and had to use daily</i> (2) <i>The pupil dilation and other signs that would make it obvious that I was high would be less noticable as well. Made it a lot easily to hide from people around me.</i>

MS Ellis, ZA Kasper, TJ Cicero. *Drug Alcohol Dep.* (2018) 193:14-20



NDEWS Hotspot Study: Co-Use of Methamphetamine and Opioids Among Patients in Treatment in Oregon, U.S. (September 2019)

- Meth perceived as safer than heroin
- Meth often used to detox/titrate the effects of heroin
- Meth considered a cost-effective way to achieve a high
- Relatively easy access to combined meth and heroin
- Polysubstance use with meth or heroin as the primary drug is concentrated among youth



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Meth Use and Opioid Treatment Retention

Buprenorphine Treatment Retention for Heroin Use: A Three-Site Study

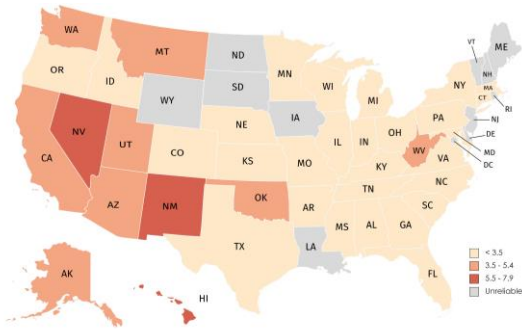
- Those who co-used meth and heroin
- had significantly shorter treatment duration
- were more likely to discontinue treatment immediately or within 3 months
- Loss to follow-up was the most common causes of non-retention

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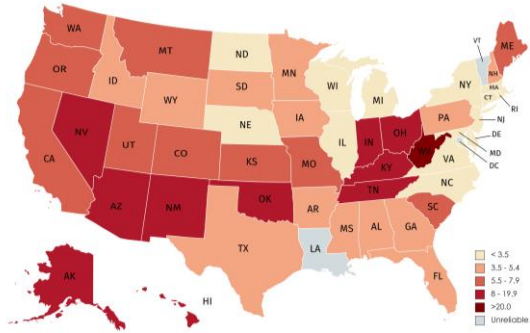
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U.S. Overdose Deaths Involving Methamphetamine* Age-Adjusted Rates/100k Persons

2015

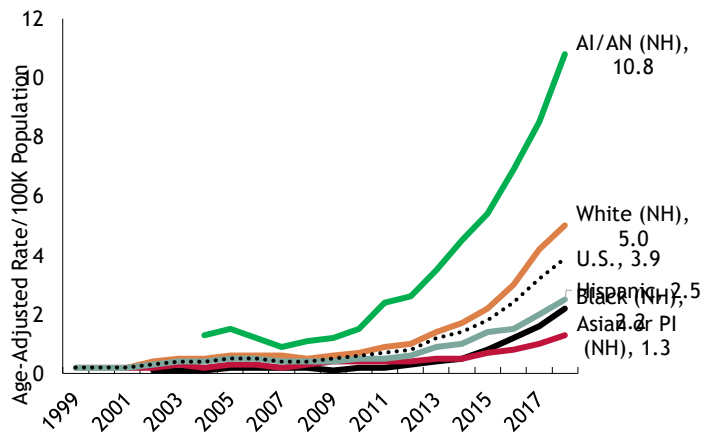


2019



*Psychostimulants With Abuse Potential ICD-10 code (T43.6). This category is dominated by methamphetamine-involved overdose deaths.
Source: CDC, National Center for Health Statistics. Multiple Cause of Death 1999-2019 on CDC WONDER Online Database, released in 2020.

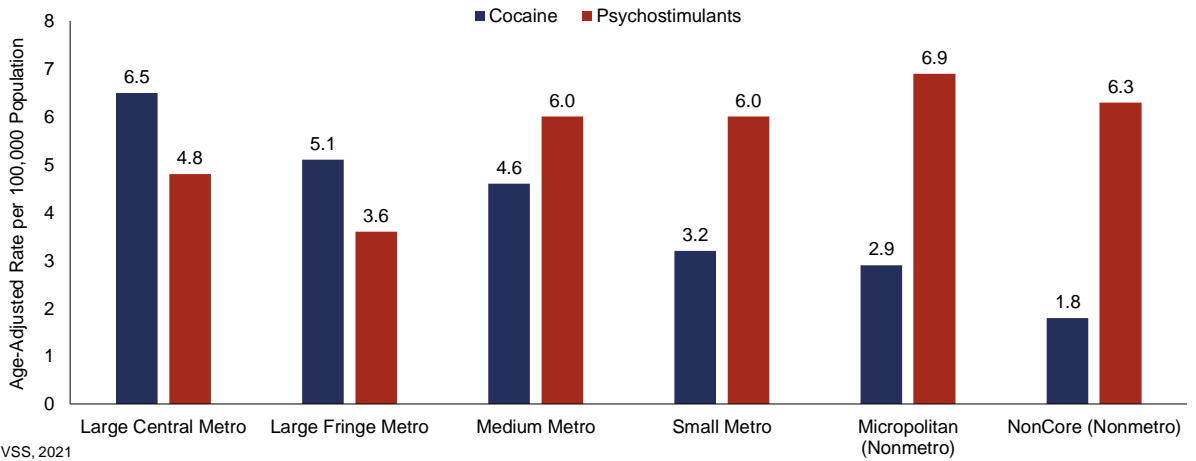
U.S. Overdose Deaths Involving Psychostimulants (i.e., Primarily Methamphetamine), by Race



CDC WONDER

ICD-10 code: T43.6,
This category is dominated by methamphetamine related-overdoses.

Cocaine and Psychostimulant Overdose Deaths, by Urbanicity, 2019



CDC NVSS, 2021

Drug Use and Addiction Can Be Prevented

EXAMPLES OF RISK AND PROTECTIVE FACTORS

Risk Factors	Domain	Protective Factors
Early Aggressive Behavior	Individual	Self-Control
Poor Social Skills	Individual	Positive Relationships
Lack of Parental Supervision	Family	Parental Monitoring and Support
Substance Abuse	Peer	Academic Competence
Drug Availability	School	Anti-Drug Use Policies
Poverty	Community	Strong Neighborhood Attachment

Reduce these



Elevate these



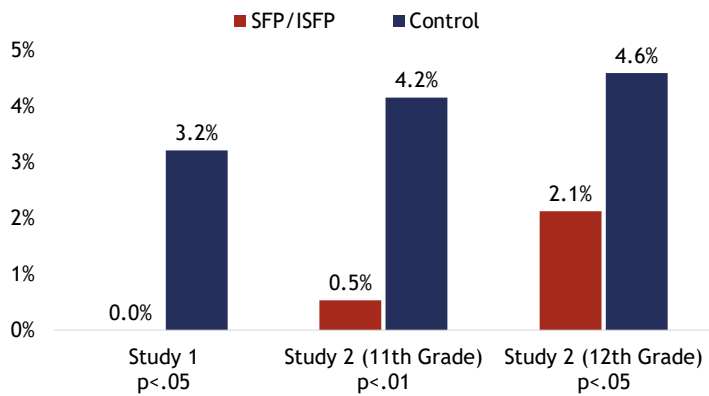
- Evidence-based universal prevention strategies :
- Communities that Care
- Life Skills Training
- Strengthening Families
- PROSPER (PROmoting School–community–university Partnerships to Enhance Resilience)

Universal Substance Use Prevention May Reduce Later Use of Opioids and Methamphetamine

Targeting Youth to Prevent Later Substance Use Disorder: An Underutilized Response to the U.S. Opioid Crisis

Compton WM, Jones CM, Baldwin GT, Harding FM, Blanco C, Wargo EM
American Journal of Public Health
 2019;109:2185-S189.

Past Year Methamphetamine Use 4½ to 6½ Years Past Baseline



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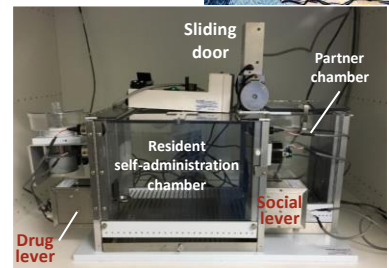
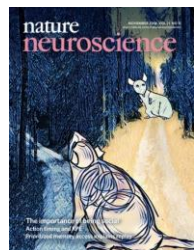
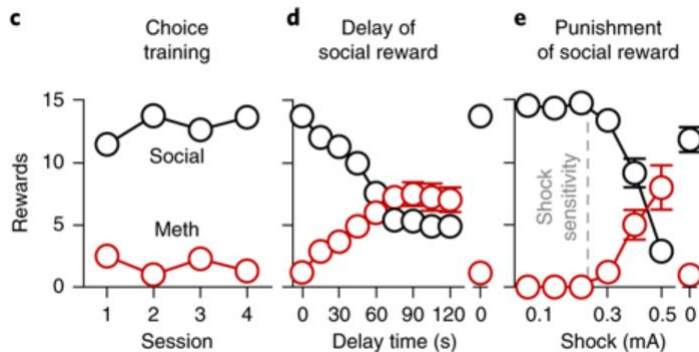
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Social Interaction Preferred Over Methamphetamine

Drug preference increases when social reward is devalued by delay or punishment



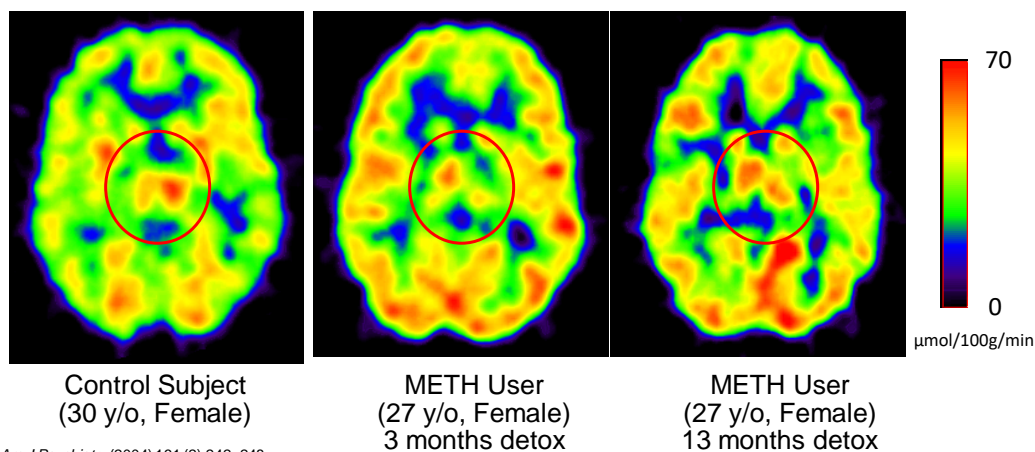
M Venniro, et al., Nature Neuroscience (2018) 21:1520-1529

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Partial Recovery of Brain Metabolism in Methamphetamine User After Protracted Abstinence



G-J Wang et al. *Am J Psychiatry* (2004) 161 (2):242–248.

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FAMILY PHYSICIANS

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Treating Methamphetamine Use Disorder

- No FDA-approved medications
- Behavioral therapies: Most effective intervention is **contingency management** (uses rewards for evidence of abstinence) **combined with a community reinforcement approach** (uses a range of recreational, familial, social, and vocational reinforcers, to make non-drug-using lifestyle more rewarding than substance use).
- Studies on the effectiveness of CM have provided over \$200 per year, and up to \$2,000/year. Most treatment programs receiving federal funds are allowed \$75/patient per year.

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Evidence-Based Treatments for Methamphetamine Use are Behavioral

Cognitive Behavioral Therapy

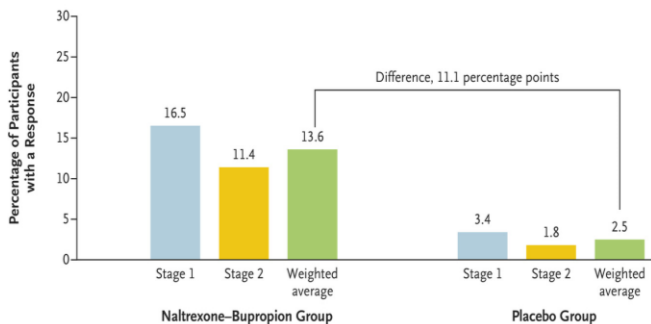
Contingency Management

12-Step Facilitation

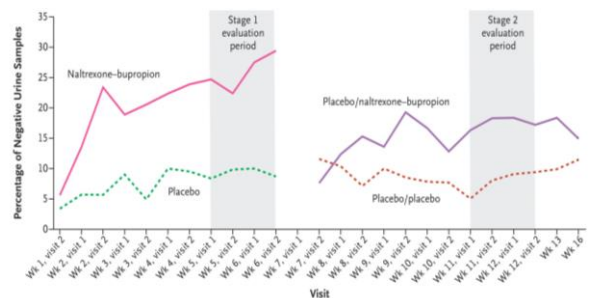
The Matrix Model

Combination Treatment (Bupropion + Naltrexone) For Methamphetamine Use Disorder

RESPONSES



METHAMPHETAMINE-NEGATIVE URINE SAMPLES



Trivedi MH, et al. *New England Journal of Medicine*. (2021) 384:140-153

NIDA Supported Stimulant (Cocaine and Methamphetamine) Use Disorder Medication Pipeline (July 2021)

Drug Discovery		Clinical Trials			
Early Preclinical T2L: (> 12 years)	Late Preclinical (10 – 12 years)	Phase I (6 – 10 years)	Phase Ib (5 – 9 years)	Phase II (4 – 6 years)	Phase III (3 – 5 years)
<ul style="list-style-type: none"> ● Cocaine hydrolase catabolic enzyme ○ Methamphetamine vaccine ● GLT-1 up-regulator ● Peptidic KOR agonists ● PTPRD ligands ○ VMAT-2 inhibitor ○ CS-1103+ Methamphetamine reversal agent 	<ul style="list-style-type: none"> ○ IXT-m200 Long-duration anti-meth mAb ○ Methamphetamine conjugate vaccine ○ IXT-v100 Methamphetamine vaccine 	<ul style="list-style-type: none"> ● dAdGNE Anti-cocaine vaccine ● h2E2 Anti-cocaine mAb ● Cocaine hydrolase gene therapy 	<ul style="list-style-type: none"> ○ Pomaglumetad methionil mGluR2/3 agonist prodrug ○ Duloxetine & Methylphenidate NET/SERT inhibitor & CNS stimulant ○ Mirtazapine NE/5HT antagonist ● Clavulanic acid GLT-1 activator ● Cariprazine D3/D2/5HT1A partial agonist 	<ul style="list-style-type: none"> ○ IXT-m200 Anti-meth mAb ● NS2359* DAT/NET/SERT inhibitor ● EMB-001 Metyrapone & oxazepam GC synth inhibitor & benzodiazepine ● Mavoglurant* mGluR5 non-competitive antagonist ● Bupropion DAT/NET inhibitor ● Guanfacine, α2A agonist ○ Naltrexone SR injection & oral Bupropion, Mu antagonist & DAT/NET inhibitor ● Ketamine NMDA antagonist ● Pioglitazone PPAR-γ agonist 	
<p>KEY: * Not currently supported by NIDA</p> <p>● NME ● New Indication ● Biologic ● Gene Therapy ● cocaine ○ meth ● both cocaine and meth</p>					

Transcranial Magnetic Stimulation: Methamphetamine Addiction

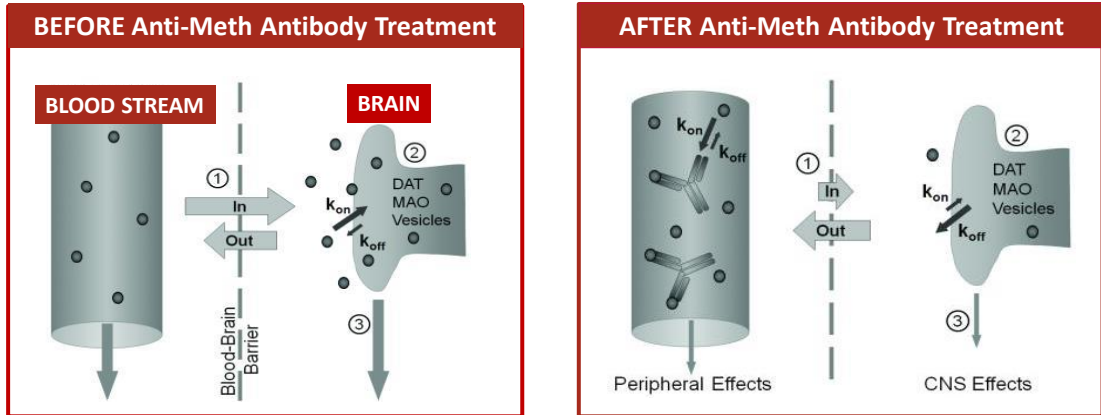
Magnetic medicine
Electric pulses in a coil held near the scalp induce a changing magnetic field that creates electric currents in the cortex. Changing the frequency and pattern of magnetic pulses delivered to the cortex can either increase or decrease neuronal firing. Multiple stimulation strategies are being used to battle cocaine addiction.

“Cold” (executive control) circuit
In one form of transcranial magnetic stimulation, pulses are delivered many times per second, on and off, for a few minutes. This “intermittent theta burst” stimulation of the dorsolateral prefrontal cortex may propagate to the midbrain (arrows, left) and strengthen the “cold” (right, dark pink) circuit that overrides drug-seeking impulses.

“Hot” (craving and reward) circuit
Continuous theta burst stimulation applied to the ventromedial prefrontal cortex is thought to inhibit the neurons of the “hot” (light pink) circuit that connects to the midbrain’s nucleus accumbens and ventral tegmental area. It is abnormally active when people addicted to cocaine are exposed to cues such as white powder.

M Wadman. *Science* (2017) 358:6365-857-848

Methamphetamine Effects in the Brain



WB Gentry, et al., *Human Vaccines* (2009) 5(4): 206-213

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Summary

- Methamphetamine is a potent, highly addictive drug associated with severe negative health effects
- Treatment development for methamphetamine has been difficult
- New tools and targets show promise
- For more information on the science of drug use and addiction, visit NIDA at www.drugabuse.gov

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 **Podcast:**
The Addiction Connection

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