

Methamphetamine

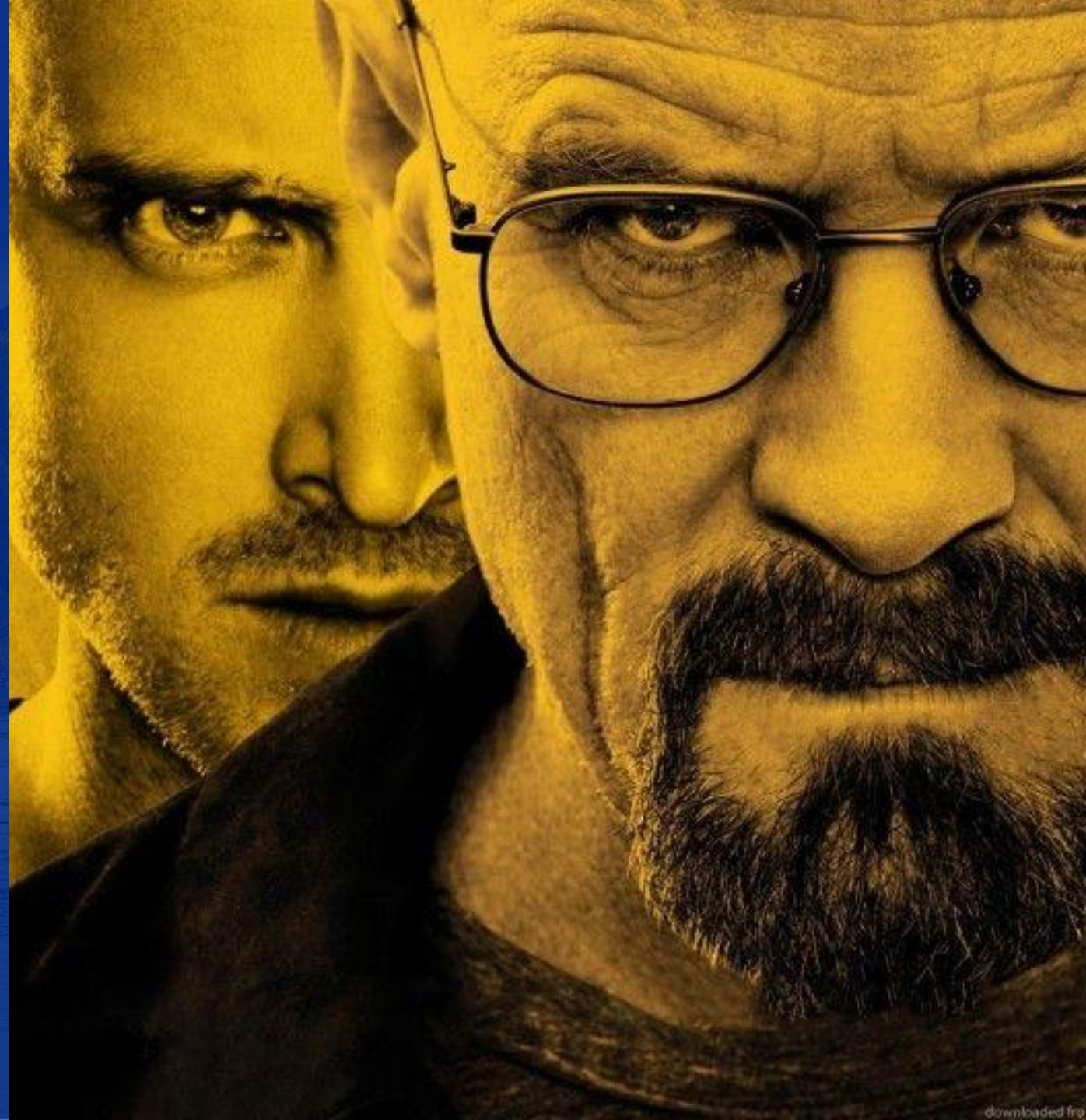
Use & Its Treatment

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Consultant, MPCA & CMS*

Addiction Medicine Network

May 2, 2024



Patient Case 1

HG is a 37-year-old man who lives between Sidney and Billings, MT who is admitted for endocarditis in the setting of IV meth use. He was recently diagnosed with cardiomyopathy (most likely meth-induced). He is currently unemployed and marginally housed, with a past psych hx of longstanding depressive symptoms, no prior hx of psychosis. Has prior h/o of IV heroin use and, more recently has been intermittently smoking fentanyl.



Patient Case 1

- Oftentimes feels extreme anxiety and has thoughts, “that scare me... I think a group of people are stalking me... I don’t know who they are... but seeing them all over.”
- Uses >1g of methamphetamine daily, remarks: “I thought I had it under control, recently I starting injecting... now I just can’t stop.”
- Notes sparse fentanyl use, he is currently on methadone 120 mg PO qday.
- Otherwise, he is currently off psychotropics: “only the meth really touches me.”
- Notes some potential interest in use reduction/cessation but voices overall ambivalence, remarks:

“I mean... it’s awesome... it makes the sex great, but I was here at the hospital not long ago... I recently ended up here because of bad burns on my skin... I’m not sure how I got them... maybe I messed up putting bleach on my athlete’s foot”



Objectives

1. Acknowledge: history & epidemiology of methamphetamine use
 2. Discuss the short & long-term effects of methamphetamine use
 3. Review how methamphetamine works in the brain
 4. Evaluate current forms of treatment for MUD
 - translate into treatment for patients with co-occurring OUD
-

DSM 5 Diagnostic Criteria

Stimulant Intoxication

- A. Recent use of stimulants
- B. Clinically significant maladaptive behavioral or psychological changes that occur during or soon after stimulant use (e.g., euphoria, alterations in sociability, impaired judgment, nervousness, tension, or anger)
- C. ≥ 2 of the following are present during or soon after stimulant use:
 - 1. Nausea or vomiting
 - 2. Weight loss
 - 3. Tachycardia (or, less commonly, bradycardia)
 - 4. Mydriasis
 - 5. Elevated BP (or, less commonly, lowered BP)
 - 6. Chills or diaphoresis
 - 7. Myalgia, hypoventilation, chest pain, or arrhythmias
 - 8. Seizures, confusion, dystonias, dyskinesias, or coma
 - 9. Psychomotor agitation (or, less commonly, retardation)
- D. Signs and symptoms of intoxication are not secondary to a medical condition or intoxication with another substance

DSM 5 Diagnostic Criteria

Stimulant Withdrawal

- A. Commonly known as a “crash”
- B. Decrease in or cessation of prolonged stimulant use
- C. Dysphoric mood and at least two of the following physiologic changes that develop within hours to days after terminating or reducing stimulant use:
 - 1. Fatigue
 - 2. Vivid, unpleasant dreams
 - 3. Insomnia or hypersomnia
 - 4. Increased desire to eat
 - 5. Psychomotor retardation or agitation
- D. Withdrawal symptoms must cause clinically significant distress or impairment in social, occupational, or other important areas of functioning and are not secondary to a medical condition or another psychiatric disorder

Signs & Symptoms



Stimulant Intoxication

Behavioral & psychological symptoms

- Feeling “high,” euphoria, restlessness, anxiety, agitation, psychosis, hyperactivity, hypervigilance, talkativeness, tension, alertness, grandiosity, anger, impaired judgment

Physical symptoms

- Pupil dilation, headache, bruxism, dyspnea, chest pain, tachycardia, ↑ BP, MI, tremor, hyperreflexia, motor tics, stereotyped movements, seizure activity, cerebral hemorrhage or infarct, N/V, myoglobinuria, acute renal failure, hyperthermia, rhabdomyolysis, death

Bath salts

- Euphoria, ↑ sociability & sex drive, paranoia, agitation, hallucinatory delirium, & psychotic and violent behavior

Stimulant Withdrawal

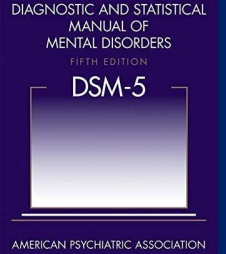
Withdrawal from stimulants causes symptoms opposite from those seen during intoxication (e.g., fatigue, hypersomnia, ↓ mood, ↑ appetite, & psychomotor retardation)

Feelings of depression may be severe enough to lead to suicidal ideation

Symptoms of craving for stimulants may persist for months, time to symptom resolution varies depending on the individual

DSM 5 Diagnostic Criteria

Stimulant Use Disorder



A problematic pattern of amphetamine-type substance, cocaine, or other stimulant use leading to clinically significant impairment or distress, as manifested by ≥ 2 of the following, occurring within a 12-month period:

1. Stimulants are often taken in larger amounts or over a longer period than was intended
2. There is a persistent desire or unsuccessful efforts to cut down or control stimulant use
3. A great deal of time is spent in activities necessary to obtain, use or recover from the stimulant
4. Craving, or a strong desire or urge to use the stimulant
5. Recurrent stimulant use resulting in a failure to fulfill major role obligations at work, school, or home
6. Continued use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the stimulant
7. Important social, occupational, or recreational activities are given up or reduced because of stimulant use
8. Recurrent stimulant use in situations in which it is physically hazardous
9. Use is continued despite having a persistent/recurrent physical/psychological problem that is caused/exacerbated by the stimulant
10. Tolerance, as defined by either of the following:
 - a. A need for markedly \uparrow amounts of the stimulant to achieve intoxication or desired effect
 - b. A markedly diminished effect with continued use of the same amount of the stimulant
11. Withdrawal, as manifested by either of the following:
 - a. The characteristic withdrawal syndrome for the stimulant
 - b. The stimulant is taken to relieve or avoid withdrawal symptoms

Methamphetamine

A focus on the historical perspective

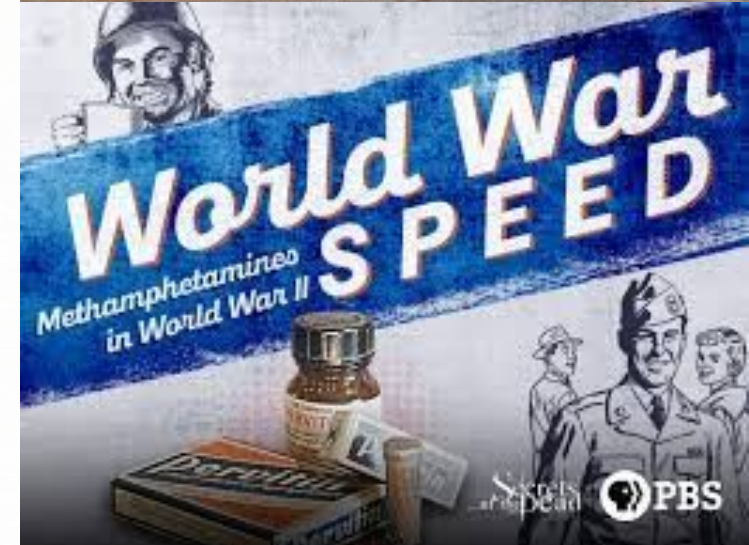
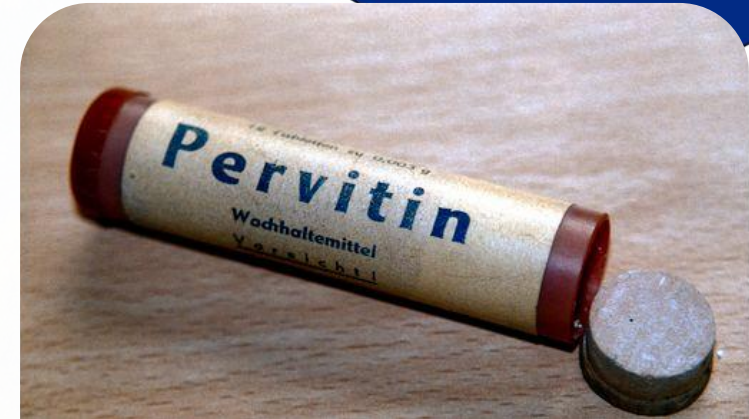
First synthesized from ephedrine in 1893 by Japanese chemist Nagai Nagayoshi

Starting in 1938, Germany began mass marketing methamphetamine under the name “Pervitin”

- Available over the counter

Central role in World War II

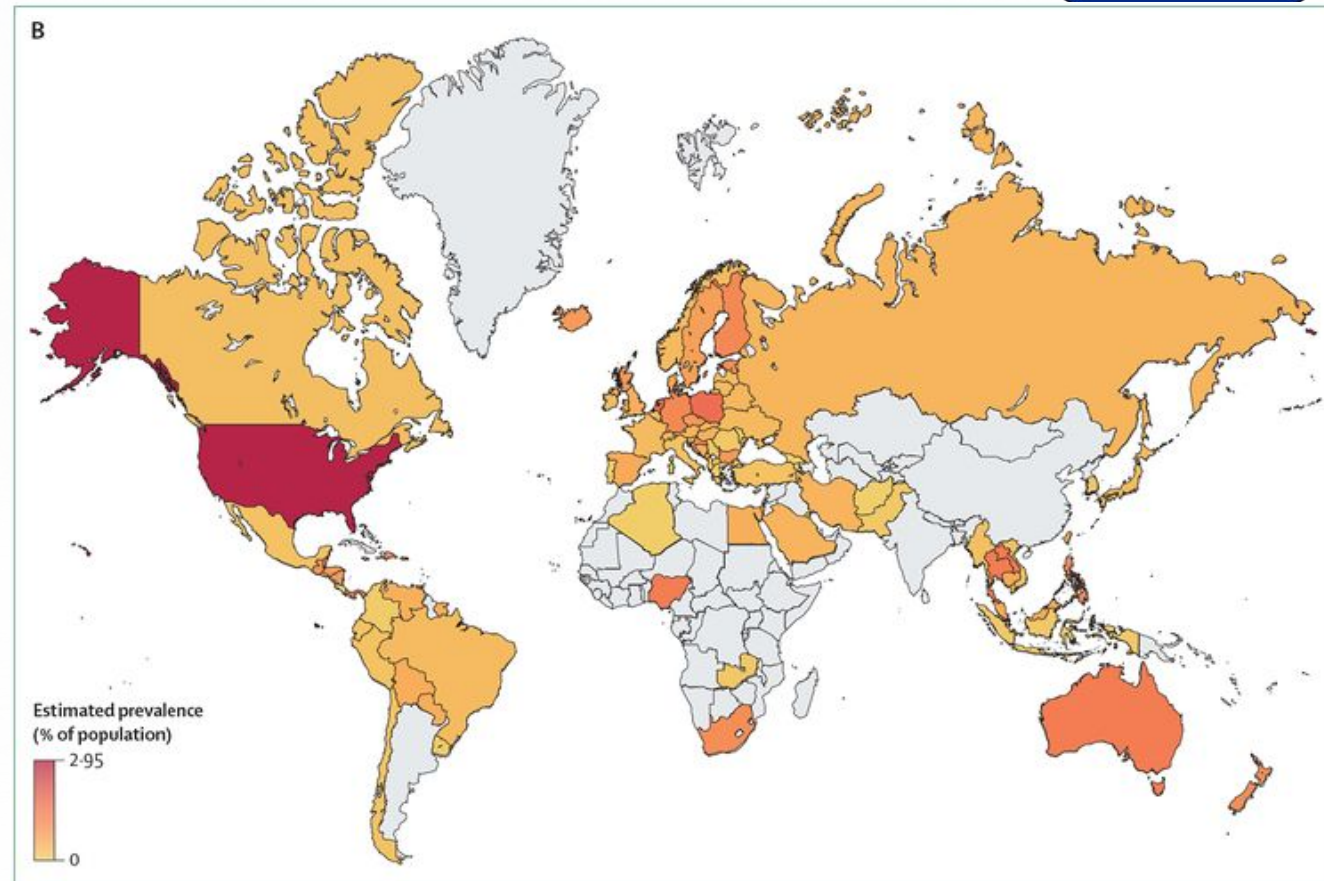
- All branches of the combined Wehrmacht armed forces of the Third Reich used it to help with ↑ energy/wakefulness
- Deleterious effects were noticed including agitation, rage & violence



Epidemiology of Use

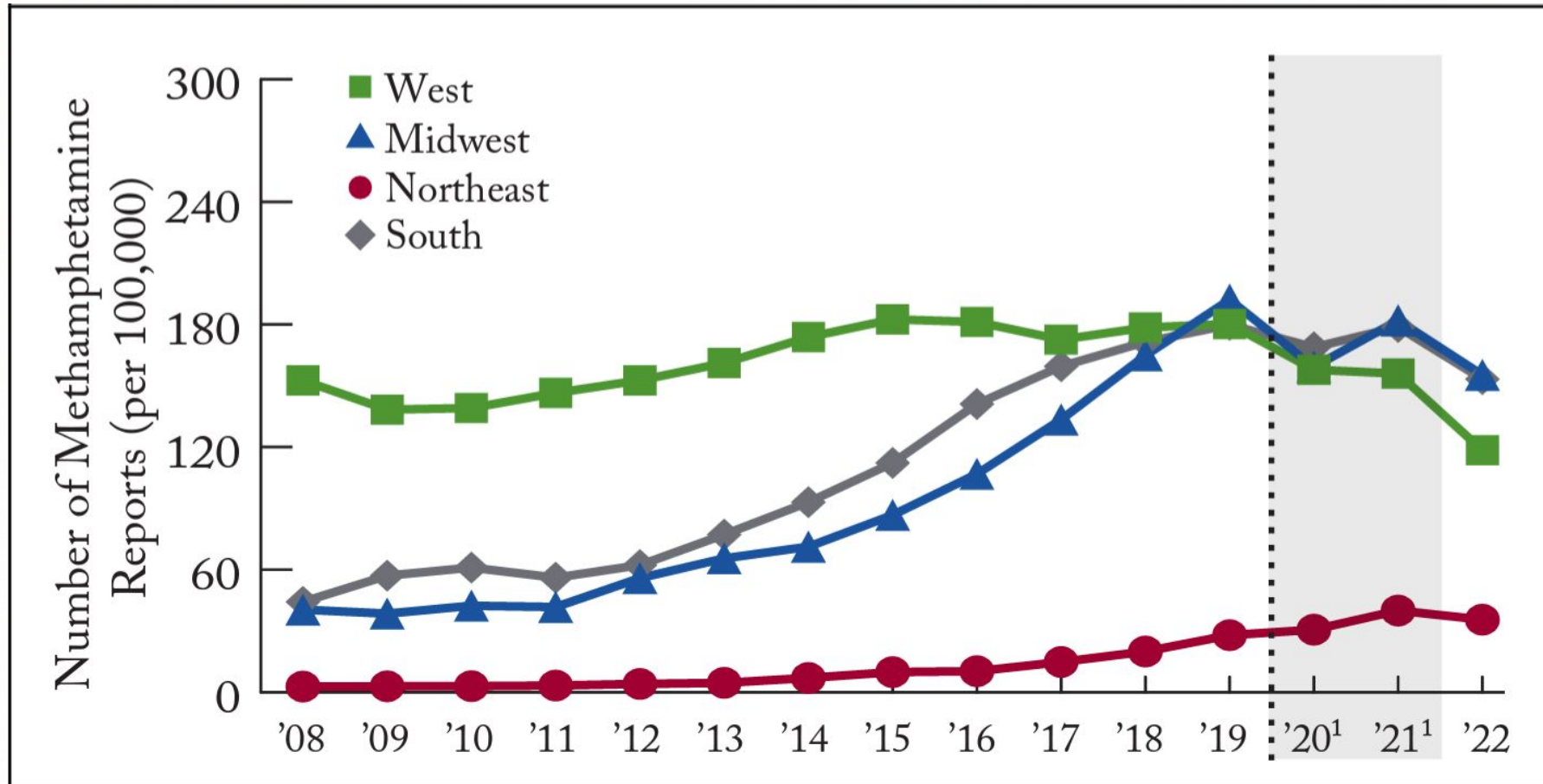
Cocaine & amphetamines are 2 of the most widely used illicit drugs worldwide

- ❖ 2018 UN Office on Drugs & Crime World Drug report estimated (15–64-year-olds):
 - **18.2 million** people used **cocaine**
 - **34.2 million** people used **amphetamines**
- ❖ The highest proportion of amphetamine use was in North America
 - **2.0 million** people (0.7% of U.S. population) used **methamphetamine** in the past year
 - **4.9 million** people (1.8% of U.S. population) misused **Rx stimulants** in the past year



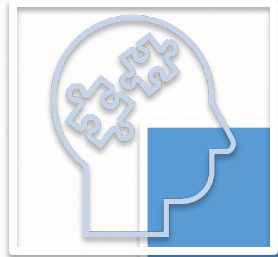
Regional Trends in Methamphetamine Use

Per 100,000 people aged 15 or older, Jan 2008-Dec 2022



Effects of Use

Clinical effects of methamphetamine are almost immediate



Short-term use

- ↑ energy and alertness
- ↓ need for sleep
- Euphoria and/or other mood changes: irritability, anxiety, aggression, and/or panic
- ↑ sexuality
- Excessive talking
- Tightened jaw muscles/ teeth grinding
- Dry mouth
- Loss of appetite
- Disorganized thinking
- Itching
- Sympathetic nervous system: diaphoresis, mydriasis, ↑ HR & other CV changes

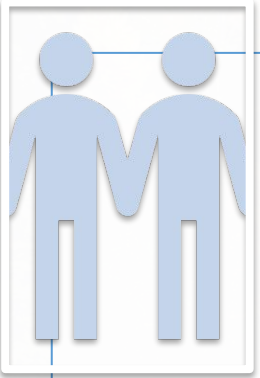


Long-term use

- **Psychosis**
- Sleep disruption/insomnia
- Apparent mania vs. mixed episode
- High risk sexual behavior/STIs
- Tooth decay/damaged dentition
- Meth sores from skin picking
- Cognitive Impairment
- Cardiovascular complications:
 - Malignant hypertension, arrhythmias, aortic dissection, myocardial infarction, stroke, & cardiomyopathy
- ↑ **mortality**

Comorbidities with Stimulant Use

Medical & Psychiatric Complications



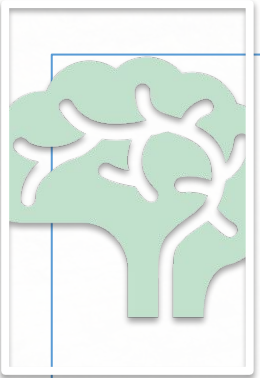
Methamphetamine use is 22.5-fold higher in MSM

- Is an independent risk factor for HIV/STI
- HIV incidence is 40-fold ↑



Proportion of total CHF patients having methamphetamine-associated cardiomyopathy is increasing

- Impaired cardiac function is correlated to methamphetamine use



Methamphetamine-induced psychosis occurs in 15-23% of individuals with recreational use

- May be up to 60% in dependent users in treatment settings



Periodontal disease

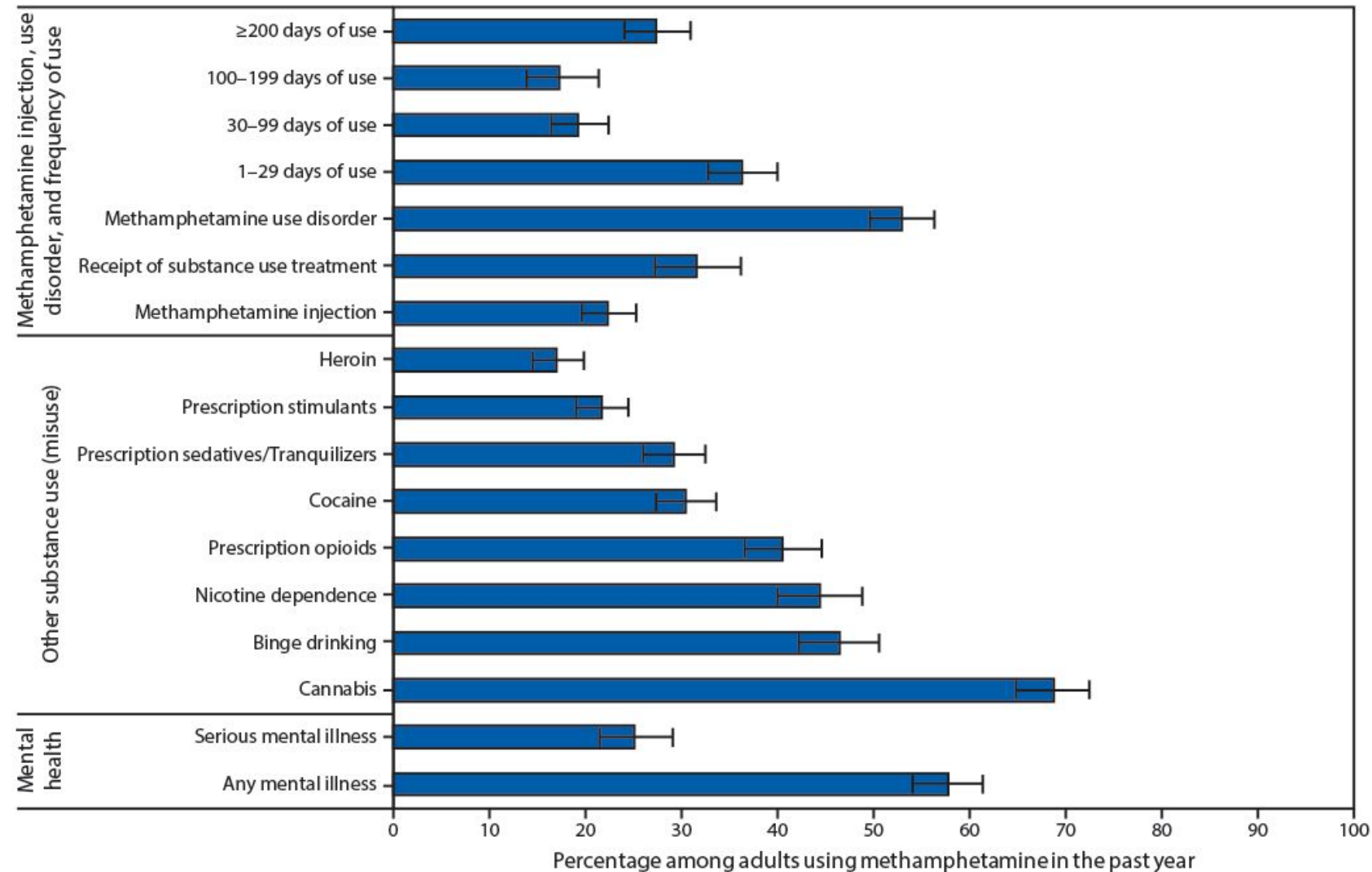
- Bruxism
- Dental caries
- Xerostomia

MSM: men who have sex with men; HIV: human immunodeficiency virus; STI: sexually transmitted infection; CHF: congestive heart failure

Comorbidity

- Individuals with chronic methamphetamine use show ↑ rates of comorbid mental health and other substance use disorders

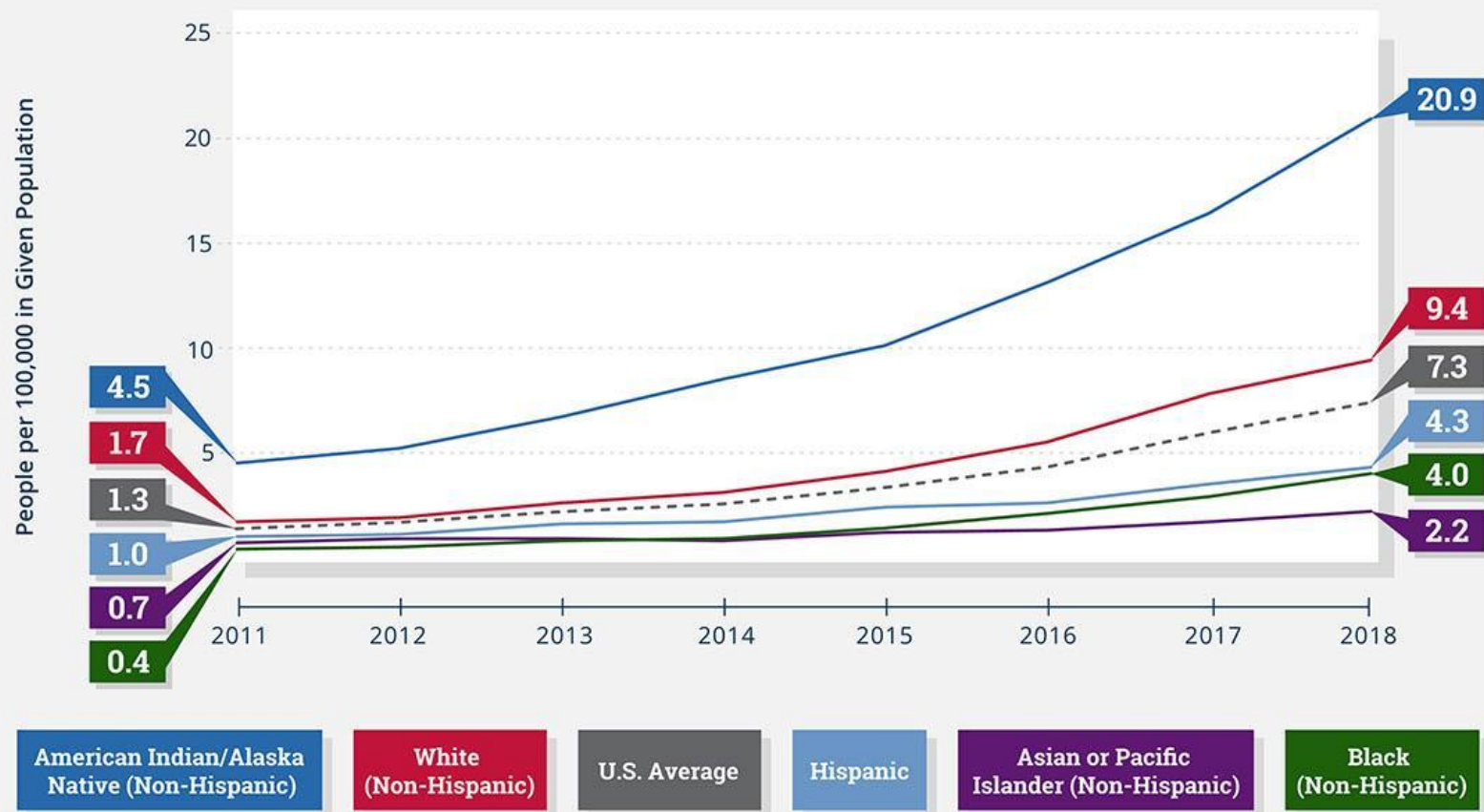
FIGURE. Methamphetamine injection, use disorder, frequency of use, receipt of substance use treatment,* other substance use,† and mental illness among adults aged ≥18 years reporting past-year methamphetamine use — United States, 2015–2018^s



Mortality Rates

Methamphetamine overdose deaths rise sharply nationwide

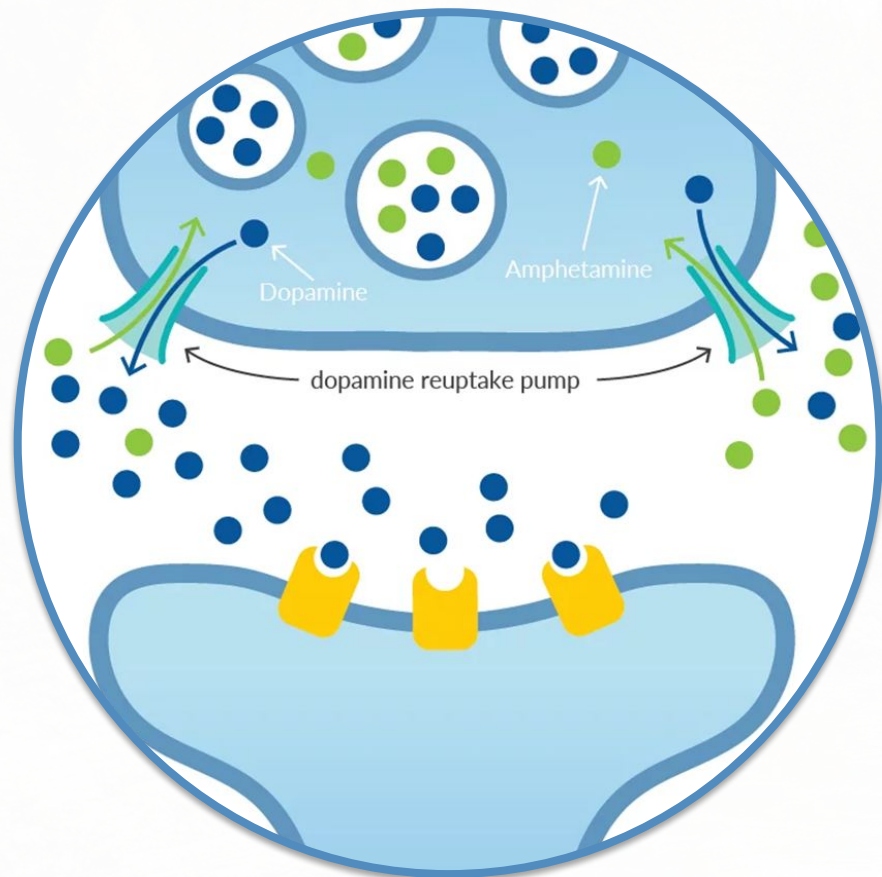
- ❖ American Indians & Alaska Natives had the ↑ death rates overall



*Recent national data show that most people who use methamphetamine are between 25 and 54 years old, so investigators limited analysis to this age group.

Pathophysiology

Methamphetamine Mechanism of Action (MOA)



Highly potent psychostimulant that \uparrow synaptic levels of **DA** \gg **NE**, & **5HT** through \uparrow release & blocked reuptake

- \uparrow **DA** production
- \uparrow availability of **DA** & **NE**
- Reversal of neurotransmitter transport through plasma membrane
- Blocking the activity & expression of transporters (especially for **DA**)
- Inhibiting enzymatic breakdown of neurotransmitters



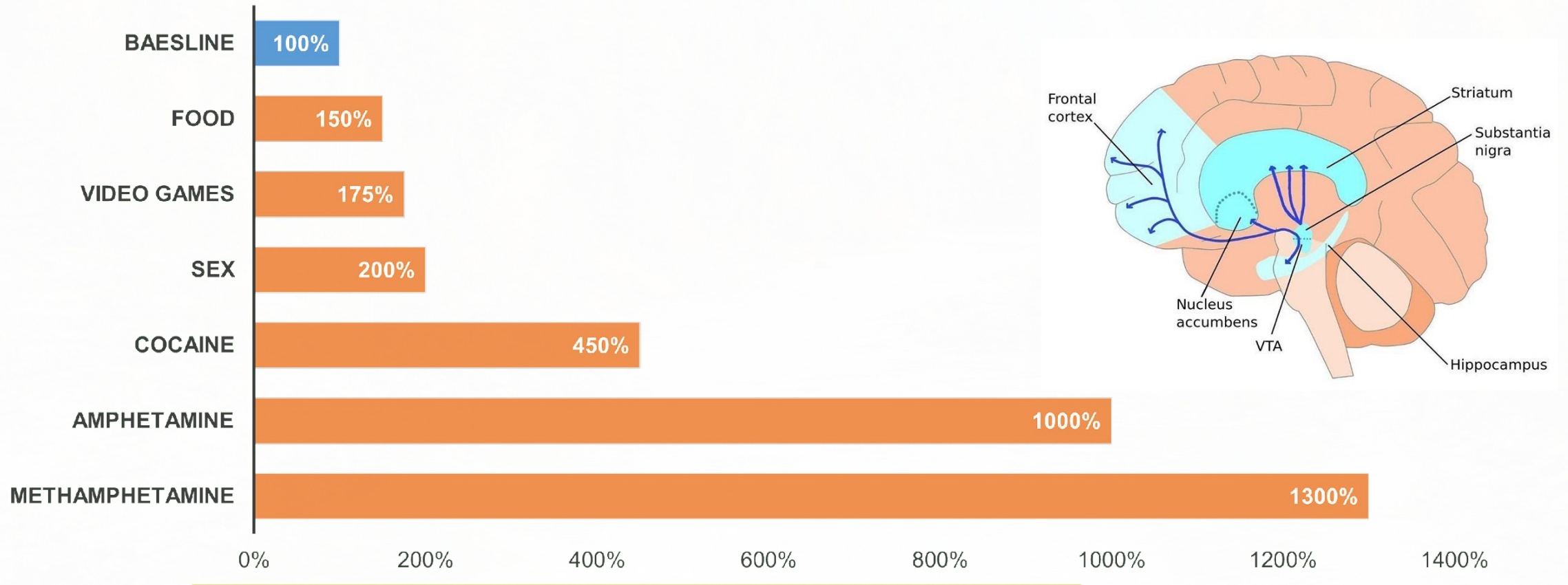
Net Effect: *¡Mucha Dopamina!*

DA: dopamine; NE: norepinephrine; 5HT: serotonin

Pathophysiology of Stimulant UD

Dopamine Release from Natural Rewards vs Stimulants

Comparisons of Dopamine Release





Psychosocial & Pharmacologic Treatment Options for StimUD

Treatment Guidance

There are no medications FDA approved for StimUD

Stimulant Intoxication

Symptomatic management – monitor vital signs for ↑ HR, temperature, & BP – may need IV hydration

Provide a quiet & cool environment – helps ↓ agitation & overreaction to external stimuli with close observation

Benzodiazepines – symptomatic approach for anxiety, agitation, seizures, & HTN

Antipsychotics

Most patients with stimulant-induced psychosis recover spontaneously – may use antipsychotics until psychosis clears

Stimulant Withdrawal

Symptomatic treatment (e.g., ↓ depressive symptoms) may prevent relapse

No specific medication management recommendations

Withdrawal symptoms (e.g., cravings, depression) may persist if untreated

Medication management with antidepressants may be necessary for significant depressive symptoms

Evidence-based Psychosocial Interventions

First-line treatment for MUD



Individual or Group Drug Counseling

- Outpatient & inpatient outpatient therapy (IOT)

Cognitive Behavioral Therapy (CBT)

Motivational Interviewing

Behavioral Approaches

- Contingency Management (NNT = 5)
 - Behavior modification intervention which reinforces desired behaviors through incentives
- Cue Exposure Therapy
 - A behavioristic psychological approach to treating SUDs whereby individuals are exposed to relevant drug cues to extinguish conditioned responses

Community Reinforcement Approach

- Focus on healthier, more adaptive ways to meet social & emotional needs than substance use by providing rewards or withholding negative consequences in response to measurable behavior



Bupropion and Naltrexone in Methamphetamine Use Disorder

Madhukar H. Trivedi, M.D., Robrina Walker, Ph.D., Walter Ling, M.D., Adriane dela Cruz, M.D., Ph.D., Gaurav Sharma, Ph.D., Thomas Carmody, Ph.D., Udi E. Ghitza, Ph.D., Aimee Wahle, M.S., Mora Kim, M.P.H., Kathy Shores-Wilson, Ph.D., Steven Sparenborg, Ph.D., Phillip Coffin, M.D., M.I.A., et al.

Why naltrexone + bupropion for MUD?

- Naltrexone:
 - Reduces reinforcing effects of amphetamine, craving
 - May decrease likelihood of relapse
- Bupropion:
 - Reduces cue craving
 - May decrease methamphetamine use

Study design:

- Multisite, double-blind, two-stage, placebo-controlled trial
- 403 adults with moderate to severe MUD
 - IM Naltrexone 380 mg every 3 weeks
 - Oral extended-release bupropion 450 mg per day
- Included psychosocial component



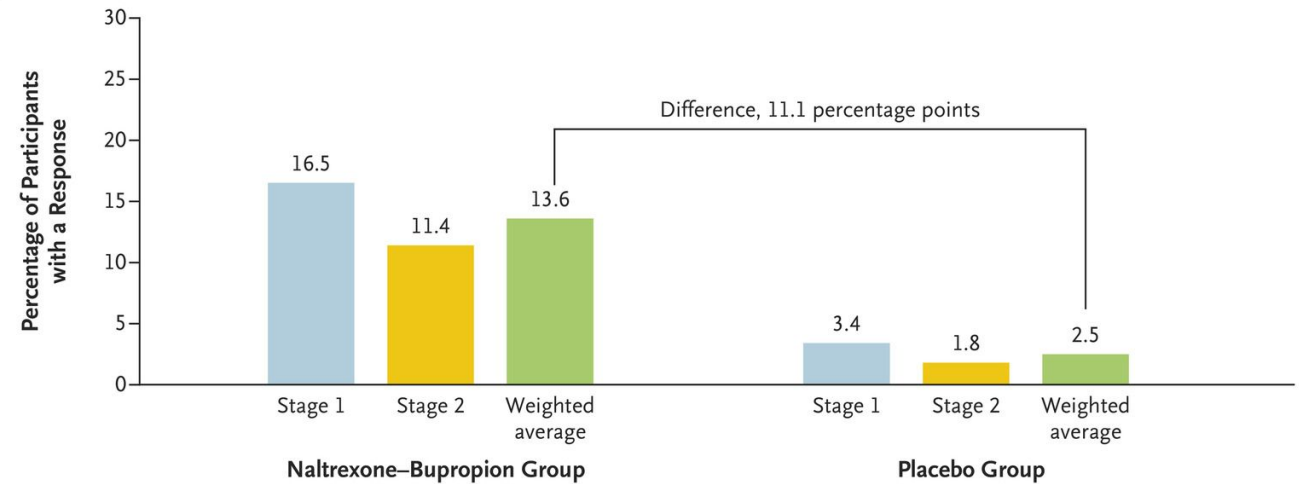
Study Results

Weighted avg. response*
across the 2 stages:

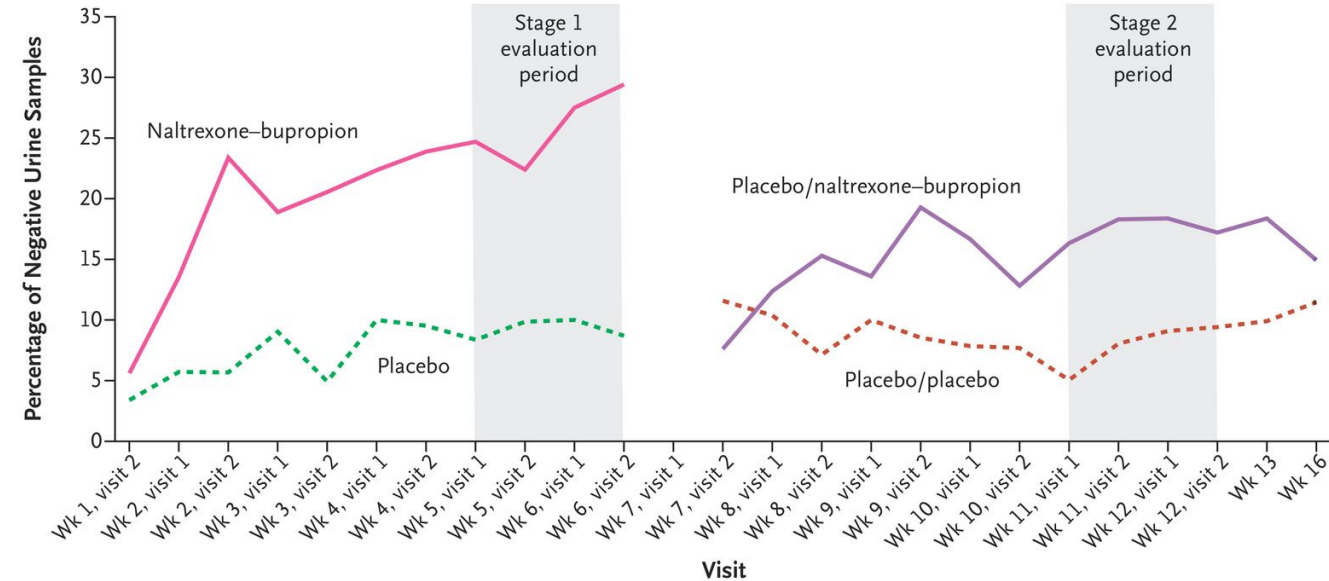
- 13.6% for naltrexone–bupropion
- 2.5% with placebo
- Overall treatment effect of 11.1% ($p < 0.001$)
- NNT = 9

*Response = at least 3/4 urine drug screens negative for methamphetamine

A Responses



B Methamphetamine-Negative Urine Samples



No. of Urine Samples Obtained at Each Visit

	Stage 1						Stage 2																	
Naltrexone-bupropion	89	96	77	90	73	85	67	81	67	80	68													
Placebo	265	280	229	266	223	260	210	239	203	240	207													
Placebo/naltrexone-bupropion												92	97	85	103	83	96	78	98	82	98	93	98	87
Placebo/placebo												95	106	84	100	82	102	91	99	87	99	85	101	96



American Academy of
Addiction Psychiatry

Translating Science. Transforming Lives.

The ASAM/AAAP

CLINICAL PRACTICE GUIDELINE ON THE

Management of Stimulant Use Disorder

Management of Stimulant Use Disorder

20. For patients with ATS use disorder, clinicians can consider prescribing a long-acting MPH formulation to promote reduced use of ATS (*Low certainty, Conditional Recommendation*).
- Clinicians can give long-acting MPH formulations additional consideration for patients with moderate or higher frequency of ATS use at treatment start (ie, 10 or more days per month; *Low certainty, Conditional Recommendation*).
 - Clinicians can give long-acting MPH formulations additional consideration for patients with co-occurring ADHD, as these medications can also reduce ADHD symptoms (*Low certainty, Conditional Recommendation*).
 - When prescribing a long-acting MPH formulation, clinicians can consider dosing at or above the maximum dose approved by the FDA for the treatment of ADHD to effectively reduce ATS use (*Low certainty, Weak Recommendation*).

Methylphenidate as Treatment of MUD: Cited Sources

- Ling W, Chang L, Hillhouse M, et al. Sustained-release methylphenidate in a randomized trial of treatment of methamphetamine use disorder: Methylphenidate for methamphetamine use. *Addiction*. 2014;109(9):1489-1500. doi:10.1111/add.12608 371.
- Miles SW, Sheridan J, Russell B, et al. Extended-release methylphenidate for treatment of amphetamine/methamphetamine dependence: a randomized, double-blind, placebo-controlled trial: Methylphenidate in amphetamine dependence. *Addiction*. 2013;108(7):1279-1286. doi:10.1111/add.12109 372.
- Minařík J, Gabrhelík R, Malcolm R, Pavlovská A, Miller P. Methylphenidate substitution for methamphetamine addiction and implications for future randomized clinical trials: a unique case series. *J Subst Use*. 2016;21(4):435-438. doi:10.3109/14659891.2015.1045047 373.
- Rezaei F, Emami M, Zahed S, Morabbi MJ, Farahzadi M, Akhondzadeh S. Sustained release methylphenidate in methamphetamine dependence treatment: a double-blind and placebo-controlled trial. *DARU J Pharm Sci*. 2015;23(1):2. doi:10.1186/s40199-015-0092-y

Review

Pharmacotherapy for methamphetamine/amphetamine use disorder—a systematic review and meta-analysis

Brian Chan ✉, Michele Freeman, Karli Kondo, Chelsea Ayers, Jessica Montgomery, Robin Paynter,

Why methylphenidate for MUD?

- Design: Systematic review and meta-analysis of pharmacotherapy options for treating methamphetamine / amphetamine use disorder.
- Key Results:
 - Methylphenidate: low-strength evidence suggests that methylphenidate may reduce MA use:
 - One study showed a slight increase in MA/A-negative urine drug screens (UDS) from 2.8% to 6.5% ($p=0.008$).
 - Another study showed an improvement from 16% to 23% in MA/A-negative urine drug screens, with a significance level of $p=0.047$: ($p=0.047$). Note: high rate of co-occurring ADHD**

*Tiihonen J., Kuoppasalmi K., Fohr J. et al. A comparison of aripiprazole, methylphenidate, and placebo for amphetamine dependence. *Am J Psychiatry* 2007; 164: 160–2.

**Konstenius M., Jayaram-Lindstrom N., Guterstam J., Beck O., Philips B., Franck J. Methylphenidate for attention deficit hyperactivity disorder and drug relapse in criminal offenders with substance dependence: a 24-week randomized placebo-controlled trial. *Addiction* 2014; 109: 440–9.



Return to Patient Case 1

Patient Case 1

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- Uses >1g of methamphetamine daily, remarks: “I thought I had it under control, recently I starting injecting... now I just can’t stop.”
- Notes sparse fentanyl use, he is currently on methadone 120 mg PO qday.
- Otherwise, he is currently off psychotropics: “only the meth really touches me.”
- Notes some potential interest in use reduction/cessation but voices overall ambivalence, remarks:

“I mean... it’s awesome... it makes the sex great, but I was here at the hospital not long ago... I recently ended up here because of bad burns on my skin... I’m not sure how I got them... maybe I messed up putting bleach on my athlete’s foot”



How do you proceed?

Select all that apply:

1. Insist on abstinence from meth prior to prescribing any medication
2. Tolerate meth use so long as he is only using < 1 g daily
3. Prescribe bupropion and IM naltrexone as medication-assisted treatment (MAT) for meth use disorder
4. Engage in motivational interviewing targeting meth use reduction/cessation
5. Proceed to treat psychosis and depression with evidence-based pharmacological treatment
6. Provide contingency management



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4. **Engage in motivational interviewing targeting meth use reduction/cessation**
5. **Proceed to treat psychosis and depression with evidence-based pharmacological treatment**
6. **Provide contingency management**



How do you proceed?

Discharge Med Regimen

1. Abilify 20 mg PO qHS (following Olanzapine 10 mg PO qHS during first few days of hospitalization)
2. Sertraline 50 mg PO qday with plan to likely increase to 100 mg PO qday in the near future

F/U:

Referred to EMCMHC to establish care via their TRUST program's SUD counseling initiative that features **contingency management**



Case 2

BN is a 38-year-old divorced woman with a history of criterion A trauma, trauma-related symptoms as well as current alcohol (began at age 15), cannabis, IV methamphetamine use, fentanyl and other opioid use. She recently lost her job and is currently homeless secondary to the financial impact of her use. She has 3 children in grade school.

- ❑ She recently started inpatient treatment and left AMA after 3 days and has continued to use many substances.
 - ❑ She presents to care noting that she wants treatment to become stable and succeed in her new job at a fast food restaurant.
-

Case 2 Continued

On assessment she notes:

- ❑ a history of suicide attempt 8 years ago by hanging
- ❑ significant concern as to whether she has Bipolar D/O as she is constantly anxious, moods are up and down and she is very “stressed out” and has difficulty sleeping
- ❑ Reports dx of ADHD and prior treatment with methylphenidate in high school.
- ❑ She is motivated to start her new job and wants to start classes at the community college and “turn her life around for her kids.”
- ❑ Last use: 8 hours ago: Oxycodone 30mg + IV methamphetamine (uncertain how much)

How would you proceed?

Select all that apply:

1. Insist on abstinence from substances prior to prescribing any medication.
2. Prescribe Narcan
3. Prescribe buprenorphine as MOUD
4. Engage in motivational interviewing targeting substance use reduction/cessation
5. Educate regarding benefits of mutual-help group involvement
6. Proceed to treat depression, anxiety, ADHD and trauma-related symptoms with pharmacotherapy
7. Engage in Contingency Management

How would you proceed?

Select all that apply:

1. Insist on abstinence from substances prior to prescribing any medication.
 2. Prescribe Narcan
 3. Prescribe buprenorphine as MOUD
 4. Engage in motivational interviewing targeting substance use reduction/cessation
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 6. Proceed to treat depression, anxiety, ADHD and trauma-related symptoms with pharmacotherapy
 7. Engage in Contingency Management
-

Urine Tox. Results after MOUD start

Day 1: 04/2021 -Initiation of Treatment

Oxycodone: 223

Methamphetamine: 377

THC: 15

Week 1:

Norbuprenorphine/Buprenorphine: 1000/490

Amphetamine: 438

Methamphetamine: 521

THC: 19

Week 2:

Norbuprenorphine/Buprenorphine: 113/198

THC: 110

Amphetamine: 438

Methamphetamine: 521

Urine Tox. Results after MOUD start *continued*

Week 3:

Hydrocodone: + 146

Norbuprenorphine/buprenorphine: 587/337

Amphetamine: 108

Methamphetamine: 231

THC: 177

Week 4:

Norbuprenorphine/buprenorphine: 617/421

Amphetamine: 0

Methamphetamine: 0

THC: 144

Objectives

1. Acknowledge: history & epidemiology of methamphetamine use
 2. Discuss the short & long-term effects of methamphetamine use
 3. Review how methamphetamine works in the brain
 4. Evaluate current forms of treatment for MUD
 - translate into treatment for patients with co-occurring OUD
-

Objectives → *Takeaways*

1. Acknowledge: history & epidemiology of methamphetamine use
Has been very prevalent for some time, since early 1900s
 2. Discuss the short & long-term effects of methamphetamine use
Strong stimulant, altered mood, psychosis and long-term cognitive impact
 3. Review how methamphetamine works in the brain
Massive synaptic surge of dopamine
 4. Evaluate current forms of treatment for MUD
Psychosocial (CM) has greatest impact, possible place for naltrexone IM + bupropion and methylphenidate (especially if patient has co-occurring ADHD and is otherwise appropriate)
→ translate into treatment for patients with co-occurring OUD
***Contingency Management** (naltrexone is frequently NOT a viable option due to opioid agonist therapy)*
***MOUD** → improved stability associated with decreased meth use*
Treat co-occurring disorders
-



Questions?

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