AETC AIDS Education & Training Center Program Mountain West

Update on Methamphetamine Use and Treatment

2024 AIDS Clinical Conference

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Disclosures

No conflicts of interest or relationships to disclose

We will discuss off-label use of medications

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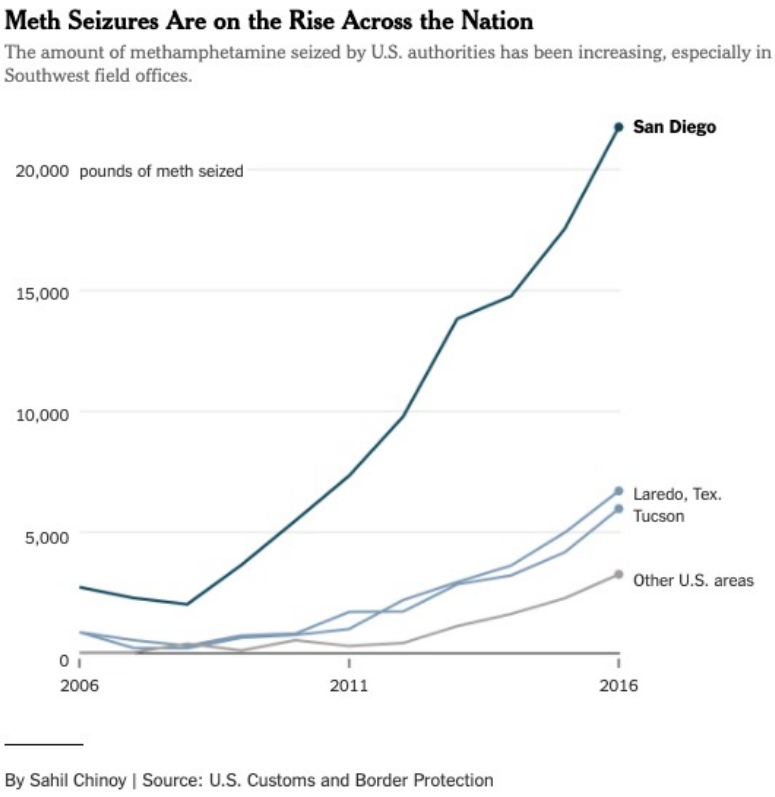
The New York Times

Meth, the Forgotten Killer, Is Back. And It's Everywhere.

"The drug, experts say, has never been purer, cheaper or more lethal."



New York Times, Feb. 13, 2018

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Agenda

- What is MA and how is it used?
- Acute and chronic effects of MA use
- Why do people use MA?
- MA + opioids: 4th wave of opioid epidemic
- Burden of MA use and overdose in U.S.
- MA use disorder treatment: psychosocial and off-label medications
- Reducing harm from MA use
- Discussion / Q&A

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Which of the following statements about MA is NOT true?

- MA is extremely reinforcing due to indirect agonism at noradrenaline, serotonin, and dopaminergic receptors
- Withdrawal from MA typically lasts days to weeks
- Cravings for MA can last months, contributing to recurrent use
- Respiratory failure is the most common mechanism of death related to MA use

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What is MA and how is it used?

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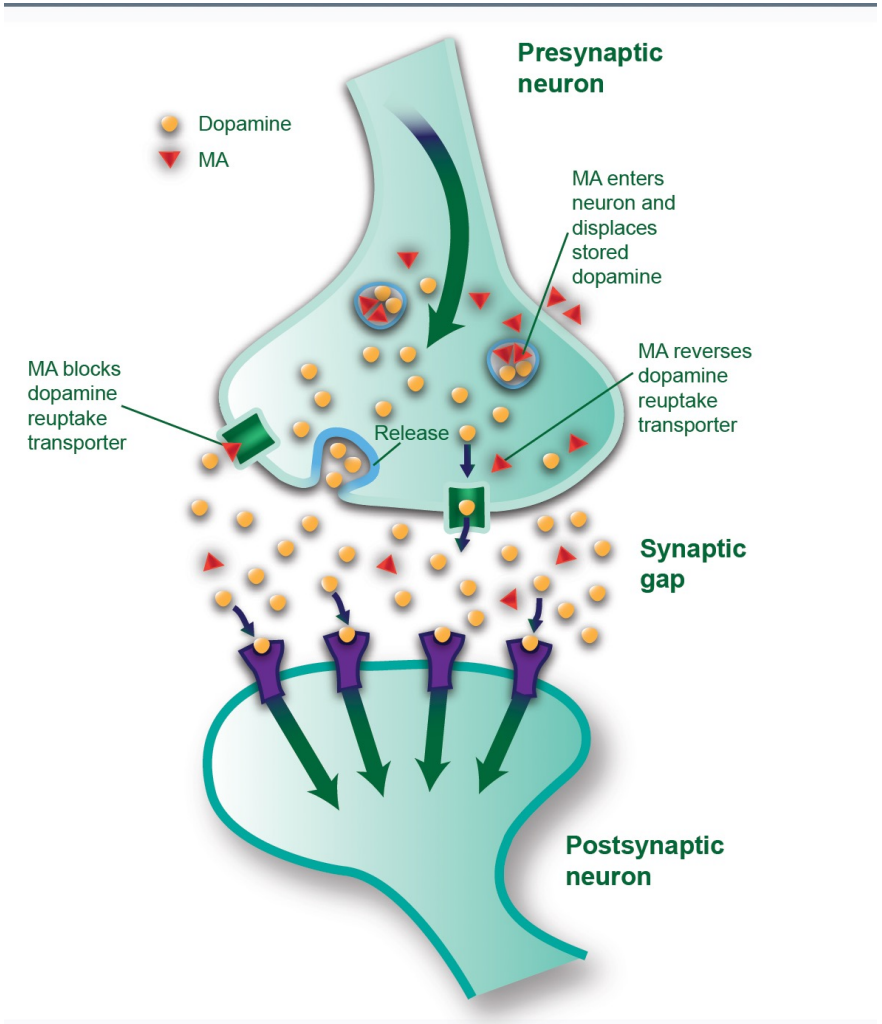
Neurobiology of MA

- Indirect agonist on major serotonergic, noradrenergic, and dopaminergic (DA) pathways
- Blocks DA reuptake and promotes DA release
- ***Extremely reinforcing***
- Opioidergic pathways also affected
- Oxidative stress, neurotoxic effects, neuroinflammation



Paulus, JAMA Psychiatry. 2020;77(9):959-966. Figure: SAMHSA TIP 33, Treatment for Substance Use Disorders

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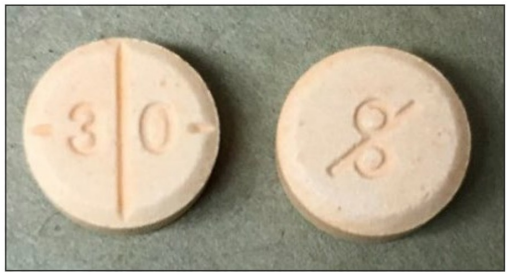
MA comes in many forms

- Powder (meth, speed)
- Crystalline (crystal, ice)
- Pills
- Liquid (rare)

Source: DEA



Source: Northwest High Intensity Drug Trafficking Area

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Use of MA

- Smoking
- Intranasal/insluffation
- Injection
- Rectal (“booty bumping”)
- Oral (“parachuting”)
- Highly variable patterns: daily, every few days, intermittent, binging

Image: NY times

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Acute and chronic effects of MA use

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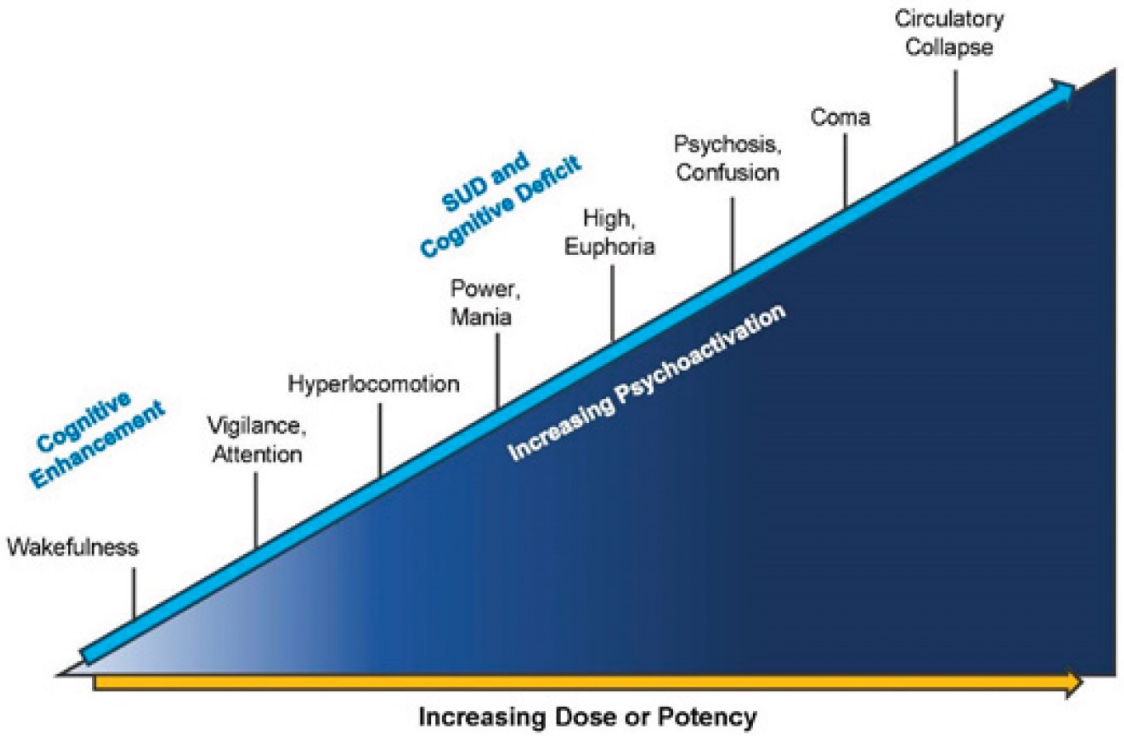
EXHIBIT 2.3. Continuum of Psychostimulant Activation



Increasing cognitive activation as stimulant dose increases initially produces increased wakefulness and cognitive enhancement. These are the beneficial effects. As dose or potency increases, a sense of power and euphoria can ensue. These are the effects people with SUD seek. Such effects are accompanied by cognitive deficits. Higher doses can result in overdose, psychosis, coma, and eventual circulatory collapse

Source: Wood et al. (2014). Adapted with permission.

Acute effects of MA

Arousal/ increased sexuality	Sympathetic overdrive
Euphoria	Psychosis, bizarre behavior
Positive mood	Anxiety, depression, hostility
Improved attention/cognition	Self-neglect
Decreased need for sleep	Trouble sleeping
Loss of appetite	Weight loss
Excessive talking	Tension, bruxism, hyperactivity
	Cardiac events
	Seizures

"Overamping:" poorly-defined term for negative, uncomfortable experience from using MA, which can become life-threatening

Paulus, JAMA Psychiatry. 2020;77(9):959-966.

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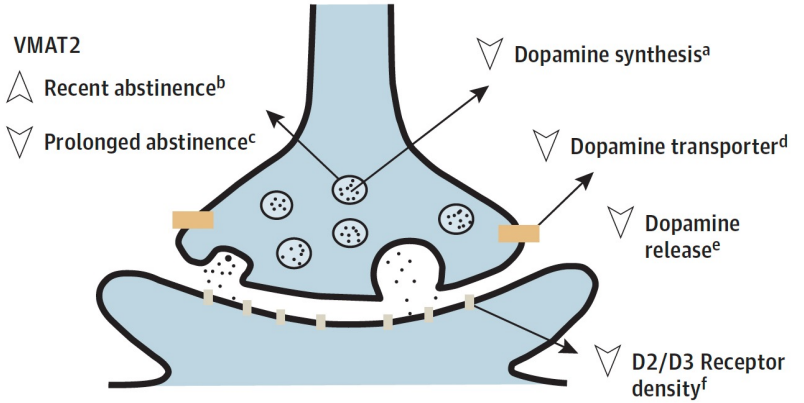
Chronic effects of MA use

- Downregulation of receptors and transporters
- Depleted monoamine stores
- Chronic neuroinflammation and neurodegeneration

➢ Withdrawal symptoms, cognitive loss, psychiatric and psychomotor symptoms

➢ Ischemic, toxic and other effects on brain, heart, lungs, kidneys

Figure 4. Summary of Dopaminergic Alterations in Stimulant Users



The synaptic location of the major dopaminergic findings is summarized from our meta-analysis and the results from studies of other aspects of the dopamine system. VMAT2 indicates vesicular monoamine transporter 2. The upward arrow indicates increased in stimulant users compared with controls; the downward arrow indicates decreased in stimulant users compared with controls.

Ciccarone and Shoptaw, Med Clin North Am. 2022 January ; 106(1): 81–97. Ashok, JAMA Psychiatry. 2017;74(5):511-519.

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MA –induced psychosis

- Often hours to days but occasionally 6 months or more
- Increased risk with high-dose, high potency, frequent use
- Positive symptoms: suspiciousness, unusual thought content, hallucinations, bizarre behavior
- Affective symptoms: depression, suicidality, somatic concerns, self-neglect

Ciccarone and Shoptaw, Med Clin North Am. 2022 January ; 106(1): 81–97. Ashok, JAMA Psychiatry. 2017;74(5):511-519.

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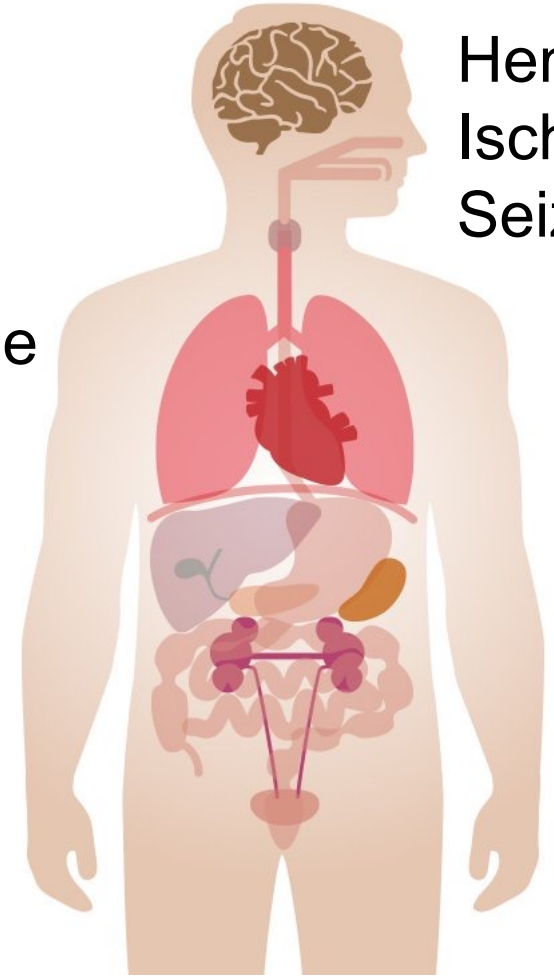
Cardiac and CNS events are common causes of death

Acute coronary syndrome
Arrhythmias
Myocarditis
Cardiomyopathy/CHF
CV collapse



Hemorrhagic stroke
Ischemic stroke
Seizures

Ciccarone and Shoptaw, Med Clin North Am. 2022 January ; 106(1): 81–97. Ashok, JAMA Psychiatry. 2017;74(5):511-519.

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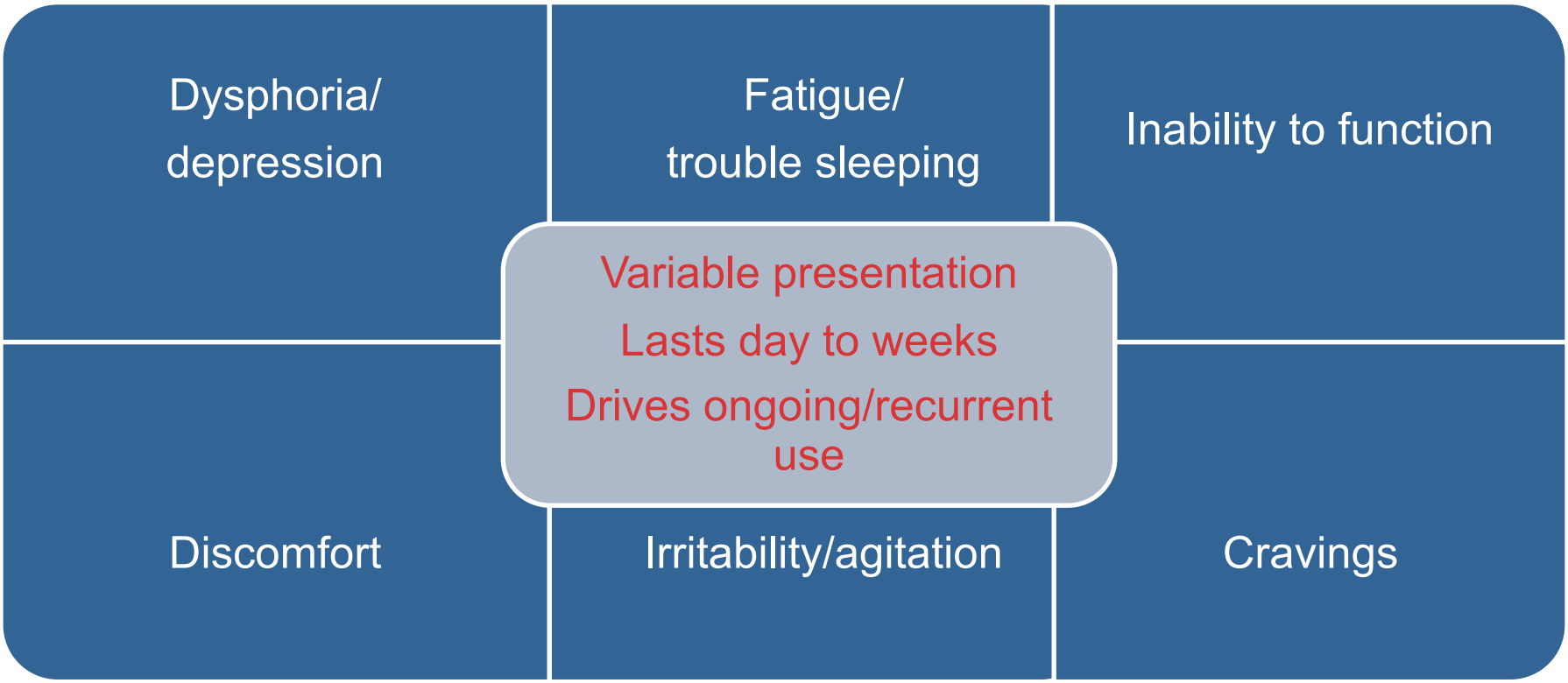
MA withdrawal



Ciccarone and Shoptaw, Med Clin North Am. 2022 January ; 106(1): 81–97. 2022

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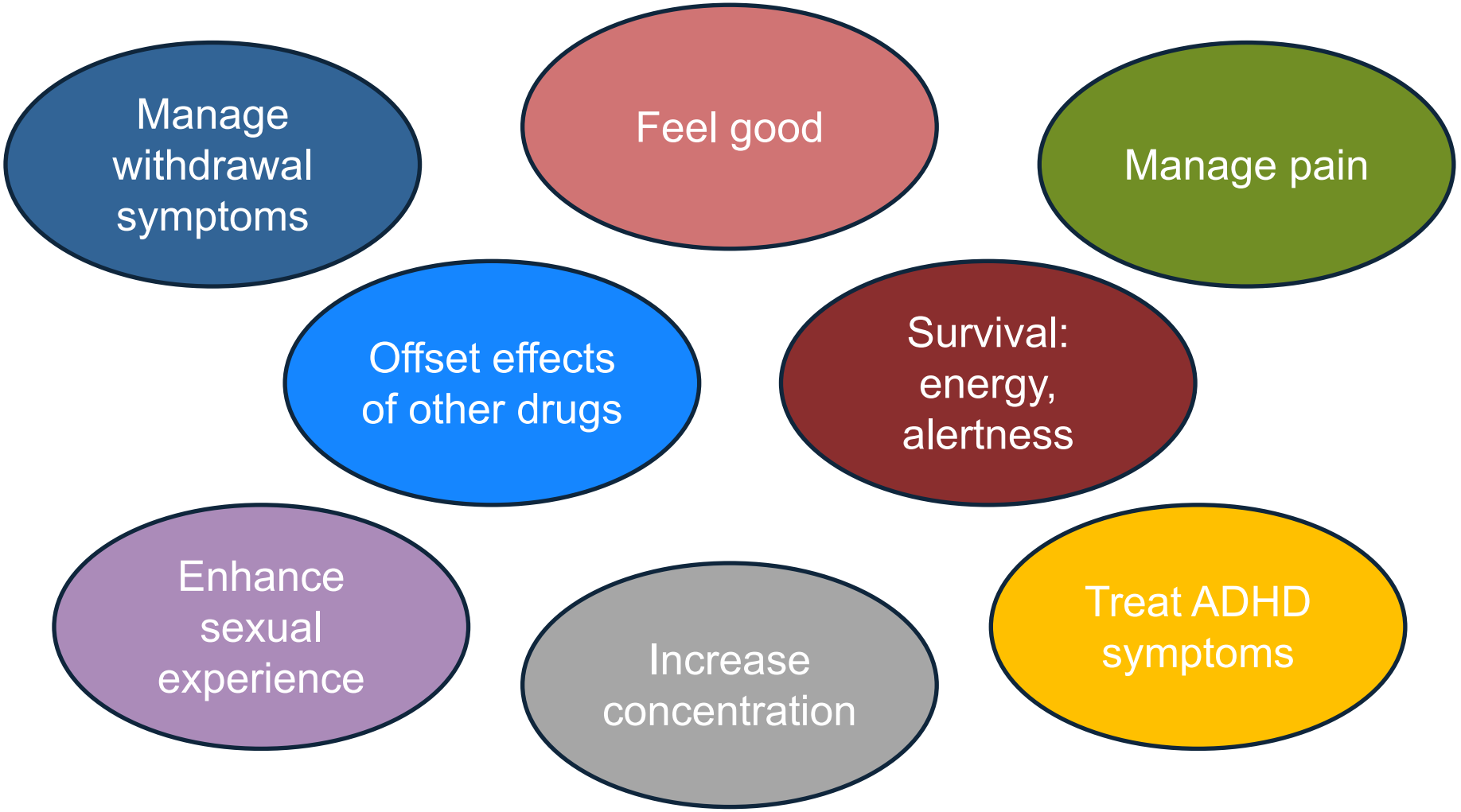
Why do people use MA?

Why use MA?



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Rose, center, with her boyfriend and another young man, all homeless, walking to a drop-in youth center in Tulsa. “Having nowhere to sleep, nothing to eat — that’s where meth comes into play,” she said. “Those things aren’t a problem if you’re using.” Joseph Rushmore for The New York Times

All of the following are reasons for co-use of opioids and stimulants, except…

- Enhance high from opioids, especially among those with opioid dependence
- Mitigate opioid withdrawal symptoms
- Decrease harm associated with opioid use
- Overlapping distribution networks
- Pain relief
- All are reasons for co-use of MA and opioids

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MA + opioids: the 4th wave of the opioid epidemic

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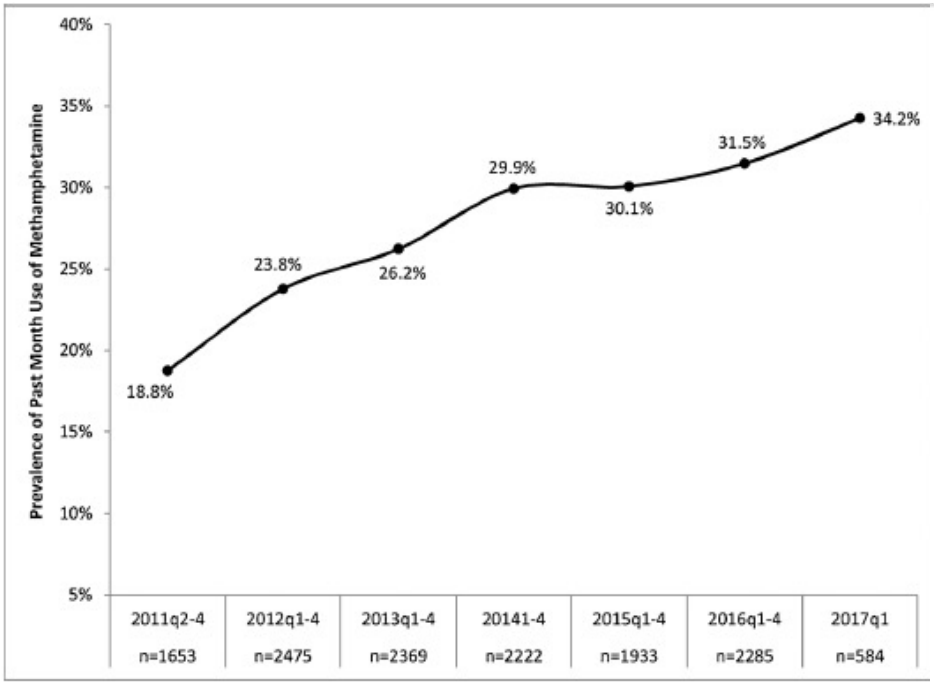
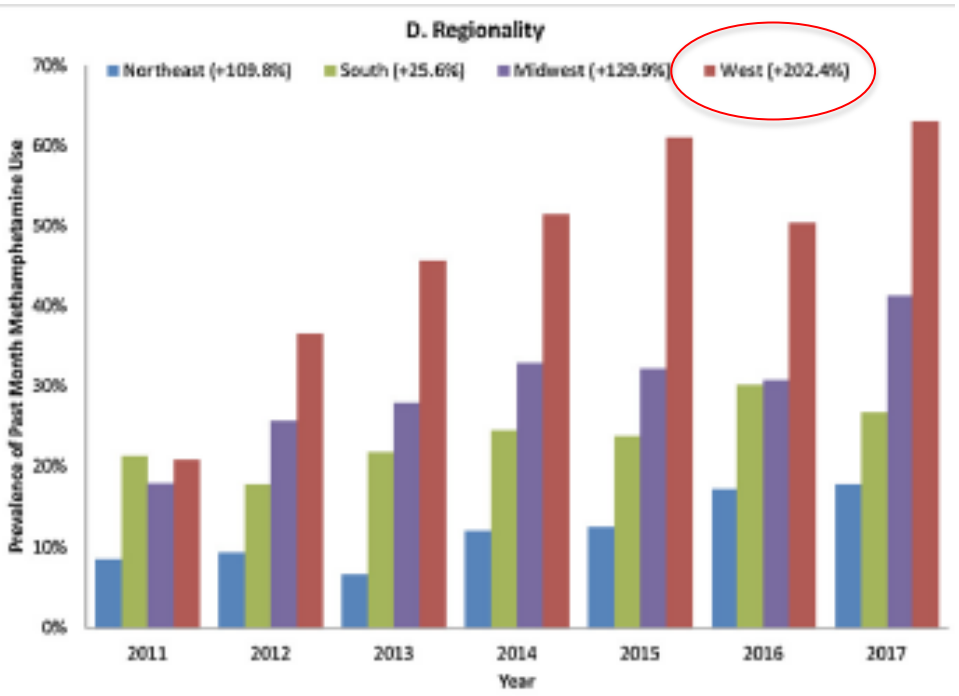
MA use rising among users of opioids

- Past-month MA use among people seeking treatment for OUD
- Majority used both drugs on same day
- Greater increases: West coast, age 35-44, women





Ellis, Drug Alcohol Dep 2018

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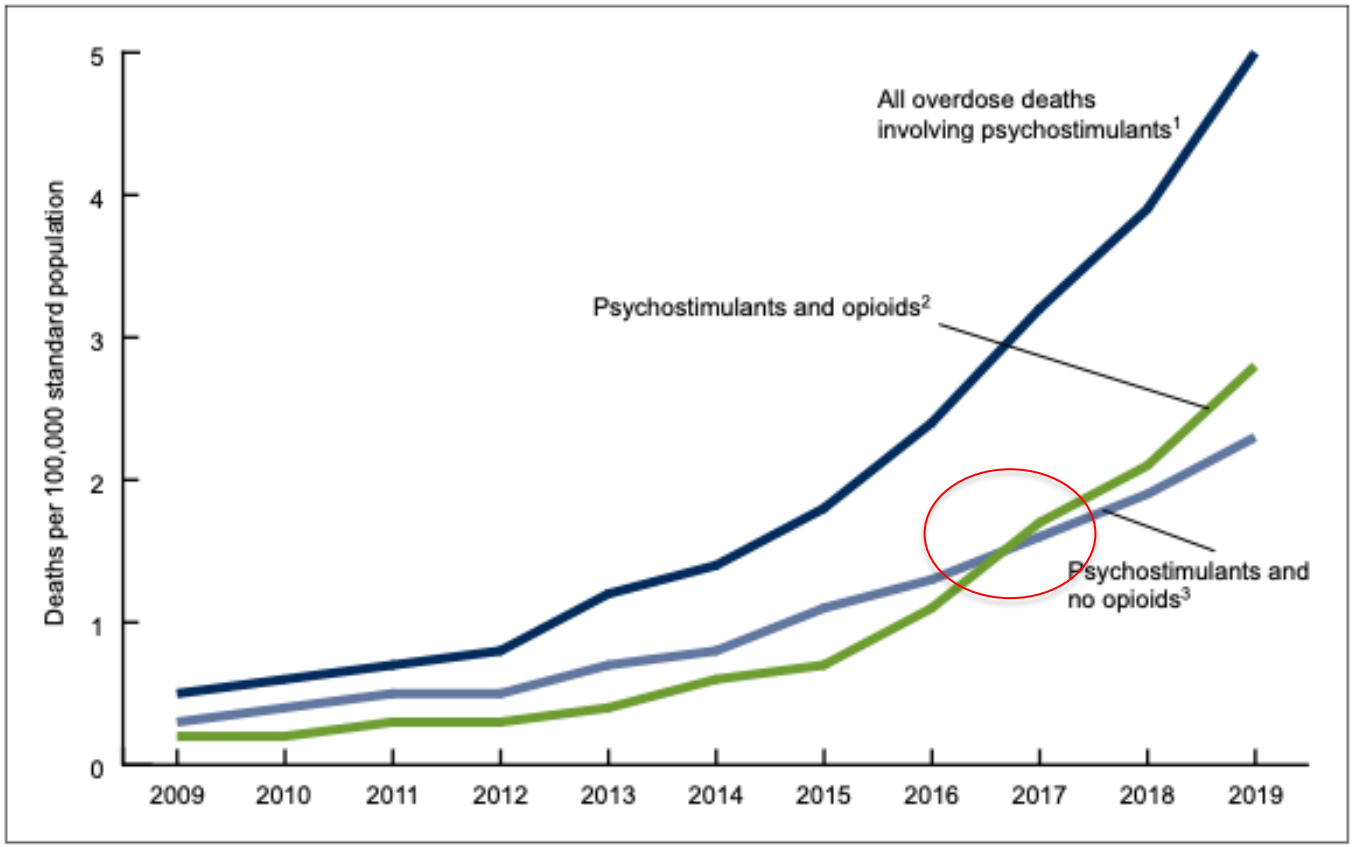
Overdose deaths related to MA + opioids

- Overdose deaths increased nearly 3x, 2015-2019

Figure 3. Age-adjusted rates of overdose deaths involving psychostimulants, by concurrent involvement of opioids: United States, 2009–2019



Han et al, JAMA Psychiatry, 2021; Figure: NCHS Data Brief No 394, Dec 2020

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Overdose among users of MA+ opioid

- Mouse model data looking at MA + fentanyl
  - MA at lower doses increases respiratory depression from fentanyl
  - MA at at higher levels reverses respiratory depression from fentanyl
- Use of depressant + stimulant drugs places immense pressure on the cardiovascular, respiratory, and central nervous systems

Glick, Drug and Alcohol Dependence 182 (2018) 86; Elder, DAD 2023; Al-Tayyib, 2017

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MA + opioid use disorder (OUD)

- Systematic review of 39 studies found that people with OUD who use MA are
  - less likely to receive life-saving treatment with methadone or buprenorphine
  - less likely to be retained in treatment with methadone / buprenorphine
  - less likely to be abstinent from opioids during treatment with methadone

Frost, Addict Sci Clin Pract. 2021

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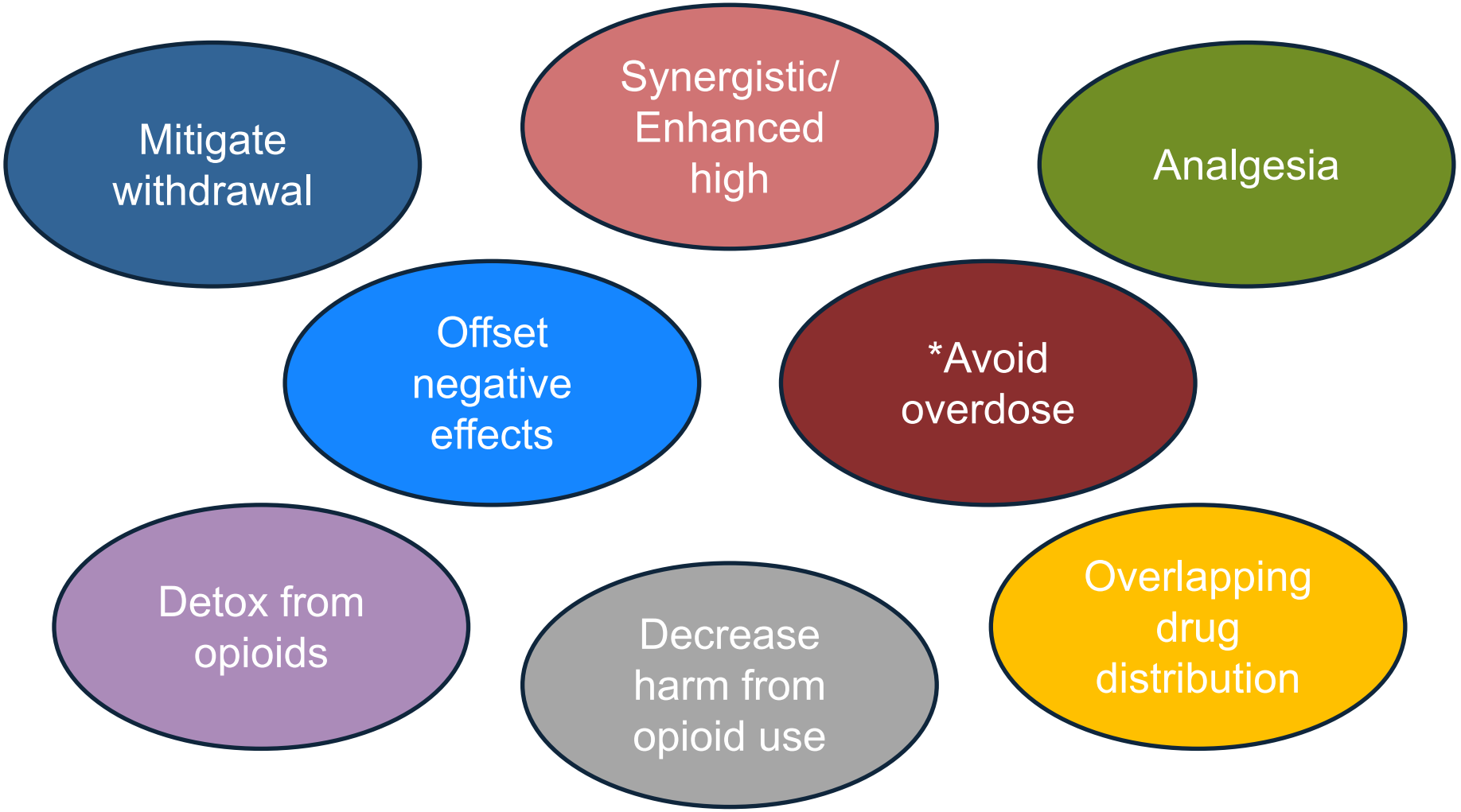
Why use opioids and stimulants together?



Ellis, 2018; Lopez, Int J Drug Policy 2021; Shiriatirad, 2013

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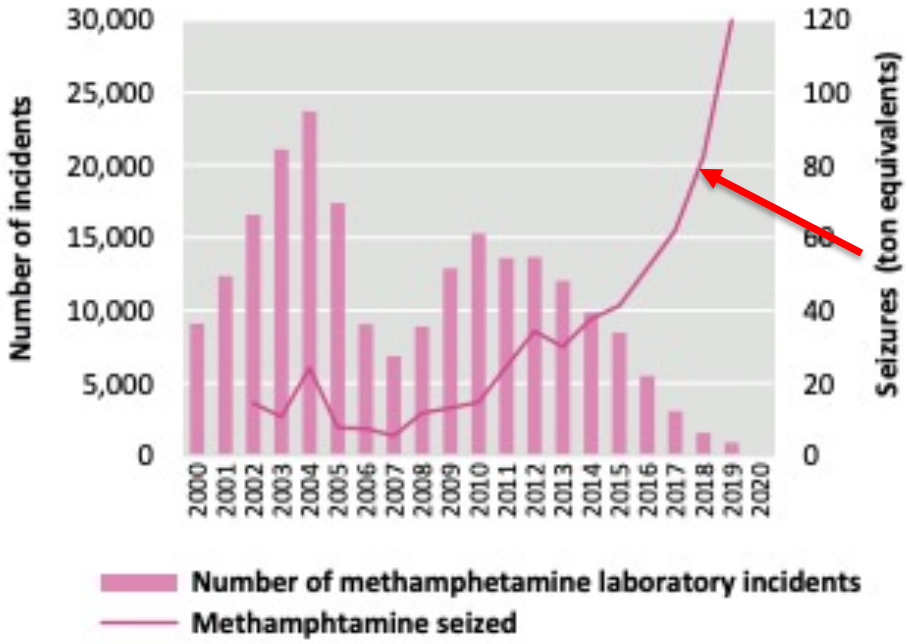
Trends in MA use and overdose in the U.S.

Availability and potency are surging

FIG. 27 Methamphetamine laboratory incidents and quantities of methamphetamine seized, United States, 2000–2019



Methamphetamine purity and potency, United States, 2011–2019

Figures: UNODC

United Nations Office on Drugs and Crime (UNODC) World Drug Report 2021

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Methamphetamine use in the U.S. is highest in world and appears to be increasing

- In 2020, 2.5 million Americans reported using methamphetamine in the last year
- 2015-2019:
  - Past-year MA use among adults increased 43%
  - MA use disorder increased 62%

Figure: United Nations Office of Drugs and Crime, 2019

Substance Abuse and Mental Health Services Administration (SAMHSA); Han et al, JAMA Psychiatry, Dec 2021

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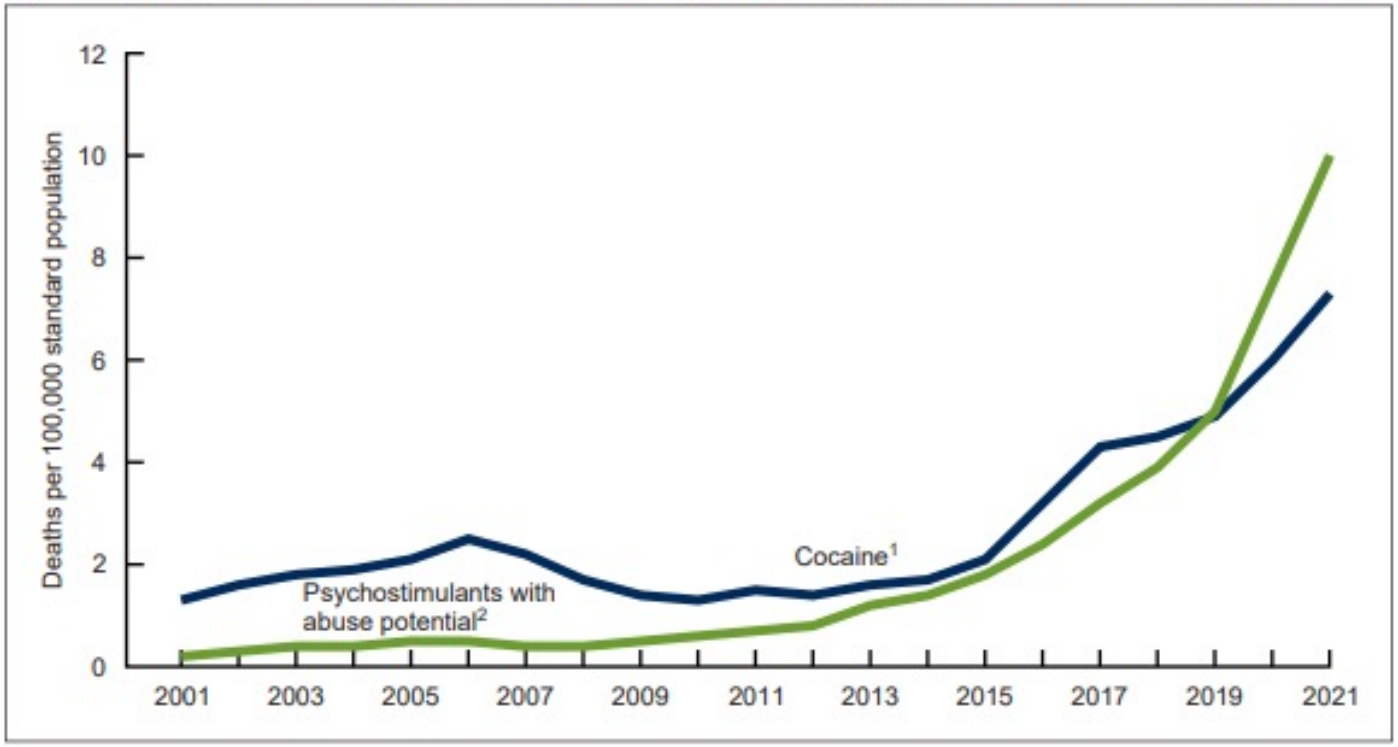
MA overdose deaths are increasing much more dramatically

- Overdose deaths increased >12x from 2008 to 2019

Figure 5. Age-adjusted rate of drug overdose deaths involving stimulants, by type of stimulant: United States, 2001–2021



National Center for Health Statistics (NCHS) Data Brief 394, 2020, and 457, 2022

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Increases in overdose out of proportion to increases in use

- Risker use: increases in
  - intentional use with fentanyl, heroin, cocaine
  - methamphetamine laced with fentanyl
  - frequent methamphetamine use
- Riskier drug?
  - Changed processes for making methamphetamine
  - Increased d- to l-isomer: ⇧ CNS activity, increased potency

Han et al, JAMA Psychiatry, 2021; 2019 DEA National Drug Threat Assessment.
Image: New York Times. P2P=phenyl-2-propanone

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Changing ingredients of methamphetamine

- Then: ephedrine method, subject to legal/regulatory actions by U.S. and Mexico to limit supply of ephedrine
- Now: P2P method, variety of legal and cheap chemicals used in wide variety of industries
- Production shifts to numerous, efficient labs in Mexico

Methamphetamine Precursor Chemicals

Controlled Examples:	Not Controlled Examples:
• Methylamine	• Ammonium chloride
• Benzaldehyde	• Formaldehyde
• Nitroethane	

2019 DEA National Drug Threat Assessment. P2P=phenyl-2-propanone

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Who is most at risk for MA use and MUD?

- Low socioeconomic status
- Housing instability
- Lack of insurance
- Criminal justice involvement
- Chronic viral infections (HIV, hepatitis C, etc.)
- Depression
- Suicidality
- Polysubstance use

Han et al, JAMA Psychiatry Dec 2021

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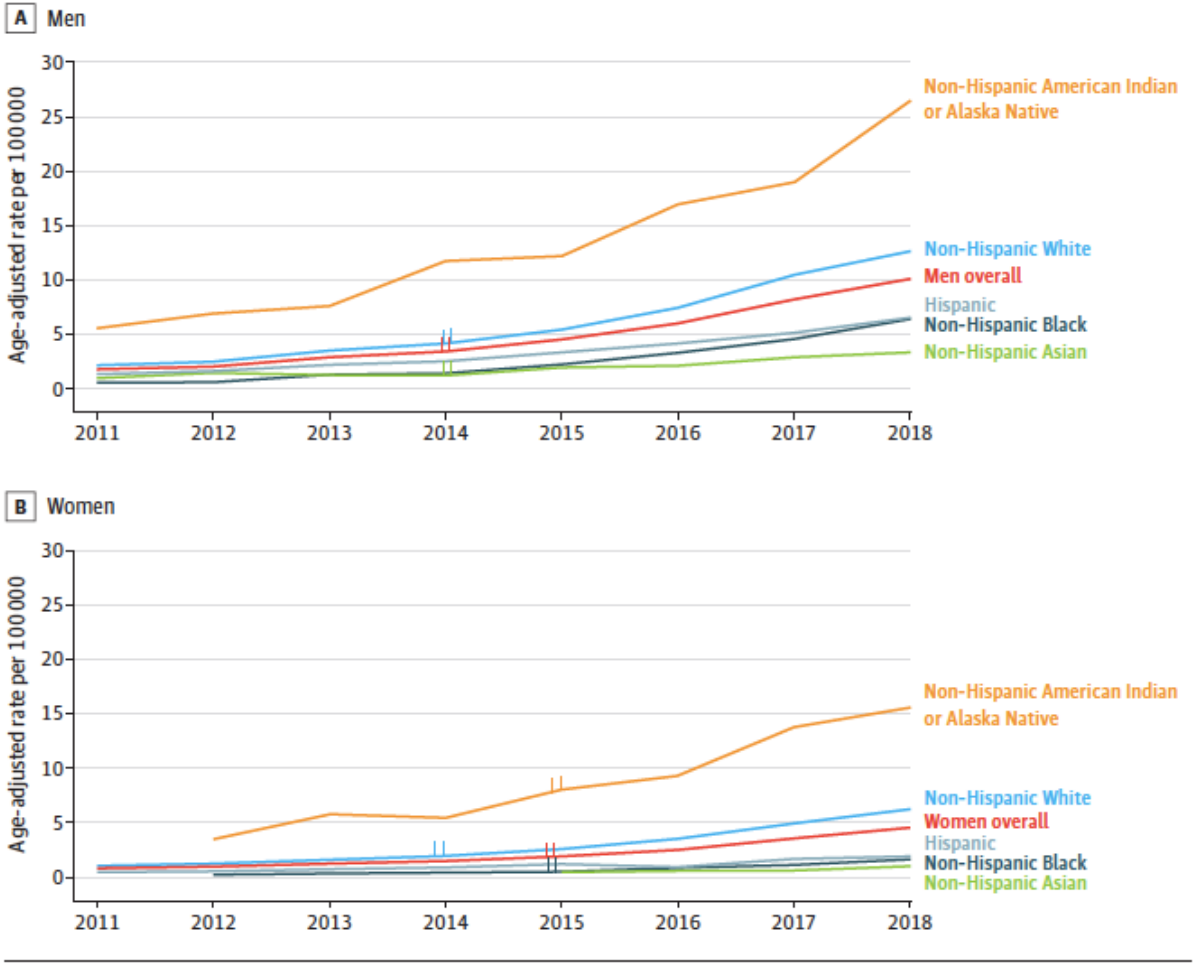
Disproportionate overdose death among American Indian / Alaska Native persons

Figure. Trends in Methamphetamine Deaths Among US Men and Women Aged 25-54 Years Overall and by Race and Ethnicity



Han et al, JAMA Psychiatry, May 2021

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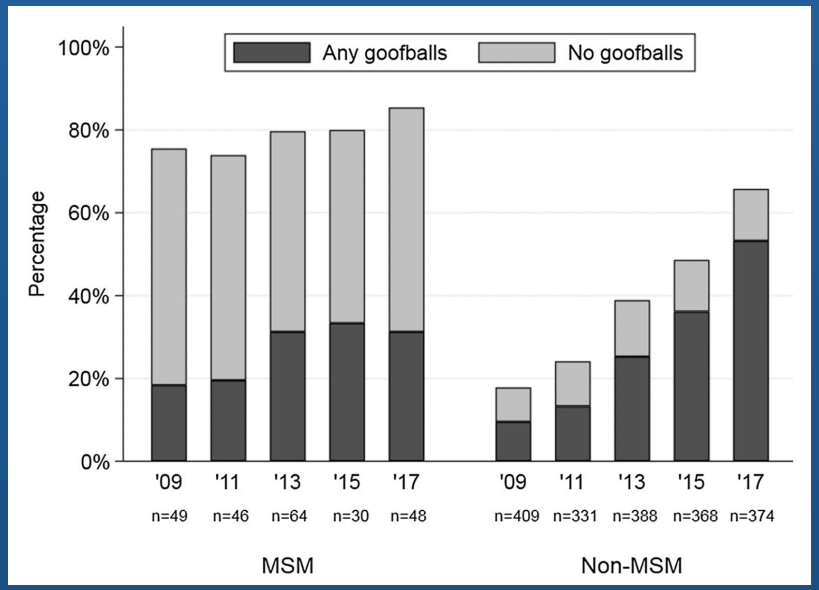
Trends in MA and risk of HIV

"Goofball" injection within 3 months, PWID in King County, 2009-2017



- MA use increases risk of HIV acquisition, transmission, and viral non-suppression
- King County PWID:
  - rising injection MA use, mostly in combination with heroin ("goofballs"), mostly driven by non-MSM
  - Significant needle sharing between non-MSM and MSM
  - Non-MSM who use MA are emerging population at risk of HIV

Glick, Drug and Alcohol Dependence 182 (2018) 86. PWID= persons who inject drugs

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Each of the following has shown promise to treat MUD, except…

- Methylphenidate
- Aripiprazole
- Topiramate
- Mirtazapine
- Buprenorphine/XR naltrexone
- All of the above have shown promise to treat MUD

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MA treatment: psychosocial and off-label use of medications

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Treatment—the big picture

↑ Use, risky use, overdose

High rates co-occurring use

Diversifying populations affected

Urgent need to

increase / improve treatment options

increase access to harm reduction

treat co-occurring disorders

target diverse populations for prevention and tx

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Making the diagnosis of MUD

- Impaired Control
  1. Larger amounts, longer time
  2. Inability to cutback
  3. More time spent, getting, using, recovering
  4. Craving
- Social Impairment
  5. Failure to fulfill major role obligations
  6. Social or interpersonal problems related to use
  7. Important social activities given up to use.
- Risky use
  8. Physically hazardous use
  9. Continued use despite associated recurrent physical or psychological problems.
- Pharmacological
  10. Tolerance
  11. Withdrawal

2-3 = mild
4-5 = moderate
6+ = severe

- A substance use disorder is defined as clinically significant impairment or distress, associated with 2 or more of these symptoms in the past year
- Tolerance and withdrawal criteria are not considered when taken appropriately by Rx.
- Severity is related by the number of symptoms.

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SUD treatment endpoints

Abstinence

- Dichotomous view of recovery
- Devalues alternative endpoints that contribute to safety and recovery
- High, unrealistic bar
- Disincentivizes medication development

Other endpoints

- Symptoms—withdrawal, sleep problems, mood
- Reduced use—decreases exposure to harms, improves health, can put people on path toward abstinence
- Retention in treatment

Volkow, Am J Psychiatry 2020; Guidance document, FDA Oct 2020; Roos et al, Drug Alcohol Depend 2019

Interest in treatment

- 2019 WA State syringe exchange survey of *non-treatment seeking population*
- 583 participants, of whom 24% reported MA was main drug
- Of those, 46% reported interest in reducing /stopping MA

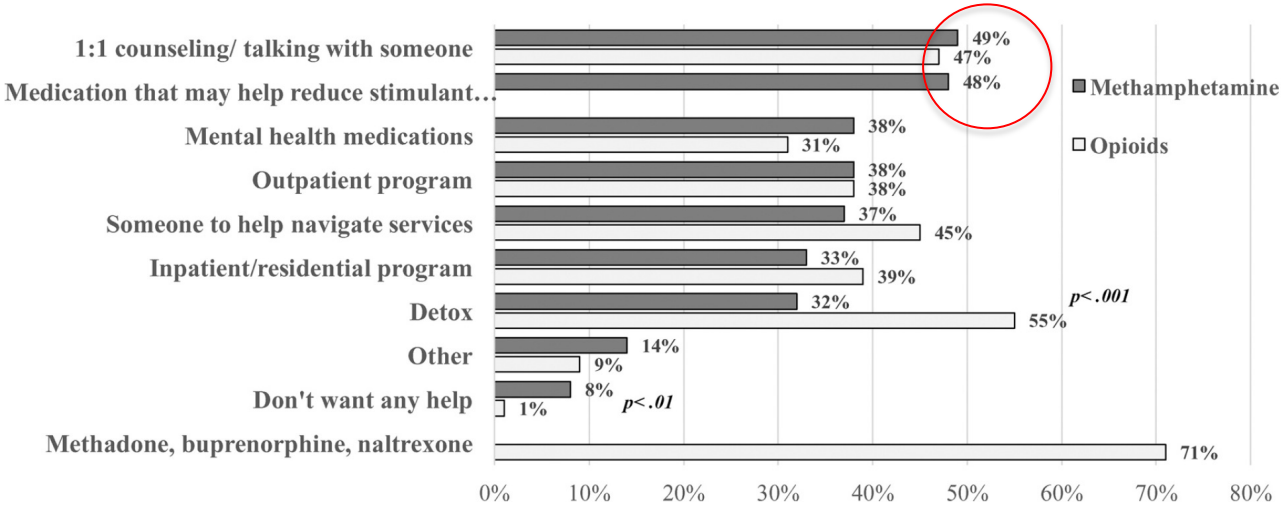

Fig. 2. Among Participants who were Interested in Reducing or Stopping their Methamphetamine or Opioid Use, the Percent who Wanted Different Types of Help by Reported Main Drug (Methamphetamine or an Opioid) (n = 474).

McMahan, Drug and Alcohol Dependence 216 (2020) 108243

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Behavioral treatments—best evidence

Outcomes

- Abstinence
- Reduced use
- Addiction severity
- HIV risk behaviors
- Sexual risk behaviors

Contingency Management

Community Reinforcement Approach

Cognitive Behavioral Therapy

SAMHSA: Treatment of Stimulant Use Disorders, 2019; (adapted) slide credit: Jared Klein

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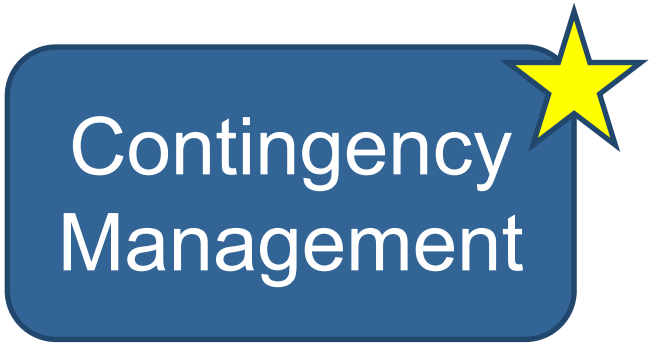
Strongest evidence

- Based on operant conditioning—reinforcing desired behavior with prizes/ cash
- Fishbowl method—earn chances to win prizes of varying value
- Vouchers of increasing value
- Incentives for
  - Stimulant-negative urines
  - Adherence to medications
  - Attending treatment



Strong evidence

- 1:1 or group short-term goal-oriented therapy
- Examine existing thought patterns that contribute to substance use
- Develop strategies to change thoughts and behaviors
- “Sleeper effect”—abstinence outcomes improves over time as participants apply the skills to real life

Cognitive Behavioral Therapy

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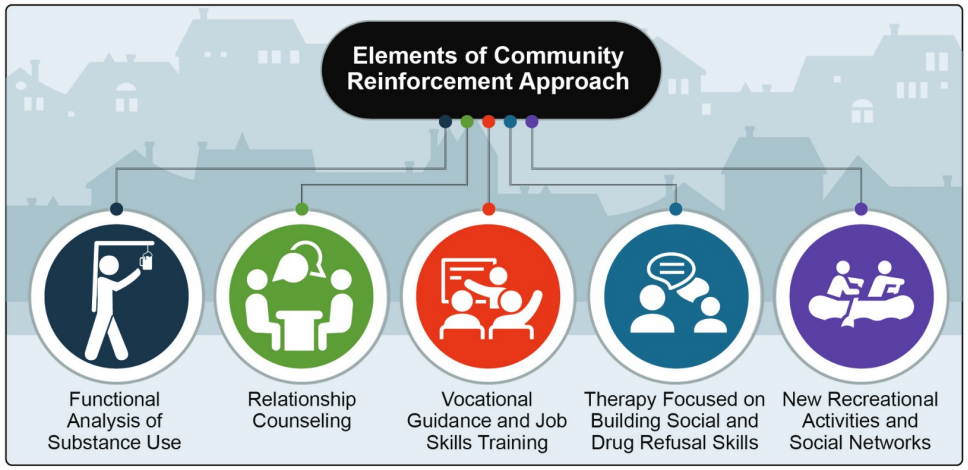
Strong evidence (cocaine)

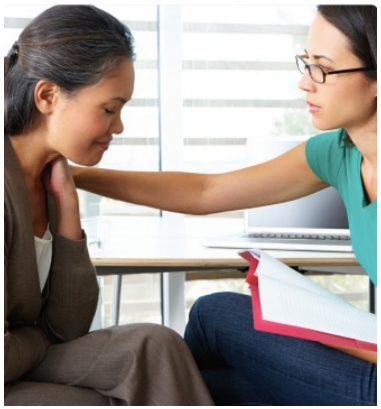
- Comprehensive behavioral therapy– work to adjust aspects of lives that interfere with health
- Goal: build a way of living without substances that is more rewarding than a life with substances
- Resource intensive

Community Reinforcement Approach



Limitations of behavioral treatments

- Cognitive effects of use may reduce ability to engage
- Dropout high and predicts recurrent use
- Regulatory and coverage barriers
- Limited access
- More evidence for cocaine vs methamphetamine



[1]Lappan et al, Addiction 2020; Images: SAMHSA

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2018 Review: Numerous Medication Trials, No FDA Approved Medication Treatments

- Dexamphetamine
- Methylphenidate
- Modafinil
- Bupropion
- Mirtazapine
- Sertraline
- Fluoxetine
- Risperidone
- Aripiprazole
- Buprenorphine
- Naltrexone
- Topiramate
- Gabapentin
- Vigabatrin
- N-acetyl cysteine
- Baclofen
- Ondansetron
- Varenicline
- Amlodipine
- Flumazenil + gabapentin
- Bupropion + naltrexone

Lee et al, Drug and Alc Dep 2018

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The ASAM/AAAP

CLINICAL PRACTICE GUIDELINE ON THE

Management of Stimulant Use Disorder

ASAM American Society of Addiction Medicine

AAP American Academy of Addiction Psychiatry

https://www.asam

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Topiramate

- RCT of topiramate vs. placebo x 12 weeks
- Topiramate uptitrated to target dose of 200 mg though few achieved that dose
- Abstinence at weeks 6-12 did not differ (primary outcome)
  - For those with negative urine prior to randomization, abstinence was significantly greater in topiramate group
- Urine MA levels and observer-rated severity of dependence were lower with topiramate (secondary outcomes)
- No serious adverse events in topiramate group

Elkashef, Addiction. 2012 July ; 107(7): 1297–1306.

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Mirtazapine

- Replicated results of small 12-week RCT
- Cisgender men and transgender women who had sex w/ men while using MA
- Excluded if major depression
- Mirtazapine 30 mg vs placebo for 24 weeks
- Primary outcome: **meth-positive urines**
- Secondary: sexual risk behaviors and AEs

Mirtazapine = mixed monoamine agonist/antagonist, facilitates release of dopamine, norepinephrine, and serotonin

Colfax et al, Archives Gen Psych 2011; Coffin, JAMA Psychiatry 2019

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Results at 24 weeks

- 120 participants, 96% cisgender men, racially diverse
- Adherence low in both groups
- ~25% fewer MA-positive urines in group taking mirtazapine
- ↓ sexual risk behavior, depression, sleepiness scores
- No serious AE from mirtazapine

Figure 2. Proportion of Participants With Positive Urine Test Results for Methamphetamine During Follow-up, by Arm

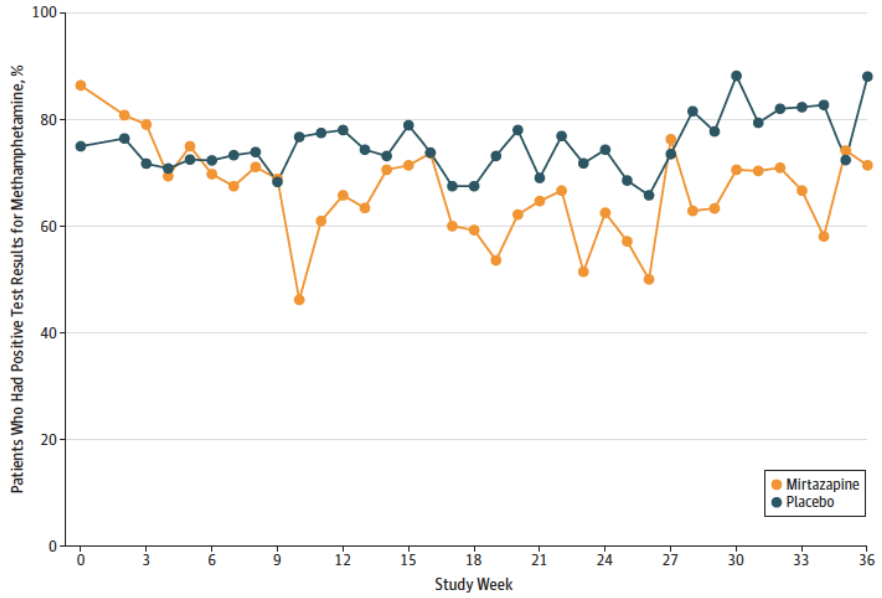

Table 2. Primary and Secondary Outcomes and Sensitivity Analyses

Outcome	Risk Ratio or Coefficient (95% CI)	*P* Value
Primary Outcomes		
Intent-to-treat analyses[a]		
Treatment effect at 12 wk	0.67 (0.51-0.87)	.003
Net treatment effect at 24 wk[b]	0.75 (0.56-1.00)	.05
Net treatment effect at 36 wk[c]	0.73 (0.57-0.96)	.02

Coffin et al, JAMA Psychiatry 2019; AE: adverse events

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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Bupropion and Naltrexone in Methamphetamine Use Disorder

- Followed small open-label pilot
- 12-week RCT of injectable ER naltrexone+ bupropion, both at high doses
- 2- stage design to enhance sample
- MUD, active MA use, desire to quit or reduce use, opioid-free
- **Response to treatment** defined by at least 3 of 4 urines negative for MA in last 2 weeks of each stage

Bupropion = stimulant-like antidepressant, may alleviate dysphoria of withdrawal

+

Naltrexone = opioid antagonist, may attenuate reinforcing effects/decrease cravings

Mooney et al, J Addiction Med 2016; Trivedi et al, NEJM 2021. ER: extended-release

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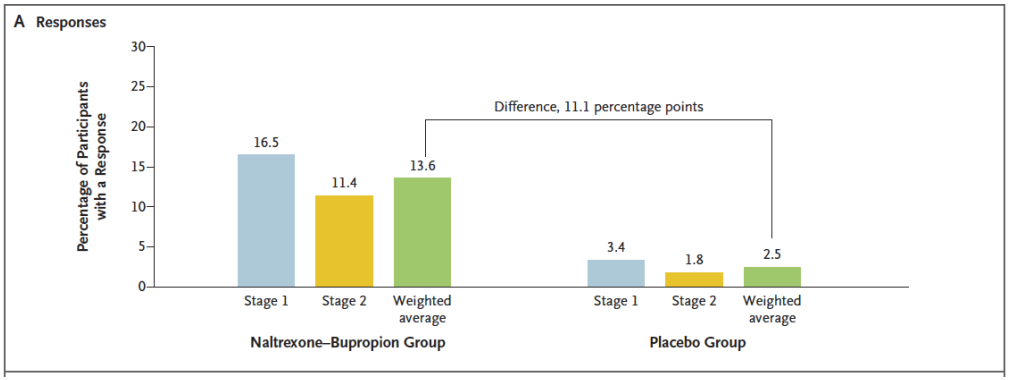
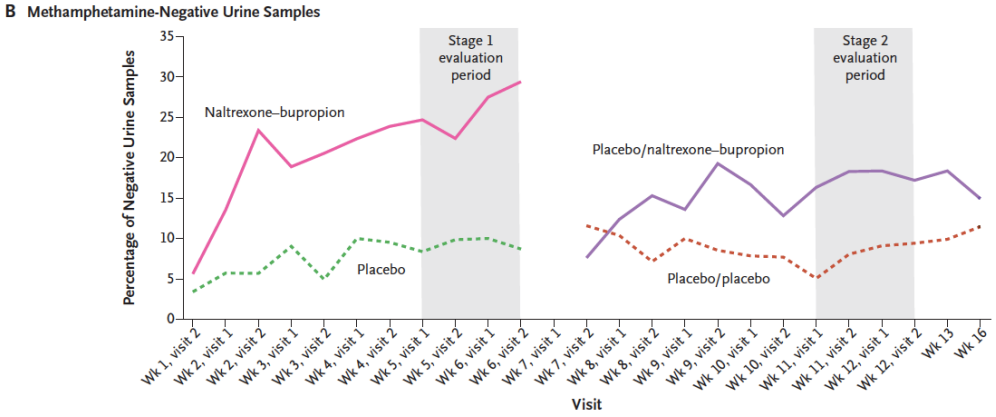
Results

- N=401, averaged 27/30 days MA use
- >75% adherence
- Overall treatment effect of 11.1% - and 18.7% in those with 4/4 samples
- Mild adverse events





Trivedi et al, NEJM 2021

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Prescription stimulants

- Long interest in potential in “agonist-type” treatment
- Meta-analysis found rx stimulants are associated with increased abstinence and decreased use of psychostimulants
- Data is *low-quality and driven by subgroup with cocaine use disorder*
- Have been shown to improve ADHD symptoms in people with ADHD who use MA

Methylphenidate = dopamine agonist, inhibits reuptake of norepinephrine and dopamine

Tardelli, Psychopharmacology (2020) 237:2233–2255

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ASAM/AAAP guideline

- Risks of psychostimulants may outweigh benefits
- “Only physician specialists board certified in addiction medicine or addiction psychiatry—or physicians with commensurate training, competencies, and capacity for close patient monitoring—should prescribe these medications for this purpose”

https://www.asam.org/quality-care/clinical-guidelines/stimulant-use-disorders

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Medication highlights

Topiramate

- Data for reducing MA use and for preventing recurrent use
- Gradual titration due to side effects
- Additional benefits in those with alcohol use disorder, seizure disorder, chronic headaches, etc.

Mirtazapine

- Weak data for small reduction in MA use
- Two trials by same study group, methodological limitations
- Specific population limits generalizability
- Safe medication with known benefits to sleep and mood

Bupropion/naltrexone

- Good quality data for reduced MA use
- NNT=9 for one patient to have a response
- Low attrition/ high adherence limit generalizability
- Safe, well-tolerated medications but used at higher than usual doses
- Not an option for people who use opioids

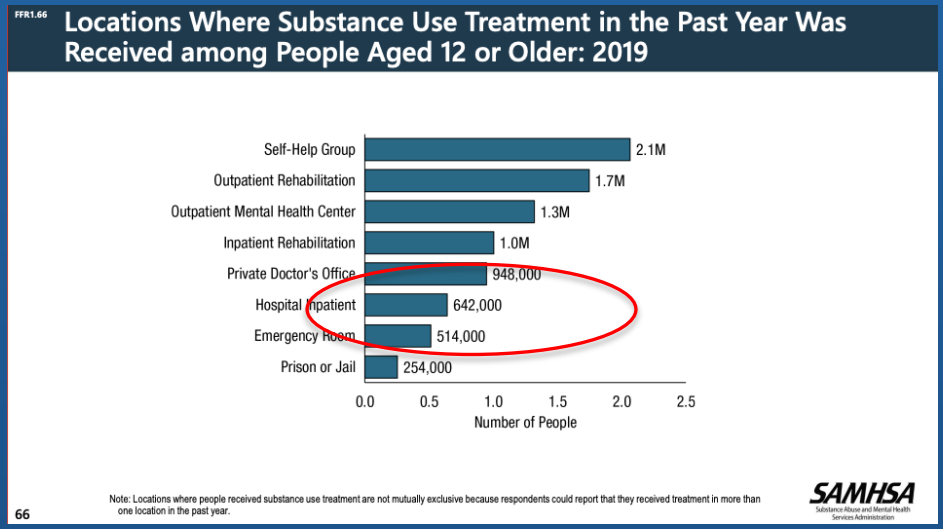
Extended-release methylphenidate

- Data for increasing abstinence and decreasing stimulant use (driven by subgroup using cocaine)
- Effective for ADHD in those who use MA
- Guidelines do not currently recommend for those without specialized training

Stigma is a barrier to treatment

- Psychosocial barriers to treatment for MA use:
  - Embarrassment/stigma – 60%
  - Belief that treatment was unnecessary – 59%
  - Preference to withdraw alone without help – 55%
  - Privacy concerns – 51%

You kind of feel sorry for the opiate addict like, "Oh, they have pain, and they're covering it up. They're not hurting anybody. They're just sitting there." Whereas meth, it's like, "That's a psychotic person. That's a dangerous, insane person." (Lopez, 2021)



Cumming, Drug and Alcohol Dependence 168 (2016) 263–273

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Reducing harm from MA use (in brief)

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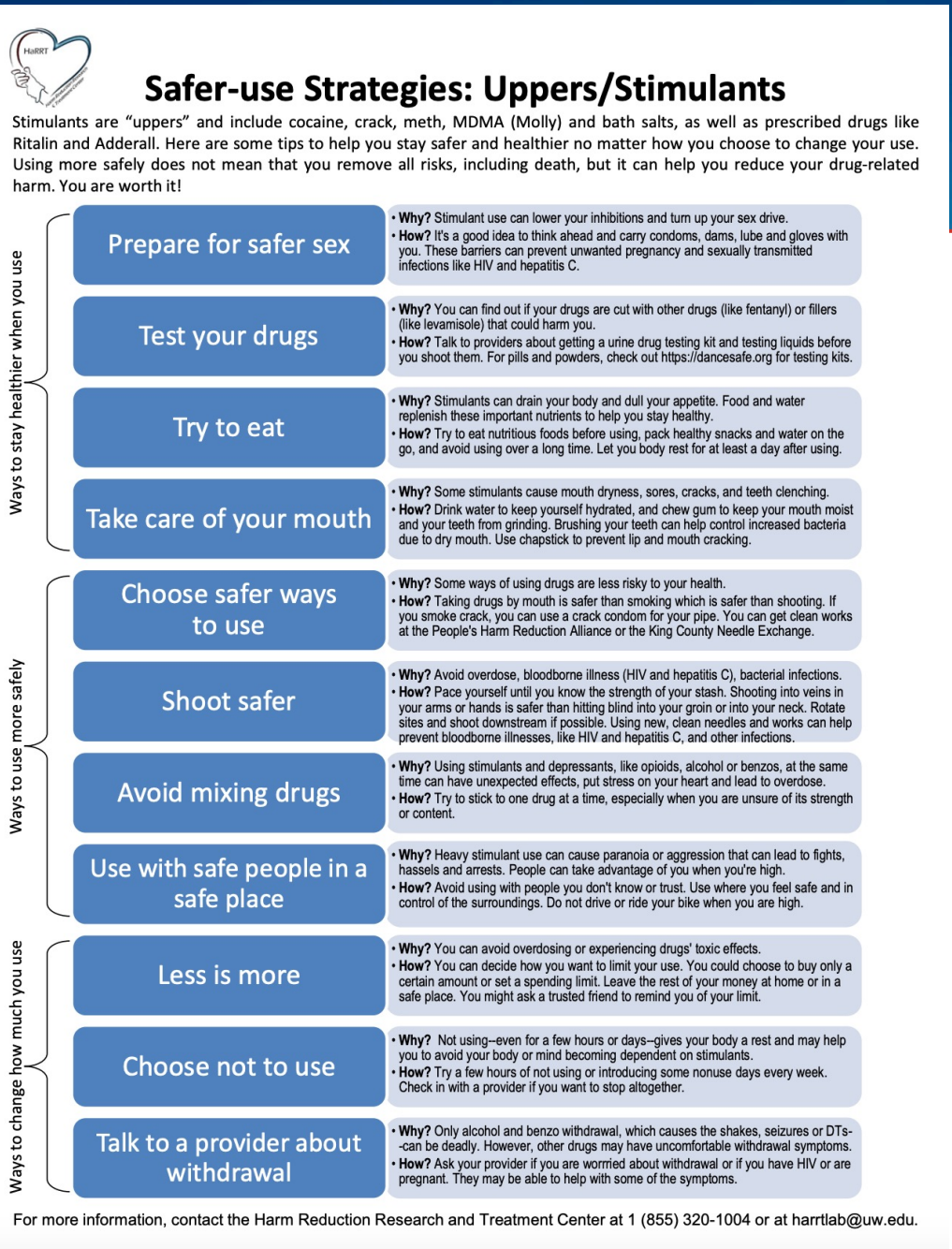
- Naloxone for all – provide multiple
- Diagnose and treat OUD – methadone and buprenorphine save lives
- Screen for HCV, HBV, HIV, syphilis
- Remember PrEP



Safer-use Strategies: Uppers/Stimulants

Stimulants are "uppers" and include cocaine, crack, meth, MDMA (Molly) and bath salts, as well as prescribed drugs like Ritalin and Adderall. Here are some tips to help you stay safer and healthier no matter how you choose to change your use. Using more safely does not mean that you remove all risks, including death, but it can help you reduce your drug-related harm. You are worth it!

Ways to stay healthier when you use	Prepare for safer sex	• **Why?** Stimulant use can lower your inhibitions and turn up your sex drive. • **How?** It's a good idea to think ahead and carry condoms, dams, lube and gloves with you. These barriers can prevent unwanted pregnancy and sexually transmitted infections like HIV and hepatitis C.
	Test your drugs	• **Why?** You can find out if your drugs are cut with other drugs (like fentanyl) or fillers (like levamisole) that could harm you. • **How?** Talk to providers about getting a urine drug testing kit and testing liquids before you shoot them. For pills and powders, check out https://dancesafe.org for testing kits.
	Try to eat	• **Why?** Stimulants can drain your body and dull your appetite. Food and water replenish these important nutrients to help you stay healthy. • **How?** Try to eat nutritious foods before using, pack healthy snacks and water on the go, and avoid using over a long time. Let you body rest for at least a day after using.
	Take care of your mouth	• **Why?** Some stimulants cause mouth dryness, sores, cracks, and teeth clenching. • **How?** Drink water to keep yourself hydrated, and chew gum to keep your mouth moist and your teeth from grinding. Brushing your teeth can help control increased bacteria due to dry mouth. Use chapstick to prevent lip and mouth cracking.
Ways to use more safely	Choose safer ways to use	• **Why?** Some ways of using drugs are less risky to your health. • **How?** Taking drugs by mouth is safer than smoking which is safer than shooting. If you smoke crack, you can use a crack condom for your pipe. You can get clean works at the People's Harm Reduction Alliance or the King County Needle Exchange.
	Shoot safer	• **Why?** Avoid overdose, bloodborne illness (HIV and hepatitis C), bacterial infections. • **How?** Pace yourself until you know the strength of your stash. Shooting into veins in your arms or hands is safer than hitting blind into your groin or into your neck. Rotate sites and shoot downstream if possible. Using new, clean needles and works can help prevent bloodborne illnesses, like HIV and hepatitis C, and other infections.
	Avoid mixing drugs	• **Why?** Using stimulants and depressants, like opioids, alcohol or benzos, at the same time can have unexpected effects, put stress on your heart and lead to overdose. • **How?** Try to stick to one drug at a time, especially when you are unsure of its strength or content.
	Use with safe people in a safe place	• **Why?** Heavy stimulant use can cause paranoia or aggression that can lead to fights, hassels and arrests. People can take advantage of you when you're high. • **How?** Avoid using with people you don't know or trust. Use where you feel safe and in control of the surroundings. Do not drive or ride your bike when you are high.
Ways to change how much you use	Less is more	• **Why?** You can avoid overdosing or experiencing drugs' toxic effects. • **How?** You can decide how you want to limit your use. You could choose to buy only a certain amount or set a spending limit. Leave the rest of your money at home or in a safe place. You might ask a trusted friend to remind you of your limit.
	Choose not to use	• **Why?** Not using--even for a few hours or days--gives your body a rest and may help you to avoid your body or mind becoming dependent on stimulants. • **How?** Try a few hours of not using or introducing some nonuse days every week. Check in with a provider if you want to stop altogether.
	Talk to a provider about withdrawal	• **Why?** Only alcohol and benzo withdrawal, which causes the shakes, seizures or DTs--can be deadly. However, other drugs may have uncomfortable withdrawal symptoms. • **How?** Ask your provider if you are worried about withdrawal or if you have HIV or are pregnant. They may be able to help with some of the symptoms.

For more information, contact the Harm Reduction Research and Treatment Center at 1 (855) 320-1004 or at harrtlab@uw.edu.

https://depts.washington.edu/harrtlab/wordpress/wp-content/uploads/2018/11/Safer-Use-Stimulants.pdf

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Closing thoughts

- MA is highly reinforcing and acute and chronic consequences are many
- Important to understand why your patient uses MA and address what symptoms/conditions you can
- Behavioral approaches work but access is limited
- Consider offering medications; think about comorbidities and symptoms
- Engaging patients in discussions about their use and treatment options is a success!

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Discussion/Q&A

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