AETC AIDS Education & Training Center Program Mountain West

Updates on Methamphetamine Use in the U.S.: rising dangers, potential treatments

Jocelyn James, MD
Assistant Professor
Division of General Internal Medicine
University of Washington School of Medicine

December 7, 2021

AETC AIDS Education & Training Center Program Mountain West

Panel Discussants

James Darnton, MD
Clinical Instructor
Division of General Internal Medicine
University of Washington School of Medicine

Jared Klein, MD, MPH
Assistant Professor
Division of General Internal Medicine
University of Washington School of Medicine

Disclosures

No conflicts of interest or relationships to disclose

We will discuss off-label use of medications

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Outline

- Trends in methamphetamine use and harms
- Evolving approaches to treatment of methamphetamine use disorder (MUD)
- Recent literature on medications for MUD
- Discussion / Q&A

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Terminology

- I will use “methamphetamine” in place of “psychostimulants with abuse potential,” as it is by far the largest contributor to this category
- The categorization “psychostimulants with abuse potential” also includes ecstasy and prescription stimulants such as methylphenidate

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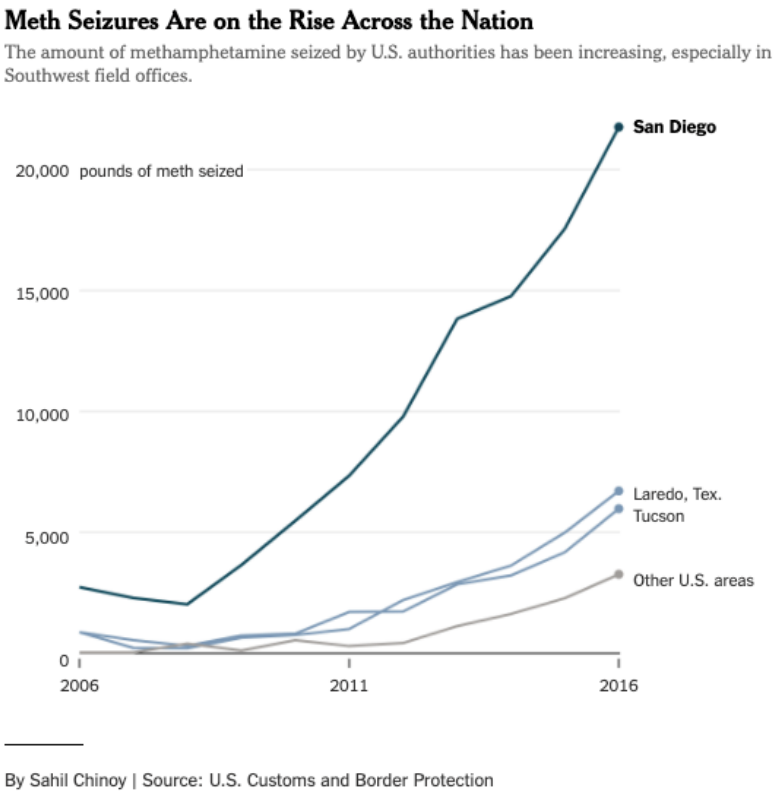
The New York Times

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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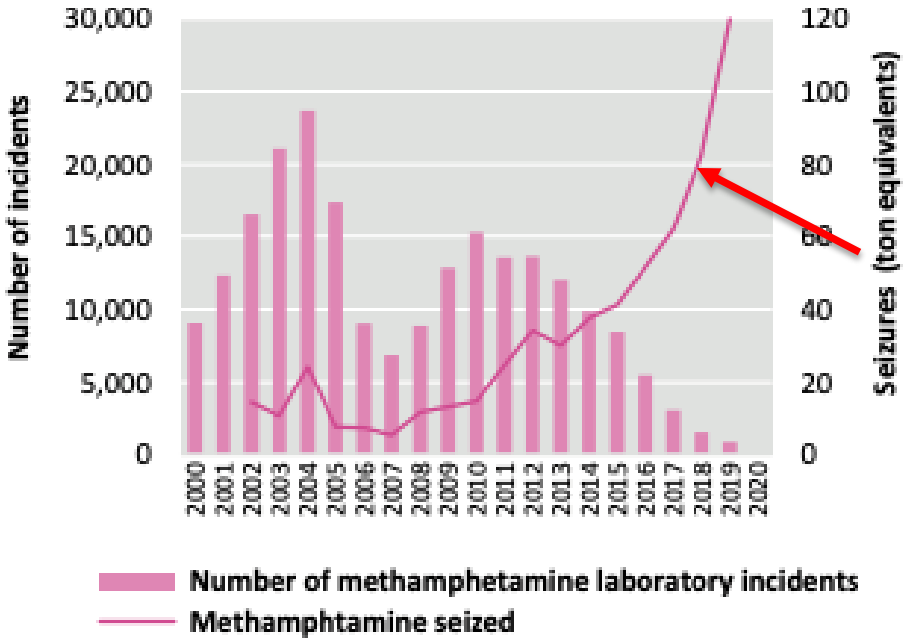
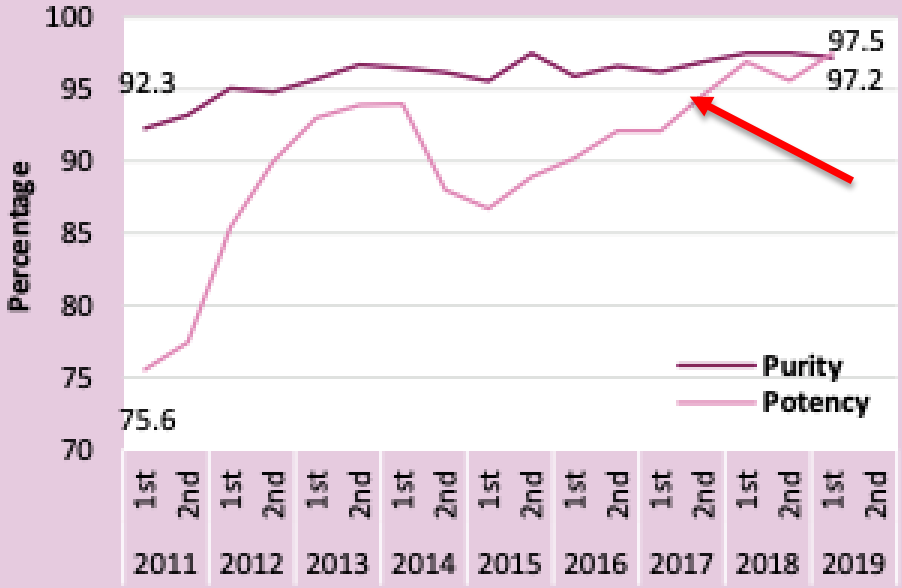
Availability and potency are surging

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[1]
- Past-year use among adults increased 43%, 2015-2019[2]
- MUD increased 62% during same period[2]

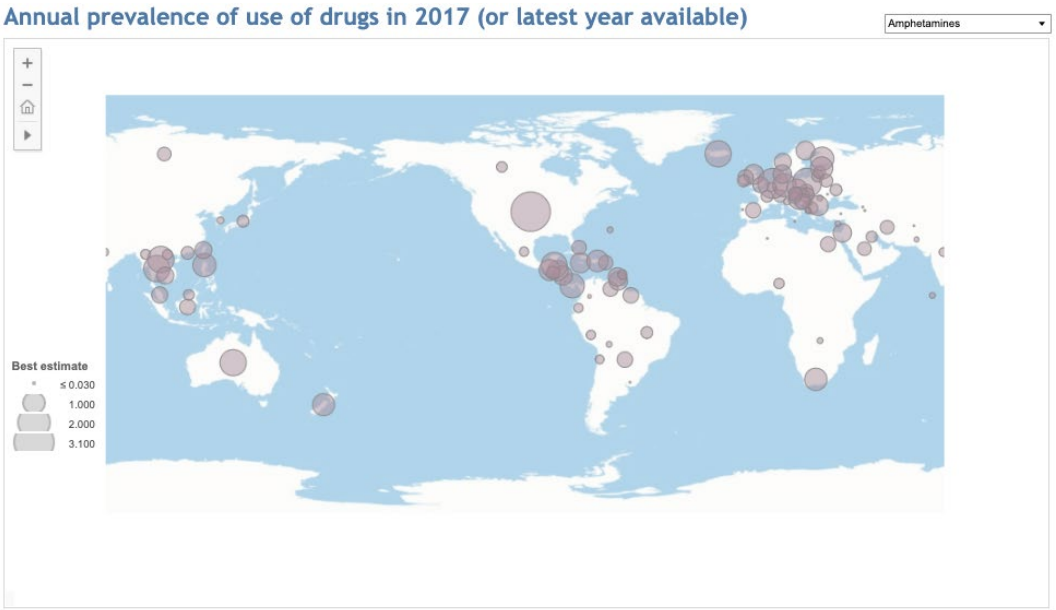

Figure: United Nations Office of Drugs and Crime, 2019

[1]Substance Abuse and Mental Health Services Administration (SAMHSA); [2]Han et al, JAMA Psychiatry, Dec 2021

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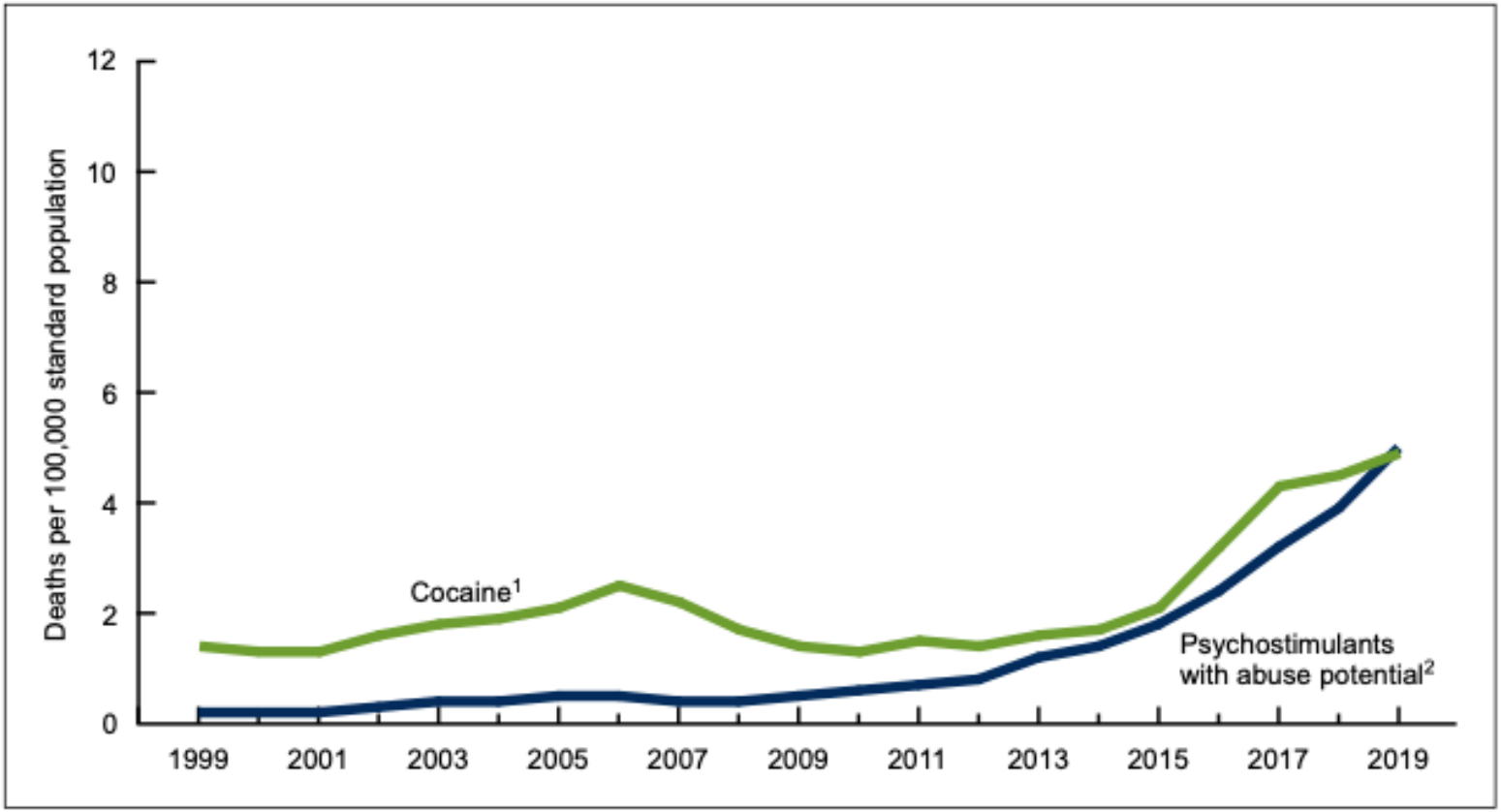
Methamphetamine overdose deaths increasing much more dramatically

- Overdose deaths increased >12x from 2008 to 2019[1]

Figure 4. Age-adjusted rates of drug overdose deaths involving stimulants, by type of stimulant: United States, 1999–2019



[1]Hedegaard et al, National Center for Health Statistics (NCHS) Data Brief 394, 2020

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Overdose deaths involving methamphetamine

Table 1. Overdose Deaths Involving Psychostimulants Other Than Cocaine and Methamphetamine Use, Use Disorder, Injection, and Frequent Use Among US Adults Aged 18 to 64 Years

Variable	Year					*P* for trend[a]
	2015	2016	2017	2018	2019	
Overdose deaths involving psychostimulants other than cocaine, No.[b]						
Overall	5526	7301	10 029	12 203	15 489	<.001
With opioids	2306	3345	5114	6269	8438	<.001
Without opioids	3220	3956	4915	5934	7051	<.001
With cocaine	370	690	1116	1433	1772	.007
Without cocaine	5156	6662	8913	10 770	13 717	<.001
Without opioids or cocaine	3102	3765	4665	5609	6698	<.001

Han et al, JAMA Psychiatry, Dec 2021

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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[1]
- Riskier drug? Changed processes for making methamphetamine

[1]Han et al, JAMA Psychiatry, 2021; Image: New York Times

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The Atlantic

SCIENCE

‘I DON’T KNOW THAT I WOULD EVEN CALL IT METH ANYMORE’

Different chemically than it was a decade ago, the drug is creating a wave of severe mental illness and worsening America’s homelessness problem.

The Atlantic, Oct. 18, 2021

Changing ingredients of methamphetamine

- Then: ephedrine method, subject to legal/regulatory actions by U.S. and Mexico to limit supply of ephedrine
- Now: P2P (phenyl-2-propanone) method, uses variety of legal and cheap chemicals used in wide variety of industries
- Consequences:
  - Production shifts increasingly to numerous, efficient labs in Mexico: availability explodes, prices fall
  - ? Increase in neuropsychiatric effects

The Atlantic, Oct. 18, 2021

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Ties to mental health decline, rising homelessness?

”…As the meth changed around 2009, so did Barrera’s life. His cravings for meth continued, but paranoia and delusions began to fill his days. “Those feelings of being chatty and wanting to talk go away,” he told me. “All of a sudden you’re stuck and you’re in your head and you’re there for hours.” He said strange things to people. He couldn’t hold a job. No one tolerated him for long… And, for the first time in more than a decade of meth use, Barrera was homeless.”

The Atlantic, Oct. 18, 2021

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Overdose deaths do not include…

…Most people who die from methamphetamine-related health and social problems, e.g.

- Stroke
- Heart attack
- Pulmonary hypertension
- Infections (HIV/AIDS, hepatitis C, hepatitis B, bacterial infections)
- Depression, violence, lack of housing, etc.

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Risk factors for methamphetamine use, risky use, MUD

- Lower 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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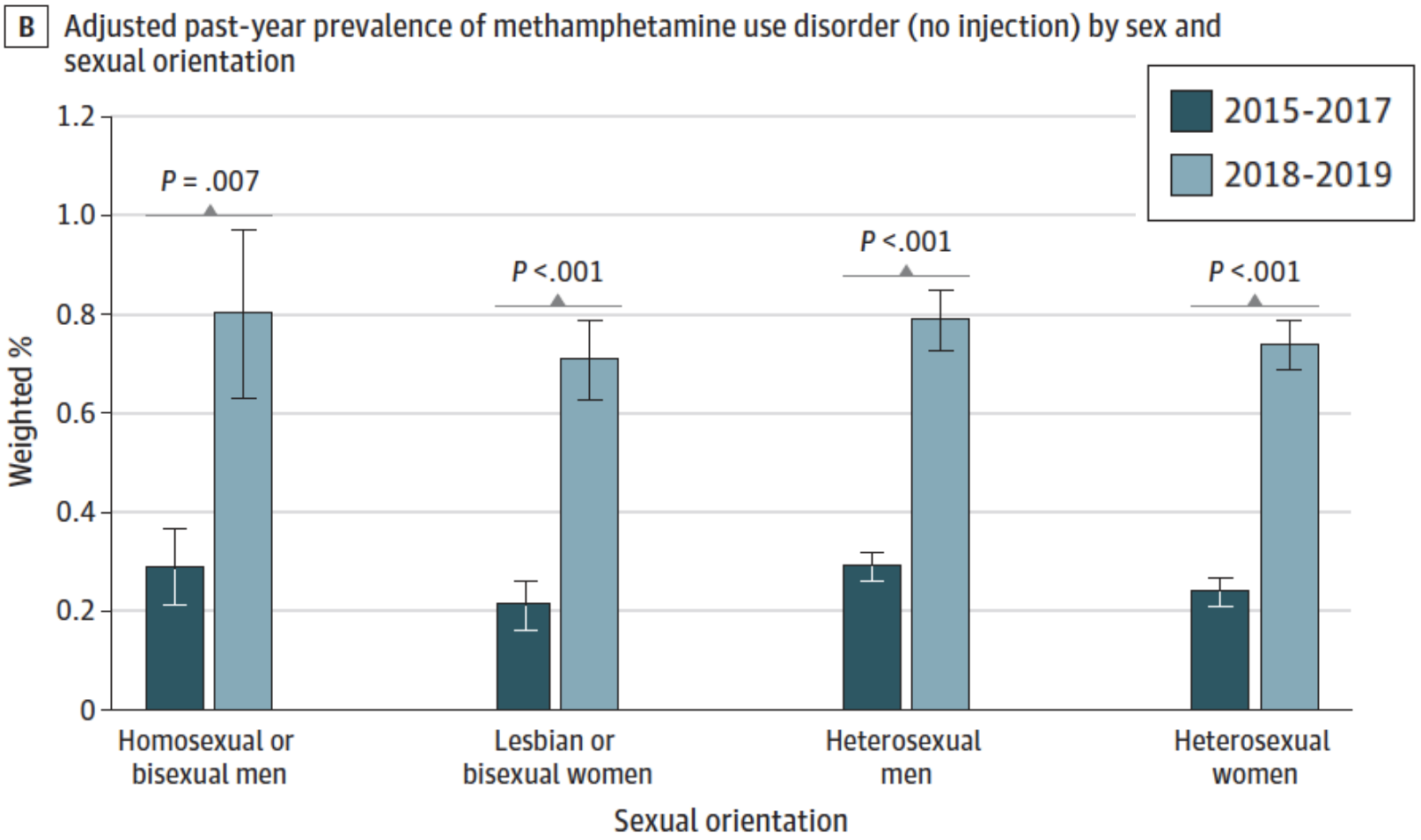
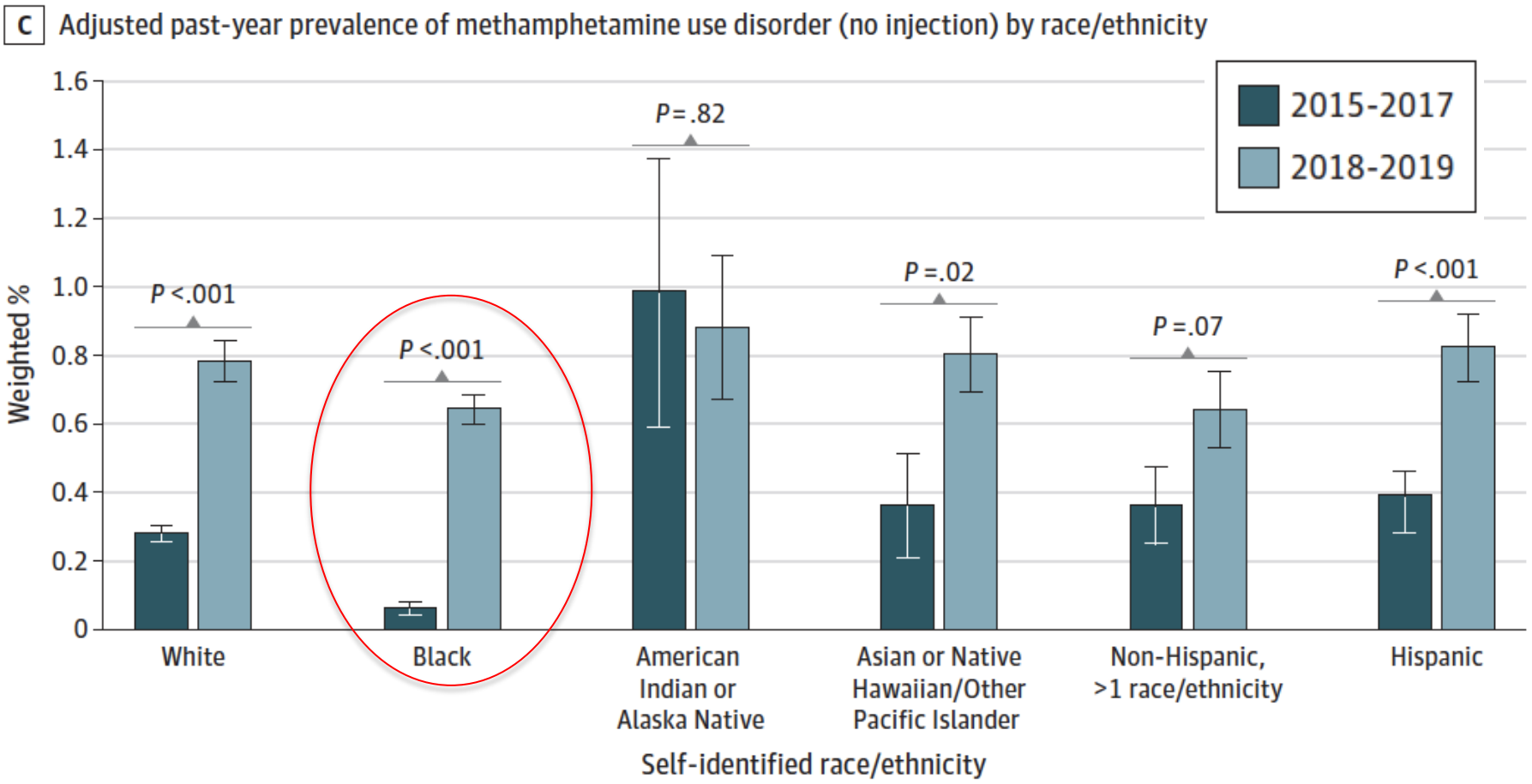
Diversifying populations with MUD



Han et al, JAMA Psychiatry Dec 2021

Diversifying populations with MUD



Han et al, JAMA Psychiatry Dec 2021

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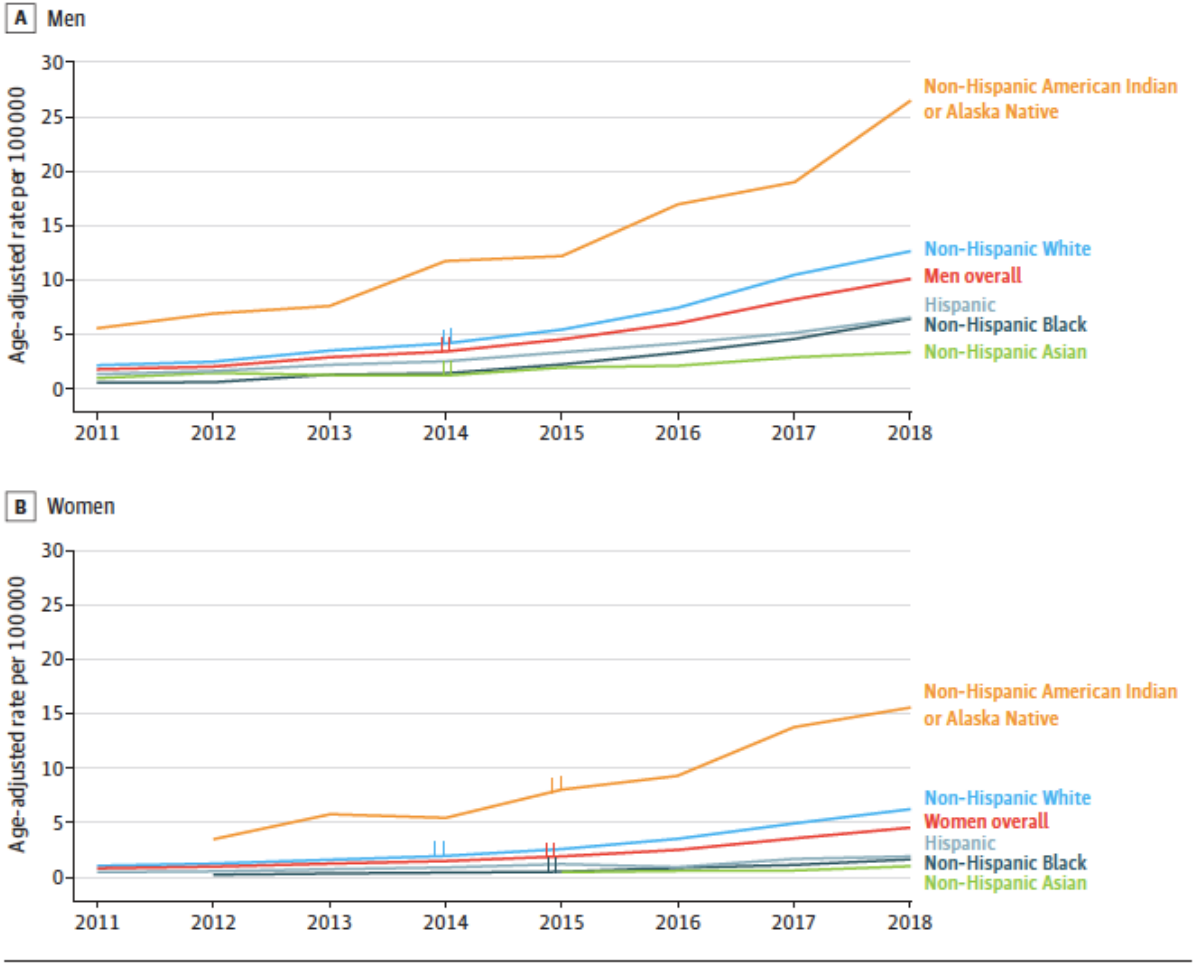
Disproportionate overdose death among American Indian / Alaska Native people

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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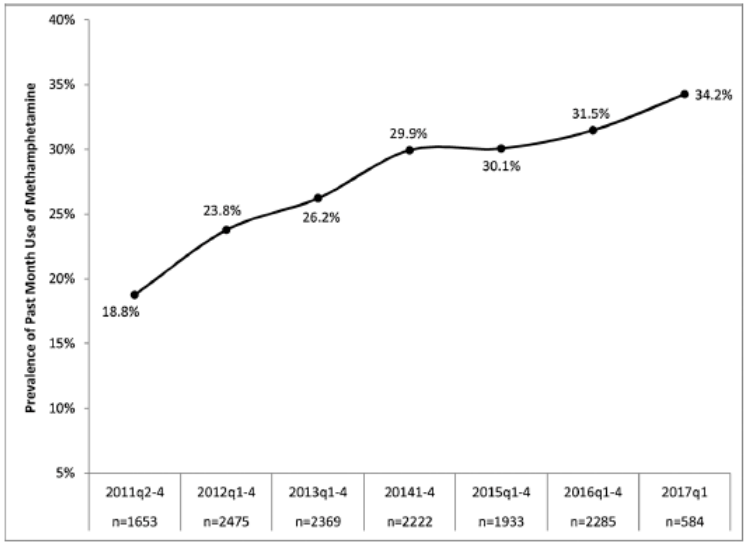
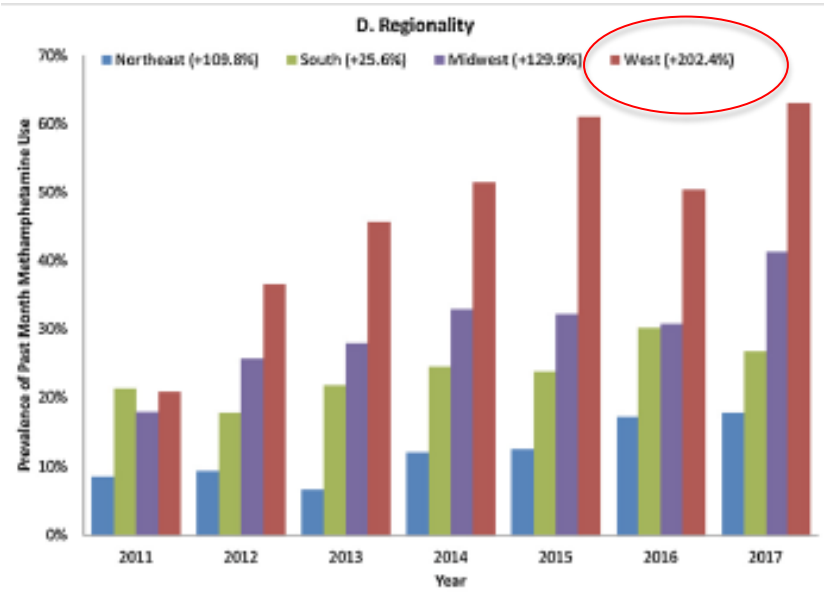
Methamphetamine use rising among users of opioids

- Provides synergistic high, serves as opioid substitute, balances out effects of opioids to function "normally"[1]
- Greater increases among 35-44 year-olds, women[1]





[1]Ellis, Drug Alcohol Dep 2018

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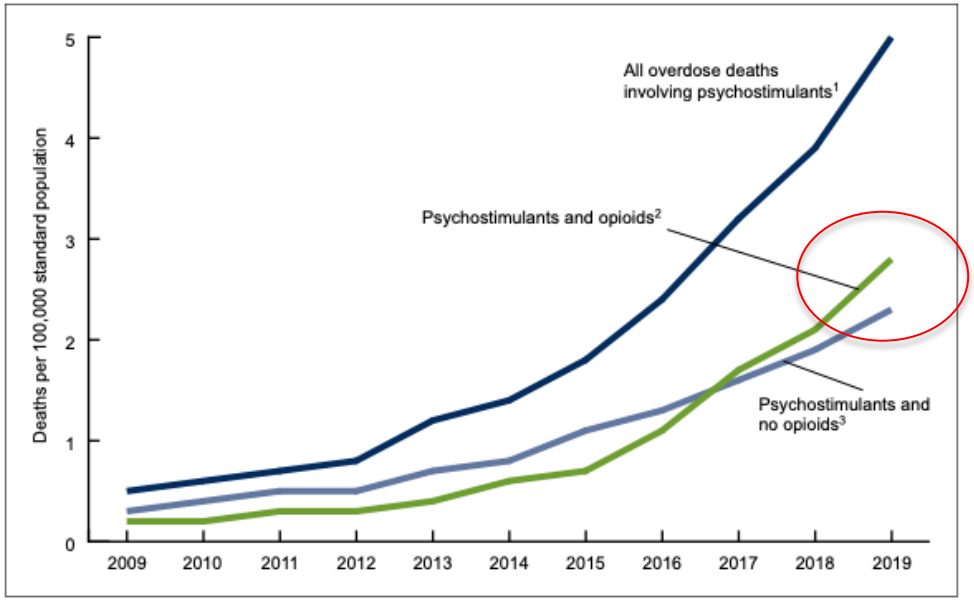
“4th wave” of opioid overdose epidemic

- Increasing use of methamphetamine among people who use opioids[1]
- Overdose deaths involving methamphetamine among people who use opioids increased nearly 3x, 2015-2019[2]

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



[1]Ellis et al, Drug and Alc Dep 2018; [2]Han et al, JAMA Psychiatry, 2021; Figure: NCHS Data Brief No 394, Dec 2020

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Treatment

↑ 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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Traditional SUD treatment endpoint—abstinence—can be problematic

- Stems from dichotomous view of recovery, whereas recovery varies by individual and over time
- Devalues alternative endpoints that contribute meaningfully to safety, recovery
- High, unrealistic bar for many individuals and for medication approval, disincentivizing pharmaceutical development

Volkow, Am J Psychiatry 2020

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Case for alternative treatment endpoints

1. **Symptoms:** patients want holistic, individualized care that addresses key symptoms (withdrawal, sleep problems, depression, pain)[1]
2. **Reduction in use**:
   - ↓exposure to harms of drug trade, contaminants, overdose risk, etc.[1]
   - clinical benefits, e.g. better health outcomes or psychosocial benefit[2]
   - can put people on path toward abstinence[3]

[1] Volkow et al, Am J Psychiatry 2020; [2] Guidance document, FDA Oct 2020; [3]Roos et al, Drug Alcohol Depend 2019

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Case for alternative treatment endpoints

1. **Symptoms:** patients want holistic, individualized care that addresses key symptoms (withdrawal, sleep problems, depression, pain)[1]
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   - can put people on path toward abstinence[3]

How do we measure this? What changes in use are clinically meaningful? How do trials of short duration apply to this chronic, dynamic disease process?

[1] Volkow et al, Am J Psychiatry 2020; [2] Guidance document, FDA Oct 2020; [3]Roos et al, Drug Alcohol Depend 2019

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Reminder: best evidence for behavioral treatments

Motivational Interviewing

Outcomes

- Abstinence
- Reduced use (quantity, frequency)
- 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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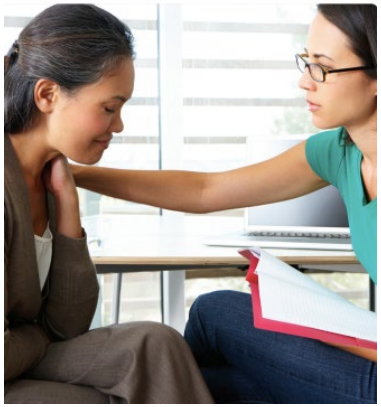
Limitations of behavioral treatments

- Dropout high[1]
- Retaining people who use stimulants in treatment is particularly difficult[1]
- Dropout from treatment predicts recurrence of use
- Access is limited
- More evidence for cocaine vs methamphetamine



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

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Neurobiology offers targets for rx development

Methamphetamine ↑ dopamine release, blocks re-uptake: extremely reinforcing

Chronic use

↓

Down regulation of dopamine transporters

↓ → *Tolerance*

Dysphoria, fatigue, cravings in absence of drug

Meds could

- target dopaminergic, serotonergic, GABAergic systems
- mimic drug's effects but less rapidly/intensely: reduce cravings, withdrawal

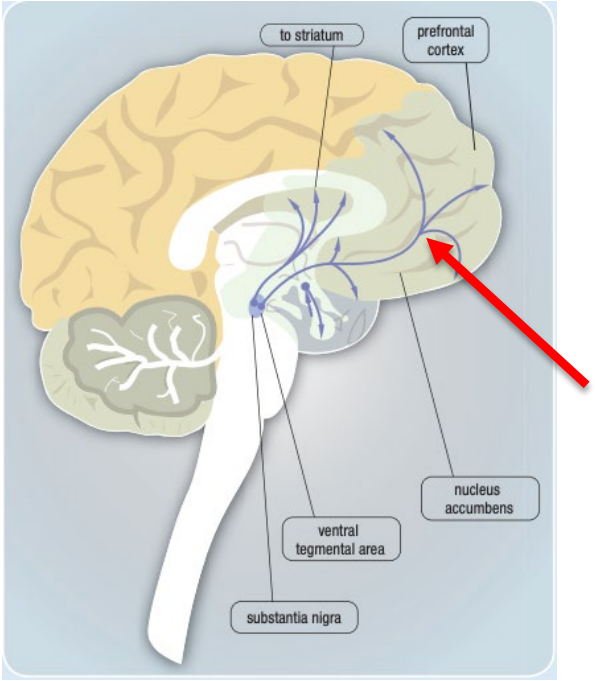

Figure: National Institute on Drug Abuse, Research Report Series, 2013

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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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Evidence of *some benefit* (↓use, craving, severity of dependence)

- Dexamphetamine
- Methylphenidate
- Modafinil
- Bupropion
- Mirtazapine
- Sertraline
- Fluoxetine
- Risperidone
- Aripiprazole
- Buprenorphine
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- Baclofen
- Ondansetron
- Varenicline
- Amlodipine
- Flumazenil + gabapentin
- Bupropion + naltrexone

Lee et al, Drug and Alc Dep 2018

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Evidence of *harm*

- 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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Evidence of *potential benefit or little-no benefit*

- Dexamphetamine
- Methylphenidate
- Modafinil
- Bupropion
- Mirtazapine
- Sertraline
- Fluoxetine
- Risperidone
- Aripiprazole
- Buprenorphine
- Naltrexone
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Lee et al, Drug and Alc Dep 2018

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Recent trials offer some promise

JAMA Psychiatry | Original Investigation

Effects of Mirtazapine for Methamphetamine Use Disorder Among Cisgender Men and Transgender Women Who Have Sex With Men

A Placebo-Controlled Randomized Clinical Trial

Phillip O. Coffin, MD, MIA; Glenn-Milo Santos, PhD, MPH; Jaclyn Hern, MPH; Eric Vittinghoff, PhD; John E. Walker, MSN; Tim Matheson, PhD, MS; Deirdre Santos, RN, MSN; Grant Colfax, MD; Steven L. Batki, MD

Clinical Trials Network (CTN)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Bupropion and Naltrexone in Methamphetamine Use Disorder

M.H. Trivedi, R. Walker, W. Ling, A. dela Cruz, G. Sharma, T. Carmody, U.E. Ghitza, A. Wahle, M. Kim, K. Shores-Wilson, S. Sparenborg, P. Coffin, J. Schmitz, K. Wiest, G. Bart, S.C. Sonne, S. Wakhlu, A.J. Rush, E.V. Nunes, and S. Shoptaw

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Mirtazapine (Coffin, JAMA Psych 2019)

- Modeled after smaller 12-week RCT which found that mirtazapine ↓ methamphetamine-positive urines and high-risk sexual behavior in MSM[1]
- Cisgender men and transgender women who had sex w/ men while using meth, methamphetamine dependence, interest in reducing/ceasing
- Those with current major depression excluded
- Mirtazapine 30 mg vs placebo for 24 weeks, background substance use counseling (CBT, MI)
- Primary outcome: **meth-positive urines**
- Secondary: sexual risk behaviors and AEs

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

[1]Colfax et al, Archives Gen Psych 2011

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Results at 24 weeks

- 120 participants
- ~96% cisgender men, mean age 44, 51% white, 26% African American, 12.5% Latinx
- Adherence low: 28% mirtazapine and 39% placebo (p=0.59)
- ~25% fewer meth-positive urines in group taking mirtazapine
- ↓ sexual risk behavior and depression, sleepiness scores
- Non-significant ↑ in abstinence in mirtazapine group (18% vs 8%)
- No serious AE from mirtazapine

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

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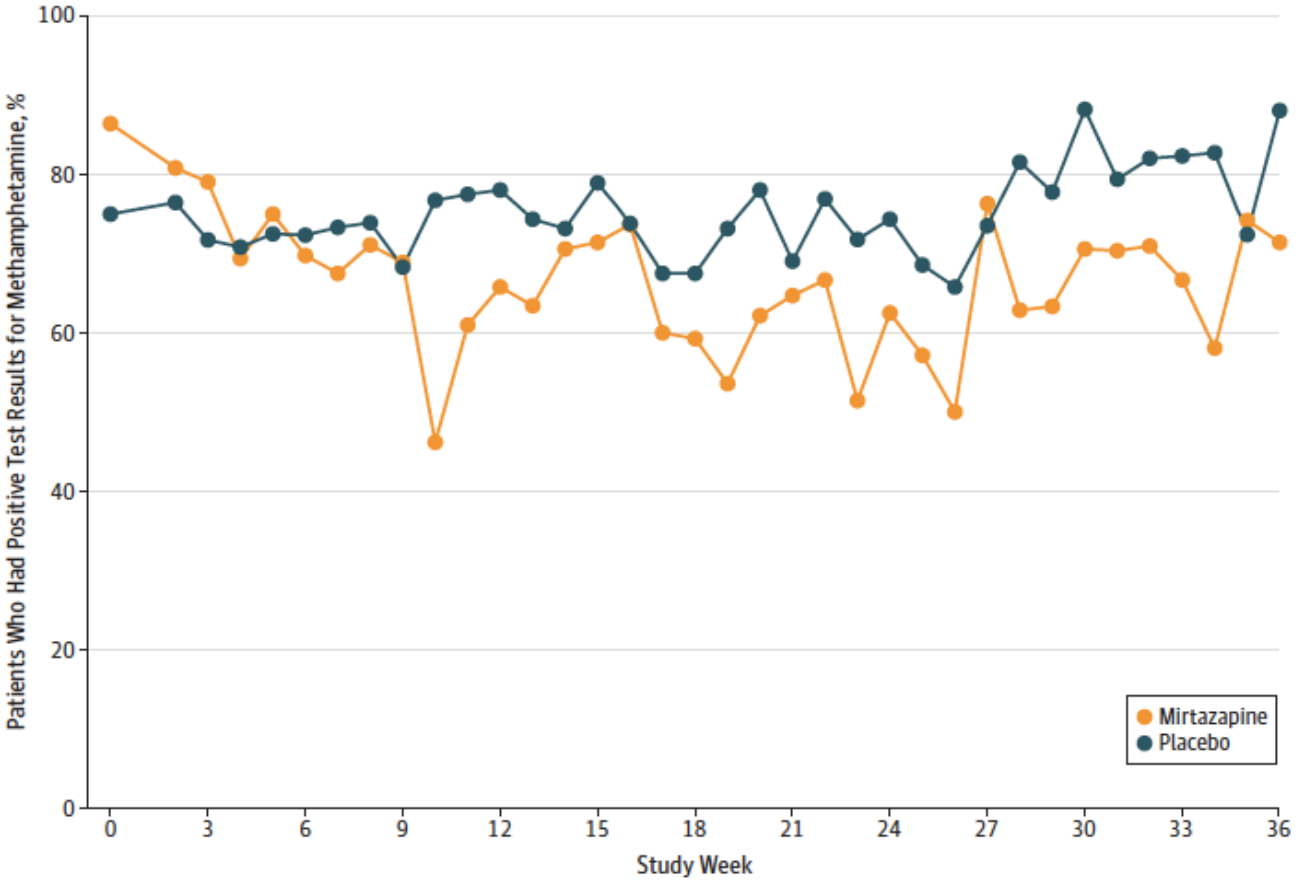
Proportion of participants with positive urine results, mirtazapine vs placebo

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



Coffin et al, JAMA Psychiatry 2019

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Treatment effect at weeks 12, 24, 36

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

Author's conclusions: "Adding mirtazapine to substance use counseling reduced meth use among men and transwomen who have sex w/ men and had lasting effects in spite of low adherence"

Coffin et al, JAMA Psychiatry 2019

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Mirtazapine: Worth offering for MUD?

Limitations

- Generalizability to other populations
- Those with major depression excluded
- Methodological issues
- Modest reduction in use

Strengths

- Some effort to mirror real-world practice (e.g. minimal adherence support)
- Main finding replicated earlier trial
- Safe medication well known to providers
- Benefits to sleep and mood

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Bupropion + naltrexone (Trivedi, NEJM 2021)

- ADAPT-2 Trial
- Based on small open-label pilot[1]
- Randomized, double-blind trial evaluating efficacy and safety of injectable ER naltrexone 380 mg q3 weeks + oral ER bupropion 450 mg daily
- Sponsored by NIDA

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

+

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

[1] Mooney et al, J Addiction Med 2016; ADAPT: Accelerated Development of Additive Pharmacotherapy Treatment for Methamphetamine Disorder; ER: extended-release; NIDA: National Institute for Drug Abuse

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Trial design

- Sequential parallel design
- 2 stages, 12 weeks total
- Twice weekly visits and urine screens
- Weekly substance use counseling by trial clinicians
- Adherence support via smartphone app and by trial clinicians
- Intention-to-treat analysis combining results from both stages

Trivedi et al, NEJM 2021

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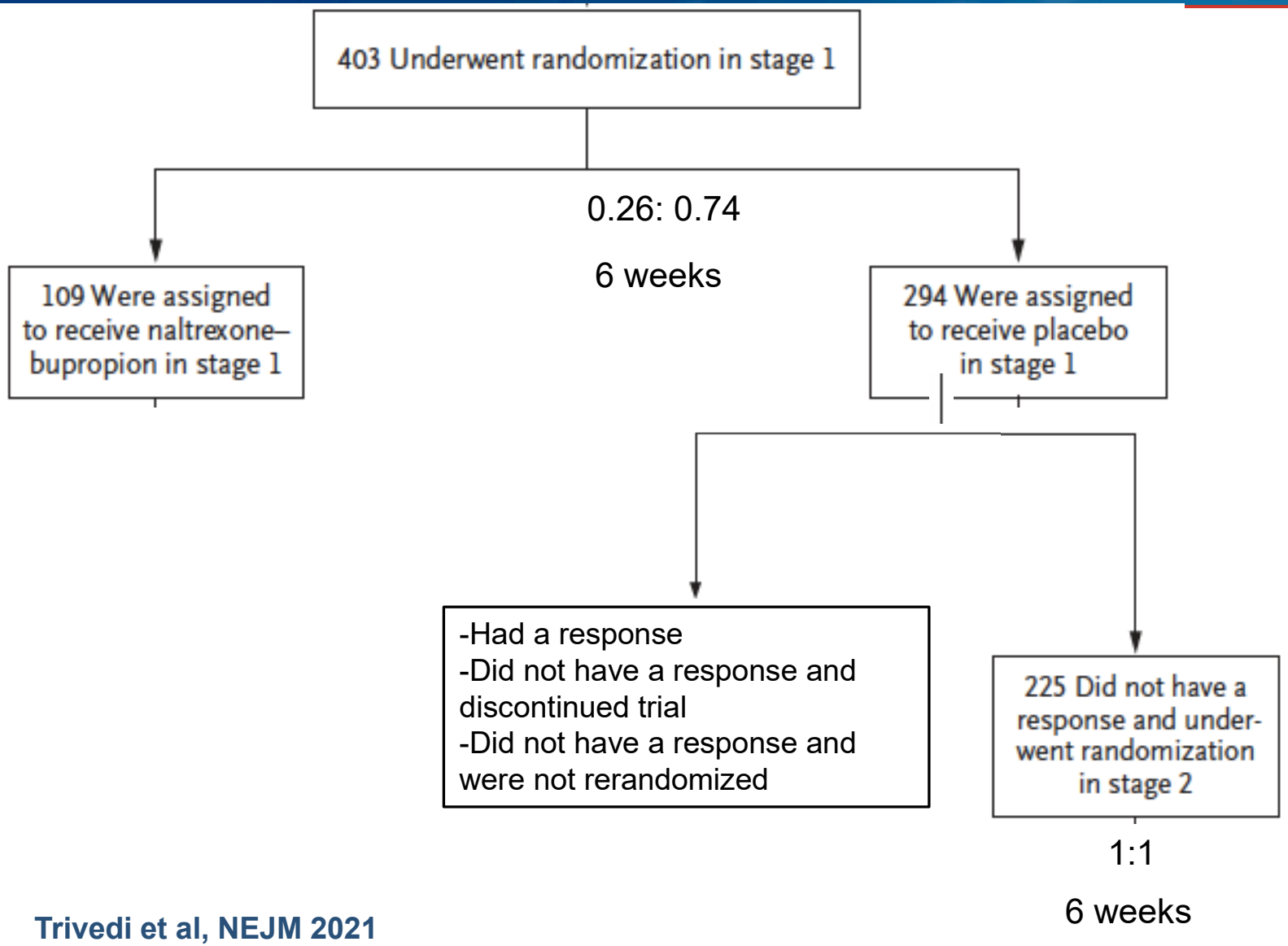
Two-stage design to enrich sample



Trivedi et al, NEJM 2021

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Participants and outcomes

- Adults with moderate-severe MUD and active use who wanted to quit or reduce use; had to be opioid-free
  - Exclusion criteria: other tx for SUD, anticipated need for opioids, safety concerns
  - Other medical and psychiatric conditions evaluated on case-by-case basis
- Primary outcome= **response to treatment**
  - at least 3 of 4 urines negative for methamphetamine in last 2 weeks of each stage, between-group difference of weighted average
- Secondary outcomes included severity of cravings, depressive symptoms

Trivedi et al, NEJM 2021

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Results

- N=401, mean age 41, 69% male, 71% white, averaged 27/30 days use
- Adherence high: >75% in all groups
- Tx response: 13.5% (bup +XR-NTX) vs 2.5% (placebo); tx effect 11.1%
- Sensitivity analysis of those with 4/4 samples last 2 wks: tx effect 18.7%
- Adverse events mild: nausea, constipation, dry mouth, etc.

Trivedi et al, NEJM 2021

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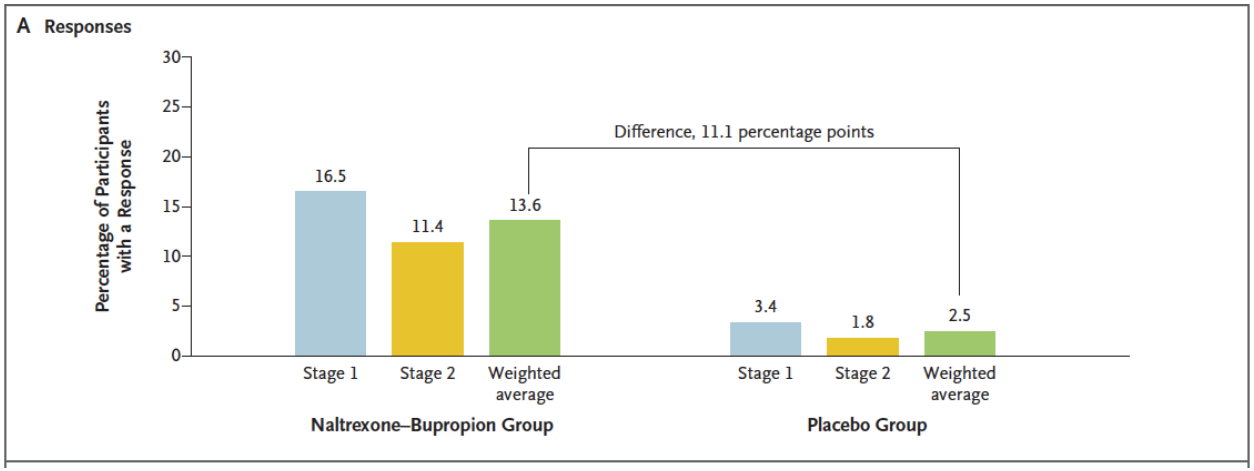
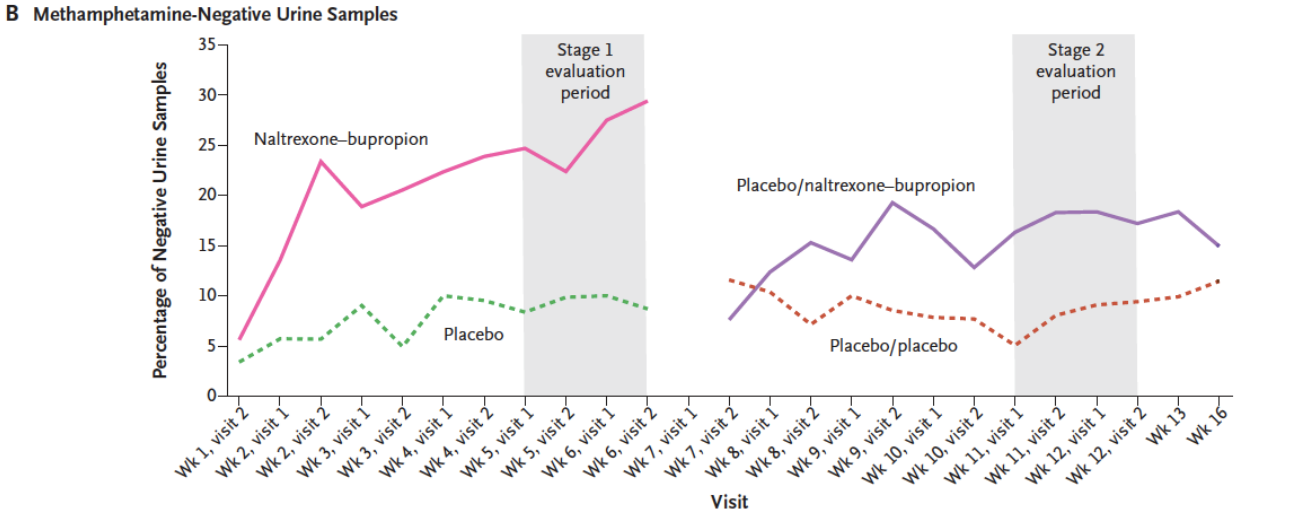
Higher treatment response in bup + NTX group





Trivedi et al, NEJM 2021

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Ready to join treatment options for MUD?

Limitations

- Short duration trial
- Complicated design
- Low attrition and high adherence limit generalizability
- Not an option for the many people who also use opioids

Strengths

- Well-done study
- NNT=9 for one patient to have a response
- Safe, well-tolerated medications familiar to internists

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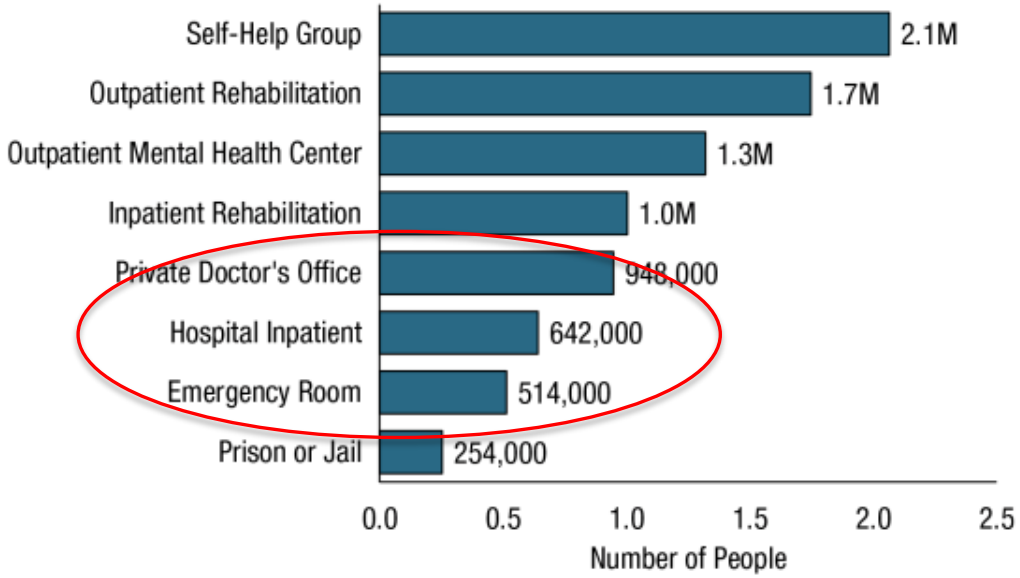
Many missed opportunities

FFR1.66

Locations Where Substance Use Treatment in the Past Year Was Received among People Aged 12 or Older: 2019



Note: Locations where people received substance use treatment are not mutually exclusive because respondents could report that they received treatment in more than one location in the past year.

SAMHSA
Substance Abuse and Mental Health Services Administration

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Closing thoughts

- ↑ rates MUD and overdose : ↑ urgency offering harm reduction and tx
- Important tx endpoints include abstinence but also reduced use, symptoms
- Behavioral approaches work and we should be doing these more
- Consider offering medications; think about comorbidities and symptoms
- Treat co-occurring SUD with FDA-approved medications
- Engaging patient in discussion of tx options is a success!

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Panel Discussion

- In what ways have you noticed changing impacts of methamphetamine, and how does this affect your view of treatment?
- How have these recent trials changed your practice, or not?

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Acknowledgment

This Mountain West AIDS Education and Training (MWAETC) program is supported by the Health Resources and Services Administration (HRSA) of the U.S. Department of Health and Human Services (HHS) as part of an award totaling $2,911,844 and as part of another award totaling $400,000 with 0% financed with non-governmental sources.

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