Understanding the 4th Wave of Opioid Overdoses: Stimulants and Opioids

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In Collaboration with Los Angeles County Department of Public Health

Almansor Court, Alhambra, CA

Disclosures

The following CME planners and faculty do not have relevant financial relationships with ineligible companies in the past 24 months:

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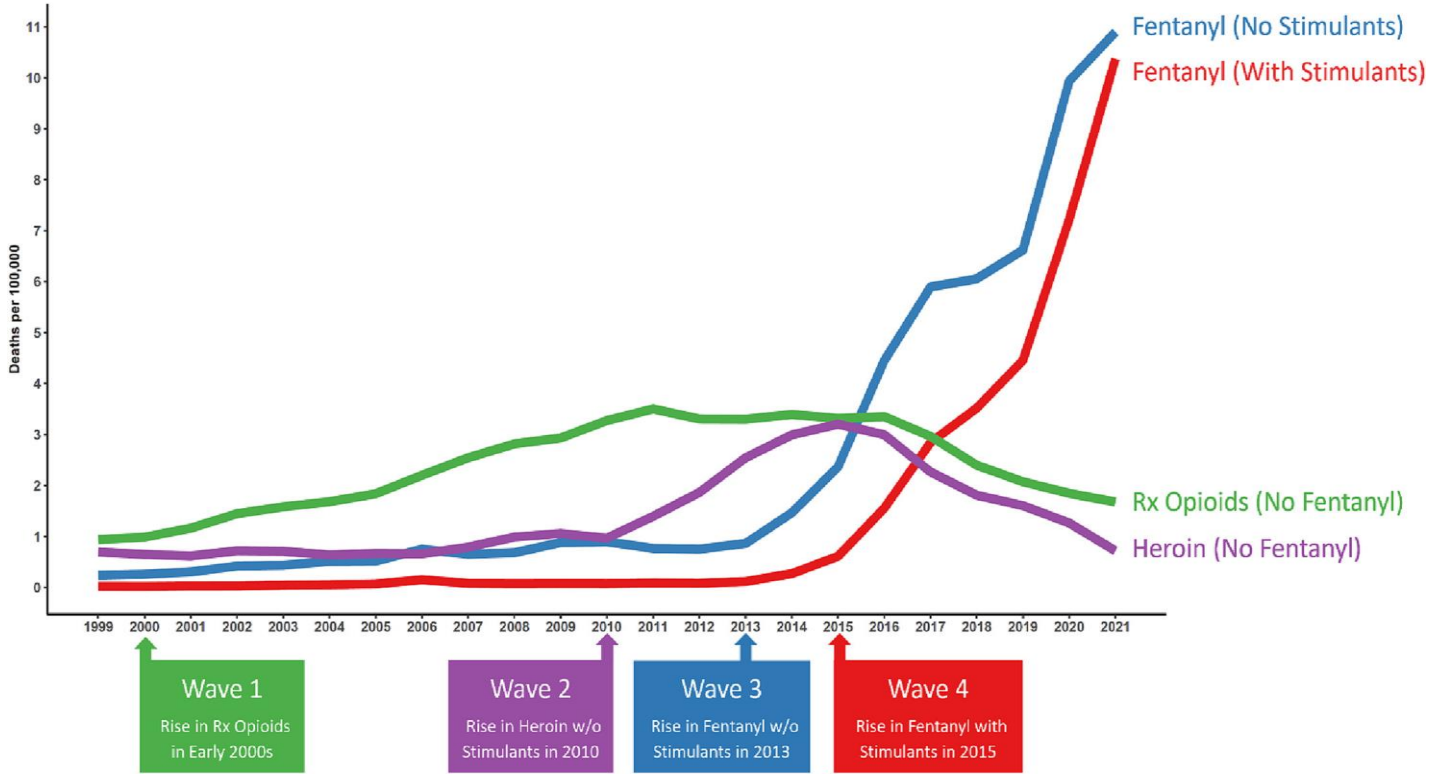
An ineligible company is any entity whose primary business is producing, marketing, selling, re-selling, or distributing healthcare products used by or on patients.

Commercial support was not received for this CME/CE activity.

Learning Objectives

- Describe at least two (2) risks of combining opioids and stimulants
- Identify four (4) risk factors with disparities in care to stimulant and opioid use
- Summarize the pharmacologic treatments of concurrent opioid and stimulant use disorder(s).
- Specify four (4) best practices for reducing harms of concomitant opioid and stimulant use.

History of Overdose Deaths



Addiction, Volume: 118, Issue: 12, Pages: 2477-2485, First published: 13 September 2023, DOI: (10.1111/add.16318)

1st Wave of Opioid Overdoses

JAMA. 2000 Jul 26;284(4):428-9. doi: 10.1001/jama.284.4.423b.

JCAHO pain management standards are unveiled. Joint Commission on Accreditation of Healthcare Organizations

D M Phillips

PMID: 10904487 DOI: 10.1001/jama.284.4.423b

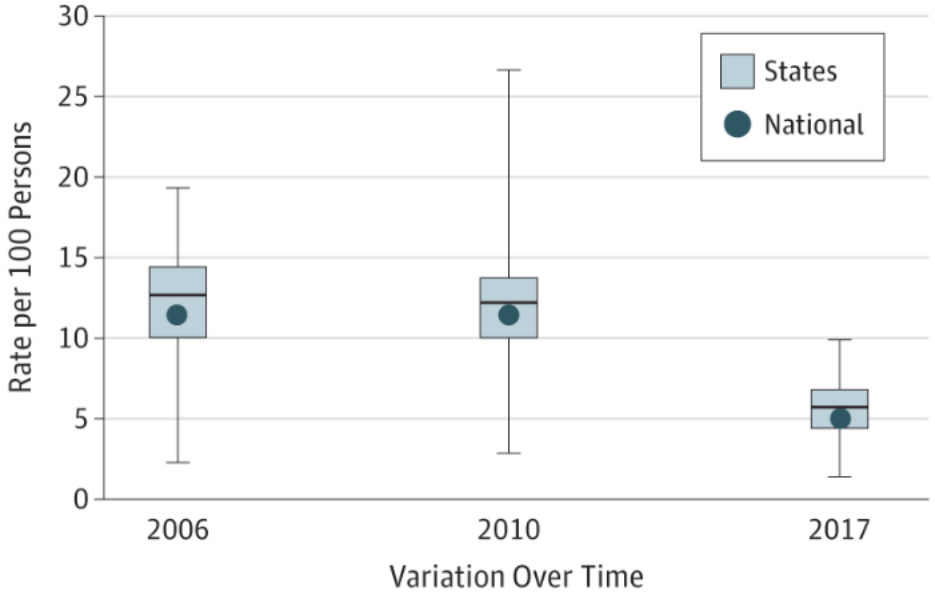
"…Awareness of pain as the fifth vital sign"

"[Physicians] may have 'opiophobia' – fear of addiction"

"The truth is that crossover in the drug culture world and those in need of medicine is very small"

2nd Wave of Opioid Overdoses

Changes in Rx Opioids >90 MME , 2006-2017



CDC Guideline for Prescribing Opioids for Chronic Pain — United States, 2016

Recommendations and Reports / March 18, 2016 / 65(1);1–49

On March 15, 2016, this report was posted online as an MMWR *Early Release.*

*JAMA Netw Open.*2019;2(3):e190665.

3rd Wave of Opioid Overdoses

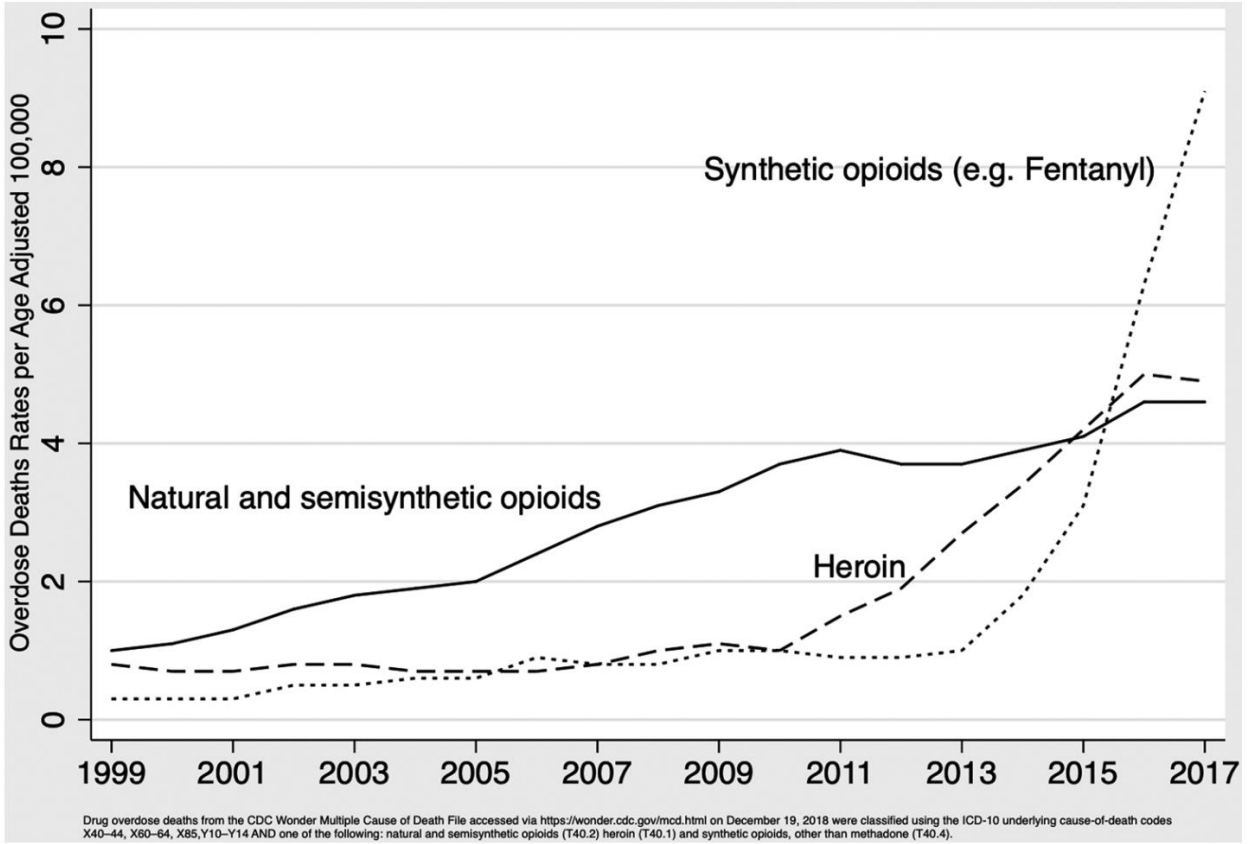


Fig. 1. Opioid Overdose Deaths by Type of Opioid.

International Journal of Drug Policy. 2019;71:183-188.

4th Wave of Opioid Overdoses

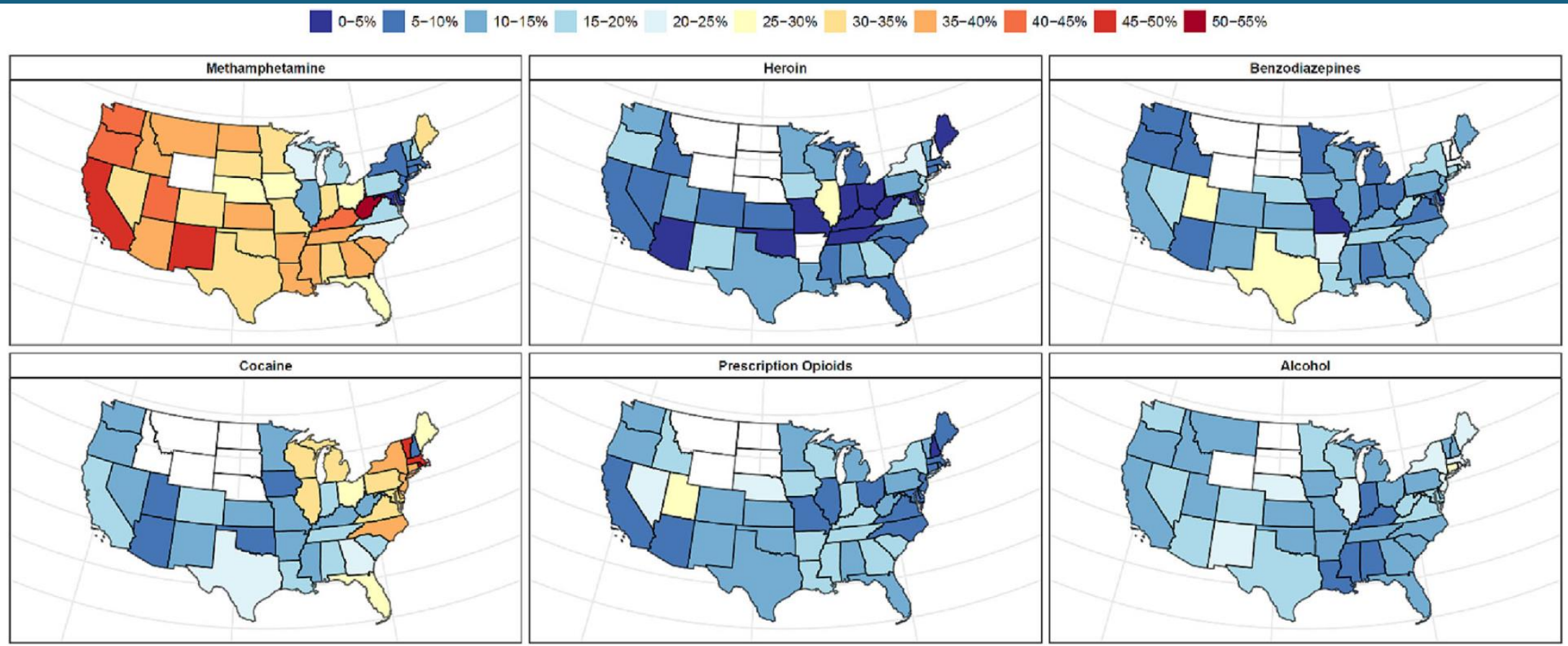


FIGURE 4 Percent of fentanyl overdose deaths containing other drug classes by state, 2021. The percent of fentanyl-involved overdose deaths co-involving other drugs in 2021 is shown for six drug classes by state. Data were obtained from Centers for Disease Control and Prevention's Wide-Ranging Online Database for Epidemiologic Research (CDC WONDER). Instances were fewer than 10 deaths involved a given substance and fentanyls are suppressed by CDC WONDER, and therefore, not shown.

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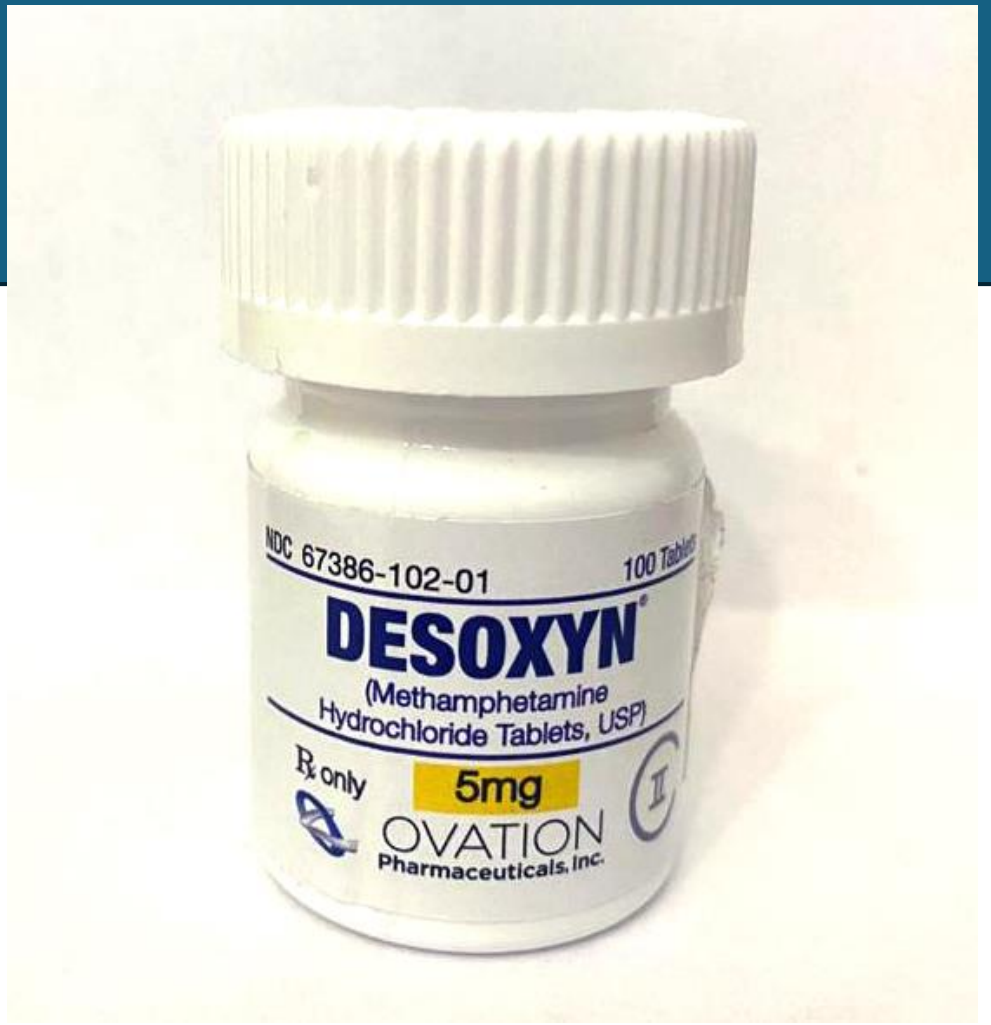
Methamphetamine

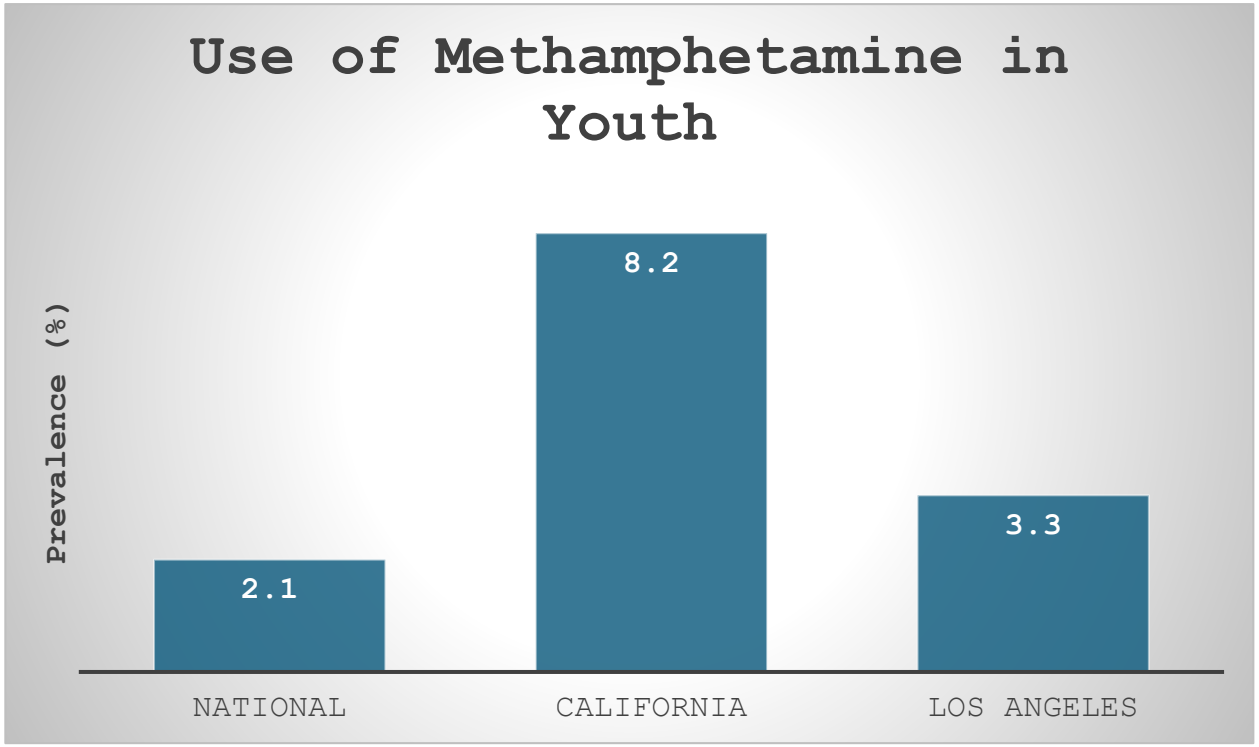
- Lifetime prevalence of methamphetamine use = 5.9%
- FDA Schedule II approved for ADHD and obesity
- More recently manufactured in clandestine labs in powder and crystal form



SAMHSA2022 National Survey on Drug Use and Health

Local Trends

- More than 20,000 ED visits and hospitalizations each year in LA County costing over $1.4 billion



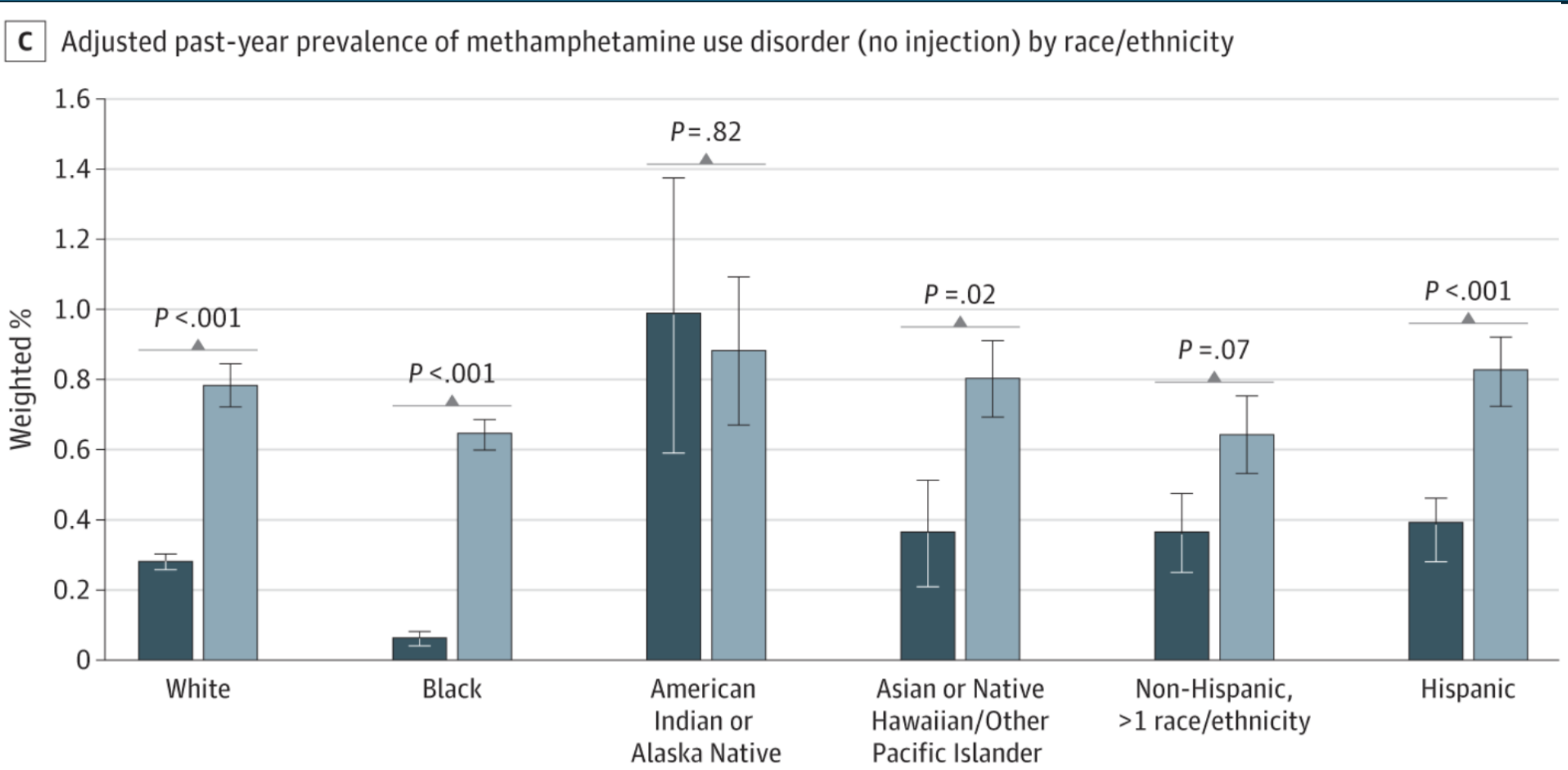
LA County Public Health SAPC Data Brief 2024.

Factors Associated with Methamphetamine Use

- Education level of high school or less
- Annual household income of <$20,000
- Medicaid only or uninsured
- Criminal justice involvement
- History of suicidal ideation
- Other substance use disorder

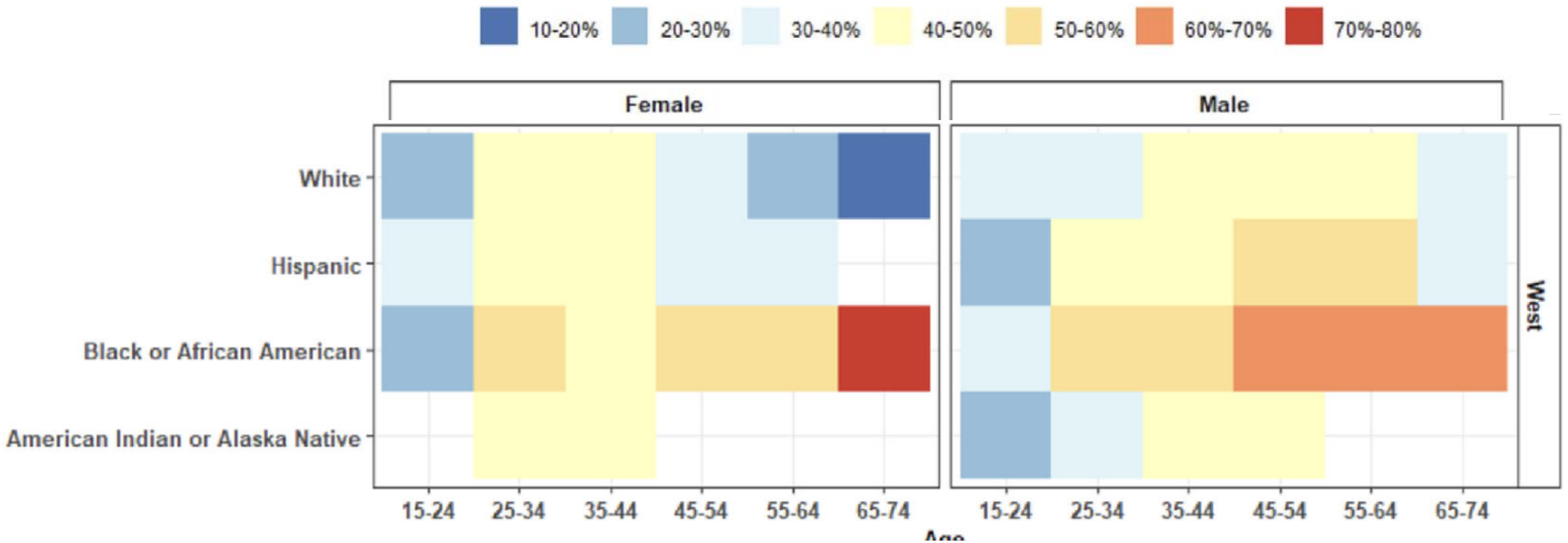
JAMA Psychiatry. 2021;78(12):1329.

Disparities in Methamphetamine Use Prevalence



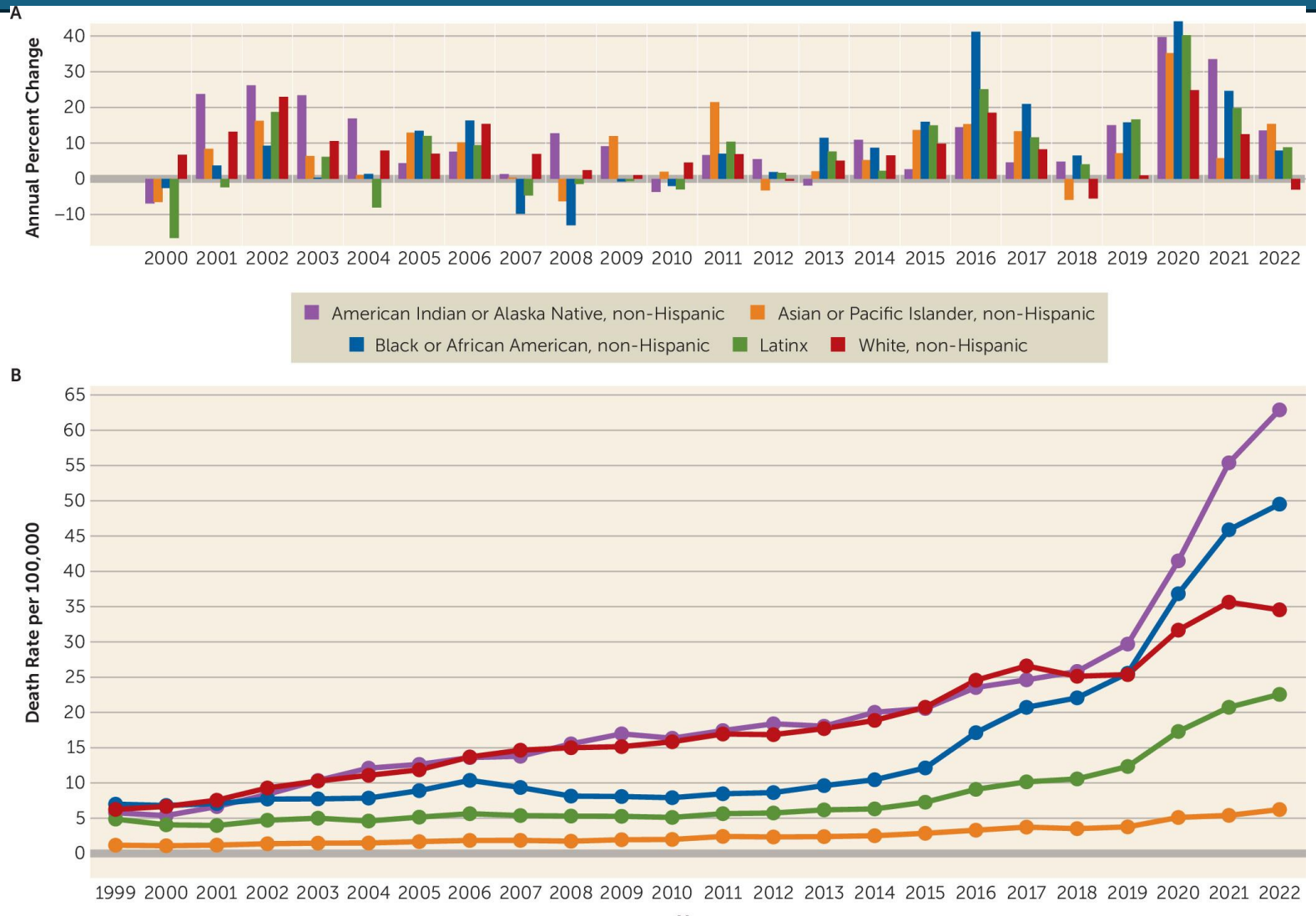
JAMA Psychiatry. 2021;78(12):1329.

Disparities in Methamphetamine and Fentanyl Deaths



Addiction, Volume: 118, Issue: 12, Pages: 2477-2485, First published: 13 September 2023, DOI: (10.1111/add.16318)

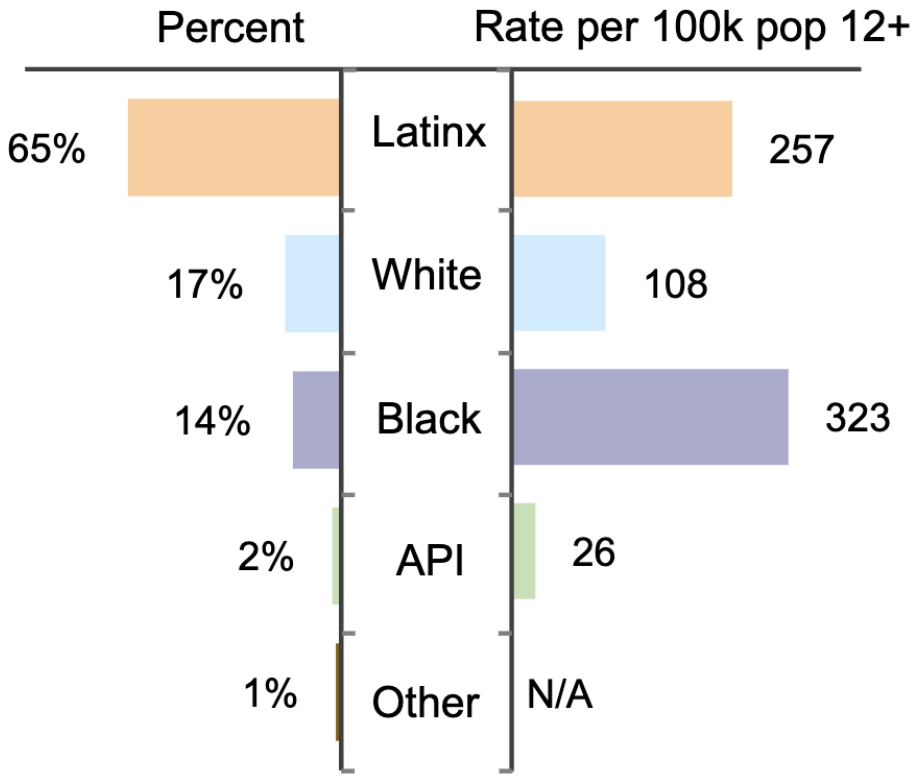
Widening Racial Disparities



American Journal of Psychiatry. 2024;181(5):381-390.

Los Angeles Data

Race/ethnicity among patients with primary meth problem, LAC, FY2223[16]



LA County Public Health SAPC Data Brief 2024.

Opioid and Stimulant Use

- Intentional stimulant and opioid use
  - Synergistic Euphoria
  - Treating adverse effects of one drug with another
  - Misconception that stimulants are protective of opioid overdose
- Unintentional opioid use through stimulants
  - Laced supply of fentanyl
  - Pressed pills

Drug Alcohol Rev. 2020;39(3):209-215.

Adverse Public Health Outcomes

- Increased risk for overdose
- Increased risky sexual behaviors
- Increase IV drug use
- Higher medical and psychiatric comorbidities
- Worsened treatment outcomes
- More likely to have a history of sexual abuse

Addiction. 2020;115(2):347-353.

Treatment

- Individuals admitted for treatment of stimulants and opioids were 35% less likely to have medications prescribed for OUD

Addiction. 2020;115(2):347-353.

OUD Treatment

- First line treatment: mu opioid receptor agonism
  - Full agonist: methadone
  - Partial agonist: buprenorphine
- Psychosocial support
  - Cognitive behavioral therapy
  - Contingency management

JAMA Psychiatry. 2021;78(10):1092.

What About With Stimulants?

- Individuals entering drug treatment for opioid use disorder report frequent use of stimulants
- On interview, individuals reported:
  - Methamphetamine is used as an opioid "substitute"
  - Balances out the opioid
- Authors conclude that supply-side reductions in prescription opioids led to seeking euphorigenic substances elsewhere
- Opioid availability and stimulant cost also contributing factors

Drug and Alcohol Dependence. 2018;193:14-2

Psychopharmacology of Stimulants

- Mechanism: increased neurotransmission of dopamine and norepinephrine
- Addiction results from stimulation of dopamine in the mesolimbic reward pathway
- Initial reward leads to compulsive use

Cocaine

- Inhibits dopamine reuptake in synapse
- Half-life: ~1 hour
- With alcohol consumption→ cocaethylene
  - Longer half-life (~2.5 hours)
  - More euphoric
  - Greater risk of cardiac toxicity

Pergolizzi Cureus, *14*(2). 2022

Amphetamine

- Inhibits reuptake of dopamine and norepinephrine in synapse
- Inhibits VMAT to displace dopamine and further increase dopamine release
- Half-life: ~10 hours

Methamphetamine

- Inhibits reuptake of dopamine and norepinephrine in synapse
- Inhibits VMAT to displace dopamine and further increase dopamine release
- Half-life: ~12 hours
- Usual dosage of 100-200 mg

Drug and Alcohol Dependence. 2022;232:109320.

Risks of Long Term Use of Stimulants

- Psychosis
- Infections (HIV, Hep C)
- Cardiovascular (heart failure, stroke, MI)
- Dental problems
- Adverse birth outcomes

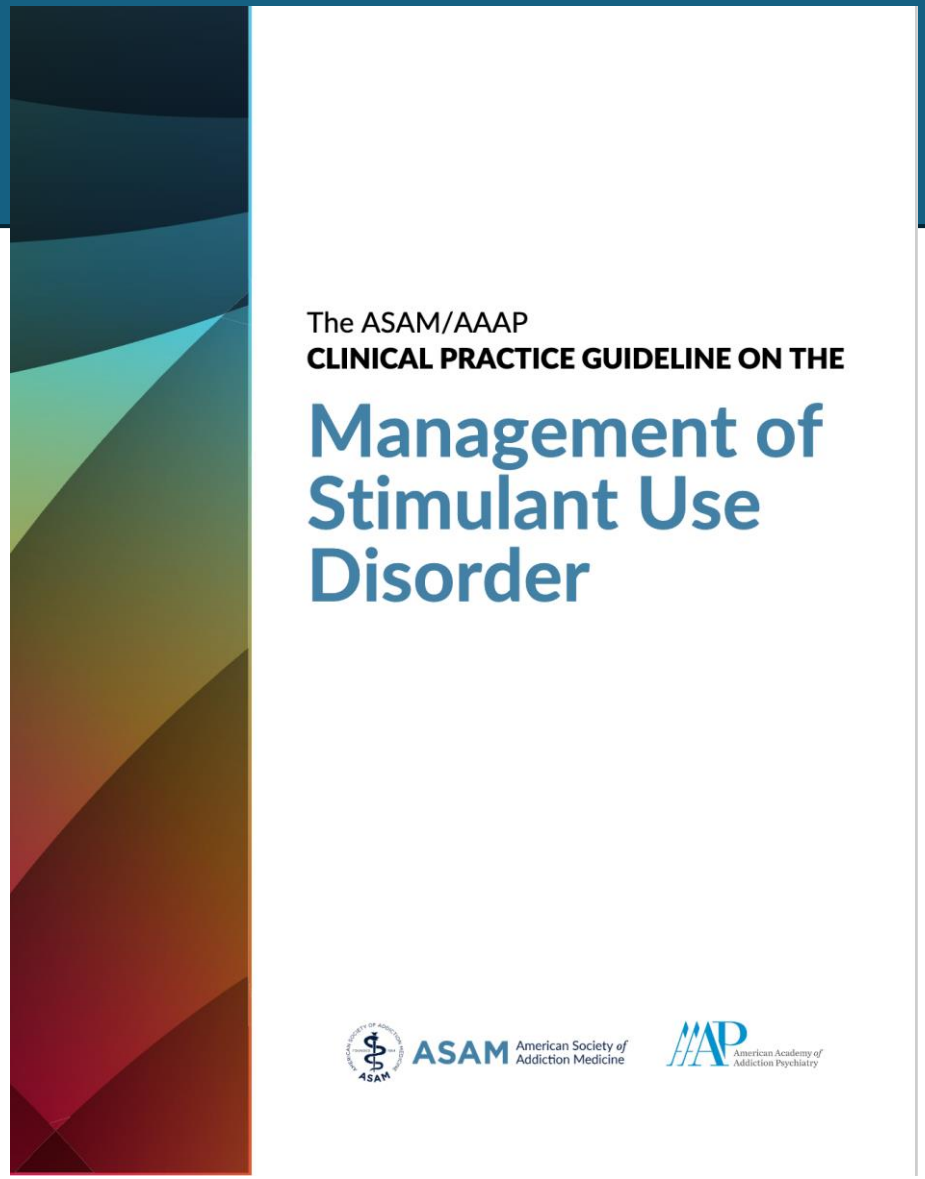
J Addict Med. 2024;18(1S):1-56

Long-term Complications: Psychosis

- High dose stimulant intoxication can present similarly to psychotic disorders
  - Hallucinations
  - Delusions
- Some individuals will experience symptom resolution when they clear the stimulant
- Methamphetamine known to be neurotoxic
- Reviews of clinical trials indicate that antipsychotics appear to be effective for acute psychosis
- Evidence unclear to suggest chronic use is effective as prophylaxis

J Addict Med. 2024;18(1S):1-56.
Schizophrenia Research. 2024;267:182-19
Front Psychiatry. 2019;10:740.

There are no FDA approved treatments



Treating StUD

Pharmacotherapy

Talk-based therapy

J Addict Med.
2024;18(1S):1-56.

Tempering Expectations

- Number needed to treat of *best* recommendation = 9
- Adherence to interventions in trials is limited (30-75%)

J Addict Med. 2024;18(1S):1-56.

Harm Reduction Principles

1. Accepts drug use and attempts to minimize harmful effects
2. Understands drug use is complex
3. Individual and community quality of life = success
4. People who use drugs (PWUD) are primary agents
5. Non-judgmental, non-coercive resources in communities
6. PWUD have a voice for services
7. Recognizes social inequities
8. Does not attempt to minimize harm associated with illicit drug use

Harm Reduction

- Overdose prevention
- Fentanyl test strips
- Safer sex practices
- Injection drug use
- PrEP
- Safe smoking practices
  - Use mouthpiece
  - Do not use pipe if cracked/broken
  - Inhale slowly, exhale immediately

Pharmacologic Treatment Options

- Naltrexone and bupropion
- Mirtazapine
- Bupropion
- Topiramate
- Agonist type therapies
  - Methylphenidate
  - Amphetamine

J Addict Med. 2024;18(1S):1-56.

Mirtazapine

- Atypical antidepressant
  - Antagonist of $Alpha_2$ adrenergic receptors
  - Antagonist of 5-HT2a
- Modest improvement in methamphetamine cravings
- Modest reductions in methamphetamine use
- Reduction in sexual risk behaviors
- Target doses used 30 mg/day

JAMA Psychiatry. 2020;77(3):246.
Drug and Alcohol Dependence. 2022;232:109295.

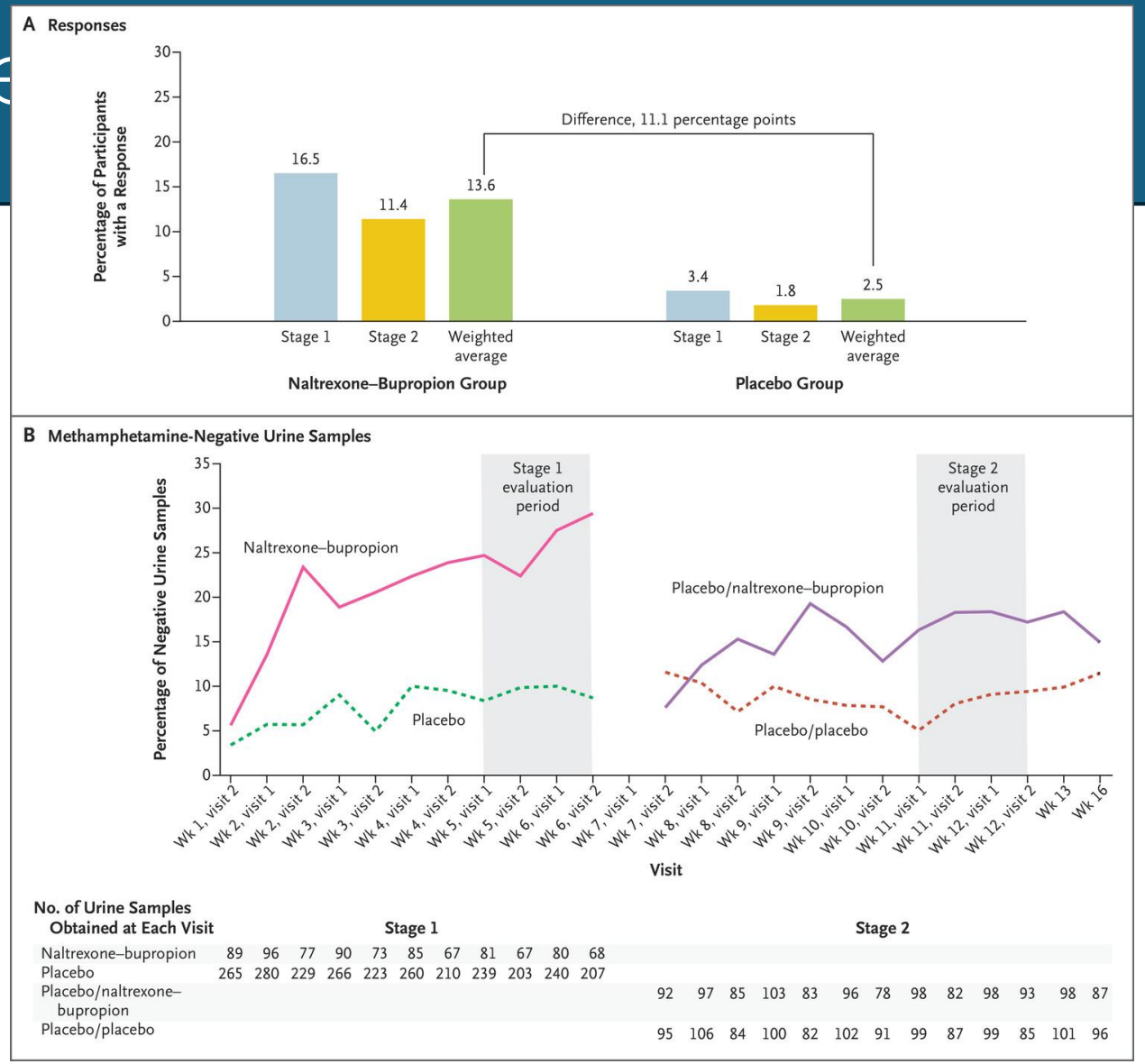
Bupropion

- Atypical antidepressant
  - Blocks reuptake of dopamine
  - Blocks reuptake of norepinephrine
- Several small studies demonstrated modest improvement in stimulant use reductions
- Better outcomes in individuals with less than daily use of stimulants
- Most trials looked at 300 mg/day

Addiction. 2014;109(11):1878-1886.
Drug Alcohol Depend. 2015;150:170-

Bupropion + Naltre

- Based on previous limited evidence of either agent alone
- Used higher dose of bupropion (450 mg/day)
- Used higher naltrexone dose (380 mg IM q 3weeks)



N Engl J Med. 2021;384(2):140-153.

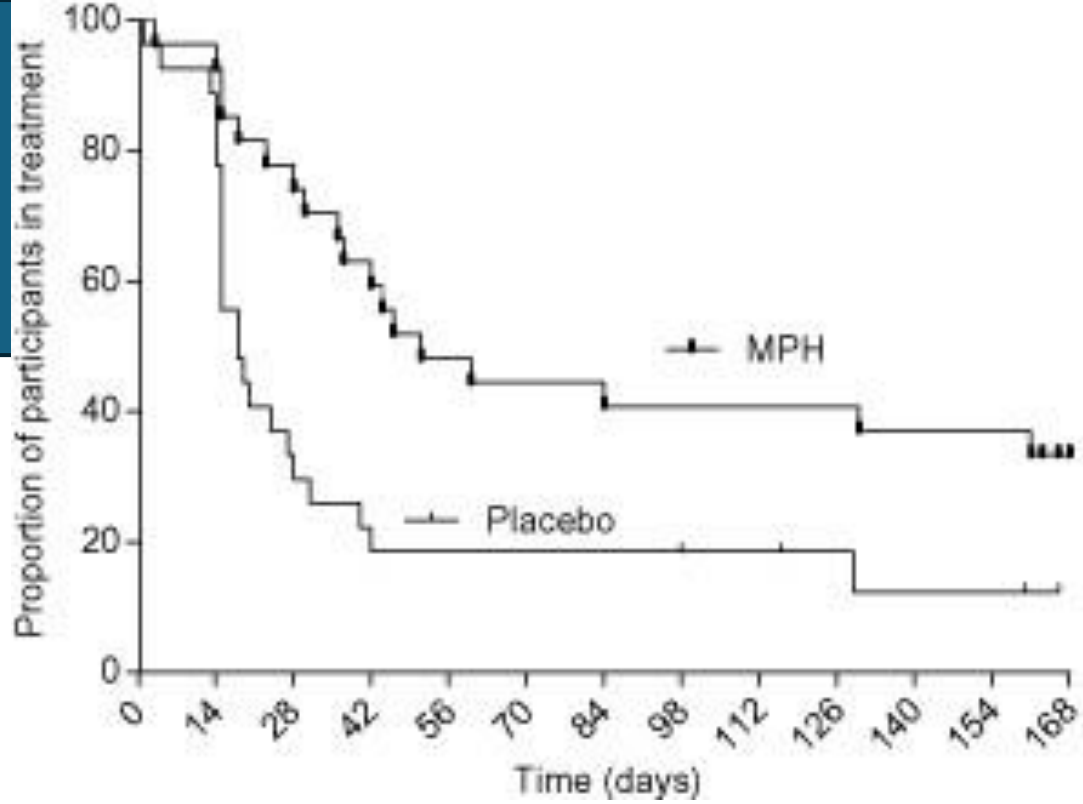
Topiramate

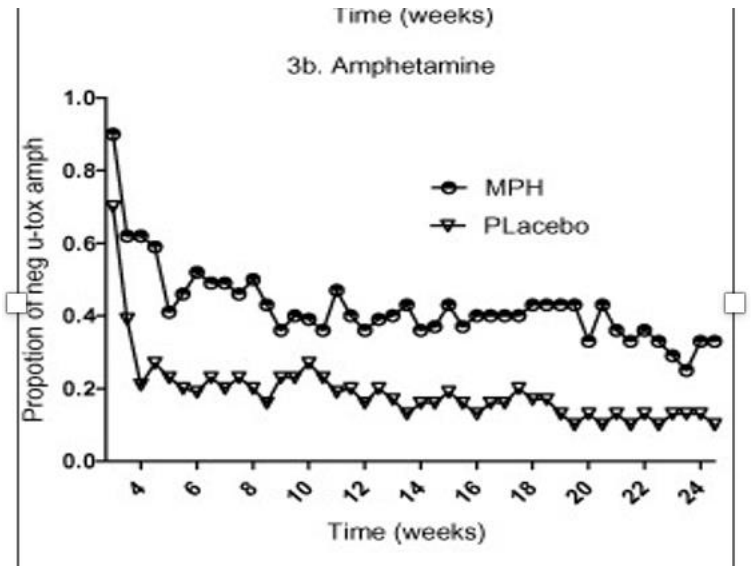
- Target doses are 200 mg per day and above
  - Titration starts at 25 mg daily and gradually to target dose
  - Tolerability often limiting
- Reduced use and severity of dependence
- Short-term (6 weeks) modest reductions in MA-positive urine drug screens
- Not sustained at 10 weeks

CNS Drugs. 2020;34(4):337-365.

Stimulants

- Methylphenidate has best evidence (of stimulants)
  - Inhibits reuptake of dopamine
  - Inhibits reuptake of norepinephrine
- Limited efficacy at "FDA doses" 60 mg/day
- Doses of up to 180 mg/day shown to improve treatment retention and negative UDS





Psychopharmacology. 2020;237(8):2233-2255.
Addiction. 2014;109(3):440-449.

Using Prescription Stimulants in StUD

- Harm reduction approach
  - Known dose
  - Known purity
- Stigma of “replacing one addiction for another”
- Duration of supply
- Ongoing monitoring

Depression in SUD

- Individuals with OUD have a high occurrence of depressive episodes
- Comorbid OUD and MDD are associated with worsened outcomes
- Treatment with MOUD (methadone, buprenorphine, and naltrexone) are associated with improvements in depression

American J Addict. 2023;32(3):291-300.

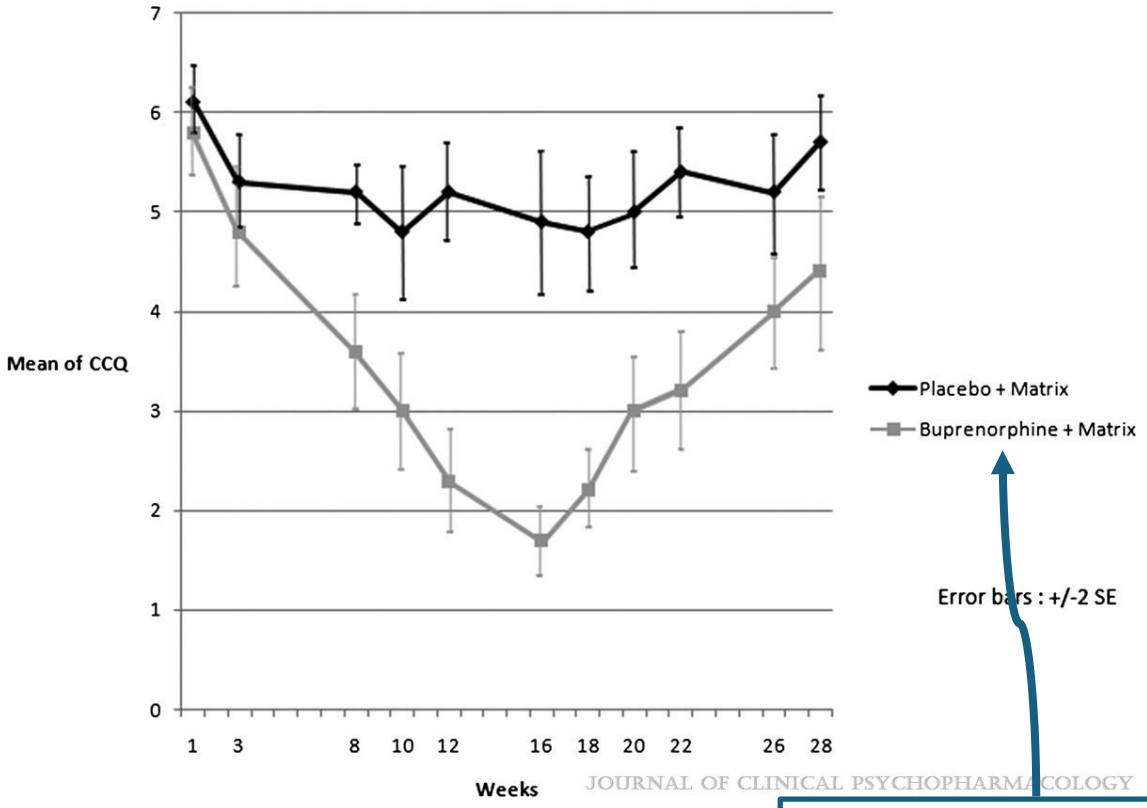
Tailoring Treatment

- Major Depressive Disorder
  - Bupropion
  - Mirtazapine
- Nicotine dependence
  - Bupropion
- Insomnia
  - Mirtazapine
  - Sedating atypical antipsychotics (with comorbid psychotic disorders)

Targeting the Opioid Pathway in StUD

- Decrease in dopamine firing through upstream mu-opioid receptor blockade
- Buprenorphine is first-line for OUD but may interact with other recommended treatments for StUD (naltrexone)
  - Clinical implication less clear, but naltrexone has a *slightly* lower affinity than buprenorphine
  - Limited data on buprenorphine outcomes in StUD

Future Directions of Buprenorphine in StUD



2-6mg/day buprenorphine

Monthly Injectable BUP for MA Use Disorder (MURB) Trial (CTN-0110)

ClinicalTrials.gov ID NCT05283304

Sponsor Madhukar H. Trivedi, MD

300 mg buprenorphine monthl

Journal of Clinical Psychopharmacology 35(6):724-727

Future Direction – Ketamine?

FIGURE 2. Time to first use or dropout, by treatment group, in a randomized controlled trial of ketamine and a mindfulness-based behavioral modification for cocaine dependence

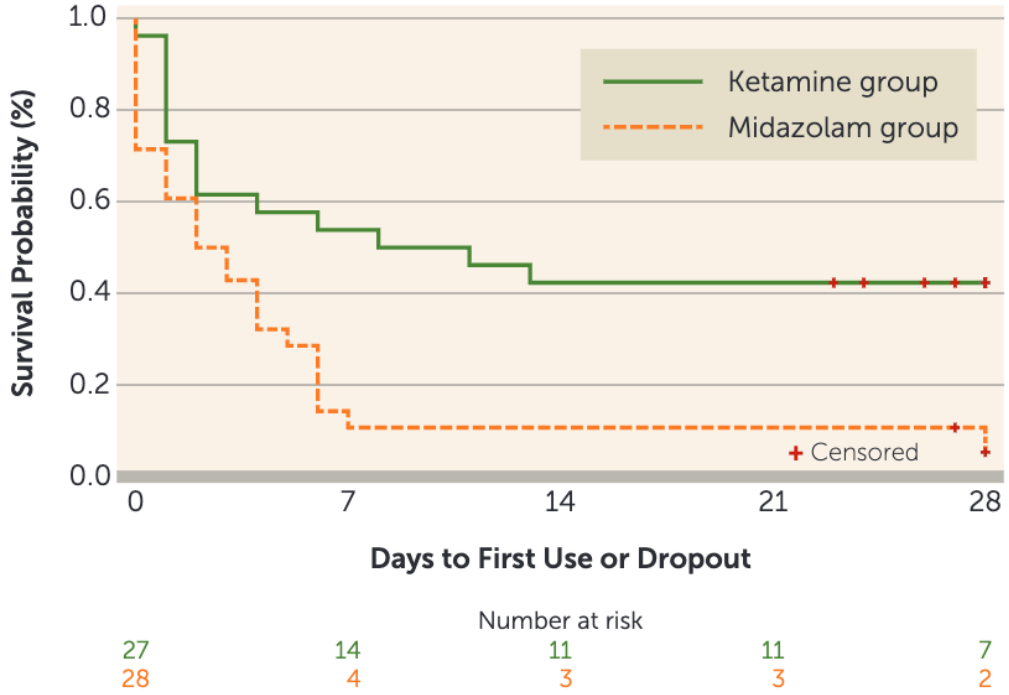
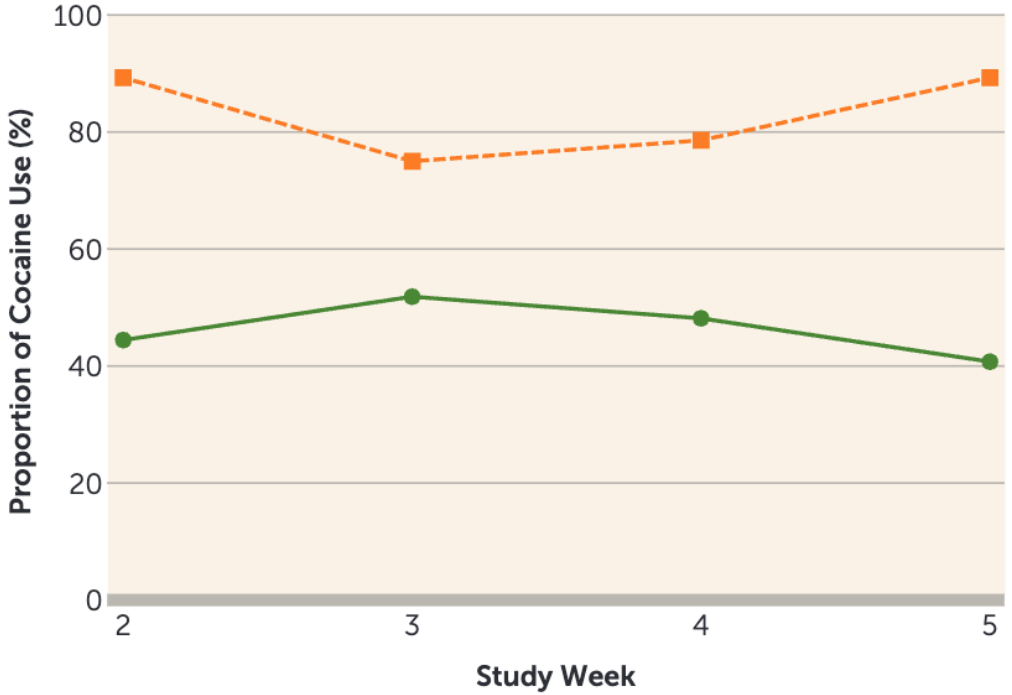


FIGURE 3. Observed proportion of cocaine use over time, by treatment group, in a randomized controlled trial of ketamine and a mindfulness-based behavioral modification for cocaine dependence



AJP. 2019;176(11):923-930.

Depot Buprenorphine Outcomes

	Baseline	Week 4	Week 16
Non-prescribed opioid use	97%	61%*	12%*
Injection drug use	81%	52%*	17%*
Methamphetamine use	25%	10%*	14%

* p<0.05

Addiction. 2022;117(2):382-391.

Contingency Management

- Considered as standard of care for stimulant use disorders
- Providing a reward for target behaviors
  - Most common: negative urine drug screen
  - Adherence with appointments
- May be combined with other interventions

PLoS ONE. 2020;15(6):e0234809.

California DHCS Contingency Management

Table 1: Sample Incentive Delivery Schedule	
Week	**Incentive for Stimulant-Free Test**
Week 1	$10.00 + $10.00 = $20
Week 2	$11.50 + $11.50 = $23
Week 3	$13.00 + $13.00 = $26
Week 4	$14.50 + $14.50 = $29
Week 5	$16.00 + $16.00 = $32
Week 6	$17.50 + $17.50 = $35
Week 7	$19.00 + $19.00 = $38
Week 8	$20.50 + $20.50 = $41
Week 9	$22.00 + $22.00 = $44
Week 10	$23.50 + $23.50 = $47
Week 11	$25.00 + $25.00 = $50
Week 12	$26.50 + $26.50 = $53
Weeks 13-18	$15.00 per week/test
Weeks 19-23	$10.00 per week/test
Week 24	$21.00 per week/test
Total	**$599**

Talk-Based Therapy

- Matrix Model – structured approach that consists of:
  - 16 week treatment
  - CBT
  - Family education
  - Social support groups
- Demonstrated reductions in methamphetamine use, cravings, and risky behaviors

Addiction. 2006;101(2):267-274.

Summary

- Stimulant related overdose deaths are increasing at an alarming rate and disproportionately impacting black and indigenous populations
- Modest improvements in care or retention in treatment can have dramatic impact
- Medications are effective and should be tailored to patient's symptoms
- Individuals who are not ready to stop using can still experience reduction of harms from substance use

Frequently Asked Questions

1. What are the risks associated with use of street stimulants?

Stimulants are increasingly containing lethal doses of fentanyl for individuals not tolerant to the effects of opioids and thus fueling a dramatic increase in stimulant related deaths. Besides overdose from laced fentanyl, methamphetamine can cause acute and chronic psychotic symptoms warranting hospitalization and medication treatment. Stimulants can also cause cardiovascular conditions.

Frequently Asked Questions

2. Are any medications effective at treating stimulant and/or opioid use disorder?

Though no medication is FDA approved to treat stimulant use disorder, there have been clinical trials demonstrating a modest benefit in reducing frequency of use, cravings or other harms associated with stimulant use disorder. Naltrexone and bupropion have shown benefit in methamphetamine use disorder, as have mirtazapine and extended-release pharmaceutical stimulants as agonist therapy. Topiramate has shown to be beneficial in cocaine use. Opioid use disorder should be treated with agonist therapy such as buprenorphine or methadone due to the substantial benefit in reducing overdose deaths, cravings, and harms associated with injection drug use.

Frequently Asked Questions

3. What are the best non-pharmacologic treatments for stimulant use disorder?

Contingency management has shown benefit in reducing stimulant use by providing incentives for positive behaviors (reduced use, safer use, abstinence). Cognitive behavioral therapy is another intervention that is effective when patients have access to this modality, as are principles of motivational interviewing for patients that are more ambivalent about their use of substances.

Frequently Asked Questions

4. What strategies can reduce the risks of harms of stimulant and/or opioid use in individuals not ready to stop using?

Harm reduction approaches that can make using drugs safer in individuals not ready to quit include providing fentanyl test strips to avoid unintended opioid exposure. Safer smoking kits that include glass pipes may limit harms from using homemade pipes that can produce toxic fumes or can shatter during use. All patients using drugs should be given naloxone in case of an opioid overdose.

Thank you!

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