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Psychostimulants 2020: An Update: Epidemiology, Clinical Challenges, and Review of Treatments

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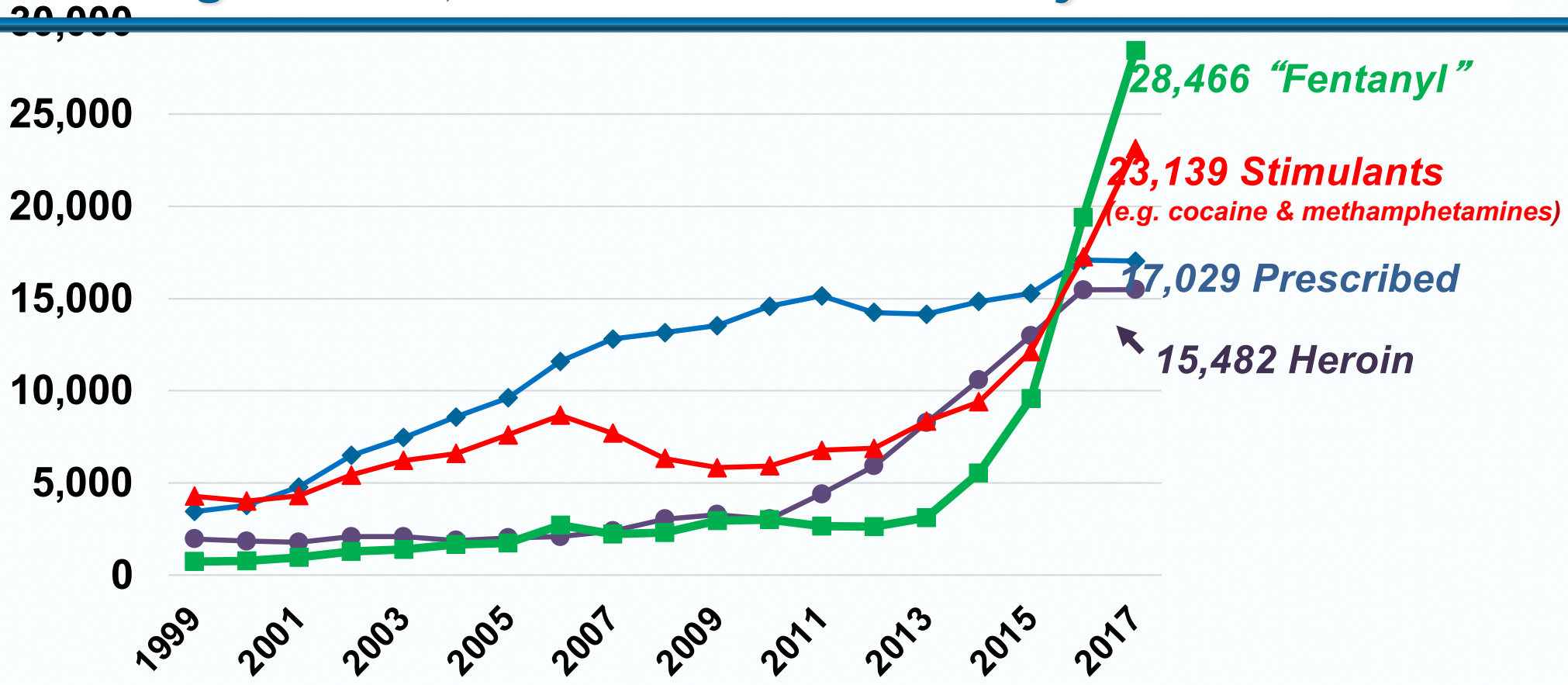
Epidemiology of Methamphetamine and Cocaine Use

Perris, CA, largest domestic meth seizure 2200 pounds on 10/2/20

Evolution of Drivers of Overdose Deaths:

Analgesics ➡ Heroin ➡ Fentanyl ➡ Stimulants



See: Compton WM & Jones CM, *Ann NY Acad Sci, 2019;* Data from CDC WONDER Database

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Hedegaard H, Miniño AM, Warner M. Drug Overdose Deaths in the United States, 1999-2018. NCHS Data Brief. 2020 Jan;(356):1-8. PMID: 32487285.

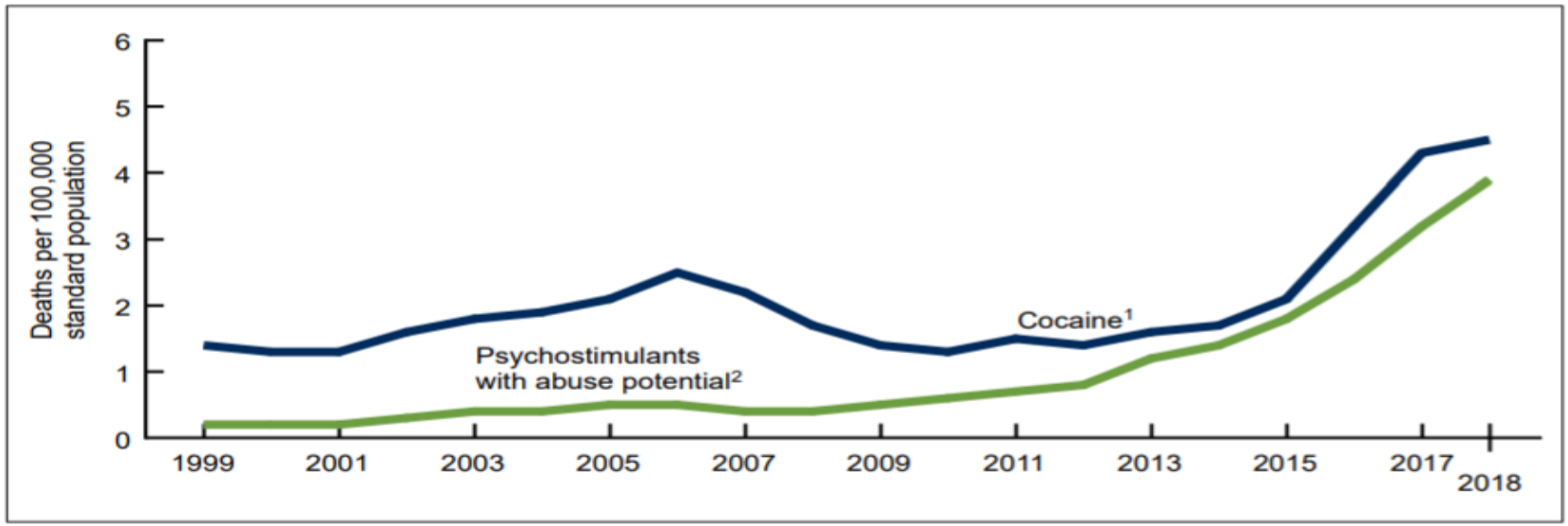
Stimulant Overdose Rates

From 2012 through 2018, the age-adjusted rate of drug overdose deaths involving cocaine more than tripled.

The rate of deaths involving psychostimulants (including methamphetamine) with abuse potential increased nearly 5-fold.

Stimulant Overdose Rates 1999-2018

Figure 4. Age-adjusted drug overdose death rates involving stimulants, by type of stimulant: United States, 1999–2018



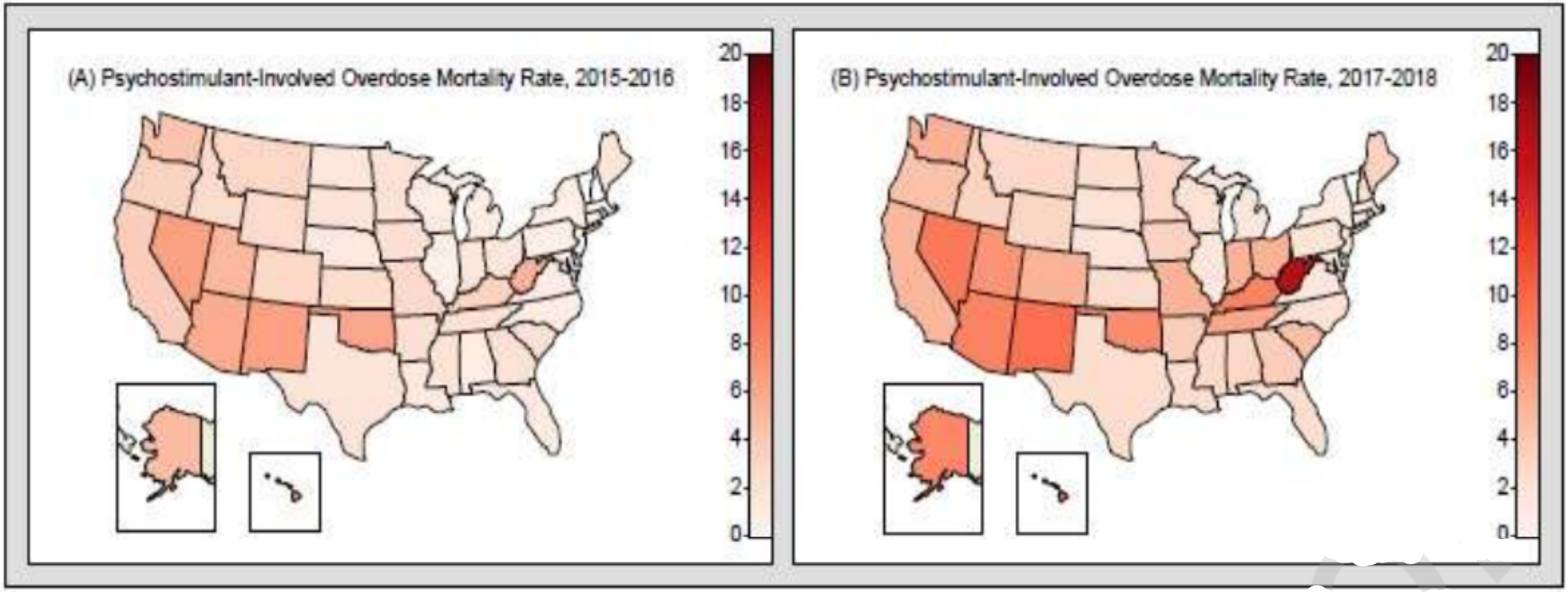
[1]Significant increasing trend from 1999 through 2006, decreasing trend from 2006 through 2012, and increasing trend from 2012 through 2018 with different rates of change over time, $p < 0.05$.
[2]Significant increasing trend from 1999 through 2005, 2008 through 2012, and 2012 through 2018 with different rates of change over time, $p < 0.05$.
NOTES: Deaths are classified using the *International Classification of Diseases, 10th Revision*. Drug-poisoning (overdose) deaths are identified using underlying cause-of-death codes X40–X44, X60–X64, X85, and Y10–Y14. Drug overdose deaths involving selected drug categories are identified by specific multiple-cause-of-death codes: cocaine, T40.5; and psychostimulants, T43.6. Deaths may involve multiple drugs. The percentage of drug overdose deaths that identified the specific drugs involved varied by year, with ranges of 75%–79% from 1999 through 2013 and 81%–92% from 2014 through 2018. Access data table for Figure 4 at: https://www.cdc.gov/nchs/data/databriefs/db356_tables-508.pdf#4.
SOURCE: NCHS, National Vital Statistics System, Mortality.

Cano M, Huang Y. Overdose deaths involving psychostimulants with abuse potential, excluding cocaine: State-level differences and the role of opioids. Drug Alcohol Depend. 2020 Oct 26:108384. doi: 10.1016/j.drugalcdep.2020.108384.

Overdose Deaths Involving Psychostimulants with Abuse Potential, Excluding Cocaine Cano et al., 2020

- In 2017 half of stimulant-involved overdose deaths in the U.S. involved opioids (Hoots et al., 2020).
- Methamphetamine use increases may be occurring in large part among opioid users.
- State-level ,age-adjusted overdose mortality rates were obtained from Multiple Cause of Death data on CDC WONDER (Wide-ranging Online Data for Epidemiologic Research).
- Rates reflect per 100,000 person years.
- Death certificate information was obtained from 50 states and DC.

State-level age-adjusted psychostimulant-involved overdose mortality rates in (A) 2015-2016 and (B) 2017-2018



Nevada, New Mexico, Hawaii, Oklahoma, Arizona

West Virginia, New Mexico, Nevada, Hawaii, Arizona

Age-adjusted psychostimulant overdose rates per 100,000 person years

2015/2016

- Nevada 6.65
- New Mexico 6.56
- Hawaii 6.35
- Oklahoma 6.20
- Arizona 5.90

2017/2018

- West Virginia 16.47
- New Mexico 9.55
- Nevada 8.92
- Hawaii 8.62
- Arizona 8.44

- Also there were significant rate increases in 42 states, no change in 5, and no data in 3 states.

Percentage of co-involvement of opioids in psychostimulant-involved overdose deaths, (A) by state, and (B) by psychostimulant-involved overdose mortality rate, 2017-2018.

Shade of red=psychostim OD; blue=involvement of opioids

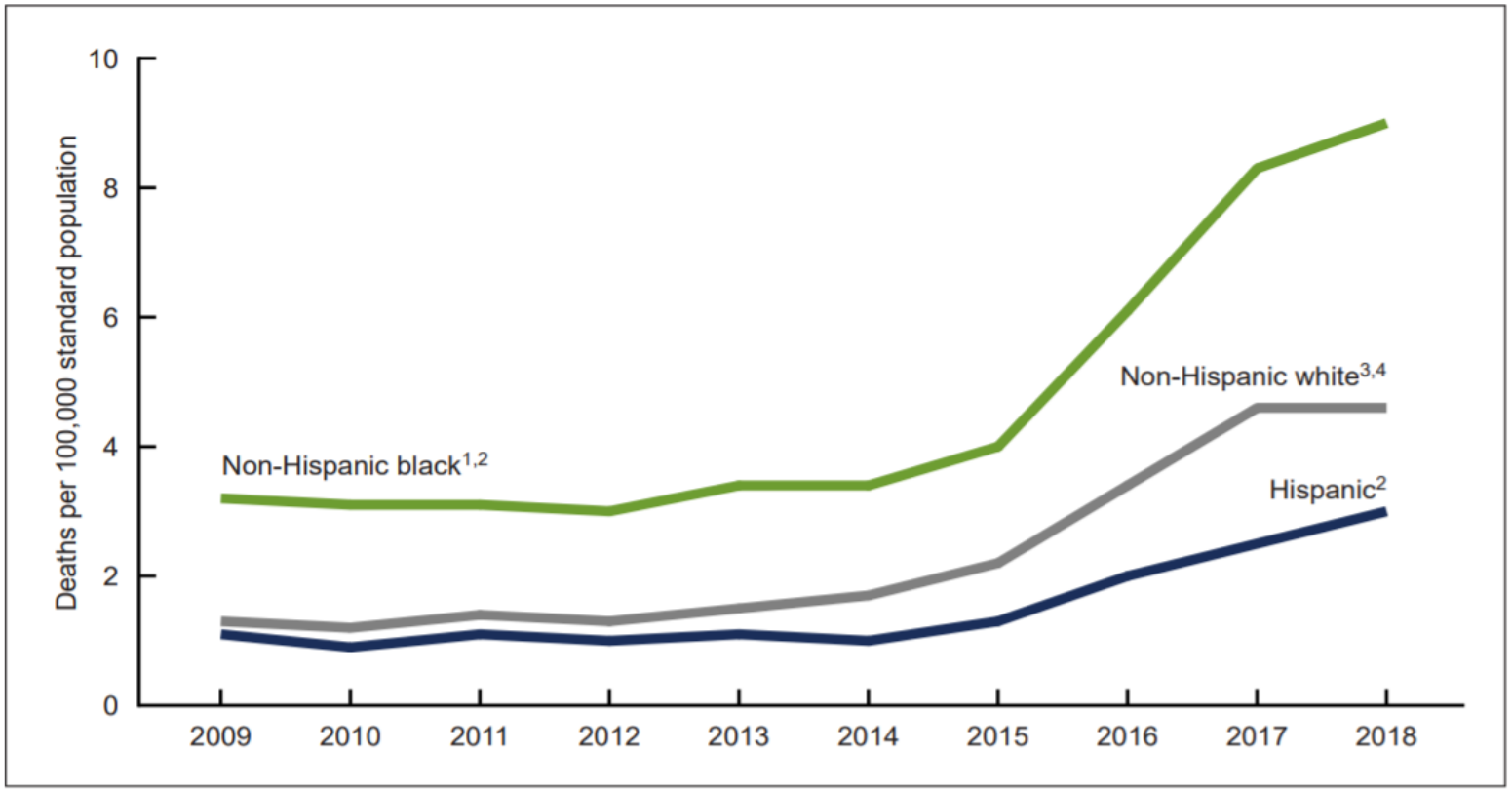
Summary

- Deaths involving methamphetamine have historically been concentrated in the western U.S.
- Results here reflect a large increase in psychostimulant involved mortality rates across the nation, especially in states heavily impacted by the opioid epidemic.
- States east of the Mississippi had higher rates of opioid involvement in psychostimulant-involved overdose deaths.

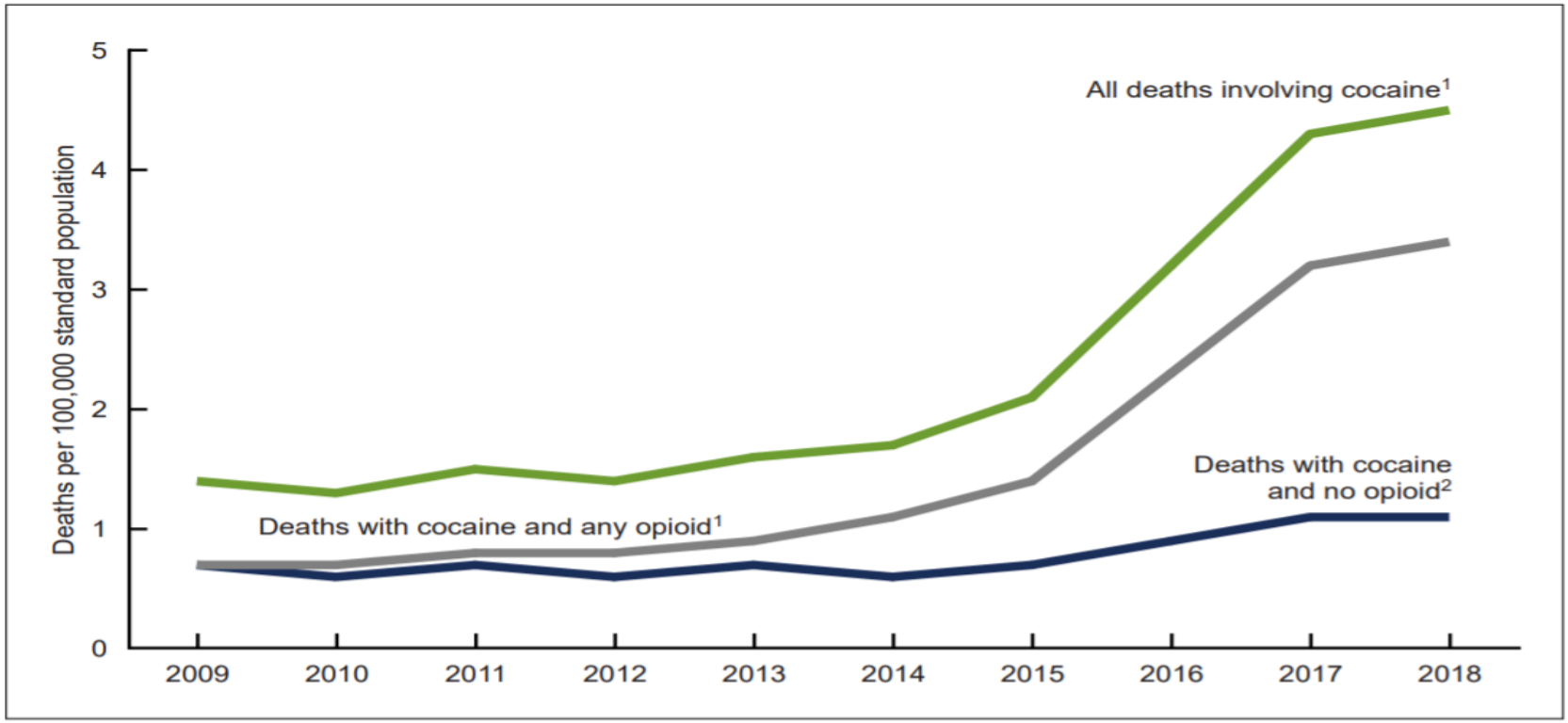
Increase in Drug Overdose Deaths Involving Cocaine: United States, 2009-2018 Hedegaard et al., 2020

- The rate of overdose deaths involving cocaine was stable from 2009-2013.
- The rate of overdose deaths nearly tripled from 2013-2018.
- From 2009-2018 the rate of OD deaths involving cocaine was highest in the non-Hispanic black population.
- In 2018 the rate in the non-Hispanic black population was nearly twice that of non-Hispanic whites, and three times that of Hispanics.

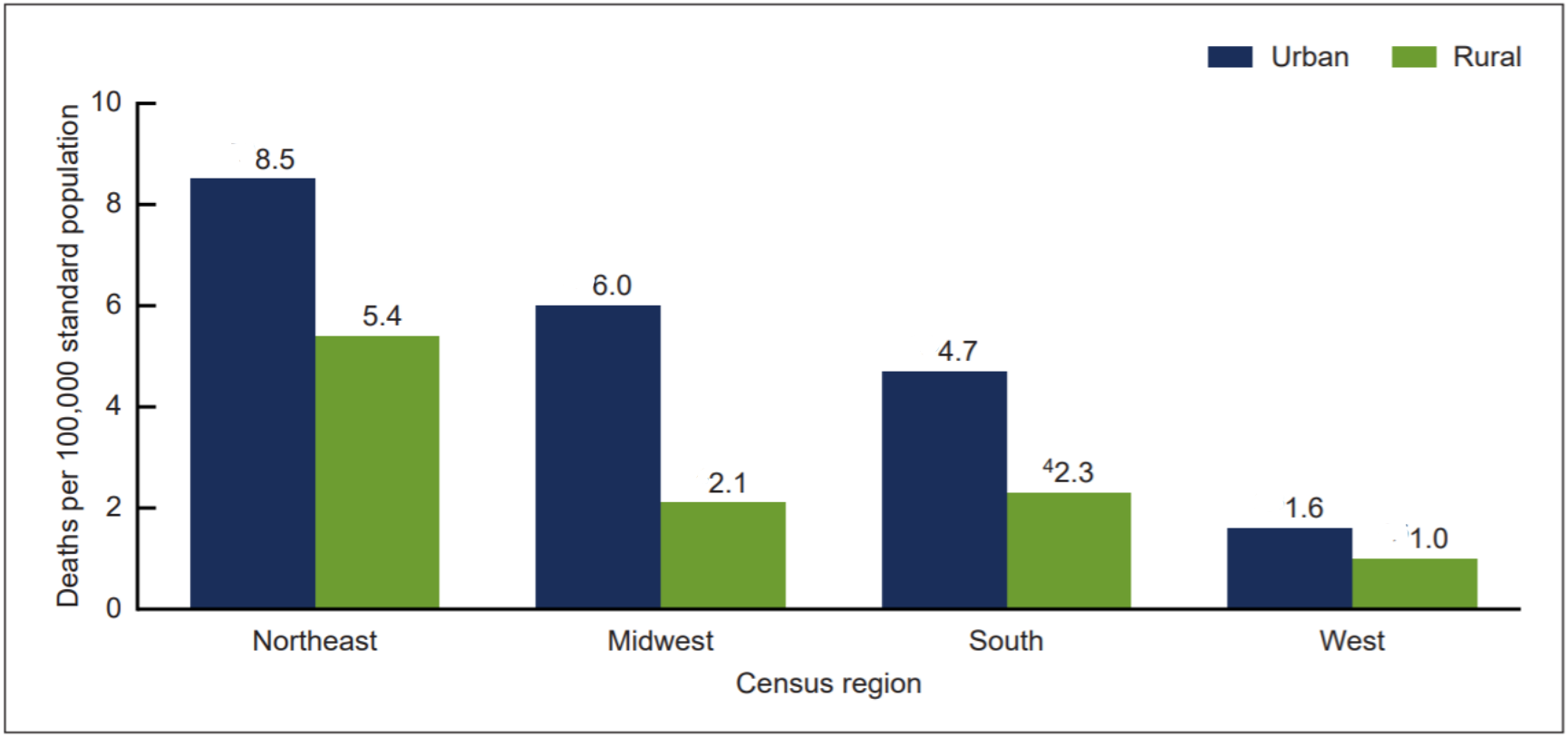
Age-adjusted rates of drug overdose deaths involving cocaine by race and H



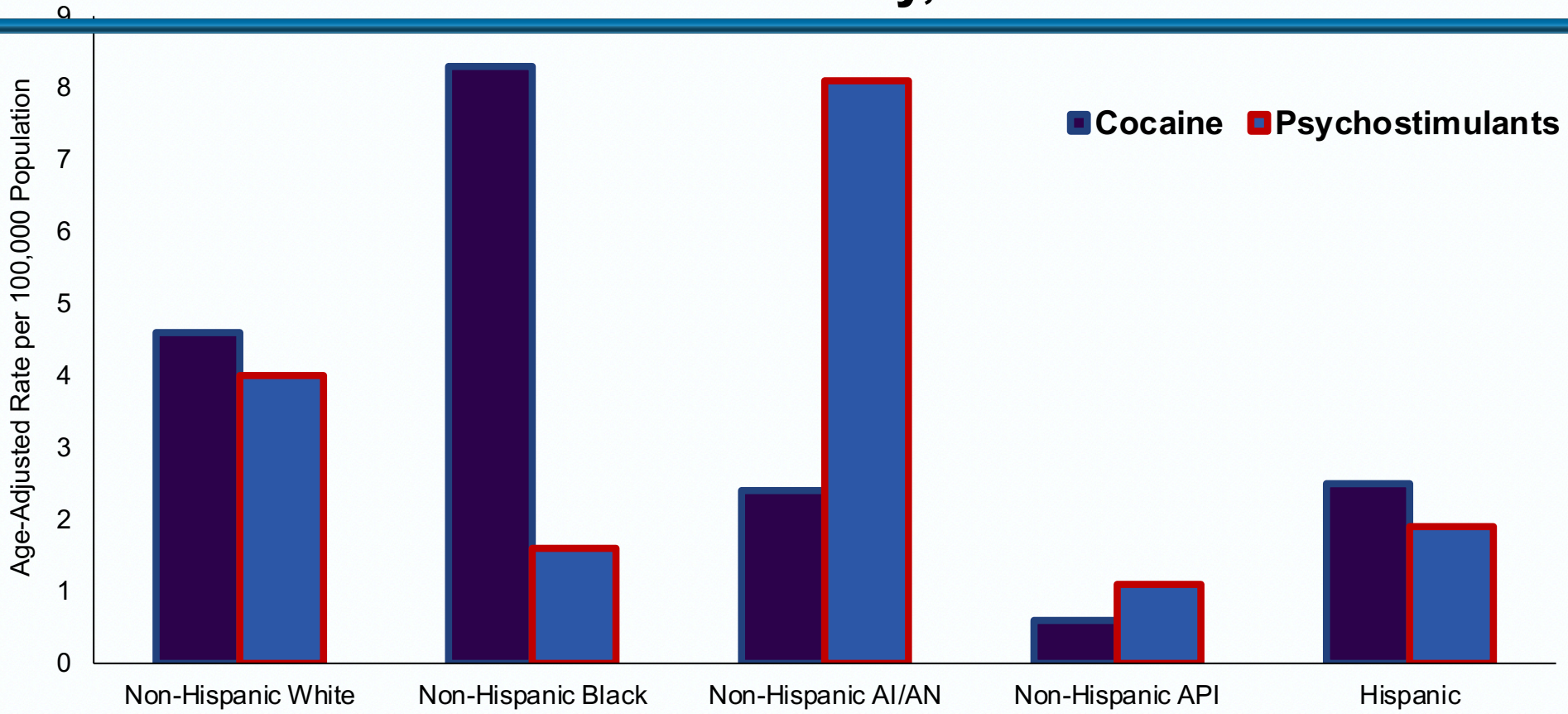
From 2014-2018 the rate of OD deaths involving cocaine with concurrent opioids increased at a faster pace than cocaine OD rates without opioids



In 2018, the rate of OD deaths involving cocaine was highest in urban counties in the northeast



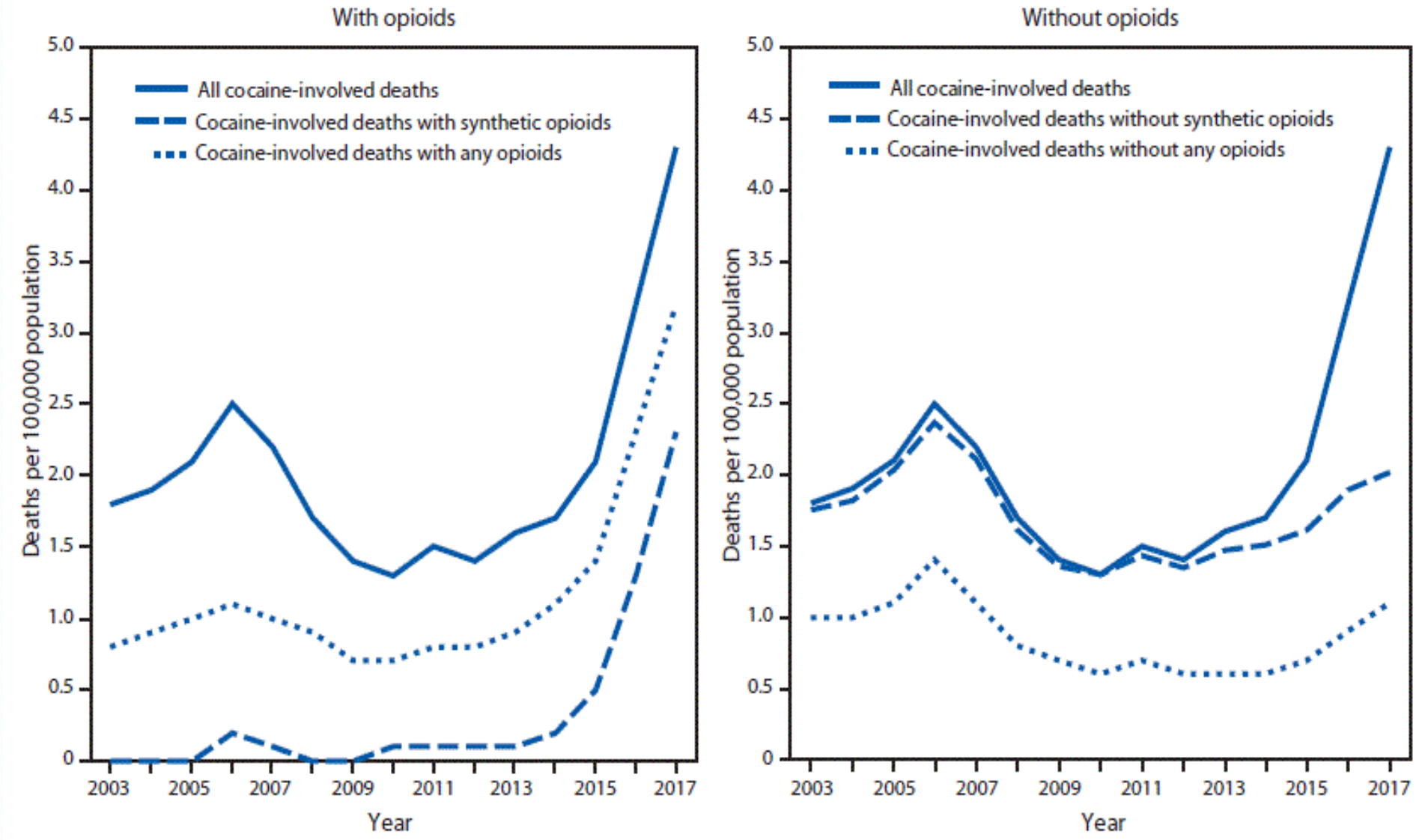
Cocaine and Psychostimulant Overdose Deaths by Race/Ethnicity, 2017



Source: CDC NVSS, 2019

Kariisa, M., et al. (2019). *MMWR Morb Mortal Wkly Rep*. *68*(17), 388–395

Cocaine-Related Deaths, 2003–2017



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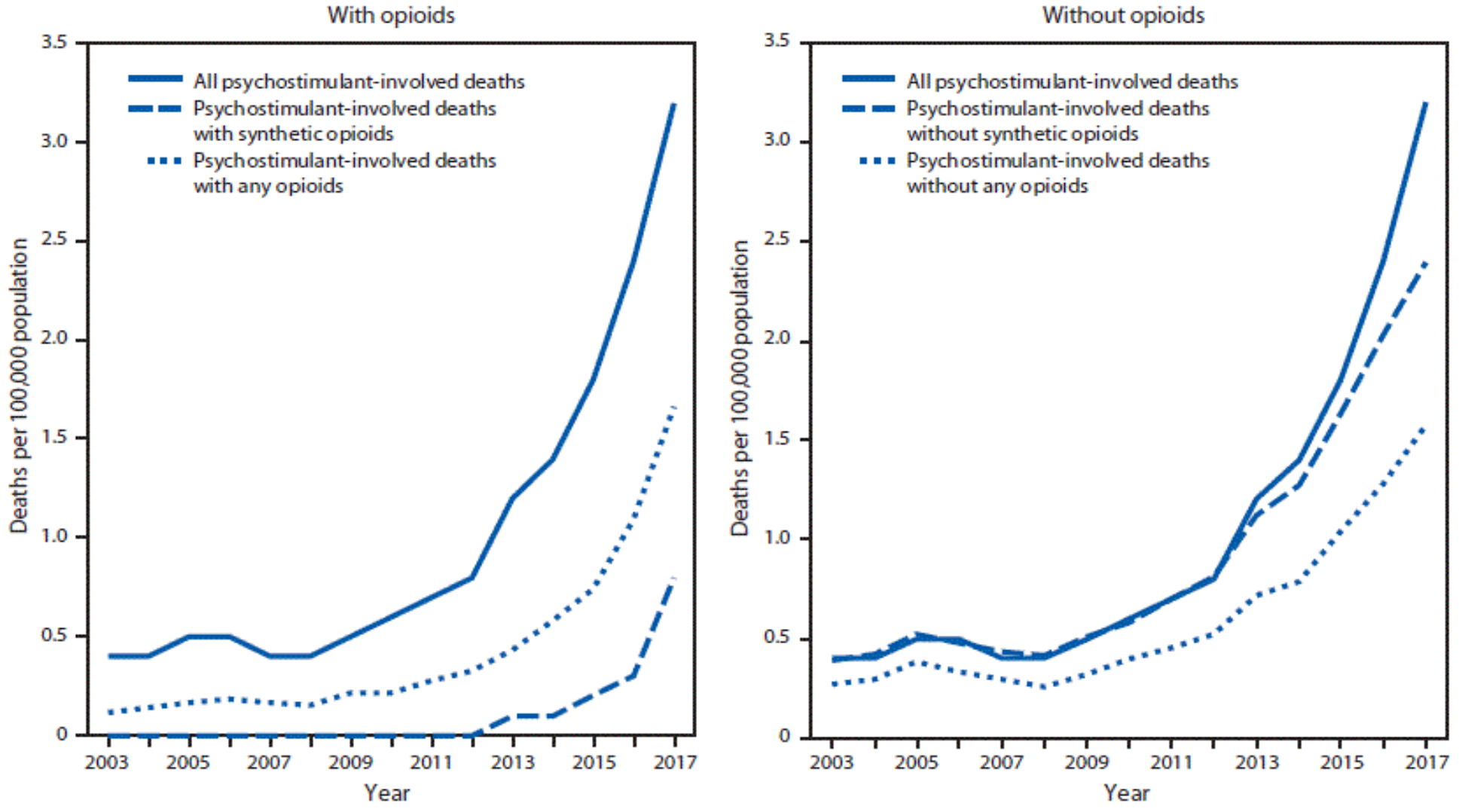
ATS-Related Deaths, 2003–2017



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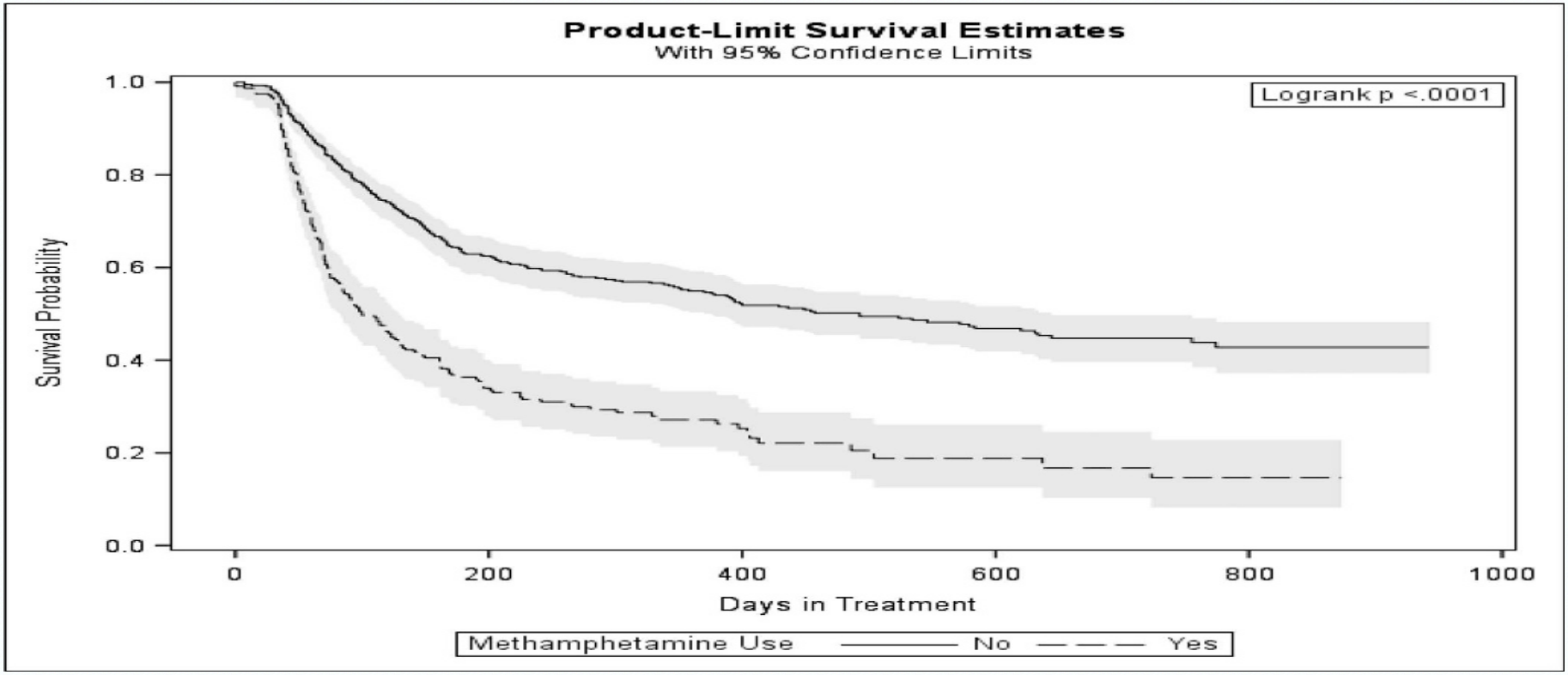
Judith I. Tsui, et al (2020) Association between methamphetamine use and retention among patients with opioid use disorders treated with buprenorphine. Journal of Substance Abuse Treatment 109:80–85

Association Between Methamphetamine Use and Retention Among Patients With Opioid Use Disorders Treated With Buprenorphine

- The study utilized data on adult patients receiving buprenorphine from Washington State Medication Assisted Treatment-Prescription Drug and Opioid Addiction program clinics between November 1, 2015, and April 31, 2018 (N=799). Past 30-day substance use data were collected at baseline, 6-months, and date of program discharge.

- 30% (n=237) of individuals reported meth use at admission. Baseline methamphetamine use was associated with more than twice the relative hazards for discharge in adjusted models (aHR=2.39; 95% CI: 1.94–2.93).

Association Between Methamphetamine Use and Retention Among Patients With Opioid Use Disorders Treated With Buprenorphine



Impacts of Methamphetamine Use

Paulus, M. P. and Stewart, J.L. , Neurobiology, Clinical Presentation and Treatment of Methamphetamine Use Disorder: A Review. JAMA Psychiatry, 77:959-966. doi:10.1001/jamapsychiatry.2020.02462020

Medical Issues Related to Methamphetamine Use

- Neurotoxicity, cognitive effects
- Cardiovascular and cerebrovascular symptoms
- Behavioral treatments effective; Need for pharmacologic interventions

Neurotoxicity

- Excessive dopamine resulting in damaged cell structures
- Cell death
- Activation of dopamine D3 receptors resulting in hyperthermia
- Disruption of the blood-brain barrier
- Overall, the altered brain state is consistent with degenerative central nervous system diseases.

Cognitive effects

Soon after cessation of methamphetamine use:

- Poor performance on motor and processing tasks
- Poor performance on verbal fluency and attention

After prolonged abstinence:

- Poor learning efficiency and comprehension
- Poor visual-spatial processing
- Slow processing and psychomotor speed

Cognitive effects

It is estimated the more than 2/3 of those with methamphetamine use disorder show cognitive impairment.

Impairment is associated with older age, longer duration of use, injection route of administration and greater frequency of use.

Impairment may limit ability to follow through with treatment, comprehend advice and direction in treatment as well as generally achieve good treatment outcomes.

Cerebrovascular and Cardiovascular Disease

Leading causes of death with methamphetamine use disorder

Strokes on rise, most often with young men

Strokes are primarily hemorrhagic

- Associated with methamphetamine use:
  - Pulmonary hypertension
  - Cardiac arrhythmia
  - Cardiomyopathy

Lappin, JM, Darke, S., and Farrell, M. (2017) Stroke and methamphetamine use in young adults: a review. J Neurol Neurosurg Psychiatry 2017;88:1079–1091. doi:10.1136/jnnp-2017-316071

Stroke and Methamphetamine Use in Young Adults: A Review Lappin et al., 2017

- 77 articles reviewed reported stroke in young adult (<45) methamphetamine users.
- 81 hemorrhagic and 17 ischemic strokes reported.
- Hemorrhagic strokes were associated with injection route of administration.
- Ischemic strokes were associated with inhalation.
- Following hemorrhagic stroke, 1/3 died.
- Following ischemic stroke, 1/5 died.

Stroke and Methamphetamine Use in Young Adults: A Review Lappin et al., 2017

Treatment providers should be aware of the heightened risk of stroke in young methamphetamine users.

Be aware of early signs and symptoms:

- Numbness
- Headache
- Speech and language difficulty
- Vision problems
- Dizziness

Smid, M., Metz and Gorden. (2019). Stimulant Use in Pregnancy: An Under-Recognized Epidemic Among Pregnant Women, Clin Obstet Gynecol. *62*(1), 168–184.

Stimulant Use in Pregnancy
Smid et al., 2019

Meta-analysis of 31 studies found cocaine use during pregnancy increased risk of pre-term delivery, low birth weight, small for gestational age, earlier gestational age at delivery (Gouin, 2011).

Meta-analysis of 8 studies found methamphetamine use during pregnancy was associated with earlier gestational age at delivery, lower birth weight, and smaller head circumference (Kalaitzopoulos, 2018).

Infants with prenatal exposure to methamphetamine exhibit jitteriness, drowsiness, and respiratory distress suggesting withdrawal.

Cocaine and methamphetamine are excreted in breastmilk and contraindicate breastfeeding.

Stimulant Use in Pregnancy
Smid et al., 2019

- Long-term follow-up of 204 methamphetamine exposed maternal-child pairs and 208 unexposed pairs (Derauf et al., 2007).
- At one month, 33% methamphetamine-exposed mothers did not have custody compared to 2% of unexposed.
- At age 3 years, heavy prenatal methamphetamine use (≥ 3days per week) was associated with anxiety/depression and attention problems.
- At age 7.5 years, methamphetamine-exposed children had poorer cognitive function.
- UCLA Study of 4-5 year olds found impoverished vocabulary and poorer fluency with language

Foulds, JA, Boden, JM, McKetin, R. and Newton, Howes, G. 2020 Methamphetamine use and violence: Findings from a longitudinal birth cohort. Drug and Alcohol Dependence, 207. 43-53.

Methamphetamine and Violence

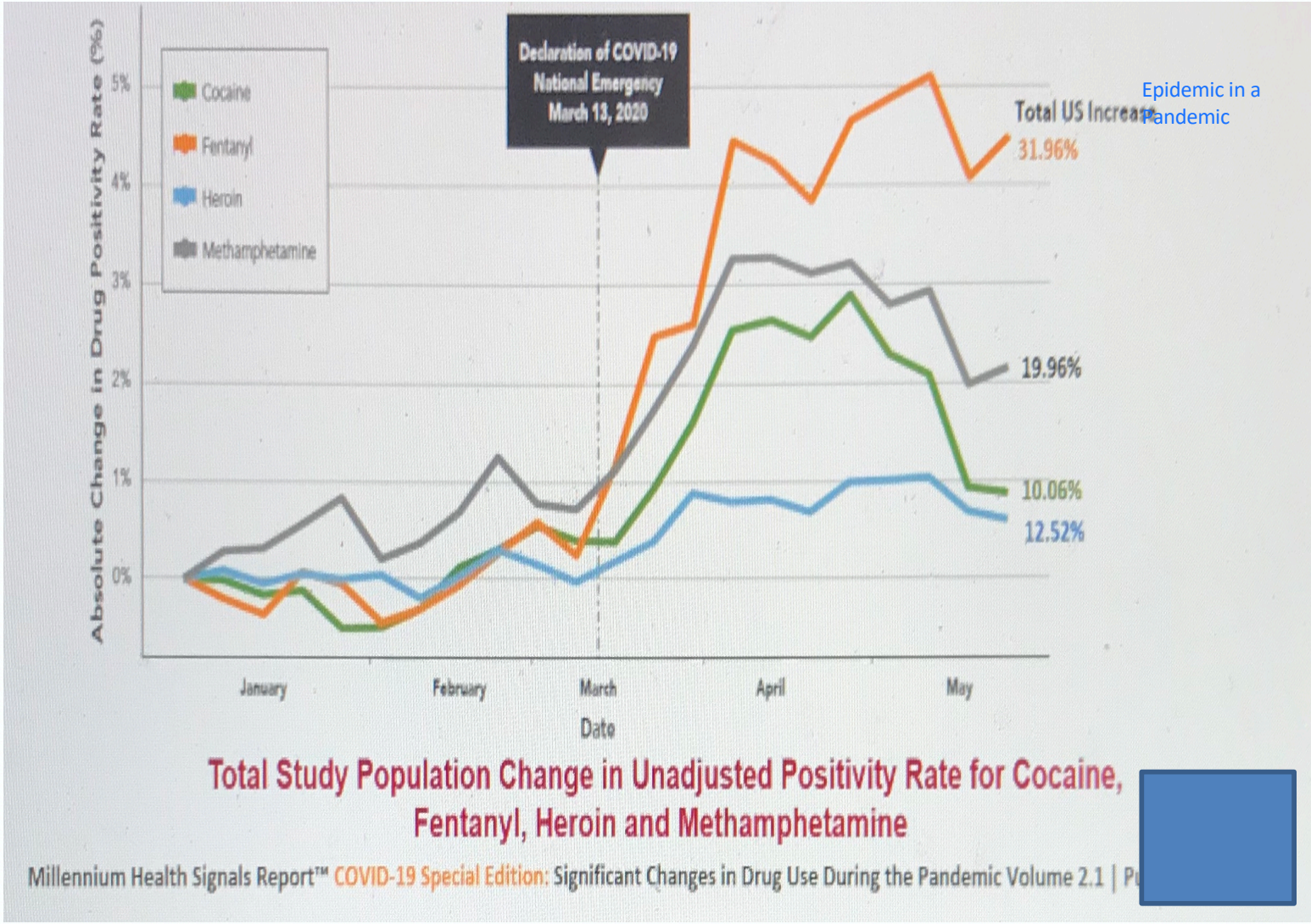
Foulds et al., 2020

- Compared to no use, amphetamines use was associated with a 2-fold increase in the odds of hostility or violence.
- Frequent and heavier/injection use increases the risk of violent behavior.
- Other risk factors included: psychotic symptoms, alcohol or other drug use, psychosocial problems, and impulsivity.
- A majority of violent episodes occurred during periods of psychosis

Collision of the COVID-19 and the Addiction Epidemics Volkow, 2020

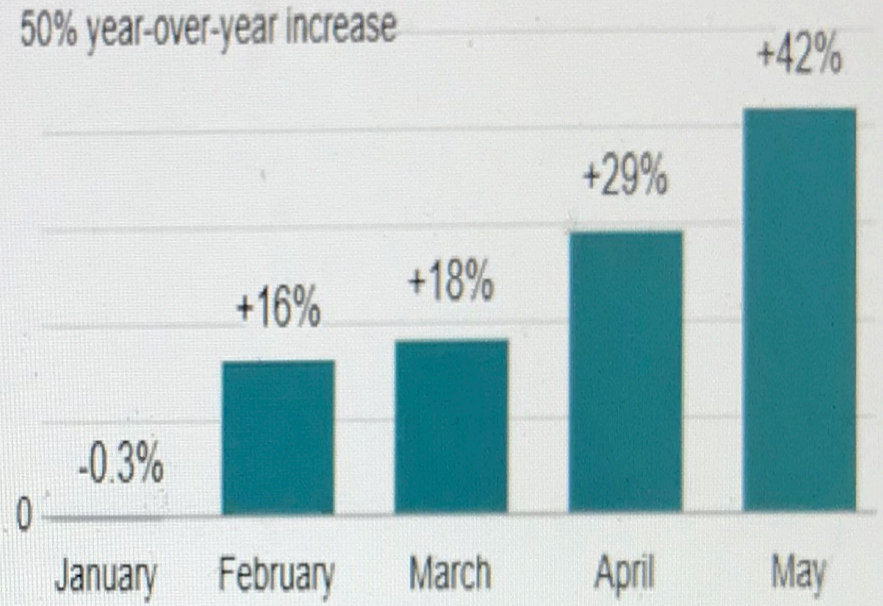
- Chinese Center for Disease Control reports a fatality rate of 6.3% for people with chronic respiratory diseases compared to 2.3% overall.
- People who smoke, vape, use opioids, or have an SUD are vulnerable.
- Opioid use causes hypoxemia.
- Methamphetamine use causes pulmonary damage.
- Social distancing increases risk of overdose with fewer people available to administer naloxone.
- **Isolation, stress, anxiety, and depression can lead to more substance use and more fatal overdoses**.

Drug Use Increase During COVID-19



Overdoses Grew Dramatically During COVID Pandemic

Overdoses increased up to 42% per month during the pandemic, as compared to the same months in 2019.



Note: Percent growth references the 1,201 agencies reporting to ODMAP by January

Source: ODMAP

ALYSSA FOWERS/THE WASHINGTON POST

Friedman J, Beletsky L, Schriger DL. Overdose-Related Cardiac Arrests Observed by Emergency Medical Services During the US COVID-19 Epidemic. JAMA Psychiatry. 2020 Dec 3:e204218. doi: 10.1001/jamapsychiatry.2020.4218.

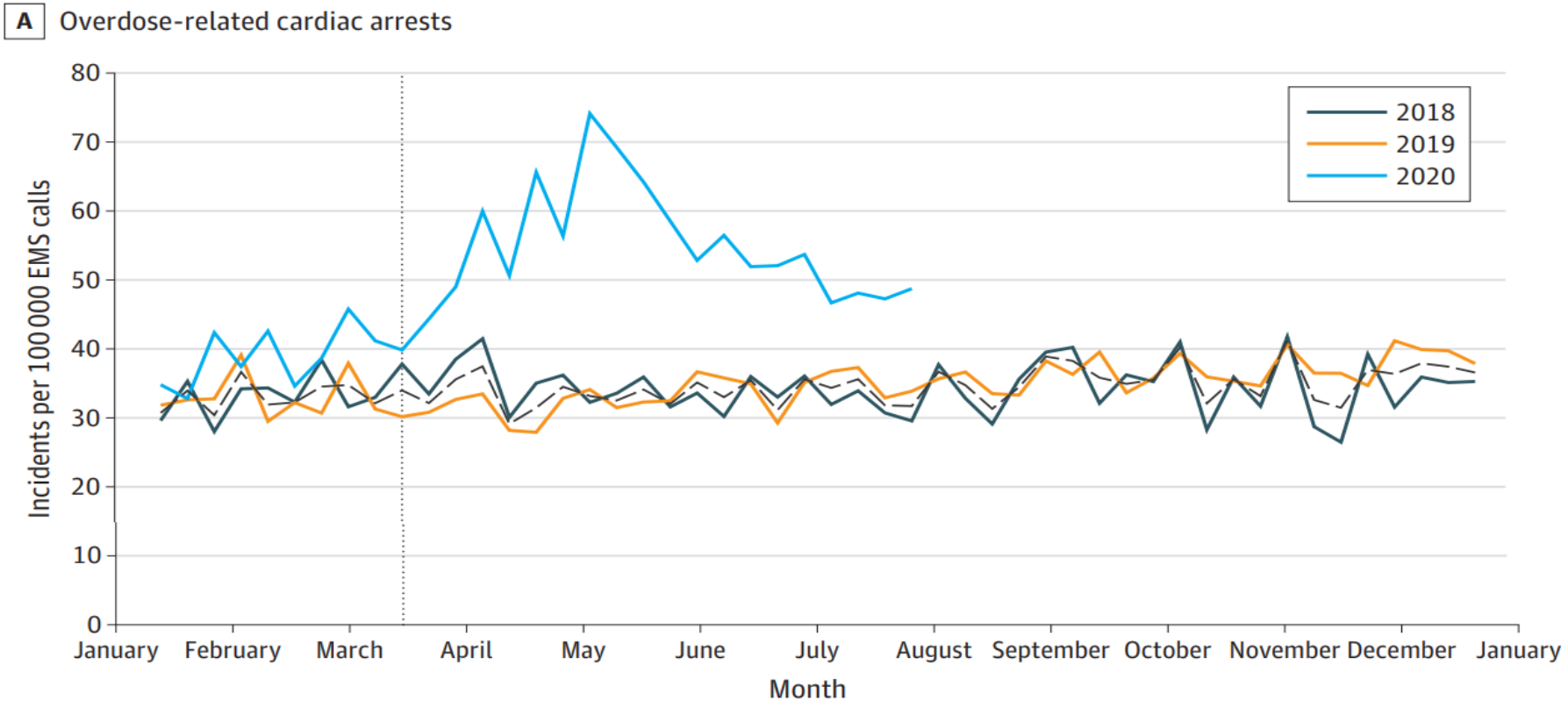
Overdose-Related Cardiac Arrests Observed by Emergency Medical Services During the US COVID-19 Epidemic

Friedman et al., 2020

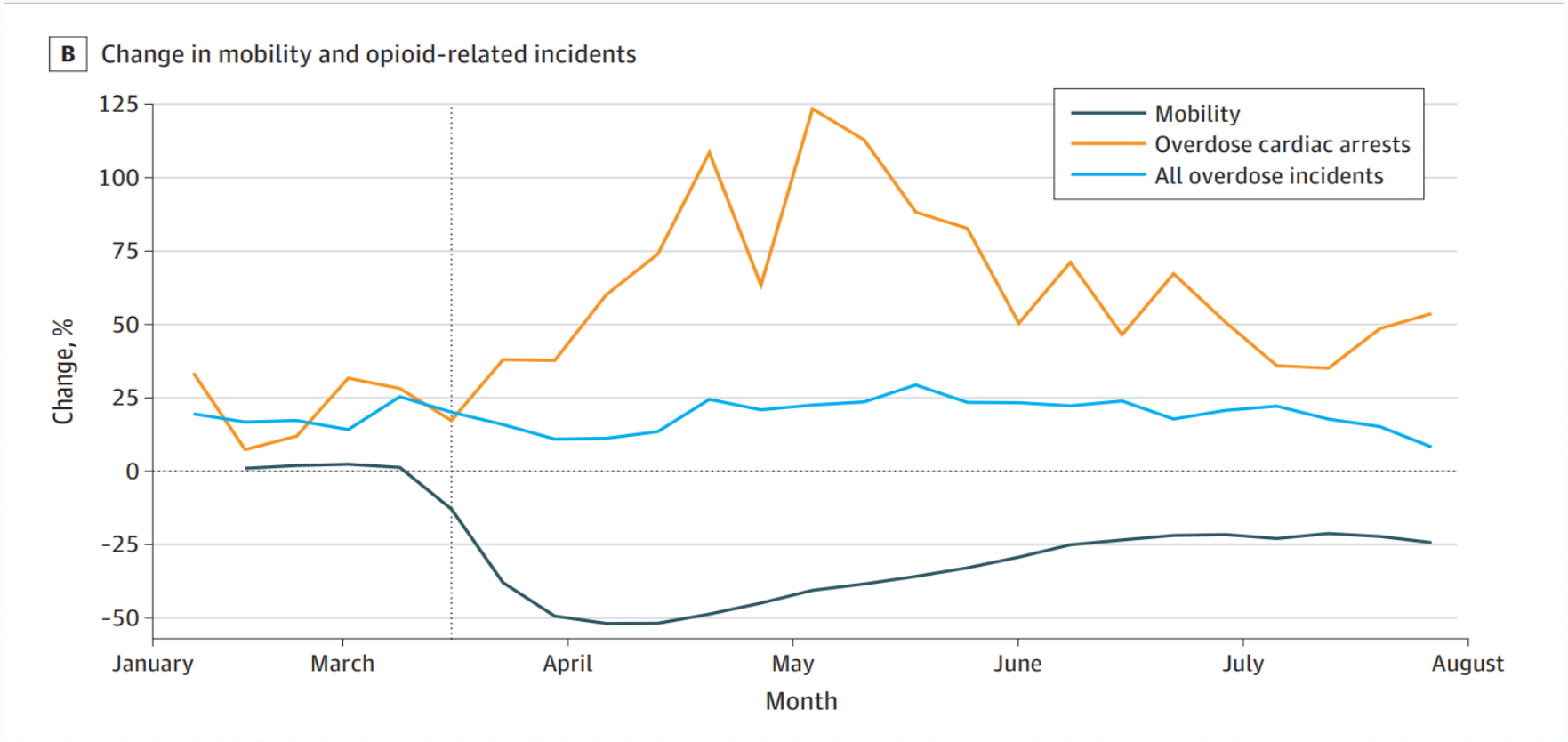
- State databases tracking overdose mortality have long lag times.
- Emergency medical services (EMS) provide near real-time information.
- This is a retrospective observational analysis using the National EMS Information System (NEMSIS).
- 10,000 EMS agencies in 47 states.

Overdose-related cardiac arrests increased by about 50% in 2020 Friedman et al., 2020

Figure. Changes in Emergency Medical Services (EMS)–Observed Overdose Incidents, Cardiac Arrests, and Mobility During the US Coronavirus Disease 2019 (COVID-19) Epidemic



Decrease in mobility (social isolation) correlates with overdose deaths Friedman et al., 2020



Clinical Challenges

Clinical Challenges With Individuals with Stimulant Use Disorder

- Overdose death
- Limited understanding of stimulant addiction
- Ambivalence about need to stop use
- Impulsivity/Poor judgement
- Cognitive impairment and poor memory

Clinical Challenges With Individuals with Stimulant Use Disorder

- Anhedonia
- Paranoia
- Hypersexuality
- Violence and psychosis
- Powerful Pavlovian trigger-craving response
- Elevated rates of psychiatric co-morbidity
- Very poor retention in outpatient treatment

Lappan SN, Brown AW, Hendricks PS. Dropout rates of in-person psychosocial substance use disorder treatments: a systematic review and meta-analysis. Addiction. 2020 Feb;115(2):201-217. doi: 10.1111/add.14793.

Dropout rates of in-person psychosocial substance abuse treatment: a systematic review and meta-analysis (Lappan et al., Addiction, 2020)

- Meta-analysis of in-person psychosocial SUD treatment.
- Drop out rates in first 90 days of treatment
- 151 studies, with 26,243 participants.
- Results yielded overall average dropout rates, and predictors of dropout.

Substance Targeted and Dropout

Treatment Target	Dropout Rate
Heroin	25.1
Tobacco	25.5%
Alcohol	26.1%
Cocaine	48.7%
Methamphetamine	53.5%

Special Treatment Consideration Should Be Made for the Following Groups

- People who inject stimulants.
- People who use stimulants daily or in very high doses.
- Women (high rates of physical/sexual abuse).
- Homeless, chronically mentally ill, and/or individuals with high levels of psychiatric symptoms at admission.
- Men who have sex with men (MSM).
- Individuals in medication treatment for OUD.

Clinical Interventions

Wang, A.Z., Lupov, I.P., and Sloan, B.K. (2019). A Novel Technique for Ice Water Immersion in Severe Drug-Induced Hyperthermia in the Emergency Department. J Emerg Med. *57*(5), 713-715. doi: 10.1016/j.jemermed.2019.08.041. PMID: 31629579.

2 cases of Hyperthermia Treatment

Wang et al., 2019

- Indiana School of Medicine
- Case 1: 21-year-old unresponsive after ingesting methamphetamine.
- Temperature was 107.9˚F.
- Cooling blankets and bags of ice applied; temp still 104.7˚F after 46 minutes.
- Patient was put in a body bag filled with an ice slurry and temp dropped to 97.7˚F.

2 cases of Hyperthermia Treatment

Wang et al., 2019

- Case 2: one week later a 46-year-old unresponsive after ingesting methamphetamine.
- Temperature was 107.2˚F.
- Patient was immediately put in a body bag filled with an ice slurry and temp dropped to 98.4˚F in 32 minutes.

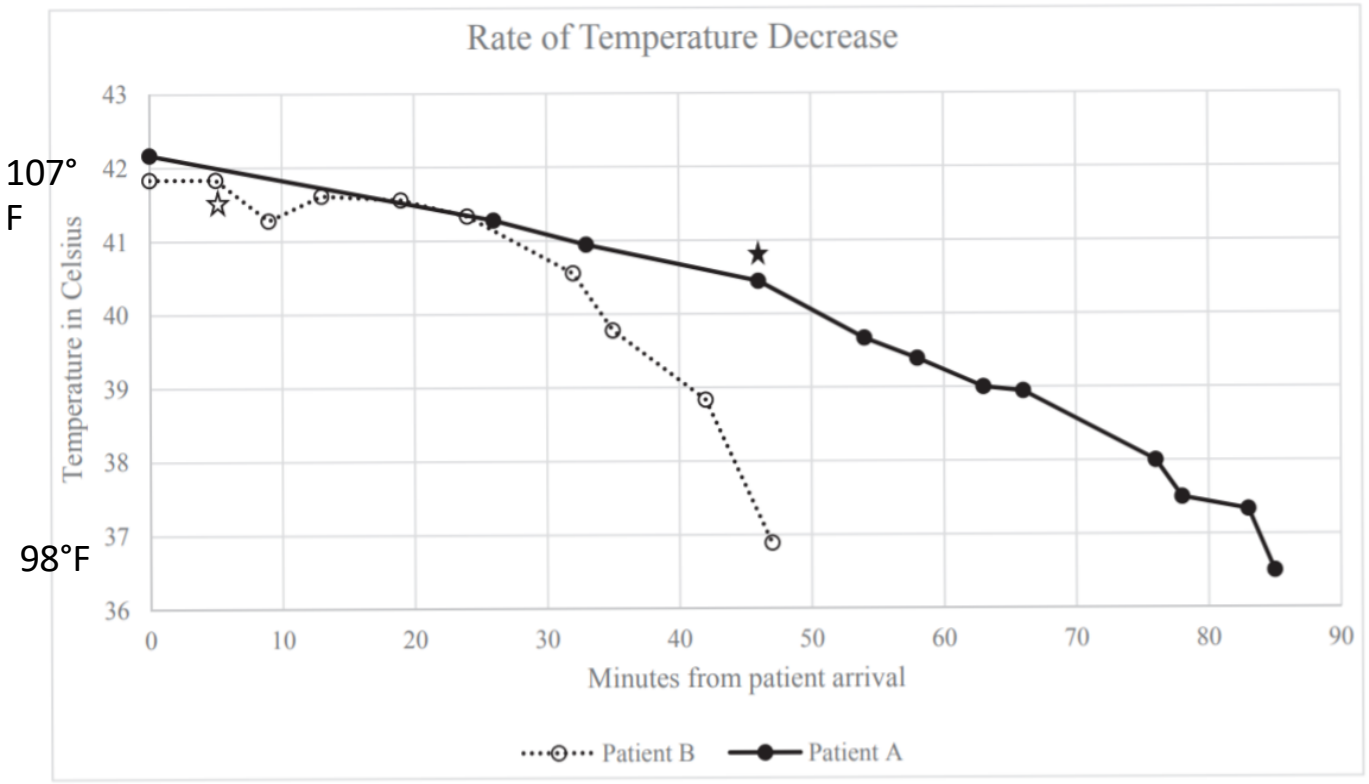


Figure 2. Rate of temperature decrease for patient A and patient B. Symbols (★ and ☆) represent time of immersion for patient A and patient B, respectively.

Isoardi KZ, Ayles SF, Harris K, Finch CJ, Page CB. Methamphetamine presentations to an emergency department: Management and complications. Emerg Med Australas. 2019 Aug;31(4):593-599. doi: 10.1111/1742-6723.13219. Epub 2018 Dec 28.

Methamphetamine Presentations to an Emergency Department: Management and Complications

Isoardi et al., 2019

- 329 patients (378 presentations) in 2016
- ED in Brisbane, Australia
- Clinical effects:
  - Behavioral disturbance, 78%
  - Tachycardia, 56%
  - Hypertension, 42%
  - Hyperthermia, 5%

Harm Reduction Strategies for Individuals who Use Stimulants

- Information about medical and psychiatric effects of meth
- Overdose education (fentanyl)
- Syringe exchanges
- Naloxone (for opioid overdose)
- Quiet rooms and wash up/shower rooms
- Condoms/safe sex education
- Topical antibiotic creams and ointments for injection sites
- Water (dehydration)
- Toothpaste/toothbrush

Interest in Reducing Methamphetamine and Opioid Use Among Syringe Services Program Participants in Washington State McMahan et al, 2020 Drug and Alcohol Dependence

- In a sample of 583 participants at a Washington state syringe exchange program (443 opioids; 140 methamphetamine), survey data were collected on their attitudes about stopping drug use.
- 82% of the individuals who reported opioids as their main drug expressed an interest in reducing/stopping opioid use.
- 46% of individuals who reported methamphetamine as their main drug expressed an interest in reducing/stopping their meth use.

Treatment for Individuals with Stimulant Use Disorder

Systematic Reviews and Meta-analyses

PLOS | MEDICINE

RESEARCH ARTICLE

Comparative efficacy and acceptability of psychosocial interventions for individuals with cocaine and amphetamine addiction: A systematic review and network meta-analysis

Franco De Crescenzo[1,2,3], Marco Ciabattini[4], Gian Loreto D'Alò[4], Riccardo De Giorgi[1,2], Cinzia Del Giovane[5], Carolina Cassar[6], Luigi Janiri[3], Nicolas Clark[7], Michael Joshua Ostacher[8,9], Andrea Cipriani[1,2]*

1 Department of Psychiatry, University of Oxford, Oxford, United Kingdom, **2** Oxford Health NHS Foundation Trust, Warneford Hospital, Oxford, United Kingdom, **3** Institute of Psychiatry and Clinical Psychology, Catholic University of the Sacred Heart, Rome, Italy, **4** School of Hygiene and Preventive Medicine, University of Rome Tor Vergata, Rome, Italy, **5** Institute of Primary Health Care (BIHAM), University of Bern, Bern, Switzerland, **6** Department of Dynamic and Clinical Psychology, Sapienza University of Rome, Rome, Italy, **7** Mental Health and Substance Abuse, World Health Organization, Geneva, Switzerland, **8** Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, California, United States of America, **9** Department of Psychiatry, VA Palo Alto Health Care System, Palo Alto, California, United States of America

PLOS Medicine | December 26, 2018

Meta-Analysis Findings

Network meta-analysis was used to analyze 50 clinical studies (6,943 participants) on 12 different psychosocial interventions for cocaine and/or amphetamine addiction.

The combination of contingency management and community reinforcement approach was the most efficacious and most acceptable treatment, both in the short and long term.

Psychosocial Interventions for Cocaine and Psychostimulant Amphetamines Related Disorders. *Werner Paulo Knapp, Bernardo Soares, Michael Farrell, Maurício Silva deLima. (2009)* ***The Cochrane Collaboration***

Twenty-seven randomized controlled studies (3663 participants) fulfilled inclusion criteria and had data that could be used for at least one of the main comparisons.

The comparisons between different type of behavioral interventions showed results in favor of treatments with some form of contingency management in respect to both reducing dropouts and lowering cocaine use.

Responding to Global Stimulant Use: Challenges and Opportunities Lancet (Farrell et al., 2019)

Psychosocial **interventions other than contingency management have weak and non-specific effects** on stimulant problems, and there are no effective pharmacotherapies. Substantial research investment is needed to develop more effective, innovative, and impactful prevention and treatment.

Non-Pharmacological Interventions for Methamphetamine Use Disorder: A Systematic Review Drug and Alcohol Dependence, AshaRani, PV, et al. 2020

- 44 Studies reviewed.
- Conclusions: While Contingency Management (CM) interventions showed the strongest evidence favoring the outcomes assessed, tailored CBT alone or with CM was also effective in the target population.

Current Status of Treatment Approaches for Stimulant Use Disorder

- **Contingency management unanimously** (5 systematic reviews and meta-analyses) found to have best evidence of effectiveness.
- Other approaches with less but clear evidence of support: Cognitive Behavioral Therapy (CBT) and Community Reinforcement Approach (CRA).
- Approach with evidence for treatment of a broad variety of SUD: Motivational Interviewing (MI).
- Approach with recent studies showing benefit to methamphetamine users: Physical Exercise (PE) (e.g., Rawson et al., 2015).

Contingency Management

A technique employing the systematic delivery of positive reinforcement for desired behaviors, critical to the reduced use of stimulants. In the treatment of methamphetamine dependence, vouchers or prizes can be "earned" for submission of methamphetamine-free urine samples.

Contingency Management for the Treatment of Methamphetamine Use Disorder: A Systematic Review Brown and DeFulio, 2020

- A review of 27 studies.
- All included a contingency management intervention for individuals with methamphetamine use disorder.
- Outcomes:
  - Drug abstinence
  - Retention in treatment
  - Attendance/treatment engagement
  - Sexual risk behavior
  - Mood/affect
  - Treatment response predictors

Results of CM Treatments

- Reduced methamphetamine use in 26 of 27 studies.
- Longer retention in treatment.
- More therapy sessions attended; higher use of other services and medical services.
- Reductions in risky sexual behavior.
- Increases in positive affect and decreases in negative affect.

The Three Major Challenges to Using CM

- Medicaid regulations that restrict the amount of incentives that can be given to patients to $75 per patient per year.
- Where does the funding for incentives come from?
- Staff resistance to the idea of incentives
  - Patients should not have to be “paid” or “bribed”; recovery is the reward.
  - Motivation needs to come from within.

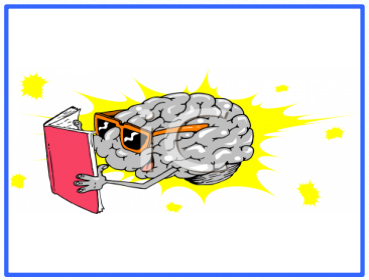
Exercise as a Treatment Intervention for Methamphetamine Dependence

Impact of Exercise on Individuals in treatment for Methamphetamine Use Disorder Rawson, et al multiple studies

Exercise Group:
1h, 3 days/wk

N=69

Health Education Group:
1h, 3 days/wk



N=66

Exercise Study Summary

- For individuals in the first 100 days of meth recovery, exercise:
  - Improves physical conditioning
  - Reduces weight gain
  - Improves cardiovascular functioning (increases heart rate variability)
  - Reduces symptoms of anxiety and depression
  - Reduces craving for methamphetamine
  - Enhances recovery of dopamine system
  - Reduces relapse to methamphetamine post discharge (except in very heavy users)

Medications

Medications for Cocaine Use Disorder

Medications with positive studies and under consideration.

- topiramate*
- modafinil*
- bupropion*
- amphetamine salts
- disulfiram (mixed, worse retention)
- propranolol (WD)
- buprenorphine+naltrexone

Medications for Methamphetamine Use Disorder

Medications with positive studies and under consideration

- bupropion
- mirtazapine *****
- naltrexone
- methylphenidate
- d-amphetamine
- topiramate

Summary/takeaways

- The methamphetamine being used in 2020 is more lethal than in earlier years due to more potent formula and addition of fentanyl.
- New research has provided a better understanding of the medical and psychiatric consequences of methamphetamine use.
- Behavioral treatments, particularly contingency management, have evidence of efficacy.
- There are no medications with FDA approval for the treatment of individuals with methamphetamine use disorder.

QUESTIONS

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