

Drug Addiction Science and the U.S. Overdose Epidemic

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Disclosures of Interests: Wilson M. Compton, MD, MPE

- **Stock Equity:**
 - 3M Company (under \$5,000)
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- **Current Position:** Deputy Director, National Institute on Drug Abuse

Virtually all U.S. regions have experienced rising overdose death rates over the past two decades.

106,699 reported deaths in 2021

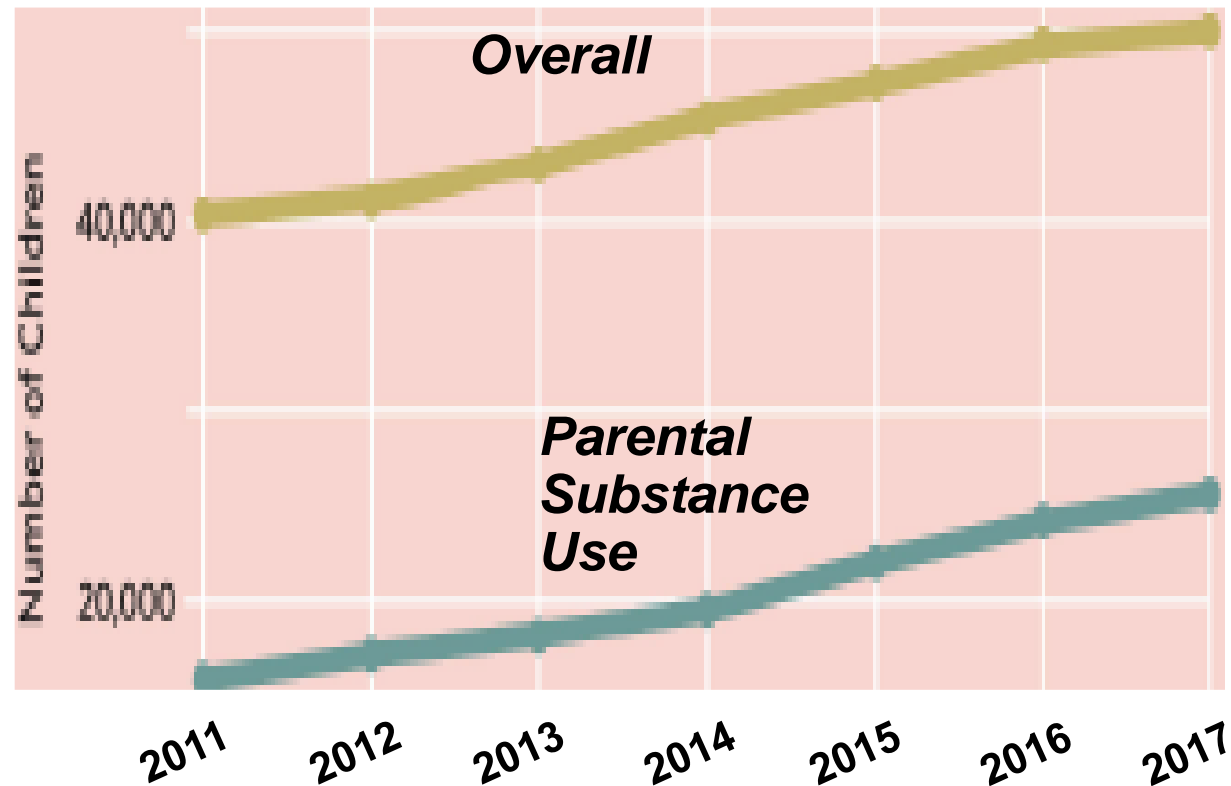
80,411 from Opioids (Prescription and Illicit)

**111,355 predicted deaths over past 12 months
(as of April 30, 2023, *provisional data*)**

Additional Consequences of Addiction

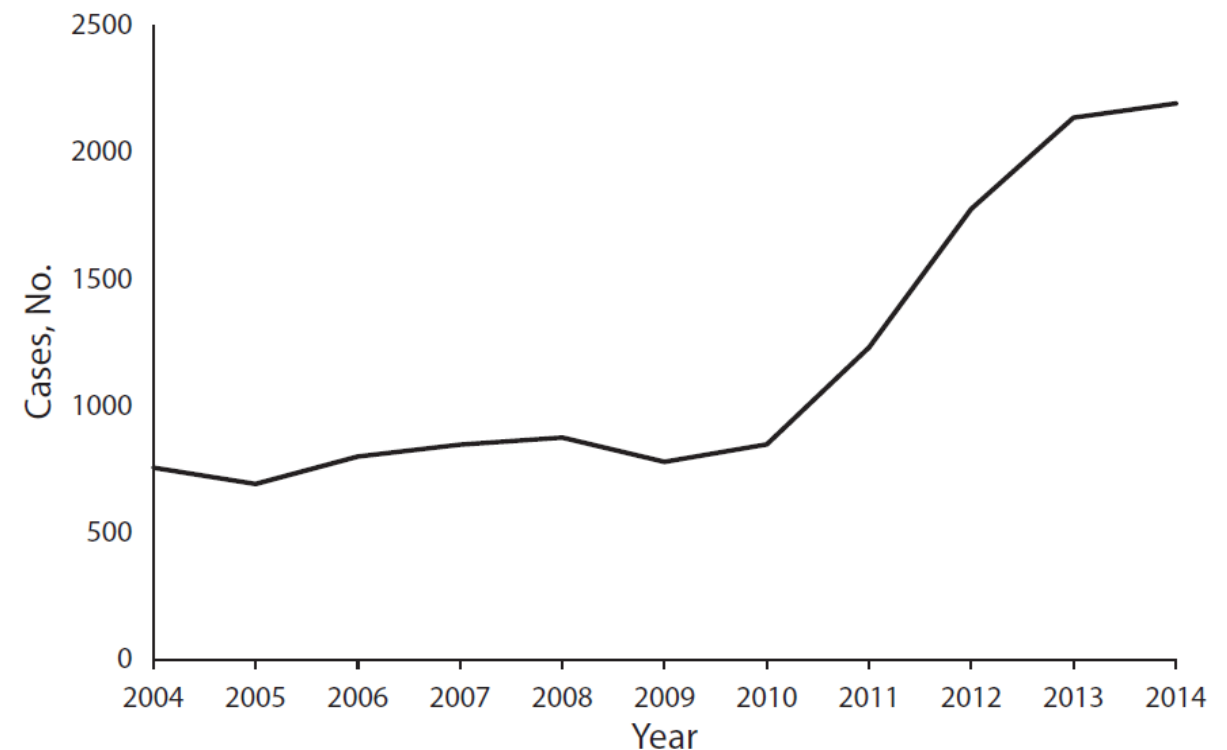
- Drug use while pregnant or parenting has led to increases in rates of neonatal abstinence syndrome and removal of children into the foster care system.
- Increased rates of injection drug use have led to increases in acute cases of Hepatitis C and outbreaks of HIV

U.S. Foster Care Removals for Infants <



Source: Patrick SW, Frank RG, et al. *Hospital Pediatrics*, 2019.

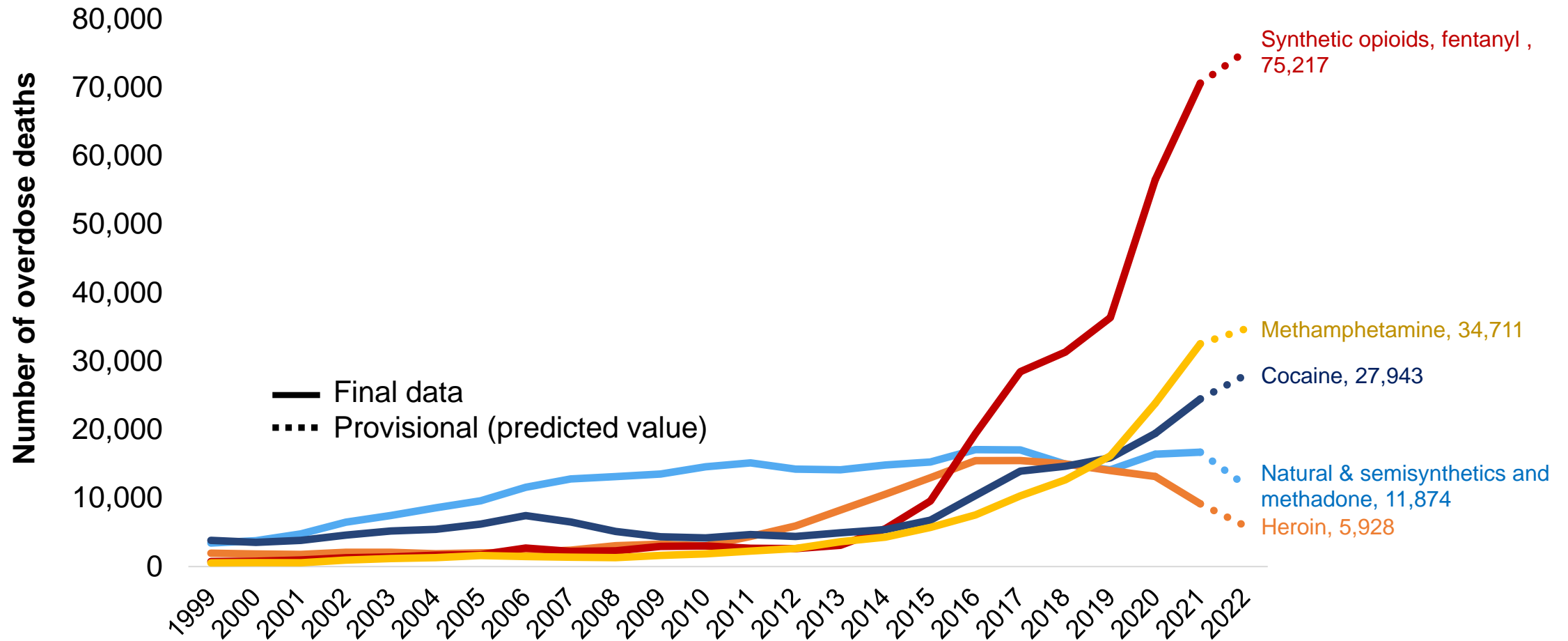
Acute Cases of HCV in USA



Zibbell et al. *Am J Public Health* 2018;108:175-181

Evolution of Drivers of Overdose Deaths, All Ages

Analgesics → Heroin → Fentanyl → Stimulants

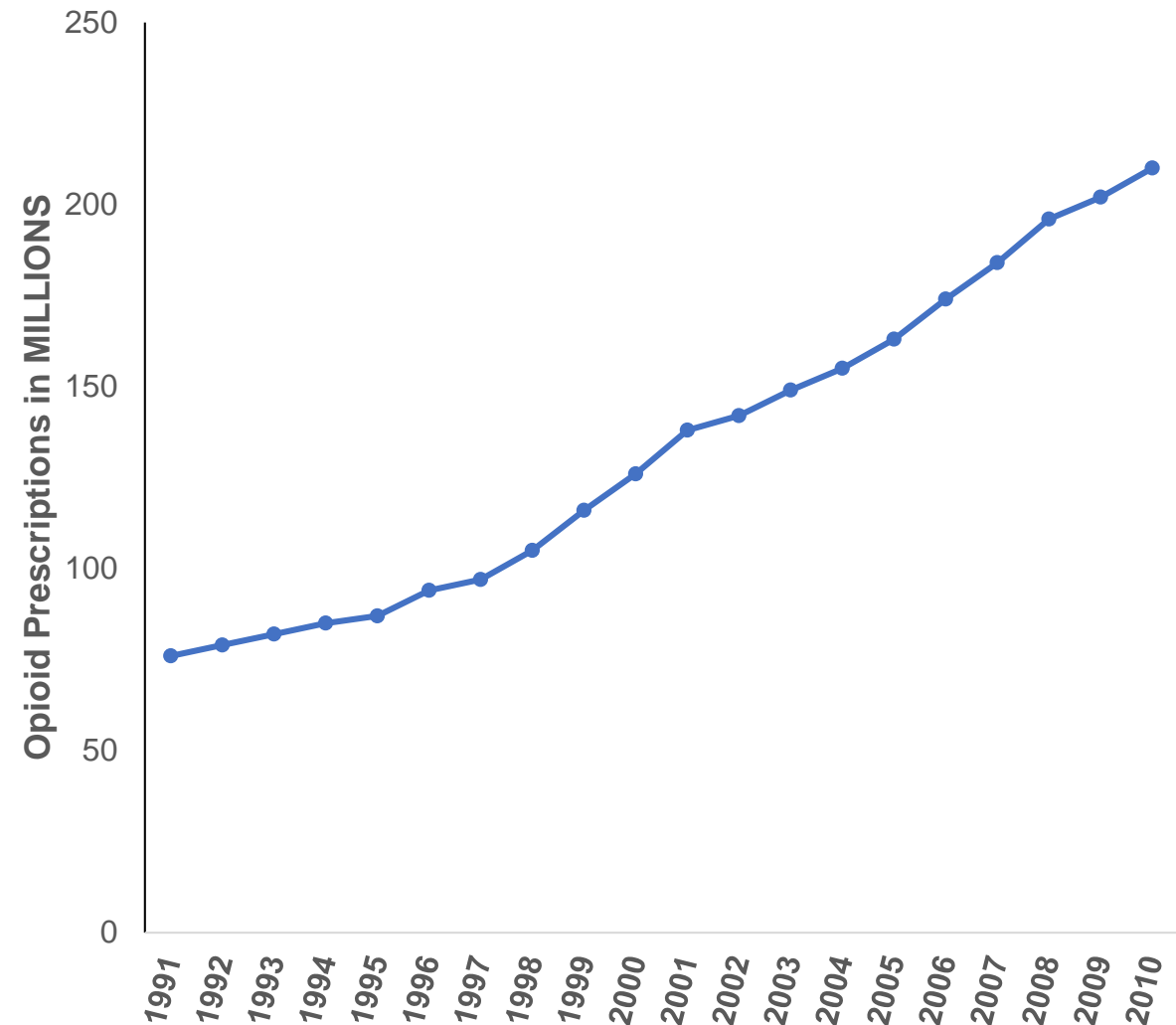


Note: Final and provisional data cannot be compared because final data includes deaths reported in US residents, whereas provisional data includes all deaths in the US including those in foreign residents. Provisional data is included here to provide a sense of what the final data may show.

Source: The Multiple Cause of Death data are produced by the Division of Vital Statistics, National Center for Health Statistics (NCHS), Centers for Disease Control and Prevention (CDC), United States Department of Health and Human Services (US DHHS).

Economics: Current Opioid Crisis Originated with Prescribing Increases

**Opioid prescriptions
*Tripled to MORE THAN
200 MILLION
prescriptions in the
2000's***



Solutions toward *Responsible Prescribing*: Guidance



Opioid Prescribing Guideline

November 4, 2022 CDC's updated Clinical Practice Guideline for Prescribing Opioids released:

The [2022 CDC Clinical Practice Guideline for Prescribing Opioids for Pain](https://www.cdc.gov/opioids/healthcare-professionals/prescribing/guideline/at-a-glance.html#print) is a clinical tool to help clinicians and patients work together to make informed, patient-centered decisions about pain care.

<https://www.cdc.gov/opioids/healthcare-professionals/prescribing/guideline/at-a-glance.html#print>

Dowell D, Ragan KR, Jones CM, Baldwin GT, Chou R. CDC Clinical Practice Guideline for Prescribing Opioids for Pain — United States, 2022. MMWR Recomm Rep 2022;71(No. RR-3):1–95. DOI: <http://dx.doi.org/10.15585/mmwr.rr7103a1>.

Continuation
Assessing risk and addressing
harms of opioid use

Challenges to tapering

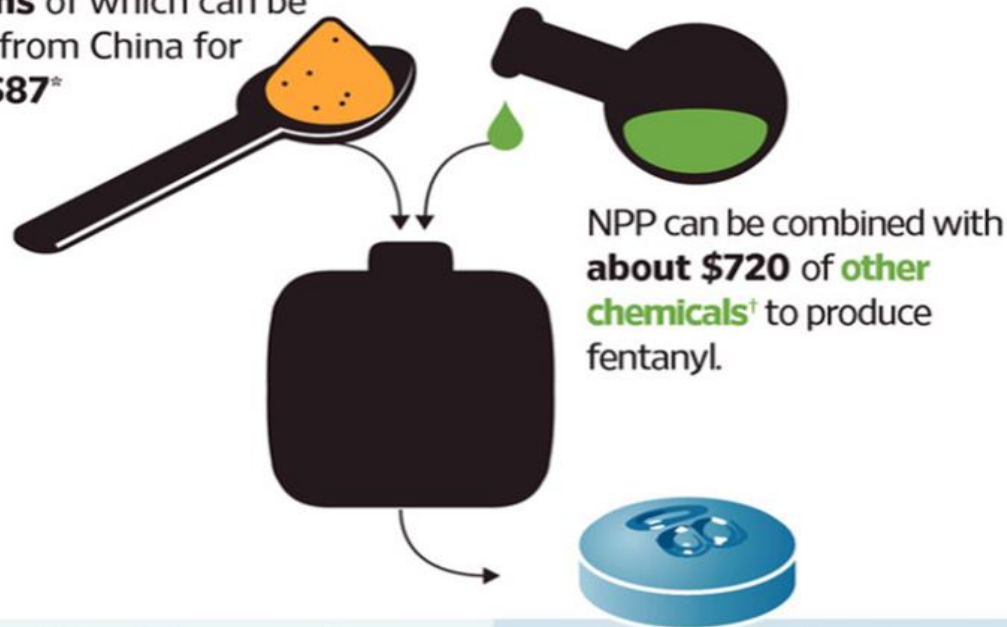
Dosage changes, particularly rapid reductions in dose, can harm patients or put them at risk if not made in a thoughtful, deliberative, collaborative, and measured manner.

Economic Drivers: Cheap precursors = fentanyl's dominance

Criminal Chemistry

Traffickers manufacturing fentanyl often purchase the key ingredient from China, which doesn't regulate its sale. Here's how the chemical building blocks become a highly profitable street drug.

The key ingredient is **NPP**,
25 grams of which can be
bought from China for
about **\$87***



**The resulting 25 grams of
fentanyl cost about \$810 to
produce...**

**...and are equivalent to up to
\$800,000 of pills on the black
market.**

*Average current price from Chinese suppliers

†Prices from U.S. suppliers

Sources: NES Inc.; Drug Enforcement Administration;
Calgary Police

THE WALL STREET JOURNAL.

September 27, 2021

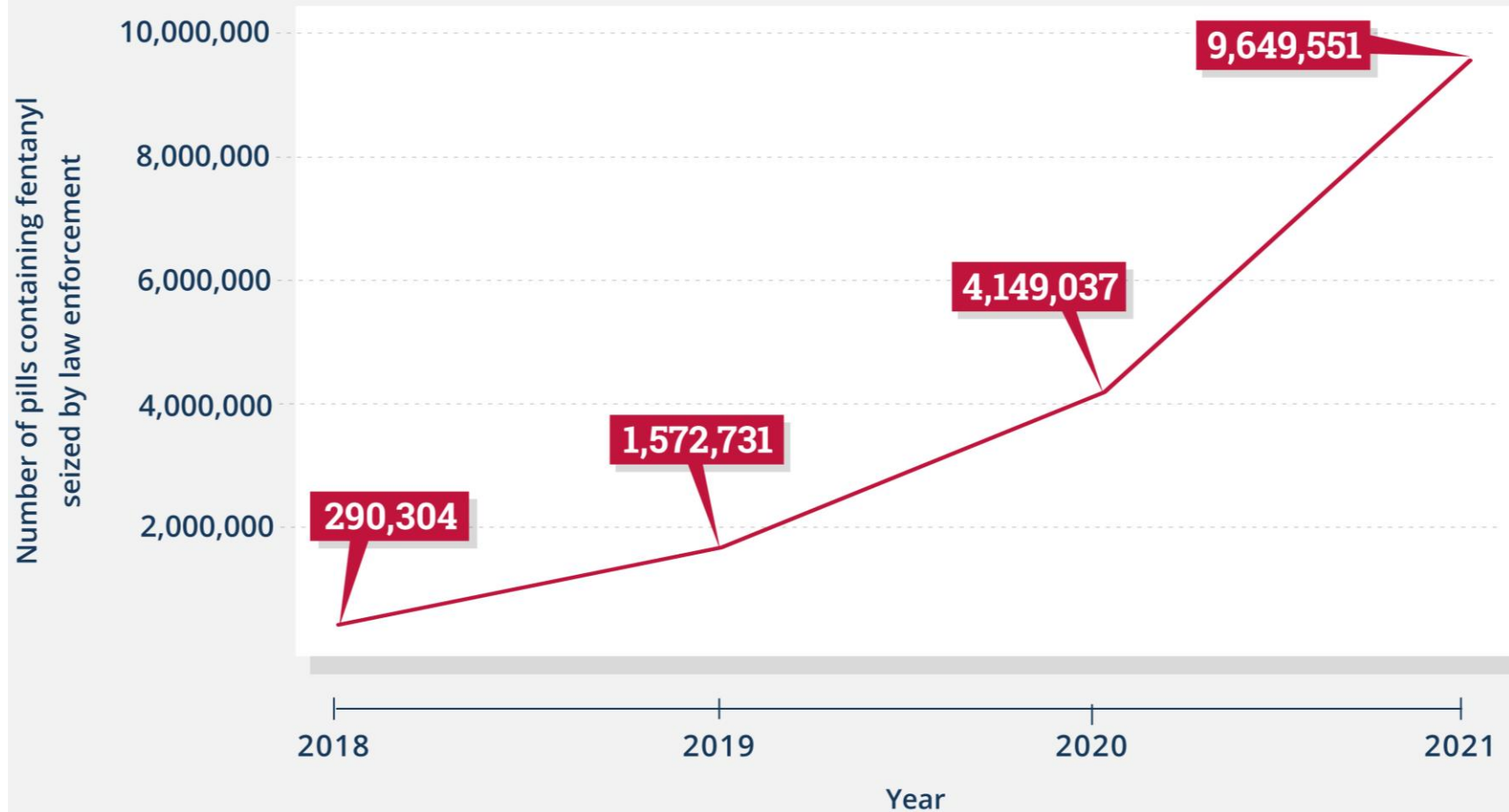
**DEA Issues Public
Safety Alert on Sharp
Increase in Fake
Prescription Pills
Containing Fentanyl
and Meth**



*DEA Warns that International and
Domestic Criminal Drug Networks are
Flooding the United States with Lethal
Counterfeit Pills*

<https://www.dea.gov/press-releases/2021/09/27/dea-issues-public-safety-alert>

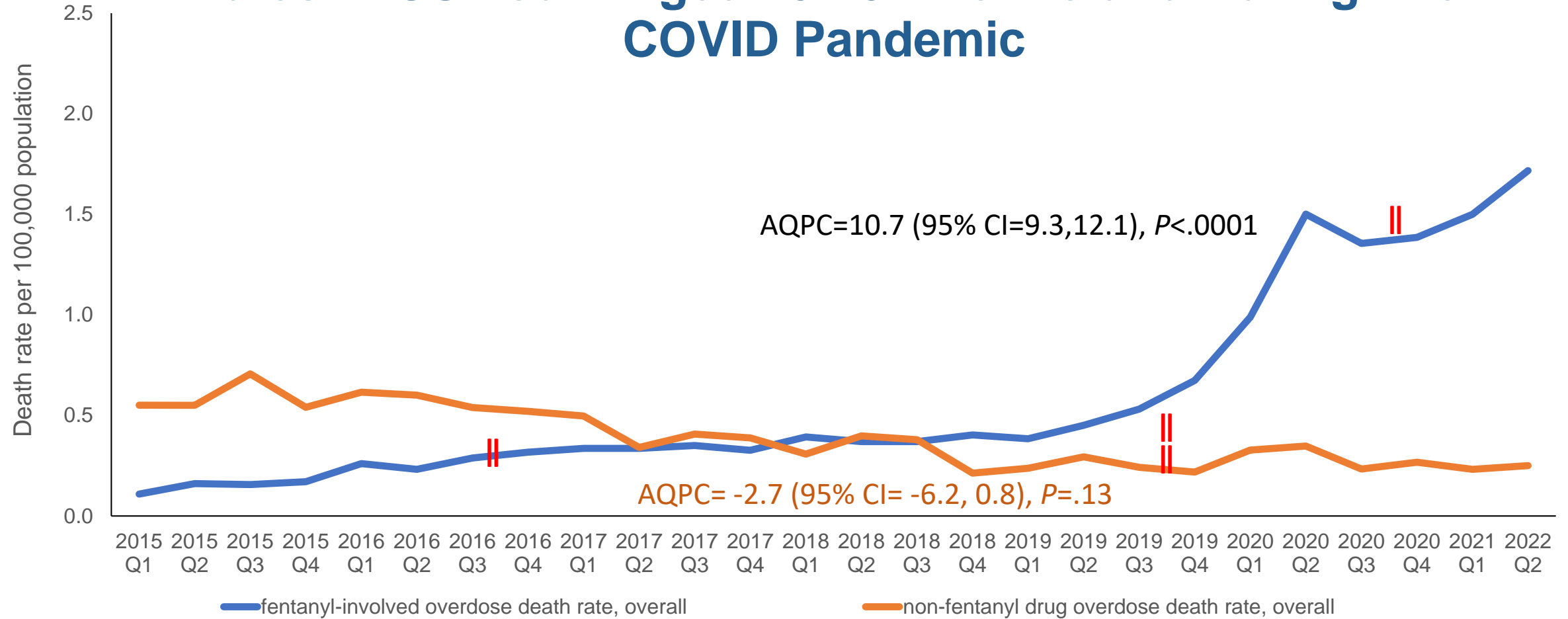
Number of Pills Containing Fentanyl Seized by Law Enforcement in the United States, 2018 – 2021



Estimates based on data reported by the Office of National Drug Control Policy's High Intensity Drug Trafficking Areas program

Reference: JJ Palamar, et al. *Drug and Alcohol Dependence*. DOI: 10.1016/j.drugalcdep.2022.109398 (2022)

Fentanyl-involved and Non-fentanyl Overdose Death Rates In US Youth Aged 15-19 Prior To and During The COVID Pandemic



National Vital Statistics System multiple-cause-of-death 2015-2020 final and 2021 provisional data U.S. census monthly data. **||**: Joinpoints indicate significant changes in nonlinear trends using Bayesian Information Criterion. AQPC=average quarter percentage change during 2015 Q1-2022 Q2. ICD-10 cause of death code: synthetic opioids other than methadone (T40.4, primarily fentanyl and analogs).

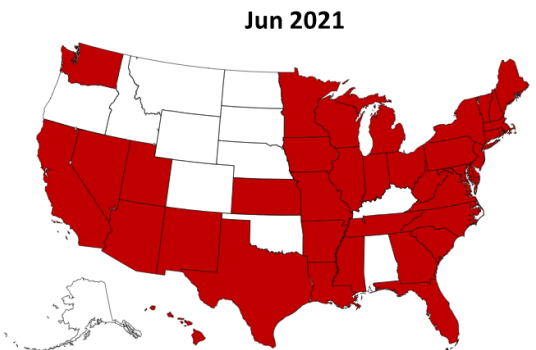
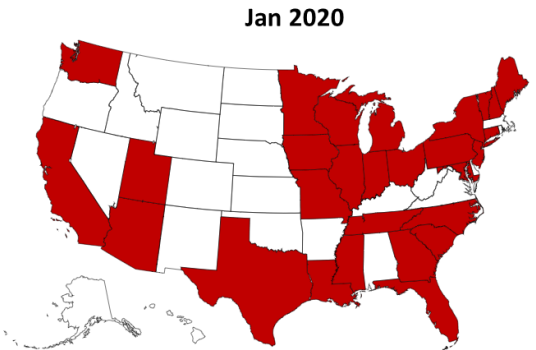
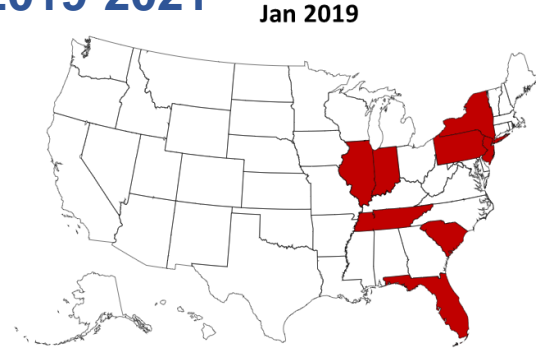
Illicit Drug Supply Evolves

States with at least one
positive xylazine detection,
2019-2021

Xylazine

- Alpha-2 adrenergic agonist used as a veterinary sedative
- Inhibits release of norepinephrine, decreasing sympathetic activity
- When combined with Fentanyl, it appears to extend the duration of their pharmacological effects (analgesia, respiratory depression, reward)
- Toxic doses in humans range from 40 to 2400 mg (0.6-34.3 mg/70 kg)
- Associated with severe tissue injury
- Appears nearly always in combination with fentanyl
- Not reversed by naloxone, but fentanyl is reversed by naloxone

Kacinko, S et al., *J Analytical Toxicology*, 46(8), 911-917.



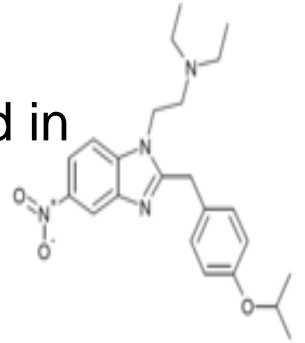
White House Office of National Drug Control Policy:
**FENTANYL ADULTERATED OR ASSOCIATED WITH XYLAZINE
RESPONSE PLAN** (released July 2023)

<https://www.whitehouse.gov/wp-content/uploads/2023/07/FENTANYL-ADULTERATED-OR-ASSOCIATED-WITH-XYLAZINE-EMERGING-THREAT-RESPONSE-PLAN-Report-July-2023.pdf>

Other drugs/contaminants also appearing...

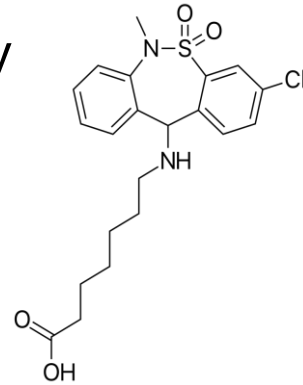
• Nitazenes

- July 2019—Isotonitazene found in U.S. toxicology and >250 overdose deaths
- August 2020—DEA classified isotonitazene as a Schedule I substance and listed in Annual Emerging Threat Report; other nitazenes (e.g., etonitazene and metonitazene) emerge
- Nitazenes detected postmortem in combination with other drugs, 2021



• Tianeptine

- Antidepressant drug that is not approved by the Food and Drug Administration (FDA). Clinical effects of tianeptine abuse and withdrawal can mimic opioid toxicity and withdrawal.
- Tianeptine exposure calls to U.S. poison control centers increased during 2014–2017, suggesting a possible emerging public health risk.
- Associated health effects included neurologic, cardiovascular, and gastrointestinal signs and symptoms, with some effects mimicking opioid toxicity and withdrawal.

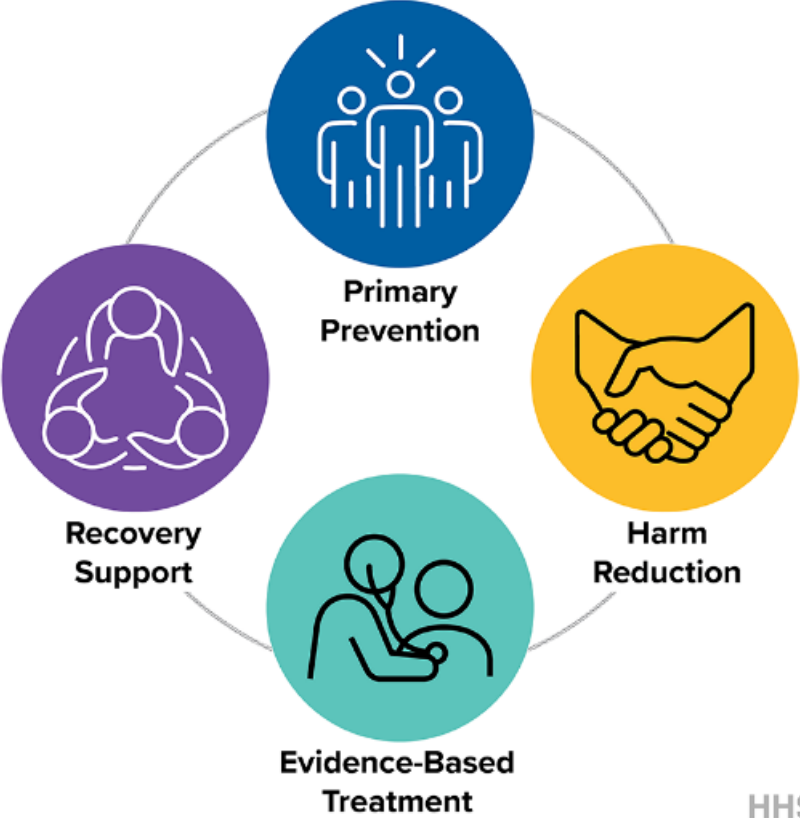


Point of care testing (e.g., urine drug screen for fentanyl or other opioids) does not detect nitazenes or tianeptine which require lab-based mass spectrometry testing that is not widely available.

Need for development of specialized detection assays?

U.S. Department of Health and Human Services (HHS): Overdose Prevention Strategy Pillars and Cross-Cutting Principles

HHS Overdose Prevention Strategy



HHS.gov

Cross-Cutting Principles

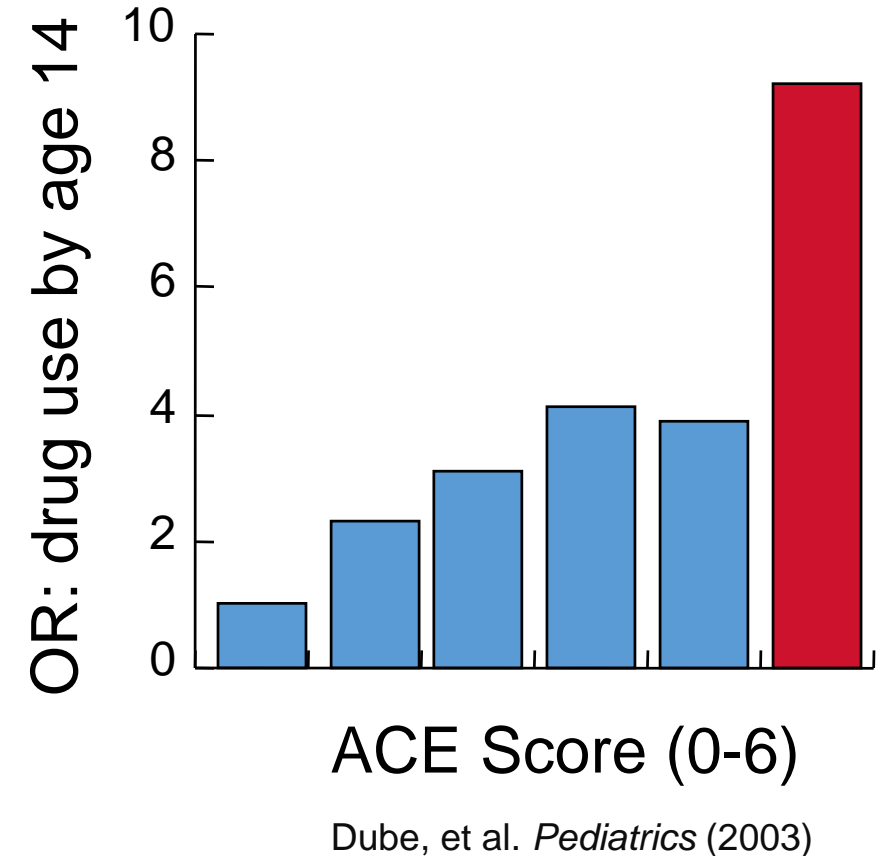
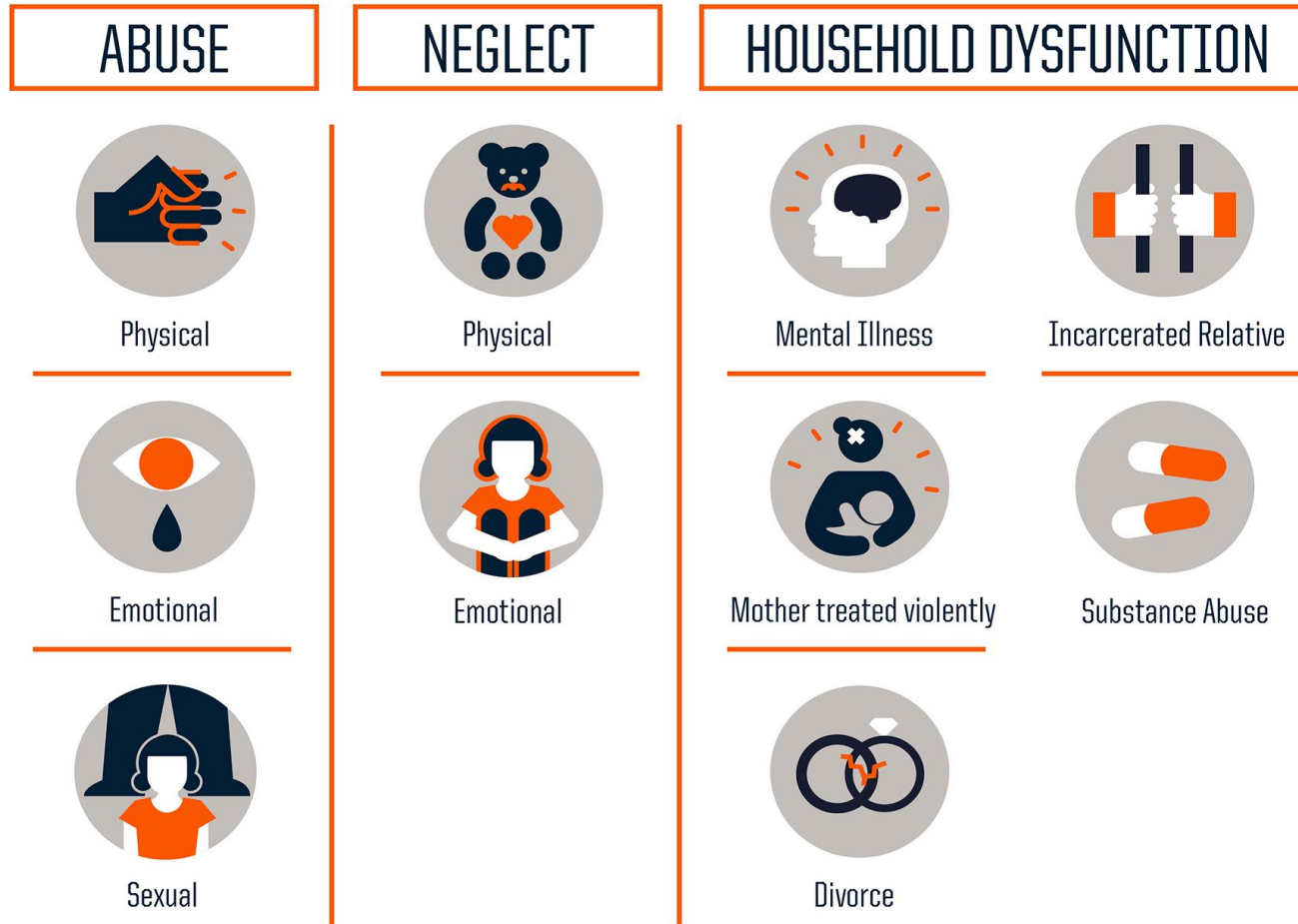
Equity

Data & Surveillance

Coordination, Collaboration & Integration

Reducing Stigma

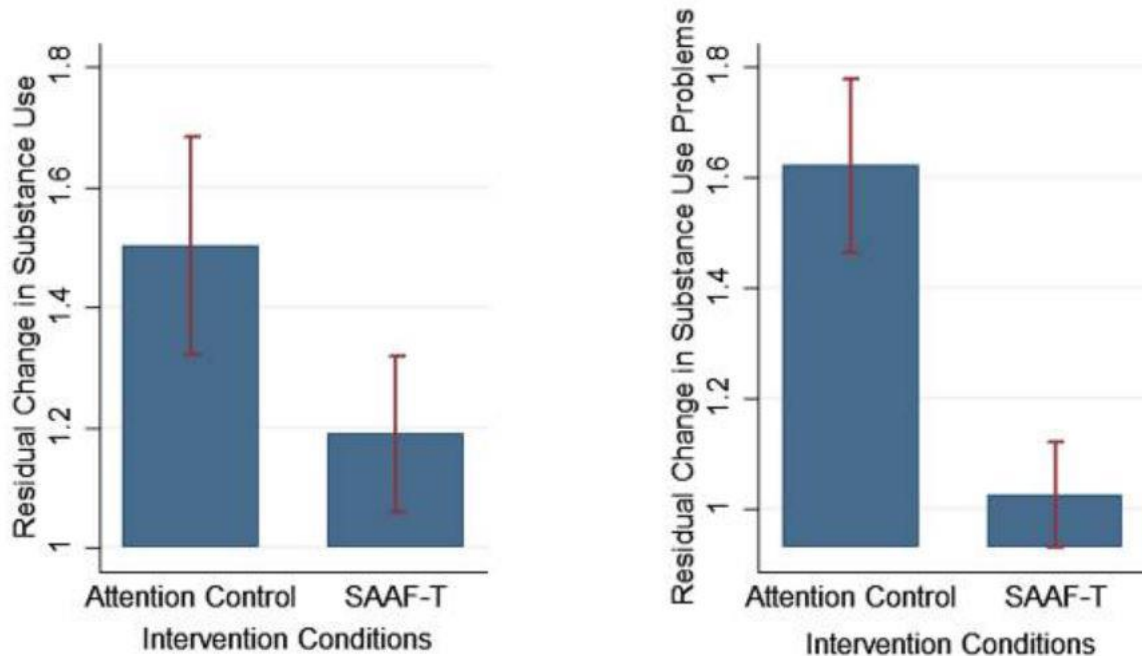
Social Determinants of Health (SDOH), including adverse childhood experiences, play a role in substance use and addiction.



ACE account for one half to two thirds of serious problems with drug use.

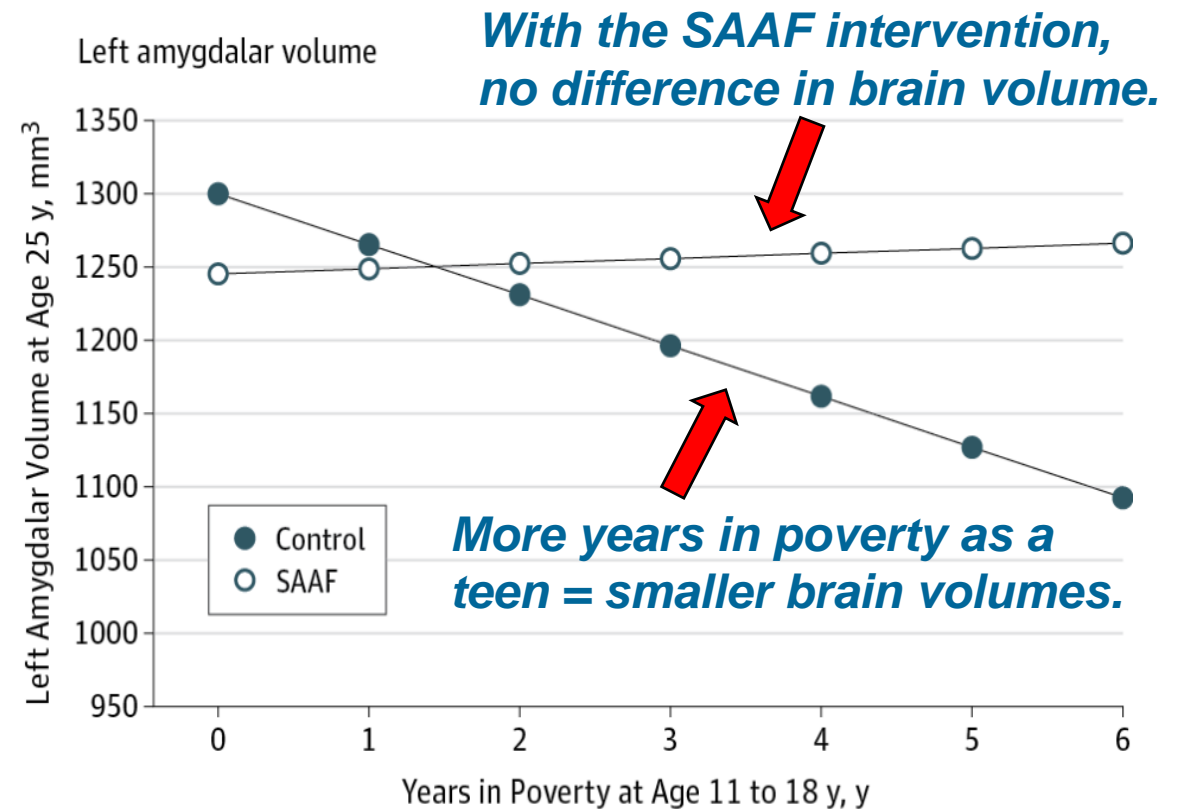
Modifying Environmental Risks:

A family-based intervention for teens reduces substance use and may help prevent changes in brain development associated with poverty.



SAAF=Strong African American Families intervention

[Brody, et al. Pediatrics \(2012\)](#)

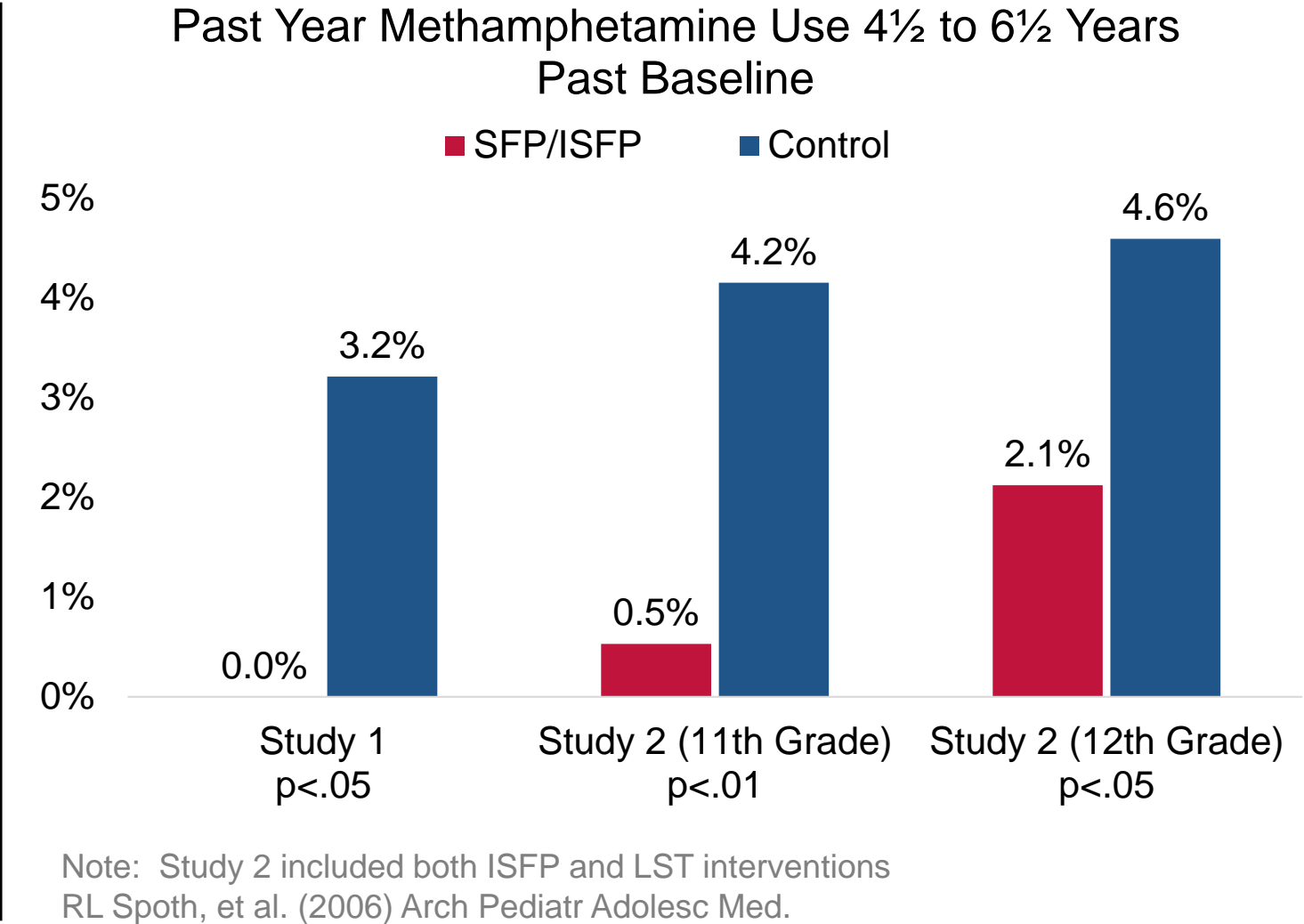


[Brody, et al. JAMA Pediatrics \(2017\)](#)

Universal Substance Use Prevention May Reduce Later Use of Opioids & Methamphetamine

Targeting Youth to Prevent Later Substance Use Disorder: An Underutilized Response to the US Opioid Crisis

WM Compton, CM Jones, GT Baldwin, et al.
AJPH. 2019;109:2185-S189.



Access to Naloxone

2014 FDA approves naloxone *autoinjector* with a prescription.

2015 FDA approves *nasal naloxone* spray with a prescription.

On March 29, 2023, FDA approved the first nasal naloxone spray available *without a prescription*.

On May 22, 2023, FDA approved *nalmefene nasal* spray with a *prescription*.

On July 28, 2023, FDA approved the first *generic* nasal naloxone spray *without a prescription*.

Inexpensive *injectable* naloxone widely available as well.

Making Addiction Treatment More Realistic And Pragmatic: The Perfect Should Not Be The Enemy Of The Good

Nora D. Volkow

“The magnitude of this crisis demands out-of-the-box thinking”

“Drug addiction is a chronic but treatable disorder with well-understood genetic and social contributors. It is not a sign of a person’s weakness or bad character.”

“Continued or intermittent use of drugs, even by people who know they have a disorder and are trying hard to recover from it, must be acknowledged as part of the reality of the disorder for many who struggle with it.”



New Harm Reduction Research Network

Goal: To increase our understanding of the effectiveness, implementation, and impact of existing and new harm reduction practices for people with SUD.

Priorities

- Novel harm reduction approaches
- Novel settings and modes of delivery
- Understanding and addressing barriers
- Ensuring access and benefits for vulnerable, understudied, and hard-to-reach populations
- Harm reduction for people who use methamphetamine and other stimulants

News Release

NIH launches harm reduction research network to prevent overdose fatalities

Scientists will test community-based approaches to prevent drug overdoses, curb high death rates

December 16, 2022

To address the overdose crisis in the United States, the National Institutes of Health has established a research network that will test harm reduction strategies in different community settings to inform efforts to help save lives. [The harm reduction research network's](#) efforts build on existing harm reduction research, and represent the largest pool of funding from NIH to date to study harm reduction strategies to address overdose deaths.

More than 107,000 people in the United States died from a drug overdose in 2021, according to provisional data from the U.S. Centers for Disease Control and Prevention. These deaths are largely driven by the proliferation of cheap, potent synthetic drugs like fentanyl contaminating the drug supply, including in heroin, cocaine, methamphetamine, and counterfeit pills.



NIDA Image

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Addressing the Stigma of Addiction



Drug and Alcohol Dependence

Volume 221, 1 April 2021, 108627



The role of stigma in physicians' treatment

Elizabeth M. Stone ^{a, b}  , Alene Kennedy-Hend
McGinty ^{a, b}

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<https://doi.org/10.1016/j.drugalcdep.2021.108627>

Highlights

- National survey of U.S. primary care physicians (PCPs) reported high levels of physician burnout and substance use disorder.

 Nora's Blog

Punishing Drug Use Heightens the Stigma of Addiction


August 9, 2021 By Dr. Nora Volkow

This essay was originally published by STAT  on August 3, 2021.

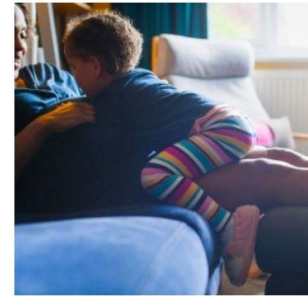


Photo by

February 15, 2023 By Dr. Nora Volkow

*This blog was also published in
STAT  on February 8, 2023.*

Though it may be hard for many to fathom, even pregnant people and new parents can have active substance use disorders. They need support, not criminalization.



©Get

The addiction and overdose crisis, which now claims **more than 100,000 lives a year**, shows little sign of abating, and emerging a startling impact on pregnant people: Overdose is now a **leading cause of death** or shortly after pregnancy.


While attitudes around drug use, particularly use of substances significantly changed in recent decades, the use and possession to be penalized. Punitive policies around drugs mark people wh

Columbia University researchers recently reported that drug overdose deaths among pregnant and postpartum people **increased by 81%** between 2017 and September 2022, the Centers for Disease Control and Prevention **reveals** that deaths related to mental health conditions, including substance use disorders (SUDs), account for **23% of deaths** during pregnancy or in the year following birth. Other leading causes of death include excessive bleeding, cardiovascular conditions, or other well-known complications of pregnancy.

 Nora's Blog

Pregnant People With Substance Use Disorders Need Treatment, Not Criminalization

February 15, 2023 By Dr. Nora Volkow

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Though it may be hard for many to fathom, even pregnant people and new parents can have active substance use disorders. They need support, not criminalization.

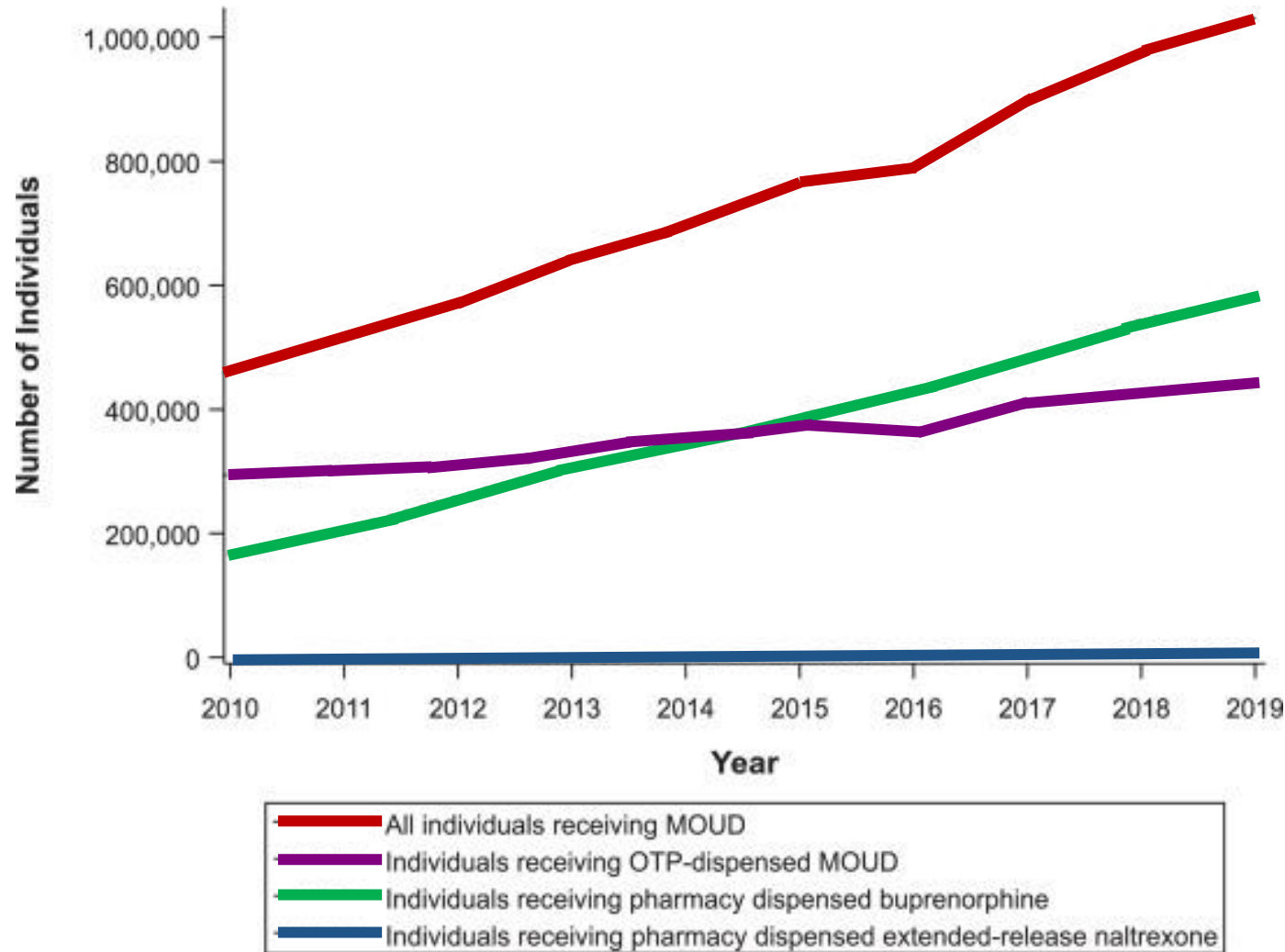
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Breaking Down the Stigma of Addiction: A Witness' Story Through Art



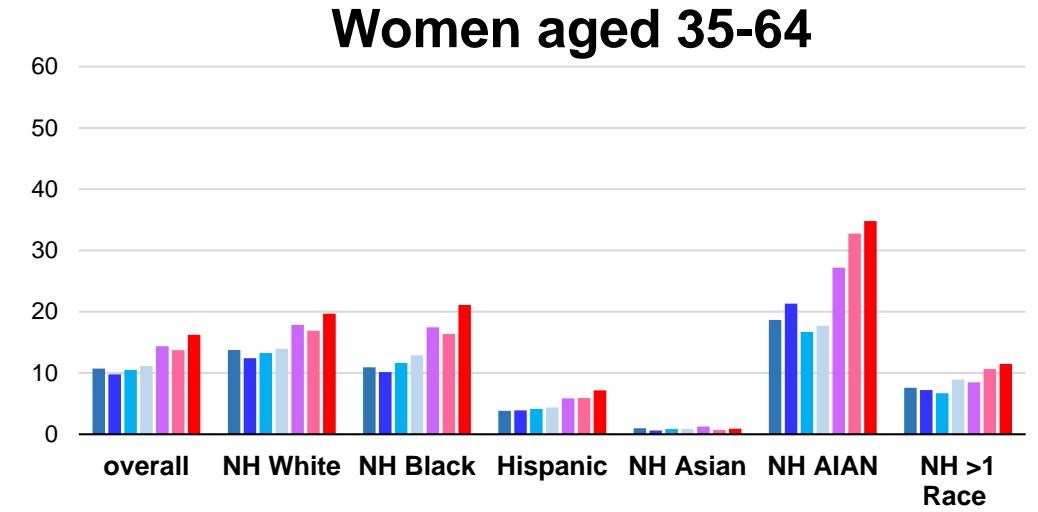
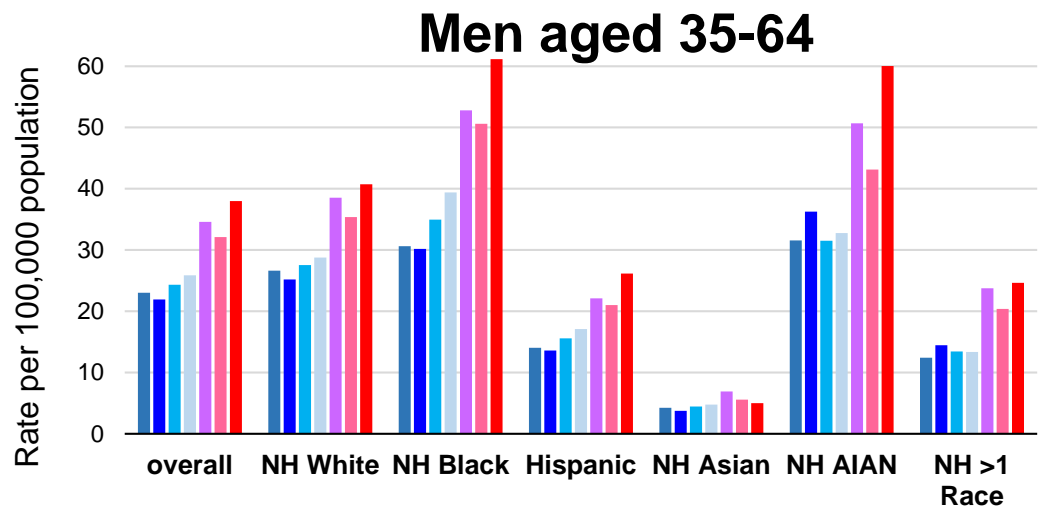
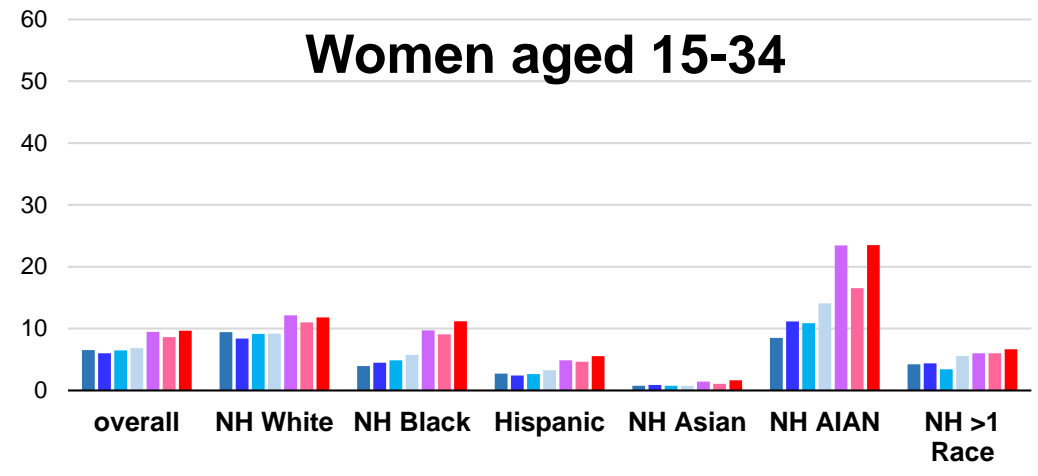
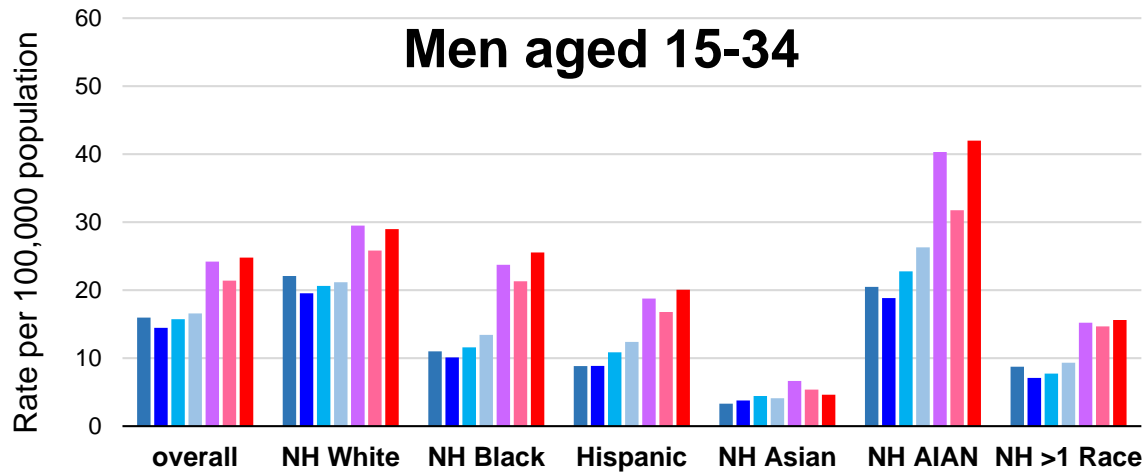
Medication treatment of OUD in the US increased from 2010 to 2019; But treatment gap is still very large



- Estimated annual prevalence of 7,631,804 individuals suffering from OUD (2723.5/100 000) in 2019
- Estimated number of individuals receiving medications for OUD 1,031,785 (368.2/100 000) in 2019
- Though MOUD treatment has increased in past 10 years **in 2019 still only 13.4% of individuals with OUD received MOUD.**



Overdose rates rose sharply for all, but especially among older Black men and AI/AN persons during the pandemic.



■ Mar-Aug 2018

■ Sep 2018-Feb 2019

■ Mar-Aug 2019

■ Sep 2019-Feb 2020

■ Mar-Aug 2020

■ Sep 2020-Feb 2021

■ Mar-Aug 2021

Han et al., JAMA Network Open, 2022

COVID-Related Temporary Policy Changes for Prescribing MOUD



Buprenorphine (available by Rx at pharmacies)

Before COVID

- BUP prescribing limited to clinicians holding X-waivers based on DEA registration and training.
- Per physician cap on the number of patients treated with BUP at a given time.
- In-person eval required for initiation.

During COVID

- Telehealth (including audio-only) allowed for initiation and follow-up.

Methadone (available only at OTPs)

Before COVID

- In-person eval at OTP required for initiation.
- In-person daily dosing required for most patients.

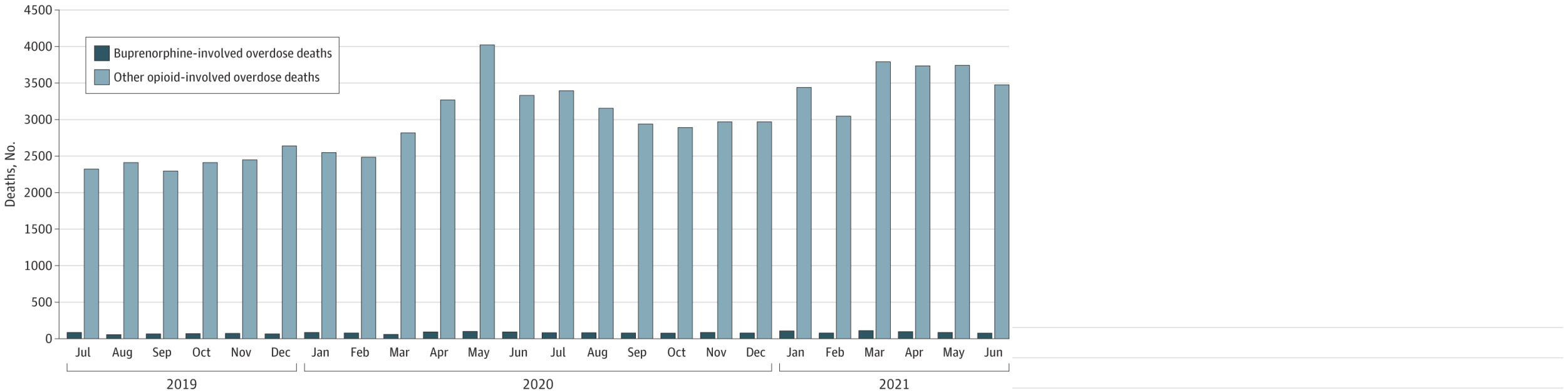
During COVID

- Up to 28 take-home doses for stable patients
- Up to 14 days for less stable patients



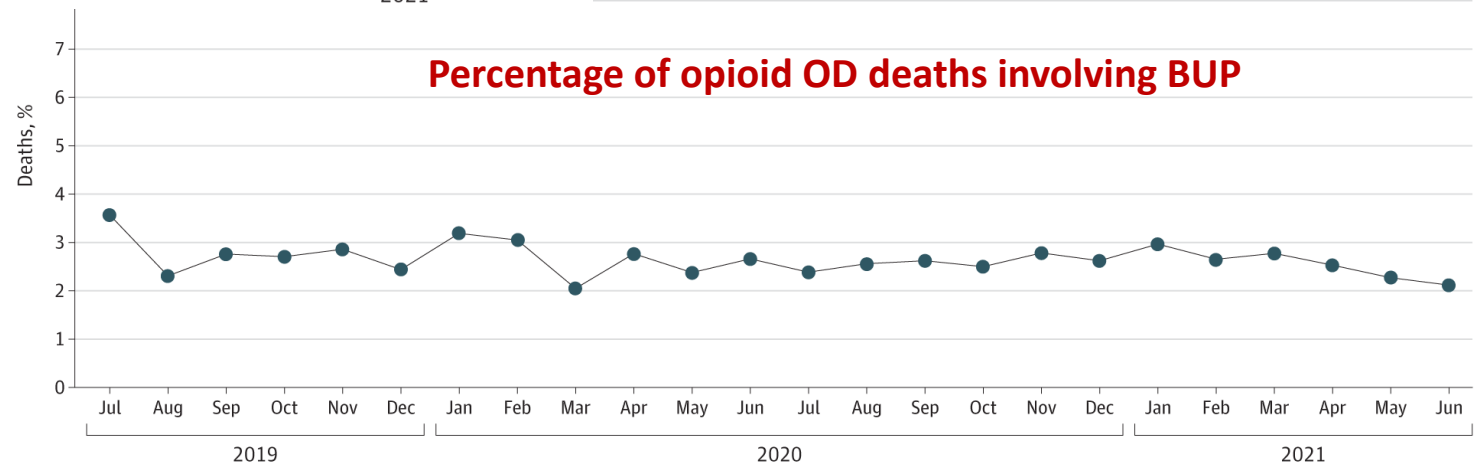
Buprenorphine-involved overdoses remained rare and did not increase as a percentage of opioid deaths.

BUP- and other opioid-involved deaths

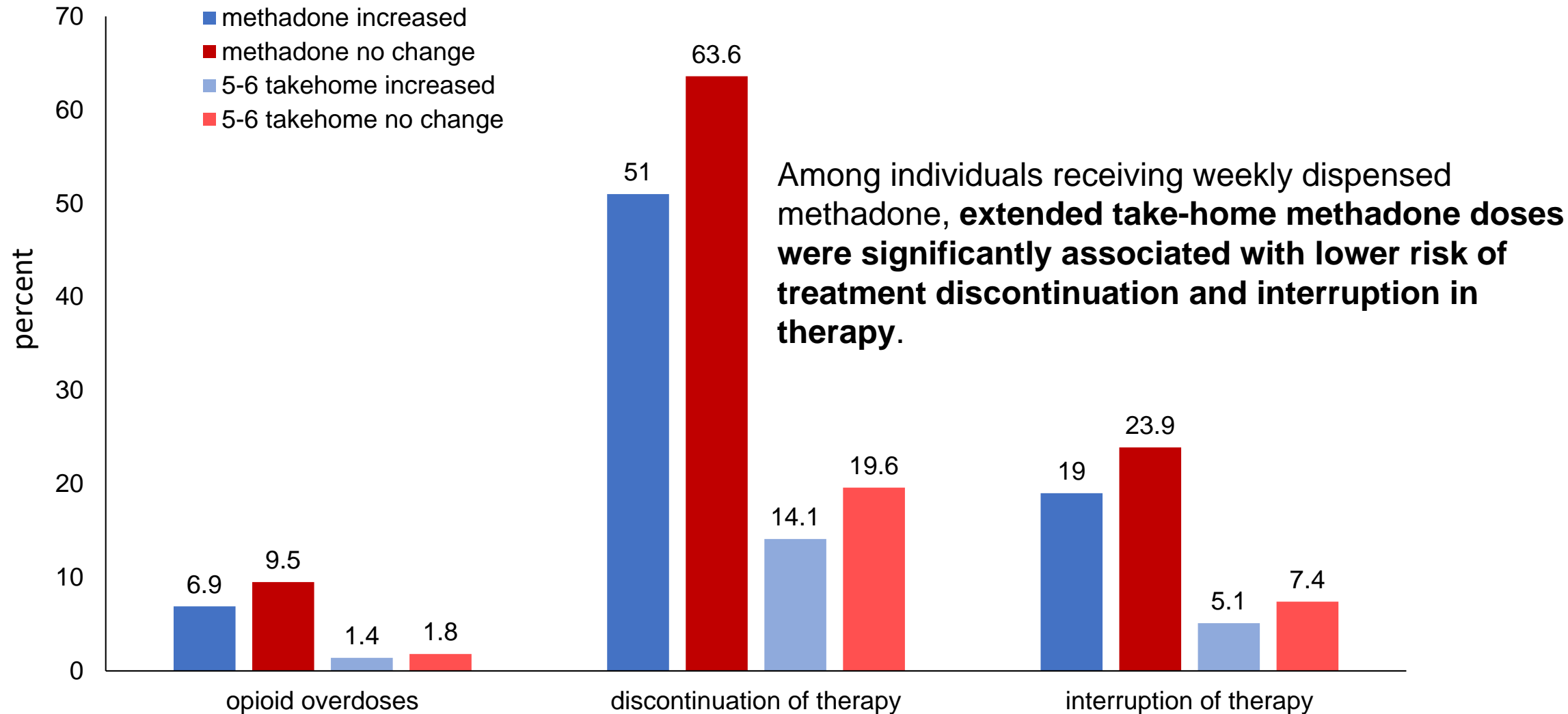


[Tanz, et al. JAMA \(2023\)](#)

Percentage of opioid OD deaths involving BUP



Take-Home Doses of Methadone Therapy Associated with Improved Outcomes



Telehealth Services, Receipt and Retention of Medications for Opioid Use Disorder (MOUD), and Medically Treated Overdose (OD) Among Medicare Beneficiaries Before and During the COVID-19 Pandemic

Characteristics Associated With MOUD Retention for at Least 80% of Eligible Days Among Beneficiaries With OUD and MOUD

Characteristic	aOR (95% CI) ^b
Total, No.	8826
Receipt of OUD-related telehealth service	1.267 (1.139-1.410) ^c

Characteristics Associated With Experiencing A Medically Attended OD During Study Period Among Beneficiaries With OUD

Characteristic	aOR (95% CI) ^b
Total, No.	70 497
Receipt of OUD-related telehealth service	0.671 (0.634-0.710) ^c

Source: Jones CM, Shoff C, Hodges BS, Blanco C, Losby JL, Ling SM, Compton WM. *JAMA Psychiatry*. 2022;79(10):981-992

Characteristics Associated With Experiencing A Fatal Drug OD During Study Period Among Beneficiaries With OUD

Characteristic	Beneficiaries, No. (%)	aOR (95% CI) ^b
Receipt of OUD-related telehealth service	13 809 (19.6)	0.67 (0.48-0.92) ^c

Source: Jones CM, Shoff C, Hodges BS, Blanco C, Losby JL, Ling SM, Compton WM. *JAMA Psychiatry*. 2023;80(5):508–514

NIDA Research pivots to address substance use and overdose trends.

- Treating OUD in the **fentanyl** era
 - Implementation and services research to expand MOUD
 - Therapeutic development: novel medications, immunotherapies, neuromodulation
 - Alternative outcomes: craving, sleep, OUD severity
- Therapeutics for StUD, **polysubstance** UD, co-morbidities
- Novel overdose treatments, including for stimulant OD
- **Prevention** of substance use and addiction
 - Social Determinants of Health
 - Pre-addiction
- **More timely data** on fatal and non-fatal overdoses, use patterns of emerging drugs (e.g., nitazenes, xylazine) and drug mixtures
- Harm reduction approaches and outcomes
- Recovery approaches and outcomes



Implementation Science: CTN, JCOIN, HCS, Prevention



Enhancing the National Drug Abuse Treatment Clinical Trials Network to Address Opioids Expand research conducted by NIDA CTN to address emergent needs presented by the opioid crisis.

Justice Community Opioid Innovation Network Study quality care for OUD in justice populations. Help create partnerships between local and state justice systems and community-based treatment providers.

HEALing Communities Study is investigating coordinated approaches for deploying evidence-based strategies to prevent and treat OUD in 67 communities in 4 states.

Developing Novel Approaches

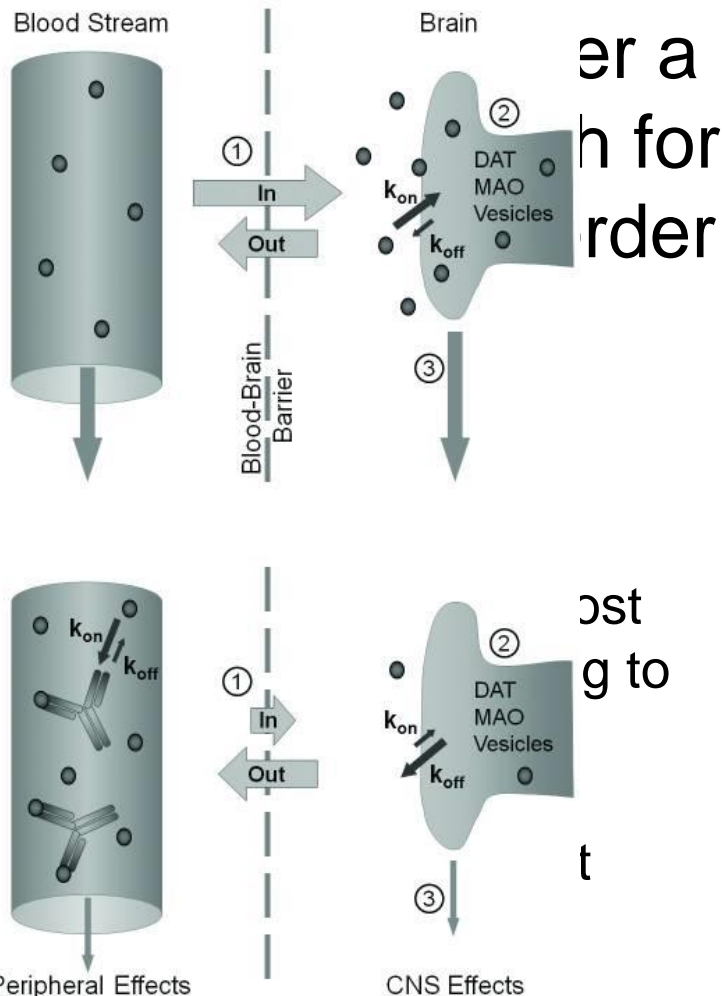
Vaccines and mAB

ADAPT-2
Meth Effects in
the Brain

BEFORE anti-
meth antibody
treatment

AFTER Anti-
meth antibody
treatment

- No FDA approved stimulant
- Contingency management is effective treatment
- Implementing NIDA priority development stimulant

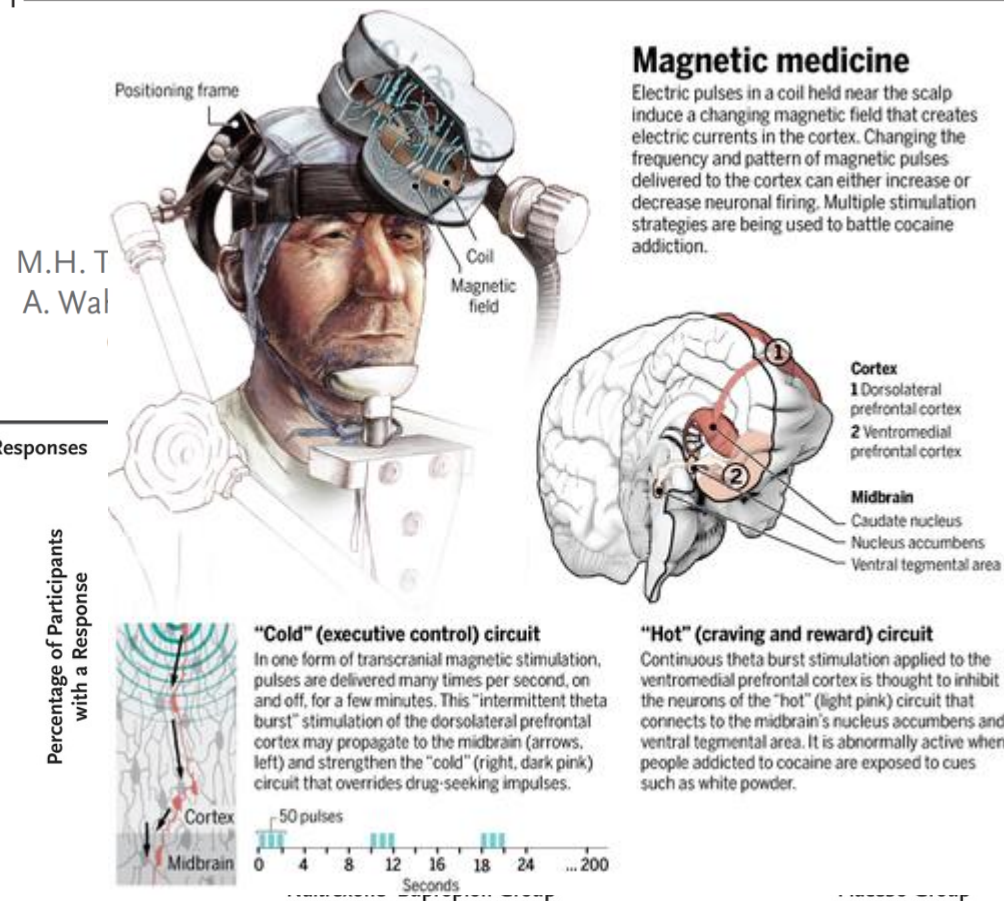


WB Gentry, et al. (2009) Human Vaccines

Transcranial Magnetic Stimulation

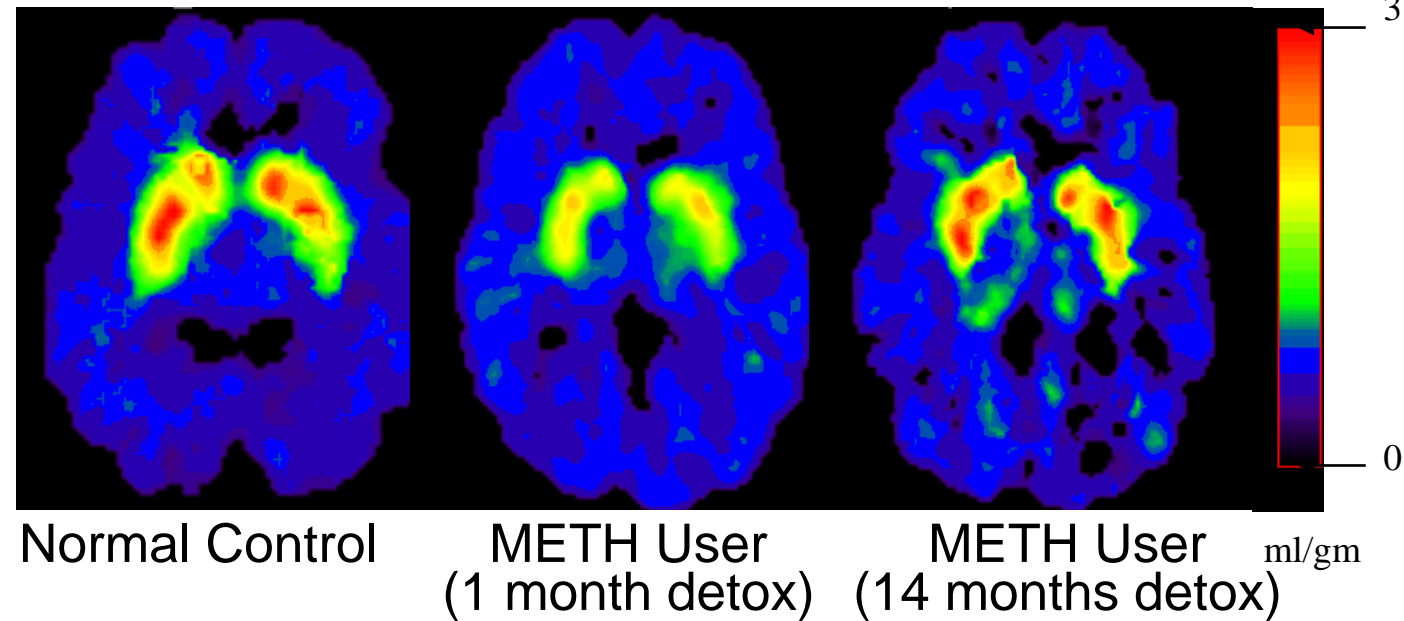
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

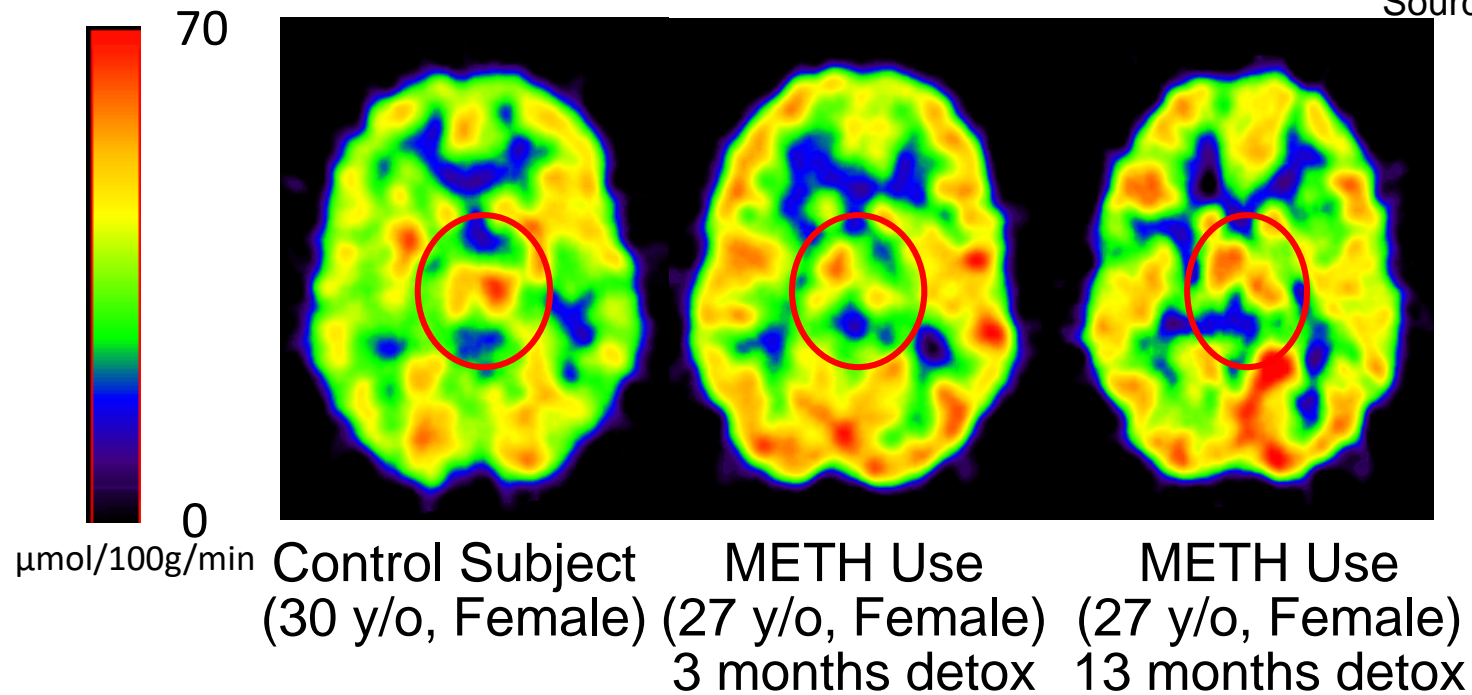


M Wadman, (2017) Science

Recovery is Possible:



Source: Volkow, ND et al., *Journal of Neuroscience* 2001



G-J Wang et al., *Am J Psychiatry* 2001

Improvements in Brain Metabolism with Prolonged Abstinence from Methamphetamine Use

Take Home Key Messages

- As the opioid epidemic continues to evolve—increases seen in synthetic opioids and polysubstance use, including opioid co-involvement with methamphetamine use
- The COVID-19 pandemic has exacerbated the overdose crisis
- Treatment addresses the underlying neurobiology of addiction: Treatment saves lives
- New tools and targets show promise; prevention is essential
- Reducing stigma and harm reduction approaches are critical components of the HHS Overdose Prevention Strategy