

Next Steps in *Public Health for Opioid Use Disorder*

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Disclosures: Wilson M. Compton, MD, MPE

Long-term Stock Equity:

- 3M Companies (under \$5,000)
- General Electric Corporation (under \$5,000)
- Pfizer, Inc. (under \$5,000)

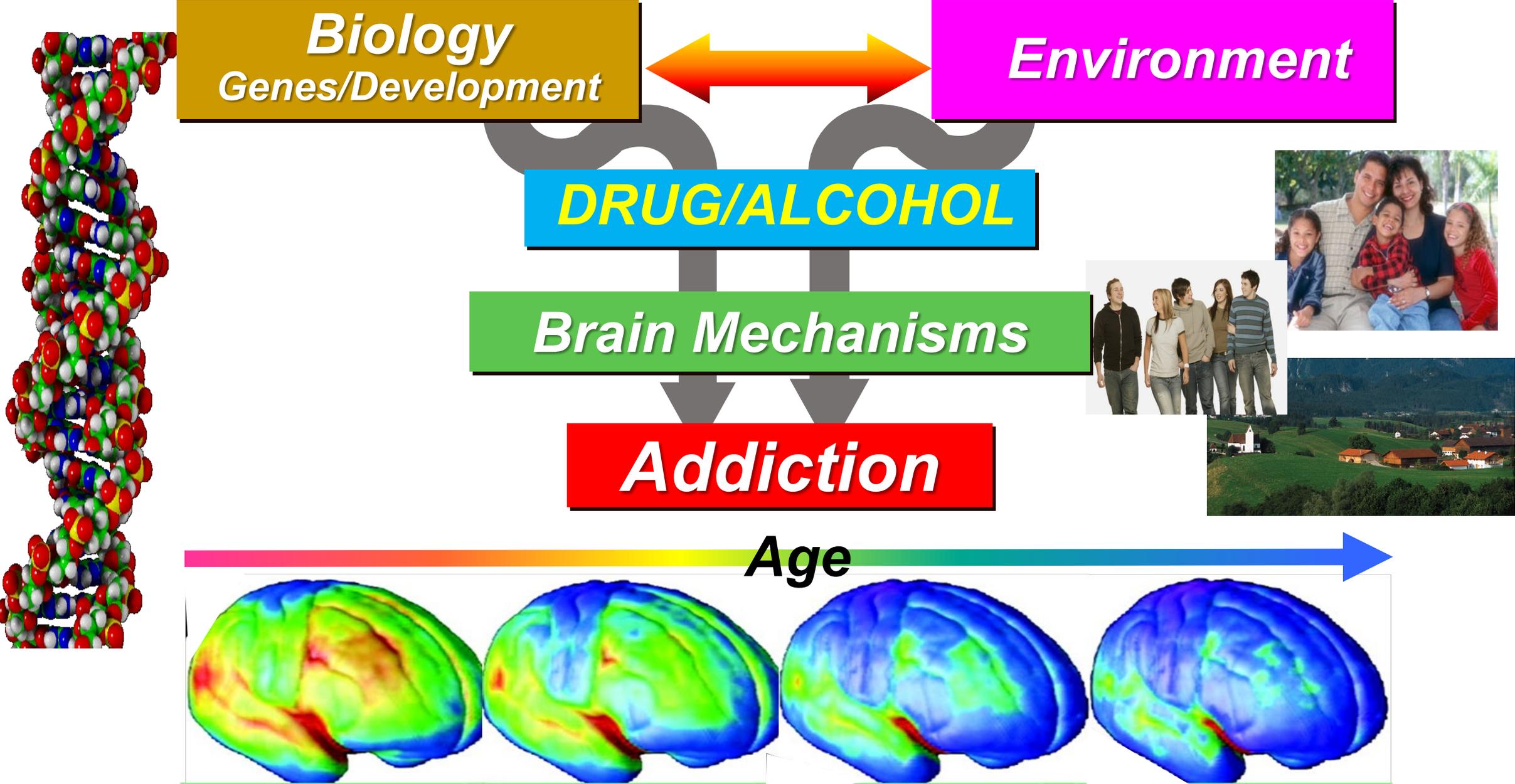
Speaker's Bureau(s): None

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Consulting Relationships: None

Current Position: Deputy Director, National Institute on Drug Abuse

ADDICTIONS as Diseases of *Gene-Environment-Development*

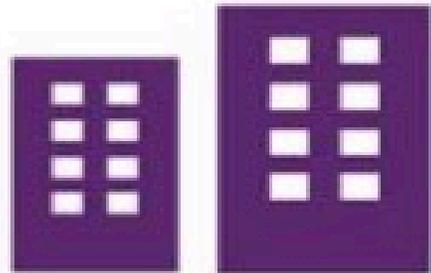


SOCIAL DETERMINANTS OF HEALTH

The social determinants of health are the conditions in which we are born, we grow and age, and in which we live and work. The factors below impact on our health and wellbeing.



Childhood experiences



Housing



Education



Social support



Family income



Employment



Our communities



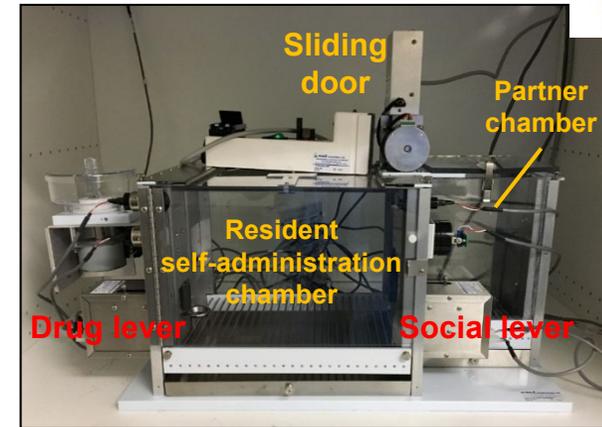
Access to health services

Source: NHS ***The wider set of forces/systems shaping the conditions of daily life***

Social Factors Influencing Drug Use

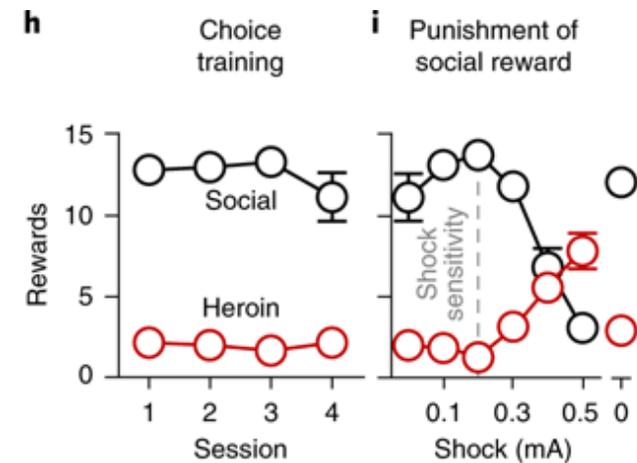


James Nachtwey. *TIME* Special Report



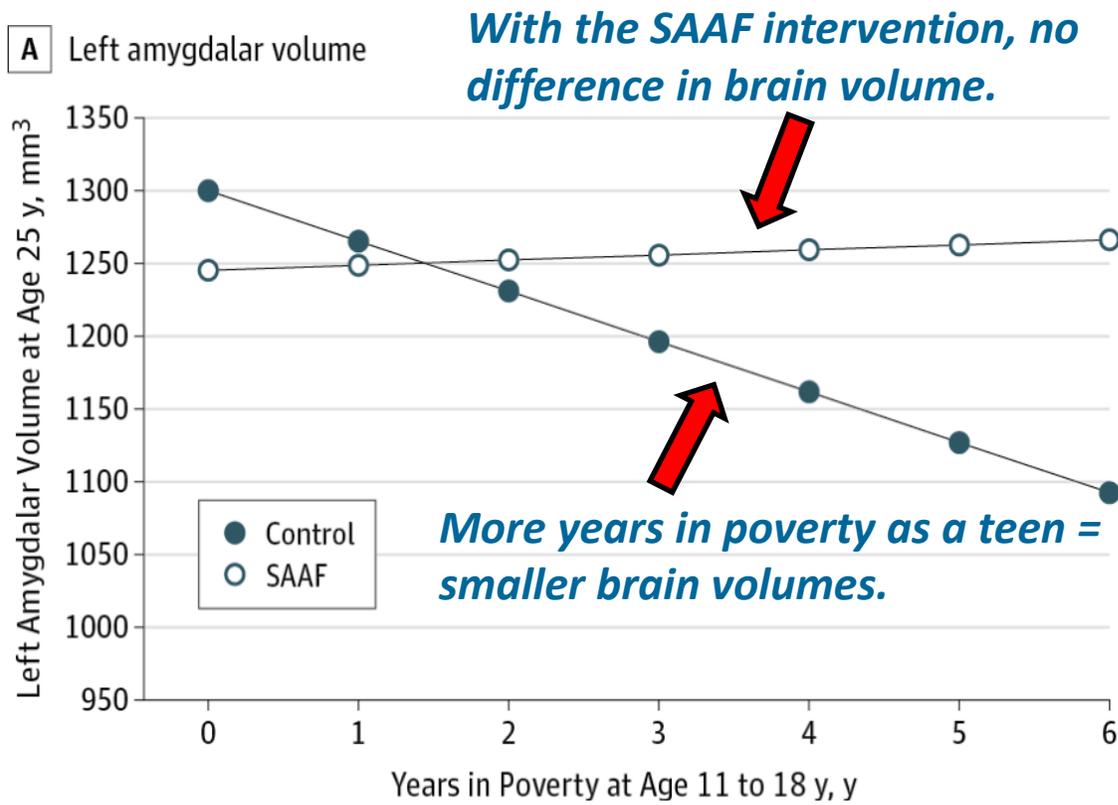
Veniro et al., 2018

HEROIN



The Environment Matters

A Family-Based intervention for young teenagers may help brain development



Brody GH, et al. *JAMA Pediatr*, 2017.

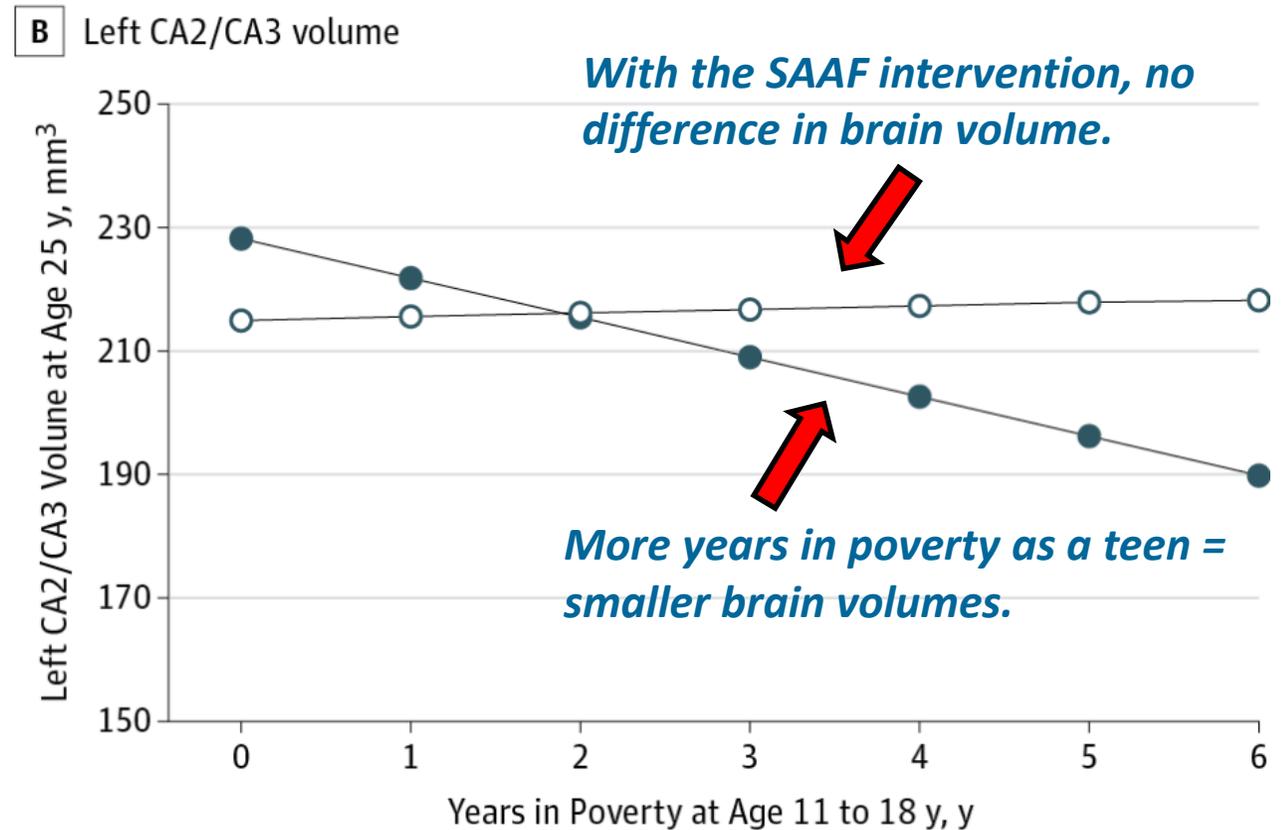


Figure: *Effect of Family Poverty on Youth Brain Region by Intervention Status.*
SAAF=Strong African American Families intervention.

U.S. Drug Overdose Deaths

70,630 Deaths in 2019—49,860 from Opioids*

93,398 Deaths in 2020—69,769 from Opioids*

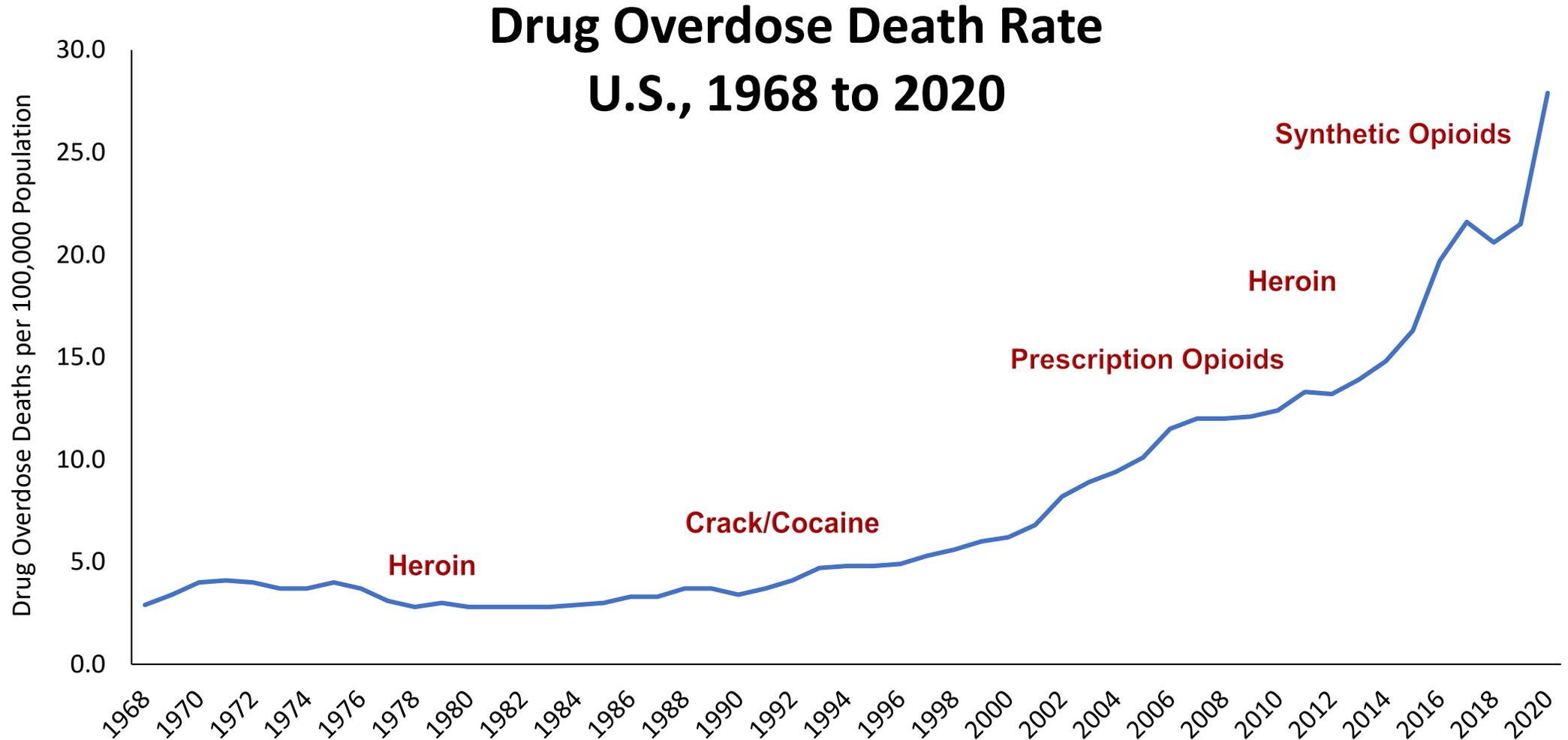
107,622[^] Deaths in 2021—80,816 from Opioids*

[^]Provisional data (predicted values) released May 2022

*Opioids include both illicit and prescription opioids

National Center for Health Statistics, National Vital Statistics System, mortality data

40 Year Exponential Increases in U.S. Overdose Deaths



See: Jalal, et al. Science 2016, and Compton, Einstein, Jones. International Journal of Drug Policy. 2022.

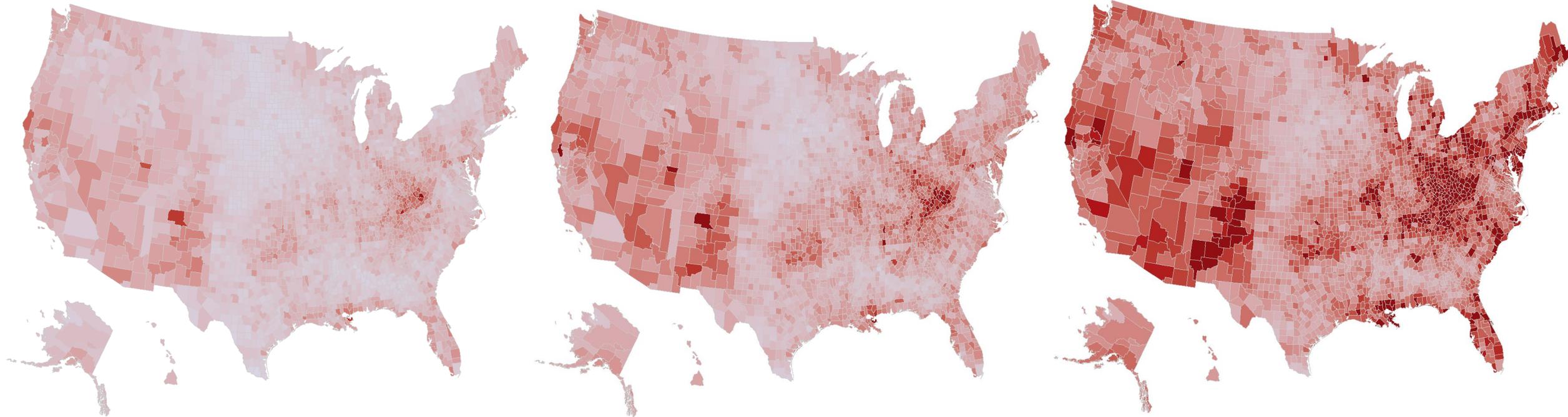
Virtually All U.S. Regions Have Increased Drug Overdoses

Estimated Age-adjusted Death Rates per 100,000 for Drug Poisoning by County

2003

2013

2020



Model-based Death Rate

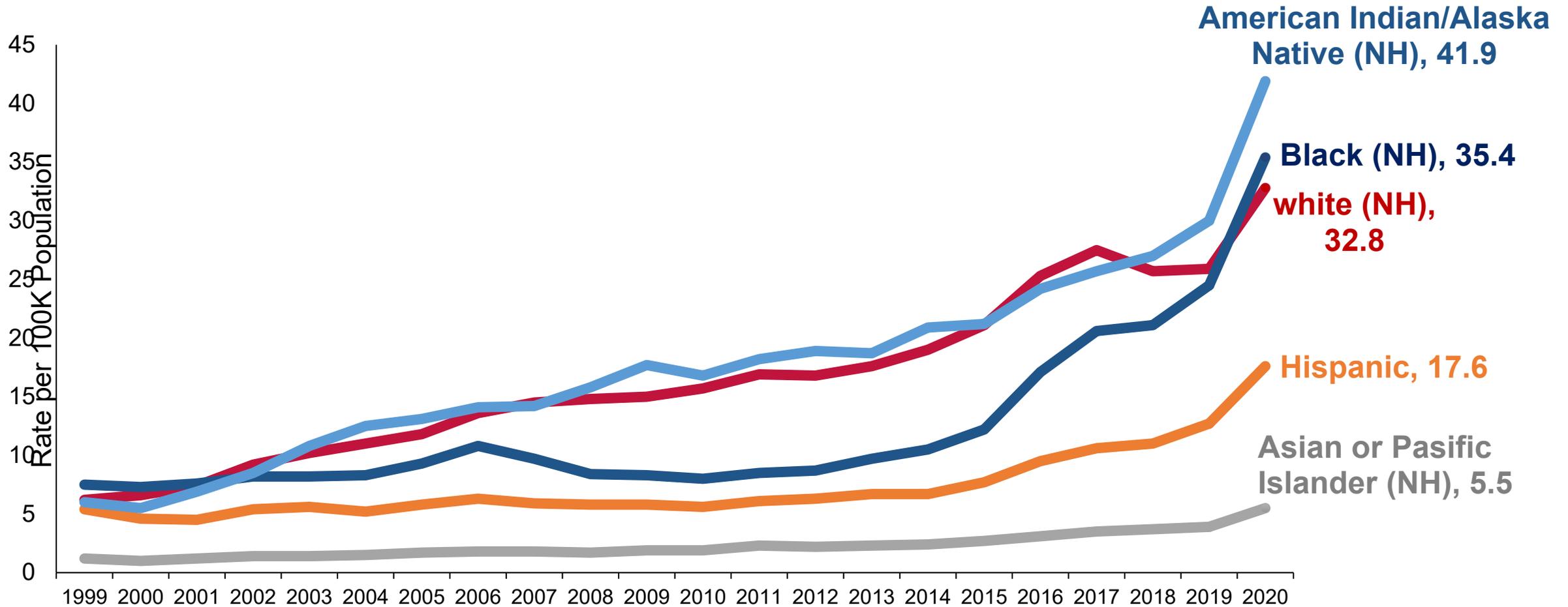
0.00



40.00

+

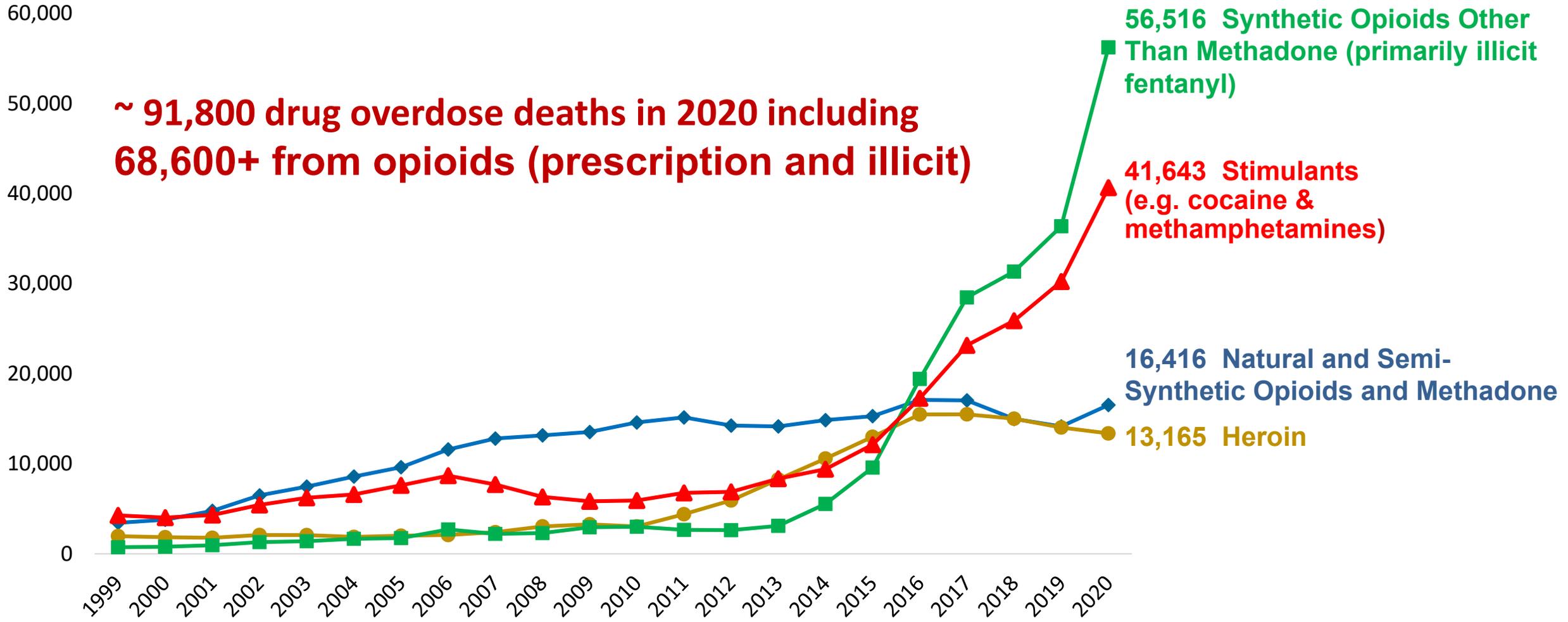
Drug Overdose Death Rates by Race/Ethnicity



NCHS, National Vital Statistics System. Estimates for 2020 are based on final data.

Evolution of Drivers of Overdose Deaths:

Analgesics ➡ **Heroin** ➡ **“Fentanyl”** ➡ **Stimulants**



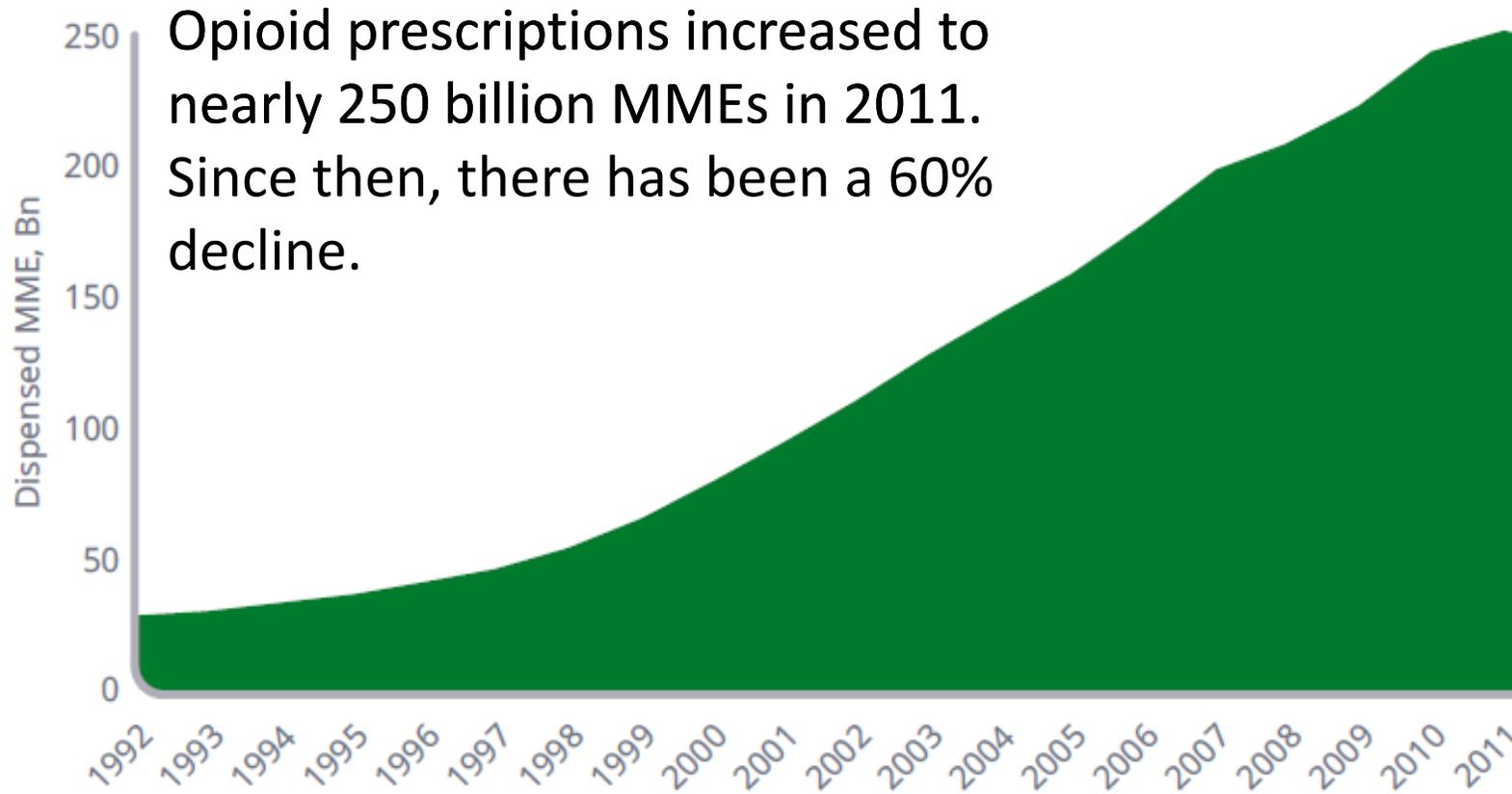
Drug Overdose Deaths* Increased in 2021

	ALL DRUGS	HEROIN	NAT & SEMI SYNTHETIC	METHADONE	SYNTHETIC OPIOIDS (mainly illicit fentanyl)	COCAINE	OTHER PSYCHO-STIMULANTS (mainly meth)
12/2020*	93,655	13,437	13,722	3,620	57,834	19,927	24,576
6/2021	101,850	11,157	13,928	3,770	65,453	21,469	29,576
12/2021*	107,622	9,137	13,503	3,612	71,238	24,538	32,856
Percent Change 12/20-12/21	14.9%	-32.0%	-1.6%	-0.02%	23.2%	23.1%	33.7%

*NCHS Provisional drug-involved overdose death counts are PREDICTED VALUES, 12 months ending in select months.

<https://www.cdc.gov/nchs/nvss/vsrr/drug-overdose-data.htm>

Environmental Availability: Prescribing Increases Contributed to Opioid Crisis

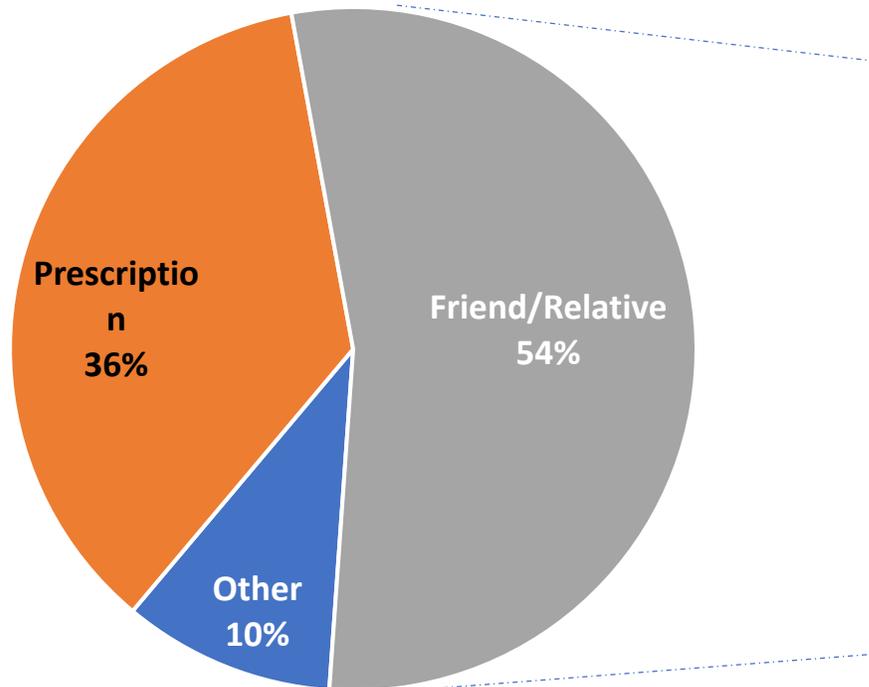


Source: IQVIA Xponent, Mar 2020; IQVIA National Prescription Audit; IQVIA Institute, Nov 2020

Direct and Indirect Pathways from Prescriptions to Misuse

People misusing analgesics, **directly** and **indirectly**, obtain them by prescription.

Source where pain relievers obtained for most recent misuse



Adolescent Exposure to Prescription Opioids Associated with Future Opioid Misuse and Heroin Use

6,220 12th graders followed up to age 23:

Legitimate opioid use before high school graduation is independently associated with a 33% increase in the risk of future opioid misuse after high school.

Richard Miech, Lloyd Johnston, Patrick M. O'Malley, Katherine M. Keyes and Kennon Heard
Pediatrics November 2015, 136 (5) e1169-e1177; DOI: <https://doi.org/10.1542/peds.2015-1364>

11,012 12th graders followed up to 35:

Adolescents who reported nonmedical prescription opioid use (with subsequent nonmedical or medical use) had greater odds of any heroin use in adulthood than population controls.

McCabe SE, Boyd CJ, Evans-Polce RJ, McCabe VV, Schulenberg JE, Veliz PT. Pills to Powder: A 17-Year Transition From Prescription Opioids to Heroin Among US Adolescents Followed Into Adulthood. J Addict Med. 2021 May-Jun 01;15(3):241-244.

Solutions toward *Responsible Prescribing*: Guidance



Opioid Prescribing Guidelines March 2016



Patient-Centered Reduction or Discontinuation of Long-Term Opioid Analgesics

February 10, 2022: CDC's updated Clinical Practice Guideline for Prescribing Opioids open for public comment

<https://www.federalregister.gov/public-inspection/2022-02802/proposed-2022-clinical-practice-guideline-for-prescribing-opioidsexternal icon>

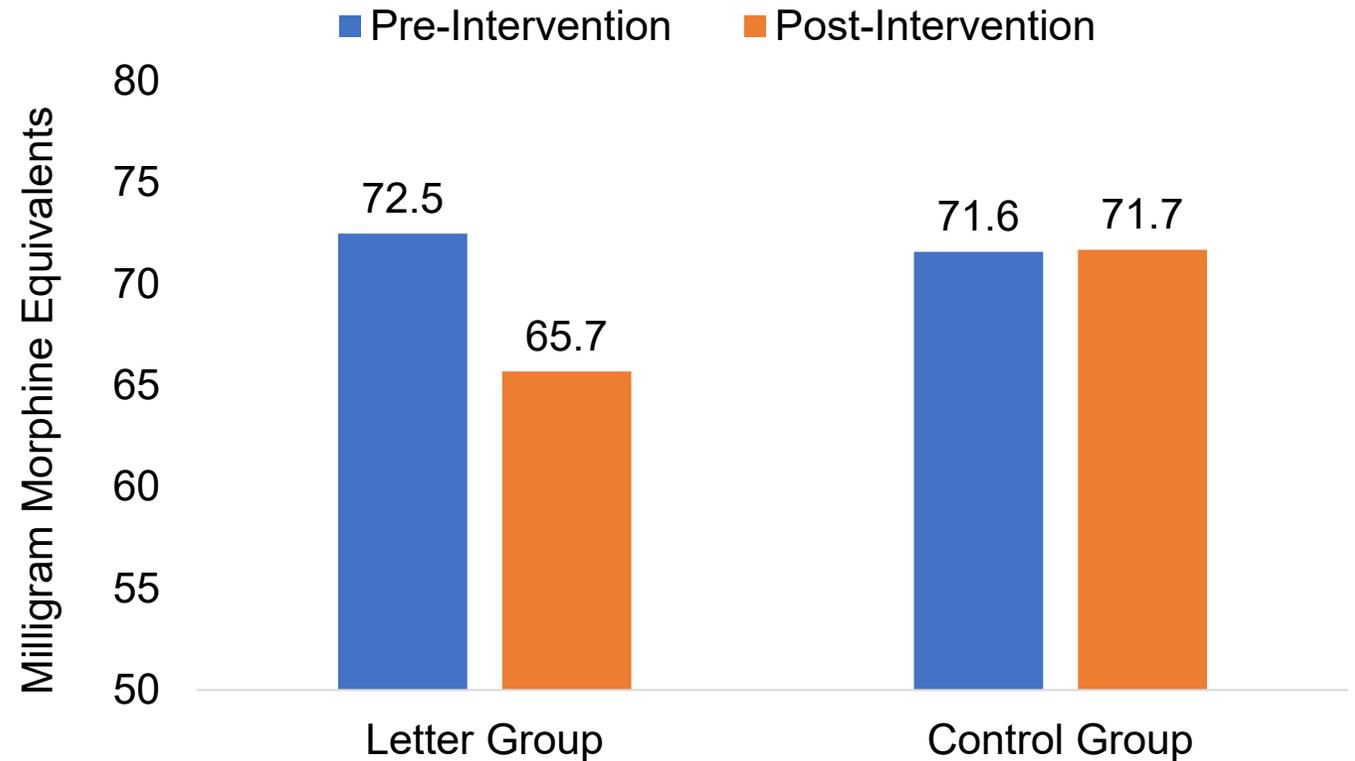
- Opioid selection, dosage, duration, follow-up and discontinuation
- Assessing risk and addressing harms of opioid use

- 6. Opioid withdrawal management
- 7. Behavioral health support
- 8. Challenges to tapering

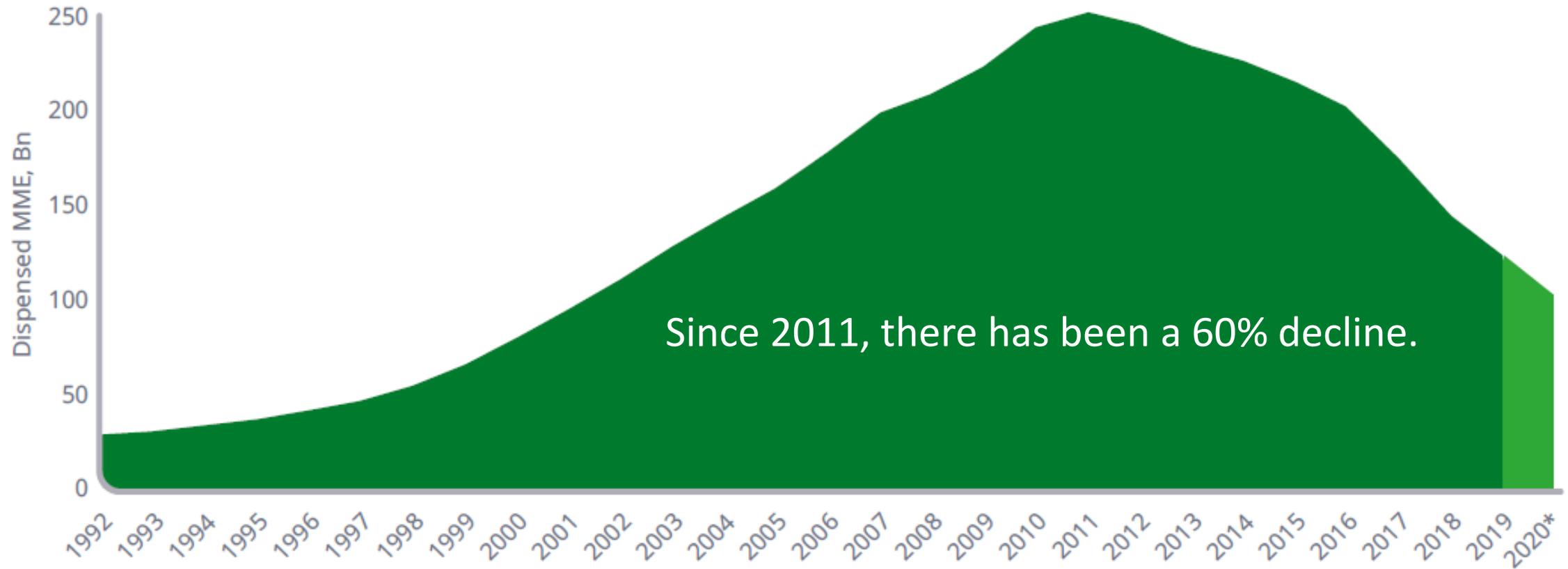
Dosage changes, particularly rapid reductions in dose, can harm patients or put them at risk if not made in a thoughtful, deliberative, collaborative, and measured manner.

Medical Examiner Letter Reduces Subsequent Prescribing: Randomized trial of 861 clinicians prescribing to 170 OD decedents

- Intervention group received notification of their patients' deaths and a safe prescribing injunction from their county's medical examiner; control group did not.
- Milligram morphine equivalents in prescriptions filled by patients of letter recipients decreased by 9.7% (95% confidence interval: 6.2 to 13.2%; $P < 0.001$) over 3 months after intervention; also, fewer opioid initiates and fewer high-dose opioid prescriptions.

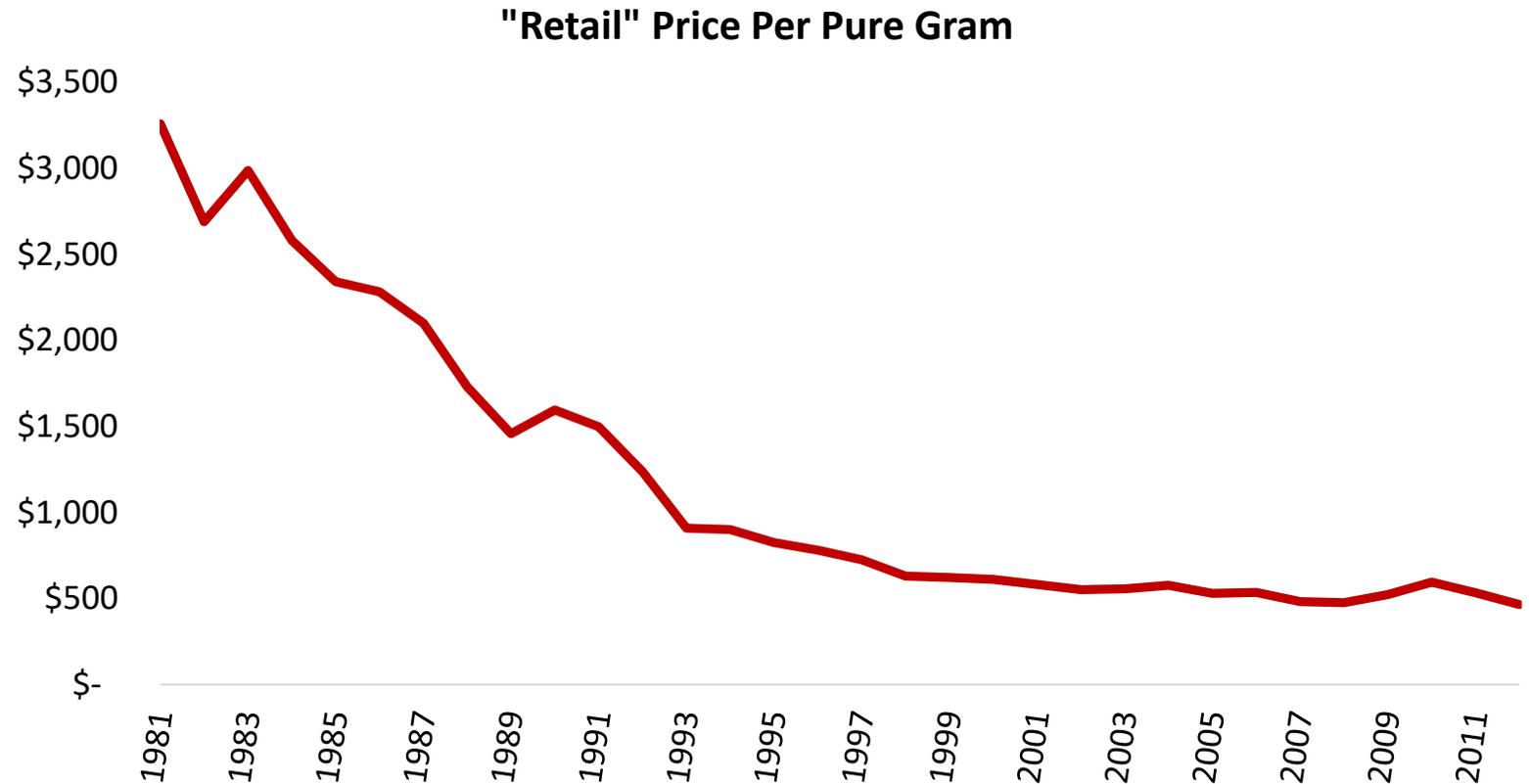
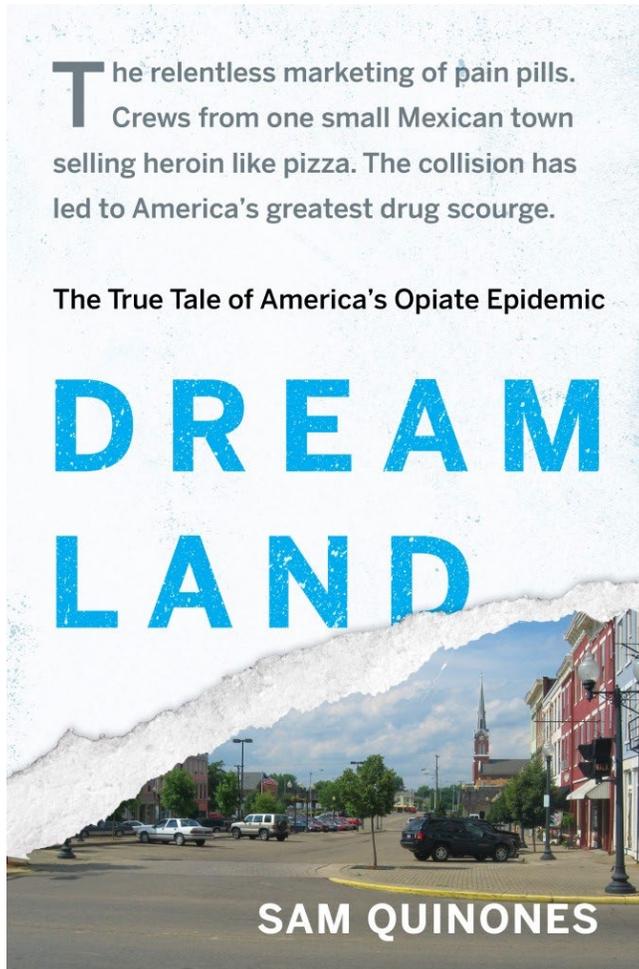


Environmental Availability: Prescribing Increases Contributed to Opioid Crisis



Source: IQVIA Xponent, Mar 2020; IQVIA National Prescription Audit; IQVIA Institute, Nov 2020

ECONOMICS: Heroin Increases Due to Lower Price and Greater Availability



National Drug Control Strategy--Data Supplement 2016.

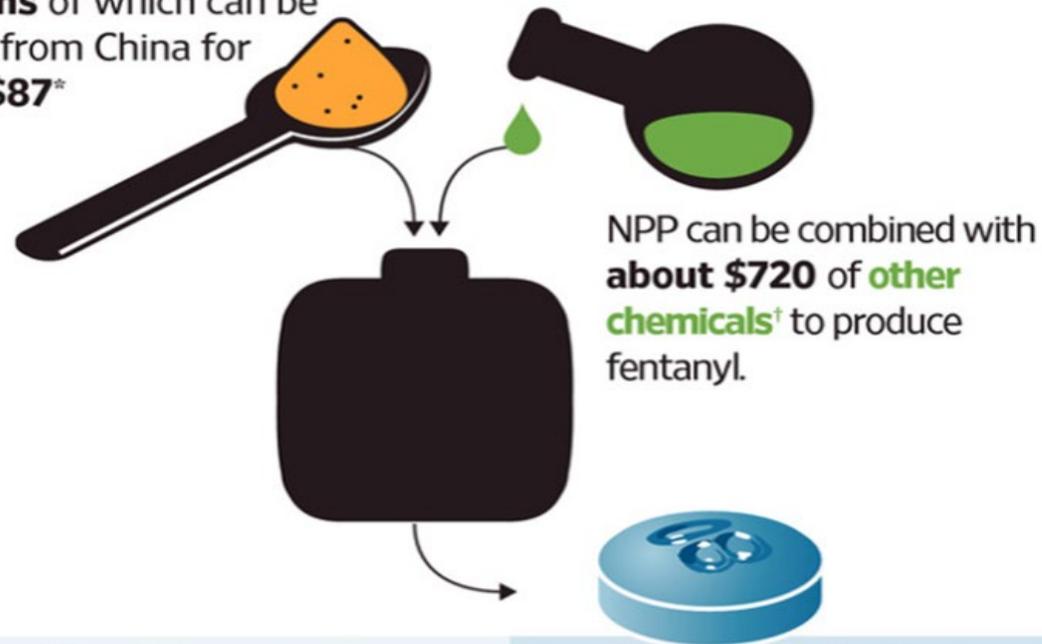
https://obamawhitehouse.archives.gov/sites/default/files/ondcp/policy-and-research/2016_ndcs_data_supplement_20170110.pdf

ECONOMICS: CHEAP Fentanyl Precursor Chemicals

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

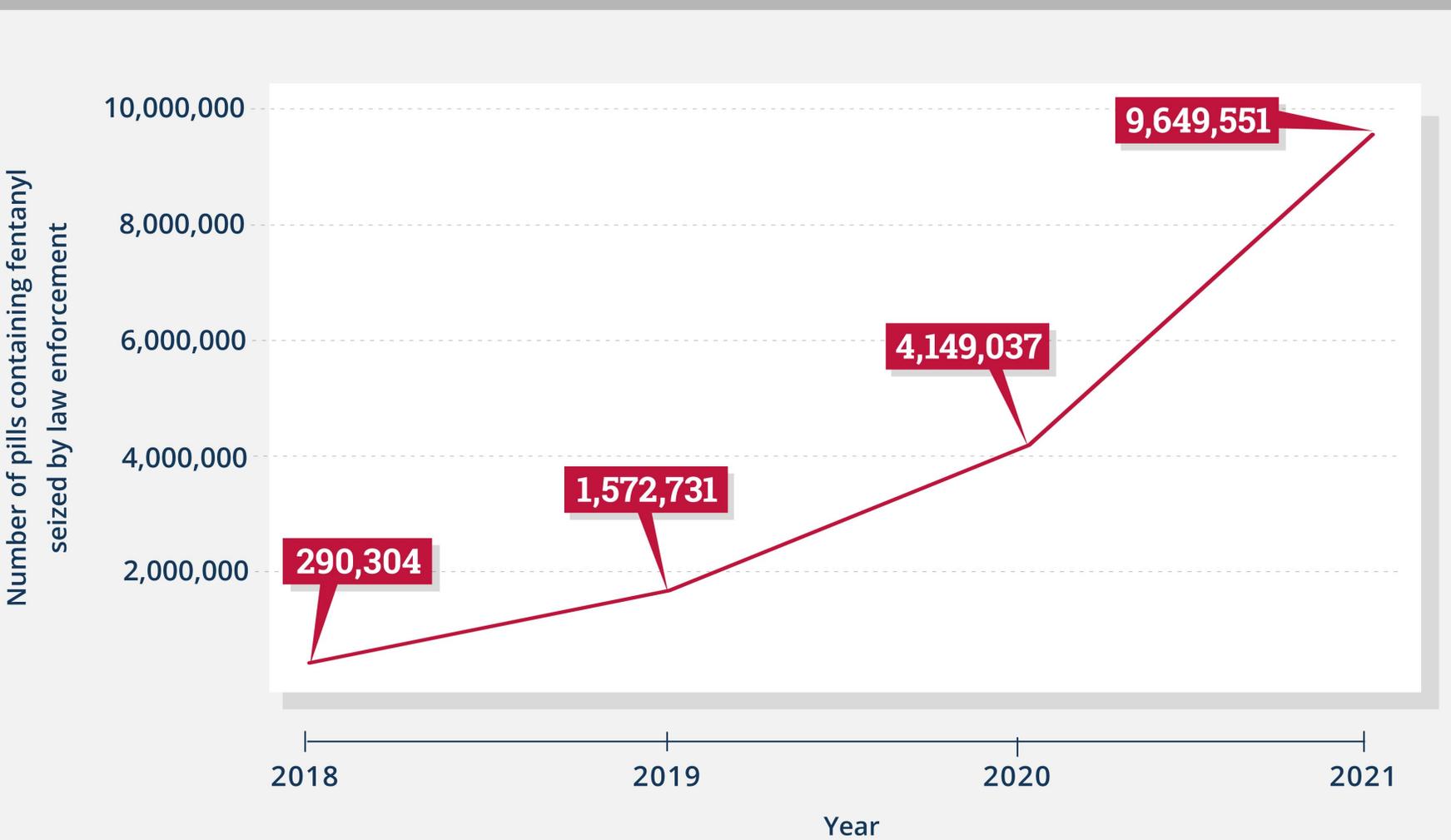
DEA Issues Public Safety Alert on Sharp Increase in Fake Prescription Pills Containing Fentanyl and Meth



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>

Fentanyl Law Enforcement Seizures, 2018-2021

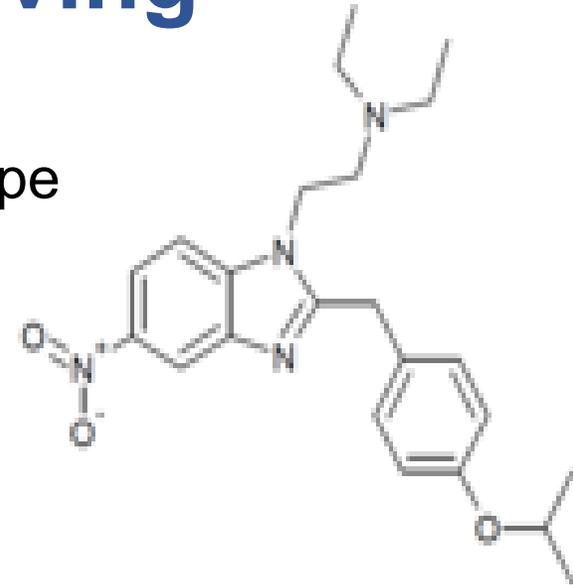


Estimates based on data reported by the Office of National Drug Control Policy's High Intensity Drug Trafficking Areas program

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

Novel Synthetic Opioids Constantly Evolving

- March 2019
 - Isotonitazene (500> morphine) first appeared in Canada and Europe
- July 2019
 - Isotonitazene found in U.S. toxicology and >250 overdose deaths
- August 2020
 - DEA classified isotonitazene as a Schedule I substance
 - DEA listed isotonitazene in Annual Emerging Threat Report
 - Other nitazines, etonitazene and metonitazene, emerge
- 2021
 - Nitazenes detected postmortem in combination with other drugs
 - Increased toxicology reports of nitazenes and other non-fentanyl NPS opioids



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

Need for development of specialized detection assays.



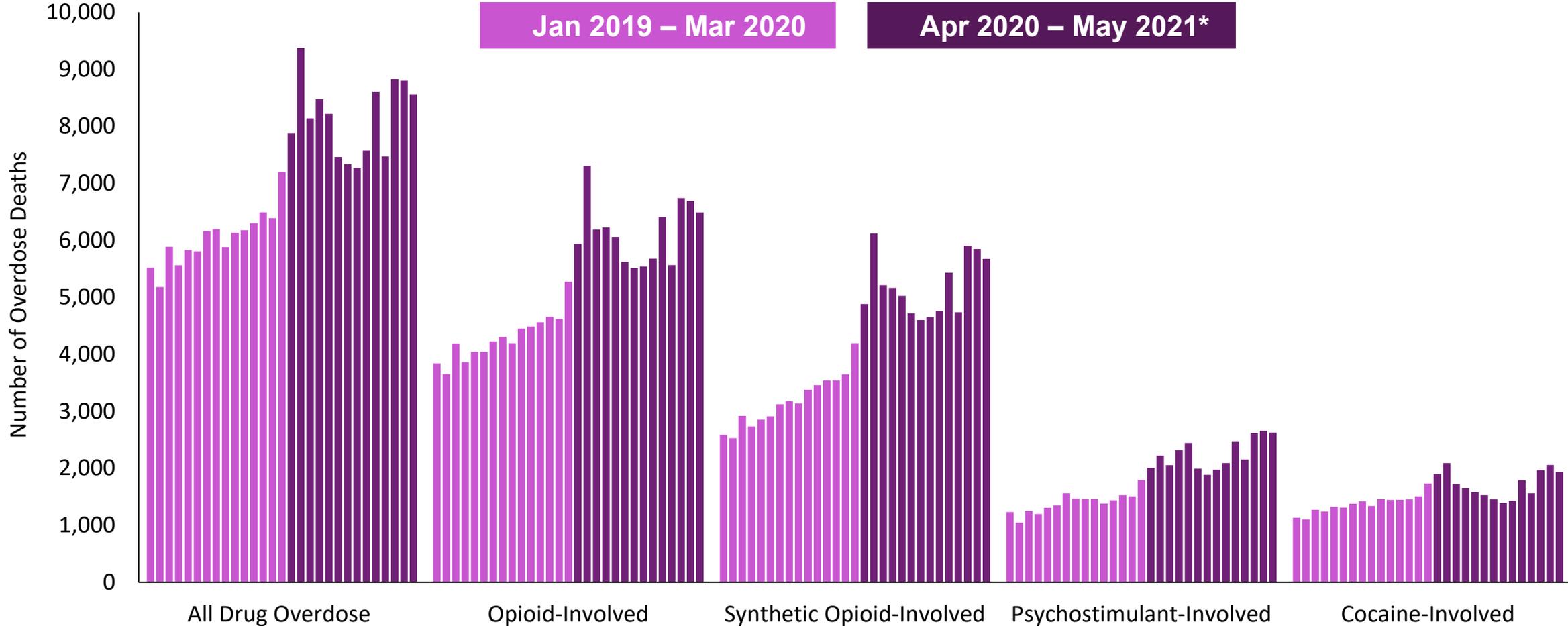
Intersection Between COVID-19 and Substance Use Disorders

Structural and Social Challenges for SUD During COVID-19

- Stress and Stigma
- Limited medication access and limited peer-support groups/social connection
- Social distancing increases likelihood of opioid overdoses happening with no observers who can administer naloxone
- Job losses
- Housing instability/homelessness
- Incarceration (>50% of U.S prisoners have SUD) and prison populations are at greatest risk SARS-CoV-2 transmission

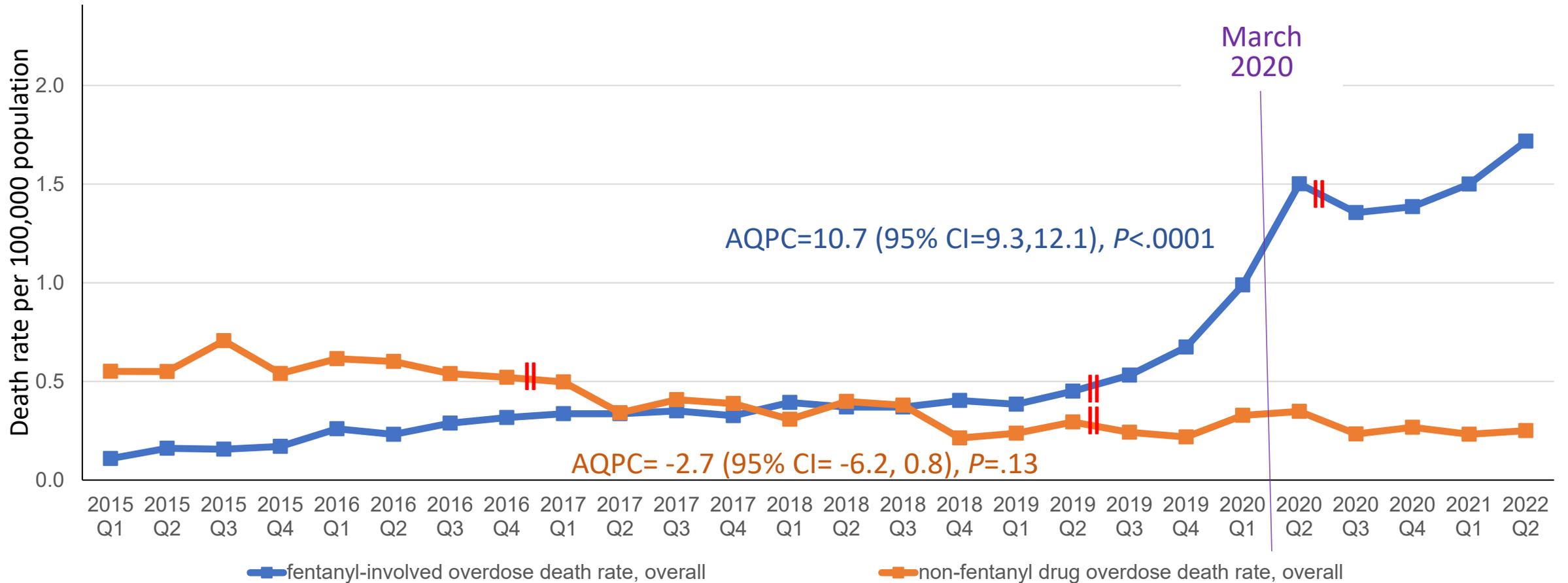


Current State of the Overdose Crisis



*January 2021-May 2021 are provisional data. CDC WONDER National Vital Statistics System, 2021.

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).

SUD Services Have Shifted During the Pandemic

- Increased use of telemedicine
- Establishment of mental health hot lines
- Deployment of virtual support meetings
- Expansion of take-home medicines for MOUD
- Buprenorphine prescribing via Telehealth
- Release of non-violent offenders with SUD from jails and prisons(might improve their outcomes)
- Development of web-based educational material that can be used to help in rehabilitation

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

HHS Overdose Prevention Strategy



Cross-Cutting Principles

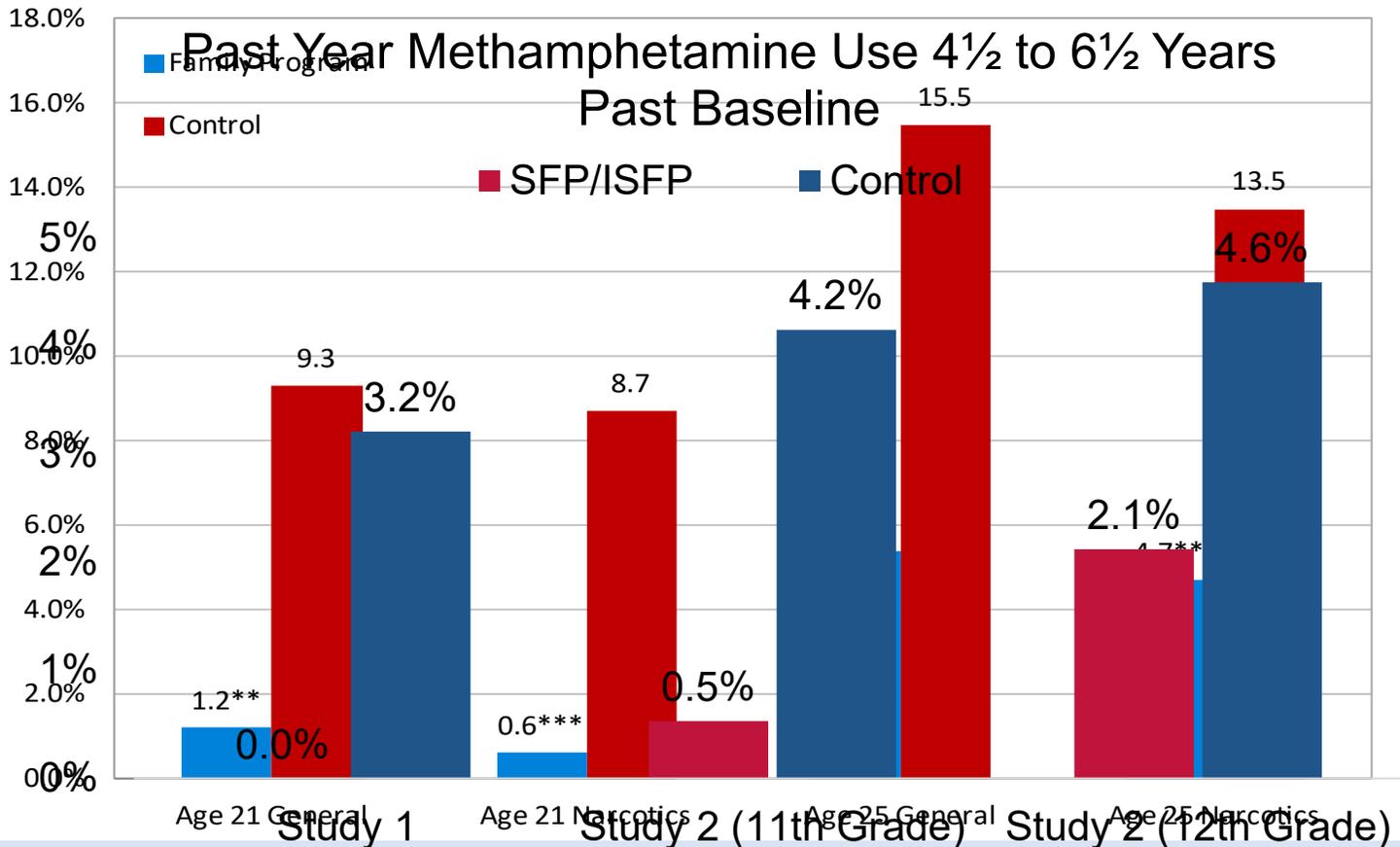
Equity

Data &
Surveillance

Coordination,
Collaboration &
Integration

Reducing Stigma

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



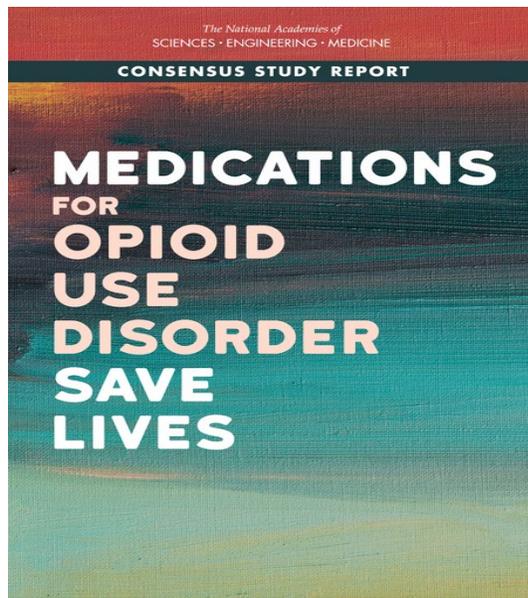
Targeting Youth to Prevent Later Substance Use Disorder: An Underutilized Response to the US Opioid Crisis

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

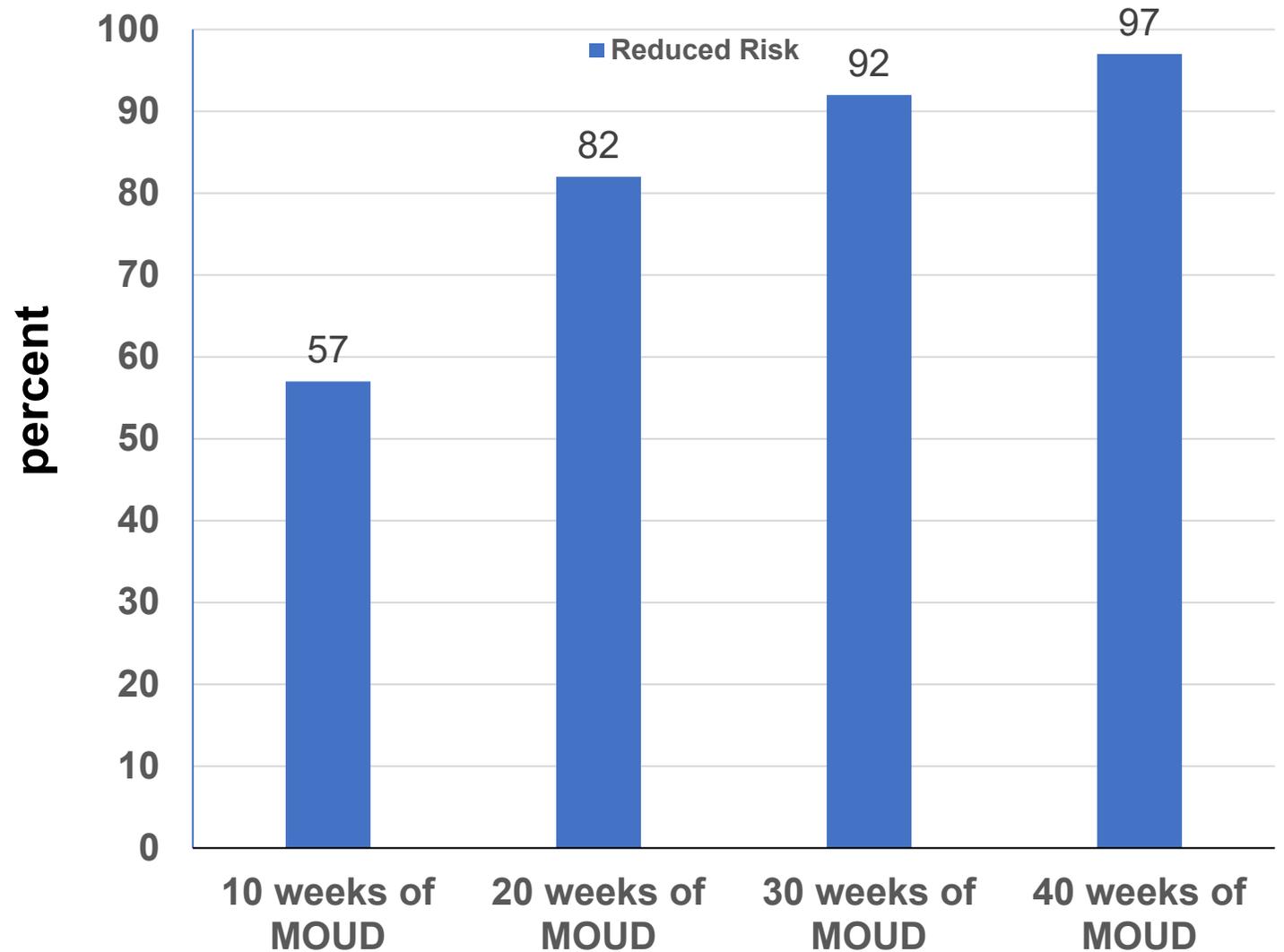
In this study, for 100 young adults in general population starting Rx abuse, only 35 young adults from an intervention community started.

Note: Study 2 included both ISFP and LST interventions
 PLSy et al. (2016) *Sch Pediatr Adolesc Med.*

Notes: General=Misuse of opioids or CNS depressants or stimulants. Source: R Spoth et al. American Journal of Public Health 2013



Reduced Risk Overdose in Pregnant Women Given Medications for OUD



FDA-Approved Medications

Methadone



In use since the 1960s, the slow-acting synthetic opioid agonist effectively treats moderate to severe heroin addiction. It is only available in heavily regulated clinics.

Buprenorphine/Suboxone



Approved in 2002, the long-acting opioid agonist relieves drug cravings with fewer side effects than other opioids and is available by prescription from certain doctors. Suboxone is designed to deter illicit use.

Naltrexone/Vivitrol



Approved in pill form in 1984, it has been available since 2010 as a 30-day time-release injectable medication called Vivitrol. Patients must be completely off all opioids for seven to 10 days. Both block the effect of opioids, do not activate the opioid receptor system, and do not cause physical dependence.

Naloxone



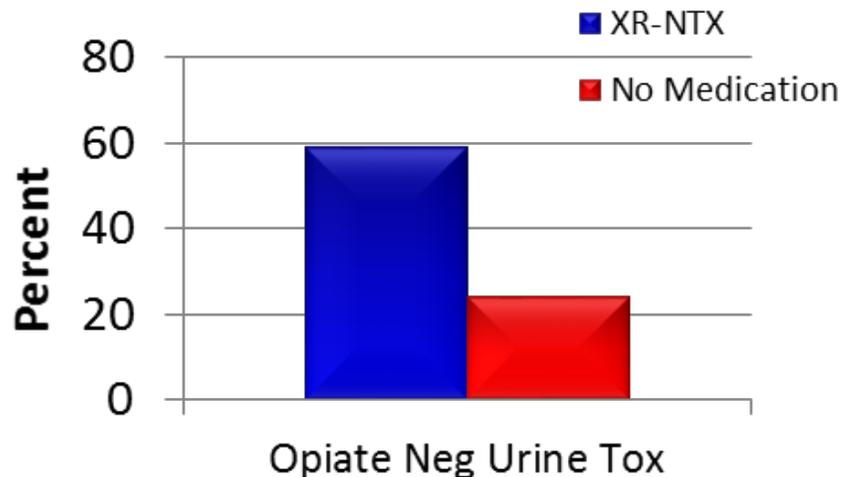
Approved in 1971, the short-acting medication, also known as Narcan and Evzio, reverses opioid overdoses but does not treat opioid addiction.

Science = Solutions: Improving Addiction Treatment

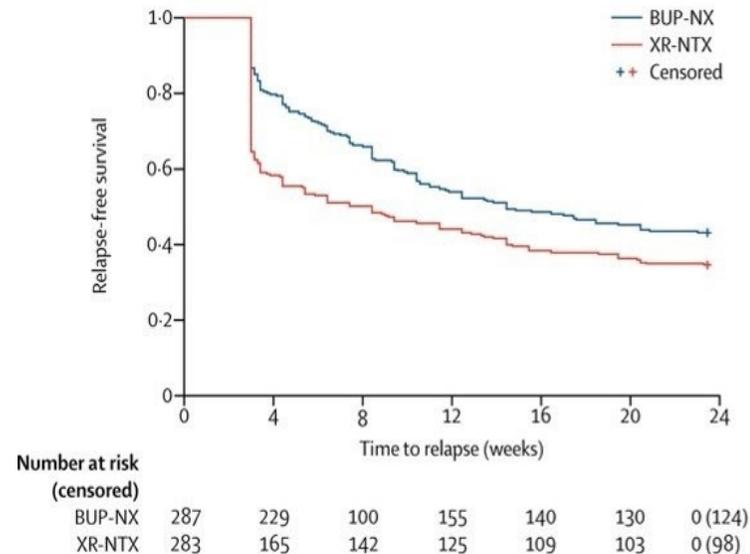
- Initiating buprenorphine treatment in the **emergency department** improves treatment engagement and reduces illicit opioid use
- Extended release naltrexone initiated in **criminal justice** relapse rates and overdoses
- **BUP-Nx** more effective than the **XR-Naltrexone** overall but also safe and effective after induction



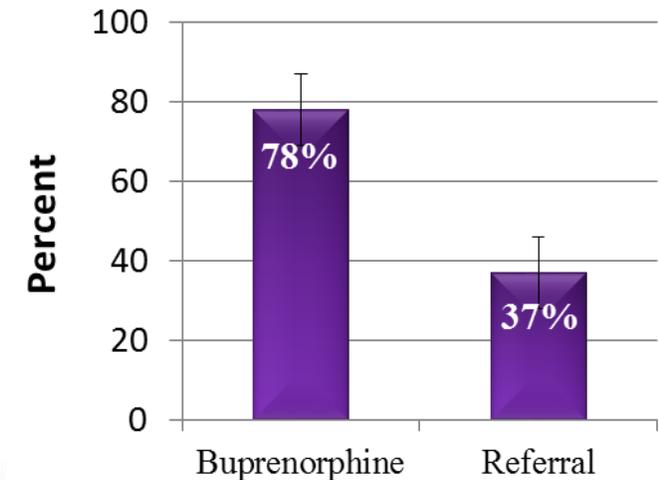
Post Prison-Release Outcomes



Relapse-free survival



ED-initiated Buprenorphine Increased TX Engagement



D'Onofrio JAMA. 2015.

Lee JD, et al., *Addiction* 2015;100:1005-1014
and *New Eng J Med* 2016;374:1232-1242

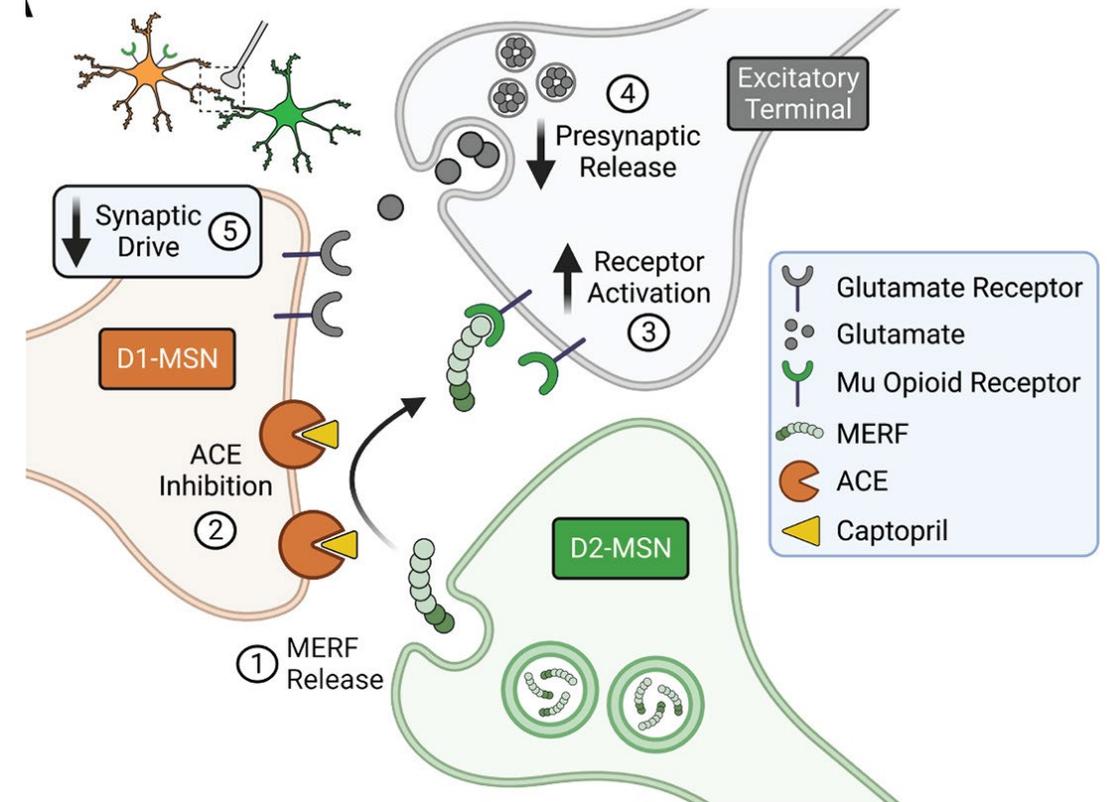
Lee JD et al., *The Lancet* Nov. 14, 2017

Treating Fentanyl OUD and Overdoses (limited data)

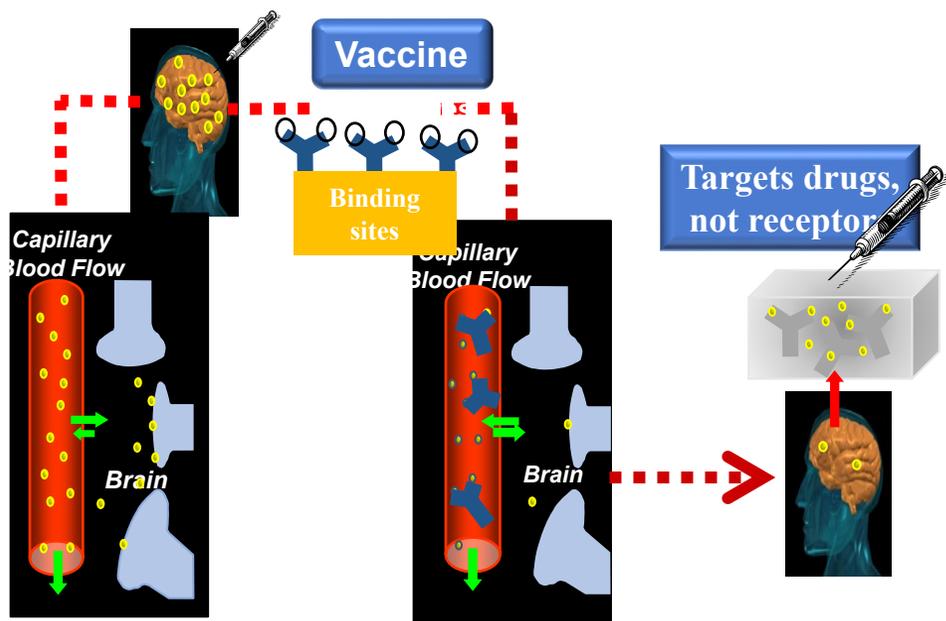
- Methadone is effective in fentanyl OUD
 - Methadone protects against death, but relapse rates high ([Stone, et al., 2018](#), [Stone, et al. 2020](#))
- Buprenorphine is effective in fentanyl OUD,
 - Harder to induct into treatment ([Wakeman, et al., 2019](#))
- Naltrexone no published data
- Fentanyl deaths increasing despite naloxone ([Torralva and Janowsky, 2019](#))
- OD from fentanyl may require multiple naloxone doses ([Schumann et al., 2007](#), [Somerville et al., 2017](#))
 - Shorter duration of naloxone ($t_{1/2}$ 1.3–2.4 h) than fentanyl ($t_{1/2}$ 7-8 h)
 - Slower clearance of fentanyl in frequent users
 - Chest wall rigidity induced by fentanyl

Systemic Captopril Reduces Excitatory Input to D1-MSNs, Counteracts Fentanyl Reward, and Increases Sociability

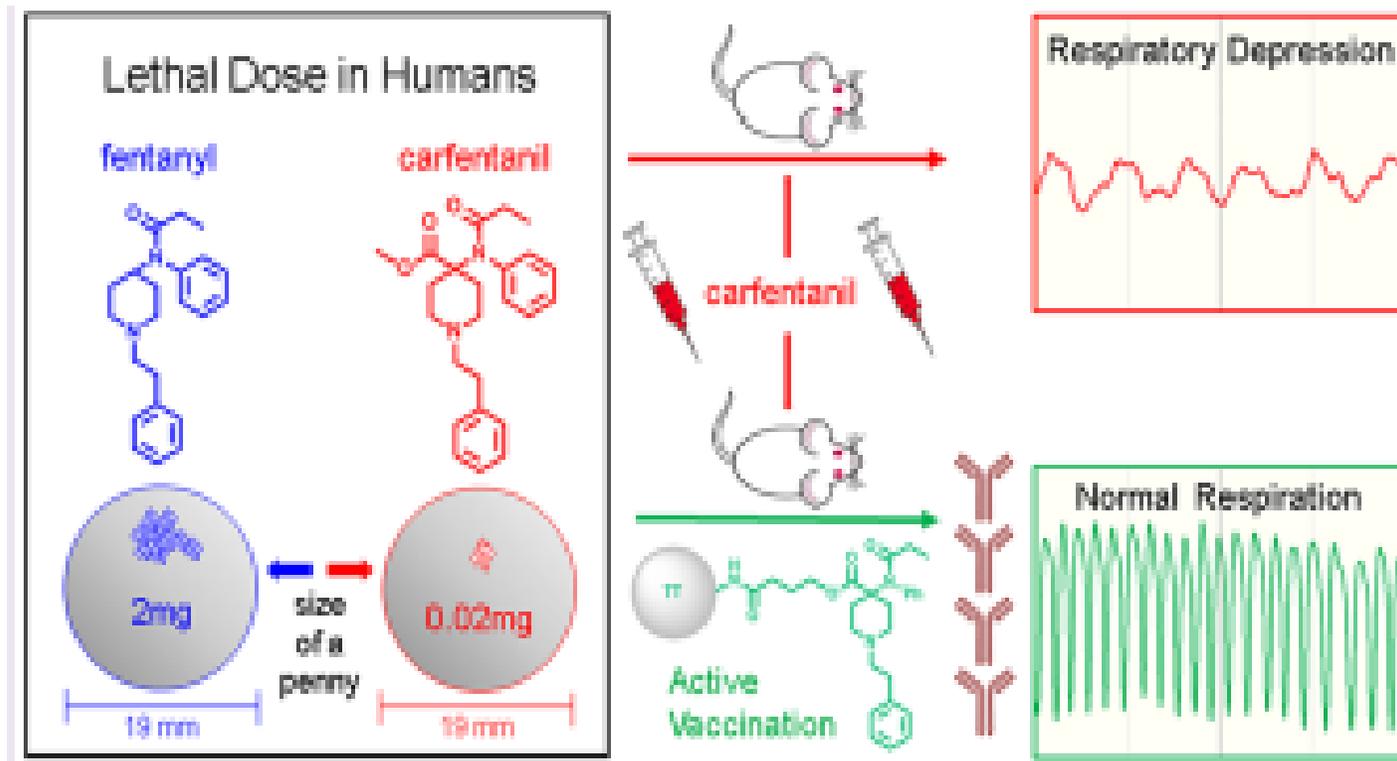
- Angiotensin-converting enzyme (ACE) regulates BP by cleaving angiotensin I to angiotensin II. In the brain, ACE is abundant in striatal tissue.
- In the NAc from mice ACE degrades an enkephalin heptapeptide, Met-enkephalin-Arg-Phe thereby enhancing endogenous MOR signaling in the NAc.
- ACE inhibition enhanced MOR activation by Met-enkephalin-Arg-Phe, causing a cell type-specific long-term depression of glutamate release onto MSN expressing DA D1R.
- Systemic ACE inhibition was not rewarding, but decreased CPP to fentanyl, and enhanced reciprocal social interaction.
- Central ACE inhibition might be of therapeutic value for pain and addiction.



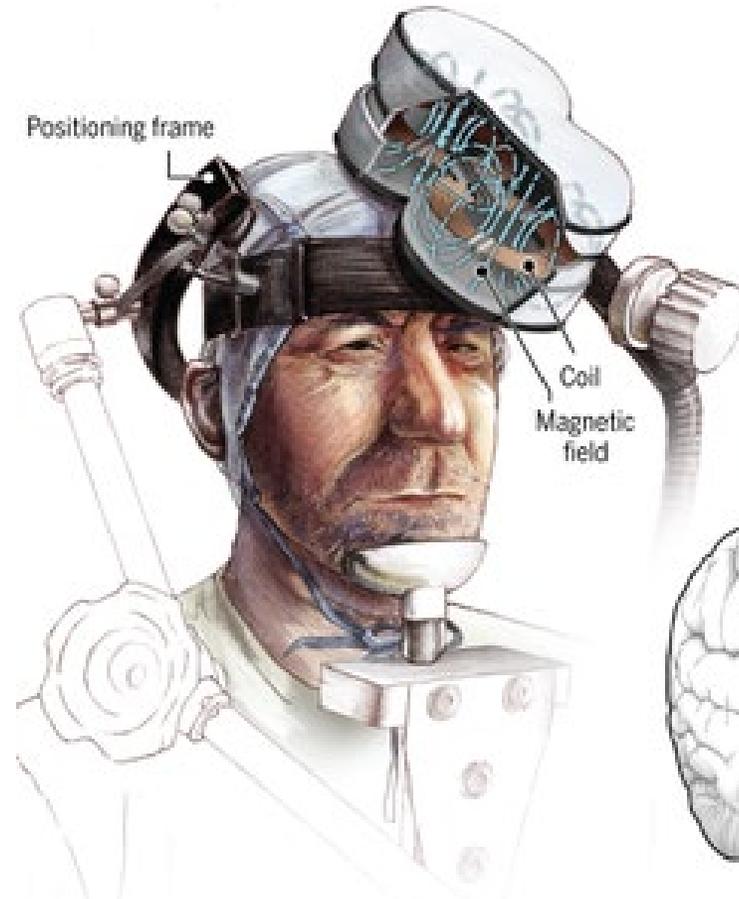
Immunotherapies for Addiction: Vaccines and mAB



Carfentanil Vaccine Blunts Opioid-Induced Antinociception and Respiratory Depression

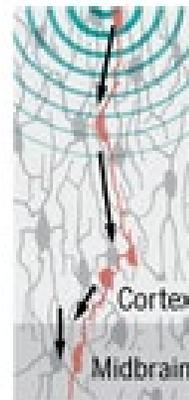
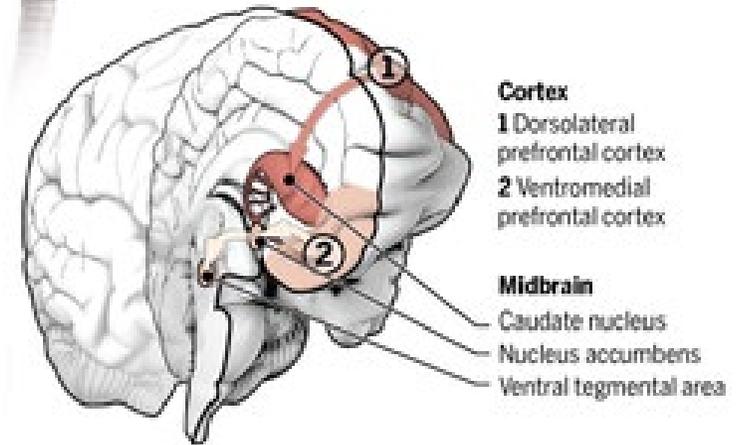


Treating Addiction: Neuromodulation



Magnetic medicine

Electric pulses in a coil held near the scalp induce a changing magnetic field that creates electric currents in the cortex. Changing the frequency and pattern of magnetic pulses delivered to the cortex can either increase or decrease neuronal firing. Multiple stimulation strategies are being used to battle cocaine addiction.



"Cold" (executive control) circuit

In one form of transcranial magnetic stimulation, pulses are delivered many times per second, on and off, for a few minutes. This "intermittent theta burst" stimulation of the dorsolateral prefrontal cortex may propagate to the midbrain (arrows, left) and strengthen the "cold" (right, dark pink) circuit that overrides drug-seeking impulses.

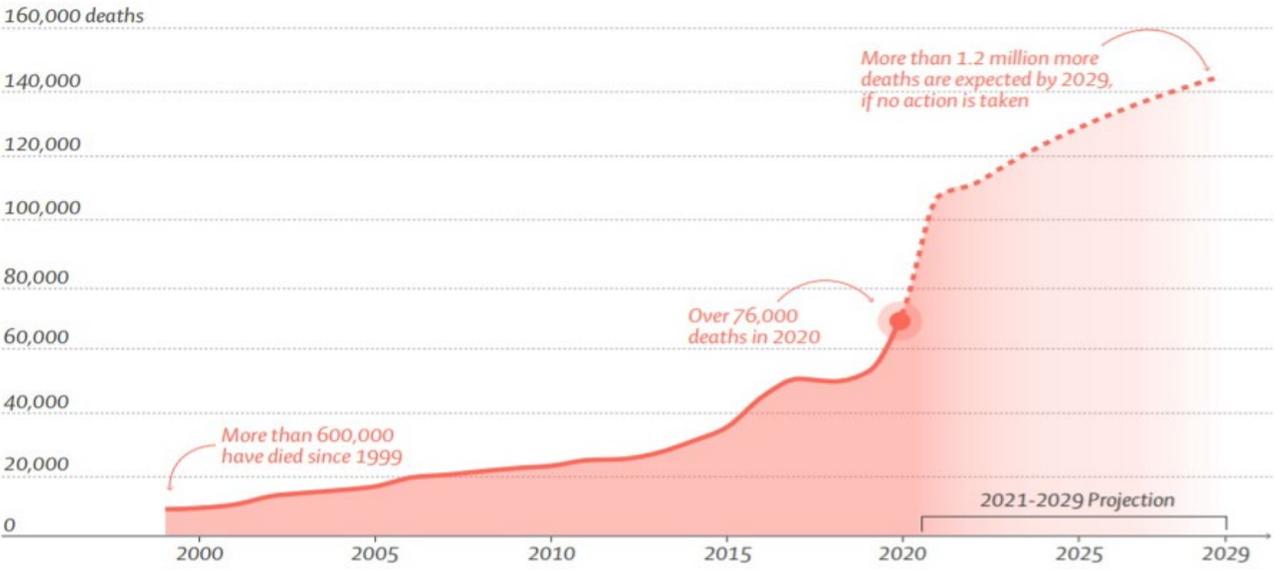


"Hot" (craving and reward) circuit

Continuous theta burst stimulation applied to the ventromedial prefrontal cortex is thought to inhibit the neurons of the "hot" (light pink) circuit that connects to the midbrain's nucleus accumbens and ventral tegmental area. It is abnormally active when people addicted to cocaine are exposed to cues such as white powder.

Stanford-Lancet Commission to the Opioid Crisis in North America

Deaths from opioid overdose in North America



Status quo predicts
1.2M deaths by 2029
Humphrey et al., Lancet 2022

Effectiveness of Policies for Addressing the US Opioid Epidemic: Model-Based Analysis

- Naloxone expansion by 30% had largest effect, averting 25% deaths
- Pharmacotherapy, syringe exchange, psychosocial treatment, PMPs reduced deaths improving life years and QALYs
- Reduced prescribing and increasing opioid disposal would reduce deaths
- Combined interventions being more effective than isolated ones

Rao et al., *Lancet Regional Health-Americas*, 2021

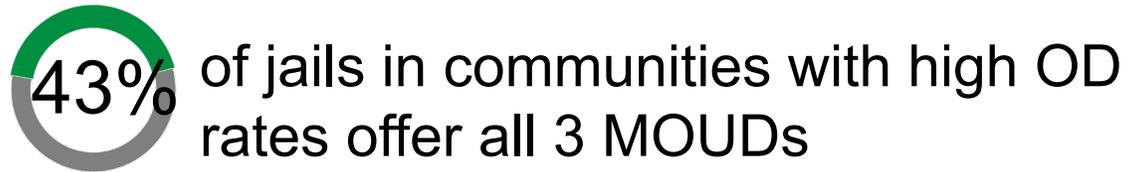
NIH Helping to End Addiction Long-Term (HEAL) Initiative

A trans-agency effort to speed scientific solutions to the opioid public health crisis



MEDICATIONS AT RE-ENTRY

Providing all FDA-approved MOUDs during incarceration could reduce overdose deaths & recidivism by ~30%



Sources: Evans et al., 2022; Scott et al., 2021, Macmadu et al., 2021

Barriers
Stigma
Funding
Training
Logistics

PILOT STUDY: EXTENDED-RELEASE BUPRENORPHINE

Extended-release buprenorphine prior to re-entry from jails increased adherence (69 vs. 35%) relative to sublingual buprenorphine

Sources: Lee et al. 2021

MEDICAID & INCARCERATION

Medicaid pre-enrollment prior to release increased Medicaid access 7-fold & decreased racial disparities.

Receiving MOUDs while incarcerated doesn't change Medicaid costs, but shifts costs away from emergency care

Sources: Burns et al., 2020, Howell et al. 2021, Hochstatter, 2021



Images of People in the Community

Intervention Accomplishments

- Implemented EBPs for OEND, MOUD, and safer prescribing in Wave 1 communities
- Communication campaigns completed on:
 - Overdose education and naloxone
 - MOUD
 - Accessing and staying in treatment
- Developing sustainability plans to maintain HCS activities

Wave 1 communities are implementing the Communities That Heal intervention through June 2022. Starting July 1, 2022, our Wave 2 communities will begin implementation.

Addressing Stigma of Addiction

Nora's Blog

Addressing the Stigma that Surrounds Addiction

April 22, 2020 By Dr. Nora Volkow

Untreated drug and alcohol use contribute to tens of thousands of deaths each year and impact the lives of many more. Healthcare already has effective medications for opioid and alcohol use disorder that cost less than \$100 a month, but they are not being utilized widely enough, and many people do not even seek them out. One important reason is the stigma surrounding addiction.

Stigma is a problem with health conditions ranging from cancer and HIV to many mental illnesses. Some gains have been made in reducing stigma around certain conditions; public education and widespread use of effective medications has demystified depression, for instance, making it somewhat less taboo now than it was in past generations. But little progress has been made in removing stigma from substance use disorders. People with addiction continue to be blamed, and although medicine long ago reached a consensus that addiction is a brain disorder with behavioral components, the public and even the justice system continue to view it as a result of moral weakness.



Nora's Blog

Punishing Drug Use Heightens the Stigma of Addiction



Drug and Alcohol Dependence

Volume 221, 1 April 2021, 108627



The role of stigma in U.S. primary care physicians' treatment of opioid use disorder

Elizabeth M. Stone^{a, b}, Alene Kennedy-Hendricks^{a, b}, Colleen L. Barry^{a, b}, Marcus A. Bachhuber^c, Emma E. McGinty^{a, b}

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

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Highlights

- National survey of U.S. primary care physicians.
- PCPs reported high levels of stigmatizing attitudes related to opioid use disorder.
- Stigma negatively associated with likelihood of prescribing OUD



Photo by [iStock.com/EvgeniyShkolenko](#)

to be informed by unfounded myths and

stigmatizing, unfounded belief that compulsive drug use reflects ongoing deliberate antisocial or deviant behavior. The criminalization of drug use and

use of substances like cannabis, have increased. The use and possession of most drugs continue to be stigmatized, and people who use them are marked as criminals, leading to stigma against people contending with an often-

NIDA Racial Equity Initiative

Workplace

- Fall 2020 NIDA Climate Survey conducted; results analyzed by an external contractor to promote trust and objectivity of the results
- Survey provide meaningful baseline data as we continue our internal racial and ethnic equity initiatives.
- Focus groups with NIDA staff will be held this spring to address actionable findings.
- A follow-on survey launched

Workforce

- NIDA Diversity Supplement Program
Annual budget increased \$750K
4 additional supplement apps from predoc & postdocs funded in FY 2021
- 3 supplements to support ESIs in Addiction Science and Related Neuroscience Pilots at NIMHD-RCMI institutions
- 3 NIDA R25 applications to support underrepresented UG, predocs, and postdocs
- 13 research and career development applications funded in FY 2021

Research Gaps and Opportunities

- 18 supplements in response to Racial Equity Initiative notices
- Supported 14 projects that characterize impact of racism on substance use outcomes, ameliorate disparities in SUD care, involve culturally tailored interventions
- Multiple research concepts presented to NIDA Council for development

NIDA's Office of Translational Initiatives and Program Innovation

 U.S. Department of Health & Human Services

Overdose Prevention Strategy



Primary Prevention

focuses on root causes and key predictors of substance use and substance use disorder, and how to safely and effectively manage pain.



Harm Reduction

focuses on reducing risks associated with substance use, including overdose and infectious disease transmission.



Evidence-Based Treatment

focuses on providing the most effective, evidence-based treatments without delay, stigma, or other barriers.

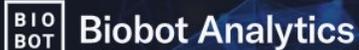


Recovery Support

focuses on funding, reimbursing, training workforces for, and developing protocols around peer, employment, and housing supports.

 invistics

 S:3 Research

 BIO BOT Biobot Analytics

 appliedVR

 SOUND life sciences

 Workit Health

 SG Sober Grid

 Woebot

 village

 emocha MOBILE HEALTH INC.

 prapela

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 Marigold HEALTH

Final Thoughts

- The U.S. Overdose Epidemic has **ACCELERATED** during COVID-19.
- Fentanyl-related and stimulant-related overdoses are an increasing concern.
- What can explain and address long-term exponential rise in OD deaths?
- Interventions
 - **Pain** treatments crucial but not sufficient.
 - **Opioid Use Disorder** treatment crucial but not sufficient (need to focus on retention and recovery)
 - **Other Substance Use Disorder** treatment is needed
 - **Overdose treatment** needed for drug combinations and **stimulant overdoses**
 - **Prevention** of drug use needed (screening and appropriate treatment intervention for mild to moderate SUD, and universal early prevention)
- **DATA:** Timely reporting of fatal and non-fatal overdoses (especially emerging new drugs and drug mixtures)
- Focus on **Social Determinants of Health** and **Harm Reduction Approaches**