

Drug Addiction Science and the U.S. Overdose Epidemic

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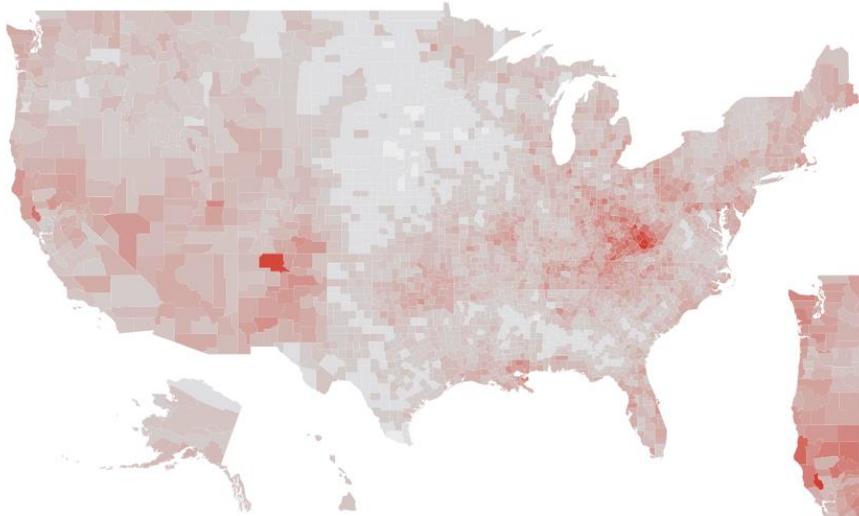
email: wcompton@nida.nih.gov



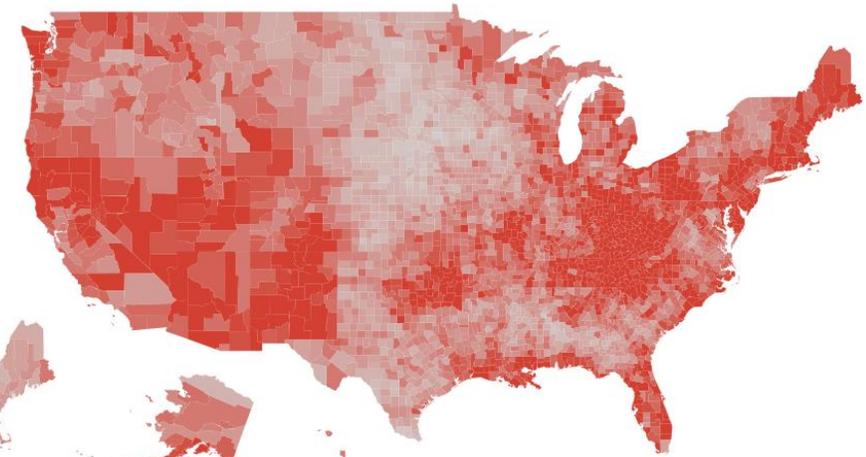
Virtually all U.S. regions have experienced rising overdose death rates over the past two decades.

Estimated Crude Death Rates for Drug Overdose by County

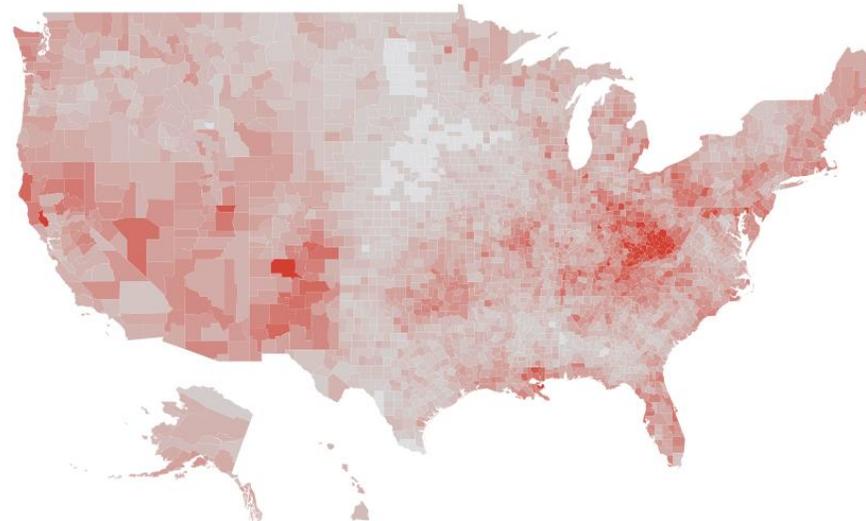
2003



2021

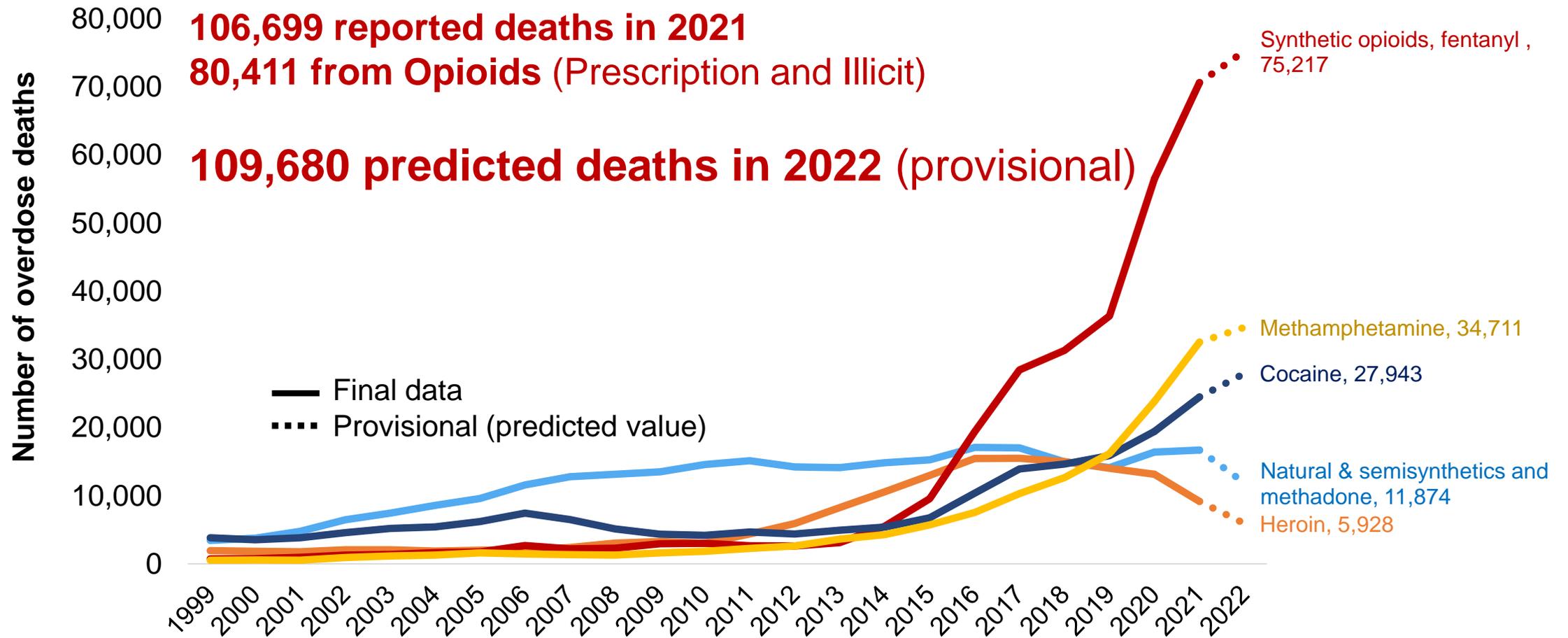


2013



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.

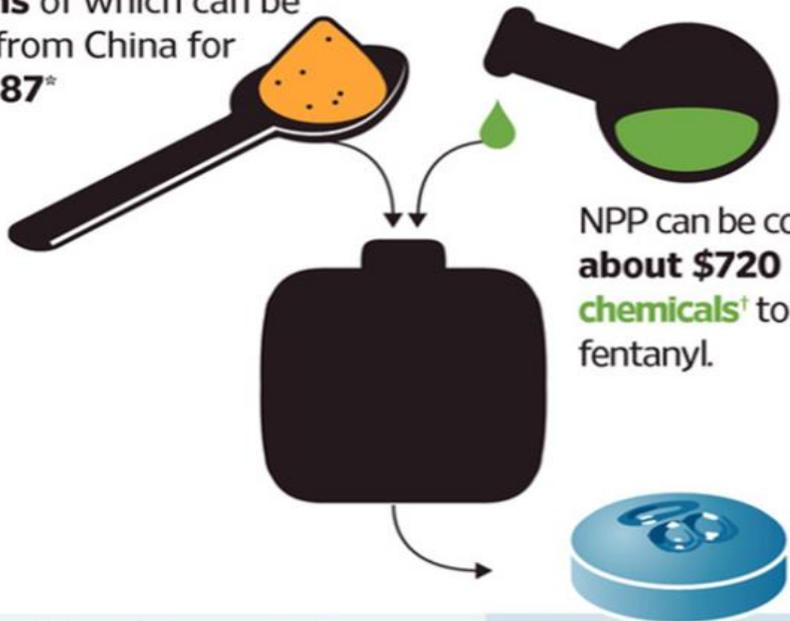
Source: The Multiple Cause of Death data are produced by the Division of Vital Statistics, National Center for Health Statistics (NCHS), Centers for Disease Control and Prevention (CDC), United States Department of Health and Human Services (US DHHS).

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***



NPP can be combined with about **\$720** of **other chemicals†** to produce fentanyl.

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

September 27, 2021

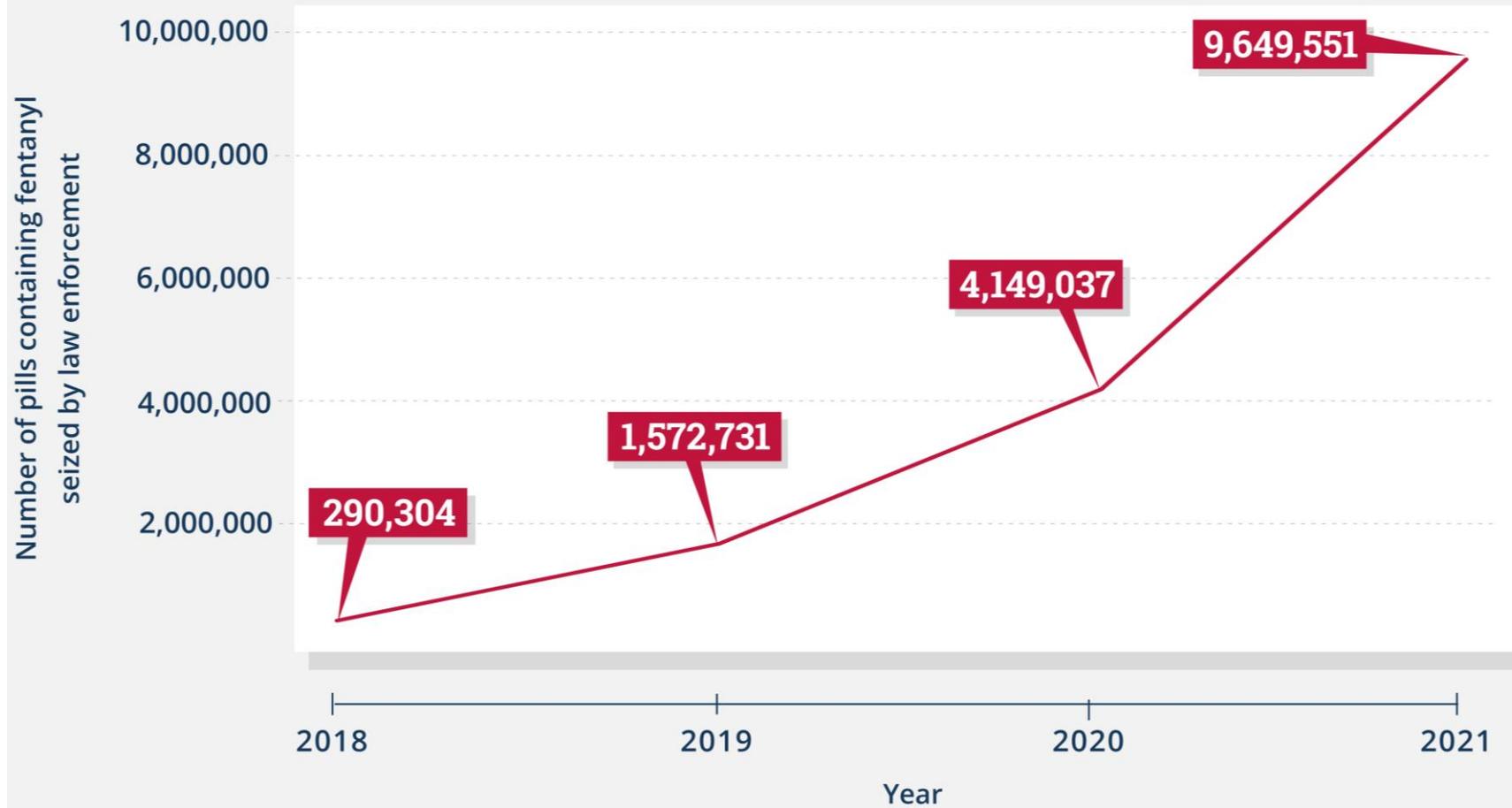


DEA Issues Public Safety Alert on Sharp Increase in Fake Prescription Pills Containing Fentanyl and Meth

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>

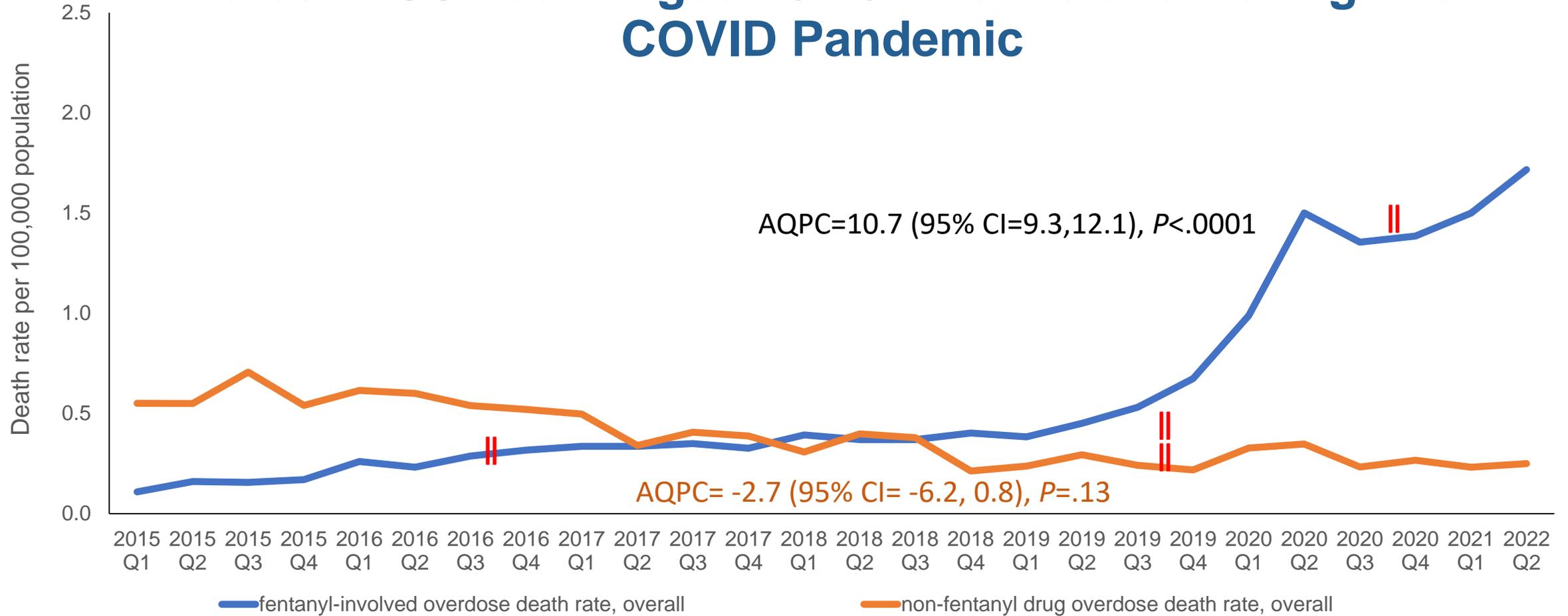
Number of Pills Containing Fentanyl Seized by Law Enforcement in the United States, 2018 – 2021



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

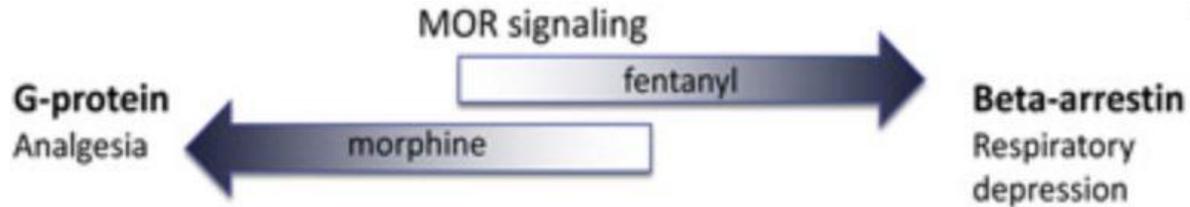
Reference: JJ Palamar, et al. *Drug and Alcohol Dependence*. DOI: 10.1016/j.drugalcdep.2022.109398 (2022)

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



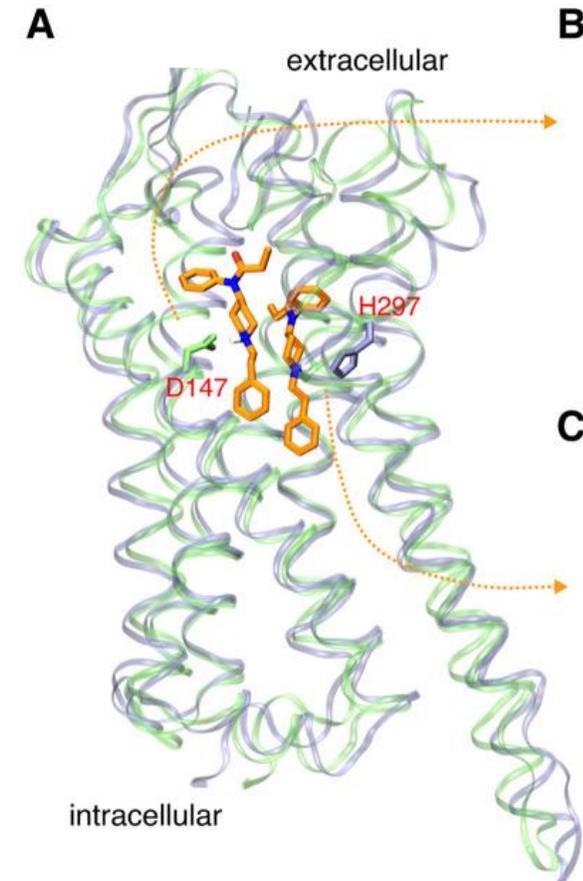
National Vital Statistics System multiple-cause-of-death 2015-2020 final and 2021 provisional data U.S. census monthly data. **||**: Joinpoints indicate significant changes in nonlinear trends using Bayesian Information Criterion. AQPC=average quarter percentage change during 2015 Q1-2022 Q2. ICD-10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

Why is fentanyl so dangerous compared to morphine and heroin?



Morphine	Fentanyl
Little to no MOR internalization	MOR internalization
beta-arrestin 2 KO mice No analgesic tolerance No locomotor sensitization Tolerance JNK-dependent	beta-arrestin-2 KO mice Tolerance not affected Locomotor sensitization not changed Tolerance JNK-independent
Tolerance is GRK3-independent	Tolerance is GRK3-dependent
RGS9-2 KO <i>increases</i> analgesia	RGS9-2 KO <i>decreases</i> analgesia
No ERK1/2 activation (via b-arrestin-2)	ERK1/2 activation (via b-arrestin-2)
Analgesic potency = 1	Equi-analgesic potency = 0.01* (i.e., fentanyl is ~100x more potent than morphine)
Less lipophilic	More lipophilic
Slow CNS entry	Rapid CNS entry
<i>OPRM1</i> A118G decreases morphine reward	<i>OPRM1</i> A118G no effect on fentanyl reward

Fentanyl binding with mOR -- Overlay of the representative simulation snapshots showing mOR is bound to fentanyl in the D147- (green) and H297- (purple) binding modes

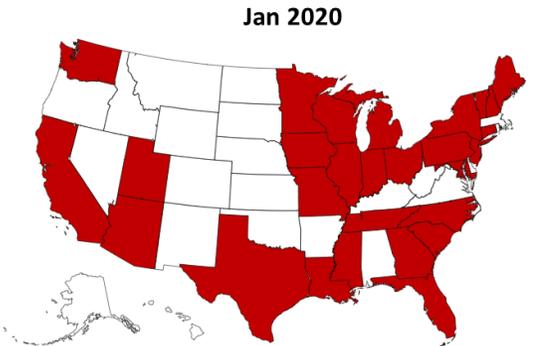


Illicit Drug Supply Evolves

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
- By itself it induces hypoxia as severe as that from fentanyl but longer lasting
- When combined with Fentanyl it blocks the compensatory hyperoxemia observed with fentanyl (also with heroin)
- When combined with Fentanyl and Heroin 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)
- Not reversed by naloxone
- Associated with severe tissue injury



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



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

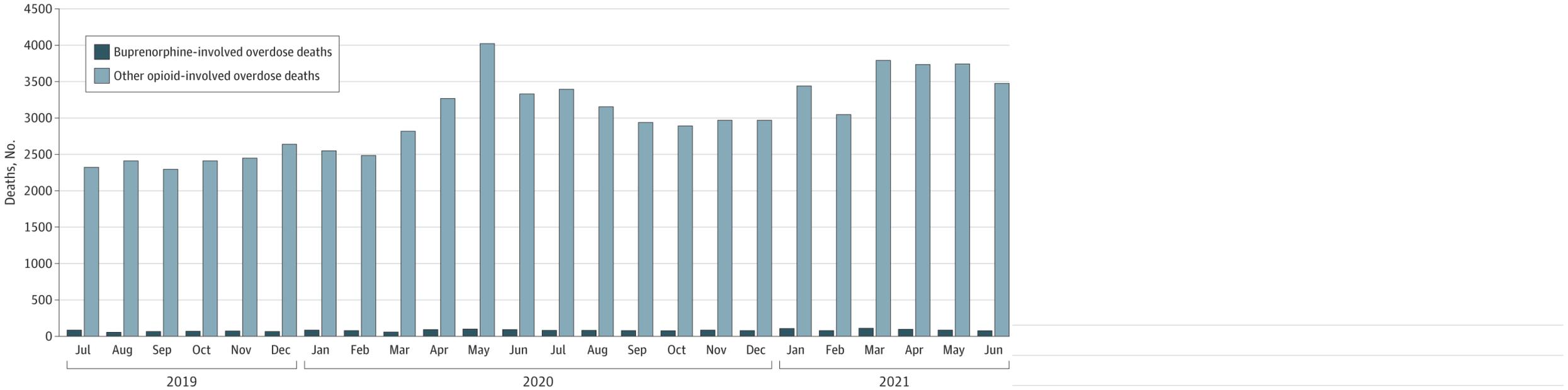
Characteristics Associated With Experiencing A Fatal Drug OD During Study Period Among Beneficiaries With OUD

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

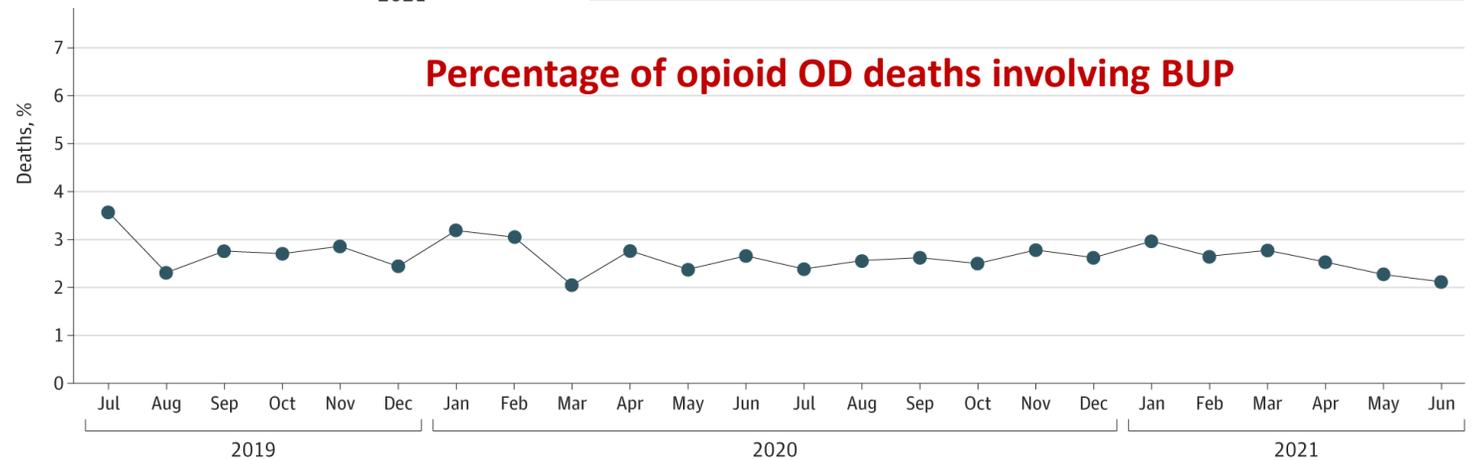
Buprenorphine-involved overdoses remained rare and did not increase as a percentage of opioid deaths.

BUP- and other opioid-involved deaths



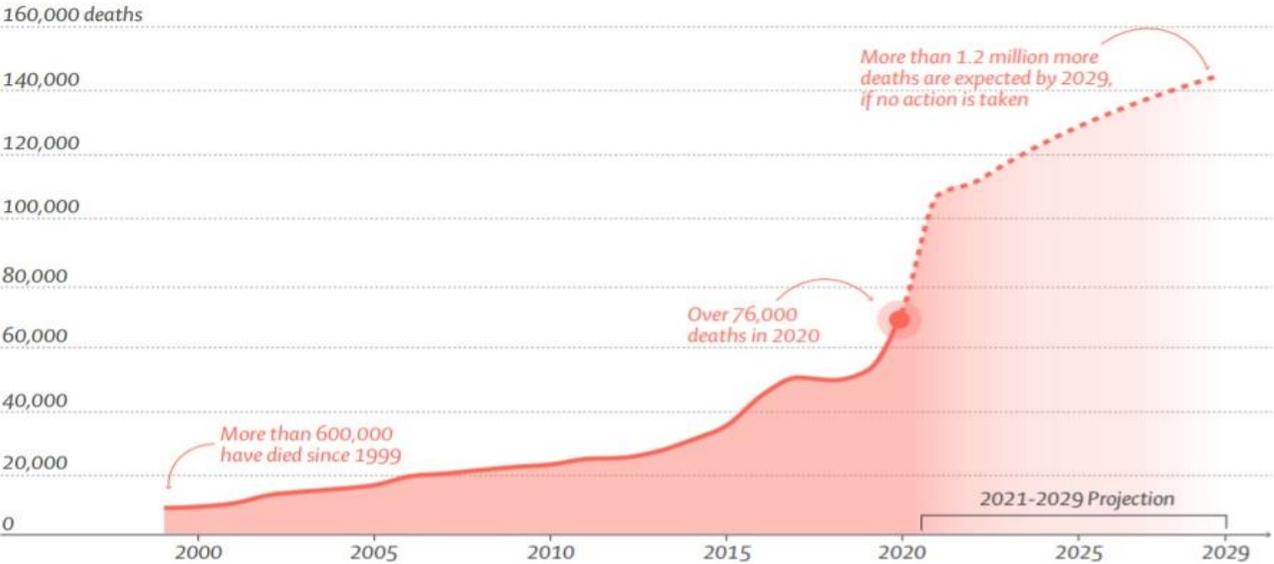
[Tanz, et al. JAMA \(2023\)](#)

Percentage of opioid OD deaths involving BUP



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

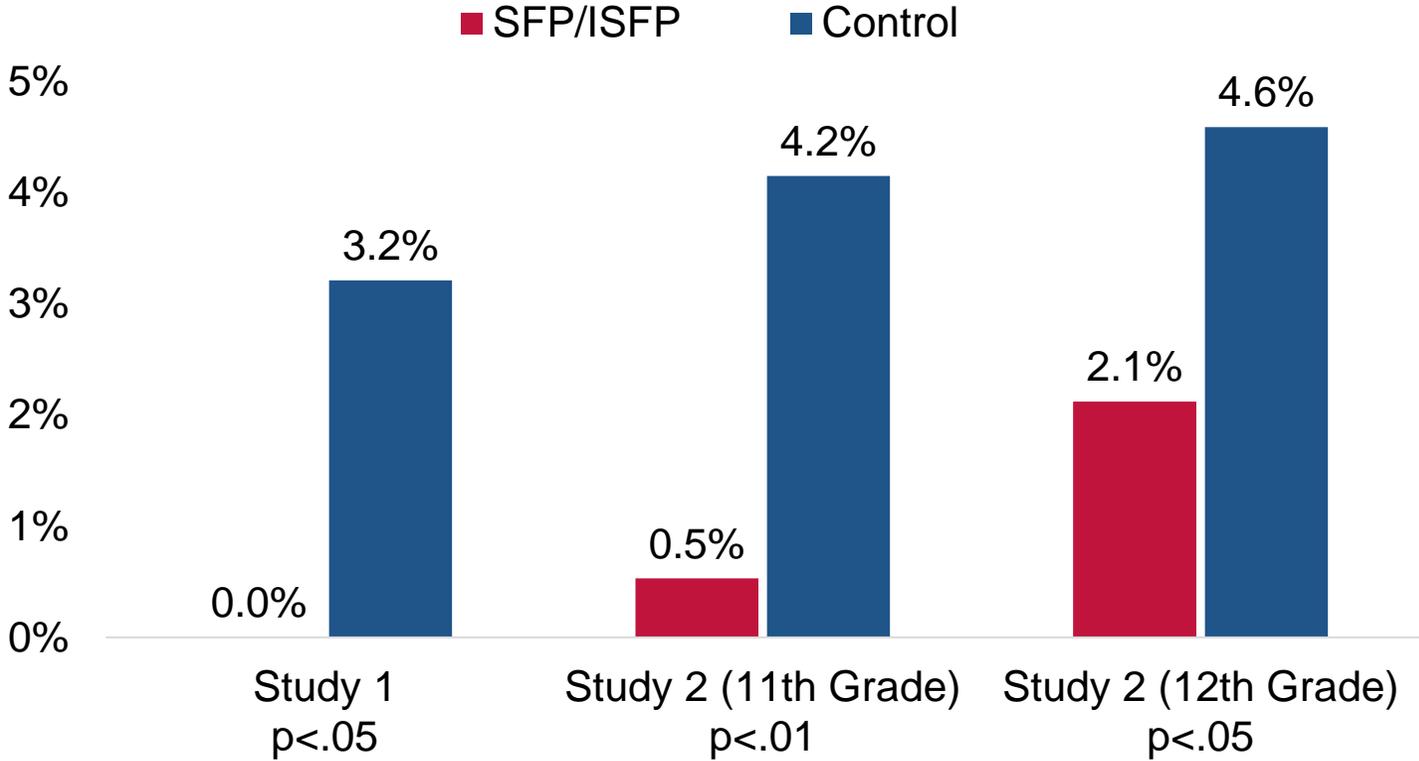
- Naloxone expansion by 30% had largest effect, averting 25% deaths
- Pharmacotherapy, syringe exchange, psychosocial treatment, PMPs reduced deaths improving life years and QALYs
- Reduced prescribing and increasing opioid disposal would reduce deaths
- Combined interventions being more effective than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

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.

Past Year Methamphetamine Use 4½ to 6½ Years Past Baseline



Note: Study 2 included both ISFP and LST interventions
RL Spoth, et al. (2006) Arch Pediatr Adolesc Med.

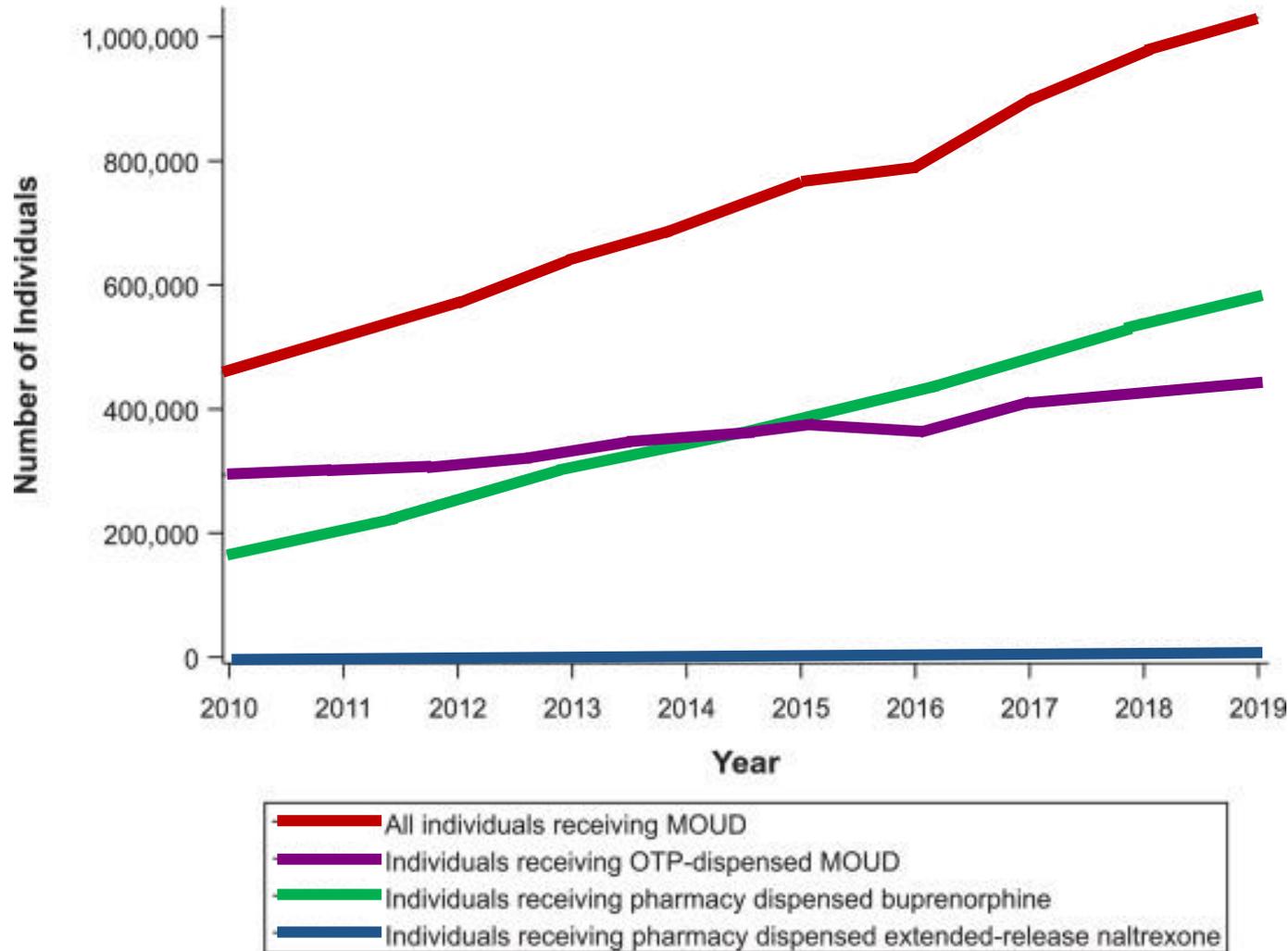
Access to Naloxone

- Naloxone na from May 20
 - In MA, fir (Chatterj
 - Limited a order wa
 - Most pharmacies in TX do not appear to be willing and able to dispense prescribed buprenorphine/naloxone films and naloxone nasal spray to patients with OUD in a timely manner (Hill, et al., 2021).
- Pharmacists express support of dispensing naloxone in rural and urban pharmacies in NY (Tofighi, et al., 2021). Still, research findings indicate underutilization of pharmacists with a specific need of programs and training to support their naloxone dispensing.

In March 2023, FDA approved the first nasal naloxone spray available without a prescription.
On May 22, 2023, FDA approved nalmeffene nasal spray for prescription.

U.S. states
orders
the standing

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.**

NIDA Research pivots to address substance use and overdose trends.

- Treating OUD in the **fantanyl** 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 Examples:



Justice Community Opioid Innovation Network

Study quality care for opioid use disorder in justice populations.

Help create partnerships between local and state justice systems and community-based treatment providers.



HEALing Communities Study

Investigating coordinated approaches for deploying evidence-based strategies to prevent and treat OUD in 67 communities in 4 states.

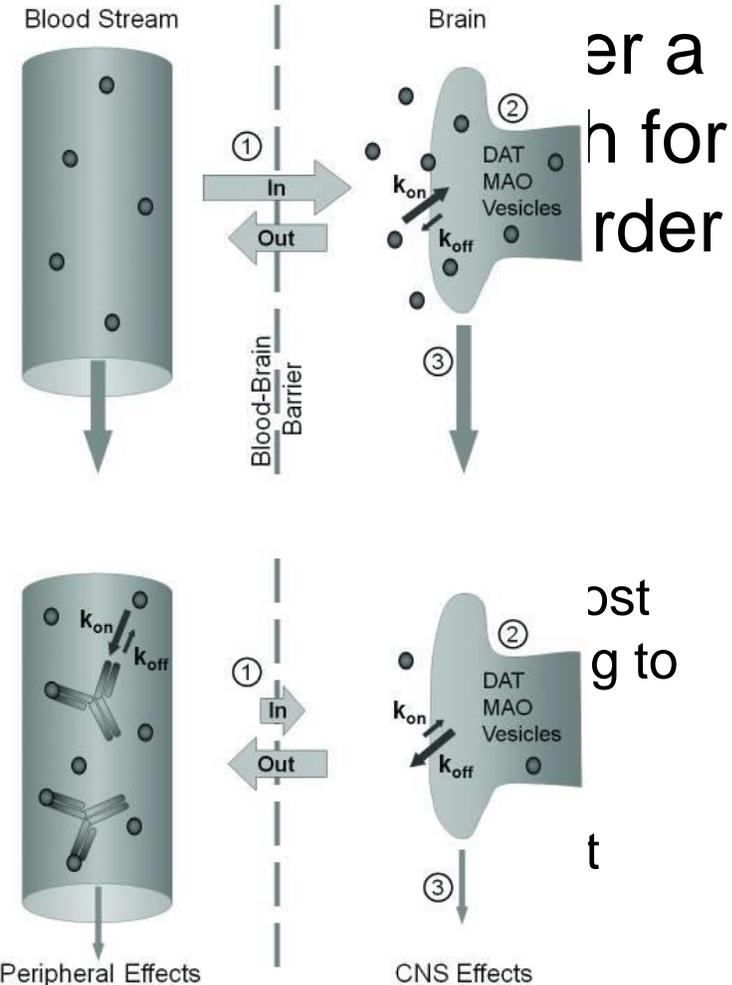
Developing Novel Approaches to Treating Addictions

Vaccines and mAB

ADAPT-2
Meth Effects in the Brain

BEFORE anti-meth antibody treatment

- No FDA approved stimulant
- Contingency effective treatment implemented
- NIDA priority development stimulant

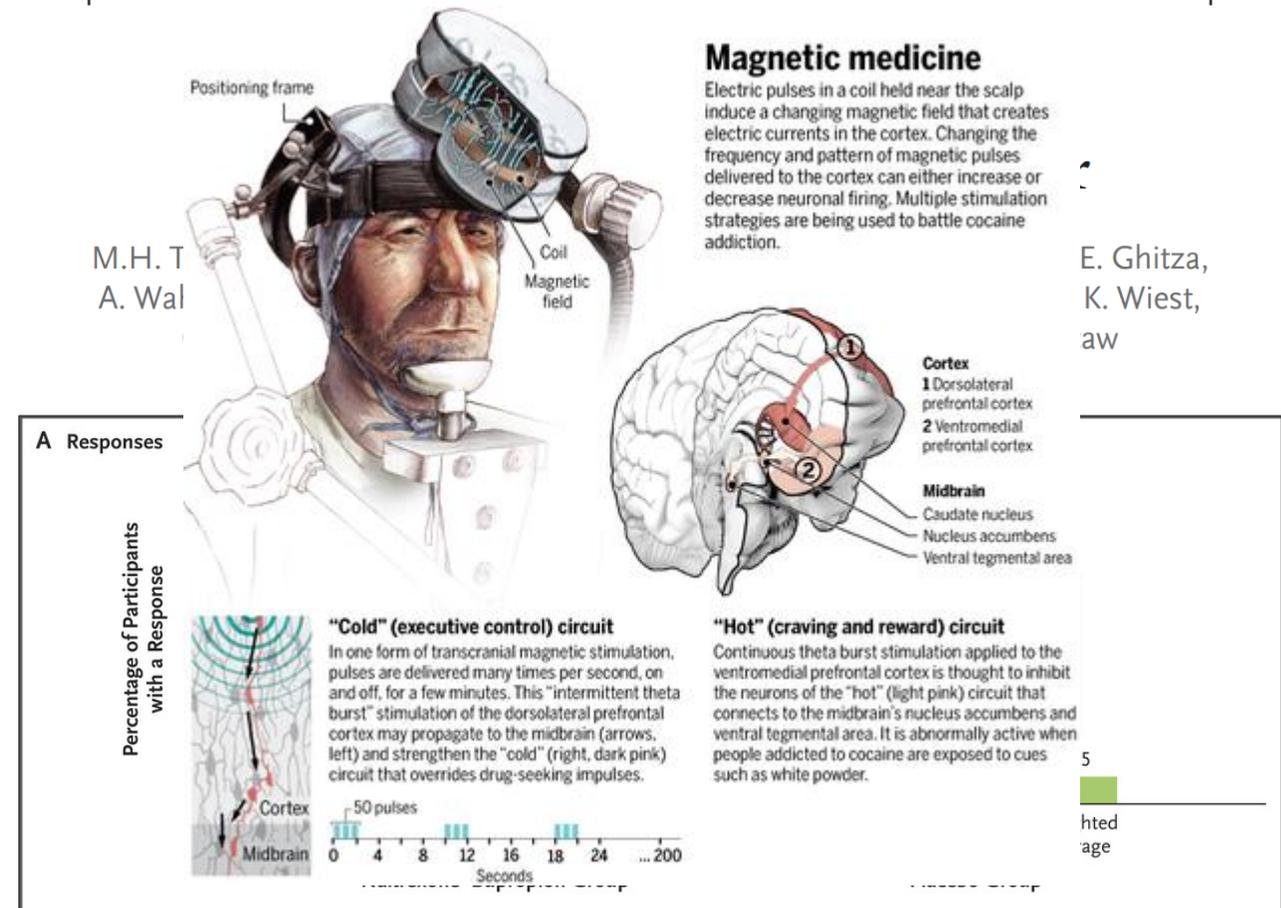


WB Gentry, et al. (2009) Human Vaccines

The NEW ENGLAND JOURNAL of MEDICINE

Transcranial Magnetic Stimulation

ORIGINAL ARTICLE



M Wadman, (2017) Science

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, c, d, e}, 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 stigma toward people with substance use disorder.

Our understanding of substance use disorders as chronic but treatable health conditions has come a long way since the dark days when they were thought of as character flaws — or worse. Yet our societal norms surrounding drug use and addiction continue to be informed by unfounded misconceptions.

Among the most harmful of these is the scientifically unfounded belief that drug-taking by individuals with addiction reflects ongoing deliberate choices. This belief contributes to the continued criminalization of addiction.

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

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.

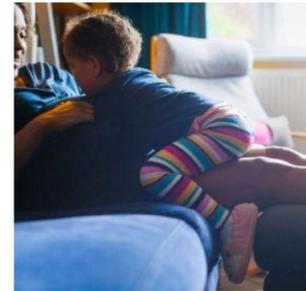
Though it may be hard for many to fathom, even pregnant people and new parents can have active substance use disorders. They need support, not criminalization.

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

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 released a report 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. This number outstrips excessive bleeding, cardiovascular conditions, or other well-known causes of death.

Nora's Blog

Pregnant People With Substance Use Disorders Need Treatment, Not Criminalization



©Getty

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



Summary

- Drug use and drug use disorders are complex concerns that are developmentally informed and shaped by many influences
- Drug use varies over time and geography
- Addressing the current U.S. overdose crisis requires a focus on multiple factors
- Research is needed across a broad range of topics