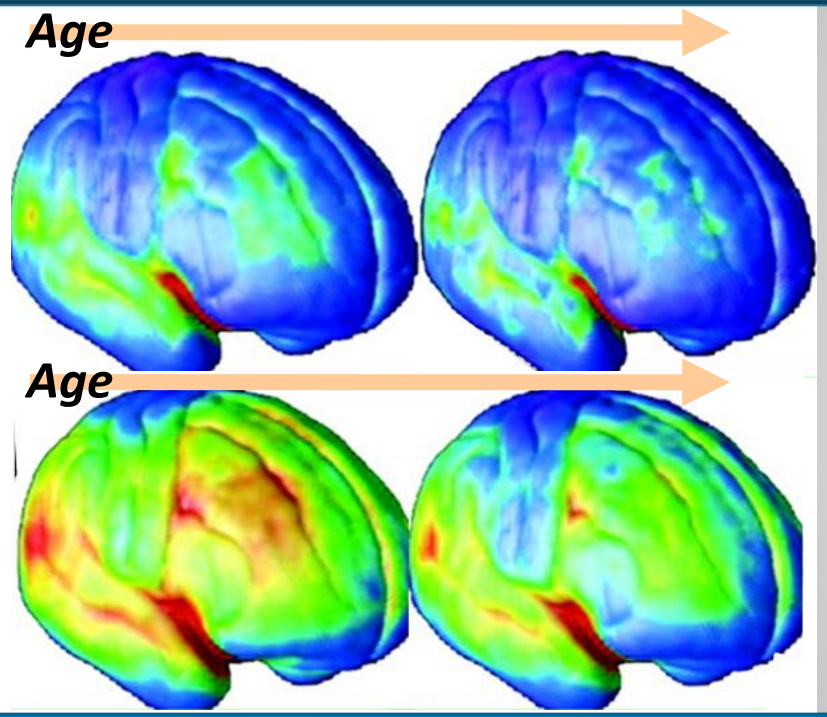
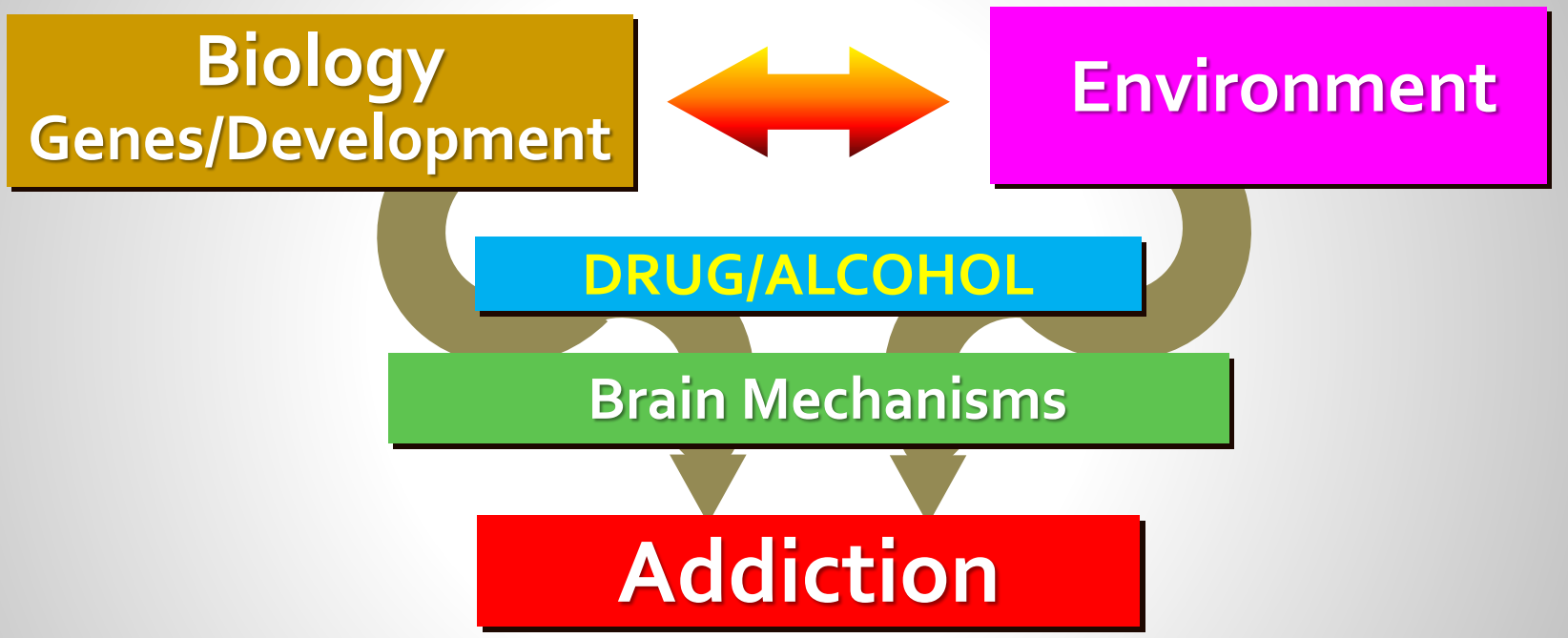
NIDA Update:
Overdose, Vaping, Cannabis, Stimulants





Wilson M. Compton, M.D., M.P.E.
Deputy Director
National Institute on Drug Abuse

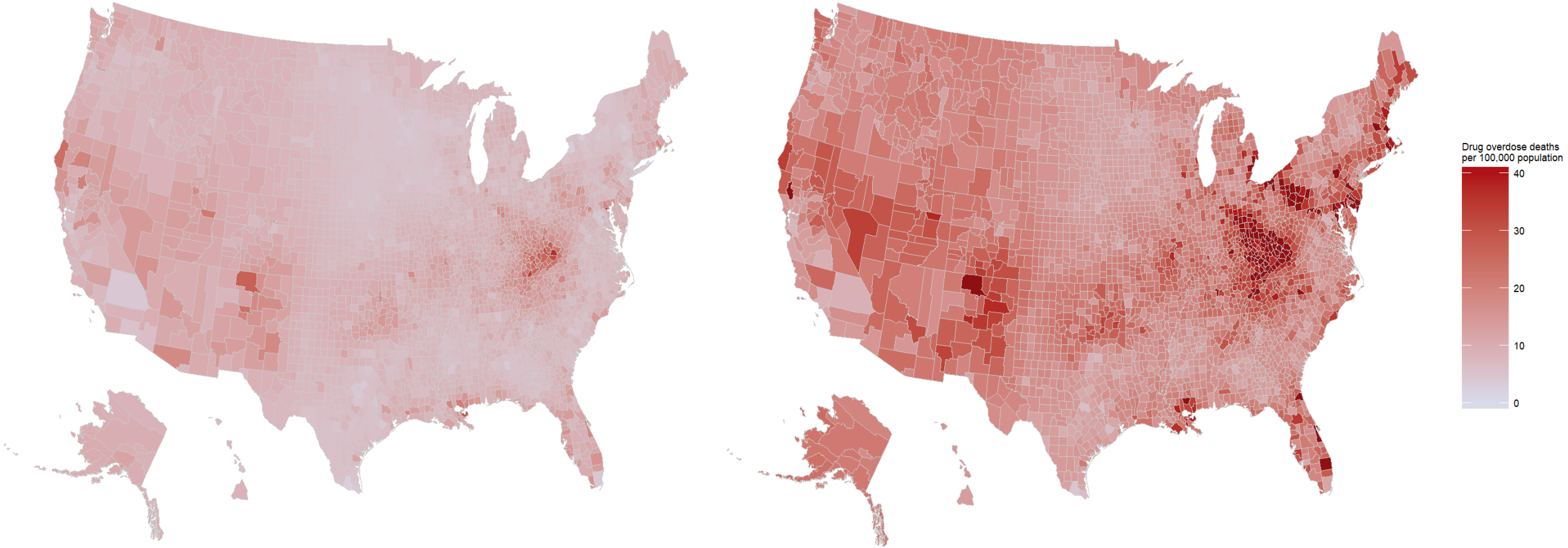
NIH National Institute on Drug Abuse
Advancing Addiction Science

Increased Drug *Overdose* Death Rates

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

2003

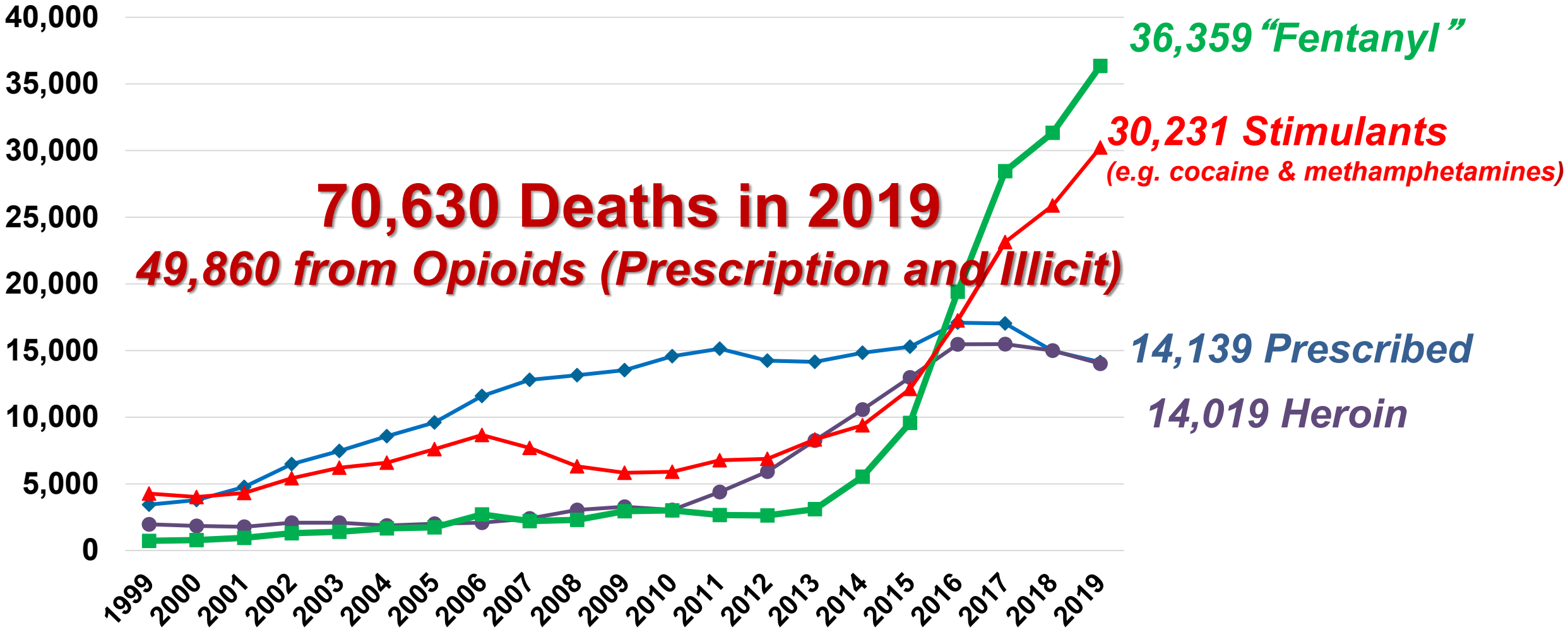
2017



SOURCE: National Center for Health Statistics, National Vital Statistics System, mortality data (http://www.cdc.gov/nchs/deaths.htm).

Evolution of Drivers of Overdose Deaths:

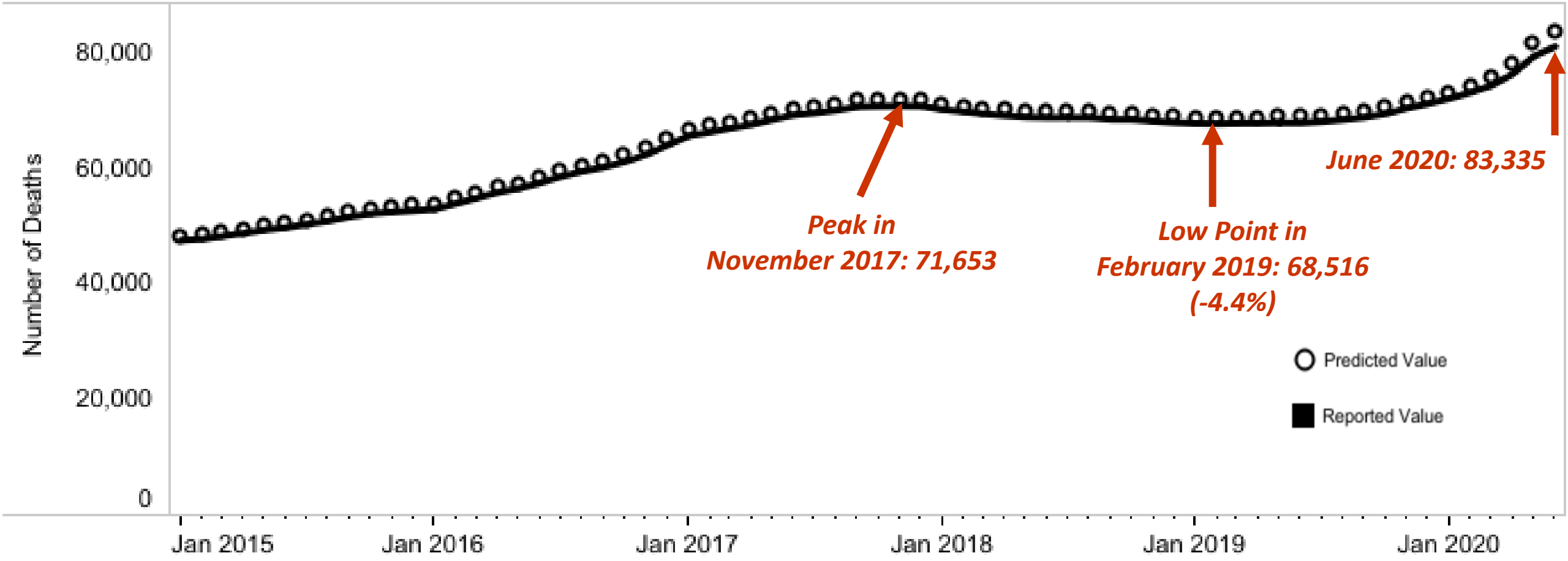
Analgesics ➡ Heroin ➡ "Fentanyl" ➡ Stimulants



See: Compton WM & Jones CM, Ann NY Acad Sci, 2019;
Updated for 2019 from WONDER Database

Recent Changes in Overdose Deaths

Figure 1a. 12 Month-ending Provisional Counts of Drug Overdose Deaths: United States



NCHS Provisional Drug Overdose Death Counts: *https://www.cdc.gov/nchs/nvss/vsrr/drug-overdose-data.htm*
(downloaded 1-18-2021)

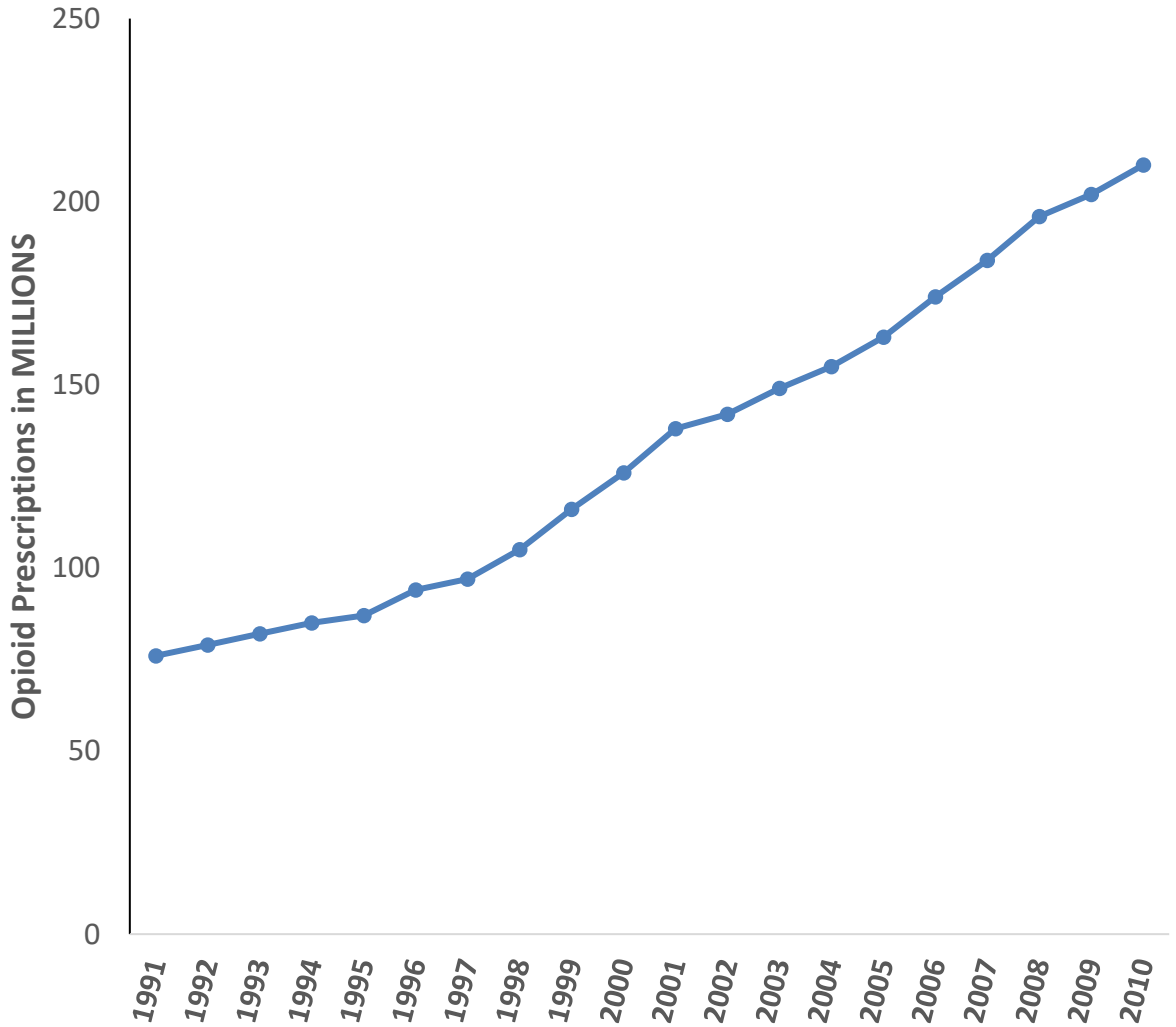
Overdose Deaths Continued to Increase in 2020

	ALL DRUGS	HEROIN	NAT & SEMI – SYNTHETIC	METHADONE	SYNTHETIC OPIOIDS	COCAINE	OTHER PSYCHO-STIMULANTS (mainly meth)
January 2020 *	**72,731**	14,175	12,107	2,795	37,054	16,522	16,882
March 2020*	**75,687**	14,145	12,349	2,837	40,756	17,465	18,033
June 2020*	**83,335**	14,480	12,966	3,195	48,006	19,215	20,318
Jan 2020-June 2020 **Change**	**14.6%**	**2.2%**	**7.1%**	**14.3%**	**29.6%**	**16.3%**	**20.4%**

NCHS Provisional Drug Overdose Death Counts: *https://www.cdc.gov/nchs/nvss/vsrr/drug-overdose-data.htm (as of January 18, 2021)*

ENVIRONMENTAL AVAILABILITY: Current Opioid Crisis Originated with Prescribing Increases

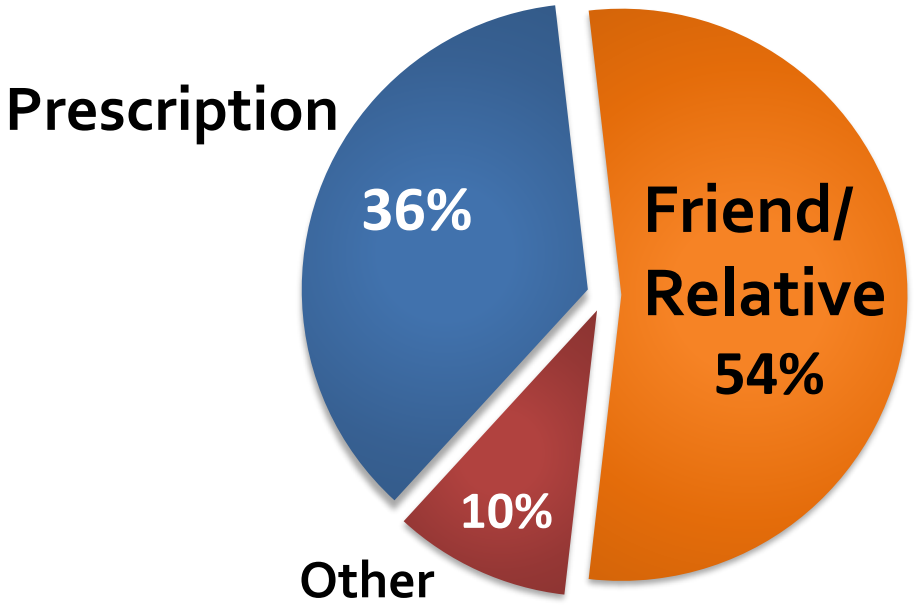
Opioid prescriptions
Tripled to MORE THAN 200 MILLION prescriptions in the 2000's



From Prescriptions to Misuse: *Direct Pathways*

- ***People misusing analgesics Directly obtain them by their own prescriptions***

Source where pain relievers obtained for most recent misuse

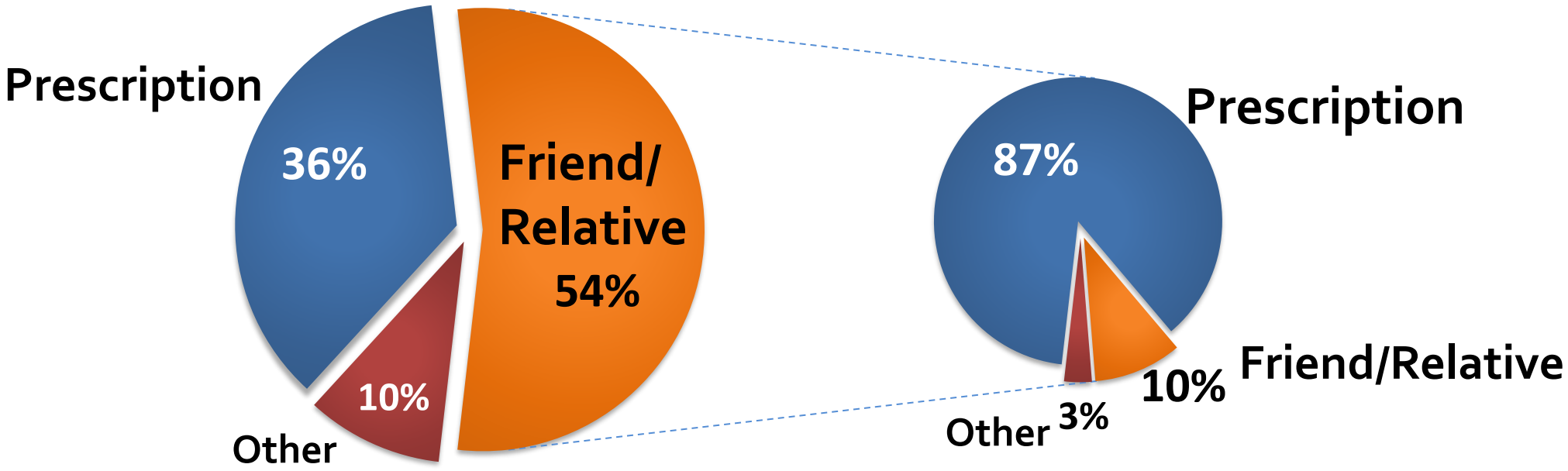


Source: Han, Compton, et al. Annals of Internal Medicine 2017

From Prescriptions to Misuse: *Direct Pathways* and *Indirect*

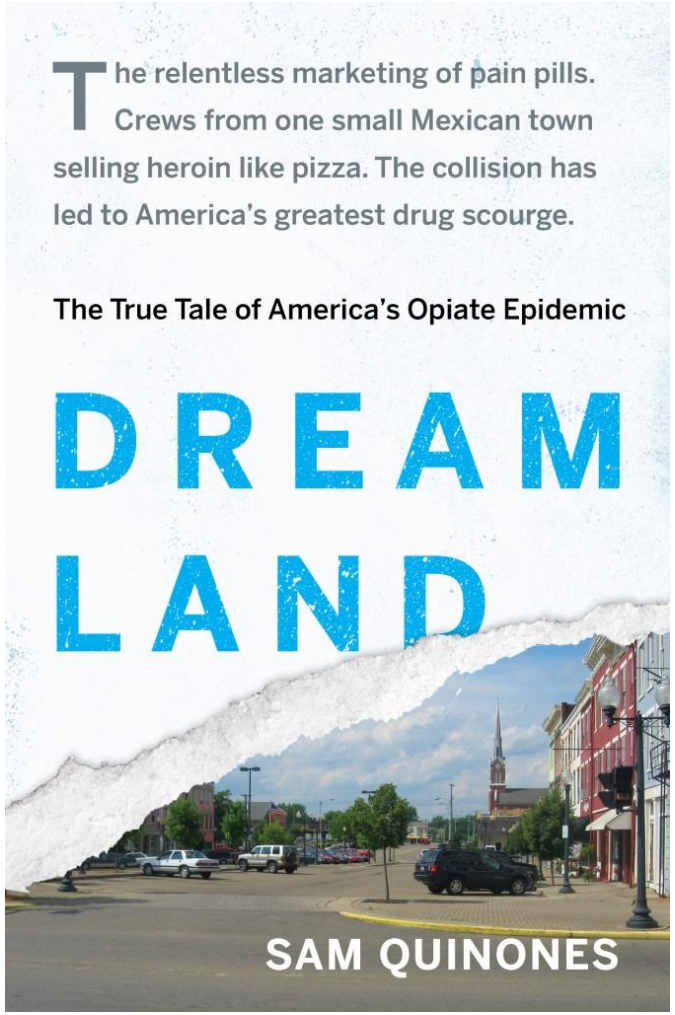
- ***People misusing analgesics Directly obtain them by their own prescriptions, as well as Indirectly from prescriptions of friends and relatives***

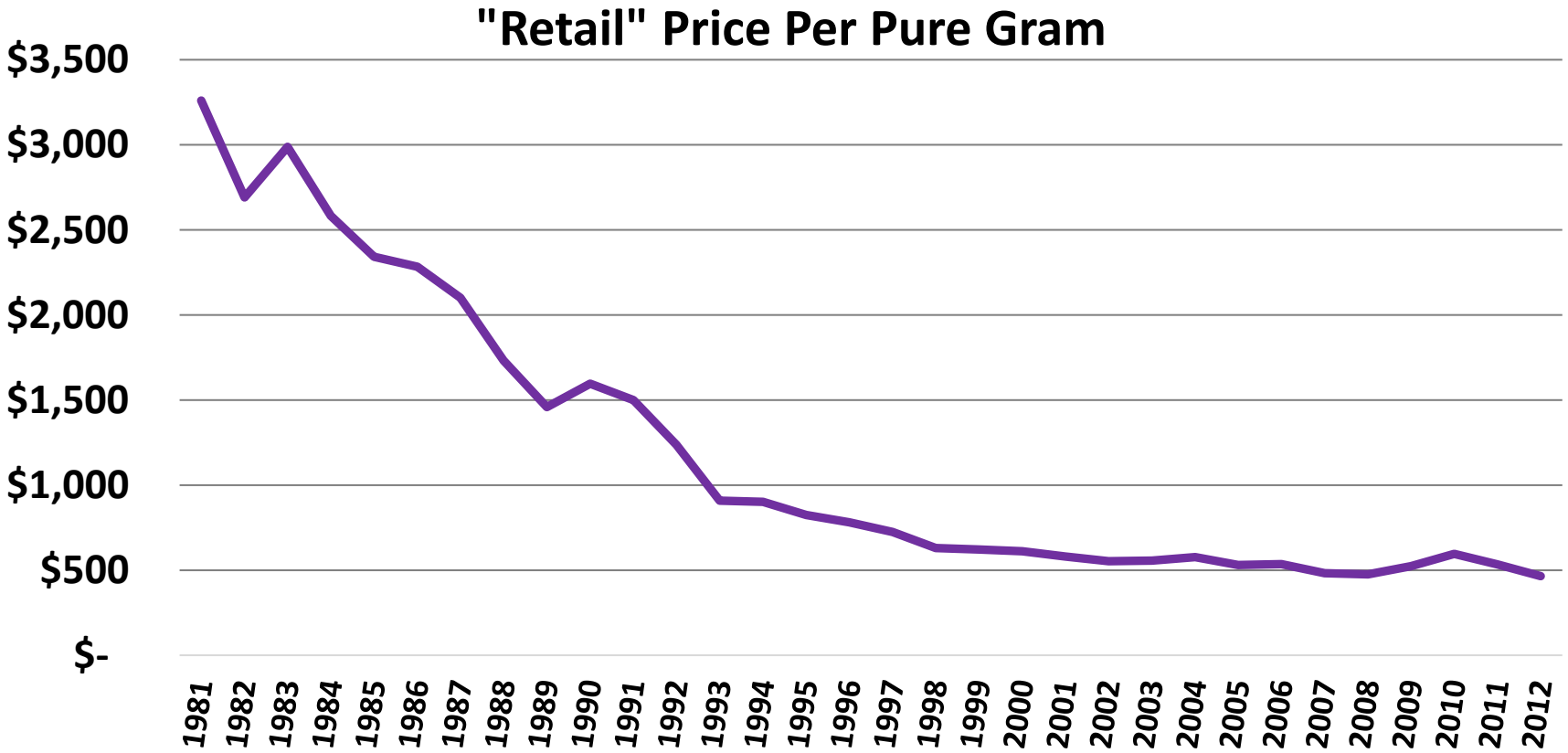
Source where pain relievers obtained for most recent misuse



Source: Han, Compton, et al. Annals of Internal Medicine 2017

ECONOMICS: Heroin Increases Due to Lower Price and Greater Availability

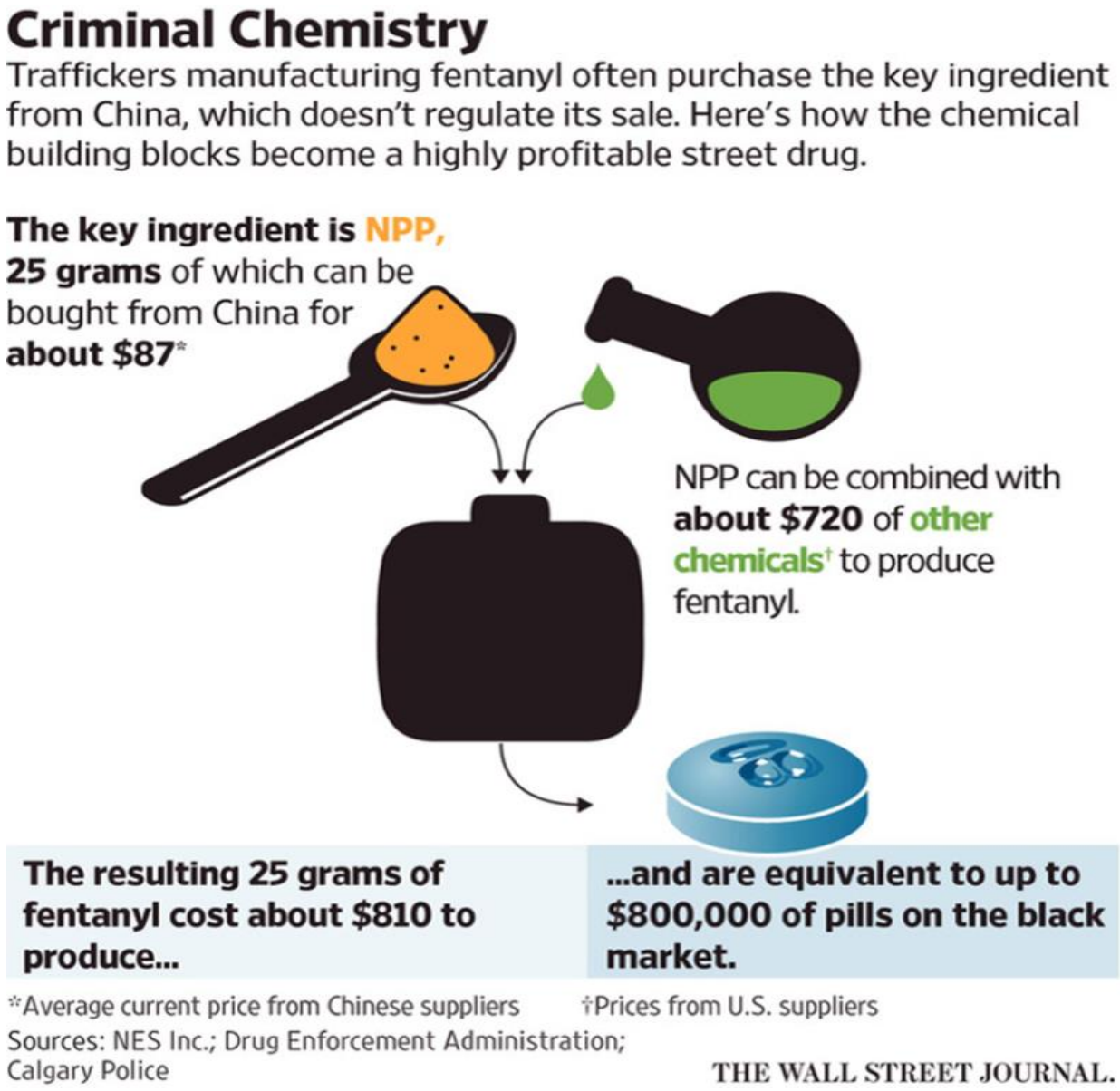




National Drug Control Strategy--Data Supplement 2014. https://www.whitehouse.gov/sites/default/files/ondcp/policy-and-research/ndcs_data_supplement_2014.pdf

ECONOMICS:

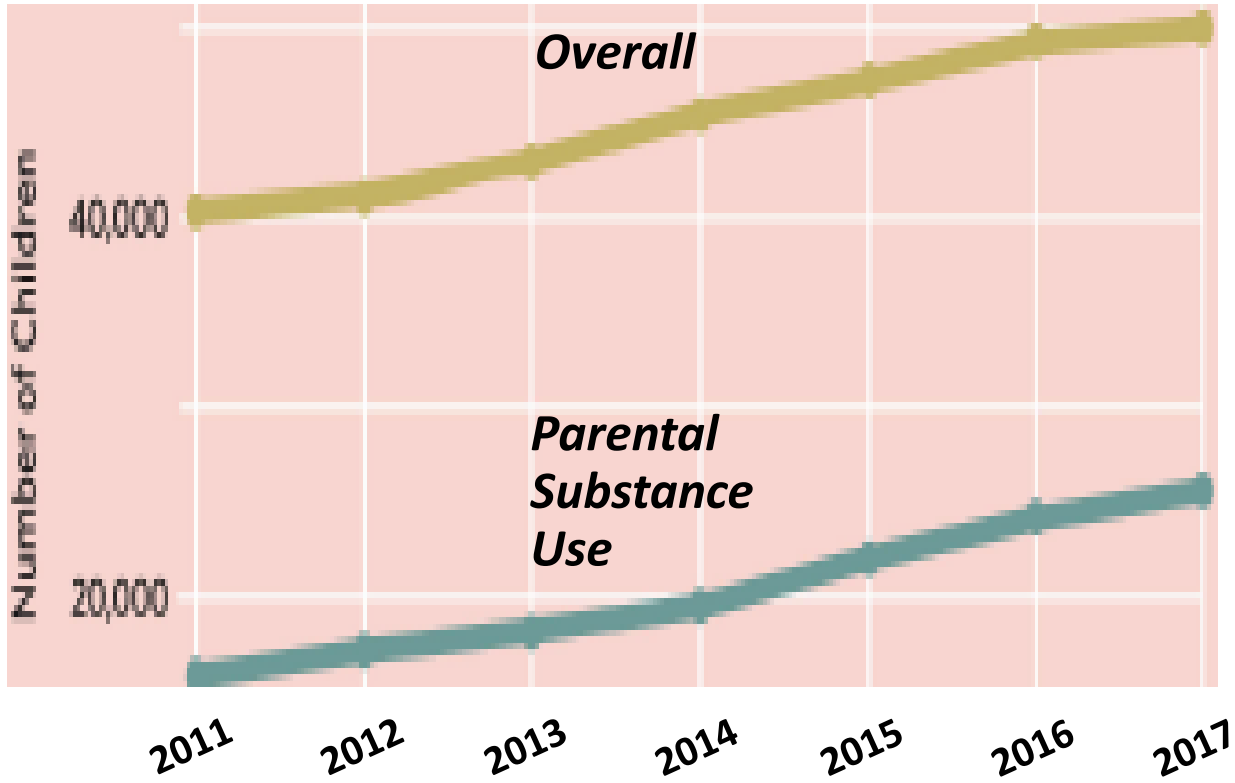
CHEAP Fentanyl Precursor Chemicals



Additional Consequences of Addiction

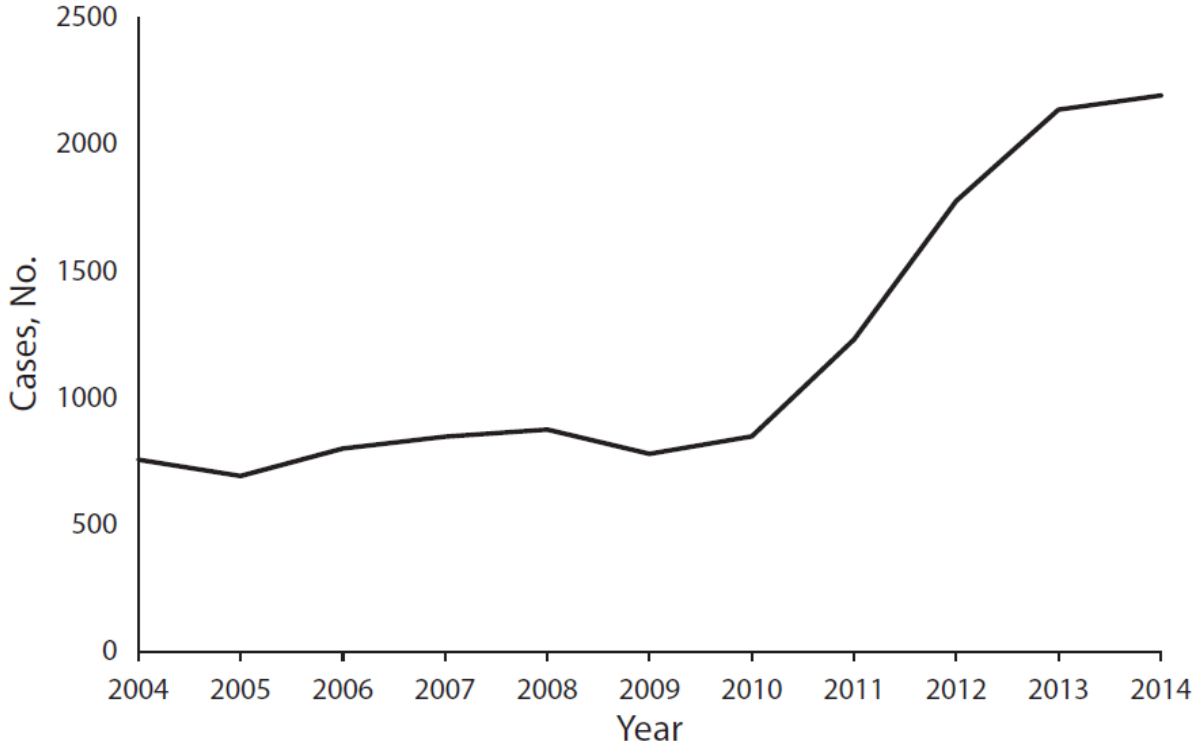
- Drug use while pregnant or parenting has led to increases in rates of neonatal abstinence syndrome and removal of children into the foster care system.
- Increased rates of injection drug use have led to increases in acute cases of Hepatitis C and outbreaks of HIV

U.S. Foster Care Removals for Infants < 1 Y.O.



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

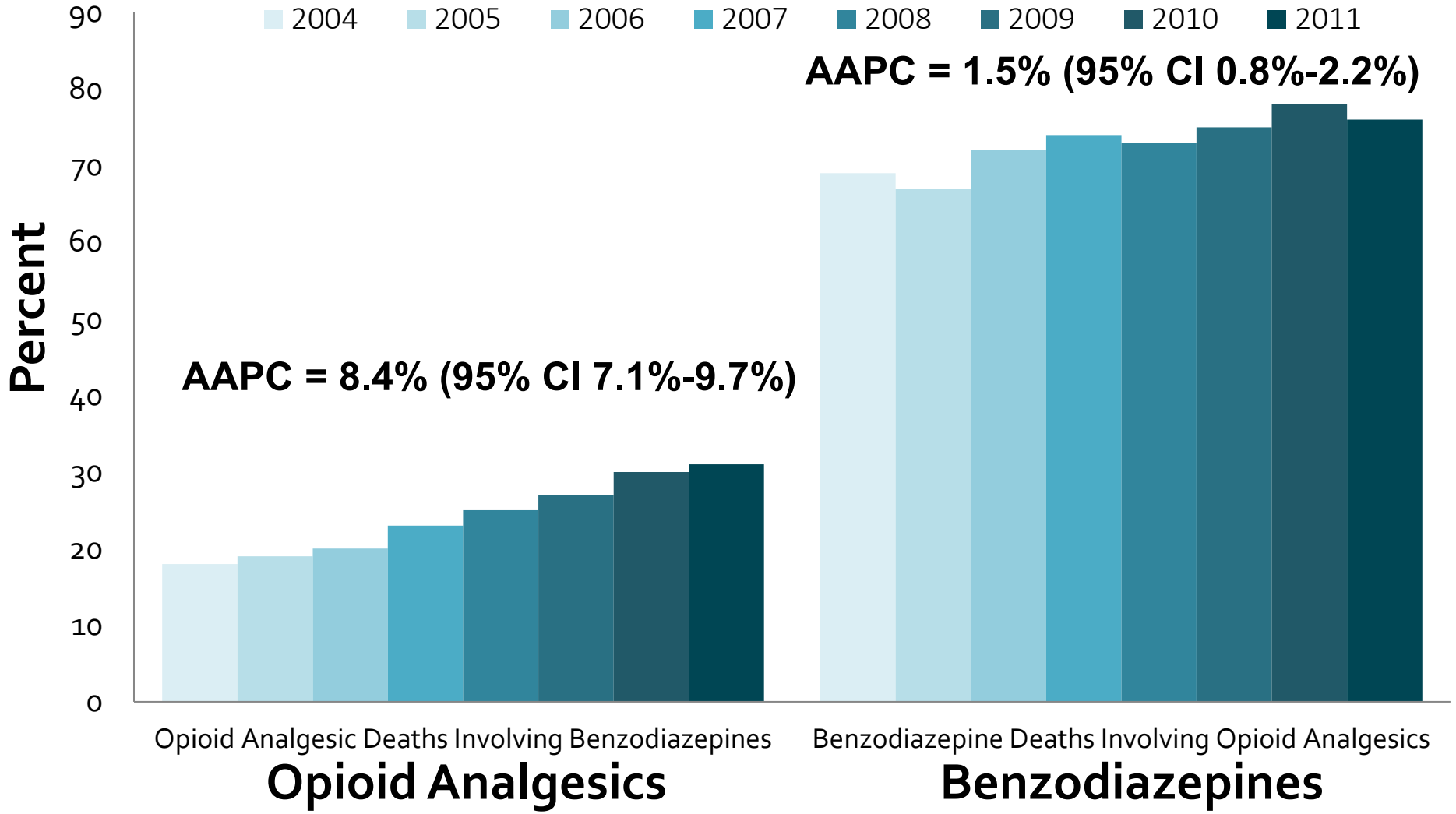
Acute Cases of HCV in USA



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

Overlap of *Benzodiazepines and Opioids*

Opioid Analgesic ED Visits and OD Deaths Involving Benzodiazepines & Benzodiazepine ED Visits and OD Deaths Involving Opioids

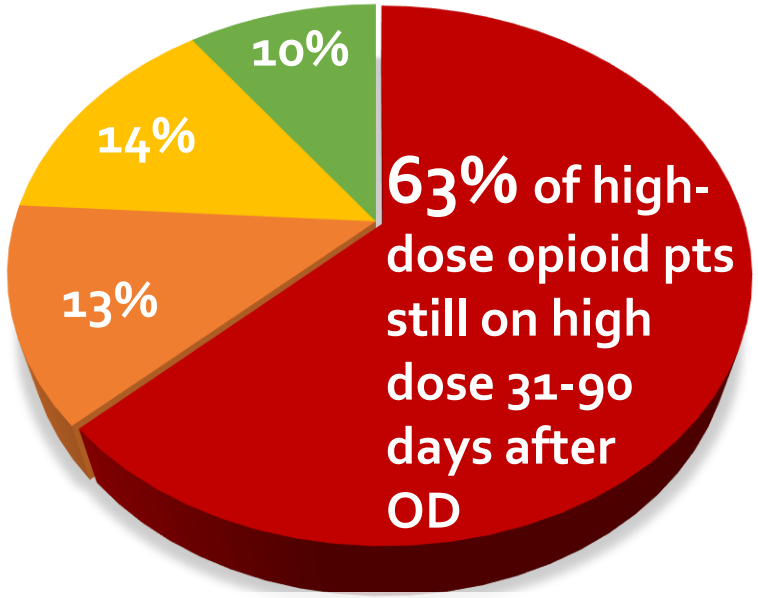


Source: CM Jones, JK McAninch. *American Journal of Preventive Medicine* 2015;49:493-501.

Science = Solutions

Doctors Continue to Prescribe Opioids for Ninety-one Percent of Overdose Patients

*In a **2-year follow-up of 2848 commercially insured patients who had a nonfatal opioid overdose** during long-term opioid therapy :*



17% *of high- dose patients overdosed again within two years*

- ***33-39% of those with active opioid prescriptions during follow-up also were prescribed benzodiazepines.***

Source: Larochelle et al. *Ann Intern Med*. 2016;164(1):1-9.

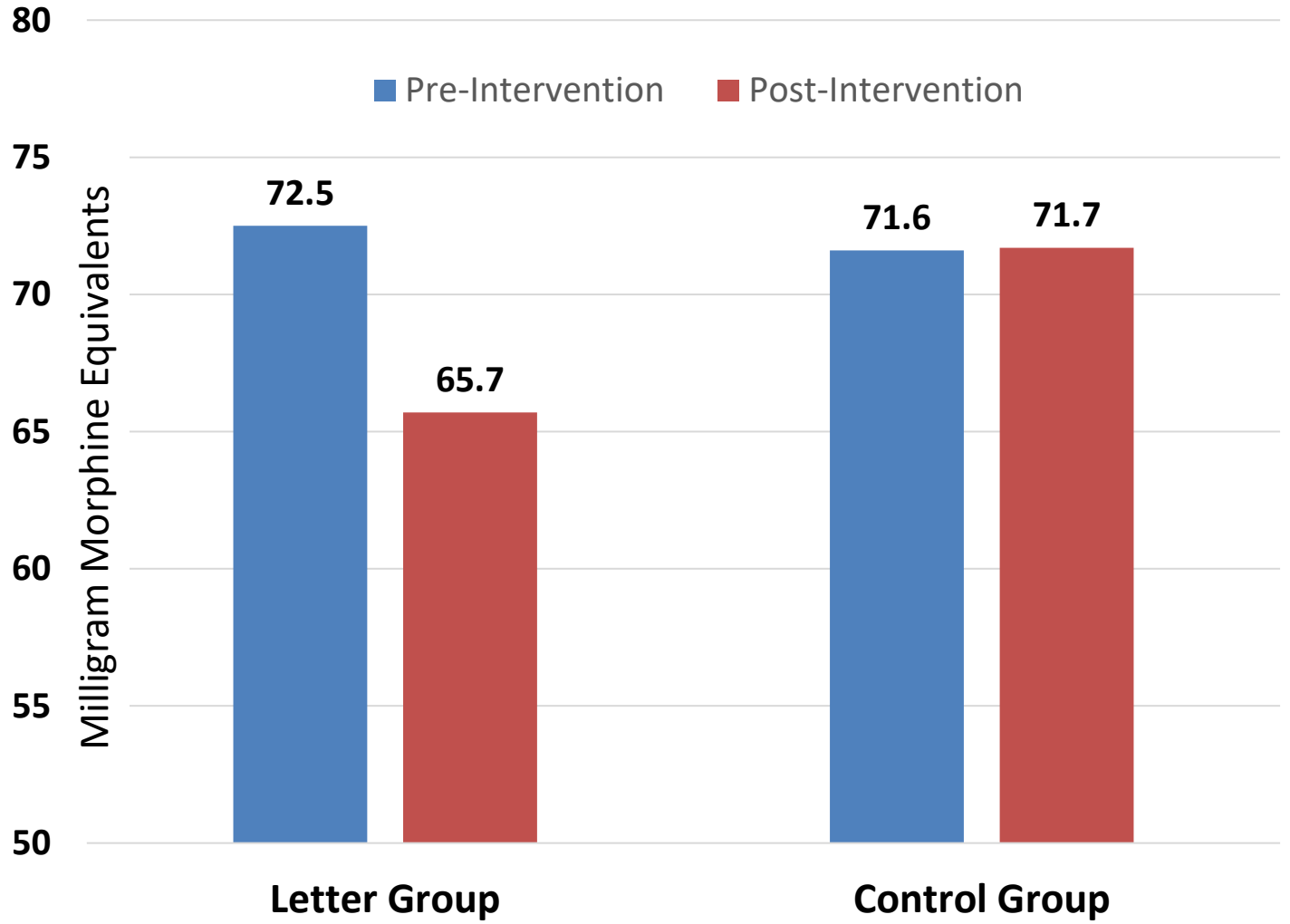
Question:

What can you do to address these issues?

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.



Source: Doctor, et al. *Science* 2018;361(6402):588-590.

Solutions toward *Responsible Prescribing*: Guidance

Opioid Prescribing Guidelines March 2016

- **Intended for primary care providers**
- **Applies to patients >18 years old in chronic pain outside of end-of-life care**
- ***Focuses on:***
  - **Determining when to initiate or continue opioids for chronic pain**
  - **Opioid selection, dosage, duration, follow-up and discontinuation**
  - **Assessing risk and addressing harms of opioid use**

JAMA® The Journal of the American Medical Association

Dowell, Compton, Giroir.
2019;322(19):1855–1856

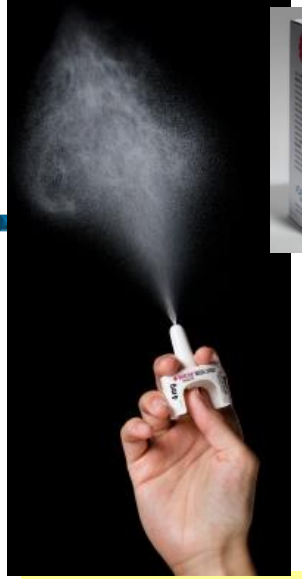
Patient-Centered Reduction or Discontinuation of Long-term Opioid Analgesics:

The HHS Guide for Clinicians

Focuses on:

(1) Criteria for reducing or discontinuing opioid therapy
(2) Considerations prior to deciding to taper opioids
(3) Ensuring patient safety prior to initiating taper
(4) Shared decision-making with patients
(5) Rate of opioid taper
(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.



Naloxone Distribution

Direct intervention to save lives:
Nasal spray and Auto-injector formulations

April 5, 2018

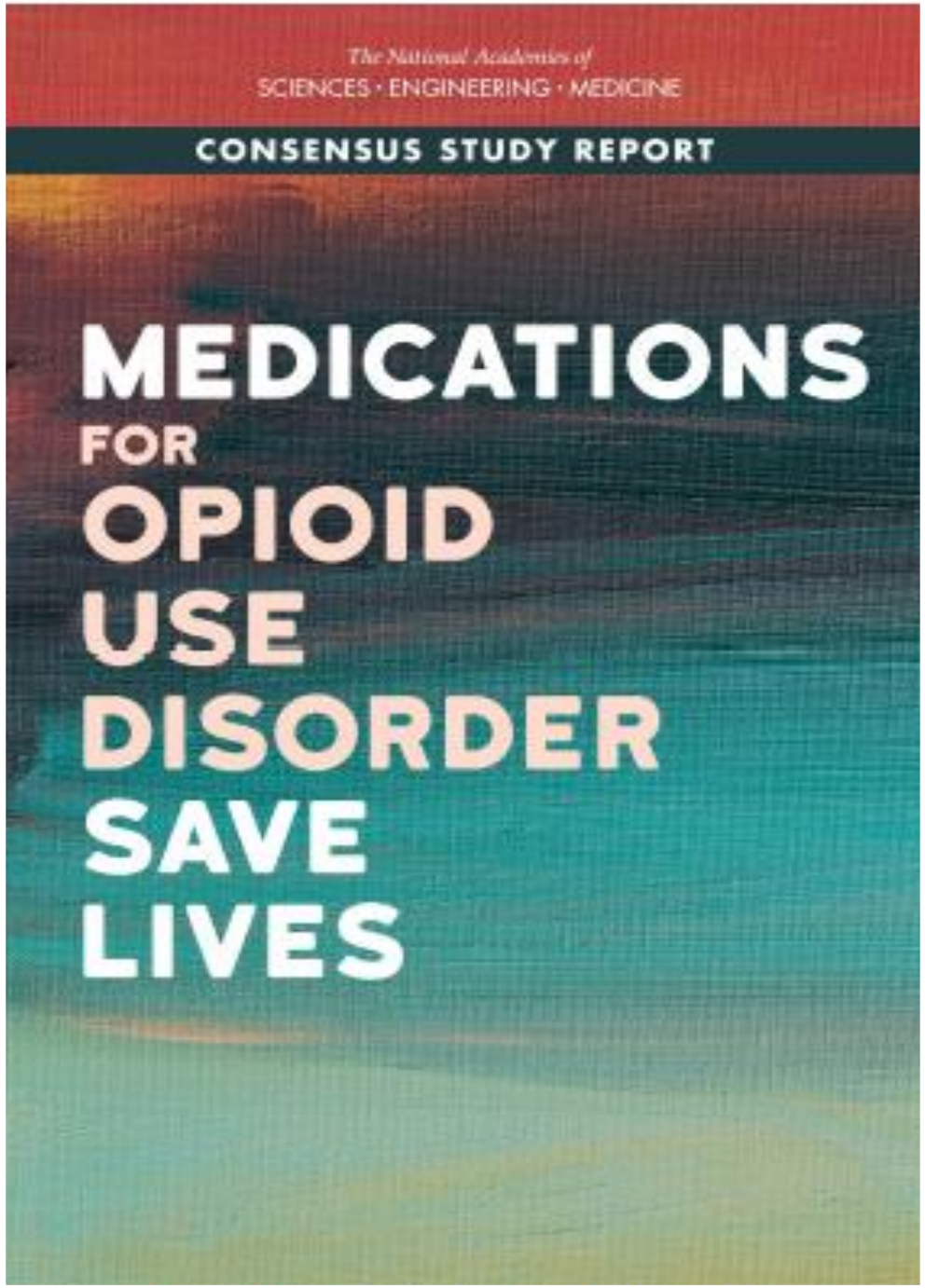
Surgeon General's Advisory on Naloxone and Opioid Overdose

I, Surgeon General of the United States Public Health Service, VADM Jerome Adams, am emphasizing the importance of the overdose-reversing drug naloxone. For patients currently taking high doses of opioids as prescribed for pain, individuals misusing prescription opioids, individuals using illicit opioids such as heroin or fentanyl, health care practitioners, family and friends of people who have an opioid use disorder, and community members who come into contact with people at risk for opioid overdose, ***knowing how to use naloxone and keeping it within reach can save a life.***

BE PREPARED. GET NALOXONE. SAVE A LIFE.

Next steps

- *Longer acting agents to address fentanyl risks?*
- *Respiratory stimulation?*
- *Device development?*

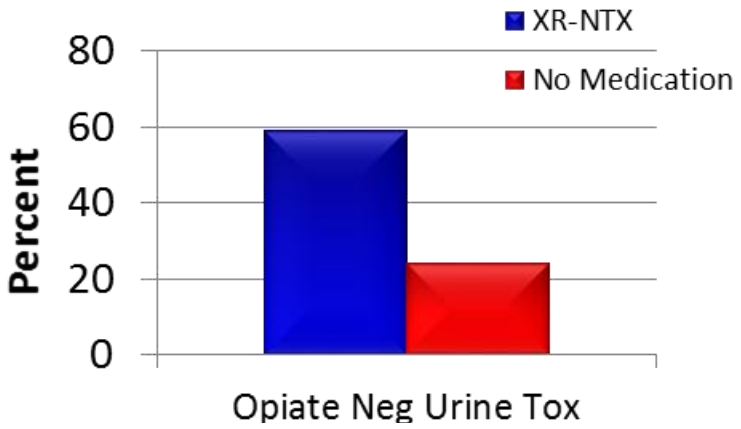


Medications for Opioid Use Disorder are underutilized, and
Relapse rates are very high!

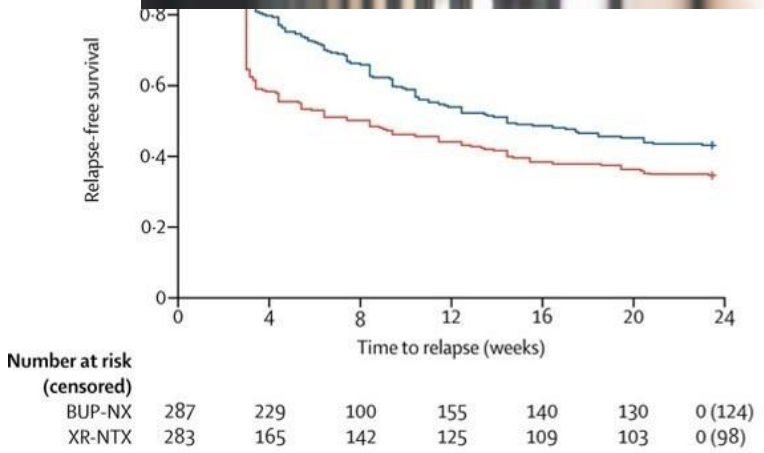
Science = Solutions: Improving Addiction Treatment

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

Post Prison-Release Outcomes

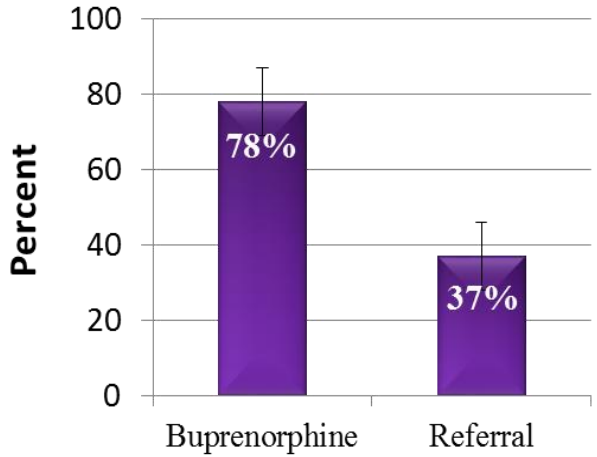


Lee JD, et al., Addiction 2015;100:1005-1014
and New Eng J Med 2016;374:1232-1242



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

ED-initiated Buprenorphine Increased TX Engagement



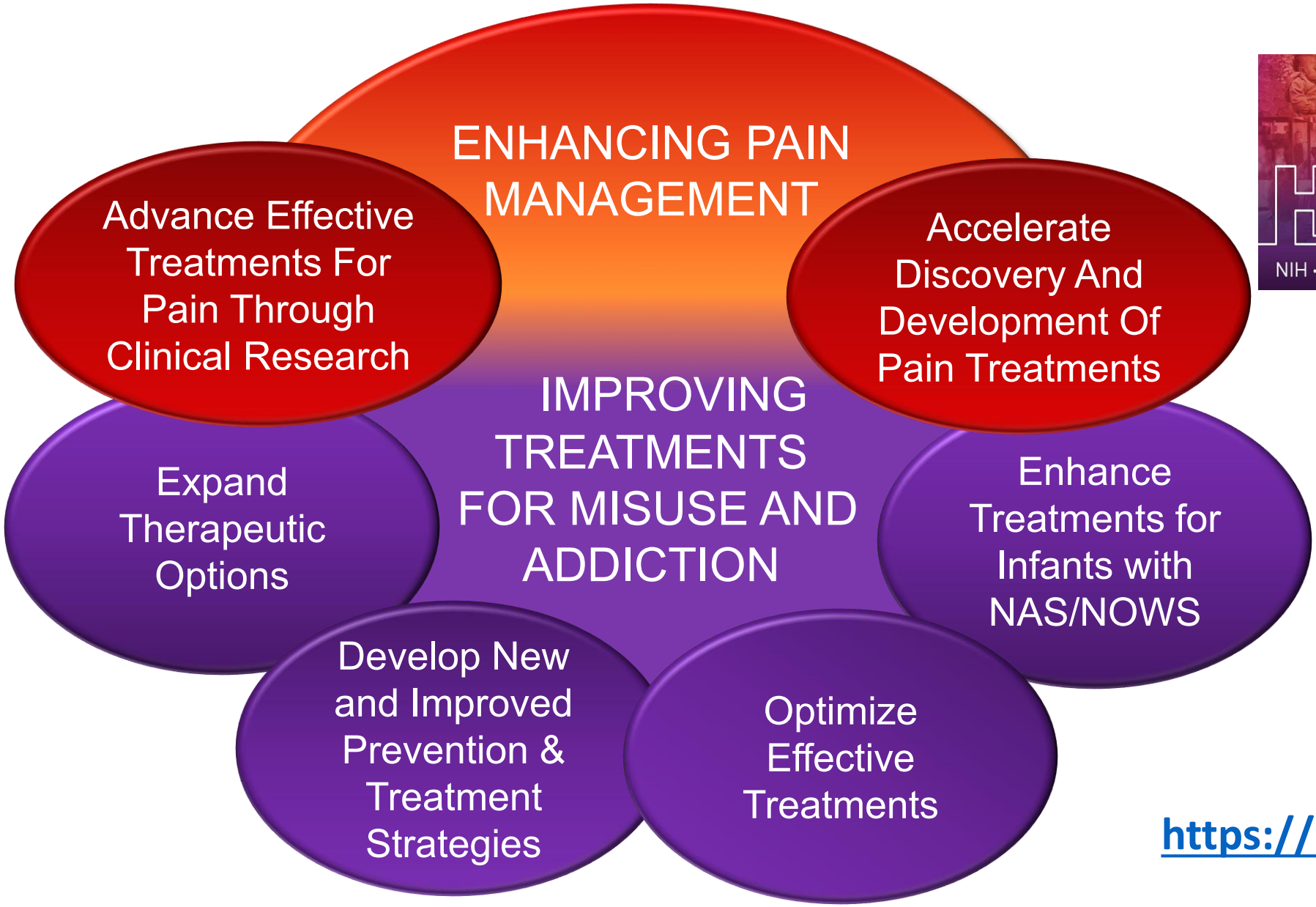
D'Onofrio JAMA. 2015.

Scientific solutions to the opioids crisis

https://heal.nih.gov/

- $500M/year effort
  - > $945M obligated in FY2019
  - 40+ funding opportunity announcements
  - 41 states
  - 400 Investigators
- > 25 HEAL research programs
  - 12 NIH Institute and Centers
  - From prevention, basic and translational research, clinical trials, to implementation science
- Research ongoing for years to come

Helping End Addiction Long Term℠ (HEAL) Initiative



https://heal.nih.gov/

Question:

How does the SARS-Cov-2 pandemic intersect with the overdose crisis?

Overdoses Grew During SARS-CoV-2 Pandemic at a Faster Pace than Early 2020

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

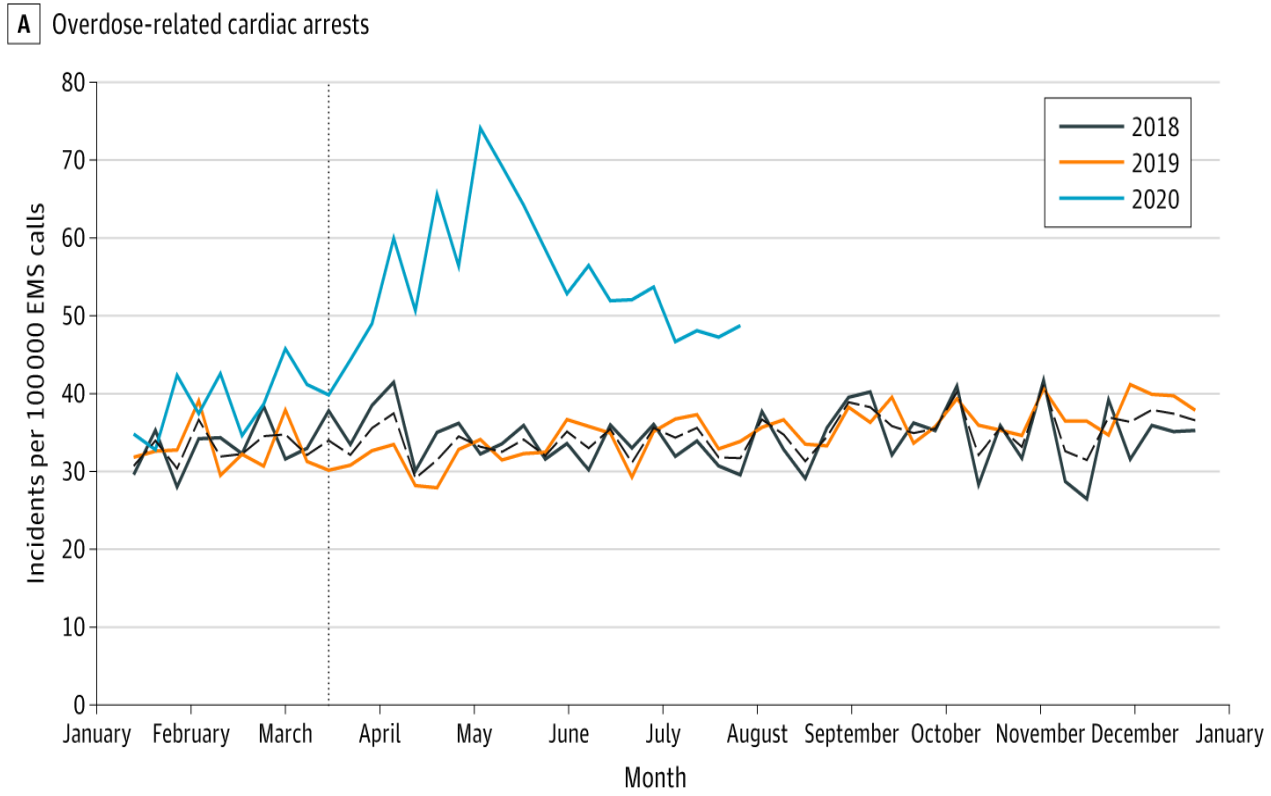
Note: Percent growth references the 1,201 agencies reporting to ODMAP by 1st January

Source: ODMAP

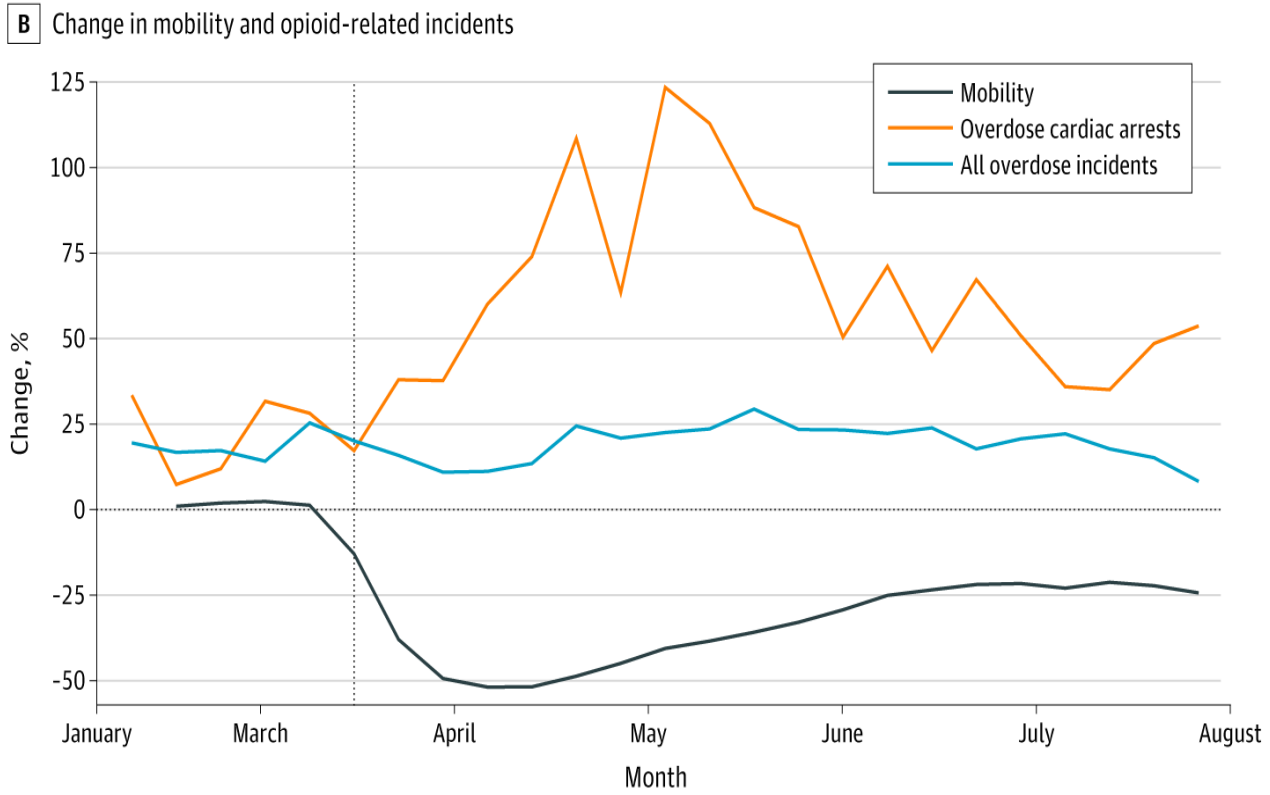
ODMAP OVERDOSE DETECTION MAPPING APPLICATION PROGRAM

ALYSSA FOWERS/THE WASHINGTON PO

Increased Overdose-Related Cardiac Arrests During the US COVID-19 Epidemic



Overdose-related cardiac arrests per 100 000 EMS calls for 2018 through August 2020. (Average of 2018 and 2019 values is the dotted black line.)

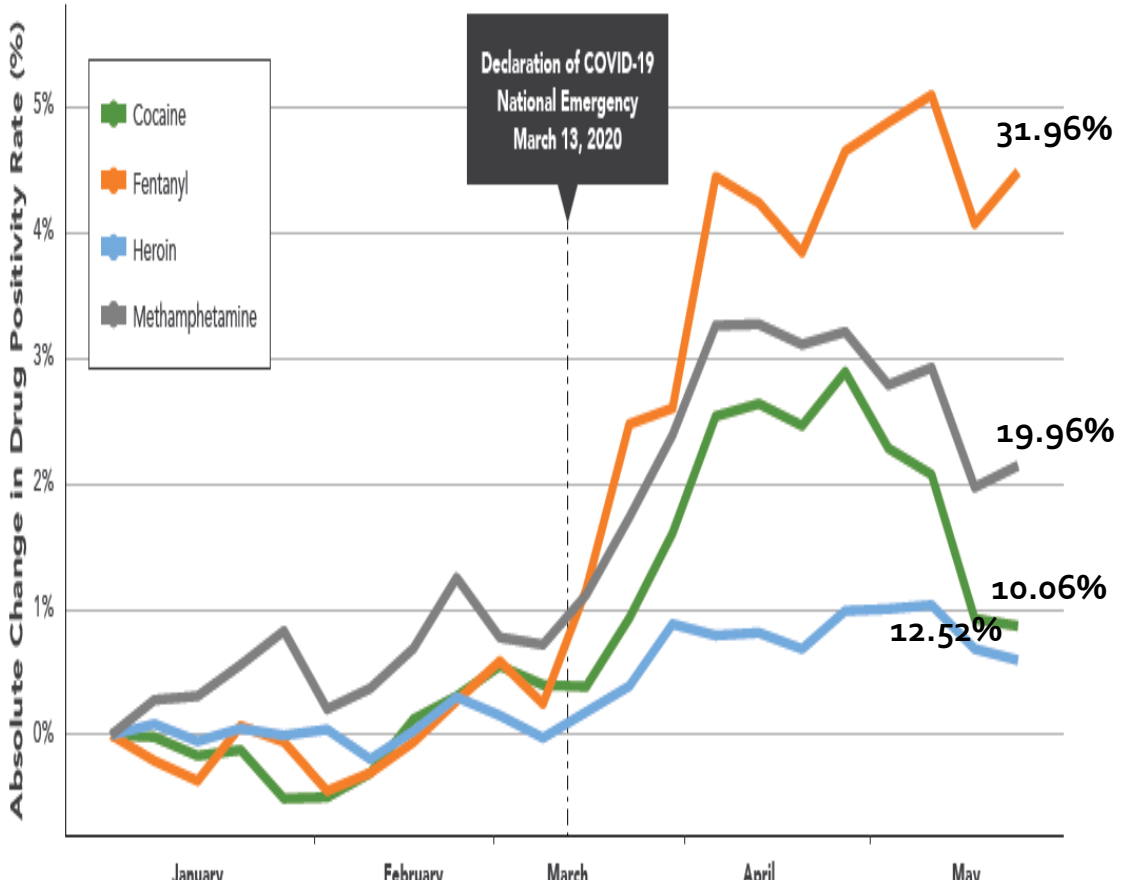


Elevation in 2020 over baseline values in overdose-related cardiac arrests and all overdose-related EMS calls alongside changes in mobility

Vertical dashed line marks March 16, when mobility first markedly decreased nationally in the US.

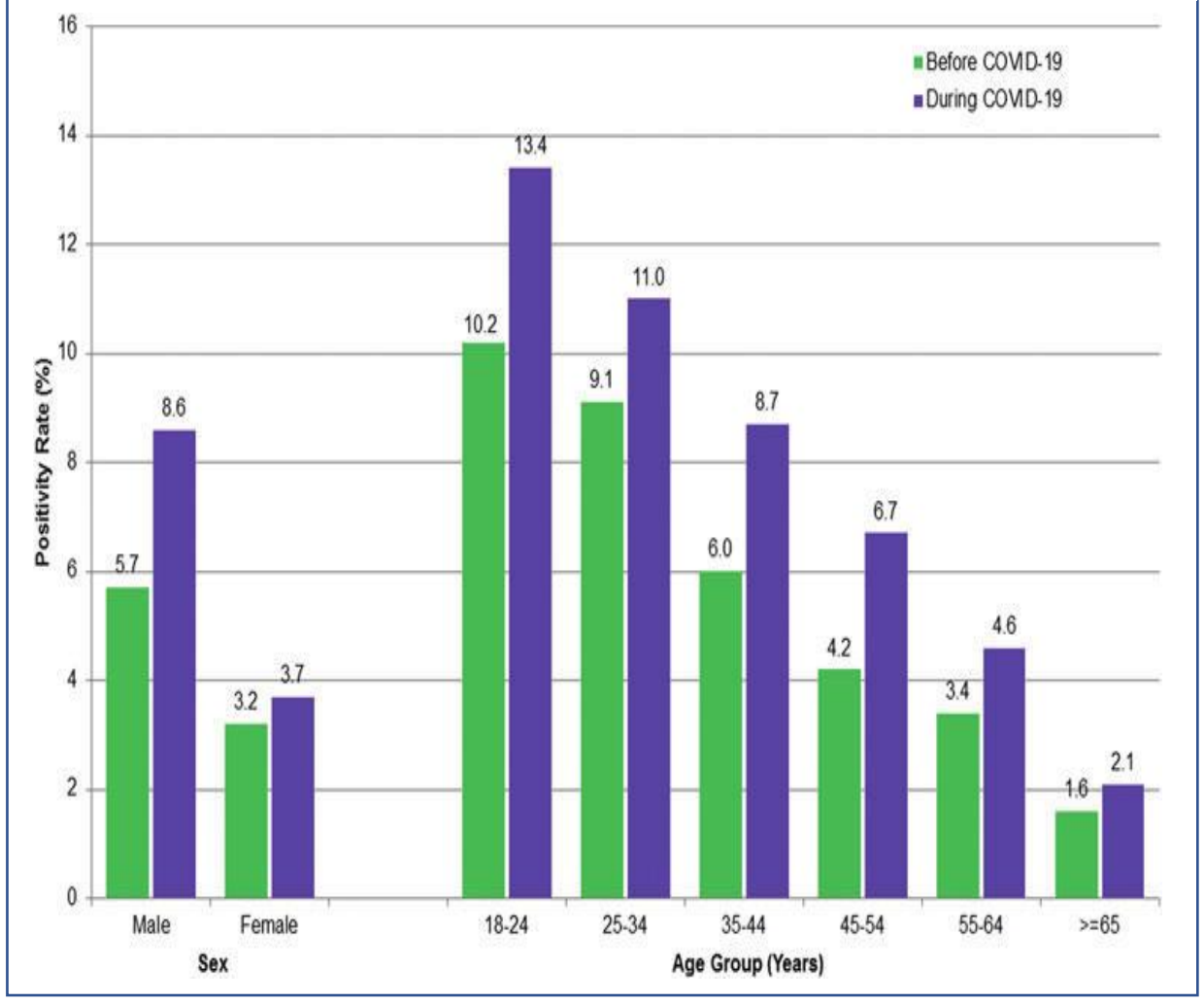
Source: J Friedman. L Beletsky, DL Schriger. *JAMA Psychiatry* December 03, 2020. doi:10.1001/jamapsychiatry.2020.4218

Drug Use Increases During Pandemic



Millennium Health Signals Report™ COVID-19 Special Edition: Significant Changes in Drug Use During the Pandemic Volume 2.1 Published July 2020

Fentanyl Positivity, by Age and Sex, Before and During COVID-19

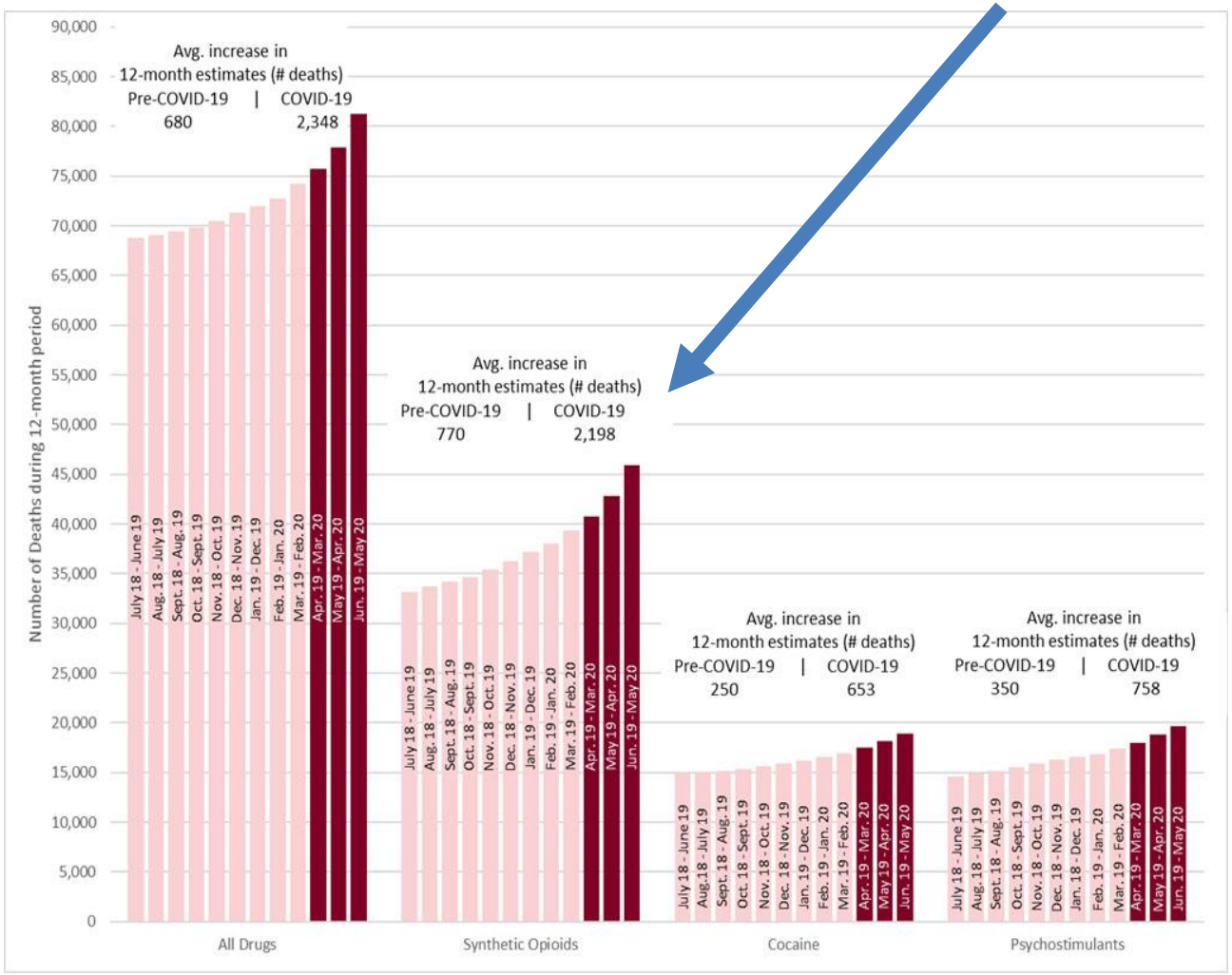


Niles JK et al., Population Health Management, 2020.

Increased Overdose Death Rates During COVID-19 Pandemic

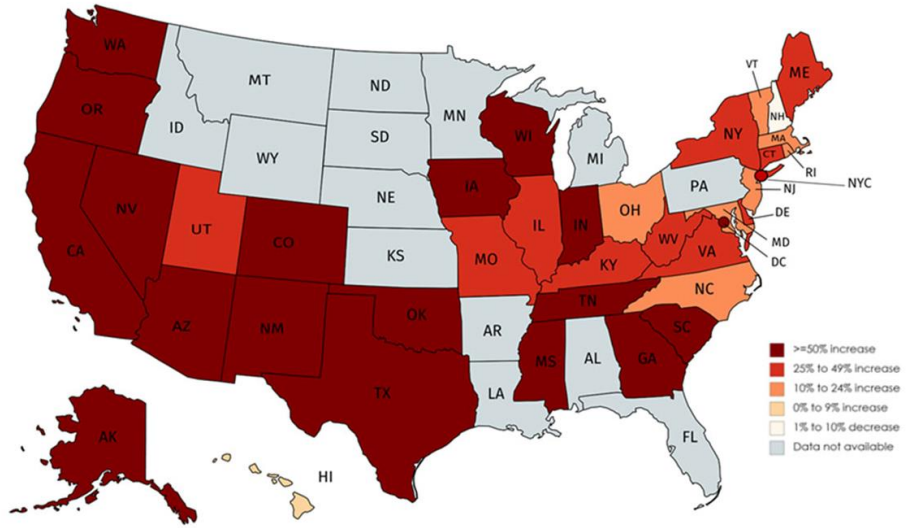
12-months Ending June 2019 Compared to 12-months Ending May 2020

Primarily Driven by Synthetic Opioids



38.4% increase in synthetic opioid OD deaths across U.S.

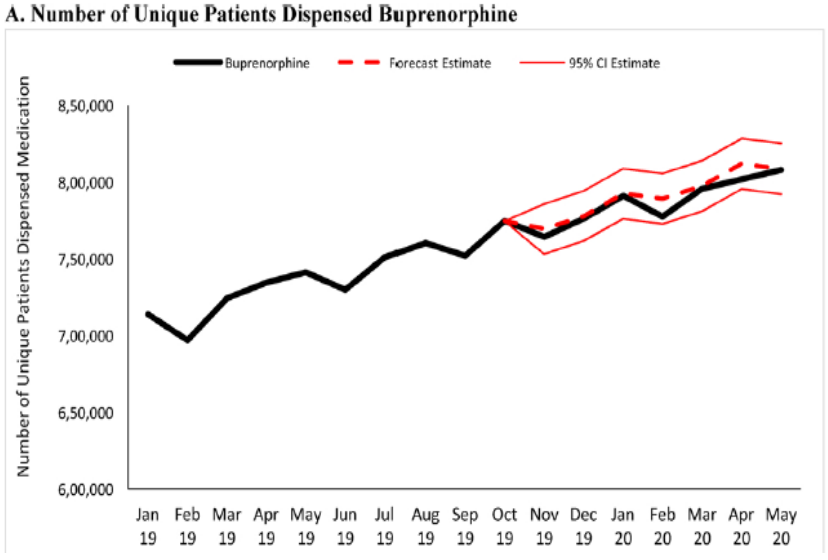
- ⬆ 98.0% - 10 western states
- ⬆ 35.4% - 12 southern states & DC
- ⬆ 32.1% - 6 midwestern states
- ⬆ 21.1% - 8 northeastern states & NYC

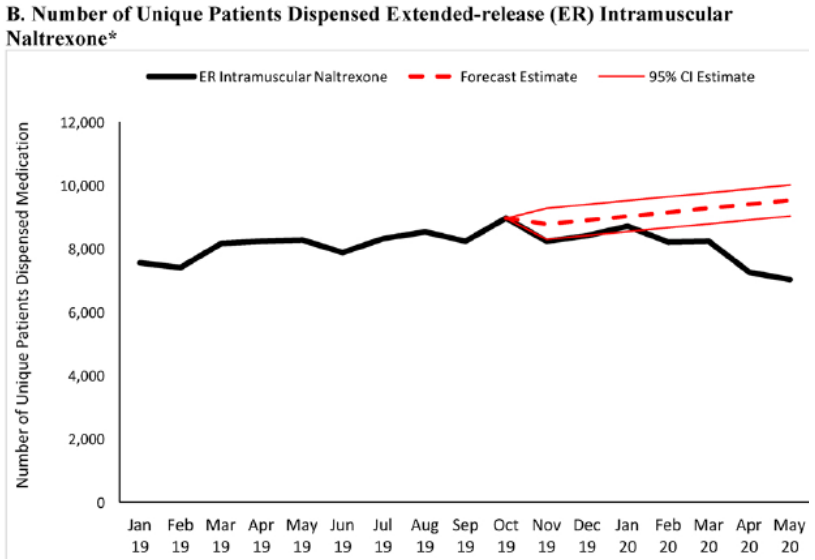


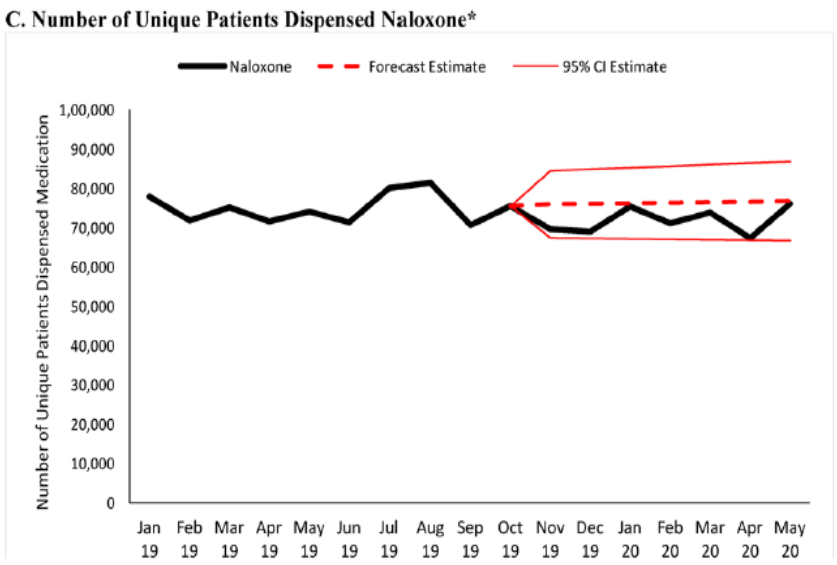
SOURCE: CDC Health Alert Network Advisory December 17, 2020, https://emergency.cdc.gov/han/2020/han00438.asp

MAT Prescribing During Early Pandemic, March 2020-May 2020

- Extended-release intramuscular naltrexone prescriptions fell statistically significantly ***below forecasted levels***
  - Suggests patients had difficulty obtaining XR-BUP due to healthcare provider office closures and need for provider to administer medication
- Buprenorphine and naloxone prescribing was at forecasted levels
- Comparison prescriptions for other conditions were ***above*** forecasted levels in March; at forecasted levels April-May
  - Reflects public health recommendations to increase medication supplies on hand





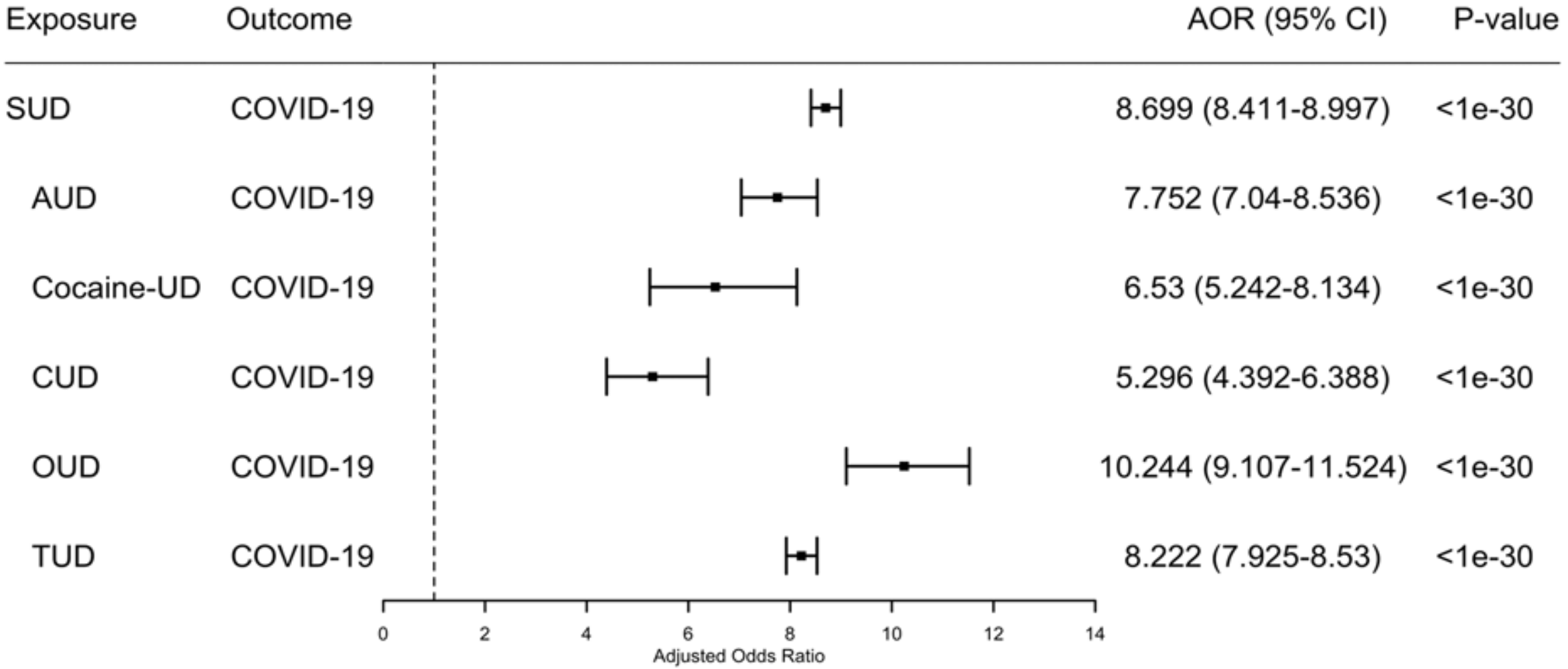


Jones CM, Guy GP Jr, Board A. Drug Alcohol Depend. 2021;219:108486. Epub ahead of print.

COVID-19 in patients with substance use disorders

(based on U.S. Electronic Health Records)

Risk Associated with Recent SUD Diagnosis and COVID-19



Wang QQ, Kaelber DC, Xu R, Vokow ND, *Mol Psychiatry* 2020

Structural and Social Challenges for SUD During SARS-CoV-2

- *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*

Buffalo NY Methadone Clinic March 2020

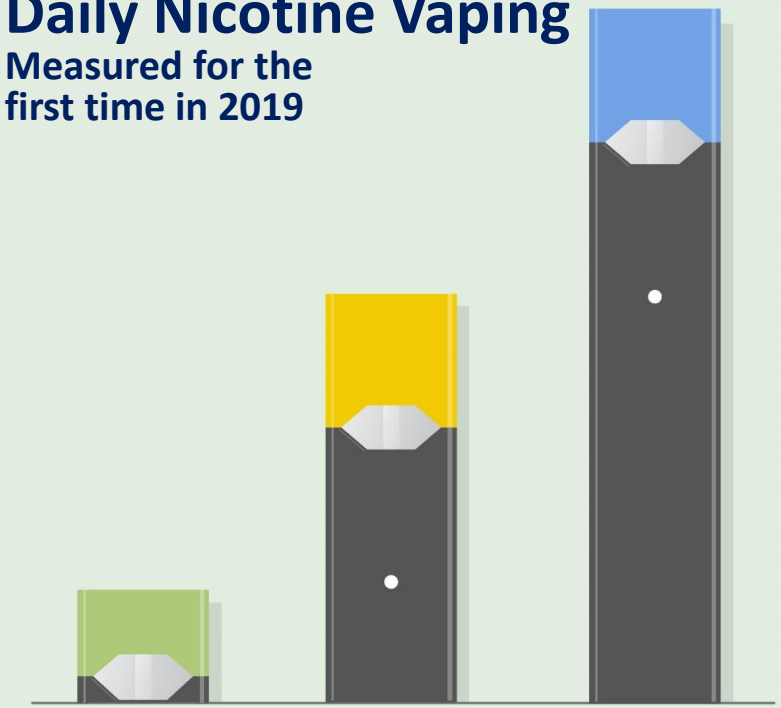
Service Shifts in SARS-CoV-2 *Pandemic*

- 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

Teen Nicotine Vaping Climbs Significantly *(and threatens progress in tobacco control)*

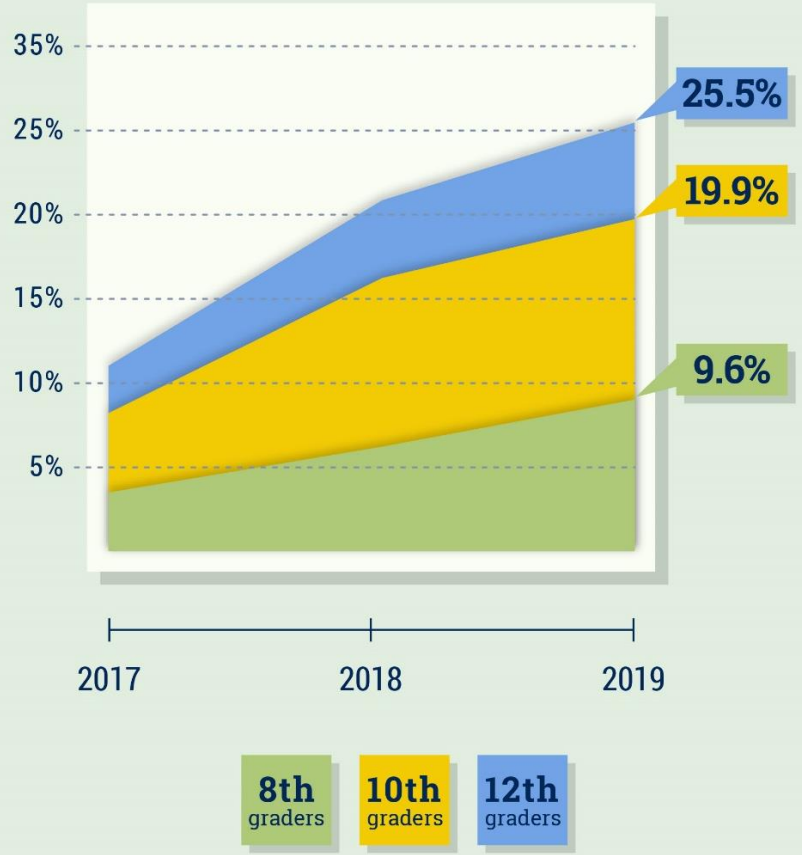
Daily Nicotine Vaping

Measured for the first time in 2019



8th graders	10th graders	12th graders
1.9%	6.9%	11.7%

Past Month Nicotine Vaping

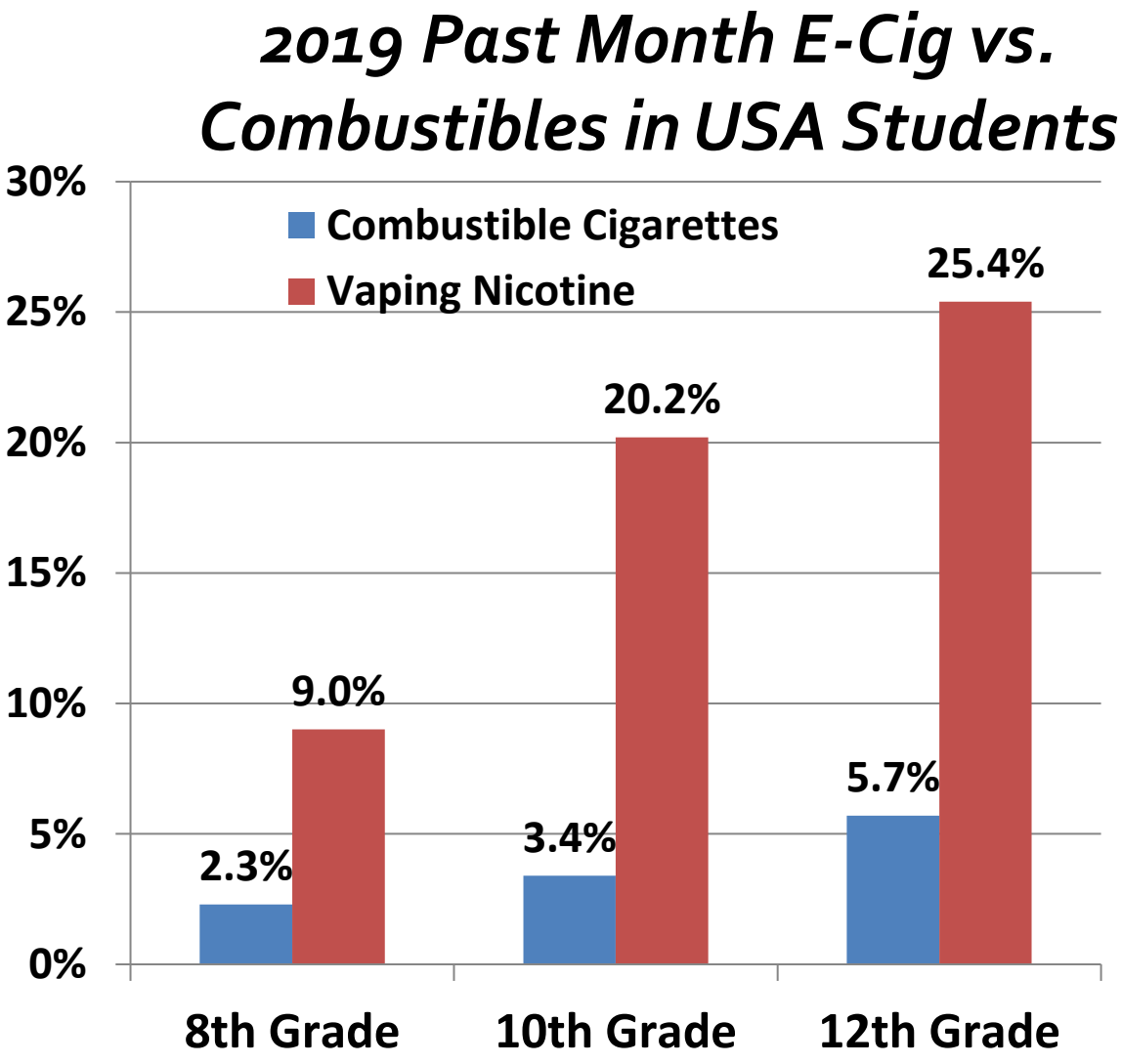


Past month nicotine vaping Equates to:

1 in 10–8th graders
1 in 5–10th graders
1 in 4–12th graders

2019 Monitoring the Future Survey

More U.S. Youth Use E-Cigs Than Combustible Cigs



5.3 million U.S. middle and high-school students reported vaping in 2019

Cullen et al. JAMA, November 5, 2019

Miech et al. *New England Journal of Medicine*, 18 September 2019

E-Cigarette Use *May Lead to Combustible Cigs*

In a prospective study of 14 year old students, *E-Cigarette use predicted onset* of—

- **Any Combustible Tobacco Product: 2.75 times more likely (*AOR*-adjusted odds ratio)**
- **Smoking Cigarettes 1.73 more likely (AOR)**

Leventhal, et al. *JAMA* 2015;314(7):700-707.

In a prospective study of 12-15 year olds, *E-Cigarette use predicting onset* 2 years later of—

- **Ever Using Cigarettes: 4.09 times more likely (AOR)**
- **Currently Smoking Cigarettes: 2.75 times more likely (AOR)**

Berry, et al. *JAMA* Network Open 2019;2(2):e187794

Safer ≠ Safe

Generally Higher Levels of Toxic Compounds in Conventional Cigarettes than E-Cigarettes (*but not zero levels*)

Toxic Compound	Conventional Cigarette (ug)	E-cigarette (ug / 15 puffs)	Conventional vs E-cigarette
Formaldehyde	1.6-5.5	0.2-5.61	9
Acetaldehyde	52-140	0.11-1.36	130
Acrolein	4.6-14	0.07-4.19	4
Toluene	6.4-9.0	0.02-0.63	23
NNN	0.012-0.37	0.00008-0.00043	145
NNK	0.009-0.08	0.00011-0.00283	30
Cd	0.03-0.35	0.001-0.022	16
Ni	0.003-0.60	0.011-0.029	15

Goniewicz et al, 2014, Tobacco Control

Question:

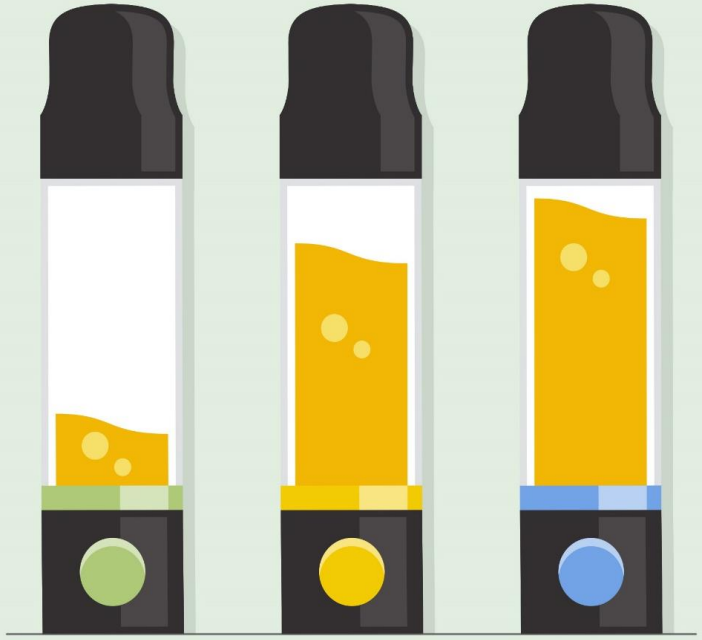
How can clinicians address youth vaping?

How do we balance potential benefits (to smokers who can't quit using other approaches) ***vs. harms from vaping?***

Teen Marijuana Vaping Climbs Significantly

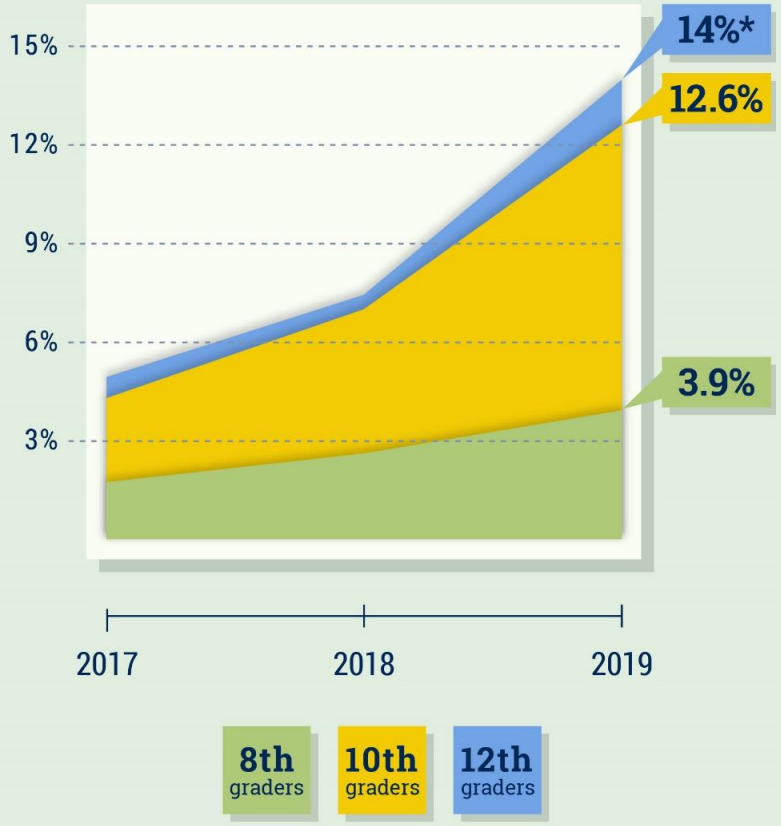
Daily Marijuana Vaping

Measured for the first time in 2019



8th graders	10th graders	12th graders
0.8%	3.0%	3.5%

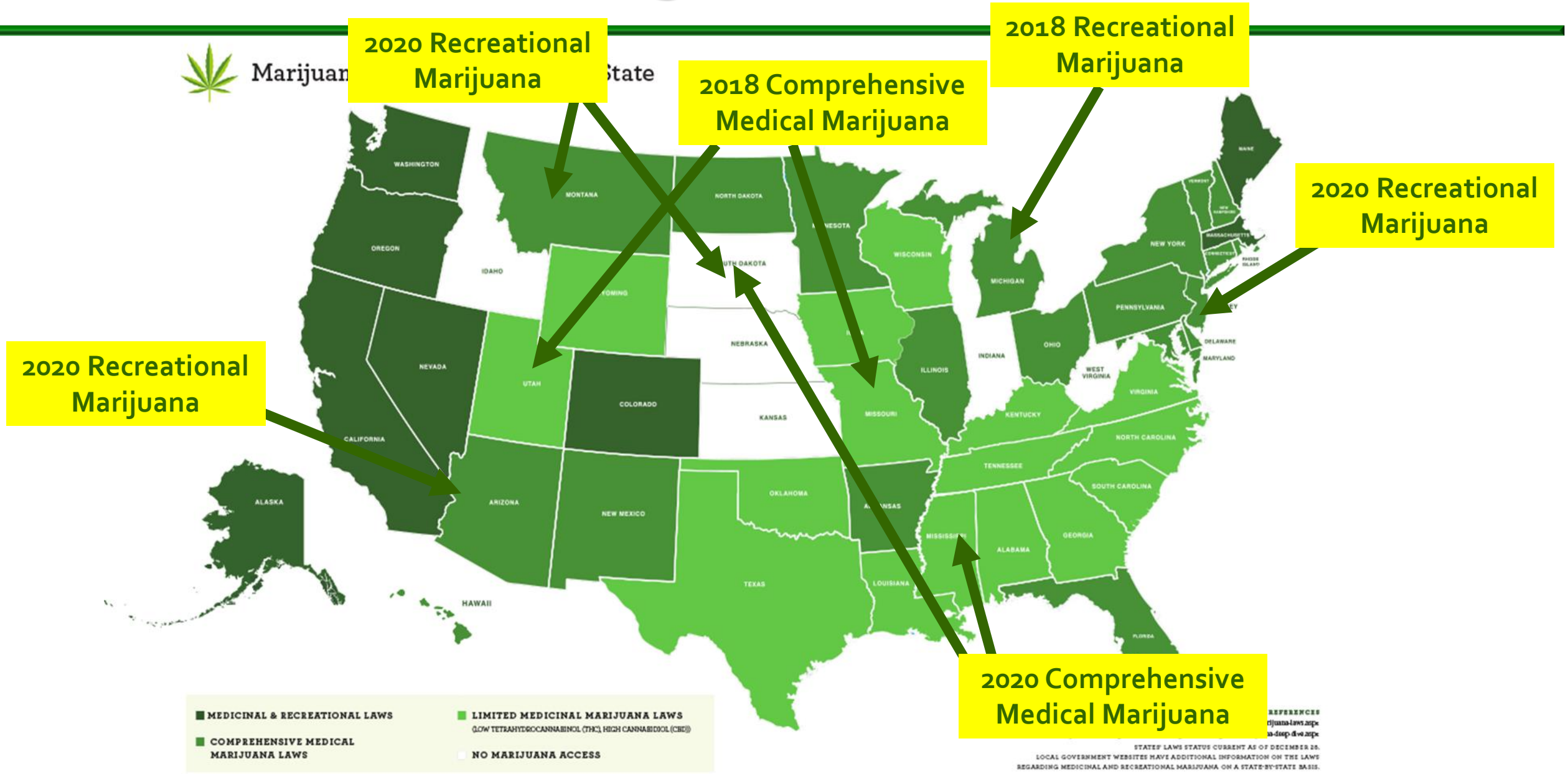
Past Month Marijuana Vaping



The 2018-2019 increase is the second largest 1-year jump ever tracked for any substance in the 45-year survey.

2019 Monitoring the Future Survey
Miech, et al. JAMA. Dec 17, 2019.

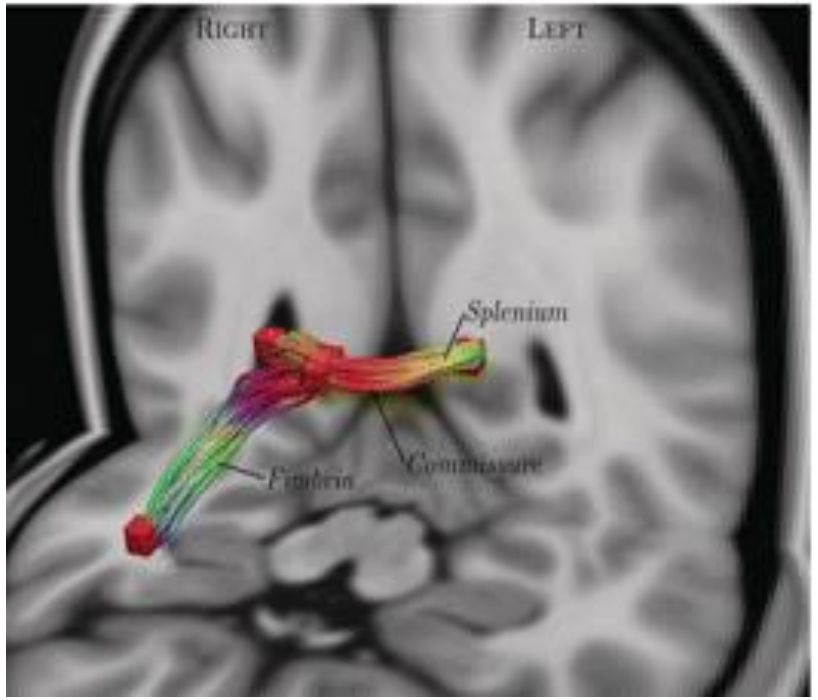
Variation in Legal Status of Cannabis



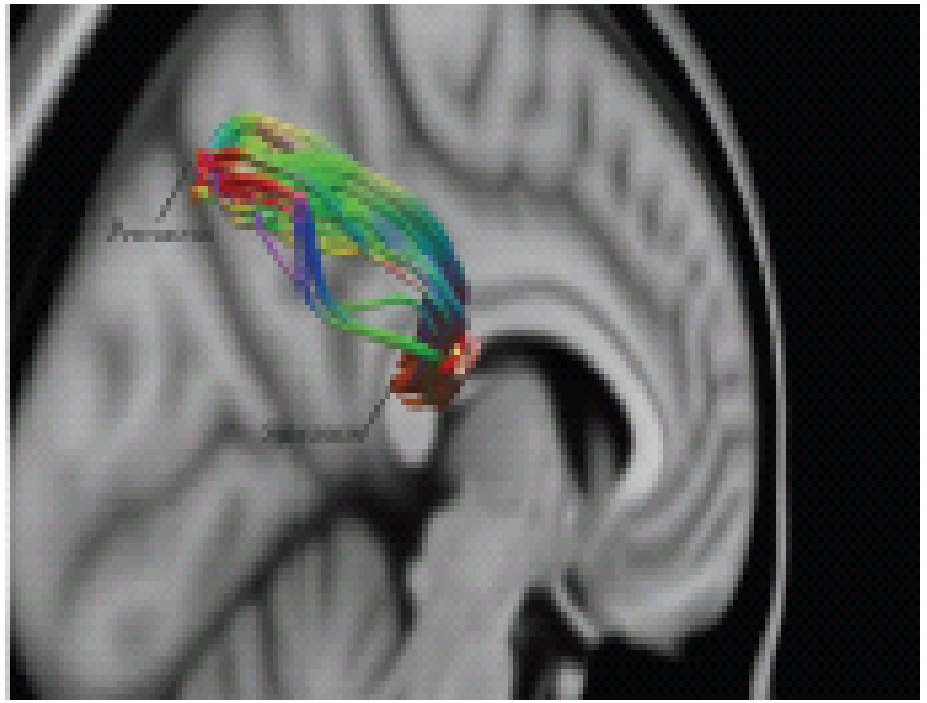
MULTIPLE STUDIES SHOW ALTERED BRAIN STRUCTURE AND FUNCTION IN YOUTH WHO REGULARLY USE CANNABIS

Early (<18y) Cannabis Use Decreases Axonal Fiber Connectivity

Precuneus to splenium



Fimbria of hippocampus, hippocampal Commissure, and splenium



Axonal paths with reduced connectivity (measured with diffusion-weighted MRI) in cannabis users (n=59) than in controls (N=33).

Source: Zalesky et al Brain 2012

PATH

Population Assessment of Tobacco and Health

A collaboration between the NIH and FDA

- **More than 5 years of data collection, starting with 45,971 adults and youth participants (ages 12 and up)**
- **Data access at http://www.icpsr.umich.edu/icpsrweb/NAHDAP/series/606**

Adolescent Brain Cognitive Development

Teen Brains. Today's Science. Brighter Future.

An NIH Collaboration: NIDA, NIAAA, NCI, NIMH, NIMHD, NICHD, NINDS, OBSSR

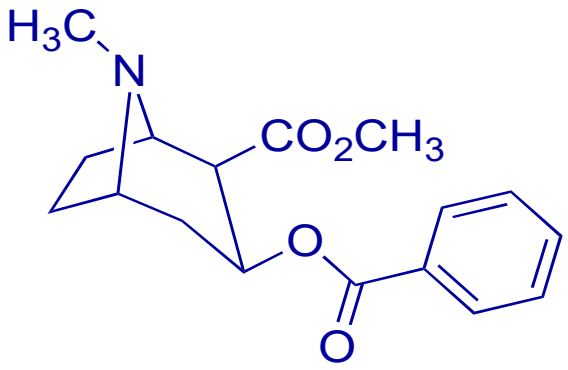
- **Baseline data collection complete—*11,878 children ages 9-10***
- **Longitudinal Data—*in process***
- **Easy and data access.**
- **See abcdstudy.org**

Question:

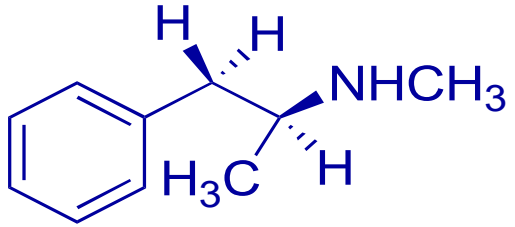
How can clinicians address cannabis use by youth?

What about for adult patients?

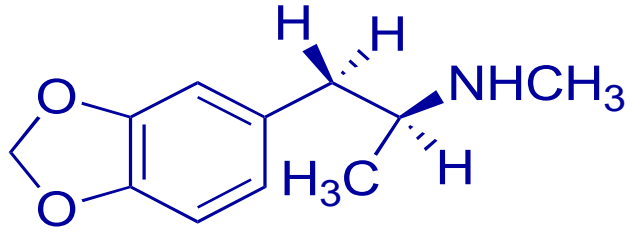
Psychostimulant Drugs



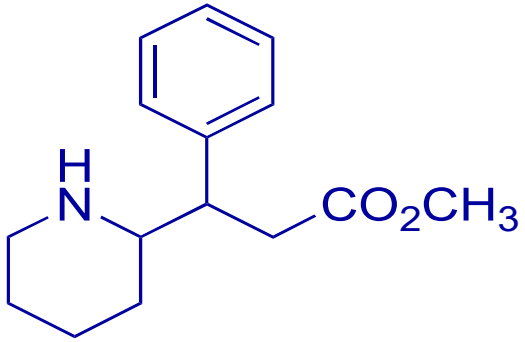
cocaine



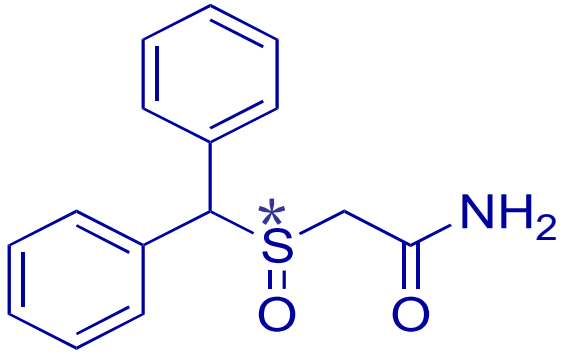
d-methamphetamine



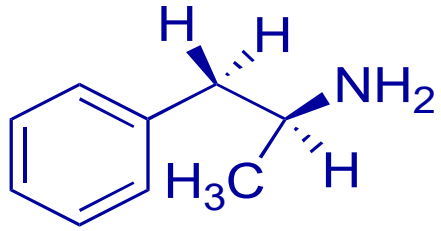
MDMA



methylphenidate



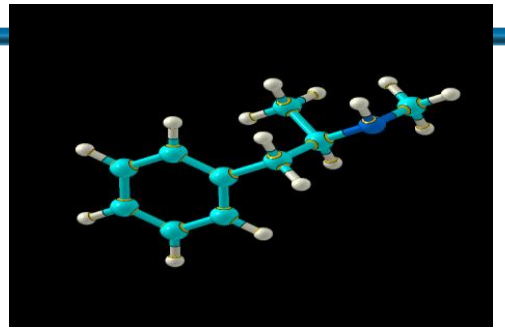
modafinil



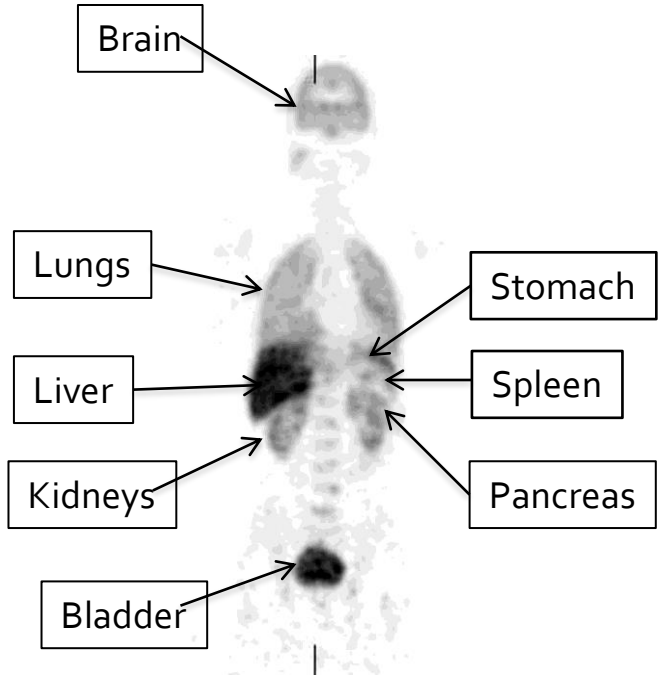
amphetamine

METH: Addictive and Toxic, Serious Mental Illness, Difficult to Treat

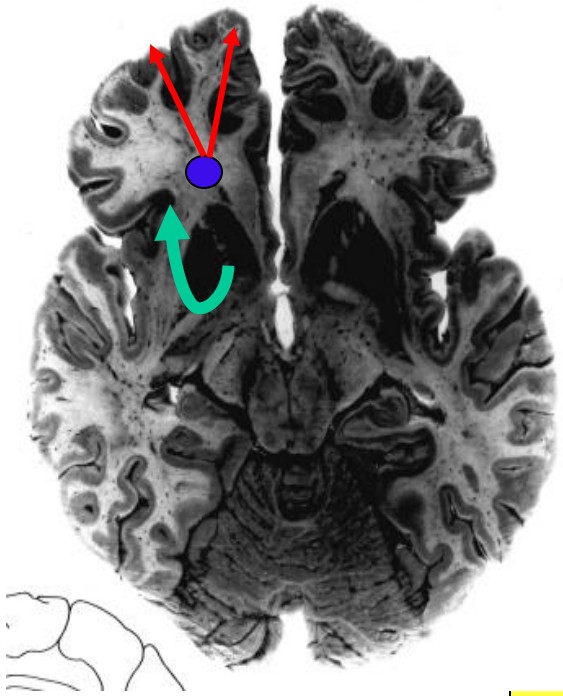
- *Acute*: increased alertness/energy, aggression/violence, psychosis, suicidality/homicidality with binge use; vasoconstrictor: HTN, cardiovascular stimulant, seizures, fatal cardiac complications and strokes; common ED presentations: trauma
- *Chronic*: difficulty feeling any pleasure other than provided by the drug
- *Co-occurring mental disorders:* psychosis, violent behaviors, depression
- *Treatment:* No medications; treat with behavioral therapies in the context of drug cravings and cognitive deficits can lead to poor retention, poor outcomes, frequent relapse



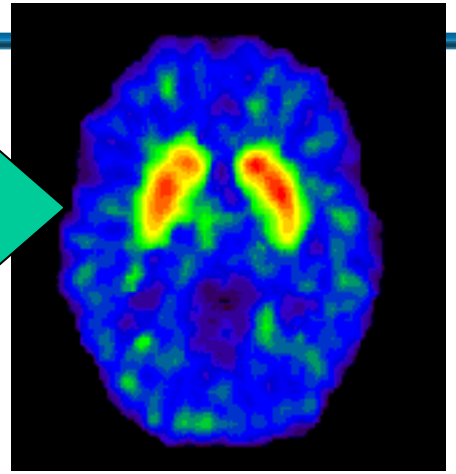
Distribution of METH in Brain and Body



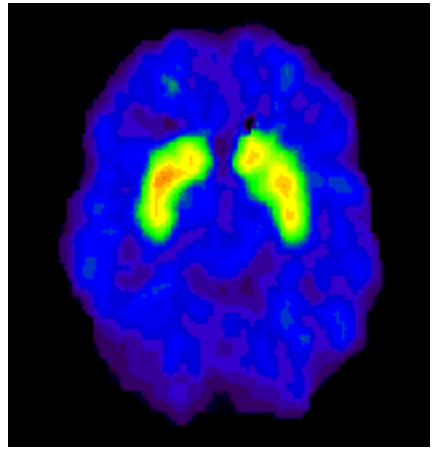
Brain Dopamine System



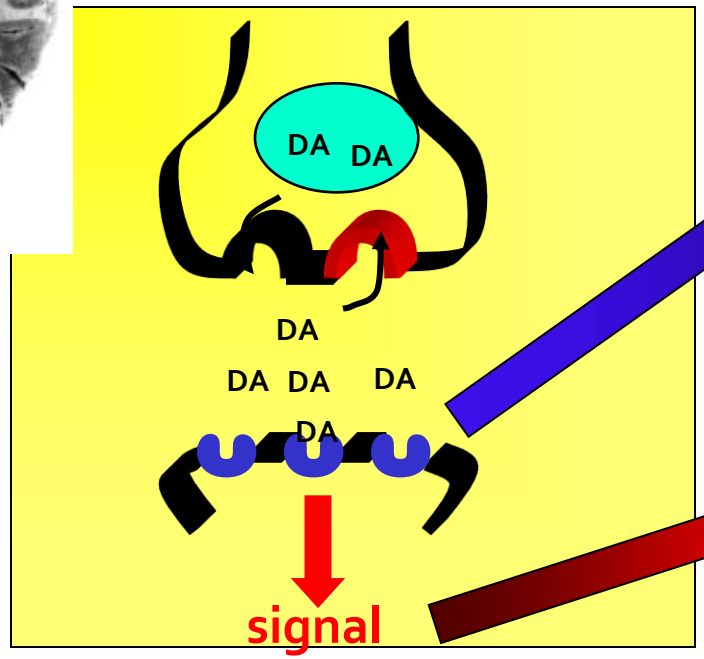
Anatomy



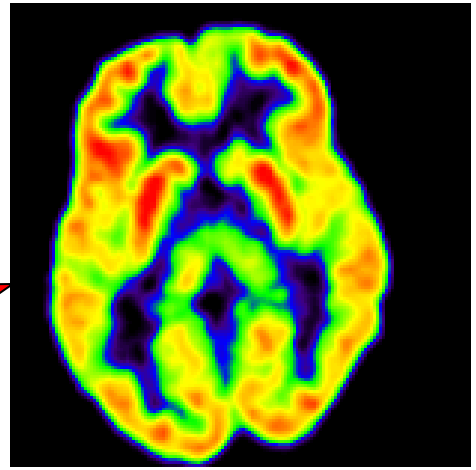
DA Transporters



DA Receptors

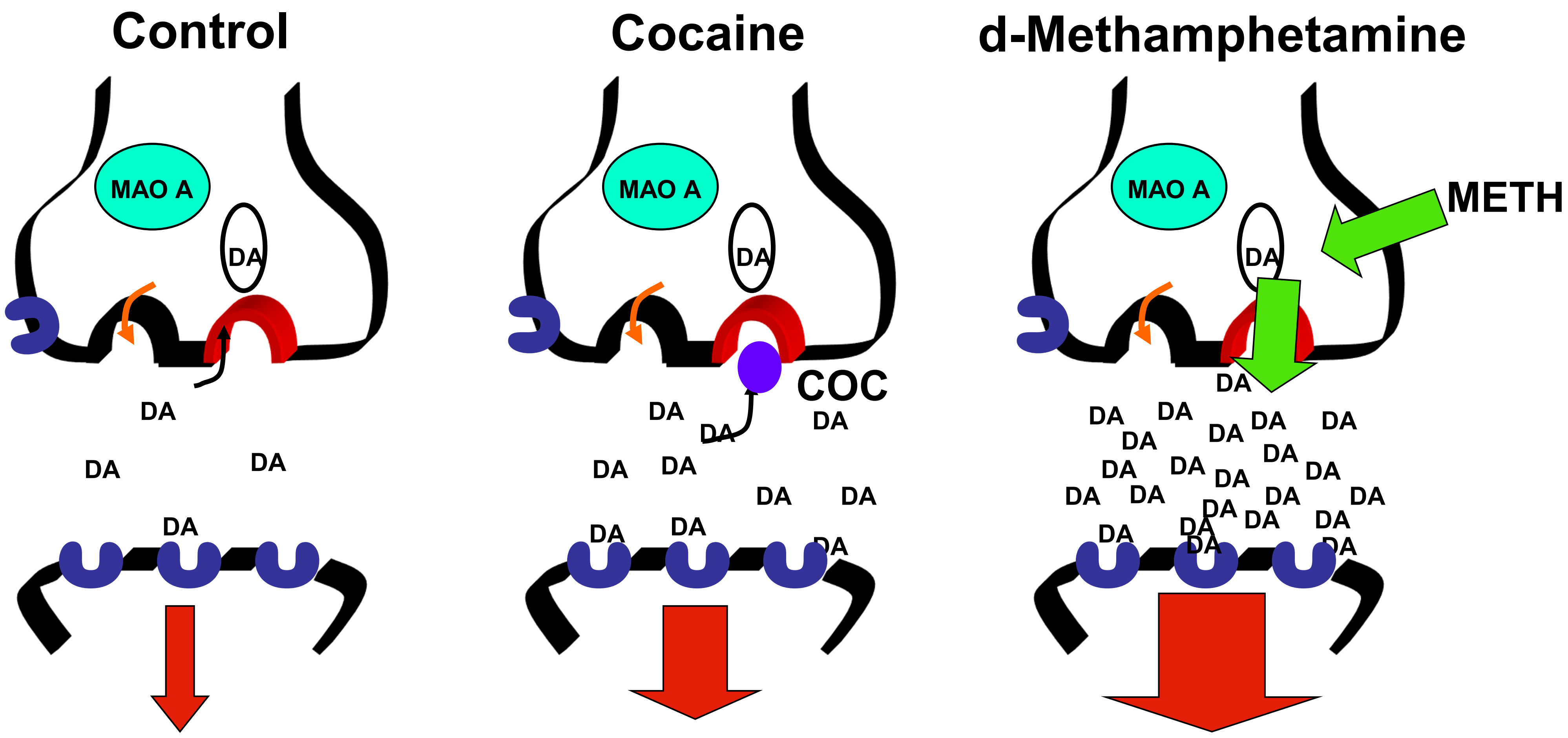


Dopamine Cell

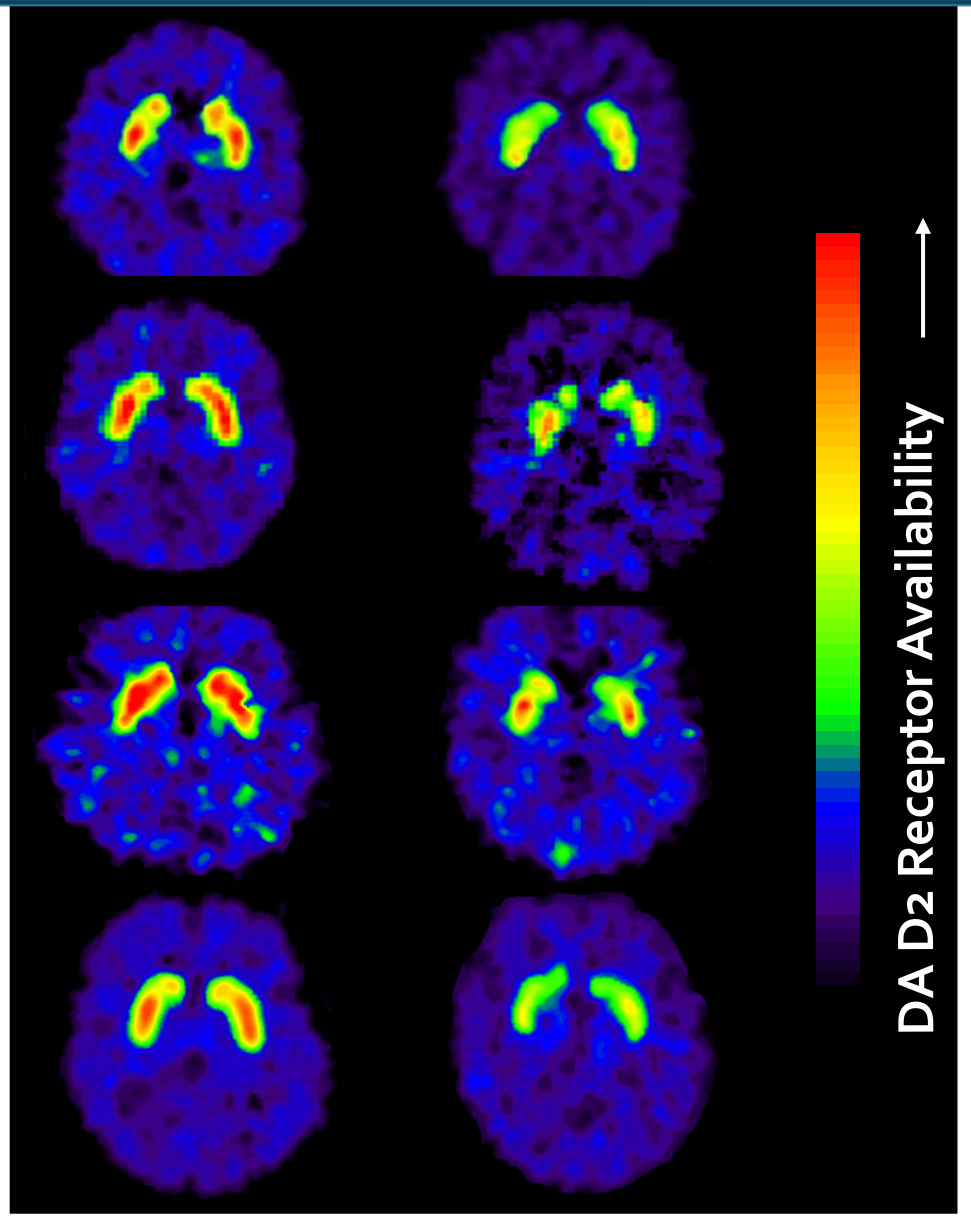


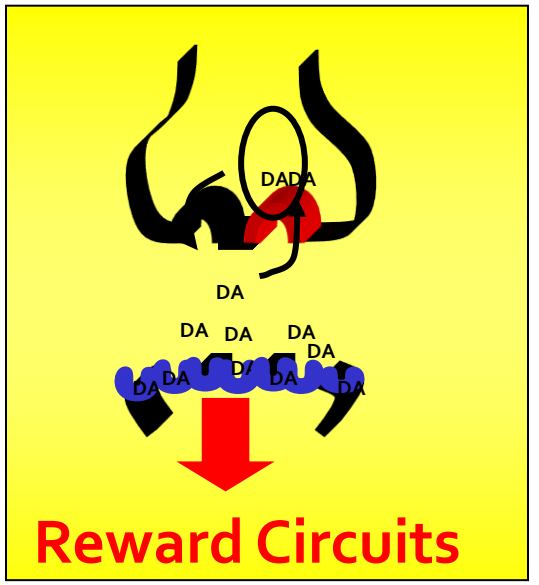
Metabolism

Cocaine blocks *DA reuptake*; Methamphetamine blocks *DA reuptake and releases DA from vesicles*

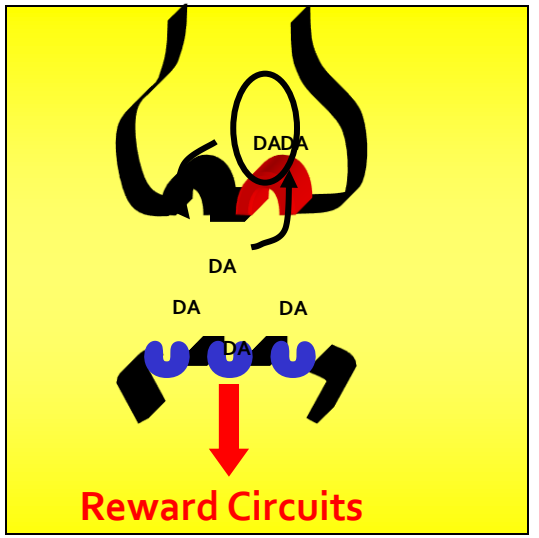


Dopamine D2 Receptors are Lower in Addiction



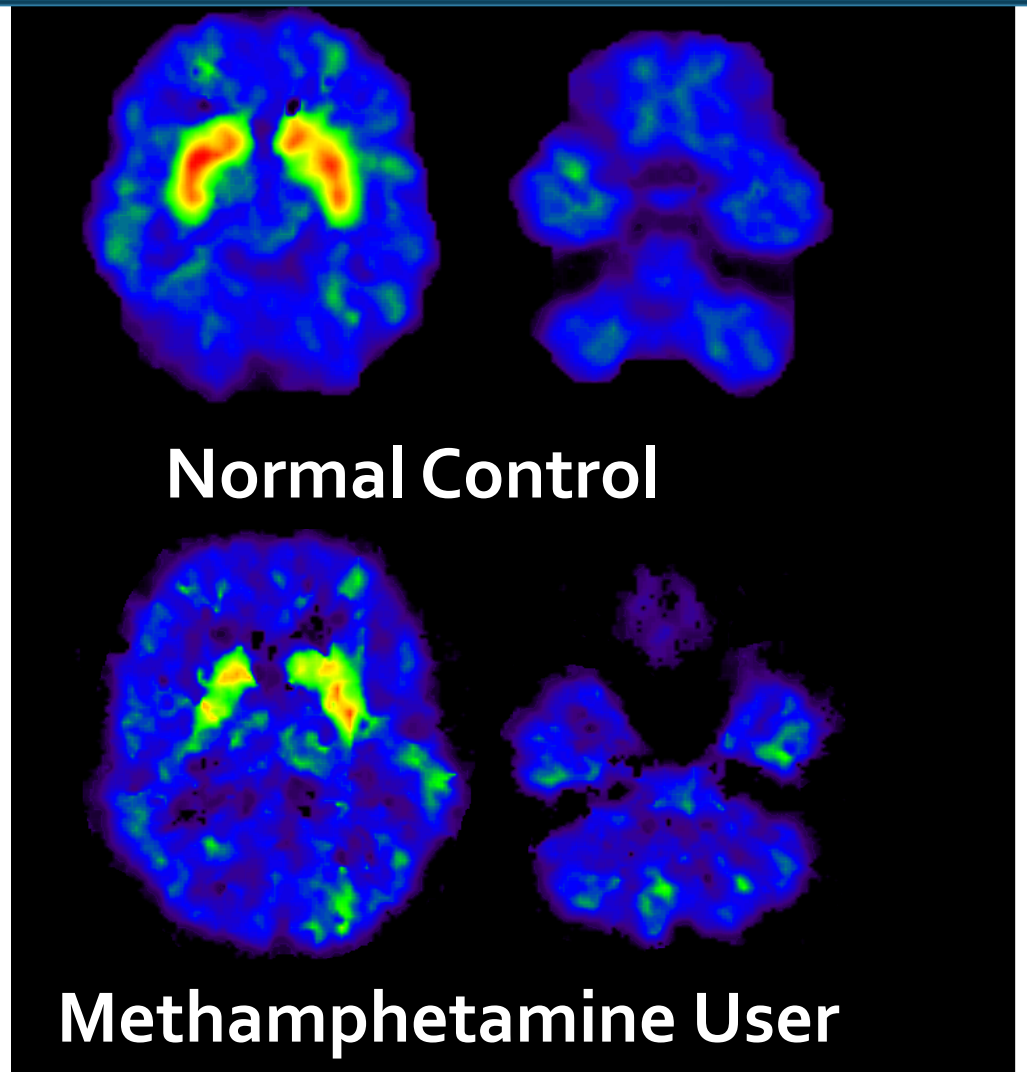


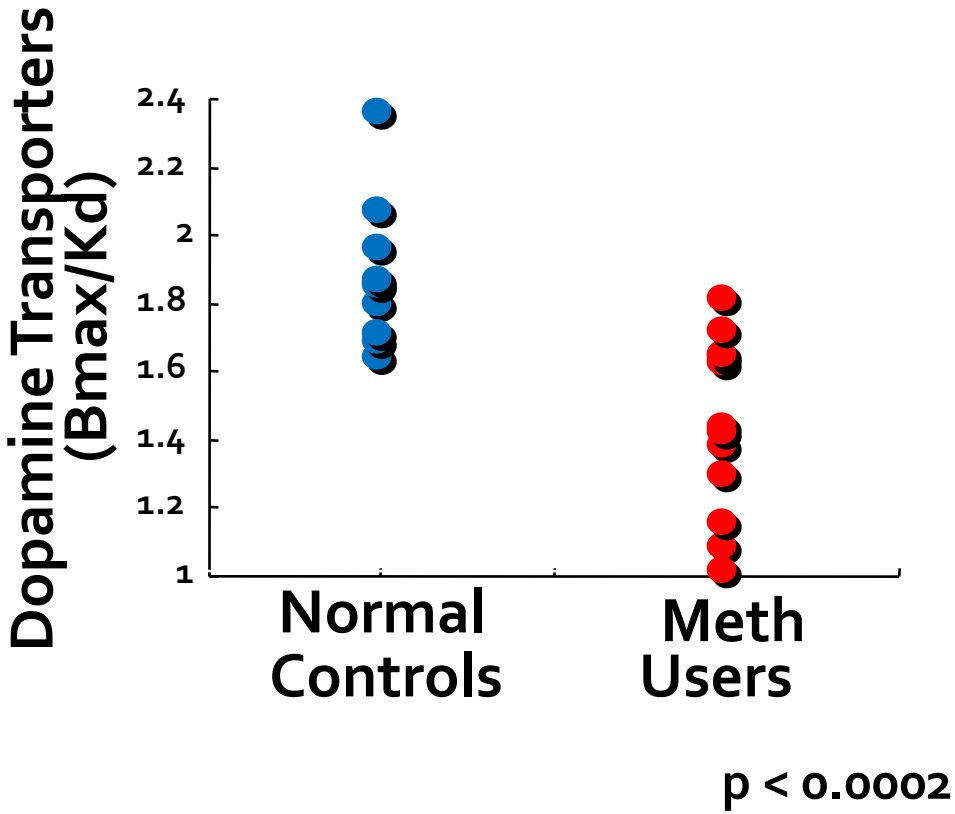
Non-Drug User



Drug User

Dopamine Transporters in Methamphetamine Users



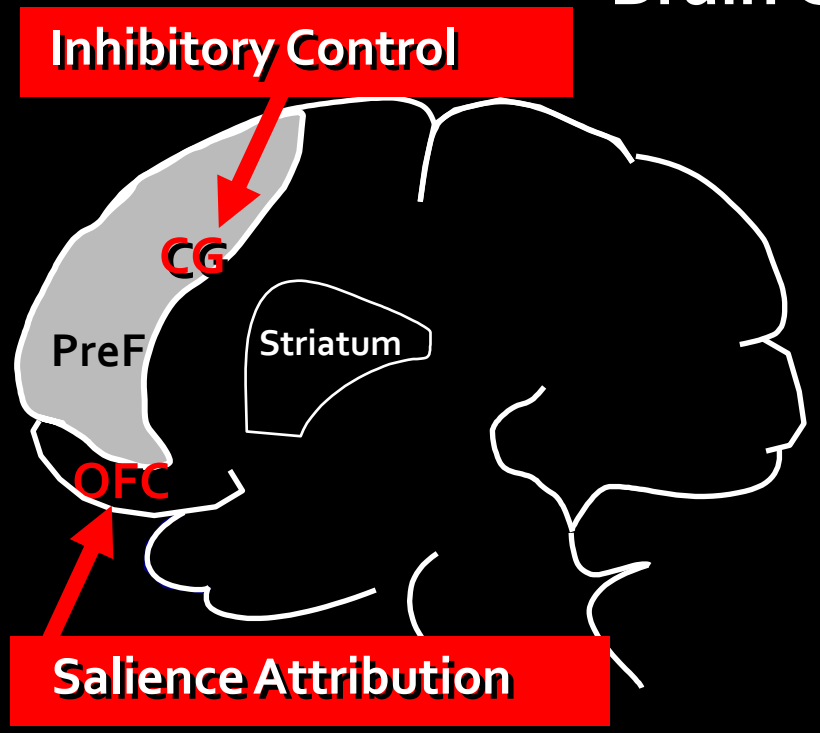


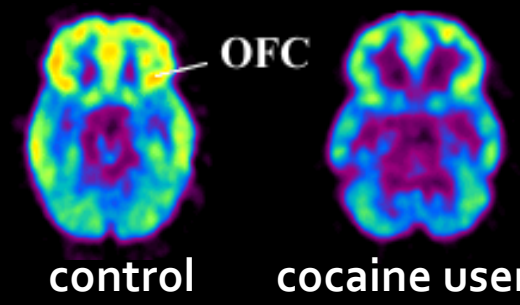
Methamphetamine users have significant reductions in dopamine transporters

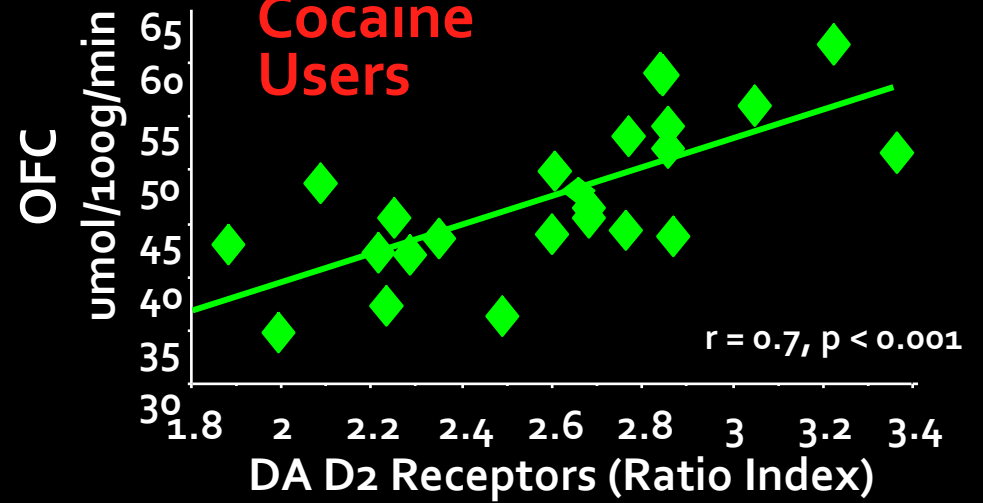
BNL
UCLA
SUNY

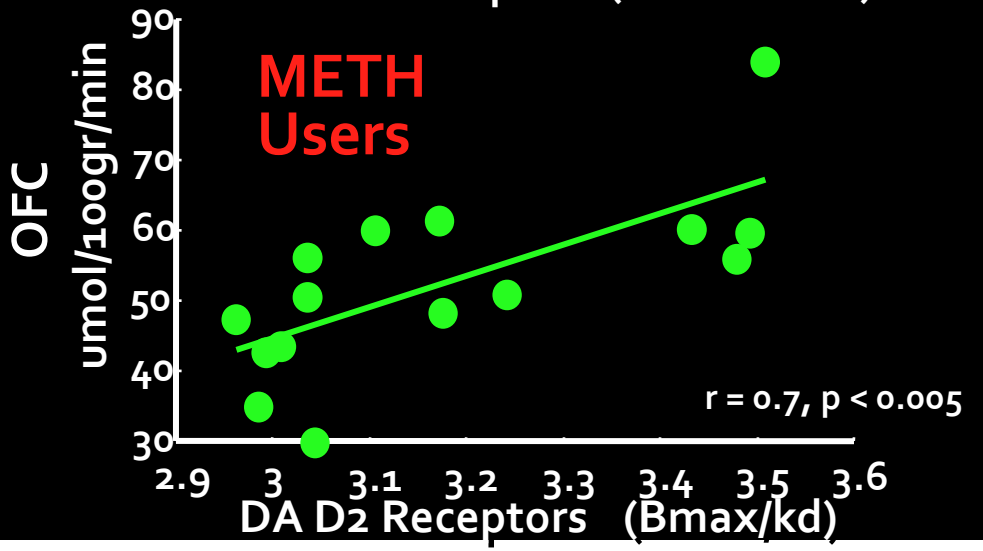
Chronic Drug Use Disrupts Inhibitory Control

Correlations Between D2 Receptors in Striatum and Brain Glucose Metabolism

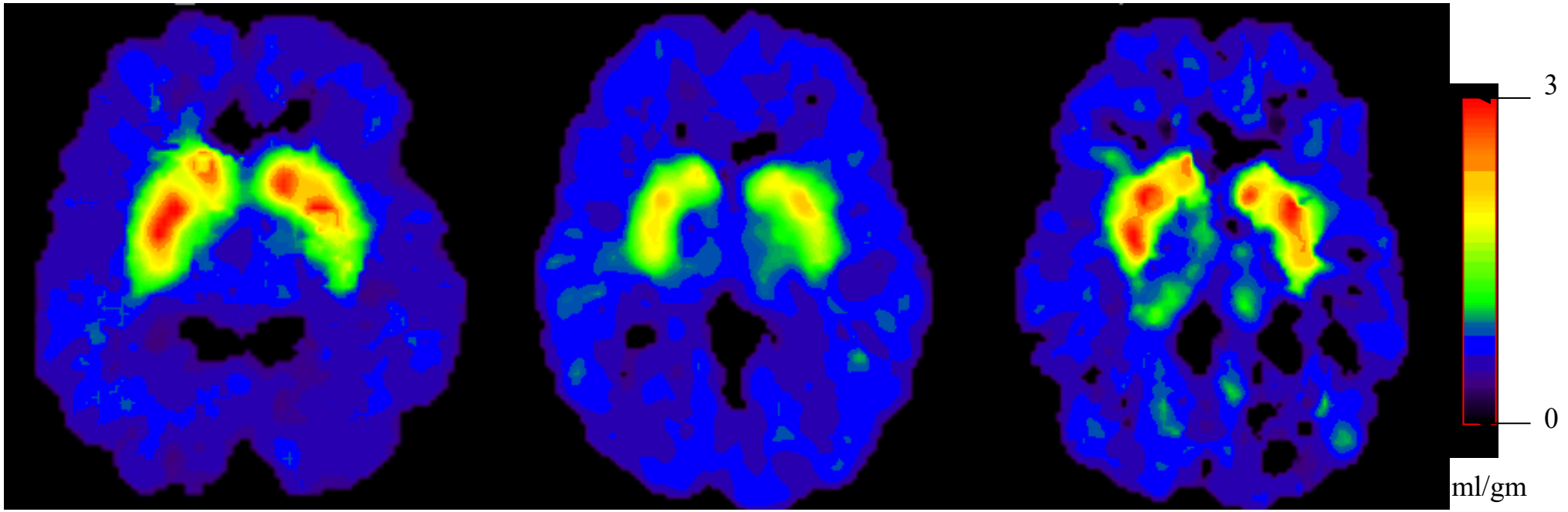








Partial *Recovery* of Brain Dopamine Transporters in Methamphetamine User After Protracted Abstinence



Normal Control

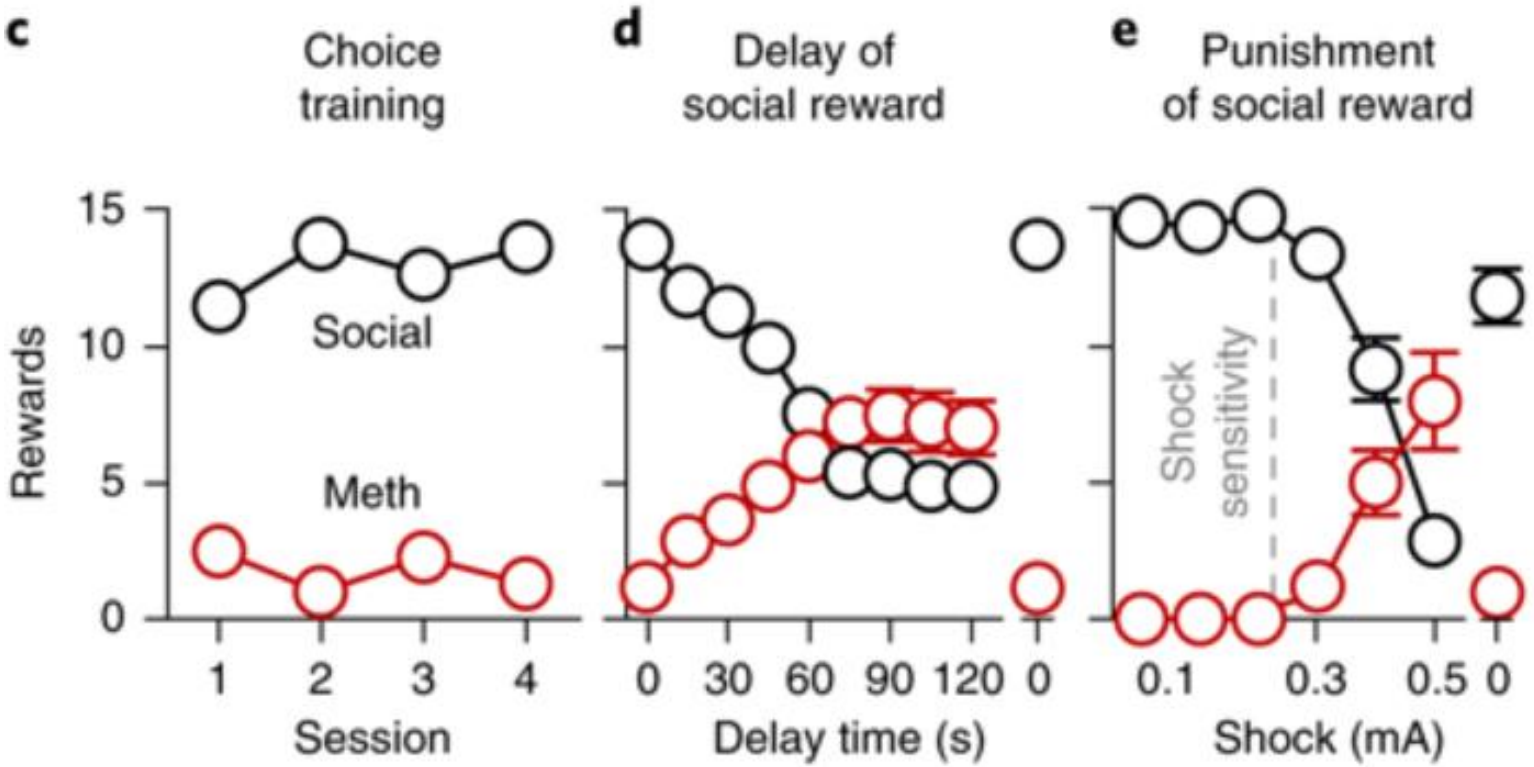
METH User
(1 month detox)

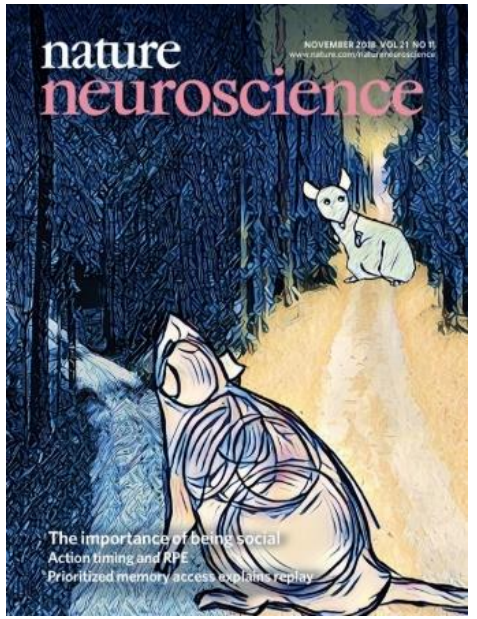
METH User
(14 months detox)

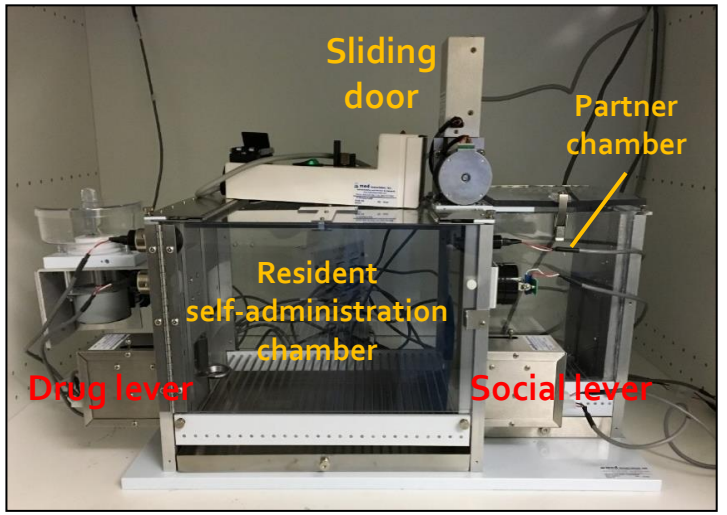
Source: Volkow, ND et al., Journal of Neuroscience 21, 9414-9418, 2001.

Social Interaction Preferred Over Methamphetamine

Drug preference increases when social reward is devalued by delay or punishment





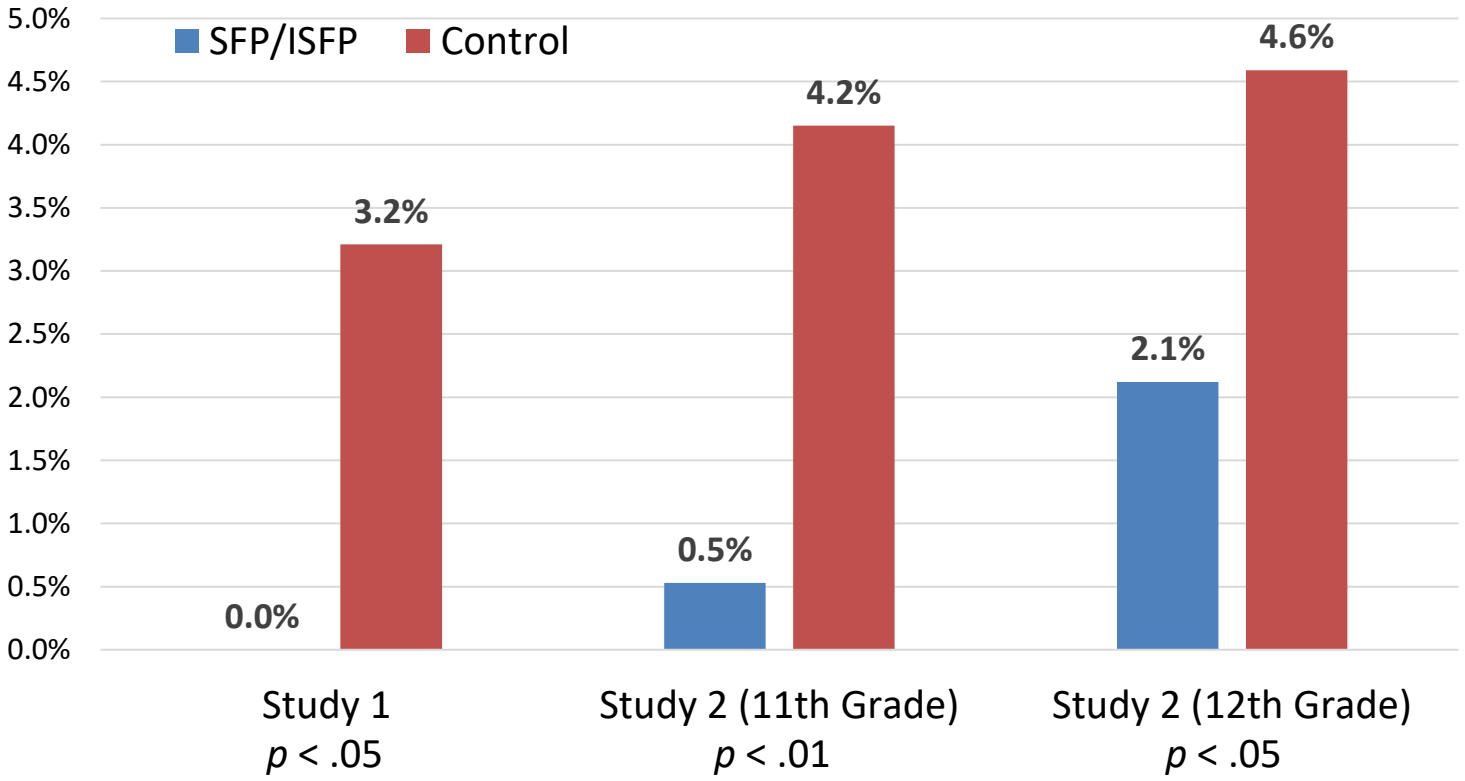


Venniro et al., 2018

Universal Drug Abuse Prevention:

Studies suggest impact on opioids and methamphetamine

Past Year Methamphetamine Use 4½ to 6½ Years Past Baseline



Note: Study 2 included both ISFP and LST interventions

Source: R Spoth et al. *Arch Pediatr Adolesc Med* 2006;160:876-882

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

Compton WM, Jones CM, Baldwin GT, Harding FM, Blanco C, Wargo EM

American Journal of Public Health 2019;109:2185-S189.

ER-Naltrexone (380 mg/month) **plus ER Buproprion** (450 mg/day) **for Methamphetamine Use Disorder** (n=403 [phase 1], 225 [phase 2])

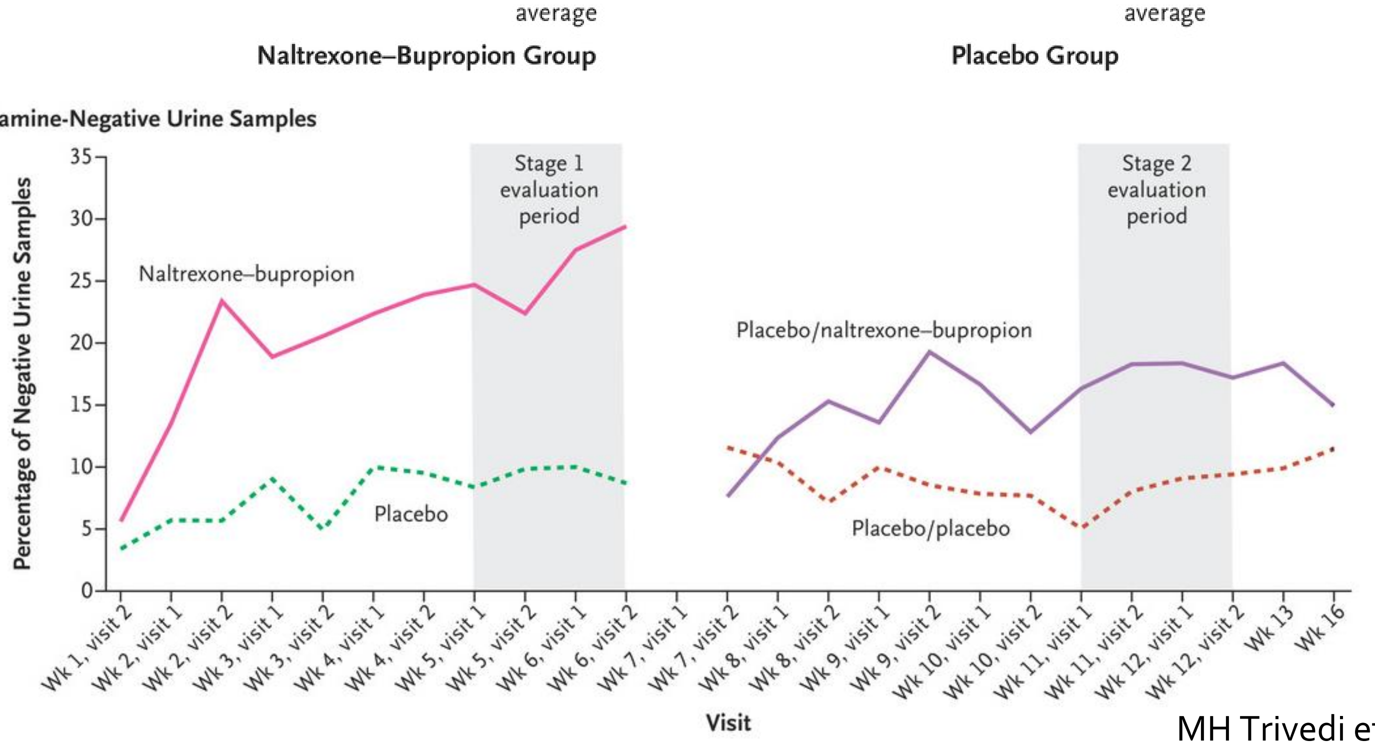
No. of Urine Samples Obtained at Each Visit

Stage 1

Naltrexone–bupropion	89	96	77	90	73	85	67	81	67	80	68
Placebo	265	280	229	266	223	260	210	239	203	240	207

Stage 2

Placebo/naltrexone–bupropion	92	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	87
Placebo/placebo	95	106	84	100	82	102	91	99	87	99	85	101	96



Conclusions:

"Among adults with methamphetamine use disorder, the response over a period of 12 weeks among participants who received extended-release injectable naltrexone plus oral extended-release bupropion was low but was higher than that among participants who received placebo."

MH Trivedi et al. N Engl J Med 2021;384:140-153.

The NEW ENGLAND JOURNAL of MEDICINE

Summary:

- Complex biological, developmental and social aspects of substance use and addiction suggest ***multipronged responses***.
- The severity of ADDICTION demands ***urgent action.***

NIDAMED

Resources for Medical Students, Resident Physicians & Faculty

www.drugabuse.gov/coe

www.drugabuse.gov

NIH National Institute on Drug Abuse

Advancing Addiction Science

Science = Solutions