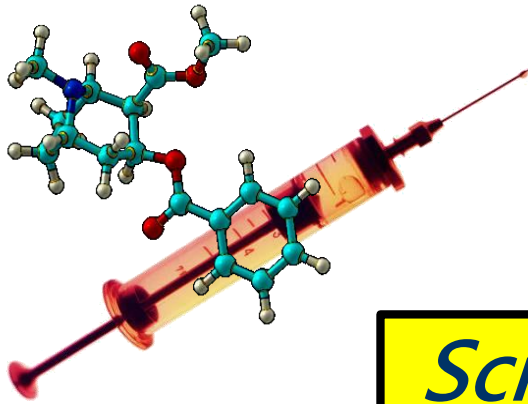
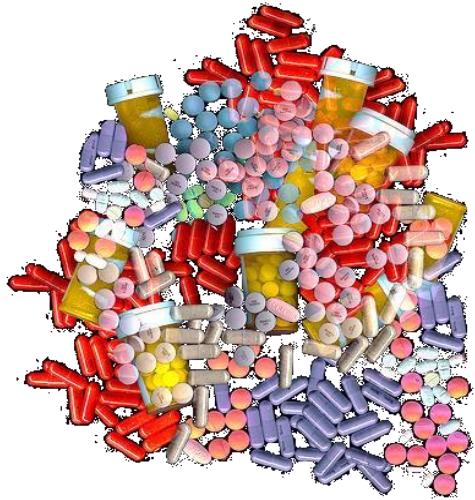
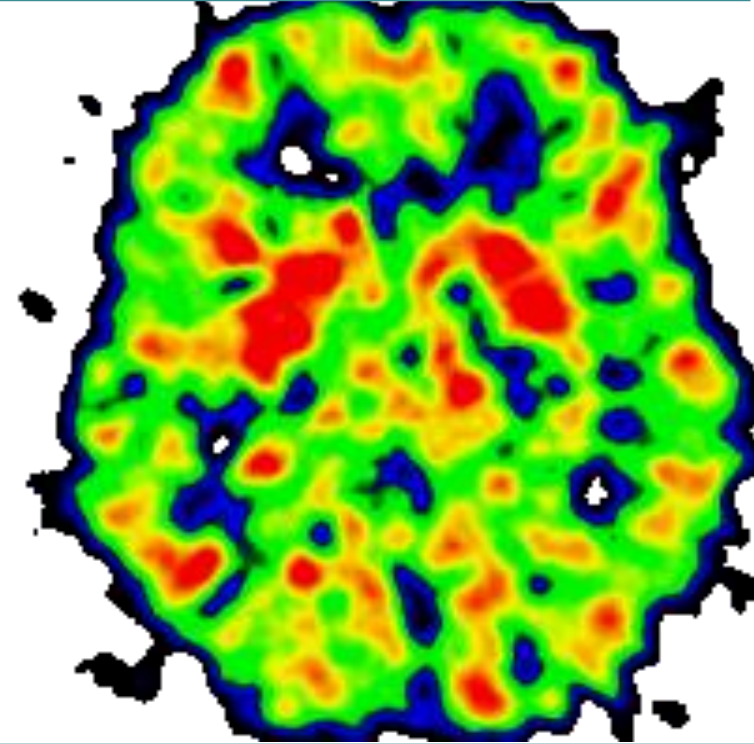


# *Advancing Addiction Science to Address the Opioid Crisis*

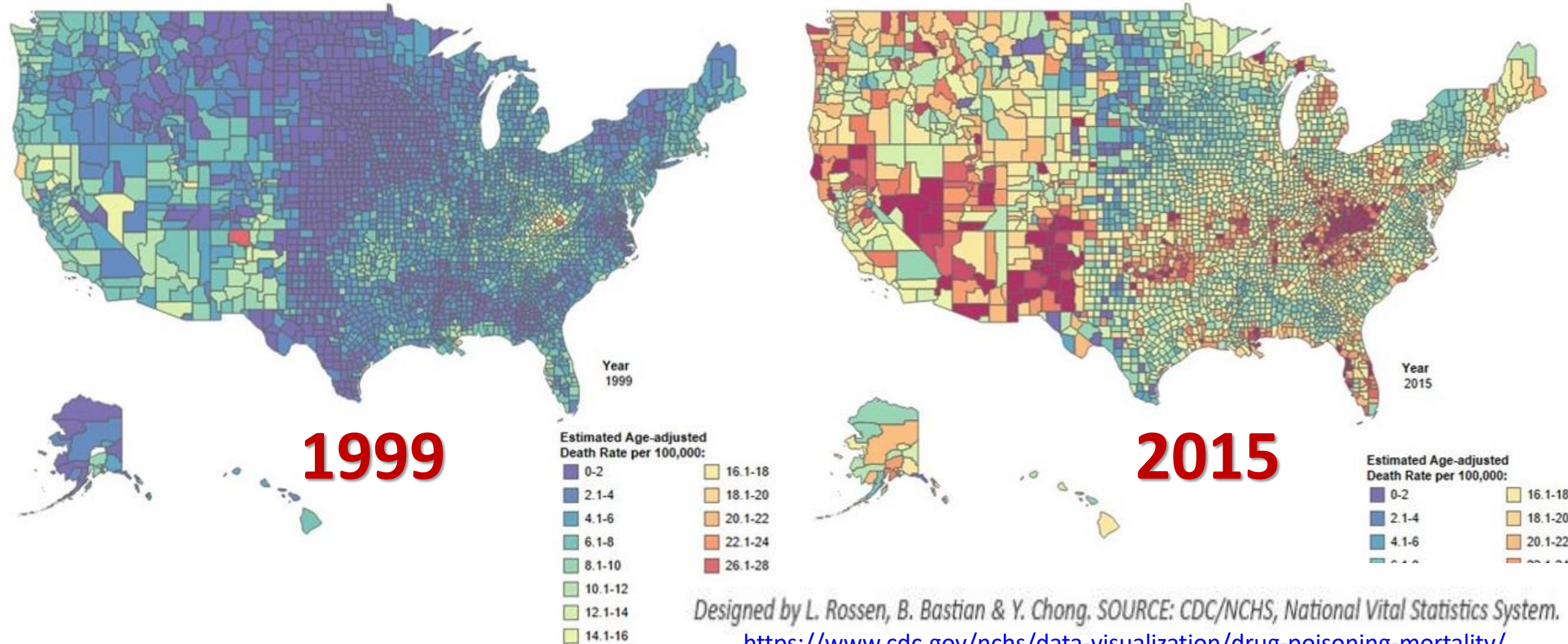


*Science =  
Solutions*



# 52,404 Overdose Deaths in 2015 (33,091 from Rx and Illicit Opioids)

## *Geographic and Temporal Variation: Estimated Age-adjusted Death Rates for Drug Poisoning by County*

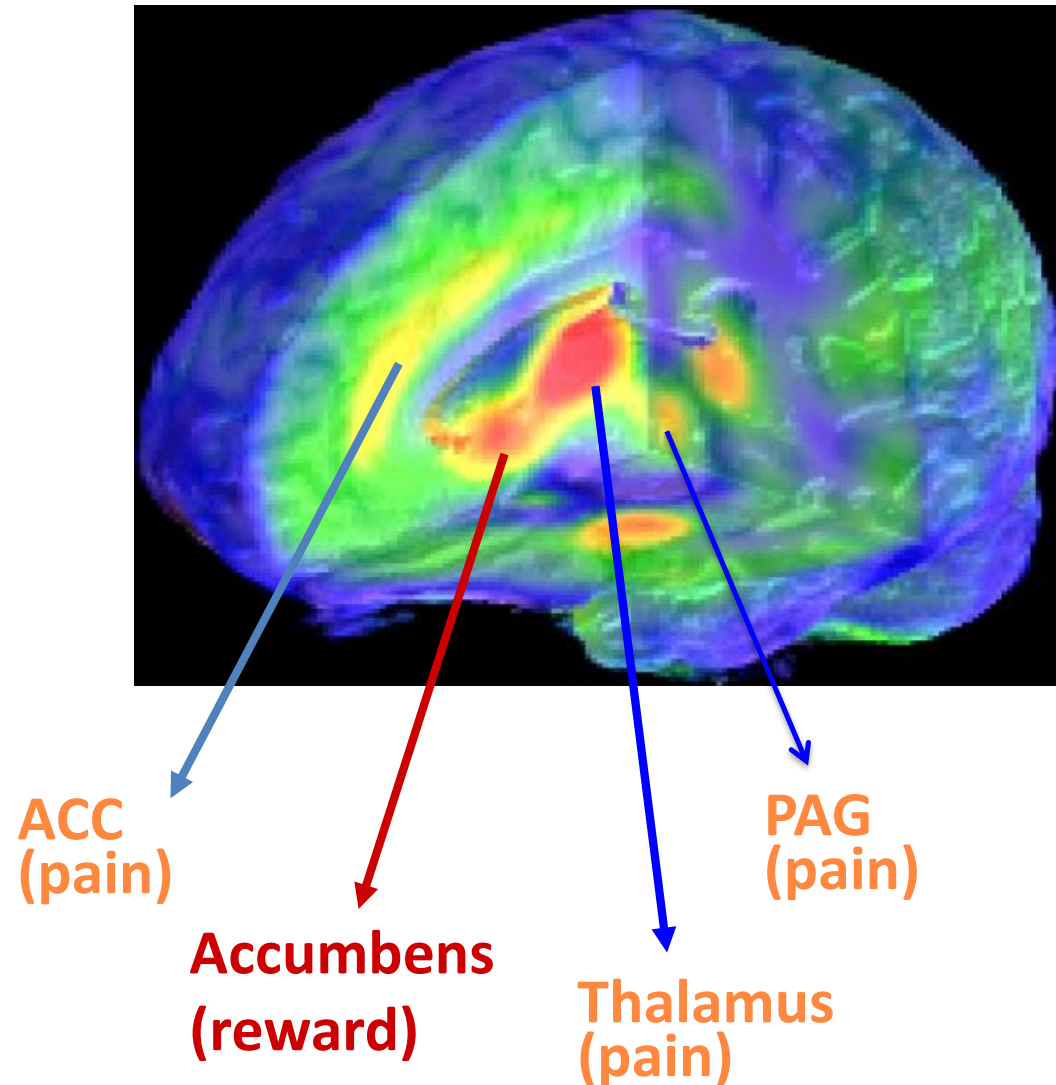


Designed by L. Rossen, B. Bastian & Y. Chong. SOURCE: CDC/NCHS, National Vital Statistics System.

<https://www.cdc.gov/nchs/data-visualization/drug-poisoning-mortality/>

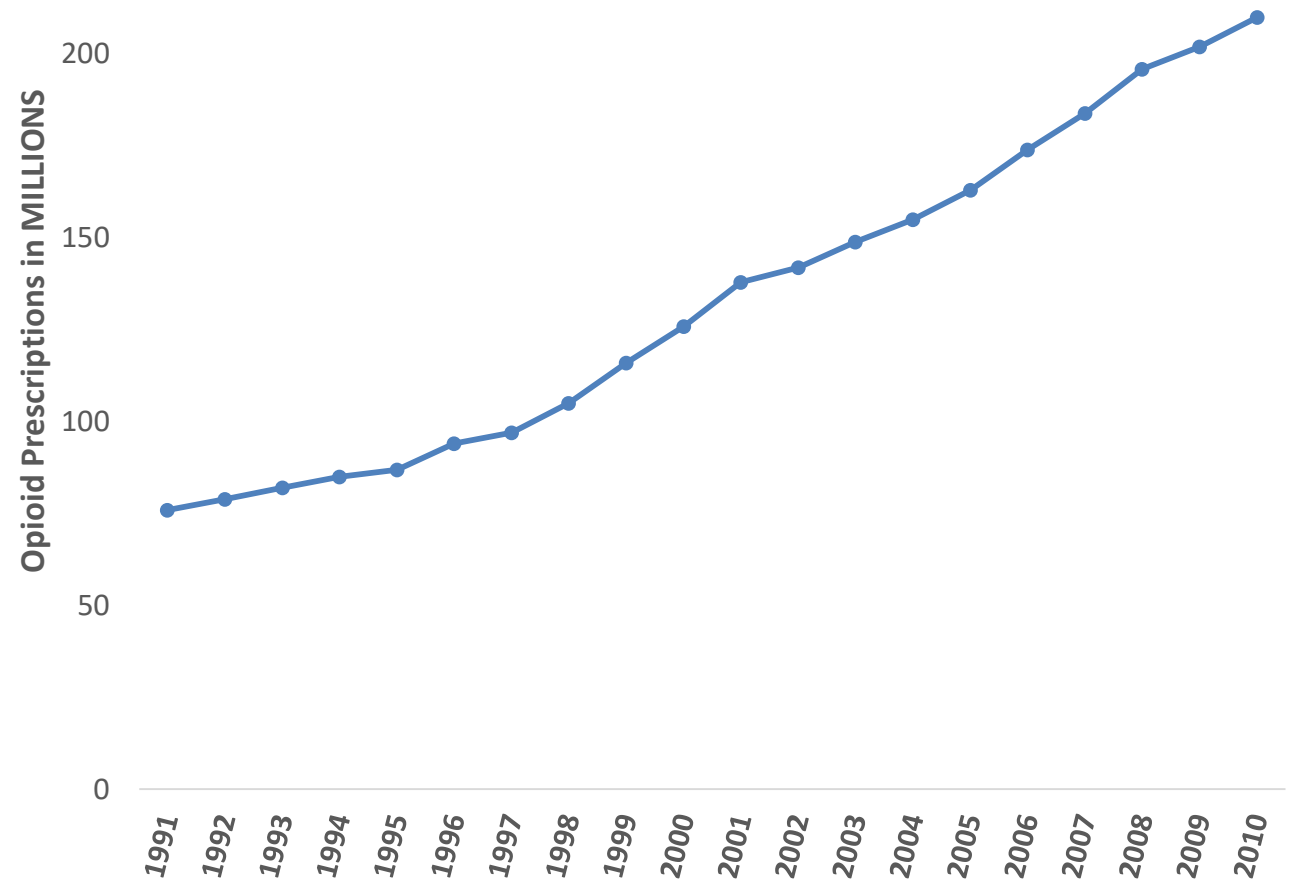


# Analgesic Mechanisms of Mu Opiate Drugs (Heroin, Vicodin, Morphine)



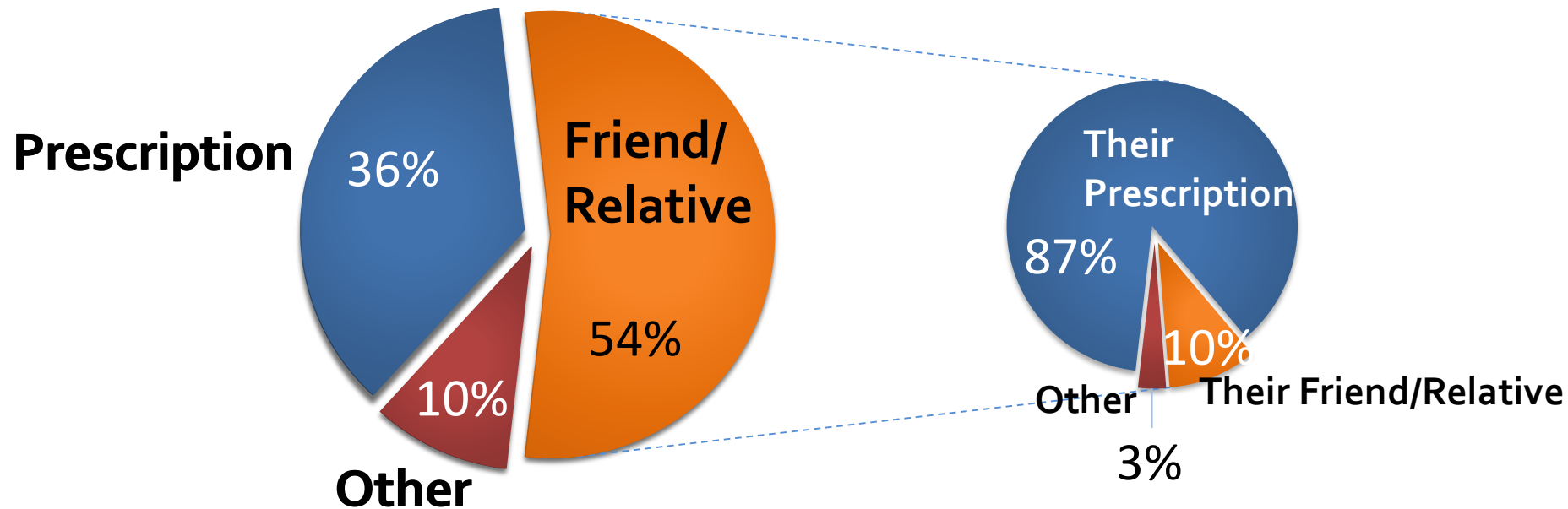
# ***ENVIRONMENTAL AVAILABILITY:*** Current Opioid Crisis Originated with Prescribing Increases

Opioid prescriptions  
*Tripled to MORE THAN 200 MILLION prescriptions in recent years*



# People Misusing Analgesics Obtain them *Directly & Indirectly* by Prescription

*Source where pain relievers obtained for most recent misuse*



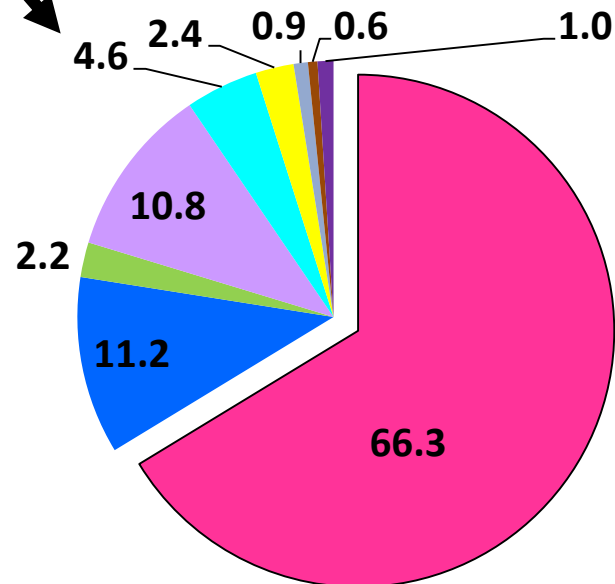
Source: Han, Compton, et al. *Annals of Internal Medicine* 2017;167(5):293-301

# Inadequate *Pain Treatment* as a Driver?

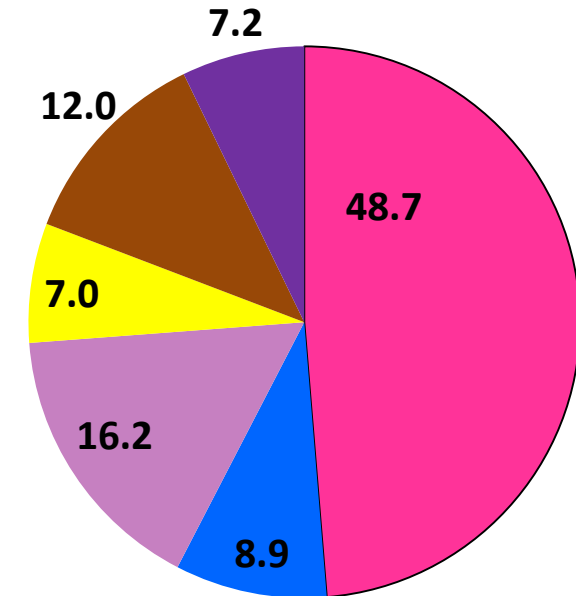
91.8 million adults **used prescription opioids** (37.8% of the U.S. adult population)

11.5 million adults **misused prescription opioids** (4.7% of the U.S. adult population)

1.9 million adults had **prescription opioid use disorders** (0.8% of the U.S. adult population)

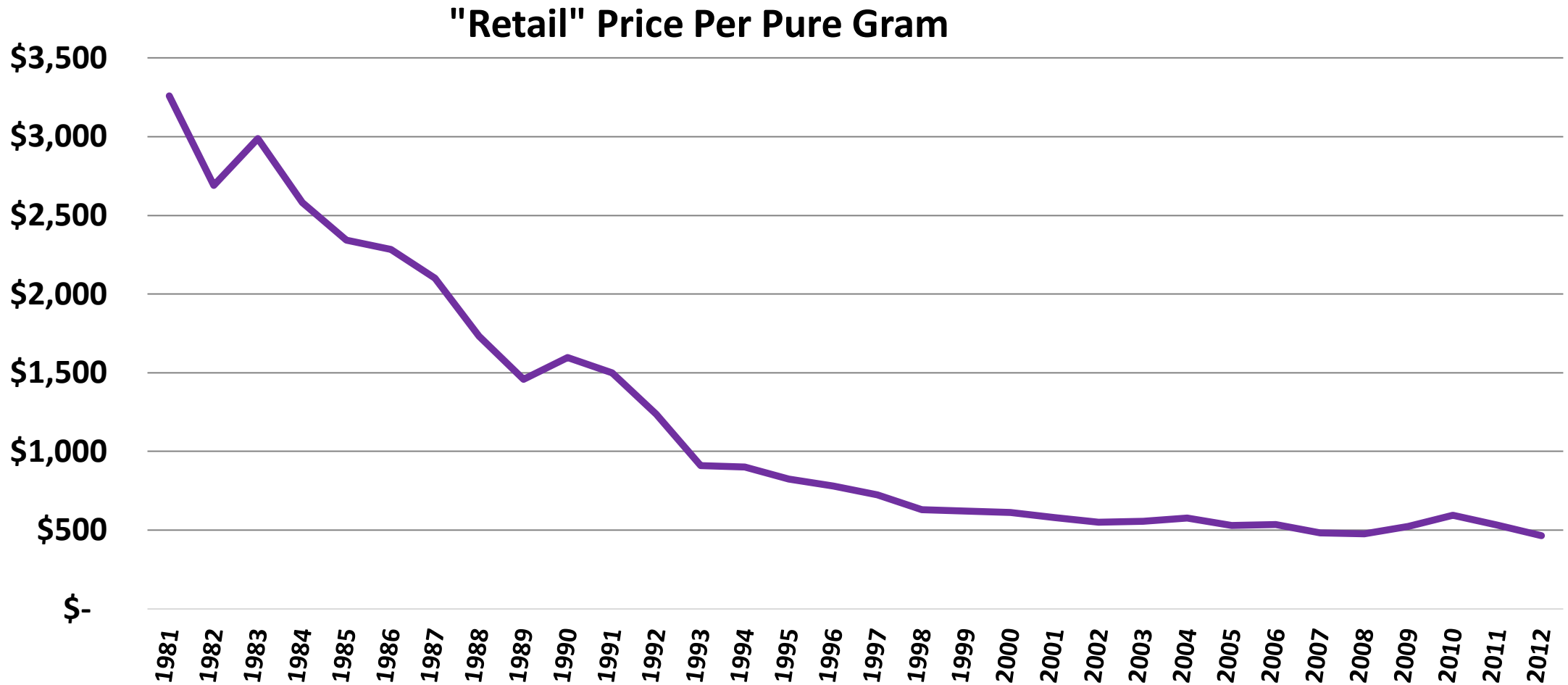


- relieve physical pain
- relax or relieve tension
- experiment
- get high or feel good
- help with sleep
- help with emotions or feelings
- increase/decrease effects of other drugs
- hooked or have to misuse
- other reason



Source: Han, Compton, et al. Annals of Internal Medicine 2017 (epub Aug 1, 2017)

# ***ECONOMICS:*** Heroin Increases Due to Lower Price and Greater Availability



National Drug Control Strategy--Data Supplement 2014.

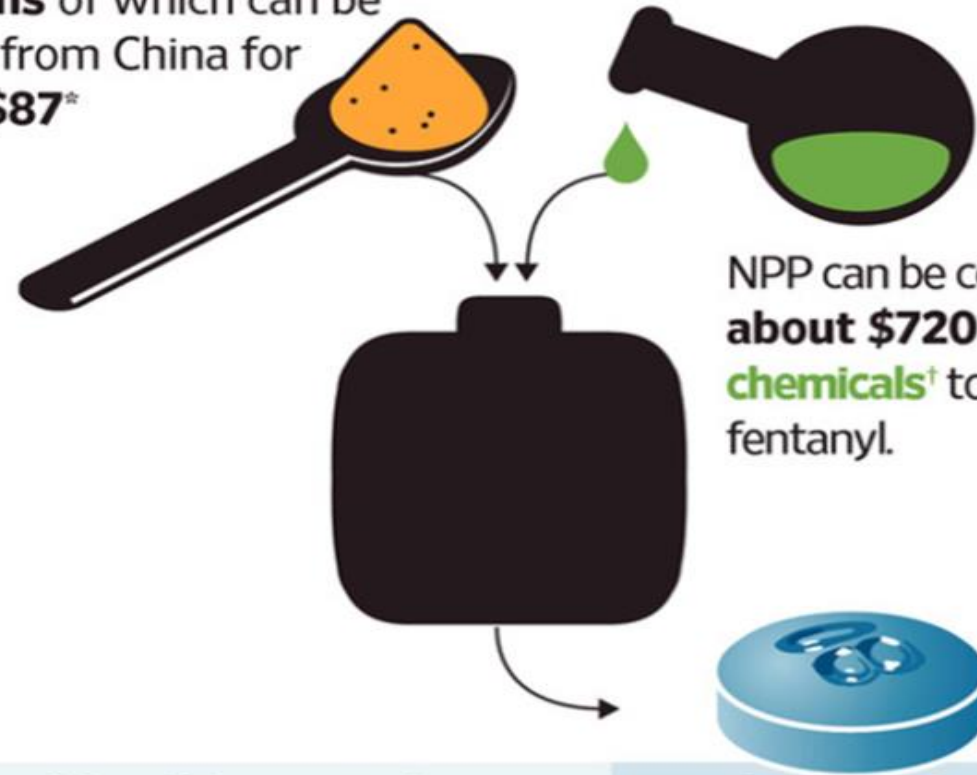
[https://www.whitehouse.gov/sites/default/files/ondcp/policy-and-research/ndcs\\_data\\_supplement\\_2014.pdf](https://www.whitehouse.gov/sites/default/files/ondcp/policy-and-research/ndcs_data_supplement_2014.pdf)

# ***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\***



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

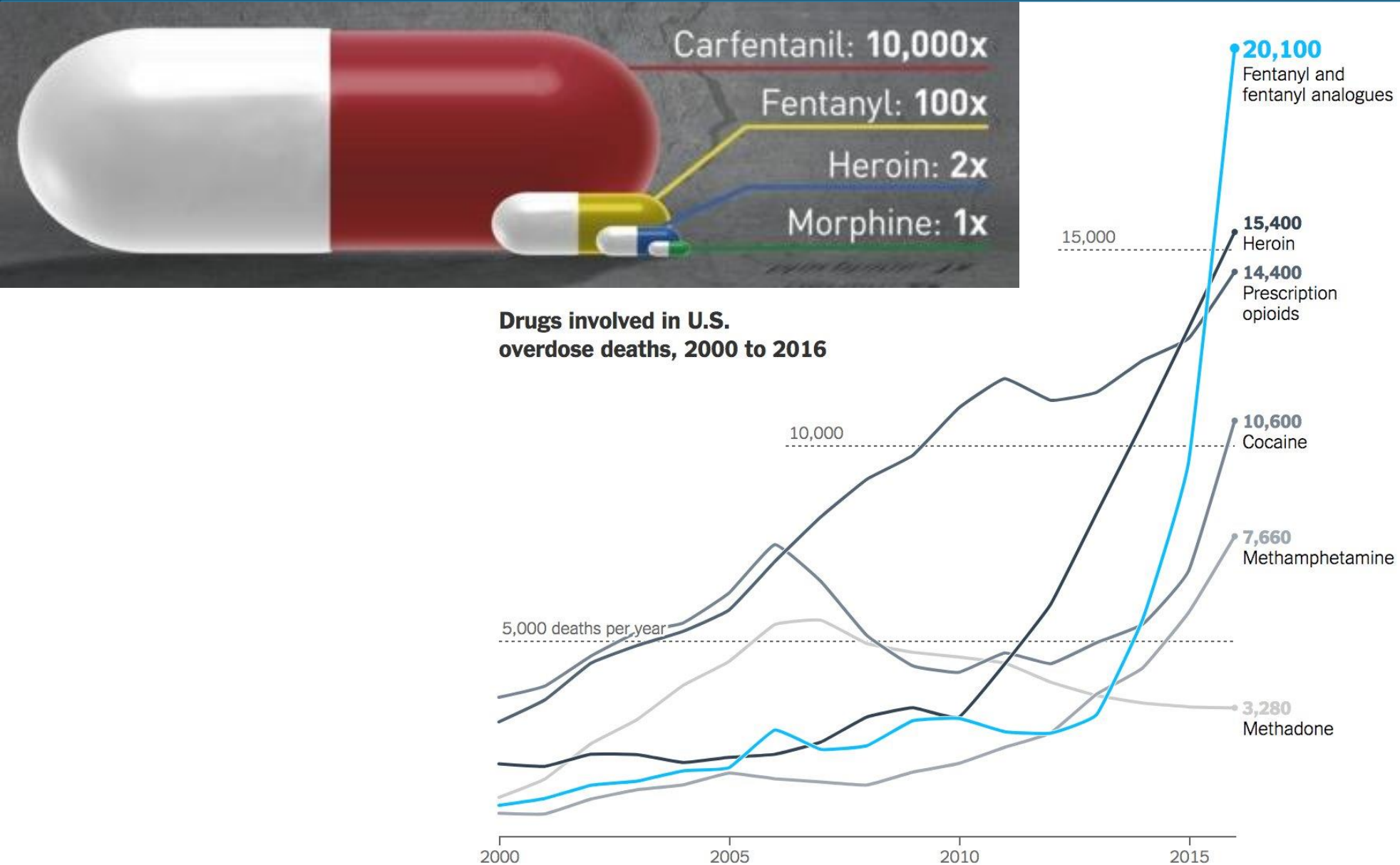
†Prices from U.S. suppliers

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

THE WALL STREET JOURNAL.



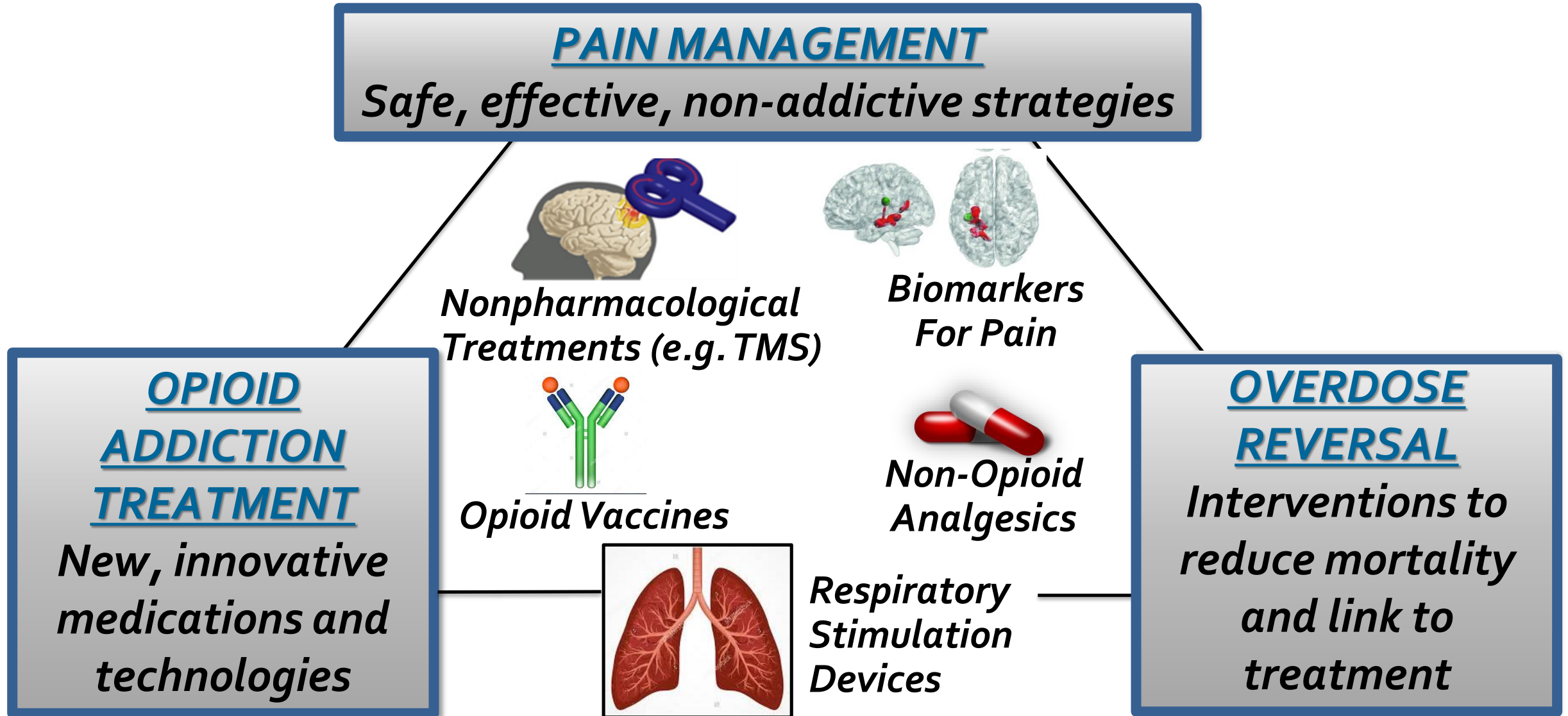
# 2016 *Fentanyl-Related Deaths* Surpassed Heroin or Rx



Graphs from [NY Times Article](#)  
based on [CDC MMWR Report](#)  
2017

# NIH Opioid Research Initiative

## *Using Research to End the Opioid Crisis*



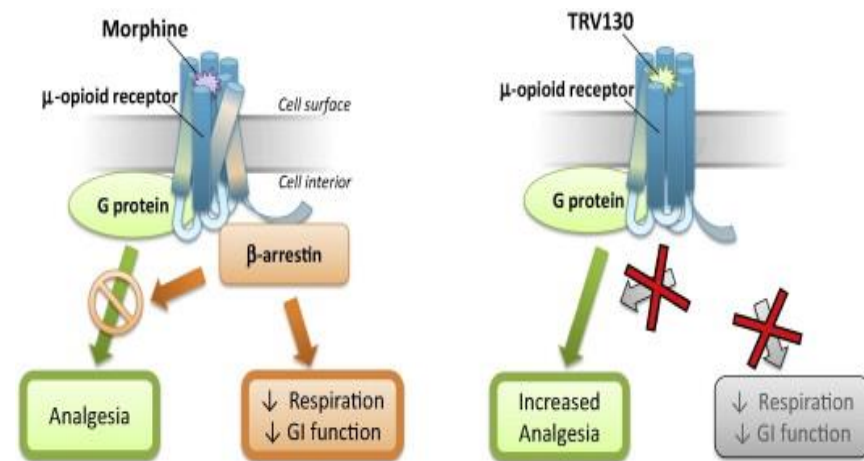
# ***Multiple Potential Targets for Pain Medication but Multiple Challenges***

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- **Regulatory** high safety & labeling hurdles
- **Poor predictive power of preclinical models**
- **Heterogeneous patient population**
  - Multiple pain conditions; wide variation in individual response
- **Lack of biomarkers in pain studies**
- **Limited clinical research resources** No clinical trials network to coordinate pain treatment
- **Limited cohorts of more homogeneous pain syndromes** (trigeminal neuralgia, CRPS,..)

# Public Private Partnership (PPP) Projects in Pain

- **Data Sharing Consortium:** share data on successful & failed drug development
- **Coordinated Clinical Testing of Novel Treatments for Select Pain Conditions in a Pain Research Network :** Develop deeply phenotyped cohorts with select pain conditions
- **Develop and Validate Biomarkers:**
  - Stratify pain populations
  - Predict clinical outcomes/response to treatment
  - Provide precise, objective measures of nociception (“pain-o-meter”)
- **Re-engineer the Pre-Clinical Platform :** Improve success of analgesic development through new pain models (including pluripotential cell models/organoids)
- **Prevention of Chronic Pain**
- **Applying new technologies to discover novel pain targets**



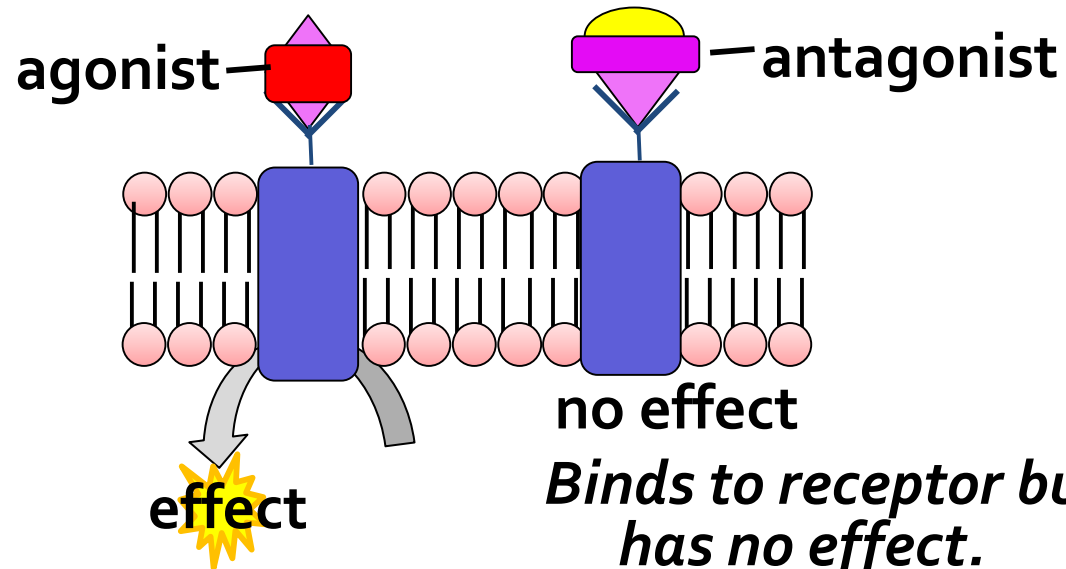


# Effective Medications for Opioid Addiction

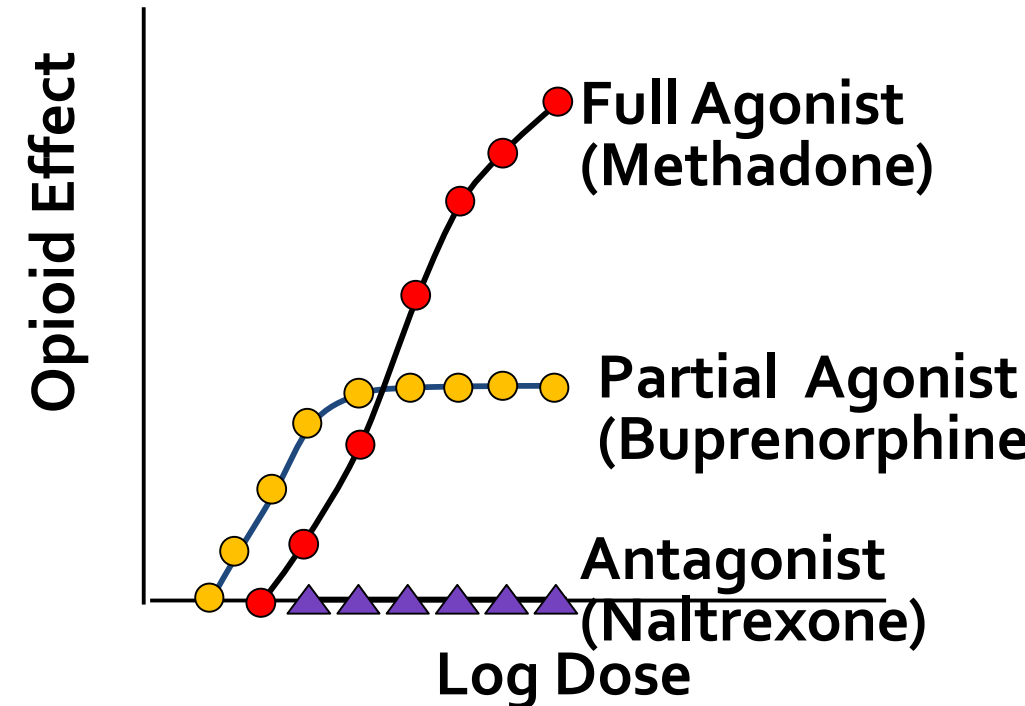
Full Agonist: **Methadone** (daily dosing)

Partial Agonist: **Buprenorphine** (3-4X week, or implant)

Antagonists: **Naltrexone** (monthly extended release)



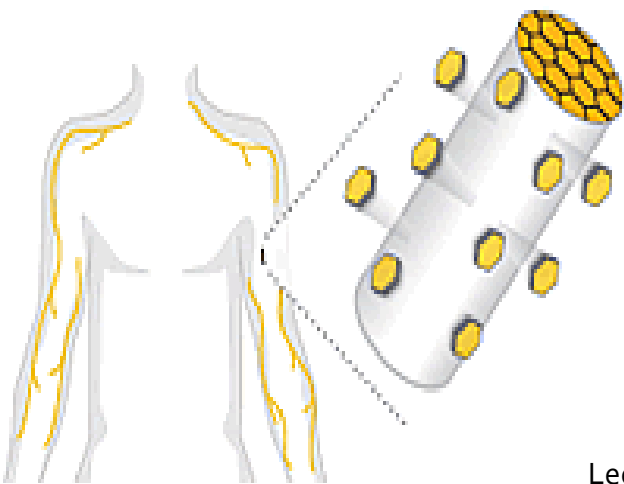
*Binds to the receptor and activates it;  
Full agonists have maximal effect.  
Partial agonist have intermediate effect.  
Prevent Heroin from binding.*



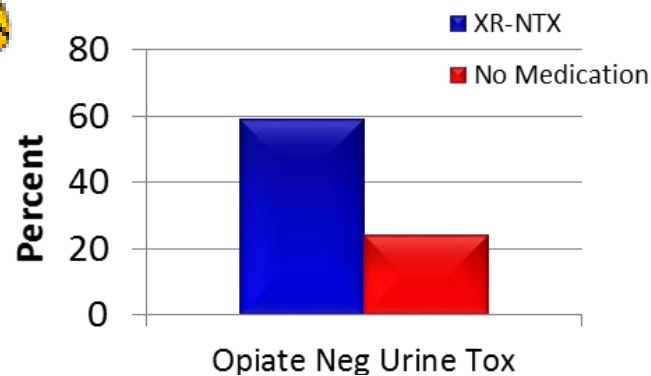
*Science = Solutions*

# Science Driven Solutions: Improving Addiction Treatment

- Probuphine: **buprenorphine implant**; releases sustained dose for up to 6 months (FDA Approval May 26, 2016)
- 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
- Abstinence from opioids over 12 Weeks with **interim buprenorphine**

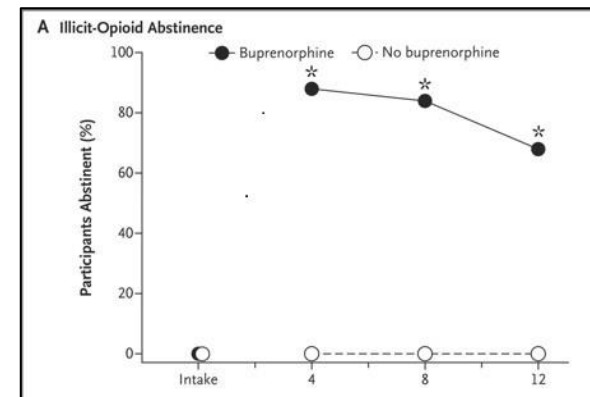


Post Prison-Release Outcomes



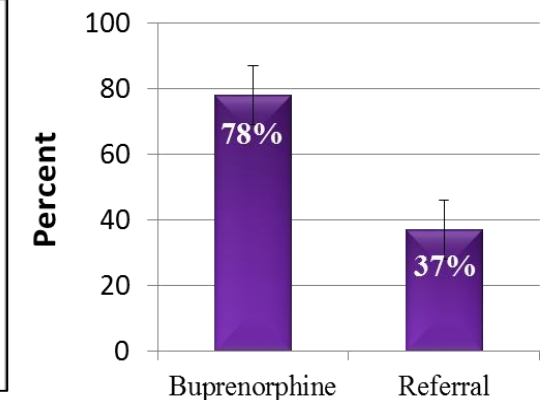
Lee JD, et al., *Addiction* 2015;100:1005-1014  
and *New Eng J Med* 2016;374:1232-1242

Abstinence with Interim Buprenorphine



Sigmon SC et al. *N Engl J Med* 2016.

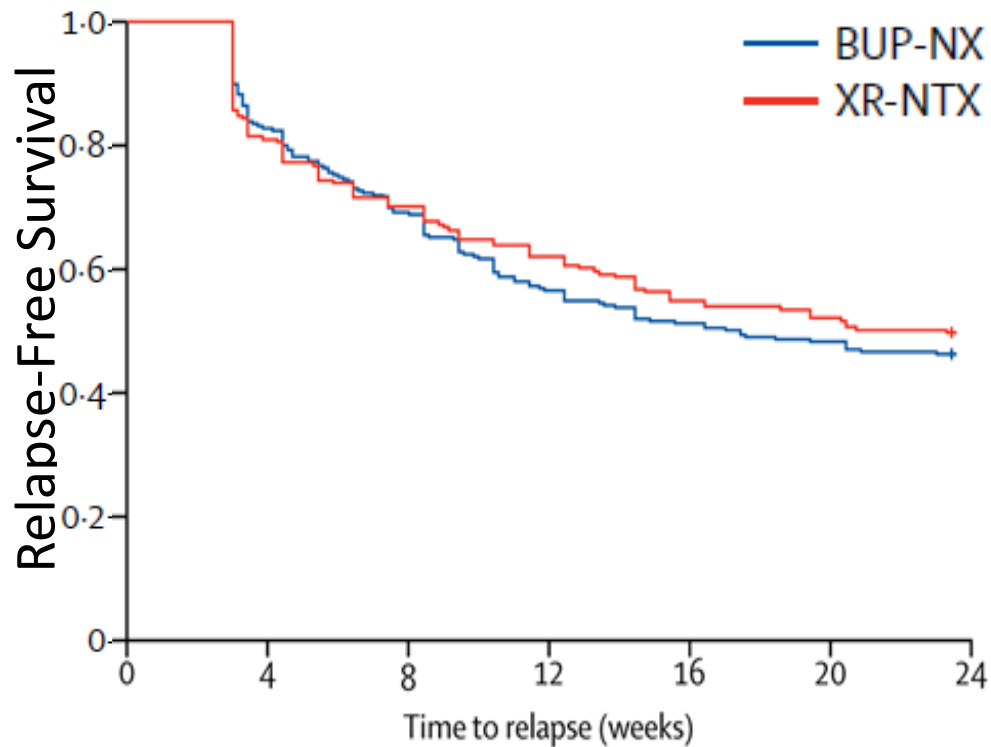
ED-initiated Buprenorphine Increased TX Engagement



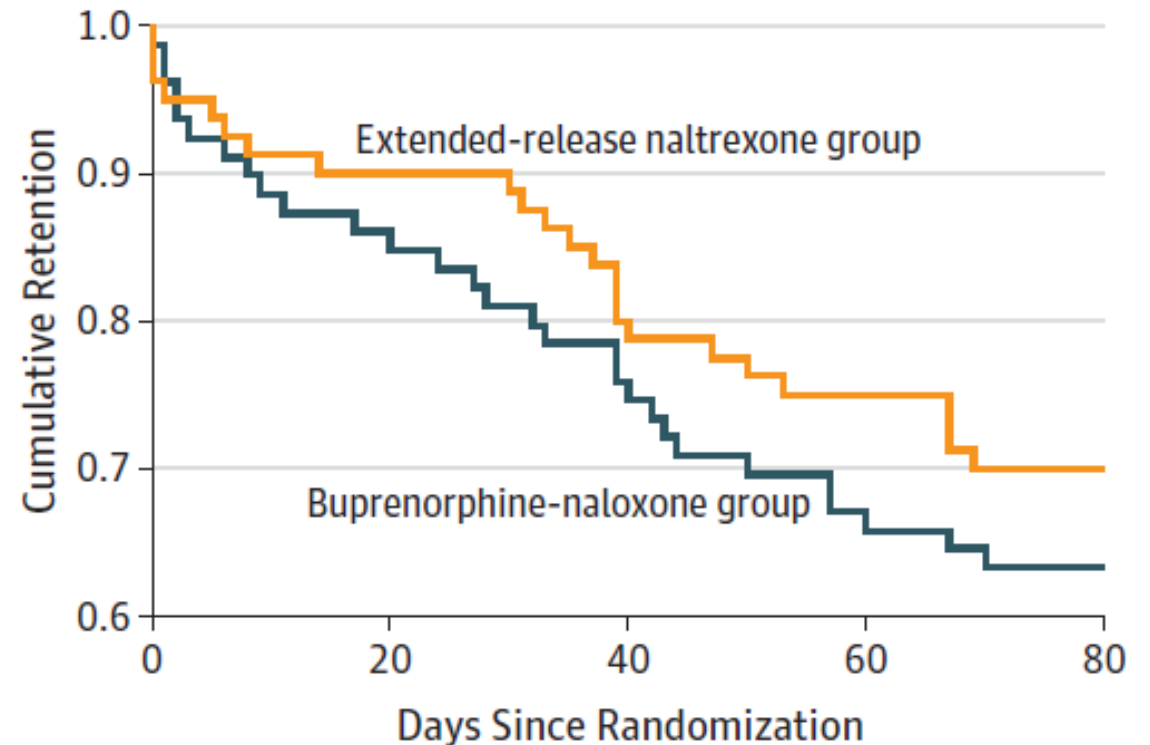
D'Onofrio *JAMA*. 2015.

# XR-Naltrexone and Buprenorphine-Nx *Equally Safe and Effective In Preventing Relapse* (After Induced to Medication)

*Two studies found that once induced onto medication outcomes were comparable.  
However, relapse rates were high for both medications.*



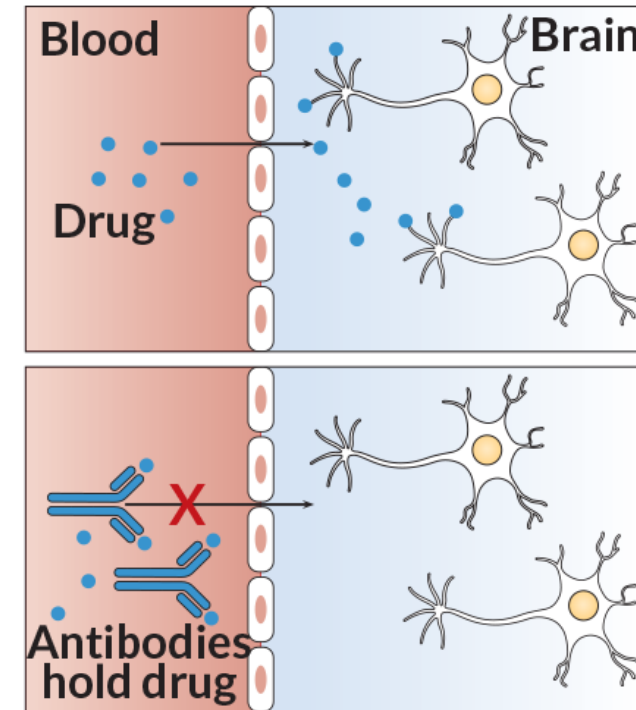
Lee J et al., Lancet November 14, 2017.



Tanum L et al., JAMA Psych. October 18, 2017.

# Monoclonal *Antibodies and Vaccines* to Treat OUD and Prevent Overdose

- Heroin vaccine validated in primate model in 2017
- First vaccine for fentanyl and fentanyl analogs reported in a mouse model in 2016
- Reduces drug reaching the brain
- Protect high-risk individuals against overdose



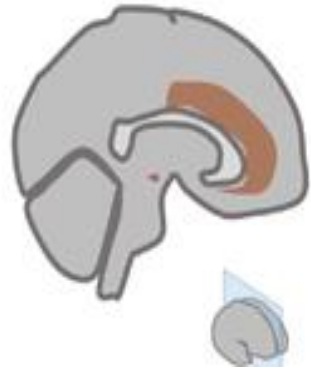
*Bremer et al, 2017;*  
*Bremer et al, 2016;*  
*Janda and Treweek, 2012.*



# *Non-Pharmacological Treatments* for Addiction



**Transcranial Magnetic Stimulation (TMS)**



**Transcranial Direct Current Stimulation (tDCS)**



**Deep Brain Stimulation (DBS)**  
Implanted electrodes emit electrical stimulation to targeted brain region



- Dorsolateral Prefrontal Cortex
- Superior Prefrontal Cortex
- Inferior Prefrontal Cortex
- Orbitofrontal Cortex
- Anterior Cingulate Cortex
- Ventral Striatum
- Amygdala
- Ventral Tegmental Area

# PPP for Opioid Use Disorder

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## ➤ *Medications for OUD*

- Extended release formulations buprenorphine, naltrexone
- Drug combinations
- Alternative therapeutics (i.e. new targets, vaccines)
- Targeting endophenotypes/circuits

## ➤ *Medications for overdose prevention and reversal*

- Stronger formulations of Naloxone or alternative antagonists to reverse OD from synthetic opioids like fentanyl, carfentanil
- Vaccines and antibodies against fentanyl and analogs

## ➤ *Devices to prevent opioid misuse, overdose prevention*

- Devices to administer buprenorphine or methadone safely at home
- Naloxone autoinjectors
- Stimulation devices (TMS, DECT, Ultrasound, Peripheral stimulation)

# Summary:

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- Biological, developmental, and social complexities of substance use and addiction suggest *multipronged responses*.
- *Medication development* is key.

Science = Solutions