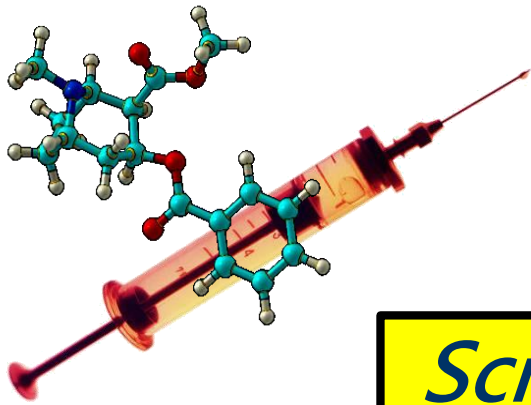
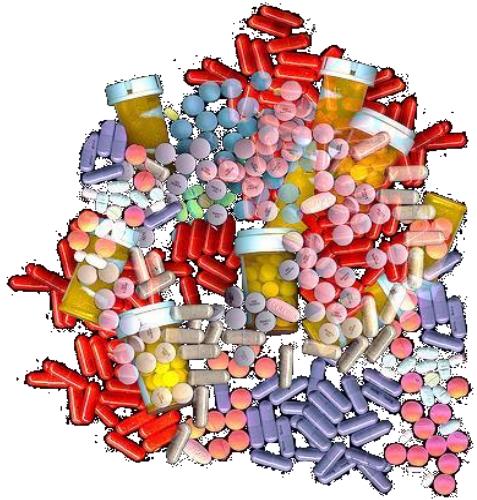
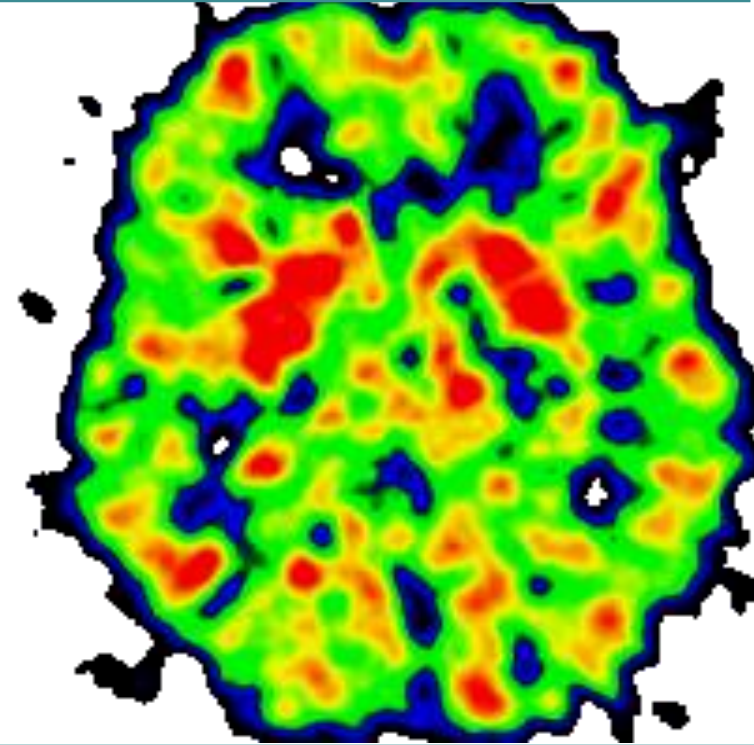


Advancing Addiction Science to Address the Opioid Crisis



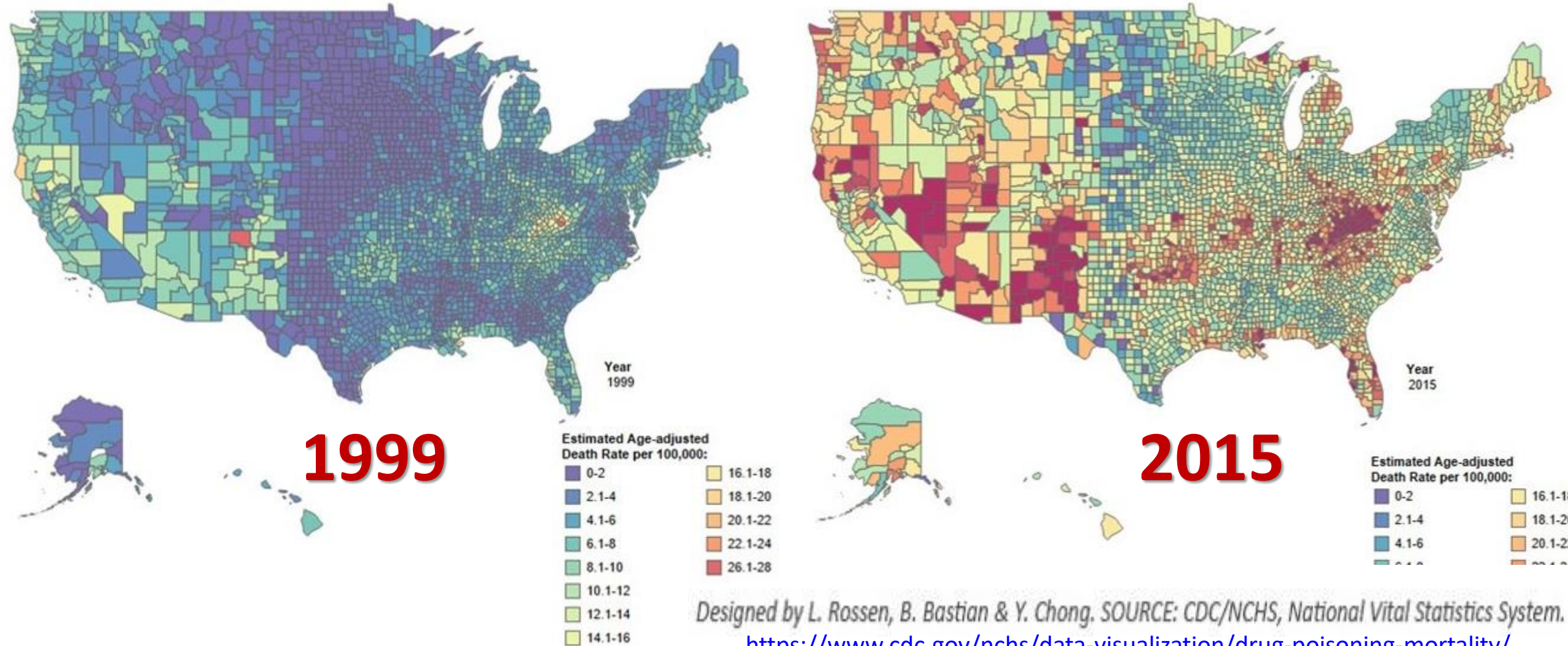
*Science =
Solutions*



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

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

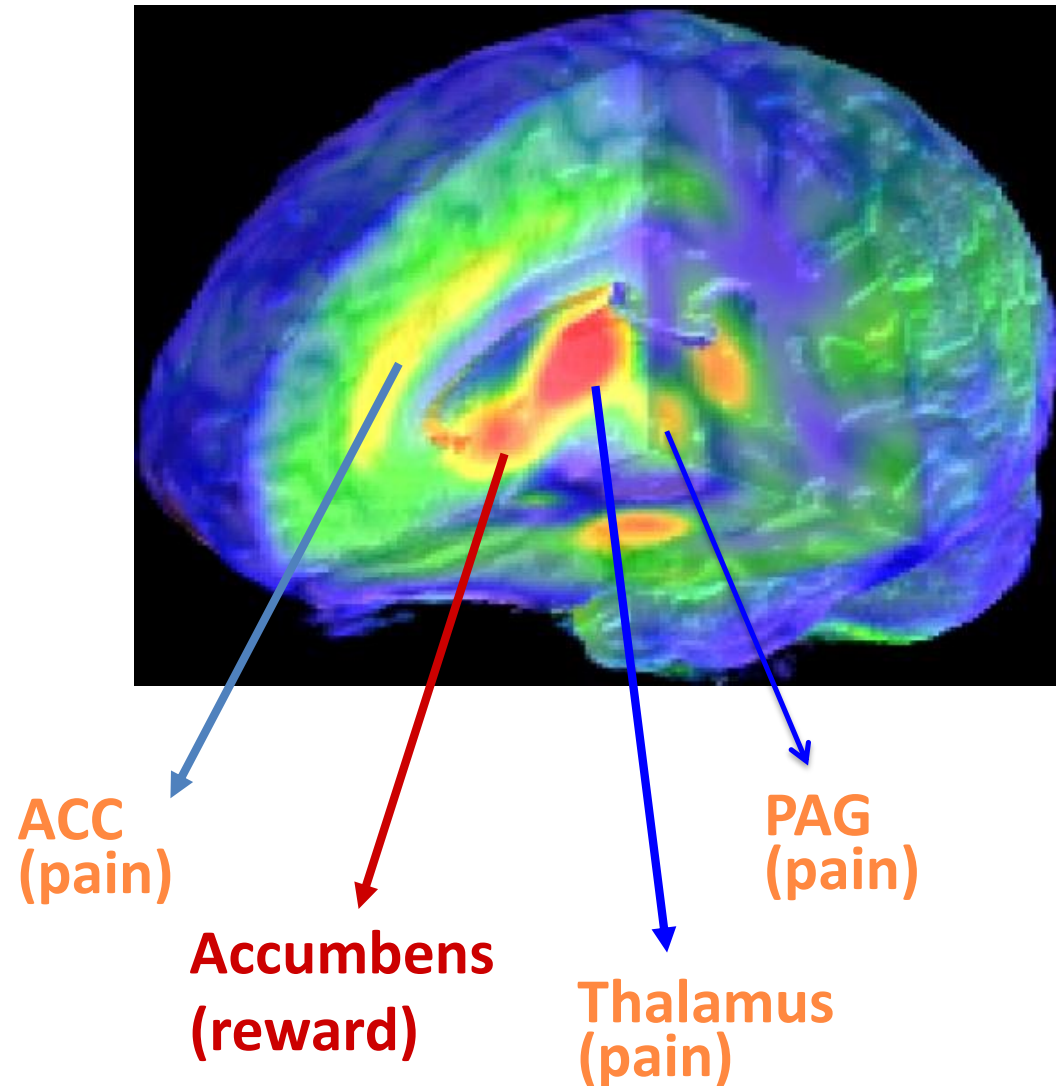
Geographic and Temporal Variation: Estimated Age-adjusted Death Rates for Drug Poisoning by County



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

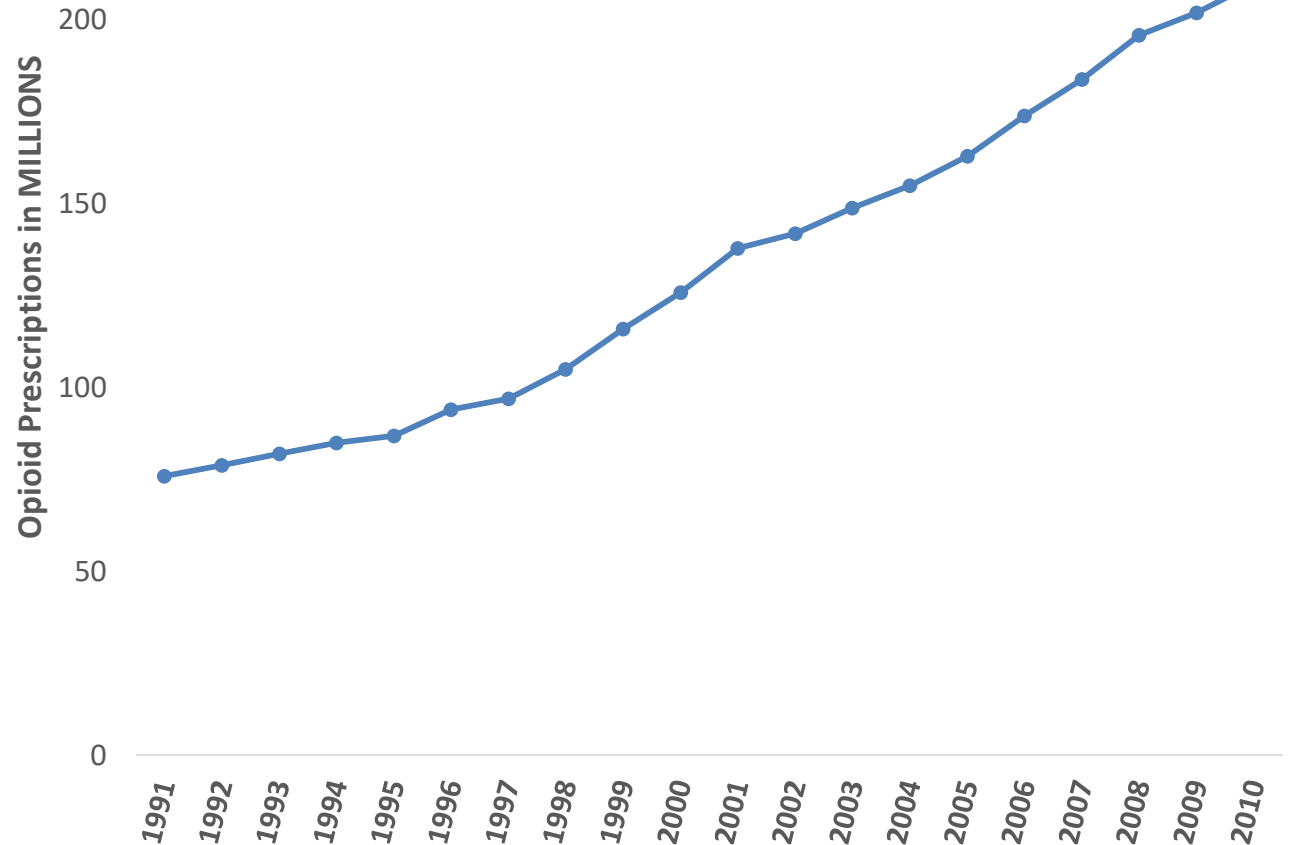
<https://www.cdc.gov/nchs/data-visualization/drug-poisoning-mortality/>

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



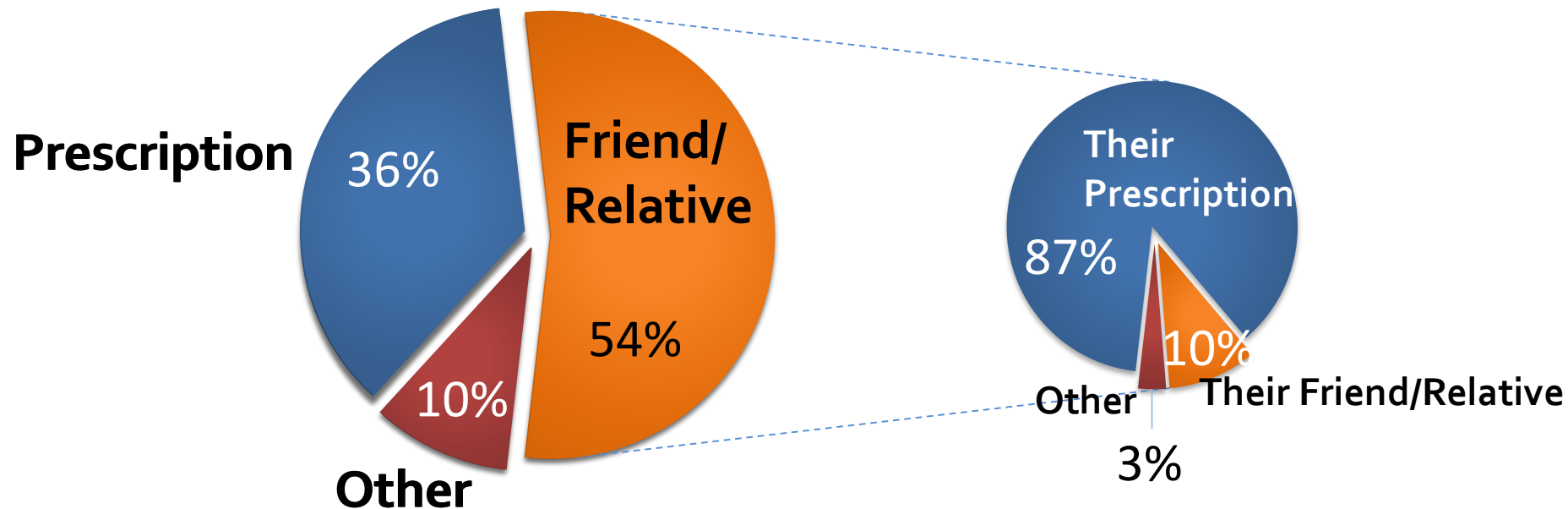
***ENVIRONMENTAL AVAILABILITY:* Current Opioid Crisis Originated with Prescribing Increases**

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



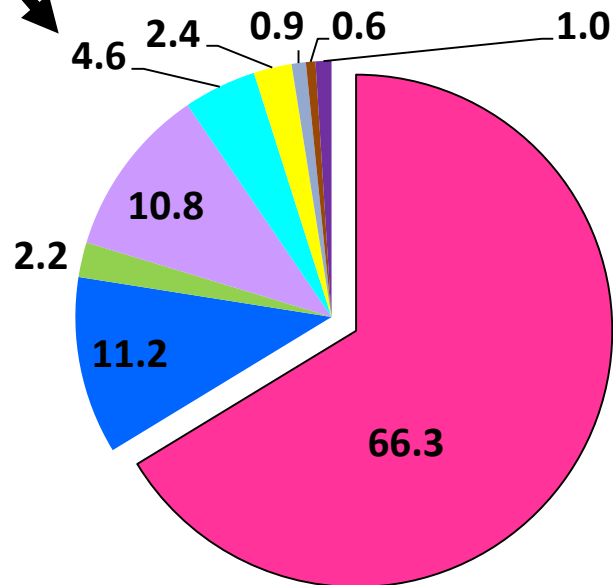
Source: Han, Compton, et al. *Annals of Internal Medicine* 2017;167(5):293-301

Inadequate *Pain Treatment* as a Driver?

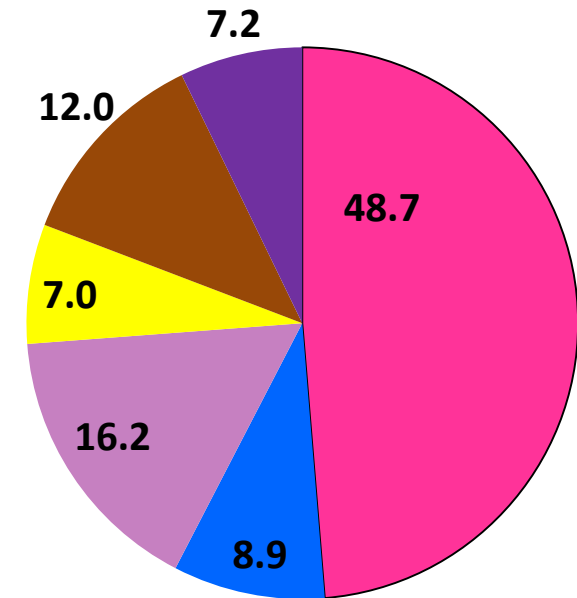
91.8 million adults used prescription opioids (37.8% of the U.S. adult population)

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)

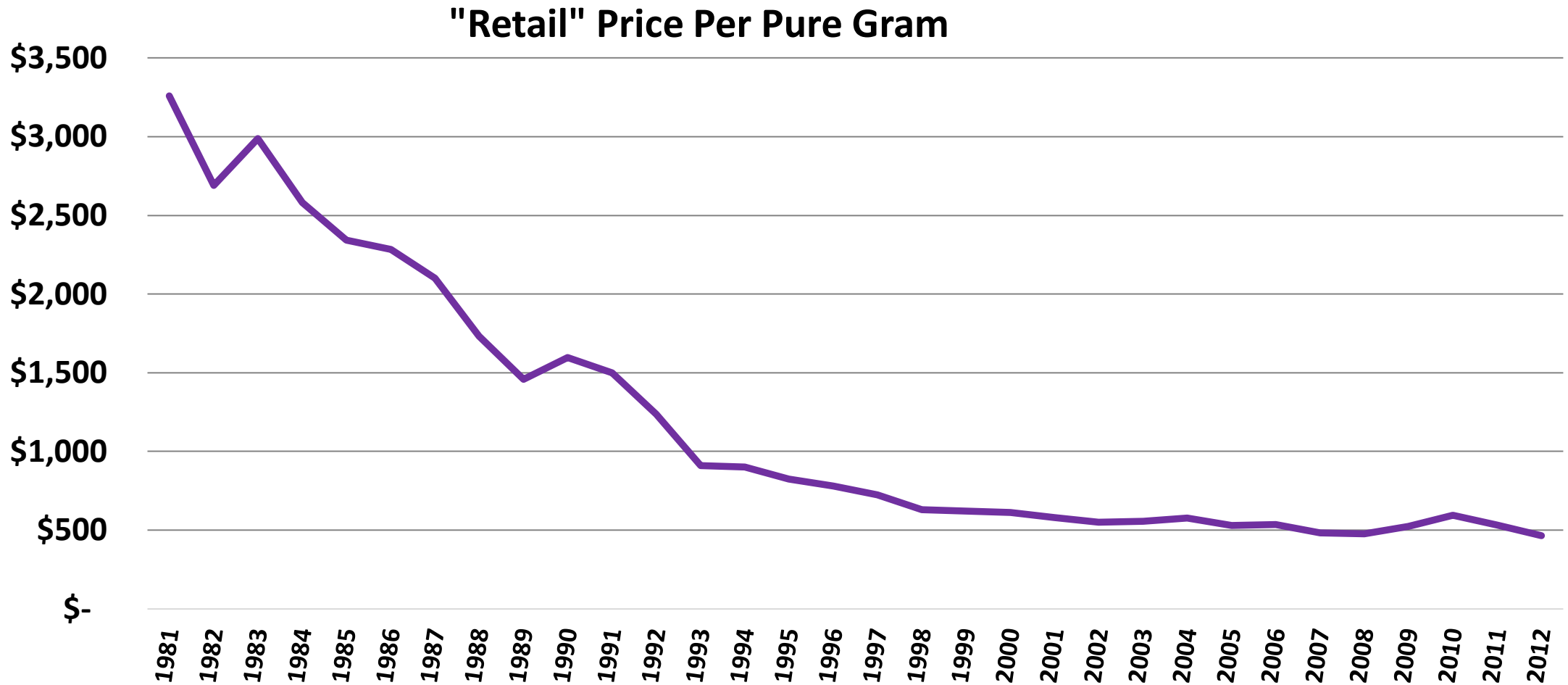


- relieve physical pain
- relax or relieve tension
- experiment
- get high or feel good
- help with sleep
- help with emotions or feelings
- increase/decrease effects of other drugs
- hooked or have to misuse
- other reason



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

ECONOMICS: Heroin Increases Due to Lower Price and Greater Availability

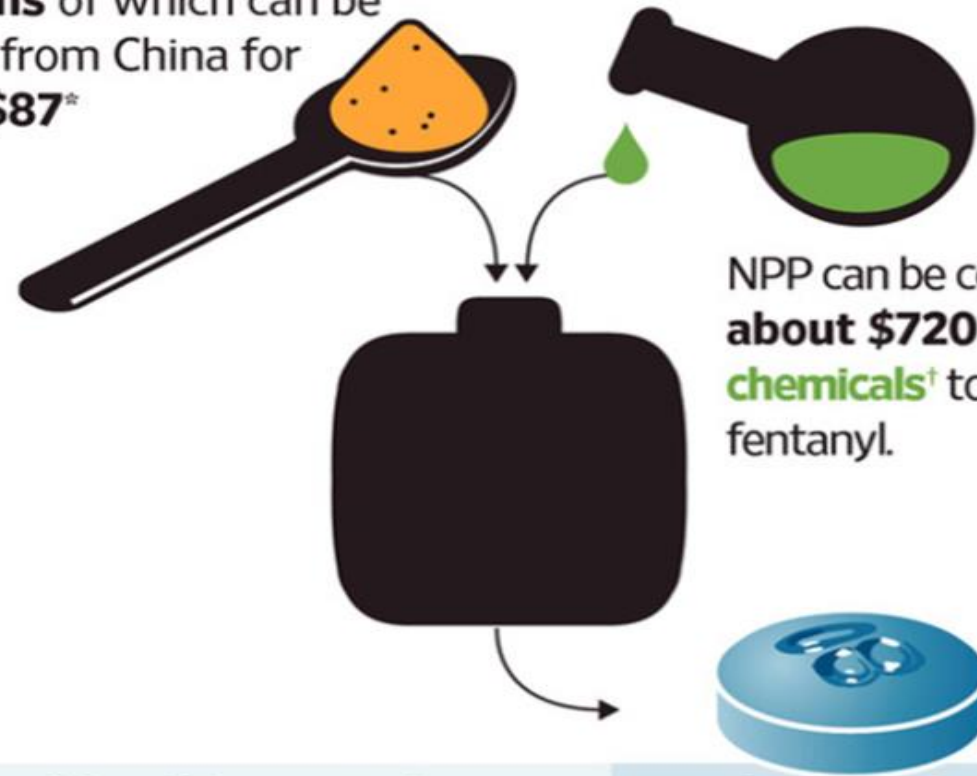


ECONOMICS: **CHEAP Fentanyl Precursor Chemicals**

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

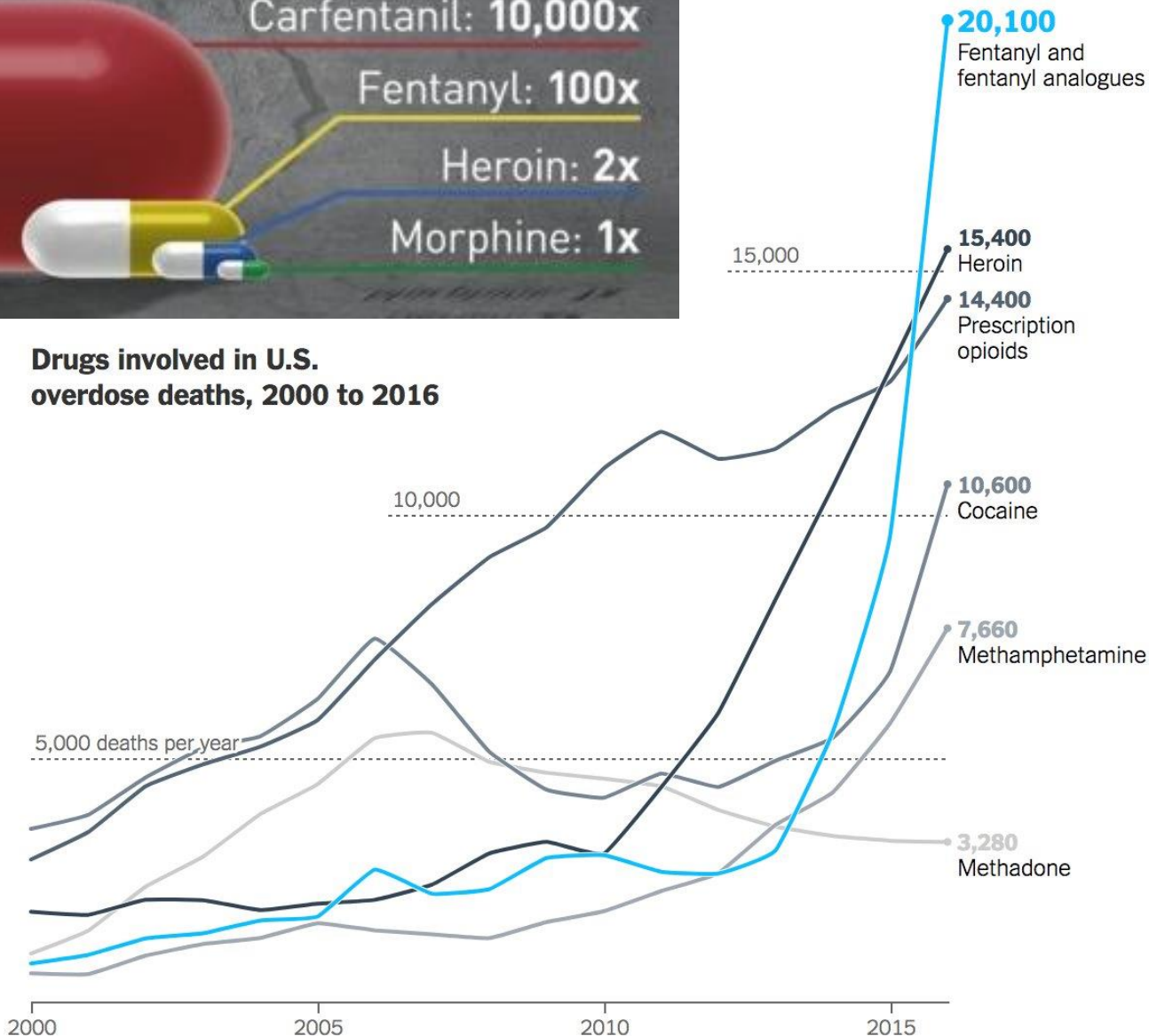
Sources: NES Inc.; Drug Enforcement Administration;
Calgary Police

THE WALL STREET JOURNAL.

2016 *Fentanyl-Related Deaths* Surpassed Heroin or Rx



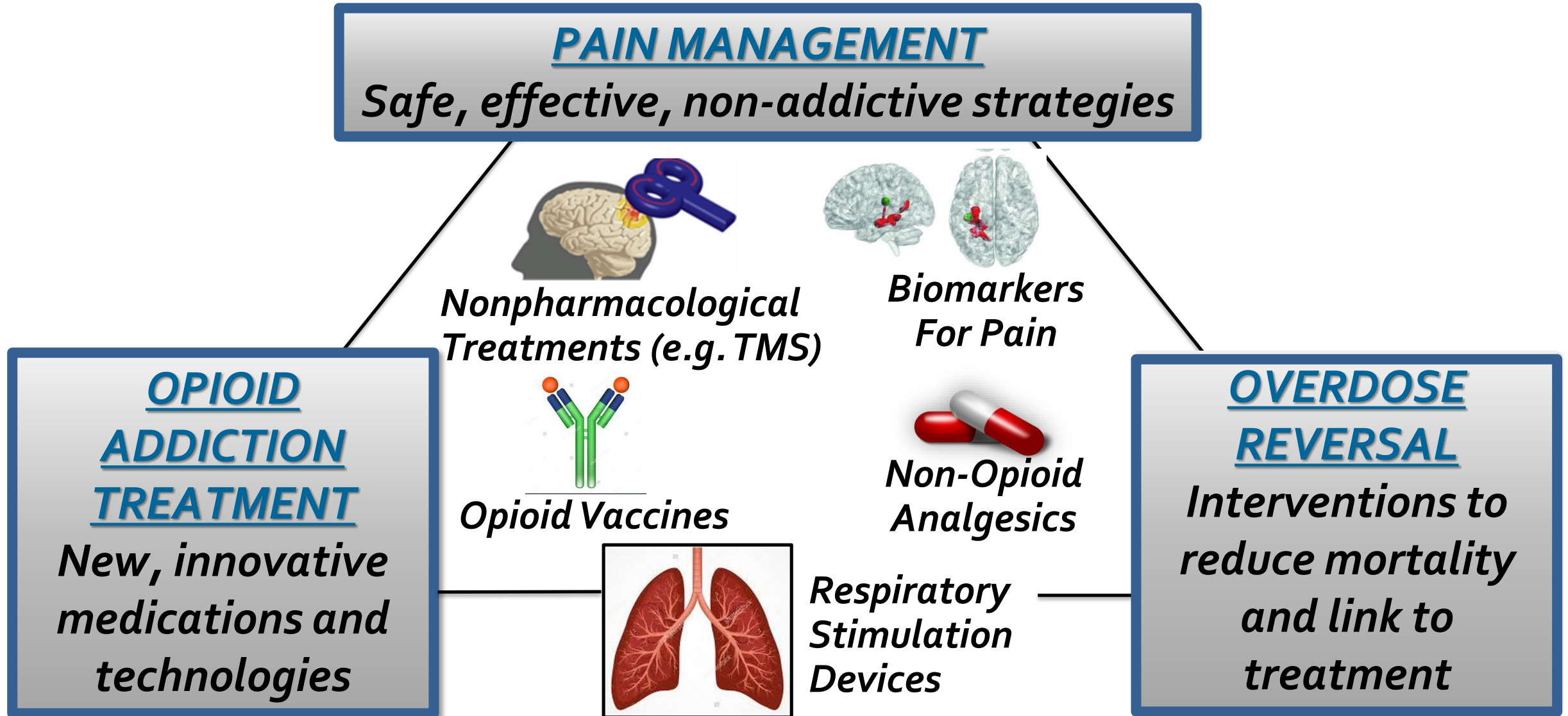
Drugs involved in U.S. overdose deaths, 2000 to 2016



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

NIH Opioid Research Initiative

Using Research to End the Opioid Crisis

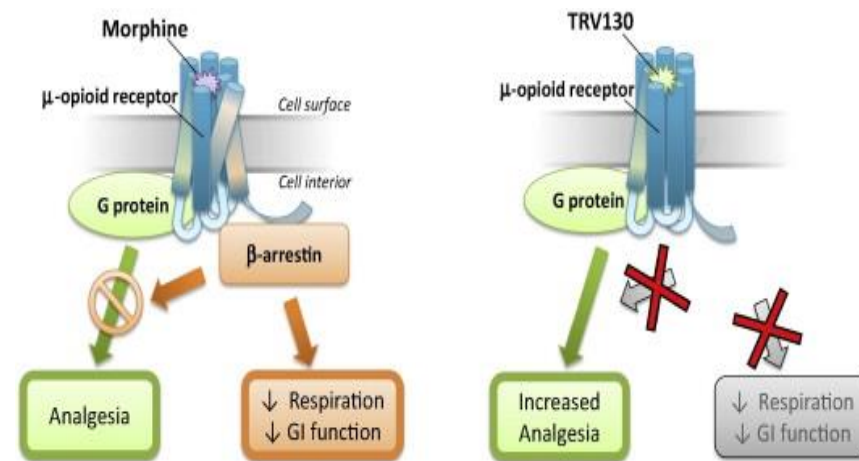


Multiple Potential Targets for Pain Medication but *Multiple Challenges*

- **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**

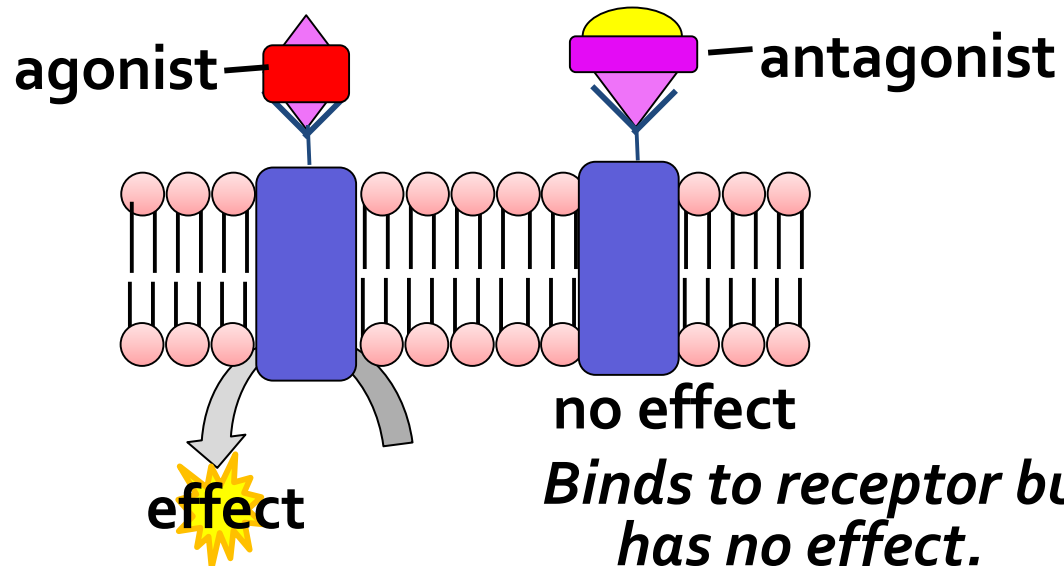


Effective Medications for Opioid Addiction

Full Agonist: *Methadone* (daily dosing)

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

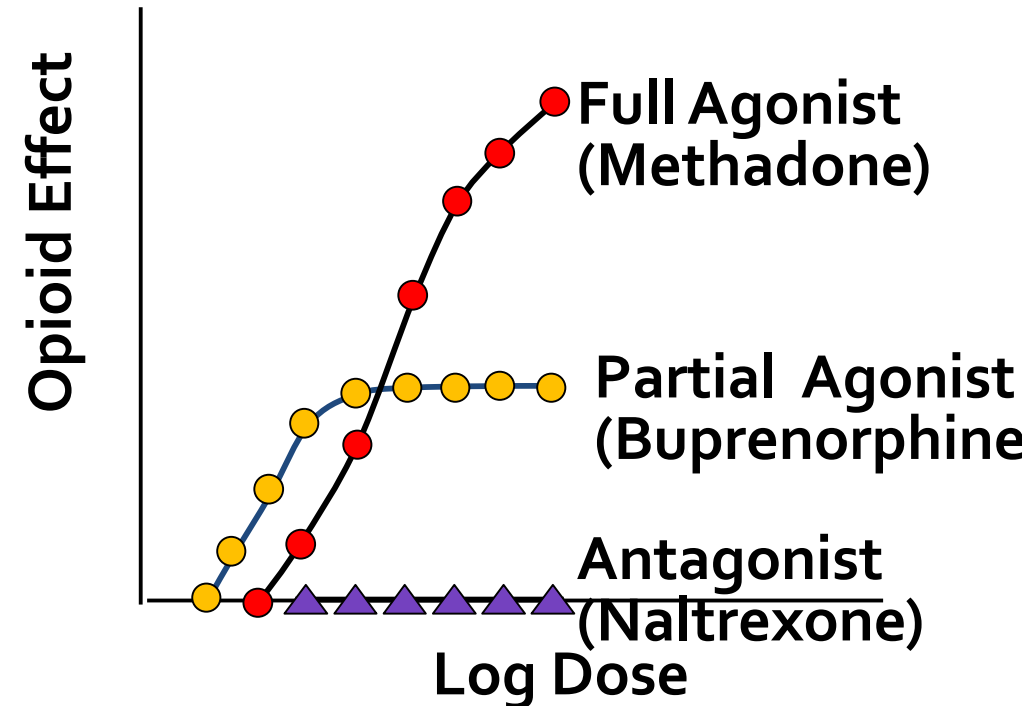
Antagonists: *Naltrexone* (monthly extended release)



Binds to the receptor and activates it; Full agonists have maximal effect.

Partial agonist have intermediate effect.

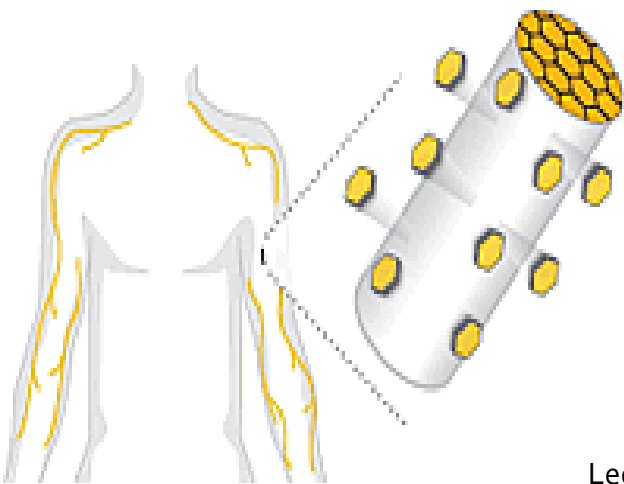
Prevent Heroin from binding.



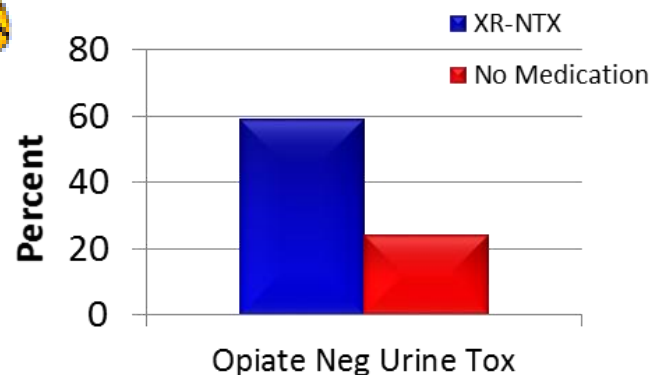
Science = Solutions

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**

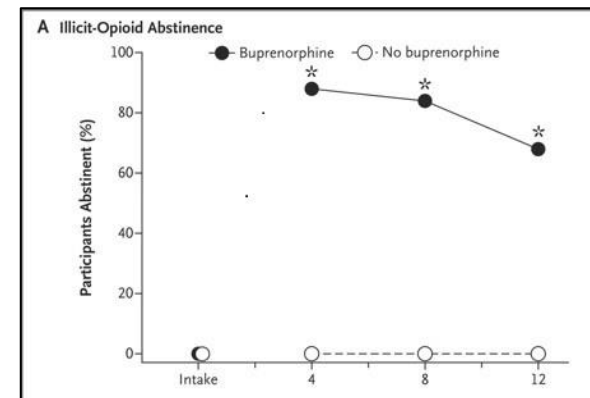


Post Prison-Release Outcomes



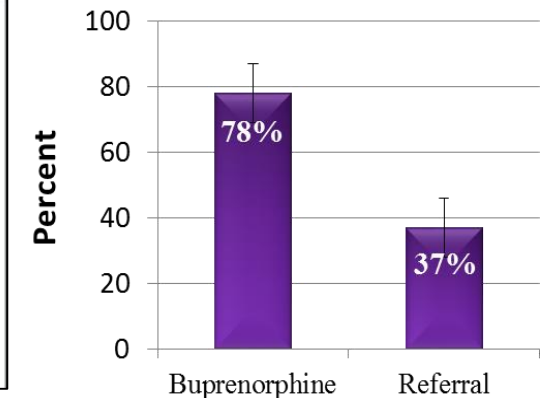
Lee JD, et al., *Addiction* 2015;100:1005-1014
and *New Eng J Med* 2016;374:1232-1242

Abstinence with Interim Buprenorphine



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

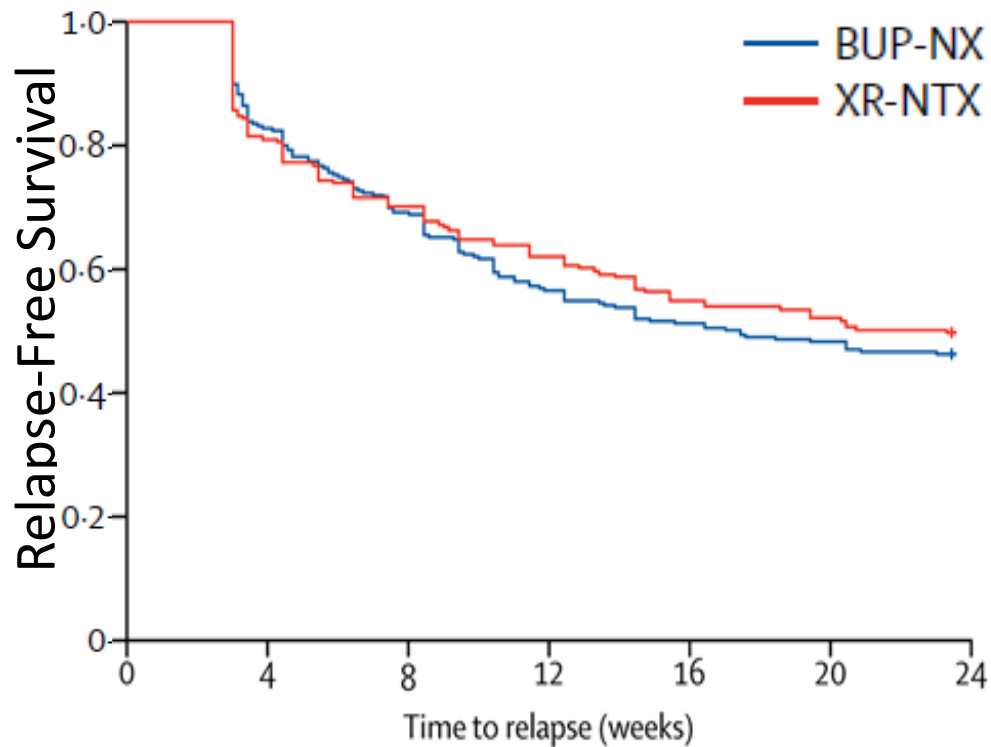
ED-initiated Buprenorphine Increased TX Engagement



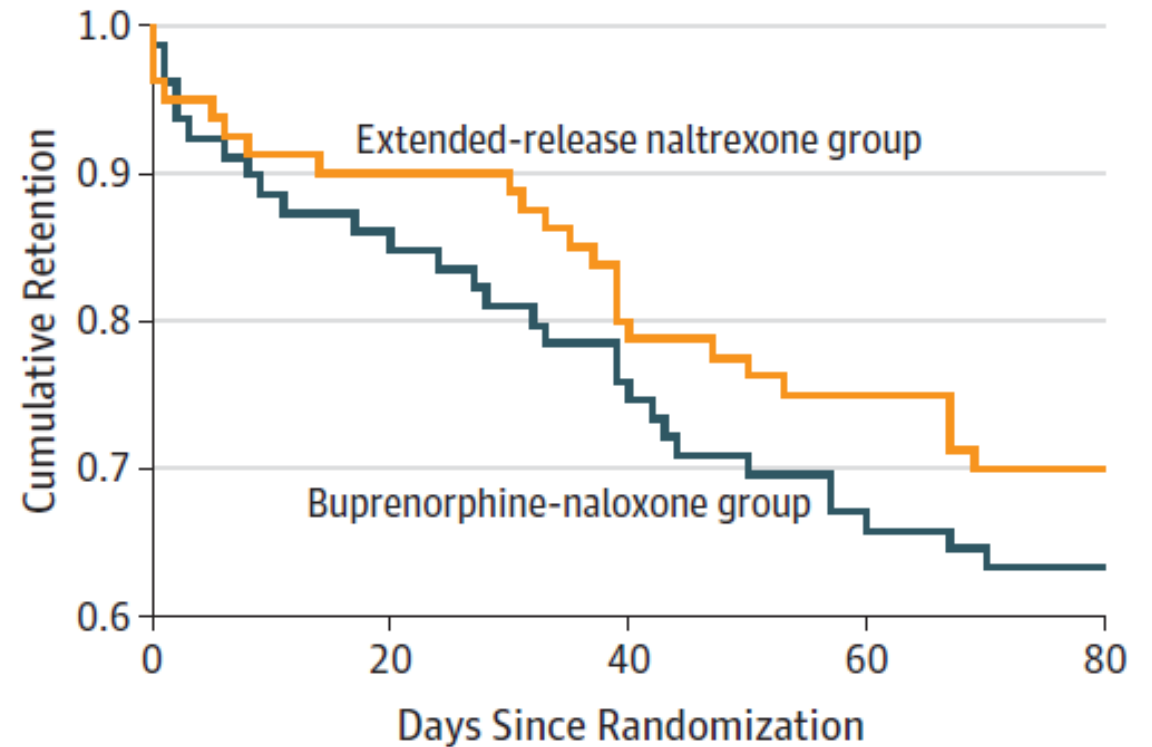
D'Onofrio *JAMA*. 2015.

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

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



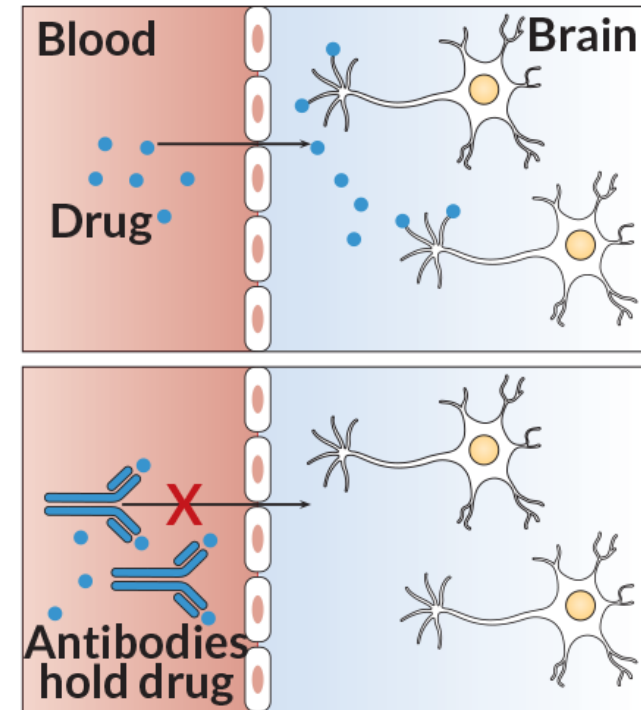
Lee J et al., Lancet November 14, 2017.



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

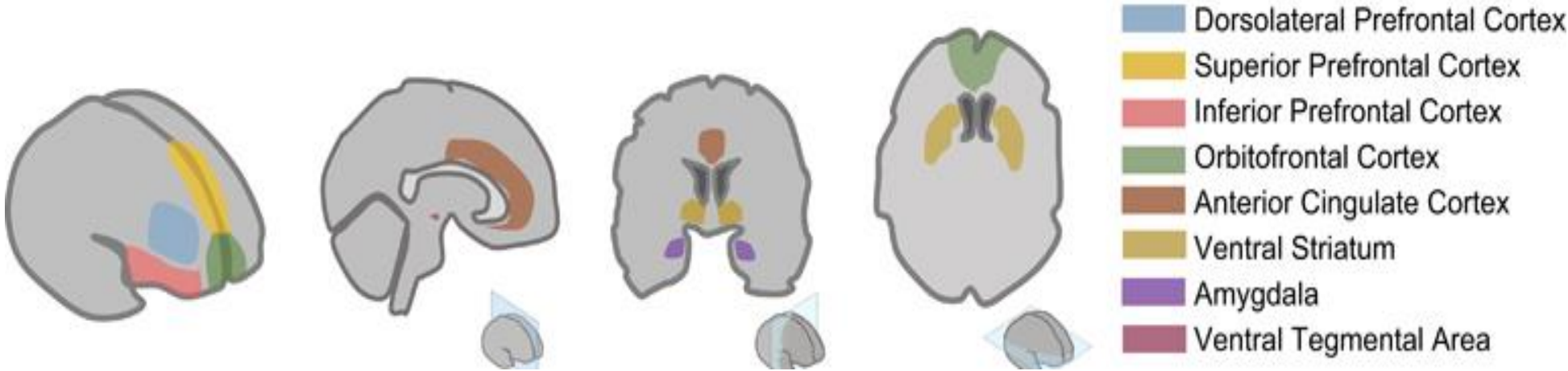
Monoclonal *Antibodies and Vaccines* to Treat OUD and Prevent Overdose

- 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



Salling and Martinez, 2016.

PPP for Opioid Use Disorder

➤ *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:

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

Science = Solutions