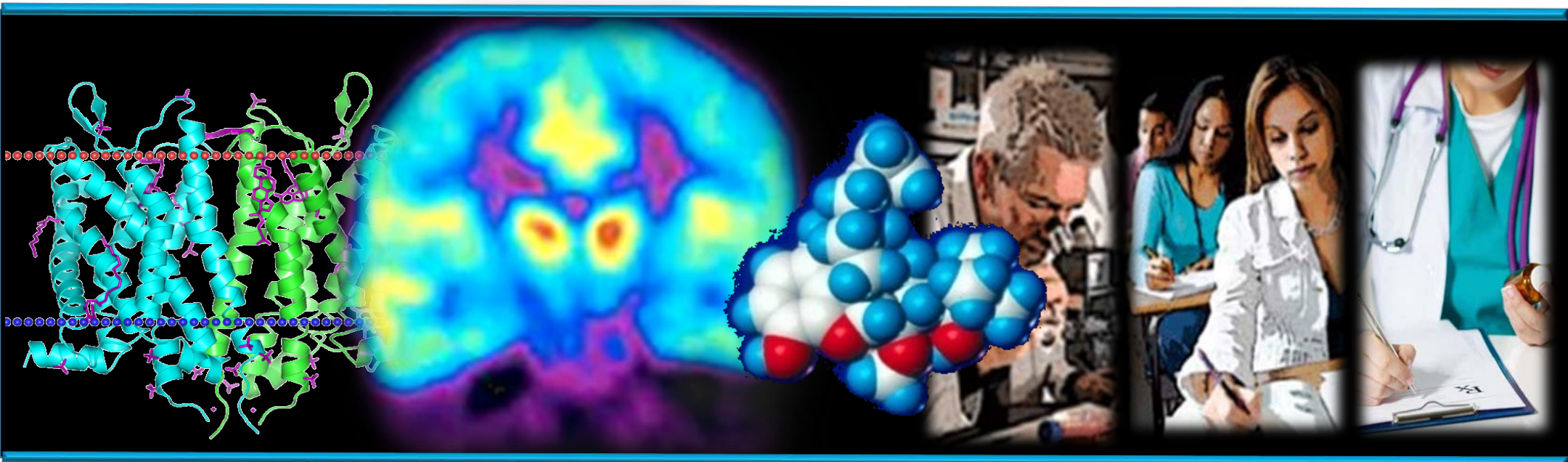


Addressing the Opioid Crisis: *A Key Role for Translational Science*



Nora D. Volkow, M.D.
Director

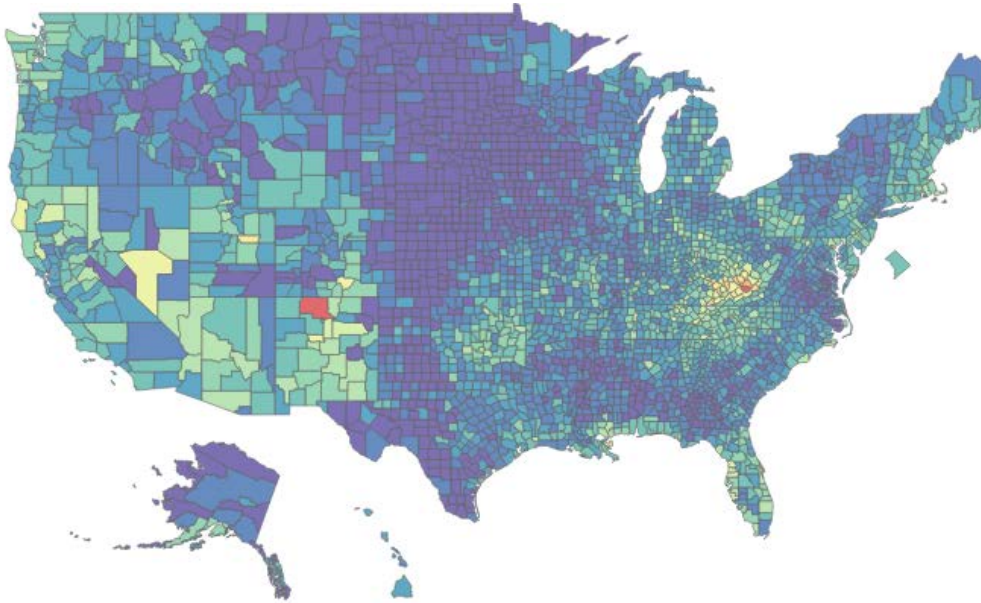


National Institute
on Drug Abuse

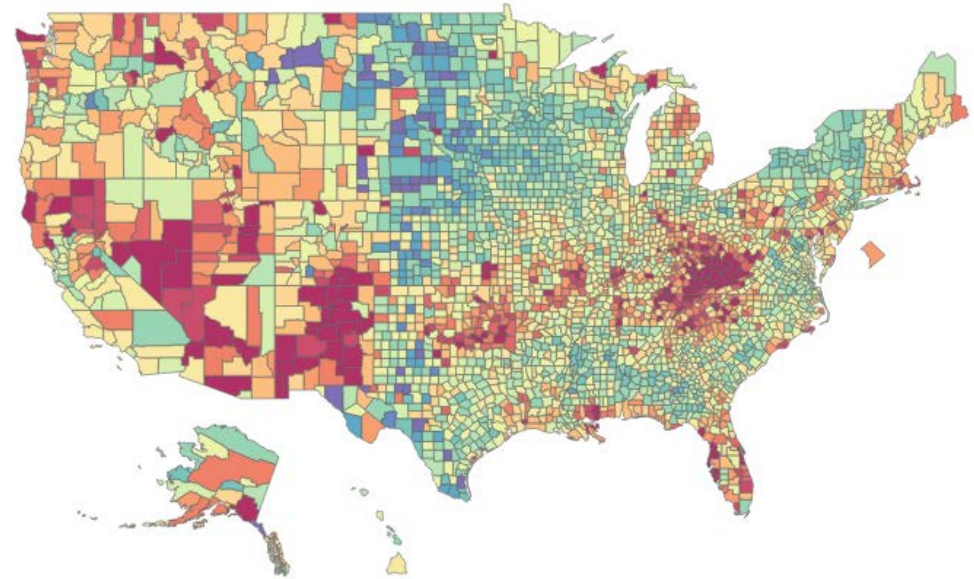
 @NIDAnews

Overdose Death Rates

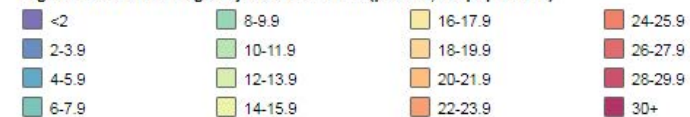
1999



2016

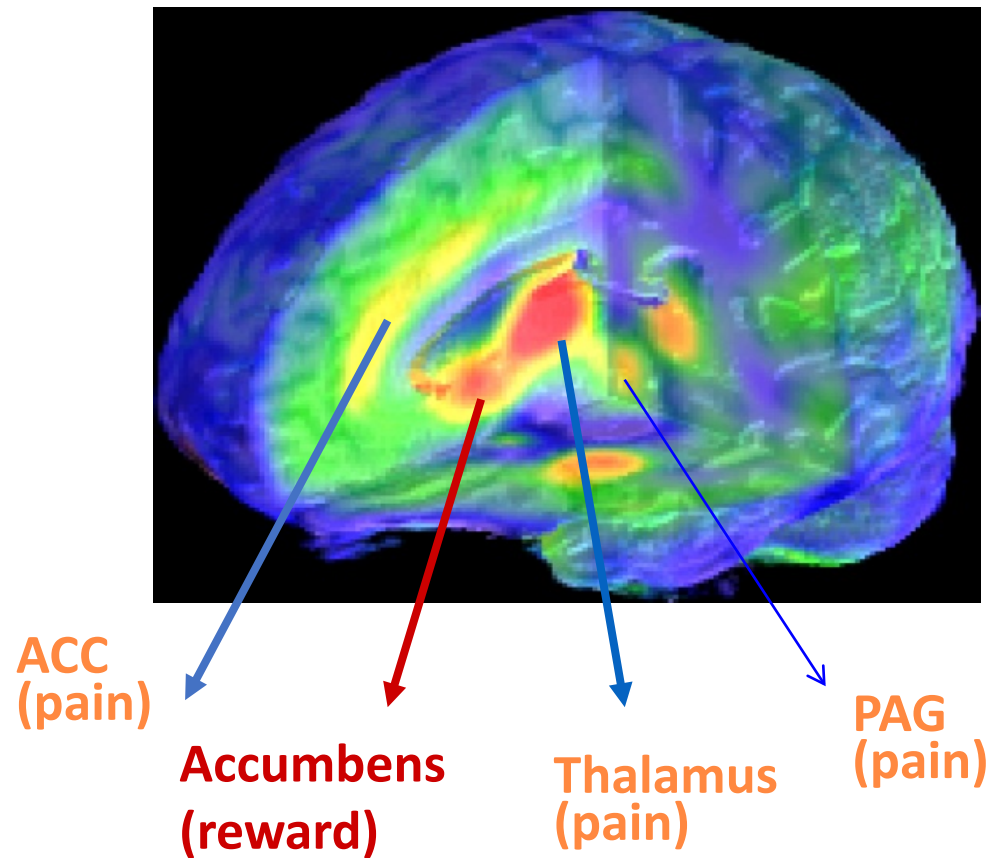


Legend for estimated age-adjusted death rate (per 100,000 population)

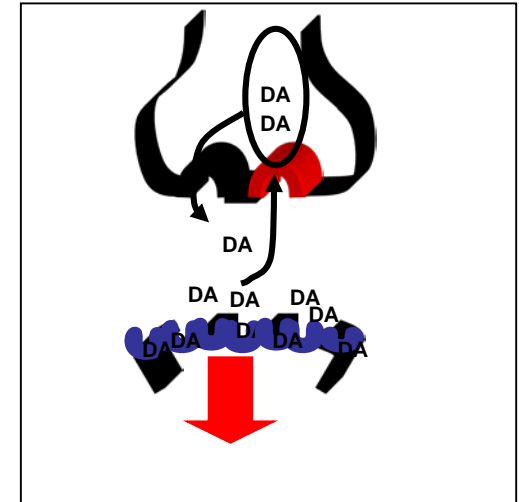
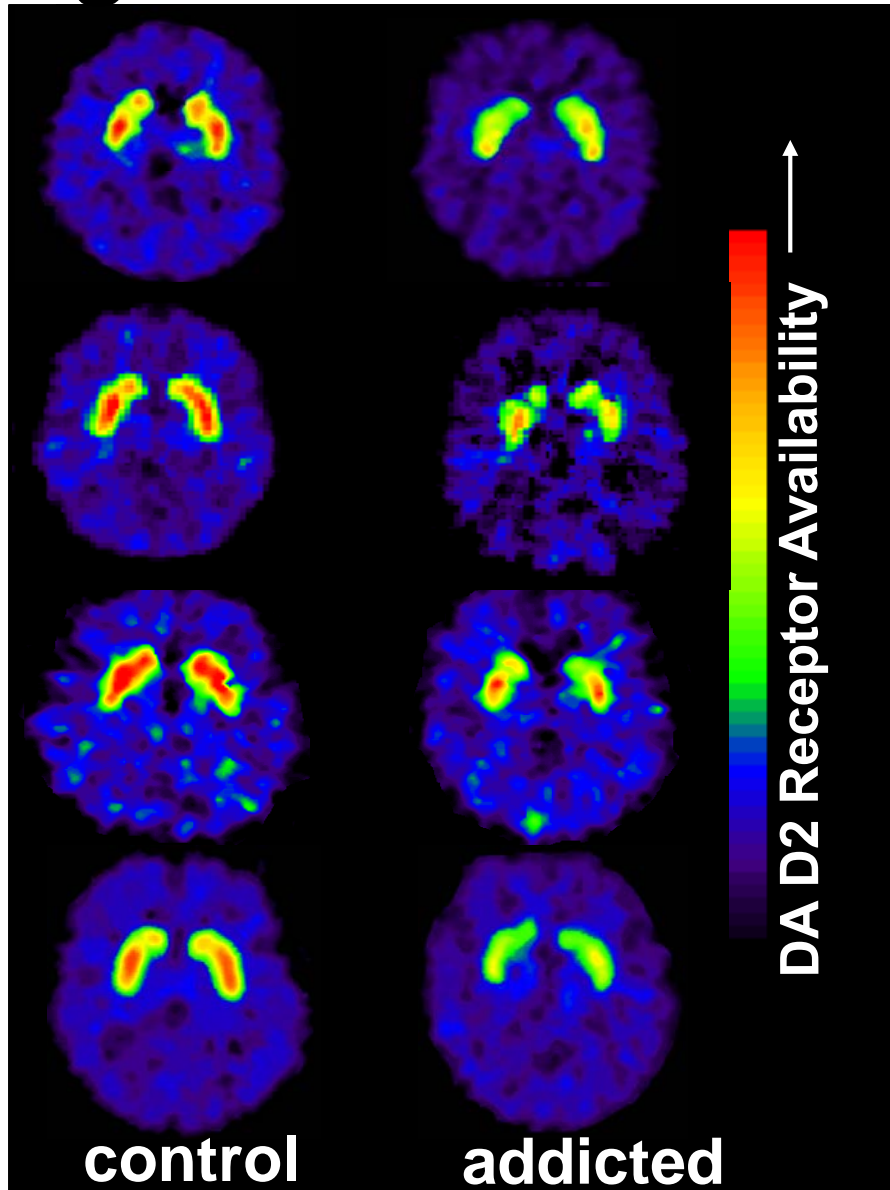
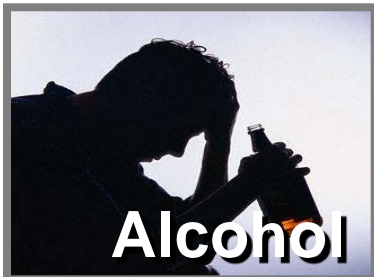


Source: <https://www.cdc.gov/nchs/data-visualization/drug-poisoning-mortality/index.htm>

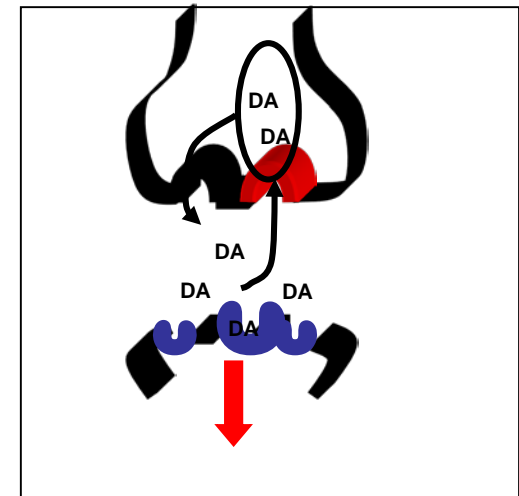
Analgesic & **Reward** Mechanisms of Mu Opiate Drugs (Heroin, Vicodin, Morphine)



Decreased Levels of DA D2 Receptors in Drug Addicted Individuals



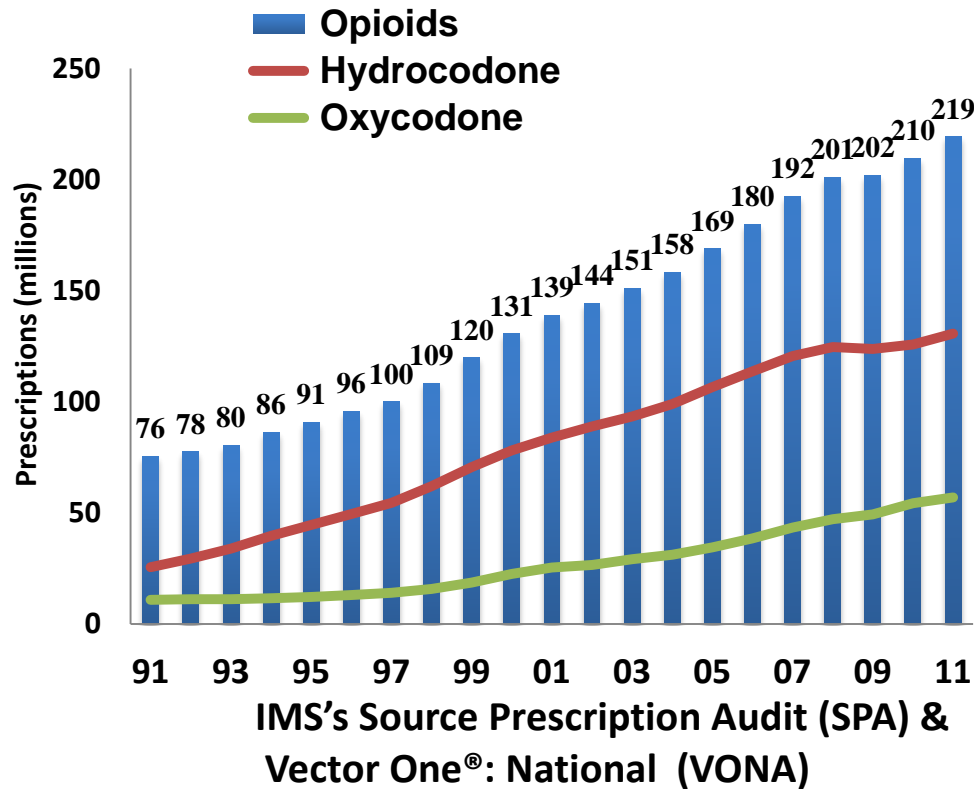
Non-Drug Abuser



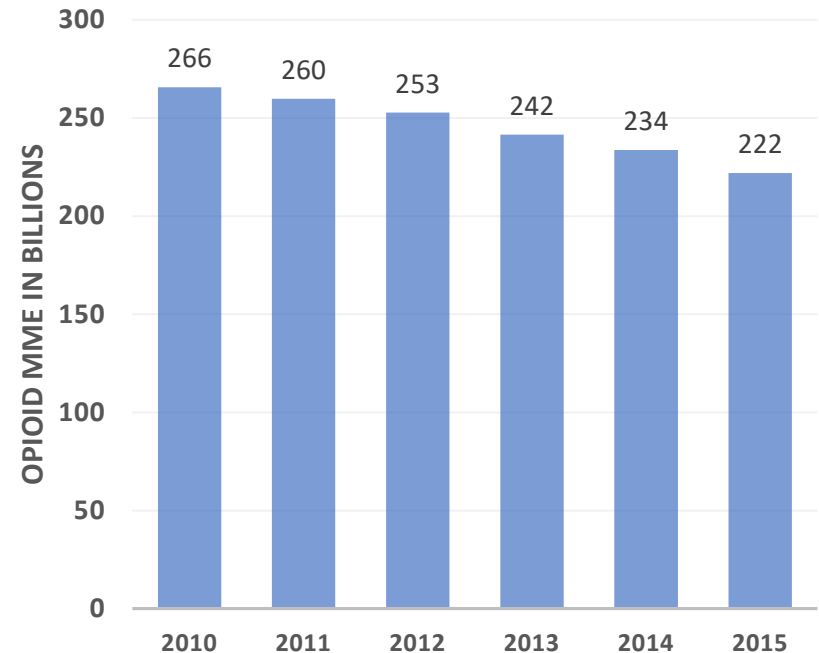
Drug Abuser

Volkow et al., PNAS 2011

Opioid Prescriptions 1991-2011

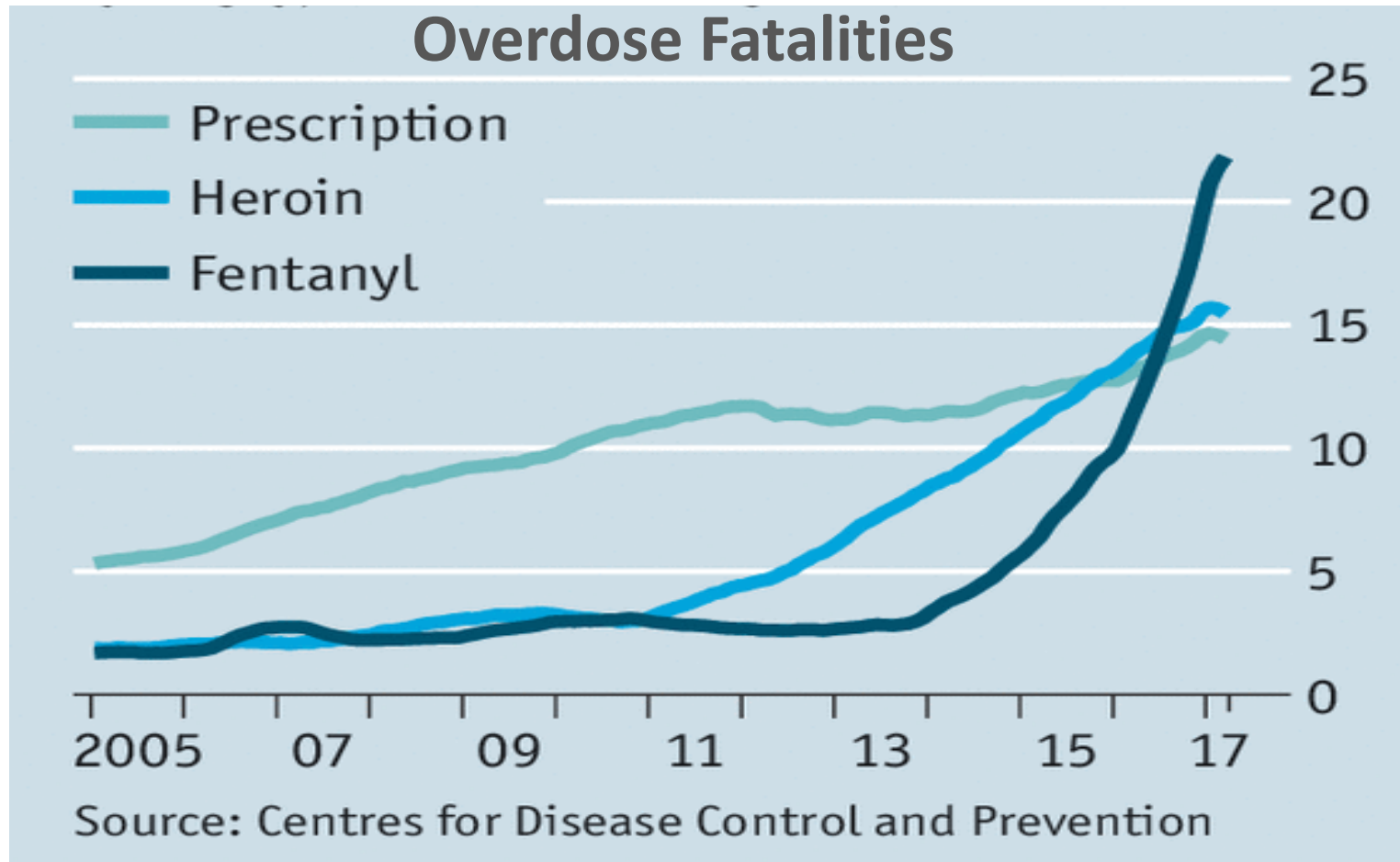


Opioid morphine milligram equivalents (MME) dispensed fell by over 15% from 2010-2015



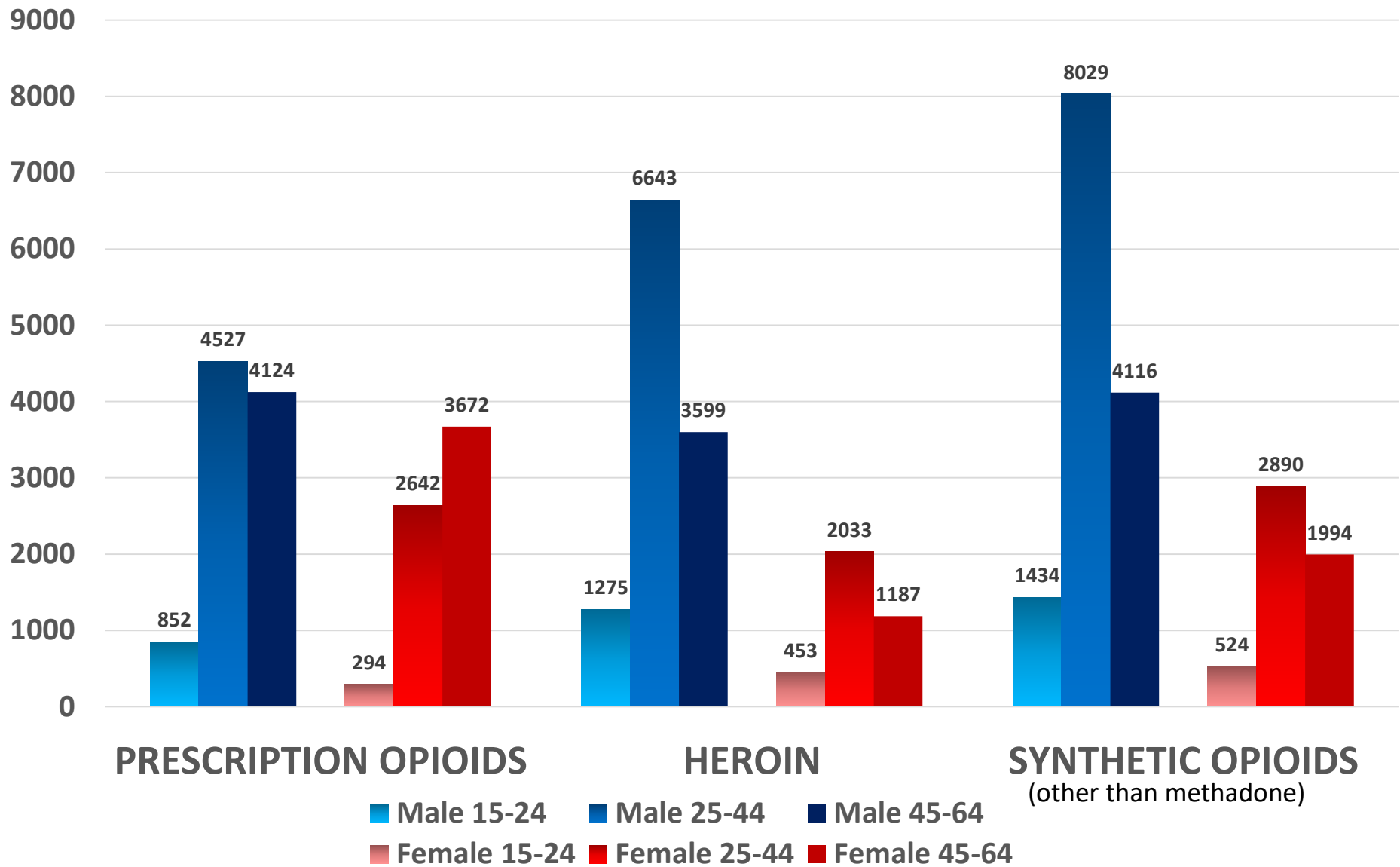
IMS Health, U.S. Outpatient Retail Setting

Evolution of the Opioid Crisis



1. Over prescription of opioid medications led to misuse
2. Addiction to prescription opioids led to heroin
3. Emergence of fentanyl(s), with higher potency and greater profitability in the black market than heroin.

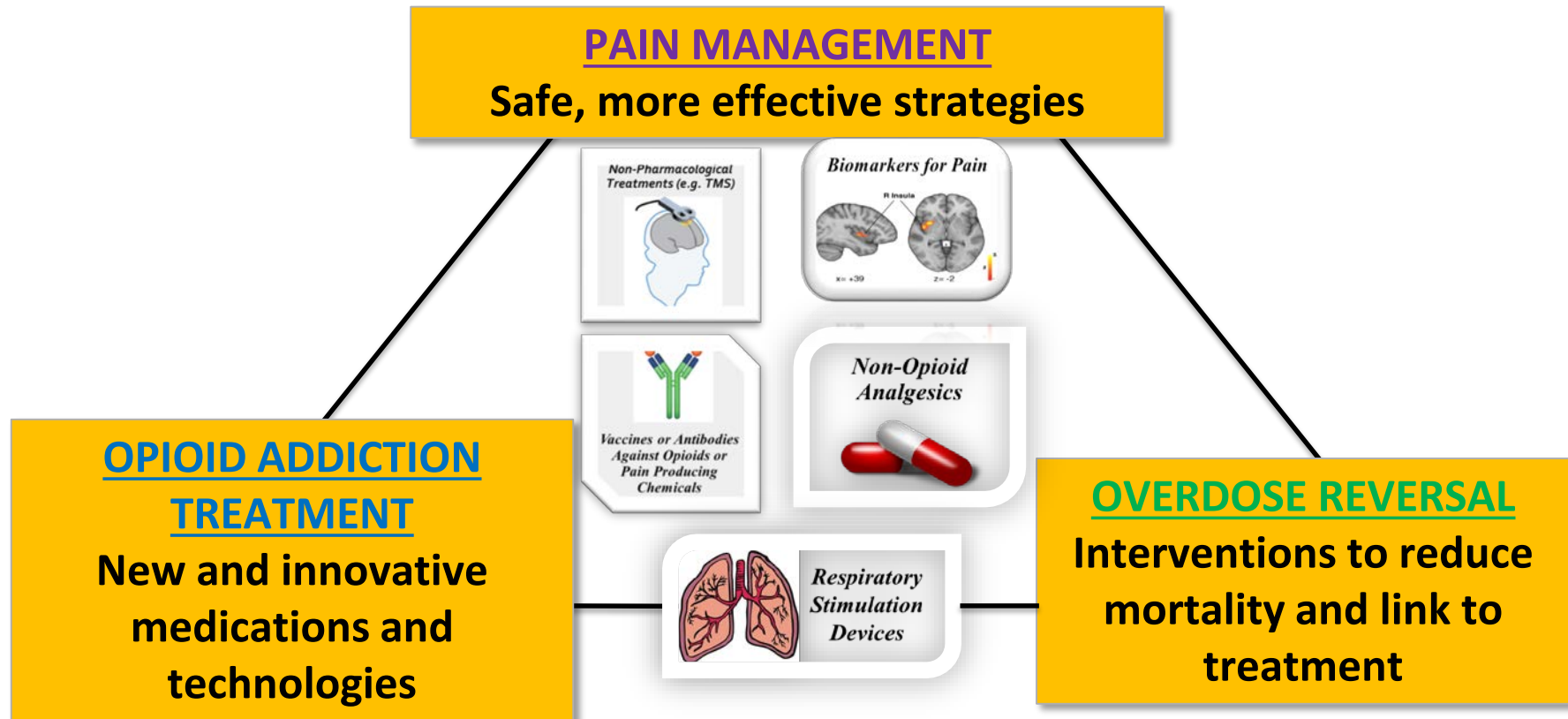
Overdose Deaths Involving Opioids, U.S., 2016



Puja Seth et al., MMWR, Weekly / March 30, 2018 / 67(12);349–358.

NIH OPIOID RESEARCH INITIATIVE

Using Research to End the Opioid Crisis



Safe, More Effective Strategies for Pain Management



Non-Opioid Analgesics
Cannabinoids;
Inflammatory mediators;
Ion channel blockers



Targeted Opioid Analgesics
with reduced potential for
addiction and overdose

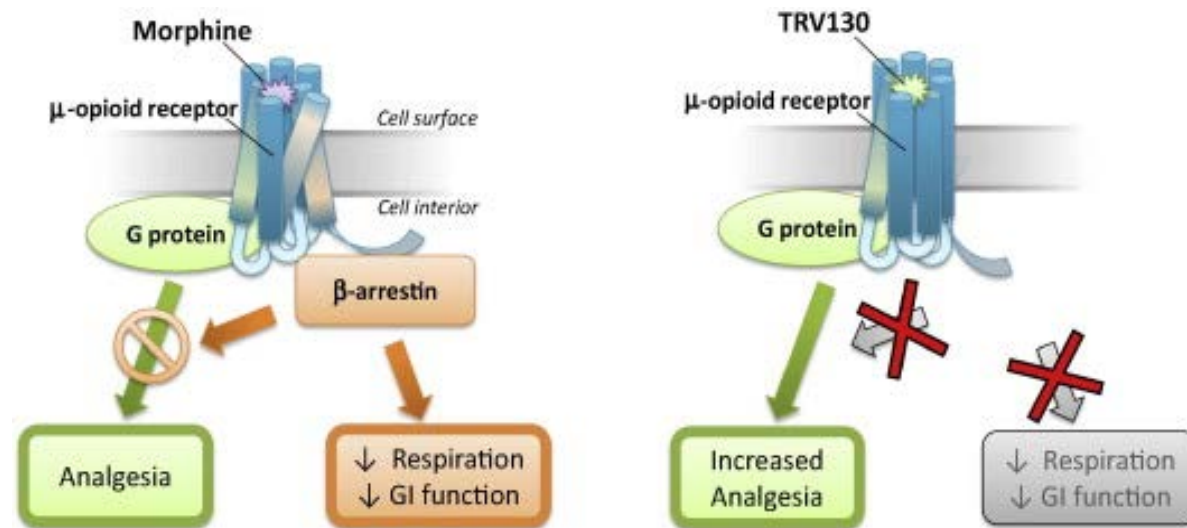


Biologics
e.g. antibodies that bind to
pain producing cytokines



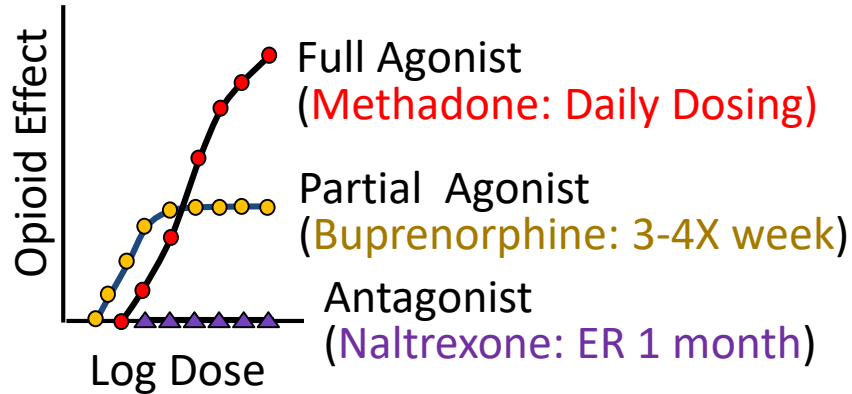
Non-pharmacological treatment
Neural stimulation;
Surgical interventions;
Meditation

Biased Mu-Opioid Receptor Ligands: New Generation Of Pain Therapeutics



Soergel DG et al., Pain 2014; 155(9):1829–1835.

Medication Assisted Treatment (MAT)



DECREASES:

- Opioid use
- Opioid-related overdose deaths
- Criminal activity
- Infectious disease transmission

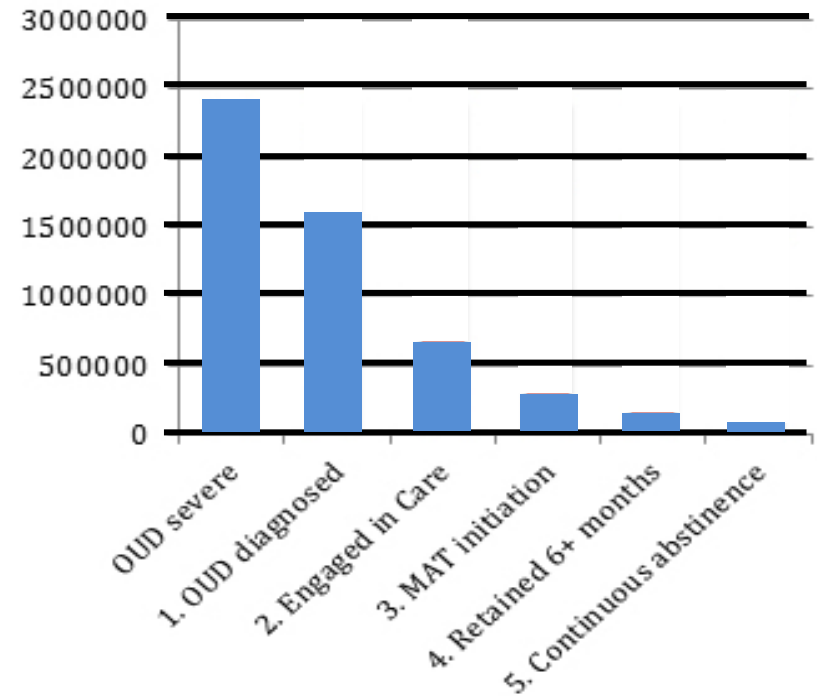
INCREASES

- Social functioning
- Retention in treatment

MAT is highly underutilized!

Relapse rates are very high (50% in 6 months)

OUD Cascade of Care in USA



Williams AR, Nunes E, Olfson M. Health Affairs Blog, 2017

Expand access to MAT

Healthcare system

Criminal Justice system

Medication development

Extended release formulations

Drug combinations

New Targets, Vaccines others

Extended Release Formulations

● **Vivitrol®**

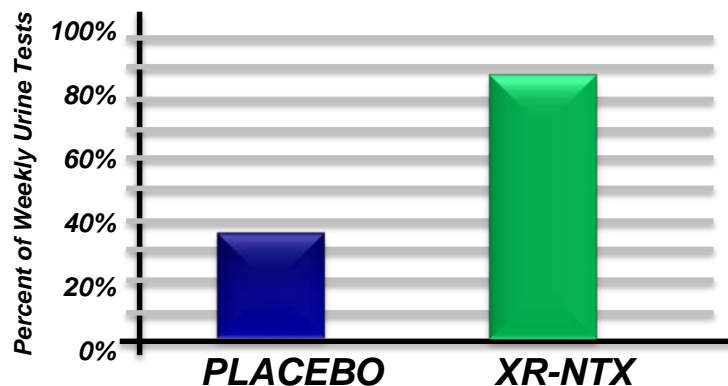


● **PROBUPHINE®**



IM Injection q 4 weeks for 24 weeks

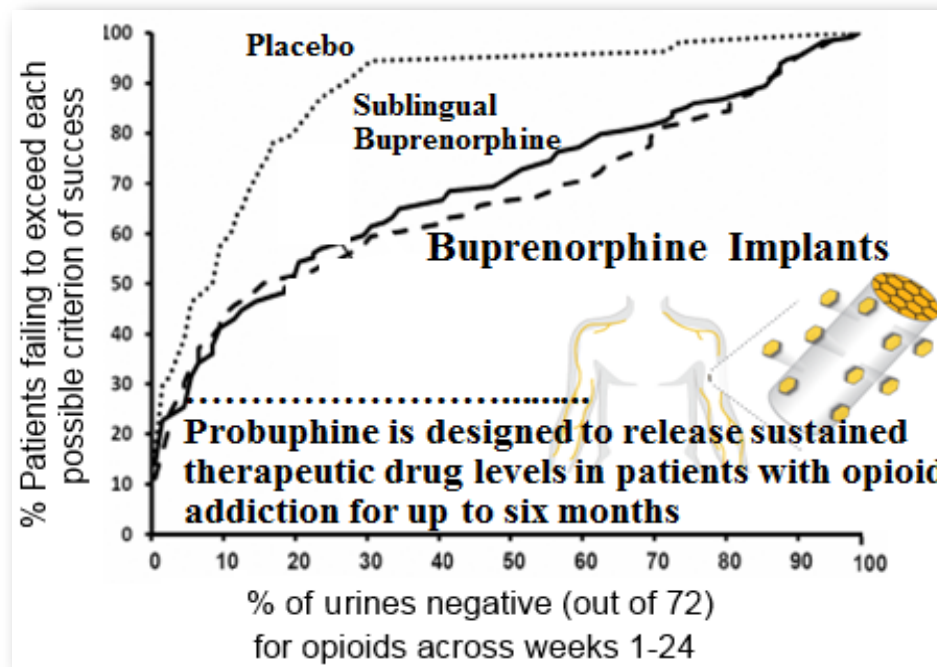
Median % Opioid-Negative Urines



■ **Placebo: N=124**

■ **XR-NTX: N=126**

Krupitzky et al., Lancet 2011



Rosenthal et al., Addiction 2013;105.

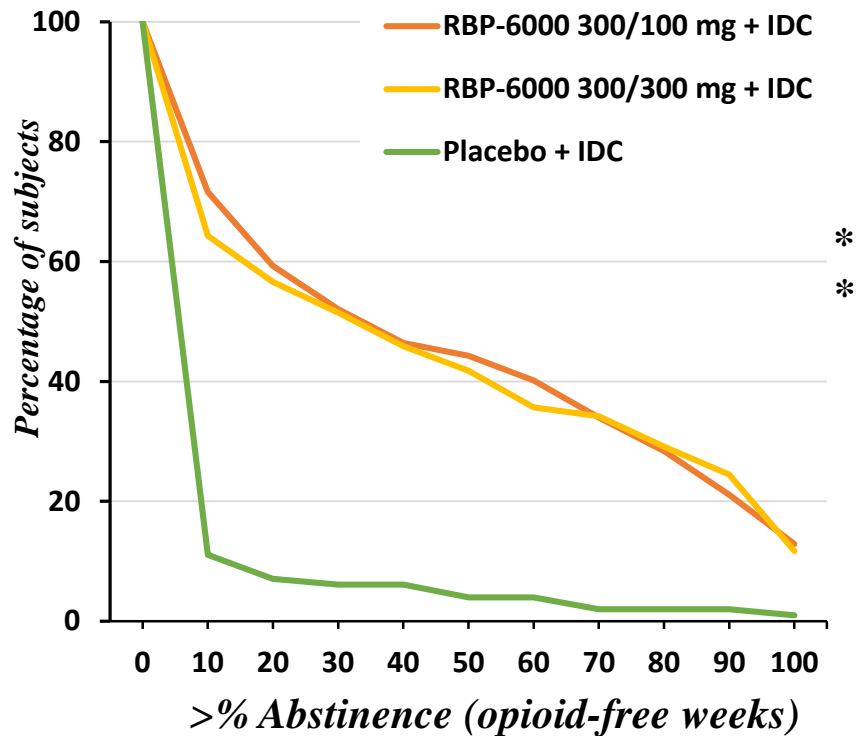
FDA approval – May 26, 2016

Opportunities for Partnership in the Development of Longer Acting Formulations and/or Drug Combinations to Improve Treatment Compliance and Retention

SUBLOCADE™
(Buprenorphine ER),
Once-Month Injectable
FDA Approval 11.30.2017



**% urine samples negative
for opioids (Weeks 5 to 24)**



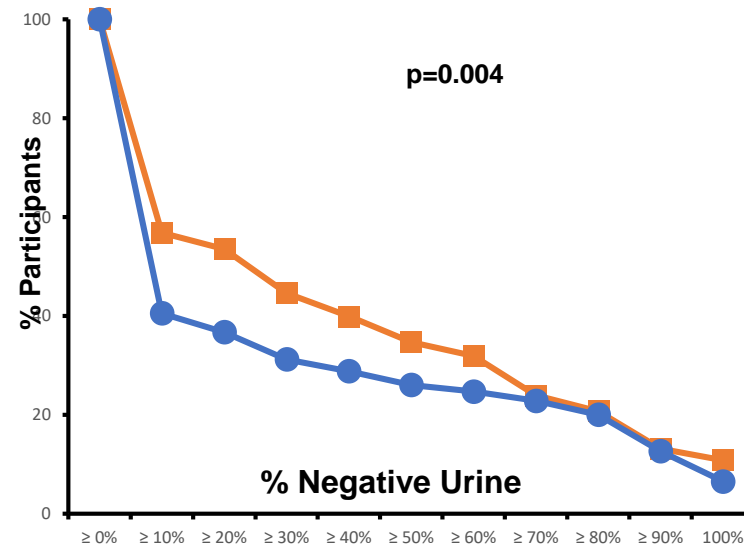
Heidbreder et al., CPDD 2017

CAM2038:
Subcutaneous ER
Buprenorphine



Weekly or monthly injection

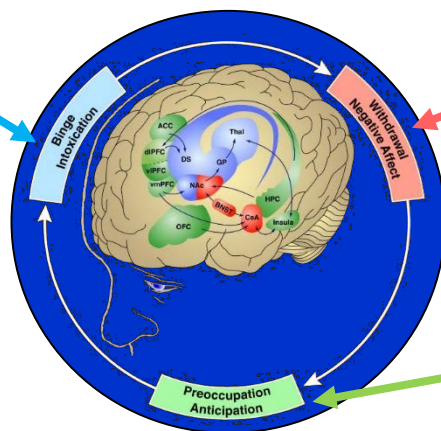
Comparison CAM2038 versus Daily SL BPN



braeburn

Target Selection on the Basis of the Neurocircuitry of Addiction

Targets to interfere with drug reward



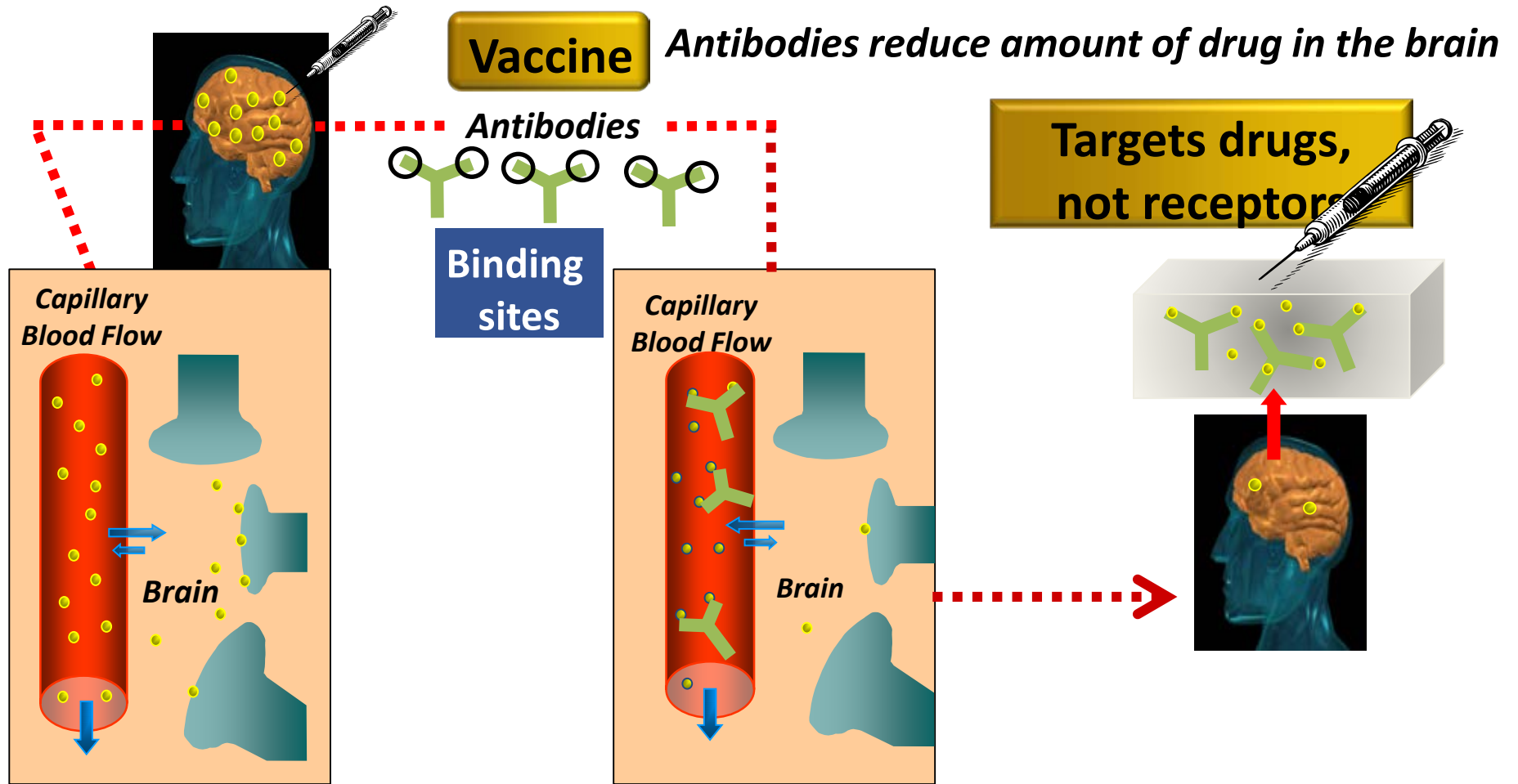
Targets to reduce stress-induced drug seeking and to improve mood

Targets to reduce cue-induced drug seeking and to improve executive function

***Diagram: Koob GF, Volkow ND.
Neuropsychopharmacol Rev, 2010***

Compounds targeted to neurocircuitry could be beneficial not just to addiction but also to diseases for which such circuits are disrupted (i.e., ADHD, depression)

Immunotherapies for Opioid Use Disorder



Expand access to MAT

Healthcare system

Criminal Justice system

Medication development

Extended release formulations

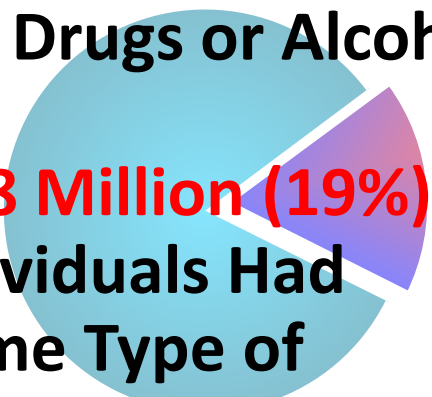
Drug combinations

New Targets, Vaccines others

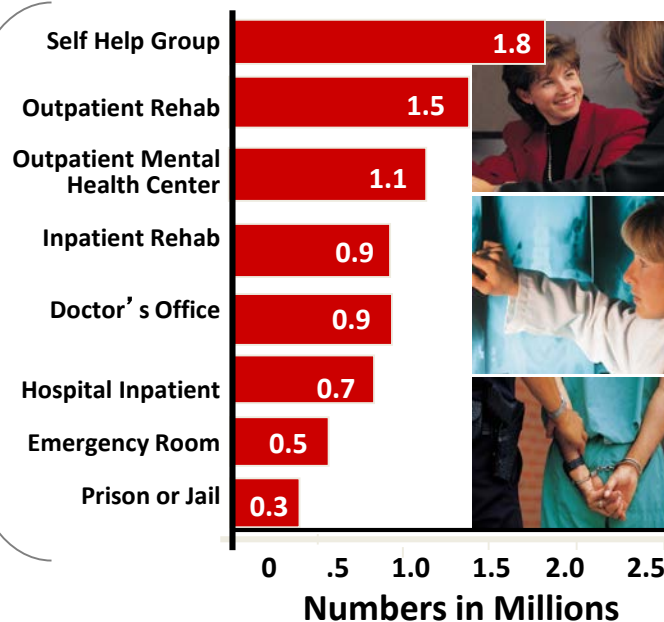
Opportunities with Health Care Reform to Expand Involvement of the Health Care System in Treatment of SUD

In 2016 An Estimated **20.1 Million Americans** 12 or Older Were Dependent On Any Illicit Drugs or Alcohol

But...Only **3.8 Million (19%)** of These Individuals Had Received Some Type of Tx In the Past Year and few involved Health Care Systems



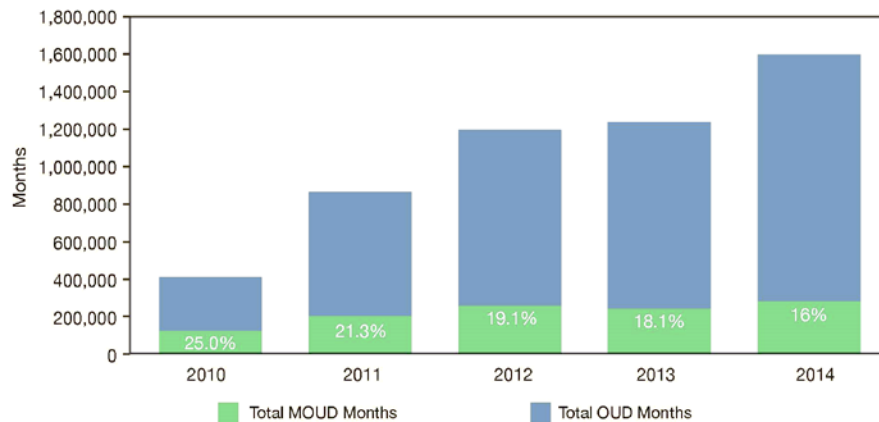
Location TX Received



“Clinicians Underutilize Available OUD Medications”

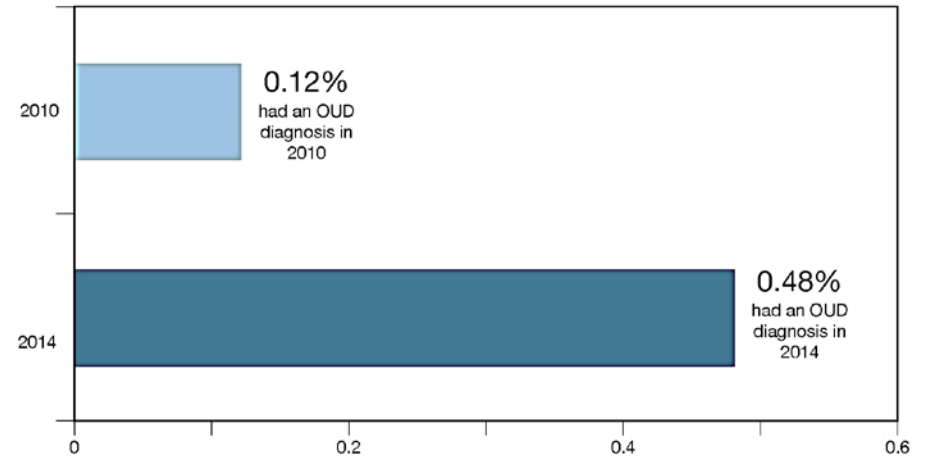


Increases in MOUD Prescriptions Did Not Keep Pace With Increased Treatment Need

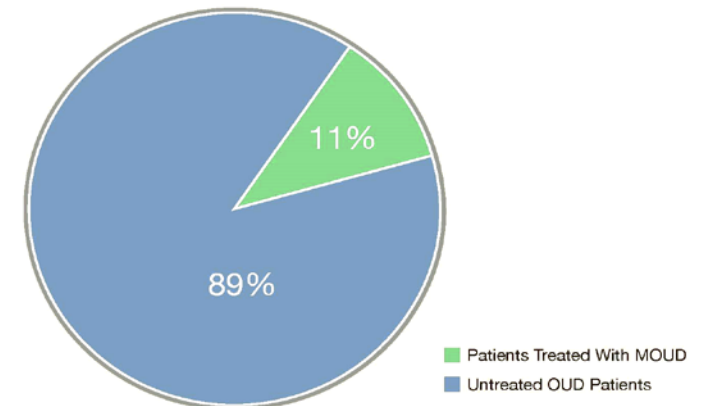


Diagnoses of OUD Quadrupled From 2010 to 2014

Of more than 100 million commercially insured individuals analyzed ...



In 2010 to 2014, Only 11 Percent of Patients With OUD Were Treated With Approved Prescription Medications



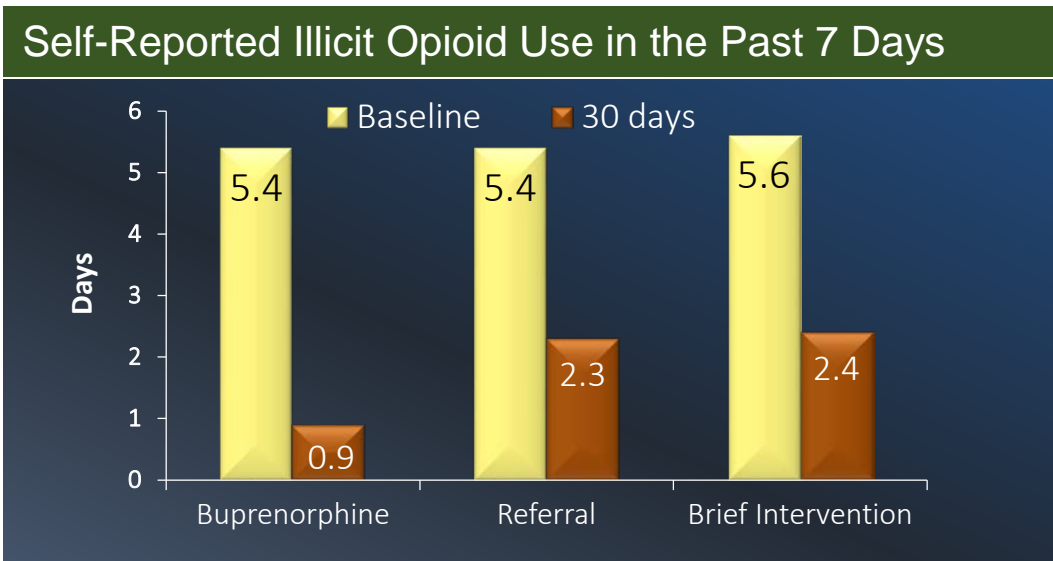
Note: OUD months = number of patients with OUD x number of months they needed treatment in a given year
MOUD months = number of person-months for which prescriptions for OUD medications were written

Adapted from Morgan et al., 2017; permission for use of data provided by Dr. J.R. Morgan. Morgan JR, Schackman BR, Leff JA, et al. J Subst Abuse Tx, 2017.

Improving Treatments for Addiction: Implementing Medication-Assisted Treatment



- Emergency department-initiated buprenorphine
 - Reduced self-reported, illicit opioid use
 - Increased engagement in addiction treatment; decreased use of inpatient addiction treatment services



D'Onofrio G et al., JAMA April 28, 2015.



JAMA

Original Investigation

April 28, 2015 Volume 313

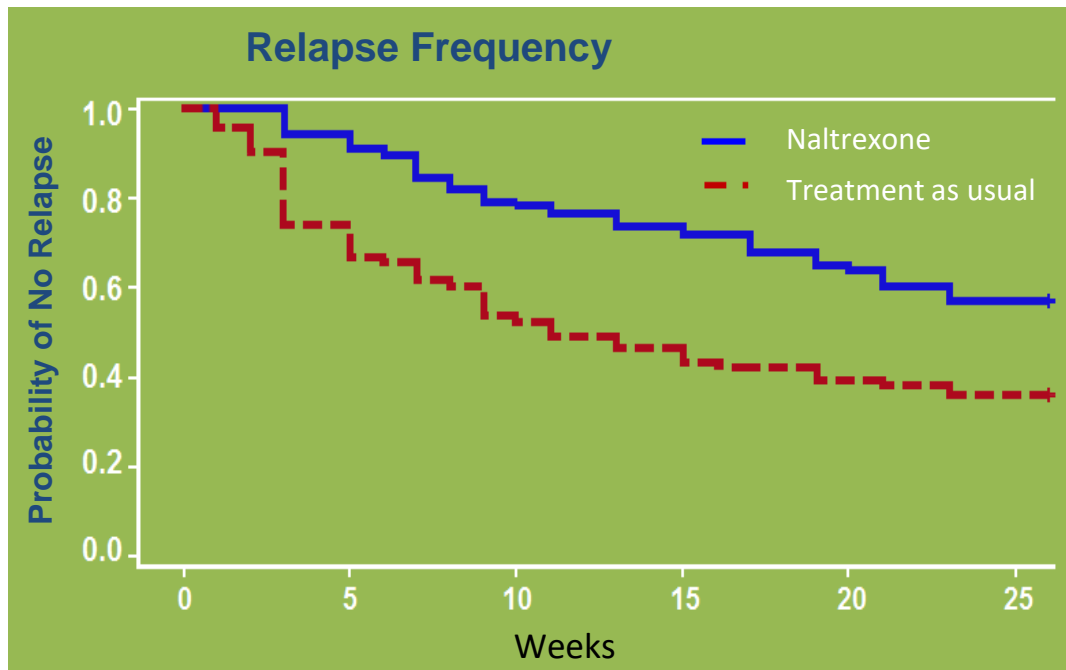
**Emergency Department-Initiated Buprenorphine/Naloxone Treatment for Opioid Dependence
A Randomized Clinical Trial**

Gail D'Onofrio, MD, MS; Patrick G. O'Connor, MD, MPH; Michael V. Pantalon, PhD; Marek C. Chawarski, PhD; Susan H. Busch, PhD; Patricia H. Owens, MS; Steven L. Bernstein, MD; David A. Fiellin, MD

Improving Treatments for Addiction: *Naltrexone Trial in CJ Populations*



- *Participants:* parolees/probationers with opioid addiction – all *volunteers* – received either
 - Monthly injections of extended release naltrexone for 6 months
 - Community treatment, including methadone or Suboxone (encouraged)



Overdoses in 78 weeks:

Control: 7
Naltrexone: 0

Lee et al. NEJM March 31, 2016.

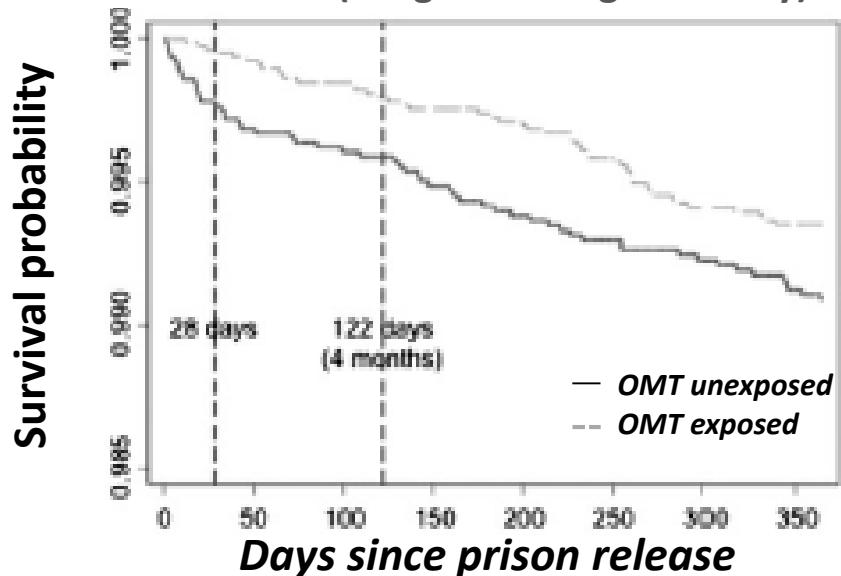


Opioid Medication Therapy (OMT) In Prison

Postincarceration Overdose Deaths After Implementing OMT in a Statewide Correctional System (Rhode Island)

Mortality Post Release

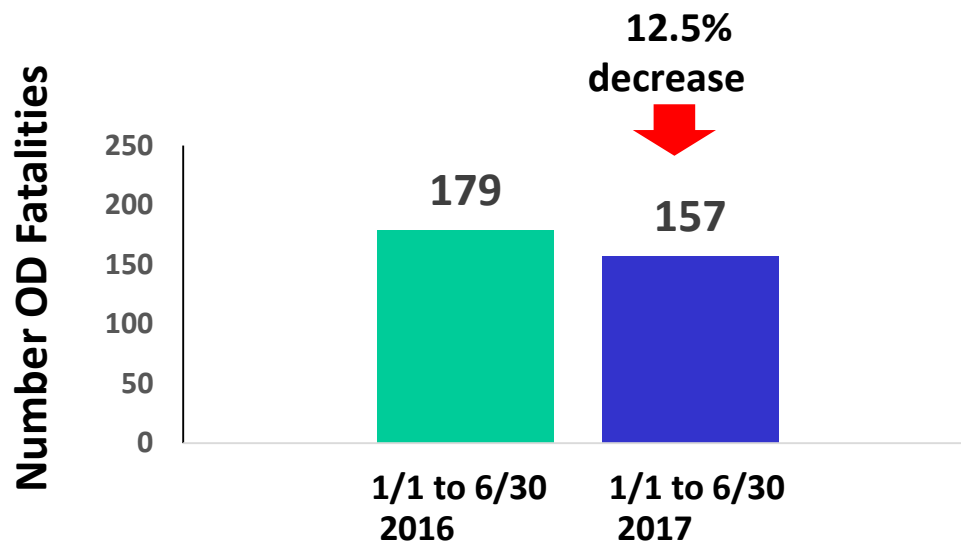
Survival Curve During the Year Following Release (Drug-Poisoning Mortality)



OMT resulted in a 75% reduction in mortality (85% reduction in overdoses) in the first month post release

Marsden J et al., *Addiction* 2017; 112:1408-1418.

Statewide Overdose Deaths



OD fatalities in those who had been incarcerated in 2017 decreased by 60% compared to 2016 (5.7% vs 14.5%)

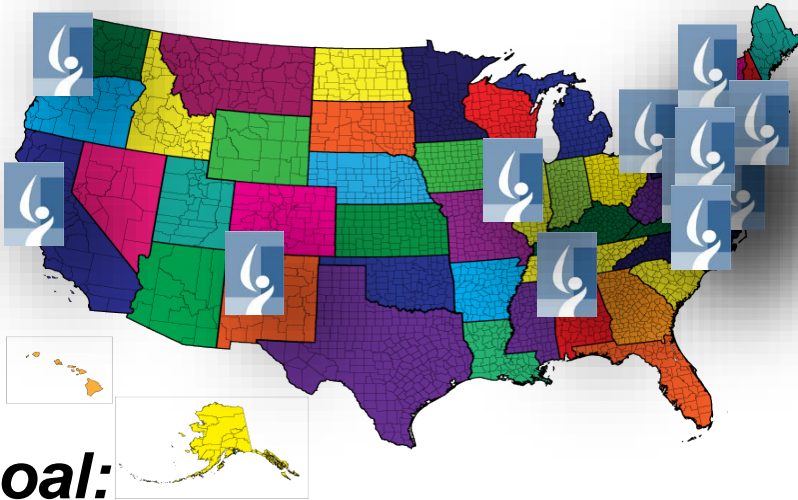
Green TC and Clarke J. *JAMA Psychiatry* 2018;75(4).

Education

PAIN

NIH Pain Consortium Centers of Excellence in Pain Education

ORWH NIA
OBSSR NINR
NIDA NICHD
NIDCR NIAMS
NINDS NCCIH



Goal:
Improve pain treatment through education

SUD



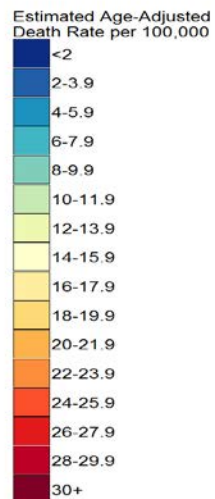
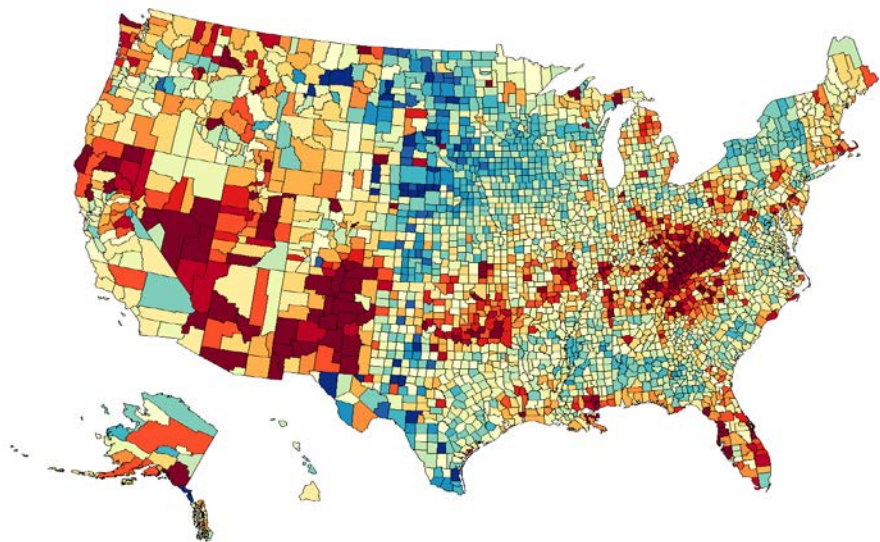
Goal:
Prevent SUD and improve outcomes in addiction through education of health care providers



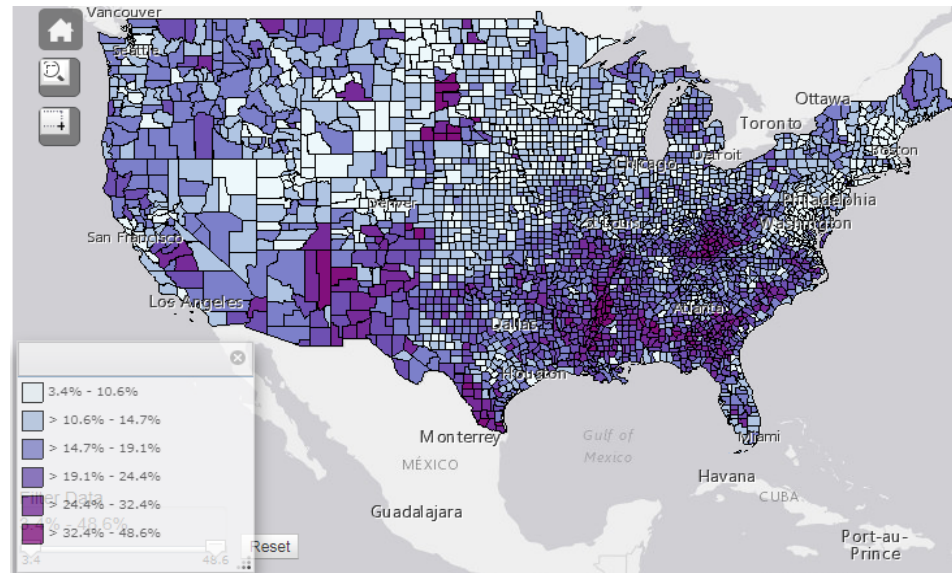
Drug Poisoning Deaths

2016

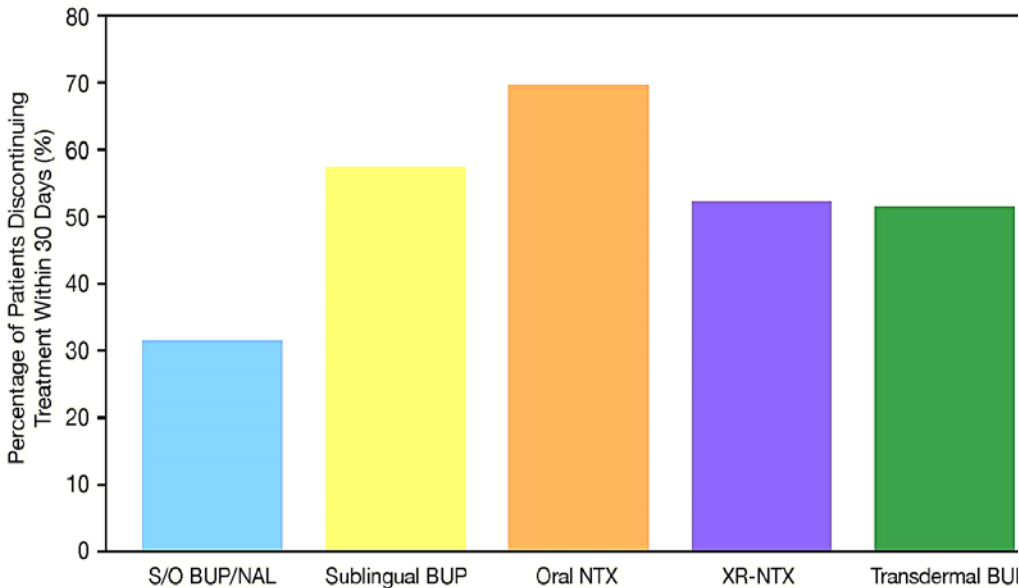
2016



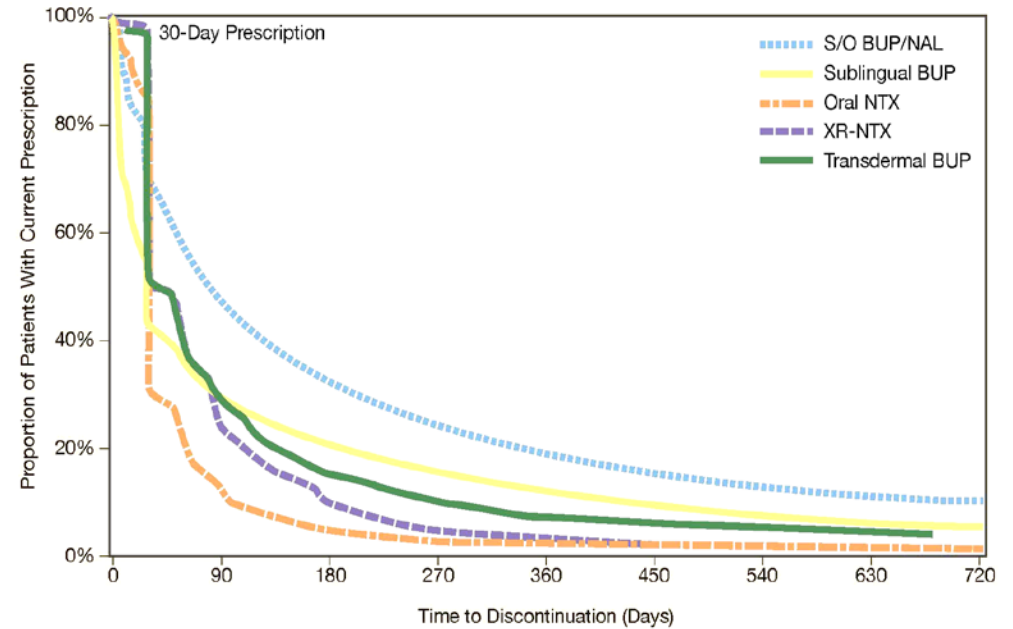
All Ages in Poverty



Patients Are More Likely To Stop Taking Certain Medications



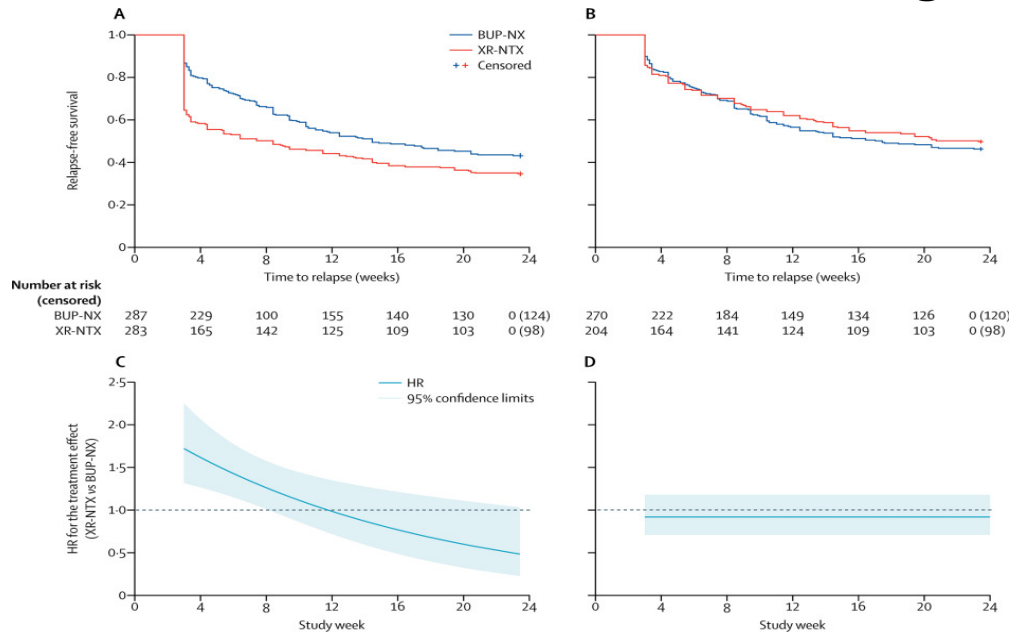
Most OUD Patients Stop Treatment Within 2 Years



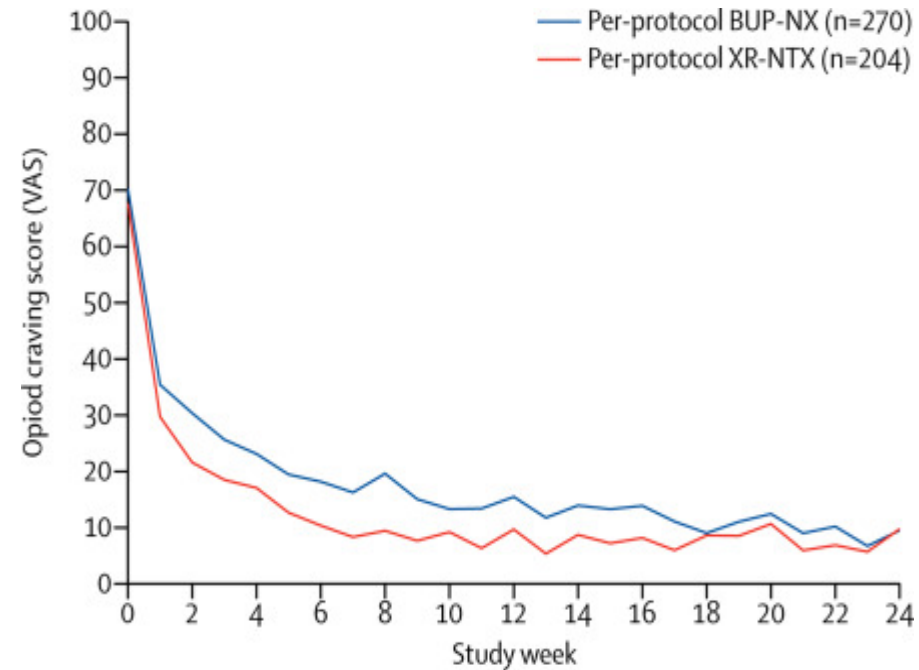
Adapted from Morgan et al., 2017; permission for use of data provided by Dr. J.R. Morgan. Morgan JR, Schackman BR, Leff JA, et al. J Subst Abuse Tx, 2017.

XR-NTX and BUP-NX Were Equally Safe and Effective In Preventing Relapse

Relapse-free survival and treatment effect over time for the XR-NTX and BUP-NX treatment groups



Opioid craving during the trial



In this population it was more difficult to initiate patients to XR-NTX than BUP-NX, and this negatively affected overall relapse. However, once initiated, both medications were equally safe and effective.

Lee JD et al., Lancet 2017, November 14 (E-pub ahead of print.)

