National Academies of Sciences, Engineering, and Medicine

Forum on Neuroscience and Nervous System Disorders

Workshop: Advancing Therapeutic Development for Pain and Opioid Use Disorders through Public-Private Partnerships

October 11-12, 2017

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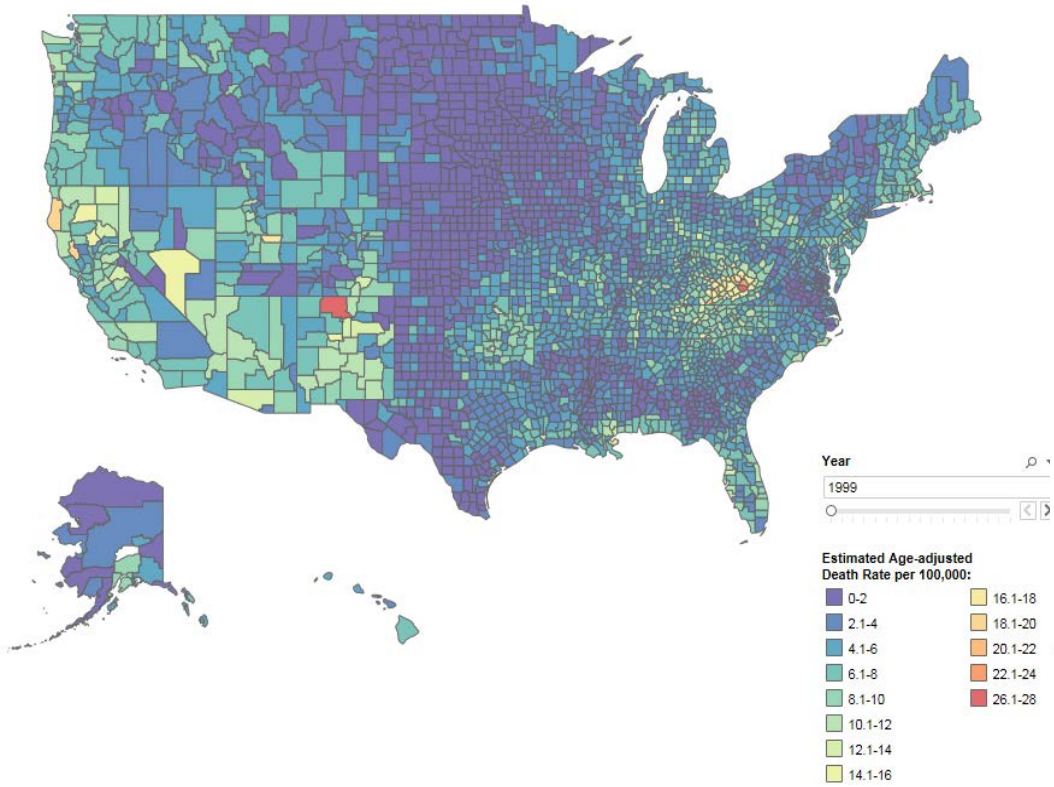
National Institute on Drug Abuse

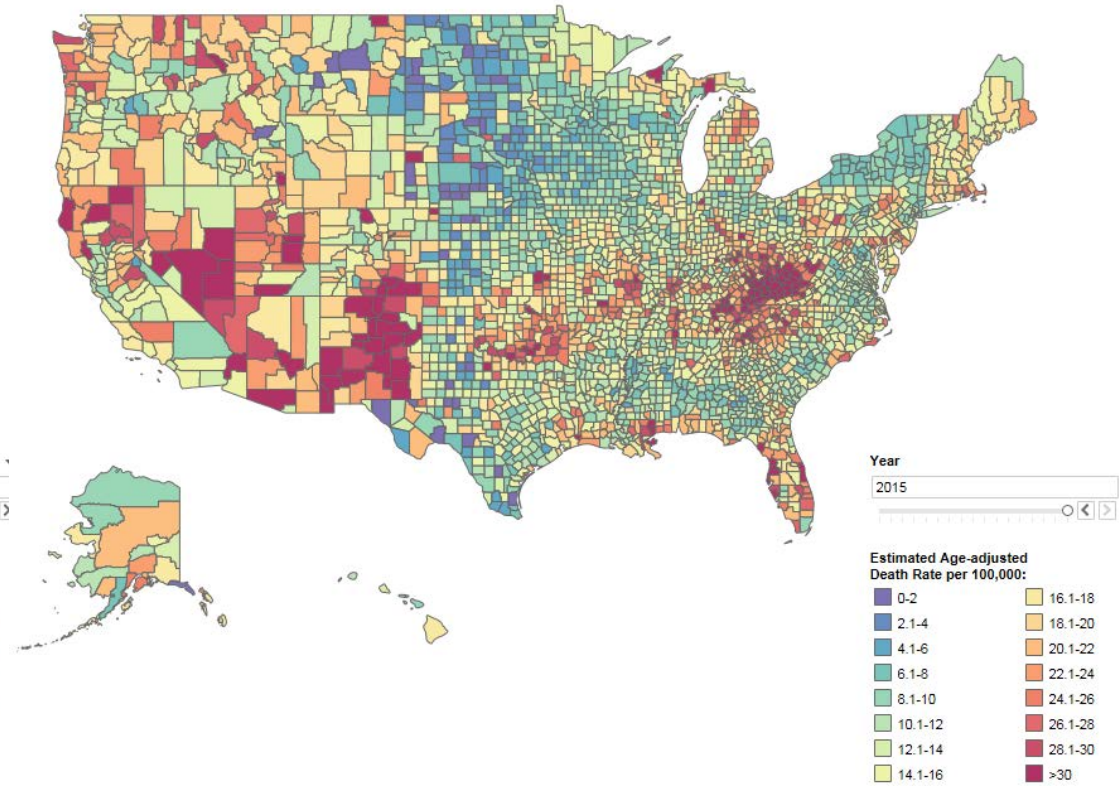
@NIDAnews

Overdose Death Rates

1999

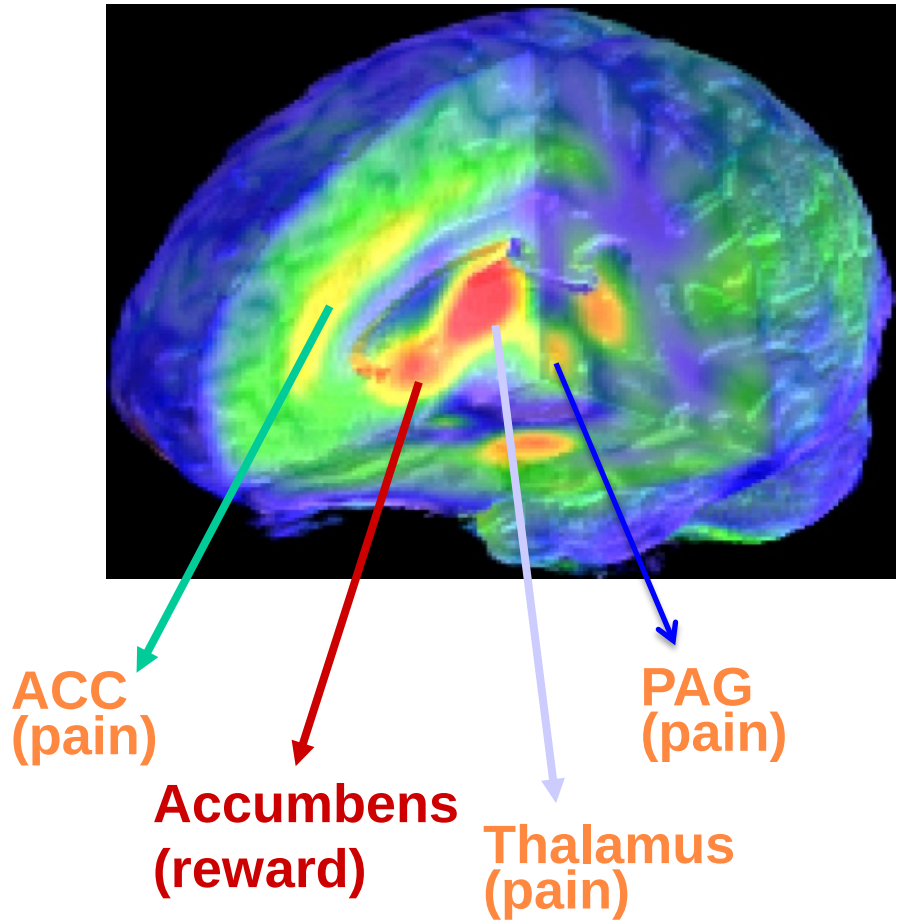


2015

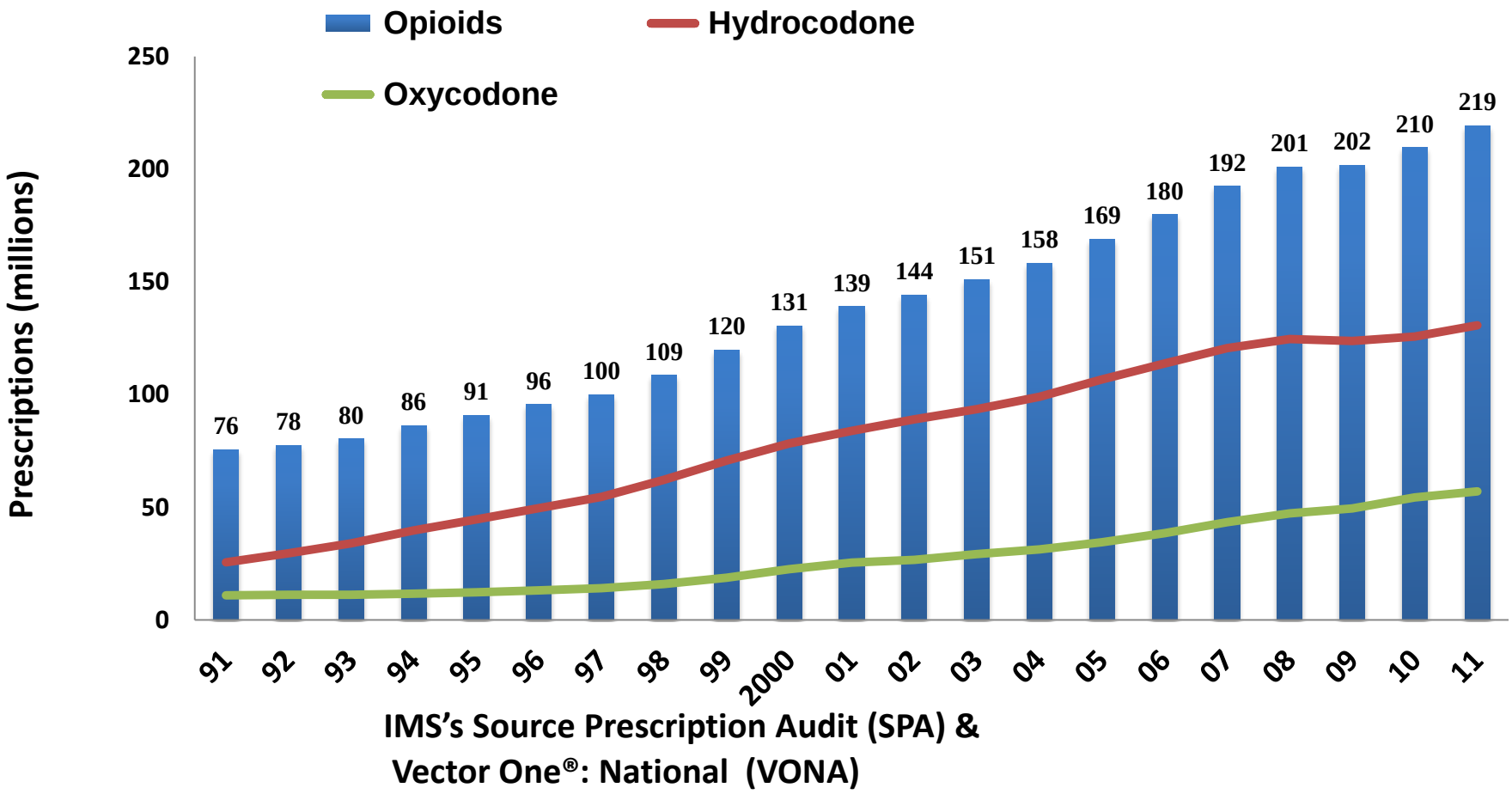


Designed by L. Rossen, B. Bastian & Y. Chong. SOURCE: CDC/NCHS, National Vital Statistics System

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

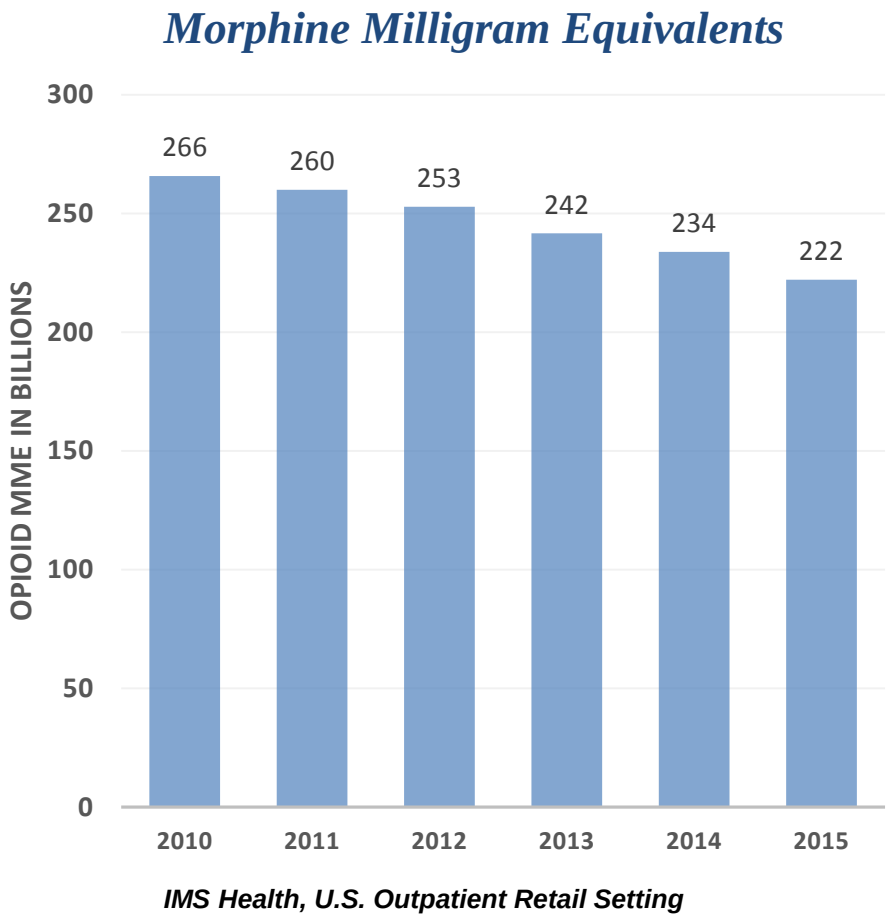


Opioid Prescriptions USA 1991-2011

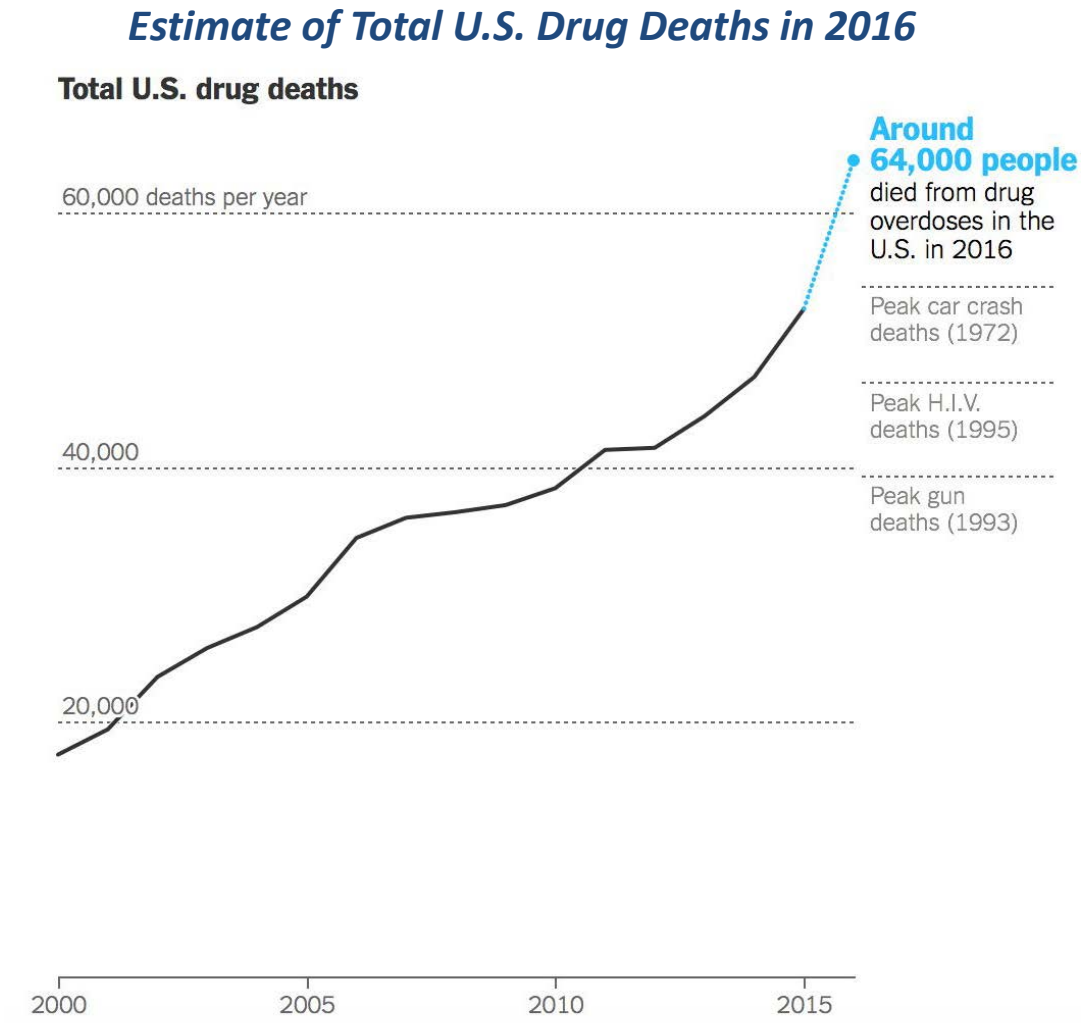


Opioids Dispensed Fell by Over 15% from 2010-2015

However Overdoses Continued to Rise



IMS Health, U.S. Outpatient Retail Setting



Fentanyl-Related Deaths Surpassed Heroin or Rx Opioids in 2016

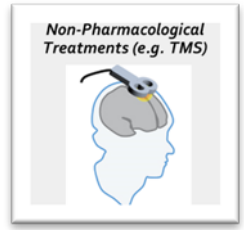
Graphs from NY Times Article based on CDC MMWR Report 2017

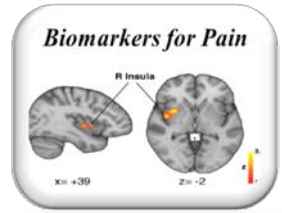
NIH OPIOID RESEARCH INITIATIVE

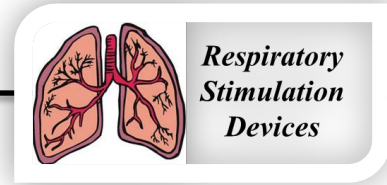
Using Research to End the Opioid Crisis

PAIN MANAGEMENT

Safe, more effective strategies







OPIOID ADDICTION TREATMENT

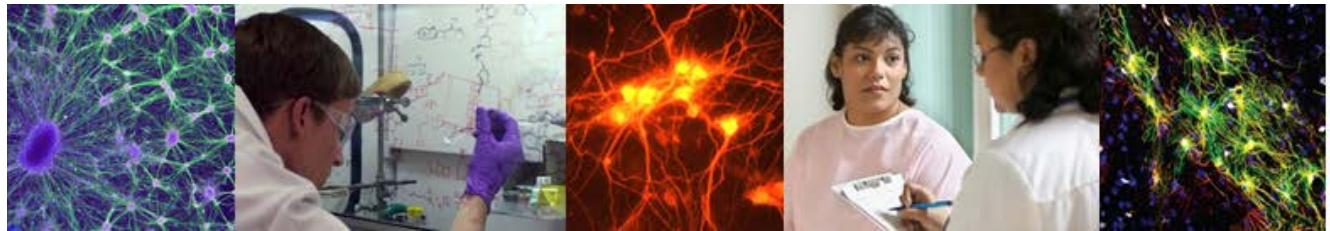
New and innovative medications and technologies

OVERDOSE REVERSAL

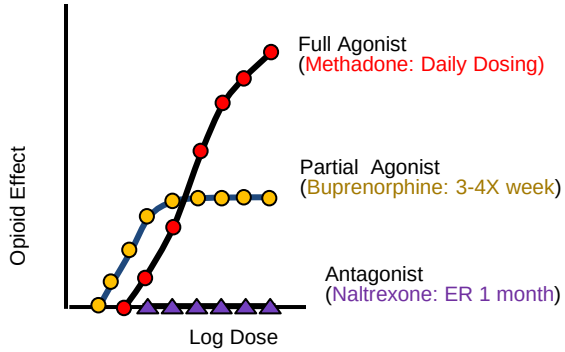
Interventions to reduce mortality and link to treatment

Case for a Public-Private Partnership for Pain and Opioid Use Disorders

- Urgent public health crisis
- Need for better alternatives for treatment of addiction
- Need for more potent treatments for overdose
- Absence of highly potent alternatives to opioids for pain
- Emergence of numerous potential drug targets
- Possibility of development/validation of biomarkers for pain relief
- Strong support at highest level of U.S. Government
  - FDA highly motivated
  - Potential for additional industry incentives



Medication Assisted Treatment (MAT)



DECREASES:

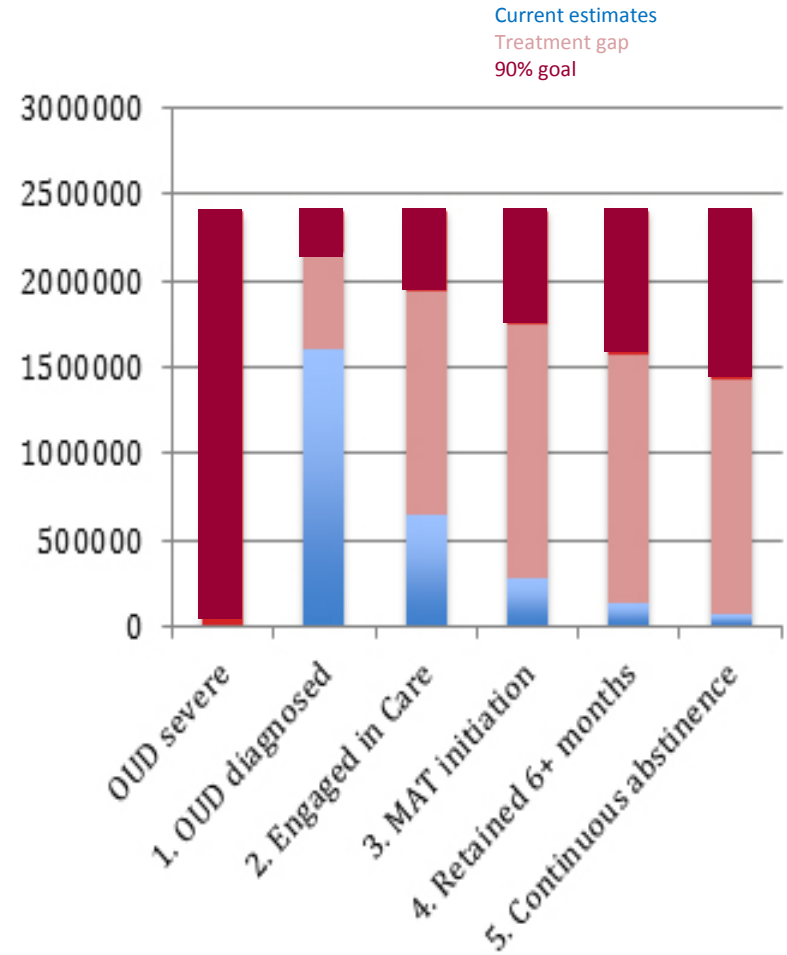
- **Opioid use**
- **Opioid-related overdose deaths**
- **Criminal activity**
- **Infectious disease transmission**

INCREASES

- **Social functioning**
- **Retention in treatment**

But MAT is highly underutilized!
Relapse rates are very high!

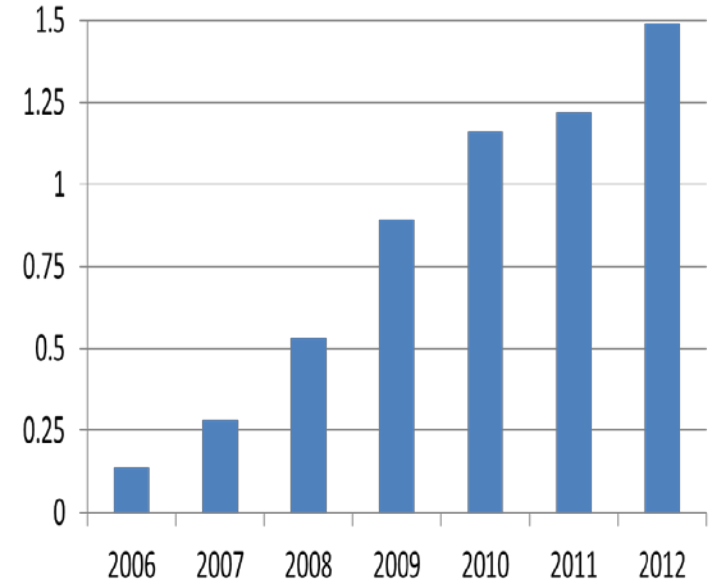
OUD Cascade of Care in USA



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

Traditionally Medications for Substance Use Disorders Are Deemed Non Profitable and Hence Development Has Been Predominantly Driven by NIH

U.S. Suboxone® sales reached
$1.49 Billion in 2012
(more than Viagra® or Adderall ®)



NIDA Med Development Program: Recent Progress

- Sublingual Buprenorphine
- Depot Naltrexone
- Intranasal Naloxone
- Buprenorphine Implant

Planning–To Date–for Public-Private Partnership for Pain and Opioid Use Disorders (OUD)

- ***April 2017:*** **case made to heads of R&D of big pharma**
  - ✓ **Industry agreed to pursue partnership**
- ***June/July 2017:*** **NIH convened 3 cutting-edge science meeting with experts from academia, industry, government**
  - **Goal: identify develop safe, effective therapeutics for opioid abuse, pain in half the time it currently takes**
    - ✓ ***June 5:*** **Medications Development for OUD and Overdose Prevention and Reversal**
    - ✓ ***June 16:*** **Development of Safe, Effective, Non-Addictive Pain Treatments**
    - ✓ ***July 7:*** **Understanding the Neurobiological Mechanisms of Pain**
- **Insights from meetings used to design two new partnership efforts**
  - **#1 Medication development for OUD and OD Prevention and reversal**
  - **#2 Medication development for safer Pain medications**

Project #1: Develop New Formulations and Combinations of Medications to Treat Opioid Use Disorders (OUD), Prevent, and Reverse Overdose (OD)

- Develop new formulations for OUD and OD prevention
- Develop combinations of existing medications to treat OUD, prevent and reverse OD
- Explore new uses for compounds (de-prioritized or available for repurposing) and related expertise, to enable development for use in treating OUD, OD prevention, and reversal
- Development of vaccines and monoclonal antibodies for high-risk individuals
- Device development, such as autoinjectors for naloxone, take home dispensers of buprenorphine
- Basic research to identify new targets for OUD (e.g., focusing on disruption of neurocircuitry) and biomarkers of vulnerability

NIDA OUD Medications Development-Relevant Mechanisms

- **Grand Opportunity in Medications Development for SUD (U01)**
- **Strategic Alliances for Medications Development for SUD (R01)**
- **NIDA Translational Avant-Garde Award for Development of Medications for SUD (UG3/UH3)**
- **SBIR and STTR Grant and Contract Solicitations**

Contract Resources (CRADA/CTA/Screening Agreement Collaborations)

- ***Confidential in vitro and in vivo pharmacology studies (ranging from receptor activity profiling to evaluation of test compound effects on drug self-administration in monkeys)***
- ***GMP synthesis and dosage formulation***
- ***Standard preclinical safety and toxicokinetic evaluations***
- ***Special, FDA-required drug interaction studies (preclinical and clinical)***
- ***Multi-site efficacy trials (IAG with VA CSP)***

Project #2: Accelerate Development of New Non-addictive Pain Therapies

- Focused data sharing effort on successful and failed drug development
- Create a clinical trial network to coordinate clinical testing of novel treatments:
  - For specific high-impact pain conditions (rare disease model)
  - For more common pain conditions
- Joint development of biomarkers
  - Of target engagement
  - To stratify pain populations (subsets of pain conditions)
  - To predict clinical outcomes/response to treatment
- Jointly develop objective measures for nociception (“pain-o-meter”)
- Partner to re-engineer preclinical platform to better predict efficacy of new treatments
- Apply new technologies to improve pain drug discovery

Planning–To Date–for Public-Private Partnership for Pain and Opioid Use Disorders (OUD)

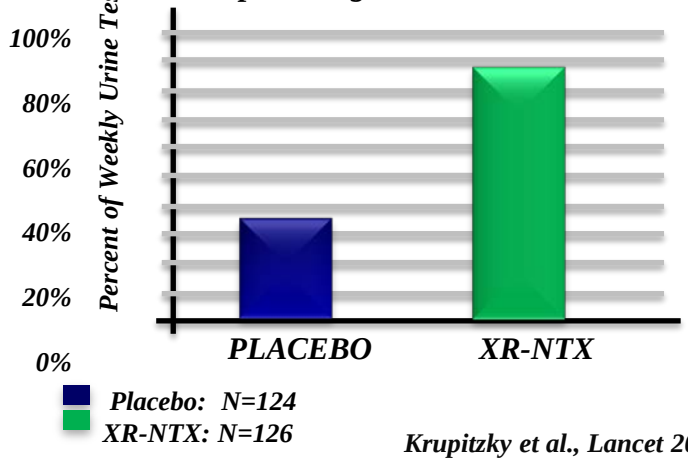
- **Informed by the three science meetings**
- **Meeting with biopharmaceutical groups to get feedback on recommendations from 3 meetings and develop plan:**
  - **Research experts from industry convened to discuss options *(9/7/17)***
  - **Biopharmaceutical industry groups convened by PhRMA *(9/11/17)***
  - **Pharmaceutical CEOs convened by Chris Christie, Chair of the President's Commission on Combating Drug Addiction and the Opioid Crisis *(9/18/17)***
  - **President's Commission on Combating Drug Addiction and the Opioid Crisis *(9/27/17)***
- **Plan will include major goals, action steps, key partners, deliverables, timeline, associated costs**
  - **Aim for alignment with Commission's final report, expected in November**
  - **Input on strategy and initiative will be solicited from all stakeholders and federal partners**
- **Final version will be posted for public viewing at:**

Extended Release Formulations

Vivitrol®

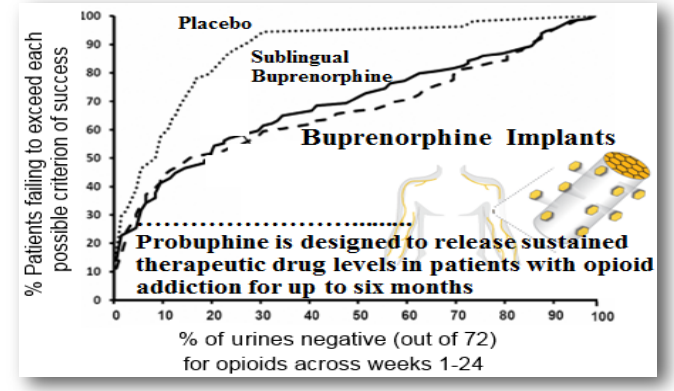
IM Injection q 4 weeks for 24 weeks

Median % Opioid-Negative Urines



Krupitzky et al., Lancet 2011

PROBUPHINE®

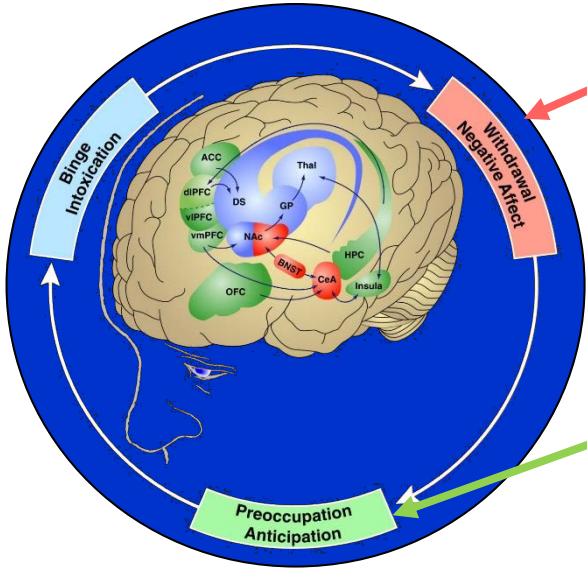


Rosenthal et al., Addiction 2013;105.

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

Target selection on the Basis of the Neurocircuitry of Addiction



Koob GF, Volkow ND. Neuropsychopharmacol Rev, 2010

Promising Targets

Mechanisms to reduce stress-induced drug seeking

- *Kappa Opioid Receptor Antagonists*
- *OX-1 Receptor Antagonists*
- *NOP Receptor Agonists*
- *α2-Adrenergic Receptor Agonists*
- *PDE7 Inhibitors*

Mechanisms to reduce cue-induced drug seeking

- *D3 Receptor Antagonists*
- *OX-1 Receptor Antagonists*
- *5-HT2C Receptor Agonists*
- *5-HT2A Receptor Inverse Agonists*
- *mGluR2 Positive Allosteric Modulators*
- *5-HT6 Receptor Inhibitors*
- *PDE7 Inhibitors*

Opportunities for Partnership: Sharing of Compounds and de-risking new targets for treatment of OUD (PK, PD, Toxicity, Testing Animal Models of SUD including NHP, Human Lab Studies)