

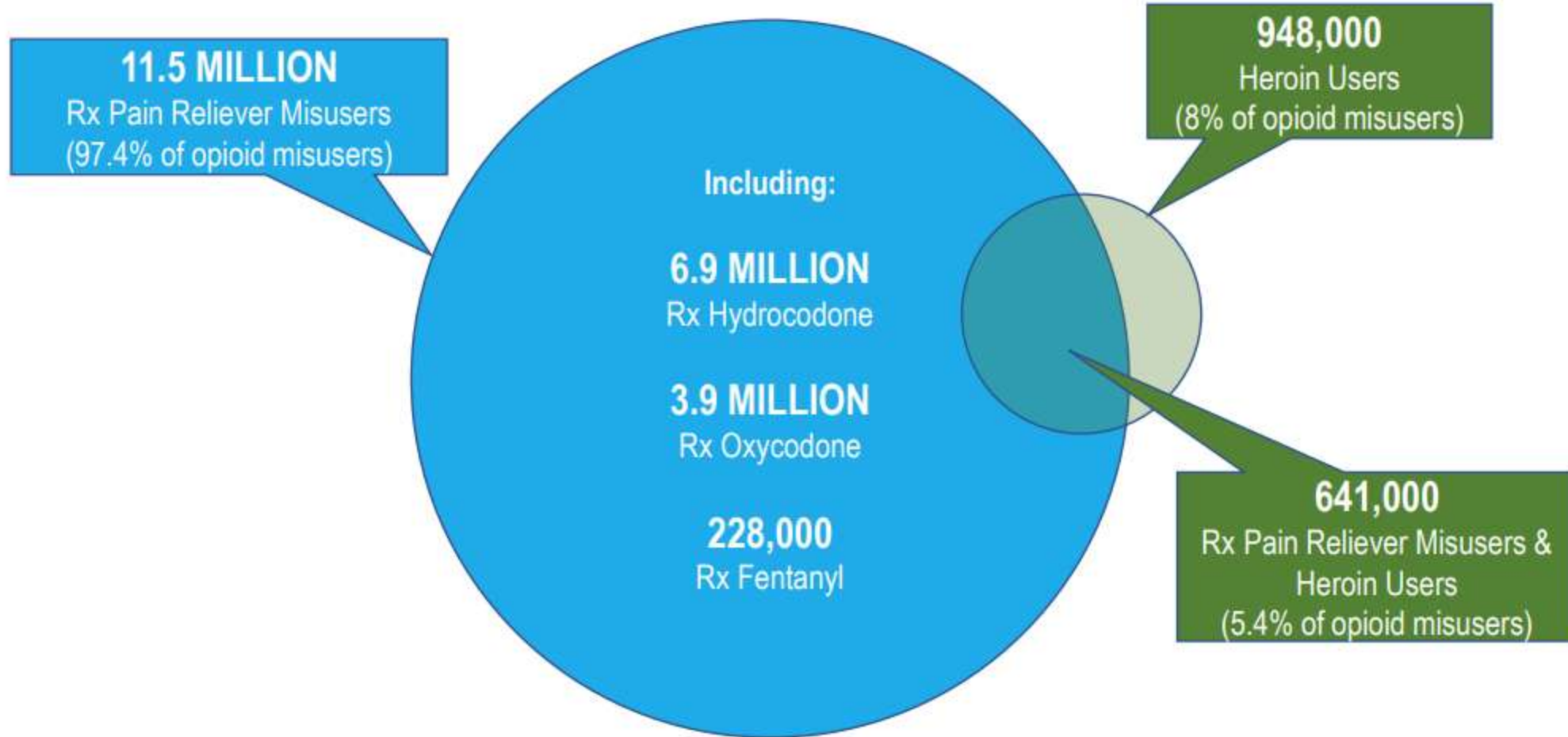
Opioid Crisis in the USA: Research Agenda

Iván D. Montoya, M.D., M.P.H.

Acting Director, Division of Therapeutics and Medical Consequences

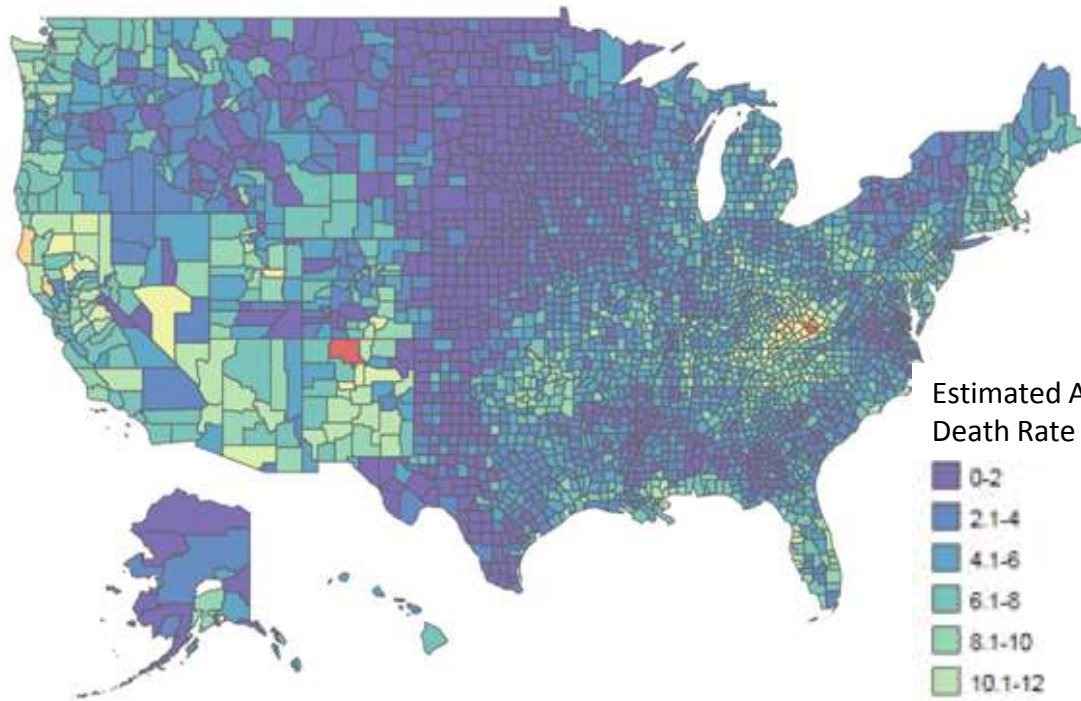
NIDA

11.8 MILLION PEOPLE WITH OPIOID MISUSE (4.4% OF TOTAL POPULATION)

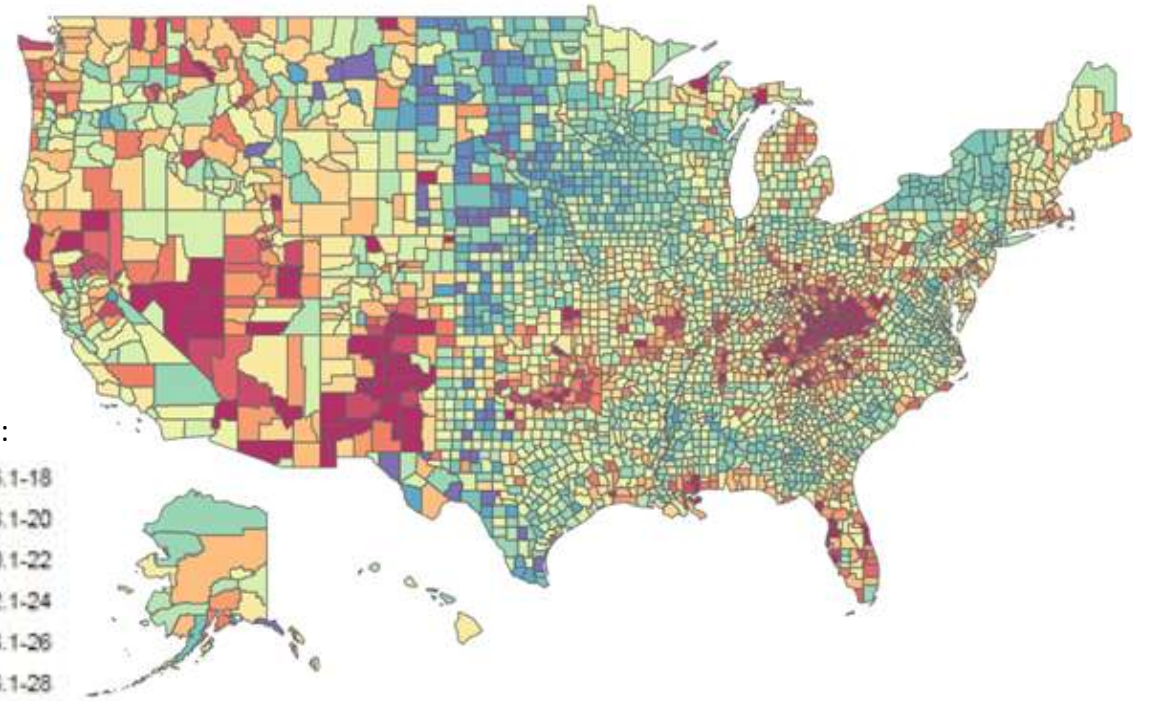


The Crisis: Overdose Death Rates

1999



2015

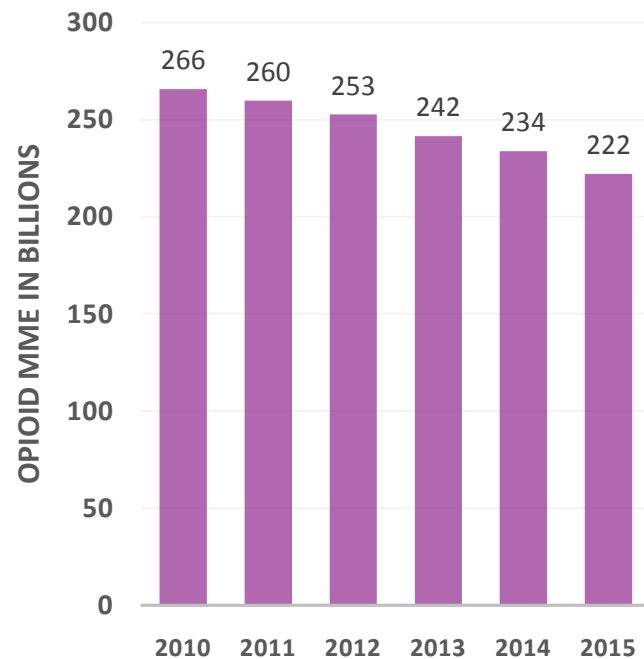


Estimated Age-adjusted
Death Rate per 100,000:



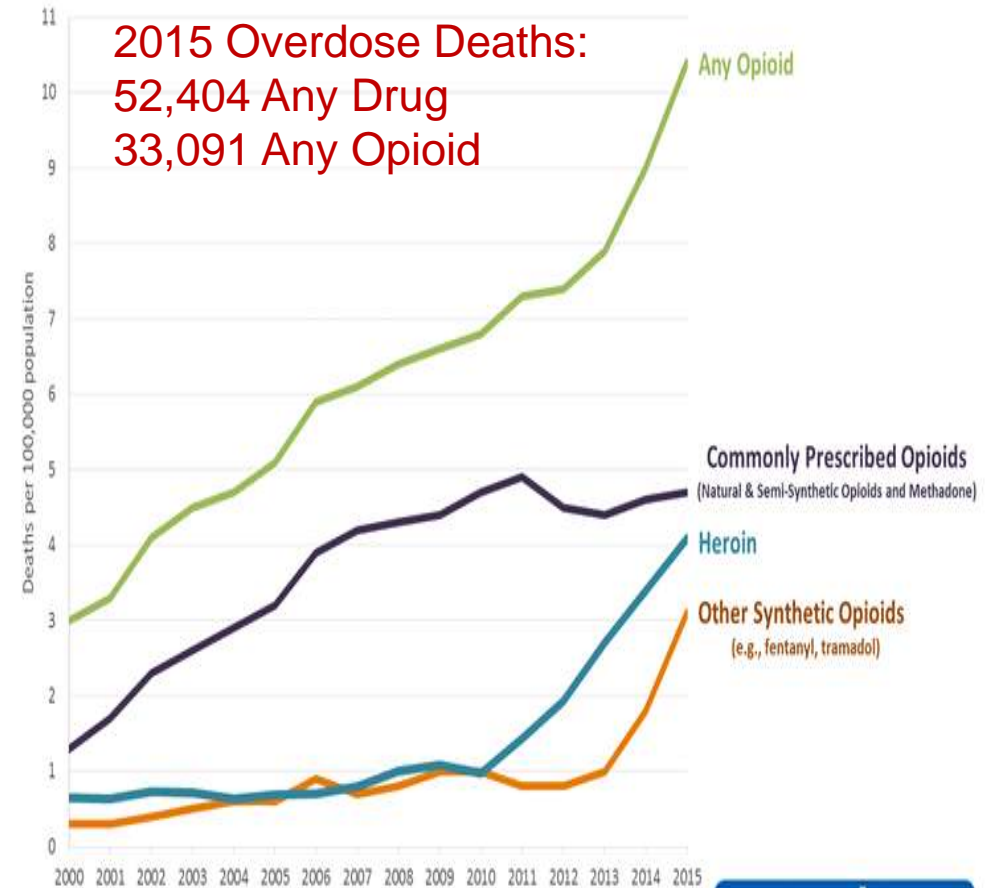
Opioid Prescriptions have started to Decrease but Opioids Fatalities are still Increasing

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



Source: IMS Health, U.S. Outpatient Retail Setting

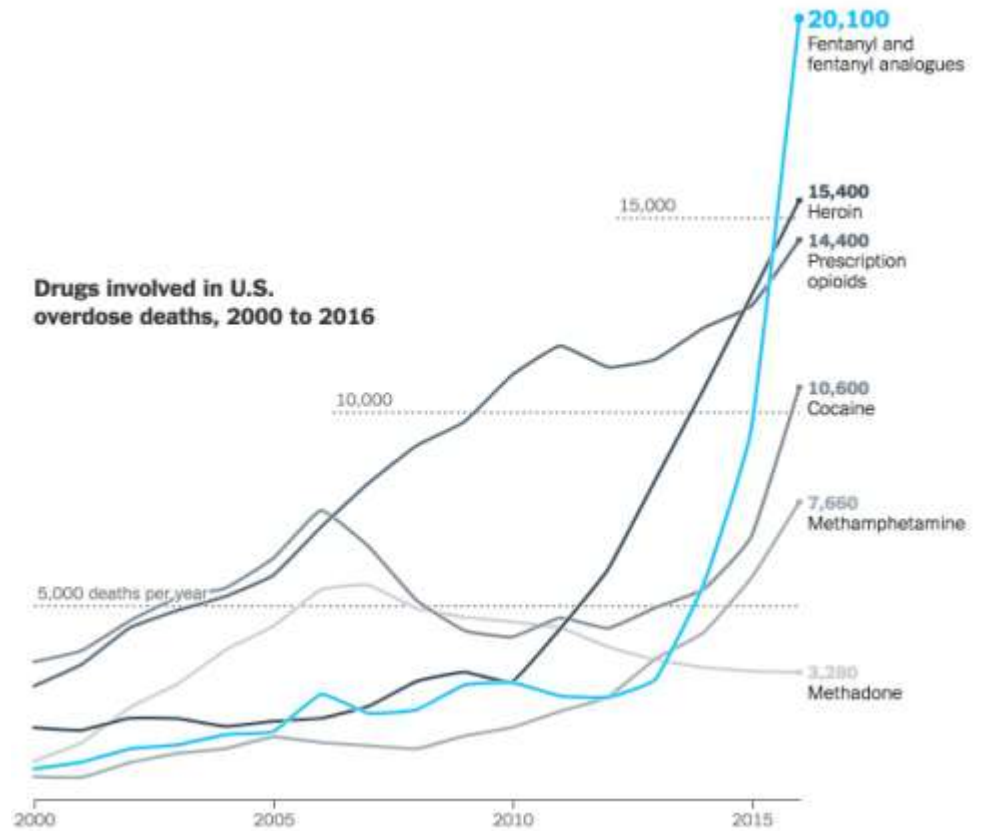
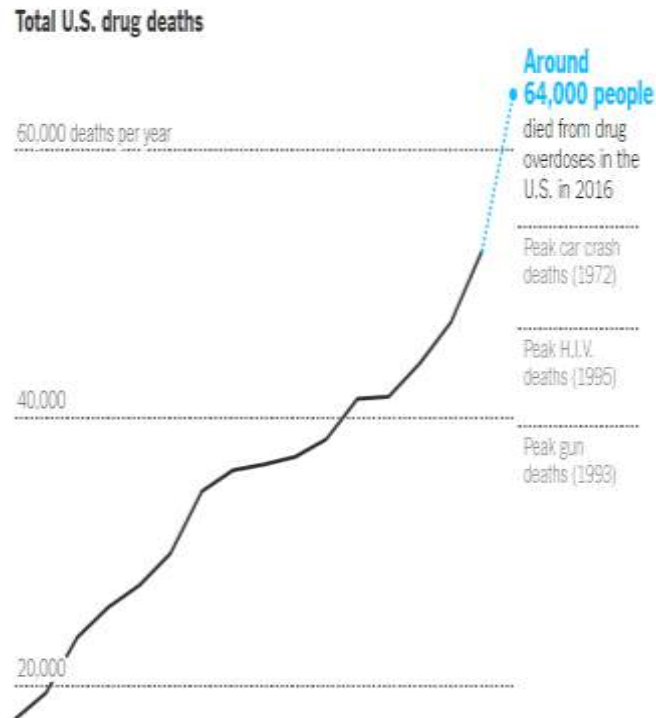
Opioid OD Deaths US, 2000-2015



SOURCE: CDC/NCHS, National Vital Statistics System, Mortality. CDC WONDER, Atlanta, GA: US Department of Health and Human Services, CDC, 2016. <https://wonder.cdc.gov/>.

Fentanyl Overtakes Heroin as Leading Cause of U.S. Drug Death

Estimate U.S. Drug Deaths in 2016



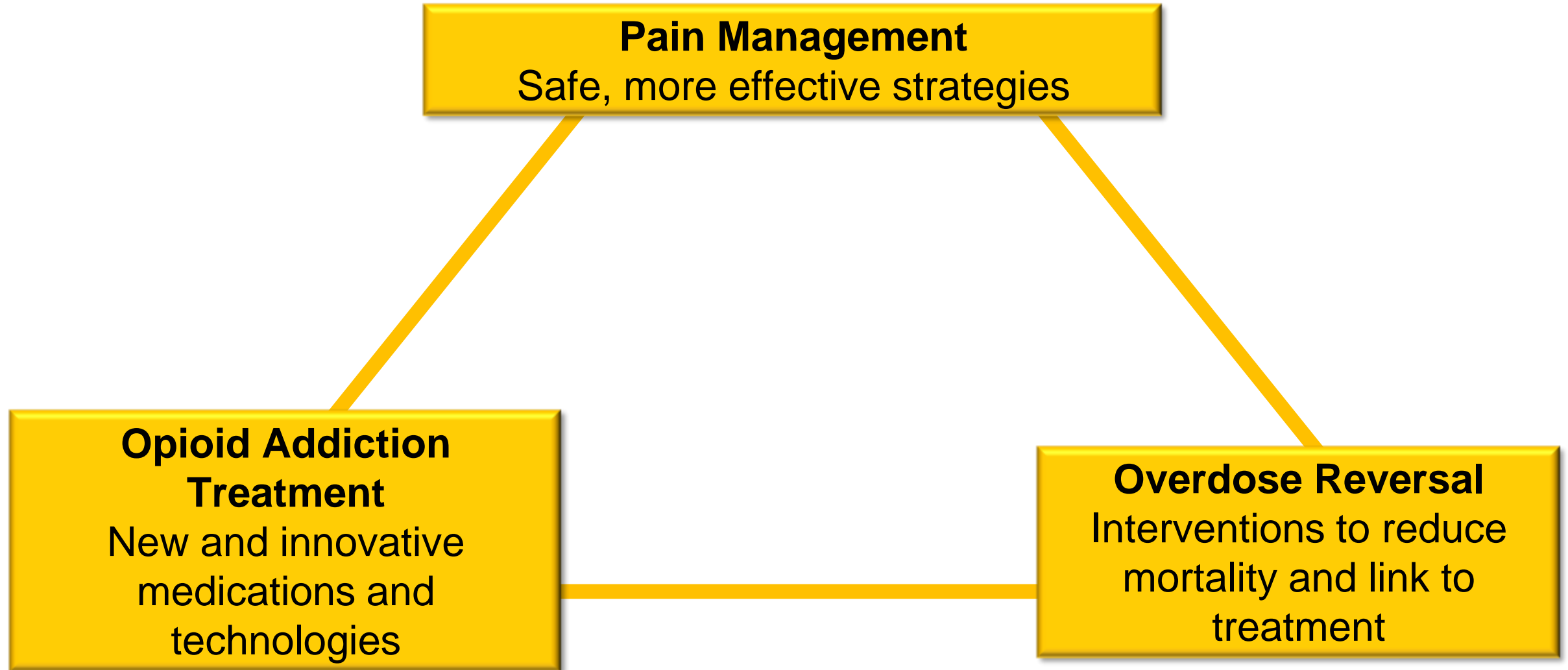
Graphs from [NY Times Article](#) based on [CDC MMWR Report 2017](#)

Challenges of the Opioid Crisis

- Opioid crisis has claimed about 200,000 lives
- Overdose deaths continue to rise. There is no end in sight.
- Medications are available to treat opioid use disorders and to prevent/reverse overdose
 - But are underutilized
 - Duration of treatment needed is not well understood
- Research has revolutionized our understanding of addiction and pain
 - But alternatives to treat addiction and overdose are limited
 - And new, non-addictive pain medicines are urgently needed

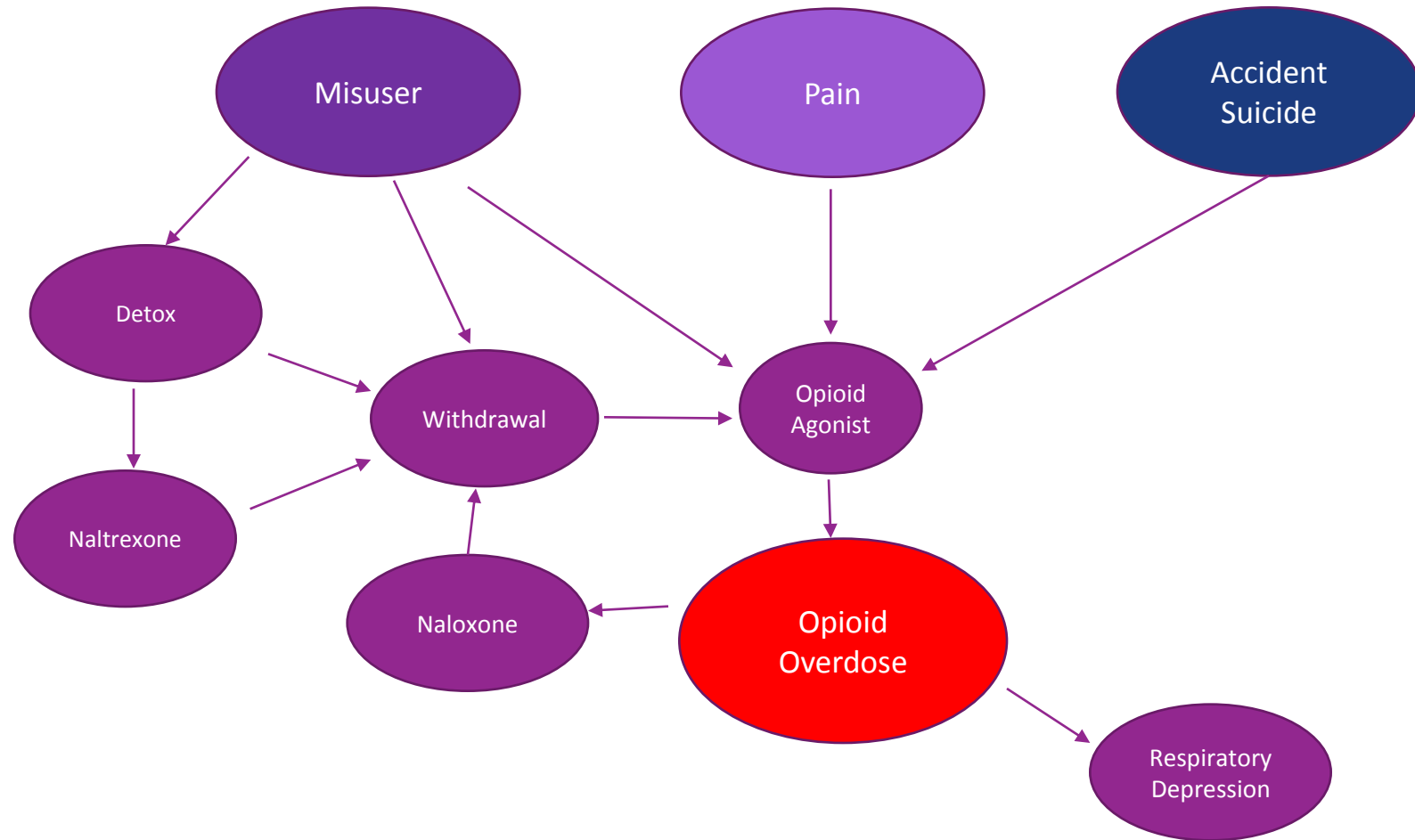
NIH Opioid Research Initiative

Using Research to End the Opioid Crisis



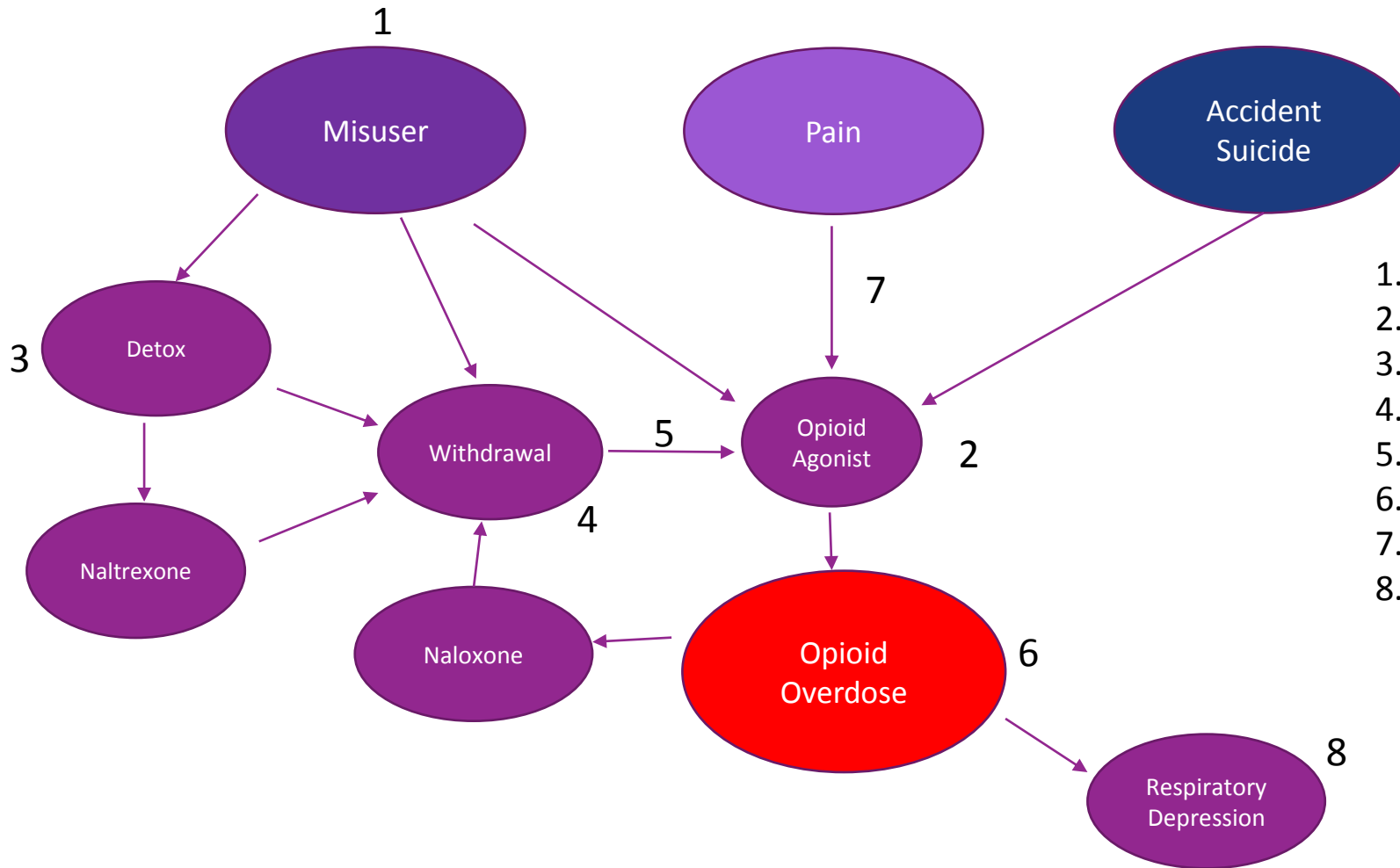
Opioid Use Trajectories

Clinical Targets



Opioid Use Trajectories

Clinical Targets



1. Prevent initiation and progression of OUDs
2. Improve OUD treatment outcomes
3. Facilitate opioid agonist discontinuation
4. Improve tx opioid withdrawal (including neonatal)
5. Reduce lethality of opioid overdose
6. Reduce overdose relapses
7. Reduce need/dose of opioids analgesics
8. Reduce risk of opioid respiratory depression

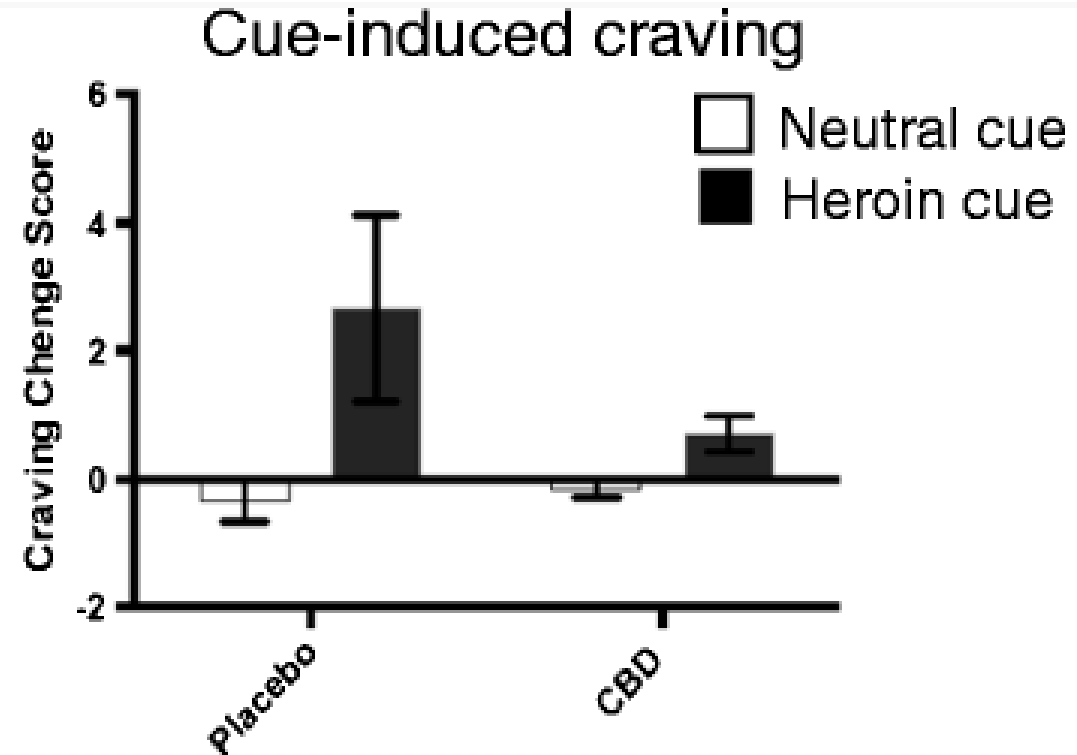
1. Prevent initiation and progression of OUDs

- Non-opioid analgesics
- Opioid analgesics with low abuse potential
- Concomitant medications to reduce the need of opioid analgesics
 - (e.g., gabapentin, cannabinoids)
- Abuse deterring formulations
- Neuromodulatory devices
- Psychosocial interventions

2. Improve OUD treatment outcomes

- Improve treatment adherence
 - Long acting formulations
 - Behavioral Interventions (contingency management)
- New pharmacological targets and medications

Cannabidiol



Component of Cannabis sativa

No psychotomimetic activity and hedonic properties

Preclinical studies: attenuates cue-induced reinstatement of heroin-seeking behavior and decreases the reward-facilitating effects of morphine [Katsidoni, 2013].

NCT01605539: Cue-induced craving in drug-abstinent heroin-dependent. CBD: 400 mg or 800 mg vs. placebo (PI: Dr. Yasmin Hurd)

Target Selection on the Basis of the Neurocircuitry of Addiction

Promising Targets

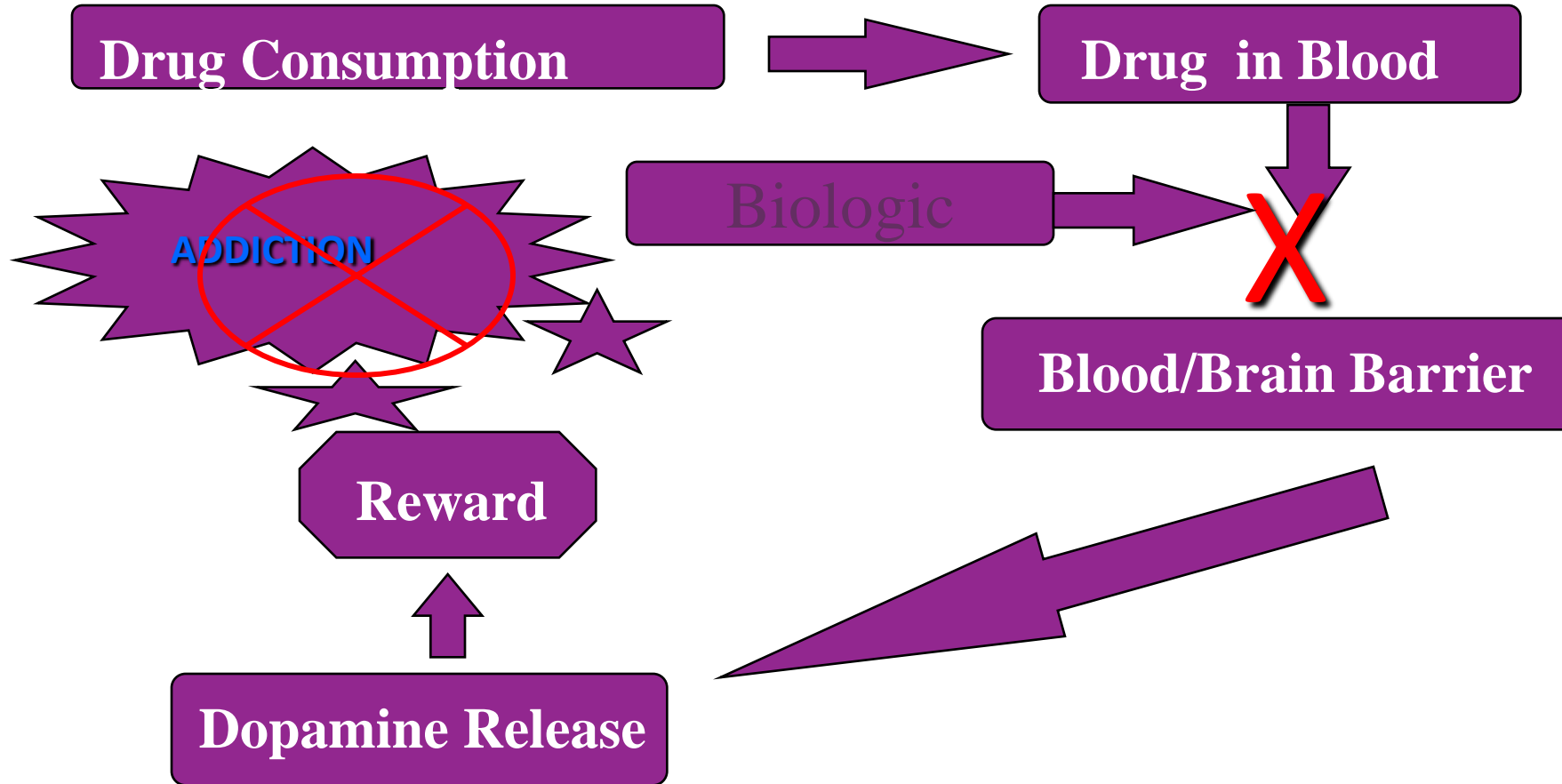
Mechanisms to reduce stress-induced drug seeking

- *Kappa Opioid Receptor Antagonists*
- *OX-1 Receptor Antagonists*
- *NOP Receptor Agonists*
- *α 2-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*

Biologics: Mechanism of Action



3. Facilitate opioid agonist discontinuation

- Anesthesia assisted rapid opioid detoxification
- Ketamine
- Low dose naltrexone
- Other medications

4. Improve tx opioid withdrawal (including neonatal)

Lofexidine for Opioid Withdrawal

- Alpha-2-adrenergic receptor agonist
- Approved in the United Kingdom for the treatment of opioid withdrawal
- More significant effects on decreasing opioid withdrawal symptoms with less hypotension than clonidine.

5. Reduce lethality of opioid overdose

- Easy to administer naloxone formulations
- Fentanyl detection kits

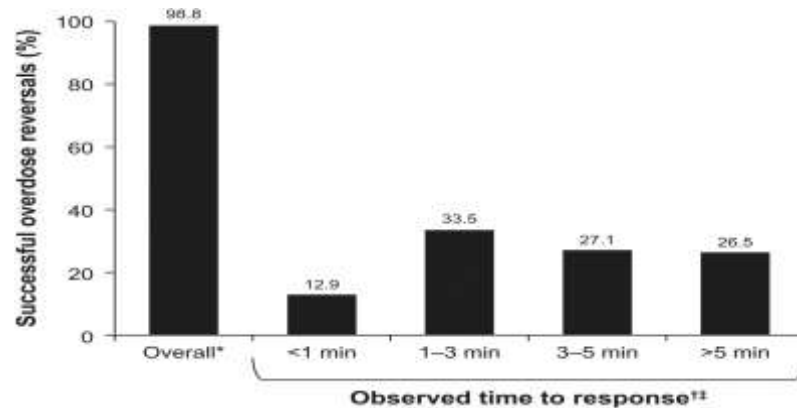
Medications for Overdose Reversal and Prevention



NARCAN® Nasal Spray device
\$37.50 per 4mg

Approved by FDA
November 2015

Opioid Overdose Reversal By Narcan® Nasal Spray



Avetian GE et al., Current Medical Research and Opinion, 23 May 2017.

Fentanyl detection kits

86% of drugs checked at Insite contain fentanyl



8/31/2016

 [Download the backgrounder](#)

Vancouver, BC – Drug checking, offered at Insite for the first time as a pilot, has found that 86 per cent of drugs were positive for fentanyl, the dangerous drug responsible for hundreds of fatal overdoses.

“These initial results confirm our suspicion that the local drug supply is overwhelmingly contaminated with fentanyl,” says Dr. Mark Lysyshyn, medical health officer with Vancouver Coastal Health (VCH). “We’re hoping this information can help people who use drugs.”

Nurses at Insite have been offering each client a test strip so they can check their drugs at their injection station. The client dilutes their substance with a few drops of water and a positive or negative for fentanyl is revealed within seconds. This method exclusively checks for fentanyl and no other substances.



BTNX, a Markham-based biotechnology company, first designed its fentanyl-detection test

6. Reduce overdose relapses

- Long-acting opioid antagonists

7. Reduce need/dose of opioids analgesics

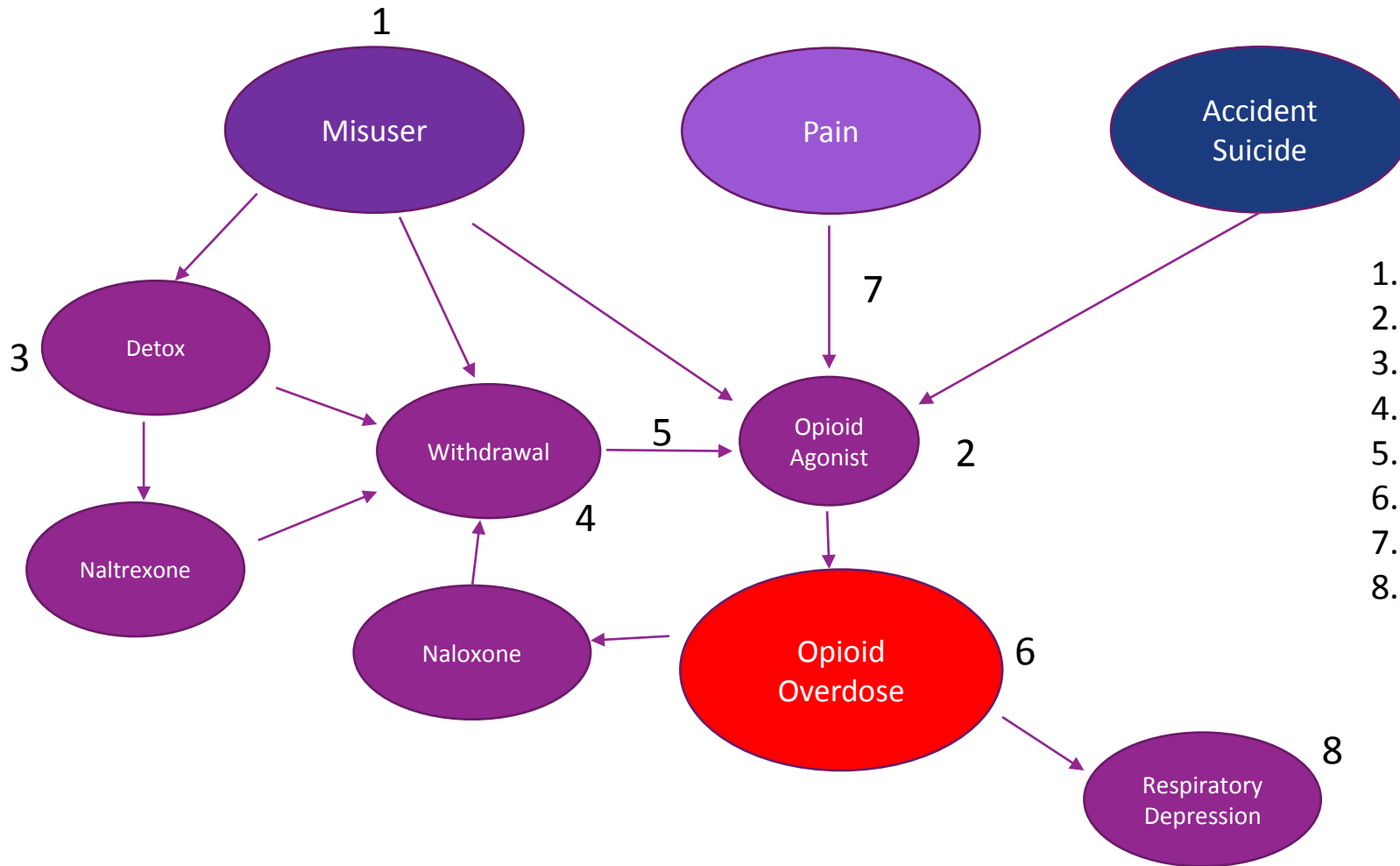
- Cannabinoids
- Gabapentin

8. Reduce risk of opioid respiratory depression

- Phrenic nerve stimulation
- Ampakines

Opioid Use Trajectories

Clinical Targets



1. Prevent initiation and progression of OUDs
2. Improve OUD treatment outcomes
3. Facilitate opioid agonist discontinuation
4. Improve tx opioid withdrawal (including neonatal)
5. Reduce lethality of opioid overdose
6. Reduce overdose relapses
7. Reduce need/dose of opioids analgesics
8. Reduce risk of opioid respiratory depression