Dean J Mariano, D.O.
Sr. Dir. Clinical Development & Medical Affairs

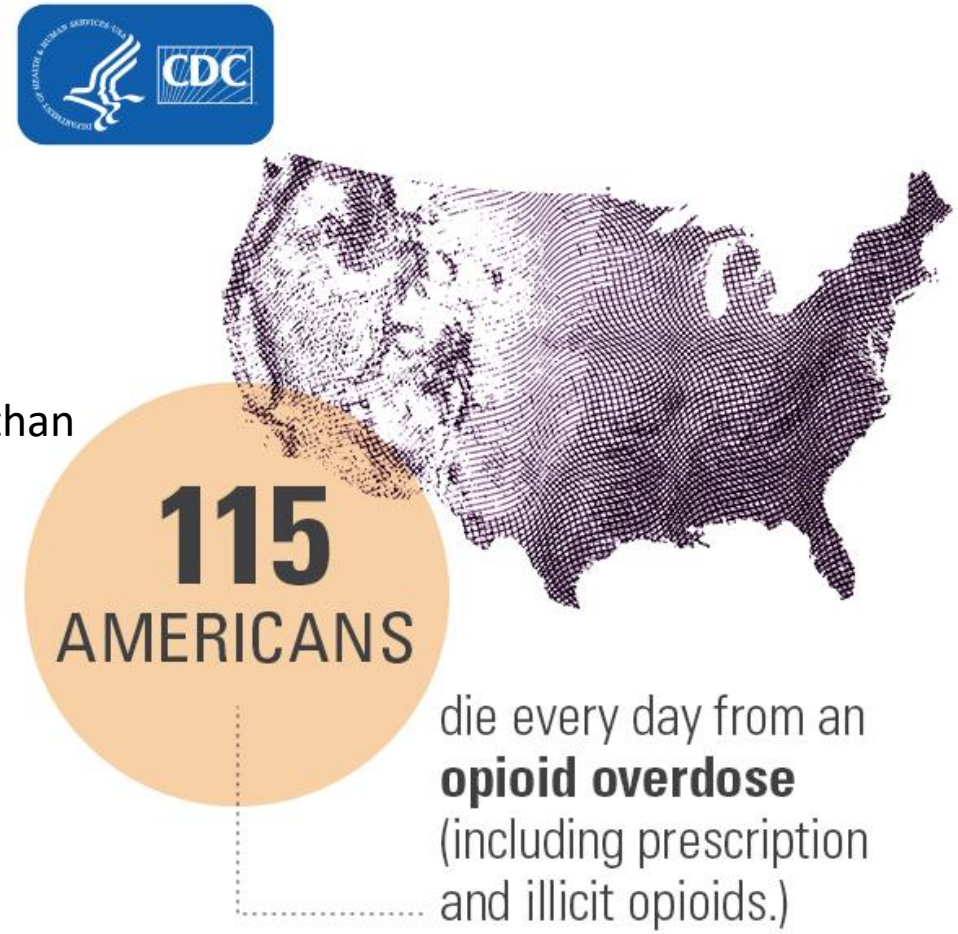
Co-Prescribing of Naloxone

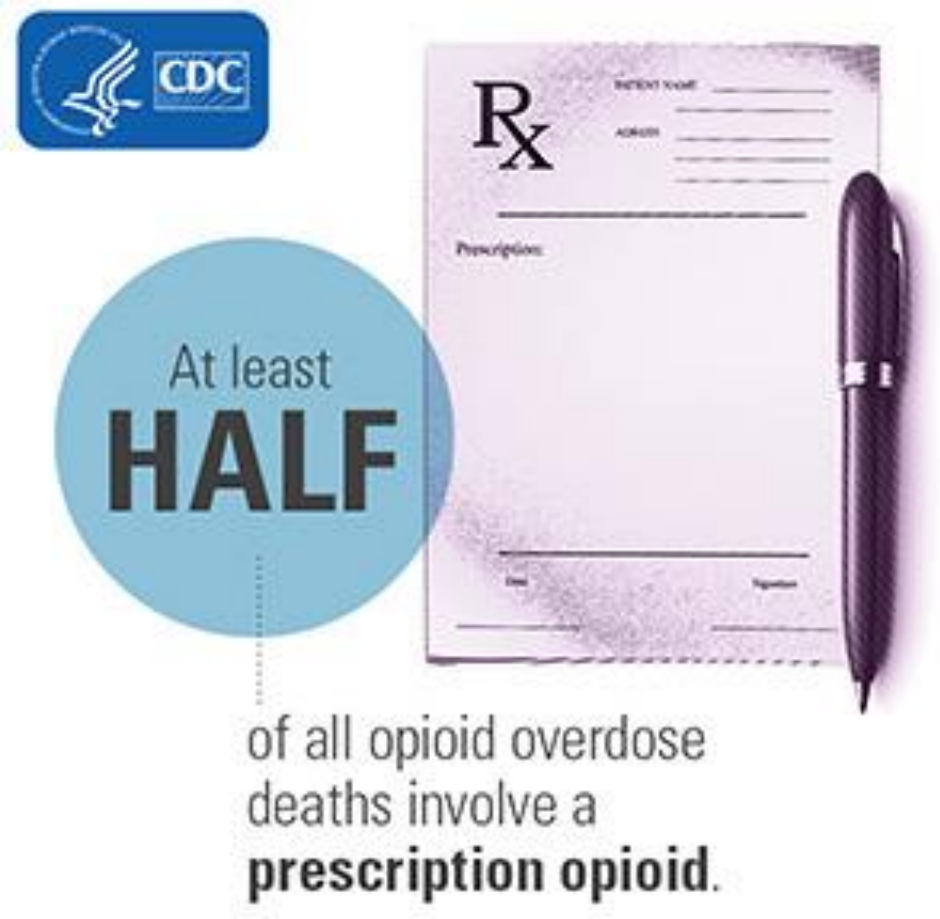
Access to Naloxone Can Save Lives

Joint Meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee

December 17-18, 2018

The Opioid Crisis

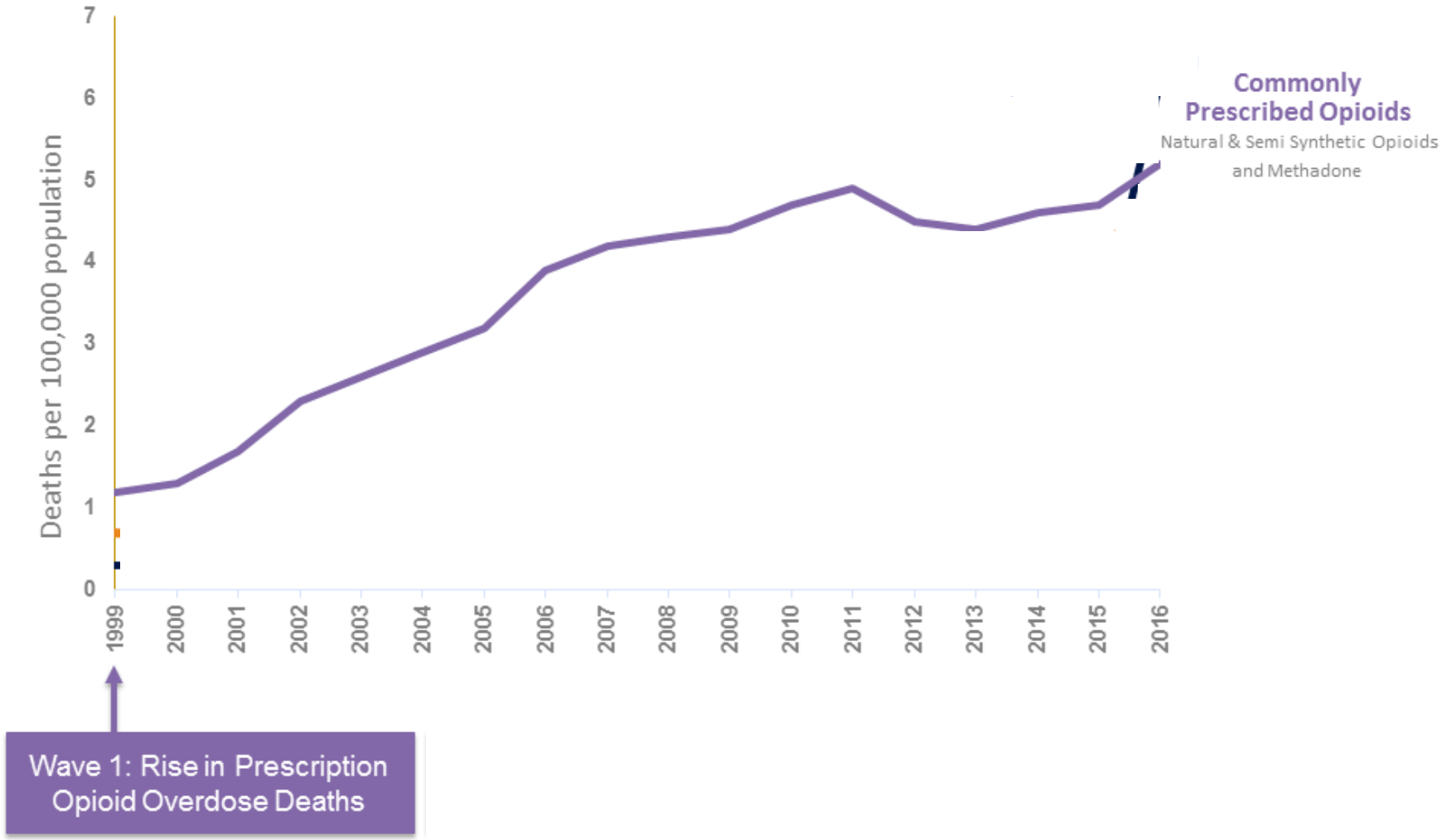




https://www.cdc.gov/drugoverdose/epidemic/index.html

Deaths Associate with Prescription Opioids

NIH National Institute on Drug Abuse



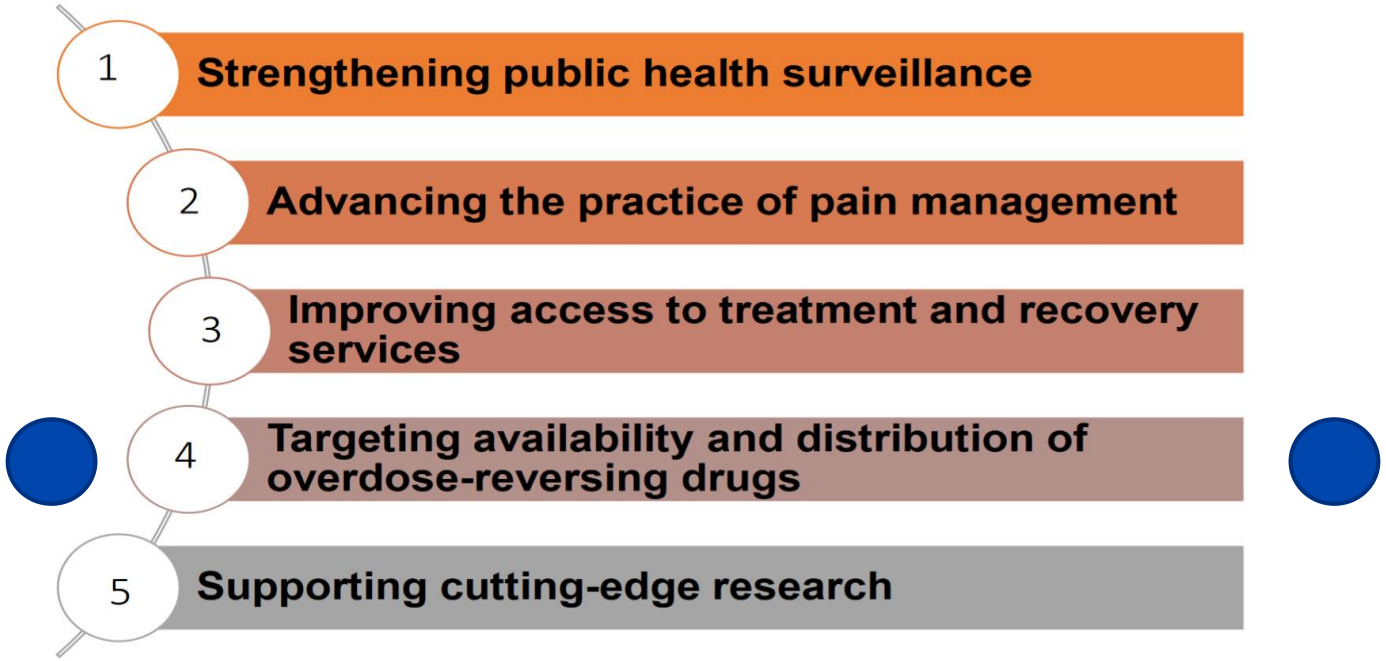
SOURCE: National Vital Statistics System Mortality File.

https://www.cdc.gov/drugoverdose/epidemic/index.html

The Government Has a Strategy

Approach of the Federal Government

HHS FIVE-POINT OPIOID STRATEGY



SAMHSA
Substance Abuse and Mental Health Services Administration

https://www.hhs.gov/opioids/about-the-epidemic/hhs-response/index.html

The US Surgeon General Endorses Co-Prescribing

Surgeon General's Advisory on Naloxone and Opioid Overdose (April 5, 2018)[1]

*"I, Surgeon General of the United States Public Health Service, VADM Jerome Adams, am **emphasizing the importance of the overdose-reversing drug naloxone**. For patients currently taking high doses of opioids as prescribed for pain, individuals misusing prescription opioids, individuals using illicit opioids such as heroin or fentanyl, health care practitioners, family and friends of people who have an opioid use disorder, and community members who come into contact with people at risk for opioid overdose, knowing how to use naloxone and keeping it within reach can save a life."*

1. Office of the Surgeon General; US Department of Health and Human Services. *Surgeon General's Advisory on Naloxone and Opioid Overdose.* www.surgeongeneral.gov/priorities/opioid-overdose-prevention/naloxone-advisory.html Accessed 4.5.2018.

Know Where To Get It and How To Use It

WHAT CAN YOU DO TO PREVENT OPIOID MISUSE?

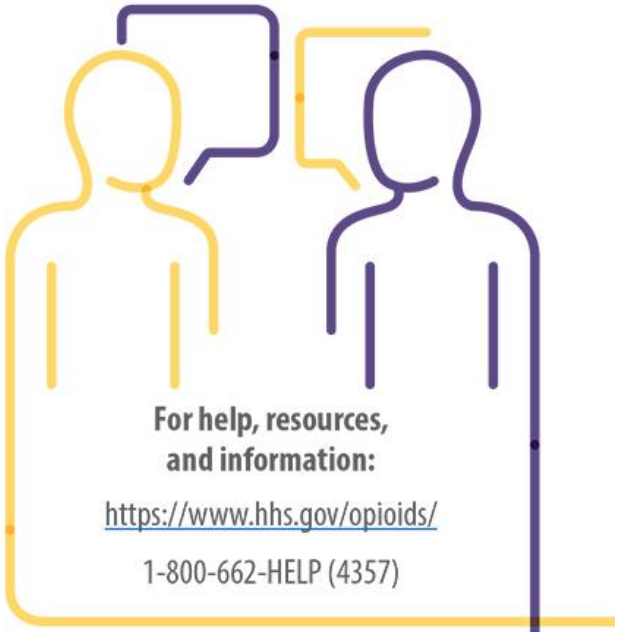
TALK ABOUT IT.
Opioids can be addictive and dangerous. We all should have a conversation about preventing drug misuse and overdose.

BE SAFE.
Only take opioid medications as prescribed. Always store in a secure place. Dispose of unused medication properly.

UNDERSTAND PAIN.
Treatments other than opioids are effective in managing pain and may have less risk for harm. Talk with your healthcare provider about an individualized plan that is right for your pain.

KNOW ADDICTION.
Addiction is a chronic disease that changes the brain and alters decision-making. With the right treatment and supports, people do recover. There is hope.

BE PREPARED.
Many opioid overdose deaths occur at home. Having naloxone, an opioid overdose reversing drug, could mean saving a life. Know where to get it and how to use it.



For help, resources, and information:

https://www.hhs.gov/opioids/

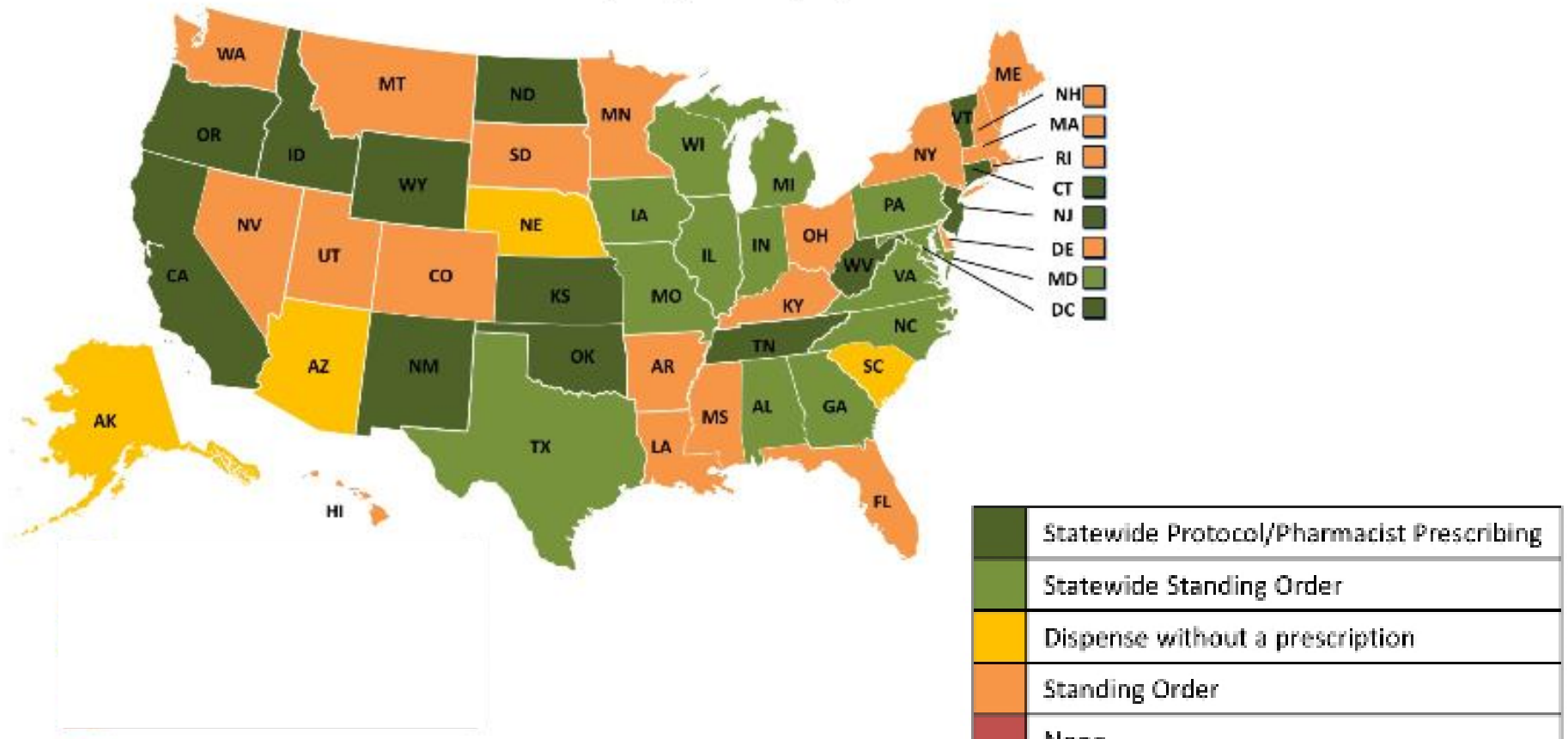
1-800-662-HELP (4357)

Naloxone Access Barriers Are Falling

NASPA
NATIONAL ALLIANCE OF STATE PHARMACY ASSOCIATIONS

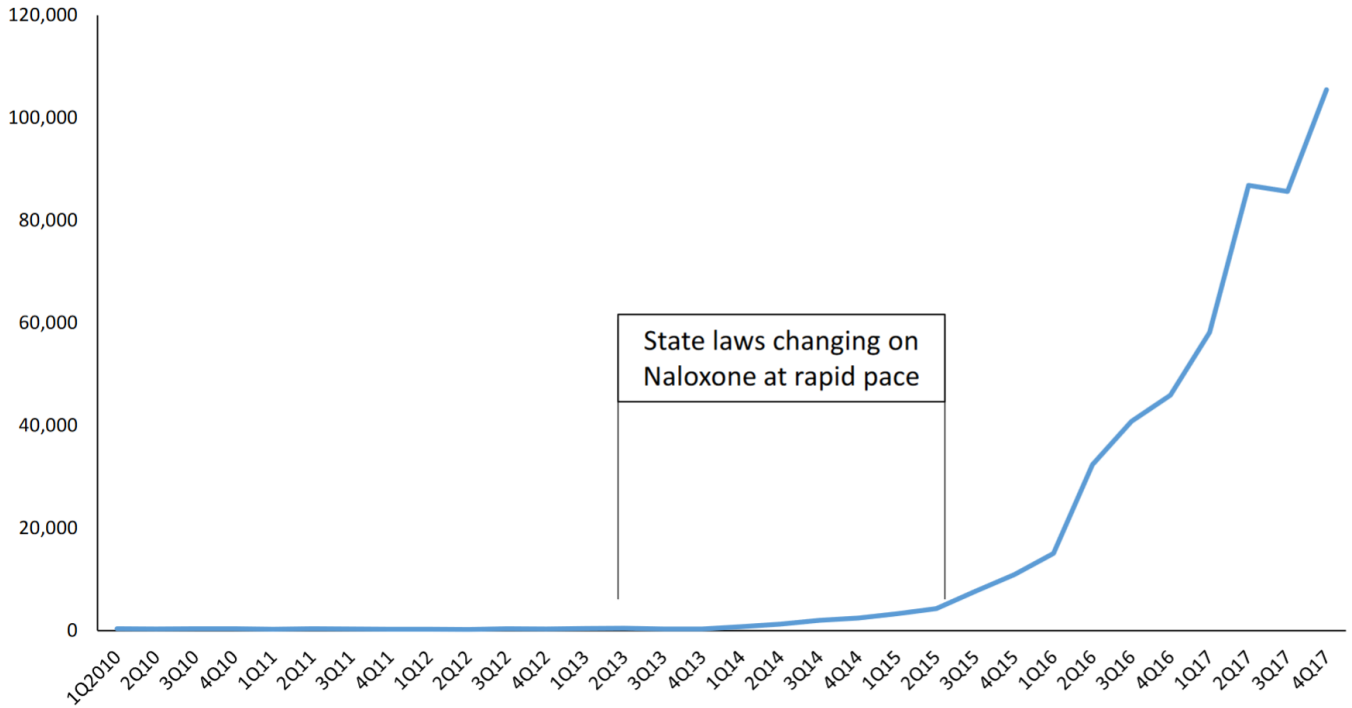
Naloxone Access in Community Pharmacies

Based on data collected by NASPA (updated January 2018)



https://naspa.us/resource/naloxone-access-community-pharmacies/

Dispensing is Rising



Source: IQVIA National Prescription Audit, data extracted 2016-2018

SAMHSA
Substance Abuse and Mental Health Services Administration

Naloxone Is Part of The Response

https://www.phsd.ca/health-topics-programs/alcohol-drugs/community-drug-strategy/education/harm-reduction

Representative Opioid Class Labeling for Life-threatening Respiratory Depression

Section 5.2 Life-threating Respiratory Depression:

- ***Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. Respiratory depression, if not immediately recognized and treated, may lead to respiratory arrest and death…***

Section 10.2 Overdose Treatment:

- ***… The opioid antagonist naloxone hydrochloride is a specific antidote against respiratory depression which may result form overdose or unusual sensitivity to opioids…***

Labels Are Not The Only Source Supporting Co-Prescribing of Naloxone

CDC Guideline for Prescribing Opioids for Chronic Pain

Recommendation #8

Before starting and periodically during continuation of opioid therapy, clinicians should evaluate risk factors for opioid-related harms. **Clinicians should incorporate into the management plan strategies to mitigate risk, including considering offering naloxone** when factors that increase risk for opioid overdose, such as **history of overdose, history of substance use disorder, higher opioid dosages (≥50 MME/day), or concurrent benzodiazepine use**, are present (recommendation category: A, evidence type: 4).

CDC Guideline for Prescribing Opioids for Chronic Pain — United States, 2016 *Recommendations and Reports* / March 18, 2016 / 65(1);1–49.

Pharmaceutical Opioid Overdose Deaths in the Presence of a Witness.

Pharmaceutical opioid overdose deaths and the presence of witnesses

Rowan P. Ogeil, Jeremy Dwyer, Lyndal Bugeja, Cherie Heilbronn, Dan I. Lubman, Belinda Lloyd

International Journal of Drug Policy 55(2018) 6-13

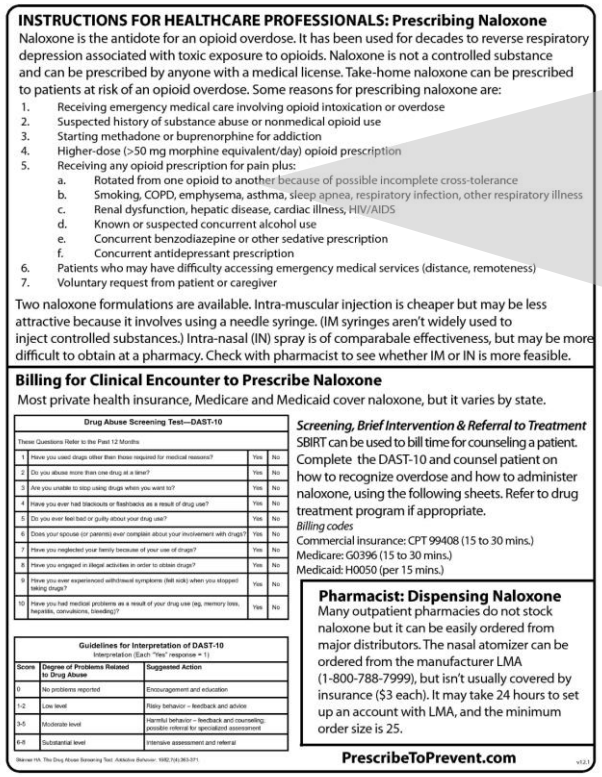
Objective: Identified a series of fatal opioid overdoses where there was evidence that witnesses had noted symptoms consistent with overdose, and examined associated contextual factors.

The Results : Pharmaceutical Opioid Overdose Deaths 2011-2013

- 587 Deaths
  - 125 (21%) were witnessed
    - 77.6% occurred in decedent's home
    - 70.4% witnesses who noted potential overdose took no action
    - 88% were co-prescribed other CNS depressants
      - 72% Benzodiazepines

- Conclusion: Most pharmaceutical opioid overdose deaths with a witness present occurred in the deceased's home, with symptoms of overdose being noted, but not acted upon. These findings support the administering of education and/or naloxone to partners and family members of people who use pharmaceutical opioids in order to reduce overdose deaths.

Guidelines are Being Adopted in Education



INSTRUCTIONS FOR HEALTHCARE PROFESSIONALS: Prescribing Naloxone

Naloxone is the antidote for an opioid overdose. It has been used for decades to reverse respiratory depression associated with toxic exposure to opioids. Naloxone is not a controlled substance and can be prescribed by anyone with a medical license. Take-home naloxone can be prescribed to patients at risk of an opioid overdose. Some reasons for prescribing naloxone are:

1. Receiving emergency medical care involving opioid intoxication or overdose
2. Suspected history of substance abuse or nonmedical opioid use
3. Starting methadone or buprenorphine for addiction
4. Higher-dose (>50 mg morphine equivalent/day) opioid prescription
5. Receiving any opioid prescription for pain plus:
   a. Rotated from one opioid to another because of possible incomplete cross-tolerance
   b. Smoking, COPD, emphysema, asthma, sleep apnea, respiratory infection, other respiratory illness
   c. Renal dysfunction, hepatic disease, cardiac illness, HIV/AIDS
   d. Known or suspected concurrent alcohol use
   e. Concurrent benzodiazepine or other sedative prescription
   f. Concurrent antidepressant prescription
6. Patients who may have difficulty accessing emergency medical services (distance, remoteness)
7. Voluntary request from patient or caregiver

Two naloxone formulations are available. Intra-muscular injection is cheaper but may be less attractive because it involves using a needle syringe. (IM syringes aren't widely used to inject controlled substances.) Intra-nasal (IN) spray is of comparabale effectiveness, but may be more difficult to obtain at a pharmacy. Check with pharmacist to see whether IM or IN is more feasible.

Billing for Clinical Encounter to Prescribe Naloxone

Most private health insurance, Medicare and Medicaid cover naloxone, but it varies by state.

Drug Abuse Screening Test—DAST-10

These Questions Refer to the Past 12 Months

1	Have you used drugs other than those required for medical reasons?	Yes	No
2	Do you abuse more than one drug at a time?	Yes	No
3	Are you unable to stop using drugs when you want to?	Yes	No
4	Have you ever had blackouts or flashbacks as a result of drug use?	Yes	No
5	Do you ever feel bad or guilty about your drug use?	Yes	No
6	Does your spouse (or parents) ever complain about your involvement with drugs?	Yes	No
7	Have you neglected your family because of your use of drugs?	Yes	No
8	Have you engaged in illegal activities in order to obtain drugs?	Yes	No
9	Have you ever experienced withdrawal symptoms (felt sick) when you stopped taking drugs?	Yes	No
10	Have you had medical problems as a result of your drug use (eg, memory loss, hepatitis, convulsions, bleeding)?	Yes	No

Guidelines for Interpretation of DAST-10

Interpretation (Each "Yes" response = 1)

Score	Degree of Problems Related to Drug Abuse	Suggested Action
0	No problems reported	Encouragement and education
1-2	Low level	Risky behavior – feedback and advice
3-5	Moderate level	Harmful behavior – feedback and counseling; possible referral for specialized assessment
6-8	Substantial level	Intensive assessment and referral

Screening, Brief Intervention & Referral to Treatment

SBIRT can be used to bill time for counseling a patient. Complete the DAST-10 and counsel patient on how to recognize overdose and how to administer naloxone, using the following sheets. Refer to drug treatment program if appropriate.

Billing codes

Commercial insurance: CPT 99408 (15 to 30 mins.)
Medicare: G0396 (15 to 30 mins.)
Medicaid: H0050 (per 15 mins.)

Pharmacist: Dispensing Naloxone

Many outpatient pharmacies do not stock naloxone but it can be easily ordered from major distributors. The nasal atomizer can be ordered from the manufacturer LMA (1-800-788-7999), but isn't usually covered by insurance ($3 each). It may take 24 hours to set up an account with LMA, and the minimum order size is 25.

PrescribeToPrevent.com

PRESCRIBE TO PREVENT

Overdose Prevention and Naloxone Rescue Kits for Prescribers and Pharmacists

EMS Has Its Limitations

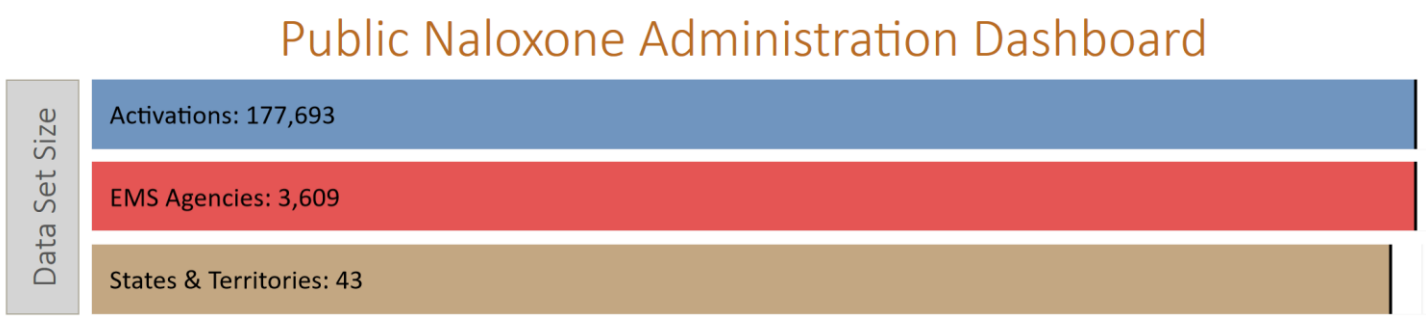
- Average time for an EMS unit to arrive on scene was **7 minutes**[1]
  - Time increased to more than **14 minutes** in rural settings
  - Nearly 1 in 10 encounters wait up to **30 minutes**
- Lack of Oxygen:
  - Permanent brain damage can occur after **4 minutes**[2]

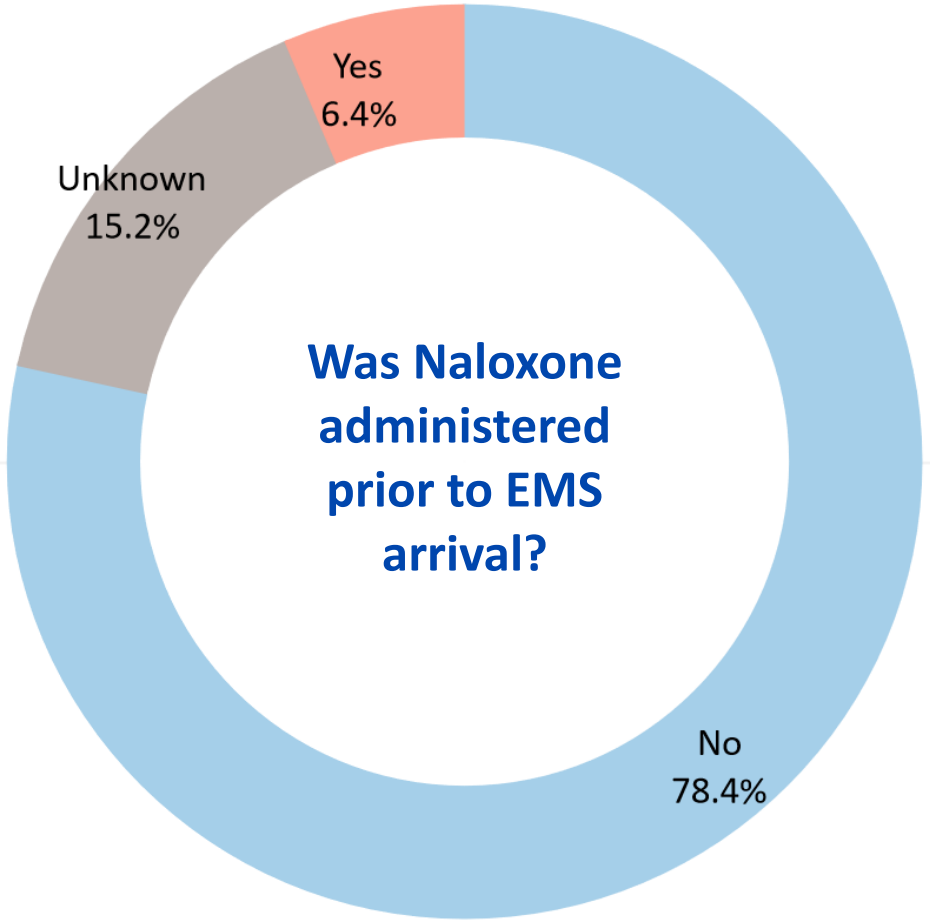
1. What is the Average Response Time for Emergency Medical Services? Medical News Bulletin-October 5, 2017

2. https://medlineplus.gov/ency/article/000013.htm

Data Concerning the Administration of Naloxone

NEMSIS
Powered by NHTSA's Office of EMS





As of December 10, 2018

Co-Prescribing Support Through Research Funded by The National Institute on Drug Abuse (NIDA)

Nonrandomized Intervention Study of Naloxone Co-prescription for Primary Care Patients Receiving Long-Term Opioid (LTO) Therapy for Pain

Phillip O. Coffin, MD, MIA; Emily Behar, MA; Christopher Rowe, MPH; Glenn-Milo Santos, PhD, MPH;

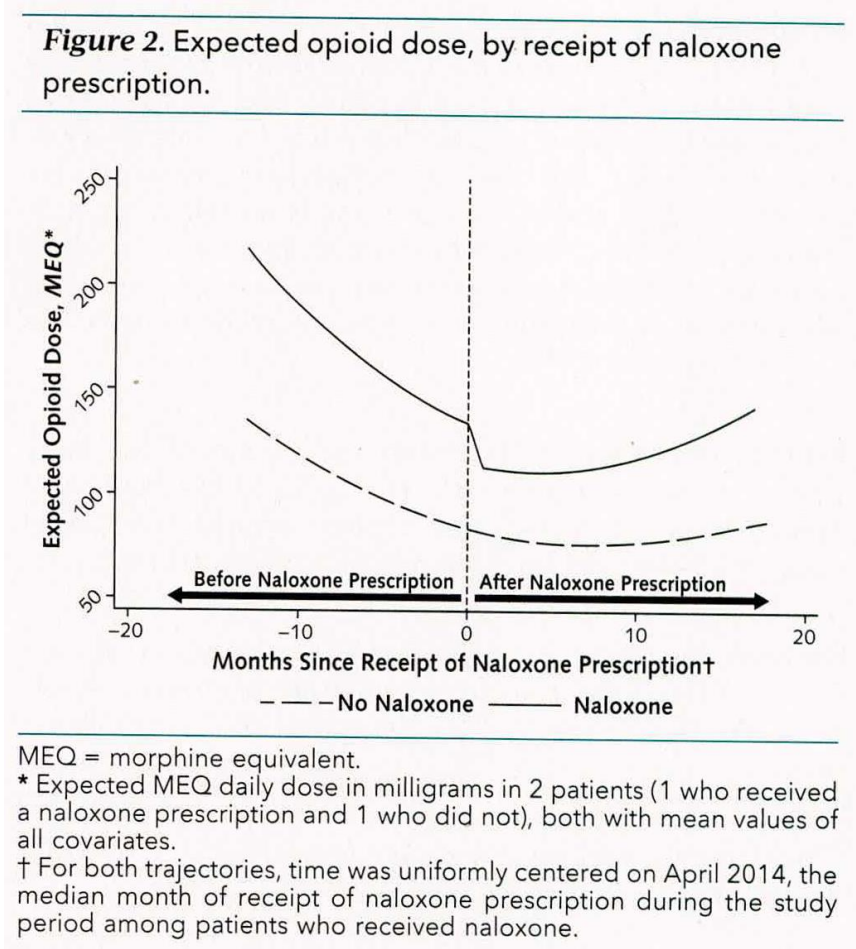
Diana Coffa, MD; Matthew Bald, MD; and Eric Vittinghoff, PhD

Ann Intern Med. 2016;165:245-252. doi:10.7326/M15-2771

Objective: To evaluate the feasibility and effect of implementing a naloxone prescription to patients prescribed opioids for chronic pain.

The Results : First Large Published Data on Co-Prescribing

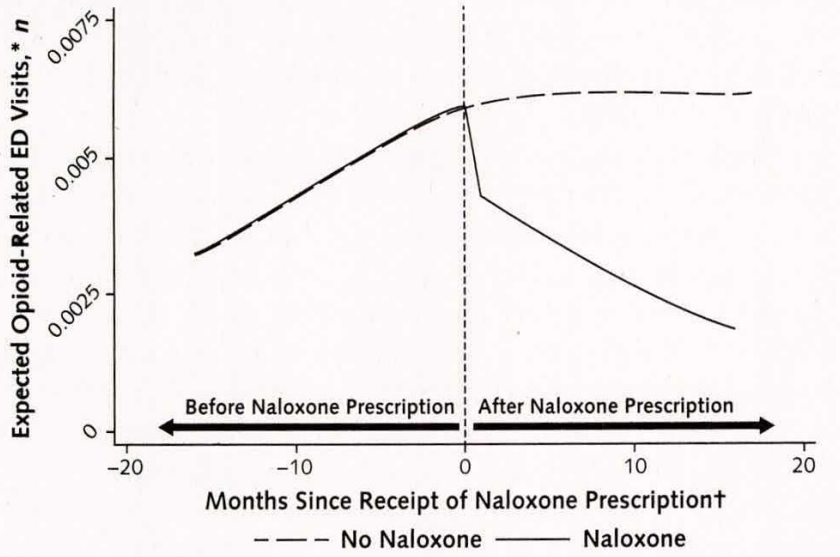
- 759 of 1985 patients receiving chronic opioids were prescribed naloxone
- Independently more likely to be prescribed
  - Patients prescribed higher doses of opioids
  - Opioid-related ED visit in the past 12 months
- There was no net change in opioid dose



The Conclusion: First Large Published Data on Co-Prescribing

- Results from providing a prescription of naloxone with opioids
  - 47% fewer opioid related Emergency Department visits after 6 months
  - 63% fewer Emergency Department visits after one year
  - Raising the possibility that providing naloxone affected patient behavior with respect to opioids.

Figure 1. Expected number of opioid-related ED visits per month, by receipt of naloxone prescription.



ED = emergency department.
* Expected number of ED visits per month calculated for 2 patients (1 who received a naloxone prescription and 1 who did not), both with mean values of all covariates.
† For both trajectories, time was uniformly centered on April 2014, the median month of receipt of naloxone prescription during the study period among patients who received naloxone.

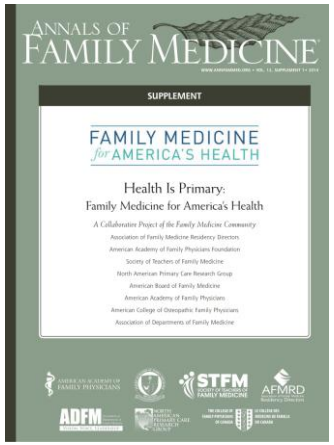
Patient's Experience With Naloxone Co-Prescribing

Primary Care Patient Experience with Naloxone Prescription

Emily Behar, MS, Christopher Rowe, MPH, Glenn-Milo Santos, PhD, MPH,

Sheigla Murphy, PhD, Phillip O. Coffin, MD, MIA

Ann Fam Med 2016;14:431-436



Objective: Evaluate chronic pain patients' attitudes toward being offered a naloxone prescription and their experience with naloxone.

The Results

60 Patients October 2013 – October 2015

- 90% previously never received a prescription
- 82% successfully filled the prescription
- 97% believed that patients prescribed opioids for pain should be offered naloxone
- Most patients had a positive (57%) or neutral (22%) response to being offered naloxone
  - Positive reactions:
    - Improved relationship with clinician
    - Appreciate the offer
    - Community benefits

The Results

- 37% reported safer opioid use behaviors after receiving the prescription
- No harmful behavior changes reported.
- 37% had personally experienced an opioid-poisoning event
- 5% reported that the prescribed naloxone had been used on them
- 77% estimated their risk of overdose as low.

- Conclusion : Primary care patients on opioids found it acceptable to receive a prescription for naloxone, the prescription reached patients who had not had access to naloxone, and having naloxone may be associated with beneficial changes in opioid use behaviors.

How Many Doses of Naloxone Does It Take?

An Innovative Model for Naloxone Use Within an OTP Setting: A Prospective Cohort Study

Joanna G. Katzman, MD, MSPH, Mikiko Y. Takeda, PharmD, MS, Snehal R. Bhatt, MD,
Monica Moya Balasch, MS, Nina Greenberg, MS, and Howard Yonas, MD

J Addict Med 2018;12: 113–118

Objective: Measure the opioid overdose reversal rate with take-home naloxone among participants with a diagnosis of opioid use disorder (OUD) in an opioid treatment program (OTP) setting.

The Results

244 Participants April 4, 2016 - July 4,2016

215 Completed 3-Month Visit

- At intake:
  - 44% personally overdosed at least once
  - 87% witnessed someone else overdose at least once
- 3-Month Interval:
  - 13% (n=31) successfully reversed opioid overdose on 38 community members
  - 1 study participant overdosed reversed by EMS
  - 87% of the reversed were family or friends of study participant

How Many Doses of Naloxone Dose It Take?

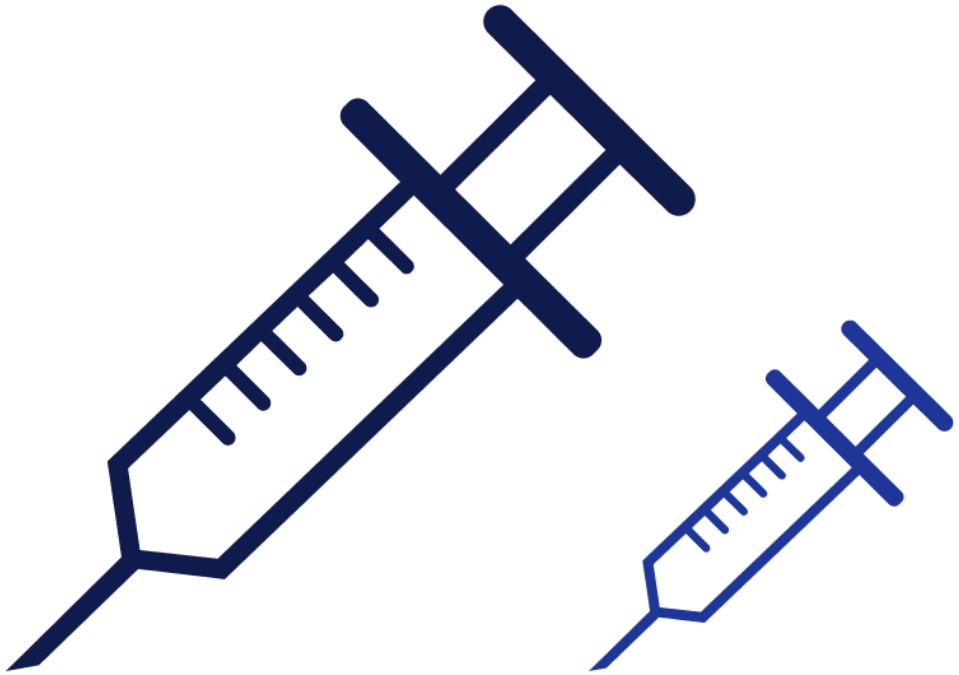
- Of the 38 reported overdose reversals:
  - 50% required 1 dose of naloxone
  - 45% required 2 doses of naloxone
  - 5% required 3 doses of naloxone
    - Third dose delivered by EMS and a study participant with an extra dose

- All reported overdose reversals were successful, and
- All involved injected heroin

1. Katzman JG et al. J Addict Med 2018;12:113-8.

National Emergency Medical Services Information Systems Database: Emergency Medical Services data from US States and Territories as of December 10, 2018

Number of Naloxone Administrations and Average per Record



1.34 Average Number of Naloxone Administrations

Number of Doses Given	1	2	3	4
Count of activations	129,094	35,151	7,213	2,350
Percent of total activations with Naloxone administration	74.29%	20.23%	4.15%	1.35%

NEMSIS Powered by NHTSA's Office of EMS

Insys Naloxone Nasal Spray

NIH Public Private Partnership To Address the Opioid Crisis

Focus Area A: Enhance medications for OUD and to prevent/reverse overdoses

- Develop *new formulations* and *combinations of medications* to treat OUD and to prevent overdoses
- Develop *more potent* or *longer lasting opioid antagonists* to reverse overdoses from fentanyl or its derivatives.
- *Develop and validate alternative endpoint* other than abstinence that are acceptable to FDA for approval of OUD medications

Focus Area B: Pain

- Establish *data sharing collaborative* between industry groups
  NIH to serve as a neutral broker
- Determine *objective measures* to understand, predict responses to pain
  Biomarkers for pain – and a "Pain-ometer"
- *Clinical trial network* to accelerate trials on common and rare pain syndromes and to evaluate biomarkers

N. Volkow, MD NIDA Update May, 2018

- Anticipated NDA filing 1Q2019.
- An 8 mg formulation
- Unique, first-in-class PK profile

Conclusion

- Co-prescribing naloxone may have a positive impact on unintentional opioid overdose deaths[1]
- It is difficult to predict who on chronic opioid therapy will experience overdose
- If naloxone is co-prescribed in a Universal Precautions manner for all patients receiving chronic opioid therapy, it may have a significant impact on intentional and unintentional opioid overdose deaths[1]

1. Takeda et al., Co-prescription of naloxone as a Universal Precautions model for patients on chronic opioid therapy – Observational study, Subst Abus. 2016 Oct-Dec;37(4):591-596.