

Naloxone for Emergency Administration: A 2017 Update On FDA Guidance

Nathan A. Painter, PharmD, CDE

Associate Clinical Professor
University of California San Diego
Skaggs School of Pharmacy and Pharmaceutical Sciences
La Jolla, California



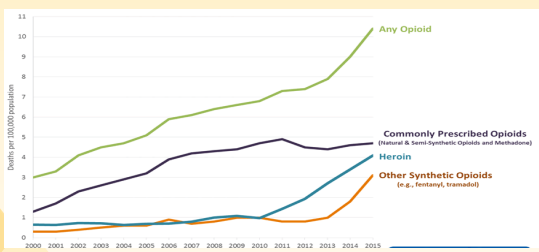
Educational Objectives

At the completion of this activity, the participant will be able to:

- Examine the severity of the opioid epidemic in the community and ways to identify patients at risk for opioid overdose
- Identify requirements needed to establish a collaborative practice agreement to dispense naloxone
- Compare the differences between intravenous (IV), intramuscular (IM), subcutaneous (SC), and intranasal (IN) routes of administration for naloxone
- Develop strategies to educate patients and caregivers in the community about naloxone, how to administer it during an emergency, and where to access available resources and programs



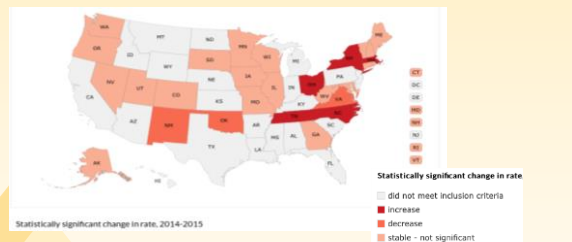
Overdose Deaths Involving Opioids, United States, 2000-2015



Printed with permission from CDC/NCHS, National Vital Statistics System, Mortality, CDC Wonder, Atlanta, GA US Department of Health and Human Services, CDC 2016. <https://wonder.cdc.gov/>. Accessed March 4, 2017.



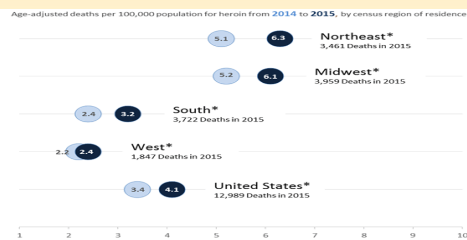
Statistically Significant Changes in Drug Overdose Death Rates Involving Natural and Semi-synthetic Opioids by Select States, United States, 2014-2015



Printed with permission from CDC. <https://www.cdc.gov/drugoverdose/data/overdose.html>. Accessed March 4, 2017.



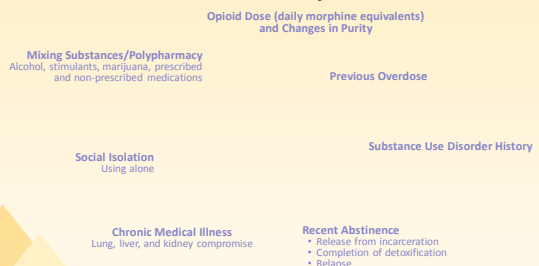
Heroin Overdose Death Rates



*Statistically significant at p<0.05 level.
Printed with permission from CDC/NCHS, National Vital Statistics System, Mortality, CDC Wonder, Atlanta, GA US Department of Health and Human Services, CDC 2016. <https://wonder.cdc.gov/>. Accessed March 4, 2017.



Common Risks for Opioid Overdose



Yolkow PD, McLellan AT. N Engl J Med. 2016;374(12):1203. Prescribe to Prevent. www.prescribetoprevent.org. Accessed March 4, 2017.



Opioid Conversion

Opioid	Oral Equianalgesic Dose (mg)
Morphine	30
Hydrocodone	30
Oxycodone	20
Codeine	200
Hydromorphone	7.5
Meperidine	300
Oxymorphone	10
Tramadol	120

McPherson ML. Amer. Soc of Health-Systems Pharm. Bethesda, MD, 2010.



Rationale for Overdose Education and Naloxone Rescue Kits

- Feasibility**
 - Piper, et al. *Suicide Life Threat*. 2008; 43: 858-70.
 - Dun-Schetter, et al. *Am J Public Health*. 2010; 100: 788-791.
 - Cohen, et al. *J Urban Health*. 2010; 87: 103-141.
 - Barnett, et al. *J Urban Health*. 2011; 88: 1020-30.
 - Walley, et al. *JAT*. 2013; 44: 241-7. (Methodology and data program)
- Increased knowledge and skills**
 - Green, et al. *Addiction*. 2009; 110: 979-83.
 - Tobias, et al. *J Drug Policy*. 2010; 35: 131-6.
 - Wagner, et al. *Int J Drug Policy*. 2010; 31: 186-93.
- No increase in use**
- Increase in treatment**
 - Katz, et al. *Urban Health*. 2009; 82: 303-11.
 - Dun-Schetter, et al. *AM J Public Health*. 2011; 101: 207.
- Reduction in overdose in communities**
 - Marswell, et al. *J Addict Dis*. 2006; 25: 89-96.
 - Covino, et al. *Am J Epidemiol*. 2012; 174: 302-8.
 - Moffitt, et al. *Am J Addict*. 2013; 124: 1178.
 - Bird, et al. *Addiction*. 2015; Dec 1.
- Cost-effective**
 - Coffin and Sullivan. *Ann Intern Med*. 2013 Jan 1; 158(1): 1-9



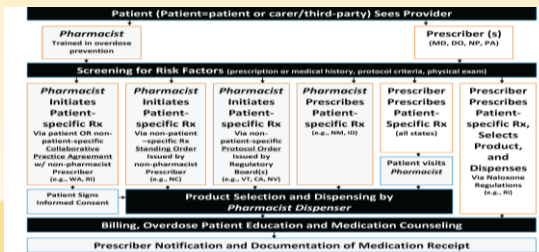
Abuse/Misuse Trends

- Rates of analgesic misuse and death are highest among:
 - Men; however, death rates increasing more rapidly for women as compared to men
 - Aged 20 to 64 years
 - Non-Hispanic whites
 - Poor and rural populations
- “Persons who have mental illness are overrepresented among both those who are prescribed opioids and those who overdose on them.”

CDC MMWR 2012; 61(1): 10-13. CDC MMWR 2013; 62(2): E07-542



Naloxone Distribution Models



Adapted from Green TC, et al. *Harm Reduct J* 2015;12:25.



Utilizing Pharmacists to Increase Naloxone Access

<https://www.pharmacytimes.org/resource-center/opioid-overdose-rescue>

Find out your state laws: www.PDAPS.org



*Based on a survey of pharmacy community pharmacists authorized to participate, no drug restrictions (they need to specify within the agreement, teaching/counseling alert) regarding the relationship between the prescriber and the patient. Note: This survey was based on the model of practice. The national model of practice is currently published in September 2015 issue of *Pharmacy Times*. State laws and regulations are courtesy of NADPA and first published in February 2015 and updated in August 2016. Abbreviations for state laws may not be in official state law or regulation. May 15. Report updated information not released from NADPA website.



Emerging Innovations: Models for Pharmacy Naloxone

- Prescriber writes prescription** (Patient fills at pharmacy)
 - Setting: clinic with insured patients
 - Pharmacies alerted to prescribing plans
 - May need to have atomizers on-site for intranasal formulation
 - Informational brochure, patient fills
- Pharmacy provides naloxone directly to customer**
 - Without prescriber contact under a standing order
 - Training needed; Range of active models: Naloxone co-prescription Universal offer, may require clear policy direction
- Pharmacy provides naloxone to patients in treatment/clinic/center**
 - Without prescriber or pharmacy contact under a standing order, distribution model
 - Patient training done on-site at clinic, facilitates facility level compliance and sustainability



Partnerships Between Substance Use Disorder Treatment Programs and Community Pharmacies

- Large pharmacy chain with pharmacy standing order 11/2014-4/2016
 - 120 pharmacies dispensing naloxone in 83 towns
 - Dispensed 1865 naloxone rescue kits – More than half to a store in Brockton
 - Stores in towns with most distributions have agreements with programs to fill naloxone rescue kits release

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Pharmacy standing order log data, slide used with permission from AY Walker, MD.

DIRECTIONS IN
Pharmacy

Expanded Access in Community Pharmacies

- Rhode Island
 - A statewide protocol involving informed consent from each patient
- New Mexico
 - First in the nation to grant prescriptive authority for naloxone
- North Carolina
 - Project Lazarus: Increasing naloxone access in community pharmacies in collaboration with Community Care of North Carolina's Chronic Pain Initiative

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<http://www.pharmacist.com/66-drug-new-life-naloxone-access-expands-community-pharmacies>. Accessed March 5, 2017.

DIRECTIONS IN
Pharmacy

Pharmacist Protocol for Furnishing Naloxone in California

Pharmacist Training

- A pharmacist must successfully complete a training program with a minimum of one hour of approved continuing education on the use of naloxone prior to furnishing

Patient Education

- Must provide education, including opioid overdose education (prevention, recognition, and response), administration of naloxone, potential side effects or adverse effects, and the requirement to seek emergency medical care for the patient.
- Must provide information about referrals and resources for drug addiction and proper drug disposal, if needed
- Must ensure that the information is understood and all questions are answered before the naloxone kit is provided

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Two Response Strategies

- Legal reform
 - 911 Good Samaritan Laws reduce risk of arrest for calling 911 in event of overdose
 - Legislation to further minimize (the already low) risk to medical providers involved in naloxone distribution
- Overdose education/naloxone distribution programs
 - Train people at risk, friends, family members, and first responders to recognize and respond to overdose

Call R, et al. N Engl J Med 374:15.

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DIRECTIONS IN
Pharmacy

911 Good Samaritan Laws

- Similar to, but different from CPR-based Good Samaritan Laws
- Protect caller, bystanders, and victim from arrest for drug charges when 911 is called in event of overdose
- Meant to minimize fear of police when calling 911
- Protects callers & victims from charges related to being under the influence or possession for personal use of drugs or drug paraphernalia
- Does not provide immunity against:
 - Sales or distribution
 - Forcibly administering a drug against a person's will
 - DUI or drugged driving

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DIRECTIONS IN
Pharmacy

Medical Liability

- Provides protection to licensed health care professionals from civil and criminal liability when they prescribe, dispense, or oversee the distribution of naloxone via standing order or in standard medical practice
- Non-medical personnel are able to distribute naloxone under a doctor's standing orders
- Permits individuals to possess and administer naloxone in an emergency and protects responder from civil or criminal prosecution for practicing medicine without a license
- Encourages licensed prescribers to prescribe naloxone to individual patients on chronic opioid pain medication

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DIRECTIONS IN
Pharmacy

Opioid Receptors

Mu:

- Analgesia
- Sedation
- Euphoria
- Respiratory depression
- Constipation
- Physical dependence

Kappa:

Mild analgesia
Less respiratory depression

Delta:

Mild analgesia



Naloxone nasal spray [prescribing information]. Redford, PA: Adapt Pharma, Inc.; 2015. <https://www.narcan.com/pdf/NARCAN-Prescribing-Information.pdf>. White, JM, Irvine RJ. Addiction. 1999; 24(10):981-92.



Naloxone

- An opioid antagonist that temporarily reverses the effects of an opioid overdose (~60 minutes)
- Prescribed/distributed to people at risk of opioid overdose
 - Accompanied by training for at-risk individual and educational materials
- An ANTIDOTE for OPIOID overdose
- Naloxone is an opioid receptor antagonist at mu, kappa, and delta receptors
- Works at the opioid receptor to displace opioid agonists
- Shows little to no agonist activity
- Shows little to no pharmacological effect in patients who have not received opioids



Naloxone nasal spray [prescribing information]. Redford, PA: Adapt Pharma, Inc.; 2015. <https://www.narcan.com/pdf/NARCAN-Prescribing-Information.pdf>.



Onset and Duration of Action

- Naloxone takes effect in 3 to 5 minutes
 - If patient is not responding in this time a second dose may need be administered
- Naloxone wears off in 30 to 90 minutes
 - Patients can go back into overdose if long acting opioids were taken (fentanyl, methadone, extended-release morphine, extended-release oxycodone)
 - Patients should avoid taking more opioids after naloxone administration so they do not go back into overdose after naloxone wears off
 - Patients may want to take more opioids during this time because they may feel withdrawal symptoms



Naloxone nasal spray [prescribing information]. Redford, PA: Adapt Pharma, Inc.; 2015. <https://www.narcan.com/pdf/NARCAN-Prescribing-Information.pdf>. Naloxone [prescribing information].

Lehto-Pearl, A, Hoegbe, Inc; 2015. <http://labeling.pfizer.com/showlabeling.aspx?label=4042>



Naloxone Safety and Tolerability

- Naloxone adverse events are **extremely rare**
- They are most likely related to **withdrawal**
- Needle stick injury
- Naloxone has **no effect**, and therefore **no adverse effects**, in people who have **no opioids** in their body



Naloxone [package insert]. Redford, PA: Adapt Pharma Inc.; 2015. *Marino FJ. Am J Emerg Med.* 1993;1(1):127-28. Pharmacy Benefits Management Services. https://www.pbm.va.gov/PBM/clinical/guidance/clinicalrecommendations/Naloxone_HQ_Renewal_X04_Recommendations_Inc_Use.pdf. Accessed March 4, 2017.



Opioid Withdrawal

- During withdrawal, there is a rebound release of norepinephrine leading to:
 - Tachycardia
 - Tremor
 - Anxiety
 - Hypertension
 - Headache
 - Sweating
 - Nausea
 - Vomiting



<https://www.drugbase.com/related/opioid/naloxone>. Accessed March 5, 2017; Downing PL. Pharmacotherapy: A Pathophysiologic Approach, 8th ed. New York: McGraw-Hill Medical; 2012.



Patient Education Steps

- Before receiving naloxone patients must have overdose prevention, identification, and response training:
 - Purpose for naloxone
 - Identifying and avoiding high risk situations for overdose
 - Risk reduction strategies
- Opioid Overdose Response
 - How to identify an overdose
 - Calling 9-1-1
 - How to administer naloxone (either IM or IN)
 - Rescue breathing
 - What to do and expect after naloxone administration (withdrawal, rescue position)



Green T, et al. *RI Med J.* 2014;31(10):29-33.



Intranasal Naloxone Kit

- 2 naloxone 1 mg/mL (2 mL) prefilled needleless syringes
- SIG: Spray one-half of syringe into each nostril upon signs of opioid overdose. Call 911. May repeat x1.
- 2 mucosal atomizer devices

VA Form Naloxone Kit #10, Sept 2014
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DIRECTIONS IN
Pharmacy

Intramuscular Naloxone

- Naloxone 0.4 mg/mL single dose vial, 2 vials
- SIG: Inject 1 mL IM upon signs of opioid overdose. Call 911. May repeat x1
- Syringe 3 mL 25G x1 inch No. 2
- SIG: Use as directed for naloxone administration
- 0.4 mg/mL
- Box of 10 (prefilled)
- Syringe device with luer-lock

https://www.ptceinjectables.com/products/Naloxone_Hydrochloride
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DIRECTIONS IN
Pharmacy

Intramuscular Auto-Injector

- Naloxone 0.4 mg/0.4 mL
- No. 1 twin pack
- SIG: Use one auto-injector upon signs of opioid overdose. Call 911. May repeat x1

Extra (generalizing information), Richmond, VA, Salix, Inc., 2014
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DIRECTIONS IN
Pharmacy

Airway Open

Rescue Breathing

If overdose is witnessed i.e., you see the person stop breathing

- Place face shield (optional)
- Tilt head back, lift chin, pinch nose
- Give **2 slow breaths**
- Chest should rise
- Give **1 breath every 5 seconds**

Chest Compressions

If overdose is UNwitnessed; i.e., you find someone not breathing

- Place heel of one hand over center of person's chest (between nipples)
- Place other hand on top of first hand, keeping elbows straight with shoulders directly above hands
- Use body weight to push straight down, at least 2 inches, at rate of 100 compressions per minute
- Place face shield (optional)
- Give 2 breaths for every 30 compressions

VA Opioid Overdose Response with Naloxone Intranasal Kit Structure
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DIRECTIONS IN
Pharmacy

Recovery Position

- If the person is breathing but unresponsive, put the person on his/her side to prevent choking if person vomits
- Because naloxone wears off in 30-90 minutes and the person may stop breathing again
 - Stay with person until emergency medical staff arrive
 - If person's breathing stops, give 2nd dose of naloxone

OPANACE Opioid Trainer's Manual
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DIRECTIONS IN
Pharmacy

Why Use Naloxone

- Not scheduled or controlled
- Fewer barriers to access
- Cannot be abused
- No euphoria from naloxone
- No effect if opioids are not present
- Effective, inexpensive, easy to administer
- Naloxone has shown success in take-home programs facilitated by community outreach programs in various states

Wheeler, L., Jones, T., Gilbert, M., Cavallaro, P. Opioid Overdose Prevention Programs Providing Naloxone to Laypersons – United States, 2014. MMWR 64(22): 634-636, June 16, 2015
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DIRECTIONS IN
Pharmacy

Conclusion

- There is an opioid epidemic in this country
- Find ways to identify patients at risk for opioid overdose
- Participate in your community based on state laws to distribute naloxone
- Various naloxone products and routes available
- Patient education is key
- Find referral sources for treatment programs

Additional Resources

- Office of National Drug Control Policy (ONDCP) supports overdose prevention and use of naloxone as part of national prevention and treatment efforts
 - <http://www.whitehouse.gov/sites/default/files/ondcp/prevent.pdf>
- SAMHSA Toolkit
 - <http://store.samhsa.gov/products/sma13-4742>
- College of Psychiatric and Neurologic Pharmacists
 - <https://cnp.org/ed/presentation/2016/naloxone-access-practical-guideline-pharmacists?view-link-0-1471882249>
- Taking Opioids Responsibly for Your Safety and the Safety of Others
 - http://www.ethics.ca.gov/foia/policy/Taking_Opioids_Responsibly_2013528.pdf
- Community Based Overdose Prevention and Naloxone Distribution Program Locator
 - <http://hopeandrecovery.org/flcatters/>
- Prescribe to Prevent
 - Patient resources and videos demonstrating overdose recognition and response, including naloxone administration
 - <http://prescribetoprevent.org/kids>
- Prescription Drug Abuse Policy System
 - <http://www.pdaps.org/>
- California Board of Pharmacy Protocol to furnish naloxone
 - http://pharmacy.ca.gov/licenses/naloxone_info.shtml
- FDA Guidance Document for the use of naloxone
 - <https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/UCM532687.pdf>