Naloxone: A Critical Tool to Fight the Opioid Crisis

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Off-label uses of naloxone will not be discussed during this presentation.

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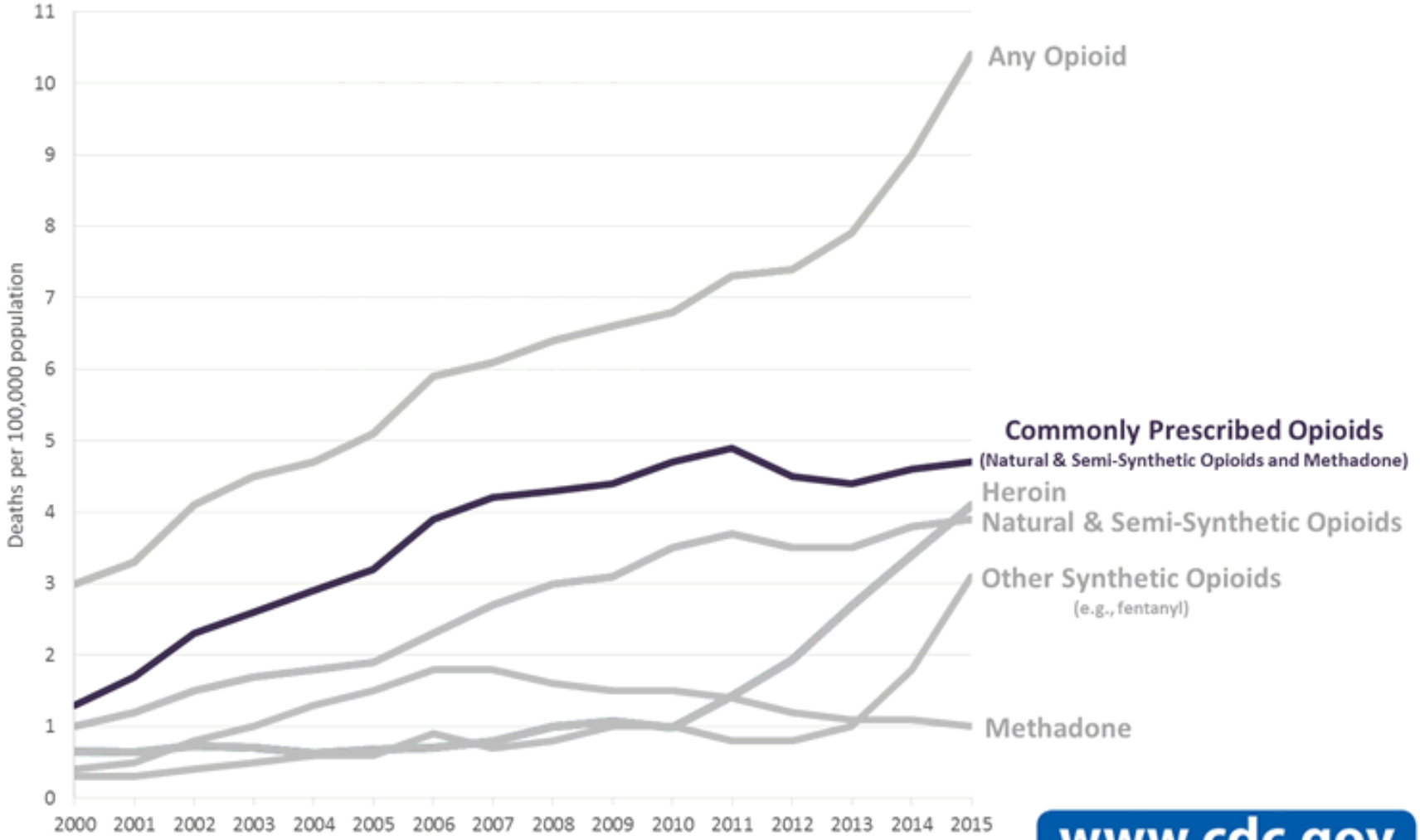
- Minnesota Board of Pharmacy
- Minnesota Poison Control System

Objectives

- State some factors that may increase risk of opioid overdose
- Identify signs and symptoms of opioid toxicity
- List pros and cons of different naloxone formulations
- Review resources patients may use to access naloxone
- Describe legal considerations for prescribing and dispensing of naloxone in Minnesota
- Discuss available naloxone and opioid resources for healthcare providers and patients

Overdose Deaths Involving Opioids, United States, 2000-2015

Deaths related to commonly prescribed opioids account for nearly half of all opioid overdose deaths in 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/.

www.cdc.gov
Your Source for Credible Health Information

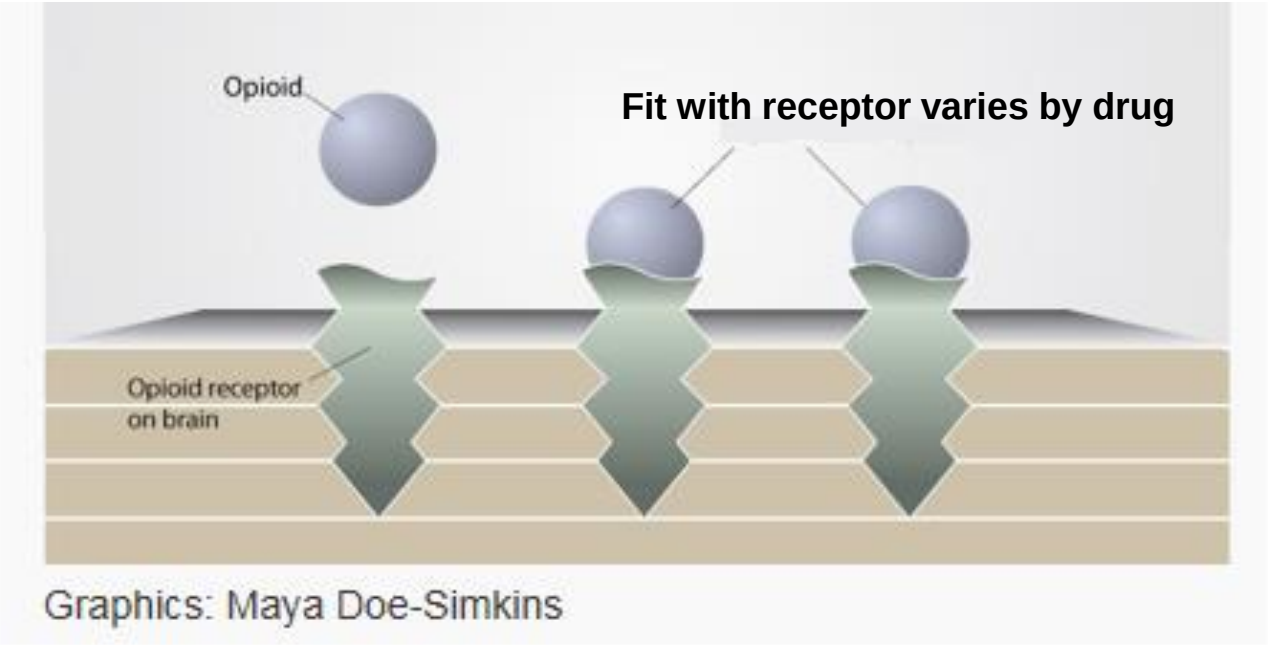
US Opioid Epidemic & Contributing Factors

- $20 billion spent annually on emergency department and inpatient care for patients with opioid poisoning

- Since 1999, more than 165,000 people have died as a result of overdose due to prescription opioids

- Addiction fails to be acknowledged and treated as a chronic medical disease and the stigma of addiction continues

Opioid Receptor Activation



- Multiple receptors including: *mu, kappa, delta, and* ORL_1
- Different effects based on specific receptor activation
- Respiratory depression may occur with *mu* receptor activation → cause of death in opioid overdose

Opioid Overdose Signs & Symptoms

Equivalent Dose Terminology

Morphine milligram equivalent (MME)

=

Morphine equivalent dose (MED)

=

Morphine dose equivalents (MDE)

*Note: CDC has a downloadable MME calculator App

CDC Guideline for Prescribing Opioids for Chronic Pain, March 2016

- When to initiate or continue opioids for chronic pain
- Opioid selection, dosage, duration, patient follow-up, and discontinuation
- Assessment of risk and addressing harms of opioid use

CDC - Opioids for Chronic Pain Highlights

- Preference for non-pharmacologic and non-opioid therapies
- Immediate-release opioid recommended over extended-release and long-acting formulations
- Lowest effective dose with appropriate duration recommended
- Insufficient evidence to recommend using immediate-release for breakthrough when already using ER/LA
- Risks vs. benefits for $\geq$ 50 morphine milligram equivalents (MME)/day
- Avoid $\geq$ 90 MME/day

CDC - Opioids for Chronic Pain Highlights

- Utilize prescription drug monitoring program
- Include urine drug screens in patient treatment plans
- Consider offering naloxone when patient is at increased risk of opioid-related harm

CDC - Opioids for Chronic Pain-Highlights
Who is at Increased Risk of Overdose?

- Higher opioid dosages: ≥ 50 MME/day
- Concurrent benzodiazepine use
- History of substance use disorder
- History of previous opioid overdose

Why Does CDC use 50 MME/day for Increased Overdose Risk?

- Retrospective cohort study looking at association of average prescribed daily opioid dose and rates of opioid overdose

When compared to patients on 1-20 MME/day:	
Patients on 50-99 MME/day	**3.7 increase in overdose risk**
Patients on ≥ 100 MME/day	**8.9 increase in overdose risk**

http://www.ncbi.nlm.nih.gov/pubmed/20083827

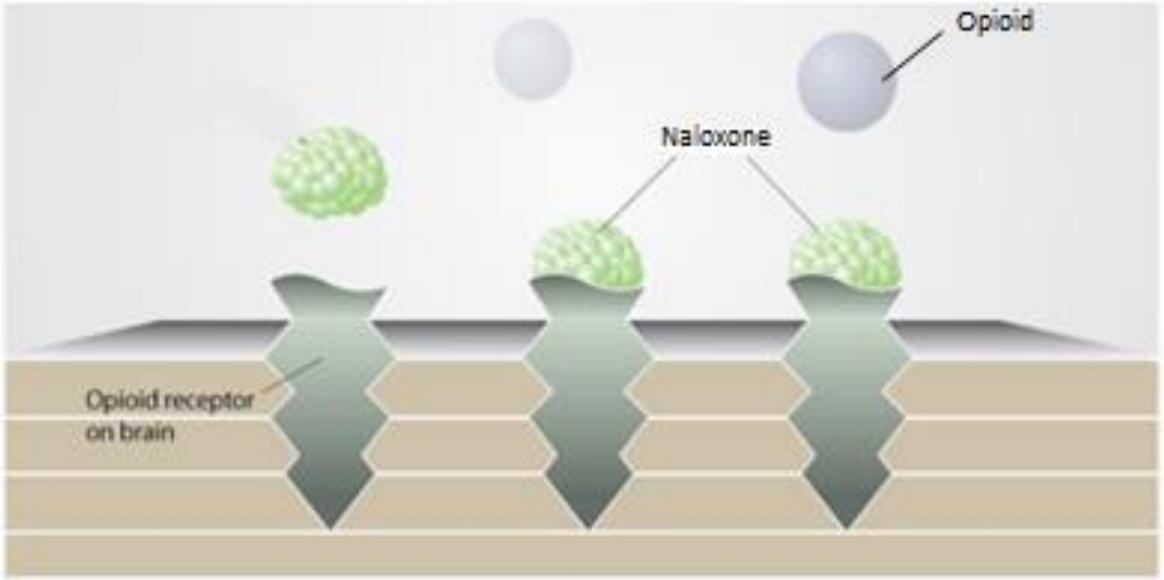
Examples of 50 and 90 MME/day

Opioid	Conversion factor	Amount equal to 50 MME/day	Amount equal to 90 MME/day
Codeine	0.15	333 mg/day	600 mg/day
Hydrocodone	1	50 mg/day	90 mg/day
Morphine	1	50 mg/day	90 mg/day
Oxycodone	1.5	33 mg/day	60 mg/day
Fentanyl transdermal	2.4	20 mcg/hr	37.5 mcg/hr
Oxymorphone	3	16 mg/day	30 mg/day
Hydromorphone	4	12.5 mg/day	22.5 mg/day
Methadone	4*	12.5 mg/day	22.5 mg/day

* Methadone conversion factor increases with total daily dose

Naloxone Mechanism

- High affinity *mu* receptor antagonist
  - Displaces opioids to reverse respiratory depression
  - Opioids still circulate in the body
- No dependence or tolerance
- No clinical effects in absence of opioids



Graphics: Maya Doe-Simkins

Comparative Pharmacokinetics of Naloxone Based on Route

	Intramuscular	Intranasal
Time to onset	2-3 minutes	2-3 minutes
Half-life	30 to 90 minutes	~120 minutes

- Similar onset of action
- Naloxone is poorly absorbed via oral route
- All patients require medical evaluation following naloxone administration
- Duration of action of most opioids is longer than the duration of action of naloxone

http://www.ncbi.nlm.nih.gov/pubmed/18641540
Package inserts for Evzio, Narcan
Micromedex for morphine and fentanyl

Acute Opioid Withdrawal Signs and Symptoms

- Headache
- Watery Eyes
- Runny Nose
- Abdominal Pain
- Nausea/vomiting
- Diarrhea
- Musculoskeletal pain
- Tremor
- Goosebumps
- Sweating
- Opioid craving
- Restlessness/Irritability

Naloxone Adverse Effects

- No expected effects if no opioids are present in the body
- Product specific reactions
  - Nasal dryness
  - IM site discomfort
- May elicit opioid withdrawal
- Pulmonary edema has been reported
  - Is a known effect of opioid toxicity and unclear if also caused by administration of naloxone
  - Rescue breaths/oxygen administration may limit its development

Naloxone Use in Special Populations

- Pregnancy: Crosses placenta, may precipitate withdrawal in fetus
- Neonatal: May cause seizures in neonates born of mothers with opioid dependence
- Lactation: Unclear excretion in breast milk, not shown to affect prolactin or oxytocin levels, poorly absorbed orally (all populations)
- Geriatric: May have increased systemic exposure due to decreased hepatic/renal/cardiac function, unclear clinical significance, no dose adjustments necessary

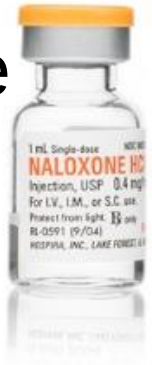
Package inserts for Evzio and Narcan

Naloxone Products

- Injectable generics: by Hospira and Mylan
- Auto-injector branded: Evzio® by Kaléo
- Injectable generic given intranasally: by IMS/Amphastar
- Intranasal branded: Narcan® by Adapt Pharma

Naloxone Intramuscular (IM) Injection

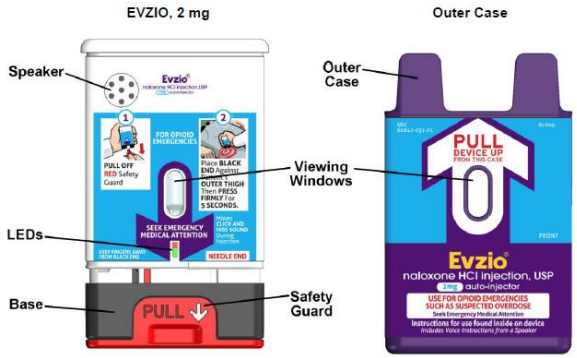
- Dose: 0.4 mg/mL
- May be vials or ampules
- Each kit contains 2 or 3 vials
- Draw medication from vial and inject one mL into shoulder or thigh muscle
- Repeat in 2-3 minutes if minimal or no response
- More difficult to use
- Lowest in cost



http://prescribetoprevent.org/wp2015/wp-content/uploads/Naloxone-product-chart.16_01_21.pdf
https://www.hospira.com/en/products_and_services/drugs/NALOXONE_HYDROCHLORIDE

Evzio® Auto-Injector

- Dose: 2mg/0.4mL
- Previous 0.4mg/0.4mL dose no longer manufactured
- Electronic voice instruction system
- Each kit contains two auto-injectors and a trainer device
- May give intramuscularly or subcutaneously
- Inject contents of one device into outer thigh and **hold in place**
- Repeat with second device in 2-3 minutes if minimal or no response
- Easiest injection formulation to use
- Most expensive



Evzio [package insert]. Richmond, VA : Kaleo Inc. 2017.

Evzio® Administration

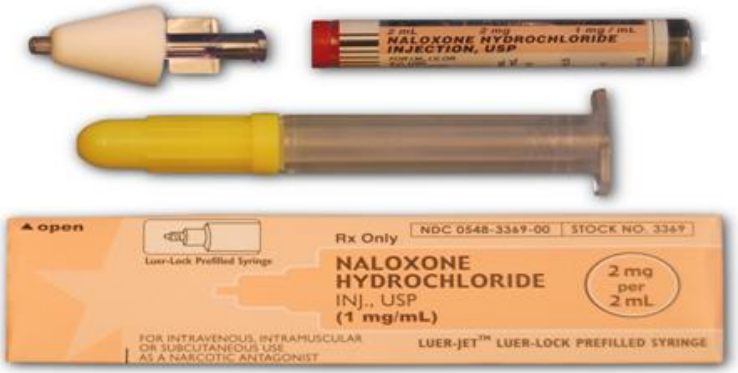
Figure B

Figure C

Figure D

Naloxone
Nasal Atomizer with Prefilled Syringe

- Dose: 2 mg/2 mL prefilled syringe
- Dispensed with atomizer for intranasal administration
- Each kit may include 1 or 2 syringes
- Attach atomizer and assemble syringe
- Spray 1 mg (1mL=1/2 of syringe) into each nostril
- Repeat after 2-3 minutes if minimal or no response
- Easier to use than injection
- More difficult to use than brand name intranasal product
- Cheaper than brand name intranasal product



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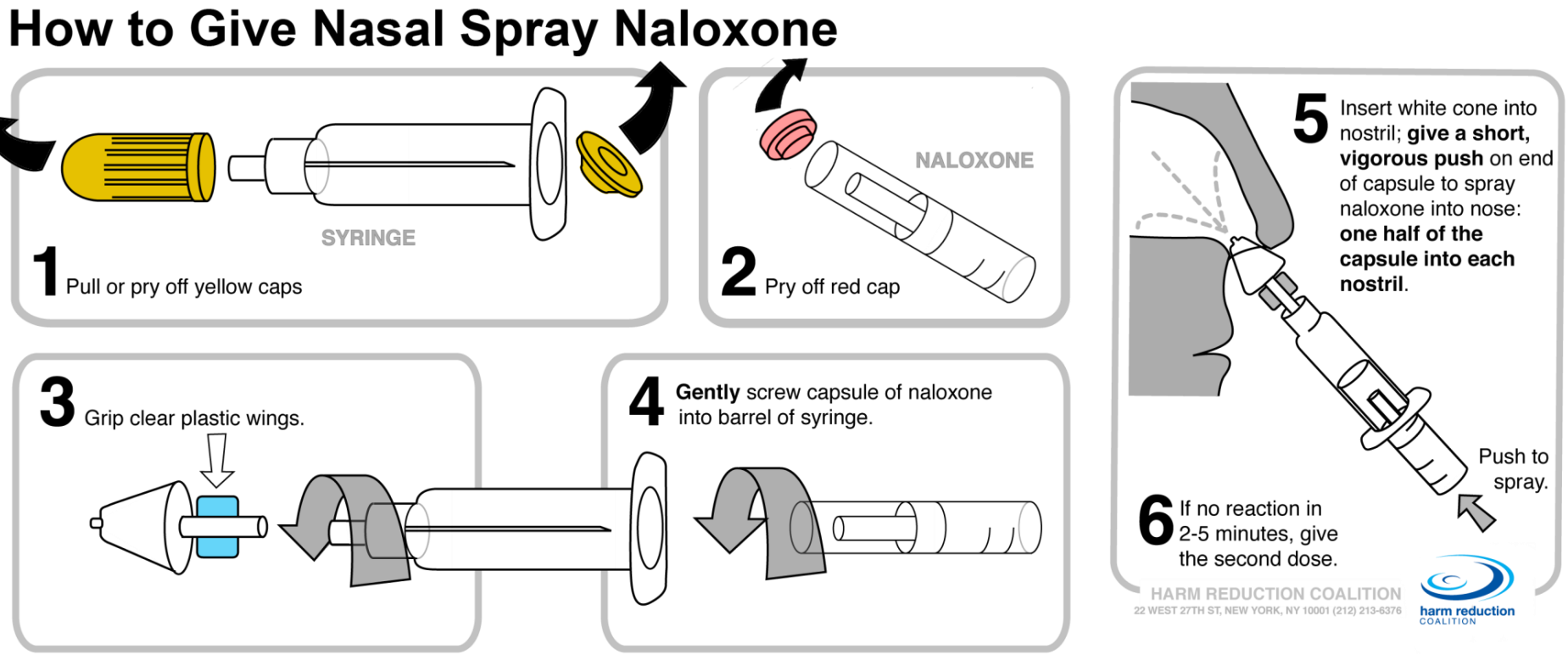
http://ireta.org/2013/08/07/drug-overdose-in-our-backyard-is-breeding-home-grown-solutions/

Naloxone Administration
Nasal Atomizer with Prefilled Syringe



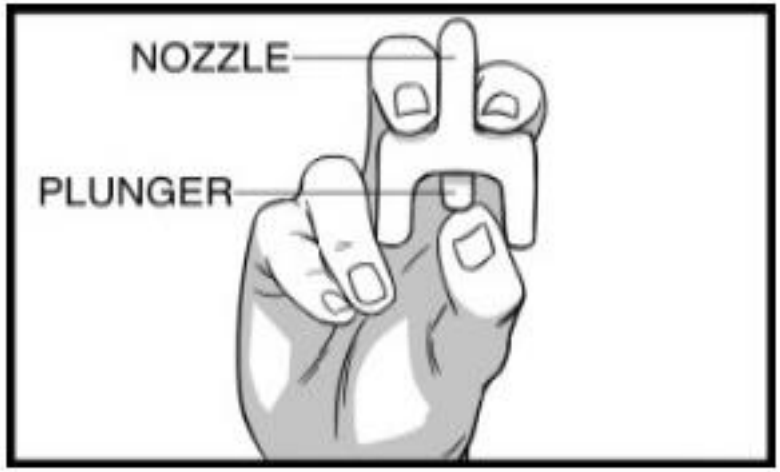
http://harmreduction.org/issues/overdose-prevention/overview/overdose-basics/responding-to-opioidoverdose/administer-naloxone/

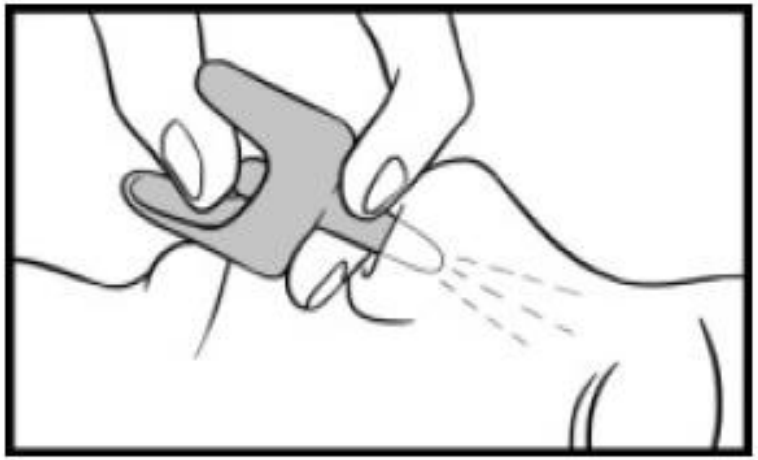
Narcan® Intranasal Device

- Dose: 4 mg/0.1 mL per device
- Each kit contains 2 devices
- Spray contents of 1 device (0.1 mL) into 1 nostril
- Repeat with second device into other nostril after 2-3 minutes if minimal or no response
- Easiest to use
- More expensive than generic prefilled syringe formulation with atomizer
- Discounted pricing available to community partners

http://www.narcan.com/pdf/NARCAN-Quick-Start-Guide.pdf
http://prescribetoprevent.org/wp2015/wp-content/uploads/Naloxone-product-chart.16_01_21.pdf

Narcan ® Nasal Spray Administration





http://www.narcan.com/pdf/NARCAN-Quick-Start-Guide.pdf

Naloxone Product Summary

	IM injection	Evzio®	Nasal atomizer	Narcan®
Strength	0.4 mg/mL	2 mg/0.4 mL	1 mg/mL	4 mg/0.1 mL
Total naloxone per kit	0.8-1.2 mg	4 mg	2-4 mg	8 mg
Rx & quantity	# 2-3 single-use 1 mL vials	#1 2 device pack	#2 2 mL syringes + atomizers	#1 2 device pack
Dosage	Inject 1 mL (0.4 mg) Repeat in 2-3 min if needed	Inject 0.4 mL (1 device) Repeat in 2-3 min if needed	Spray 1 mL (1/2 of syringe) into each nostril Repeat in 2-3 min if needed	Spray 0.1 mL (1 device) into 1 nostril Repeat in 2-3 min (with 2nd device into other nostril) if needed
Cost	$	$$$	$$	$$
Unique considerations	Assembly required	Not covered by most insurance, Voice instructions	Assembly required	Easier to use than atomizer, insurance coverage improving

http://prescribetoprevent.org/wp2015/wp-content/uploads/Naloxone-product-chart.16_01_21.pdf

Addressing Naloxone Myths

Myth #1

Availability of naloxone encourages risky opioid use behavior.

Addressing the Myth

- No data exists to support the concern that naloxone encourages risky opioid use behavior.

Addiction

- Is a disease that causes continued risky opioid use behavior despite the consequences
- Is not cured by naloxone
- Naloxone saves lives, providing an opportunity to consider addiction treatment

- Walley *et.al.* (2013) in Massachusetts showed education of opioid users at risk of overdose, and their family and friends, had a significant reduction (27-46%) in the adjusted rate ratio of opioid overdose.

- Systematic review (McDonald *et al.* 2016) showed that take-home naloxone programs decreased overdose mortality in program participants and in the community.

- Bird *et al.* (2015) suggests that opioid overdose related deaths can be decreased by at least 25% through opioid education and naloxone distribution services for those at risk following prison release or hospital discharge.

Walley AY, Xuan Z, Hackman HH, et al. (2013)
Bird , et al. (2015)
McDonald R, Strang, J. Systemic Review (2016)

- Wagner *et al.* (2010) found in a study of injectable drug users, 53% reported decreased drug use 3 months after participating in an opioid education and naloxone distribution program.

- Doe-Simkins *et.al.* (2014) showed no change in heroin use 30 days after take-home naloxone.
  - 38% reported decreased use
  - 35% reported increased use
  - 27% reported no change in their use
  - p = 0.52

. Wagner, KD, Valente TW, *et al.* 2010.

Doe-Simkins M., Quinn E., *et. al*. 2014.

Myth #2

It is difficult to offer naloxone to patients without offending them.

Addressing the Myth

- Offering naloxone can be done in a non-judgmental manner

- Naloxone should be offered to any individual who might benefit from its availability.
  - This could include those at risk for opioid overdose or those individuals who may be present to administer it

Addressing the Myth

- Important to convey safety perspective
  - It is recommended that naloxone be available to individuals using a higher than 50 MME dose or who take medications that may have harmful interactions
- Consider it like epinephrine for anaphylaxis or glucagon for hypoglycemia
- Goal is that it is never needed but that it is available

Supporting Referral to Treatment

Provide non-judgmental stance	“Thank you for sharing your concern. I have resources to help you.”
Assess	“Do you have a primary care doctor, nurse, counselor, case manager, or care coordinator who you can talk to more about this?”
Refer	Ensure they have a point person to call and schedule an appointment. If no clinic, offer to look up the clinic nearest to their home (use the referral list provided for treatment providers if needed).
Ask Permission	“Would it be okay if we looked at a list of resources together to see what would be the best fit?”

Supporting Referral to Treatment

- SAMHSA National Helpline
  - Treatment referral routing service
  - 1-800-622-HELP (4357)
  - Can be used to connect to local treatment facilities
- Fast Tracker
  - For identifying mental health and substance use treatment facilities with openings
  - MDH Opioid Dashboard -> Use Misuse -> Substance Use Disorder -> Resources Tab

Myth #3

The risks of potential harm to the patient and others during acute opioid withdrawal are too high to use naloxone.

Addressing the Myth

- Generally, opioid withdrawal is not life-threatening but is often very uncomfortable
- More severe adverse effects typically occur following more “severe poisonings”
- Reports of person receiving naloxone becoming agitated or combative

Buajordet, I.m Naess, A. et.al. 2006.

Legal Considerations

Legal protection exists for health care providers prescribing and dispensing naloxone.

Statutes Vary State to State

- As examples, MN, WI, and ND provide criminal and civil liability immunity to prescribers and pharmacists who prescribe, distribute, dispense, and administer naloxone lawfully

  - MN Stat § 604A.04
  - WI Act 200, Section 9.448.037 and 14.450.11
  - ND Century Code Section 23-01-42

MN Statute 151.37 Sec 3

Emergency medical responders, police officers, and staff of designated community programs may be authorized to administer opiate antagonists

- Authorized by prescribers
- Standing order or protocol
- Individual must be trained to recognize signs of opiate overdose and use of opiate antagonists

Minnesota Statutes

- “Good Samaritan” or “Steve Law”
- Non-health professional acting in good faith may administer an opiate antagonist and be immune from criminal prosecution as well as not be liable for civil damages
  - MN Statute 151.37 Sec 3
  - MN Statute 604A.04
- Also applies to licensed health professional who prescribes, dispenses, distributes, or administers an opiate antagonist directly or by standing order
  - Minnesota Statute 151.37 Subd. 12
  - MN Statute 604A.04

Methods to Access Naloxone

- Minnesota
  - Valid patient prescription direct to patient from prescriber
  - Organizations: RAAN, Steve Rummler HOPE Network, Adapt Pharmaceuticals
  - Pharmacists may have protocol agreement from authorized prescribers
    - Any MN licensed prescriber (MD/DO, APRN, PA)

Minnesota Opiate Antagonist Protocol

- Any Minnesota licensed prescriber (MD/DO, APRN, PA)
  - MN Protocol or other individualized template

- Community Health Board Medical Consultant
- County Public Health Medical Consultant
- Minnesota Department of Health Medical Director

Minnesota Opiate Antagonist Protocol

- Template offered on Board of Pharmacy Website
- Written in response to the statutes presented
- Content areas include:
  - Requirements for implementation
  - Educational resources for pharmacists
- Submit request to MDH if requesting MDH medical director as prescriber of record

Prescribing and Dispensing Naloxone

Education for Prescription Recipient

- Identify signs of opioid toxicity
- For inadequate breathing such as slow rate, gurgling respirations, or apnea
  - Provide rescue breaths using barrier device
  - Call 911
  - Administer naloxone
- All patients need transport to a medical facility

Training video: https://www.youtube.com/watch?v=tGdUFMrCRh4
Training module: http://training.mnpoison.org/training-courses/training-course/

The Importance of Language

- Stigma is a major barrier to seeking help for substance use disorder
  - Of the 23 million Americans who meet criteria for a substance use disorder each year, only ~11% access treatment
  - Words that moralize and criminalize contribute
  - “Dirty” urine drug test vs. “positive” urinalysis
  - “Drug seeker” & “junkie” versus person with substance use disorder

https://www.drugabuse.gov/publications/drugfacts/treatment-statistics

“Stop Talking Dirty” http://www.amjmed.com/article/S0002-9343(14)00770-0/abstract

Summary

- Stigma kills.
- Multiple factors contributed to this epidemic, we need to work together to end it.
- Several formulations of naloxone are available.
- There are several ways patients and third parties can access naloxone.
- MN statutes offer legal protection for prescribers and dispensers of naloxone.
- Naloxone saves lives.

Resources

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Questions?

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