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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• Rural AIDS Action Network (RAAN)
• University of Minnesota College of Pharmacy
• Minnesota Department of Health
• Minnesota Pharmacists’ Association
• 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.

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

Graphics: Maya Doe-Simkins
**Opioid Overdose Signs & Symptoms**

- **Breathing will be slow or absent**
- **Lips and nails are blue**
- **Person is not moving**
- **Person may be choking**
- **You can hear gurgling sounds or snoring**
- **Can’t be woken up**
- **Skin feels cold and clammy**
- **Pupils are tiny**
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 > 50 morphine milligram equivalents (MME)/day

• Avoid > 90 MME/day

Centers for Disease Control and Prevention
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

<table>
<thead>
<tr>
<th>When compared to patients on 1-20 MME/day:</th>
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<tbody>
<tr>
<td>Patients on 50-99 MME/day</td>
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<tr>
<td>Patients on ≥ 100 MME/day</td>
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</tbody>
</table>

Examples of 50 and 90 MME/day

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

* 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
Comparative Pharmacokinetics of Naloxone Based on Route

<table>
<thead>
<tr>
<th></th>
<th>Intramuscular</th>
<th>Intranasal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to onset</td>
<td>2-3 minutes</td>
<td>2-3 minutes</td>
</tr>
<tr>
<td>Half-life</td>
<td>30 to 90 minutes</td>
<td>~120 minutes</td>
</tr>
</tbody>
</table>

- 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

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

http://www.evzio.com
http://druginserts.com
https://www.hospira.com
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

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® 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 (1 mL = 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

Naloxone Administration
Nasal Atomizer with Prefilled Syringe

How to Give Nasal Spray Naloxone

1. Pull or pry off yellow caps

2. Pry off red cap

3. Grip clear plastic wings.

4. Gently screw capsule of naloxone into barrel of syringe.

5. Insert white cone into nostril: give a short, vigorous push on end of capsule to spray naloxone into nose: one half of the capsule into each nostril.

6. If no reaction in 2-5 minutes, give the second dose. Push to spray.

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

Narcan® Nasal Spray Administration

# Naloxone Product Summary

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

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)  
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
- \( p = 0.52 \)
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

<table>
<thead>
<tr>
<th>Provide non-judgmental stance</th>
<th>“Thank you for sharing your concern. I have resources to help you.”</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assess</td>
<td>“Do you have a primary care doctor, nurse, counselor, case manager, or care coordinator who you can talk to more about this?”</td>
</tr>
<tr>
<td>Refer</td>
<td>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).</td>
</tr>
<tr>
<td>Ask Permission</td>
<td>“Would it be okay if we looked at a list of resources together to see what would be the best fit?”</td>
</tr>
</tbody>
</table>
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
“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
References

• “Administer Naloxone Overdose Response” Harm Reduction Coalition

• Adapt Pharmaceuticals Naloxone training link: https://www.youtube.com/watch?v=tGdUFMrCRh4


• "Calculating Total Shareholder Return." Centers for Disease Control and Prevention


• Dowell, Deborah, MD, Tamara Haegerich M., PhD, and Roger Chou, MD. "CDC Guideline for Prescribing Opioids for Chronic Pain—United States, 2016." JAMA 315.15 (2016): 1624


• Minnesota Poison Control Center Naloxone Module: http://training.mnpoison.org/training-courses/training-course/


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- www.shatterpoof.org
Questions?

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