Naloxone: Access, Pharmacology, Practicality and Politics

Jeffrey Fudin, B.S., Pharm.D., FCCP, FASHP
Diplomate, American Academy of Pain Management
Clinical Pharmacy Specialist & PGY2 Pain Residency Director;
Stratton VA Medical Center

East Tennessee State University, Common Misconceptions in Prescribing for Chronic Pain
Friday the 13th (November)

Adjunct Affiliations;
UCONN School of Pharmacy, Albany College of Pharmacy & Health Sciences,
SUNY/University at Buffalo, Western New England University

Disclosure Statement
• Astra Zeneca (Speakers Bureau, Advisory Board)
• DepoMed (Advisory Board)
• Endo (Consultant)
• Kaléo (Speakers Bureau, Advisory Board)
• KemPharm (Consultant)
• Millennium Health, LLC (Speakers Bureau, Advisory Board, Expert Witness)
• Practical Pain Management Development of Online Opioid Conversion Calculator
• Remitigate, LLC (Founder, Owner)
• Scilex Pharmaceuticals (Consultant)
• Zogenix (Consultant)
• Faculty (PainWeek; PainWeekEnds)

Audience Poll
• Who has prescribed or recommended a home naloxone rescue kit or auto injector for a patient? Yes / No
• Who has experience with administering a naloxone rescue kit or auto injector? Yes / No
Learning Objectives

- Differentiate between intranasal, intramuscular (traditional and auto-injector), and intravenous routes of administration
- Identify unexpected risks for opioid-induced respiratory depression
- Integrate RIOSORD analysis into decision making when considering dual therapy
- Communicate with patients and caregivers regarding a plan of action when faced with an OIRD casualty

US Prescription Opioid-Related Deaths

- Approximately 16,000 deaths in 2014 from RX opioids
- Approximately 9,000 deaths in 2014 from heroin
- according to the CDC (center for Disease Control)
  - ~85% unintentional = 13,600 deaths
    - ~37 unintentional deaths/day
    - ~1 unintentional death every 40 minutes
- Children/Infant Deaths
  - ~3300 in 2014 (down from 5187 in 2004)

Life-Threatening Opioid-Induced Respiratory Depression Facts / Numbers

- ~60% of patients taking opioids were prescribed potentially dangerous medication combinations (e.g., opioid + a benzodiazepine)
  - Two-thirds by ≥2 HCPs
- ~20%-30% of opioid-related deaths involve alcohol
  - Alcohol may cause some extended-release formulations to rapidly release opioid
- In 2014, ~3,000 children aged ≤5 years were admitted to the ED for accidental opioid ingestion

References:
**Patient profile: Pain Clinic Patient**

- 47-year-old female with 3 failed back surgeries & DM Type II
  - 5'6" tall and weighs 200 lbs.
- Medication regimen at pain clinic (for last 2 years):
  - Oxycodone ER 30mg PO q12h and oxycodone IR 10mg PO q4h PRN
- Do you think this patient is at elevated risk (Low, Med, High)?
  - She has obstructive sleep apnea
  - Medications prescribed by PCP:
    - Lorazepam 0.5 mg q8h for anxiety
  - What if the patient is:
    - Placed of pregabalin 75mg PO TID (endocrine)
    - Placed on a macrolide antibiotic? (PCP)
    - Goes on a grapefruit diet?
    - Is an ultra-‐rapid 2D6 metabolizer?
    - Develops an URTI, takes OTC meds?

**INTRODUCTION**

**Opioid Overdose**

- For every 1 opioid-related death, there are 10 treatment admissions for abuse, 32 emergency department visits, 130 persons that abuse or are dependent on opioids, and 825 nonmedical users.
- Prescription opioid misuse and abuse resulted in approximately 660,000 emergency department visits in 2010, double the number seen in 2004.

Recommendations That Naloxone Be Readily Accessible

SAMHSA: "With proper education, patients on long-term opioid therapy and others at risk for overdose may benefit from having a naloxone kit containing naloxone, syringes and needles or prescribing Evzio® which delivers a single dose of naloxone via a handheld auto-injector that can be carried in a pocket or stored in a medicine cabinet to use in the event of known or suspected overdose."

"The AMA has been a longtime supporter of increasing the availability of naloxone for patients, first responders and bystanders who can help save lives."

Risks for Opioid Overdose

- Substance abuse
- High daily morphine equivalent dose (MDE)
- Gender
- Concurrent use of benzodiazepines and/or alcohol with or without other sedative-hypnotics
- Chronic kidney and/or liver impairment
- Sleep apnea
- Accidental exposure to young children in the home
- Age
- Chronic lung disease


Naloxone for Opioid Reversal

- Naloxone is a potent, competitive mu-opioid receptor antagonist
- Reverses opioid-induced respiratory depression
- Since 1996, overdose education and naloxone distribution (OEND) programs have offered naloxone and other opioid overdose educational services
- OEND programs are supported both in the US and abroad

Pharmacology

- Pure opioid mu-receptor agonist
- Partial opioid agonist
- Partial opioid agonist/antagonist
- Opioid receptor antagonist

Opioid Receptor Pharmacology 101


Signs of Opioid Overmedication

- Unusual sleepiness, drowsiness, or difficulty staying awake despite loud verbal stimulus or vigorous sternal rub
- Mental confusion, slurred speech, intoxicated behavior
- Slow or shallow breathing
- Pinpoint pupils
- Slow heartbeat, low blood pressure
- Difficulty waking the person from sleep

Signs of Opioid Overdose

- Extreme sleepiness, inability to awaken verbally or upon sternal rub
- Breathing problems (ranges from slow to shallow breathing)
- Fingernails or lips turning blue/purple
- Pinpoint pupils
- Slow heartbeat and/or low blood pressure

What were Scarecrow, Lion, Dorothy and friends missing in the poppy field?

- Scarecrow was missing a brain
- Lion was missing courage
- Dorothy was missing home!
- All were missing naloxone!

Intramuscular (IM) Naloxone Rescue Kit
**Directions for Use of IM Naloxone Kit**

**HOW TO GIVE INTRAMUSCULAR NALOXONE**

1. Place the drug in a syringe, remove cap from syringe and insert needle.
2. Insert needle through skin with needle held parallel to skin. Insert needle horizontally into the skin for deep injections.
3. Inject 1 ml of naloxone subcutaneously at the site of injection. Avoid injecting at the site of injection.

**IT INSTRUCTIONS**

- Have a kit available at the time of injection.
- Have a kit available at the time of administration.
- Have a kit available at the time of administration.
- Have a kit available at the time of administration.
- Have a kit available at the time of administration.

---

**Intranasal (IN) Naloxone Rescue Kit**


---

**Directions for Use of IN Naloxone Kit**

**HOW TO GIVE INTRANASAL NALOXONE**

1. Place the drug in a syringe, remove cap from syringe and insert needle.
2. Insert needle through skin with needle held parallel to skin. Insert needle horizontally into the skin for deep injections.
3. Inject 1 ml of naloxone subcutaneously at the site of injection. Avoid injecting at the site of injection.

**IT INSTRUCTIONS**

- Have a kit available at the time of injection.
- Have a kit available at the time of administration.
- Have a kit available at the time of administration.
- Have a kit available at the time of administration.
- Have a kit available at the time of administration.
Naloxone Auto Injector (AI)

Directions for Use of AI Naloxone

How to Use EVZIO

1. Hold the EVZIO from the outer case.
2. Unlock the safety clip.
3. Insert one end of the needle into the neck vein under the jaw, insert the needle into the neck vein under the jaw, or insert the needle into the abdomen under the belly button. The needle should be perpendicular to the skin in all directions.


Directions for Use of AI Naloxone (continued)

If you give EVZIO to an infant or child under 1 year old, place the middle of the needle against the area where you can safely give EVZIO and continue to push until you feel the needle penetrate the skin.

If you give EVZIO to a child older than 1 year old, place the middle of the needle against the area where you can safely give EVZIO and continue to push until you feel the needle penetrate the skin.


Important Steps with ALL Forms of Naloxone Administration

1. If the person is unresponsive, give naloxone
2. Call 911
3. Assess the person’s airway
   1. Rescue breathing (if overdose witnessed)
   2. Chest compressions (if overdose is unwitnessed)
4. Consider repeat naloxone administration
5. Place the person in the recovery position
   1. Put the person on his/her side to prevent choking if vomiting occurs

Naloxone Legislation

2001: New Mexico amends state law
As of May 8, 2015: 33 other states + Washington, DC have followed suit


Naloxone Good Samaritan Laws

2007: New Mexico amends state law
As of April 10, 2015: 25 other states + Washington, DC have followed suit

Edwards et al

- 42 patients 18-65 years of age were randomly assigned to administer a simulated dose of IN or AI naloxone that involved 3 phases
  - Phase 1: no naloxone training
  - Phase 2: training from healthcare professional on naloxone use
  - Phase 3: 7-8 days later participants returned to administer a naloxone dose with no additional training


Edwards et al

- Phase 1
  - 90.5% of participants administering AI naloxone were successful compared to 0% of IN users
    - P<0.0001
- Phase 2
  - 100% of participants were successful in both groups
- Phase 3
  - 100% of participants giving AI naloxone were successful while 57.1% of IN were successful
    - P<0.0001


Kelly et al

- 155 patients suspected of having opioid overdose were administered naloxone
  - 71 patients received IM naloxone
  - 84 patients received IN naloxone
- 82% of patients administered IM naloxone had more than 10 spontaneous respirations per minute within 8 minutes compared to 63% of IN naloxone (p=0.0173)

**IM Route**

- Formulation manufactured for this route
- Similar response rates vs. IV naloxone in prehospital settings
- Fewer steps to assemble
- Simpler for some to use (diabetics, others familiar with using injections)

**Al Administration**

- Pocket-sized (convenient and portable)
- Easy to use, even without prior training
- Retractable needle may reduce accidental needle sticks and transmission of blood-borne virus
- No needle visibility which may appeal to those with aversion to sight of needles
- Storage in wider temperature range

**Time to “Response”**

- IM naloxone: mean 6-8 min
- AI naloxone: mean 6-8 min
- IN naloxone: Similar or longer by 2 min than IM
  - Range 2-13 min
Summary

• AI shown to be relatively easy to use even without prior training in English-speaking individuals
• IM or AI naloxone may provide a faster “time to response” compared to IN naloxone
• IM naloxone has fewer assembly steps
• AI naloxone provides voice instruction and even if voice instruction fails, label instructions can be followed on the cartridge

CON: NALOXONE IM/AUTO-INJECTOR VS. INTRANASAL

IN Route

- Rapid onset
- High bioavailability
- Delivery to CNS via olfactory mucosa
- Avoids first pass metabolism
- Eliminates need for needles
- Nose easily accessible

Efficacy of Intranasal Naloxone

- Barton et al
  - 95 patients were included in the study with altered mental status, being found down, or suspected opioid overdose
  - 52 patients responded to IN or IV naloxone
  - 43 patients responded to IN naloxone
  - 7 patients required IV doses following IN naloxone due to recurrent somnolence or slow response
  - 9 patients only responded to IV naloxone


Exposure to Bloodborne Pathogens

- IN route could be considered as a safer route of naloxone administration in high-risk patients encountered in the field by paramedics and first-responders
- Injecting drug users have higher risk of infection with blood-borne viruses
  - Human immunodeficiency virus (HIV)
  - Hepatitis B (HBV)
  - Hepatitis C (HCV)

Risk after Occupational Exposure

- Risk of infection after an occupational exposure:
  - HBV: in an unvaccinated person, 6-30% risk from a single needlestick or cut exposure
  - HCV: 1.8% risk from a single needlestick or cut exposure
  - HIV: 0.3% risk from a single needlestick or cut exposure

Kerr et al

- Study aim: determine the effectiveness and safety of concentrated (2mg/mL) IN naloxone vs. IM naloxone in the pre-hospital setting
- N = 172 patients (IN naloxone: 83, IM naloxone: 89)
- No significant difference found in patients achieving an adequate response within 10 minutes of initial naloxone treatment
  - IN naloxone: 60 (72.3%)
  - IM naloxone: 69 (77.5%)
- No significant difference found in the mean response time between groups
  - IN naloxone: 8.0 min
  - IM naloxone: 7.9 min


Patient Attitudes and Preferences

- N = 99 injecting drug users (IDUs) interviewed regarding peer naloxone distribution
- Majority of the sample reported positive attitudes toward naloxone distribution
  - Good to very good idea: 89%
- 92% said they were willing to participate in a related training program
- 74% preferred IN administration compared to other routes


Summary

- IN naloxone eliminates the use of needles
  - Reduce risk of occupational exposure in paramedics and first responders
  - IDUs prefer the IN route of administration
- IN naloxone is administered through the nose, which is often easily accessible
- IN naloxone mean response time is not statistically significantly different from IM naloxone
How do I know who should get in-home naloxone?

**SELECTION OF “AT RISK” PATIENTS**

### RIOSORD Risk Index for Overdose or Serious Opioid-induced Respiratory Depression

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Risk Score</th>
<th>All Patients (n = 8,617)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Average Predicted Probability (95% CI)</td>
</tr>
<tr>
<td>1</td>
<td>1-24</td>
<td>16.0 (9.8%)</td>
</tr>
<tr>
<td>2</td>
<td>25-39</td>
<td>14.0 (8.7%)</td>
</tr>
<tr>
<td>3</td>
<td>40-59</td>
<td>12.0 (7.4%)</td>
</tr>
<tr>
<td>4</td>
<td>60-79</td>
<td>10.0 (6.1%)</td>
</tr>
<tr>
<td>5</td>
<td>80-99</td>
<td>8.0 (4.8%)</td>
</tr>
<tr>
<td>6</td>
<td>100-119</td>
<td>6.0 (3.6%)</td>
</tr>
<tr>
<td>7</td>
<td>120-139</td>
<td>4.0 (2.4%)</td>
</tr>
<tr>
<td>8</td>
<td>140-159</td>
<td>2.0 (1.2%)</td>
</tr>
<tr>
<td>9</td>
<td>160-179</td>
<td>0.0 (0.0%)</td>
</tr>
</tbody>
</table>

**RIOSORD** Risk Index for Serious Prescription Opioid-induced Respiratory Depression or Overdose in Veterans’ Health Administration Patients.


---

**Prediction**

<table>
<thead>
<tr>
<th>Risk Class</th>
<th>Risk Score (Points)</th>
<th>All Patients (n = 8,617)</th>
<th>Average Predicted Probability (95% CI)</th>
<th>Observed Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1-24</td>
<td>16.0 (9.8%)</td>
<td>0.02 (0.02, 0.03)</td>
<td>0.02 (0.02, 0.03)</td>
</tr>
<tr>
<td>2</td>
<td>25-39</td>
<td>14.0 (8.7%)</td>
<td>0.01 (0.01, 0.02)</td>
<td>0.01 (0.01, 0.02)</td>
</tr>
<tr>
<td>3</td>
<td>40-59</td>
<td>12.0 (7.4%)</td>
<td>0.01 (0.01, 0.02)</td>
<td>0.01 (0.01, 0.02)</td>
</tr>
<tr>
<td>4</td>
<td>60-79</td>
<td>10.0 (6.1%)</td>
<td>0.00 (0.00, 0.01)</td>
<td>0.00 (0.00, 0.01)</td>
</tr>
<tr>
<td>5</td>
<td>80-99</td>
<td>8.0 (4.8%)</td>
<td>0.00 (0.00, 0.01)</td>
<td>0.00 (0.00, 0.01)</td>
</tr>
<tr>
<td>6</td>
<td>100-119</td>
<td>6.0 (3.6%)</td>
<td>0.00 (0.00, 0.01)</td>
<td>0.00 (0.00, 0.01)</td>
</tr>
<tr>
<td>7</td>
<td>120-139</td>
<td>4.0 (2.4%)</td>
<td>0.00 (0.00, 0.01)</td>
<td>0.00 (0.00, 0.01)</td>
</tr>
<tr>
<td>8</td>
<td>140-159</td>
<td>2.0 (1.2%)</td>
<td>0.00 (0.00, 0.01)</td>
<td>0.00 (0.00, 0.01)</td>
</tr>
<tr>
<td>9</td>
<td>160-179</td>
<td>0.0 (0.0%)</td>
<td>0.00 (0.00, 0.01)</td>
<td>0.00 (0.00, 0.01)</td>
</tr>
</tbody>
</table>

**Model performance**

R^2 = 0.286

Reamer et al. guideline of fit statistics.
Non-VA population

- Retrospective case-control study of 18,365,497 patients IMS
- PharMetrics Plus integrated commercial health plan opioid claims in the U.S.
- 7,234 patients experience OSORD
- OSORD found to be associated with:
  - ER/LA opioid formulations
  - Daily morphine equivalence dose
  - Interacting medications
  - ED visits and hospital admissions
  - Coexisting health conditions

REBUTTAL PRO: NALOXONE IM/AUTO-INJECTOR VS. INTRANASAL
Intranasal Route

- Injectable formulation of naloxone
- Administered by Mucosal Atomization Device
- FDA approved drug via an FDA approved medical device but in a non-FDA approved indication
- How does a pharmacist dispensing this drug treat it and bill for it?


Intranasal Limitations

- Formulation not concentrated for retention
- Delivery is larger than typically used
- Loss of drug from the nasal cavity
- Integrity of nasal mucosa
- Involves more steps to assemble
  - IM kit: 3 steps
  - AI cartridge: 3 steps
  - IN kit: 5 steps, required dexterity and manipulation


Kerr et al

- Study aim: determine the effectiveness and safety of concentrated (2mg/mL) IN naloxone vs. IM naloxone in the pre-hospital setting
- N = 172 patients (IN naloxone: 83, IM naloxone: 89)
- Rescue naloxone administered more often to patients in IN naloxone group (18.1%) compared to IM naloxone group (4.5%)
  - Statistically significant difference (OR 4.8 (95% CI 1.4, 16.3))

Contraindications to IN Naloxone

Contraindications
- Nasal septal abnormalities
- Nasal trauma
- Epistaxis
- Excessive nasal mucus
- Intranasal damage caused by cocaine use

Relative contraindications
- Severe hypotension
- Recent use of vasoconstrictors


REBUTTAL CON: NALOXONE IM/AUTO-INJECTOR VS. INTRANASAL

Cost of Auto-injector
- Naloxone auto-injector $450-$600
- Drug company is offering discount program
- Naloxone otherwise $7 per dose

Green et al 2014

- Case report of 2 patients recently released from prison who self-administered naloxone to reverse heroin overdose
  - Patient A
    - Trained friend who used with how to use IN naloxone
    - Friend administered 1 mL of IN naloxone which allowed patient to administer remaining 1 mL
  - Patient B
    - Left naloxone kit and drug dealers house where she used heroin
    - When she regained partial consciousness, requested kit
    - Patient assembled and administered 2 IN naloxone doses


Kelly et al 2005

- Randomized, unblended trial comparing IM and IN naloxone
- Patients receiving IM naloxone were more likely to experience
  - An adverse effect 21% compared to the IN naloxone group 12% (p=0.1818)
  - Agitation/irritation with 13% for IM group and 2% for the IN group (p=0.0278)


Patient/Family Discussions

- Why now?
- Why Me?
- What if patient refuses?
- Insurance coverage?
- Liability and documenting refusal
Questions?