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

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 hand-held 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

<table>
<thead>
<tr>
<th>Substance abuse</th>
<th>High daily morphine equivalent dose (MED)</th>
<th>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Concomitant use of benzodiazepines and/or alcohol with or without other sedative-hypnotics</td>
<td>Chronic lung disease</td>
</tr>
<tr>
<td>Chronic kidney and/or liver impairment</td>
<td>Sleep apnea</td>
<td>Accidental exposure to young children in the home</td>
</tr>
</tbody>
</table>

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?

Lion was missing courage

Dorothy was missing home!

Scarecrow was missing a brain

All were missing naloxone!
Intramuscular (IM) Naloxone Rescue Kit
Directions for Use of IM Naloxone Kit

**HOW TO GIVE INTRAMUSCULAR NALOXONE**

1. Put on gloves (optional), remove cap from naloxone vial and uncover the needle.

2. Insert needle through rubber plug with vial upside down. Pull back on plunger and pull down to 1 mL.

3. Inject 1 mL of naloxone at a 90° angle into a large muscle (upper arm/thigh, outer buttocks).

4. If no reaction in 3-5 minutes or if the person stops breathing again, give the second dose of naloxone (i.e., using new needle and naloxone vial, inject 1 mL of naloxone into a large muscle).

**KIT INSTRUCTIONS**

- Keep naloxone kit with you at all times
- Store naloxone kit at room temperature, away from light
- Keep naloxone kit out of the heat—e.g., do not store in your car—otherwise naloxone will lose its effectiveness
- If you use your naloxone kit or it expires, see your provider as soon as possible to replace the kit
- Contact your pharmacy about the proper disposal of your naloxone kit
- Be sure to properly dispose of used needles; do not reuse them
Directions for Use of IN Naloxone Kit

**HOW TO GIVE INTRANASAL NALOXONE**

1. Pull or pry off end caps
2. Pry off end cap
3. Grip clear plastic wings below cone; screw into tip of syringe
4. Screw cartridge of naloxone into syringe barrel
5. Insert cone into nostril; give a short, vigorous push on end of naloxone cartridge to spray naloxone into nose; spray one half of the naloxone cartridge into each nostril
6. If no reaction in 3-5 minutes or if the person stops breathing again, give the second dose of naloxone (spray one half of the second cartridge into each nostril)

**KIT INSTRUCTIONS**

- Keep naloxone kit with you at all times
- Store naloxone kit at room temperature, away from light
- Keep naloxone kit out of the heat--e.g., do not store in your car--otherwise naloxone will lose its effectiveness
- If you use your naloxone kit or it expires, see your provider as soon as possible to replace the kit
- Contact your pharmacy about the proper disposal of your naloxone kit
Naloxone Auto Injector (AI)

Directions for Use of AI Naloxone

How to Use EVZIO

Visual and voice instructions help guide the way

EVZIO is designed to be easy to use for patients, their family members, and other caregivers who do not have medical training. It contains the Intellject® Prompt System (IPS™) with visual and voice instructions that help guide the user through the injection process.

Administration steps

1. Pull EVZIO from the outer case.

Do not go to Step 2 (do not remove the red safety guard) until you are ready to use EVZIO. If you are not ready to use EVZIO, put it back in the outer case for later use.

2. Pull off the red safety guard.

To reduce the chance of an accidental injection, do not touch the black base of the auto-injector, which is where the needle comes out. If an accidental injection happens, get medical help right away.

Note: The red safety guard is made to fit tightly. Pull firmly to remove.

Do not replace the red safety guard after it is removed.

Directions for Use of Al Naloxone (continued)

3. Place the black end against the middle of the patient’s outer thigh, through clothing (pants, jeans, etc) if necessary, then press firmly and hold in place for 5 seconds.

If you give EVZIO to an infant less than 1 year old, pinch the middle of the outer thigh before you give EVZIO and continue to pinch while you give EVZIO.

Note: EVZIO makes a distinct sound (click and hiss) when it is pressed against the thigh. This is normal and means that EVZIO is working correctly. Keep EVZIO firmly pressed on the thigh for 5 seconds after you hear the click and hiss sound. The needle will inject and then retract back up into the EVZIO auto-injector and is not visible after use.

4. After using EVZIO, the user should immediately seek emergency medical help.

If symptoms return after an injection with EVZIO, an additional injection using another EVZIO may be needed. Give additional injections using a new EVZIO auto-injector every 2 to 3 minutes and continue to closely watch the person until emergency help is received.

EVZIO cannot be reused. After use, place the auto-injector back into its outer case. Do not replace the red safety guard.

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 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

• 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)

Naloxone Kits and Naloxone Autoinjectors: Recommendations for Issuing Naloxone Kits and Naloxone Autoinjectors for the VA Overdose Education and Naloxone Distribution (OEND) Program. Washington, DC: Veterans Affairs Pharmacy Benefits Management, Medical Advisory Panel, and VISN Pharmacist Executives in collaboration with the VA OEND National Support and Development Work Group, Veterans Health Administration, Department of Veterans Affairs; May 2015.
AI Administration

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

Naloxone Kits and Naloxone Autoinjectors: Recommendations for Issuing Naloxone Kits and Naloxone Autoinjectors for the VA Overdose Education and Naloxone Distribution (OEND) Program. Washington, DC: Veterans Affairs Pharmacy Benefits Management, Medical Advisory Panel, and VISN Pharmacist Executives in collaboration with the VA OEND National Support and Development Work Group, Veterans Health Administration, Department of Veterans Affairs; May 2015.
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

Naloxone Kits and Naloxone Auto-injectors: Recommendations for Issuing Naloxone Kits and Naloxone Autoinjectors for the VA Overdose Education and Naloxone Distribution (OEND) Program. Washington, DC: Veterans Affairs Pharmacy Benefits Management, Medical Advisory Panel, and VISN Pharmacist Executives in collaboration with the VA OEND National Support and Development Work Group, Veterans Health Administration, Department of Veterans Affairs; May 2015.
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

• 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>DESCRIPTION</th>
<th>YES/NO</th>
<th>POINTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>In the past 6 months, has the patient had a healthcare visit (outpatient, inpatient or ED) involving any of the following health conditions?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Opioid dependence?</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>Chronic hepatitis or cirrhosis?</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>Bipolar disorder or schizophrenia?</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Chronic pulmonary disease (e.g., emphysema, chronic bronchitis, asthma, pneumoconiosis, asbestosis)?</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Chronic kidney disease with clinically significant renal impairment?</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>An active traumatic injury, excluding burns (e.g., fracture, dislocation, contusion, laceration, wound)?</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Sleep apnea?</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td><strong>Does the patient consume:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>An extended-release or long-acting (ER/LA) formulation of any prescription opioid or opioid with long and/or variable half-life? (e.g., OxyContin, Oramorph-SR, methadone, fentanyl patch, levorphanol)</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>Methadone? (Methadone is a long-acting opioid so also check “ER/LA formulation”)</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>Oxycodone? (If it has an ER/LA formulation [e.g., OxyContin] also check “ER/LA formulation”)</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>A prescription antidepressant? (e.g., fluoxetine, citalopram, venlafaxine, amitriptyline)</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>A prescription benzodiazepine? (e.g., diazepam, alprazolam)</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td><strong>Is the patient’s current maximum prescribed opioid dose#:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;100 mg morphine equivalents per day?</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>50-100 mg morphine equivalents per day?</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>20-50 mg morphine equivalents per day?</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td><strong>In the past 6 months, has the patient:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Had one or more emergency department (ED) visits?</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Been hospitalized for one or more days?</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td><strong>TOTAL=</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

## Prediction

<table>
<thead>
<tr>
<th>Risk Class</th>
<th>Risk Index Score (Points)</th>
<th>All Patients $(n = 8,987)$, $n (%)$</th>
<th>Average Predicted Probability (95% CI)</th>
<th>Observed Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0–24</td>
<td>7,133 (79.4)</td>
<td>0.03 (0.03, 0.03)</td>
<td>0.03</td>
</tr>
<tr>
<td>2</td>
<td>25–32</td>
<td>780 (8.7)</td>
<td>0.14 (0.14, 0.15)</td>
<td>0.14</td>
</tr>
<tr>
<td>3</td>
<td>33–37</td>
<td>306 (4.5)</td>
<td>0.24 (0.24, 0.24)</td>
<td>0.23</td>
</tr>
<tr>
<td>4</td>
<td>38–42</td>
<td>238 (2.7)</td>
<td>0.34 (0.34, 0.35)</td>
<td>0.37</td>
</tr>
<tr>
<td>5</td>
<td>43–46</td>
<td>133 (1.5)</td>
<td>0.46 (0.45, 0.46)</td>
<td>0.51</td>
</tr>
<tr>
<td>6</td>
<td>47–49</td>
<td>77 (0.9)</td>
<td>0.55 (0.54, 0.55)</td>
<td>0.55</td>
</tr>
<tr>
<td>7</td>
<td>50–54</td>
<td>101 (1.1)</td>
<td>0.64 (0.64, 0.65)</td>
<td>0.60</td>
</tr>
<tr>
<td>8</td>
<td>55–59</td>
<td>87 (1.0)</td>
<td>0.76 (0.75, 0.76)</td>
<td>0.79</td>
</tr>
<tr>
<td>9</td>
<td>60–66</td>
<td>73 (0.8)</td>
<td>0.85 (0.84, 0.85)</td>
<td>0.75</td>
</tr>
<tr>
<td>10</td>
<td>≥67</td>
<td>59 (0.7)</td>
<td>0.94 (0.93, 0.95)</td>
<td>0.86</td>
</tr>
</tbody>
</table>

Model performance
- C-statistic = 0.88
- Hosmer–Lemeshow goodness-of-fit statistic = 10.8 ($P > 0.05$)
Validation of a Screening Risk Index for Overdose or Serious Prescription Opioid-Induced Respiratory Depression

Barbara Zaleda, MD, MPH; William Sopruh, PhD, MPH; Jennifer Logue, PhD; Catharine Vics, MD; Lynn Maruri, MPH, PhD

BACKGROUND

Population住院 data and deaths from overdoses or opioid-induced respiratory depression have increased steadily in the United States over the past decade. To reduce the number of cases, it is necessary to identify patients at risk of overdosing before the onset of symptoms. This study aims to develop a screening index of risk for overdose or serious opioid-induced respiratory depression (OIRD) to identify patients at risk of overdosing. Since the risk factors for OIRD have not been clearly defined, this study used data from patients treated in hospital outpatient departments. The study population included patients who were prescribed opioids for chronic non-malignant conditions and who had at least one prescription for a high-risk opioid before being prescribed a benzodiazepine. The index was developed using a stepwise logistic regression model to identify the most significant risk factors for OIRD. The index was validated on a separate dataset to confirm its predictive ability.

OBJECTIVE

To validate and assess the index for overdose or serious opioid-induced respiratory depression (OIRD) as a potential risk indicator for patients prescribed high-risk opioids.

METHODS

This study is a prospective, observational, cohort study of 1,482 patient episodes with a pharmacy claim for an opioid between January 1, 2011, and December 31, 2013. The study was conducted in hospital outpatient departments. The index was developed using a stepwise logistic regression model to identify the most significant risk factors for OIRD. The index was validated on a separate dataset to confirm its predictive ability.

RESULTS

Among the 1,482 patient episodes with an opioid claim during the study period, 42 had a serious opioid-related event (OIRD). The independent risk factors associated with OIRD included a higher age, a prior prescription for benzodiazepines, a history of drug use, and a history of mental health disorders. The index was validated on a separate dataset to confirm its predictive ability.

CONCLUSIONS

The index for overdose or serious opioid-induced respiratory depression is a potential risk indicator for patients prescribed high-risk opioids. The index can be used to identify patients at risk of OIRD and to develop targeted interventions to reduce the risk of overdose or serious respiratory depression.
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?