Prescribing Naloxone to Patients for Overdose Reversal

Julie Kmiec, DO
Assistant Professor of Psychiatry
University of Pittsburgh School of Medicine
Disclosures

- Financial – none
- This presentation will discuss intranasal use of naloxone solution 1 mg/mL which is an off-label use of this product
Educational Objectives

- At the conclusion of this activity participants should be able to:
  - Discuss how the opioid prescribing epidemic is associated with the overdose epidemic
  - Discuss opioid overdose risk factors
  - Describe the basic pharmacology of naloxone
  - Describe studies demonstrating the efficacy of naloxone in bystander overdose
  - Name the four different forms of naloxone available for bystander reversal of overdose and discuss to prescribe it
Overview

• Opioid epidemic
• Overdose epidemic
• Overdose risk factors
• Naloxone
• Opioid overdose prevention programs
• How you can prescribe naloxone
OPIOID EPIDEMIC
Opioid Epidemic

• From 1999 to 2008, the number of opioids prescribed in the US quadrupled (CDC, 2011)
  • Consensus statement from American Pain Society and American Academy of Pain Medicine in 1997
    • Little risk of addiction and overdose in pain patients
    • “Fewer than 1% of patients become addicted to opioids” (based on Letter to Editor to NEJM by Porter and Jick, 1980)
  • Greater emphasis in assessing and treating pain (TJC; Berry & Dahl, 2000), 5th vital sign (APS, VHA)
  • Purdue Pharma: OxyContin as safe and effective, funded >20,000 educational programs on pain, encouraged long-term opioid for pain, supported professional societies, FSMB, TJC (Kolodny et al., 2015)
ADDICTION RARE IN PATIENTS TREATED WITH NARCOTICS

To the Editor: Recently, we examined our current files to determine the incidence of narcotic addiction in 39,946 hospitalized medical patients1 who were monitored consecutively. Although there were 11,882 patients who received at least one narcotic preparation, there were only four cases of reasonably well documented addiction in patients who had no history of addiction. The addiction was considered major in only one instance. The drugs implicated were meperidine in two patients,2 Percodan in one, and hydromorphone in one. We conclude that despite widespread use of narcotic drugs in hospitals, the development of addiction is rare in medical patients with no history of addiction.

JANE PORTER
Hershel Jick, M.D.
Boston Collaborative Drug Surveillance Program
Waltham, MA 02154

Boston University Medical Center


Number and Type of Citations of the 1980 Letter, According to Year.

Total 608 citations

439 (72.2%) cited as addiction rare

491 (80.8%) did not cite that pts were hospitalized and given opiates

Introduction of OxyContin
Opioid Misuse

- Roughly 21-29% of patients prescribed opioids for chronic pain misuse them
- Between 8-12% develop an opioid use disorder
- An estimated 4-6% who misuse prescription opioids transition to heroin
- About 80% of people who use heroin first misused prescription opioids

Vowles et al., 2015; Muhuri et al., 2013; Cicero et al., 2014; Carlson et al., 2016
Fig. 1. First opioid of regular use among opioid initiates from 2005 to 2015 (N = 5885). Cochran-Armitage trend tests showed significant changes for heroin (< .001), hydrocodone (< 0.001), other prescription opioids (< 0.001), but not oxycodone (p = 0.13).
OVERDOSE EPIDEMIC
Overdose Deaths

• From 2000-2014, there was a 200% increase in deaths involving opioids
• Opioid overdoses increased 30% from July 2016 through September 2017 in 52 areas in 45 states

Rudd et al., 2016; Vivolo-Kantor et al., 2017
Figure 2. National Drug Overdose Deaths Number Among All Ages, 1999-2017

Source: Centers for Disease Control and Prevention, National Center for Health Statistics. Multiple Cause of Death 1999-2017 on CDC WONDER Online Database, released December, 2018
Figure 5. National Drug Overdose Deaths Involving Heroin Number Among All Ages, 1999-2017

Source: Centers for Disease Control and Prevention, National Center for Health Statistics. Multiple Cause of Death 1999-2017 on CDC WONDER Online Database, released December, 2018.
Allegheny County Overdose Data

Adapted from https://www.overdosefreepa.pitt.edu/
OVERDOSE RISK FACTORS
Overdose Risk Factors

• Using >50 mg of oral morphine equivalents daily (Bohnert et al., 2011; Zedler et al., 2014; Liang and Turner, 2015; Yang et al., 2015)
• Recent release from controlled environment
  • Incarceration (Binswanger et al., 2013; Binswanger et al., 2007)
  • Treatment (Strang et al., 2003)
• Mixing opioids with benzos, alcohol, other drugs (Powis et al., 1999)
• Medical conditions (renal, hepatic, pulmonary diseases, HIV)
Respiration

• Respiration is principally controlled by medullary respiratory center with peripheral input from chemoreceptors

• Control of respiration from dorsal respiratory group (DRG) likely produces breathing rhythm, has influence on ventral respiratory group (VRG) which has efferent fibers that innervate muscles of respiration

• Respiration involves phasic activation (excitatory amino acids like glutamate) and inhibition (GABA mediated)

• GABA receptors (A and B) have high density in DRG and VRG

• Chemoreceptors are located in carotid and aortic bodies, respond to changes in blood gases; they are stimulated by decreases in oxygen, and also, but to lesser extent by increase in CO2 or decrease in pH

White & Irvine, 1999
Opioids and Respiration

• Opioid peptides can modulate respiration, depress respiration through reduction in glutamate induced excitation
• Agonist activity at medullary mu or delta receptors causes respiratory depression
  • Opioids may affect tidal volume and respiratory frequency
• Agonist activity at kappa receptor has either no effect on respiration or may stimulate respiration slightly
• At chemoreceptors, inhibition is mediated by mu opioid receptor binding, resulting in decreased sensitivity to changes in oxygen and CO2, particularly the response to increased CO2

White & Irvine, 1999
Other Factors Influencing Overdose Risk

• Glutamate and GABA mediate the control of respiration, explaining contribution of benzodiazepines and alcohol to overdose
  • Benzodiazepines and alcohol facilitate the inhibitory effect of GABA at GABA-A receptors
  • Alcohol decreases excitatory effect of glutamate at NMDA receptors
• Individual differences in susceptibility to overdose may be mediated by an individual's metabolism
  • Glucuronidation
  • CYP 3A4 and 2D6
• Overdose may occur when there is loss of tolerance at cellular and/or pharmacokinetic level
• High tolerance may also increase risk, as person will need to use higher doses to get an effect
• Pulmonary edema is also consequence of opioid overdose and may contribute to death

White & Irvine, 1999
Opioid Overdose

- Decreased oxygenation of brain and heart leads to
  - Unresponsiveness
  - Anoxia, cyanosis
  - Death
- Respiratory depression can last 1-3 hours, is reversible with naloxone

Boyer, 2012
Possible Complications of Non-fatal Overdoses

- Anoxic brain injury
- Pulmonary edema
- Acute respiratory distress syndrome
- Hypothermia
- Renal failure
- Compartment syndrome
- Liver failure
- Seizures (depending on substance ingested)
NALOXONE
Naloxone

- Naloxone is opioid antagonist
  - High affinity for mu receptor
  - Displaces bound agonist
  - Prevents other agonists from binding
  - Works within minutes
  - Lasts 20-90 mins
  - FDA approved for IV, SC, IM use
    - Recent FDA approved intranasal naloxone; also off-label intranasal use of naloxone for injection

- Naloxone has been used for opioid reversal for 40 years in hospitals
- Naloxone has been used for overdose in ED and by paramedics for years
- Since mid-1990s, provision for use outside medical setting for people at risk of overdose

Boyer, 2012
Possible Adverse Effects of Naloxone

• If administered in usual dose to someone not using opioids, there are no adverse effects
• Tachycardia
• Hypertension
• Hypotension
• Seizure – due to anoxia
• Nausea, vomiting
• Diaphoresis
• Other opioid withdrawal symptoms
• Severe symptoms listed in prescribing info were seen in post-op reversals
Naloxone IM vs IN

- Kerr et al. (2009)
- Concentrated naloxone 2 mg/1 mL IM vs. IN randomized, controlled, open-label trial
- 172 patients with suspected overdose treated by EMS
  - 83 received 1 mg/0.5 mL in each nostril
  - 89 received 2 mg/1 mL IM
- 129 had adequate response within 10 mins (95% CI -18.2, 7.7%)
  - 60 in IN group (72.3%)
  - 69 in IM group (77.5%)
- Adverse events were similar between groups
- Mean response time was similar between groups, about 8 mins
<table>
<thead>
<tr>
<th>Article</th>
<th>Location</th>
<th>N</th>
<th>Population</th>
<th>Study design</th>
<th>Question addressed by study</th>
<th>Summary of key findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Merlin et al., 2010&lt;sup&gt;65&lt;/sup&gt;</td>
<td>Urban setting, USA</td>
<td>277</td>
<td>Patients who received naloxone by paramedics</td>
<td>Retrospective cohort study with chart review</td>
<td>Determine if intranasal naloxone is noninferior to intravenous naloxone</td>
<td><strong>Intranasal naloxone was noninferior to intravenous naloxone at reversing the effects of opioid OD in terms of changes in Glasgow Coma Score and respiratory rate, but 42% of the intranasal naloxone recipients required redosing compared with 20% of the intravenous naloxone recipients.</strong></td>
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<td>Barton et al., 2005&lt;sup&gt;62&lt;/sup&gt;</td>
<td>Denver, Colorado, USA</td>
<td>95</td>
<td>Adult patients in a prehospital setting with a suspected opiate OD, found down, or with and altered mental status who received intranasal (IN) naloxone</td>
<td>Prospective cohort study</td>
<td>Determine if intranasal naloxone is effective for suspected OD in prehospital settings</td>
<td><strong>83% of patients who responded to naloxone (n = 52) responded to IN and did not require intravenous naloxone.</strong></td>
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<td>Buajordet et al., 2004&lt;sup&gt;63&lt;/sup&gt;</td>
<td>Oslo, Norway</td>
<td>1192</td>
<td>Patients who received naloxone by paramedics for heroin OD</td>
<td>Prospective observational study</td>
<td>Determine the frequencies and characteristics of adverse events related to out of hospital administration of naloxone by paramedics over a 1-year period</td>
<td><strong>Adverse events of naloxone administration included 32% with confusion, 22% with headache, 9% with nausea/vomiting, 8% with aggressiveness, and 6% with tachycardia. Serious adverse events from naloxone requiring hospitalization occurred in only 3 cases (0.3%).</strong></td>
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<tr>
<td>Study</td>
<td>Dose and route</td>
<td>Naloxone administrations and reversal success rate</td>
<td>Withdrawal symptoms</td>
<td>Recurrence of respiratory depression</td>
<td>Location; other</td>
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<td>Rando and colleagues¹⁴²</td>
<td>2 mg IN × 1 and call EMS</td>
<td>Naloxone administered to 67/individuals; 77.6% survival (11% lost to follow-up, 10.5% died)</td>
<td>NR</td>
<td>NR</td>
<td>Lorain County, OH; 2011–2014; police officers trained to administer naloxone. Quarterly number of opioid OD deaths decreased by 4.1 individuals per quarter in contrast to pre-program quarterly increase by 1.5 deaths</td>
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<td>Rowe and colleagues¹⁶³</td>
<td>2 × IM or IN kits (dose NR)</td>
<td>Out of 702 administrations there were 10 deaths (1.4%) (in 6 cases the participant knew it was ‘too late’ but administered naloxone anyway)</td>
<td>NR</td>
<td>NR</td>
<td>San Francisco, CA; 2010–2013; data obtained only from participants returning from refill rather than active data collection; &gt;90% reported using heroin; EMS was called in 27.4% cases</td>
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<td>Chronister and colleagues¹⁶⁴</td>
<td>0.4 mg IM × 2</td>
<td>30 administrations, 100% successful  40% of ODs responded within 2 min, another 40% within 2–5 min</td>
<td>Four treated individuals were reportedly angry due to withdrawal; no other issues</td>
<td>NR</td>
<td>Sydney, Australia; two-thirds who witnessed an OD called EMS</td>
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<td>Madah-Amiri and colleagues¹⁶⁵</td>
<td>0.8 ml IN (divided as 0.4 ml in each nostril) via atomizer and repeat × 1; given 2 ml of 1 mg/ml</td>
<td>277 administrations of which 265 survived (96%; remaining unknown or missing) Doses titrated and 24% of participants reported using all the doses available: 73% used 2 doses or less while 27% used the whole 2 ml and one used 4 ml</td>
<td>In 27% of administrations, no adverse symptoms were reported, while after given naloxone, 27% were confused, 11% were angry, 7% were nauseous, 1% vomited, 5% were tired, 3% ‘shock’ and 8% had other adverse symptoms</td>
<td>NR</td>
<td>Norway; 2014–2015; 66% called EMS for OD; 84% of naloxone uses were for heroin OD</td>
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Naloxone and Fentanyl

- Fentanyl is highly lipophilic and rapidly equilibrates between the plasma and the CSF, resulting in fast onset of analgesia and respiratory depression
- Fentanyl may be extensively redistributed to less highly perfused tissues
- Large doses of fentanyl can prolong duration of action due to saturation of tissue
- Fentanyl has been shown to be resistant to reversal with standard doses of naloxone
- In 2015, almost 1/5 of patients receiving naloxone from EMS required more than one administration, up from 1/6 of patients in 2012
- Fentanyl overdoses may be unresponsive to IN naloxone and only transiently reversed with IV naloxone and required additional IV doses or continuous infusions to prevent recurrence of toxicity and respiratory depression

Rzasa et al., 2017
Refusing Medical Treatment After Naloxone

- Retrospective review of San Diego EMS database and medical examiner’s database
- Looked at paramedic data, who received naloxone and who signed AMA form (n = 998)
- Looked at ME data, who died of heroin OD (n=601)
- Cross-referenced lists, no one released AMA had died of OD within 12 hours

Vilke et al., 2003
OPIOID OVERDOSE PREVENTION PROGRAMS
Opioid Overdose Prevention Programs (OOPP)

- Started 1996, first program in Chicago
- Started in harm prevention programs
- OOPP train people at risk for overdose how to prevent overdose as well as how to recognize and respond to overdose
- Participants are trained to seek help (call 911), rescue breath, administer naloxone IN or IM, and stay with the person who has overdosed
## OOPP Providing Naloxone, 2014

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<tr>
<th></th>
<th>2010</th>
<th>2014</th>
<th>% increase</th>
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<tbody>
<tr>
<td>Number of sites providing naloxone</td>
<td>188</td>
<td>644</td>
<td>243%</td>
</tr>
<tr>
<td>Number of persons provided kits</td>
<td>53,032</td>
<td>152,283</td>
<td>187%</td>
</tr>
<tr>
<td>Number of reversals reported</td>
<td>10,171</td>
<td>26,463</td>
<td>160%</td>
</tr>
<tr>
<td>Number of states with OOPP</td>
<td>16</td>
<td>30</td>
<td>94%</td>
</tr>
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Wheeler et al., 2015
Implementation of OOPP in MA

• Between 2006-2009, 4857 people were enrolled in OOPP programs and 545 naloxone rescue attempts reported
  • From the 19 communities meeting study criteria, 2912 were enrolled and 327 rescue attempts made
  • 327 rescue attempts were made by 212 individuals
  • 87% were by people who used opioids
  • Most rescue attempts occurred in private settings
  • Rescuer and person who overdosed were usually friends

Walley et al., 2013
Implementation of OOPP in MA

- Naloxone was successful in 98% (150/153) of rescue attempts
  - The remaining 3 people received care by medical system and survived
- Reduced death rates in communities that implemented OOPP
  - Low implementers (1-100 enrollments per 100,000) had 27% decrease
  - High implementers (>100 enrollments per 100,000) had 46% decrease

Walley et al., 2013
1/17/11 Does the jurisdiction have a naloxone access law?
2017

7/1/17 Does the jurisdiction have a naloxone access law?

http://pdaps.org/datasets/laws-regulating-administration-of-naloxone-1501695139
Naloxone Laws

7/1/17 (26 jurisdictions)

http://pdaps.org/datasets/laws-regulating-administration-of-naloxone-1501695139
Naloxone for bystander administration

- Intramuscular
  - Traditional
  - Auto-injector
- Intranasal
  - With MAD (off-label)
  - NARCAN nasal spray
HOW TO PRESCRIBE NALOXONE TO PATIENTS
Talk to Patients about Overdose

- Have you ever had an accidental overdose?
  - What were the circumstances, what happened, how did you survive?
- Have you ever witnessed an overdose?
  - What did you do?
- What do you do to protect yourself from overdose?
- What are some risk factors for overdose?
- Have you heard about naloxone/Narcan for reversal of overdose?
Patient Selection (1)

- History of opioid overdose (Silva et al., 2013, Wines et al., 2007)
- Emergency treatment for opioid overdose or intoxication (SAMHSA, 2014)
- Suspected or known heroin or nonmedical opioid use (SAMHSA, 2014)
- Buprenorphine or methadone maintenance (Paulozzi et al., 2012; Britton et al., 2010)
- Receiving >50-100 morphine equivalents of opioid per day (Bohnert et al., 2011; Dunn et al., 2010)
- Changing from one opioid to another (incomplete cross-tolerance; SAMHSA, 2014)
- Living in remote location or difficulty accessing EMS
- Request from patient or concerned significant other
Patient Selection (2)

- Patient receiving opioid prescription and:
  - Smoking, COPD, asthma, sleep apnea, respiratory infection, other respiratory illness (Warner-Smith et al., 2001; Darke et al., 2006)
  - Renal disease, liver disease, cardiac disease, HIV/AIDS (Warner-Smith et al., 2001; Darke et al., 2006; Green et al., 2012)
  - Known or suspected heavy alcohol use (UNODC/WHO, 2013; Häkkinen et al., 2011)
  - Concurrent benzodiazepine or other sedative prescription (Paulozzi et al., 2012; Silva et al., 2013)
  - Concurrent antidepressant prescription (Darke & Ross, 2000) or psychiatric diagnosis (Bohnert et al., 2011)
  - Recently released from incarceration, detoxification, mandatory abstinence program (SAMHSA, 2014)
Educational Videos for Patients

• Prescribetoprevent.org
  • http://prescribetoprevent.org/patient-education/videos/

• Study showed first time recipients of naloxone receiving 5-10 minute education on overdose education and naloxone demonstrated high level of knowledge on Brief Overdose Recognition and Response Assessment (Behar et al., 2015)
Prescription for IM Naloxone

Naloxone HCl 0.4 mg/mL (Narcan)
1 x 10 mL as one flip top vial (NDC 0409-1219-01) OR
2 x 1mL single dose vials (NDC 0409-1215-01)

Refills: _____

Intramuscular (IM) syringe, 23 G, 3cc, 1 inch

Qty: _____ Refills: _____

Sig: For suspected opioid overdose,
inject 1mL IM in shoulder or thigh.
Repeat after 3 minutes if no or minimal response.

Prescription for Naloxone with MAD

Naloxone HCl 1 mg/mL
2 x 2 mL as pre-filled Luer-Lock needless syringe
(NDC 76329-3369-1)

Refills: _____

2 x Intranasal Mucosal Atomizing Device (MAD 300)

Refills: _____

For suspected opioid overdose, spray 1mL in each nostril. Repeat after 3 minutes if no or minimal response.

Pharmacist: Call 1-800-788-7999 to order MAD 300.

Prescription for Auto-injector

• Naloxone Auto-Injector 2 mg/0.4 mL
  • Disp #1 twin pack
  • Use 1 auto-injector upon signs of opioid overdose. Repeat after 3 minutes if minimal or no response.
  • Refills ____

• *Dose was changed from 0.4 mg/0.4 mL in 2016
Writing Prescription for Naloxone Nasal Spray

- Naloxone nasal spray 4 mg/0.1 mL (1 box, pack of 2)
  - Sig: For suspected overdose, spray in one nostril. May repeat in 3 mins if minimal or no response.
  - Disp: #1 (pack of two)
  - Refills _____
Common Issues

- Covered by commercial insurance, Medicaid, Medicare
- Cost of naloxone has gone up in recent years due to increased demand
- MAD may not be covered, typically $4-8/each
- Naloxone nasal spray may cost $130, covered by insurance, including Medicaid
- Auto-injector may cost $3750, covered by some insurances and Medicaid with prior auth
- Regularly stocked by pharmacies; if not, see if pharmacist will order
- Shelf life 12-24 months
Standing Orders

7/1/17  How are pharmacists allowed to dispense or distribute naloxone without a patient-specific prescription from another medical professional?

http://pdaps.org/datasets/laws-regulating-administration-of-naloxone-1501695139
Collaborative Pharmacy Practice Agreements (CPA)

- CPA permit pharmacists to work in collaboration with a prescriber on drug therapy management
  - 48 states allow CPA to manage pharmaceutical care under agreement
  - 21 states permit pharmacists to initiate medication under agreement

Green et al., 2015
Questions/Comments
References

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