WHO says Narcan? Intranasal that is!

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Pharmacy/Anesthesiology

October 2015
Review the background on the current opioid crisis

Describe the recent interest in the use of prehospital naloxone for suspected opioid overdoses

Identify risks and benefits associated with its use

Identify its current role in practice
### WHO Guidelines Summary

<table>
<thead>
<tr>
<th>No.</th>
<th>Recommendation</th>
<th>Strength of recommendation</th>
<th>Quality of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>People likely to witness an opioid overdose should have access to naloxone and be instructed in its administration to enable them to use it for the emergency management of suspected opioid overdose.</td>
<td>Strong</td>
<td>Very low</td>
</tr>
<tr>
<td>2</td>
<td>Naloxone is effective when delivered by intravenous, intramuscular, subcutaneous and intranasal routes of administration. Persons using naloxone should select a route of administration based on the formulation available, their skills in administration, the setting and local context.</td>
<td>Conditional</td>
<td>Very low</td>
</tr>
<tr>
<td>3</td>
<td>In suspected opioid overdose, first responders should focus on airway management, assisting ventilation and administering naloxone.</td>
<td>Strong</td>
<td>Very low</td>
</tr>
<tr>
<td>4</td>
<td>After successful resuscitation following the administration of naloxone, the level of consciousness and breathing of the affected person should be closely observed until full recovery has been achieved.</td>
<td>Strong</td>
<td>Very low</td>
</tr>
</tbody>
</table>

WHO Library Cataloguing-in-Publication Data
Community management of opioid overdose.
The Problem

“If one of us dies of an overdose, probably 10 who were about to won’t...”

Phillip Seymour Hoffman
(In Time reported by Aaron Sorkin)
NOTES: Drug poisoning deaths are a subset of poisoning deaths. Unintentional drug poisoning deaths are a subset of drug poisoning deaths.


Steady rise in drug overdose deaths since 1992
- 117% increase from 1999 to 2012
- In the United States (US), 100 people die every day from opioid overdose
- >16,000 people died from an overdose of prescription opioids in US in 2013
Oh What a Pretty Flower
“the entire jungle is a house of death”

America's Growing Population of Heroin Users
People age 12 and over who report using heroin increased by 68 percent since 2002

Source: National Survey on Drug Use and Health

Bloomberg
“it’s just a straight plummet to certain death”

**Heroin Deaths Nearly Tripled Since 2010**

The age-adjusted rates for drug overdose deaths

- **Opioids**
- **Heroin**

Source: CDC National Center for Health Statistics

Bloomberg
Opioid-Analgesic Poisoning Deaths by Opioid Analgesic Category in the U.S. (1999-2011)

NOTE: Access data table for Figure 3 at: http://www.cdc.gov/nchs/data/databriefs/db166_table.pdf#3.

Number of Opioid-Analgesic Poisoning Deaths, by Involvement of Benzodiazepines in the U.S. (1999-2011)

# Opioids Alone are Not to Blame

## Table 4. Contributory Drugs Involved in Unintentional Pharmaceutical Overdose Fatalities, West Virginia, 2006

<table>
<thead>
<tr>
<th>Contributory Prescription Drug</th>
<th>Deaths, Total (%)</th>
<th>Prescribed, %a</th>
<th>Dispensed Within 30 d of Death, %b</th>
<th>Other Prescription Drugs</th>
<th>Illicit Drugsc</th>
<th>Alcohol</th>
<th>None</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opioid analgesic</td>
<td>275 (93.2)</td>
<td>44.4</td>
<td>29.1</td>
<td>63.3</td>
<td>16.0</td>
<td>13.5</td>
<td>21.5</td>
</tr>
<tr>
<td>Methadone</td>
<td>112 (40.0)</td>
<td>32.1</td>
<td>25.8</td>
<td>62.5</td>
<td>13.4</td>
<td>9.8</td>
<td>25.9</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>67 (22.7)</td>
<td>85.1</td>
<td>NA</td>
<td>83.6</td>
<td>9.0</td>
<td>11.9</td>
<td>7.5</td>
</tr>
<tr>
<td>Oxycodeone</td>
<td>61 (20.7)</td>
<td>60.7</td>
<td>39.3</td>
<td>70.5</td>
<td>14.8</td>
<td>9.8</td>
<td>18.0</td>
</tr>
<tr>
<td>Morphine</td>
<td>46 (15.6)</td>
<td>21.7</td>
<td>15.2</td>
<td>54.3</td>
<td>28.3</td>
<td>28.3</td>
<td>21.7</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>31 (10.5)</td>
<td>41.9</td>
<td>32.3</td>
<td>77.4</td>
<td>19.4</td>
<td>9.7</td>
<td>12.9</td>
</tr>
<tr>
<td>Other Schedule II opioid analgesic</td>
<td>4 (1.4)</td>
<td>25.0</td>
<td>25.0</td>
<td>100</td>
<td>25.0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Other Schedule III opioid analgesic</td>
<td>24 (8.1)</td>
<td>50.0</td>
<td>NA</td>
<td>91.7</td>
<td>8.3</td>
<td>8.3</td>
<td>0</td>
</tr>
<tr>
<td>Psychotherapeutic</td>
<td>144 (48.8)</td>
<td>54.9</td>
<td>NA</td>
<td>93.8</td>
<td>8.3</td>
<td>20.8</td>
<td>0.7</td>
</tr>
<tr>
<td>Diazepam</td>
<td>65 (22.4)</td>
<td>45.5</td>
<td>NA</td>
<td>92.4</td>
<td>7.6</td>
<td>19.7</td>
<td>0</td>
</tr>
<tr>
<td>Alprazolam</td>
<td>54 (18.3)</td>
<td>64.8</td>
<td>NA</td>
<td>100</td>
<td>5.6</td>
<td>11.1</td>
<td>0</td>
</tr>
<tr>
<td>Other benzodiazepine</td>
<td>5 (1.7)</td>
<td>80.0</td>
<td>NA</td>
<td>100</td>
<td>0</td>
<td>20.0</td>
<td>0</td>
</tr>
<tr>
<td>Antidepressant</td>
<td>49 (16.6)</td>
<td>71.4</td>
<td>NA</td>
<td>93.9</td>
<td>10.2</td>
<td>20.4</td>
<td>2.0</td>
</tr>
<tr>
<td>Other psychotherapeutic</td>
<td>16 (5.4)</td>
<td>68.8</td>
<td>NA</td>
<td>93.8</td>
<td>0</td>
<td>37.5</td>
<td>0</td>
</tr>
<tr>
<td>Other prescription drug</td>
<td>33 (11.2)</td>
<td>60.1</td>
<td>NA</td>
<td>97.0</td>
<td>9.1</td>
<td>12.1</td>
<td>3.0</td>
</tr>
<tr>
<td>All decedents</td>
<td>295 (100)</td>
<td>36.9</td>
<td>NA</td>
<td>62.4</td>
<td>15.9</td>
<td>17.3</td>
<td>20.7</td>
</tr>
</tbody>
</table>

Abbreviation: NA, not applicable.

aFor decedents with multiple contributory drugs from a given category, percentage includes only those who had all drugs prescribed to them.

bApplicable to 227 decedents with Schedule II drugs, which can be dispensed as no more than a 30-day supply with no refills in West Virginia. For decedents with multiple contributory drugs from a given category, percentage includes only those who had all drugs dispensed to them within 30 days of death.

cIncludes cocaine, heroin, and methamphetamine.

dIncludes hydromorphone and meperidine.

eIncludes codeine, dihydrocodeine, and propoxyphene.

fIncludes chlordiazepoxide, clonazepam, and temazepam.

gIncludes amitriptyline, bupropion, clonazepam, desipramine, doxepin, fluoxetine, imipramine, mirtazapine, nortriptyline, paroxetine, sertraline, trazodone, and venlafaxine.

hIncludes carbamazepine, hydroxyzine, phenobarbital, quetiapine, topiramate, and zolpidem.

iIncludes butalbital, carisoprodol, cyclobenzaprine, diltiazem, phenytoin, promethazine, and tramadol.
The Scope of the Prescribing Problem in the United States

Number of painkiller prescriptions per 100 people

- 52-71
- 72-82.1
- 82.2-95
- 96-143

SOURCE: ME. National Prescription Audit (NPA™, 2013)
What About Michigan?

Fatal overdoses reach record levels in Michigan

Data from Michigan Department of Community Health
“a person’s a person, no matter how small”

- Approximately 2% of heroin users die each year
- ½-2/3 of heroin users experience at least one nonfatal overdose
- 80% have observed an overdose

Why Do We Have an Opioid Overdose Epidemic?

According to a recent Nationwide survey:

MORE DOCTORS SMOKE CAMELS
THAN ANY OTHER CIGARETTE

CAMELS Cigarette Tobacco
People coming out of jail or treatment have highest risk of overdose

Most deaths are among opiate users who are in their late twenties to early thirties and have been actively using for the past five to ten years

Only 17% of opiate related deaths are among new users.
What is Driving the Increase in Overdose?

- **New Drug Use Patterns**
  - New Initiates to prescription drugs
  - Vicodin/Percocet/oxycodone >>> heroin

- **Heroin Availability/Purity/Lethal Mixture**
  - Heroin is the leading drug threat in New England
  - From ‘93-’10 Heroin reported as primary drug increased from 20% - 40% of treatment admissions in MA
  - Combination with Fentanyl

- **Prescribing Patterns**
  - Schedule II Opioid prescriptions increased more than 4 fold from 1999-2010
Risk Factors for Prescription Overdose

- Male gender
- Older age
- Lower socioeconomic status
- Mental health disorders
- Higher doses $\geq 100$mg morphine equivalents daily
- Polypharmacy
Risks Associated with Diversion and Doctor Shopping

Table 3. Substance Abuse Indicators Among Unintentional Pharmaceutical Overdose Deaths Involving Pharmaceutical Diversion and Doctor Shopping, West Virginia, 2006

<table>
<thead>
<tr>
<th>Substance Abuse Indicator</th>
<th>All Deaths, No. (%)</th>
<th>Any Diverted Pharmaceuticals&lt;sup&gt;a&lt;/sup&gt;</th>
<th>≥5 Clinicians&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>All Deaths, No. (%)</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>History of substance abuse</td>
<td>231 (78.3)</td>
<td>153 (82.3)</td>
<td>1.8 (1.0-3.4)</td>
</tr>
<tr>
<td>Any diverted pharmaceuticals&lt;sup&gt;a&lt;/sup&gt;</td>
<td>186 (63.1)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Nonmedical route of administration</td>
<td>66 (22.4)</td>
<td>49 (26.3)</td>
<td>1.9 (1.0-3.8)</td>
</tr>
<tr>
<td>≥5 Clinicians prescribed controlled substances&lt;sup&gt;b&lt;/sup&gt;</td>
<td>63 (21.4)</td>
<td>24 (12.9)</td>
<td>0.3 (0.1-0.5)</td>
</tr>
<tr>
<td>Contributory alcohol</td>
<td>51 (17.3)</td>
<td>34 (18.3)</td>
<td>1.2 (0.6-2.4)</td>
</tr>
<tr>
<td>Previous overdose</td>
<td>50 (16.9)</td>
<td>29 (15.6)</td>
<td>0.8 (0.4-1.5)</td>
</tr>
<tr>
<td>Contributory illicit drug&lt;sup&gt;e&lt;/sup&gt;</td>
<td>47 (15.9)</td>
<td>36 (19.4)</td>
<td>2.1 (1.0-4.9)</td>
</tr>
<tr>
<td>Current OTP enrollment</td>
<td>12 (4.1)</td>
<td>4 (2.2)</td>
<td>0.3 (0.1-1.1)</td>
</tr>
<tr>
<td>Any indicator&lt;sup&gt;f&lt;/sup&gt;</td>
<td>279 (94.6)</td>
<td>167 (89.8)</td>
<td>1.5 (0.7-3.3)</td>
</tr>
<tr>
<td>Total</td>
<td>295 (100)</td>
<td>186 (100)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; NA, not applicable; OR, odds ratio; OTP, opiate treatment program.

<sup>a</sup> Diverted pharmaceuticals include those that contributed to death but that were not prescribed to the decedent.

<sup>b</sup> Includes clinicians who prescribed controlled substances to the decedent during the year prior to death, based on Controlled Substances Monitoring Program records.

<sup>c</sup> Percentages among those with any diverted pharmaceuticals or ≥5 clinicians (column percentages) are reported.

<sup>d</sup> Odds ratio compares those with a given substance abuse indicator vs those without as the reference group.

<sup>e</sup> Includes cocaine, heroin, and methamphetamine.

<sup>f</sup> Excludes not applicable indicators, as noted.
Most Likely Time of Day

Knowlton A. Prehospital Emergency Care. 17; 2013
Most Likely Day of the Week

Knowlton A. Prehospital Emergency Care. 17; 2013
Most Likely Time of Year

Knowlton A. Prehospital Emergency Care. 17; 2013
Opioid Overdose Costs

- $20.4 billion per year in 2009
  - $2.2 billion direct costs
    - inpatient, ED, MDs, ambulance
  - $18.2 billion indirect costs
    - lost productivity from absenteeism and mortality
- $37,274 cost per opioid overdose event

Inocencio TJ et al. Pain Medicine 2013
It Costs's Us All

<table>
<thead>
<tr>
<th></th>
<th>Cost per Case ($)</th>
<th>Total Cost ($, thousands)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Absenteeism costs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heroin</td>
<td>581</td>
<td>79,307</td>
</tr>
<tr>
<td>Prescription opioid</td>
<td>618</td>
<td>256,173</td>
</tr>
<tr>
<td>All</td>
<td>608</td>
<td>334,648</td>
</tr>
<tr>
<td><strong>Mortality costs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heroin</td>
<td>30,010</td>
<td>4,075,566</td>
</tr>
<tr>
<td>Prescription opioid</td>
<td>33,664</td>
<td>13,887,512</td>
</tr>
<tr>
<td>All</td>
<td>32,657</td>
<td>17,907,232</td>
</tr>
<tr>
<td><strong>All productivity costs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heroin</td>
<td>30,594</td>
<td>4,155,966</td>
</tr>
<tr>
<td>Prescription opioid</td>
<td>34,285</td>
<td>14,143,685</td>
</tr>
<tr>
<td>All</td>
<td>33,267</td>
<td>18,241,881</td>
</tr>
</tbody>
</table>

Inocencio. Pain Med. 14; 2013
Results of Sensitivity Analysis: Naloxone distribution was cost-effective in all deterministic and probabilistic sensitivity and scenario analyses, and it was cost-saving if it resulted in fewer overdoses or emergency medical service activations. In a “worst-case scenario” where overdose was rarely witnessed and naloxone was rarely used, minimally effective, and expensive, the ICER was $14,000. If national drug-related expenditures were applied to heroin users, the ICER was $2429.
Cost-effectiveness of Distributing Naloxone to Heroin Users for Overdose Reversal

- One heroin overdose death prevented for every 164 kits distributed
- Cost for naloxone distribution would range between:
  - $438-$14,000 (best-worst case scenario) for every quality-adjusted life year gained
- Generally accepted threshold is $50,000/year
  - For dialysis: recently calculated as $129,000
  - For primary care-based SBIRT: recently calculated as $6960

Cost by Opioid...A Picture is Worth a Thousand Words

Inocencio TJ. Pain Med. 14; 2013
PrescribeToPrevent.org does not receive funds or other support from any manufacturer of any component of naloxone rescue kits, nor does PrescribeToPrevent.org endorse specific products. We mention manufacturers only to facilitate access. To our knowledge, we mention all sources of the components of naloxone rescue kits.

Billing

Some insurance plans, including Medicaid and Medicare in some states, reimburse for naloxone. Compiling a list of insurance plans in your area that will cover naloxone and collaborating with a pharmacist will be helpful. Because naloxone is not an expensive medication, even patients whose insurance will not cover the medicine may be willing to pay for naloxone.

Advocates in some locations have been successful in persuading insurers to cover the cost of naloxone or have it added to local ADAP (AIDS Drug Assistance Program)
## Good Samaritan Protection

<table>
<thead>
<tr>
<th>Protection</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prescriber immunity from criminal &amp; civil liability for prescribing, dispensing, or administering naloxone</td>
<td>✔️</td>
</tr>
<tr>
<td>Pharmacist protection from criminal &amp; civil liability for dispensing or administering naloxone</td>
<td>✔️</td>
</tr>
<tr>
<td>Layperson immunity from civil liability when administering naloxone</td>
<td>✔️</td>
</tr>
<tr>
<td>3\textsuperscript{rd} Party Prescribing (Naloxone access law)</td>
<td>✔️</td>
</tr>
<tr>
<td>Protection from criminal liability for possession of controlled substances</td>
<td>❌</td>
</tr>
<tr>
<td>Standing order prescriptions</td>
<td>❌</td>
</tr>
</tbody>
</table>
Good Samaritan Laws July 2015

- Teal: States with naloxone access and drug overdose Good Sam laws
- Light blue: States with drug overdose Good Sam laws only
- Yellow: States with naloxone access laws only
All 53 jurisdictions permit Paramedics to administer naloxone.

Of the 48 jurisdictions with mid-level EMS personnel, all but one authorize those personnel to administer naloxone.

Only twelve jurisdictions explicitly permit EMTs to administer naloxone.

Five additional states permit some or all EMTs to administer the drug through pilot programs or agency medical director authority.

‘there’s a tiny person on that speck that needs my help!’

Naloxone Could Prevent More Than 20,000 U.S. Overdose Deaths, WHO Says

Reuters
Posted: 11/04/2014 6:57 am EST | Updated: 01/04/2015 5:39 am EST
Opioids are used primarily in medicine for pain relief, treatment of opioid use disorders, and cough relief.

All categories have overdose risk
“is everything okay down there?”

- Weak/Thready pulse
- Slow or Absent Respirations
- Constricted Pupils
- Weakness
- Unresponsiveness
Naloxone Basics 101

- **MOA**: Competitively displaces opioids from receptors
- **Half-life**: ~ 30 min - 1 hour
- Complete, temporary reversal of opioid overdose effects
- May cause acute and severe opioid withdrawal
- Inactivated by first pass metabolism
## Properties of Nasal Absorption

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>High absorption for lipophilic drugs with MW &lt; 1 kDa</td>
<td>Poor permeability for hydrophilic drugs or drugs with MW &gt; 1 kDa (peptides, proteins...)</td>
</tr>
<tr>
<td>Avoidance of gastrointestinal and hepatic first-pass effect</td>
<td>Absorption time limited by mucociliary clearance</td>
</tr>
<tr>
<td>Plasma profile similar to the intravenous route: fast onset of action</td>
<td>Low absorption surface in comparison to intestinal mucosa</td>
</tr>
<tr>
<td>Ease of administration, non-invasive: self-medication</td>
<td>Enzymatic activity of the nasal mucosa, especially with proteins- and peptides-degrading enzymes</td>
</tr>
<tr>
<td>Ease of use in patients with nausea and vomiting</td>
<td>Variability in the absorption in case of chronic alterations of the nasal mucosa or with simultaneous administration of vasoconstrictive drugs</td>
</tr>
<tr>
<td>Cheap drug delivery devices</td>
<td>Local intolerance towards nasal mucosa</td>
</tr>
</tbody>
</table>

Grassin-Delyle S. Pharmacol Therap. 134; 2012
The Nose Knows

NASAL PHYSIOLOGY

ABSORPTION PATHWAYS

Chhajed S. Int J Pharm Sci Res. 6; 2012
Why High Cerebral Spinal Fluid Levels

NOSE TO BRAIN TRANSPORT

PLASMA VS CSF CONCENTRATIONS

Illum L. Eur J Pharm Sci. 11; 2000
Ideal Drug Characteristics

- The more lipophilic the better
- Smaller is better
- Volume is important
Strategies to Improve Nasal Bioavailability

- Increase nasal residual time
- Enhance nasal absorption
- Modify drug to change the physiochemical properties
<table>
<thead>
<tr>
<th>Product</th>
<th>Route of Administration</th>
<th>Available Strengths</th>
<th>Dosing</th>
<th>Advantage</th>
<th>Price per Dose* (7/2015)</th>
<th>FDA Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Auto-injector</td>
<td>IM</td>
<td>0.4mg/ml</td>
<td>0.4mg</td>
<td>No training required Easy to use No assembly Decreased risk of needle stick</td>
<td>$345</td>
<td>Yes</td>
</tr>
<tr>
<td>Multi-use Vial</td>
<td>IM, IV, SC</td>
<td>0.4mg/ml</td>
<td>0.4mg</td>
<td>Multiple doses</td>
<td>$11.84</td>
<td>Yes</td>
</tr>
<tr>
<td>Single Dose Vial</td>
<td>IM, IV, SC</td>
<td>0.4mg/ml</td>
<td>0.4mg</td>
<td>Individual dose</td>
<td>$18.99</td>
<td>Yes</td>
</tr>
<tr>
<td>Prefilled Syringe</td>
<td>Intranasal</td>
<td>1mg/ml</td>
<td>1mg</td>
<td>Easy to use Decreased risk of needle stick</td>
<td>$19.80</td>
<td>Yes</td>
</tr>
</tbody>
</table>
FDA Rapidly Approves Naloxone Auto-Injector For Heroin And Prescription Opioid Overdose
Time and Number of Doses

Robertson TM. Prehospital Emergency Care 13; 2009
## Time to Opioid Overdose Reversal

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Intrasal Mean</th>
<th>Intrasal SD</th>
<th>Intrasal Total</th>
<th>Intramuscular Mean</th>
<th>Intramuscular SD</th>
<th>Intramuscular Total</th>
<th>Weight</th>
<th>Mean Difference IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kerr 2009 (1)</td>
<td>8</td>
<td>4.6811</td>
<td>63</td>
<td>7.9</td>
<td>4.6811</td>
<td>89</td>
<td>49.9%</td>
<td>0.10 [1.30, 1.50]</td>
</tr>
<tr>
<td>Kelly 2005 (2)</td>
<td>8.2</td>
<td>4.23</td>
<td>84</td>
<td>7.6</td>
<td>8.9</td>
<td>71</td>
<td>0.0%</td>
<td>0.50 [-1.24, 2.44]</td>
</tr>
<tr>
<td>Kelly 2005 (3)</td>
<td>8</td>
<td>4.608</td>
<td>84</td>
<td>6</td>
<td>4.2248</td>
<td>71</td>
<td>60.1%</td>
<td>2.00 [0.61, 3.39]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>167</strong></td>
<td></td>
<td></td>
<td><strong>160</strong></td>
<td><strong>100.0%</strong></td>
<td></td>
<td></td>
<td><strong>1.05 [-0.81, 2.91]</strong></td>
</tr>
</tbody>
</table>

Heterogeneity: $\tau^2 = 1.30; \chi^2 = 3.56, df = 1 (P = 0.06); I^2 = 72\%$

Test for overall effect: $Z = 1.11 (P = 0.27)$

(1) RR $\geq 10$ and/or GCS $\geq 13$
(2) GCS $> 11$
(3) RR $\geq 10$/min
Opioid Withdrawal Reaction to Naloxone agitation/irritation/violence

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Intranasal Events</th>
<th>Intramuscular Events</th>
<th>Total Events</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kelly 2005 (1)</td>
<td>2</td>
<td>9</td>
<td>11</td>
<td>0.19 [0.04, 0.84]</td>
</tr>
<tr>
<td>Kerr 2009 (2)</td>
<td>5</td>
<td>7</td>
<td>89</td>
<td>0.77 [0.25, 2.32]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>167</td>
<td>160</td>
<td>100.0%</td>
<td>0.42 [0.10, 1.65]</td>
</tr>
</tbody>
</table>

Total events: 167 Intranasal, 160 Intramuscular

Heterogeneity: Tau² = 0.55, Chi² = 2.23, df = 1 (p = 0.14), I² = 55%

Test for overall effect: Z = 1.25 (p = 0.21)

(1) Classified as agitation/irritation
(2) Classified as agitation/violence
**Route of Administration Comparison**

**Level of Consciousness**

<table>
<thead>
<tr>
<th>Level of consciousness</th>
<th>Before Naloxone</th>
<th>After Naloxone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intranasal administration, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coma</td>
<td>12 (24%)</td>
<td>0</td>
</tr>
<tr>
<td>Stupor</td>
<td>24 (48%)</td>
<td>0</td>
</tr>
<tr>
<td>Obtundation</td>
<td>14 (28%)</td>
<td>0</td>
</tr>
<tr>
<td>Lethargic</td>
<td>0</td>
<td>28 (56%)</td>
</tr>
<tr>
<td>Conscious</td>
<td>0</td>
<td>22 (44%)</td>
</tr>
<tr>
<td>Intravenous administration, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coma</td>
<td>10 (20%)</td>
<td>0</td>
</tr>
<tr>
<td>Stupor</td>
<td>28 (56%)</td>
<td>0</td>
</tr>
<tr>
<td>Obtundation</td>
<td>12 (24%)</td>
<td>20 (40%)</td>
</tr>
<tr>
<td>Lethargic</td>
<td>0</td>
<td>18 (36%)</td>
</tr>
<tr>
<td>Conscious</td>
<td>0</td>
<td>12 (24%)</td>
</tr>
</tbody>
</table>

**Response Comparison**

- Intramuscular naloxone
- Intranasal naloxone

NS

Proportion of each group with (a) respiratory rate > 10 per minute, and (b) with Glasgow Coma Scale score > 11 per minute.

Sabzghabaee AM. Arch Med Sci 10; 2014
Kelly A. MJA. 182; 2005
“sorry this is where we get off”

Dahan A Anesthesiology. 2010;112
How Much Does it Take?

Dahan A. Anesthesiology. 2010; 112
Pulmonary Edema

- First case in 1977
- Occurs with doses as low as 80 mcg IV
- Onset within 1-60 minutes
- Majority in healthy men < 50 yo

Naloxone & Catecholamines

- Increases catecholamine release
  - especially in the presence of hypercapnoea
  - The correction of hypercapnoea reduces haemodynamic effects.
    - Mills CA (1988)
- There is no clinical evidence to support hypercapnoea correction prior to administration of naloxone.
Plasma Norepinephrine Levels

Mills CA. Anesth Anal. 1988
Plasma Epinephrine Levels

Mills CA. Anesth Anal. 1988
The Solution

- A multi-faceted approach to overdose prevention is required.
Strategies to Address Overdose

- Prescription monitoring programs
  - Paulozzi et al. Pain Medicine 2011
- Prescription drug take back events
  - Safe disposal
- Safe opioid prescribing education
- Expansion of opioid agonist treatment
  - Clausen et al. Addiction 2009;104;1356-62
- Safe injection facilities
Evaluations of OEND programs

- **Feasibility**
  - Piper et al. Subst Use Misuse 2008; 43; 858-70
  - Enteen et al. J Urban Health 2010; 87: 931-41
  - Walley et al. JSAT 2013; 44:241-7 (Methadone and detox programs)

- **Increased knowledge and skills**
  - Green et al. Addiction 2008: 103;979-89

- **No increase in use, increase in drug treatment**

- **Reduction in overdose in communities**
  - Maxwell et al. J Addict Dis 2006;25; 89-96
  - Walley et al. BMJ 2013; 346: f174
State to State Data
West Virginia

- 1999-2004 Largest increase in drug overdose mortality rates
- 295 unintentional deaths from pharmaceutical overdose
- 93% from opioids
- 90% were men age 18-70 yo
- 63% were associated with drug diversion
- 21% due to doctor shopping
- Substance abuse indicators present in 95%
Opioid Overdose Deaths in Florida 2003-2009

Cobaugh DJ. AJHP. 71; 2014
Enrollments and Rescues: 2006-2012 Massachusetts

- **Enrollments**
  - 16,379 individuals
  - >10 per day

- **Rescues**
  - 1,741 reported
  - >1 per day

- AIDS Action Committee
- AIDS Project Worcester
- AIDS Support Group of Cape Cod
- Brockton Area Multi-Services Inc. (BAMSI)
- Bay State Community Services
- Boston Public Health Commission
- Greater Lawrence Family Health Center
- Holyoke Health Center
- Learn to Cope
- Lowell House/ Lowell Community Health Center
- Manet Community Health Center
- Northeast Behavioral Health
- Seven Hills Behavioral Health
- Tapestry Health
- SPHERE
### Enrollee Characteristics: 2006-2012

<table>
<thead>
<tr>
<th></th>
<th>User n=11,002</th>
<th>Non-User n=5,377</th>
</tr>
</thead>
<tbody>
<tr>
<td>Witnessed overdose ever</td>
<td>75%</td>
<td>42%</td>
</tr>
<tr>
<td>Lifetime history of overdose</td>
<td>49%</td>
<td></td>
</tr>
<tr>
<td>Receive naloxone ever</td>
<td>41%</td>
<td></td>
</tr>
<tr>
<td>Inpatient detox, past year</td>
<td>64%</td>
<td></td>
</tr>
<tr>
<td>Incarcerated, past year</td>
<td>28%</td>
<td></td>
</tr>
<tr>
<td>Reported at least one overdose</td>
<td>7.5%</td>
<td>2.0%</td>
</tr>
</tbody>
</table>

Program data
## Adverse Events:
### Sept 2006-Dec 2012

<table>
<thead>
<tr>
<th>Event</th>
<th>Count/Total</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deaths</td>
<td>7/1729</td>
<td>0.4%</td>
</tr>
<tr>
<td>OD requiring 3 or more doses</td>
<td>72/1604</td>
<td>4%</td>
</tr>
<tr>
<td>Recurrent overdose</td>
<td>3/1741</td>
<td>0.2%</td>
</tr>
<tr>
<td>Withdrawal symptoms after naloxone</td>
<td>107/219</td>
<td><strong>49%</strong></td>
</tr>
<tr>
<td>Difficulty with device</td>
<td>11/1741</td>
<td>0.6%</td>
</tr>
<tr>
<td>Negative interactions with public safety</td>
<td>114/466</td>
<td>24%</td>
</tr>
<tr>
<td>Confiscations</td>
<td>205/5271</td>
<td>4%</td>
</tr>
</tbody>
</table>

N=1,741

Program data
Fatal Opioid OD Rates by OEND Implementation

## Challenges for Community Programs

<table>
<thead>
<tr>
<th>Prescription and prescriber typically required</th>
<th>Co-prescribe naloxone with opioids for pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naloxone cost is increasing, funding is minimal</td>
<td>Co-prescribe with methadone/buprenorphine for addiction</td>
</tr>
<tr>
<td>Missing people who don’t identify as drug users, but have high risk</td>
<td>Insurance should fund this</td>
</tr>
<tr>
<td>CBOs target IDU, people w/substance use disorders, HIV prevention</td>
<td>Increase patient, provider &amp; pharmacist awareness</td>
</tr>
<tr>
<td></td>
<td>Universalize overdose risk</td>
</tr>
</tbody>
</table>
Opioid overdose is a public health crisis
Naloxone is a safe and effective opioid reversal agent
Multiple routes of administration are available
Diversion and prescribing of opioids must be addressed
Questions???