Disclosures

- Jeffrey Fudin declares the following: Astra Zeneca (Speakers Bureau, Advisory Board), Depoject (Advisory Board), Endo (Consultant), Kello (Speakers Bureau, Advisory Board), KerfPharm (Consultant), Millennium Health, LLC (Speakers Bureau, Advisory Board, Expert Witness), Practical Pain Management (Developer of Online Opioid Conversion Calculator), Reingate, LLC (Founder, Owner), Scotts Pharmaceuticals (Consultant)
- Chris Herndon and Tony Tommasello declare no conflicts of interest, real or apparent, and no financial interests in any company, product, or service mentioned in this program, including grants, employment, gifts, stock holdings, and honoraria.

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Learning Objectives

- Review clinical guidelines and evidence findings regarding chronic opioid therapy in chronic pain management.
- Discuss strategies that enhance safe use of chronic opioid therapy in chronic pain management.
- Describe naloxone's role in attenuating death and disability from the opioid overdose epidemic.
- Review clinical guidelines and evidence findings regarding naloxone use and overdosage deaths.

Target Audience: Pharmacists

ACPE#: 0202-0000-16-045-L01-P

Activity Type: Knowledge-based

Schedule

- Opioids for chronic noncancer pain
  - Moderator: Dr. Tommasello
  - Pro: Dr. Fudin
  - Con: Dr. Herndon
- Increasing naloxone access for opioid overdose
  - Moderator: Dr. Herndon
  - Pro: Dr. Tommasello
  - Con: Dr. Fudin
- Panel discussion
Which of the following guidelines for opioid prescribing provides specific recommendations on duration of therapy?

a) American Academy of Physicians / American Pain Society
b) American Geriatrics Society
c) American Society of Anesthesiologists
d) Centers for Disease Control
e) American Academy of Neurology

Which of the following are considered proven methods for reducing risk of opioid misuse / abuse?

a) Prescription Drug Monitoring Programs
b) Urine / Saliva / Blood Drug Testing
c) Patient-Prescriber Treatment Agreements
d) Observed Pill Counts
e) Insurance Mandated Quantity Limits

Why are patients most likely to overdose with extended release (ER) opioids during the first 2 weeks of treatment?

a) Because the pharmacokinetics of ER opioids make them more dangerous than short-acting opioids
b) Because health care providers struggle with appropriate equianalgesic conversions
c) Because patients are more likely to abuse ER opioids than short-acting opioids
d) Because patients do not receive appropriate education about the use of ER opioids

Which of the following statements is true about naloxone?

a) It is a Schedule 5 drug due to its abuse potential
b) It can trigger symptoms of withdrawal in opioid-naive individuals.
c) It reverses symptoms of opioid overdose within 1 to 2 minutes
d) Patients may require more than one dose of naloxone

Community distribution of naloxone has been proven to reduce the rate of:

a) Unintentional opioid overdose deaths
b) Opioid misuse and abuse
c) Heroin use
d) Patients seeking treatment for opioid addiction

Use of Chronic Opioid Therapy in Chronic Pain Management

Introduction
Tony Tommasello, Ph.D.
Risks and Benefits

- I am an addiction specialist, not a pain specialist
- Aware of the benefit to millions of patients for whom opioids provide substantial short-term pain relief and also the societal and individual risks posed by excessive and illicit opioid use
- The right drug, for the right patient, in the right dose, at the right time

Pain Management in the United States

- In 2012, there were 258 million opioid prescriptions
  - Prescription opioid sales increased 300% since 1999
  - There has not been an overall change in the amount of pain Americans report
- In 2013, nearly 2 million individuals either abused or were dependent on opioids
- In 2013, 16,000 individuals died from opioid-related overdoses
  - Four times the number in 1999

http://www.cdc.gov/drugoverdose/prescribing/guideline.html

Responsible Opioid Prescribing

- Patient evaluation, including risk assessment
- Treatment plans that incorporate functional goals
- Informed consent and prescribing agreements
- Periodic review and monitoring of patients
- Referral and patient management
- Documentation
- Compliance with state and federal law

The American Academy of Pain Medicine (AAPM)
Use of Opioids for the Treatment of Chronic Pain

- 2013 clinical guideline, notes that:
  - 100 million Americans suffer from pain
  - Treatment of pain costs the United States more than half a trillion dollars per year
  - Pain is one of the most common reasons patients seek health care
  - It frequently is inappropriately treated
- Offers statements on the use of opioids


AAPM 2013 Clinical Guideline Statements

- Legislation and regulatory policies should limit inappropriate prescribing
  - But should not discourage or prevent prescription of opioids where medically indicated and appropriately managed
- Prescription of opioids for chronic, intractable pain is appropriate when
  - More conservative methods are ineffective, and
  - The treatment plan is reasonably designed to avoid diversion, addiction, and other adverse effects

AAPM 2013 Clinical Guideline Statements (cont.)

- Health care providers should be sensitive to and seek to minimize the risks of addiction, respiratory depression and other adverse effects, tolerance, and diversion
  - However, some commonly held assumptions about these issues need to be reviewed.
- Opioids should be prescribed only after
  - A thorough evaluation of the patient
  - Consideration of alternatives
  - Development of a treatment plan tailored to the needs of the patient and minimization of adverse effects, and
  - Ongoing monitoring and documentation

Opioids, Overdoses, and Pain Management

Jeffrey Fudin, PharmD, DAAPM, FCCP, FASHP
Clinical Pharmacy Specialist & PGY2 Pain Residency Director;
Straton VA Medical Center
Adjunct Affiliations: Albany College of Pharmacy & Health Sciences,
Western New England University, UCONN School of Pharmacy

Learning Objectives

1. Summarize clinical guidelines and evidence findings regarding chronic opioid therapy in chronic pain management.
2. Discuss strategies that enhance safe use of chronic opioid therapy in chronic pain management.

Second Hour

1. Describe the role of naloxone in attenuating death and disability from the opioid overdose epidemic.
2. Summarize clinical guidelines and evidence findings regarding naloxone use and overdose deaths.

Is Fudin “Pro-Opioid” for Chronic Non-Cancer Pain?

- A matter of semantics...
  - Pro-opioid
  - Anti-opioid
- Absence of Evidence is Evidence of Absence
- I am anti...
  - Myths and Hysteria
  - And then there’s the guidelines...

Pain Guidelines


Risk Assessment Tools

<table>
<thead>
<tr>
<th>Question</th>
<th>Form Fats</th>
<th>Indicators</th>
<th>Advantages</th>
<th>Disadvantages</th>
<th>Scoring</th>
<th>Validated</th>
</tr>
</thead>
<tbody>
<tr>
<td>DOAPP2</td>
<td>%, %</td>
<td>Pain, assess for high pain risk, moderate risk, low risk</td>
<td>[details]</td>
<td>[details]</td>
<td>[details]</td>
<td>[details]</td>
</tr>
<tr>
<td>DOAPP-R</td>
<td>%</td>
<td>Pain, assess for high pain risk, moderate risk, low risk</td>
<td>[details]</td>
<td>[details]</td>
<td>[details]</td>
<td>[details]</td>
</tr>
<tr>
<td>CRT</td>
<td>1</td>
<td>Eligibility criteria for treatment</td>
<td>[details]</td>
<td>[details]</td>
<td>[details]</td>
<td>[details]</td>
</tr>
<tr>
<td>DIRE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Opioid Misuse Tools</td>
<td>Question Formats</td>
<td>Indication</td>
<td>Advantages</td>
<td>Disadvantages</td>
<td>Scoring</td>
<td>Validated</td>
</tr>
<tr>
<td>--------------------</td>
<td>-----------------</td>
<td>-----------</td>
<td>------------</td>
<td>--------------</td>
<td>---------</td>
<td>-----------</td>
</tr>
<tr>
<td>PAD*</td>
<td>SA.</td>
<td>To assess adherence to treatment and to identify patients at risk of opioid misuse</td>
<td>Helps clinicians identify patients at risk of misuse</td>
<td>Risk assessment tool</td>
<td>PAD</td>
<td>PAD</td>
</tr>
<tr>
<td>COMM*</td>
<td>General Hospital</td>
<td>To assess compliance with treatment and to identify patients at risk of opioid misuse</td>
<td>Helps clinicians identify patients at risk of misuse</td>
<td>Risk assessment tool</td>
<td>COMM</td>
<td>COMM</td>
</tr>
<tr>
<td>ABC*</td>
<td>7 items</td>
<td>To assess compliance with treatment and to identify patients at risk of opioid misuse</td>
<td>Helps clinicians identify patients at risk of misuse</td>
<td>Risk assessment tool</td>
<td>ABC</td>
<td>ABC</td>
</tr>
</tbody>
</table>

## Myths

- Extended-release opioids are more dangerous than immediate-release opioids.
  - Is 20mg of extended-release morphine somehow more potent than 30mg of immediate-release morphine?
  - Does blunting the Cmax by slowly releasing the same amount of medication over a period of 10-12 hours compared to 1-2 hours make opioids more dangerous?
    - **ABSURD**
    - yet interpretation of several studies recently have endorsed those exact conclusions.1,2

## The truth?

- Studies have shown increased risk of adverse effects in patients on extended-release opioids
  - but often define chronic pain inappropriately and/or do not adjust for post-surgical pain and acute pain prescriptions.
- Data from a recent study highlights overdose rates dramatically increase the first two weeks of treatment with ER opioids
  - Inappropriate conclusion
    - The dosage form itself is more dangerous and short-acting opioids should be used if possible.1
  - Correct conclusion
    - Healthcare providers struggle with appropriate equianalgesic conversions when performing spin opioid rotations.2,3

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Variability in Opioid Equivalence Survey

- Sept 13 thru December 31, 2013.
- 411 Respondents, adjusted after stats to 319
- RPhs, MD/DOs, NPs, PAs
- Convert to Daily MEQ:
  - Hydrocodone 80mg; Fentanyl 75mcg/hr;
  - Methadone 40mg; Oxycodone 120mg;
  - Hydromorphone 48mg

Available Online Opioid Conversion Calculators

- Med Calc
- WA State Agency
- Pain Research
- Pain Physicians
- Hopkins
- Palliative Care
- Global RPh
- Practical Pain Management (PPM)

What do you think were the most outrageous conversions?

Table 1: Comparison of Proposed Conversion To Methadone Conversion Parameters

<table>
<thead>
<tr>
<th>Source</th>
<th>Conversion Factors</th>
<th>morphine (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>morphine 100</td>
<td>2.238</td>
<td>0.0985</td>
</tr>
<tr>
<td>morphine 200</td>
<td>4.476</td>
<td>0.1971</td>
</tr>
<tr>
<td>morphine 300</td>
<td>6.714</td>
<td>0.3957</td>
</tr>
<tr>
<td>morphine 400</td>
<td>8.952</td>
<td>0.5943</td>
</tr>
</tbody>
</table>

Morphine (mg)

Equianalgesic Dose of Morphine to Methadone

- 100mg Morphine = 60mg Methadone
- 300mg Morphine = 90mg Methadone
- 302mg Morphine = 90mg Methadone

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Original Research Article
Cohort Study of the Impact of High-dose Opioid Analgesics on Overdose Mortality

Design. Prospective observational cohort with one year follow-up.
Setting. One year in one state (NC) using a controlled substances prescription monitoring program, with name-linked morality data.
Subjects. 2,182,374 opioid analgesic patients.
Results.
• Of 2,182,374, there were 478 overdose deaths (0.022% per year).
• 60.0% of opioid analgesic deaths in pts who received benzodiazepines.
• Rates of overdose death among those co-prescribed benzodiazepines and opioid analgesics were ten times higher: (7.0 per 10,000 person-years, 95% CI: 3.3, 7.8)

Desquette, N., Laran, U., Might, J., Forsk, S. (Prospective study, 2019). Expanding Opportunities through Patient Care?

And then there's the CDC Guidelines.

Chronic Pain Sufferers Have Something to Say About "Opioid Epidemic"

Strategies that enhance safe use of chronic opioid therapy
• Encourage the use of risk stratification tools (See pained.org)
• Education for all prescribers & pharmacists
  – Close attention to drug interactions
  – Sedative hypnotics, enzyme (and pGP) inhibitors/inducers, natural food products and vitamin supplements, pharmacogenetics, etc.
• Slow escalation of opioid doses upon conversion
• Recognize unique population variables
• Realize the value of a pharmacist "provider" to mitigate drug risks and encourage

HERE'S SOME OXYCODONE FOR YOUR HANGNAIL

Chris Herndon, PharmD, BCPS, CPE
Associate Professor, Southern Illinois University

Risk vs. Benefit
• Benefit Risk Assessment (BRA)
• Naturalistic vs. randomized evidence
• Quite simply
  – Number Needed to Treat: Number Needed to Harm
  – Should be > 1
• Quality-Adjusted Time Without Sx and Tox (QALYs)
• How do we assess??

Benefit (efficacy)

- Undeniably effective for short term use in acute pain
  - we think...
- "No high, moderate, or low evidence to suggestion opioids effective long term for persistent noncancer pain"
- Long term prescribing and dose escalation based on anecdotal and naturalistic experience
- Do we really lack controlled evidence of benefit?

Pseudo-Placebo Controlled, All Pain

- Low dose (fixed or placebo) vs. escalating dose
  - used in refractory epilepsy registration trials
  - assumes low dose either superior or equal to placebo
- 2 arm randomized placebo controlled 12-month trial
- n = 135
- No difference in any of 3 primary outcome measures
  - usual pain (p = 0.31)
  - pain relief (p = 0.06)
  - functional disability (p = 0.06)

Neuropathic Pain

Table 4: Multivariate (adjusted) analysis assessing mean disability and physical functioning scores for each opioid dose group at baseline and 12-months

<table>
<thead>
<tr>
<th>Pain Group</th>
<th>Mean (SD)</th>
<th>Pain Disability Score</th>
<th>Physical Functioning Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>0mg</td>
<td>25.5 (14.5)</td>
<td>41.8 (13.5)</td>
<td>40.5 (15.0)</td>
</tr>
<tr>
<td>50mg</td>
<td>32.5 (24.2)</td>
<td>27.1 (17.2)</td>
<td>40.5 (15.0)</td>
</tr>
<tr>
<td>100mg</td>
<td>27.5 (15.1)</td>
<td>27.1 (17.2)</td>
<td>40.5 (15.0)</td>
</tr>
</tbody>
</table>

P-value:
- p < 0.05

LOWER BETTER!

Fibromyalgia

- 12 month observational study, n = 1700
- 3 cohorts
  - no opioid
  - tramadol
  - any opioid
- Compared to those taking no opioid, opioid users had:
  - Worse pain severity
  - Worse pain interference
  - Worse disease impact
  - Worse insomnia
  - Worse disability
  - Worse depression scores

Is hyperalgesia really a thing?

  - 2 studies involving 144 patients
  - hyperalgesic pain associated with higher post-op pain intensity and post-op opioid consumption
  - 58-month follow-up, n = 54
  - pre-op opioid use associated with higher post-op opioid requirement, hospital length of stay, and lower functional scores
  - women only; placebo and experimental heat pain

Drugs Used to Get High

(all responders)

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Draft CDC Guidelines for Opioids

1. Non-pharmacologic therapy and non-opioid pharmacologic therapy are preferred for chronic pain. Providers should only consider adding opioid therapy if expected benefits for both pain and function are anticipated to outweigh risks.

2. Before starting long-term opioid therapy, providers should establish treatment goals with all patients, including realistic goals for pain and function. Providers should continue opioid therapy only if there is clinically meaningful improvement in pain and function that outweighs risks to patient safety.

Draft CDC Guidelines for Opioids

3. Before starting and periodically during opioid therapy, providers should discuss with patients risks and realistic benefits of opioid therapy and patient and provider responsibilities for managing therapy.

4. When starting opioid therapy, providers should prescribe short-acting opioids instead of extended release/long-acting (ER/LA) opioids.

5. When opioids are started, providers should prescribe the lowest possible effective dosage. Providers should implement additional precautions when increasing dosage to > 50 MME/day and should avoid increasing dosages to > 90 MME/day.
Draft CDC Guidelines for Opioids

6. When opioids are started, providers should prescribe the lowest possible effective dosage. Providers should implement additional precautions when increasing dosage to > 50 MME/day and should avoid increasing dosages to > 90 MME/day.

7. Long-term opioid use often begins with treatment of acute pain. When opioids are used for acute pain, providers should prescribe the lowest effective dose of short-acting opioids and should prescribe no greater quantity than needed for the expected duration of pain severe enough to require opioids. Three or fewer days will usually be sufficient for non-traumatic pain not related to major surgery.

Draft CDC Guidelines for Opioids

8. Providers should evaluate patients within 1 to 4 weeks of starting long-term opioid therapy or of dose escalation to assess benefits and harms of continued opioid therapy. Providers should evaluate patients receiving long-term opioid therapy every 3 months or more frequently for benefits and harms of continued opioid therapy. If benefits do not outweigh harms of continued opioid therapy, providers should work with patients to reduce opioid dosage and to discontinue opioids when possible.

9. Before starting and periodically during continuation of opioid therapy, providers should evaluate risk factors for opioid-related harms. Providers should incorporate into the management plan strategies to mitigate risks, including considering offering naloxone when factors that increase risk for opioid-related harms are present.

Draft CDC Guidelines for Opioids

10. Providers should review the patient’s history of controlled substance prescriptions using state PDMP data to determine whether the patient is receiving excessive opioid dosages or dangerous combinations that put him/her at high risk for overdose. Providers should review PDMP data when starting opioid therapy and periodically during long-term opioid therapy, ranging from every prescription to every 3 months.

11. Providers should use urine drug testing before starting opioids for chronic pain and consider urine drug testing at least annually for all patients on long-term opioid therapy to assess for prescribed medications as well as other controlled substances and illicit drugs.

12. Providers should avoid prescribing of opioid pain medication and benzodiazepines concurrently whenever possible.

Data from my service

Table 2. Changes in Brief Pain Inventory Parameters

<table>
<thead>
<tr>
<th>Assessment Parameter</th>
<th>Mean Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>BPI - Severity - Now</td>
<td>na</td>
</tr>
<tr>
<td>BPI - Severity - Average</td>
<td>na</td>
</tr>
<tr>
<td>BPI - Severity - Worst</td>
<td>na</td>
</tr>
<tr>
<td>BPI - Interference - Activity</td>
<td>-0.21 (p = .02)</td>
</tr>
<tr>
<td>BPI - Interference - Mood</td>
<td>-0.21 (p = .04)</td>
</tr>
<tr>
<td>BPI - Interference - Social Function</td>
<td>-0.21 (p = .02)</td>
</tr>
<tr>
<td>BPI - Interference - Pain</td>
<td>-0.21 (p = .03)</td>
</tr>
<tr>
<td>BPI - Total Pain Interference</td>
<td>-0.21 (p = .02)</td>
</tr>
</tbody>
</table>

Other “time tested” therapies....

- Intravenous EIOH for premature labor
- Cocaine for toothaches
- Insulin “shock therapy” for schizophrenia
- Crocodile dung contraception
- Arsenic for malaria and syphilis
- Mercury for constipation

Is it time we add long-term, high dose opioids for persistent noncancer pain to this list?

NALOXONE AVAILABILITY LEADS TO RISKIER BEHAVIOR

Chris Hemdon, PharmD, BCPs

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Naloxone
- Patented in 1961
- Received FDA approval for opioid reversal 1971
- World Health Organization List of Essential Medicines

Naloxone Regulatory Considerations
- Good samaritan
- Liability protection
- Collaborative practice agreement

Immunity: Prescribers & Dispensers

Prescribing via standing orders

Prescribing to third party

Naloxone Rescue

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Naloxone for Reversal of Opioid Overdose

- Semi-synthetic competitive opioid antagonist at the mu-opioid receptor
- Reverses clinical signs of opioid overdose including respiratory depression, sedation and hypotension
- May be administered via intravenous (IV), intramuscular (IM), subcutaneous (SC) or intranasal (IN) administration
- No known abuse potential and no effect in opioid-naive individuals
- Minimal adverse effects with the exception of withdrawal symptoms. Severity of symptoms proportional to naloxone dose and degree of opioid dependence
- Clinical response generally seen within 3-5 min, with effects lasting between 30-60 min depending on the dose and route of administration
- More than one dose may be required, particularly if long-acting opioids were taken

Intranasal naloxone pharmacokinetics

Intrinsic Activity and Affinity for the μ Opioid Receptor

<table>
<thead>
<tr>
<th>Compound</th>
<th>Intrinsic Activity</th>
<th>Log[dissociation constant] (μM) to achieve 50% binding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methadone</td>
<td>Agonist</td>
<td>1.3</td>
</tr>
<tr>
<td>Morphine</td>
<td>Agonist</td>
<td>0.9</td>
</tr>
<tr>
<td>Naloxone</td>
<td>Antagonist</td>
<td>0.87</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>Partial Agonist</td>
<td>0.22</td>
</tr>
</tbody>
</table>

Concentration of Prescription Opioid Drugs in the United States has been increasing over the last decade

- From 2000-2002, the United States has remained the highest consumer of prescription opioids
- Rate of consumption slowed from 2009-2011 and 2010-2012

Opioid-related Emergency Department (ED) Visits Have Been Increasing

- Most frequent analgesics in 2011:
  - Oxycodone/combinations
  - Hydrocodone/combinations
  - Methadone
  - Morphine/combinations

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Opioid-Related Deaths and Treatment Admissions Have Tended Upward With Increasing Retail Sales

- Opioid-related poisoning deaths have increased 2
- Death rate quadrupled from 1999 through 2011
- Rate has slowed since 2010

Major Sources of Painkillers Used Nonmedically (2012-2013)

<table>
<thead>
<tr>
<th>Percentage of Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Friend or relative (free)</td>
</tr>
<tr>
<td>Friend or relative (bought or taken)</td>
</tr>
<tr>
<td>Prescription (1 MD)</td>
</tr>
<tr>
<td>Drug dealer or stranger</td>
</tr>
</tbody>
</table>

Reported Heroin Use Coincided With the Introduction of Abuse-Deterrent OxyContin

- 82.6% of heroin initiates reported that their initial drug was a prescription opioid
- Rate of heroin death was inversely related to the
  prescription opioid market

Dose Associated With Risk of Death

Adjusted Hazard Ratios (HRs) Associated With Maximum Prescribed Dose of 2100 mg MED by Medical Condition

<table>
<thead>
<tr>
<th>Condition</th>
<th>Adjusted HR (95% CI)</th>
<th>Absolute Risk Difference (MED)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Substance use disorders</td>
<td>0.54 (0.48-0.62)</td>
<td>0.14</td>
</tr>
<tr>
<td>Acute pain</td>
<td>0.65 (0.51-0.83)</td>
<td>0.21</td>
</tr>
<tr>
<td>Chronic pain</td>
<td>0.70 (0.63-0.79)</td>
<td>0.20</td>
</tr>
<tr>
<td>Cancer</td>
<td>1.59 (1.51-1.67)</td>
<td>0.65</td>
</tr>
</tbody>
</table>

Community Education and Naloxone Distribution Effects Overdose Rate

Unadjusted unintentional opioid-related overdose death rates in 19 communities with no, low, and high enrollment in overdose education and naloxone distribution program in Massachusetts, 2002-09.

Summary

- Naloxone is a time-tested proven antidote for opioid overdose
- Intranasal insufflation is an efficacious means of naloxone administration
- The number of opioid overdoses is increasing for a variety of reasons
- Overdose education and naloxone distribution can reduce opioid overdose events

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Opioids, Overdoses, and Pain Management

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Stratton VA Medical Center
Adjunct Affiliates, Albany College of Pharmacy & Health Sciences,
Western New England University, UCONN School of Pharmacy

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 RX coverage! And, they had no $$$ to pay for it.

Is naloxone for everyone?
Is each dosage form therapeutically interchangeable?

Recommendations That Naloxone Be Readily Accessible

Are You Kidding ME?

Pitfalls of Outpatient Naloxone

• Access to in-home an EMS naloxone matters But...
  – Know what you dispense and if it works
  – Payment for product, prior approval
  – Payment for counseling
  – Liability
  • non-FDA approved use
  • failed reversal attempts

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Pharmacology

- Pure opioid mu-receptor agonist
- Partial opioid agonist
  - Tramadol risk?
- Partial opioid agonist/antagonist
  - Buprenorphine?
- Opioid receptor antagonist

Available Naloxone Comparisons

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


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)


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**IM 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)

**Time to “Response”**

- IM naloxone: mean 6-8 min
- Auto-injector naloxone: mean 6-8 min
- Intra-nasal naloxone: Similar or extended by 2 min than IM
  - Range 2-13 min

**IN Route**

- Rapid onset ???
- High bioavailability ???
- Delivery to CNS via olfactory mucosa
- 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 responded to IV naloxone ONLY

**Exposure to Bloodborne Pathogens**

- IN route could be considered as a safer route of naloxone administration of traditional IM 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)

**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
  - IN kit: 3 steps
- IN kit: 5 steps, required dexterity and manipulation

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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

Cost of Auto-injector
- Naloxone auto-injector: $1700 per dose
- Newest intranasal dosage form: $10.75 per dose
- Naloxone otherwise $1 per dose for non-FDA intranasal

Questions?

Which of the following guidelines for opioid prescribing provides specific recommendations on duration of therapy?

a) American Academy of Physicians / American Pain Society
b) American Geriatrics Society
c) American Society of Anesthesiologists
d) Centers for Disease Control
e) American Academy of Neurology

Which of the following are considered proven methods for reducing risk of opioid misuse / abuse?

a) Prescription Drug Monitoring Programs
b) Urine / Saliva / Blood Drug Testing
c) Patient-Prescriber Treatment Agreements
d) Observed Pill Counts
e) Insurance Mandated Quantity Limits

Why are patients most likely to overdose with extended release (ER) opioids during the first 2 weeks of treatment?

a) Because the pharmacokinetics of ER opioids make them more dangerous than short-acting opioids
b) Because health care providers struggle with appropriate equianalgesic conversions
c) Because patients are more likely to abuse ER opioids than short-acting opioids
d) Because patients do not receive appropriate education about the use of ER opioids

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Which of the following statements is true about naloxone?

a) It is a Schedule 5 drug due to its abuse potential
b) It can trigger symptoms of withdrawal in opioid-naive individuals.
c) It reverses symptoms of opioid overdose within 1 to 2 minutes
d) Patients may require more than one dose of naloxone

Community distribution of naloxone has been proven to reduce the rate of:

a) Unintentional opioid overdose deaths
b) Opioid misuse and abuse
c) Heroin use
d) Patients seeking treatment for opioid addiction