Opioid REMS: Policy, Education, & Dosing Risks

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Sciences Section Editor, Pain Medicine
Chairman/Founder, Professionals for Rational Opioid Monitoring and Pharmcotherapy

OBJECTIVES:

1. Discuss the benefits and risks associated with opioids in pain management
2. Comprehend the rationale for FDA implementation of opioid REMS education
3. Describe the components of currently proposed opioid REMS programs
4. Describe dosing conversion risks associated with morbidity and mortality
5. Explain the role of opioid REMS in pharmacy practice and patient care

BIBIOLGRAPHY & SUGGESTED READINGS

5. Fudin J. Update on Risk Evaluation and Mitigation Strategies (REMS) associated with long-acting opioids, CE program of the University of Connecticut School of Pharmacy and Drug Topics. Drug topics. 2011 October: 45-58.
Opioid REMS
Policy, Education, & Dosing Risks

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Disclosures

- Speakers’ Bureaus
  - Janssen Pharmaceuticals
  - Purdue Pharma
  - Cadence Pharmaceuticals
  - Cumberland Pharmaceuticals
- Consultant
  - Practical Pain Management
  - Author, Online Opioid Calculator

Practice Pearls to Mitigate Opioid Risks

- Political Unrest and Current Events
- REMS History & Updates
- Underappreciated drug interactions risks
- Dose conversion disasters
- Equivalent dose of morphine
  - Is it possible to determine?
  - How do drug interactions affect equivalency?
- What can I do to mitigate risks?
  - Education and Slow Titration
  - Understanding the UDS versus Serum Analysis

The Opioid Pendulum

Avoidance
Even dying people at risk of addiction

Balance
Risk stratification and principles of addiction medicine applied to opioid prescribing regardless of the pain problem at hand

Widespread Use
Opophobia must go

With permission from Dr. Steven Passik

Highly Prescribed Products Compared With Opioid Products Commonly Prescribed in the US

- Atorvastatin
- Amoxicillin
- Hydrocodone/Combo
- Oxycodone/Combo
- Tramadol/Combo
- Codeine/Combo
- Oxycodone
- Fentanyl
- Morphine
- Hydromorphone

Highly Prescribed Products in US

Number of Prescriptions (in Millions)

120
100
80
60
40
20
0

Multiple Barriers Exist to Opioid Utilization

- HCP Factors
  - Communication between HCP and patient
  - Fear of disciplinary action or prosecution
  - Concern about potential for abuse
  - Inadequate training
  - Reimbursement issues

- Patient Factors
  - Fear of addiction and side effects
  - Socioeconomic and psychological factors
  - Poor patient knowledge

HCP = Healthcare professional.
Pain Relievers Obtained for Nonmedical Use: Sources Reported by Users*  

<table>
<thead>
<tr>
<th>Source of Drugs</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Friend/Relative</td>
<td>59.8</td>
</tr>
<tr>
<td>One Doctor</td>
<td>16.8</td>
</tr>
<tr>
<td>Dealer/Stranger</td>
<td>4.3</td>
</tr>
<tr>
<td>Internet</td>
<td>0.8</td>
</tr>
</tbody>
</table>

*Source of drugs for the most recent nonmedical use of pain relievers reported by persons aged 12 or older in the United States 2005.


Current Events

- January 25, 2013
  - FDA advisory panel voted 19/10 recommending to the FDA commissioner to reschedule hydrocodone combinations to C-II status.

- February 7-8, 2013
  - FDA held a public hearing on the “Impact of Approved Drug Labeling on Chronic Opioid Therapy.”

The purpose?

- next slide


Citizen’s Petition (from PROP)

The petition requested 3 labeling changes by the FDA

1) Strike the term “moderate” from the indication of opioids for noncancer pain
   - Leaving “severe pain” as the only indication
2) MDD daily opioid dose, equivalent to 100mg of morphine for noncancer pain
3) Add a maximum duration of 90 days for continuous (daily) opioid use for noncancer pain.

Label Changes for Opioids, FOR or AGAINST
http://paindr.com/label-changes-for-opioids-for-or-against/

We Intend to be PROMPT with a Challenge to PROP FDA Letter
http://paindr.com(prompt-challenges-prop-fda-letter)

TOLERANCE ≠ ADDICTION

PHYSICAL DEPENDENCE
**FDA 4-Pronged Approach**

- **Education**
  - Pharmaceutical manufacturers will be required to fund educational initiatives about safe and appropriate use devoted to both health care providers and patients.

- **Monitoring**
  - There will be implementation of prescription monitoring programs across the United States.

- **Disposal**
  - Issues surrounding drug disposal and drug “take-back” programs need to be made more available and consistent.

- **Enforcement**
  - “Pill mills” and other health care providers contributing to the problem through illegal or unethical practices, need to be brought to justice, and shut down.

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**Opioids included in REMS**

- Targeted Opioids Include (long-acting and extended-release)
  - fentanyl
  - Hydromorphone
  - Methadone
  - Oxycodone
  - Oxymorphone

- ROOs: Approved formulations in the US and Europe
  - Oral transmucosal fentanyl citrate
  - Fentanyl effervescent buccal tablet
  - Bio-erodable mucoadhesive (BEMA™) patch
  - Fentanyl solution nasal spray
  - Sublingual fentanyl tablet

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**What is REMS?**

A. Risks Emulated from Morphine Substances
B. Rational Exceptions to Morphine Substances
C. Risk Evaluation Mitigation Strategies
D. None of the Above

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**Risk Evaluation and Mitigation Strategies (REMS) for Transmucosal Immediate Release Fentanyl (TIRF) Products**

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**TIRF Program Goals**

The goals of the TIRF REMS Access program are to mitigate the risk of misuse, abuse, addiction, overdose, and serious complications due to medication errors by:

1. Prescribing and dispensing TIRF medicines only to appropriate patients, which includes use only in opioid tolerant patients.
2. Preventing inappropriate conversion between fentanyl products.
3. Preventing accidental exposure to children and others for whom it was not prescribed.
4. Educating prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction, and overdose.

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**Overview**

- Appropriate patient selection
- Understanding risk factors for misuse, abuse, addiction and overdose
- Dosage and administration
- Patient counseling
- Effective patient management and follow-up
**Patient Selection**

- Indicated for adult patients with **cancer** pain
  - 18+ years old (16+ for Actiq only)
  - Opioid Tolerant*
  - Current treatment with regular opioid (ATC)
  - In need of pain management for **persistent breakthrough pain**

**Opioid Tolerance**

- Patients considered opioid-tolerant are those who are taking, **for one week or longer, at least**:
  - 60 mg oral morphine/day
  - 25 mcg transdermal fentanyl/hour
  - 30 mg oral oxycodone/day
  - 8 mg oral hydromorphone/day
  - 25 mg oral oxymorphone/day
  - OR an equianalgesic dose of another oral opioid
  - List available at [www.TIRFREMSaccess.com](http://www.TIRFREMSaccess.com)

**Contraindications**

- Opioid non-tolerant patients
- Management of acute or postoperative pain
  - Specific lists available in Full Prescribing Information packet for each product
  - Patients with known intolerance or hypersensitivity

**Products**

- Abstral® (fentanyl) sublingual tablets
- Actiq® (fentanyl citrate) oral transmucosal lozenge
- Fentora® (fentanyl citrate) buccal tablet
- Lazanda® (fentanyl) nasal spray
- Onsolis® (fentanyl) buccal soluble film
- Subsys™ (fentanyl) sublingual spray
- Approved generic equivalents of these products are also covered under this program

**Conversion Cautions**

- As a result of PK differences, TIRF-to-TIRF conversions may result in fatal overdose
- ***Again, TIRF conversions must not be done on a mcg-to-mcg basis***
- Titrate according to labeled dosing instructions
  - EACH TIME a new TIRF medication is started
    - Only exception is Brand-Generic conversions
    - Conversion information from Actiq to Fentora is available in Full Prescribing Information packet

**Pharmacokinetic and Therapeutic Considerations**
Metabolic Pathway for RX Elimination

<table>
<thead>
<tr>
<th>DRUG</th>
<th>OPIOID CLASS</th>
<th>MEJOR METABOLIC PATHWAY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>Phenanthrene</td>
<td>Glucuronidation</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>Phenanthrene</td>
<td>Glucuronidation</td>
</tr>
<tr>
<td>Codeine</td>
<td>Phenanthrene</td>
<td>Glucuronidation</td>
</tr>
<tr>
<td>Levoephedrine</td>
<td>Phenanthrene</td>
<td>Glucuronidation</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>Phenanthrene</td>
<td>Glucuronidation, deamination, glucuronidation</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>Phenanthrene</td>
<td>Glucuronidation</td>
</tr>
<tr>
<td>Methadone</td>
<td>Phenanthrene</td>
<td>Glucuronidation, deamination, glucuronidation</td>
</tr>
</tbody>
</table>

Values DF, McGory R. Pharmacokinetic considerations, 1999.1

Opioid Analgesic P-Kinetics

<table>
<thead>
<tr>
<th>Agent</th>
<th>Time to Peak (hr)</th>
<th>Half-life (hr)</th>
<th>Analgesic Onset (min)</th>
<th>Analgesic Duration (hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine (IM)</td>
<td>0.5-1</td>
<td>2</td>
<td>10-20</td>
<td>3-5</td>
</tr>
<tr>
<td>Hydromorphone (IM)</td>
<td>0.5-1</td>
<td>2-3</td>
<td>10-20</td>
<td>3-5</td>
</tr>
<tr>
<td>Levoephedrine (PO)</td>
<td>0.5-1</td>
<td>12-16</td>
<td>10-20</td>
<td>5-8</td>
</tr>
<tr>
<td>Hydrocodone (PO)</td>
<td></td>
<td>1</td>
<td>30-60</td>
<td>4-6</td>
</tr>
<tr>
<td>Codeine (IM)</td>
<td>0.5-1</td>
<td>3</td>
<td>10-20</td>
<td>8</td>
</tr>
<tr>
<td>Oxycodone (PO)</td>
<td>0.5-1</td>
<td>2-3</td>
<td>30-60</td>
<td>4-6</td>
</tr>
<tr>
<td>Meperidine (IM)</td>
<td>0.5-1</td>
<td>3-4</td>
<td>10-20</td>
<td>2-5</td>
</tr>
<tr>
<td>Fentanyl (IM)</td>
<td>0.5-1</td>
<td>10-20</td>
<td>3-4</td>
<td>1-2</td>
</tr>
<tr>
<td>Methadone (IM)</td>
<td>0.5-1</td>
<td>15-30</td>
<td>10-20</td>
<td>&gt;8 (chronic)</td>
</tr>
</tbody>
</table>

**Combined data from:** Reisine T, Paternak G 1995 and Pasero C, Portenoy RK, McCaffery M. 1999

Select Opioid Analgesic Choices

- **Extended Release Products:**
  - Buprenorphine Transdermal Patch
  - Transdermal Fentanyl Patch
  - Hydromorphone-ER
  - Morphine-ER (several products available)
  - Oxycodone-ER
  - Oxymorphone-ER

- **Synthetic Atypical:**
  - Long Biological T_{1/2} & intermediate analgesic T_{1/2}
  - Levorphanol
  - Methadone

Chemical Classes of Opioids

- **PHENANTHRENES**
- **BENZOMORPHANS**
- **PHENYLPIPERIDINES**
- **DIPHENYLHEPTANES**

Rx EXAMPLES:

- MORPHINE
- Codeine
- Hydrocodone
- Hydromorphone
- Oxycodone
- Oxymorphone
- Propoxyphene

X-SENSITIVITY > PROBABLE POSSIBLE LOW RISK LOW RISK

- **PHENANTHRENES**
- **BENZOMORPHANS**
- **PHENYLPIPERIDINES**
- **DIPHENYLHEPTANES**

See handout for tapentadol & tramadol

Opioid Rotation

- Switching a chronic pain patient from one opioid to another
- Reported to provide more effective analgesia
- Interpatient variability of response
- Incomplete cross-tolerance
- Indications for opioid rotation
- Poorly controlled pain with inability to increase dose due to side effects
- Adverse event or toxicity with current opioid
- Rapid development of tolerance
- Development of opioid hyperalgesia

Morphine 100mg equivalent?

- “Recent evidence suggests that the use of dose conversion ratios published in equianalgesic tables may lead to fatal or near-fatal opioid overdoses.”

  - What source(s) do you reply upon to convert doses?
    A. Package inserts
    B. Primary Literature
    C. Textbooks
    D. Websites
    E. Online Opioid Calculators


Available Online Opioid Conversion Calculators

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

Shaw/Fudin 2012

New Opioid Calculator

http://opioidcalculator.practicalpainmanagement.com/

ACPHS Pain Elective Assignment-2013

- Convert 5 different opioids to their morphine equivalents.
- 15 students selected 3 different readily available resources
- Calculate the conversion to morphine 3 different times
- All students chose three references which mathematically allowed for 45 possible selections
- 16 unique reference sources were identified by all students combined.

http://paindr.com/the-answer-is-morphine-100mg-equivalent-morphine-jeopardy/

Raw Data

<table>
<thead>
<tr>
<th>Convert From</th>
<th>CALCULATED MORPHINE EQUIVALENT BY RESOURCE</th>
<th>Average (mg)</th>
<th>Range (mg)</th>
<th>Standard Deviation of Sample (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrocodone 80mg</td>
<td></td>
<td>88</td>
<td>67 - 144</td>
<td>20</td>
</tr>
<tr>
<td>Fentanyl 1800mcg as (25mcg/hour)</td>
<td></td>
<td>259</td>
<td>133 - 540</td>
<td>132</td>
</tr>
<tr>
<td>Methadone 40mg</td>
<td></td>
<td>103</td>
<td>50 - 160</td>
<td>33</td>
</tr>
<tr>
<td>Oxycodeone 120mg</td>
<td></td>
<td>176</td>
<td>80 - 240</td>
<td>37</td>
</tr>
<tr>
<td>Hydromorphone 8mg</td>
<td></td>
<td>199</td>
<td>170 - 384</td>
<td>48</td>
</tr>
</tbody>
</table>

(+/-) % Variation (Compared to Manual Calculation)

RISKS: Overdose & Death


Conversion of Fentanyl (1800mcg)
Serum Fentanyl Concentrations Following Multiple Applications of DURAGESIC® 100mcg/h (n=10)

Transdermal Fentanyl Conversion

- Conversion suggested in manufacturer’s package insert:
- Donner & Colleagues, Breibart & Colleagues, American Academy of Hospice & Palliative Medicine suggested conversion:

Methadone Statistics, CDC 2012

- 2% of prescriptions for opioid analgesics are for methadone
- Methadone accounts for nearly 1 in 3 prescription opioid overdose deaths in the U.S., 6X the number in 2009

http://www.cdc.gov/features/vitalsigns/methadoneoverdoses/

Methadone Conversion Study

- Ripamonti, et al 1998
  - Cross-sectional
  - Morphine to methadone
  - 38 patients
  - Dose Ranges

<table>
<thead>
<tr>
<th>Morphine (mg)</th>
<th>Morphine to Methadone Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-90</td>
<td>3.70 to 1</td>
</tr>
<tr>
<td>91-300</td>
<td>7.75 to 1</td>
</tr>
<tr>
<td>301 and higher</td>
<td>12.25 to 1</td>
</tr>
</tbody>
</table>

Methadone (mg)  | Morphine (mg)  
---|---
60mg  | 60mg
30mg  | 30mg
15mg  | 15mg

**Case 1 (Monitoring!)**
- A 42 year old man with documented chronic back pain post-surgery for back x 2 is receiving
  - MSContin® 100mg PO TID
  - MSContin® 60mg PO BID
  - Morphine sulfate 30mg IR PO Q4H PRN
- For 10 years, the patient fills the prescriptions regularly.
  - AWP vs. ASP?

**Case 1 Questions**
A. Morphine 600mg PO per day is too high
B. There is never maximum dose of morphine
C. MDD is based on monitoring by prescriber and ability to tolerate RX
D. If 600mg per day is required, it would be best to switch to a different opioid

**Questions to Ponder**
A. What will a UDS tell us?
B. What will a serum tell us?
C. When should a serum be ordered?
D. When is the cost justified?
### Sample Urine Drug Screen Cutoff Levels

<table>
<thead>
<tr>
<th>Screen</th>
<th>Cutoff (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphetamine</td>
<td>1000</td>
</tr>
<tr>
<td>Barbiturate</td>
<td>200</td>
</tr>
<tr>
<td>Benzodiazepine</td>
<td>200</td>
</tr>
<tr>
<td>Cocaine</td>
<td>300</td>
</tr>
<tr>
<td>Opiates</td>
<td>2000 / 300</td>
</tr>
<tr>
<td>Cannabinoids</td>
<td>50</td>
</tr>
<tr>
<td>Methadone</td>
<td>300</td>
</tr>
<tr>
<td>PCP (phencyclidine)</td>
<td>25</td>
</tr>
</tbody>
</table>

### Chemical Adulterants

#### HOUSEHOLD PRODUCTS

<table>
<thead>
<tr>
<th>Adulterant</th>
<th>Drug Test Affected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorine Bleach</td>
<td>Marijuana, Morphine, Amphetamine</td>
</tr>
<tr>
<td>Liquid Drain Cleaner</td>
<td>Morphine, Amphetamine</td>
</tr>
<tr>
<td>Vinegar</td>
<td>Amphetamine</td>
</tr>
</tbody>
</table>

#### PROMOTIONAL PRODUCTS

<table>
<thead>
<tr>
<th>Adulterant</th>
<th>Drug Test Affected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyridinium Chlorochromate</td>
<td>Amphetamine, Cocaine, Morphine</td>
</tr>
<tr>
<td>(PCC)</td>
<td>Marijuana, Phencyclidine</td>
</tr>
<tr>
<td>UR'n Kleen</td>
<td>All of the above except Amphetamine</td>
</tr>
</tbody>
</table>


### The Clean Whiz Kit

(http://www.cleanwhiz.com/cleankit.html)

### Case 2: Rifampin & Morphine

<table>
<thead>
<tr>
<th>DATE</th>
<th>PLAN</th>
<th>PATIENT RESPONSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>7/19</td>
<td>Discontinue hydromorphone</td>
<td>3/10 Serum Level Ordered</td>
</tr>
<tr>
<td></td>
<td>Initiate morphine SA 75 mg PO q8h</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No IV opioids under any circumstances, Clonidine 0.2 mg PO</td>
<td></td>
</tr>
<tr>
<td></td>
<td>QAM and 0.1 mg PO QPM</td>
<td></td>
</tr>
<tr>
<td></td>
<td>36.9 (±15.1) ng/mL of serum free morphine for every 100 mg of morphine SA</td>
<td></td>
</tr>
<tr>
<td>7/24</td>
<td>Morphine SA 60 mg PO q8h</td>
<td>3/10, No BT RX requested</td>
</tr>
<tr>
<td></td>
<td>Morphine sulfate 15 mg IR PO q8h PRN</td>
<td></td>
</tr>
<tr>
<td>7/30</td>
<td>Morphine SA 45 mg 6 AM and 2 PM</td>
<td>3/10, No BT RX requested</td>
</tr>
<tr>
<td></td>
<td>Morphine SA 60 mg q 10 PM IR coverage provided</td>
<td></td>
</tr>
</tbody>
</table>

### Why is the serum morphine so low?

A. Rifampin is a potent CYP450 inducer that will lower serum morphine levels  
B. Rifampin is a potent CYP450 inhibitor that will lower serum morphine levels  
C. Rifampin doesn’t affect CYP450  
D. Morphine levels are diminished for another reason
Case 2: Rifampin & Morphine

A. Buprenorphine transdermal is okay based on the prescribed dose
B. Based on FDA labeling, buprenorphine transdermal is contraindicated
C. Based on Serum morphine of 19ng/mL, buprenorphine transdermal is plausible
D. B and C above

Resolution Strategies

- Encourage the use of risk stratification tools
  - See painedu.org
- Education for all prescribers & pharmacists
- Slow escalation of opioid doses upon conversion
- Know the advantages & pitfalls of conversion schematics
- Pharmacists must act as ambassadors for the healthcare team and work with regulatory agencies to achieve a balance

Old, New, & Future Options

- Buprenorphine Patches (Butrans®)
  - Dosage Units: 5, 10, 20mcg/hour
- BUZZ WORDS TO WATCH FOR...
  - Abuse Deterrent Opioids
  - Tamper Resistant products
  - Abuse Liability

Looming Questions

- Should the scheduling of hydrocodone change at the federal level?
- Should we adopt PROP’s proposal?
- Will Bloomberg’s taskforce have an impact?
- How will ISTOP affect pharmacists?
  - Federal institutions?
  - Electronic ordering?

Conclusions-1

- Chronic pain is common and under-treated
- Identify chronic pain patients who would most likely benefit from opioid therapy and dispense/monitor it responsibly
- Dispense opioid treatment with a plan for ongoing monitoring
- Assess and monitor pain, side effects, and drug-related behaviors
- Prospectively recommend opioid therapies commensurate with potential diversion risk
- Adjust dosage
- Manage side effects

Conclusions-2

- Need to monitor patients using opioids
  - Medical
  - Legal
- Monitor patients appropriately for opiate use
  - Urine screen as a preliminary indicator (provider)
- Investigate further with serum opioid levels PRN
  - Correlate patient specific values with known pharmacokinetic data
- React appropriately to lab results
  - Do not jump to conclusions
  - Advise appropriately with appropriate lab tests

Chemical Classes of Opioids

PHENANTHRENES  BENZOMORPHANS  PHENYLPIPERIDINES  DIPHENYLHEPTANES

MORPHINE  PENTAZOCINE  MEPERIDINE  METHADONE

Rx EXAMPLES > morphine  pentazocine  meperidine  methadone
codeine  diphenoxylate  fentanyl  propoxyphene
hydrocodone*  loperamide  sufentanil
hydromorphone*  oxycodone*  alfentanil
levorphanol*  oxymorphone*  remifentanil
diphenoxylate  buprenorphine*
hydromorphone  nalbuphine
*These agents lack the 6-OH group of morphine, possibly decreasing cross- sensitivity within the phenanthrene group.

PROBABLE  POSSIBLE  LOW RISK  LOW RISK

References:

Courtesy of Dr. Jeffrey Fudin (http://www.paindr.com)
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