Inconspicuous and Miscalculated Opioid Risks
Plus Updates on Rescheduling Hydrocodone

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Learning Objectives

1. Describe recent changes to NYS Regulation regarding rescheduling hydrocodone, including expectations, potential pitfalls, and current outcomes.
2. Differentiate among the various chemical classes of opioids.
3. Identify the various Cytochrome P450 iso-enzymes that affect metabolism of commonly prescribed opioid analgesic therapy.
4. Understand the usefulness and pitfalls of serum and UDS analysis with respect to opioids.
5. Recognize important drug interactions resulting from P450 metabolic and p-glycoprotein absorption pharmacokinetics.

Suggested Readings

Inconspicuous and Miscalculated Risks of Opioid Therapy

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Practice Pearls to Mitigate Opioid Risks

- 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
Opipophobia must go

With permission from Dr. Steven Passik

Disclosures

- Speakers Bureau for Millennium Laboratories, Inc.
- Author, Opioid Conversion Calculator in collaboration with Practical Pain Management

Multiple Barriers Exist to Opioid Utilization

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

<table>
<thead>
<tr>
<th>Product</th>
<th>Highly Prescribed Products In US</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin</td>
<td></td>
</tr>
<tr>
<td>Amoxicillin</td>
<td></td>
</tr>
<tr>
<td>Hydrocodone/Combo</td>
<td></td>
</tr>
<tr>
<td>Oxycodone/Combo</td>
<td></td>
</tr>
<tr>
<td>Tramadol/Combo</td>
<td></td>
</tr>
<tr>
<td>Codeine/Combo</td>
<td></td>
</tr>
<tr>
<td>Oxycodone</td>
<td></td>
</tr>
<tr>
<td>Fentanyl</td>
<td></td>
</tr>
<tr>
<td>Morphine</td>
<td></td>
</tr>
<tr>
<td>Hydromorphone</td>
<td></td>
</tr>
</tbody>
</table>

Number of Prescriptions (in Millions)

<table>
<thead>
<tr>
<th>Product</th>
<th>Number of Prescriptions (in Millions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin</td>
<td>120</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>114</td>
</tr>
<tr>
<td>Hydrocodone/Combo</td>
<td>100</td>
</tr>
<tr>
<td>Oxycodone/Combo</td>
<td>90</td>
</tr>
<tr>
<td>Tramadol/Combo</td>
<td>80</td>
</tr>
<tr>
<td>Codeine/Combo</td>
<td>70</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>60</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>50</td>
</tr>
<tr>
<td>Morphine</td>
<td>40</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>30</td>
</tr>
</tbody>
</table>
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.

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 23, 2013
  - NYS officially rescheduled hydrocodone to CII
- February 7-8, 2013
  - FDA held a public hearing on the “Impact of Approved Drug Labeling on Chronic Opioid Therapy.”
  - The purpose? (Next Slide)

Pharmacokinetic and Therapeutic Considerations

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</td>
<td>0.5-1</td>
<td>2</td>
<td>10-20</td>
<td>3-5</td>
</tr>
<tr>
<td>Levorphanol (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>1</td>
<td>4</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>4-6</td>
</tr>
<tr>
<td>Oxycodeone (PO)</td>
<td>0.5-1</td>
<td>2.5</td>
<td>30-60</td>
<td>4-6</td>
</tr>
<tr>
<td>Methadone (IM)</td>
<td>0.5-1</td>
<td>4</td>
<td>10-20</td>
<td>2-5</td>
</tr>
<tr>
<td>Fentanyl (IM)</td>
<td>10-20</td>
<td>2</td>
<td>7-15</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>&lt;8 (chronic)</td>
</tr>
</tbody>
</table>

Metabolic Pathway for RX Elimination

<table>
<thead>
<tr>
<th>DRUG</th>
<th>OPIOID CLASS</th>
<th>MAJOR 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>Oxycodone</td>
<td>Phenanthrene</td>
<td>Glucuronidation, O-demethylation</td>
</tr>
<tr>
<td>Meperidine</td>
<td>Phenanthrene</td>
<td>Glucuronidation, O-demethylation</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>Phenylethanol</td>
<td>Oxidation, hydrolysis, glucuronidation</td>
</tr>
<tr>
<td>Methadone</td>
<td>Diphenylheptane</td>
<td>Glucuronidation</td>
</tr>
</tbody>
</table>

Select Opioid Analgesic Choices

- Extended Release Products:
  - Buprenorphine Transdermal Patch
  - Transdermal Fentanyl Patch
  - Hydromorphone-ER
  - Morphine-ER (several products available)
  - Oxycodone-ER
  - Oxymorphone-ER
  - Hydrocodone-ER (Zohydro, HydroContin®)

- Synthetic Atypical:
  - Long Biological T1/2 & intermediate analgesic T1/2
    - Levoxcodone
    - Methadone

Chemical Classes of Opioids

- Examples:
  - Phenanthrenes: morphine, codeine
  - Benzomorphans: oxycodone, oxymorphone, buprenorphine, methadone
  - Phenylpiperidines: levorphanol, cetomorphine
  - Diphenylheptanes: sufentanil

- X-Sensitivity:
  - High: (atypical-morphine)
  - Probable: (possible-morphine)
  - Possible: (low-risk morphine)
  - Low Risk: (low-risk morphine)

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


See handout for tapentadol & tramadol

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

Variability in Opioid Equivalence Survey

• Sept 13 thru Nov 4, 2013, 362 Respondents
• RPhs, MD/DOs, NPs, PAs
• Convert to Daily MEQ:
  • Hydrocodone 80mg; Fentanyl 75mcg/hr; Methadone 40mg; Oxycodone 120mg; Hydromorphone 48mg

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 times the number in 2009

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

Transdermal Fentanyl Conversion

- Conversion suggested in manufacturer’s package insert:

Donner & Colleagues, Breitbart & Colleagues, American Academy of Hospice & Palliative Medicine suggested conversion:

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

<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>

J Clin Oncol 1998;16:3216-3221

Table 1. Comparison of Proposed Morphine to Methadone Conversion Parameters

<table>
<thead>
<tr>
<th>Morphine dose (mg)</th>
<th>Morphine/Methadone (mg/mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-90</td>
<td>3.30</td>
</tr>
<tr>
<td>91-300</td>
<td>7.75</td>
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<td>301 and higher</td>
<td>12.25</td>
</tr>
</tbody>
</table>

Aromatase 2000

Methadone (mg) to Morphine (mg) Equianalgesic Dosing Ratios

- 300mg Morphine = 60mg Methadone
- 302.5mg Morphine = 30mg Methadone

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 (Lab Dependent)</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>

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
UDS vs. Serum

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?

Chemical Adulterants

<table>
<thead>
<tr>
<th>HOUSEHOLD PRODUCTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adulterant</td>
</tr>
<tr>
<td>Chlorine Bleach</td>
</tr>
<tr>
<td>Liquid Drain Cleaner</td>
</tr>
<tr>
<td>Vinegar</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PROMOTIONAL PRODUCTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adulterant</td>
</tr>
<tr>
<td>Pyridinium Chlorochromate (PCC)</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>UR'n Kleen</td>
</tr>
</tbody>
</table>

Case Study: Jack

- 34-year-old man, history of chronic trigeminal neuralgia, multiple interventional procedures and multiple medication trials with no sustained benefit
- Past Medical History (PMH): otherwise negative
- Current pharmacologic regimen includes:
  - Gabapentin (Neurontin®)
  - Hydromorphone ER (Exalgo®)
  - Hydrocodone + APAP (Vicodin®)
  - Venlafaxine (Effexor®)

In-Office Test Results

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opiate</td>
<td>Negative</td>
</tr>
<tr>
<td>PCP (phencyclidine)</td>
<td>Positive</td>
</tr>
</tbody>
</table>

LC-MS/MS Laboratory Test Results

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydromorphone</td>
<td>Negative</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>Negative</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>Positive</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>Positive</td>
</tr>
<tr>
<td>PCP (phencyclidine)</td>
<td>Negative</td>
</tr>
</tbody>
</table>

The Clean Whiz Kit
(http://www.youtube.com/watch?v=91knqnsu_hU)

Dr. Jeffrey Fudin

www.paindr.com
Street Value Perspective

- 120 Percocet 5/325 (brand name)
  - $600.00
- 120 Lortab 10/500 (any brand)
  - $600.00
- 60 Oxycontin 80mg
  - $1500.00
- 120 Actiq Lollipop 200mcg
  - $3240.00
- Knowing when your patient is diverting drug...
  - PRICELESS!

http://streetrx.com/

Case #2: Rifampin & Morphine

- 51 YOWM with hx of heroin abuse
- Admitted to hospital with endocarditis
- RX on admission:
  - Oxacillin 2 g, infuse over 30 min q4h IV
  - Hydromorphone 2 mg/1 mL q4h PRN IV
  - Nystatin 500,000 units/5 mL PO TID
  - Gentamicin 100 mg, infuse over 30 min q8h
  - Warfarin 7.5 mg PO daily
  - Lactobaccilus 1 tab PO BID
  - Omeprazole 40 mg PO BID
  - Enoxaparin 80 mg/0.8 mL BID SQ
  - Rifampin 600 mg PO daily


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 Initiate morphine SA 75 mg PO q8h No IV opioids under any circumstances, Clonidine 0.2 mg PO QAM and 0.1 mg PO QPM 36.9 (±15.1) ng/mL of serum free morphine for every 100 mg of morphine SR</td>
<td>3/10 SERUM LEVEL ORDERED</td>
</tr>
<tr>
<td>7/24</td>
<td>Morphine SA 60 mg PO q8h Morphine sulfate 15 mg IR PO q8h PRN</td>
<td>3/10, No BT RX requested</td>
</tr>
<tr>
<td>7/30</td>
<td>Morphine SA 45 mg 6 AM and 2 PM Morphine SA 60 mg q 10 PM IR coverage provided</td>
<td>3/10, No BT RX requested</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

The Answer

\[ \text{Rifampin induces the gastric p-glycoprotein efflux pump} \]
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
Chemical Classes of Opioids

**PHENANTHRENES**
- Morphine
- Codeine
- Hydrocodone*
- Hydromorphone*
- Levoorphanol*
-oxycodeone*
-oxymorphone*
buprenorphine*
nalbuphine
-butorphanol*
naloxone*
-heroin (diacetyl-morphine)

**BENZOMORPHANS**
- Pentazocine
- Diphenoxylate

**PHENYLPIPERIDINES**
- Meperidine
- Fentanyl
- Alfentanil
- Remifentanil

**DIPHENYLHEPTANES**
- Methadone
- Propoxyphene**

**PROBABLE**

**POSSIBLE**

**LOW RISK head

<table>
<thead>
<tr>
<th>Rx EXAMPLES</th>
<th>MORPHINE</th>
<th>PENTAZOCINE</th>
<th>MEPERIDINE</th>
<th>METHADONE</th>
</tr>
</thead>
<tbody>
<tr>
<td>morphine</td>
<td>pentazocine</td>
<td>meperidine</td>
<td>methadone</td>
<td></td>
</tr>
<tr>
<td>codeine</td>
<td>diphenoxylate</td>
<td>fentanyl</td>
<td>propoxyphene**</td>
<td></td>
</tr>
<tr>
<td>hydrocodone*</td>
<td>loperamide</td>
<td>sufentanil</td>
<td></td>
<td></td>
</tr>
<tr>
<td>hydromorphone*</td>
<td></td>
<td>alfentanil</td>
<td></td>
<td></td>
</tr>
<tr>
<td>levoorphanol*</td>
<td></td>
<td>remifentanil</td>
<td></td>
<td></td>
</tr>
<tr>
<td>oxycodone*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>oxymorphone*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>buprenorphine*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>nalbuphine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>butorphanol*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>naloxone*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>heroin (diacetyl-morphine)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*CROSS-SENSITIVITY > RISK

PROBABLE  POSSIBLE  LOW RISK  LOW RISK

*These agents lack the 6-OH group of morphine, possibly decreasing cross-sensitivity within the phenanthrene group.
*No longer available on the U.S. market, propoxyphene is included because previous use history is often a predictor of a patient’s ability to tolerate methadone.

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Tapentadol is a 3-[(1R,2R)-3-(dimethylamino)-1-ethyl-2-methylpropyl]phenol monohydrochloride.

Tramadol is a (±)cis-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl cyclohexanol hydrochloride.

REFERENCES:

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