Individual Patient & Medication Factors that Invalidate Morphine Milligram Equivalents

Presented on June 7-8, 2021 at FDA Collaborative with various Federal Government Agency Stakeholders

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## Disclosures

<table>
<thead>
<tr>
<th>Affiliation</th>
<th>Role/Activities</th>
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<tr>
<td>Abbott Laboratories</td>
<td>Speaking, non-speakers bureau</td>
</tr>
<tr>
<td>AcelRx Pharmaceuticals</td>
<td>Acute perioperative pain (speakers bureau, consulting, advisory boards)</td>
</tr>
<tr>
<td>BioDelivery Sciences International</td>
<td>Collaborative publications, consulting, advisory boards</td>
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<tr>
<td>Firstox Laboratories</td>
<td>Micro serum testing for substances of abuse (consulting)</td>
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<td>GlaxoSmithKline (GSK)</td>
<td>Collaborative non-paid poster presentations)</td>
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<td>Advisory Board</td>
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<td>Hikma Pharmaceuticals</td>
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<tr>
<td>Scilex Pharmaceuticals</td>
<td>Collaborative non-paid publications</td>
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<tr>
<td>Salix Pharmaceuticals</td>
<td>Speakers bureau, consultant, advisory boards</td>
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<tr>
<td>Torrent Pharmaceuticals</td>
<td>Lecture, non-speakers bureau</td>
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Learning Objectives

At the completion of this activity, participants will be able to:

1. Explain opioid conversion and calculation strategies when developing a care plan for patients with chronic pain.
2. Assess patient-specific factors that warrant adjustment to an opioid regimen.
3. Identify important drug interactions that can affect opioid serum levels.
4. Describe how pharmacogenetic differences can affect opioid efficacy, toxicity, and tolerability.
Not All Opioids are Created Equally

<table>
<thead>
<tr>
<th>PHENANTHRENES</th>
<th>BENZOMORPHANS</th>
<th>PHENYLPIPERIDINES</th>
<th>DIPHENYLHEPTANES</th>
<th>PHENYLPROPYL AMINES</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Morphine" /></td>
<td><img src="image2" alt="Pentazocine" /></td>
<td><img src="image3" alt="Fentanyl" /></td>
<td><img src="image4" alt="Methadone" /></td>
<td><img src="image5" alt="Tramadol" /></td>
</tr>
</tbody>
</table>

**MORPHINE**
- Buprenorphine
- Butorphanol
- Codene
- Dextromorphan
- Dihydrocodeine
- Heroin (diacetyl morphine)
- Hydrocodone
- Hydromorphone
- Levoorphanol
- Methylmorphinone
- Morphine (Opium, conc)
- Nalbuphine
- Naloxone
- Naltrexone
- Naloxegol
- Oxycodone
- Oxymorphone

**PENTAZOCINE**
- Pentazocine

**FENTANYL**
- Alfentanil
- Fentanyl
- Remifentanil
- Sufentanil
- Meperidine
- Diphenoxylate
- Loperamide

**METHADONE**
- Methadone
- Propoxyphene

**TRAMADOL**
- Tapentadol
- Tramadol

**Illicit Fentanyl**
- Furanyl fentanyl
- Acetyl fentanyl
- Fluoro-fentanyl
- Carfentanil
- Others

**CROSS-SENSITIVITY RISK**

<table>
<thead>
<tr>
<th>PROBABLE</th>
<th>POSSIBLE</th>
<th>LOW RISK</th>
<th>LOW RISK</th>
<th>LOW RISK</th>
</tr>
</thead>
</table>

*Agents lacking the 6-OH group of morphine, possibly decreases cross-tolerability within the phenanthrene group.
**6-position is substituted with a ketone group and tolerability is similar to hydroxylation.

Jeffrey Fudin, BSPharm, PharmD, DAAPM, FCCP, FASHP, FFSMB

http://painsk.com/resources/quick-references/ (See “Opioid Chemistry”)

- Previously incorrectly listed as “Benzomorphans”
Issues with MEDD & Opioid Conversion\textsuperscript{1-4}

› Pharmacogenetic variability
› Drug interactions
› Lack of universal morphine equivalence
› Specific opioids that should never have an MEDD
  – Methadone, Buprenorphine, Tapentadol, Tramadol

Conceptual Dose-Response Curves of Three Opioids

A rose by any other name...

- DDD
  - defined daily dose

- OMEQ
  - oral morphine equivalent dose

- MEDD
  - morphine equivalent daily dose

- Or more accurately, perhaps we need a...
  - MAE (morphine analgesic equivalent)
  - MTE (morphine toxic equivalent)
## Mu Receptor Binding Affinity versus Partition Coefficient (Select Opioids)

<table>
<thead>
<tr>
<th>Opioid</th>
<th>Binding affinity (Ki value, nM)</th>
<th>Partition Coefficient (Log P)</th>
<th>Molecular Weight (Da)</th>
<th>Equivalent Equianalgesic IM dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sufentanil</td>
<td>0.1380</td>
<td>3.95</td>
<td>386</td>
<td>~500-1000 times more potent</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>0.2157</td>
<td>4.98</td>
<td>468</td>
<td>~40 times more potent</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>0.3654</td>
<td>1.84</td>
<td>285</td>
<td>1.5</td>
</tr>
<tr>
<td>Oxymorphone</td>
<td>0.4055</td>
<td>0.83</td>
<td>301</td>
<td>1</td>
</tr>
<tr>
<td>Levorphanol</td>
<td>0.4194</td>
<td>3.14</td>
<td>257</td>
<td>2</td>
</tr>
<tr>
<td>Morphine</td>
<td>1.168</td>
<td>0.76</td>
<td>285</td>
<td>10</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>1.346</td>
<td>4.05</td>
<td>336</td>
<td>0.1 – 0.2</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>25.87</td>
<td>0.82</td>
<td>315</td>
<td>20</td>
</tr>
<tr>
<td>Codeine</td>
<td>734.2</td>
<td>1.14</td>
<td>299</td>
<td>130</td>
</tr>
</tbody>
</table>

*Log P corresponds to the logarithm of the ratio of the concentrations of the studied compound in octanol and in water: LogP = Log (C_{oct}/C_{water}).

For Equianalgesic IM doses, time of peak analgesia in non-tolerant patients ranges from one-half to one hour and the duration of four to six hours. Doses are expressed in milligram strength.

Potency when calculated for buprenorphine is relative, given it has different pharmacologic effects on opioid receptors than traditional opioid agonist medications.

The MEDD myth: the impact of pseudoscience on pain research and prescribing-guideline development

With the opioid-misuse and -abuse problem on the rise, pain practitioners and lawmakers are scrambling for strategies to help mitigate opioid risks. Approaches include opioid-treatment agreements, urine drug testing, prescription-monitoring programs, assorted validated risk-assessment tools for abuse/misuse and opioid-induced respiratory depression (OIRD), biopsychosocial support, and other strategies. Nonopioid pain therapies should be considered and maximized prior to initiating opioid treatment; however, in some cases opioids are the optimal choice for both noncancer
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

### Variability Survey Results

**Morphine equivalent doses (mg) for each opioid medication by specialty**

<table>
<thead>
<tr>
<th>Specialty</th>
<th>Fentanyl</th>
<th>Hydrocodone</th>
<th>Hydromorphone</th>
<th>Methadone</th>
<th>Oxycodone</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pain Management</strong></td>
<td>166 ± 115</td>
<td>85 ± 43</td>
<td>191 ± 68</td>
<td>162 ± 111</td>
<td>167 ± 45</td>
</tr>
<tr>
<td>(n=39)</td>
<td>(150)</td>
<td>(80)</td>
<td>(192)</td>
<td>(120)</td>
<td>(180)</td>
</tr>
<tr>
<td><strong>Palliative Care</strong></td>
<td>168 ± 57</td>
<td>84 ± 17</td>
<td>188 ± 67</td>
<td>251 ± 166</td>
<td>154 ± 38</td>
</tr>
<tr>
<td>(n=35)</td>
<td>(150)</td>
<td>(80)</td>
<td>(192)</td>
<td>(240)</td>
<td>(180)</td>
</tr>
<tr>
<td><strong>None of the Above</strong></td>
<td>177 ± 124</td>
<td>88 ± 43</td>
<td>191 ± 50</td>
<td>169 ± 115</td>
<td>177 ± 37</td>
</tr>
<tr>
<td>(n=247)</td>
<td>(150)</td>
<td>(80)</td>
<td>(192)</td>
<td>(160)</td>
<td>(180)</td>
</tr>
</tbody>
</table>

Available Online Opioid Conversion Calculators

› Med Calc
› WA State Agency
› Pain Research
› Pain Physicians
› Hopkins
› Palliative Care
› Global RPh
› Practical Pain Management

### Comparison of Proposed Morphine to Methadone Equivalents

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Morphine dose (mg/day)</strong></td>
<td>30-90</td>
<td>91-300</td>
<td>301+</td>
<td>30-90</td>
</tr>
<tr>
<td><strong>Morphine:Methadone</strong></td>
<td>3.70:1</td>
<td>7.75:1</td>
<td>12.25:1</td>
<td>&lt;100</td>
</tr>
<tr>
<td></td>
<td>3:1</td>
<td>5:1</td>
<td>10:1</td>
<td>12:1</td>
</tr>
</tbody>
</table>

**Fudin et al, 2012**

\[ \text{Methadone (mg)} = \frac{X}{21} \left\{ 5.7 - 3 \sin \left[ \frac{90}{\sqrt{\frac{110}{X} + 1}} \right] - \sin \left[ \frac{90}{\sqrt{\frac{320}{X} + 1}} \right] \right\} \]

Let \( X = \text{Morphine (mg)} \) | EDR=equianalgesic dose ration

Equianalgesic Dose of Morphine to Methadone

300mg Morphine = 60mg Methadone
302.5mg Morphine = 30mg Methadone
CDC Calculator (methadone) is most consistent with Ayonrinde’s formula


### Calculating morphine milligram equivalents (MME)

<table>
<thead>
<tr>
<th>OPIOID (doses in mg/day except where noted)</th>
<th>CONVERSION FACTOR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Codeine</td>
<td>0.15</td>
</tr>
<tr>
<td>Fentanyl transdermal (in mcg/hr)</td>
<td>2.4</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>1</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>4</td>
</tr>
<tr>
<td>Methadone</td>
<td></td>
</tr>
<tr>
<td>1-20 mg/day</td>
<td>4</td>
</tr>
<tr>
<td>21-40 mg/day</td>
<td>8</td>
</tr>
<tr>
<td>41-60 mg/day</td>
<td>10</td>
</tr>
<tr>
<td>≥ 61-80 mg/day</td>
<td>12</td>
</tr>
<tr>
<td>Morphine</td>
<td>1</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>1.5</td>
</tr>
<tr>
<td>Oxymorphone</td>
<td>3</td>
</tr>
</tbody>
</table>

These dose conversions are estimated and cannot account for all individual differences in genetics and pharmacokinetics.
When converting opioids, there could be unanticipated risks of opioid-induced respiratory depression (OIRD).
Serum Fentanyl Concentrations Following Multiple Applications of DURAGESIC® 100mcg/h (n=10)

Fentanyl TD


Huge risk even with 50% dose reduction!
Shown in red are the major cytochrome P450 enzymes involved in phase I metabolism; patterns of drug metabolites may reflect the metabolic phenotype of the patient. Actual proportions of individual metabolites will vary. Pharmacogenetic testing is available for CYP2D6 and CYP3A4. | Phase II reactions (eg, glucuronide conjugation) are not shown but are prominent for most opioids.

* Not specifically detected by the Opiate screen. Definitive urine testing by chromatography may be necessary.
<table>
<thead>
<tr>
<th>Phase of Metabolism</th>
<th>Key Enzymes Involved</th>
<th>Examples: Opioid Medication Metabolized</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase I</td>
<td>Cytochrome P450 (CYP450) Examples: CYP2D6, CYP2C19, CYP2B6, CYP2C9, CYP3A4 &amp; CYP3A5</td>
<td>Codeine, hydrocodone, oxycodone, tramadol, fentanyl, methadone, buprenorphine</td>
</tr>
<tr>
<td>Phase II</td>
<td>Uridine 5'-diphosphogluconosyltransferase (UDP-glucuronosyltransferase, UGT) Examples: UGT2B7 &amp; UGT1A9</td>
<td>Morphine, oxymorphone, hydromorphone, tapentadol</td>
</tr>
</tbody>
</table>

Pharmacogenetic Variability & Response\textsuperscript{1-3}

- General population has 40-60% phenotype variability
- CYP450 enzymes most frequently involved
  - CYP2D6, CYP2C19, CYP2C9, CYP3A4, CYP1A2, CYP2E1
- Genetic differences impact 25% of all drugs

Individual Response to Treatment

Pharmacogenetics
The science of how genetic variability impacts individual responses to medications

CYP450 Nomenclature

› Cytochrome is designated CYP
› CYP (#) - # identifying the enzyme family
› CYP (#) (A,C) - Subfamily designation
› CYP (#) (A,C) (#) - Individual enzyme
  (this is based on when enzyme was discovered)

› EXAMPLES:
  – CYP3A4, CYP2D6, CYP1A2
Deciphering Drug Interactions Among Assorted Analgesics
Terminology

› Inducer
› Inhibitor
› Substrate
› What is Genetic Polymorphism?
Personalizing Medication with Pharmacogenetic (PGT) Interpretation
P-gp drug interaction are not included in most pharmacy software packages!

Published Cases


PGT Variability & Response\textsuperscript{1-3}

› General population has 40-60% phenotype variability

› CYP450 enzymes most frequently involved
  – CYP2D6, CYP2C19, CYP2C9, CYP3A4, CYP1A2, CYP2E1

› Genetic differences impact 25% of all drugs


Phenotypes & Variants

› Allele Variations
  - wild:wild vs variant:wild vs wild:variant

Poor Metabolizer (PM)
  DDDD → M

Intermediate Metabolizer (IM)
  DDDD → MMm

Extensive Metabolizer (EM)
  DDDD → MMM

Ultra Rapid Metabolizer (UM)
  DDDD → MMMMmmmm
Discuss Cases, if time permits
Case: JB

› JB is a 45 year old Caucasian male who has a history of cervical stenosis at C5-6 with myelopathy. He has been on tramadol for a number of years but he comes to you for assistance with optimal control of neuropathic pain. You initiate Carbamazepine 100mg PO Daily x 7 days then 200mg PO Daily.

› Three weeks later JB calls the clinic in distress and he reports being in the worst pain he has experienced in years.

› Why is JB suddenly in pain?
Case: RC

- PT is a 48-year-old man with a past medical history significant for ADHD, OSA, PTSD, and CLBP
- Pain level VAS 0-10 reported as 9/10
- Intolerant to many antidepressants: duloxetine, venlafaxine, citalopram, sertraline, bupropion, and mirtazapine
- Mild response to morphine
- Pharmacogenetic Testing:
  - COMT – Reduced Activity
  - MTHFR – Reduced Activity
  - CYP3A4 and CYP3A5 – Intermediate Metabolizer
  - CYP2C19 – Normal Metabolizer
  - CYP2D6 – Normal Metabolizer
  - UGT2B15 – Normal Metabolizer

RC and the Role of MTHFR

› MTHFR is responsible for converting 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, and 5-methyltetrahydrofolate is the predominant circulating form of folate

› Reduced folate levels linked to depression and ADHD

› Treatment:
  – L-methylfolate
  – Leucovorin (folinic acid)

› Outcome after initiating Leucovorin
  – After 1-week of leucovorin 10mg QAM and ZnSulf 220mg QPM
  – Pain level 2/10, ADHP and depression improved
  – 8-month later, patient remains stable, **NO OPIOIDS**


Case: Patient SR

- SR 47-year-old female patient with 3 failed back surgeries and DM type 2
  - 5’ 6” tall and weighs 200 lbs
- Medication regimen at pain clinic (for last 2 years):
  - Oxycodone CR 30 mg PO q12h and Oxycodone IR 10 mg PO q4h PRN
- Do you think this patient is at elevated risk (Low, Med, High)?

- Medications prescribed by psychiatrist:
  - Lorazepam 0.5 mg q8h for anxiety
- What if the patient:
  - Is placed on pregabalin 75 mg PO TID (Endocrine for DPN)
  - Goes on a grapefruit diet? (Self)
  - Is an ultra-rapid 2D6 metabolizer? (Ohhhh Nooo!)
  - Develops an URTI?
  - Takes OTC meds?
Transforming Negative Perception in a Perfect World

› What opioids are really killing our community and how? Fentanyl vs Fentalogues


› Patents and Community
  - Educate and seek education from...
    › Medical providers and pharmacists
  - Support Pharmacy Provider Status
    › Pharmacists can prescribe nationwide, but aren’t paid by insurance carriers to see patients and mitigate risks