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Chief Executive Officer, REMITIGATE LLC

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Stratton VA Medical Center (WOC)

Adjunct Associate Professor

Albany College of Pharmacy & Health Sciences &
Western New England University College of Pharmacy
Demystifying Opioid Conversion Calculations
Disclosures

› Astra Zeneca (Speakers Bureau)
› Daiichi Sankyo (Advisory Board, Speakers Bureau, Software Collaboration)
› Egalet (Consultant, Advisory Board, Speaker)
› Quest Labs (Advisory Board)
› Remitigate, LLC (Owner)
Learning Objectives

At the completion of this activity, the pharmacist 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.
Morphine Equivalent Daily Dose (MEDD) is the same in all healthy patients of same gender and weight in the absence of drug interactions.

A. True
B. False
Self-Assessment Question 2

Online opioid conversion calculators are most **inaccurate** for...

A. Hydrocodone and oxycodone  
B. Hydromorphone and oxymorphone  
C. Methadone and fentanyl  
D. None of the above
Self-Assessment Question 3

When converting from an IR opioid to a different ER opioid, the FDA suggests what percent dosage reduction for cross-tolerance?

A. 50%
B. 25%
C. 15%
D. 10%
### Comparative Opioid Chemistry

<table>
<thead>
<tr>
<th>PHENANTHRENES</th>
<th>BENZOMORPHANS</th>
<th>PHENYLPIPERIDINES</th>
<th>DIPHENYLHEPTANES</th>
<th>PHENYLPROPYL AMINES</th>
</tr>
</thead>
<tbody>
<tr>
<td>MORPHINE</td>
<td>PENTAZOCINE</td>
<td>FENTANYL</td>
<td>METHADONE</td>
<td>TRAMADOL</td>
</tr>
<tr>
<td>Buprenorphine* Butorphanol* Codeine Dextramethorphan* Dihydrocodeine Heroin (diacetyl-morphine) Hydrocodone* Hydromorphone* Levorphanol* MethylNaltrexone** Morphine (Opium, conc) Nalbuphine* Naloxone* Naloxegol* Naltrexone** Oxycodone* Oxymorphone* Diphenoxylate Loperamide Pentazocine Allentanil Fentanyl Fentanyl Meperidine Remifentanil Sufentanil Methadone Propoxyphene Tapentadol Tramadol</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Illicit Fentanyl</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Furanyl fentanyl Acetyl fentanyl Fluoro-fentanyl Carfentanil</td>
<td></td>
<td></td>
<td></td>
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</table>

#### 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, DAIPM, FCCP, FASHP, FFsMB


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Not All Opioids are Created Equal!
States with MEDD Thresholds (a moving target)

<table>
<thead>
<tr>
<th>Dosage Amount</th>
<th>0</th>
<th>20</th>
<th>40</th>
<th>60</th>
<th>80</th>
<th>100</th>
<th>120</th>
<th>140</th>
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<tbody>
<tr>
<td>CDC</td>
<td>0-50</td>
<td>50-90</td>
<td>90+</td>
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<td>Indiana</td>
<td>15-60</td>
<td>60+</td>
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<tr>
<td>Maine</td>
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<td>New Hampshire</td>
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<td>100+</td>
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</tr>
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</tr>
</tbody>
</table>

Issues with MEDD & Opioid Conversion

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

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

Jeffrey Fudin
Jacqueline Pratt Cleary
Michael E Schatman

Western New England University College of Pharmacy, Springfield, MA,
Stratton VA Medical Center, Albany, NY, US Pain Foundation, Bellevue, WA, USA

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.\textsuperscript{1-3} 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

What Do You Think Were the Most Outrageous Conversions?

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

How can I contribute to a methadone death?

Let me count the ways...
### Comparison of Proposed Morphine to Methadone Equivalents

<table>
<thead>
<tr>
<th>Ripamonti et al, 1998</th>
<th>Morphine dose (mg/day)</th>
<th>30-90</th>
<th>91-300</th>
<th>301+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine:Methadone EDR</td>
<td>3.70:1</td>
<td>7.75:1</td>
<td>12.25:1</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ayonrinde et al, 2000</th>
<th>Morphine dose (mg/day)</th>
<th>&lt;100</th>
<th>101-300</th>
<th>301-600</th>
<th>601-800</th>
<th>801-1000</th>
<th>&gt;1001</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine:Methadone EDR</td>
<td>3:1</td>
<td>5:1</td>
<td>10:1</td>
<td>12:1</td>
<td>15:1</td>
<td>20:1</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Mercadante et al, 2001</th>
<th>Morphine dose (mg/day)</th>
<th>30-90</th>
<th>91-300</th>
<th>301+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine:Methadone EDR</td>
<td>4:1</td>
<td>8:1</td>
<td>12:1</td>
<td></td>
</tr>
</tbody>
</table>

| Fudin et al, 2012 | Methadone (mg) = \[ \frac{X}{21} \left\{ 5.7 - 3 \sin \left( \frac{90}{\frac{110}{X} + 1} \right) - \sin \left( \frac{90}{\frac{320}{X} + 1} \right) \right\} \]
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>X=morphine (mg)</td>
<td>EDR=equianalgesic dose ratio</td>
</tr>
</tbody>
</table>

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Equianalgesic Dose of Morphine to Methadone

- 300mg Morphine = 60mg Methadone
- 302.5mg Morphine = 30mg Methadone
<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'-diphospho-glucuronosyltransferase (UDP-glucuronosyltransferase, UGT) Examples: UGT2B7 &amp; 2B15</td>
<td>Morphine, oxymorphone, hydromorphone, tapentadol</td>
</tr>
</tbody>
</table>

CDC Advert for CDC Online Opioid Calculator

https://www.cdc.gov/drugoverdose/prescribing/app.html
CDC Calculator lacks accuracy with methadone conversion!

1. **DETERMINE** the total daily amount of each opioid the patient takes.

2. **CONVERT** each to MMEs—multiply the dose for each opioid by the conversion factor. (see table)

3. **ADD** them together.

### 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>
</tbody>
</table>
| Methadone
  - 1-20 mg/day                            | 4                 |
  - 21-40 mg/day                            | 8                 |
  - 41-60 mg/day                            | 10                |
  - > 61-80 mg/day                          | 12                |
| Morphine                                  | 1                 |
| Oxycodone                                 | 1.5               |
| Oxymorphone                                | 3                 |

*These dose conversions are estimated and cannot account for all individual differences in genetics and pharmacokinetics.*

An Actual Example from CDC Smart Phone App

<table>
<thead>
<tr>
<th>“Morphine Equivalent” (mg)</th>
<th>Methadone Daily Dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>80</td>
<td>20</td>
</tr>
<tr>
<td>168</td>
<td>21</td>
</tr>
<tr>
<td>320</td>
<td>40</td>
</tr>
<tr>
<td>410</td>
<td>41</td>
</tr>
</tbody>
</table>

Safety concerns with the Centers for Disease Control opioid calculator

Introduction
Morphine milligram equivalence (MME) and other comparable acronyms have been employed in federal pain guidelines and used by policy makers to limit opioid prescribing. On March 18, 2016, the Centers for Disease Control (CDC) released
Serum Fentanyl Concentrations Following Multiple Applications of **Fentanyl TD** 100mcg/h (n=10)

This presents a huge risk even with 50% dose reduction!

When converting opioids, there could be unanticipated risks of opioid-induced respiratory depression (OIRD).
Opiates and Opioid Metabolism

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.

Phase II reactions (e.g., glucuronide conjugation) are not shown but are prominent for most compounds.

*Not specifically detected by the Opiates – Confirmation/Quantification, Urine, assay
Individual Response to Treatment

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

PGT Variability & Response

› 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
Let's Discuss Cases
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?
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

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?
Example Converting to MEDD

- Oxycodone 10mg PO Q6H around the clock
  - Equal to morphine 60mg / See chart
- Hydromorphone 2mg PO Q4H
  - Equal to morphine 48mg / See chart
  - Total MEDD: 60 + 48 = **108mg** PO morphine
- Convert to Morphine ER
  - \( (108\text{mg})(50\%) = 54\text{mg} \) PO morphine total
  - Morphine SR 30mg PO Q12H = **60mg**
  - Breakthrough IR medication discussion?

<table>
<thead>
<tr>
<th>Drug</th>
<th>Parenteral</th>
<th>Oral</th>
</tr>
</thead>
<tbody>
<tr>
<td>Codeine</td>
<td>100mg</td>
<td>200mg</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>0.1mg</td>
<td>N/A</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>N/A</td>
<td>30mg</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>1.5mg</td>
<td>7.5mg</td>
</tr>
<tr>
<td>Methadone</td>
<td>*</td>
<td>N/A</td>
</tr>
<tr>
<td>Morphine</td>
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Example Converting to MEDD

Current Meds:
- Oxycodone 10mg PO Q6H around the clock
  - Equal to morphine 60mg / See chart
- Hydromorphone 2mg PO Q4H
  - Equal to morphine 48mg / See chart
  - Total MEDD: 60 + 48 = **108mg PO morphine**

Convert to Morphine ER
- \((108mg)(50\%) = 54mg\) PO morphine total
  ~Morphine SR 30mg PO Q12H = **60mg**
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<td>1mg</td>
<td>10mg</td>
</tr>
</tbody>
</table>

Morphine Equivalent Daily Dose (MEDD) is the same in all healthy patients of same gender and weight in the absence of drug interactions.

A. True

B. False
Self-Assessment Question 2

Online opioid conversion calculators are most inaccurate for...

A. Hydrocodone and oxycodone
B. Hydromorphone and oxymorphone
C. Methadone and fentanyl
D. None of the above
Self-Assessment Question 3

When converting from an IR opioid to a different ER opioid, the FDA suggests what percent dosage reduction for cross-tolerance?

A. 50%
B. 25%
C. 15%
D. 10%
Discussion

Questions?