



Jeffrey Fudin, PharmD, FCCP, FASHP, FFSMB

Diplomate, Academy of Integrative Pain Management (AIPM)

Chief Executive Officer, REMITIGATE LLC

Clinical Pharmacy Specialist & PGY2 Pain Residency Director
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 effect opioid efficacy, toxicity, and tolerability.



Self-Assessment Question 1

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

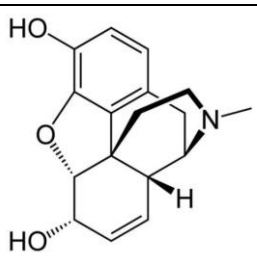
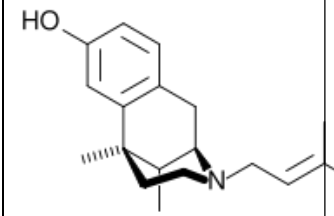
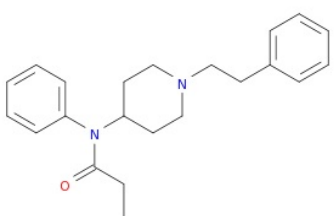
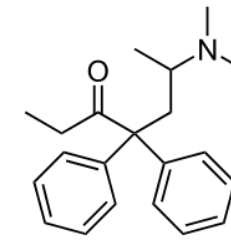
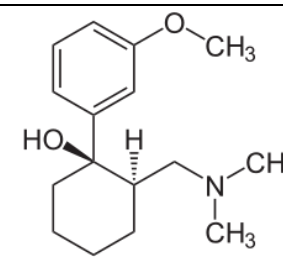
Self-Assessment Question 3

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%

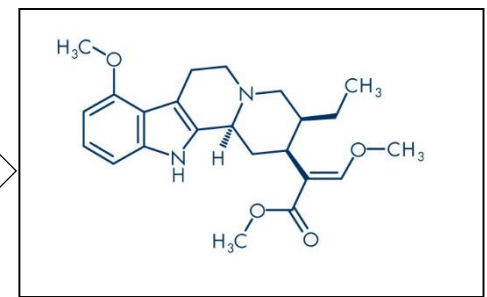


Comparative Opioid Chemistry

PHENANTHRENES	BENZOMORPHANS	PHENYLPIPERIDINES	DIPHENYLHEPTANES	PHENYLPROPYL AMINES
				
MORPHINE	PENTAZOCINE	FENTANYL	METHADONE	TRAMADOL
Buprenorphine* Butorphanol* Codeine Dextromethorphan* Dihydrocodeine Heroin (diacetyl-morphine) Hydrocodone* Hydromorphone* Levorphanol* Methylnaltrexone** Morphine (Opium, conc) Nalbuphine* Naloxone* Naloxegol* Naltrexone** Oxycodone* Oxymorphone*	Diphenoxylate Loperamide Pentazocine	Alfentanil Fentanyl Meperidine Remifentanyl Sufentanyl Illicit Fentanyl Furanyl fentanyl Acetyl fentanyl Fluoro-fentanyl Carfentanyl	Methadone Propoxyphene	Tapentadol Tramadol
CROSS-SENSITIVITY RISK				
PROBABLE	POSSIBLE	LOW RISK	LOW RISK	LOW RISK

Not All
Opioids are
Created
Equal!

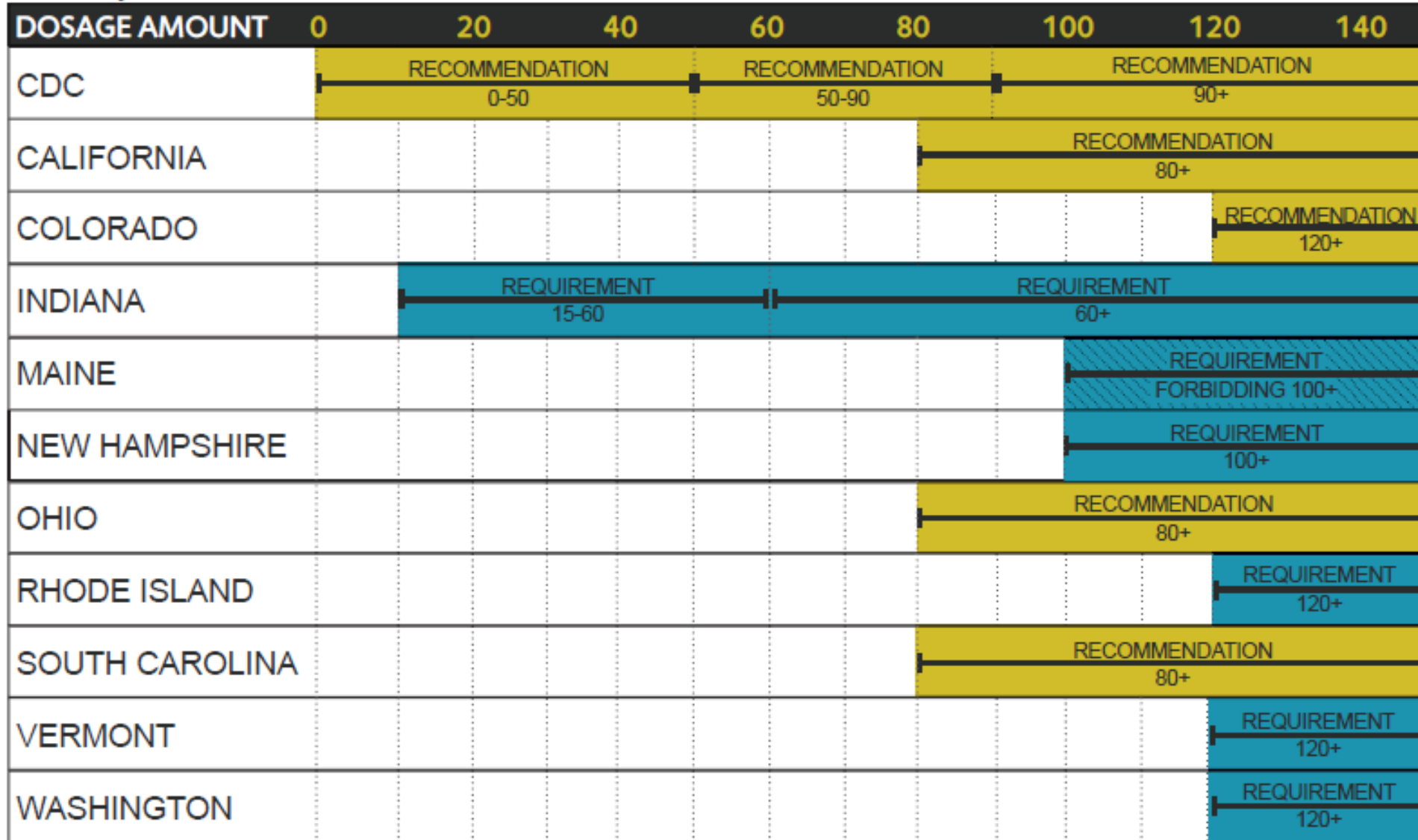
Mitragynine (Kratom)



*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

States with MEDD Thresholds (a moving target)

(MME/Day)



Opioid Dosage and Morphine Equivalency: Implications for Meeting the Standard of Care when Comparing CDC Recommendations to State Policies. State Pain Policy Advocacy Network (SPPAN). August 2016. Available at <http://blog.aapainmanage.org/wp-content/uploads/Opioid-Dosage-and-Morphine-Equivalency.pdf>

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
-
- Fudin J, Marcoux MD, Fudin JA. Mathematical Model For Methadone Conversion Examined. Practical Pain Management. Sept. 2012. 46-51.
 - Donner B, et al. Direct conversion from oral morphine to transdermal fentanyl: a multicenter study in patients with cancer pain. Pain. 1996;64:527–534.
 - Breitbart W, Chandler S, Egel B, et al. An alternative algorithm for dosing transdermal fentanyl for cancer-related pain. Oncology. 2000;14:695–705.
 - Shaw K, Fudin J. Evaluation and Comparison of Online Equianalgesic Opioid Dose Conversion Calculators. Practical Pain Management. 2013 August; 13(7):61-66.



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

This article was published in the following Dove Press journal:

Journal of Pain Research

23 March 2016

Number of times this article has been viewed

Jeffrey Fudin¹
Jacqueline Pratt Cleary²
Michael E Schatman³

¹Western New England University
College of Pharmacy, Springfield, MA,
²Stratton VA Medical Center, Albany,
NY, ³US 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.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

Fudin J, Pratt Cleary J, Schatman ME. The MEDD myth: the impact of pseudoscience on pain research and prescribing-guideline development. Journal of Pain Research. 2016 March; 9:153-156.





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


Rennick A, Atkinson TJ, Cimino NM, Strassels SA, McPherson ML, Fudin J. Variability in Opioid Equivalence Calculations. Pain Medicine. 2016;17: 892–898.

What Do You Think Were the Most Outrageous Conversions?

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

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

Rennick, A., Atkinson, T., Cimino, N. M., Strassels, S. A., McPherson, M. L., & Fudin, J. Variability in opioid equivalence calculations. Pain Medicine. 2016;17:5:892-898.

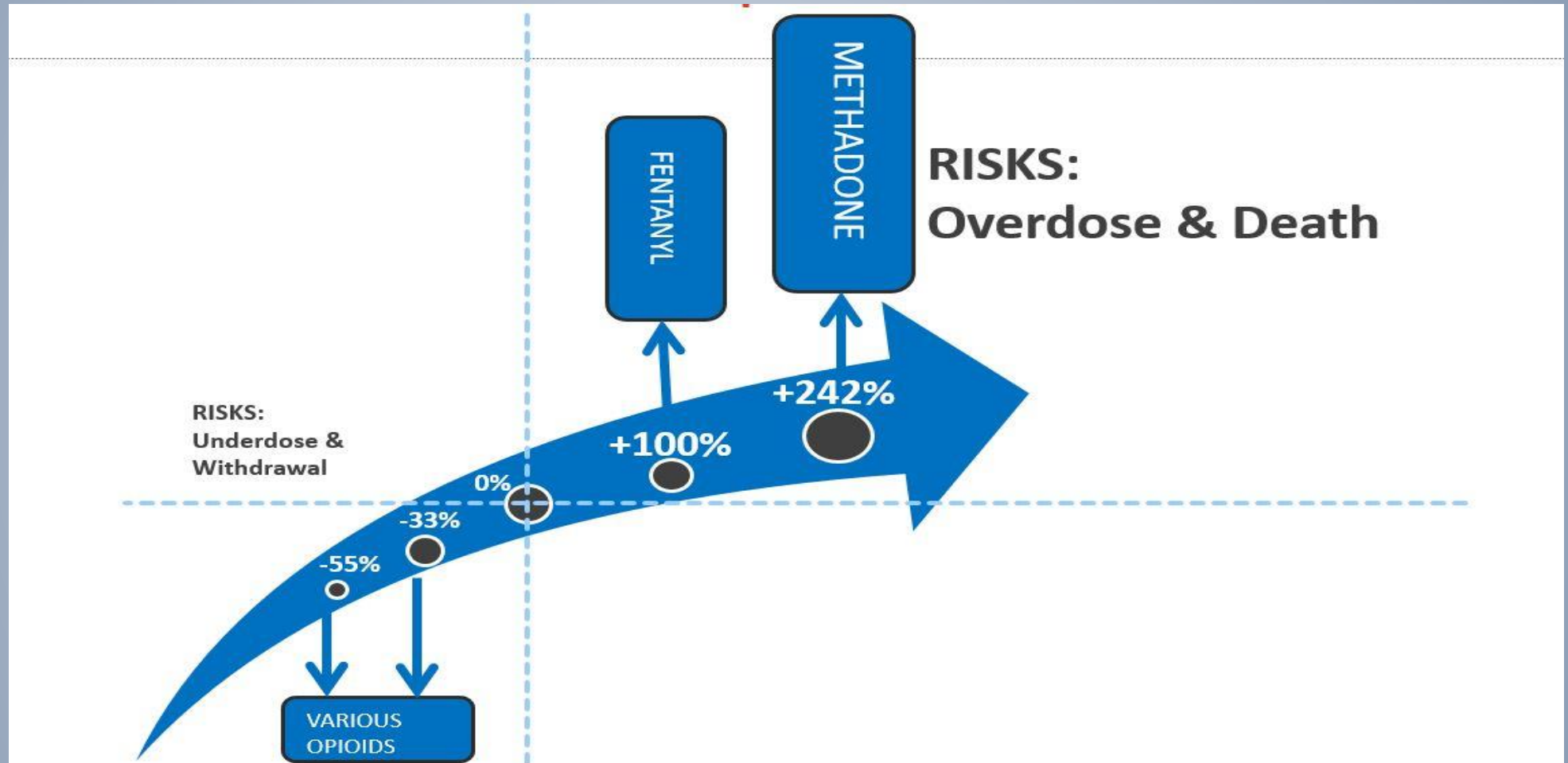


Available Online Opioid Conversion Calculators

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

Ref. Shaw K, Fudin J. Evaluation and Comparison of Online Equianalgesic Opioid Dose Conversion Calculators. *Practical Pain Management*. 2013 August; 13(7):61-66.

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



Shaw K, Fudin J. Evaluation and Comparison of Online Equianalgesic Opioid Dose Conversion Calculators. Practical Pain Management. 2013 August; 13(7):61-66. PPM 2013



How can I contribute to a
methadone death?

Let me count the ways...



Comparison of Proposed Morphine to Methadone Equivalents

Ripamonti et al, 1998						
Morphine dose (mg/day)	30-90		91-300		301+	
Morphine:Methadone EDR	3.70:1		7.75:1		12.25:1	
Ayonrinde et al, 2000						
Morphine dose (mg/day)	<100	101-300	301-600	601-800	801-1000	>1001
Morphine:Methadone EDR	3:1	5:1	10:1	12:1	15:1	20:1
Mercadante et al, 2001						
Morphine dose (mg/day)	30-90		91-300		301+	
Morphine:Methadone EDR	4:1		8:1		12:1	

Fudin et al, 2012

$$\text{Methadone (mg)} = \frac{X}{21} \left\{ 5.7 - 3 \sin \left[\frac{90}{\left[\frac{110}{X} \right]^5 + 1} \right] - \sin \left[\frac{90}{\left[\frac{320}{X} \right]^7 + 1} \right] \right\}$$

Let X = Morphine (mg)

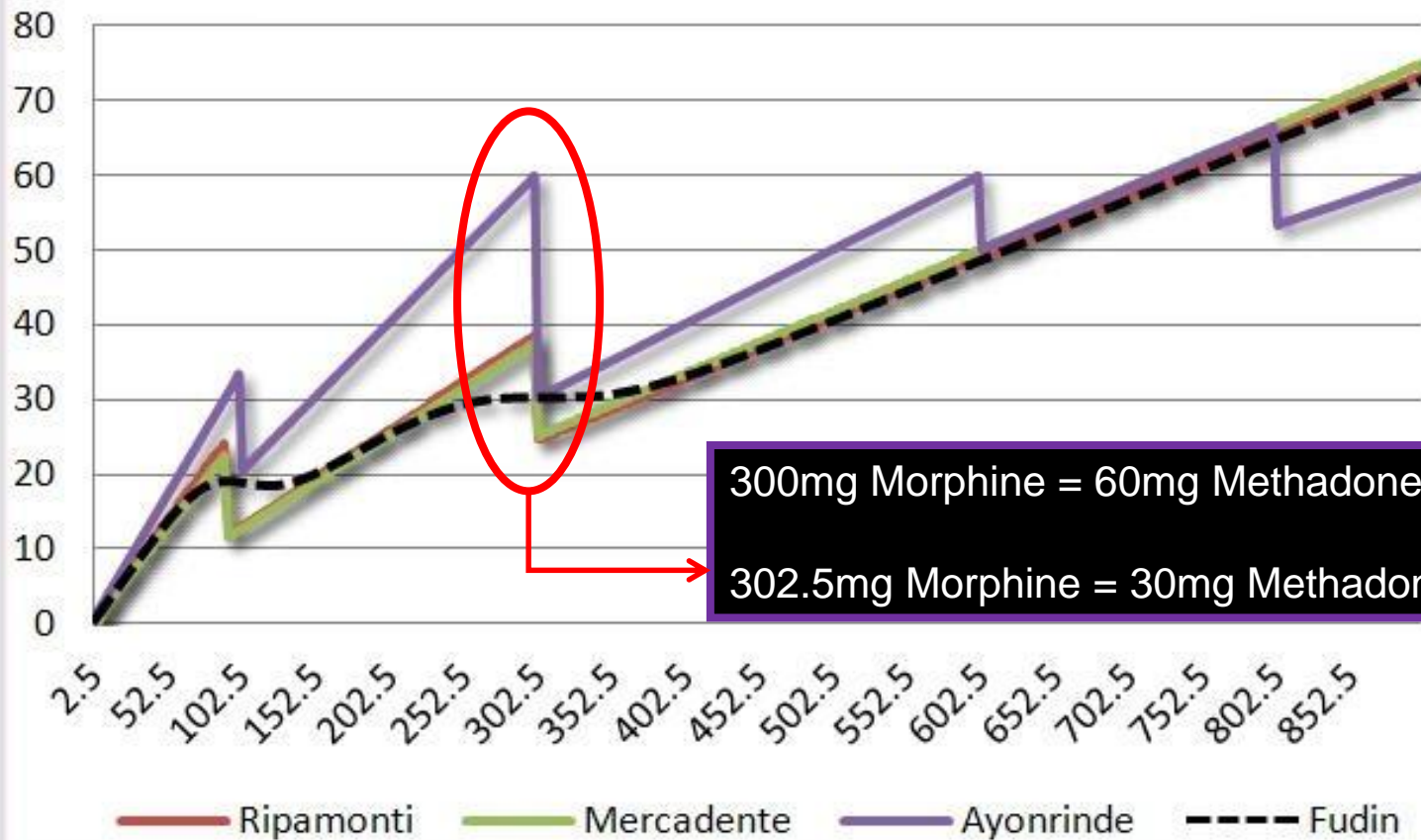
X=morphine (mg) | EDR=equianalgesic dose ration

Fudin J, Marcoux MD, Fudin JA. Mathematical Model For Methadone Conversion Examined. Practical Pain Management. 2012 September; 12(8): 46-51.



Equianalgesic Dose of Morphine to Methadone

Methadone (mg)



Morphine (mg)

Medication Metabolism

Phase of Metabolism	Key Enzymes Involved	Examples: Opioid Medication Metabolized
Phase I	Cytochrome P450 (CYP450) Examples: CYP2D6, CYP2C19, CYP2B6, CYP2C9, CYP3A4 & CYP3A5	Codeine, hydrocodone, oxycodone, tramadol, fentanyl, methadone, buprenorphine
Phase II	Uridine 5'-diphospho- glucuronosyltransferase (UDP- glucuronosyltransferase, UGT) Examples: UGT2B7 & 2B15	Morphine, oxymorphone, hydromorphone, tapentadol

Smith HS. Opioid metabolism. Mayo Clin Proc. 2009;84(7):613-624.



CDC Advert for CDC Online Opioid Calculator

Injury Prevention & Control: Opioid Overdose

[CDC](#) > [Opioid Overdose](#) > [CDC Guideline for Prescribing Opioids for Chronic Pain](#) > [Guideline Resources](#)

Guideline Resources: CDC Opioid Guideline Mobile App

[f](#) [t](#) [+](#)

CDC's new Opioid Guideline App is designed to help providers apply the recommendations of CDC's Guideline for Prescribing Opioids for Chronic Pain into clinical practice by putting the entire guideline, tools, and resources in the palm of their hand. Managing chronic pain is complex, but accessing prescribing guidance has never been easier.

The application includes a Morphine Milligram Equivalent (MME) calculator*, summaries of key recommendations and a link to the full Guideline, and an interactive motivational interviewing feature to help providers practice effective communications skills and prescribe with confidence.

Free Download

The new CDC Opioid Guideline App is now available for free download on [Google Play](#) (Android devices) and in the [Apple Store](#) (iOS devices).

[Download on the App Store](#) [ANDROID APP ON Google play](#)

Related Pages

[Guideline Resources](#) [Guideline Resources: Posters](#)

CDC Opioid Guideline App: Prescribe with Confidence



[Opioid Prescribing Guideline Mobile App](#)
[PDF - 652 KB]

<https://www.cdc.gov/drugoverdose/prescribing/app.html>

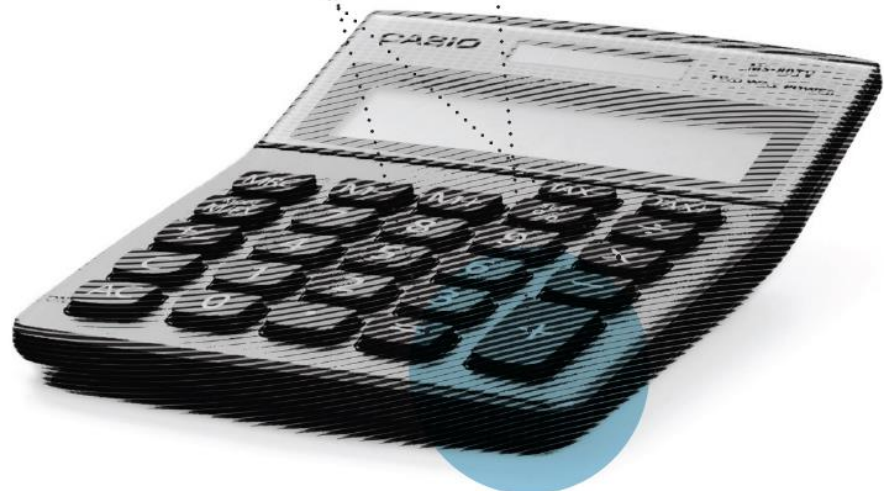
CDC Calculator lacks accuracy with methadone conversion!



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)

OPIOID (doses in mg/day except where noted)	CONVERSION FACTOR
Codeine	0.15
Fentanyl transdermal (in mcg/hr)	2.4
Hydrocodone	1
Hydromorphone	4
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.

https://www.cdc.gov/drugoverdose/pdf/calculating_total_daily_dose-a.pdf

An Actual Example from CDC Smart Phone App

Guideline Resources: CDC Opioid Guideline Mobile App

“Morphine Equivalent” (mg)	Methadone Daily Dose (mg)
80	20
168	21
320	40
410	41

Fudin J, Raouf M, Wegrzyn EL, Schatman ME. Safety concerns with the Centers for Disease Control opioid calculator. *Journal of Pain Research*. 2018;11:1.



Safety concerns with the Centers for Disease Control opioid calculator

This article was published in the following Dove Press journal:
Journal of Pain Research

Jeffrey Fudin¹⁻⁴
Mena Raouf²
Erica L Wegrzyn²⁻⁴
Michael E Schatman^{5,6}

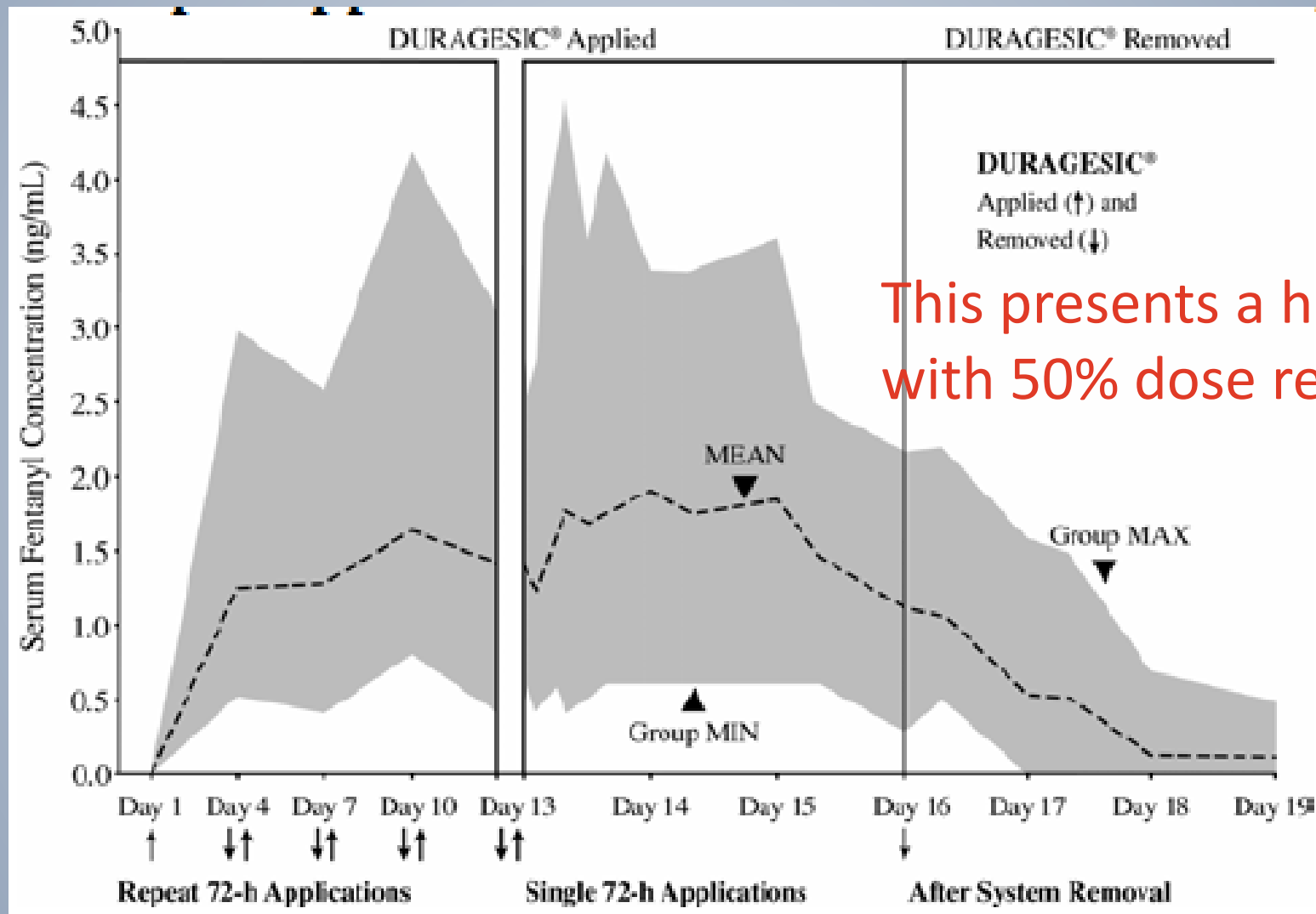
Introduction

Morphine milligram equivalence (MME) and other comparable acronyms have been employed in federal pain guidelines and used by policy makers to limit opioid prescribing.¹⁻⁵ On March 18, 2016, the Centers for Disease Control (CDC) released

Fudin J, Raouf M, Wegrzyn EL, Schatman ME. Safety concerns with the Centers for Disease Control opioid calculator. Journal of Pain Research. 2018;11:1.



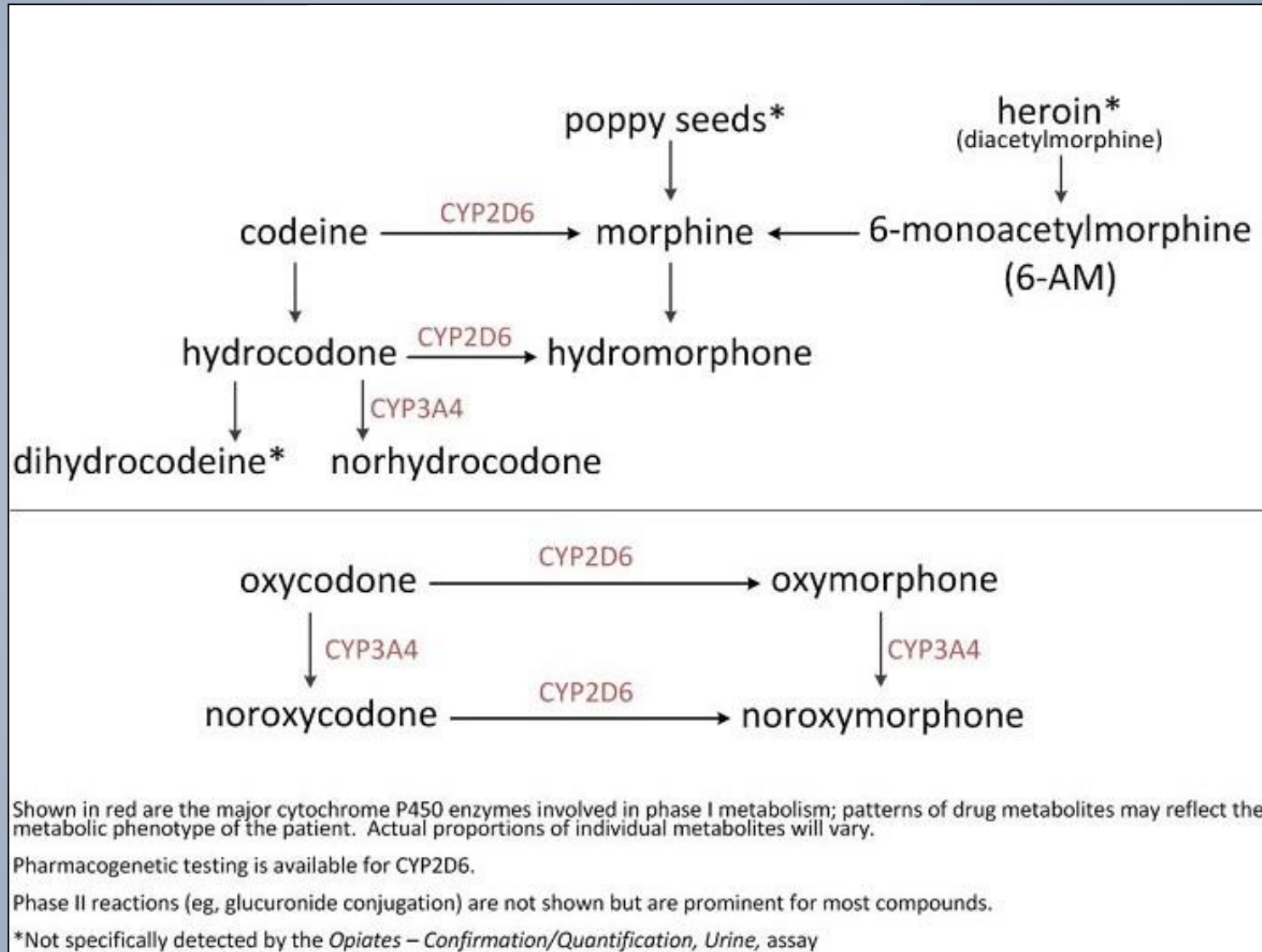
Serum Fentanyl Concentrations Following Multiple Applications of Fentanyl TD 100mcg/h (n=10)



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



Individual Response to Treatment

How the
body alters
the drug

Pharmacokinetics



How the drug
affects the
body

Pharmacodynamics

Pharmacogenetics

The science of how genetic variability impacts
individual responses to medications

- Argoff CE. Clinical implications of opioid pharmacogenetics. Clin J Pain. 2010;26(1):S16-S20.
- Belle DJ, Singh H. Genetic factors in drug metabolism. Am Fam Physician. 2008;77(11):1553-1560.





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
-
- Cavallari LH, Limdi NA. Warfarin pharmacogenomics. *Curr Opin Mol Ther.* 2009 Jun;11(3):243-51.
 - Lynch T, Price A. The effect of cytochrome P450 metabolism on drug response, interactions and adverse effects. *Am Fam Physician.* 2007; 76(3):391-6.
 - Ma JD, Lee KC, Kuo GM. Clinical application of pharmacogenomics. *J Pharm Pract.* 2012 Aug;25(4):417–27.



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 → MMMMmmm



Lets 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?**

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
- Papakostas GI, Shelton RC, Zajecka JM, et al. L-methylfolate as adjunctive therapy for SSRI-resistant major depression: results of two randomized, double-blind, parallel-sequential trials. *Am J Psychiatry*. 2012;169(12):1267-74.
- Dragic LL, Wegrzyn EL, Schatman M, Fudin J. Pharmacogenetic Guidance: Thorough Testing Results in Enhanced Pain Outcomes. 2017; in print at time of slide prep.






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**
-
- Papakostas GI, Shelton RC, Zajecka JM, et al. L-methylfolate as adjunctive therapy for SSRI-resistant major depression: results of two randomized, double-blind, parallel-sequential trials. *Am J Psychiatry*. 2012;169(12):1267-74.
 - Dragic LL, Wegrzyn EL, Schatman M, Fudin J. Pharmacogenetic Guidance: Thorough Testing Results in Enhanced Pain Outcomes. 2017; in print at time of slide prep.

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
 - (**108mg**)(50%) = **54mg** PO morphine total
 - ~Morphine SR 30mg PO Q12H = **60mg**
 - Breakthrough IR medication discussion?

Drug	Parenteral	Oral
Codeine	100mg	200mg
Fentanyl	0.1mg	N/A
Hydrocodone	N/A	30mg
Hydromorphone	1.5mg	7.5mg
Methadone	*	N/A
Morphine	10mg	30mg
Oxycodone	10mg	20mg
Oxymorphone	1mg	10mg

McPherson ML.
Demystifying opioid
conversion calculations:
a guide for effective
dosing. Bethesda (MD):
American Society of
Health-System
Pharmacists; 2010.



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: $60 + 48 = 108\text{mg PO morphine}$

Convert to Morphine ER

- › $(108\text{mg})(50\%) = 54\text{mg PO morphine total}$
~Morphine SR 30mg PO Q12H = 60mg
- › Breakthrough IR medication discussion?

Drug	Parenteral	Oral
Codeine	100mg	200mg
Fentanyl	0.1mg	N/A
Hydrocodone	N/A	30mg
Hydromorphone	1.5mg	7.5mg
Methadone	*	N/A
Morphine	10mg	30mg
Oxycodone	10mg	20mg
Oxymorphone	1mg	10mg



Self-Assessment Question 1

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?