


Demystifying Opioid Conversions and Calculations


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Disclosure


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Disclosures

Affiliation	Role
Abbott Laboratories	Speaker
AcelRx Pharmaceuticals	Advisory Board
Acutis Diagnostics, Inc	Speaker
Astra Zeneca	Speakers Bureau
BioDelivery Sciences International	Advisory Board, Consultant
Daiichi Sankyo	Advisory Board, Speakers Bureau
Firstox Laboratories	Consultant
GlaxoSmithKline (GSK)	Advisory Board, Collaborative Presentations
Human Half-Cell, Inc	Advisory Board
Quest Diagnostics	Advisory Board
Scilex Pharmaceuticals	Advisory Board, Collaborative Publications
Salix Pharmaceuticals	Advisory Board, Speakers Bureau, Publications

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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 effect opioid efficacy, toxicity, and tolerability.

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Pretest 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

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Pretest 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

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Pretest 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%

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Not All Opioids are Created Equally

PHENANTHERINES	BENZOMORPHANS	PHENYLPIPERIDINES	DIPHENYLPYRANS	PHENYLPROPYLAMINES
MORPHINE Buprenorphine* Buprenorphine* Codeine Diamorphine* Dihydrocodeone Hydrocodone* Hydrocodone* Hydrocodone* Levorphanol* Methadone (Optans, oral) Nalbuphine* Naloxone* Nalmefene* Oxycodone* Oxycodone* Oxycodone*	PENTACONS Fentanyl	PENTANS Alfentanil Fentanyl Remifentanyl Sufentanil Meprobamate Diphenhydramine* Loperamide*	METHADONS Methadone Propoxyphene	TRAMADOLS Loperamide Tramadol
PROBABLE		POSSIBLE	CROSS-SENSITIVITY RISK	
			LOW RISK	LOW RISK

Methadone (Optans) is highlighted with a red box and an arrow pointing to it.

* Again, lacking the 6-OH group of morphine, possibly decreases cross-tolerance within the phenanthrene group.
* Diamorphine is considered with a separate group and is not similar to morphine in tolerance induction.
* Methadone is considered with a separate group and is not similar to morphine in tolerance induction.
* Partially agonist/antagonist (see "Opioid Conversion").
* Fentanyl is listed as "Sufentanil".
* Benzene (C₆H₆) is listed as "Propoxyphene".
* Differences between tramadol and other opioids and their analogues (see [www.painmanagement.org](#) and [www.painmanagement.org](#)).

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States with MEDD Thresholds (a moving target)

(MEDD)	DOSAGE AMOUNT	0	20	40	60	80	100	120	140
CDC	RECOMMENDATION		5-50	50-50	50-50	50-50	50-50	50-50	50-50
CALIFORNIA	RECOMMENDATION								
COLORADO	RECOMMENDATION								
INDIANA	REQUIREMENT								
MAINE	REQUIREMENT								
NEW HAMPSHIRE	REQUIREMENT								
OHIO	RECOMMENDATION								
RHODE ISLAND	REQUIREMENT								
SOUTH CAROLINA	RECOMMENDATION								
VERMONT	REQUIREMENT								
WASHINGTON	REQUIREMENT								

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.painmanagement.org/wp-content/uploads/Opioid-Dosage-and-Morphine-Equivalency.pdf>

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Issues with MEDD & Opioid Conversion¹⁻⁴

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

1. Fudin J, Marcoux MD, Fudin JA. Mathematical Model For Methadone Conversion Examined. Practical Pain Management. Sept. 2012; 48-51.
2. Donnerer H, et al. Direct conversion from oral morphine to transdermal fentanyl: a multicenter study in patients with cancer pain. Pain. 1996;84:527-534.
3. Breitbart W, Charney S, Engel B, et al. An alternative algorithm for dosing transdermal fentanyl for cancer-related pain. Oncology. 2000; 14:695-705.
4. Shaw K, Fudin J. Evaluation and Comparison of Online Equianalgesic Opioid Dose Conversion Calculators. Practical Pain Management. 2013 August; 13(7):61-66.

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Journal of Pain Research

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

Jeffrey Fudin¹
Jacqueline Pratt Cleary²
Michael E Schatzman³

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.^{1,2} Non-opioid 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, Schatzman ME. The MEDD myth: the impact of pseudoscience on pain research and prescribing-guideline development. Journal of Pain Research. 2016 March; 9:153-156.

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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.

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Variability Survey Results

What do you think were most outrageous conversions?

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

Specialty	Fentanyl	Hydrocodone	Hydromorphone	Methadone	Oxycodone
Pain Management (n=39)	165 ± 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)

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

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Available Online Opioid Conversion Calculators

- > Med Calc
- > WA State Agency
- > Pain Research
- > Pain Physicians
- > Hopkins
- > Palliative Care
- > Global RPh
- > 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.

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(+/-) % 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

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How can I contribute to a methadone death?

Let me count the ways...

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Comparison of Proposed Morphine to Methadone Equivalents

Ripamonti et al, 1998						
Morphine dose (mg/day)	30-90	91-300	301+			
Morphine:Methadone	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	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	4:1	8:1	12:1			
Fudin et al, 2012						
Methadone (mg) = X	$\left\{ 5.7 - 3 \sin \left[\frac{90}{\left[\frac{10}{X} + 1 \right]} \right] - \sin \left[\frac{90}{\left[\frac{320}{X} + 1 \right]} \right] \right\}$					
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.

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Equianalgesic Dose of Morphine to Methadone

Methadone (mg)

Morphine (mg)

— Ripamonti — Mercadante — Ayonrinde -.- Fudin

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

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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'-diphosphoglucuronosyltransferase (UDP-glucuronosyltransferase, UGT) Examples: UGT2B7 & 2B15	Morphine, oxymorphone, hydromorphone, tapentadol

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

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CDC Advert for CDC Online Opioid Calculator

Guideline Resources: CDC Opioid Guideline Mobile App

The 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 multistep learning feature to help providers practice effective communications skills and exercise 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).

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

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CDC Calculator lacks accuracy with methadone conversion!

Calculating morphine milligram equivalents (MME)

OPIOID (list in mg/ml or mg/ml/30 min)	CONVERSION FACTOR
Codeine	0.15
Fentanyl transdermal (in mcg/hr)	2.4
Hydrocodone	1
Hydromorphone	4
Morphine	1
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

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An Actual Example from CDC Smart Phone 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.

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Safety concerns with the Centers for Disease Control opioid calculator

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

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.¹⁻³ 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.

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

Huge risk even with 50% dose reduction!

Graph showing Serum Fentanyl Concentration (ng/mL) over time (Day 1 to Day 19). The graph is divided into three phases: DURAGESIC® Applied (Repeat 72-h Applications), DURAGESIC® Applied (Single 72-h Applications), and DURAGESIC® Removed (After System Removal). The graph shows a significant increase in concentration during the single 72-h application phase, reaching a peak of approximately 4.5 ng/mL. The graph also shows a significant decrease in concentration during the After System Removal phase, reaching a minimum of approximately 0.5 ng/mL.


<https://dailymed.nlm.nih.gov/dailymed/archives/fdaDrugInfo.cfm?archived=49245>

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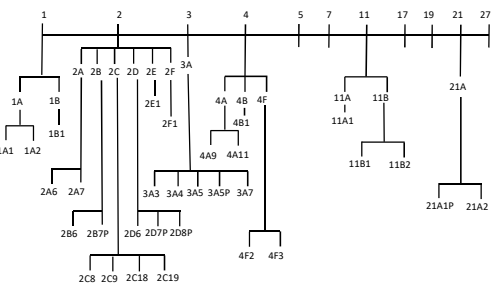


When converting opioids, there could be unanticipated risks of opioid-induced respiratory depression (OIRD).

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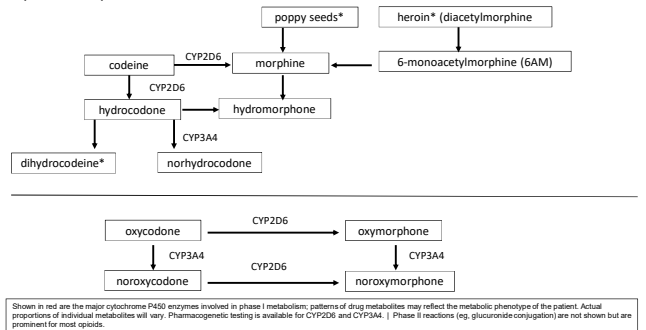
CYP450 Enzyme Tree



Adapted from: Riddick DS. Drug biotransformation. In: H Kalant, W Roschla (Ed), Principles of Medical Pharmacology, 6th ed, Oxford University Press: NY, 1997.

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Opiates / Opioid Metabolism



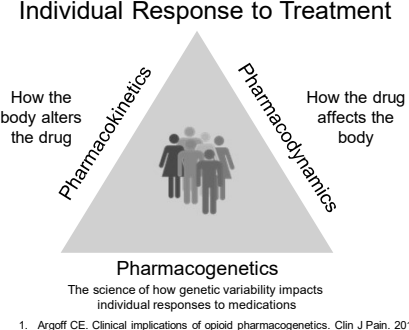
Shown in red are the major cytochrome P450 enzymes involved in phase I metabolism; patterns of drug metabolites may reflect the metabolic phenotype of the patient. Actual proportions of individual metabolites will vary. Pharmacogenetic testing is available for CYP2D6 and CYP3A4. (Phase II reactions (eg, 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.

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Individual Response to Treatment



- 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.

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PGT Variability & Response¹⁻³

- > 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

- 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; 75(3):391-5.
- Ma JD, Lee KC, Kuo GM. Clinical application of pharmacogenomics. *J Pharm Pract.* 2012 Aug;25(4):417-27.

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Phenotypes & Variants

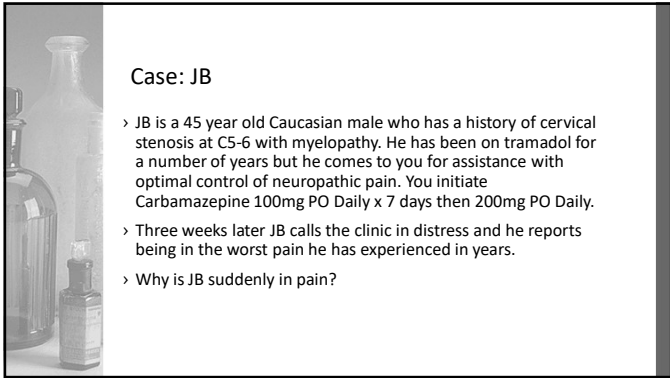
- > Allele Variations
 - wild:wild vs variant:wild vs wild:variant vs variant:variant

Poor Metabolizer (PM)
 DDDD → M
 Intermediate Metabolizer (IM)
 DDDD → MMm
 Extensive Metabolizer (EM)
 DDDD → MMM
 Ultra Rapid Metabolizer (UM)
 DDDD → MMMMmm

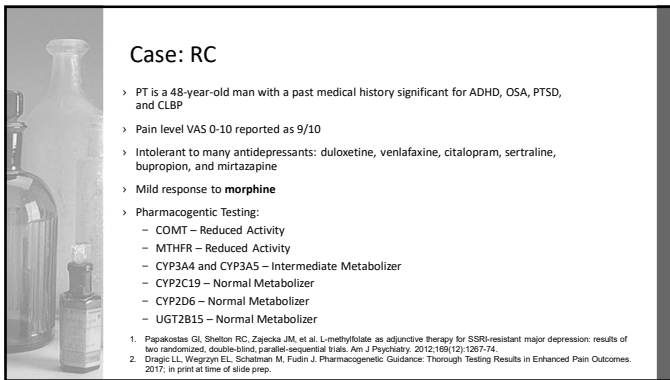
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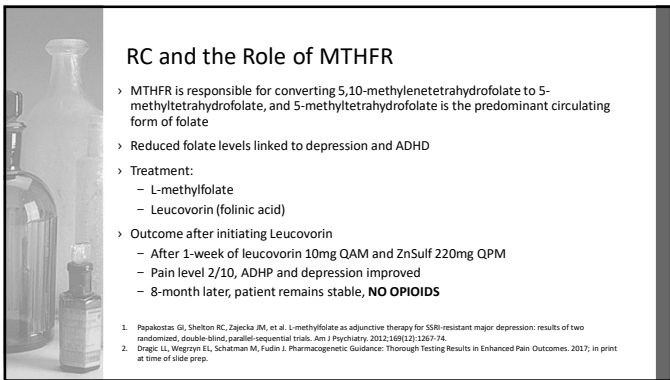
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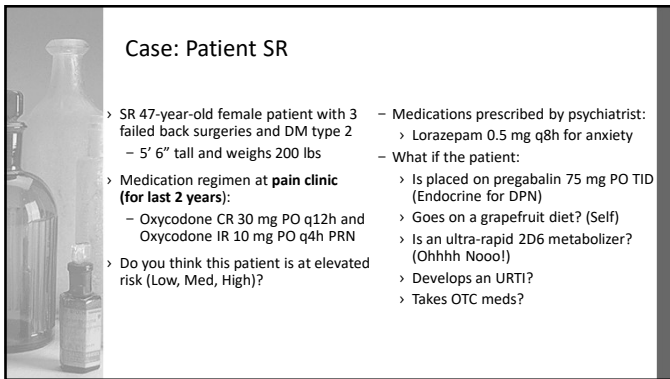
32



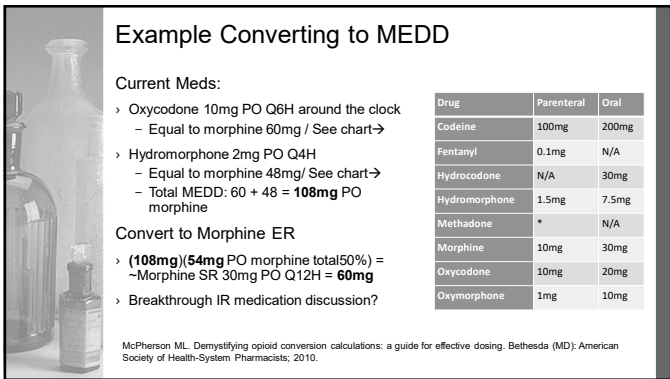
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Lets Discuss Cases

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?

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
1. Papanicolaou 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.
2. Dragic LL, Wegryn 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 (folic 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**
1. Papanicolaou 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.
2. Dragic LL, Wegryn EL, Schatman M, Fudin J. Pharmacogenetic Guidance: Thorough Testing Results in Enhanced Pain Outcomes. 2017; in print at time of slide prep.

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 Noooo!)
 - > Develops an URTI?
 - > Takes OTC meds?

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)(54mg PO morphine total50%) =**
- Morphine SR 30mg PO Q12H = **60mg**
- > Breakthrough IR medication discussion?

Drug	Parenteral	Oral
Codéine	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.




Post Test 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

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Post Test Question #2

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

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Questions?

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