Individual Patient & Medication Factors that Invalidate Morphine Milligram Equivalents

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

Jeffrey Fudin, PharmD, FCCP, FASHP, FFSMB

Clinical Pharmacy Specialist & PGY2 Pain Residency Director Stratton VAMC, Albany NY
Adjunct Associate Professor Albany College of Pharmacy & Health Sciences, Albany NY
Western New England University College of Pharmacy, Springfield MA
President, Remitigate Therapeutics, Delmar NY

Disclosures

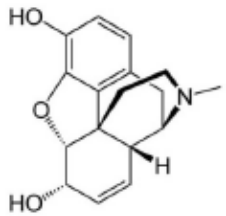
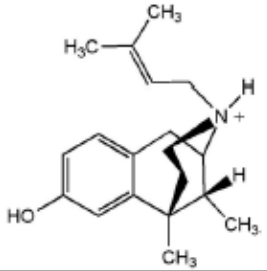
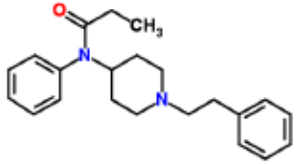
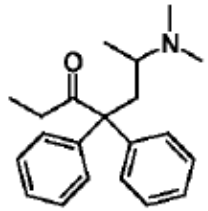
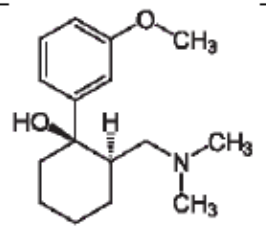
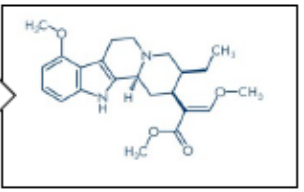
Affiliation	Role/Activities
Abbott Laboratories	Speaking, non-speakers bureau
AcelRx Pharmaceuticals	Acute perioperative pain (speakers bureau, consulting, advisory boards)
BioDelivery Sciences International	Collaborative publications, consulting, advisory boards
Firstox Laboratories	Micro serum testing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

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

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*	Pentazocine	Alfentanil Fentanyl Remifentanil Sufentanil Meperidine Diphenoxylate[a] Loperamide[a] **Illicit Fentanyl** Furanyl fentanyl Acetyl fentanyl Fluoro-fentanyl Carfentanil Others[b]	Methadone Propoxyphene **Mitragynine (Kratom)**	Tapentadol Tramadol 
CROSS-SENSITIVITY RISK				
PROBABLE	POSSIBLE	LOW RISK	LOW RISK	LOW RISK

*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

http://paindr.com/resources/quick-references/ (See "Opioid Chemistry")

a. Previously incorrectly listed as "Benzomorphans"

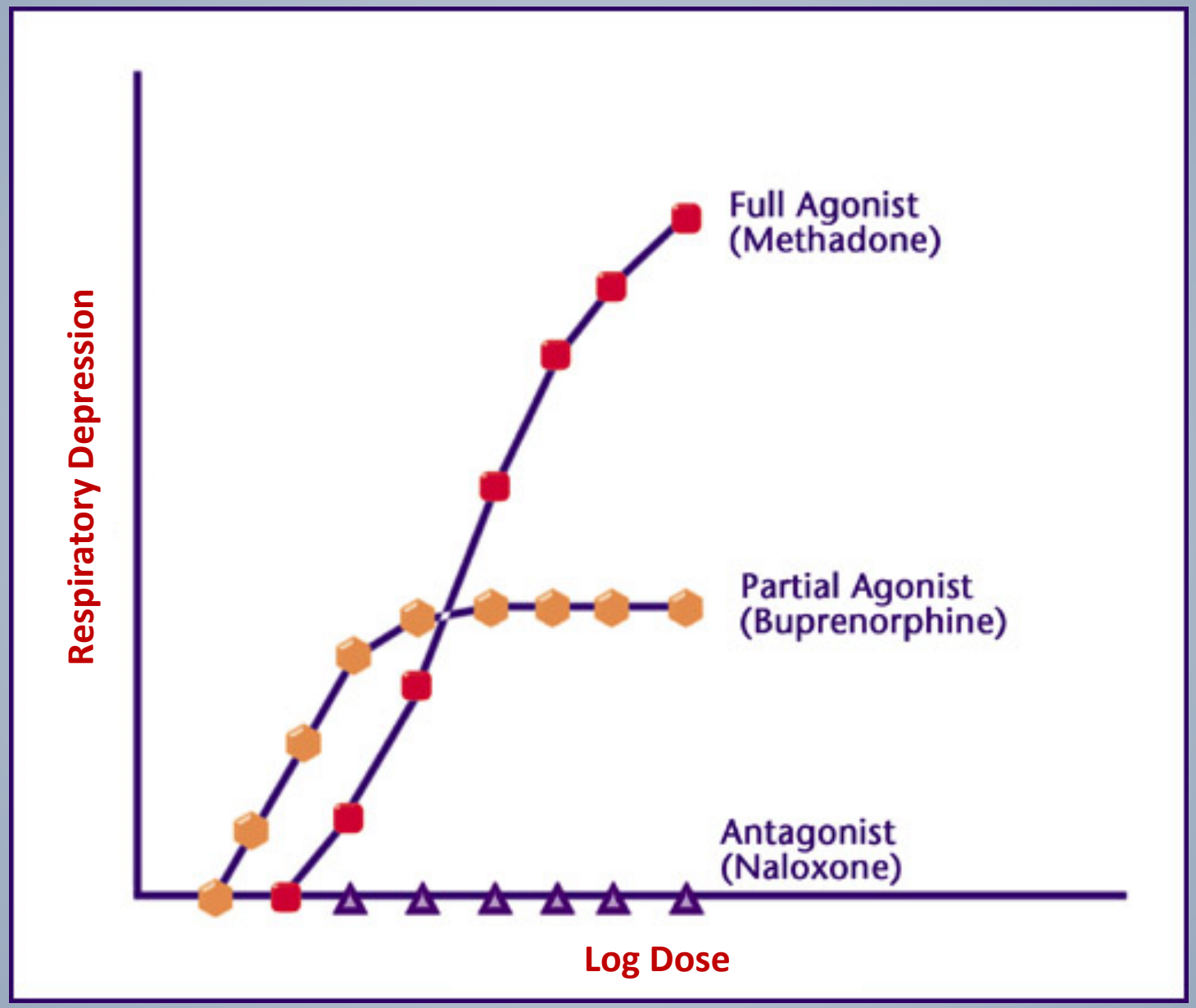
b. Bettinger JJ, Trotta ND, Fudin J. Wegrzyn EL, Schatman ME. Understanding the differences between pharmaceutical and illicit fentanyl and their analogues could save the opioid crisis. Practical Pain Management. 2018. July/August 18(5):59-67.

Issues with MEDD & Opioid Conversion[1-4]

- 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. 46-51.
2. 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.
3. Breitbart W, Chandler S, Eagel 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.

Conceptual Dose-Response Curves of Three Opioids



Adapted from: McNicholas L. US Department of Health and Human Services. 2004. Pages 11-24.

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)

Opioid:	Binding affinity (Ki value, nM)[1]	Partition Coefficient (Log P)[a]	Molecular Weight (Da)[2]	Equivalent Equianalgesic IM dose (mg)[b]
Sufentanil	0.1380	3.95	386	~500-1000 times more potent
Buprenorphine	0.2157	4.98	468	~40 times more potent[c]
Hydromorphone	0.3654	1.84	285	1.5
Oxymorphone	0.4055	0.83	301	1
Levorphanol	0.4194	3.1[4]	257[4]	2
Morphine	1.168	0.76	285	10
Fentanyl	1.346	4.05	336	0.1 – 0.2
Oxycodone	25.87	0.82	315	20
Codeine	734.2	1.14	299	130

[a]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}).
[b]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.
[c]Potency when calculated for buprenorphine is relative, given it has different pharmacologic effects on opioid receptors than traditional opioid agonist medications.

Journal of Pain Research

Dovepress
open access to scientific and medical research

Open Access Full Text Article

EDITORIAL

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 Fudin[1]
Jacqueline Pratt Cleary[2]
Michael E Schatman[3]

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

Variability Survey Results

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

Specialty	Fentanyl	Hydrocodone	Hydromorphone	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)

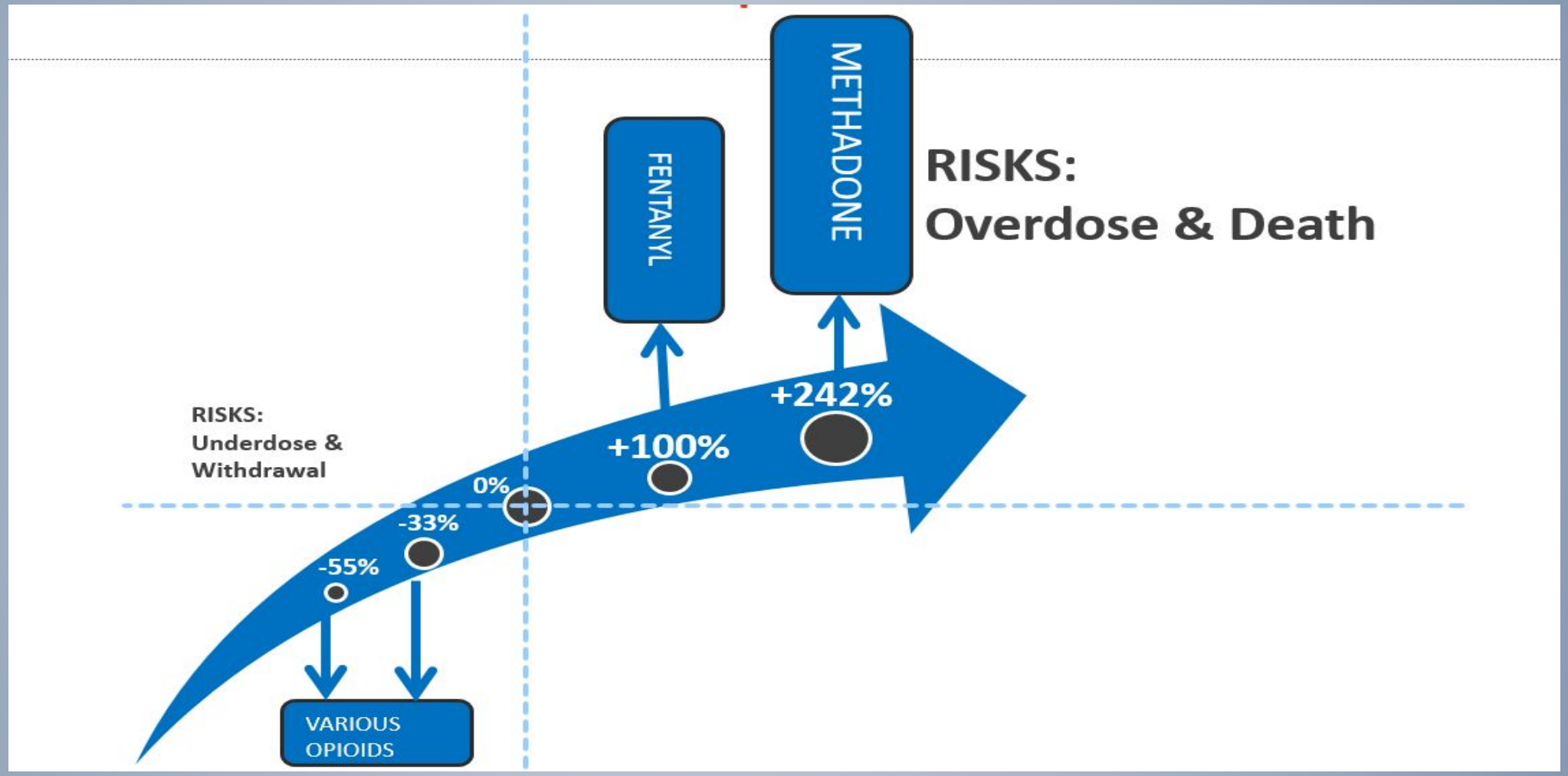
Rennick, A., Atkinson, T., Cimino, N. M., Strassels, S. A., McPherson, M. L., & Fudin, J. Variability in opioid equivalence calculations. Pain Medicine. 2016;17:5:892-898.

Available Online Opioid Conversion Calculators

- Med Calc
- 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.

(+/-) % 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

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						

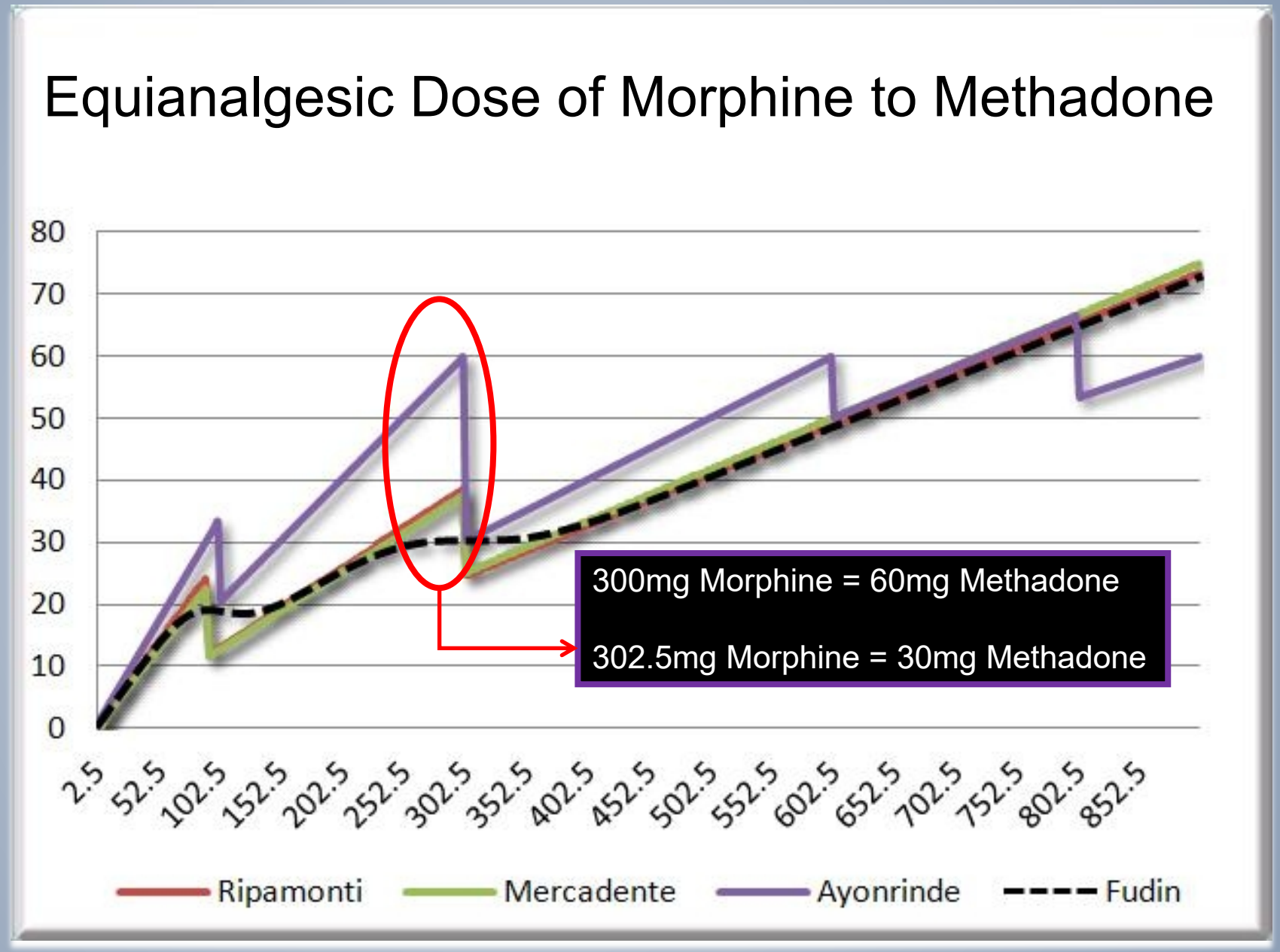
$$\text{Methadone (mg)} = \frac{X}{21}\left\{5.7 - 3\sin\left[\frac{90}{\left[\frac{110}{X}\right]^{5}+1}\right] - \sin\left[\frac{90}{\left[\frac{320}{X}\right]^{7}+1}\right]\right\}$$

$$\text{Let } X = \text{Morphine (mg)}$$

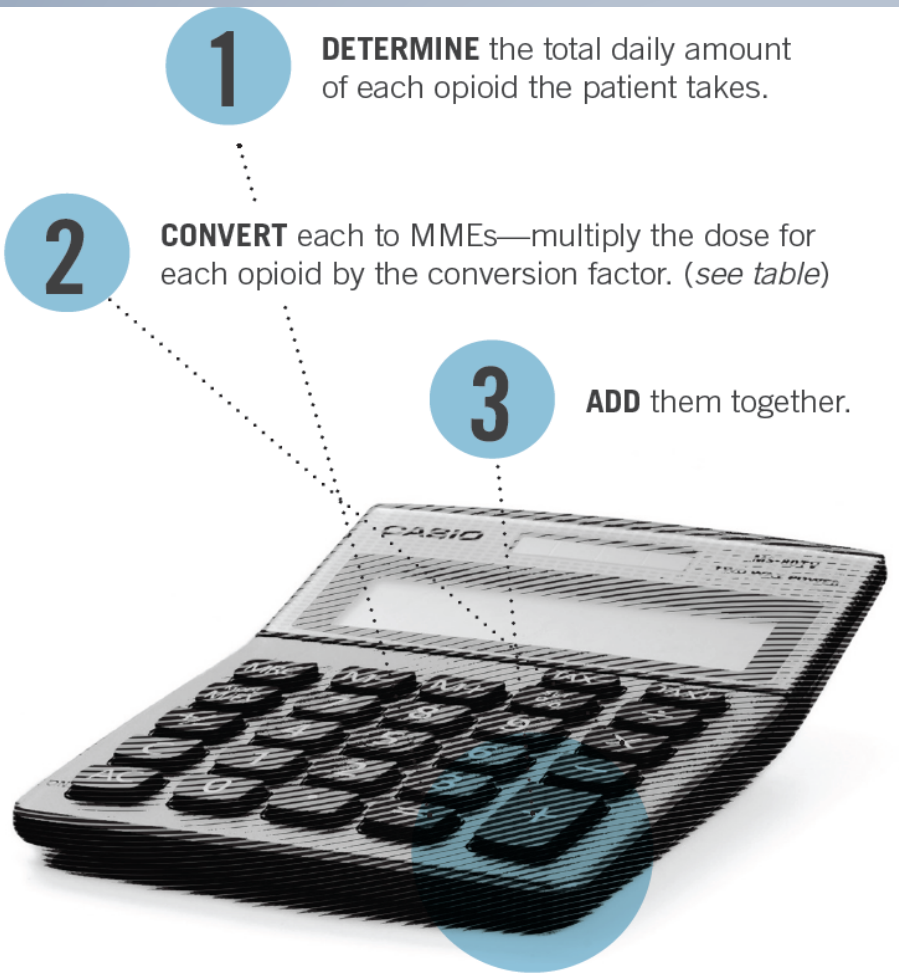
X=morphine (mg) | EDR=equianalgesic dose ration

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



CDC Calculator (methadone) is most consistent with Ayonrinde's formula



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

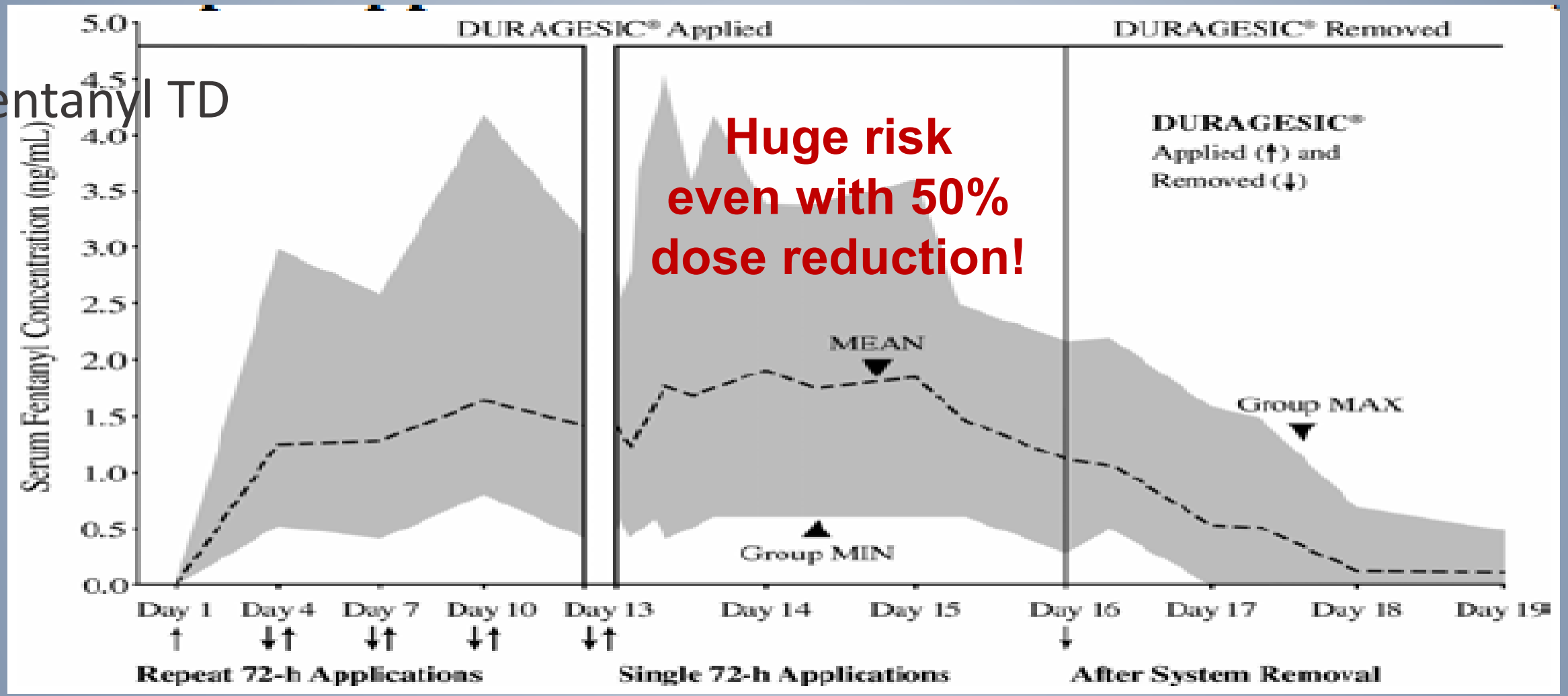
These dose conversions are estimated and cannot account for all individual differences in genetics and pharmacokinetics.

1. https://www.cdc.gov/drugoverdose/pdf/calculating_total_daily_dose-a.pdf
2. Ayonrinde OT, Bridge DT. The rediscovery of methadone for cancer pain management. pain. 2000 Nov;10(14):17.

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

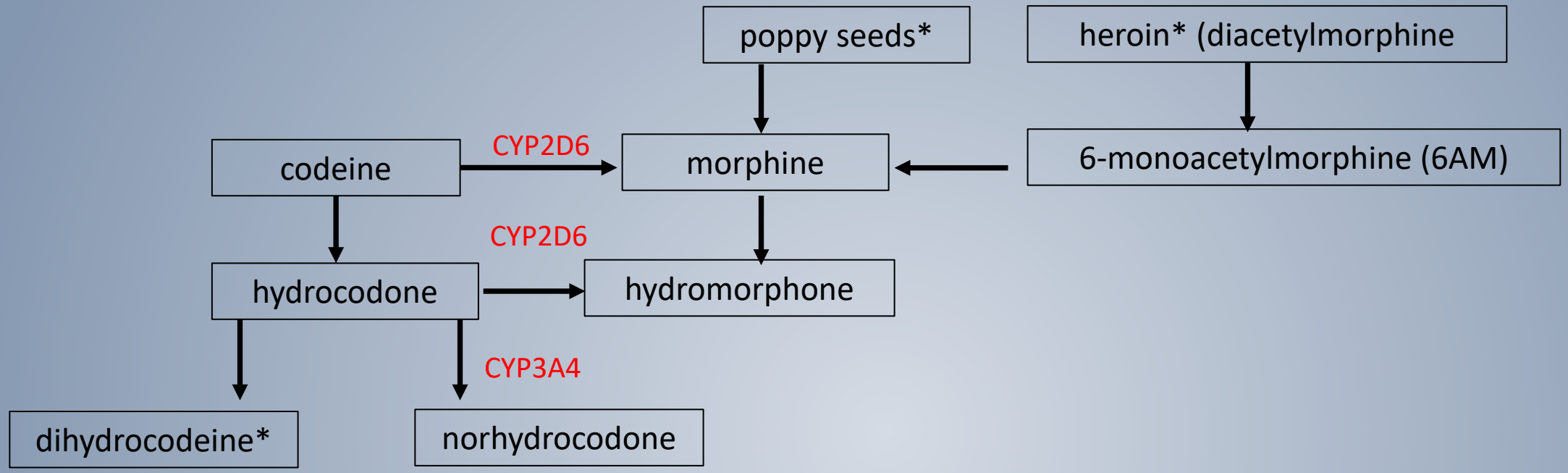
Serum Fentanyl Concentrations Following Multiple Applications of DURAGESIC® 100mcg/h (n=10)

Fentanyl TD



https://dailymed.nlm.nih.gov/dailymed/archives/fdaDrugInfo.cfm?archiveid=49245

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.

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 &	Morphine, oxymorphone, hydromorphone, tapentadol

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

Pharmacogenetic Variability & Response[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

1. Cavallari LH, Limdi NA. Warfarin pharmacogenomics. *Curr Opin Mol Ther*. 2009 Jun;11(3):243-51.
2. 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.
3. Ma JD, Lee KC, Kuo GM. Clinical application of pharmacogenomics. *J Pharm Pract.* 2012 Aug;25(4):417–27.

Individual Response to Treatment

How the body alters the drug

Pharmacokinetics

Pharmacodynamics

How the drug affects the body

Pharmacogenetics

The science of how genetic variability impacts individual responses to medications

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

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

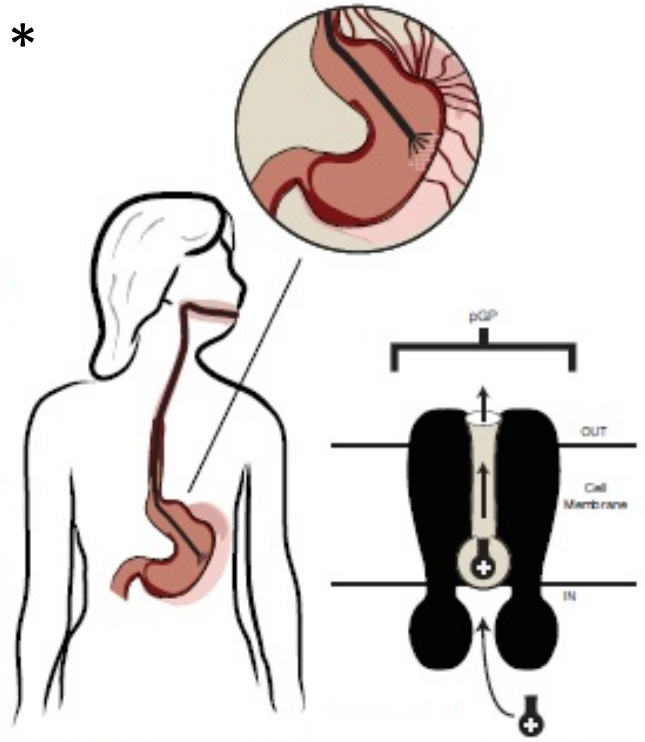
Terminology

- 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!

*



P-gp inducer
Causes the creation of more of the P-gp, and blood levels go down. P-gp inducers reduce the amount of some toxin ingestion as well, by pumping them back into the gut.

P-gp inhibitor
Inhibits the drug-pump-inhibitor and, consequently, blood levels of the drug increase.

There are other "transporters" or "pumps" that block the movement or facilitate movement of compounds through biological membranes; P-gp is the most important for drugs.

Published Cases

1. Fudin J, Fontenelle DV, Fudin HR, Carlyn C, Ashley CC, Hinden DA. Potential P-glycoprotein Pharmacokinetic Interaction of Telaprevir with Morphine or Methadone. Journal of Pain and Palliative Care Pharmacotherapy. 2013 August;. 27(3): 261-267.

2. Fudin J, Fontenelle DV, Payne A. Rifampin Reduces Oral Morphine Absorption; A Case of Transdermal Buprenorphine Selection Based on Morphine Pharmacokinetics. Journal of Pain & Palliative Care Pharmacotherapy. 2012 December;26(4):362–367.

*Fudin J, Fudin H, Zamora F. Drug Interactions. In Shapiro K, Brown SA, McNatty D, RxPrep Course Book. 2014 Ed. RxPrep Inc. Chap. 12, Page 190-202.

PGT Variability & Response[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

1. Cavallari LH, Limdi NA. Warfarin pharmacogenomics. *Curr Opin Mol Ther*. 2009 Jun;11(3):243-51.
2. 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.
3. 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

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**
- Pharmacogentic Testing:
  - COMT – Reduced Activity
  - MTHFR – Reduced Activity
  - CYP3A4 and CYP3A5 – Intermediate Metabolizer
  - CYP2C19 – Normal Metabolizer
  - CYP2D6 – Normal Metabolizer
  - UGT2B15 – Normal Metabolizer

1. 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.
2. 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**

1. 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.
2. 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.

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

1. Persico AL, Wegrzyn EL, Fudin J, Schatman ME. Fentalogues. Journal of Pain Research. 2020;13:2131.
2. Costantino RC, Gressler LE, Onukwugha E, McPherson ML, Fudin J, Villalonga-Olives E, Slejko JF. Initiation of Transdermal Fentanyl Among US Commercially Insured Patients Between 2007 and 2015. Pain Medicine. 2020 May 7.
3. Bettinger JJ, Trotta ND, Fudin J. Wegrzyn EL, Schatman ME. Fentanyl: Separating Fact from Fiction. 2018. July/August 8(5):59-67.

- 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