# CLINICAL PEARLS OF PHARMACOGENOMICS

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## DISCLOSURES

- The presenter does not have any conflicts of interest to disclose pertaining to this presentation.

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## OBJECTIVES

- Describe common pharmacogenetic variants involved in the effects of medications used in pain management
- Identify clinical situations in which obtaining a pharmacogenetic profile could be useful in pain management
- Develop individualized pain management regimens based on a given pharmacogenetic profile

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## PRE QUESTION 1

Pharmacogenomic variability only effects how drugs are metabolized by the body?

A. True
B. False

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## PRE QUESTION 2

Antidepressant activity is not impacted by pharmacogenomic variability.

A. True
B. False

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## PRE QUESTION 3

Which of the following medications can be significantly effected by pharmacogenomic characteristics?

A. Codeine
B. Oxycodone
C. Tramadol
D. All of the above

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## INTRODUCTION TO PHARMACOGENOMICS

- The study of how actions of and reactions to drugs vary due to the patient's genome
- Combines pharmacology (the science of drugs) with genomics (study of genes)
- Can impact pharmacodynamic characteristics
  - Receptor expression and signal transduction elements
- Can impact pharmacokinetic characteristics
  - Metabolizing enzymes and transporters

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## PHARMACODYNAMIC IMPACTS OF PHARMACOGENOMICS

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## VARIABLE PHENOTYPES THAT CAN EFFECT PHARMACODYNAMICS

- Opioid Receptor expression (OPMR-1)
- Catechol-O-Methyltransferase (COMT)
- Methylenetetrahydrofolate Reductase (MTHFR)
- Other genes/receptors that can impact mood disorders:
  - Brain-derived neurotrophic factor (BDNF)
  - Serotonin Receptor 2A (HTR2A)
  - Serotonin Transporter (SLC6A4)

Papakostas GI et al. Am J Psychiatry. 2012;169:1267-1274
Botto LD et al. Am J Epidemiol. 2000;161(9):862-877

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## GENETIC VARIABILITY TO OPRM-1

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## OPMR-1

- The gene that encodes for human mu-opioid receptors
  - Highly polymorphic → >100 variants identified
- Binds endogenous opioids (endorphins, enkephalins, and dynorphins)
  - Also exogenous opioids (morphine, hydrocodone, oxycodone, etc)
- It is involved in pain perception and opioid response

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## OPRM-1 POLYMORPHISMS

- A118G polymorphism leads to N40D substitution (single nucleotide polymorphism)
  - Genotype A118A; AA: opioid responder
    - Higher endorphin binding ability to mu-receptors
  - Genotype A118G; AG: decreased opioid responder
  - Genotype A118G; GG: poor opioid responder
    - Negatively associated with protein and mRNA yield
- Hypermethylation of OPRM-1
  - Decrease response to analgesic effects of opioids in cancer pain

Kaye AD et al. Pharmgenomics Pers Med. 2019;12:15-143
Viet CT et al. J Pain. 2017;18(9):1046-1059
Nielsen LM et al. Pain Pract. 2015;15(6):580-94

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## STUDIES INVOLVING SINGLE OPRM-1 GENE MUTATIONS

| Authors, year: | Gene: | Population: | Medication: | Outcomes: |
|---|---|---|---|---|
| ***Positive Associations:*** | | | | |
| Zhang et al, 2011 | A118G | Postoperative analgesia | Fentanyl | GG variants required more fentanyl to achieve adequate analgesia than AA or AG |
| Fukunda et al, 2009 | A118G | Postoperative orofacial surgery | Fentanyl | AG variants had lower analgesic response than AA patients |
| Boswell et al, 2013 | A118G | Postoperative analgesia | Hydrocodone | Pain relief significantly associated with total hydrocodone dose in AA group, but not in AG or GG groups |
| Gong et al, 2013 | A118G | Cancer-related pain | Morphine | MEDD needed to achieve adequate analgesia significantly lower in AA group than AG or GG |
| Klepstad et al, 2004 | A118G | Cancer-related pain | Morphine | Patients with GG required significantly higher MEDD to achieve pain control compared to AA |
| Chou et al, 2006 | A118G | Postoperative analgesia post-knee arthroplasty | Morphine | Patients with GG consumed significantly larger amounts of IV morphine than AA or AG groups |
| Cajanus et al, | A118G | Postoperative analgesia post-mastectomy | Oxycodone | Patient with GG required highest doses of oxycodone to achieve adequate analgesia vs AA or AG |
| Hayashida et al, 2008 | A118G | Postoperative analgesia | Total opioid doses | GG required greater 24-h postop analgesic requirements than AA or AG |
| Baber et al, 2015 | A118G | Post-cesarean section analgesia | Codeine | AG and GG variants required greater codeine consumption than AA |

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## STUDIES INVOLVING SINGLE OPRM-1 GENE MUTATIONS

| Authors, year: | Gene: | Population: | Medication: | Outcomes: |
|---|---|---|---|---|
| ***Negative Associations:*** | | | | |
| Zwisler et al, 2012 | A118G | Postoperative analgesia | Oxycodone | No association between A118G mutation and analgesic effects |
| Coulbault et al, 2006 | A118G | Postoperative analgesia | Morphine | No significant association between A118G polymorphism and MEDD |
| Kelpstad et al, 2011 | A118G | Cancer-related pain | Morphine | No significant association between A118G polymorphism and MEDD |

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## HOW THIS DICTATES TREATMENT?

- If AA genotype:
  - Will likely respond better to opioids and require ***lower*** overall doses
  - Thus, opioids could potentially work better for appropriate candidates
- If GG genotype:
  - Will likely not respond as well to opioid treatment and require ***higher*** overall doses
  - Thus, opioids should probably be avoided, or if used may require higher doses!

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## GENETIC VARIABILITY TO COMT AND MTHFR

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## COMT

- Enzyme present on nerve terminals that is involved in metabolism of neuroamines
  - Including dopamine, norepinephrine, and epinephrine
- Can be involved in pain modulation, sensitivity, and opioid response
  - Descending pain pathway is sensitive to noradrenergic modulation

Kaye AD et al. Pharmgenomics Pers Med. 2019;12:15-143

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## COMT POLYMORPHISM

| rs4680 SNP | | |
|---|---|---|
| **Genotype:** | **COMT Enzyme Activity:** | **Neuroamine Outcome:** |
| GG (Val/Val) | HIGH COMT activity | Increased metabolism of neuroamines in synaptic cleft |
| AG (Met/Val) | MODERATE COMT activity | Normal metabolism of neuroamines in synaptic cleft |
| AA (Val/Val) | LOW COMT activity (defective enzymes) | Decreased metabolism of neuroamines in synaptic cleft |

Kaye AD et al. Pharmgenomics Pers Med. 2019;12:15-143
Hu B et al. Neurosignals. 2018;26(1):11-21.

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## STUDIES INVOLVING RS4680 GENE MUTATIONS

| Authors, year: | Population: | Medication: | Outcomes: |
|---|---|---|---|
| Candiotti et al, 2014 | Postoperative analgesia after nephrectomy | Opioids | Val/Val patients consumed significantly greater opioids in 24-H and 48-H postop than Met/Met patients |
| Rakvag et al, 2005 | Cancer pain | Morphine | Val/Val patients required significantly more morphine than Val/Met and Met/Met genotypes |
| Tan et al, 2016 | Postoperative pain after total hysterectomy | Morphine | Val/Val patient required significantly more morphine than Val/Met and Met/Met genotypes |
| De Gregori et al, 2013 | Postoperative pain | Morphine | Met/Met and Met/Val genotypes both consumed significantly lower morphine doses than other patients |
| Tammimaki et al, 2012 | Fibromyalgia, migraines, and chronic widespread pain | Opioids | • Low COMT activity increases risk of fibromyalgia and chronic widespread pain; NOT migraines.<br>• Low COMT activity increases opioids receptors and enhances opioid analgesia |

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## HOW THIS DICTATES TREATMENT?

- If COMT Met/Met genotype:
  - Lower metabolism of synaptic neuroamines
  - Will likely respond better to opioids and require ***lower*** overall doses
  - Thus, opioids could potentially work better for appropriate candidates
- If COMT Val/Val genotype:
  - Will likely not respond as well to opioid treatment and require ***higher*** overall doses
  - Thus, opioids should probably be avoided, or if used may require higher doses!
  - Potentially could benefit from antidepressants?

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## MTHFR

- Catalyzes transformation of homocysteine to methionine
  - Body uses methionine as building block for proteins and neuroamines
  - Also allows for activation of dietary folate
- Similarly to COMT, can be involved in pain modulation, sensitivity, and opioid response
  - Descending pain pathway is sensitive to noradrenergic modulation
- 50-60% of individuals have reduced activity

Yigit S et al. Mol Vis. 2013;1626-1630.
Papakostas GI et al. Am J Psychiatry. 2012;169:1267-1274
Botto LD et al. Am J Epidemiol. 2000;161(9):862-877

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## MTHFR POLYMORPHISM

| C677T | | |
|---|---|---|
| **Genotype:** | **MTHFR Enzyme Activity:** | **Outcome:** |
| CC | REGULAR MTHFR activity | Normal conversion of methionine and activation of folate |
| CT | DECREASED MTHFR activity | Reduced conversion of methionine and activation of folate |
| TT | LOW MTHFR activity | Low conversion of methionine and activation of folate |

Yigit S et al. Mol Vis. 2013;1626-1630.
Papakostas GI et al. Am J Psychiatry. 2012;169:1267-1274

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## STUDIES INVOLVING C677T GENE MUTATIONS

- Unfortunately, there are not many studies that have attempted to associate C677T mutations with chronic pain conditions
- There have been several case studies and series that have noted some correlation in treating a C677T mutation with reduction in pain levels
  - Specifically by using L-methylfolate (active version of folate)
- There have been a multitude of studies showing an association between increased rates of depression, anxiety, bipolar disorder, and schizophrenia in those that are MTHFR poor metabolizers (677TT genotypes)

Wan et al. Transl Psychiatry. 2018;8:242.

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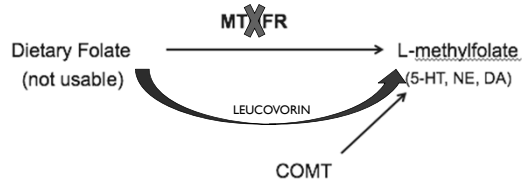
## HOW THIS DICTATES TREATMENT?




If MTHFR deficient, supplement with leucovorin!

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PATIENT CASE BREAK!

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## PATIENT CASE: JC

JC is a newly seen patient with chronic maxillofacial pain maintained on fentanyl 50mcg/hr apply once every 72 hours (has not responded to traditional therapies). The referring PCP was interested in a pharmacogenomic evaluation, as patient's pain was still not controlled despite escalating doses of fentanyl. The OPRM-1 gene was found to have a SNP mutation at A118G of GG genotype. What would be the expected outcome from this mutation?

A. We would expect patient to be an opioid RESPONDER, which explains why he requires MORE opioids
B. We would expect patient to be an opioid POOR RESPONDER, which explains why he requires MORE opioids
C. We would expect patient to metabolize neuroamines more rapidly, which explains why he is in more pain
D. OPRM-1 has nothing to do with pain or opioid response

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PHARMACOKINETIC IMPACTS OF PHARMACOGENOMICS

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## CYTOCHROME (CYP) 450

- Enzymes bound within cell membranes (cyto) and contains heme pigment (chrome and P), absorbs light at a wavelength of 450nm
- There are greater than 50 CYP eznymes
- Expressed mainly in liver
  - Also in small intestine, lungs, placenta, and kidneys
- CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4
  - Responsible for metabolizing about 90% of currently approved drugs
  - 40-60% phenotypic variability

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## PHENOTYPES AND VARIANTS

| Allelic Expression Inducing Phenotypes | | |
|---|---|---|
| **Poor Metabolizer** | Two nonfunctional alleles | The lowest rate of metabolism of drug into metabolite |
| **Intermediate Metabolizer** | At least one nonfunctional allele | The second lowest rate of metabolism of drug into metabolite |
| **Extensive Metabolizer** | At least one functional allele | The second fastest rate of metabolism of drug into metabolite |
| **Ultrarapid Metabolizer** | Multiple functional alleles and/or promoter mutations | Fastest rate of metabolism of drug into metabolite |

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## POTENTIAL OUTCOMES

| Phenotype | Active Parent Drug | Pro Drugs |
|---|---|---|
| **Poor Metabolizer** | ➢ Increased efficacy, toxicity<br>➢ Consider lower doses | ➢ Decreased efficacy, toxicity(?)<br>➢ Consider higher doses |
| **Intermediate Metabolizer** | ➢ Possible increased efficacy , toxicity<br>➢ +/- lower doses | ➢ Possible decreased efficacy, toxicity<br>➢ +/- Consider lower doses |
| **Extensive Metabolizer** | Average efficacy & toxicity if we know what that is… | Average efficacy & toxicity if we know what that is… |
| **Ultrarapid Metabolizer** | Decreased efficacy, toxicity<br>Consider higher doses | Increased efficacy, toxicity<br>Consider lower doses |

Don't forget that some drugs have multiple metabolites and phases!

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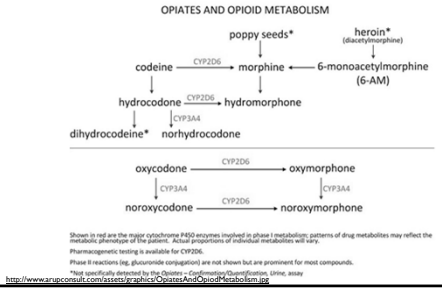
## REVIEW OF OPIOID METABOLISM



http://www.aruplconsult.com/assets/graphics/OpiatesAndOpioidMetabolism.jpg

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## OTHER OPIOID METABOLISM

| Drug Name (Brand) | FDA-Approved Neuropathic Pain Condition | Metabolism/Elimination | Other Metabolism and Transport Effects |
|---|---|---|---|
| Tramadol (Ultram®) | • Moderate to severe pain | • 30% renally<br>• 60% metabolism via CYP2D6 into active and 3A4 into inactive metabolites | None |
| Tapentadol (Nucynta®) | • Moderate to severe pain<br>• Diabetic neuropathy | • Primarily phase II metabolism into inactive metabolites | None |
| Methadone (Dolophine®) | • Chronic pain | • Primarily CYP3A4, 2B6, and 2C19 metabolism into inactive metabolites | • Weakly inhibits CYP2D6 |
| Levorphanol | • Moderate to severe pain | • Primarily phase II metabolism into inactive metabolites | None |
| Fentanyl | • Moderate to severe pain | • Primarily via CYP3A4 into inactive metabolite (norfentanyl) | None |

Smith HS. Pain Physician. 2012; 15(3 Suppl):ES93-110.
Pham TC, et al. Pain Med. 2015; 16(9):1673-9.

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## REVIEW OF SNRI METABOLISM

| Drug Name (Brand) | FDA-Approved Neuropathic Pain Condition | Metabolism/Elimination | Other Metabolism/Transport Effects |
|---|---|---|---|
| Venlafaxine (Effexor®) | None | • Primarily metabolism through CYP2D6 into active metabolites | • Weakly inhibits CYP enzyme 2D6 |
| Desvenlafaxine (Pristiq®) | None | • 50% renally<br>• 50% phase II metabolism | • Weakly inhibits CYP2D6<br>• Weakly induces CYP3A4 |
| Duloxetine (Cymbalta®) | • Diabetic neuropathy<br>• Fibromyalgia | • Almost entirely through CYP1A2 and CYP2D6 | • Moderately inhibits CYP2D6 |
| Milnacipran (Savella®) | • Fibromyalgia | • 55% renally<br>• 45% hepatically | None |
| Levomilnacipran (Fetzima®) | None | • 58% renally<br>• 42% hepatically | None |

Sindrup SH, et al. Basic Clin Pharmacol Toxicol. 2005; 96(6):399-409.

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## REVIEW OF ANTICONVULSANT METABOLISM

| Drug Name (Brand) | FDA-Approved Neuropathic Pain Condition | Metabolism/Elimination | Other Metabolism/Transport Effects |
|---|---|---|---|
| Carbamazepine (Tegretol®) | • Trigeminal neuralgia<br>• Glossopharyngeal neuralgia | • Primarily metabolism through CYP3A4 into active metabolites | • Strongly induces CYP3A4, 1A2, 2C19, 2C8, 2C9, PGP, UGT1A1 |
| Oxcarbazepine (Trileptal®) | None | • Primarily phase II metabolism into active metabolites | • Weakly induces CYP3A4 |
| Topiramate (Topamax®) | • Prophylaxis of migraines | • 70% renally<br>• 30% phase II metabolism | • Weakly inhibits CYP2C19 |
| Lamotrigine (Lamictal®) | None | • 10% renally<br>• 90% phase II metabolism | • Inhibits OCT2 |

Eisenberg E, et al. Drugs. 2007; 67(9): 1265-1289.

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## P-GLYCOPROTEIN VARIABILITY

- ATP-Binding Cassette sub-family B member 1 (ABCB1 gene) → encodes for p-glycoprotein (PGP) efflux transporter
- Present within membranes of blood-brain-barrier (BBB) and throughout intestinal tract
- Responsible for transport of different substrates, INCLUDING OPIOIDS
- EFFLUX → when a substrates binds within the membrane, PGP sends the substrate back to where it originally came from
  - For example, morphine is a substrate for PGP, thus when morphine is trying to cross the BBB from blood to the brain, PGP prevents morphine from reaching the brain

Kaye AD et al. Pharmgenomics Pers Med. 2019;12:15-143

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## POLYMORPHISMS TO THE ABCB1 GENE

- SNP at C3435T
  - TT genotype associated with potential lower expression of PGP
  - TT genotype associated with higher max cerebrospinal fluid concentration of morphine[1]
  - TT genotype associated with LOWER weight-surface area-adjusted opioid doses than CC or CT genotypes[2]
- SNP at rs9282564
  - Associated with prolonged PACU stay due to respiratory depression and increased odds of respiratory depression in PACU by 4.7-fold in children receiving morphine for perioperative analgesia[3]

1. Meineke L, et al. Br J Clin Pharmacol. 2002;54(6):592-603
2. Gong XD et al. Asian Pac J Cancer Prev. 2013;14(5):2937-43
3. Sadhasivam S et al. Pharmacogenomics J. 2015;15(2):119-26

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## CLINICAL RELEVANCE OF PGP?

- Clinical studies are lacking, and slightly contradicting
- Most genetic tests do not test for PGP expression
- We don't really know what the clinical relevance is yet

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PATIENT CASE BREAK!

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## CASE JC CONTINUED

JC, patient with chronic maxillofacial pain on fentanyl 50mcg/hr apply Q72H, was also found to be a CYP3A4 ultrarapid metabolizer. Due to the fact that he continues to be in pain, his PCP decides to convert directly to morphine extended-release capsules 150mg PO once daily. What could be a potential outcome?

A. Potential withdrawal: the patient would have had HIGHER than normal fentanyl levels, therefore conversion to the morphine dose above would be an UNDER DOSE

B. 100% PAIN RELIEF: the patient's genetics do NOT impact fentanyl metabolism, thus the above conversion makes sense

C. Potential overdose/death: the patient would have had LOWER than normal fentanyl levels, therefore conversion to the morphine dose above would be an OVER DOSE

D. I have no clue!

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## SUMMARY

- Pharmacogenomics has shown to play an important role in impacting both pharmacodynamic and pharmacokinetic characteristics
- Pharmacogenomic variability can not only impact pain itself, but can influence the potential response and tolerability to pain medications
- Understanding pharmacogenomics can help optimally guide treatment selection and safe management of pain patients

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THANK YOU!
ANY QUESTIONS?

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