CLINICAL PEARLS OF PHARMACOGENOMICS

Jeffrey Bettinger, PharmD
Pain Management Clinical Pharmacist
Saratoga Hospital Medical Group
Saratoga Springs, NY

Jacqueline Cleary, PharmD, BCACP
Assistant Professor of Pharmacy Practice
Albany College of Pharmacy and Health Sciences
Albany, NY

DISCLOSURES

- Dr. Bettinger would like to disclose that he is on the national advisory board for Hisamitsu America, Inc
- Dr. Cleary would like to disclose that she is a consultant and on the speakers board for Genomind

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

INTRODUCTION TO PHARMACOGENOMICS

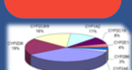
- The study of how actions of and reactions to drugs vary due to the patient's genome
- Combines pharmacology (the science of drugs) with genomics (study of genes)
- Can impact pharmacodynamic characteristics
  - Receptor expression and signal transduction elements
- Can impact pharmacokinetic characteristics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

PHARMACODYNAMIC IMPACTS OF PHARMACOGENOMICS

CANDIDATE GENES: KINETIC VS. DYNAMIC

Pharmacokinetic Genes:

CYP3A4/5
CYP2D6
CYP2C19
CYP1A2
CYP2B6
CYP2C9
UGT
ABCB1



Pharmacodynamic Genes:

SLC6A4
COMT
ADRA2A
DRD2
MC4R
5HT2A
5HT2C
OPRM1
GRIK1
MTHFR
BDNF
HLA-A/B

Häggström, Mikael. "Medical gallery of Mikael Häggström 2014". *Wikiversity Journal of Medicine* **1** (2). DOI:10.15347/wjm/2014.008. ISSN 20018762.

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

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

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

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

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

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!

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

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.

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. • Low COMT activity increases opioids receptors and enhances opioid analgesia

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?

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

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

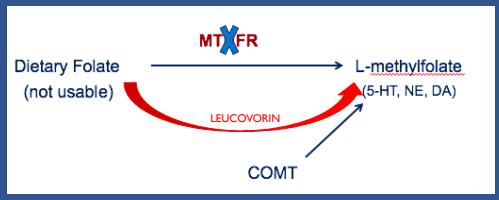
Yigit S et al. Mol Vis. 2013;1626-1630.
Papakostas GI et. al. Am J Psychiatry 2012;169:1267-1274

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.

HOW THIS DICTATES TREATMENT?



If MTHFR deficient, supplement with leucovorin!

PHARMACOKINETIC IMPACTS OF PHARMACOGENOMICS

CYTOCHROME (CYP) 450

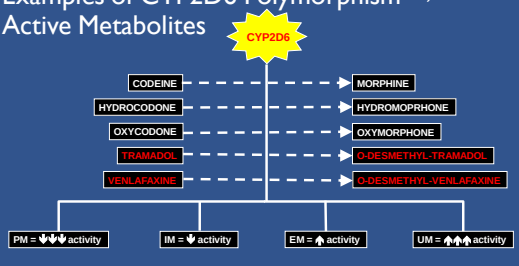
- Enzymes bound within cell membranes (cyto) and contains heme pigment (chrome and P), absorbs light at a wavelength of 450nm
- There are greater than 50 CYP eznymes
- Expressed mainly in liver
  - Also in small intestine, lungs, placenta, and kidneys
- CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4
  -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

POTENTIAL CLINICAL OUTCOMES

Phenotype	Active Parent Drug	Prodrugs
(PM) DDDD → M	➢ Increased efficacy, toxicity ➢ Consider lower doses	➢ Decreased efficacy, toxicity (?) ➢ Consider higher doses
(IM) DDDD → MMm	➢ Possible increased efficacy , toxicity ➢ +/- lower doses	➢ Possible decreased efficacy, toxicity ➢ +/- lower doses
(EM) DDDD → MMM	Average efficacy & toxicity (if known)	Average efficacy & toxicity (if known)
(UM) DDDD → MMMMmmm	➢ Decreased efficacy, toxicity ➢ Consider higher doses	➢ Increased efficacy, toxicity ➢ Consider lower doses

REMEMBER some drugs have multiple metabolites and phases!

Examples of CYP2D6 Polymorphism → Active Metabolites



OPIOID	METABOLISM	METABOITES
Fentanyl	3A4 (N-dealkylation)	Norfentanyl, hydroxyfentanyl
Morphine	Phase II glucuronidation	Morphine-3-glucuronide; morphine-6-glucuronide; hydromorphone (<5%)
Hydromorphone	Phase II glucuronidation	hydromorphone-3-glucuronide; hydromorphone-6-glucuronide
Hydrocodone	2D6 (O-demethylation); 3A4 (N-demethylation); 6-keto reduction	Hydromorphone (active, ~5.4 times more potent); norhydrocodone (active, ~70 times less potent); 6-alpha and 6-beta hydroxymetabolites
Codeine	2D6 (O-demethylation); phase II glucuronidation; 3A4 (N-demethylation)	Morphine (active); codeine-6-glucuronide; norcodeine (inactive)
Oxycodone	2D6 (O-demethylation); 3A4 (N-demethylation)	Oxymorphone (active, 2 time more potent); noroxycodone)
Oxymorphone	Phase II glucuronidation	oxymorphone-3-glucuronide
Methadone	3A4, 2B6, 2C19 (n-demethylation)	2- ethylidene-1, 5-dimethyl-3,3- diphenylpyrrolidene (EDDP)
Tapentadol	Phase II glucuronidation; 2C9/2C19 (methylation)	O-glucuronide; n-desmethyl-tapentadol

Courtesy of: http://pamdr.com/wp-content/uploads/2012/05/Pharmacodynamic-and-Pharmacokinetic-Properties-of-Commonly-Prescribed-Opioids_Fudin-Perkins.pdf

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 • 50% phase II metabolism	• Weakly inhibits CYP2D6 • Weakly induces CYP3A4
Duloxetine (Cymbalta®)	• Diabetic neuropathy • Fibromyalgia	• Almost entirely through CYP1A2 and CYP2D6	• Moderately inhibits CYP2D6
Milnacipran (Savella®)	• Fibromyalgia	• 55% renally • 45% hepatically	None
Levomilnacipran (Fetzima®)	None	• 58% renally • 42% hepatically	None

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

REVIEW OF ANTICONVULSANT METABOLISM

Drug Name (Brand)	FDA-Approved Neuropathic Pain Condition	Metabolism/Elimination	Other Metabolism/Transport Effects
Carbamazepine (Tegretol®)	• Trigeminal neuralgia • 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 • 30% phase II metabolism	• Weakly inhibits CYP2C19
Lamotrigine (Lamictal®)	None	• 10% renally • 90% phase II metabolism	• Inhibits OCT2

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

REVIEW OF NSAID METABOLISM (CELECOXIB, FLURBIPROFEN, IORNOXICAM, IBUPROFEN)

Phenotype of 2C9	Therapeutic Recommendation	Classification of Recommendation	Other Considerations
Normal	Initiate therapy with recommended starting dose	Strong	
Intermediate AS 1.5	Initiate therapy with recommended starting dose	Moderate	IMs may have a higher than normal risk of adverse events
Intermediate AS 1	Initiate therapy with recommended starting dose	Moderate	IMs may have a higher than normal risk of adverse events
Poor	Initiate 25-50% of the lowest recommended starting dose Titrate upward to clinical effect or 25-50% of maximum recommended dose with caution Dosage increases only once steady state has reached	Moderate	Therapies not metabolized by 2C9- aspirin, ketorolac, naproxen, sulidac

AS- activity score
Published June 2020 by CPIC- 2C9 and NSAID
https://cpicpgx.org/content/guideline/publication/NSAID/2020/32189324.pdf

REVIEW OF NSAID METABOLISM (MELOXICAM)

Phenotype of 2C9	Therapeutic Recommendation	Classification of Recommendation	Other Considerations
Normal	Initiate therapy with recommended starting dose	Strong	
Intermediate AS 1.5	Initiate therapy with recommended starting dose	Moderate	IMs may have a higher than normal risk of adverse events
Intermediate AS 1	Initiate therapy with 50% of the lowest recommended starting dose. Titrate dose upward to clinical effect or 50% of the maximum recommended dose with cuation	Moderate	IMs may have a higher than normal risk of adverse events. Therapies not metabolized by 2C9- aspirin, ketorolac, naproxen, sulidac
Poor	Choose an alternative therapy not metabolized by 2C9	Moderate	

AS- activity score
Published June 2020 by CPIC- 2C9 and NSAID
https://cpicpgx.org/content/guideline/publication/NSAID/2020/32189324.pdf

AVAILABLE EVIDENCE

- FDA guidance
  - FDA maintains a list of actionable genetic biomarkers (over 200 drugs)
  - https://www.fda.gov/downloads/Drugs/ScienceResearch/UCM572698.pdf
- CPIC guidance
  - CPIC creates dosing guidelines for many drugs (SSRIs, TCAs, Anticoagulants, etc.)
  - https://cpicpgx.org/
- PharmGKB
  - Aggregates PGx literature
  - Levels of evidence
  - https://www.pharmgkb.org/

DRUG	GENE	GUIDELINE
amitriptyline	CYP2C19	guideline
	CYP2D6	
citalopram	CYP2C19	guideline
clomipramine	CYP2C19	guideline
	CYP2D6	
clopidogrel	CYP2C19	guideline
codeine	CYP2D6	guideline
desipramine	CYP2D6	guideline
doxepin	CYP2C19	guideline
	CYP2D6	
fluvoxamine	CYP2D6	guideline
imipramine	CYP2C19	guideline
	CYP2D6	
nortriptyline	CYP2D6	guideline
ondansetron	CYP2D6	guideline
paroxetine	CYP2D6	guideline
phenytoin	CYP2C9	guideline
sertraline	CYP2C19	guideline
tacrolimus	CYP3A5	guideline
tamoxifen	CYP2D6	guideline
trimipramine	CYP2C19	guideline
	CYP2D6	
tropisetron	CYP2D6	guideline
voriconazole	CYP2C19	guideline
warfarin	CYP2C9	guideline

WHAT CAN CPIC TELL US?

- ~40 gene-drug pairs with associated guidelines
- Over 150 drugs contain PGX information in FDA approved drug label
- Allele frequencies
- CONSTANTLY EVOLVING!

PATIENT CASE BREAK

PATIENT CASE- HL

- HL is a 42 y.o. Caucasian MALE with PMH of severe depression and anxiety seen in pain clinic for uncontrolled chronic low back pain
- Allergies: NKDA
- Medications:
  - Bupropion 150mg PO BID for depression
  - Venlafaxine SA 300mg PO daily for depression
  - Paroxetine 40mg PO daily for anxiety
  - Alprazolam 1mg PO TID PRN for anxiety
  - Celecoxib 200mg PO daily PRN for pain
  - Oxycodone IR 15mg PO Q6H PRN for breakthrough pain
  - Oxycodone SA 80mg PO Q8H for pain

33

PATIENT CASE- HL

- Pharmacogenetic testing completed for HL (response per the patient)
- Medications:
  - Bupropion 150mg PO BID for depression
  - Venlafaxine SA 300mg PO daily for depression (poor response)
  - Paroxetine 40mg PO daily for anxiety (poor response)
  - Alprazolam 1mg PO TID PRN for anxiety
  - Celecoxib 200mg PO daily PRN for pain
  - Oxycodone IR 15mg PO Q6H PRN for breakthrough pain (poor response)
  - Oxycodone SA 80mg PO Q8H for pain (poor response)

34

PATIENT CASE- HL

Gene	Reported Phenotype	Medication
CYP1A2	Intermediate metabolizer	
CYP2B6	Extensive metabolizer	Bupropion
CYP2C9	Extensive metabolizer	Celecoxib
CYP2C19	Intermediate metabolizer	
CYP2D6	Poor metabolizer	Oxycodone, venlafaxine, paroxetine
CYP3A4	Extensive metabolizer	Alprazolam

35

PATIENT CASE- HL

Clinical considerations to improve pain and depression

- Potential drug interactions:
  - CYP 2D6 substrates: venlafaxine, oxycodone, paroxetine
  - CYP 2D6 inhibitors: bupropion, paroxetine, celecoxib
- Change SNRI
  - Duloxetine? Milnacipran?
- Change opioid
  - Morphine? Fentanyl? Methadone?
  - Serum oxycodone level!!!

36

PATIENT CASE- HL

- Patient brings with him his pharmacogenomic profile which shows the following:
  - C677T MTHFR genotype (LOW ACTIVITY)
  - Val/Val COMT genotype (DECREASED PAIN SENSITIVITY)
  - OPRM1- A118G;AG (DECERASED OPIOID RESPONDER)

37

PATIENT CASE- HL

Clinical considerations to improve pain and depression

- Optimize nonopioid options
  - If utilizing antidepressant(s), consider L-methylfolate supplementation
  - If the patient has comorbid depression, consider L-methylfolate supplementation
- May require higher doses of opioids*

38

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

THANK YOU!
ANY QUESTIONS?

Jeffery Bettinger: jbettinger@remitigate.com
Jacqueline Cleary: Jacqueline.cleary@acphs.edu