



The Pharmacogenomics of Pain Management

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Interprofessional Clinical Pharmacogenomics Certificate Program

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WSU

Conflict of Interest Disclosure

- I have no relevant financial relationships to disclose.

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Learning Objectives

- Determine the impact of genetic variation on drug pharmacokinetics, pharmacodynamics, and drug response
- Interpret pharmacogenomic test results by identifying clinically actionable drug-gene pairs using high-quality, evidence-based pharmacogenomic databases and guidelines to formulate therapeutic recommendations
- Describe the benefits, limitations, and risks of pharmacogenomic information for individuals, family members and communities, and recognize when to refer the patient to a genetic counselor

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Today's session on The Pharmacogenomics of Pain Management

- In addition to this lecture, this week's 1-hour home study session also includes reading 2 CPIC guidelines

Clinical Pharmacogenetics Implementation Consortium Guideline (CPIC) for CYP2C9 and Nonsteroidal Anti-Inflammatory Drugs

Katherine N Theken, Craig R Lee, Li Gong, Kelly E Caudle, Christine M Formea, Andrea Gaedigk, Teri E Klein, José A G Agúndez, Tilo Grosser

Clinical Pharmacogenetics Implementation Consortium Guideline for CYP2D6, OPRM1, and COMT Genotypes and Select Opioid Therapy

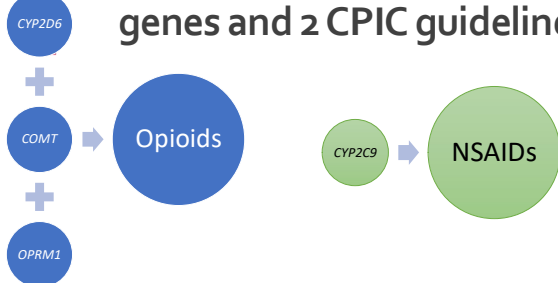
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Crews KR, et al. Clinical Pharmacogenetics Implementation Consortium Guideline for CYP2C9, OPRM1, and COMT Genotypes and Select Opioid Therapy. Clin Pharmacol Ther. 2021 Oct 1;110(4):888-896.

Theken KN, et al. Clinical Pharmacogenetics Implementation Consortium Guideline for CYP2C9 and Nonsteroidal Anti-Inflammatory Drugs. Clin Pharmacol Ther. 2021 Aug 1;110(2):455-466.

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Today's session will cover 4 genes and 2 CPIC guidelines



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Nonsteroidal anti-inflammatory drugs (NSAIDs) Background

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Many NSAIDs are readily available over the counter

Generic	Brand	OTC/Rx
Aspirin	Bayer Aspirin®	OTC
Celecoxib	Celebrex®	Rx
Diclofenac	Zipsor®	Rx
Ibuprofen	Advil®	OTC/Rx
Ketorolac	Toradol®	Rx
Meloxicam	Mobic®	Rx
Naproxen	Aleve®	OTC/Rx

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NSAIDs are among the most commonly used analgesics

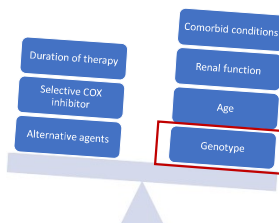
- 43.6 million U.S. adults take aspirin regularly
- 29.4 million U.S adults take other NSAIDs regularly
 - Regular use defined as at least 3xweekly for at least 3 months



Phong T. et al. Trends in the use of aspirin and nonsteroidal anti-inflammatory drugs in the general U.S. population. Pharmacotherapy. 2014;34(11):151-59.

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There are many factors to consider when initiating an NSAID

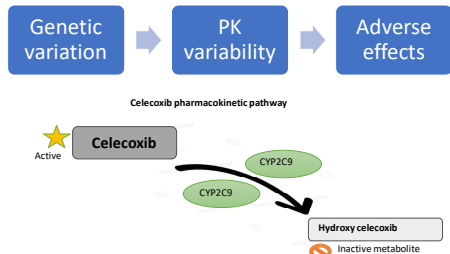


- Multiple patient specific factors can influence NSAID pharmacokinetics, efficacy, and toxicity

Thaler W et al. Clinical Pharmacogenetics Implementation Consortium Guideline: CYP2C9 for CYP2C9 and Nonsteroidal Anti-inflammatory Drugs. Clin Pharmacol Ther. 2020 Aug;108(2):391-200.

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Genetic variations in CYP2C9 can increase drug exposure and the risk for toxicities



U.S. et al. Celecoxib enzyme pharmacokinetics and pharmacokinetics. Pharmacokinetics and genetics. 2010.

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CYP2C9 genetic variation can decrease NSAID metabolism and increase plasma concentrations

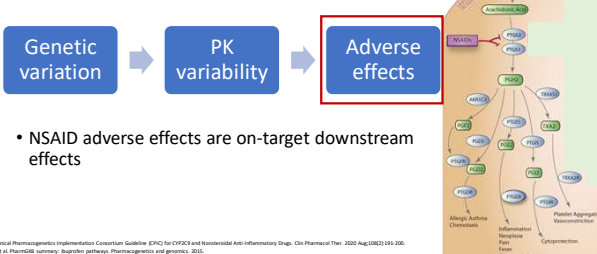


Allele	NSAID metabolism	NSAID plasma concentrations
CYP2C9 *1	↔	↔
CYP2C9 *2	↓	↑
CYP2C9 *3	↓↓	↑↑

Thaler W et al. Clinical Pharmacogenetics Implementation Consortium Guideline: CYP2C9 for CYP2C9 and Nonsteroidal Anti-inflammatory Drugs. Clin Pharmacol Ther. 2020 Aug;108(2):391-200.

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Increased drug exposure increases risk for adverse effects



- NSAID adverse effects are on-target downstream effects

Thaler W et al. Clinical Pharmacogenetics Implementation Consortium Guideline: CYP2C9 for CYP2C9 and Nonsteroidal Anti-inflammatory Drugs. Clin Pharmacol Ther. 2020 Aug;108(2):391-200.

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Adverse effects of NSAIDs are concentration dependent

Adverse Effect	Proposed Mechanism
Gastrointestinal Bleeding	Inhibition of mucosal cell protection
Renal damage	Inhibition of vasoconstriction causes decreased renal blood flow
Hypertension	Increased sodium and water retention
Myocardial infarction	Hypertension Drug interaction: NSAID blocking antiplatelet effects of aspirin



Hendrick, J. Adverse Events Associated with NSAIDs. *US Pharm.* 2008; 20(3):463-463.
Green GA. Understanding NSAIDs: from aspirin to COX-2. *Clin Cornerstone.* 2001; 3(5):59-60.
Thelen WB et al. Clinical Pharmacogenetics Implementation Consortium Guideline (CPIC) for CYP2C9 and Nonsteroidal Anti-inflammatory Drugs. *Clin Pharmacol Ther.* 2020 Aug;108(2):191-205.

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Clinical Pharmacogenetics Implementation Consortium Guideline (CPIC) for CYP2C9 and Nonsteroidal Anti-Inflammatory Drugs

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CYP2C9 and NSAIDs: CPIC Guideline

Thelen WB et al. Clinical Pharmacogenetics Implementation Consortium Guideline (CPIC) for CYP2C9 and Nonsteroidal Anti-inflammatory Drugs. *Clin Pharmacol Ther.* 2020 Aug;108(2):191-205.

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Clinical Pharmacogenetics Implementation Consortium Guideline (CPIC) for CYP2C9 and Nonsteroidal Anti-Inflammatory Drugs

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FOCUSED LITERATURE REVIEW

A systematic literature review focused on CYP2C9 genotype and NSAID (celecoxib, diclofenac, flurbiprofen, ibuprofen, indomethacin, lornoxicam, meloxicam, nabumetone, naproxen, piroxicam, tenoxicam, and sulindac) use and CYP2C8 genotype and ibuprofen, piroxicam, and diclofenac use was conducted (details in **Supplementary Material**). Evidence summarized in Tables S1–S10.

Evidence for 12 NSAIDs extensively reviewed

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CYP2C9 and NSAID CPIC Guideline

- Provides evidence review and therapeutic recommendations for

Short-acting NSAIDs	Intermediate-acting NSAID	Long-acting NSAID
- celecoxib - flurbiprofen - ibuprofen	meloxicam	piroxicam

Thelen WB et al. Clinical Pharmacogenetics Implementation Consortium Guideline (CPIC) for CYP2C9 and Nonsteroidal Anti-inflammatory Drugs. *Clin Pharmacol Ther.* 2020 Aug;108(2):191-205.

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The 2020 CPIC guideline assigns activity values to CYP2C9 alleles

Allele Function	Allele Activity Value	Example CYP2C9 alleles
Normal function	1	*1
Decreased function	0.5	*2, *5, *8, *11
No function	0	*3, *6

- CYP2C9 allele activity scores are added to determine a genotype activity score

Thelen WB et al. Clinical Pharmacogenetics Implementation Consortium Guideline (CPIC) for CYP2C9 and Nonsteroidal Anti-inflammatory Drugs. *Clin Pharmacol Ther.* 2020 Aug;108(2):191-205.

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Genes covered

THE TEST ANALYZES MORE THAN 100 ALLELES IN 27 GENES

Gene	Alleles
CYP2A2	*1C, *1D, *1E, *1F, *1G, *1H, *1I, *1J, *1K, *1L, *1M, *1N
CYP2B6	*1, *2, *3, *4, *5, *6, *7, *8, *9, *10, *11, *12, *13, *14, *15, *16, *17, *18, *19, *20, *21, *22, *23, *24, *25, *26, *27, *28, *29, *30, *31, *32, *33, *34, *35, *36, *37, *38, *39, *40, *41, *42, *43, *44, *45, *46, *47, *48, *49, *50, *51, *52, *53, *54, *55, *56, *57, *58, *59, *60, *61, *62, *63, *64, *65, *66, *67, *68, *69, *70, *71, *72, *73, *74, *75, *76, *77, *78, *79, *80, *81, *82, *83, *84, *85, *86, *87, *88, *89, *90, *91, *92, *93, *94, *95, *96, *97, *98, *99, *100, *101, *102, *103, *104, *105, *106, *107, *108, *109, *110, *111, *112, *113, *114, *115, *116, *117, *118, *119, *120, *121, *122, *123, *124, *125, *126, *127, *128, *129, *130, *131, *132, *133, *134, *135, *136, *137, *138, *139, *140, *141, *142, *143, *144, *145, *146, *147, *148, *149, *150, *151, *152, *153, *154, *155, *156, *157, *158, *159, *160, *161, *162, *163, *164, *165, *166, *167, *168, *169, *170, *171, *172, *173, *174, *175, *176, *177, *178, *179, *180, *181, *182, *183, 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The 2020 CPIC guideline includes a new process for phenotype assignment based on activity score

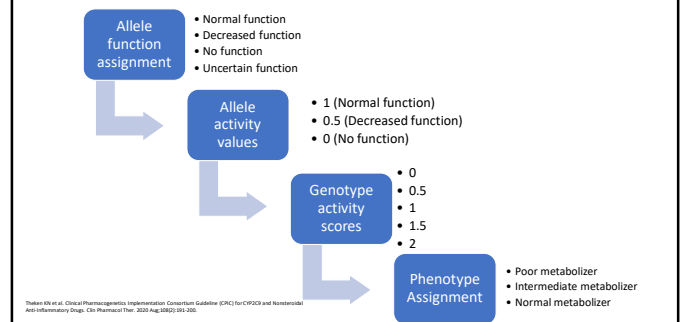
Phenotype	Activity Score	Example Genotypes
Normal Metabolizer	2	Two normal function alleles (*1/*1)
Intermediate Metabolizer	1.5	One normal function and one decreased function allele (*1/*2)
	1	One normal function and one no function allele (*1/*3) Two decreased function alleles (*2/*2)
Poor Metabolizer	0.5	One decreased function and one no function allele (*2/*3)
	0	Two no function alleles (*3/*3)
Indeterminate	N/A	One or more uncertain function alleles (*1/*7)

Prior to 2020, two decreased function alleles were assigned a Poor Metabolizer phenotype

Thaler KB et al. Clinical Pharmacogenetics Implementation Consortium Guideline (CPIC) for CYP2C9 and Nonsteroidal Anti-inflammatory Drugs. Clin Pharmacol Ther. 2020 Aug;108(2):191-205.

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CYP2C9 updates in the CPIC guideline



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Self-Assessment

If the activity value for *CYP2C9* *1 is 1 and the activity value for *2 is 0.5, what is the activity score for the genotype *1/*2?

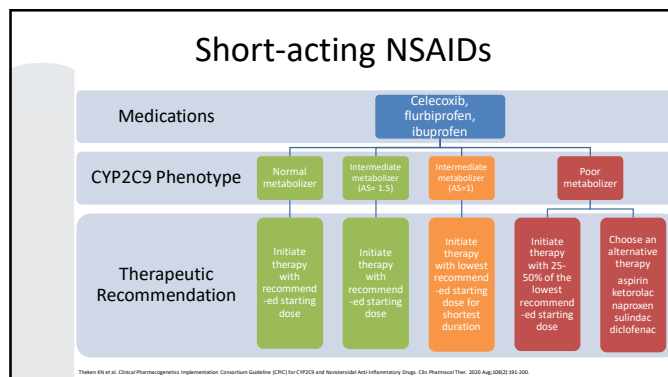
- 0
- 1
- 1.5
- 2

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Therapeutic Recommendations

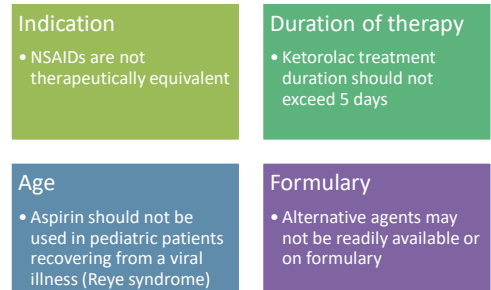
22

Short-acting NSAIDs

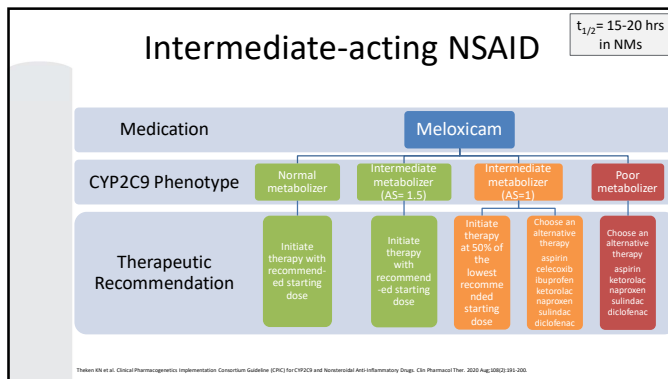


23

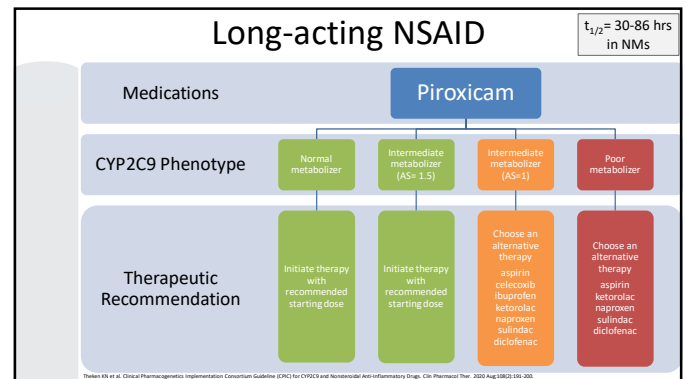
Alternative Therapy Considerations



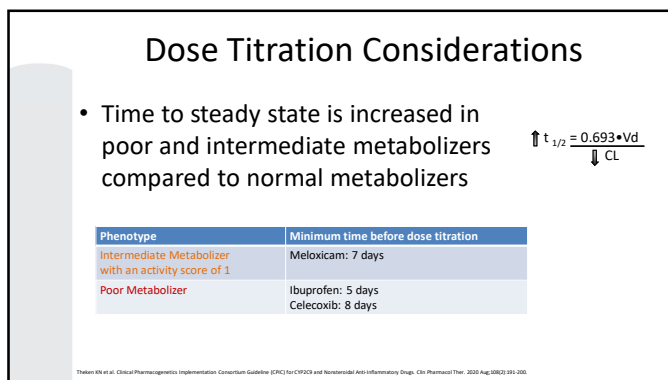
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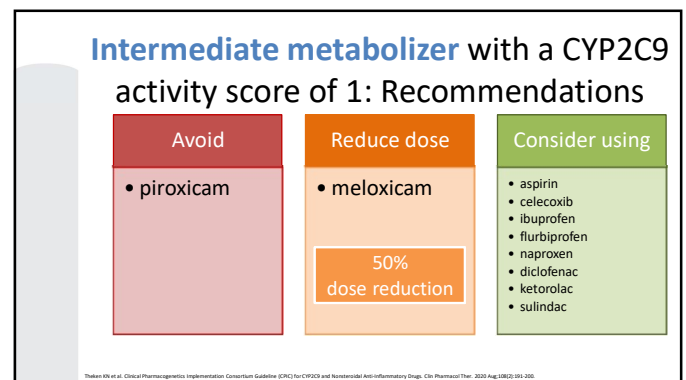
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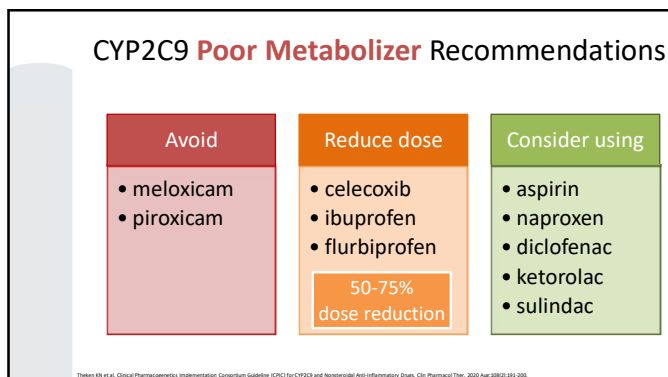
26



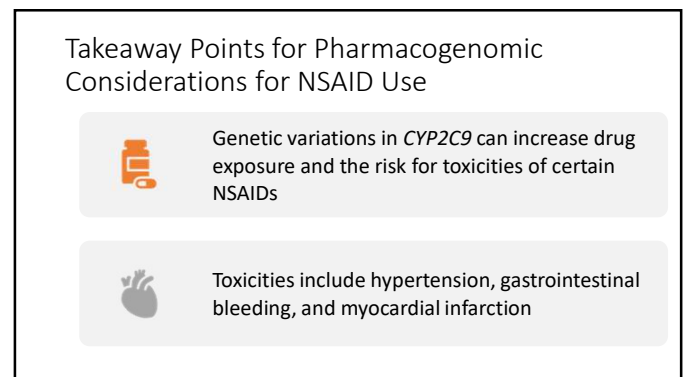
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Clinical Pharmacogenetics Implementation Consortium Guideline for *CYP2D6*, *OPRM1*, and *COMT* Genotypes and Select Opioid Therapy

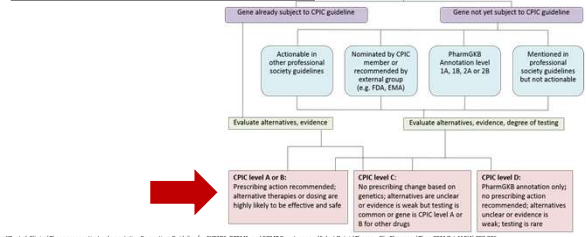
Kristine R. Crews^{1*}, Andrew A. Monte², Rachel Huddart³, Kelly E. Caudle¹, Evan D. Kharasch⁴, Andrea Gaedigk^{5,6}, Henry M. Dunnenberger⁷, J. Steven Leeder^{5,6}, John T. Callaghan⁸, Caroline Flora Samer⁹, Teri E. Klein³, Cyrene E. Haidar³, Sara L. Van Driest¹⁰, Gualberto Ruano¹¹, Katrin Sangkuhl¹², Larisa H. Cavallari¹², Daniel J. Müller¹³, Cynthia A. Prows¹⁴, Mohamed Nagy¹⁵, Andrew A. Somogyi¹⁶ and Todd C. Skarr⁸

Crews KR, et al. Clinical Pharmacogenetics Implementation Consortium Guideline for *CYP2D6*, *OPRM1*, and *COMT* Genotypes and Select Opioid Therapy. *Clin Pharmacol Ther*. 2021 Oct 1;101(4):888-896.

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Clinical Pharmacogenetics Implementation Consortium Guideline for *CYP2D6*, *OPRM1*, and *COMT* Genotypes and Select Opioid Therapy

Kristine R. Crews^{1*}, Andrew A. Monte², Rachel Huddart³, Kelly E. Caudle¹, Evan D. Kharasch⁴, Andrea Gaedigk^{5,6}, Henry M. Dunnenberger⁷, J. Steven Leeder^{5,6}, John T. Callaghan⁸, Caroline Flora Samer⁹, Teri E. Klein³, Cyrene E. Haidar³, Sara L. Van Driest¹⁰, Gualberto Ruano¹¹, Katrin Sangkuhl¹², Larisa H. Cavallari¹², Daniel J. Müller¹³, Cynthia A. Prows¹⁴, Mohamed Nagy¹⁵, Andrew A. Somogyi¹⁶ and Todd C. Skarr⁸



Crews KR, et al. Clinical Pharmacogenetics Implementation Consortium Guideline for *CYP2D6*, *OPRM1*, and *COMT* Genotypes and Select Opioid Therapy. *Clin Pharmacol Ther*. 2021 Oct 1;101(4):888-896.

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The genes *COMT* and *OPRM1* have made their way onto some multigene panels for pain therapy personalization. Do they pull their weight, though?

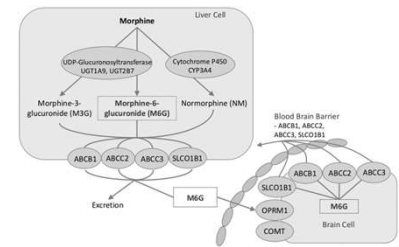
# (N=448)	GENE (N=102) = 10%	DRUG (N=102) = 21%	GUIDELINE	CPIC LEVEL	CPIC LEVEL STATUS	PHARMGKB LEVEL OF EVIDENCE	PDA OR FDA LABEL	CPIC PUBLICATIONS (PMID)
228	COMT	alfentanil	Guideline	C	Final			• 33387367
236	COMT	buprenorphine	Guideline	C	Final	3		• 33387367
241	COMT	choline		E	Provisional			
247	COMT	codeine	Guideline	C	Final			• 33387367
258	COMT	enkephalin		E	Provisional			
263	COMT	fentanyl	Guideline	C	Final	3		• 33387367
274	COMT	hydrocodone	Guideline	C	Final			• 33387367

<https://cpic.org>

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Catechol-O-methyltransferase gene

- COMT protein- catalyzes the metabolism of catecholamine neurotransmitters and catechol drugs which affect pain modulation
- 84 variants reported
- The CPIC evidence review examined 122 articles



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The most widely studied *COMT* allele is rs4680

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Genes covered

THE TEST ANALYZES MORE THAN 100 ALLELES IN 27 GENES

Gene	Alleles
CYP2A2	*6, *10, *16, *18, *19, *21, *22, *23, *24, *25, *26, *27, *28, *29, *30, *31, *32, *33, *34, *35, *36, *37, *38, *39, *40, *41, *42, *43, *44, *45, *46, *47, *48, *49, *50, *51, *52, *53, *54, *55, *56, *57, *58, *59, *60, *61, *62, *63, *64, *65, *66, *67, *68, *69, *70, *71, *72, *73, *74, *75, *76, *77, *78, *79, *80, *81, *82, *83, *84, *85, *86, *87, *88, *89, *90, *91, *92, *93, *94, *95, *96, *97, *98, *99, *100, *101, *102, *103, *104, *105, *106, *107, *108, *109, *110, *111, *112, *113, *114, *115, *116, *117, *118, *119, *120, *121, *122, *123, *124, *125, *126, *127, *128, *129, *130, *131, *132, *133, *134, *135, *136, *137, *138, *139, *140, *141, *142, *143, *144, *145, *146, *147, *148, *149, *150, *151, *152, *153, *154, *155, *156, *157, *158, *159, *160, *161, *162, *163, *164, *165, *166, *167, *168, *169, *170, *171, *172, *173, *174, *175, *176, *177, *178, *179, *180, *181, *182, *183, *184, *185, *186, *187, *188, *189, *190, *191, *192, *193, *194, 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Neurosignals 2018;26:11-21
DOI: 10.1155/2018/1121
Published online January 31, 2018
© 2018 The Author(s)
Published by Taylor & Francis Group, LLC
www.tandfonline.com

Original Paper

Association between COMT Polymorphism Val158Met and Opioid Consumption in Patients with Postoperative Pain: A Meta-Analysis

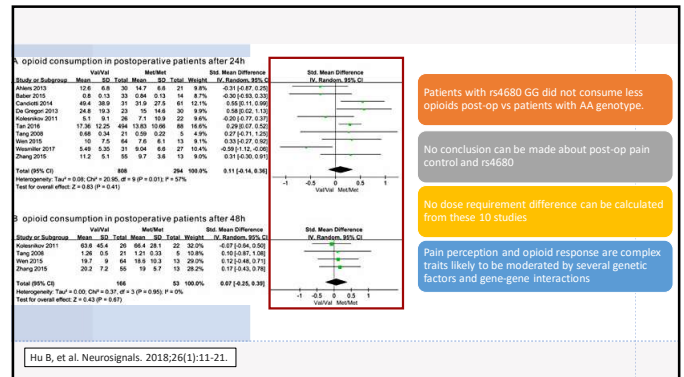
Bo Hu^a, Xiaomin Zhang^b, Guangtao Xu^a, Qinmei Zhang^a, Ping Qian^a, Shengbing Liu^a, Jia Zhu^a, Ruilin Shen^a

^aDepartment of Immunopathology and Diabetes Institute, Jiangsu Hospital of Traditional Chinese Medicine, Jiangsu University, Jiangsu, Zhejiang; ^bDepartment of Physiology, Kunming Medical University, Kunming, Yunnan, P.R.China

Key Words
Postoperative pain • COMT • Single-nucleotide polymorphism • Opioid

Hu B, et al. Neurosignals. 2018;26(1):11-21. Several factors influencing postoperative pain and the effect of opioid analgesics have been investigated on an individual level. The aim of this study was to clarify

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CPIC evidence review found no consensus on *COMT* and opioids

Genotype	Implications	Recommendations	Classification of recommendation ^a	Considerations
rs4680 A	No effect for opioid adverse events. Insufficient evidence for an association between <i>COMT</i> rs4680 genotype, analgesia and opioid dose requirements.	No recommendation	No recommendation	Many factors contribute to variability in opioid response including other gene variants, age, psychological status, indication and duration of opioid use. Mixed evidence indicates both supporting and non-supporting evidence for an association with neither direction dominating.

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Does *COMT* pull its weight on multigene panels for pain therapy personalization?

No- CPIC evidence review found no clinical actionability for *COMT* rs4680

Chen BB, et al. Clinical Pharmacogenetics Implementation Consortium Guidelines for CYP2D6, CYP2A6, and COMT Genotypes and Select Opioid Therapy. Clin Pharmacol Ther. 2021;110(5):888-895.

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ONEOME[™]
Gene and phenotype summary (cont.)

Gene	Variant	Activity
CYP2D6	*1	Normal activity
COMT	rs4680 GG	High activity
DPYD	*12A	Intermediate
DRD2	rs1799737 AA	Normal receptor expression

<https://oneome.com/nightmed-test/>

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COMT has a CPIC Level of C (Not actionable).

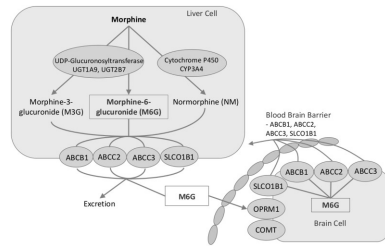
# (N=448)	GENE	DRUG	GUIDELINE	CPIC LEVEL	CPIC STATUS	PHARMACOKINETIC EVIDENCE	PKC ON FDA LABEL	CPIC PUBLICATIONS (PMIDs)
228	COMT	alfentanil	Guideline	C	Final			• 33387367
236	COMT	buprenorphine	Guideline	C	Final	3		• 33387367
341	COMT	choline	Guideline	C	Provisional			
347	COMT	codeine	Guideline	C	Final			• 33387367
356	COMT	metoprolol	Guideline	C	Provisional			
263	COMT	fentanyl	Guideline	C	Final	3		• 33387367
274	COMT	hydrocodone	Guideline	C	Final			• 33387367

<https://cpic.org/>

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OPRM1

- The *OPRM1* gene encodes the mu-opioid receptor mu 1
- The CPIC evidence review examined 278 articles



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The most widely studied
OPRM1 allele is rs1799971.

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Genes covered

THE TEST ANALYZES MORE THAN 100 ALLELES IN 27 GENES

Gene	Alleles
NUDT15	Ars199Cys (rs19855232)
OPRM1	Ars199Cys (rs1799971)
SLC6A4	~900A-G (rs25325, 497, 48756443 (rs74876466))
SLC6A8	~16, ~15, ~15, ~15, ~15
TPMT	~2, ~15A, ~15B, ~15C, ~15
UGT1A1	~16, ~28 (8A)
VKORC1	~1050G-A (rs9923275, 842C-T (rs7200748))

NOTE: The test does not detect all known and unknown variations in the gene(s) tested. For drug metabolism enzymes, the absence of a detectable variant (designated as "B" does not rule out the presence of other variants not tested.

<https://oneome.com/rightmed-test/>

OneOme reports *OPRM1* allele rs1799971

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PAIN MEDICINE

OPRM1 A118G Gene Variant and Postoperative Opioid Requirement

A Systematic Review and Meta-analysis

In Chae Hwang, M.D., Ph.D., Ji-Young Park, M.D., Ph.D., Seung Kwon Myung, M.D., Ph.D., Hong Yup Ahn, Ph.D., Ken-ichi Fukuda, M.D., Ph.D., Qin Liao, M.D., Ph.D.

ABSTRACT

Background: Although a number of studies have investigated the association of the *OPRM1* A118G polymorphism with pain response, a consensus has not yet been reached.

Methods: The authors searched PubMed, EMBASE, and the Cochrane Library to identify gene-association studies that explored the impact of the *OPRM1* A118G polymorphism on postoperative opioid requirements through July 2013. Two evaluators independently reviewed and selected articles on the basis of prespecified selection criteria. The authors primarily investigated the standardized mean difference (SMD) of required amounts of opioids between AA homozygotes and G-allele carriers. The authors also performed subgroup analyses for race, opioid use, and type of surgery. Potential bias was assessed using the Egger's test with a trim and fill procedure.

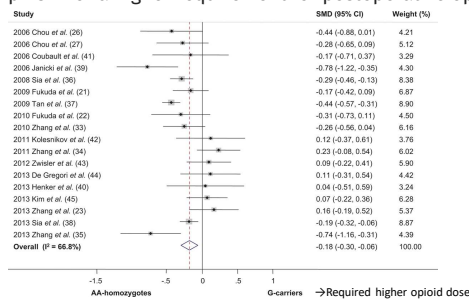
Results: Three hundred forty-six articles were retrieved from databases, and 18 studies involving 4,607 participants were included in the final analysis. In a random-effect meta-analysis, G-allele carriers required a higher mean opioid dose than AA homozygotes (SMD, -0.18; $P = 0.003$). Although there was no evidence of publication bias, heterogeneity was present among studies ($I^2 = 66.8\%$). In the subgroup meta-analyses, significance remained robust in Asian patients (SMD, -0.21; $P = 0.001$), morphine users (SMD, -0.20; $P < 0.001$), and patients who received surgery for a vicious (SMD, -0.20; $P = 0.008$).

Conclusions: The *OPRM1* A118G polymorphism was associated with interindividual variability in postoperative response to opioids. In a subpopulation, identifying *OPRM1* A118G polymorphism may provide valuable information regarding the individual analgesic doses that are required to achieve satisfactory pain control. (*Anesthesiology* 2014; 121:825-34)

Hwang IC, et al. *Anesthesiology*. 2014 Oct;121(4):825-34.

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Meta-analysis found a small effect of the *OPRM1* rs1799971 (G variant) polymorphism for a higher requirement for postoperative opioids



Hwang IC, et al. *Anesthesiology*. 2014 Oct;121(4):825-34.

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CPIC evidence review found a small (~10%) increase in morphine dose requirements with *OPRM1* rs1799971 variant

Genotype	Implications	Recommendations	Classification of recommendation*	Considerations
rs1799971 G	The rs1799971 G allele is associated with small but statistically significant decreases in analgesia and/or increases in morphine requirements in some studies. However, this does not appear to translate into clinically actionable dose alterations.	No recommendation	No recommendation	Most publications focus on morphine for postoperative pain. Many factors contribute to variability in postoperative morphine response including age, psychological status, tolerance, surgery type and duration, genetics and presurgical pain and opioid use. Due to the marginal difference in dose between genotypes and numerous other factors affecting this outcome, the safest recommendation is to "start low and go slow."

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OPRM1 has a CPIC Level of C (Not actionable).

# (n=448)	GENE (CPIC ID)	DRUG (CPIC ID)	GUIDELINE	CPIC LEVEL	CPIC LEVEL (CPIC ID)	PHARMACOGENOMIC LEVEL OF EVIDENCE	POC ON FDA LABEL	CPIC PUBLICATIONS (PMID)
229	OPRM1	alfentanil	Guideline	C	Final	3		• 33387367
237	OPRM1	buprenorphine	Guideline	C	Final	3		• 33387362
381	OPRM1	codeine	Guideline	C	Final	3		• 33387362
354	OPRM1	fentanyl	Guideline	C	Final	3		• 33387362
275	OPRM1	hydromorphone	Guideline	C	Final	3		• 33387362
277	OPRM1	hydromorphone	Guideline	C	Final	3		• 33387362
234	OPRM1	levorphanolone	Guideline	C	Final	3		• 33387362
388	OPRM1	mefenorex	Guideline	C	Final	3		• 33387362
298	OPRM1	mefenorex	Guideline	C	Final	3		• 33387362

<https://cpic.org>

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Gene and phenotype summary (cont.)

HLA-B	Negative	Normal risk
HTR2A	rs799702 AA	Normal risk
HTR2C	rs381929 TT	Normal risk
IFNL4	rs1297860 CC	Normal risk
NUDT15	rs16855232 CC	Normal risk
OPRM1	rs1799971 GG	Normal risk

<https://oneome.com/rightmed-test/>

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Takeaway Points of Pharmacogenomic Considerations for *COMT* and *OPRM1* and Opioids



COMT and *OPRM1* are pharmacodynamic genes which may affect a patient's response to pain or to opioid therapy.



After extensive evidence review, both have a CPIC Level C (not actionable).

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Highlights of the CPIC recommendations for *CYP2D6* and opioids

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CYP2D6 Activity Score can be used to assign phenotype

- Each allele is assigned an activity value:

Activity value	CYP2D6 Alleles	Type of Allele
1	*1, *2, *2A	Wild-type
0.25	*10	Decreased Function
0.5	*9, *17, *29, *41	Decreased function
0	*3, *4, *5, *6, *7, *8, *11, *12, *14, *14A, *14B, *15, *18, *19, *20, *21, *38, *40, *42, *44, *56, *56A, *56B	No function

- CYP2D6* activity score is calculated by adding up the activity value for each allele as follows:

$$\text{Activity score for } CYP2D6 (*1/*2A)2N = 1 + 1 = 2$$

$$\text{Activity score for } CYP2D6 (*2/*10)2N = 1 + 0.25 = 1.25$$

$$\text{Activity score for } CYP2D6 (*4/*4)2N = 0 + 0 = 0$$

$$\text{Activity score for } CYP2D6 (*3/*9)2N = 0 + 0.5 = 0.5$$

Gaedigk, A. et al. Clin Pharmacol Ther. 83: 234-42, 2008

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Table 2 Codeine therapy recommendations based on *CYP2D6* phenotype

Phenotype	Activity score	Implications	Recommendations	Classification of recommendation*
<i>CYP2D6</i> ultrarapid metabolizer	> 2.25	Increased formation of morphine leading to higher risk of toxicity	Avoid codeine use because of potential for serious toxicity. If opioid use is warranted, consider a non-tramadol opioid.	Strong
<i>CYP2D6</i> normal metabolizer	$1.25 \leq x \leq 2.25$	Expected morphine formation	Use codeine label recommended age-specific or weight-specific dosing.	Strong
<i>CYP2D6</i> intermediate metabolizer	$0 < x < 1.25$	Reduced morphine formation	Use codeine label recommended age-specific or weight-specific dosing. If no response and opioid use is warranted, consider a non-tramadol opioid.	Moderate
<i>CYP2D6</i> poor metabolizer	0	Greatly reduced morphine formation leading to diminished analgesia.	Avoid codeine use because of possibility of diminished analgesia. If opioid use is warranted, consider a non-tramadol opioid.	Strong
<i>CYP2D6</i> indeterminate	n/a	n/a	No recommendation	No recommendation

n/a, not applicable.

*Rating scheme described in the Supplementary Material.

Chen, H, et al. Clinical Pharmacogenetics Implementation Consortium Guidelines for *CYP2D6*, *OPRM1*, and *COMT* Genotypes and Select Opioid Therapy. Clin Pharmacol Ther. 2021 Dec; 110(6):889-895.

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Table 3 Tramadol therapy recommendations based on CYP2D6 phenotype

Phenotype	Activity score	Implications	Recommendations	Classification of recommendation ^a
CYP2D6 ultrarapid metabolizer	> 2.25	Increased formation of O-desmethytramadol (active metabolite) leading to higher risk of toxicity	Avoid tramadol use because of potential for toxicity. If opioid use is warranted, consider a non-codeine opioid.	Strong
CYP2D6 normal metabolizer	1.25 ≤ x ≤ 2.25	Expected O-desmethytramadol (active metabolite) formation	Use tramadol label recommended age-specific or weight-specific dosing.	Strong
CYP2D6 intermediate metabolizer	0 < x < 1.25	Reduced O-desmethytramadol (active metabolite) formation	Use tramadol label recommended age-specific or weight-specific dosing. <u>If no response and opioid use is warranted, consider non-codeine opioid.</u>	Optional
CYP2D6 poor metabolizer	0	Greatly reduced O-desmethytramadol (active metabolite) formation leading to diminished analgesia.	Avoid tramadol use because of possibility of diminished analgesia. If opioid use is warranted, consider a non-codeine opioid.	Strong
CYP2D6 indeterminate	n/a	n/a	No recommendation	No recommendation

n/a, not applicable.
^aRating scheme described in the **Supplementary Material**.

Crowe SR, et al. Clinical Pharmacogenetics Implementation Consortium Guidelines for CYP2D6, OPRM1, and COMT Genotypes and Select Opioid Therapy. Clin Pharmacol Ther. 2021 Oct 1;110(4):888-896.

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Updated recommendations for hydrocodone for IMs and PMs are to switch from hydrocodone if no response is obtained (minimal evidence; Level B)

Table 4 Hydrocodone therapy recommendations based on CYP2D6 phenotype

Phenotype	Activity score	Implications	Recommendations	Classification of recommendation ^a
CYP2D6 ultrarapid metabolizer	> 2.25	Minimal evidence for pharmacokinetic or clinical effect.	No recommendation for hydrocodone therapy because of minimal evidence regarding adverse events or analgesia.	No recommendation
CYP2D6 normal metabolizer	1.25 ≤ x ≤ 2.25	Normal hydromorphone formation	Use hydrocodone label recommended age-specific or weight-specific dosing.	Strong
CYP2D6 intermediate metabolizer	0 < x < 1.25	Minimal evidence for pharmacokinetic or clinical effect.	Use hydrocodone label recommended age-specific or weight-specific dosing. <u>If no response and opioid use is warranted, consider non-codeine or non-tramadol opioid.</u>	Optional
CYP2D6 poor metabolizer	0	Decreased metabolism of hydrocodone to active metabolite, hydromorphone, but there is insufficient evidence to determine if these effects on pharmacokinetics translate into decreased analgesia or side effects.	Use hydrocodone label recommended age-specific or weight-specific dosing. <u>If no response and opioid use is warranted, consider non-codeine and non-tramadol opioid.</u>	Optional
CYP2D6 indeterminate	n/a	n/a	No recommendation	No recommendation

n/a, not applicable.
^aRating scheme described in the **Supplementary Material**.

Crowe SR, et al. Clinical Pharmacogenetics Implementation Consortium Guidelines for CYP2D6, OPRM1, and COMT Genotypes and Select Opioid Therapy. Clin Pharmacol Ther. 2021 Oct 1;110(4):888-896.

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New to the 2021 CPIC guideline update for opioids: limited and/or weak data for CYP2D6 and:

hydrocodone	CPIC Level B (for IMs and PMs)
oxycodone	CPIC Level C
methadone	CPIC Level C

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Takeaway Points of Pharmacogenomic Considerations for Pain Management



Many genetic and non-genetic factors affect a patient's response to pain management.



Pharmacogenomics can be used to provide evidence-based recommendations to personalize a patient's pain management.

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See you for our Live Discussion

- In addition to this lecture, this week's 1-hour home study session also includes reading 2 CPIC guidelines

Clinical Pharmacogenetics Implementation Consortium Guideline (CPIC) for CYP2C9 and Nonsteroidal Anti-Inflammatory Drugs

Katherine N Theken, Craig R Lee, Li Gong, Kelly E Caudle, Christine M Formea, Andrea Gaedigk, Teri E Klein, José A G Agúndez, Tilo Grosser

Clinical Pharmacogenetics Implementation Consortium Guideline for CYP2D6, OPRM1, and COMT Genotypes and Select Opioid Therapy

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www.cpicpgx.org/guidelines

Crowe SR, et al. Clinical Pharmacogenetics Implementation Consortium Guidelines for CYP2D6, OPRM1, and COMT Genotypes and Select Opioid Therapy. Clin Pharmacol Ther. 2021 Oct 1;110(4):888-896.

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