Clinical Applications in Pain Management Pharmacogenetics

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Disclosure

- I declare no conflicts of interest, real or apparent, and no financial interests in any company, product, or service mentioned in this program, including grants, employment, gifts, stock holdings, and honoraria.

- The University of Florida College of Pharmacy is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education.

Overview

1. Describe clinical implications of genetic variability in **pain management**

2. Discuss clinical, patient-specific, **genetic**, and other factors that inform drug therapy changes for select **opioids**

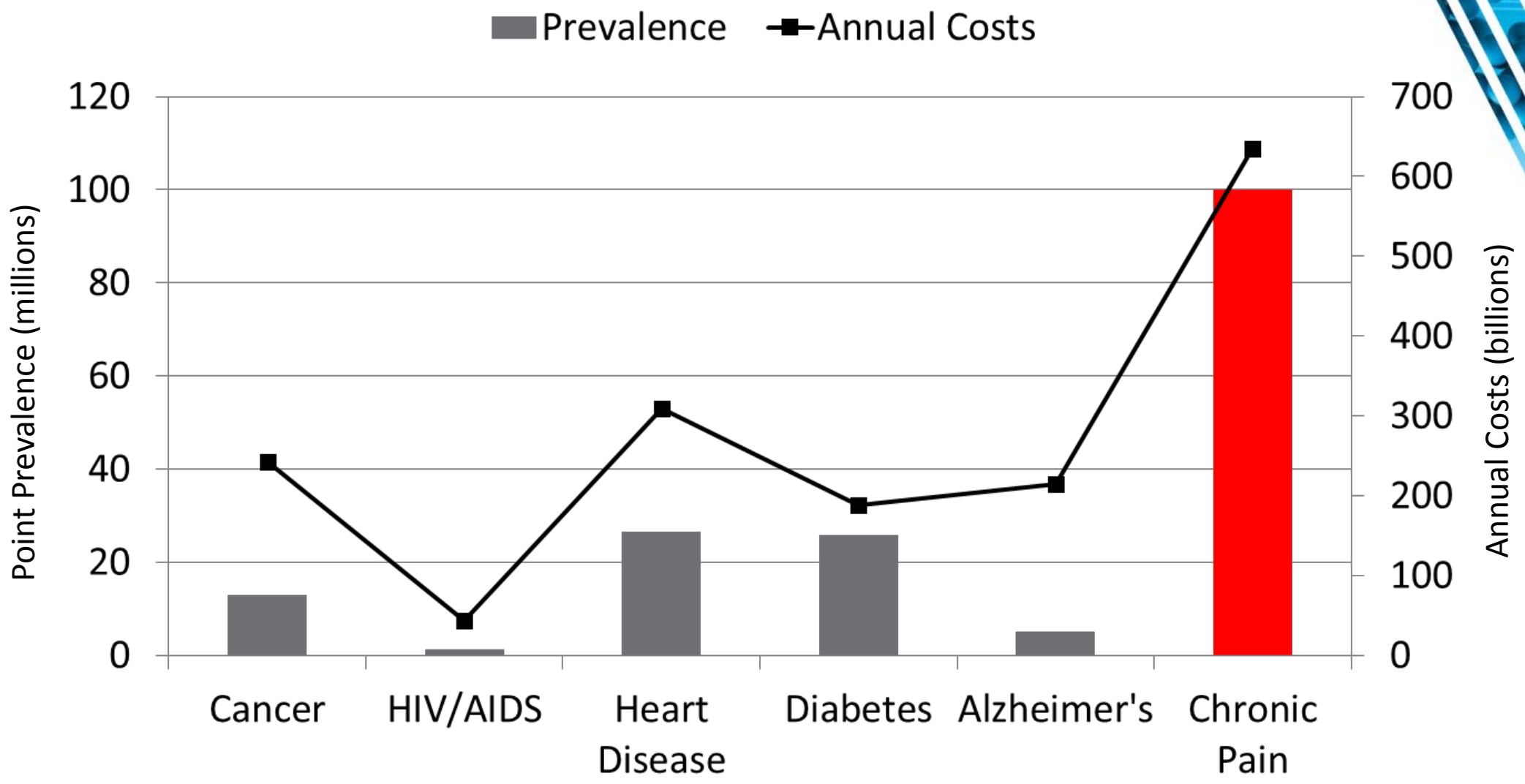
3. Summarize the steps of **implementing** pain management pharmacogenetics

Before we get started…

HJ just received a root canal, and her dentist asks for you to recommend the best dose of codeine for her. Based on a previous genotype order in her EHR, you note that HJ has *CYP2D6* *1/*4 genotype. Based on the patient's genetic results, what would you recommend?

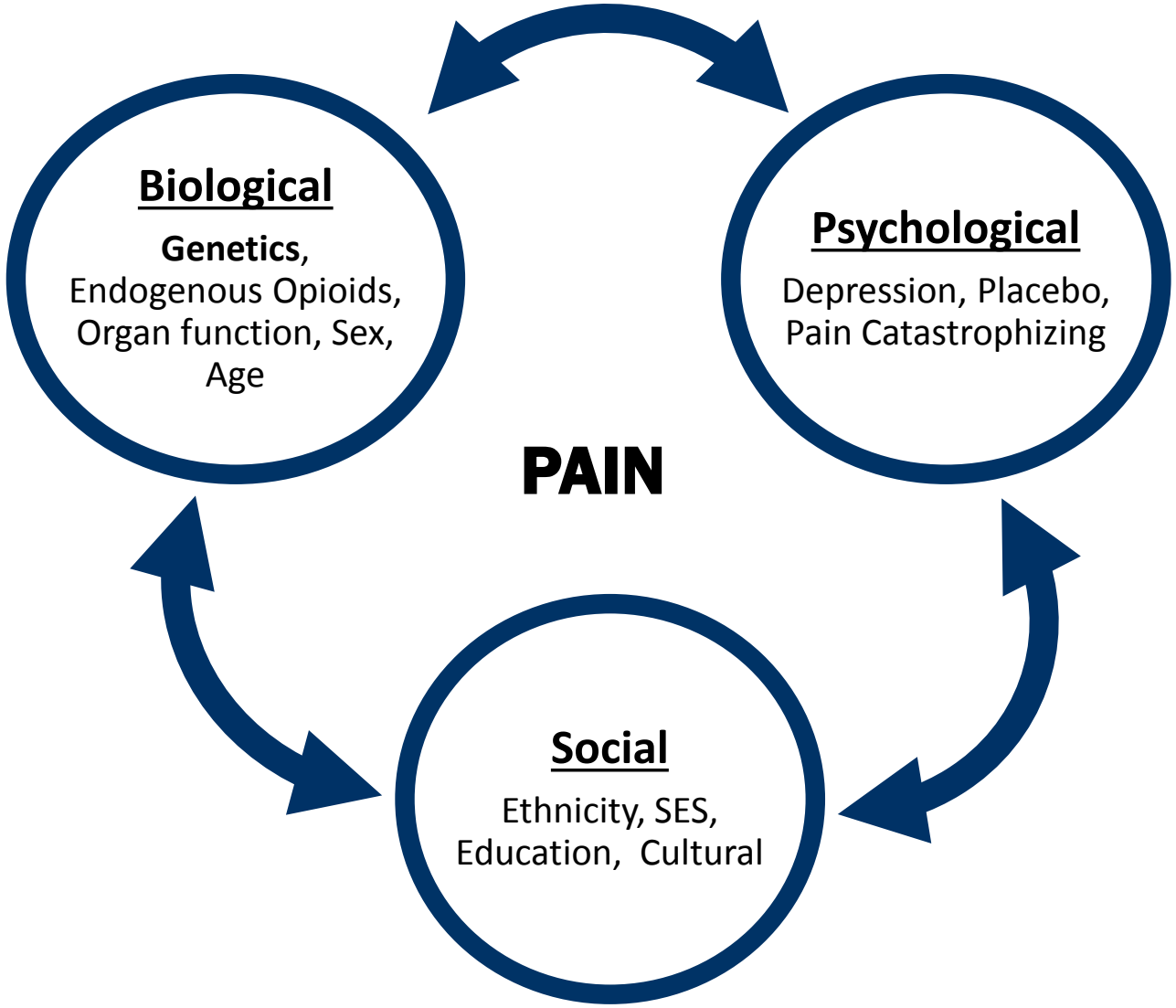
A. HJ has an activity score of 5, a CYP2D6 ultra-rapid metabolizer (UM). Avoid codeine due to potential for toxicity.
B. HJ has an activity score of 1, a CYP2D6 normal metabolizer (NM). Prescribe the label recommended dose of codeine.
C. HJ has an activity score of 0.5, a CYP2D6 intermediate metabolizer (IM). Prescribe twice the recommended dose of codeine.
D. HJ has an activity score of 0, a CYP2D6 poor metabolizer. Avoid codeine due to lack of efficacy.

Prevalence of Pain in the US



AAPM Facts and Figures on Pain. http://www.painmed.org/patientcenter/facts_on_pain.aspx

Factors When Considering Pain Management



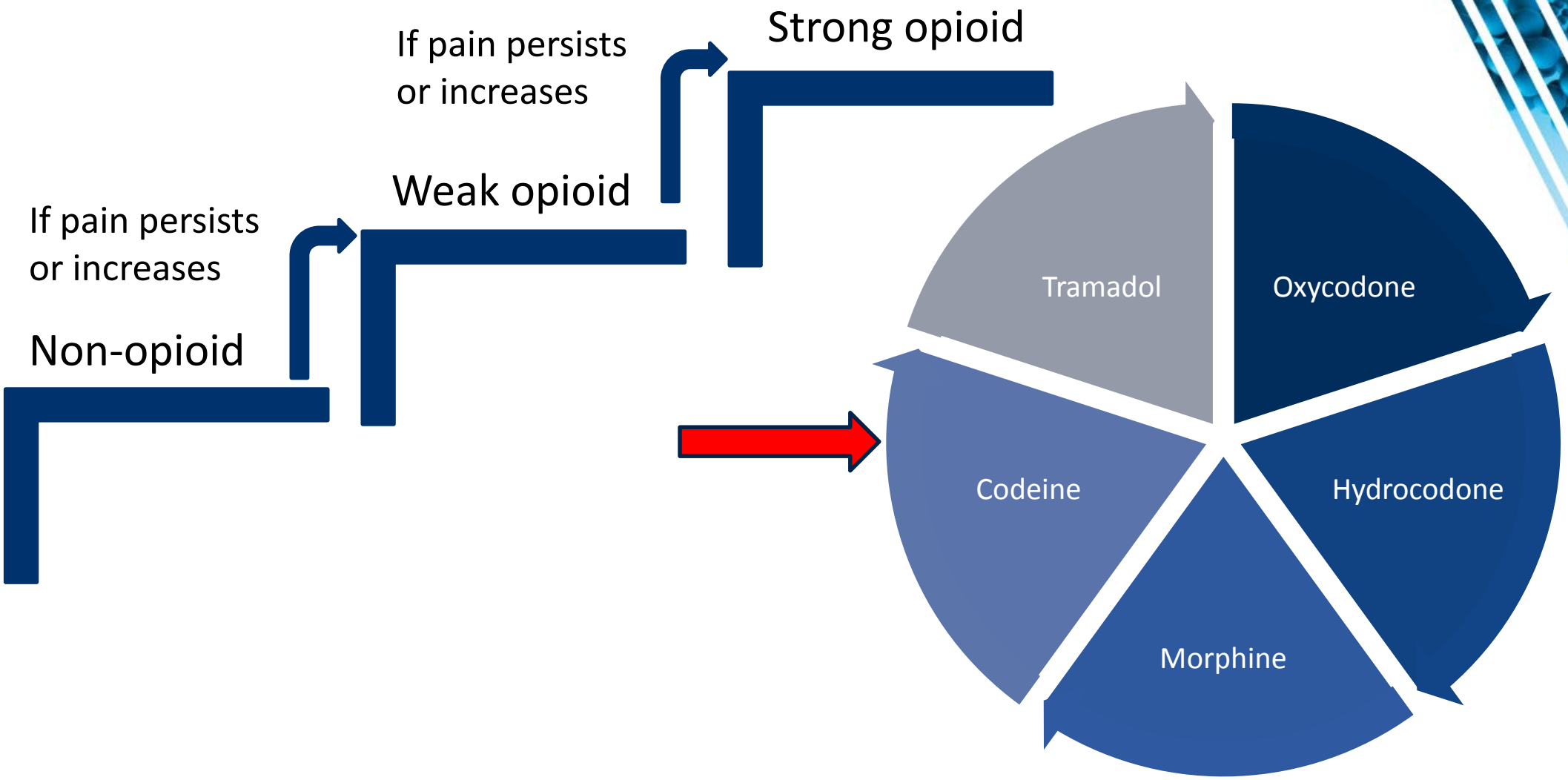
Opioids

- Cornerstone of clinical pain management[1]
  - Most potent drugs for pain relief
  - Commonly prescribed with 259 million prescriptions in 2012

- Important factors for PGx consideration[2]
  - Narrow therapeutic window
  - Wide dosage variability

1. Opioid Addiction 2016 Facts and Figures. American Society of Addiction Medicine. Accessed on Feb 27, 2017. [Internet]. Available from: http://www.asam.org/docs/default-source/advocacy/opioid-addiction-disease-facts-figures.pdf
2. Somogyi AA, Coller JK, Barratt DT. Pharmacogenetics of Opioid Response. Clin Pharmacol Ther. Feb 2015. 97 (2): 125 - 127

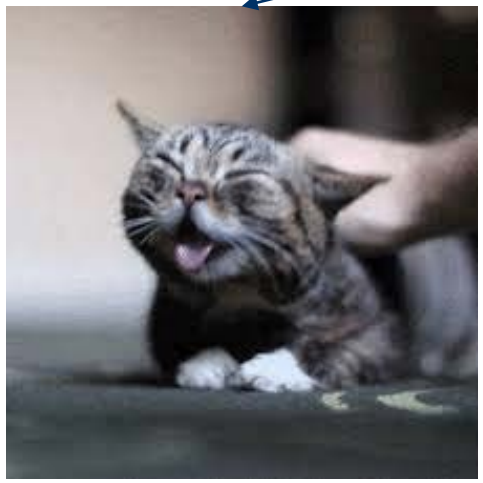
WHO Analgesic Ladder



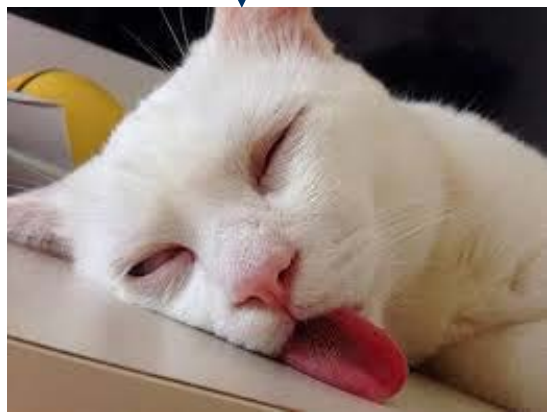
World Health Organization. Geneva, Switz: World Health Organization; 1987.

Pain

Opioid



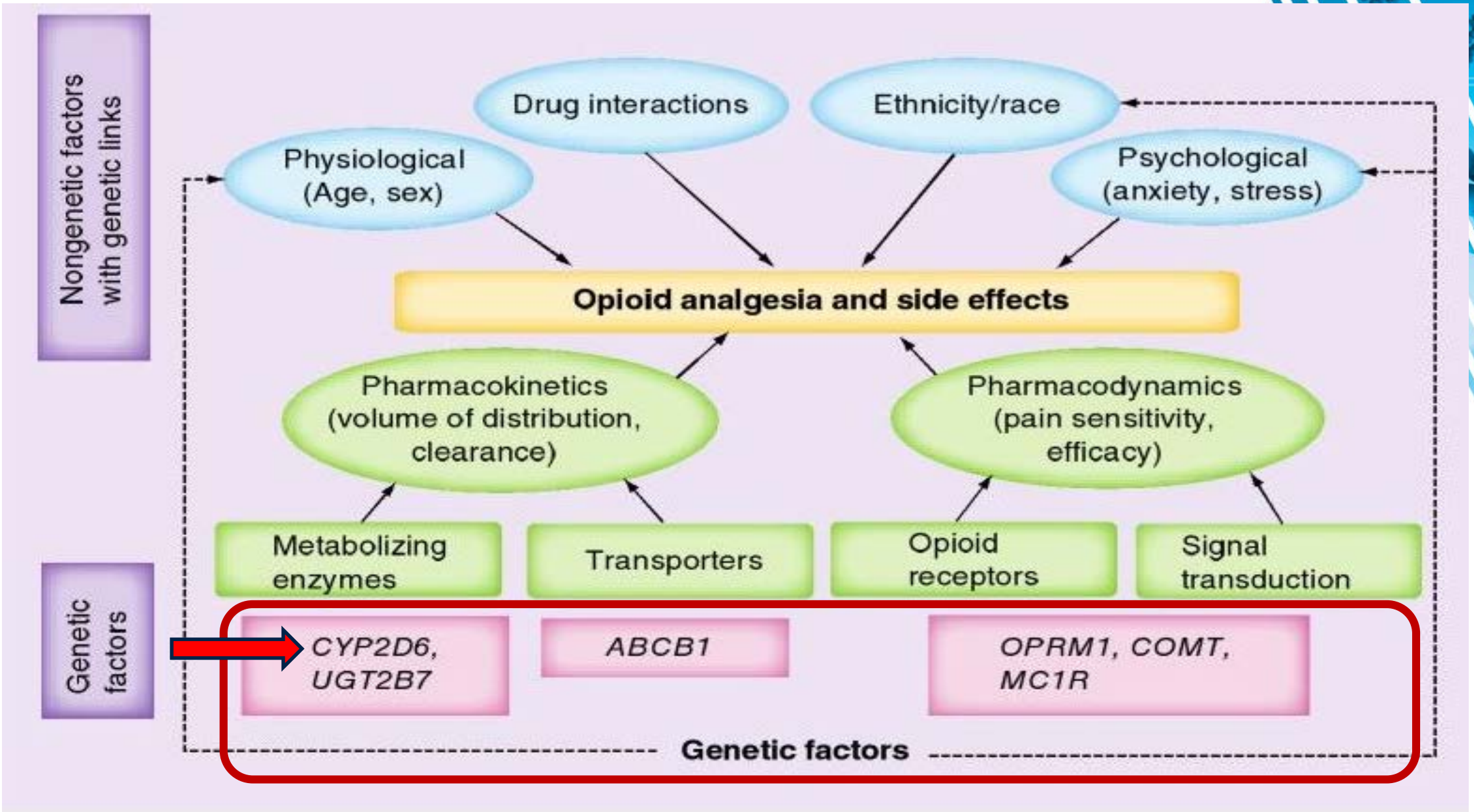
Feel Better



Feel Terrible

Feel Nothing

Factors Related to Opioid Response



Sadhasivam, S, *et al*. Pharmacogenomics of opioids and perioperative pain management."Pharmacogenomics **13**(15): 1719-1740.

If you participated in personal genotyping, what is your CYP2D6 phenotype?

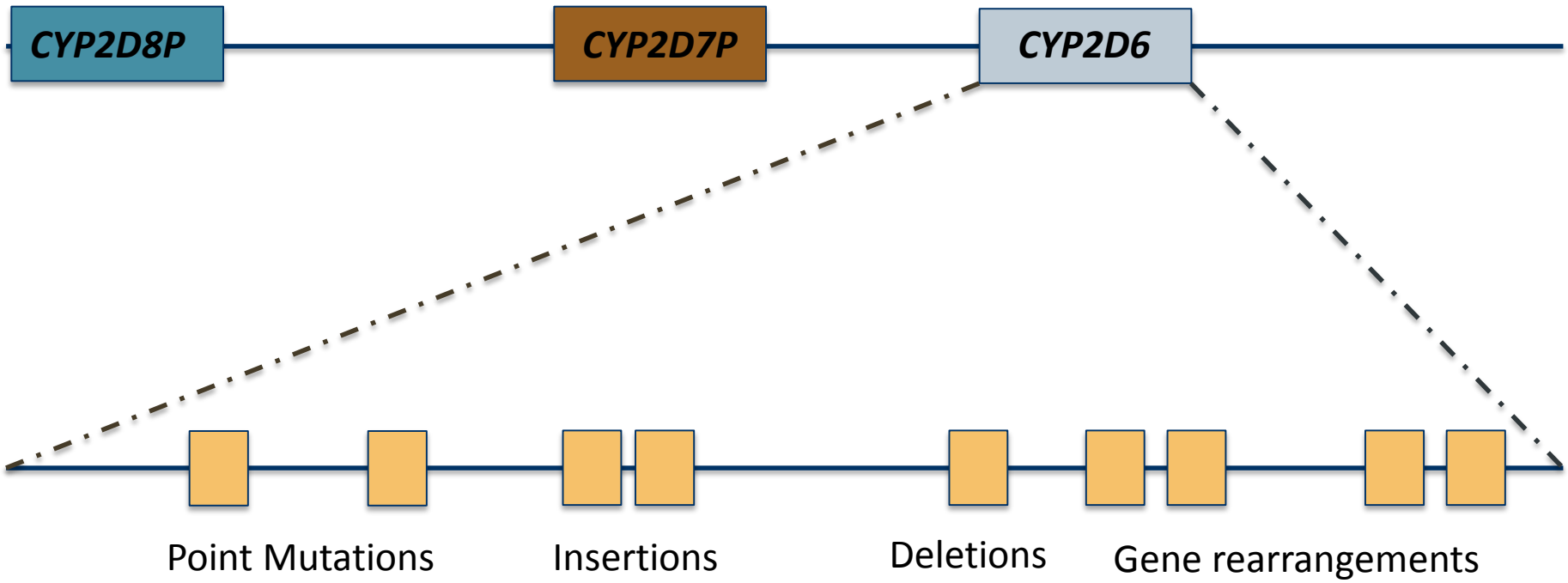
- A. Ultra-rapid metabolizer
- B. Normal metabolizer
- C. Intermediate Metabolizer
- D. Poor Metabolizer

Cytochrome P450 2D6 *(CYP2D6)*

- Codes for hepatic enzyme that metabolizes 25% of all drugs
  - Metabolizes codeine, tramadol, oxycodone, and hydrocodone into more potent metabolites
  - High risk for **drug interactions**

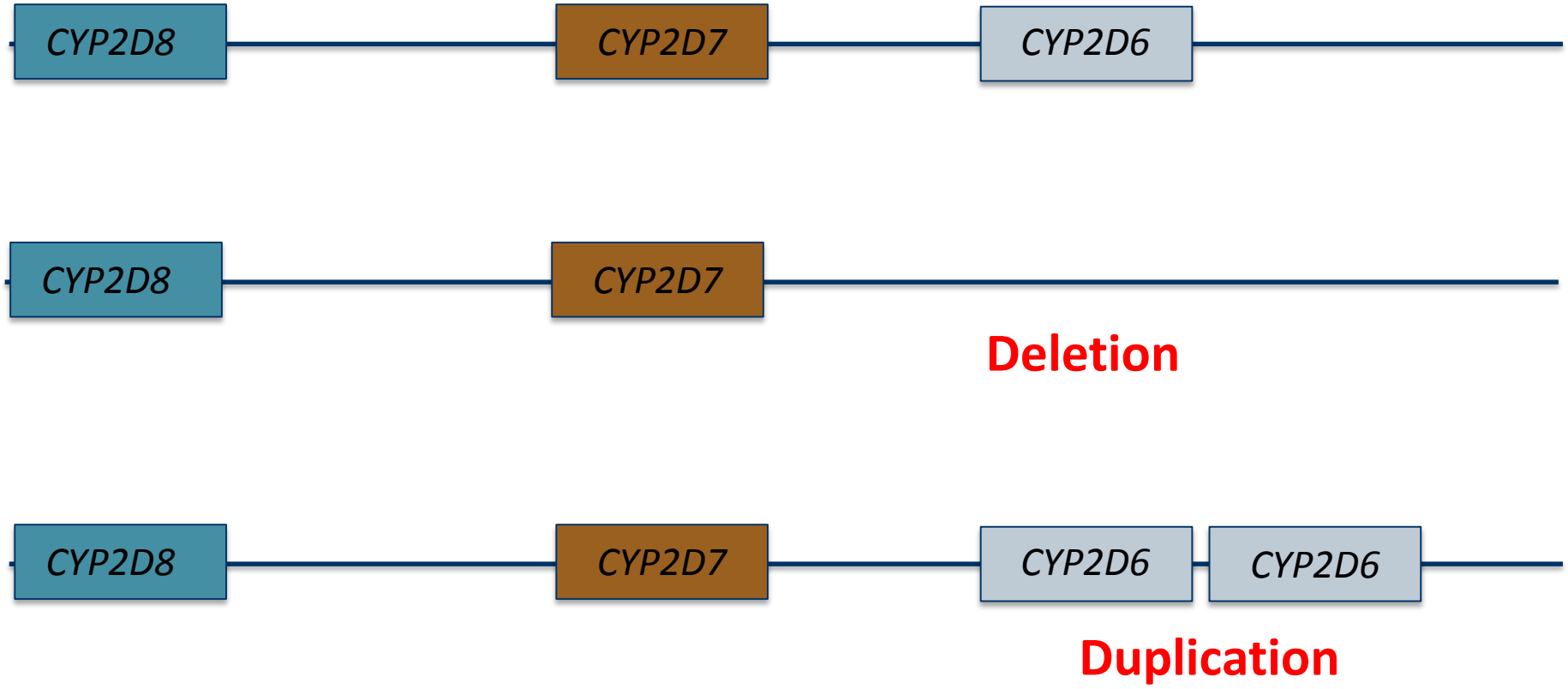
- **Wide variability** in CYP2D6 enzyme activity
  - Highly polymorphic gene (>100 allelic variants)
  - Allele frequencies vary among different populations
  - Important to test for the appropriate alleles in a given race/ethnic group

CYP2D6 Gene



Koch WH. Nat Rev Drug Discov. 2004 Sep;3(9):749-61.

CYP2D6



Koch WH. Nat Rev Drug Discov. 2004 Sep;3(9):749-61.

CYP2D6 Variability

Allele	Enzyme Function	African	African American	Caucasian‡	Middle Eastern	East Asian	South/ Central Asian	Oceanian
*1	Normal	39.23	40.6	53.63	58.04	34.17	53.7	70.15
*2	Normal†	20.12	14.15	26.91	21.72	12.82	31.9	1.2
*4	None	3.36	6.23	18.5	7.8	0.42	6.56	1.13
*10	Decreased#	6.77	4.18	3.16	3.49	42.31	19.76	1.6
*17	Decreased†	19.98	18.22	0.32	1.58	0.01	0.38	0.05
*41	Decreased†	10.94	9.41	8.56	20.37	1.97	10.5	0
*1xN	Increased	1.47	0.44	0.8	3.07	0.28	0.5	11.83

Percentage
>40
20 to 40
5 to 19.99
< 5

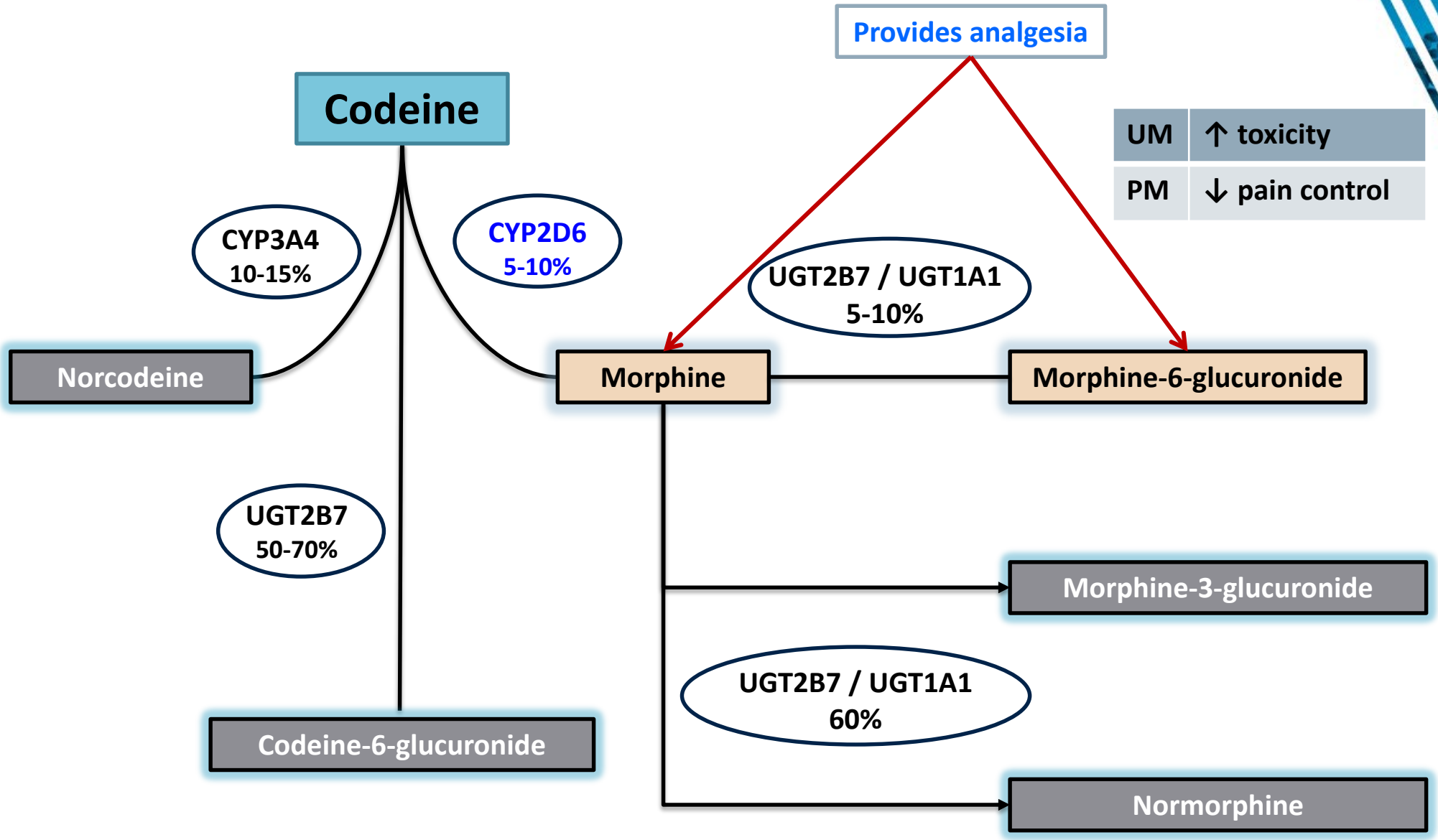
†Frequency may vary due to risk of misclassification
#Data linking to phenotype is controversial
‡European + North American

Crews KR, et al. *Clin Pharmacol Ther.* 2014 Apr;95(4):376-82.

Codeine

- Opioid analgesic indicated for mild to moderate pain
- Analgesic properties stem from metabolites formed via CYP2D6
- Common adverse reactions
  - Drowsiness, lightheadedness, dizziness, sedation, shortness of breath, nausea, vomiting, sweating
- Serious adverse reactions
  - Respiratory depression, circulatory depression, respiratory arrest, shock, cardiac arrest
- Antitussive properties

Codeine Metabolism



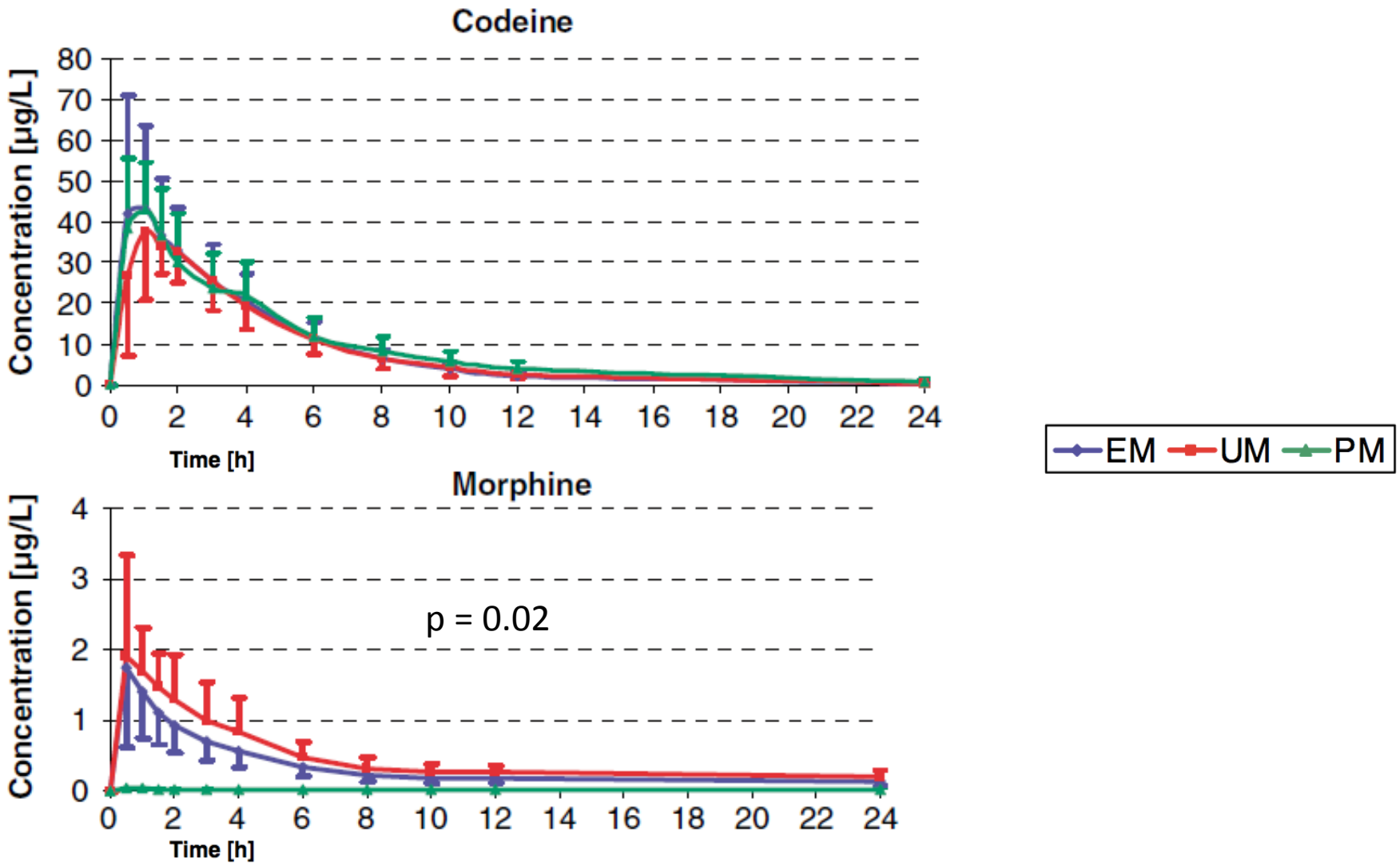
UM	↑ toxicity
PM	↓ pain control

Crews KR, et al. *Clin Pharmacol Ther.* 2014 Apr;95(4):376-82.

Codeine → Morphine via CYP2D6

- UM: Codeine $\xrightarrow{2D6}$ Morphine
- NM: Codeine $\xrightarrow{2D6}$ Morphine
- IM: Codeine $\xrightarrow{2D6}$ Morphine
- PM: Codeine $\xrightarrow{2D6}$ Morphine

Study	Patients	Objective	Result
Cross-sectional cohort	Healthy Caucasian males (n = 26)	Assess pharmacokinetic differences of codeine between UM and EM after a single dose of codeine 30 mg	Significant difference in concentrations of morphine, M3G, and M6G between UM and EM (p = 0.02). Also seen with PM.



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- MedWatch The FDA Safety Information and Adverse Event Reporting Program
- Safety Information
- Safety Alerts for Human Medical Products
- 2014 Safety Alerts for Human Medical Products
- 2013 Safety Alerts for Human Medical Products
- 2012 Safety Alerts for Human Medical Products

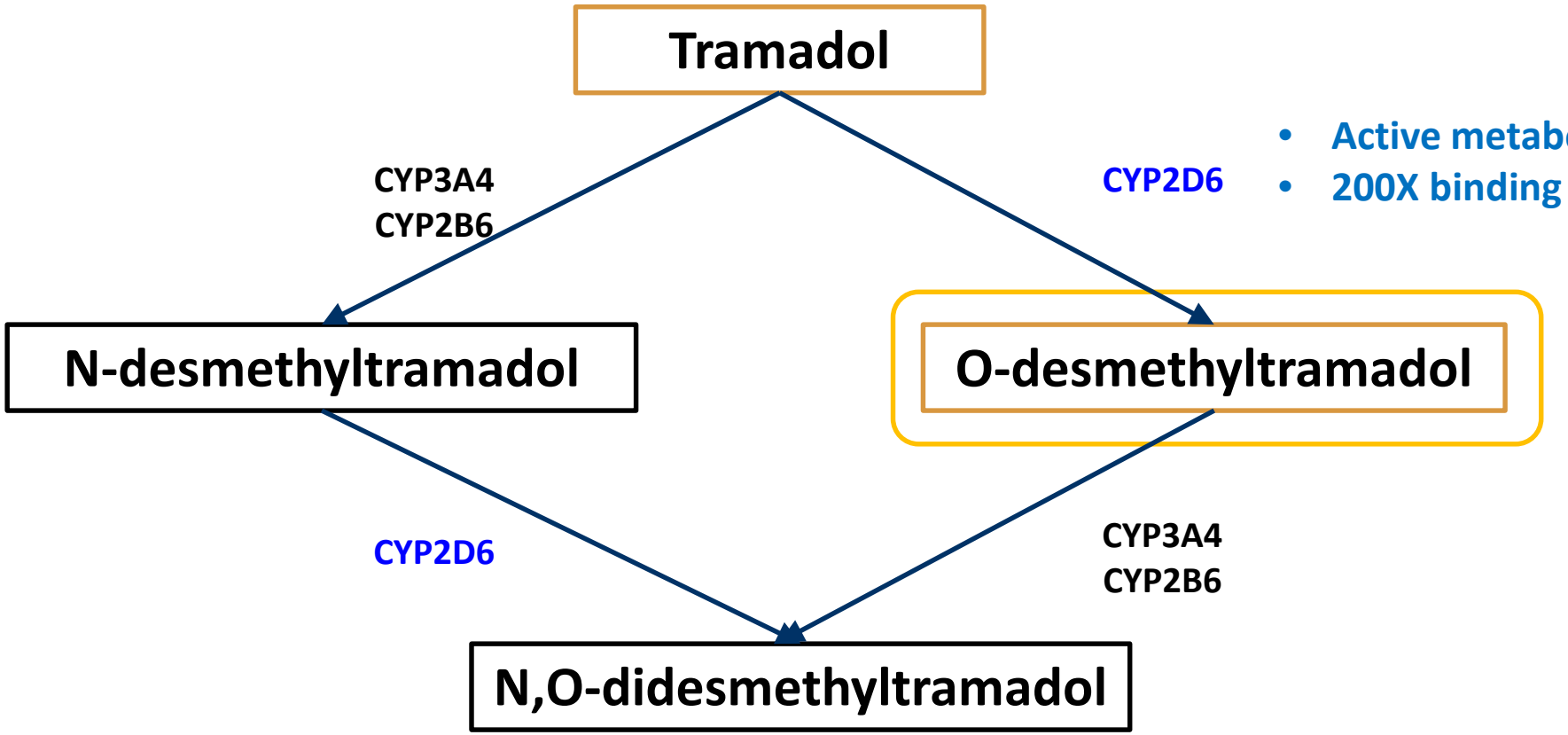
Codeine Use in Certain Children After Tonsillectomy and/or Adenoidectomy: Drug Safety Communication - Risk of Rare, But Life-Threatening Adverse Events or Death

[UPDATED 02/20/2013] FDA notified the public about new actions being taken to address a known safety concern with codeine use in certain children after tonsillectomy and/or adenoidectomy (surgery to remove the tonsils and/or adenoids). A new **BOXED WARNING**, FDA's strongest warning, will be added to the drug label of codeine-containing products about the risk of codeine in post-operative pain management in children following tonsillectomy and/or adenoidectomy. A Contraindication, which is a formal means for FDA to make a strong recommendation against use of a drug in certain patients, will be added to restrict codeine from being used in this setting. The Warnings/Precautions, Pediatric Use, and Patient Counseling Information sections of the drug label will also be updated.

WARNING: DEATH RELATED TO ULTRA-RAPID METABOLISM OF CODEINE TO MORPHINE

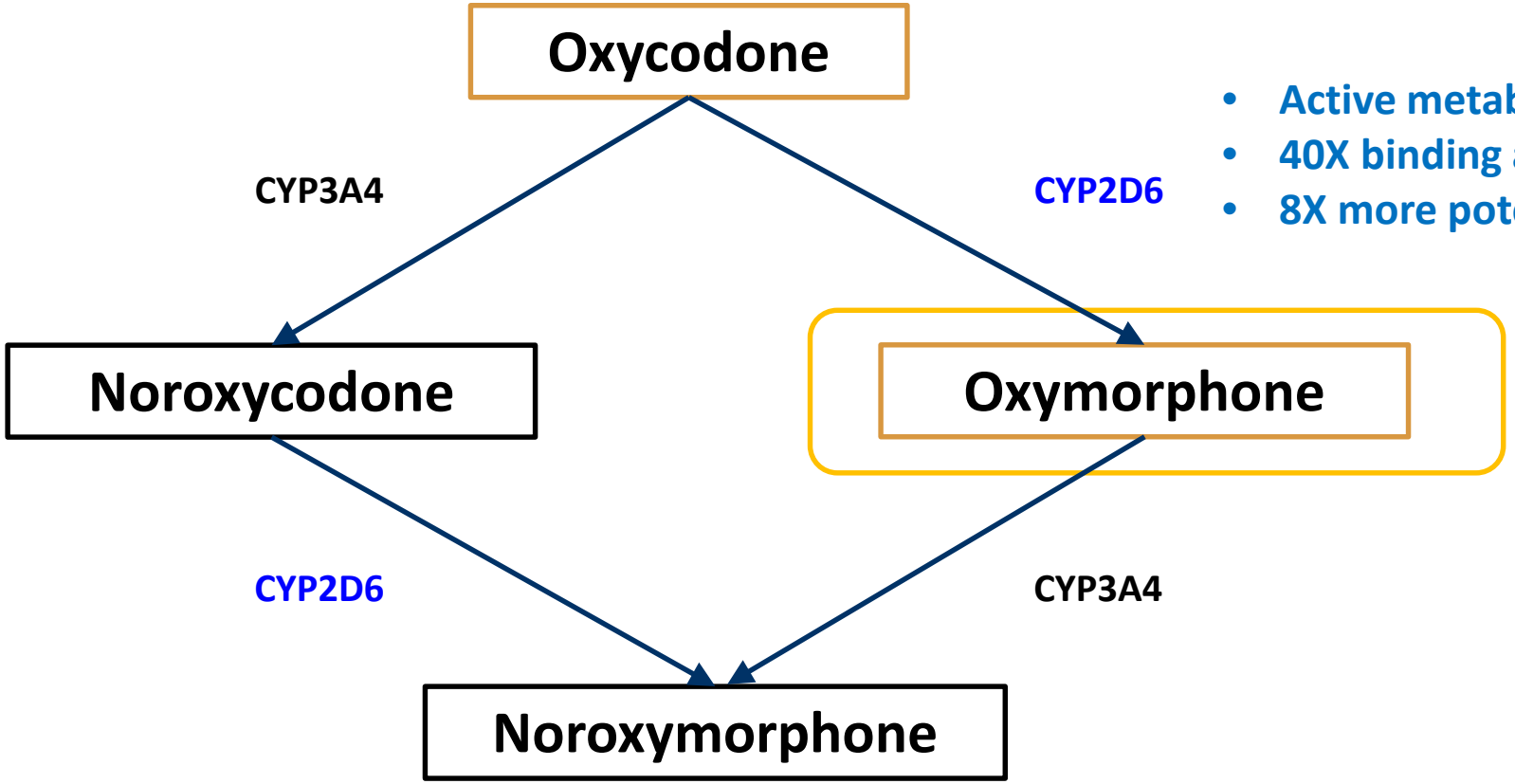
Respiratory depression and death have occurred in children who received codeine following tonsillectomy and/or adenoidectomy and had evidence of being ultra-rapid metabolizers of codeine due to a CYP2D6 polymorphism.

Tramadol



- Active metabolite
- 200X binding affinity

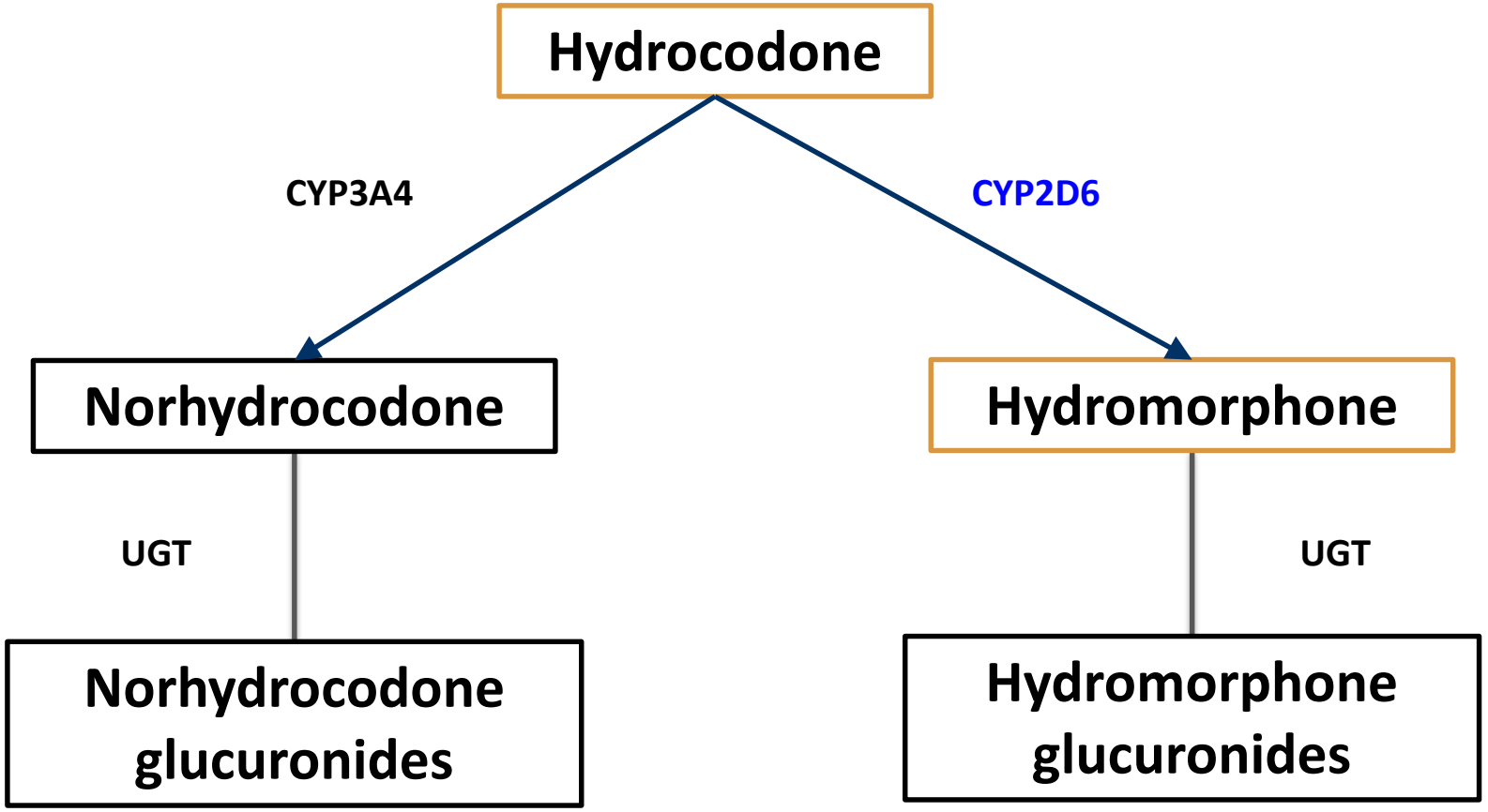
Oxycodone



- Active metabolite
- 40X binding affinity
- 8X more potent

Vuilleumier PH, et al. Pharmgenomics Pers Med. 2012;5:73-87

Hydrocodone



PharmGKB Guidelines

- Clinical Pharmacogenetics Implementation Consortium (CPIC)
  - https://www.pharmgkb.org/guideline/PA166104996
- Royal Dutch Association for the Advancement of Pharmacy - Pharmacogenetics Working Group (DPWG)
  - https://www.pharmgkb.org/page/dpwg
- The Canadian Pharmacogenomics Network for Drug Safety (CPNDS)
  - https://www.pharmgkb.org/pmid/24214521

CYP2D6 genotype guided codeine therapy

Clinical Pharmacogenetics Implementation Consortium Guidelines for Cytochrome P450 2D6 Genotype and Codeine Therapy: 2014 Update

KR Crews[1], A Gaedigk[2,3], HM Dunnenberger[1], JS Leeder[2,3], TE Klein[4], KE Caudle[1], CE Haidar[1], DD Shen[5,6], JT Callaghan[7,8], S Sadhasivam[9,10], CA Prows[11,12], ED Kharasch[13] and TC Skaar[7]

Codeine is bioactivated to morphine, a strong opioid agonist, by the hepatic cytochrome P450 2D6 (CYP2D6); hence, the efficacy and safety of codeine are governed by CYP2D6 activity. Polymorphisms are a major cause of CYP2D6 variability. We summarize evidence from the literature supporting this association and provide therapeutic recommendations for codeine based on *CYP2D6* genotype. This document is an update to the 2012 Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for *CYP2D6* genotype and codeine therapy.

FOCUSED LITERATURE REVIEW AND UPDATE

A systematic literature review focused on CYP2D6 and codeine use was conducted (**Supplementary Data** online). In addition to the information provided in the 2012 Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for *CYP2D6* genotype and codeine therapy,[1] this document also addresses the recent US Food and Drug Administration (FDA) warning regarding codeine use in children following tonsillectomy with or without adenoidectomy, pediatric considerations, and additional considerations for use of alternative opioids metabolized by cytochrome P450 2D6 (CYP2D6). Furthermore, the accompanying **Supplementary Data** online has been updated.

GENE: *CYP2D6*

Background

More than 100 *CYP2D6* alleles have been defined by the Cytochrome P450 Nomenclature Committee at http://www.cypalleles.ki.se. Clinical phenotype data are available for common alleles (**Supplementary Tables S1–S5** online). However, many alleles have not been evaluated in clinical trials, and their clinical phenotypes are predicted based on the expected functional impact of their defining genetic variation or are extrapolated based on *in vitro* functional studies using different substrates.

Genetic test interpretation

Most clinical laboratories report *CYP2D6* genotype using the star (*) allele nomenclature and may provide interpretation of the patient's predicted metabolizer phenotype. Single-nucleotide polymorphisms (SNPs) and other sequence variations, including insertions and deletions, are determined by genetic laboratory tests. The reference SNP number (rs number) for a SNP defines the specific genomic nucleotide alteration. Each star (*) allele (or haplotype) is defined by the presence of a specific combination of SNPs and/or other sequence alterations within the *CYP2D6* gene locus. The key alleles are shown in **Supplementary Table S1** online, and the key allele-defining SNPs and their respective impacts on CYP2D6 enzyme function are provided in **Supplementary Table S2** online. Genetic results are reported as a diplotype, which includes one maternal and one paternal allele (e.g., *CYP2D6*1/*4*). In some cases, patients have more than two copies of the *CYP2D6* gene; up to 13 gene copies have been described.[2] Those alleles are denoted by an "*xN*" following the allele designation, e.g., *CYP2D6*2x2* (duplication; see **Supplementary Data** online for details). Additional details

[1]Department of Pharmaceutical Sciences, St. Jude Children's Research Hospital, Memphis, Tennessee, USA; [2]Division of Clinical Pharmacology and Therapeutic Innovation, Children's Mercy Hospitals and Clinics, Kansas City, Missouri, USA; [3]Department of Pediatrics, University of Missouri–Kansas City, Kansas City, Missouri, USA; [4]Department of Genetics, Stanford University, Stanford, California, USA; [5]Department of Pharmaceutics, School of Pharmacy, University of Washington, Seattle, Washington, USA; [6]Department of Pharmacy, School of Pharmacy, University of Washington, Seattle, Washington, USA; [7]Division of Clinical Pharmacology, Department of Medicine, Indiana University School of Medicine, Indianapolis, Indiana, USA; [8]Department of Veterans Affairs, RLR VA Medical Center, Indianapolis, Indiana, USA; [9]Department of Pediatrics, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, USA; [10]Department of Anesthesia, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, USA; [11]Division of Human Genetics, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, USA; [12]Division of Patient Services, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, USA; [13]Division of Clinical and Translational Research, Department of Anesthesiology, Washington University in St. Louis, St. Louis, Missouri, USA. Correspondence: KR Crews (kristine.crews@stjude.org)

Received 3 October 2013; accepted 17 December 2013; advance online publication 29 January 2014. doi:10.1038/clpt.2013.254

CY2D6 Activity Score

Functional Status	Activity Value	Alleles
Increased function	>1	*1xN, *2xN, *35xN, *45xN
Normal or Increased function	1 or >1	*9xN, *10xN, *17xN, *29xN, *41xN
Normal function	1	*1, *2, *27, *33, *34, *35,*39, *45, *46, *48, *53
Decreased function	0.5	*9, *10, *14B,*17, *29, *41, *49, *50, *54, *55, *59, *72
No function	0	*3, *3xN, *4, *4xN, *5, *6, *6xN, *7, *8, *11, *12, *13, *14A, *15, *18, *19, *20, *21, *31, *36, *36xN, *38, *40, *42, *44, *47, *51, *56, *57, *62,*68, *69, *92, *100, *101
Unknown	N/A	*22, *23, *24, *25, *26, *28, *30, *32, *37, *43, *43xN, *52, *58, *60, *61, *63, *64, *65, *70, *71, *73, *74, *75, *81, *82, *83, *84, *85, *86, *87, *88, *89, *90, *91, *93, *94, *95, *96, *97, *98, *102, *103, *104, *105

Determining CYP2D6 Phenotype from Activity Score

- Add activity score of 2 alleles together to determine phenotype:

Allele Diplotype	Individual Scores	Activity Score	Phenotype
*1/*2	1+1	2	Normal Metabolizer (NM)
*3/*41	0+0.5	0.5	Intermediate Metabolizer (IM)
*3/*4	0+0	0	Poor Metabolizer

Type of Allele	Alleles	Activity Score
Functional	*1, *2	1
Reduced Function	*9, *10, *17, *29, *41	0.5
Non-functional	*3, *4, *5, *6, *7, *8, *11, *15	0

CYP2D6 Activity Score	Phenotype
>2	UM
1-2	NM
0.5	IM
0	PM

Crews KR, et al. *Clin Pharmacol Ther.* 2014 Apr;95(4):376-82.

CPIC Recommendations by CYP2D6 Phenotype

Table 2 Codeine therapy recommendations based on cytochrome P450 2D6 (CYP2D6) phenotype

Phenotype	Implications for codeine metabolism	Recommendations for codeine therapy	Classification of recommendation for codeine therapy[a]	Considerations for alternative opioids
Ultrarapid metabolizer	Increased formation of morphine following codeine administration, leading to higher risk of toxicity	Avoid codeine use due to potential for toxicity.	Strong	Alternatives that are not affected by this CYP2D6 phenotype include morphine and nonopioid analgesics. Tramadol and, to a lesser extent, hydrocodone and oxycodone are not good alternatives because their metabolism is affected by CYP2D6 activity.[b,c]
Extensive metabolizer	Normal morphine formation	Use label-recommended age- or weight-specific dosing.	Strong	—
Intermediate metabolizer	Reduced morphine formation	Use label-recommended age- or weight-specific dosing. If no response, consider alternative analgesics such as morphine or a nonopioid.	Moderate	Monitor tramadol use for response.
Poor metabolizer	Greatly reduced morphine formation following codeine administration, leading to insufficient pain relief	Avoid codeine use due to lack of efficacy.	Strong	Alternatives that are not affected by this CYP2D6 phenotype include morphine and nonopioid analgesics. Tramadol and, to a lesser extent, hydrocodone and oxycodone are not good alternatives because their metabolism is affected by CYP2D6 activity; these agents should be avoided.[b,c]

CYP2D6 Phenotypes

Phenotype	Population Prevalence	Genotype	Enzyme Activity	Recommendation
PM	~5-10%	No functional alleles present	Absent	Avoid codeine use due to lack of efficacy
IM	~2-11%	1 reduced-function AND 1 nonfunctional allele.	Decreased	Use label-recommended doses. If no response consider alternative analgesic
NM	~77-92%	2 alleles with full or reduced function OR 1 fully functioning allele AND 1 non/reduced-function allele	Normal	Use label-recommended doses.
UM	~1-2%	> 2 functional alleles	Increased	Avoid codeine use due to potential for toxicity

Crews KR, et al. *Clin Pharmacol Ther.* 2014 Apr;95(4):376-82.

Phenoconversion

- Modification of the predicted phenotype by drug interactions
- Drug-Drug-Gene Interactions: CYP2D6 Inhibitors

Inhibition	PK Effect	Examples
Strong	≥ 5-fold increase in AUC or > 80% decrease in CL	Bupropion, fluoxetine, paroxetine, quinidine, terbinafine
Moderate	≥ 2 but < 5-fold increase in AUC or 50-80% decrease in CL	Cimetidine, cinacalcet, duloxetine, fluvoxamine, mirabegron
Weak	≥ 1.25 but < 2-fold increase in AUC or 20-50% decrease in CL	Amiodarone, celecoxib, desvenlafaxine, diltiazem, diphenhydramine, Echinacea, escitalopram, febuxostat, gefitinib, hydralazine, hydroxychloroquine, imatinib, methadone, oral contraceptives, propafenone, ranitidine, ritonavir, sertraline, telithromycin, verapamil

Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers. FDA. Last Updated: Sept 27, 2016. Accessed on Feb 26, 2016. [Internet]. Available from: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm

CYP2D6 Inhibitors and Activity Score

- Strong Inhibitors:
  - CYP2D6 activity score is adjusted to 0
  - Predicted phenotype is a poor metabolizer
- Weak or Moderate Inhibitors:
  - CYP2D6 activity score is multiplied by 0.5
  - Convert calculated activity score to the predicted phenotype
- Example:
  - CYP2D6 *2/*4 → activity score = 1; predicted phenotype is NM
  - Patient taking duloxetine (moderate inhibitor) will have activity score multiplied by 0.5 → 1 x 0.5 = 0.5 (modified activity score)
  - Activity score of 0.5; predicted phenotype is IM

Crews, KR, et al. Clin Pharmacol Ther. **95:** 376-382

Drugs not Dependent upon CYP2D6

Alternative Analgesics
Acetaminophen
NSAIDs
Morphine
Hydromorphone
Oxymorphone
Fentanyl
Methadone
Buprenorphine

Pharmacogenetic Checkpoint

According to the CPIC guideline, which CYP2D6 phenotypes carry a strong recommendation to avoid codeine for pain relief?

A. Poor Metabolizer (PM) and Intermediate Metabolizer (IM)
B. Poor Metabolizer (PM) and Ultra-Rapid Metabolizer (UM)
C. Normal Metabolizer (NM) and Ultra-Rapid Metabolizer (UM)

Future directions

- Further guidance on oxycodone and hydrocodone
- Determine if implementing guidelines increases quality of life
- Determine economic value for pre-emptive genotyping

Summary

- *CYP2D6* genotype is an important factor to help guide pain management
- CYP2D6 enzyme is highly variable and is involved in the metabolic pathway of several opioids such as codeine, tramadol, hydrocodone and oxycodone
- Codeine use is not recommended in CYP2D6 ultra-rapid metabolizers and poor metabolizers. Tramadol, oxycodone, and hydrocodone may not be good options because they are also metabolized via CYP2D6
- Codeine is contraindicated in children post tonsillectomy and/or adenoidectomy
- CYP2D6 genetic testing is currently being utilized in practice to guide pain management.

Now that we have covered the basics…

HJ just received a root canal, and her dentist asks for you to recommend the best dose of codeine for her. Based on a previous genotype order in her EHR, you note that HJ has *CYP2D6* *1/*4 genotype. Based on the patient's genetic results, what would you recommend?

A. HJ has an activity score of 5, a CYP2D6 ultra-rapid metabolizer (UM). Avoid codeine due to potential for toxicity.
B. HJ has an activity score of 1, a CYP2D6 normal metabolizer (NM). Prescribe the label recommended dose of codeine.
C. HJ has an activity score of 0.5, a CYP2D6 intermediate metabolizer (IM). Prescribe twice the recommended dose of codeine.
D. HJ has an activity score of 0, a CYP2D6 poor metabolizer. Avoid codeine due to lack of efficacy.