Clinical Applications in Pain Management
Pharmacogenetics

Scott Mosley, PharmD
Postdoctoral Fellow, Center for Pharmacogenomics
Department of Pharmacotherapy and Translational Research
University of Florida College of Pharmacy
Email: samosley@ufl.edu

March 10, 2017
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
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.

Before we get started...
Prevalence of Pain in the US

<table>
<thead>
<tr>
<th>Condition</th>
<th>Point Prevalence (millions)</th>
<th>Annual Costs (billions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>HIV/AIDS</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Heart Disease</td>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td>Diabetes</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Alzheimer's</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Chronic Pain</td>
<td>600</td>
<td>600</td>
</tr>
</tbody>
</table>

Factors When Considering Pain Management

**Biological**
- Genetics
- Endogenous Opioids
- Organ function
- Sex
- Age

**Psychological**
- Depression
- Placebo
- Pain Catastrophizing

**Social**
- Ethnicity
- SES
- Education
- Cultural

**PAIN**
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

---

WHO Analgesic Ladder

If pain persists or increases

Weak opioid

If pain persists or increases

Strong opioid

Non-opioid

Oxycodone

Hydrocodone

Morphine

Codeine

Tramadol

Pain

Opioid

Feel Better
Feel Terrible
Feel Nothing
Factors Related to Opioid Response

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**

- Point Mutations
- Insertions
- Deletions
- Gene rearrangements

Duplication

CYP2D6

CYP2D6

Deletion

CYP2D6

# CYP2D6 Variability

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

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

![Percentage](Percentage.png)

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

**Codeine**

- CYP3A4: 10-15%
- CYP2D6: 5-10%
- UGT2B7: 50-70%

**Norcodeine**

**Codeine-6-glucuronide**

**Morphine**

- CYP2D6: 5-10%
- UGT2B7 / UGT1A1: 5-10%

**Morphine-6-glucuronide**

**Morphine-3-glucuronide**

- UGT2B7 / UGT1A1: 60%

**Normorphine**

Provides analgesia

UM ↑ toxicity
PM ↓ pain control

Codeine $\rightarrow$ Morphine via CYP2D6

- UM: Codeine $\rightarrow$ Morphine
- NM: Codeine $\rightarrow$ Morphine
- IM: Codeine $\rightarrow$ Morphine
- PM: Codeine $\rightarrow$ Morphine
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.
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

**Tramadol**

- CYP3A4
- CYP2B6

**N-desmethyltramadol**

- CYP2D6

**O-desmethyltramadol**

- CYP2D6

- CYP3A4
- CYP2B6

**N,O-didesmethyltramadol**
Oxycodone

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

Hydrocodone

- Hydrocodone
  - Norhydrocodone
    - Norhydrocodone glucuronides
  - Hydromorphone
    - Hydromorphone glucuronides

Enzymes involved:
- CYP3A4
- CYP2D6
- UGT
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

KR Crews1, A Gedigk2,3,1, HM Dunnenberger1, JS Leeder2,4,5, TE Klein1, KE Caudle1, CE Haldar1, DD Shen6, JT Callaghan7,8, S Sadhasivam9,10, CA Proven11,12,13, ED Kharasch13 and TC Skarin7

Codeine is biactivated 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) guideline 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 consensatory with or without antidepressant, 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.info. Clinical phenotype data are available for common alleles (Supplementary Tables S1–S8 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 variants, including insertions and deletions, are determined by genomic laboratory tests. The reference SNP number (rs number) for a SNP defines the specific genetic nucleotide alteration. Each star (*) allele (or haplotype) is defined by the presence of a specific combination of SNPs and other sequence alterations within the CYP2D6 gene locus. The key alleles are shown in Supplementary Table S8 online, and the key allele-defining SNPs and their respective impacts on CYP2D6 enzyme function are provided in Supplementary Table S2 online. Genomic results are reported as a diplotype, which includes one maternal and one paternal allele (e.g., CYP2D6*10*4). In some cases, patients have more than two copies of the CYP2D6 gene; up to 11 gene copies have been described.2 These alleles are denoted by an "a" following the allele designation, e.g., CYP2D6*10*4a (duplication), see Supplementary Data online for details. Additional details...

1Department of Pharmaceutical Sciences, St. Jude Children's Research Hospital, Memphis, Tennessee, USA. 2Division of Clinical Pharmacology and Therapeutics Innovation, Children's Mercy Hospital and Clinics, Kansas City, Missouri, USA. 3Department of Pediatrics, University of Minnesota, Minneapolis, Minnesota, USA. 4Department of Pediatrics and Division of Hematology/Oncology, University of California, San Francisco, San Francisco, California, USA. 5Department of Pharmacy, University of Washington, Seattle, Washington, USA. 6Department of Pharmacy, School of Pharmacy, University of Washington, Seattle, Washington, USA. 7Division of Clinical Pharmacology, Department of Medicine, Indiana University School of Medicine, Indianapolis, Indiana, USA. 8Division of Clinical Pharmacology and Laboratory Medicine, Indiana University School of Medicine, Indianapolis, Indiana, USA. 9Department of Pediatric Hematology/Oncology, Children's Hospital, Columbus, Ohio, USA. 10Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, Minnesota, USA. 11Department of Pharmacy, University of California, San Francisco, San Francisco, California, USA. 12Yale University School of Medicine, New Haven, Connecticut, USA. 13Division of Hematology/Oncology, Children's Hospital, Columbus, Ohio, USA. 14Division of Genomic Medicine, Children's Hospital, Columbus, Ohio, USA. 15Division of Pediatric Rheumatology, Nationwide Children's Hospital, Columbus, Ohio, USA. 16Division of Adolescent Medicine, Children's Hospital, Columbus, Ohio, USA. 17Division of Adolescent Medicine, Children's Hospital, Columbus, Ohio, USA. 18Division of Clinical and Translational Research, Department of Anesthesiology, Washington University School of Medicine, St. Louis, Missouri, USA. 19Corresponding author. Received 8 October 2013; revised 17 December 2013; accepted 28 December 2013; published online 29 January 2014. DOI: 10.1038/nph.2013.294
## CY2D6 Activity Score

<table>
<thead>
<tr>
<th>Functional Status</th>
<th>Activity Value</th>
<th>Alleles</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased function</td>
<td>&gt;1</td>
<td>*1xN, *2xN, *35xN, *45xN</td>
</tr>
<tr>
<td>Normal or Increased function</td>
<td>1 or &gt;1</td>
<td>*9xN, *10xN, *17xN, *29xN, *41xN</td>
</tr>
</tbody>
</table>
Determining CYP2D6 Phenotype from Activity Score

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

<table>
<thead>
<tr>
<th>Allele Diplotpe</th>
<th>Individual Scores</th>
<th>Activity Score</th>
<th>Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>*1/*2</td>
<td>1+1</td>
<td>2</td>
<td>Normal Metabolizer (NM)</td>
</tr>
<tr>
<td>*3/*41</td>
<td>0+0.5</td>
<td>0.5</td>
<td>Intermediate Metabolizer (IM)</td>
</tr>
<tr>
<td>*3/*4</td>
<td>0+0</td>
<td>0</td>
<td>Poor Metabolizer</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Type of Allele</th>
<th>Alleles</th>
<th>Activity Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Functional</td>
<td>*1, *2</td>
<td>1</td>
</tr>
<tr>
<td>Reduced Function</td>
<td>*9, *10, *17, *29, *41</td>
<td>0.5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CYP2D6 Activity Score</th>
<th>Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;2</td>
<td>UM</td>
</tr>
<tr>
<td>1-2</td>
<td>NM</td>
</tr>
<tr>
<td>0.5</td>
<td>IM</td>
</tr>
<tr>
<td>0</td>
<td>PM</td>
</tr>
</tbody>
</table>

# CPIC Recommendations by CYP2D6 Phenotype

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

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Implications for codeine metabolism</th>
<th>Recommendations for codeine therapy</th>
<th>Classification of recommendation for codeine therapy</th>
<th>Considerations for alternative opioids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultrarapid metabolizer</td>
<td>Increased formation of morphine following codeine administration, leading to higher risk of toxicity</td>
<td>Avoid codeine use due to potential for toxicity.</td>
<td>Strong</td>
<td>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})</td>
</tr>
<tr>
<td>Extensive metabolizer</td>
<td>Normal morphine formation</td>
<td>Use label-recommended age- or weight-specific dosing.</td>
<td>Strong</td>
<td>—</td>
</tr>
<tr>
<td>Intermediate metabolizer</td>
<td>Reduced morphine formation</td>
<td>Use label-recommended age- or weight-specific dosing. If no response, consider alternative analgesics such as morphine or a nonopioid.</td>
<td>Moderate</td>
<td>Monitor tramadol use for response.</td>
</tr>
<tr>
<td>Poor metabolizer</td>
<td>Greatly reduced morphine formation following codeine administration, leading to insufficient pain relief</td>
<td>Avoid codeine use due to lack of efficacy.</td>
<td>Strong</td>
<td>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})</td>
</tr>
</tbody>
</table>
## CYP2D6 Phenotypes

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

Phenoconversion

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

<table>
<thead>
<tr>
<th>Inhibition</th>
<th>PK Effect</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Strong</strong></td>
<td>≥ 5-fold increase in AUC or &gt; 80% decrease in CL</td>
<td>Bupropion, fluoxetine, paroxetine, quinidine, terbinafine</td>
</tr>
<tr>
<td><strong>Moderate</strong></td>
<td>≥ 2 but &lt; 5-fold increase in AUC or 50-80% decrease in CL</td>
<td>Cimetidine, cinacalcet, duloxetine, fluvoxamine, mirabegron</td>
</tr>
<tr>
<td><strong>Weak</strong></td>
<td>≥ 1.25 but &lt; 2-fold increase in AUC or 20-50% decrease in CL</td>
<td>Amiodarone, celecoxib, desvenlafaxine, diltiazem, diphenhydramine, Echinacea, escitalopram, febuxostat, gefitinib, hydralazine, hydroxychloroquine, imatinib, methadone, oral contraceptives, propafenone, ranitidine, ritonavir, sertraline, telithromycin, verapamil</td>
</tr>
</tbody>
</table>
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 \(\rightarrow\) activity score = 1; predicted phenotype is NM
  - Patient taking duloxetine (moderate inhibitor) will have activity score multiplied by 0.5 \(\rightarrow\) 1 x 0.5 = 0.5 (modified activity score)
  - Activity score of 0.5; predicted phenotype is IM

## Drugs not Dependent upon CYP2D6

<table>
<thead>
<tr>
<th>Alternative Analgesics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen</td>
</tr>
<tr>
<td>NSAIDs</td>
</tr>
<tr>
<td>Morphine</td>
</tr>
<tr>
<td>Hydromorphone</td>
</tr>
<tr>
<td>Oxymorphone</td>
</tr>
<tr>
<td>Fentanyl</td>
</tr>
<tr>
<td>Methadone</td>
</tr>
<tr>
<td>Buprenorphine</td>
</tr>
</tbody>
</table>
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.
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.

Now that we have covered the basics...