Cytochrome P450 2D6 (CYP2D6) Pharmacogenomic Competency
An 18-year-old patient who is a CYP2D6 poor metabolizer is prescribed codeine 30 mg PO Q4-6hrs as needed for pain. Which of the following therapeutic recommendations is most appropriate based their CYP2D6 phenotype?

a) Dispense codeine as prescribed
b) Do not use codeine, recommend using another agent
c) Dispense codeine and recommend increasing the dose
d) Dispense codeine and recommend decreasing the dose
Question #2

Which of the following medications is primarily metabolized via by the CYP2D6 enzyme system?

a) Paroxetine
b) Sertraline
c) Escitalopram
d) Citalopram
CYP2D6 ultra-rapid metabolizers (UM) clear ondansetron faster than CYP2D6 normal metabolizers. Which of the following ondansetron recommendations is most appropriate for a patient who is a CYP2D6 UM?

a) Dispense ondansetron at higher than package insert recommended doses
b) Dispense ondansetron at package insert recommended doses
c) Substitute another agent for ondansetron
d) Dispense ondansetron at package insert recommended doses and administer more frequently
Objectives

• Upon completion of this competency, participants will be able to:
  • Recognize the different CYP2D6 allele variants
  • Recognize the different CYP2D6 phenotypes
  • Calculate a CYP2D6 activity score
  • Assign the correct phenotype based upon the activity score
  • Make therapeutic recommendations for medications metabolized by CYP2D6 based on a patient’s predicted CYP2D6 phenotype
CYP2D6 and Drug Metabolism

- CYP2D6 is an enzyme that metabolizes up to 25% of currently prescribed medications
- CYP2D6 can either activate or inactivate a medication

Diagram:
- Codeine (pro-drug; inactive) → CYP2D6 → Morphine (active)
- Ondansetron (active) → CYP2D6 → 6-hydroxy-ondansetron (inactive)

GOAL: Know the patient’s CYP2D6 status prior to prescribing a medication that affected by CYP2D6 polymorphisms.
CYP2D6 Allele Function
CYP2D6 Allele Function

- Normal function
- Decreased function
- No function
CYP2D6 Normal Function Alleles

- Certain CYP2D6 alleles are characterized as normal function alleles
  - These alleles will encode for CYP2D6 enzymes that will have normal metabolic function

- CYP2D6 normal function alleles include:
  - *1, *2, *33
Certain *CYP2D6* alleles are characterized as decreased function alleles. These alleles will encode for *CYP2D6* enzymes that have less metabolic activity than normal function alleles but more activity than no function alleles.

*CYP2D6* decreased function alleles include:
CYP2D6 No Function Allele

• Certain CYP2D6 alleles are characterized as no function alleles
  • These alleles will encode for CYP2D6 enzymes that have little or no metabolic activity

• CYP2D6 no function alleles include:
  • *3,*4,*5,*6,*7,*8,*11,*12,*13
  • Note that the *5 allele is a deleted allele
CYP2D6 Activity Score Assignment

- Each allele is assigned an activity value as shown below:

<table>
<thead>
<tr>
<th>Function</th>
<th>Example Alleles</th>
<th>Activity Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal function</td>
<td>*1, *2</td>
<td>1</td>
</tr>
<tr>
<td>Decreased function</td>
<td>*14, *17, *29, *49, *59</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>*9, *10, *41</td>
<td>0.25</td>
</tr>
</tbody>
</table>

- CYP2D6 activity score is calculated by adding up the activity value for each allele as follows:
  
  - Activity score for $CYP2D6 \; (*1/*2)2N = 1 + 1 = 2$
  - Activity score for $CYP2D6 \; (*2/*14)2N = 1 + 0.5 = 1.5$
  - Activity score for $CYP2D6 \; (*3/*9)2N = 0 + 0.5 = 0.5$
  - Activity score for $CYP2D6 \; (*4/*4)2N = 0 + 0 = 0$
• While most people have two copies of a gene (one inherited from each parent), the number of CYP2D6 gene copies a person can have may vary from zero copies to more than three copies.

• It is important to select a clinical laboratory that can assess the number of CYP2D6 copies in addition to interrogating the most commonly known variations in the population.

• Reference laboratories differ in the way they report duplicated alleles:
  • Some indicate which allele is duplicated
  • Others indicate the total number of copies of the CYP2D6 gene
What is the activity score for CYP2D6 (*2/*14)3N? What are the possibilities?

\[
\begin{align*}
*2 + *2 + *10 & \text{ (3 alleles total)} = 1 + 1 + 0.25 = 2.5 \\
& \text{Ultra-rapid metabolizer} \\
OR \quad *2 + *10 + *10 & \text{ (3 alleles total)} = 1 + 0.25 + 0.25 = 1.50 \\
& \text{Normal metabolizer}
\end{align*}
\]

<table>
<thead>
<tr>
<th>Function</th>
<th>Alleles</th>
<th>Activity Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal function</td>
<td>*1, *2</td>
<td>1</td>
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<td>Decreased function</td>
<td>*14, *17, *29, *49, *59</td>
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</tr>
<tr>
<td></td>
<td>*9, *10, *41</td>
<td>0.25</td>
</tr>
</tbody>
</table>
Assigning CYP2D6 Phenotype
CYP2D6 Phenotypes

- There are four known CYP2D6 phenotypes:
  - Ultra-rapid metabolizer (UM)
  - Normal metabolizer (NM)
  - Intermediate metabolizer (IM)
  - Poor metabolizer (PM)
The exact percent of each phenotype group varies by race and ethnicity.
Assigning CYP2D6 Phenotype

CYP2D6 phenotype assignment is based on the diplotype’s total activity score:

<table>
<thead>
<tr>
<th>CYP2D6 activity score</th>
<th>Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;2.25</td>
<td>Ultra-rapid metabolizer</td>
</tr>
<tr>
<td>1.25-2.25</td>
<td>Normal metabolizer</td>
</tr>
<tr>
<td>0.25-1</td>
<td>Intermediate metabolizer</td>
</tr>
<tr>
<td>0</td>
<td>Poor metabolizer</td>
</tr>
</tbody>
</table>

Gene-Based Dosing Recommendations
Codeine
Codeine and CYP2D6 Ultra-rapid Metabolizers

- Codeine’s analgesic effect is closely related to CYP2D6 metabolism
  - CYP2D6 ultra-rapid metabolizers
    - Convert codeine to morphine at a greater extent than normal leading to an increased risk of toxicities such as over sedation, respiratory depression, or constipation
    - Breastfeeding mothers who are CYP2D6 UMs should NOT take codeine while breastfeeding because codeine and its metabolites (including morphine) are secreted into human breast milk

https://cpicpgx.org/guidelines/guideline-for-codeine-and-cyp2d6/
Codeine and CYP2D6 Poor Metabolizers

- CYP2D6 poor metabolizers cannot activate the codeine to morphine and will have no analgesic benefit

https://cpicpgx.org/guidelines/guideline-for-codeine-and-cyp2d6/
Codeine Therapeutic Recommendations

Alternatives to codeine should be chosen based on each institution’s formulary. Example of alternative medications include non-opioid analgesics such as NSAIDs, morphine, hydromorphone, acetaminophen/hydrocodone.

CYP2D6 Phenotype | Therapeutic Recommendations
--- | ---
Ultra-rapid metabolizer | Avoid codeine use – potential for serious toxicity
Normal metabolizer | Use codeine label recommended age-specific or weight-specific dosing
Intermediate metabolizer | Use codeine label recommended age-specific or weight-specific dosing
Poor metabolizer | Avoid codeine use – possibly of diminished analgesia

Tramadol
Tramadol and CYP2D6 Ultra-rapid and Poor Metabolizers

- Tramadol analgesia is related to CYP2D6 metabolism
  - CYP2D6 ultra-rapid metabolizers
    - Convert tramadol to O-desmethyltramadol at a greater rate than normal leading to an increased risk of side effects
  - CYP2D6 poor metabolizers
    - Cannot metabolize tramadol to the more active form O-desmethyltramadol; therefore, resulting in little to no analgesic benefit

Tramadol Therapeutic Recommendations

Alternatives to tramadol should be chosen based on each institution’s formulary. Example of alternative medications include non-opioid analgesics such as NSAIDs, morphine, hydromorphone, and acetaminophen/hydrocodone.

<table>
<thead>
<tr>
<th>CYP2D6 Phenotype</th>
<th>Therapeutic Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultra-rapid metabolizer</td>
<td>Avoid tramadol use – potential for serious toxicity</td>
</tr>
<tr>
<td>Normal metabolizer</td>
<td>Use tramadol label recommended age-specific or weight-specific dosing</td>
</tr>
<tr>
<td>Intermediate metabolizer</td>
<td>Use tramadol label recommended age-specific or weight-specific dosing</td>
</tr>
<tr>
<td>Poor metabolizer</td>
<td>Avoid tramadol use – possibly of diminished analgesia</td>
</tr>
</tbody>
</table>

Ondansetron
CYP2D6 (along with other CYP450 enzymes) metabolizes ondansetron to major inactive metabolites 7- and 8-hydroxy ondansetron and minor inactive metabolites 6- hydroxy and N-desmethyl ondansetron.
• CYP2D6 ultrarapid metabolizers have increased clearance of ondansetron which can lead to inadequate anti-emetic control

<table>
<thead>
<tr>
<th>CYP2D6 Phenotype</th>
<th>Therapeutic Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultra-rapid metabolizer</td>
<td>Avoid ondansetron – consider granisetron or anti-emetic not metabolized by CYP2D6</td>
</tr>
</tbody>
</table>

https://cpicpgx.org/guidelines/guideline-for-codeine-and-cyp2d6/
Amitriptyline
Amitriptyline Metabolism

- **CYP2C19** metabolizes amitriptyline to an active metabolite: nortriptyline
- **CYP2D6** metabolizes amitriptyline and nortriptyline to less active hydroxy-metabolites

![Diagram showing the metabolic pathways of amitriptyline and nortriptyline]

• **CYP2C19** metabolizes amitriptyline to an active metabolite: nortriptyline
• **CYP2D6** metabolizes amitriptyline and nortriptyline to less active hydroxy-metabolites
Tricyclic Antidepressants

• Because the tricyclic antidepressants have comparable pharmacokinetic properties, the dosing recommendations for amitriptyline may be applied to other tricyclic antidepressants including:
  • Clomipramine, imipramine, doxepin, and trimipramine
<table>
<thead>
<tr>
<th>CYP2D6 Phenotype</th>
<th>Therapeutic Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultra-rapid metabolizer</td>
<td>Avoid tricyclic use – consider alternative drug not metabolized by CYP2D6</td>
</tr>
<tr>
<td>Normal metabolizer</td>
<td>Initiate therapy with recommended starting dose</td>
</tr>
<tr>
<td>Intermediate metabolizer</td>
<td>Consider 25% reduction of recommended starting dose</td>
</tr>
<tr>
<td>Poor metabolizer</td>
<td>Avoid tricyclic use – consider alternative drug not metabolized by CYP2D6</td>
</tr>
</tbody>
</table>

# Summary of Tricyclic Antidepressant Therapeutic Recommendations Based on CYP2C19 and CYP2D6 Phenotypes

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>CYP2D6 ultra-rapid metabolizer</th>
<th>CYP2D6 normal metabolizer</th>
<th>CYP2D6 intermediate metabolizer</th>
<th>CYP2D6 poor metabolizer</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2C19 ultra-rapid metabolizer</td>
<td>Avoid use</td>
<td>Consider alternative drug not metabolized by CYP2C19</td>
<td>Consider alternative drug not metabolized by CYP2C19</td>
<td>Avoid use</td>
</tr>
<tr>
<td>CYP2C19 rapid metabolizer</td>
<td>Avoid use</td>
<td>Consider alternative drug not metabolized by CYP2C19</td>
<td>Consider alternative drug not metabolized by CYP2C19</td>
<td>Avoid use</td>
</tr>
<tr>
<td>CYP2C19 normal metabolizer</td>
<td>Avoid use</td>
<td>Initiate therapy with recommended starting dose</td>
<td>Consider 25% reduction of recommended starting dose</td>
<td>Avoid use – if use is warranted, consider a 50% reduction of recommended starting dose</td>
</tr>
<tr>
<td>CYP2C19 intermediate metabolizer</td>
<td>Avoid use</td>
<td>Initiate therapy with recommended starting dose</td>
<td>Consider 25% reduction of recommended starting dose</td>
<td>Avoid use – if use is warranted, consider a 50% reduction of recommended starting dose</td>
</tr>
<tr>
<td>CYP2C19 poor metabolizer</td>
<td>Avoid use</td>
<td>Avoid use – if use is warranted, consider a 50% reduction of recommended starting dose</td>
<td>Avoid use</td>
<td>Avoid use</td>
</tr>
</tbody>
</table>

Selective Serotonin Reuptake Inhibitors
Paroxetine, vortioxetine, and venlafaxine are primarily metabolized by CYP2D6 to inactive metabolites.
Selective-Serotonin Inhibitors

**Medications**
- Sertraline
- Escitalopram
- Citalopram
- Paroxetine
- Fluoxetine
- Fluvoxamine

**Mechanism of action**
- Inhibit the reuptake of serotonin → increase serotonin activity

**Indications**
- Major depression disorder
- Generalized anxiety disorder
- Obsessive-compulsive disorder
- Panic disorder
- Posttraumatic stress disorder
- Social anxiety disorder

**Adverse Effects**
- Irritability, hyperactivity
- Agitation, shakiness or anxiousness
- Gastrointestinal (N/V/D)
- Headache
- Drowsiness
- Dizziness
- Blurred vision
- Prolong QT interval
- Weight gain
- Decreased libido
# Paroxetine Therapeutic Recommendations

<table>
<thead>
<tr>
<th>CYP2D6 Phenotype</th>
<th>Therapeutic Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultra-rapid metabolizer</td>
<td>Avoid paroxetine use – consider alternative drug not predominantly metabolized by CYP2D6</td>
</tr>
<tr>
<td>Normal metabolizer</td>
<td>Initiate therapy with recommended starting dose</td>
</tr>
<tr>
<td>Intermediate metabolizer</td>
<td>Consider a lower starting dose and slow titration</td>
</tr>
<tr>
<td>Poor metabolizer</td>
<td>Consider a 50% reduction in recommended starting dose, slower titration schedule, and a 50% lower maintenance dose</td>
</tr>
</tbody>
</table>

# Fluvoxamine Therapeutic Recommendations

<table>
<thead>
<tr>
<th>CYP2D6 Phenotype</th>
<th>Therapeutic Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultra-rapid metabolizer</td>
<td>No recommendation due to minimal evidence</td>
</tr>
<tr>
<td>Normal metabolizer</td>
<td>Initiate therapy with recommended starting dose</td>
</tr>
<tr>
<td>Intermediate metabolizer</td>
<td>Initiate therapy with recommended starting dose</td>
</tr>
<tr>
<td>Poor metabolizer</td>
<td>Consider alternative agent not predominantly metabolized by CYP2D6. Alternatively, consider a 25-50% lower starting doses and slower titration</td>
</tr>
</tbody>
</table>

# Venlafaxine Therapeutic Recommendations

<table>
<thead>
<tr>
<th>CYP2D6 Phenotype</th>
<th>Therapeutic Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultra-rapid metabolizer</td>
<td>No recommendation due to minimal evidence</td>
</tr>
<tr>
<td>Normal metabolizer</td>
<td>Initiate therapy with recommended starting dose</td>
</tr>
<tr>
<td>Intermediate metabolizer</td>
<td>No recommendation due to minimal evidence</td>
</tr>
<tr>
<td>Poor metabolizer</td>
<td>Avoid venlafaxine use – consider alternative drug not predominantly metabolized by CYP2D6</td>
</tr>
</tbody>
</table>

## Vortioxetine Therapeutic Recommendations

<table>
<thead>
<tr>
<th>CYP2D6 Phenotype</th>
<th>Therapeutic Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultra-rapid metabolizer</td>
<td>Avoid vortioxetine use – consider alternative drug not predominantly metabolized by CYP2D6</td>
</tr>
<tr>
<td>Normal metabolizer</td>
<td>Initiate therapy with recommended starting dose</td>
</tr>
<tr>
<td>Intermediate metabolizer</td>
<td>No recommendation due to minimal evidence</td>
</tr>
<tr>
<td>Poor metabolizer</td>
<td>Consider alternative agent not predominantly metabolized by CYP2D6. Alternatively, consider a 50% lower starting doses and titrate to a maximum of 10 mg (in adult populations)</td>
</tr>
</tbody>
</table>

• For more information about CYP2D6 and medications affected by CYP2D6 polymorphisms, visit the CPIC guideline page at https://cpicpgx.org/gene/cyp2d6/

• For more information about the St. Jude implementation efforts for CYP2D6 visit www.stjude.org/CYP2D6
An 18-year-old patient who is a CYP2D6 poor metabolizer is prescribed codeine 30 mg PO Q4-6hrs as needed for pain. Which of the following therapeutic recommendations is most appropriate based on their CYP2D6 phenotype?

a) Dispense codeine as prescribed
b) Do not use codeine, recommend using another agent
c) Dispense codeine and recommend increasing the dose
d) Dispense codeine and recommend decreasing the dose
An 18-year-old patient who is a CYP2D6 poor metabolizer is prescribed codeine 30 mg PO Q4-6hrs as needed for pain. Which of the following therapeutic recommendations is most appropriate based their CYP2D6 phenotype?

a) Dispense codeine as prescribed
b) Do not use codeine, recommend using another agent
c) Dispense codeine and recommend increasing the dose
d) Dispense codeine and recommend decreasing the dose

Correct Answer: B
Which of the following medications is primarily metabolized via the CYP2D6 enzyme system?

a) Paroxetine
b) Sertraline
c) Escitalopram
d) Citalopram
Which of the following medications is primarily metabolized via
by the CYP2D6 enzyme system?

a) Paroxetine  
b) Sertraline  
c) Escitalopram  
d) Citalopram  

Correct Answer: A
CYP2D6 ultra-rapid metabolizers (UM) clear ondansetron faster than CYP2D6 normal metabolizers. Which of the following ondansetron recommendations is most appropriate for a patient who is a CYP2D6 UM?

a) Dispense ondansetron at higher than package insert recommended doses
b) Dispense ondansetron at package insert recommended doses
c) Substitute another agent for ondansetron
d) Dispense ondansetron at package insert recommended doses and administer more frequently
CYP2D6 ultra-rapid metabolizers (UM) clear ondansetron faster than CYP2D6 normal metabolizers. Which of the following ondansetron recommendations is most appropriate for a patient who is a CYP2D6 UM?

a) Dispense ondansetron at higher than package insert recommended doses
b) Dispense ondansetron at package insert recommended doses
c) **Substitute another agent for ondansetron**
d) Dispense ondansetron at package insert recommended doses and administer more frequently

Correct Answer: C
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