Cytochrome P450 2D6 (CYP2D6) PharmacogenomicCompetency

Revised: August 2023

Question #1

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

Question #3

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

Petrović, J, *et al. Eur J Hum Genet.* 2020;28:88–94.
https://cpicpgx.org/guidelines/guideline-for-ondansetron-and-tropisetron-and-cyp2d6-genotype/ *Accessed 09/09/2022*
https://cpicpgx.org/guidelines/guideline-for-codeine-and-cyp2d6/ *Accessed 09/09/2022*

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*

CYP2D6 Decreased Function Alleles

- 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 that no function alleles

- *CYP2D6* decreased function alleles include:
  - **9,*10,*14,*17,*29,*41*

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

CYP2D6 Activity Score Assignment

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

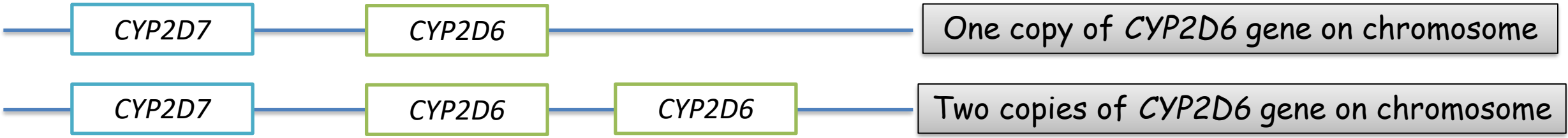
Function	Example Alleles	Activity Score
Normal function	**1, *2*	1
Decreased function	**14, *17, *29, *49, *59*	0.5
	**9,*10,*41*	0.25
No function	**3, *4, *5, *6, *7, *8, *12, *15, *21, *31, *40, *42, *56*	0

- 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

Gaedigk A, *et al. Clin Pharmacol Ther*. 2008;83(2):234-242;
Crews KR, *et al. Clin Pharmacol Ther*. 2021;110(4):888-896.

CYP2D6 Copy Number Variation

- While most people have two copies of a gene (one inherited from each parent), the number *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

Gaedigk A, *et al. Clin Pharmacol Ther*. 2008;83(2):234-242;
Crews KR, *et al. Clin Pharmacol Ther*. 2021;110(4):888-896.

CYP2D6 Copy Number Variation, Activity Score Calculation, and Phenotype Assignment

Function	Alleles	Activity Score
Normal function	**1, *2*	1
Decreased function	**14, *17, *29, *49, *59*	0.5
	**9, *10, *41*	0.25
No function	**3, *4, *5, *6, *7, *8, *12, *15, *21, *31, *40, *42, *56*	0

What is the activity score for *CYP2D6 (*2/*14)3N*?

What are the possibilities?

*2 + *2 + *10 (3 alleles total) = 1 + 1 + 0.25 = 2.5

OR

*2 + *10 + *10 (3 alleles total) = 1 + 0.25 + 0.25 = 1.50

Phenotype Assignment

2.5 → **Ultra-rapid metabolizer**

1.50 → **Normal metabolizer**

Gaedigk A, *et al. Clin Pharmacol Ther*. 2008;83(2):234-242;
Crews KR, *et al. Clin Pharmacol Ther*. 2021;110(4):888-896.

Assigning CYP2D6 Phenotype

CYP2D6 Phenotypes

- There are four known CYP2D6 phenotypes

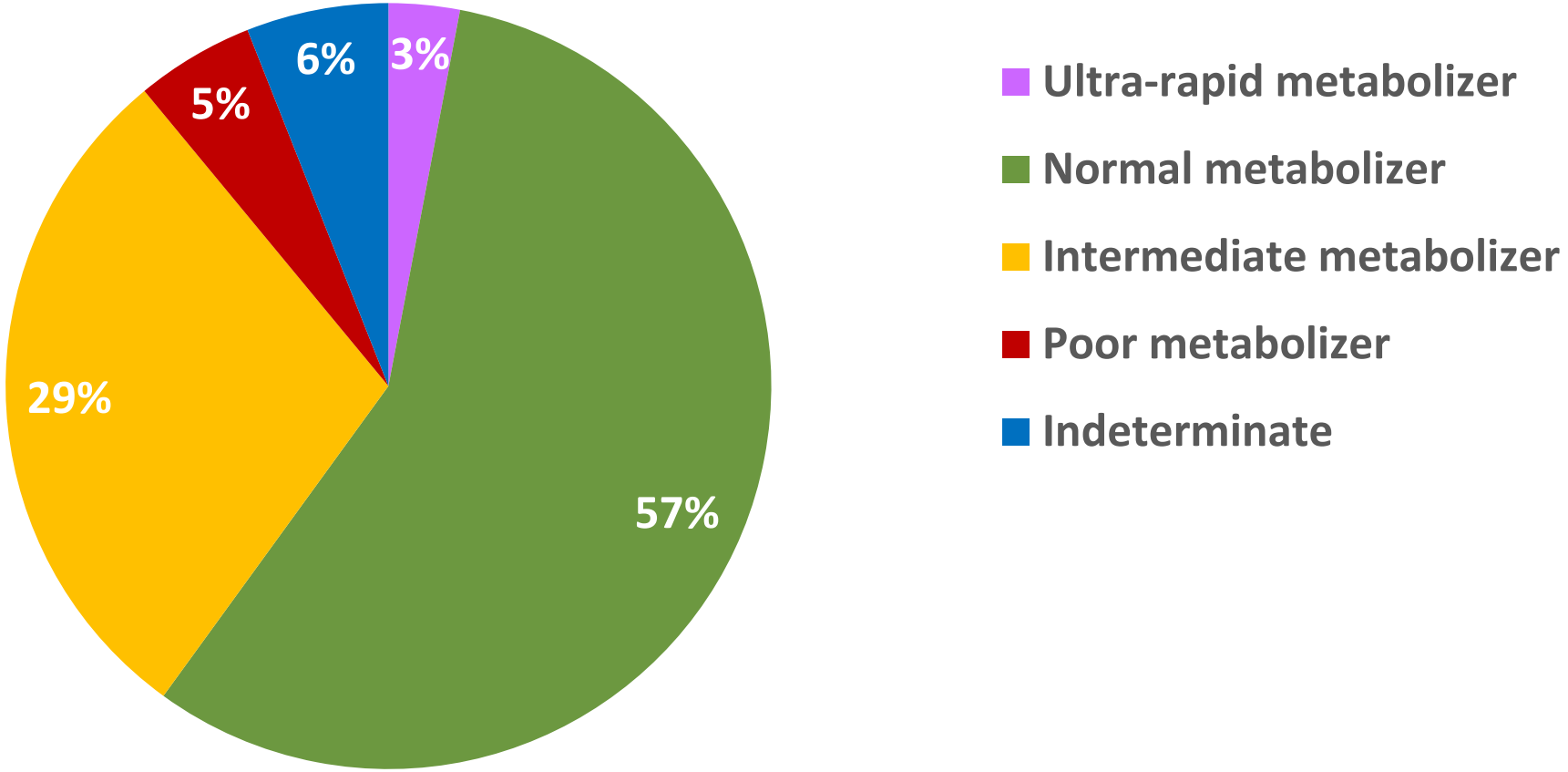
Ultra-rapid metabolizer (UM)

Normal metabolizer (NM)

Intermediate metabolizer (IM)

Poor metabolizer (PM)

CYP2D6 Phenotype Frequencies



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:

CYP2D6 activity score	Phenotype
>2.25	Ultra-rapid metabolizer
1.25-2.25	Normal metabolizer
0.25-1	Intermediate metabolizer
0	Poor metabolizer

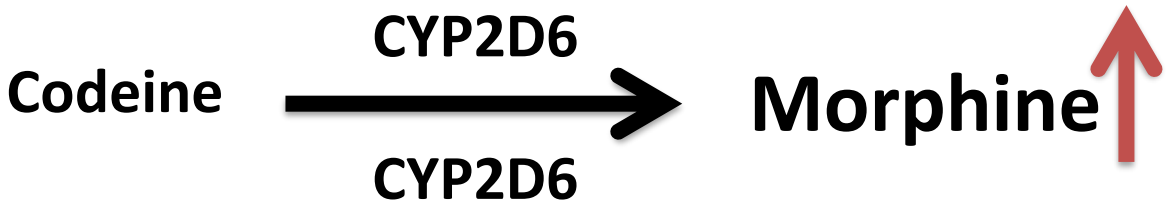
Gaedigk A, *et al. Clin Pharmacol Ther*. 2008;83(2):234-242;
Crews KR, *et al. Clin Pharmacol Ther*. 2021;110(4):888-896.

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



CYP2D6 ultra-rapid metabolizers should NOT receive codeine

Codeine and CYP2D6 Poor Metabolizers

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

CYP2D6 poor metabolizers should NOT receive codeine

Codeine Therapeutic Recommendations

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

- 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

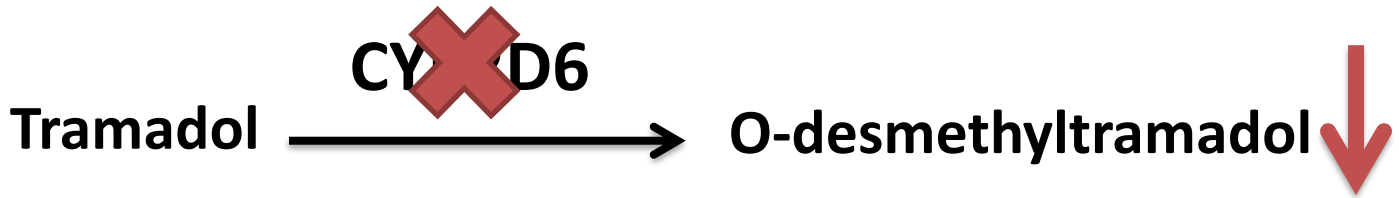
Crews KR, *et al. Clin Pharmacol Ther*. 2021;110(4):888-896.

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

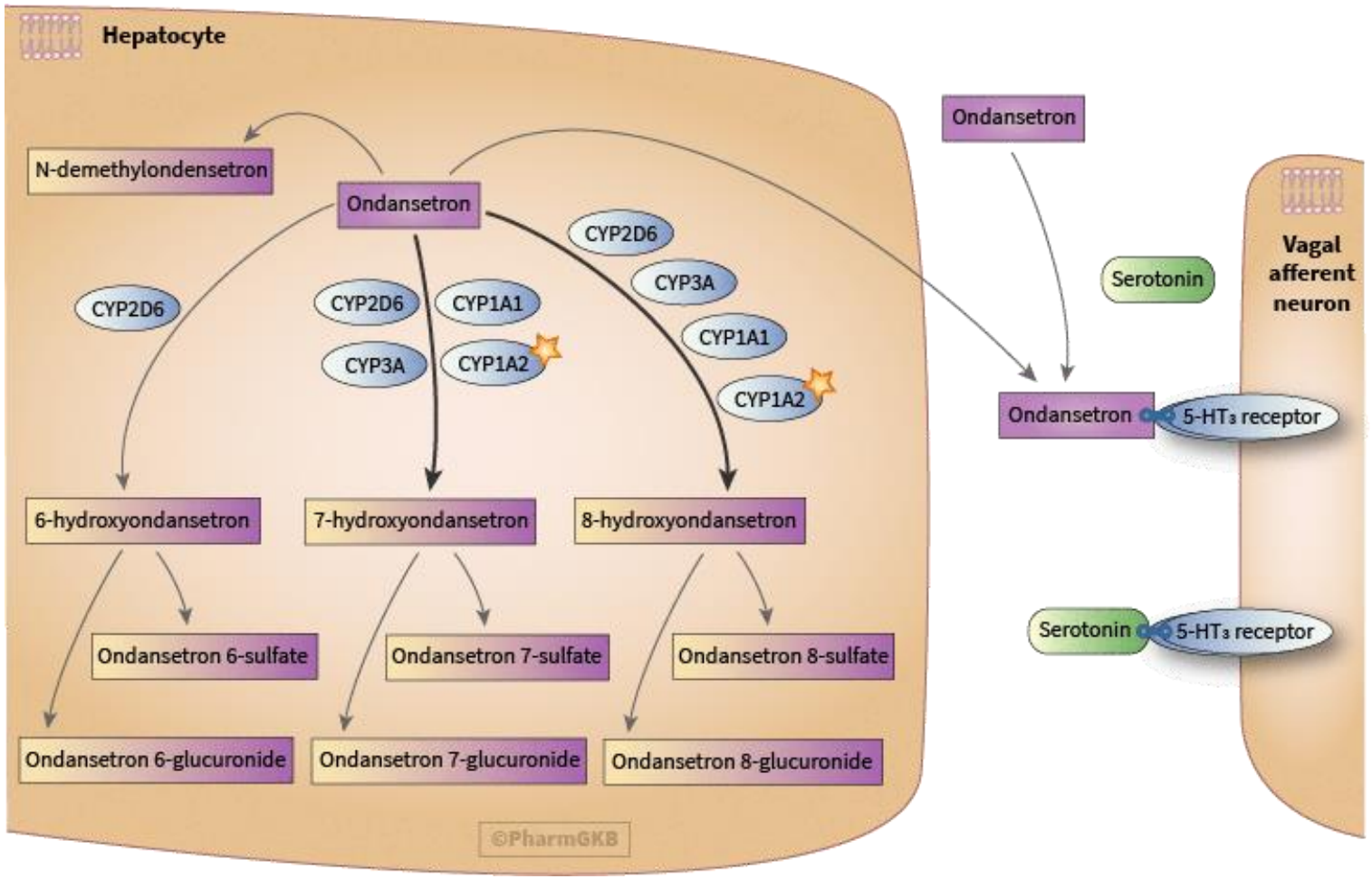
CYP2D6 Phenotype	Therapeutic Recommendations
Ultra-rapid metabolizer	Avoid tramadol use – potential for serious toxicity
Normal metabolizer	Use tramadol label recommended age-specific or weight-specific dosing
Intermediate metabolizer	Use tramadol label recommended age-specific or weight-specific dosing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

- 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

Crews KR, et al. *Clin Pharmacol Ther*. 2021;110(4):888-896.

Ondansetron

Ondansetron Metabolism



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.

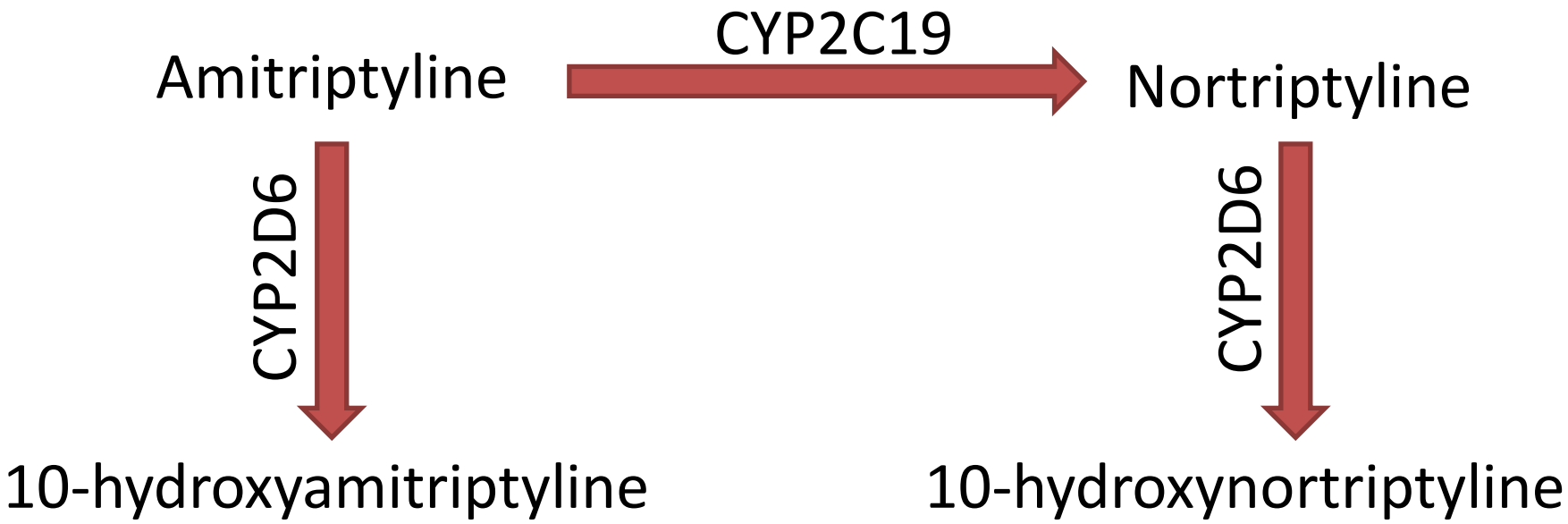
Ondansetron Therapeutic Recommendations

- CYP2D6 ultrarapid metabolizers have increased clearance of ondansetron which can lead to inadequate anti-emetic control

CYP2D6 Phenotype	Therapeutic Recommendations
Ultra-rapid metabolizer	Avoid ondansetron – consider granisetron or anti-emetic not metabolized by CYP2D6

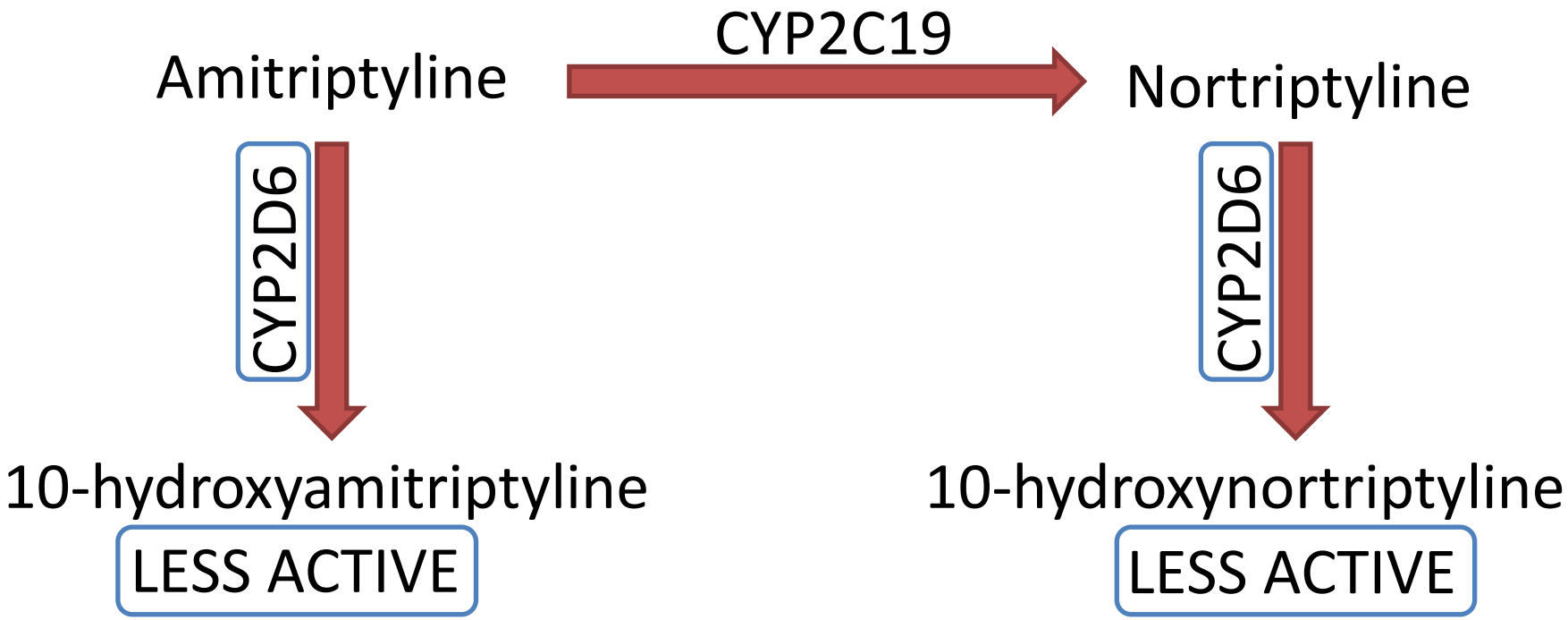
Amitriptyline

Amitriptyline Metabolism



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

Amitriptyline Metabolism



- **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

Tricyclic Antidepressant Therapeutic Recommendations

CYP2D6 Phenotype	Therapeutic Recommendations
Ultra-rapid metabolizer	Avoid tricyclic use – consider alternative drug not metabolized by CYP2D6
Normal metabolizer	Initiate therapy with recommended starting dose
Intermediate metabolizer	Consider 25% reduction of recommended starting dose
Poor metabolizer	Avoid tricyclic use – consider alternative drug not metabolized by CYP2D6

Hicks JK, et al. *Clin Pharmacol Ther.* 2017;102(1):37-44.

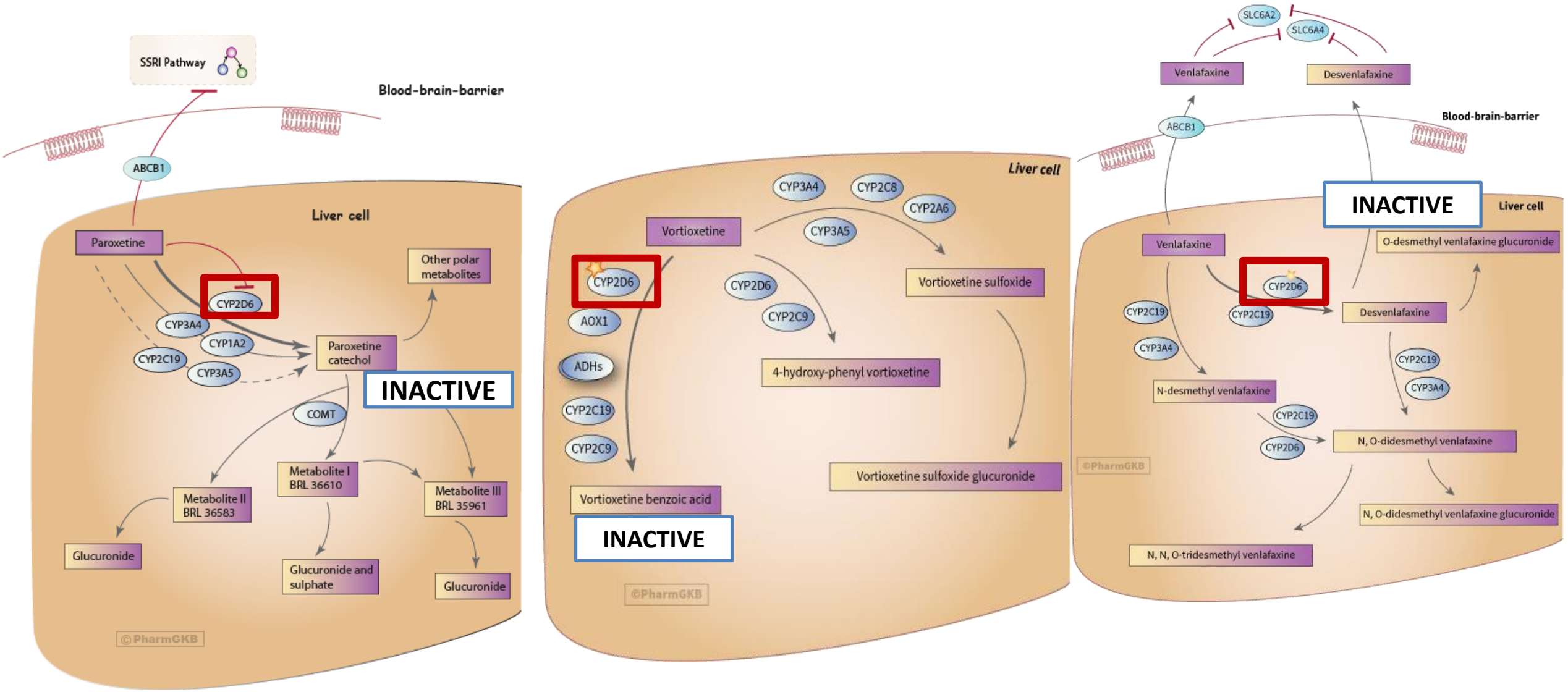
Summary of Tricyclic Antidepressant Therapeutic Recommendations Based on CYP2C19 and CYP2D6 Phenotypes

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

Adapted from: Hicks JK, et al. *Clin Pharmacol Ther.* 2017;102(1):37-44.

Selective Serotonin Reuptake Inhibitors

Paroxetine, vortioxetine, and venlafaxine are primarily metabolized by CYP2D6 to inactive metabolites



Whirl-Carillo M, et al. *Clin Pharmacol Ther*. 2021;110(13):563-572;
Sangkuhl K, et al. *Pharmacogenet Genomics*. 2014;22(1):62-72.

Selective-Serotonin Inhibitors

Medications	Mechanism of action	Indications	Adverse Effects
• Sertraline • Escitalopram • Citalopram • Paroxetine • Fluoxetine • Fluvoxamine	• Inhibit the reuptake of serotonin → increase serotonin activity	• Major depression disorder • Generalized anxiety disorder • Obsessive-compulsive disorder • Panic disorder • Posttraumatic stress disorder • Social anxiety disorder	• 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

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

Bousman CA, et al. *Clin Pharmacol Ther*. 2023;114(1):51-68.

Fluvoxamine Therapeutic Recommendations

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

Bousman CA, et al. *Clin Pharmacol Ther*. 2023;114(1):51-68.

Venlafaxine Therapeutic Recommendations

CYP2D6 Phenotype	Therapeutic Recommendations
Ultra-rapid metabolizer	No recommendation due to minimal evidence
Normal metabolizer	Initiate therapy with recommended starting dose
Intermediate metabolizer	No recommendation due to minimal evidence
Poor metabolizer	Avoid venlafaxine use – consider alternative drug not predominantly metabolized by CYP2D6

Bousman CA, et al. *Clin Pharmacol Ther*. 2023;114(1):51-68.

Vortioxetine Therapeutic Recommendations

CYP2D6 Phenotype	Therapeutic Recommendations
Ultra-rapid metabolizer	Avoid vortioxetine use – consider alternative drug not predominantly metabolized by CYP2D6
Normal metabolizer	Initiate therapy with recommended starting dose
Intermediate metabolizer	No recommendation due to minimal evidence
Poor metabolizer	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)

For More Information…

- 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*

Question #1

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

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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

Question #2

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

a) Paroxetine

b) Sertraline

c) Escitalopram

d) Citalopram

Question #2

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

Question #3

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b) Dispense ondansetron at package insert recommended doses

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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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