Cytochrome P450 2C19 (CYP2C19) Pharmacogenetic Competency

Updated on 6/2015

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Pre-test Question # 1

A patient has a reported pharmacogenetic test result of *CYP2C19 *1/*12*. What is the assigned phenotype?

a) Ultra-rapid metabolizer (UM)
b) Intermediate metabolizer (IM)
c) Poor metabolizer (PM)
d) Indeterminate

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Pre-test Question # 2

A patient with a reported pharmacogenetic test result of *CYP2C19 *2A/*2A* who is receiving clopidogrel is at ____ risk of suffering from an adverse cardiovascular event (e.g. thrombosis) due to treatment failure.

a) Increased
b) Moderate
c) Decreased

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Pre-test Question # 3

JH has an indication to start clopidogrel therapy. He has a reported pharmacogenetic test result of *CYP2C19 *2A/*3*. What is your recommendation to the physician regarding the use of clopidogrel?

a) Use clopidogrel at an increased dose
b) Use clopidogrel at a reduced dose
c) Use clopidogrel at a standard dose
d) Use an alternative antiplatelet agent

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Pre-test Question # 4

Which of the following statements is most correct about a *CYP2C19 *17/*17* genotype?

a) Patients convert clopidogrel to an inactive metabolite to a greater extent than **1/*1* and therefore a decrease in clopidogrel dose is recommended

b) Patients convert clopidogrel to an active metabolite to a greater extent than **1/*1* but no change in clopidogrel dose is recommended

c) Patients convert clopidogrel to an active metabolite to a lesser extent than **1/*1* and therefore a decrease in clopidogrel dose is recommended

d) Patients convert clopidogrel to an active metabolite to a lesser extent than **1/*1* and therefore a change in therapy is recommended

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Objectives

- **Upon completion of this competency, participants will be able to:**
  - **Recognize the different *CYP2C19* allele variants**
  - **Describe the different CYP2C19 phenotypes**
  - **Assign the correct phenotype based upon the allele variants**
  - **Make therapeutic recommendations for clopidogrel dosing based on a patient's predicted CYP2C19 phenotype**

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Patient Case

- A 74-year-old patient with severe coronary artery disease started on clopidogrel following a percutaneous coronary intervention (PCI).
- After multiple episodes of restenosis, clopidogrel resistance was suspected.
- Platelet reactivity testing measured while on clopidogrel returned was high (suggestive of resistance).
- *CYP2C19* genotyping revealed that the patient was homozygous for two non-functional alleles (*2/*2 genotype). The patient was classified as having a CYP2C19 poor metabolizer phenotype.
- Switched to prasugrel, reduction in platelet reactivity by 86% and no cardiovascular events since switching agents.

Rai M, et al. *Conn Med*. 2012;76(5):267-72.

CYP2C19 Pharmacogenetics

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CYP2C19

- **CYP2C19 is an enzyme that metabolizes some commonly prescribed drugs**

- **Metabolism by CYP2C19 can either activate or inactivate a drug**
  - **Clopidogrel is a prodrug that is metabolized to an active form by CYP2C19**
  - **Amitriptyline is metabolized by CYP2C19 to a less active form**

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CYP2C19

- **Genetic variations in the *CYP2C19* gene may lead to changes in metabolic activity of the CYP2C19 enzyme (increased or reduced function)**

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CYP2C19 Allele Variants

- ***CYP2C19* alleles are characterized into different groups:**
  - **Wild-type (normal function) alleles**
  - **Reduced function alleles**
  - **Increased function alleles**
  - **Uncharacterized alleles**

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CYP2C19 Allele Variants

- ***CYP2C19* wild-type (normal function) allele:**
  - **This allele encodes for CYP2C19 enzymes with normal metabolic function**
  - ****1***

Scott SA, et al. *Clin Pharmacol Ther.* 2013;94(3):317-23.

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CYP2C19 Allele Variants

- **Certain *CYP2C19* alleles are characterized as reduced function alleles**
  - **These alleles will encode for a CYP2C19 enzyme that has little or no metabolic function**

- **Reduced function *CYP2C19* alleles include:**
  - ***2, *2A, *2B, *3, *4, *5, *6, *7, *8**

Scott SA, et al. *Clin Pharmacol Ther.* 2013;94(3):317-23.

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CYP2C19 Allele Variants

- ***CYP2C19* has an allele characterized by a increased expression of the enzyme**
  - **This results in increased CYP2C19 metabolic activity compared to the wild-type (normal function) allele**

- **The *CYP2C19* gain-of-function allele that is test for the most in clinical practice is the **17* allele**

Scott SA, et al. *Clin Pharmacol Ther.* 2013;94(3):317-23.

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CYP2C19 Allele Variants

- **For certain *CYP2C19* alleles, the function of the enzyme is unknown and considered uncharacterized**

- ***CYP2C19* uncharacterized alleles include:**
  - ****9, *10, *12, *13, *14,*15***

Scott SA, et al. *Clin Pharmacol Ther.* 2013;94(3):317-23.
www.pharmgkb.org

Assigning a CYP2C19 Phenotype

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CYP2C19 Phenotypes

- **The assignment of CYP2C19 phenotype is based on the two alleles that the patient carries (also called genotype or diplotype)**
- **There are four CYP2C19 phenotypes**
  - **Ultra-rapid metabolizer (UM)**
  - **Extensive metabolizer (EM)**
  - **Intermediate metabolizer (IM)**
  - **Poor metabolizer (PM)**

Scott SA, et al. *Clin Pharmacol Ther.* 2013;94(3):317-23.

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CYP2C19 Phenotypes

Phenotype	Definition
Ultra-rapid Metabolizer (UM)	• Two copies of an increased function allele. • One copy of a normal function allele and one copy of an increased function allele.
Extensive Metabolizer (EM)	• Two copies of a normal function allele.
Intermediate Metabolizer (IM)	• One copy of a reduced function allele and one copy of a normal function allele. • One copy of an increased function allele (*17) with one copy of a reduced function allele (either *2, *2A and *2B).[1]
Poor Metabolizer (PM)	• Two copies of a reduced function allele.
Indeterminate	• Two copies of an indeterminate function allele. • One copy of an indeterminate function allele with one copy of a known function allele. • One copy of an increased function allele with one copy of a reduced function allele (other than *2, *2A and *2B).

[1.] As per the CYP2C19/Clopidogrel CPIC guideline update (2013): The currently available evidence indicates that the *17 gain-of-function allele is unable to completely compensate for the *2 loss-of-function allele; however, these data have not been consistently replicated and is therefore a provisional classification.

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CYP2C19 Phenotypes

- **Ultra-rapid Metabolizers (UM)**
  - **Have CYP2C19 enzyme function higher than normal**
  - **Approximately 17% of the population**
  - **Diplotype examples:**
    - ***17/*17**
    - ***1/*17**

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CYP2C19 Phenotypes

- **Extensive (normal) metabolizers (EM)**
  - **Have normal CYP2C19 enzyme function**
  - **Homozygous wild-type/normal**
  - **Approximately 43% of the population**
  - **Patient carrying two functional alleles**
  - **Diplotype examples:**
    - ****1/*1***

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CYP2C19 Phenotypes

- **Intermediate metabolizers (IM)**
  - **Have decreased CYP2C19 enzyme function. The activity is in between extensive and poor metabolizer patients**
  - **Approximately 30% of the population**
  - **Diplotype examples:**
    - ****1/*2A***
    - ****2A/*17***

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CYP2C19 Phenotypes

- **Poor metabolizers (PM)**
  - **Have little or no CYP2C19 enzyme function**
  - **Approximately 10% of the population**
  - **Patient carrying two reduced-function alleles**
  - **Diplotype examples:**
    - ****2A/*2A***
    - ****2A/*2B***

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CYP2C19 Phenotypes

- **Indeterminate**
  - **The expected phenotype cannot be determined based upon the *CYP2C19* genotype result**
  - **For example, a patient may have two copies of an indeterminate function allele or one copy of an indeterminate function allele and one copy of a known function allele**
    - ***1/*12***
    - ***12/*14***

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CYP2C19 Phenotypes

- **Phenotypes associated with *17 allele**
  - **Only a few diplotypes which include the *17 allele have known functional activity:**
    - ***1/*17* is assigned an ultra-rapid metabolizer phenotype**
    - ***2/*17, *2A/*17* and *2B/*17* are assigned an intermediate function phenotype**
  - ***17 plus any other allele is assigned an indeterminate phenotype**

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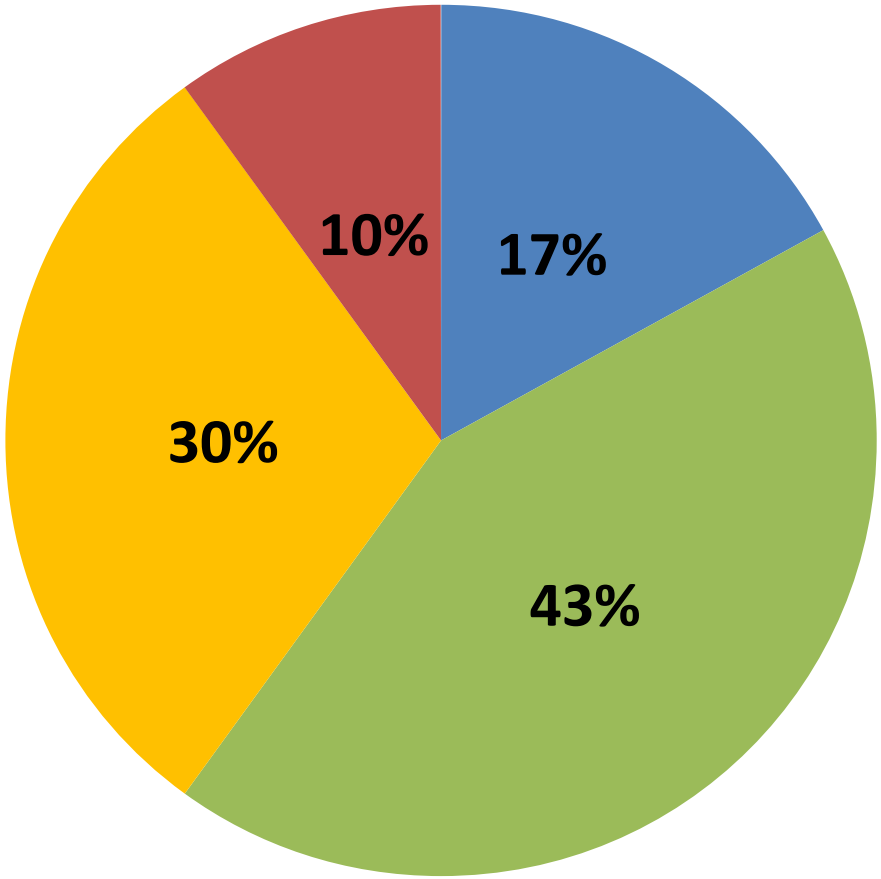
CYP2C19 Phenotypes



- Ultrarapid Metabolizer- very high activity
- Extensive Metabolizer-normal activity
- Intermediate Metabolizer- lower activity
- Poor Metabolizer- low or no activity

* The exact percent of each phenotype group varies by ethnicity

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CYP2C19 Phenotypes

- ***CYP2C19*** **allele frequencies are dependent on ethnicity**
- ***2 and *3 alleles are the most common variations**
  - ***2 allele:**
    - **~30% of Asians**
    - **~15% of Caucasians and African-Americans**
  - ***3 allele:**
    - **~8% of Asians**
    - **Less than 1% in Caucasians and African-Americans**
- **Prevalence of poor metabolizer phenotype:**
  - **Up to 25% of Asians**
  - **~5% of Caucasians and African-Americans**

Gene-Based Dosing Recommendations

Clopidogrel

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Clopidogrel

- **Clopidogrel is an antiplatelet drug which inhibits ADP-induced platelet aggregation**
- **Clopidogrel is commonly used in patients undergoing percutaneous coronary intervention (PCI) with stent placement**
- **Other indications:**
  - **Acute coronary syndrome (ACS)**
  - **Stroke**
  - **Peripheral artery disease**
- **The 2013 CPIC guideline on clopidogrel and CYP2C19 mainly focuses on ACS/PCI patients**

Scott SA, et al. *Clin Pharmacol Ther.* 2013;94(3):317-23.

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Clopidogrel

- **Clopidogrel is a pro-drug that requires hepatic bioactivation**
  - **85% of the drug is hydrolyzed by carboxylesterase 1, leaving only 15% to be converted to the active form**
- **The activation of clopidogrel is a two step process**
  - **Clopidogrel is converted to 2-oxoclopidogrel via CYP2C19 (45%), CYP1A2 (36%), and CYP2B6 (19%)**
  - **2-oxoclopidogrel is converted to the active thiol metabolite via CYP3A4/5 (40%), CYP2B6 (33%), CYP2C19 (21%), and CYP2C9 (7%)**

Scott SA, et al. *Clin Pharmacol Ther.* 2013;94(3):317-23.
Kazui M, et al. *Drug Metab Dispos.* 2010;38:92-99.

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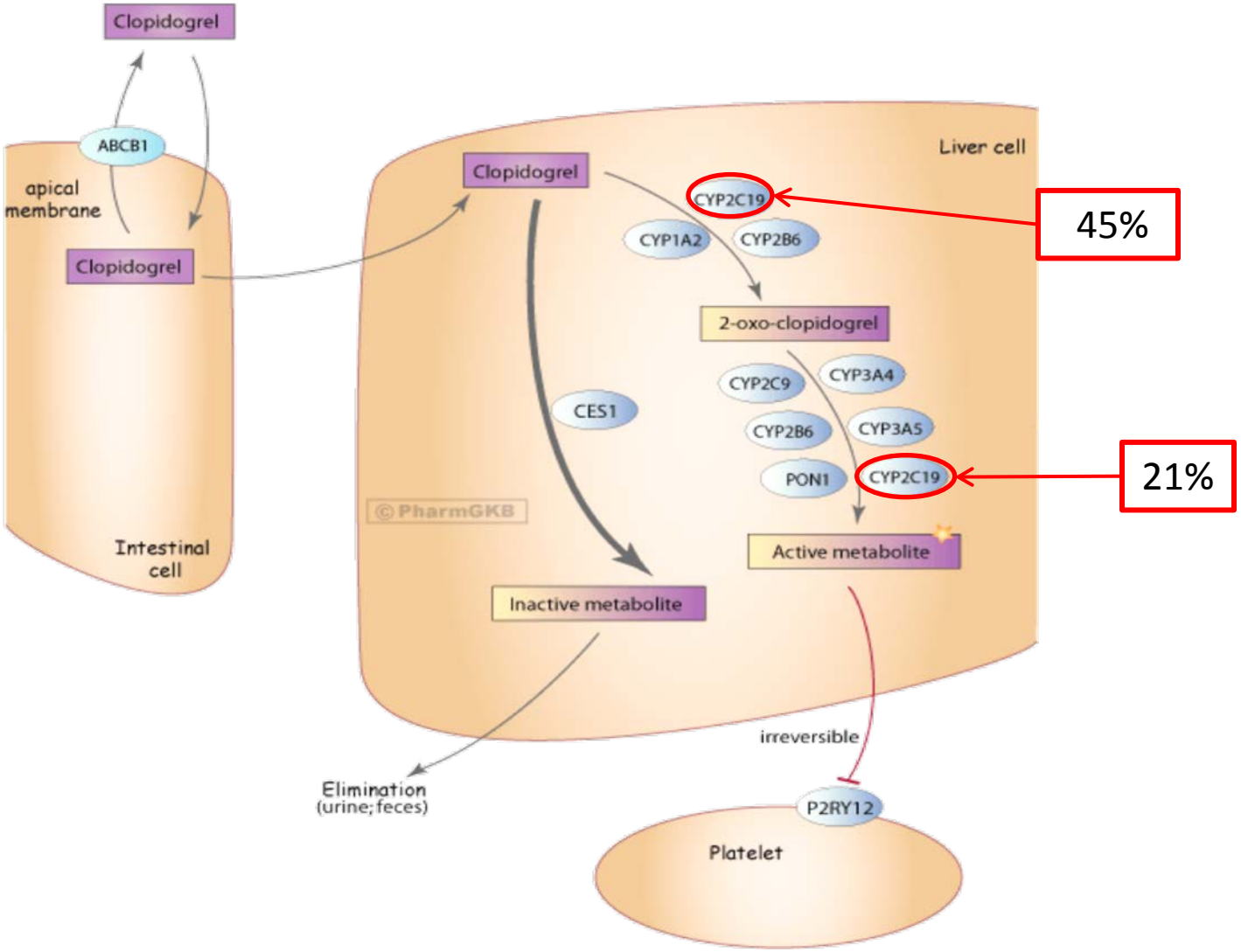
Clopidogrel



Sangkuhl K, et al. *Pharmacogenet Genomics* 2010;20:463-465.

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Clopidogrel

- **Clopidogrel's anti-platelet effect is closely related to CYP2C19 metabolism**
  - **<u>Ultra-rapid metabolizers</u>**
    - **Convert clopidogrel to the active metabolite at a greater extent than normal**
    - **Possible increase in antiplatelet activity**
    - **No recommended dosage change**
  - **<u>Extensive metabolizers</u>**
    - **Normal bioactivation**
    - **No recommended dosage change**

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Clopidogrel

- **Clopidogrel anti-platelet effect is closely related to CYP2C19 metabolism**
  - **<u>Intermediate metabolizers</u>**
    - **Reduced bioactivation of clopidogrel to the active metabolite**
    - **Decreased platelet inhibition leading to increased residual platelet aggregation**
    - **Increased risk for adverse cardiovascular events (e.g., thrombosis)**
- **CYP2C19 intermediate metabolizers generally should NOT receive clopidogrel**
  - **Consider alternatives such as prasugrel or ticagrelor**

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Clopidogrel

- **Clopidogrel anti-platelet effect is closely related to CYP2C19 metabolism**
  - **<u>Poor metabolizers</u>**
    - **Poor bioactivation of clopidogrel to the active metabolite**
    - **Significantly reduced platelet inhibition leading to increased residual platelet aggregation**
    - **Significant increased risk for adverse cardiovascular events (e.g., thrombosis)**
- **CYP2C19 poor metabolizers should NOT receive clopidogrel**
  - **Consider alternatives such as prasugrel or ticagrelor**

Amitriptyline

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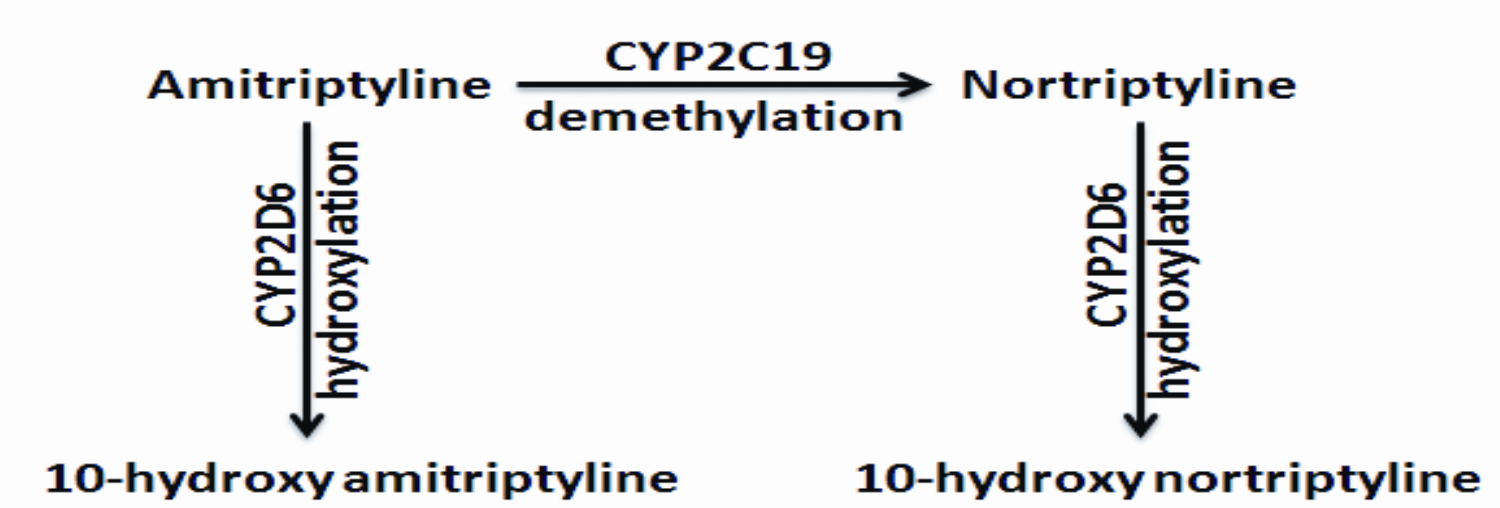
Amitriptyline



- **CYP2C19 metabolizes amitriptyline to an active metabolite: nortriptyline**

- **CYP2D6 metabolizes amitriptyline and nortriptyline to less active hydroxy-metabolites**

Hicks JK, et al. *Clin Pharmacol Ther.* 2013;93(5):402-8.

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Amitriptyline

- **Amitriptyline's efficacy is closely related to CYP2D6 and CYP2C19 metabolism**
  - **<u>Ultra-rapid metabolizers of CYP2C19 and/or CYP2D6</u>**
    - **Convert amitriptyline to nortriptyline at a greater extent than extensive metabolizers (for CYP2C19)**
    - **Increased metabolism of amitriptyline to less active compounds compared to extensive metabolizers (for CYP2D6)**
    - **Lower plasma concentrations increase the probability of therapeutic failure**
    - **Consider an alternative agent not metabolized by CYP2C19 or CYP2D6**

Hicks JK, et al. *Clin Pharmacol Ther.* 2013;93(5):402-8.

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Amitriptyline

- **Amitriptyline's efficacy is closely related to CYP2D6 and CYP2C19 metabolism**
  - **<u>Extensive metabolizers of CYP2C19 or CYP2D6</u>**
    - **Normal bioactivation**
    - **No recommended dosage change**

Hicks JK, et al. *Clin Pharmacol Ther.* 2013;93(5):402-8.

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Amitriptyline

- **Amitriptyline's efficacy is closely related to CYP2D6 and CYP2C19 metabolism**
  - **<u>Intermediate metabolizers of CYP2C19 or CYP2D6</u>**
    - **Reduced metabolism of amitriptyline when compared to extensive metabolizers**
    - **For CYP2D6 IM patients, consider a 25% reduction of the initial amitriptyline dose and titrate to effect. Utilize therapeutic drug monitoring as appropriate**
    - **For CYP2C19 IM patients, initiate therapy with the recommended starting doses of amitriptyline**

Hicks JK, et al. *Clin Pharmacol Ther.* 2013;93(5):402-8.

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Amitriptyline

- **Amitriptyline's efficacy is closely related to CYP2D6 and CYP2C19 metabolism**
  - **<u>Poor metabolizers of CYP2C19 or CYP2D6</u>**
    - **Greatly reduced metabolism of amitriptyline when compared to extensive metabolizers and an increased likelihood of side effects**
    - **Consider an alternative agent not metabolized by CYP2C19 or CYP2D6**
- **A table providing recommendations for dosing of amitriptyline according to the *CYP2D6* and *CYP2C19* genotype test results can be found here**

Hicks JK, et al. *Clin Pharmacol Ther.* 2013;93(5):402-8.

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For More Information…

- **For more information about CYP2C19 and clopidogrel dosing click here.**
- **For more information about CYP2C19 and amitriptyline dosing click here.**
- **For more information about pharmacogenetics visit the following website: www.pharmgkb.org**
- **For more pharmacogenetic service implementation resources visit the following website: www.stjude.org/pg4kds/implement**

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Question # 1

A patient has a reported pharmacogenetic test result of *CYP2C19 *1/*12*. What is the assigned phenotype?

a) Ultra-rapid metabolizer (UM)
b) Intermediate metabolizer (IM)
c) Poor metabolizer (PM)
d) Indeterminate

Correct answer: d

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Question # 2

A patient with a reported pharmacogenetic test result of *CYP2C19 *2A/*2A* who is receiving clopidogrel is at ____ risk of suffering from an adverse cardiovascular event (e.g. thrombosis) due to treatment failure.

a) Increased
b) Moderate
c) Decreased

Correct answer: a

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Question # 3

JH has an indication to start clopidogrel therapy. He has a reported pharmacogenetic test result of *CYP2C19 *2A/*3*. What is your recommendation to the physician regarding the use of clopidogrel?

a) Use clopidogrel at an increased dose
b) Use clopidogrel at a reduced dose
c) Use clopidogrel at a standard dose
d) Use an alternative antiplatelet agent

Correct answer: d

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Question # 4

Which of the following statements is most correct about a *CYP2C19 *17/*17* genotype?

a) Patients convert clopidogrel to an inactive metabolite to a greater extent than **1/*1* and therefore a decrease in clopidogrel dose is recommended

b) Patients convert clopidogrel to an active metabolite to a greater extent than **1/*1* but no change in clopidogrel dose is recommended

c) Patients convert clopidogrel to an active metabolite to a lesser extent than **1/*1* and therefore a decrease in clopidogrel dose is recommended

d) Patients convert clopidogrel to an active metabolite to a lesser extent than **1/*1* and therefore a change in therapy is recommended

Correct answer: b

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