Cytochrome P450 2D6 (CYP2D6) Pharmacogenetic Competency

Updated on 6/2015

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Pre-test Question # 1

What is the activity score for the pharmacogenetic test result of *CYP2D6 (*1/*1)2N*?

a) 0.5
b) 1.0
c) 1.5
d) 2.0

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Pre-test Question # 2

What is the predicted CYP2D6 phenotype for the test result of *CYP2D6 (*2/*17)2N*?

a) Ultra-rapid metabolizer
b) Extensive metabolizer
c) Intermediate metabolizer
d) Poor metabolizer

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Pre-test Question # 3

ZB is experiencing pain following a minor surgical procedure. A clinician wants to prescribe codeine to treat the pain and asks you for the appropriate dose. The patient has a pharmacogenetic test result of *CYP2D6 (*4/*4)* duplication.

Based on the pharmacogenetic test result, what recommendation would you give to the clinician?

a) Use label recommended dosing
b) Reduce the initial starting codeine dose by 50%
c) Avoid codeine due an increased risk of adverse events
d) Avoid codeine due to a lack of analgesic effects

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Pre-test Question # 4

MJ is about to be prescribed amitriptyline for treatment of depression. The patient has a reported pharmacogenetic test result of *CYP2D6 (*1/*4)2N*. Based on the pharmacogenetic test result, which of the following statements is correct?

a) The patient should not receive amitriptyline due to decreased plasma concentrations of the drug and likely therapeutic failure

b) The patient should not receive amitriptyline due to increased plasma concentrations of the drug and likely development of side effects

c) There is no reason to adjust the dose of amitriptyline based on the *CYP2D6* genotype test result

d) The patient's initial dose should be increased by 25%

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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**

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Patient Case

- A 14-year old girl received a prescription for a codeine-containing analgesic for hip pain.
- The patient received 15 mg of codeine and the mother noticed that she was having trouble breathing, gasping and opening her mouth widely to search for air.
- She was admitted to the ER and given a dose of naloxone which seemed to relieve the symptoms.
- Genotyping revealed that she a *CYP2D6 *4/*5* genotype. The patient was assigned a CYP2D6 poor metabolizer phenotype.

Shaw KD, et al. *Ther Drug Monit*. 2012;34:121-3.

CYP2D6 Pharmacogenetics

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CYP2D6 Enzyme

- **CYP2D6 is an enzyme that metabolizes many commonly prescribed drugs**

- **Metabolism by CYP2D6 can either activate or inactivate a drug:**
  - **Codeine is a prodrug that is metabolized to an active form (morphine) by CYP2D6**
  - **Amitriptyline is metabolized by CYP2D6 to a less active form**

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CYP2D6

- **Genetic variations in the *CYP2D6* gene may lead to changes in metabolic activity of the CYP2D6 enzyme (increased or reduced activity)**

- **For certain medications, such as codeine, dose adjustments or an alternative therapy may be necessary in instances where metabolic activity is altered**

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CYP2D6 Allele Variants

- **Certain *CYP2D6* alleles are characterized as wild-type (normal function) alleles**
  - **These alleles will encode for CYP2D6 enzymes that will have normal (extensive) metabolic activity**

- ***CYP2D6* wild-type (normal) function alleles include:**
  - ****1*, **2*, and **2A***

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CYP2D6 Allele Variants

- **Certain *CYP2D6* alleles are characterized as reduced function alleles**
  - **These alleles will encode for CYP2D6 enzymes that have less metabolic activity than wild-type (normal function) alleles**

- ***CYP2D6* reduced function alleles include:**
  - ****9, *10, *17, *29,* and **41***

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CYP2D6 Allele Variants

- **Certain *CYP2D6* alleles are characterized as non-functional alleles**
  - **These alleles will encode for CYP2D6 enzymes that have little or no metabolic activity**

- ***CYP2D6* non-functional alleles include:**
  - ****3, *4, *5, *6, *7, *8, *11, *12, *14, *14A, *14B, *15, *18, *19, *20, *21, *38, *40, *42, *44, *56, *56A, *56B***
  - **Please note that *5 is the nomenclature for a deleted allele**

Gaedigk A, et al. *Clin Pharmacol Ther.* 2008;83:234-42.
Crews KR, et al. *Clin Pharmacol Ther.* 2014;95:376-82.
http://www.cypalleles.ki.se/cyp2d6.htm

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CYP2D6 Allele Variants

- **If no variant alleles are detected, the reference lab (e.g., ARUP) may report the result as "negative"**
  - **A negative result is the same as *CYP2D6*1***

CYP2D6 Activity Score

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CYP2D6 Copy Number

- **Most patients have two copies of the *CYP2D6* gene, one allele inherited from the maternal parent and one allele inherited from the paternal parent**
- **A small percentage of patients will have multiple copies of a *CYP2D6* gene, the result will display in two different ways in the medical record:**
  - **Some reference laboratories will give an exact copy number (*xN)***
    - **The result of "*xN*" does NOT indicate which allele is duplicated**
  - **Some reference laboratories display the result as "duplication"**
    - **The result of "duplication" does NOT indicate the exact number of alleles present or which allele is duplicated**

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CYP2D6 Copy Number

- **A small percentage of patients will have one or both *CYP2D6* genes deleted, indicated by the **5* allele. For example:**
  - ****1/*5*** **patients will have one copy of a functional (*1) allele and one deleted allele (*5)**
  - ****5/*5*** **patients will have both *CYP2D6* alleles deleted**

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CYP2D6 Activity Score Calculation

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

Activity value	Alleles	Type of Allele
1	*1, *2, *2A, *27, *33, *35, *45, *39, *48, *53	Wild-type
0.5	*9, *10, *17, *29, *41, *49, *50, *54, *55, *59, *69, *72	Reduced function
0	*3, *4, *5, *6, *7, *8, *11, *12, *13, *14, *14A, *14B, *15, *16, *18, *19, *20, *21, *31, *36, *38, *40, *42, *44, *47, *51, *56, *56A, *56B, *57, *62	Non-functional

- **CYP2D6 activity score is calculated by adding up the activity value for each allele as follows:**

Activity score for *CYP2D6 (*1/*2A)2N* = 1 + 1 = <u>2</u>

Activity score for *CYP2D6 (*2/*10)2N* = 1 + 0.5 = <u>1.5</u>

Activity score for *CYP2D6 (*4/*4)2N* = 0 + 0 = <u>0</u>

Activity score for *CYP2D6 (*3/*9)2N* = 0 + 0.5 = <u>0.5</u>

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

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CYP2D6 Activity Score

- **When duplicated alleles are reported, the reference laboratory may not:**
  - **Indicate which allele is duplicated**
  - **Quantify the number of additional *CYP2D6* allele copies**

- **For the purpose of calculating a CYP2D6 activity score when a duplication is reported, assume the patient has 1 additional CYP2D6 allele (a total of 3 copies of the gene)**

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CYP2D6 Activity Score

- **For a result of *CYP2D6* (**4/*9*) duplication:**
  - **The patient may have two **4* alleles and one **9* allele (for a total of 3 alleles)**

OR

  - **The patient may have one **4* allele and two **9* alleles (for a total of 3 alleles)**

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CYP2D6 Activity Score Calculation

Activity value	Alleles	Type of Allele
1	*1, *2, *2A, *27, *33, *35, *45, *39, *48, *53	Wild-type
0.5	*9, *10, *17, *29, *41, *49, *50, *54, *55, *59, *69, *72	Reduced function
0	*3, *4, *5, *6, *7, *8, *11, *12, *13, *14, *14A, *14B, *15, *16, *18, *19, *20, *21, *31, *36, *38, *40, *42, *44, *47, *51, *56, *56A, *56B, *57, *62	Non-functional

What is the CYP2D6 activity score for the result of *CYP2D6* (4/*9*) duplication?**

1. **First, we assume 3 alleles are present but do not know which allele is duplicated**
2. **What are the possibilities?**

   ****4* + **4* + **9* (3 alleles total)**

   OR

   ****4* + **9* + **9* (3 alleles total)**

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

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CYP2D6 Activity Score Calculation

Activity value	Alleles	Type of Allele
1	*1, *2, *2A, *27, *33, *35, *45, *39, *48, *53	Wild-type
0.5	*9, *10, *17, *29, *41, *49, *50, *54, *55, *59, *69, *72	Reduced function
0	*3, *4, *5, *6, *7, *8, *11, *12, *13, *14, *14A, *14B, *15, *16, *18, *19, *20, *21, *31, *36, *38, *40, *42, *44, *47, *51, *56, *56A, *56B, *57, *62	Non-functional

3. Calculate the different possibilities

If **4* is duplicated:

****4* + **4* + **9* = 0 + 0 + 0.5 = <u>0.5</u>**

If **9* is duplicated:

****4* + **9* + **9* = 0 + 0.5 + 0.5 = <u>1.0</u>**

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

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CYP2D6 Activity Score

What is the CYP2D6 activity score for a diplotype result of **4/*9* with a duplication?

The activity score will range from 0.5-1.0

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CYP2D6 Activity Score

- **A reference laboratory may report the exact allele copy number but may NOT indicate which allele is duplicated**
  - **For the result of *(*2A/*10)3N***
    - **We already know that the patient has at least one **2A* allele and at least one **10* allele. Because there are three alleles present, indicated by *3N*, there will be an additional copy of either **2A* or **10***

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CYP2D6 Activity Score Calculation

Activity value	Alleles	Type of Allele
1	*1, *2, *2A, *27, *33, *35, *45, *39, *48, *53	Wild-type
0.5	*9, *10, *17, *29, *41, *49, *50, *54, *55, *59, *69, *72	Reduced function
0	*3, *4, *5, *6, *7, *8, *11, *12, *13, *14, *14A, *14B, *15, *16, *18, *19, *20, *21, *31, *36, *38, *40, *42, *44, *47, *51, *56, *56A, *56B, *57, *62	Non-functional

What is the activity score for a *CYP2D6* diplotype result of (*2A/*10)3N?

1. **First, we do not know which allele is duplicated**
2. **What are the possibilities?**

***2A + *2A + *10 (3 total)**

OR

***2A + *10 + *10 (3 total)**

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

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CYP2D6 Activity Score Calculation

Activity value	Alleles	Type of Allele
1	*1, *2, *2A, *27, *33, *35, *45, *39, *48, *53	Wild-type
0.5	*9, *10, *17, *29, *41, *49, *50, *54, *55, *59, *69, *72	Reduced function
0	*3, *4, *5, *6, *7, *8, *11, *12, *13, *14, *14A, *14B, *15, *16, *18, *19, *20, *21, *31, *36, *38, *40, *42, *44, *47, *51, *56, *56A, *56B, *57, *62	Non-functional

3. Calculate the different possibilities

If **10* is duplicated :

****2A* + **10* + **10* = 1 + 0.5 + 0.5 = <u>2.0</u>**

If **2A* is duplicated:

****2A* + **2A* + **10* = 1 + 1 + 0.5 = <u>2.5</u>**

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

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CYP2D6 Activity Score

What is the CYP2D6 activity score for a diplotype result of **2A/*17* duplicated ?

The activity score will range from 2.0-2.5

Assigning a CYP2D6 Phenotype

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CYP2D6 Phenotypes

- There are four CYP2D6 phenotypes
  - Ultra-rapid metabolizer (UM)
  - Extensive metabolizer (EM)
  - Intermediate metabolizer (IM)
  - Poor metabolizer (PM)

- In some cases the *CYP2D6* genotype result may be ambiguous and additional phenotype terminology is needed including
  - Possible ultra-rapid metabolizer
  - Possible intermediate metabolizer
  - Possible poor metabolizer

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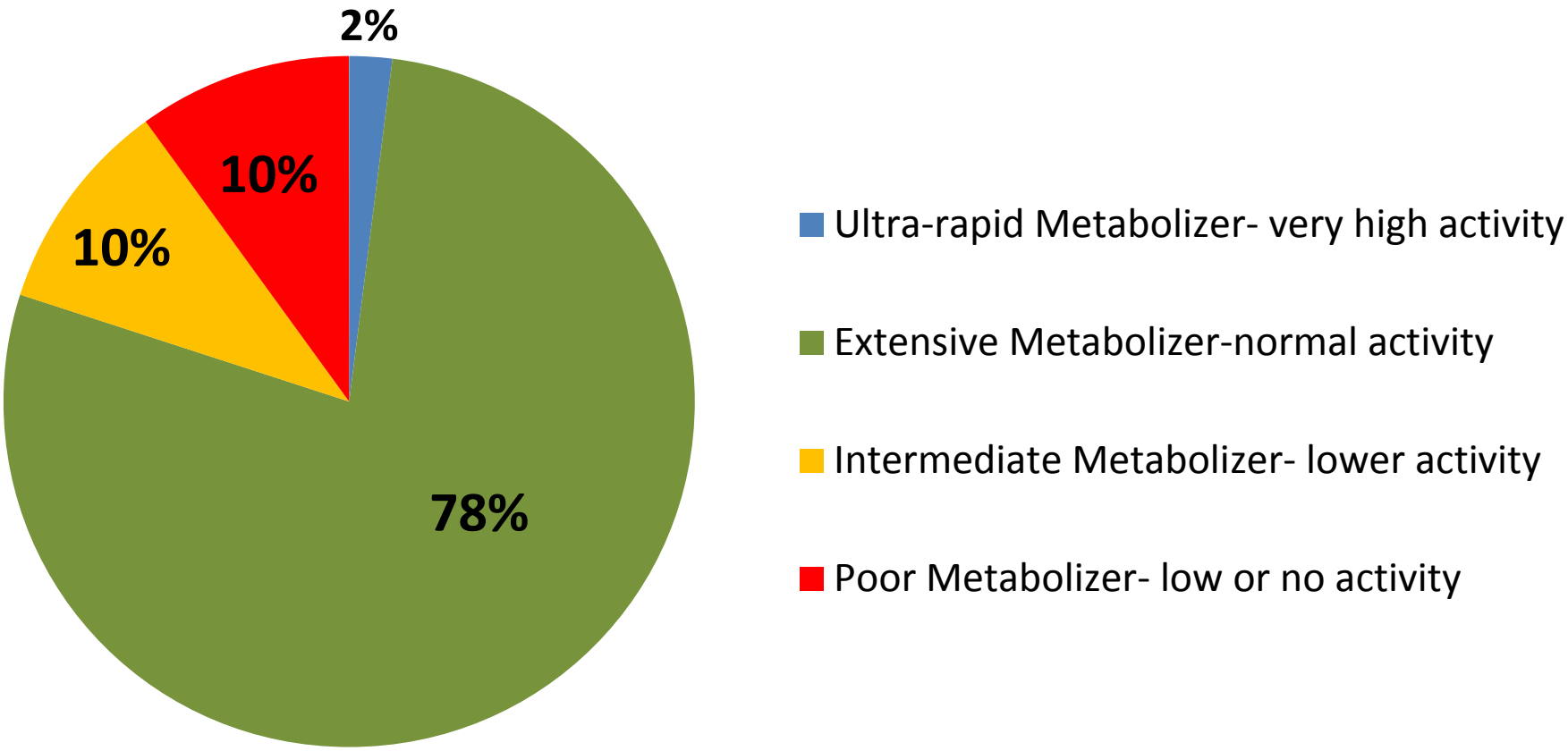
Percentage of CYP2D6 Phenotypes in the Population



*** The exact percent of each phenotype group varies by ethnicity**

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CYP2D6 Phenotype Assignment

CYP2D6 activity score	Phenotype
>2	Ultra-rapid metabolizer
1-2	Extensive metabolizer
0.5	Intermediate metabolizer
0	Poor metabolizer

- **Please note that reference laboratories or other institutions may have different guidelines for assigning a CYP2D6 phenotype**

- **In particular, some reference laboratories and institutions may classify a patient with a CYP2D6 activity score of 1.0 as an intermediate metabolizer**

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

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CYP2D6 Phenotype Assignment

CYP2D6 activity score	Phenotype
>2	Ultra-rapid metabolizer
1-2	Extensive metabolizer
0.5	Intermediate metabolizer
0	Poor metabolizer

- **If an activity score (e.g. 2.0-2.5) indicates the patient MAY be an ultra-rapid metabolizer, the phenotype assigned will be: CYP2D6 possible ultra-rapid metabolizer**
- **If an activity score (e.g. 0-0.5) indicates the patient MAY be a poor metabolizer, the phenotype assigned will be: CYP2D6 possible poor metabolizer**

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CYP2D6 Allele Variants

- ***CYP2D6*** **is highly polymorphic, with over 100 known allele variants**
  - **The majority of these allele variants are very rare and not routinely tested for**
- **Note that a patient may have an allele variant that is not tested for**
  - **If variants are not tested for, the patient is assumed to have wild-type alleles (*CYP2D6**1)**
  - **Therefore, a small chance exists that the assigned phenotype (based on the genotype test) may be wild-type but the patient may actually have a rare inactivating variant that makes the actual phenotype poor or intermediate metabolizer**
- **This is a rare risk for any genetic test**

http://www.cypalleles.ki.se/cyp2d6.htm

Gene-Based Dosing Recommendations

Codeine

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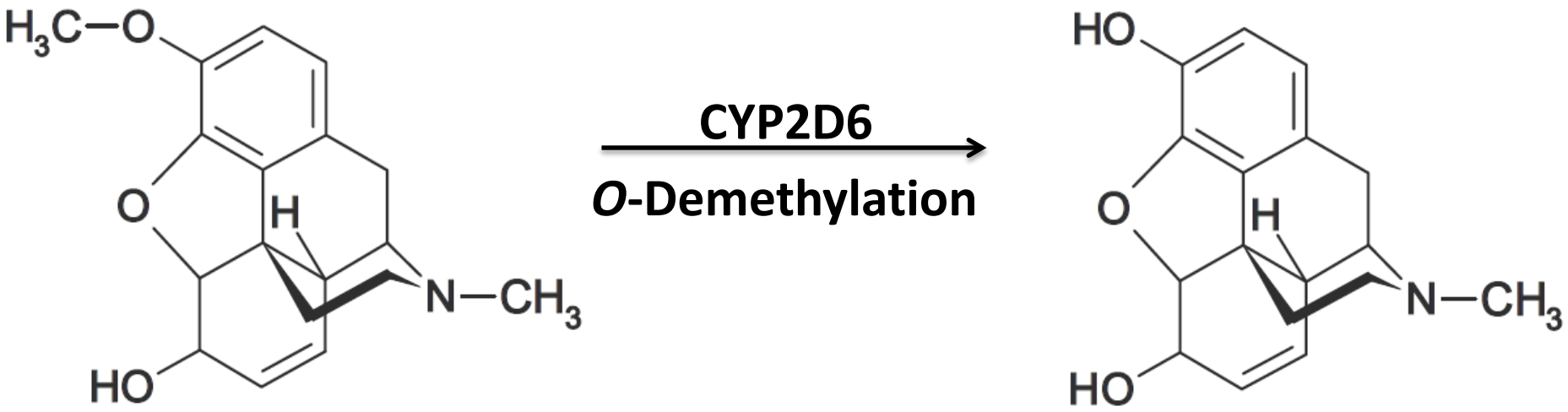
Codeine



Codeine **Morphine**

CYP2D6 metabolizes codeine to the active metabolite morphine

Lotsch J, et al. *Clin Pharmacol Ther.* 2006;79:35-48.

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Codeine

- **Codeine analgesia is closely related to CYP2D6 metabolism**
  - **Ultra-rapid metabolizers**
    - **Convert codeine to morphine at a greater extent than normal leading to an increased risk of toxic side effects, such as over sedation or respiratory depression**
    - **Because infants may be more susceptible to adverse effects from morphine, breastfeeding mothers who are ultra-rapid metabolizers should NOT take codeine**
- **CYP2D6 ultra-rapid metabolizers should NOT receive codeine**

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

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Codeine

- **Codeine analgesia is closely related to CYP2D6 metabolism**
  - **Poor metabolizers**
    - **Cannot activate the prodrug codeine to morphine and will have no analgesic benefit**
- **CYP2D6 poor metabolizers should NOT receive codeine**
- **Oxycodone and tramadol are not a good choice in CYP2D6 ultra-rapid and poor metabolizers because they are also affected by CYP2D6 (hydrocodone is affected by CYP2D6 but to a much lesser extent)**

Tramadol

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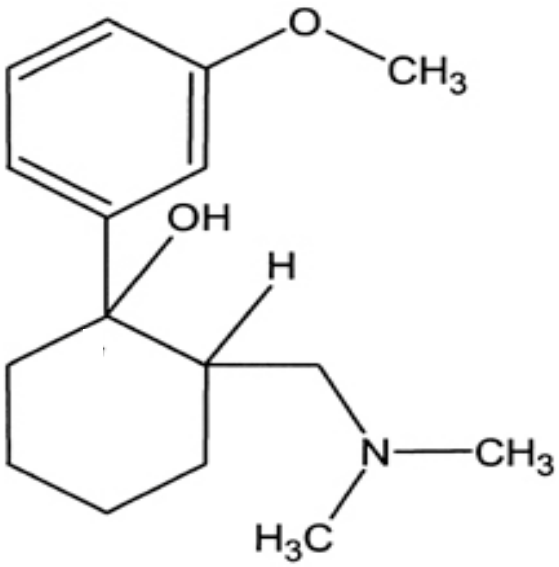
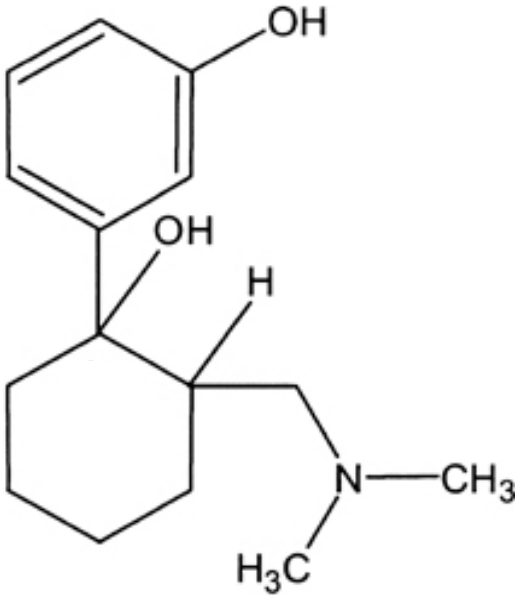
Tramadol



Tramadol

CYP2D6

***O*-Demethylation**



O-desmethyltramadol

CYP2D6 metabolizes tramadol to a more active metabolite O-desmethyltramadol

Pedersen RS, et al. *Clin Pharmacol Ther.* 2005;77:458-67.

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Tramadol

Tramadol analgesia is related to CYP2D6 metabolism

- **Ultra-rapid metabolizers**
  - **Convert tramadol to O-desmethyltramadol at a greater extent than normal leading to an increased risk of side effects**
- **Poor metabolizers**
  - **Cannot metabolize tramadol to the more active form O-desmethyltramadol, therefore resulting in little to no analgesic benefit**

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Tramadol

- **CYP2D6 extensive and intermediate metabolizers may receive the usual dose of tramadol**
  - **Monitor intermediate metabolizers for analgesic response**

- **Similar to codeine, CYP2D6 ultra-rapid and poor metabolizers should NOT receive tramadol**

Oxycodone

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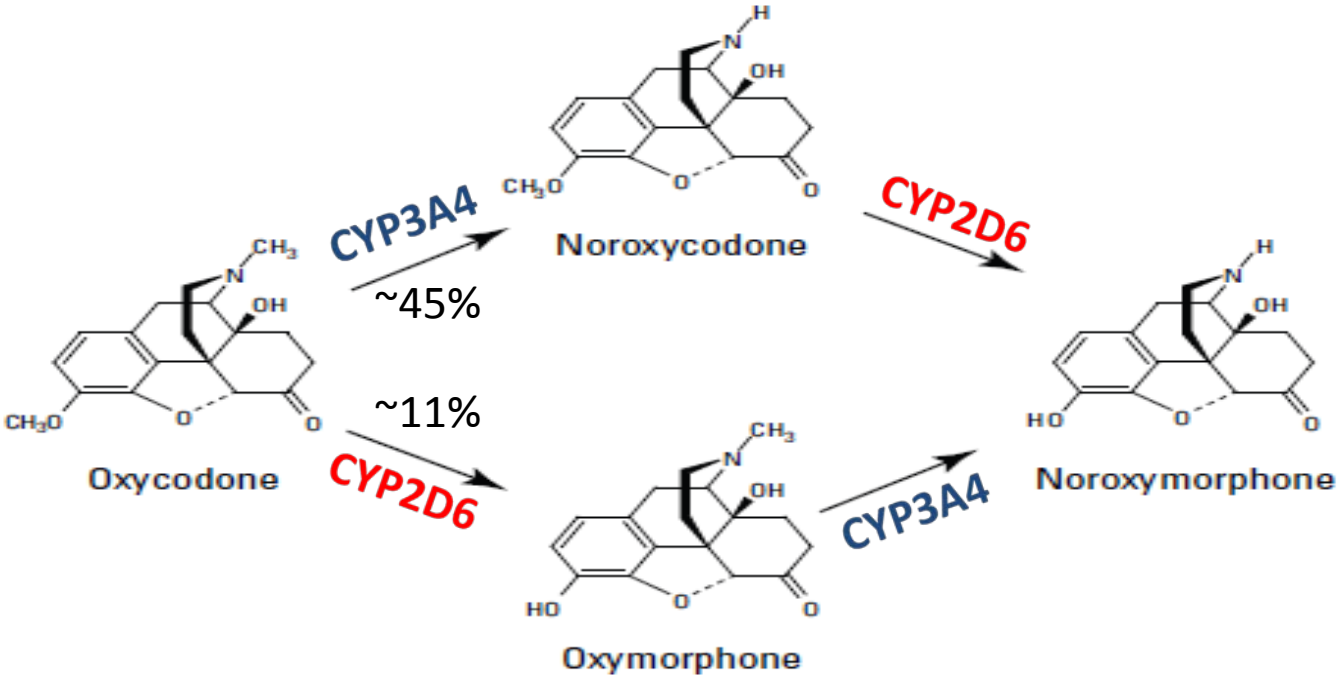
Oxycodone



- **CYP2D6 metabolizes oxycodone to the active metabolite oxymorphone**
- **Oxymorphone is a potent opioid that has a 3 to 5 times higher μ-opioid receptor affinity than morphine**
- **When compared to morphine, oxymorphone has a higher affinity for the μ-opioid receptor than the parent compound oxycodone**

Vuilleumier PH, et al. *Pharmgenomics Pers Med*. 2012;5:73-87.
http://www.chem.agilent.com/Library/applications/5990-3815EN.pdf

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Oxycodone

- **Oxycodone analgesia is related to CYP2D6 metabolism**
  - **Ultra-rapid metabolizers**
    - **Convert oxycodone to oxymorphone at a greater extent than normal leading to an increased risk of toxic side effects, such as over sedation or respiratory depression**
    - **Other pain medications such as morphine, HYDROmorphone (e.g.: Dilaudid®), or acetaminophen/hydroCODONE (e.g. Lortab®, Vicodin®) should be considered**

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Oxycodone

- **Oxycodone analgesia is related to CYP2D6 metabolism**
  - **Extensive/Intermediate metabolizers**
    - **No dosage change**
  - **Poor metabolizers**
    - **Other pain medications such as morphine, HYDROmorphone (e.g.: Dilaudid®), or acetaminophen/hydroCODONE (e.g.: Lortab®, Vicodin®) should be considered**

Ondansetron

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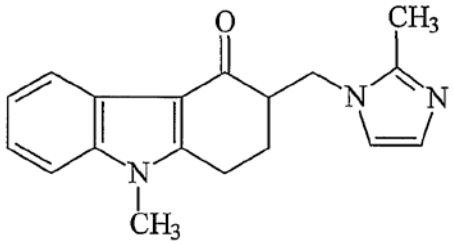
Ondansetron



CYP1A2
CYP3A4/5
CYP2D6
CYP1A1

CYP3A4/5
CYP2D6
CYP1A1
CYP1A2

CYP3A4/5
CYP2D6
CYP1A1
CYP1A2

7-hydroxy ondansetron
8-hydroxy ondansetron
(major)

N-desmethyl ondansetron
(minor)

6-hydroxy ondansetron
(minor)

Glucuronide or Sulfate conjugation

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.

Dixon CM, et al. *Drug Metab Dispos.* 1995;23:1225-30.
Fischer V, et al. *Drug Metab Dispos*. 1994;22:269-74.

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Ondansetron

- CYP2D6 ultra-rapid metabolizers have increased metabolism and therapeutic failure is possible. Consider another drug not metabolized by CYP2D6 such as granisetron.
- Data are not convincing that CYP2D6 poor metabolizers have more adverse effects to ondansetron.

Amitriptyline

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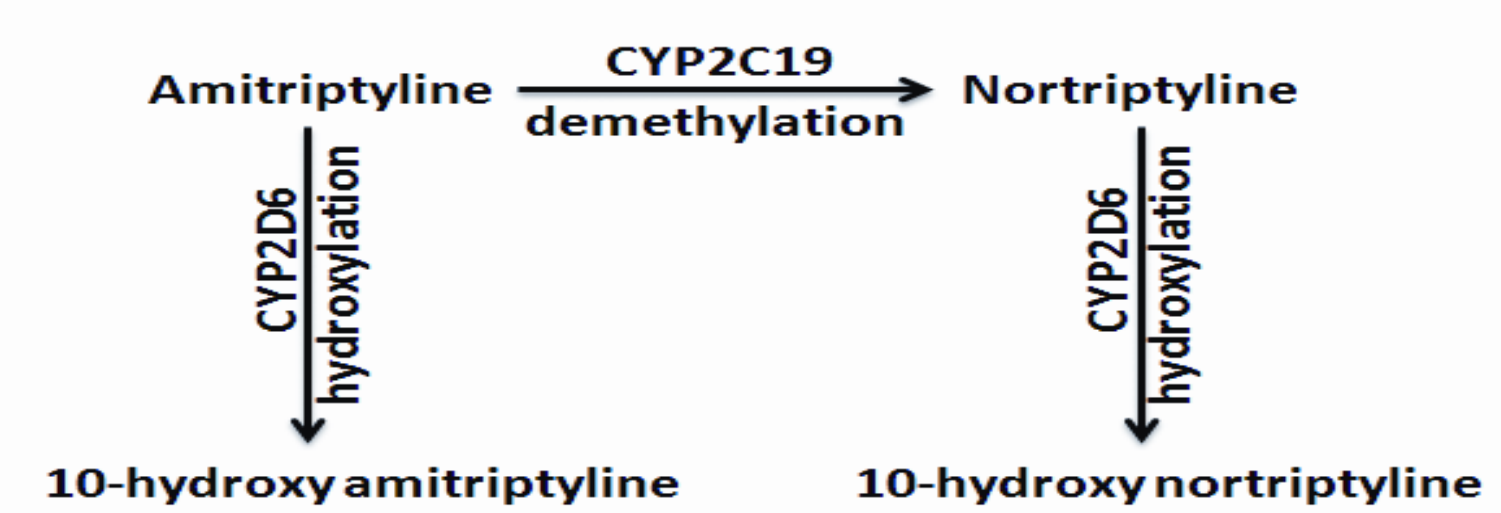
Amitriptyline



- **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 has a wide range of dosing recommendations depending on the indication**
- **For treatment of conditions such as depression, patients usually receive a higher dose**
- **For treatment of conditions such as neuropathic pain, patients usually receive a lower dose**
- **Therapeutic drug monitoring is available for amitriptyline, and may be a useful adjunct to genetic testing especially in poor, intermediate and ultra-rapid CYP2D6 metabolizers**

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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**

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Amitriptyline

- **Amitriptyline's efficacy is closely related to CYP2D6 and CYP2C19 metabolism**
  - **Poor metabolizers of CYP2C19 or CYP2D6**
    - **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 CYP2D6 and drug 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

What is the activity score for the pharmacogenetic test result of *CYP2D6 (*1/*1)2N*?

a) 0.5
b) 1.0
c) 1.5
d) 2.0

Correct answer: d

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Question # 2

What is the predicted CYP2D6 phenotype for the test result of *CYP2D6 (*2/*17)2N*?

a) Ultra-rapid metabolizer
b) Extensive metabolizer
c) Intermediate metabolizer
d) Poor metabolizer

Correct answer: b

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Question # 3

ZB is experiencing pain following a minor surgical procedure. A clinician wants to prescribe codeine to treat the pain and asks you for the appropriate dose. The patient has a pharmacogenetic test result of *CYP2D6 (*4/*4)* duplication.

Based on the pharmacogenetic test result, what recommendation would you give to the clinician?

a) Use label recommended dosing
b) Reduce the initial starting codeine dose by 50%
c) Avoid codeine due an increased risk of adverse events
d) Avoid codeine due to a lack of analgesic effects

Correct answer: d

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Question # 4

MJ is about to be prescribed amitriptyline for treatment of depression. The patient has a reported pharmacogenetic test result of *CYP2D6 (*1/*4)2N*. Based on the pharmacogenetic test result, which of the following statements is correct?

a) The patient should not receive amitriptyline due to decreased plasma concentrations of the drug and likely therapeutic failure

b) The patient should not receive amitriptyline due to increased plasma concentrations of the drug and likely development of side effects

c) There is no reason to adjust the dose of amitriptyline based on the *CYP2D6* genotype test result

d) The patient's initial dose should be increased by 25%

Correct answer: c

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