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Amitriptyline Therapy and *CYP2D6* and *CYP2C19* Genotype

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Introduction

Amitriptyline is a tricyclic antidepressant used in the treatment of several psychiatric disorders, including major depression, obsessive-compulsive disorder, panic attacks, generalized anxiety disorder, post-traumatic stress disorder, and bulimia. Amitriptyline also has different off-label uses, including migraine prevention, neuropathic pain management, fibromyalgia, and enuresis (bedwetting) (1).

Tricyclic antidepressants (TCAs) primarily mediate their therapeutic effect by inhibiting the reuptake of both serotonin and norepinephrine, leaving more neurotransmitter in the synaptic cleft stimulating the neuron. Because tricyclics can also block different receptors (H1 histamine, alpha 1 α1-adrenergic, and muscarinic receptors), side effects are common. As such, more specific selective serotonin reuptake inhibitors (SSRIs) have largely replaced the use of them. However, TCAs still have an important use in specific types of depression and other conditions.

Amitriptyline is metabolized mainly via CYP2C19 and CYP2D6 pathways. Metabolism by CYP2C19 results in active metabolites, including nortriptyline, which is also a tricyclic antidepressant. Metabolism catalyzed by CYP2D6 results in the formation of the less active 10-hydroxy metabolite. Individuals who are "CYP2D6 ultrarapid metabolizers" carry more than two normal function alleles (i.e., multiple copies) (Table 1, 2), whereas "CYP2C19 ultrarapid metabolizers" carry two increased function alleles (Table 3, 4). Individuals who are CYP2D6 or CYP2C19 "poor metabolizers" carry two no function alleles for *CYP2D6* or *CYP2C19*, respectively.

The FDA-approved drug label for amitriptyline states that CYP2D6 poor metabolizers have higher than expected plasma concentrations of tricyclic antidepressants when given usual doses. The FDA recommendations also include monitoring tricyclic antidepressant plasma levels whenever a tricyclic antidepressant is going to be co-administered with another drug known to be an inhibitor of CYP2D6 (1).

In 2016, the Clinical Pharmacogenetics Implementation Consortium (CPIC) made dosing recommendations for tricyclic antidepressants based on *CYP2C19* and *CYP2D6* genotypes (2). For CYP2D6 ultrarapid metabolizers, CPIC recommends avoiding the use of a tricyclic due to the potential lack of efficacy, and to consider an alternative drug not metabolized by CYP2D6. If a TCA is still warranted, CPIC recommends considering titrating the TCA to a higher target dose (compared to normal metabolizers) and using therapeutic drug monitoring to guide dose adjustments. For CYP2D6 intermediate metabolizers, CPIC recommends considering a 25% reduction of the starting dose, and for CYP2D6 poor metabolizers, to avoid the use of tricyclics because of the potential for side effects. If a tricyclic is still warranted for CYP2D6 poor metabolizers, CPIC recommends

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considering a 50% reduction of the starting dose while monitoring drug plasma concentrations to avoid side effects.

For CYP2C19 ultrarapid metabolizers, CPIC recommends avoiding the use of tertiary amines (e.g., amitriptyline) due to the potential for a sub-optimal response, and to consider an alternative drug not metabolized by CYP2C19, such as the secondary amines nortriptyline or desipramine. For CYP2C19 poor metabolizers, CPIC recommends avoiding tertiary amine use due to the potential for sub-optimal response, and to consider an alternative drug not metabolized by CYP2C19. If a tertiary amine is still warranted for CYP2C19 poor metabolizers, CPIC recommends considering a 50% reduction of the starting dose while monitoring drug plasma concentrations while monitoring plasma concentrations to avoid side effects (2).

Drug Class: Tricyclic Antidepressants

Tricyclic antidepressants (TCAs) are mixed serotonin-norepinephrine reuptake inhibitors. They increase the amount of neurotransmitter in the synaptic cleft, thought to mediate their antidepressant effects.

From the 1960s to the 1980s, tricyclics were the first-line treatment for depression, until the introduction of SSRIs, which have fewer side effects and are safer. The common side effects of tricyclics include anticholinergic side effects (e.g., blurred vision, dry mouth, constipation, and sedation), cardiac effects, and orthostatic hypotension.

Today, the main therapeutic use of tricyclics is chronic pain management, such as neuropathic pain. However, tricyclics are still used in the treatment of depression as well as other psychiatric disorders, including obsessive–compulsive disorder, panic attacks, generalized anxiety disorder, post-traumatic stress disorder, bulimia nervosa, smoking cessation, and enuresis (bedwetting).

Tricyclics are named after their chemical structure of three central rings and a side chain important for its function and activity. Its structure determines whether a drug is classified a tertiary amine (amitriptyline, clomipramine, doxepin, imipramine, and trimipramine) or secondary amine (desipramine and nortriptyline).

Whereas tertiary amines are generally more potent in blocking reuptake of serotonin, the secondary amines are more potent in blocking the reuptake of norepinephrine. Secondary amines are better tolerated and are also associated with fewer anticholinergic side effects.

The CYP2C19 enzyme metabolizes tertiary amines to active metabolites, which include desipramine (the active metabolite of imipramine) and nortriptyline (the active metabolite of amitriptyline). Both the tertiary and secondary amines are metabolized by CYP2D6 to less active metabolites.

The effectiveness and tolerability of tricyclics are affected by CYP2D6 metabolism and partially by CYP2C19 metabolism. Individuals who carry *CYP2D6* or *CYP2C19* variants that influence enzyme activity may be at an increased risk of treatment failure (if plasma drug levels are decreased) or drug toxicity (if plasma drug levels are increased).

Drug: Amitriptyline

Amitriptyline is used to relieve the symptoms of depression, with endogenous depression being more likely to respond to treatment than other depressive states (e.g., reactive depression) (1). Off-label uses of amitriptyline include migraine prevention, and the treatment of neuropathic pain, fibromyalgia, and enuresis (bedwetting).

Amitriptyline blocks the uptake of both serotonin and norepinephrine, but more potently blocks the reuptake of serotonin. Amitriptyline also has strong affinities for histamine (H1), alpha-1 adrenergic, and muscarinic (M1) receptors, which account for its side effects, including sedation, weight gain, blurred vision, dry mouth, and

constipation. The intensity of these side effects tends to be greater for amitriptyline compared to other tricyclics (3).

Amitriptyline is metabolized by CYP2C19 to the active metabolite, nortriptyline, which is also a tricyclic antidepressant thought to be approximately twice as potent as other TCAs. In contrast to amitriptyline, nortriptyline blocks the reuptake of norepinephrine more potently than serotonin (3).

Because both the parent drug (amitriptyline) and the CYP2C19 metabolite (nortriptyline) are pharmacologically active compounds, the plasma levels of both drugs should monitored (4). The sum of amitriptyline plus nortriptyline plasma levels may correlate with an individual's response to amitriptyline therapy (5).

The optimal therapeutic range for amitriptyline has been well-defined (6). Most individuals display an optimal response to amitriptyline when combined serum levels of amitriptyline and nortriptyline are between 80 and 200 ng/mL. Higher levels are associated with an increased risk of adverse events. At levels greater than 300 ng/ml, cardiac toxicity occurs. This is characterized by ECG changes (widening of QRS), which may lead to potentially fatal ventricular tachycardia. In some individuals, cardiac toxicity may occur at lower concentrations or even when they are within the recommended therapeutic range (7, 8).

Nortriptyline is metabolized by CYP2D6 to hydroxyl metabolites, which have been associated with cardiac toxicity. Safe levels of hydroxyl metabolites have not yet been defined (4).

Individuals who are carriers of certain *CYP2D6* and/or *CYP2C19* variants may have drug levels that are outside the therapeutic range after treated with standard doses of amitriptyline. As a result, they may have an increased risk of toxicity (if the level of amitriptyline and its active metabolites are too high) or treatment failure (if drug levels are too low).

Gene: *CYP2D6*

The cytochrome P450 superfamily (CYP) is a large and diverse group of enzymes that form the major system for metabolizing lipids, hormones, toxins, and drugs. The CYP genes are very polymorphic and can result in reduced, absent, or increased drug metabolism.

CYP2D6 is responsible for the metabolism of many commonly prescribed drugs, including antipsychotics, analgesics, beta-blockers, and TCAs such as amitriptyline.

CYP2D6 is highly polymorphic, with over 100 star (*) alleles described and currently catalogued at the Pharmacogene Variation (PharmVar) database (9).

CYP2D6 is a particularly complex gene that is difficult to genotype, partly because of the large number of variants, but also because of the presence of gene deletions, duplications, and its neighboring pseudogenes. The complexity of genetic variation at this locus complicates the ability to interrogate *CYP2D6*.

There is substantial variation in *CYP2D6* allele frequencies among different populations (10). *CYP2D6*1* is the wild-type allele and is associated with normal enzyme activity and the "normal metabolizer" phenotype. The *CYP2D6* alleles **2*, **33*, and **35* are also considered to have normal activity.

Other alleles include no function variants that produce a non-functioning enzyme (e.g., **3*, **4*, **5*,**6*, **7*, **8*, and **12*) or an enzyme with decreased activity (e.g., **10*, **17*, *29, and **41*) (see Table 1) (11) . There are large inter-ethnic differences in the frequency of these alleles, with **3*, **4*, **5*, **6*, and **41* being more common in the Caucasian population, **17* more common in Africans, and **10* more common in Asians (12).

Table 1: 2016 Assignment of *CYP2D6* phenotypes by CPIC

Phenotype	Activity Score	Genotypes	Examples of diplotypes
CYP2D6 ultrarapid metabolizer (approximately 1–20% of patients)[a]	Greater than 2.0	An individual carrying duplications of functional alleles	*(*1/*1)xN* *(*1/*2)xN* *(*2/*2)xN* [b]
CYP2D6 normal metabolizer (approximately 72–88% of patients)	1.0 – 2.0[c]	An individual carrying two normal function alleles or two decreased function alleles or one normal and no function allele or one normal function and decreased function allele or combinations of duplicated alleles that result in an activity score of 1.0 to 2.0	**1/*1* **1/*2* **2/*2* **1/*9* **1/*41* **41/*41* **1/*5* **1/*4*
CYP2D6 intermediate metabolizer (approximately 1–13% of patients)	0.5	An individual carrying one decreased function and one no function allele	**4/*41* **5/*9* **4/*10*
CYP2D6 poor metabolizer (approximately 1–10% of patients)	0	An individual carrying two no function alleles	**4/*4* **4/*4xN* **3/*4* **5/*5* **5/*6*

[a] For population-specific allele and phenotype frequencies, please see (2).
[b] Where *xN* represents the number of *CYP2D6* gene copies (N is 2 or more).
[c] Patients with an activity core of 1.0 may be classified as intermediate metabolizers by some reference laboratories.
For more information about activity scores, please see the Genetic Testing section.
This table has been adapted from Hicks J.K., Sangkuhl K., Swen J.J., Ellingrod V.L., Müller D.J., Shimoda K., Bishop J.R., Kharasch E.D., Skaar T.C., Gaedigk A., Dunnenberger H.M., Klein T.E., Caudle K.E. Clinical Pharmacogenetics Implementation Consortium Guideline (CPIC®) for *CYP2D6* and *CYP2C19* Genotypes and Dosing of Tricyclic Antidepressants: 2016 Update. Clinical pharmacology and therapeutics. 2016 Dec 20 [Epub ahead of print] (2).

Individuals who are intermediate or poor metabolizers carry copies of decreased or no function *CYP2D6* alleles, respectively (Table 1). Approximately 30% of Asians and individuals of Asian descent are intermediate metabolizers. In these populations, only half of *CYPD6* alleles are fully functional, with the reduced function **10* variant being very common (~40%, compared to ~2% in Caucasians) (13). As a result, Asians are more likely to be intermediate metabolizers than Caucasians (14). Similarly, in Africans and African Americans, only half of *CYPD6* alleles are functional. However, a wider range of variants account for the remaining alleles (14, 15, 16).

Approximately 6–10% of European Caucasians and their descendants are poor metabolizers, mainly due to no function **4* and **5* alleles (14). Notably, less than 40% are homozygous normal metabolizers (carrying two copies of **1* allele) (17, 18, 19).

Individuals who are CYP2D6 poor metabolizers have higher plasma levels of amitriptyline, compared to normal metabolizers, after standard doses of amitriptyline (20). Individuals who carry at least one non-functional *CYP2D6* variant have been found to be at medium to high risk of developing side effects (21).

Because standard doses of amitriptyline may lead to an increased risk of adverse events in individuals who are CYP2D6 poor metabolizers, CPIC recommends avoiding the use of amitriptyline or other tricyclic antidepressants, and to consider using an alternative drug that is not metabolized by CYP2D6. If a tricyclic is warranted, CPIC recommends considering a 50% reduction of the recommended starting dose, and they strongly recommend therapeutic drug monitoring to guide dose adjustments (4).

Individuals who have more than two copies of normal function *CYP2D6* alleles are *CYP2D6* ultrarapid metabolizers. The increased rate of metabolism of amitriptyline leads to less active drug being available and a poor therapeutic response. Because of the potential lack of efficacy, CPIC recommends considering an alternative drug to amitriptyline that is not metabolized by CYP2D6. If a tricyclic is warranted, CPIC recommends increasing the starting dose and using therapeutic drug monitoring to guide dose adjustments (4) (Table 2).

Table 2. 2016 CPIC Dosing recommendations for tricyclic antidepressants based on *CYP2D6* phenotype

Phenotype	Implication	Therapeutic recommendation
CYP2D6 ultrarapid metabolizer	Increased metabolism of TCAs to less active compounds compared to normal metabolizers	Avoid tricyclic use due to potential lack of efficacy. Consider alternative drug not metabolized by CYP2D6
	Lower plasma concentrations of active drugs will increase probability of pharmacotherapy failure	If a TCA is warranted, consider titrating to a higher target dose (compared to normal metabolizers)[a]. Utilize therapeutic drug monitoring to guide dose adjustments.
CYP2D6 normal metabolizer	Normal metabolism of TCAs	Initiate therapy with recommended starting dose[b].
CYP2D6 intermediate metabolizer	Reduced metabolism of TCAs to less active compounds compared to normal metabolizers	Consider a 25% reduction of recommended starting dose[b]. Utilize therapeutic drug monitoring to guide dose adjustments[a].
	Higher plasma concentrations of active drug will increase the probability of side effects	
CYP2D6 poor metabolizer	Greatly reduced metabolism of TCAs to less active compounds compared to normal metabolizers	Avoid tricyclic use due to potential for side effects. Consider alternative drug not metabolized by CYP2D6
	Higher plasma concentrations will increase the probability of side effects	If a TCA is warranted, consider a 50% reduction of recommended starting dose[b]. Utilize therapeutic drug monitoring to guide dose adjustments[a].

TCAs: Tricyclic Antidepressants
Dosing recommendations only apply to higher initial doses of TCAs for treatment of conditions such as depression.
The therapeutic recommendations for amitriptyline are classified as "moderate" for intermediate CYP2D6 metabolizers and "strong" for ultrarapid, normal, and poor CYP2D6 metabolizers.
[a] Titrate dose to observed clinical response with symptom improvement and minimal (if any) side effects.
[b] Patients may receive an initial low dose of tricyclic, which is then increased over several days to the recommended steady-state dose. The starting dose in this guideline refers to the recommended steady-state dose.
Table has been adapted from Hicks J.K., Sangkuhl K., Swen J.J., Ellingrod V.L., Müller D.J., Shimoda K., Bishop J.R., Kharasch E.D., Skaar T.C., Gaedigk A., Dunnenberger H.M., Klein T.E., Caudle K.E. Clinical Pharmacogenetics Implementation Consortium Guideline (CPIC®) for *CYP2D6* and *CYP2C19* Genotypes and Dosing of Tricyclic Antidepressants: 2016 Update. Clinical pharmacology and therapeutics. 2016 Dec 20 [Epub ahead of print] (2).

One issue with increasing the dose of amitriptyline dose for CYP2D6 metabolizers is increasing the level of hydroxyl-metabolites, which have been associated with cardiotoxicity (22, 23). Currently, the safe range of hydroxy-metabolite plasma concentrations is not known. In addition, there are few studies on how the combination of *CYP2D6* and *CYP2C19* phenotypes influences an individual's response to amitriptyline (4).

Gene: CYP2C19

The CYP2C19 enzyme contributes to the metabolism of a range of clinically important drugs, such as several proton pump inhibitors, clopidogrel, benzodiazepines, and several tricyclic antidepressants, including amitriptyline.

The *CYP2C19* gene is highly polymorphic as 35 variant star (*) alleles are available from the Pharmacogene Variation Consortium (PharmVar) https://www.pharmvar.org/.

The *CYP2C19*1* wild-type allele is associated with normal enzyme activity and the "normal metabolizer" phenotype, whereas the *CYP2C19*17* allele is associated with increased enzyme activity and the "rapid" and "ultrarapid" metabolizer phenotypes (24).

The most common no function variant is *CYP2C19*2*, which is characterized by c.681G>A in exon 5 that results in an aberrant splice site and the production of a truncated and non-functioning protein. The *CYP2C19*2* allele frequencies are ~15% in Caucasians and Africans, and ~29–35% in Asians (24, 25).

Another commonly tested no function variant is *CYP2C19*3*, which is characterized by c.636G>A in exon 4 that causes a premature stop codon. The *CYP2C19*3* allele frequencies are ~2–9% in Asian populations, but rare in other racial groups. Other no function variants occur in less than 1% of the general population, and include *CYP2C19*4-*8* (24, 25).

"CYP2C19 intermediate metabolizers" carry one copy of an allele that encodes decreased or no function (e.g. *1/*2), whereas "poor metabolizers" are homozygous or compound heterozygous for two no function alleles (e.g., *2/*2, *2/*3) (Table 3).

Table 3: Assignment of *CYP2C19* phenotypes by CPIC

Phenotype	Genotypes	Examples of diplotypes
CYP2C19 ultrarapid metabolizer (approximately 2–35% of patients)[a]	An individual carrying two increased function alleles	**17/*17*
CYP2C19 rapid metabolizer (approximately 2–30% of patients)	An individual carrying one normal function allele and one increased function allele	**1/*17*
CYP2C19 normal metabolizer (approximately 35–50% of patients)	An individual carrying two normal function alleles	**1/*1*
CYP2C19 Intermediate metabolizer (approximately 18–45% of patients)	An individual carrying one normal function and one no function allele or one no function allele and one increased function allele	**1/*2* **1/*3* **2/*17*[b]
CYP2C19 Poor metabolizer (approximately 2–15% of patients)	An individual carrying two no function alleles	**2/*2* **2/*3* **3/*3*

[a] For population-specific allele and phenotype frequencies, please see (2).
[b] The predicted metabolizer phenotype for the *2/*17 genotype is a provisional classification.
Table has been adapted from Hicks J.K., Sangkuhl K., Swen J.J., Ellingrod V.L., Müller D.J., Shimoda K., Bishop J.R., Kharasch E.D., Skaar T.C., Gaedigk A., Dunnenberger H.M., Klein T.E., Caudle K.E. Clinical Pharmacogenetics Implementation Consortium Guideline (CPIC®) for *CYP2D6* and *CYP2C19* Genotypes and Dosing of Tricyclic Antidepressants: 2016 Update. Clinical pharmacology and therapeutics. 2016 Dec 20 [Epub ahead of print] (2).

Individuals who are CYP2C19 poor metabolizers have a reduced rate of metabolism of amitriptyline compared to normal metabolizers. As a result, standard doses of amitriptyline lead to higher plasma levels of amitriptyline, lower levels of nortriptyline, and may increase the risk of side effects (20, 26, 27, 28). Therefore, for CYP2C19 poor metabolizers, CPIC recommends considering a 50% reduction of the recommended starting dose, and to use therapeutic drug monitoring to guide dose adjustments (4).

Individuals who are ultrarapid metabolizers may be at an increased risk of treatment failure and/or metabolites adverse effects. Being a carrier of the increased activity allele *CYP2C19*17* is not associated with an increased level of the sum of amitriptyline plus nortriptyline levels, but the ratio is altered. A higher level of nortriptyline is seen, which may be linked to increased side effects. Therefore, for ultrarapid metabolizers, CPIC have an

optional recommendation of considering using an alternative drug to amitriptyline that is not metabolized by CYP2C19, or if a tricyclic is warranted, to use therapeutic drug monitoring to guide dose adjustments (4, 26) (Table 4, Table 5).

Table 4. 2016 CPIC Dosing recommendations for amitriptyline based on *CYP2C19* phenotype

Phenotype	Implication	Therapeutic recommendation
CYP2C19 ultrarapid metabolizer and CYP2C19 rapid metabolizer	Increased metabolism of tertiary amines as compared to normal metabolizers Greater conversion of tertiary amines to secondary amines may affect response or side effects	Avoid tertiary amine use due to potential for sub-optimal response. Consider alternative drug not metabolized by CYP2C19. TCAs without major CYP2C19 metabolism include the secondary amines nortriptyline and desipramine.
		If a tertiary amine is warranted, utilize therapeutic drug monitoring to guide dose adjustments[a].
CYP2C19 normal metabolizer	Normal metabolism of tertiary amines	Initiate therapy with recommended starting dose[b].
CYP2C19 intermediate metabolizer	Reduced metabolism of tertiary amines compared to normal metabolizers	Initiate therapy with recommended starting dose[b].
CYP2C19 poor metabolizer	Greatly reduced metabolism of tertiary amines compared to normal metabolizers	Avoid tertiary amine use due to potential for sub-optimal response. Consider alternative drug not metabolized by CYP2C19. TCAs without major CYP2C19 metabolism include the secondary amines nortriptyline and desipramine. For tertiary amines, consider a 50% reduction of recommended starting dose[b]. Utilize therapeutic drug monitoring to guide dose adjustments[a].
	Decreased conversion of tertiary amines to secondary amines may affect response or side effects	

Dosing recommendations apply only to higher initial doses of amitriptyline for treatment of conditions such as depression. The therapeutic recommendations for amitriptyline are classified as "strong" for normal and intermediate CYP2C19 metabolizers, "moderate" for poor metabolizers, and "optional" for ultrarapid metabolizers.
[a] Titrate dose to observed clinical response with symptom improvement and minimal (if any) side effects).
[b] Patients may receive an initial low dose of tricyclic, which is then increased over several days to the recommended steady-state dose. The starting dose in this guideline refers to the recommended steady-state dose.
Table has been adapted from Hicks J.K., Sangkuhl K., Swen J.J., Ellingrod V.L., Müller D.J., Shimoda K., Bishop J.R., Kharasch E.D., Skaar T.C., Gaedigk A., Dunnenberger H.M., Klein T.E., Caudle K.E. Clinical Pharmacogenetics Implementation Consortium Guideline (CPIC®) for *CYP2D6* and *CYP2C19* Genotypes and Dosing of Tricyclic Antidepressants: 2016 Update. Clinical pharmacology and therapeutics. 2016 Dec 20 [Epub ahead of print] (2).

Table 5. 2016 CPIC Dosing recommendations for amitriptyline based on both CYP2D6 and CYP2C19 phenotypes [a,b]

Phenotype	CYP2D6 Ultrarapid metabolizer	CYP2D6 Normal metabolizer	CYP2D6 Intermediate metabolizer	CYP2D6 Poor metabolizer
CYP2C19 ultrarapid or rapid metabolizer	Avoid amitriptyline use[c] Classification of recommendation[d]: Optional	Consider alternative drug not metabolized by CYP2C19[c,e] Classification of recommendation[d]: Optional	Consider alternative drug not metabolized by CYP2C19 [c,e] Classification of recommendation[d]: Optional	Avoid amitriptyline use[c] Classification of recommendation[d]: Optional
CYP2C19 normal metabolizer	Avoid amitriptyline use. If amitriptyline is warranted, consider titrating to a higher target dose (compared to normal metabolizers)[f,g] Classification of recommendation[d]: Strong	Initiate therapy with recommended starting dose[h] Classification of recommendation[d]: Strong	Consider a 25% reduction of recommended starting dose[f,h] Classification of recommendation[d]: Moderate	Avoid amitriptyline use. If amitriptyline is warranted, consider a 50% reduction of recommended starting dose[f,h] Classification of recommendation[d]: Strong

Table 5. continued from previous page.

Phenotype	CYP2D6 Ultrarapid metabolizer	CYP2D6 Normal metabolizer	CYP2D6 Intermediate metabolizer	CYP2D6 Poor metabolizer
CYP2C19 intermediate metabolizer	Avoid amitriptyline use[c] Classification of recommendation[d]: Optional	Initiate therapy with recommended starting dose[h] Classification of recommendation[d]: Strong	Consider a 25% reduction of recommended starting dose[f,h] Classification of recommendation[d]: Optional	Avoid amitriptyline use. If amitriptyline is warranted, consider a 50% reduction of recommended starting dose[f,h] Classification of recommendation[d]: Optional
CYP2C19 poor metabolizer	Avoid amitriptyline use[c] Classification of recommendation[d]: Optional	Avoid amitriptyline use. If amitriptyline is warranted, consider a 50% reduction of recommended starting dose[f,h] Classification of recommendation[d]: Moderate	Avoid amitriptyline use[c] Classification of recommendation[d]: Optional	Avoid amitriptyline use[c] Classification of recommendation[d]: Optional

[a] Dosing recommendations only apply to higher initial doses of TCAs for treatment of conditions such as depression.
[b] The dosing recommendations are based on studies focusing on amitriptyline. Because tricyclic antidepressants have comparable pharmacokinetic properties, it may be reasonable to apply these guidelines to other tertiary amines including clomipramine, doxepin, imipramine and trimipramine (the classification of this recommendation is optional).
[c] If amitriptyline is warranted, utilize therapeutic drug monitoring to guide dose adjustment.
[d] The rating scheme for the recommendation classification is described in Supplementary Data (2). See CYP2D6 and CYP2C19 combined dosing recommendations for explanation of classification of recommendations for this table.
[e] TCAs without major CYP2C19 metabolism include the secondary amines nortriptyline and desipramine.
[f] Utilizing therapeutic drug monitoring if a tricyclic is prescribed to a patient with CYP2D6 ultrarapid, intermediate or poor metabolism in combination with CYP2C19 ultrarapid, intermediate or poor metabolism is strongly recommended.
[g] Titrate dose to observed clinical response with symptom improvement and minimal (if any) side effects.
[h] Patients may receive an initial low dose of TCAs, which is then increased over several days to the recommended steady-state dose. The starting dose in this guideline refers to the recommended steady-state dose.
Table has been adapted from Hicks J.K., Sangkuhl K., Swen J.J., Ellingrod V.L., Müller D.J., Shimoda K., Bishop J.R., Kharasch E.D., Skaar T.C., Gaedigk A., Dunnenberger H.M., Klein T.E., Caudle K.E. Clinical Pharmacogenetics Implementation Consortium Guideline (CPIC®) for *CYP2D6* and *CYP2C19* Genotypes and Dosing of Tricyclic Antidepressants: 2016 Update. Clinical pharmacology and therapeutics. 2016 Dec 20 [Epub ahead of print] (2).

Genetic Testing

Clinical genotyping tests are available for many CYP2D6 and *CYP2C19* alleles. The NIH's Genetic Testing Registry (GTR) provides a list of test providers for "amitriptyline response," and the CYP2D6 and CYP2C19 genes.

Results are typically reported as a diplotype, such as *CYP2D6 *1/*1*. A result for copy number, if available, is also important when interpreting *CYP2D6* results (29). However, it is important to note that the number of variants tested can vary among laboratories, which can result in diplotype result discrepancies between testing platforms and laboratories (30).

If the test results include an interpretation of the patient's predicted metabolizer phenotype, this should be confirmed by checking the diplotype and assigning an activity score to each allele (e.g., 0 for nonfunctional, 0.5 for reduced function, and 1 for each copy of a functional allele). The phenotype is defined by the sum of the two scores:

- A normal (previously referred to as "extensive") metabolizer phenotype has an activity score of 1 to 2
- An intermediate metabolizer has an activity score of 0.5

- A poor metabolizer has an activity score of 0
- An ultrarapid metabolizer has an activity score greater than 2 (2, 31)

Therapeutic Recommendations based on Genotype

This section contains excerpted[1] information on gene-based dosing recommendations. Neither this section nor other parts of this review contain the complete recommendations from the sources.

2016 Statement from the US Food and Drug Administration (FDA): The biochemical activity of the drug metabolizing isozyme cytochrome P450 2D6 (debrisoquin hydroxylase) is reduced in a subset of the caucasian population (about 7 to 10% of Caucasians are so called "poor metabolizers"); reliable estimates of the prevalence of reduced P450 2D6 isozyme activity among Asian, African and other populations are not yet available. Poor metabolizers have higher than expected plasma concentrations of tricyclic antidepressants (TCAs) when given usual doses. Depending on the fraction of drug metabolized by P450 2D6, the increase in plasma concentration may be small, or quite large (8 fold increase in plasma AUC of the TCA).

In addition, certain drugs inhibit the activity of this isozyme and make normal metabolizers resemble poor metabolizers. An individual who is stable on a given dose of TCA may become abruptly toxic when given one of these inhibiting drugs as concomitant therapy. The drugs that inhibit cytochrome P450 2D6 include some that are not metabolized by the enzyme (quinidine; cimetidine) and many that are substrates for P450 2D6 (many other antidepressants, phenothiazines, and the Type 1C antiarrhythmics propafenone and flecainide). While all the selective serotonin reuptake inhibitors (SSRIs), e.g., fluoxetine, sertraline, and paroxetine, inhibit P450 2D6, they may vary in the extent of inhibition. The extent to which SSRI-TCA interactions may pose clinical problems will depend on the degree of inhibition and the pharmacokinetics of the SSRI involved. Nevertheless, caution is indicated in the coadministration of TCAs with any of the SSRIs and also in switching from one class to the other. Of particular importance, sufficient time must elapse before initiating TCA treatment in a patient being withdrawn from fluoxetine, given the long half-life of the parent and active metabolite (at least 5 weeks may be necessary).

Concomitant use of tricyclic antidepressants with drugs that can inhibit cytochrome P450 2D6 may require lower doses than usually prescribed for either the tricyclic antidepressant or the other drug. Furthermore, whenever one of these other drugs is withdrawn from co-therapy, an increased dose of tricyclic antidepressant may be required. It is desirable to monitor TCA plasma levels whenever a TCA is going to be coadministered with another drug known to be an inhibitor of P450 2D6.

Please review the complete therapeutic recommendations that are located here: (1).

2016 Statement from the Clinical Pharmacogenetics Implementation Consortium (CPIC):

CYP2D6 dosing recommendations.

[…]. The recommended starting dose of amitriptyline or nortriptyline does not need adjustment for those with genotypes predictive of CYP2D6 normal metabolism. A 25% reduction of the recommended dose may be considered for CYP2D6 intermediate metabolizers. The strength of this recommendation is classified as "moderate" because patients with a CYP2D6 activity score of 1.0 are inconsistently categorized as intermediate or normal metabolizers in the literature, making these studies difficult to evaluate.

CYP2D6 ultrarapid metabolizers have a higher probability of failing amitriptyline or nortriptyline pharmacotherapy due to subtherapeutic plasma concentrations, and alternate agents are preferred. There are documented cases of CYP2D6 ultrarapid metabolizers receiving large doses of nortriptyline in order to achieve

[1] The FDA labels specific drug formulations. We have substituted the generic names for any drug labels in this excerpt. The FDA may not have labeled all formulations containing the generic drug.

therapeutic concentrations. However, very high plasma concentrations of the nortriptyline hydroxy-metabolite were present, which may increase the risk for cardiotoxicity. If a tricyclic is warranted, there are insufficient data in the literature to calculate a starting dose for a patient with CYP2D6 ultrarapid metabolizer status, and therapeutic drug monitoring is strongly recommended. Adverse effects are more likely in CYP2D6 poor metabolizers due to elevated tricyclic plasma concentrations; therefore, alternate agents are preferred. If a tricyclic is warranted, consider a 50% reduction of the usual dose, and therapeutic drug monitoring is strongly recommended.

CYP2C19 dosing recommendations.

[…]. The usual starting dose of amitriptyline may be used in CYP2C19 normal and intermediate metabolizers. Although CYP2C19 intermediate metabolizers would be expected to have a modest increase in the ratio of amitriptyline to nortriptyline plasma concentrations, the evidence does not indicate that CYP2C19 intermediate metabolizers should receive an alternate dose.

Patients taking amitriptyline who are CYP2C19 rapid or ultrarapid metabolizers may be at risk for having low plasma concentrations and an imbalance between parent drug and metabolites causing treatment failure and/or adverse events. Although the CYP2C19*17 allele did not alter the sum of amitriptyline plus nortriptyline plasma concentrations, it was associated with higher nortriptyline plasma concentrations, possibly increasing the risk of adverse events. For patients taking amitriptyline, extrapolated pharmacokinetic data suggest that CYP2C19 rapid or ultrarapid metabolizers may need a dose increase. Due to the need for further studies investigating the clinical importance of CYP2C19*17 regarding tricyclic metabolism and the possibility of altered concentrations, we recommend to consider an alternative tricyclic or other drug not affected by CYP2C19. This recommendation is classified as optional due to limited available data. If amitriptyline is administered to a CYP2C19 rapid or ultrarapid metabolizer, therapeutic drug monitoring is recommended.

CYP2C19 poor metabolizers are expected to have a greater ratio of amitriptyline to nortriptyline plasma concentrations. The elevated amitriptyline plasma concentrations may increase the chance of a patient experiencing side effects. Use an alternative agent not metabolized by CYP2C19 (e.g., nortriptyline and desipramine) or consider a 50% reduction of the usual amitriptyline starting dose along with therapeutic drug monitoring.

Please review the complete therapeutic recommendations that are located here: (2).

2011 Summary of recommendations from the Pharmacogenetics Working Group of the Royal Dutch Association for the Advancement of Pharmacy (KNMP)

For CYP2D6 ultrarapid metabolizers:

The genetic polymorphism leads to increased metabolic capacity of CYP2D6, which may cause a decrease in the plasma concentrations of amitriptyline and its active metabolite nortriptyline and increased plasma concentrations of the active metabolites E-10-OH-amitriptyline and E-10-OH- nortriptyline.

Recommendation:

1. Choose an alternative if possible. Antidepressants that are not metabolized via CYP2D6 - or to a lesser extent - include, for example, citalopram and sertraline.
2. If an alternative is not an option: increase the dose to 1.25 times the standard dose, monitor the plasma concentrations and be alert to potential therapy failure due to decreased amitriptyline plus nortriptyline plasma concentrations and to increased plasma concentrations of the potentially cardiotoxic, active hydroxy metabolites.

For CYP2D6 intermediate metabolizers:

The genetic polymorphism leads to decreased metabolic capacity of CYP2D6, which may cause an increase in the plasma concentrations of amitriptyline and its active metabolite nortriptyline and decreased plasma concentrations of the active metabolites E-10-OH-amitriptyline and E-10-OH- nortriptyline.

Recommendation:

1. Choose an alternative if possible. Antidepressants that are not metabolized via CYP2D6 - or to a lesser extent - include, for example, citalopram and sertraline.
2. If an alternative is not an option: use 60% of the standard dose and monitor the plasma concentrations of amitriptyline and nortriptyline

As side effects are related to nortriptyline plasma concentrations and the efficacy to amitriptyline plus nortriptyline plasma concentrations, which are influenced to a lesser extent by CYP2D6, it is not known whether it is possible to reduce the dose to such an extent that the side effects disappear, but the efficacy is maintained.

For CYP2D6 poor metabolizers:

The genetic polymorphism leads to decreased metabolic capacity of CYP2D6, which may cause an increase in the plasma concentrations of amitriptyline and its active metabolite nortriptyline and decreased plasma concentrations of the active metabolites E-10-OH-amitriptyline and E-10-OH- nortriptyline.

Recommendation:

1. Choose an alternative if possible. Antidepressants that are not metabolized via CYP2D6 - or to a lesser extent - include, for example, citalopram and sertraline.
2. If an alternative is not an option: use 50% of the standard dose and monitor the plasma concentrations of amitriptyline and nortriptyline

As side effects are related to nortriptyline plasma concentrations and the efficacy to amitriptyline plus nortriptyline plasma concentrations, which are influenced to a lesser extent by CYP2D6, it is not known whether it is possible to reduce the dose to such an extent that the side effects disappear, but the efficacy is maintained.

Please review the complete therapeutic recommendations that are located here: (32).

Nomenclature

Nomenclature for selected *CYP2D6* alleles

Common allele name	Alternative names	HGVS reference sequence		dbSNP reference identifier for allele location
		Coding	Protein	
*CYP2D6*4*	1846G>A	NM_000106.5:c.506-1G>A	Not applicable - variant occurs in a non-coding region	rs3892097
*CYP2D6*5*	Not applicable - variant results in a whole gene deletion			
*CYP2D6*6*	1707 del T Trp152Gly	NM_000106.5:c.454delT	NP_000097.3:p.Trp152Glyfs	rs5030655
*CYP2D6*10*	100C>T Pro34Ser	NM_000106.5:c.100C>T	NP_000097.3:p.Pro34Ser	rs1065852
*CYP2D6*17*	Includes at least two functional variants*: 1023C>T (Thr107Ile) 2850C>T (Cys296Arg)	NM_000106.5:c.320C>T NM_000106.5:c.886T>C	NP_000097.3:p.Thr107Ile NP_000097.3:p.Cys296Arg	rs28371706 rs16947

Nomenclature for selected continued from previous page.

Common allele name	Alternative names	HGVS reference sequence		dbSNP reference identifier for allele location
		Coding	Protein	
*CYP2D6*41*	2988G>A	NM_000106.5:c.985+39G>A	Not applicable – variant occurs in a non-coding region	rs28371725

* In the literature, 1023C>T is also referred to as 1111C>T, and 2850C>T is also referred to 2938C>T.

Nomenclature for selected *CYP2C19* alleles

Common allele name	Alternative names	HGVS reference sequence		dbSNP reference identifier for allele location
		Coding	Protein	
*CYP2C19*2*	681G>A Pro227Pro	NM_000769.1:c.681G>A	NP_000760.1:p.Pro227=	rs4244285
*CYP2C19*3*	636G>A Trp212Ter	NM_000769.1:c.636G>A	NP_000760.1:p.Trp212Ter	rs4986893
*CYP2C19*17*	-806C>T	NM_000769.2:c.-806C>T	Not applicable—variant occurs in a non-coding region	rs12248560

Guidelines for the description and nomenclature of gene variations are available from the Human Genome Variation Society (HGVS): http://www.hgvs.org/content/guidelines

Nomenclature for Cytochrome P450 enzymes is available from the Pharmacogene Variation Consortium (PharmVar) https://www.pharmvar.org/.

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