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Imipramine Therapy and *CYP2D6* and *CYP2C19* Genotype

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Introduction

Imipramine is a tricyclic antidepressant used in the treatment of several psychiatric disorders including major depression, obsessive-compulsive disorder, generalized anxiety disorder, post-traumatic stress disorder, and bulimia. Imipramine may also be useful as an adjunctive treatment in the management of panic attacks, neuropathic pain, attention-deficit disorder, and childhood 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 (histamine H1, 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.

Imipramine is primarily metabolized via CYP2C19 to active metabolites, including desipramine, also a tricyclic antidepressant. Further metabolism is catalyzed by CYP2D6. Individuals who are "CYP2D6 ultrarapid metabolizers" carry more than two normal function alleles (i.e., multiple copies) (Table 1, 2), whereas individuals who are "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 imipramine states that CYP2D6 poor metabolizers have higher than expected plasma concentrations of tricyclic antidepressants when given usual doses. Their recommendations 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. Amitriptyline and nortriptyline were used as model drugs for this guideline because the majority of pharmacogenomic studies have focused on these two drugs. According to the CPIC guideline, because TCAs have comparable pharmacokinetic properties, it may be reasonable to apply the recommendations to other tricyclics, including imipramine (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

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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 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., imipramine) 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 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 their 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: Imipramine

Imipramine was the first tricyclic used in the treatment of depression in the late 1950s. Imipramine is still used to relieve the symptoms of major depressive disorder, and it may be useful too as temporary adjunctive therapy in reducing enuresis (bedwetting) in children aged 6 years and older. Off-label uses of imipramine also include the treatment of neuropathic pain and attention deficit disorder.

Imipramine is a tertiary amine and is similar in structure to amitriptyline, another tertiary amine. Both drugs potently block the reuptake of serotonin and to a lesser degree norepinephrine. Imipramine has also strong affinities for alpha-1 adrenergic, histamine H1, and muscarinic M1 receptors, which account for its side effects of orthostatic hypotension, sedation, weight gain, and anticholinergic effects. However, the intensity of these side effects is generally less than it is for amitriptyline (3).

Imipramine is metabolized by CYP2C19 to desipramine, which is also a tricyclic antidepressant with distinct clinical features that differ from the imipramine. Desipramine is then metabolized by CYP2D6 to the less active hydroxy-imipramine. For therapeutic drug monitoring, the levels of imipramine and hydroxy-imipramine should be monitored (4).

The optimal therapeutic range for imipramine is well-defined (5). Most individuals display an optimal response to imipramine when combined serum levels of imipramine and desipramine are between 175 and 300 ng/mL (6). However, individuals who are carriers of certain *CYP2D6* and/or *CYP2C19* variants may have drug levels that are outside this range even after being treated with standard doses of imipramine. As a result, they may have an increased risk of side effects (if the level of imipramine 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 imipramine.

CYP2D6 is highly polymorphic, with over 100 star (*) alleles described and currently catalogued at the Pharmacogene Variation Consortium database (7).

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 (8). *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) (9). 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 (10).

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]

Table 1 continued from previous page.

Phenotype	Activity Score	Genotypes	Examples of diplotypes
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 reduced-activity 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 *CYP2D6* alleles are fully functional, with the reduced function **10* variant being very common (~40%, compared to ~2% in Caucasians) (11). As a result, Asians are more likely to be intermediate metabolizers than Caucasians (12). Similarly, in Africans and African Americans, only half of *CYPD6* alleles are functional; however, a wider range of variants account for the remaining alleles (12-14).

Approximately 6-10% of European Caucasians and their descendants are poor metabolizers, mainly due to no function **4* and **5* alleles (12). Notably, less than 40% are homozygous normal metabolizers (carrying two copies of **1* allele) (15-17).

Individuals who are CYP2D6 poor metabolizers require a lower dose of imipramine to be in therapeutic range than CYP2D6 normal metabolizers (18). When treated with standard doses of imipramine, individuals who are CYP2D6 poor metabolizers will also have higher plasma concentrations of imipramine and desipramine compared to CYP2D6 normal metabolizers (19).

Because adverse effects are more likely due to elevated tricyclic plasma concentrations, CPIC recommends alternative agents for individuals who are CYP2D6 poor metabolizers. If a tricyclic is warranted, CPIC recommends considering a 50% reduction of the usual starting dose, and they strongly recommend therapeutic drug monitoring (4).

Individuals who have more than two copies of normal function *CYP2D6* alleles are *CYP2D6* ultrarapid metabolizers. These individuals require higher doses of imipramine to be within therapeutic range compared to normal metabolizers (18). However, increasing the dose of imipramine can lead to high plasma concentrations of desipramine, which may increase the risk for cardiotoxicity. Therefore, CPIC recommends that an alternative

agent be used for CYP2D6 ultrarapid metabolizers. However, if a tricyclic is warranted, there is insufficient evidence to calculate a starting dose, and so therapeutic drug monitoring is strongly recommended (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 and nortriptyline are classified as "moderate" for intermediate CYP2D6 metabolizers, and "strong" for ultrarapid, normal, and poor CYP2D6 metabolizers. CPIC state that it may be reasonable to apply these recommendations to other TCAs also metabolized by CYP2D6, including clomipramine, desipramine, doxepin, imipramine, and trimipramine.
[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).

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 imipramine.

The *CYP2C19* gene is highly polymorphic as 35 variant star (*) alleles are currently catalogued at the Pharmacogene Variation Consortium database: (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 (20).

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 (20, 21).

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* (20, 21).

"CYP2C19 intermediate metabolizers" carry one copy of a no function allele (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: 2016 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).

Studies have found that individuals who are CYP2C19 poor metabolizers have a lower plasma clearance of imipramine compared to normal metabolizers. When given standard doses of imipramine, CYP2C19 poor metabolizers have greater concentrations of imipramine and its active metabolite desipramine (22-24). Increased drug levels could potentially lead to an increased risk of adverse events. CPIC recommends considering a 50% reduction in the starting dose of tricyclics for CYP2C19 poor metabolizers (4)

Individuals who are CYP2C19 ultrarapid metabolizers may require an increased dose of tricyclics (25).

One study found that the imipramine plasma concentration was significantly lower in ultrarapid metabolizers (i.e., *CYP2C19*17/*17*) when compared to normal metabolizers (i.e., *CYP2C19*1/*1*) patients. However, the imipramine + desipramine plasma concentrations were not significantly different between *CYP2C19* genotypes (26). Because of the possibility of altered tricyclic plasma concentrations, CPIC recommends an alternative tricyclic or other drug for ultrarapid metabolizers (4) (Table 4).

Table 4. 2016 CPIC Dosing recommendations for tertiary amines 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. CPIC state that it may be reasonable to apply these recommendations to other TCAs also metabolized by CYP2C19, including clomipramine, doxepin, imipramine, and trimipramine.
[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).

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 "imipramine 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 (27). 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 (28).

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, 29)

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 interaction may pose clinical problems will depend on the degree of inhibition and the pharmacokinetics of the SSRI involved. Nevertheless, caution is indicated in the co-administration 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 co-administered 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):

Because the TCAs have comparable pharmacokinetic properties, it may be reasonable to extrapolate this guideline to other TCAs including clomipramine, desipramine, doxepin, imipramine, and trimipramine, with the acknowledgement that there are fewer data supporting dose adjustments for these drugs than for amitriptyline or nortriptyline. […]

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.

[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.

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 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 poor metabolizers, defined as patients carrying two inactive alleles, reduce the dose of imipramine by 70% and monitor imipramine and desipramine plasma concentrations.

For CYP2D6 intermediate metabolizers, defined as patients carrying two decreased-activity alleles or one active/decreased-activity allele and one inactive allele, reduce the dose of imipramine by 30% and monitor imipramine and desipramine plasma concentrations.

For CYP2D6 ultrarapid metabolizers, defined as patients carrying a gene duplication in the absence of inactive or decreased-activity alleles, select an alternative drug (e.g., citalopram, sertraline) or increase dose by 70% and monitor imipramine and desipramine plasma concentration (Table 5).

For CYP2C19 poor metabolizers, reduce the dose of imipramine by 30% and monitor plasma concentration of imipramine and desipramine or select an alternative drug (e.g., fluvoxamine, mirtazapine).

For CYP2C19 intermediate metabolizers, there is insufficient data to allow calculation of dose adjustment for imipramine, select an alternative drug (e.g., fluvoxamine, mirtazapine)

There are no data for dose recommendations for CYP2C19 ultrarapid metabolizers (Table 6).

Table 5. *CYP2D6* phenotypes and the therapeutic recommendations for imipramine therapy, from The Dutch Pharmacogenetics Working Group (2011)

Phenotype	Recommendations for imipramine therapy
Ultrarapid metabolizer	Select alternative drug (e.g., citalopram, sertraline) or increase dose by 70% and monitor imipramine and desipramine plasma concentration
Intermediate metabolizer	Reduce dose by 30% and monitor imipramine and desipramine plasma concentrations
Poor metabolizer	Reduce dose by 70% and monitor imipramine and desipramine plasma concentrations

The level of evidence for the therapeutic (dose) recommendations is 4/4 ("good quality") for all metabolizer types. There are no data for ultrarapid metabolizers. The Table is adapted from Swen J.J., Nijenhuis M., de Boer A., Grandia L. et al. Pharmacogenetics: from bench to byte - an update of guidelines. Clinical pharmacology and therapeutics. 2011;89(5):662–73 (30).

Table 6. *CYP2C19* phenotypes and the therapeutic recommendations for imipramine therapy, from The Dutch Pharmacogenetics Working Group (2011)

Phenotype	Recommendations for imipramine therapy
Ultrarapid metabolizer	No dose recommendations
Intermediate metabolizer	No dose recommendations
Poor metabolizer	Reduce dose by 70% and monitor plasma concentration of imipramine and desipramine or select alternative drug (e.g., fluvoxamine, mirtazapine)

The level of evidence for the therapeutic (dose) recommendations is 4/4 ("good quality") for all metabolizer types. The table is adapted from (31)

Please review the complete therapeutic recommendations that are located here: (30, 31).

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
*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 database: https://www.pharmvar.org/

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