

## Pharmacogenomics of Antidepressant Medications

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### Review

#### ABSTRACT

Tricyclic antidepressants and SSRIs, prescribed for major depressive disorders, anxiety and/or neuropathic pain, are associated with therapeutic failures in approximately 40% of patients after initial dosing. Pharmacogenetic variances play a significant role in these failures and therefore, using genetic data in decision-making to personalize dosing may both enhance efficacy and reduce adverse effects. Polymorphisms affect several pharmacodynamic and pharmacokinetic variables that modulate efficacy and adverse effects; however, clinical data at this time most strongly associate variant diplotypes of cytochrome P450 (CYP) enzymes with potentially altered metabolism. Four potential patient phenotypes can result from these variants: normal-, poor-, and intermediate- and ultrarapid-drug metabolizers. Plasma concentrations of amitriptyline, nortriptyline and fluvoxamine, paroxetine, citalopram, escitalopram, and sertraline are strongly influenced by the actions of two CYP450s: CYP2D6 and CYP2C19. These CYPs are two of the most polymorphic cytochromes. Pharmacogenetic genotyping of these CYPs has led to phenotype-guided TCA and SSRI recommendations, although current guidelines are limited to drugs with sufficient accumulated clinical evidence. Overall, these guidelines call for patients phenotyped as CYP2D6 or CYP2C19 poor or ultrarapid metabolizers to consider modifications such as dose adjustments or alternative antidepressants. Most newer antidepressants are not supported by the volume or strength of clinical data as are TCAs and SSRIs and thus fewer genomic-based guidelines exist for these newer drugs, although some recommendations are being made. Pharmacogenomic testing is likely to be most useful in early treatment and is limited by identification of known variants, sufficient clinical data sets, epigenetic factors such as pheno-conversion, other drug-drug interactions and comorbidities such as liver disease.

**Keywords:** Pharmacogenetics, Pharmacogenomics, Single nucleotide polymorphisms, Metabolizers, CYP2D6, CYP2C19.

**Abbreviations:** CPIC: Clinical Pharmacogenetics Implementation Consortium; CYP: Cytochrome P450; DPWG: Dutch Pharmacogenetics Working Group (Royal Dutch Pharmacist Association Pharmacogenetics Working Group); FDA: Food and Drug Administration (U.S.); NDRI: Norepinephrine and Dopamine Reuptake Inhibitor; PD: Pharmacodynamic; PK: Pharmacokinetic; SNP: Single Nucleotide Polymorphisms; SNRI: Serotonin Norepinephrine Reuptake Inhibitor; SSRI: Selective Serotonin Reuptake Inhibitor; TCA: Tricyclic Antidepressants.

#### INTRODUCTION

Antidepressant medications of the tricyclic antidepressant (TCA) and selective serotonin reuptake inhibitor (SSRI) classes are prescribed for major depressive disorders, anxiety and/or neuropathic pain. Traditional empiric therapy with these classes has been associated with therapeutic failures in approximately 40% of patients after initial dosing and it is believed that pharmacogenetic variances play a significant role in these failures [1]. Therefore, personalizing antidepressant selection and dosing for individual patients could significantly enhance efficacy and/or reduce adverse effects. Personalized medicine, which has been characterized often as “the right patient with the right drug at the right dose at the right time” [1] is the use of genomic and other data to select a drug and/or a dose for a patient that will provide efficacy with minimal undesired toxicity when they first present with an illness. This strategy aims to improve upon the estimated 40 – 70% of drugs that are not initially effective or the approximately 7% which produce serious adverse effects [2]. Efficacy and adverse effects for an individual patient or population of patients are governed by both pharmacokinetic and pharmacodynamic drug properties [3]. Pharmacokinetics (PK), the effect of the body on drug,

includes variables involved in absorption, distribution, metabolism and excretion (ADME). Pharmacodynamics (PD), the effect of drug on the body, encompasses targets such as receptors, enzymes, nucleotides, lipids, etc. The most reasonable approach to personalizing antidepressant therapy would involve accurate profiling of a patient's PD and PK as they pertain to specific antidepressants. This personalization could involve both understanding of genetic (such as gene sequences) as well as epigenetic factors (such as drug-drug interactions or liver disease). At this point in time, insufficient clinical data exists to completely personalize antidepressant therapies; however, pharmacogenomic data do now support potential dosing adjustments for some TCAs and SSRIs. This review begins with an overview of several pharmacologic variables that can in theory be used to guide personalized medication decisions for antidepressants followed by identification of metabolic enzymes that are being used now. Next, we provide a brief, general description of nomenclature relevant to pharmacogenomics and then current guidelines for specific antidepressants.

### **Variables that Affect Personalized Responses to Antidepressants**

Ideally, pharmacogenomics should be applied to relevant aspects of both a patient's PD and PK. Of potential pharmacodynamic effectors relevant to antidepressants, the serotonin transporter linked polymorphic region, 5-HTTLPR, has been intensely studied; however, conflicting clinical responses do not presently allow strong enough evidence for dosing recommendations based on genetic variances and protein expression of this transporter [3]. Three other genes which encode proteins relevant to the PD of antidepressants have been investigated through large population clinical trials: the serotonin 2A receptor (*HTR2A*), the FK506 binding protein 5 and the glutamate receptor ionotropic, kainite 4 (*GRIK4/GluK4*). As with the 5-HTTLPR transporter, conflicting clinical correlative results have prevented recommendations for dose adjustments [3]. Therefore, although PD effectors of antidepressant drugs should ideally be part of the basis of therapeutic decision making, available clinical evidence does not support use of variances in PD genes to predict clinical outcomes.

Of potential pharmacokinetic effectors, the cytochrome P450 (CYP) enzymes are the major family of drug-metabolizing enzymes that influence antidepressant metabolism. Genetic polymorphisms are generally common in drug metabolizing enzymes and particularly so in CYP enzymes [4]. CYP2D6 is considered the most relevant of the CYP enzymes and CYP2C19 the second most relevant CYPs for antidepressant metabolism [2]. Both are extensively polymorphic and have allelic frequencies that vary by ethnicity [5]. Clinical evidence backs the use of several variant alleles to guide dosing of some antidepressants [5-7].

Other pharmacokinetic effectors that ideally should be included in the pharmacogenomics of antidepressants are the protein transporters that allow antidepressants to cross from the brain capillaries into the neuronal tissues. These include the major P-glycoprotein, a 170-KDa glycoprotein encoded by the *ABCB1* (ATP-Binding Cassette transporter, also known as MDR1 - multi drug resistance 1) gene. However clinical correlations between allele variants and clinical responses are not established sufficiently at the present time [3]. Therefore, in the field of antidepressant pharmacogenomics, therapeutic recommendations are not yet largely based on PD variables or on PK variables other than the cytochrome P450 subtypes 2D6 and 2C19 that have gained sufficient correlative clinical evidence for dosing recommendations based upon patient genotypes.

### **Pharmacogenomic Nomenclature**

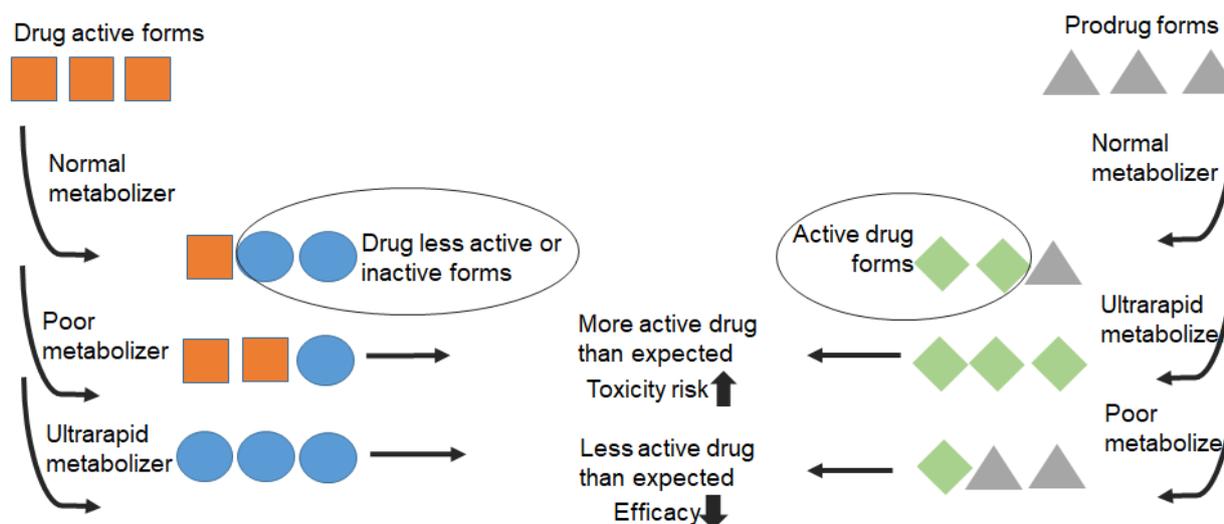
Pharmacogenomic testing laboratories determine a patient's diplotypes for each gene analyzed. The diplotypes represent haplotypes from maternal and paternal sources and typically, the panel tests for the most common genetic variants. Haplotypes are composed of a set of alleles and alleles are described by multiple nomenclatures; however, the star (\*) nomenclature is often the basis for grouping CYP450 genes into categories such as allele typing listed in CPIC Guidelines [8]. In this nomenclature, a symbol of a star precedes a number corresponding to a uniquely identified variant in the genetic code for an enzyme. A diplotype is reported by a listing both star (\*) haplotypes. As an example, a CYP450 2D6 diplotype may be expressed as CYP2D6 \*1/\*1. The \*1 corresponds to the most common allele set and is considered the population norm. i.e., if sequencing detects no variation in the alleles, the star 1 (\*1) is assigned. Variances from the most common sequence are assigned different numbers, for instance, CYP2D619\*1/\*10, has one allele set that is the common \*1 sequence while the second allele set sequence is a variant identified as \*10. Gene duplications can be reported by listing the number of copies if known or pharmacogenetic reports may only indicate that additional copies are present [8].

Variances most often arise from single nucleotide polymorphisms (SNPs). SNPs are the most common genetic variation in people and result when a single nucleotide in a gene sequence is different than the wild-type. SNPs occur on average of every 300 nucleotides and usually have no functional effect on the final protein product coded by a gene. However, if a SNP occurs within a gene's coding region or in a regulatory region near a gene, it may affect the gene's function [9]. For instance, for *CYP2D6*, the \*10 variant has a thymidylate at position 100 substituted for the normal cytidylate at that position (100XC>T). As a result of this substitution, the translated amino acid sequence changes from a proline to a serine at position 34, and the modified enzyme has decreased activity [5].

Pharmacogenetic genotypes show the allelic sequences; however, these data must be translated into an understandable clinical outcome to be useful. The genotypes must indicate a clinical phenotype, which in turn must be strongly correlated with patient outcomes. For CYP genes, the clinical phenotypes are the overall enzyme activities, which can be normal, increased, decreased/absent, or in some cases, unknown.

If a predictive association is determined to exist between a polymorphic genotype and enzymatic activity, then the genotype can be used as one tool to predict responses and perhaps modify the regimen to provide personalized medicine. Two major bodies have evaluated pharmacogenomic associations with clinical drug responses and set predictive guidelines based on an individual's genotype: the Dutch Pharmacogenetics Working Group (DPWG) and the Clinical Pharmacogenetics Implementation Consortium (CPIC) [10]. CPIC publishes peer-reviewed guidelines and posts them to the website PharmGKB.org along with supplemental data. CPIC member institutions are largely in the U.S. and DPWG members largely European. Although many recommendations between CPIC and DPWG overlap, in this review, we have summarized CPIC guidelines where they exist [11].

Polymorphisms can give rise to four potential populations. Those with "normal" metabolism shared by the majority of the human population have been referred to as "extensive metabolizers", but are now referred to as normal metabolizer by CPIC [8]. Individuals with low or no metabolism compared to the general population are referred to as "poor metabolizers" and those with less metabolism compared to the general population are termed "intermediate metabolizers" [5,7]. Individuals with greater enzymatic metabolism compared to the general population are referred to as "ultrarapid metabolizers". While the first three populations result through polymorphic sequences, often SNPs, the ultrarapid metabolizers usually result from the expression of multiple functional allele copies or increased transcription of a gene due to variant sequences in the promoter [5,7]. All four genotypes may affect efficacy or safety response to a drug. As shown in **Figure 1**, if an individual's drug metabolizing phenotype leads to more active drug than expected by the dosing regimen, the risk of toxicity increases.



**Figure 1.** Drug metabolizing enzymes regulate the PK of drug molecules by inactivating active drugs or by activating prodrugs. Active drug forms (left side of Figure) are generally dosed at a level that anticipates they become inactivated at the rate of an extensive metabolizer's enzymes. This normal metabolism leaves fewer biologically active molecules and more less-active or inactive metabolites before the next dosing interval. Poor metabolizers inactivate at a slower rate leaving more active drug than anticipated, while ultrarapid metabolizers inactivate at a faster rate leaving less active drug than anticipated in a general dosing scheme. Prodrugs (right side of Figure) are dosed in anticipation that some molecules will be metabolized into the active form(s) at a normal rate. Ultrarapid metabolizers produce more active drug than anticipated, while poor metabolizers produce less active drug than anticipated. In both scenarios, when more active drug than expected is present, the risk of toxicity increases (active drug and poor metabolizer or prodrug and ultrarapid metabolizer). When less active drug than expected is present, the risk of therapeutic efficacy decreases (active drug and ultrarapid metabolizer or prodrug and poor metabolizer).

This can occur as the result of administering normal doses of active drug to a poor metabolizer because the poor metabolizer cannot clear the active drug as expected. More-than-expected active drug can also occur when a prodrug is administered to an ultrarapid metabolizer since the prodrug is converted faster. Alternatively, if an individual's drug metabolizing phenotype leads to less active drug than anticipated by dosing, the risk of therapeutic failure increases. This can occur as the result of an active drug being inactivated by an ultrarapid metabolizer or a prodrug not being activated by a poor metabolizer. Clinical pharmacogenomics laboratories commonly give an interpretation of the genotype result and provide a predicted phenotype [5]. An example of the application of an identified diplotype to a clinical phenotype is *CYP2D6*\*10/\*10. This diplotype individual inherited two copies of the \*10 variant. This variant encodes a

protein with reduced enzymatic activity. This individual is predicted to have less than full activity and could be described phenotypically as an intermediate metabolizer. An example of a poor metabolizer would be an individual who inherited two non-functional allele sets such as CYP2D6\*5/\*6 since both \*5 and \*6 encode non-functional protein products [5].

In addition to inherited genomic effects, an individual's clinical phenotype may be influenced by other molecules that affect a metabolic enzyme. The process of phenoconversion occurs when one or more factors such as drug molecules convert an existing phenotype to another phenotype. An example of enzymatic phenoconversion is when an individual with a normal diplotype for a metabolic enzyme expresses a poor metabolizer phenotype due to a drug-drug or drug-enzyme interaction [4]; for example, enzyme inducers or inhibitors can phenoconvert an individual's CYP activities.

### Pharmacogenomic Guidelines for TCAs based on Metabolic Enzyme Activity Phenotyping

TCA drugs are used as options to treat depression, although they are now more commonly prescribed at lower doses for neuropathic pain management. Mechanistically, tricyclic antidepressants inhibit the reuptake of the neurotransmitters serotonin and norepinephrine. Tricyclics with a tertiary amine show greater inhibition of serotonin uptake while TCAs with a secondary amine show greater inhibition of norepinephrine. Thus, tertiary amines amitriptyline, clomipramine, doxepin, imipramine, and trimipramine are greater serotonin reuptake inhibitors. The secondary amines desmethyl-clomipramine, desmethyl-doxepin, desmethyl-trimipramine, desipramine, and nortriptyline are greater norepinephrine reuptake inhibitors [5].

Plasma TCA levels are strongly influenced by cytochrome P450 enzymes CYP2D6 and CYP2C19 [4]. As of 2014, CYP2D6 had 105 allelic variants and CYP2C19 had 34 [5]. CYP2D6 metabolizes TCAs into less active molecules, thereby reducing a drug's activity. CYP2C19 de-methylates tertiary amines producing secondary amines, thereby shifting serotonin reuptake towards norepinephrine. The genetic sequences encoding some CYP2D6 and 2C19 variants have correlated strongly enough with clinical phenotypes and patient dosing outcomes that they support guidelines for dosing of amitriptyline and nortriptyline and potentially other TCAs [5,6].

The 2D6 enzyme has at least two variants which encode functional enzymes, designated in the star nomenclature as CYP2D6\*1 and CYP2D6\*2. Three reduced function allele sets exist and are designated CYP2D6\*9, \*10, and \*41. Four nonfunctional allele sets are designated CYP2D6\*3- \*6. Of these non-functional alleles, the \*5 is a deletion of one allele. The most common allele set, \*1 of CYP2D6 has been found to be duplicated in instances in which a patient holds multiple copies of the gene [5]. Such duplications are identified by an "xN" after the name of the haplotype, i.e., a patient with three copies of the 2D6 gene would be identified as "CYP2D6\*1X3".

The CYP2C19 is encoded mainly by three of the 34 identified allelic variants: CYP2C19\*1 (most common or wild-type), \*2 (encodes a loss of function enzyme) and \*17 (enhanced transcription and therefore more copies of the enzyme). Based upon 2D6 and 2C19 genotyping, patients are assigned to a phenotype of either poor metabolizers, intermediate metabolizers, normal metabolizers or ultrarapid metabolizers [5]. The approximate percentage of the population with these phenotypes for 2D6 is: poor metabolizer, 5-10%; intermediate metabolizer, 2-11%; normal metabolizer, 77-92%; ultrarapid metabolizer, 2%. For 2C19 the population percentages are approximately, poor metabolizer, 2-15%; intermediate metabolizer, 18-45%; normal metabolizer, 35-50%; ultrarapid metabolizer, 5-30% [5].

Dosing recommendations which follow are categorized by the CYP enzyme and then list the drug guidelines according to patient phenotype (e.g., poor metabolizers, intermediate metabolizers, ultrarapid metabolizers). The strength of clinical evidence used to make recommendations is generally considered by CPIC to be strong for 2D6 phenotypes; for 2C19 phenotypes, recommendations are stronger for normal and intermediate metabolizers than for poor or ultrarapid metabolizers [6]. Although most data acquired and used to guide dosing recommendations for TCAs are based upon amitriptyline and nortriptyline [5], CPIC has recently also made recommendations for other TCAs based on PK similarities [6].

For the use of TCAs to treat neuropathic pain, 2D6 or 2C19 poor or intermediate metabolizer patients do not need dose modifications since neuropathic pain generally is dosed with TCAs at lower levels than for depression. For 2D6 ultrarapid metabolizers, an alternative therapy is recommended since these patients may fail therapy. For 2C19 ultrarapid metabolizers, no CPIC recommendation exists [5]. Normal metabolizers (i.e., those who carry the common, functional alleles) should receive initial therapy at the recommended starting doses.

For therapy of depression (Table 1) with amitriptyline or nortriptyline, for 2D6 poor metabolizers, an alternative therapy or a 50% dose reduction is recommended; for intermediate metabolizers, a dose reduction of 25% is recommended; for ultrarapid metabolizers, alternative drug therapy is recommended [5]. Normal metabolizers receive initial therapy at the recommended starting doses are therefore not listed in the Tables.

For therapy of depression with other TCAs, recommendations are considered optional since they are supported by less clinical data. Poor metabolizers should avoid other tertiary amine TCAs or receive a reduced initial dose and therapeutic drug monitoring. Ultra-rapid metabolizers should avoid other tertiary amines [6].

**Table 1.** Pharmacogenomic guidelines for amitriptyline, nortriptyline and other TCAs based on metabolic enzyme activity phenotyping.

Clinical Phenotype of CYP2D6 <sup>a</sup>	Amitriptyline/ Nortriptyline	<sup>b</sup> other TCAs
Poor	Alternative drug or 50% dose reduction	<sup>c</sup> <b>Optional:</b> Alternative drug or 50% dose reduction
Intermediate	Consider 25% reduction and therapeutic drug monitoring	<b>Optional:</b> Consider 25% reduction and therapeutic drug monitoring
Ultrarapid	Alternative drug	<b>Optional:</b> Avoid TCAs or consider higher dose and therapeutic drug monitoring.
Clinical Phenotype of CYP2C19	Amitriptyline	<sup>d</sup> other Tertiary TCAs
Poor	50% dose reduction	<b>Optional:</b> Avoid tertiary amines such as amitriptyline, clomipramine, imipramine, trimipramine, doxepin or consider a 50% reduction of starting dose of tertiary amines and use therapeutic drug monitoring.
Intermediate	No change to dosing	No change to dosing
Ultrarapid	Consider alternative drug	Optional: Avoid tertiary amines or use therapeutic drug monitoring

<sup>a</sup> Extensive-metabolizers receive routine starting dosing are therefore not listed in the Table. <sup>b</sup> Other TCAs include both secondary and tertiary classes.  
<sup>c</sup> Recommendations for other TCAs are considered optional because of less direct PK or trial data.  
<sup>d</sup> Other Tertiary TCAs include clomipramine, imipramine, trimipramine, doxepin.

**Legend:** Dosing recommendations are based on published CPIC guidelines <sup>[5,6]</sup> and are for CYP2D6 and CYP2C19 phenotypes. These guidelines pertain to the use of amitriptyline, nortriptyline and for other TCAs for treatment of conditions such as depression, not neuropathic pain. Because CYP2C19 affects metabolism of tertiary amine TCAs, recommendations for 2C19 variants apply only to tertiary amine TCAs. For therapy of depression with amitriptyline in 2C19 phenotypes, poor metabolizers should receive a 50% dose reduction; intermediate metabolizers receive no dose change; Ultrarapid metabolizers should consider either an alternative drug or no changes (**Table 1**)<sup>[5]</sup>. For therapy of depression with other tertiary amines in 2C19 phenotypes, recommendations are considered optional. Poor metabolizer status patients should either avoid tertiary amines or else consider a 50% dose reduction and therapeutic drug monitoring. Ultrarapid metabolizers should either avoid tertiary amines or use therapeutic drug monitoring <sup>[6]</sup>.

For patients with genetic variants in both 2D6 and 2C19, recent CPIC guidelines make recommendations for amitriptyline (not shown). These guidelines suggest avoiding amitriptyline use in patients with opposite CYP phenotypes (i.e., phenotyped as a poor metabolizer for one CYP and an ultrarapid metabolizer for the other) <sup>[6]</sup>. For patients phenotyped as normal metabolizers for one CYP, recommendations are to follow guidelines for the other CYP phenotype if it is variant. Patients who are intermediate metabolizers for both CYPs should consider a 25% reduction of the recommended starting dose <sup>[6]</sup>.

### Pharmacogenomic Guidelines for SSRIs based on Metabolic Enzyme Activity Phenotyping

SSRIs are the most common options for depression and anxiety <sup>[12]</sup>. Other uses are for social anxiety disorder, posttraumatic stress disorder and obsessive-compulsive disorder, and bulimia nervosa <sup>[13]</sup>. These agents act by inhibiting the reuptake of the neurotransmitter serotonin. Up to 50% of patients treated with SSRIs fail therapy and accumulating data suggest polymorphisms of either CYP2D6 or CYP2C19 contribute to clinical drug failures or adverse effects <sup>[7]</sup>. Adverse effects associated with SSRIs include gastrointestinal upsets, sexual dysfunction, headache, insomnia, and with citalopram and escitalopram, prolongation of the QT interval which can precipitate arrhythmias <sup>[12]</sup>. Dosing recommendations based on *CYPs 2D6* and *2C19* genotypes exist for fluvoxamine, paroxetine, citalopram, escitalopram, and sertraline <sup>[7]</sup>.

CYP2D6 metabolizes SSRIs paroxetine and fluvoxamine to more inactive molecules and therefore decreased or increased activity of 2D6 can alter response to these SSRIs. Fluoxetine, the most frequently prescribed SSRI, is metabolized by both CYPs 2D6 and 2C19 resulting in a mixture of active and inactive metabolites with varying half-lives. The net effect of parent and metabolites on a patient's clinical phenotype and response to fluoxetine is unclear, and at this time, there are no pharmacogenetic-based guidelines for fluoxetine <sup>[7]</sup>.

Notably however, the FDA label warns that fluoxetine should be used with caution in patients with conditions that predispose to QT prolongation and that such conditions include use of CYP2D6 inhibitors and CYP2D6 poor metabolizer

status [14]. CYP2C19 also plays a role in SSRI metabolism; however, as with TCAs, its role is not inactivation but rather a shift in substrate affinity; in this case leading to weakened serotonin inhibition for citalopram, escitalopram and sertraline.

Therapeutic recommendations for SSRIs based on CYP2D6 genotyping are as follows (Table 2): for patients identified as poor metabolizers, paroxetine and fluvoxamine should be replaced with alternatives not metabolized by 2D6; for intermediate metabolizers, no changes are recommended; for ultrarapid metabolizers, an alternative therapy is recommended for paroxetine [7].

Therapeutic recommendations for SSRIs based on CYP2C19 genotyping are as follows (Table 2) for poor metabolizers, citalopram, escitalopram and sertraline should be replaced with alternatives or else the initial dose should be reduced by 50%; for intermediate metabolizers, no changes are recommended; for ultrarapid metabolizers, citalopram, escitalopram should be replaced with alternatives, while for sertraline, no dosing change is recommended [7].

**Table 2.** Pharmacogenomic Guidelines for Paroxetine, Fluvoxamine, Citalopram, Escitalopram and sertraline based on metabolic enzyme activity.

Clinical Phenotype of CYP2D6 <sup>a</sup>	Paroxetine	Fluvoxamine
Poor	<sup>c</sup> Alternative drug or 50% dose reduction	Alternative drug or 25-50% dose reduction
Intermediate	No change to dosing	No change to dosing
Ultrarapid	Alternative drug	No recommendation
Clinical Phenotype of CYP2C19	Citalopram / Escitalopram	Sertraline
Poor	Alternative drug or 50% dose reduction	Alternative drug or 50% dose reduction
Intermediate	No change to dosing	No change to dosing
Ultrarapid	Alternative drug	No change to initial dosing; consider alternative for lack of efficacy.

<sup>a</sup> Extensive metabolizers receive routine starting dosing are therefore not listed in the Table.  
<sup>b</sup> Clinical phenotype based on genotype interpretation;  
<sup>c</sup> Alternative drugs should not be extensively metabolized by the CYP enzyme

As with TCAs, phenoconversion of normal to poor metabolizer status is possible if patients are co-administered CYP2D6 inhibitors such as paroxetine or fluoxetine. Dosing recommendations are based on published CPIC guidelines [7] and are for CYP2D6 and CYP2C19 phenotypes.

For fluoxetine, recommendations have not been written because of inconsistent and conflicting clinical studies; however, polymorphisms of SLC6A4, HTR1A and MAO-A genotypes are involved in patient's response to fluoxetine and several other gene products as well as gender and ethnicity may modulate therapeutic activities [15].

### Genomic-Based Recommendations for Newer Antidepressants

Although SSRIs are generally first-line drugs, newer generation antidepressants present alternatives with less adverse effects than TCAs. These new generation agents include newer Serotonin Norepinephrine Reuptake Inhibitors (SNRIs), the serotonin and  $\alpha$ 2-adrenergic receptor antagonist mirtazapine, the norepinephrine and dopamine reuptake inhibitor (NDRI) bupropion and mixed serotonergic medications.

Of the newer SNRIs (Table 3), Venlafaxine is extensively metabolized by CYP2D6 into O-desmethyl-venlafaxine, which is an active metabolite. 2D6 poor metabolizers have much higher serum venlafaxine to O-desmethyl-venlafaxine ratios and although these patients have similar efficacy to other phenotype groups, 2D6 poor metabolizers experience greater adverse effects such as nausea, vomiting and diarrhea [16]. CPIC guidelines are not established for venlafaxine; however, the Dutch Pharmacogenetics Working Group (DPWG) evaluated overall available data for venlafaxine based on CYP2D6 genotypes and recommend the selection of either an alternative drug or adjustment of venlafaxine dosage for poor and also for intermediate metabolizers. For ultra-rapid 2D6 metabolizers, DPWG recommends dosing to a maximum of 150% of the normal dose or selecting an alternative drug [17]. The new SNRI duloxetine is also metabolized by CYP2D6; however, after evaluating dose recommendations for duloxetine based on CYP2D6 genotype, the DPWG concluded no therapeutic dose changes should be recommended [18]. CPIC also makes no recommendations for duloxetine [19]. Milnacipran, a third new SNRI, appears to undergo minimal CYP metabolism; patients who are poor metabolizers for

either CYP 2D6 or 2C19 show no altered levels of either milnacipran or its metabolites [20]. Neither CPIC nor DPWG recommend altering Milnacipran based on genotyping.

**Table 3.** Pharmacogenomic status for newer generation antidepressants.

Drug	CYP in metabolism	Pharmacogenomic Guidelines Recommendations (Yes and source or No)	or Clinical Phenotype of Metabolism & Applicable Recommendations
<b>Serotonin-Norepinephrine Reuptake Inhibitors (SNRI)</b>			
Venlafaxine	2D6	Yes (DPWG)	Poor/Intermediate -alternative drug or dose adjustment. Ultrarapid - alternative drug or dose to a maximum of 150% of the normal dose
Duloxetine	2D6	No	<sup>a</sup> N/A
Milnacipran	Minimal	No	N/A
<b>Serotonin and <math>\alpha</math>2-Adrenergic antagonist</b>			
Mirtazapine	2D6	No	N/A
<b>Norepinephrine and Dopamine Reuptake Inhibitor (NDRI)</b>			
Bupropion	2B6	No	N/A
<b>Mixed Serotonergic Medication</b>			
Vortioxetine	2D6	Yes (FDA)	Poor – dose reduction
Vilazodone	3A4	No	N/A

Newer agents are shown with their major CYP involved in metabolism, genomic-based recommendations if available with the source of recommendations and brief explanation of recommendations for metabolizer phenotype.

The serotonin and  $\alpha$ 2-adrenergic receptor antagonist mirtazapine is metabolized by CYP2D6 and has been evaluated by DPWG based on CYP2D6 genotype; however, neither they nor CPIC recommend dosing adjustments [21]. The NDRI bupropion is metabolized by CYP2B6, a liver CYP with at least 28 allelic variants [22] into a less active metabolite, hydroxy bupropion. However, clinical evidence associated with variants has not been strong enough to lead to altered dosing guidelines by either CPIC or DPWG [19].

Of drugs in the newer mixed serotonergic medications class, vortioxetine is metabolically inactivated by CYP2D6 and though no CPIC or DPWG recommendations have been published, the FDA label calls for a dose reduction in 2D6 poor metabolizers [23]. Vilazodone is metabolized primarily by CYP 3A4 and a kinetics study has recommended a dose reduction when co-administered with strong 3A4 inhibitors [24]; however, genotype-based dosing guidelines have not been developed by either CPIC or DPWG [19].

### Limitations of Pharmacogenomics in Dosing Guidelines

Testing for pharmacogenomic interactions is most relevant when a drug therapy is initiated. Once patients have begun antidepressant pharmacologic therapies and achieve efficacy with the therapy, pharmacogenomic testing is of less benefit [5]. Alleles, both normal and variants, are searched for using known sequences and therefore a new or rare or undiscovered variant will not be identified and in these instances the patient would be assumed to encode a normal allele [5]. Therefore, a small possibility exists for a patient to be falsely assigned a \*1 if they have an undiscovered variant sequence. In addition, the genetics of other nonmetabolic enzyme factors regulate the PD and PK of drug responses, yet reliable genetic assays for these nonmetabolic factors have not been developed and clinically validated, and thus their pharmacogenomics are not currently used to make dosing recommendations [4]. As mentioned above, phenoconversion factors can override predicted phenotypes and CYP2D6 is a commonly phenoconverted enzyme.

## CONCLUSION

The benefit of genotype testing is its potential to enhance efficacy and/or reduce adverse effects. Antidepressant pharmacogenetics play a relevant role in achieving efficacy and reducing risks of adverse effects, yet at this time, guidelines for drug or dosing changes exist for only some agents and are largely based on CYP450 enzyme genotypes. CYP2D6 and 2C19 test results are only one of multiple variables that must be considered in determining therapies for

depression and existing guidelines do not yet encompass the many potential variables outside of drug metabolizing enzymes such as neurotransmitter receptors and transport proteins. When these other variables gather sufficient evidence to also warrant pharmacogenomic guidelines, one clear challenge will be to integrate multiple phenotypes encompassing both PD and PK variables in a manner that will still lead to sensitive and specific personalized recommendations. The foundation however, for a process of genotype testing and application of some genotypes to drug management decisions has been established and can be used to accommodate future data.

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