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Technical Bulletin

Antidepressants

SSRIs (selective serotonin reuptake inhibitors)

Report Type: Pharmacogenetics

Reported Medications: citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, vilazodone

About

Selective serotonin reuptake inhibitors (SSRIs) are prescribed to treat various psychiatric conditions, including depression, anxiety and personality disorders. Less than 50% of the depressed patients using SSRIs experience a complete remission of symptoms.[1,2,3] Furthermore, suboptimal responses can delay the use of effective medications and remission of symptoms.[2] SSRI treatment is also associated with gastrointestinal side effects,[4] and gastrointestinal adverse effects occur in up to 40% of patients. These effects can be severe enough to cause early treatment discontinuation.[5] Genetic differences can play an important role in determining patient responses.[6]

Genetics

Introduction

SSRIs block serotonin reuptake by serotonin transporters, resulting in increased serotonin levels in the synaptic cleft for binding to serotonin receptors. Patient response to SSRIs can be influenced by variants in the SLC6A4 gene that encodes the serotonin transporter, the HTR2A gene that encodes one of the serotonin receptors, or genes related to drug metabolism, such as members of the cytochrome P450 (CYP) enzyme family. CYP2D6 and CYP2C19 alleles fall into one of four categories: non-functional, reduced function, normal function or increased function. Based on the combination of alleles, patients are classified by metabolizer type: poor metabolizer (PM, low or no enzyme activity), intermediate metabolizer (IM, intermediate enzyme activity), extensive metabolizer (EM, normal enzyme activity) or ultrarapid metabolizer (UM, higher than normal enzyme activity).

Citalopram

CYP2C19 gene

CYP2C19 metabolizer status is associated with the rate of clearance of drug metabolites and the likelihood of toxicity. Citalopram is a racemate metabolized by three CYP enzymes to less active compounds. CYP2C19 is the main enzyme, which catalyzes the enantioselective demethylation of citalopram.[7] The two most common CYP2C19 loss-of-function alleles are CYP2C19 *2 and CYP2C19 *3.[8] CYP2C19 PMs have impaired citalopram metabolism and decreased clearance. PMs are at increased risk of citalopram accumulation and drug-associated toxicity.[1,7,9,10,11]

UMs have lower citalopram plasma concentrations and increased risk of non-response. The CYP2C19 *17 allele is associated with higher enzyme activity due to an extra transcription factor-binding site in the promoter region.[11] CYP2C19

*17 homozygous individuals have decreased plasma levels of citalopram and are less likely to respond to standard doses of the drug.[12] White non-Hispanic individuals who have the CYP2C19 *17 allele showed a lower rate of remission among citalopram-tolerant patients.[1] Thus, the identification of CYP2C19 UMs can provide a possible explanation for therapeutic failure or help to exclude non-compliance of patients.[12,13,14]

HTR2A gene

HTR2A mutations are associated with response to citalopram in patients with major depression, susceptibility to schizophrenia or obsessive-compulsive disorder. Significant association was detected between a variant in the HTR2A gene and citalopram treatment response in a mixed-race sample.[15] In a large study of patients with major depressive disorder who were treated with citalopram, the association between response to the drug and the A allele of the rs7997012 marker was found in Caucasian patients. No significant association between the A allele and either treatment response or remission was detected in black patients. However, 79.9% of white patients homozygous for the A allele were classified as "responders" compared to 63.5% of white patients homozygous for the G allele. The homozygous A genotype at rs7997012 conferred a 16-18% reduction in absolute risk of being a nonresponder in this sample.[15]

SLC6A4 gene

The most studied variant of SLC6A4 is a variable number tandem repeat called 5-HTTLPR. A 20-23 base pair segment is repeated 14 times in the short (S) allele or 16 times in the long (L) allele, which leads to twice the expression of the S allele.[16]

The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial is a multicenter trial in which DNA samples were collected from almost 2,000 individuals diagnosed with depression. These patients were treated with citalopram and followed by regular assessment of outcome and adverse events. This study found an association between the low expression alleles and increased risk of citalopram-related adverse effects.[17]

FDA-approved drug labels recommend initiating treatment at half the recommended dose or prescribing alternative medications for PMs[14,18,19] The Royal Dutch Association for the Advancement of Pharmacy's Pharmacogenetics Working Group (PWG) recommends alternative therapies to escitalopram, such as fluoxetine or paroxetine, for CYP2C19 UMs.[20] A recent FDA Drug Safety Communication advises against citalopram doses greater than 40 mg per day due to dose-dependent QT interval prolongation; thus, titrating the citalopram dose for UMs to a maximum of 150%, as PWG suggests, is not recommended.[20,21]

Escitalopram

CYP2C19 gene

CYP2C19 metabolizer status is associated with escitalopram plasma concentrations. Escitalopram is the pharmacologically active S-enantiomer of citalopram and one of the most commonly prescribed SSRIs.[22] CYP2C19 PMs are at risk of up to 5.7-fold higher plasma levels of escitalopram compared to EMs and have significantly reduced clearance compared to patients with other CYP2C19 metabolizer statuses.[22,23,24]

CYP2C19 UMs have lower escitalopram plasma concentrations. The CYP2C19 *17 allele is associated with higher enzyme activity due to an extra transcription factor-binding site in the promoter region.[11] CYP2C19 *17 homozygous individuals have increased metabolism and decreased plasma levels of escitalopram, which may indicate a risk of therapeutic failure.[24,25] EMs and UMs can clear escitalopram approximately 34% faster than individuals with loss-of-function CYP2C19 *2 or CYP2C19 *3 alleles.[22] The identification of CYP2C19 ultrarapid metabolizers can provide a possible explanation for treatment failure or help exclude non-compliance of patients.[13]

CYP2C19 activity decreases with increasing age, and dose adjustments may be important for older PMs.[22] Recent studies have proposed taking both age and CYP2C19 genotype into account when prescribing escitalopram.[22,25] The bioavailability and half-life of escitalopram increase approximately 50% in elderly patients.[26] Long-term excessive exposure in these patients may increase the risk of hyponatremia, gastrointestinal bleeding, falls and fractures, and bradycardia.[22]

The Royal Dutch Association for the Advancement of Pharmacy's Pharmacogenetics Working Group recommends alternative therapies to escitalopram, such as fluoxetine or paroxetine, for CYP2C19 UMs.[20] The U.K. label for citalopram recommends that CYP2C19 PMs be administered an initial dose of 10 mg daily during the first two weeks of treatment; dose may be increased to 20 mg depending on patient response.[27]

Fluoxetine

CYP2D6 gene

Fluoxetine is a racemic drug mixture of 50% S-fluoxetine and 50% R-fluoxetine. S-fluoxetine and R-fluoxetine are demethylated to S-norfluoxetine and R-norfluoxetine, respectively, by CYP2D6. Both forms are bioactive metabolites, but S-norfluoxetine is more active than R-norfluoxetine.[28] Clinical Pharmacogenetics Implementation Consortium (CPIC) dosing guidelines note that "CYP2D6 poor metabolizers have been demonstrated to possess significantly higher fluoxetine plasma concentrations than extensive metabolizers".[28]

SLC6A4 gene

The 5-HTTLPR variant in the SLC6A4 gene has been the subject of numerous studies using a variety of SSRIs, including citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine and sertraline.[29] A meta-analysis of eight studies, which included mixed populations of Caucasians and Asians, found an association of SSRI-induced side effects with the S/S genotype of the 5-HTTLPR variant.[30] The eight studies included in this meta-analysis examined fluvoxamine, fluoxetine and paroxetine.[30]

Fluvoxamine

CYP2D6 gene

Fluvoxamine is metabolized to inactive metabolites, mainly by CYP2D6 and CYP1A2 enzymes.[31] Before 2003, CYP2D6 metabolizer status could be biochemically determined, and PMs were known to have higher maximum plasma concentrations of fluvoxamine, longer drug half-life, and lower oral clearance compared to EMs.[31,32,33,34]

Variants in the CYP2D6 gene have been shown to contribute to an individual's clearance of fluvoxamine. The plasma concentration of fluvoxamine can be up to 3-fold higher in individuals with two defective alleles compared to normal individuals.[35,36,37] The clearance rate of the primary fluvoxamine metabolite is 78% lower in PMs compared to EMs in urine.[31] CYP2D6 genotype may only impact fluvoxamine plasma concentrations at low doses (50 mg/day).[35,36] This effect may be due to fluvoxamine being a CYP2D6 inhibitor and saturating the enzyme at higher doses.[38] Furthermore, factors other than CYP2D6 may affect fluvoxamine metabolism at higher doses.[36]

CYP2D6 genotype is also associated with risk of adverse effects. Gastrointestinal side effects and paroxysmal supraventricular tachycardia have been described in PMs and IMs.[5,32,33]

The CYP1A2 enzyme is induced by smoking, which could mask the impact of CYP2D6 variants on fluvoxamine metabolism. Smokers have increased fluvoxamine metabolism, lower plasma concentrations, and increased oral clearance of fluvoxamine compared to non-smokers.[31,35,39]

HTR2A gene

Two of the most studied HTR2A variants are 102C>T (rs6313) and -1438G>A (rs6311).[40,41,42] The 102C>T locus has no known function, but the −1438 G allele is associated with decreased promoter activity compared to the A allele.[43] According to a recent meta-analysis, these variants can be used to predict intolerance to SSRIs; individuals with the -1438G or 102C alleles are at increased risk.[30] Additionally, in depressed patients treated with fluvoxamine, the risk of developing gastrointestinal side effects was 2.171-fold higher and 2.926-fold higher in patients with one and two -1428G alleles, respectively.[5]

SLC6A4 gene

Please see "SLC6A4 gene" under "Fluoxetine".

Paroxetine

CYP2D6 gene

Paroxetine is both a substrate and potent inhibitor of the CYP2D6 enzyme, one of the main metabolizing enzymes of paroxetine,[44,45,46] and CYP2D6 genotype is associated with paroxetine pharmacokinetics.

CYP2D6 PMs have two inactive CYP2D6 alleles, which may lead to higher paroxetine plasma concentrations than UMs or EMs.[47,48,49,50] Consistent with these observations, PMs have increased risk of accumulating high levels of unmetabolized drug, greater potential for drug-drug interactions and increased risk of lower efficacy.[47] However, there is inconsistency in the literature regarding an association between increased paroxetine plasma concentrations and the occurrence of adverse effects.[51]

CYP2D6 UMs have an increased drug metabolism, which may lead to therapeutic failure at standard doses. UMs have three or more active CYP2D6 alleles. UMs present with extremely low or undetectable paroxetine plasma or serum concentrations.[49,50,52,53] Identifying a patient as a CYP2D6 UM may be useful to predict therapeutic failure, explain low

serum or plasma concentrations or exclude noncompliance.[49,54] Multiple dosing causes decreased CYP2D6 metabolism of paroxetine and may result in conversion of UM to EM.[55]

CYP2D6 activity is known to vary significantly, even in CYP2D6 EMs.[56] In some EMs, CYP2D6 may be maximally inhibited, which can cause conversion to PM status and increased risk of sexual dysfunction.[54,55,57,58]

The Royal Dutch Association for the Advancement of Pharmacy's Pharmacogenetics Working Group recommends alternative therapies to paroxetine for CYP2D6 UMs.[20] Dose increase of paroxetine for treatment of EMs and UMs is not recommended due to the reported teratogenic effects of parexetine and the availability of alternative medication.[45,59]

HTR2A gene

Two of the most studied HTR2A variants are 102C>T (rs6313) and -1438G>A (rs6311).[40,41,42] The 102C>T locus has no known function, but the −1438 G allele is associated with decreased promoter activity compared to the A allele.[43] The -1438G>A (102C>T) genotype is associated with paroxetine-induced adverse effects and tolerance in Asian and Caucasian patients.[2,4] In one study, the homozygous G genotype of -1438G>A was associated with severe nausea and greater severity of all adverse drug reactions, including gastrointestinal symptoms, sexual dysfunction, headache, dizziness and the appearance of psychotic symptoms.[2] Another study showed that 46.3% of homozygous 102C individuals discontinued paroxetine use compared to 16% of other users. Reasons included gastrointestinal complaints, somnolence and difficulty concentrating, agitation, sleep disturbance, dizziness, sweating, headache, and sexual dysfunction. The severity of side effects in homozygous 102C individuals was also greater.[4]

SLC6A4 gene

Please see "SLC6A4 gene" under "Fluoxetine".

Sertraline

CYP2C19 gene

The CYP2C19 enzyme is a main enzyme involved in metabolizing sertraline to inactive compounds,[60] and CYP2C19 genotypes are associated with the pharmacokinetics of sertraline.[61,62] In studies of Caucasian and Asian patients, CYP2C19 PMs had higher plasma concentrations of sertraline compared to EMs.[61,63] A 3.2-fold difference was observed between Caucasian EMs and PMs,[63] which may be important for clinical outcome of treatment. However, little is known about the relationship between sertraline systemic exposure and clinical response to treatment. Some PMs may experience nausea, diarrhea, dizziness and dry mouth.[61]

The Royal Dutch Association for the Advancement of Pharmacy's Pharmacogenetics Working Group recommends dose reduction of 50% for CYP2C19 PMs.[20]

Vilazodone

CYP3A4 gene

CYP3A4 contributes significantly in the metabolism of vilazodone while CYP2C19 and CYP2D6 play a minor role.[64] Clinical effects of vilazodone are direct through the drug with no other active metabolites.[65] In vitro studies and FDA drug label recommends reducing the dose of vilazodone if administered concomitantly with strong or moderate CYP3A4 inhibitors.[64,65]

Markers or Alleles Tested

CYP2C19 gene

CYP2C19 alleles tested: [CYP2C19 *2, CYP2C19 *3, CYP2C19 *4, CYP2C19 *5, CYP2C19 *6, CYP2C19 *7, CYP2C19 *8, CYP2C19 *17]

Predicted CYP2C19 Metabolizer Status

Metabolizer Status	CYP2C19 Diplotype
Poor Metabolizer	*2-*8/*2-*8
Intermediate Metabolizer	*1/*2-*8, *17/*2-*8
Extensive Metabolizer	*1/*1
Ultrarapid Metabolizer	*1/*17, *17/*17

CYP2D6 gene

CYP2D6 alleles are classified as non-functional, reduced-function, normal-function and increased-function.

Non-functional alleles: *3, *4, *5, *6, *7, *8, *11, *12, *14A, *15, *36, *4xN, and *36xN
Reduced-function alleles: *9, *10, *17, *29, *41, *9xN, *10xN, *17xN, *41xN and *36-*10
Normal-function alleles: *1, *2 and *35
Increased-function alleles: *1xN, *2xN and *35xN

Predicted CYP2D6 Metabolizer Status

Metabolizer Status	CYP2D6 Genotype
Poor metabolizer	Two non-functional alleles
Intermediate metabolizer	One non-functional allele and one reduced-function allele OR Two reduced-function alleles
Extensive metabolizer	One or two normal-function copies of the CYP2D6 gene
Ultrarapid metabolizer	Three or more normal-function copies of the CYP2D6 gene

CYP3A4 gene

Reduced-function alleles: *4, *5, *6, *20, *22 and *26

HTR2A gene

This test includes the 102C>T (rs6313) and -1438G>A (rs6311) alleles.

SLC6A4 gene

This test includes the 5-HTTLPR variant, which is a variable number tandem repeat with a segment that is repeated 14 or 16 times in the short (S) allele or long (L) allele, respectively. It also includes an assay for an A>G substitution present on the L allele (rs25531).

Ethnic Distribution of Tested Alleles or Phenotypes

CYP2C19 gene

The frequency of CYP2C19 PMs is distinctly higher in Asians (13-23%) compared to Caucasians (2-5%). Combinations of CYP2C19 *2 and CYP2C19 *3 alleles can account for 100% of Asian PMs.[11] In Caucasians, the homozygous CYP2C19 *2 carriers represent 75-93% of the PMs.[12]

The CYP2C19 panel detects alleles that have a combined frequency of over 99% in major ethnic groups.[66]

Allele	Enzyme activity	CYP2C19 marker	Caucasian	African	East Asian	Middle Eastern
*1	Normal	Wild-type	63%	68%	60%	87%
*2	None	rs4244285	15%	15%	29%	12%
*3	None	rs4986893	0.42%	0.52%	8.9%	1.1%
*4	None	rs28399504	0.25%	0.093%	0.049%	ND[a]
*5	Reduced	rs56337013	0.0073%	ND	0.062%	ND
*6	None	rs72552267	0.017%	0%	0%	ND
*7	None	rs72558186	ND	ND	0%	ND
*8	Reduced	rs41291556	0.35%	0%	0%	ND
*17	Increased	rs12248560	21%	16%	2.7%	ND

[a]Not Determined

CYP2D6 phenotypes[47,67,68]

Metabolizer Status	African American	Caucasian	East Asian	Hispanic
Poor Metabolizer	2-8%	5-10%	<2%	3-10%
Intermediate Metabolizer	~30%	10-17%	50-60%	No data
Extensive Metabolizer	60-70%	70-80%	40-50%	No data
Ultrarapid Metabolizer	~5%	3-10%	<1%	0-5%

CYP3A4 alleles[69]

Reduced function allele: *4, *5, *6, *20, *22 and *26

Allele	Enzyme activity	CYP3A4 marker	Caucasian	African American	Asian
*4	Reduced	rs55951658	ND[a]	ND	0.015-0.003
*5	Reduced	rs55901263	ND	ND	0.006
*6	Reduced	rs4646438	ND	ND	0.005
*20	Reduced	rs67666821	<0.006	ND	ND
*22	Reduced	rs35599367	0.083	0.043	0.043
*26	Reduced	rs138105638	ND	ND	ND

[a]Not Determined

HTR2A alleles[70]

Gene	Allele	Caucasian	African	Asian
HTR2A	102C	54%	64%	45%
HTR2A	102T	46%	36%	55%
HTR2A	-1438G	54%	63%	44%
HTR2A	-1438A	46%	37%	56%

SLC6A4 alleles[71]

5-HTTLPR Allele	Caucasian	Native American	African American
S	35%	64%	25%
L(A)	50%	35%	51%
L(G)	15%	1%	24%

Limitations and Warnings

Many rare CYP2C19, CYP2D6 and CYP3A4 variants have been identified, but are not part of this test. It is possible that the patient may have a variant that is not included in this test.

TCAs (tricyclic antidepressants)

Report Type: Pharmacogenetics

Reported Medications: amitriptyline, clomipramine, desipramine, doxepin, imipramine, nortriptyline, protriptyline, trimipramine

About

Tricyclic antidepressants (TCAs) are prescribed to treat depression and various other psychiatric conditions.[72] However, these medications are ineffective or poorly effective in 30% of the depressed patients.[73,74] TCAs act by blocking the neuronal uptake of norepinephrine and serotonin;[75] the binding of TCAs to cholinergic, alpha-adrenergic, serotonin and histamine receptors contributes to various side effects. Acute poisoning with TCAs is potentially life threatening.[76]

Genetics

Introduction

Multiple members of the cytochrome P450 enzyme family are involved in the metabolism of TCAs, including CYP2C19, CYP2D6 and CYP1A2. Correlations between genotypes and drug plasma concentrations or adverse effects are best studied for CYP2D6 and CY2C19 variants. Therefore, outcomes of the TCAs included in this test are based on CYP2D6 and CYP2C19 genotype. Amitriptyline, clomipramine, doxepin, imipramine, and trimipramine are demethylated by CYP2C19 to pharmacologically active metabolites. These drugs and their metabolites, along with desipramine and nortriptyline, undergo hydroxylation by CYP2D6 to less active metabolites. The CPIC guidelines for dosing of tricyclic antidepressants states that "both amitriptyline and nortriptyline are used as model drugs for this guideline because the majority of pharmacogenomic studies have focused on these two drugs. However, the results of these studies may apply to other tricyclics because these drugs have comparable pharmacokinetic properties".[75]

CYP2D6 and CYP2C19 alleles fall into one of four categories: non-functional, reduced function, normal function or increased function. Based on the combination of alleles, patients are classified by metabolizer type: poor metabolizer (PM, low or no enzyme activity), intermediate metabolizer (IM, intermediate enzyme activity), extensive metabolizer (EM, normal enzyme activity) or ultrarapid metabolizer (UM, higher than normal enzyme activity).

Amitriptyline

CYP2D6 and CYP2C19 genes

CYP2D6 genotype is associated with risk of amitriptyline-related adverse effects. Amitriptyline and its active metabolite, nortriptyline, are converted to hydroxylated compounds, mainly by the CYP2D6 enzyme.[77,78] The Clinical Pharmacogenetics Implementation Consortium (CPIC) Dosing Guideline for amitriptyline recommends an alternative drug for CYP2D6 or

CYP2C19 ultrarapid metabolizers and for CYP2D6 poor metabolizers. There is substantial evidence linking CYP2D6 and CYP2C19 genotypes to phenotypic variability in tricyclic side effect and pharmacokinetic profiles.[79,80,81,82] Modifying pharmacotherapy for patients who have CYP2D6 or CYP2C19 genetic variants that affect drug efficacy and safety could potentially improve clinical outcomes and reduce the failure rate of initial treatment.

The CPIC guidelines also suggest that a 50% dose reduction for CYP2C19 poor metabolizers and a 25% dose reduction for CYP2D6 intermediate metabolizers should be considered if tricyclic is warranted.[75] Similarly, the Dutch Pharmacogenetics Working Group Guideline for amitriptyline recommends selecting an alternative drug or monitor amitriptyline and nortriptyline plasma concentration for patients who are CYP2D6 poor or ultrarapid metabolizers. Reduce the initial dose for patients who are intermediate metabolizers or select an alternative drug.[83]

Concurrent use of amitriptyline with CYP2D6 inhibitors may affect plasma concentrations of amitriptyline.[84] Concurrent use of amitriptyline with CYP2C19 inducers can increase risk of adverse effects.[85]

Clomipramine

CYP2D6 and CYP2C19 genes

Variants of the CYP2D6 and CYP2C19 genes are associated with risk of adverse effects and therapeutic failure.[75,86,87,88,89] The CYP2D6 enzyme catalyzes the elimination of clomipramine and its active metabolite, desmethylclomipramine.[90]

The CPIC Dosing Guideline for tricyclics recommends an alternative drug for CYP2D6 or CYP2C19 ultrarapid metabolizers and for CYP2D6 poor metabolizers. There is substantial evidence linking CYP2D6 and CYP2C19 genotypes to phenotypic variability in tricyclic side effect and pharmacokinetic profiles.[79,80,81,82] Modifying pharmacotherapy for patients who have CYP2D6 or CYP2C19 genomic variants that affect drug efficacy and safety could potentially improve clinical outcomes and reduce the failure rate of initial treatment." The CPIC guidelines also suggest that a 50% dose reduction for CYP2C19 poor metabolizers and a 25% dose reduction for CYP2D6 intermediate metabolizers should be considered if tricyclic is warranted.[75]

The Royal Dutch Association for the Advancement of Pharmacy's Pharmacogenetics Working Group (PWG) recommends a 50% dose reduction for CYP2D6 PMs and alternative drugs, such as citalopram or sertraline, for UMs; monitoring of plasma concentrations is also recommended.[20,83]

Clomipramine is an inhibitor of CYP2D6, CYP2C19 and CYP1A2,[86,87,88,89,91,92,93] and CYP2D6 EMs are at risk of phenotype conversion to PMs if treated with clomipramine.[92,94] Concurrent use of clomipramine with CYP2D6 inhibitors or other drugs that are metabolized by CYP2D6 can lead to an excessive accumulation of clomipramine.[95] Clomipramine blocks hERG channels, which may induce QT prolongation; QT prolongation is a marker for Torsades de Pointes.[96] The clinically appropriate combined plasma concentrations of clomipramine and desmethylclomipramine should be below 500 ng/ml to avoid cardiac and central nervous system toxicity.[97,98]

Desipramine

Desipramine is an active metabolite of imipramine. Please see the imipramine section.

Doxepin

CYP2D6 and CYP2C19 genes

Variants of the CYP2D6 and CYP2C19 genes are associated with plasma concentrations of nordoxepin and adverse effects. The CYP2D6 enzyme catalyzes the elimination of doxepin and its active metabolite, nordoxepin.[75,90,99]

The CPIC Dosing Guideline for tricyclics recommends an alternative drug for CYP2D6 or CYP2C19 ultrarapid metabolizers and for CYP2D6 poor metabolizers. There is substantial evidence linking CYP2D6 and CYP2C19 genotypes to phenotypic variability in tricyclic side effect and pharmacokinetic profiles.[79,80,81,82,100,100,101] Modifying pharmacotherapy for patients who have CYP2D6 or CYP2C19 genomic variants that affect drug efficacy and safety could potentially improve clinical outcomes and reduce the failure rate of initial treatment." The CPIC guidelines also suggest that a 50% dose reduction for CYP2C19 poor metabolizers and a 25% dose reduction for CYP2D6 intermediate metabolizers should be considered if tricyclic is warranted.[75]

The Royal Dutch Association for the Advancement of Pharmacy's Pharmacogenetics Working Group (PWG) recommends dose adjustments for PMs and IMs and the selection of alternative medications, such as citalopram or sertraline, for UMs. For all three metabolizer statuses, adjustments of maintenance doses based on (nor)doxepin plasma concentrations are recommended.[20]

Imipramine

CYP2D6 and CYP2C19 genes

Variants in the CYP2D6 and CYP2C19 genes are associated with imipramine and desipramine clearance and plasma concentrations of the drugs. Imipramine is a founding member of the TCA drug class that has been in use since the 1950s.[75,102,103] The CYP2D6 enzyme catalyzes the elimination of imipramine and its active metabolite, desipramine, via hydroxylation.[104]

The CPIC Dosing Guideline for tricyclics recommends an alternative drug for CYP2D6 or CYP2C19 ultrarapid metabolizers and for CYP2D6 poor metabolizers. There is substantial evidence linking CYP2D6 and CYP2C19 genotypes to phenotypic variability in tricyclic side effect and pharmacokinetic profiles.[79,80,81,82] Modifying pharmacotherapy for patients who have CYP2D6 or CYP2C19 genetic variants that affect drug efficacy and safety could potentially improve clinical outcomes and reduce the failure rate of initial treatment." The CPIC guidelines also suggest that a 50% dose reduction for CYP2C19 poor metabolizers and a 25% dose reduction for CYP2D6 intermediate metabolizers should be considered if tricyclic is warranted.[75]

Compared to CYP2D6 EMs, PMs excrete decreased levels of hydroxylated imipramine and increased levels of desipramine.[105,106] The ratio of imipramine to its metabolites in plasma are reflected in the ratio excreted in the urine.[105] Additionally, CYP2D6 genotype is associated with combined imipramine and desipramine plasma concentrations,[107] which may increase risk of adverse effects at high levels.[108]

Nortriptyline

CYP2D6 gene

Variants of the CYP2D6 gene are associated with nortriptyline plasma concentrations. Nortriptyline is a prescribed antidepressant and an active metabolite of amitriptyline. The CYP2D6 enzyme metabolizes nortriptyline to its major metabolite,[109] which is less active than the parent drug.[110] After adjustment for dose, nortriptyline plasma concentrations have a negative correlation with CYP2D6 activity.[79,111,112,113,114,115,116] The correlation between CYP2D6 genotype and nortriptyline efficacy or risk of adverse effects has not been consistently confirmed.[79,85,117,118] Therefore, recommendations for nortriptyline dosing that are based on CYP2D6 genotype[20,119] are derived from pharmacokinetic data.

Protriptyline

CYP2D6 gene

Variants of the CYP2D6 gene are associated with protriptyline plasma concentrations. Protriptyline is a prescribed antidepressant, which is found to have rapid onset of action than imipramine or amitriptyline;[120] however, the exact mechanism of action of protriptyline is not known at present. In CYP2D6 PMs, higher than expected plasma concentrations of the tricyclic antidepressants are observed when usual doses of the drug are given. Due to lack of studies reporting genotype association, the categories for protriptyline have been assigned on the basis of FDA drug label and kinetic studies.[120,121,122]

Trimipramine

CYP2D6 and CYP2C19 genes

The CYP2D6 enzyme catalyzes the elimination of trimipramine and its active metabolite, desmethyltrimipramine.[123,124,125,126] In CYP2D6 PMs, the average bioavailability of trimipramine and desmethyltrimipramine is 40-fold and 3-fold higher, respectively, than EMs.[127] PMs also have increased risk of adverse effects and sedation eight hours after an initial dose.[124] CYP2D6 IMs have been reported to display increased plasma bioavailability of desmethyltrimipramine.[127] Conversely, UMs have been reported to display very low bioavailability of trimipramine and may be at increased risk of therapeutic failure if dose adjustments are not made.[126] CYP2D6 PMs excrete higher amounts of trimipramine and desmethyltrimipramine in their urine than EMs or UMs.[126]

The Clinical Pharmacogenetics Implementation Consortium (CPIC) Dosing Guideline for amitriptyline recommends an alternative drug for CYP2D6 or CYP2C19 ultrarapid metabolizers and for CYP2D6 poor metabolizers. There is substantial evidence linking CYP2D6 and CYP2C19 genotypes to phenotypic variability in tricyclic side effect and pharmacokinetic profiles.[79,80,81,82] Modifying pharmacotherapy for patients who have CYP2D6 or CYP2C19 genetic variants that affect drug efficacy and safety could potentially improve clinical outcomes and reduce the failure rate of initial treatment.

The CPIC guidelines also suggest that a 50% dose reduction for CYP2C19 poor metabolizers and a 25% dose reduction for CYP2D6 intermediate metabolizers should be considered if tricyclic is warranted.[75] Similarly, the Dutch Pharmacogenetics Working Group Guideline for amitriptyline recommends selecting an alternative drug or monitor amitriptyline and nortriptyline plasma concentration for patients who are CYP2D6 poor or ultrarapid metabolizers. Reduce the initial dose for

patients who are intermediate metabolizers or select an alternative drug.[83]

Markers and Alleles Tested

CYP2D6 gene

CYP2D6 alleles are classified as non-functional, reduced-function, normal-function and increased-function.

Non-functional alleles: *3, *4, *5, *6, *7, *8, *11, *12, *14A, *15, *36, *4xN, and *36xN
Reduced-function alleles: *9, *10, *17, *29, *41, *9xN, *10xN, *17xN, *41xN and *36-*10
Normal-function alleles: *1, *2 and *35
Increased-function alleles: *1xN, *2xN and *35xN

Predicted CYP2D6 Metabolizer Status

Metabolizer Status	CYP2D6 Genotype
Poor metabolizer	Two non-functional alleles
Intermediate metabolizer	One non-functional allele and one reduced-function allele OR Two reduced-function alleles
Extensive metabolizer	One or two normal-function copies of the CYP2D6 gene
Ultrarapid metabolizer	Three or more normal-function copies of the CYP2D6 gene

CYP2C19

CYP2C19 alleles tested: [CYP2C19 *2, CYP2C19 *3, CYP2C19 *4, CYP2C19 *5, CYP2C19 *6, CYP2C19 *7, CYP2C19 *8, CYP2C19 *17]

Predicted CYP2C19 Metabolizer Status

Metabolizer Status	CYP2C19 Diplotype
Poor Metabolizer	*2-*8/*2-*8
Intermediate Metabolizer	*1/*2-*8, *17/*2-*8
Extensive Metabolizer	*1/*1
Ultrarapid Metabolizer	*1/*17, *17/*17

Ethnic Distribution of Alleles or Phenotypes

CYP2D6 Phenotypes[47,67,68]

Metabolizer Status	African American	Caucasian	East Asian	Hispanic
Poor Metabolizer	2-8%	5-10%	<2%	3-10%
Intermediate Metabolizer	~30%	10-17%	50-60%	No data
Extensive Metabolizer	60-70%	70-80%	40-50%	No data
Ultrarapid Metabolizer	~5%	3-10%	<1%	0-5%

CYP2C19 gene

The frequency of CYP2C19 PMs is distinctly higher in Asians (13-23%) compared to Caucasians (2-5%). Combinations of CYP2C19 *2 and CYP2C19 *3 alleles can account for 100% of Asian PMs.[11] In Caucasians, the homozygous CYP2C19 *2 carriers represent 75-93% of the PMs.[12]

The CYP2C19 panel detects alleles that have a combined frequency of over 99% in major ethnic groups.[66]

Allele	Enzyme activity	CYP2C19 marker	Caucasian	African	East Asian	Middle Eastern
*1	Normal	Wild-type	63%	68%	60%	87%
*2	None	rs4244285	15%	15%	29%	12%
*3	None	rs4986893	0.42%	0.52%	8.9%	1.1%
*4	None	rs28399504	0.25%	0.093%	0.049%	ND[a]
*5	Reduced	rs56337013	0.0073%	ND	0.062%	ND
*6	None	rs72552267	0.017%	0%	0%	ND
*7	None	rs72558186	ND	ND	0%	ND
*8	Reduced	rs41291556	0.35%	0%	0%	ND
*17	Increased	rs12248560	21%	16%	2.7%	ND

[a]Not Determined

Limitations and Warnings

Many rare CYP2D6 and CYP2C19 variants have been identified but are not part of this test. It is possible that the patient may have a variant that is not included in this test.

Other antidepressants

Report Type: Pharmacogenetics

Reported Medications: bupropion, buspirone, duloxetine, levomilnacipran, mirtazapine, nefazodone, trazodone, venlafaxine, vortioxetine

About

The Other Antidepressants category of this report consists of non-SSRI and non-TCA antidepressants, including buspirone, levomilnacipran, nefazodone, trazodone and vortioxetine. Bupropion is a norepinephrine dopamine reuptake inhibitor (NDRI) and a non-competitive antagonist of the nicotine receptors. Duloxetine is a potent serotonin and norepinephrine reuptake inhibitor (SNRI) that is primarily used to treat major depressive disorder, generalized anxiety disorder and pain related to diabetic peripheral neuropathy.[128] Mirtazapine is a commonly prescribed second-generation tetracyclic antidepressant that inhibits adrenergic alpha2-autoreceptors and serotonin 5-HT2 and 5-HT3 receptors.[129,130] Venlafaxine is an SNRI that used to treat depression and a variety of anxiety disorders.[131] Plasma concentrations of each of these medications are associated with genetic variants.

Bupropion is a commonly prescribed medication used in the treatment of major depressive disorder (MDD), seasonal affective disorder, and aid in smoking cessations. Bupropion is a norepinephrine and dopamine reuptake inhibitor (NDRI) and a non-competitive antagonist of the nicotine receptors.

Buspirone is used for the treatment of anxiety disorder or short-term relief of the symptoms of anxiety. The FDA drug label states that 'Buspirone differs from typical benzodiazepine anxiolytics in that it does not exert anticonvulsant or muscle relaxant effects. It also lacks the prominent sedative effect that is associated with more typical anxiolytics. Some studies suggest that buspirone may have indirect effects on other neurotransmitter system'.[132]

Levomilnacipran is a serotonin-norepinephrine reuptake inhibitor (SNRI) indicated for the treatment of major depressive disorder (MDD) in adults, approved by FDA for the use in the US only.[133] Levomilnacipran is an active enantiomer of milnacipran, which is approved in the United States in 2009 for treatment of fibromyalgia and in Europe for depression.

Vortioxetine is a multimodal antidepressant indicated in the treatment of major depressive treatment and suggestive in treatment of cognitive dysfunction. The multimodal activity of vortioxetine can be a useful alternative to serotonergic antidepressants for some patients who are partial responders or non-responders. Tolerability is comparable with other serotonergic antidepressants.[134,135]

Genetics

Introduction

Multiple members of the cytochrome P450 enzyme family are involved in the metabolism of duloxetine, mirtazapine and venlafaxine, including CYP2D6, CYP1A2 and CYP3A4. Evidence for a correlation between genotype and drug plasma concentrations or adverse effects is most compelling for CYP2D6 variants. Therefore, outcomes of the drugs included in this test are based on CYP2D6 genotype. CYP2D6 alleles fall into one of four categories: non-functional, reduced function, normal function or increased function. Based on the combination of alleles, patients can be classified by metabolizer type: poor metabolizer (PM, low or no enzyme activity), intermediate metabolizer (IM, intermediate enzyme activity), extensive metabolizer (EM, normal enzyme activity) or ultrarapid metabolizer (UM, higher than normal enzyme activity).

The main target for many antidepressants is the serotonin transporter, which is encoded by the SLC6A4 gene. Variants in this gene are associated with patient response to venlafaxine.[136,137]

Bupropion

CYP2B6 gene

Bupropion is converted to its active metabolite hydroxybupropion by CYP2B6 family enzyme whereas other CYPs play a minor role.[138] CYP2B6 alleles fall into three categories: non-functional, reduced-function and normal-function. Based on the combination of alleles, patients can be classified by metabolizer type: poor metabolizer (PM, low or no enzyme activity), intermediate metabolizer (IM, intermediate enzyme activity) or extensive metabolizer (EM, normal enzyme activity).

Bupropion is primarily metabolized to its active metabolite hydroxybupropion by the cytochrome P450 CYP2B6 while CYP1A2, CYP2A6, CYP2C9, CYP3A4 and CYP2E1 are less involved.[138] Individuals with CYP2B6 PM and EM genotypes are likely to have lower plasma concentrations of hydroxybupropion, which is a major, active and chemically stable metabolite of bupropion.[139] At present due to lack of clinical evidence, these are no specific recommendations for dose adjustments for bupropion.

Buspirone

CYP3A4 gene

Buspirone is metabolized primarily by CYP3A4 and several hydroxylated derivatives and 1-pyrimidinylpiperazine (1-PP), a pharmacologically active metabolite, is produced. The FDA drug label suggests that concurrent use of buspirone with CYP3A4 inhibitors (eg: nefazodone, itraconazole, erythromycin) leads to increases in the plasma concentrations of buspirone. This could potentially lead to adverse effects, and subsequent dose adjustment may be necessary.[132]

Duloxetine

CYP2D6 gene

Duloxetine is metabolized by CYP2D6 and CYP1A2 to compounds without significant pharmacological activity.[140,141,142,143] Limited data on pharmacogenetics suggest that CYP2D6 PMs and IMs may have higher plasma drug concentrations compared to EMs.[144,145] In a study of Chinese patients, duloxetine exposures in IMs were 16% higher than EMs.[145] Similarly, in a study of Japanese and Caucasian patients, two out of four PMs had duloxetine exposures up to 3-fold higher than IMs, EMs and UMs; the other two PMs had duloxetine exposures comparable to the other individuals.[144] There are insufficient data to connect CYP2D6 genetic variants to duloxetine-related adverse effects or therapeutic efficacy.

CYP1A2 inhibitors, such as fluvoxamine or paroxetine,[140,141,142] and CYP2D6 inhibitors can cause increased plasma concentrations of duloxetine. Duloxetine strongly inhibits CYP2D6 and CYP2B6 and inhibits CYP1A2, CYP2C19, and CYP3A4/5 to a lesser extent,[146] which can lead to increased concentrations of some drugs, such as desipramine, when co-administered with duloxetine.[142,147]

Levomilnacipran

CYP3A4 gene

Levomilnacipran undergoes desethylation to form desethyl levomilnacipran and hydroxylation to form p-hydroxy-levomilnacipran. Both oxidative metabolites undergo further conjugation with glucuronide to form conjugates. The desethylation is catalyzed primarily by CYP3A4 with minor contribution by CYP2C8, CYP2C19, CYP2D6, and CYP2J2.[133] Due to lack of clinical evidence, there is no recommendation for the drug, however, levomilnacipran dose should not exceed 80mg once daily when it is co-administered with strong CYP3A4 inhibitors, including ketoconazole, clarithromycin and ritonavir.[133]

Mirtazapine

CYP2D6 gene

Mirtazapine is a racemic mixture of S(+) and R(-) enantiomers, both of which are pharmacologically active. The S(+)-mirtazapine enantiomer is metabolized by CYP2D6, and the major mirtazapine metabolite is formed primarily by CYP2D6 activity; therefore, the role of CYP1A2 and CYP3A4 activity is likely not clinically significant for mirtazapine metabolism.[148,149] The metabolites of mirtazapine are inactive except for desmethylmirtazapine which is reported to have 3-10% of the parent drug's activity.[130]

Though CYP2D6 variants are not associated with mirtazapine-related adverse or therapeutic effects,[4,150,151,152] CYP2D6 PMs have significantly higher steady-state serum concentrations and reduced clearance of mirtazapine compared to CYP2D6 EMs.[129,151,153,154] Studies of healthy patients in Germany and Spain show that CYP2D6 PMs and IMs have reduced clearance of mirtazapine and higher mirtazapine plasma concentrations compared to CYP2D6 EMs and UMs.[129,151,153] Similar results are found in depressed patients in Germany and Sweden.[154,155] However, in elderly patients with major depression, CYP2D6 variants were not associated with mirtazapine plasma concentrations.[4]

Nefazodone

CYP2D6 gene

Nefazodone is a phenylpiperazine antidepressant not related to SSRIs, TCAs and monoamine oxidase inhibitors.[156,157] The three pharmacologically active metabolites of nefazodone are hydroxy-nefazodone, triazoledione and m-chlorophenylpiperazine (mCPP).[156] In CYP2D6 PMs, increased plasma concentrations of mCPP, a minor active metabolite of nefazodone, are observed as compared to CYP2D6 EMs.[158] The FDA approved drug label does not recommend dose adjustments for nefazodone due to the lack of clinical evidence.[159]

Trazodone

CYP3A4 gene

Trazodone is a serotonin antagonist and a serotonin reuptake inhibitor (SARI) indicated for the treatment of major depressive disorder (MDD). CYP3A4 contributes significantly to the metabolism of trazodone and FDA drug label states that co-administration with CYP3A4 inhibitors (e.g. ritonavir) may lead to substantial increase in trazodone plasma concentrations with the potential for adverse effects including nausea, hypotension, and syncope.[160] Concurrent use of

trazodone with a CYP3A4 inducer (carbamazepine) reduced plasma concentrations of trazodone and m-chlorophenlypiperazine (m-CPP), an active metabolite.

Venlafaxine

CYP2D6 gene

Among all serotonergic drugs, venlafaxine has the highest fatal toxicity index, though it is much lower than the tricyclic antidepressants.[76] Venlafaxine overdose has been associated with adverse events, such as tachycardia, high blood pressure and prolonged QTc intervals.[161] The CYP2D6 enzyme converts approximately 80% of venlafaxine to O-desmethylvenlafaxine, which is the only active metabolite of venlafaxine.[162]

CYP2D6 metabolizer status correlates with the pharmacokinetics of venlafaxine. Measurements of the ratio of O-desmethylvenlafaxine to venlafaxine revealed that CYP2D6 UMs have higher ratios than EMs, who have higher ratios than PMs.[163,164,165,166] Studies have also shown that CYP2D6 PMs have lower oral clearance of venlafaxine and lower plasma concentrations of O-desmethylvenlafaxine than EMs.[165,167,168] IMs demonstrate higher plasma concentrations of venlafaxine than EMs.[169,170] Additionally, recovery of venlafaxine in urine is higher in PMs than EMs, indicating that less venlafaxine is metabolized in PMs.[167,168]

The effects of CYP2D6 genotype on venlafaxine efficacy and adverse effects have yet to be clarified. While some studies find an increase of venlafaxine-related adverse effects in PMs and IMs compared to EMs or UMs,[163,167,171] other studies do not find such an correlation.[172,173] Similarly, there are conflicting reports regarding the association between CYP2D6 genotype and venlafaxine efficacy.[163,173] Discrepancies may be due to differences in dosage regimens, definitions of adverse effects or the method used to measure efficacy.

SLC6A4 gene

The most studied variant of SLC6A4 is a variable number tandem repeat called 5-HTTLPR. A 20-23 base pair segment is repeated 14 times in the short (S) allele or 16 times in the long (L) allele, which leads to twice the expression of the S allele.[16] In addition, the L allele can exist in two forms, L(A) or L(G), such that the L(G) form has reduced expression of SLC6A4 as compared to the L(A) form.[16]

SLC6A4 genotype is associated with the likelihood of venlafaxine efficacy. One study in a Korean population treated for major depressive disorder with venlafaxine found an association between increased response to venlafaxine and being homozygous for the L allele. Being homozygous for the S allele was associated with decreased response to venlafaxine.[136] In a separate study of a mixed population of patients being treated with venlafaxine for generalized anxiety disorder, a better response was seen in L(A)/L(A) patients than in either L(A)/S or S/S patients.[137]

Vortioxetine

CYP2D6 gene

Vortioxetine is primarily metabolized by enzyme CYP2D6 into its pharmacologically inactive form.[174] CYP2D6 PMs have approximately twice the plasma concentration of the drug, as compared to CYP2D6 EMs. The recommended dose of vortioxetine for CYP2D6 PMs is 10mg/day.[175] The drug label also recommends reducing dose by one half in the patients receiving strong CYP2D6 inhibitors (e.g. bupropion or paroxetine) or a dose increase in the patients receiving concomitant CYP2D6 inducers (e.g. rifampicin or phenytoin).

Markers and Alleles Tested

CYP2B6 gene

The *1 allele is the wild type allele.

Predicted CYP2B6 Metabolizer Status[176,177,178,179,180]

CYP2B6 Diplotype	Predicted Metabolizer Status
*6/*6, *6/*9, *6/*18, *9/*9, *9/*18, *18/*18	Poor Metabolizer
*1/*6, *1/*9, *1/*18, *4/*6, *4/*18, *5/*6, *5/*9, *5/*18	Intermediate Metabolizer
*1/*1, *1/*4, *1/*5, *4/*4, *4/*5, *5/*5	Extensive Metabolizer

CYP2D6 gene

CYP2D6 alleles are classified as non-functional, reduced-function, normal-function and increased-function.

Non-functional alleles: *3, *4, *5, *6, *7, *8, *11, *12, *14A, *15, *36, *4xN, and *36xN
Reduced-function alleles: *9, *10, *17, *29, *41, *9xN, *10xN, *17xN, *41xN and *36-*10
Normal-function alleles: *1, *2 and *35
Increased-function alleles: *1xN, *2xN and *35xN

Predicted CYP2D6 Metabolizer Status

Metabolizer Status	CYP2D6 Genotype
Poor metabolizer	Two non-functional alleles
Intermediate metabolizer	One non-functional allele and one reduced-function allele OR Two reduced-function alleles
Extensive metabolizer	One or two normal-function copies of the CYP2D6 gene
Ultrarapid metabolizer	Three or more normal-function copies of the CYP2D6 gene

CYP3A4 gene
Reduced function allele: *4, *5, *6, *20, *22 and *26

SLC6A4 gene

This test includes the 5-HTTLPR variant, which is a variable number tandem repeat with a segment that is repeated 14 or 16 times in the short (S) allele or long (L) allele, respectively. It also includes an assay for an A>G substitution present on the L allele (rs25531).

Ethnic Distribution of Alleles or Phenotypes

CYP2B6 alleles[180,181,182,183,184,185,186,187,188,189,190,191,192,193,194,195]

Allele	Enzyme Activity	Marker(s)	Caucasian	African American	Asian	Hispanic
*2	Normal	rs8192709	3.0-5.3%	3.0-4.3%	3.4-13.2%	0-3.0%
*4	Increased	rs2279343	2.0-6.2%	0-2.0%	4.0-11.8%	3.0-14.3%
*5	Normal	rs3211371	3.0-12.2%	5.0-8.3%	0-4.0%	5.0-11.4%
*6	Reduced	rs2279343, rs3745274	20.0-28.1%	32.8-34.8%	12.0-27.0%	21.4-30.0%
*9	Reduced	rs3745274	0-1.4%	0-1.8%	0-1.8%	1.4-5.0%
*18	Reduced	rs28399499	0%	2.9-7.5%	0%	0%

CYP2D6 phenotypes[47,67,68]

Metabolizer Status	African American	Caucasian	East Asian	Hispanic
Poor Metabolizer	2-8%	5-10%	<2%	3-10%
Intermediate Metabolizer	~30%	10-17%	50-60%	No data
Extensive Metabolizer	60-70%	70-80%	40-50%	No data
Ultrarapid Metabolizer	~5%	3-10%	<1%	0-5%

CYP3A4 alleles[69]

Allele	Enzyme activity	CYP3A4 marker	Caucasian	African American	Asian
*4	Reduced	rs55951658	ND[a]	ND	0.015-0.003
*5	Reduced	rs55901263	ND	ND	0.006
*6	Reduced	rs4646438	ND	ND	0.005
*20	Reduced	rs67666821	<0.006	ND	ND
*22	Reduced	rs35599367	0.083	0.043	0.043
*26	Reduced	rs138105638	ND	ND	ND

[a]Not Determined

SLC6A4 alleles[71]

5-HTTLPR Allele	Caucasian	Native American	African American
S	35%	64%	25%
L(A)	50%	35%	51%
L(G)	15%	1%	24%

Limitations and Warnings: Many rare CYP2D6, CYP2B6 and CYP3A4 variants have been identified but are not part of this test. It is possible that the patient may have a variant that is not included in this test.

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Antipsychotics

Atypical antipsychotics

Report Type: Pharmacogenetics

Reported Medications: aripiprazole, asenapine, clozapine, iloperidone, lurasidone, olanzapine, paliperidone, quetiapine, risperidone, ziprasidone

About

Atypical antipsychotics are prescribed to treat various psychiatric disorders, including schizophrenia, schizoaffective disorder and bipolar mania.[1,2] These medications bind serotonin and dopamine receptors.[3,4,5,6,7,8] Stimulation of serotonin receptor 2C (5-HT2C, 5-HTR2C, HTR1C) results in secretion of pro-opiomelanocortin (POMC), enhanced satiety and decreased food intake; therefore, serotonergic agents can decrease food intake and promote weight loss.[9,10] Indeed, one of the major side-effects associated with atypical antipsychotics is significant weight gain.[9]

Most atypical antipsychotics have a lower incidence of developing extrapyramidal side effects, such as dystonia, akathisia and parkinsonism, than typical antipsychotics.[1,11] However, additional adverse effects like bodyweight gain, sedation and prolongation of the corrected QT interval (QTc) are associated with some atypical antipsychotics.[1,11,12]

Genetics

Introduction

Multiple members of the cytochrome P450 (CYP) enzyme family are involved in the metabolism of atypical antipsychotics, including CYP2D6 and CYP1A2. Evidence for a correlation between genotype and drug plasma concentrations or adverse effects is most compelling for CYP2D6 and CYP1A2 alleles. Therefore, outcomes of the atypical antipsychotics included in this test are based on genotypes for these genes. CYP2D6 and CYP1A2 alleles fall into one of four categories: non-functional, reduced function, normal function or increased function. Based on the combination of alleles, patients are classified by metabolizer type: poor metabolizer (PM, low or no enzyme activity), intermediate metabolizer (IM, intermediate enzyme activity), extensive metabolizer (EM, normal enzyme activity) or ultrarapid metabolizer (UM, higher than normal enzyme activity).

Variants in the HTR2C gene, which encodes a serotonin receptor, are associated with antipsychotics-related weight gain for multiple atypical antipsychotics. Additionally, variants in the DRD2 gene, which encodes a dopamine receptor, are associated with the likelihood of responding to risperidone treatment.

Aripiprazole

CYP2D6 gene

The CYP2D6 enzyme metabolizes aripiprazole to its active metabolite dehydroaripiprazole, and CYP2D6 variants are associated with combined plasma concentrations of aripiprazole plus dehydroaripiprazole.[13,14] CYP2D6 PMs have twice the elimination half-life and approximately 60% higher exposure to active compounds compared to EMs.[15] Thus, failure to metabolize aripiprazole in PMs can result in its accumulation in plasma and drug-related adverse effects.[16] CYP2D6 PMs may be at an increased risk of adverse effects from aripiprazole treatment. There is not enough evidence to connect CYP2D6 gene variants to aripiprazole efficacy.

The Royal Dutch Association for the Advancement of Pharmacy's Pharmacogenetics Working Group (PWG) recommends a 33% aripiprazole dose reduction for CYP2D6 PMs.[17] According to the drug label, concurrent use of aripiprazole with CYP2D6 inhibitors in EMs doubles exposure to aripiprazole.[15]

HTR2C gene

Variants in the HTR2C gene, which encodes a serotonin receptor, are associated with antipsychotic-induced weight gain and metabolic syndrome.[18,19,20,21] In response to atypical antipsychotics (clozapine, olanzapine, risperidone, quetiapine, aripiprazole and ziprasidone), individuals with the -759T allele of the HTR2C gene (rs3813929) demonstrated reduced weight gain or had a lower risk of weight gain compared to individuals with the -759C allele. The -759T allele decreases the interaction between the promoter and transcription factors, which may result in lower HTR2C expression and plasma concentrations of leptin, a hormone involved in the maintenance of body weight.[22,23]

Asenapine

HTR2C gene

Please see the "HTR2C gene" under "Aripiprazole".

Clozapine

CYP1A2 gene

CYP1A2 is the major enzyme responsible for metabolizing clozapine to its active metabolite N-desmethylclozapine (norclozapine), and CYP1A2 activity level correlates with clozapine metabolism.[24,25,26] The clearance of clozapine correlates with caffeine clearance, and the role of the CYP1A2*1F (-163C>A) allele in regulation of CYP1A2 activity and caffeine clearance is well supported.[24,27,28,29] In addition to genetic factors, smoking affects CYP1A2 activity by inducing enzyme activity. Clozapine plasma concentrations have been found to be higher in non-smokers than smokers.[26,30]

Though some studies support an association between the CYP1A2 *1F and clozapine plasma levels, some do not. One study found that four smoking schizophrenic patients who were homozygous for CYP1A2 *1F had lower plasma levels of clozapine compared to control group. Increasing clozapine doses to high levels or introducing fluvoxamine, a potent CYP1A2 inhibitor, improved the clinical state of the patients.[31] In a separate study, a patient who was homozygous for the CYP1A2 *1F haplotype had extremely low serum concentrations of clozapine and its metabolite norclozapine; introduction of fluvoxamine increased plasma concentrations of both compounds and increased therapeutic efficacy of clozapine.[32] Additionally, a study of schizophrenic patients reported differences in clozapine and N-desmethylclozapine concentration-to-

dose ratios between patients carrying 0, 1, or 2 CYP1A2 variants that were expected to reduce the CYP1A2 activity.[33] In contrast, some studies of schizophrenic patients did not find an association between CYP1A2 *1F and decreased concentrations of clozapine.[34,35,36]

The concurrent use of clozapine with compounds that inhibit or induce the activity of CYP1A2 may significantly affect plasma clozapine concentrations.[31]

HTR2C gene

The C allele of an intragenic variant in HTR2C, rs1414334, has been associated with metabolic syndrome for patients who take clozapine, olanzapine or risperidone.[19,20,21] Metabolic syndrome includes risk factors that collectively increase an individual's risks of heart diseases, type 2 diabetes and stroke.[37] Please see the "HTR2C gene" under "Aripiprazole" for the HTR2C -759T allele (rs3813929).

Iloperidone

CYP2D6

The CYP2D6 enzyme catalyzes the elimination of iloperidone and its active metabolite, P88;[38] variants in the CYP2D6 gene are associated with plasma concentrations, which affect QTc prolongation. PMs of CYP2D6 have increased exposure to iloperidone and P88 compared to EMs.[39,40] The combined plasma levels of the active iloperidone and P88 in CYP2D6 *4 homozygous PMs were greater than in EMs, as indicated by the ratio (iloperidone + P88)/P95; P95 is an inactive metabolite. The increased plasma levels were associated with prolonged QTcF interval.[40] QTc prolongation was also associated with iloperidone exposure that was regulated by CYP2D6 activity, such as concurrent use of CYP2D6 inhibitors or CYP2D6 variants.[41] Iloperidone and P88 have high affinity for the potassium voltage-gated channel hERG; inhibition of the hERG channel can prolong the QT interval.[40,42]

IMs have reduced CYP2D6 activity, and patients with this metabolizer status may have higher exposure to iloperidone.

Due to the risk of QT prolongation, the manufacturer recommends 50% dose reduction in PMs and the use of caution when prescribing the drug to patients with reduced CYP2D6 activity.[43]

HTR2C gene

Please see the "HTR2C gene" under "Aripiprazole".

Lurasidone

HTR2C gene

Please see the "HTR2C gene" under "Aripiprazole".

Olanzapine

CYP1A2 gene

CYP1A2 is a major enzyme responsible for metabolizing olanzapine, and CYP1A2 activity levels correlate with olanzapine metabolism.[44,45] The role of the CYP1A2*1F (-163C>A) allele in regulation of CYP1A2 activity and caffeine clearance is well supported, and olanzapine clearance is related to caffeine clearance.[27,28,29,46] In addition to genetic factors, smoking affects CYP1A2 activity by inducing enzyme activity. The enzyme encoded by CYP1A2 *1F has higher activity only if induced; otherwise, the enzyme has wild-type activity. Therefore, smoking status is a key aspect in estimating a CYP1A2 *1F individual's metabolism. In the absence of information about smoking status, individuals who are homozygous for CYP1A2 *1F may have increased CYP1A2 activity and olanzapine metabolism. It should be noted that there are limited studies that have examined the effect of CYP1A2 *1F genotype on olanzapine metabolism.[44,45]

HTR2C gene

Please see the "HTR2C gene" under "Clozapine".

Paliperidone

HTR2C gene

Please see the "HTR2C gene" under "Aripiprazole".

Quetiapine

HTR2C gene

Please see the "HTR2C gene" under "Aripiprazole".

Risperidone

CYP2D6 gene

The CYP2D6 enzyme metabolizes risperidone to 9-hydroxyrisperidone, which is the most abundant fraction in the plasma and has similar pharmacological activity as the parent drug.[47,48,49] CYP2D6 metabolizer status is associated with the ratio of risperidone to 9-hydroxyrisperidone, which may increase risk of adverse effects. There are insufficient data to support an association between the therapeutic effect of risperidone and CYP2D6 metabolizer status.

The ratio of risperidone to 9-hydroxyrisperidone is higher in CYP2D6 PMs than IMs, EMs and UMs.[50,51] The ratio was also found to be significantly different between IMs and EMs.[52,53] However, since both risperidone and 9-hydroxyrisperidone have similar receptor binding affinity,[54] the plasma concentrations of active moiety (risperidone plus 9-hydroxyrisperidone) are similar in all patients, regardless of metabolizer status.[48,49,50,55] Therefore, the therapeutic effect of risperidone is not dependent on CYP2D6 variants.[53,53,55,56,57,58]

Evidence suggests an association between CYP2D6 variants and risperidone-related adverse effects, though the topic is still being debated. Risperidone crosses the blood brain barrier more efficiently than 9-hydroxyrisperidone, which may be

the molecular basis of potentially higher toxicity in PMs.[59] Two studies have shown that PMs are at increased risk of adverse effects, such as longer QTc intervals, upon risperidone treatment.[51,60] Additionally, a larger study concluded that, compared to other patients, PMs had over three-fold higher risk of risperidone-related adverse effects and six-fold higher risk of discontinuing risperidone due to adverse effects.[51] In contrast, two other studies found no correlation between CYP2D6 variants and risperidone-related adverse effects,[50,58] though one study[58] did not find any PMs in the study population (PM frequency is low in Asians). The other study[50] was done on healthy individuals with single dose of risperidone and reported no significant adverse effects in PMs, but it may have had a different outcome when done in schizophrenia patients with multiple long term treatments.

The number of active CYP2D6 copies correlates with prolactin levels in risperidone-treated children, suggesting that UMs may have increased risk of prolactin-related toxicity.[61]

The Royal Dutch Association for the Advancement of Pharmacy's Pharmacogenetics Working Group (PWG) recommends using alternative drugs or a change in dose if risperidone-related adverse effects are observed in PMs and IMs or if therapeutic inefficacy is observed in UMs.[17] Fluoxetine and paroxetine can increase plasma concentrations of risperidone 2.5- to 2.8-fold and 3- to 9- fold, respectively.[62]

DRD2 gene

The -141C Ins and Del alleles of the DRD2 gene are associated with patient response to risperidone; the Ins allele reported as being favorable for treatment outcome.[63,64,65] However, there are also studies that do not observe association between Ins allele and risperidone treatment outcome.[66,67]

Overall, there is a trend towards patients who are Ins homozygotes showing increased treatment benefit from risperidone. Complementing that trend, a study of schizophrenic patients in the U.S. found that patients with the Del allele took a significantly longer time to respond to antipsychotics (risperidone or olanzapine) than homozygous Ins patients.[63] A study of schizophrenic patients treated with haloperidol, fluphenazine, zuclopenthixol or risperidone demonstrated that patients with who were homozygous for the Ins allele scored lower on negative symptom of stereotypy than patients with an Ins/Del genotype.[64] Furthermore, a meta-analysis of six studies of the tested DRD2 alleles concluded that the individuals who have the Del allele had poorer antipsychotic drug response compared to the individuals who were homozygous for the Ins allele.[65] In vitro and in vivo data have demonstrated that the Del allele might be associated with lower DRD2 expression and consequently lower D2 receptor density in brain striatum.[68,69]

In contrast, studies that included Chinese schizophrenic or Caucasians with non-affective psychotic disorders showed no association of -141C Ins/Del genotype with efficacy of risperidone treatment; however, the study of Chinese patients was included in the aforementioned meta-analysis that did find an association.[65,66,67]

HTR2C gene

Please see the "HTR2C gene" under "Clozapine".

Ziprasidone

HTR2C gene

Please see the “HTR2C gene” under “Aripiprazole”.

Markers and Alleles Tested

CYP1A2 gene

This test includes the following CYP1A2 marker: rs762551. In Caucasians, the A allele of this marker is mostly found in the CYP1A2 *1F haplotype, but in Asians, it is mostly found in other haplotypes that contain additional mutations. In Asians, the CYP1A2 *1F haplotype cannot be identified by testing for rs762551 alone and there is a lack of association of the A allele of rs762551 with increased enzyme activity or inducibility.[29]

CYP2D6 gene

CYP2D6 alleles are classified as non-functional, reduced-function, normal-function and increased-function.

Non-functional alleles: *3, *4, *5, *6, *7, *8, *11, *12, *14A, *15, *36, *4xN, and *36xN
Reduced-function alleles: *9, *10, *17, *29, *41, *9xN, *10xN, *17xN, *41xN and *36-*10
Normal-function alleles: *1, *2 and *35
Increased-function alleles: *1xN, *2xN and *35xN

Predicted CYP2D6 Metabolizer Status

Metabolizer Status	CYP2D6 Genotype
Poor metabolizer	Two non-functional alleles
Intermediate metabolizer	One non-functional allele and one reduced-function allele OR Two reduced-function alleles
Extensive metabolizer	One or two normal-function copies of the CYP2D6 gene
Ultrarapid metabolizer	Three or more normal-function copies of the CYP2D6 gene

DRD2 gene

This test includes the rs1799732 marker in the DRD2 gene.

HTR2C gene

This test includes the rs3813929 and rs1414334 markers in the HTR2C gene.

Ethnic Distribution of Alleles or Phenotypes

CYP1A2 gene

The frequency of the of the A allele at rs762551 is not significantly different between Asians (63%, Koreans) and Caucasians (71%, Swedes), but the frequency of CYP1A2*1F haplotype was found to be significantly lower in Asians (0.4 to 7.7%) compared to Caucasians (57%)[29,70] because the A allele of rs762551 is found in haplotypes besides CYP1A2*1F.[71]

CYP2D6 Phenotypes[72,73,74]

Metabolizer Status	African American	Caucasian	East Asian	Hispanic
Poor Metabolizer	2-8%	5-10%	<2%	3-10%
Intermediate Metabolizer	~30%	10-17%	50-60%	No data
Extensive Metabolizer	60-70%	70-80%	40-50%	No data
Ultrarapid Metabolizer	~5%	3-10%	<1%	0-5%

DRD2 gene

The -141C Del allele frequency is approximately 22% in Japanese population, 9% in Chinese and Caucasians and more than 50% in Africans.[75]

HTR2C gene

The -759T allele frequency in Caucasians is 18%[67] and 10-15% in Asians.[76,77] The frequency of rs1414334:C allele in Caucasians is 10-15%, while in Africans is 49% and in Asians is 1-8%.[78,79]

Limitations and Warnings

Many rare CYP2D6 variants have been identified but are not part of this test. It is possible that the patient may have a variant that is not included in this test.

Some CYP1A2 variants have been identified but are not part of this test. It is possible that the patient may have a variant that can cause altered CYP1A2 enzyme activity and is not included in this test. In Asians, the CYP1A2 *1F haplotype cannot be identified by testing for rs762551 alone, and there is a lack of association of the A allele of rs762551 with increased enzyme activity or inducibility.[29] Therefore, this test is not recommended for Asians.

Typical antipsychotics

Report Type: Pharmacogenetics

Reported Medications: haloperidol, perphenazine, pimozide, thioridazine, zuclopenthixol

About

Typical antipsychotics (TAPs), also known as first generation antipsychotics, are prescribed to treat various psychiatric disorders, including schizophrenia, mania, agitated behavior and severe anxiety.[80,81] This class of drugs acts by blocking dopamine D1 and D2 receptors,[82,83,84,85] but approximately 14% of patients using TAPs experience poor clinical outcomes or develop abnormal movement disorders, such as extrapyramidal symptoms (EPS).[86] Genetic differences can play an important role in determining patient responses.

Genetics

Introduction

Multiple members of the cytochrome P450 enzyme family are involved in the metabolism of TAPs, including CYP2D6 and CYP3A4. Evidence for a correlation between genotype and drug plasma concentrations or adverse effects is most compelling for CYP2D6 variants. Therefore, outcomes of the TAPs included in this test are based on CYP2D6 genotype. CYP2D6 alleles fall into one of four categories: non-functional, reduced function, normal function or increased function. Based on the combination of alleles, patients are classified by metabolizer type: poor metabolizer (PM, low or no enzyme activity), intermediate metabolizer (IM, intermediate enzyme activity), extensive metabolizer (EM, normal enzyme activity) or ultrarapid metabolizer (UM, higher than normal enzyme activity).

Haloperidol

Haloperidol is metabolized to multiple compounds with various binding properties and target receptors.[82,82,87] Though both CYP2D6 and CYP3A4 are involved in haloperidol metabolism, good evidence of pharmacogenetic effects is only found in studies of CYP2D6 variants. The CYP2D6 enzyme converts reduced haloperidol, a pharmacologically active metabolite of haloperidol, to haloperidol.[82,88] Concentrations of haloperidol and reduced haloperidol are associated with adverse effects.[87]

CYP2D6 PMs are likely to have slow clearance of haloperidol, high plasma concentrations of reduced haloperidol, and high ratio of reduced haloperidol to haloperidol at standard doses.[87,89,90,91] Accumulation of haloperidol and reduced haloperidol in the blood are associated with increased risk of adverse drug reactions. PMs have an increased risk of extrapyramidal symptoms and neurological side effects. Reported symptoms include pseudoparkinsonism, acute dystonic reaction, akathisia, prolonged oversedation, drowsiness, stiffness, blunting, paresthesias and restlessness.[87,90,92] IMs have a decreased metabolism of haloperidol and may have increased plasma concentrations of reduced haloperidol.[87,89,93]

CYP2D6 UMs are likely to have a fast metabolism of haloperidol at standard doses may have a slightly increased risk of extrapyramidal symptoms.[87]

The Royal Dutch Association for the Advancement of Pharmacy's Pharmacogenetics Working Group (PWG) recommends dose adjustment and use of alternative medications for PMs.[17] The German AGNP (Psychiatry Association of Neuropsychopharmacology and Pharmacopsychiatry) strongly recommends therapeutic drug monitoring (TDM) of haloperidol plasma concentrations as a part of their Consensus Guidelines for Therapeutic Drug Monitoring.[94]

Perphenazine

The CYP2D6 enzyme is responsible for metabolizing perphenazine to 7-OH-perphenazine, which has 70% of perphenazine's activity; CYP2D6 variants are associated with perphenazine plasma concentrations and clearance rates. PMs and IMs have higher concentrations and decreased clearance rates compared to EMs.[95,96,97,98] CYP2D6 PMs may be at increased risk of adverse effects from perphenazine treatment.[99,100,101] However, there is not sufficient evidence to link CYP2D6 variants to perphenazine efficacy.

Pimozide

Pimozide is an antidepressant, metabolized by the CYP3A4, CYP1A2 and the CYP2D6 enzyme.[102] Variants in the CYP2D6 gene are associated with altered plasma drug concentrations and drug clearance. CYP2D6 PMs exhibit higher concentrations of the drug than the EMs.[103] In case of CYP2D6 UMs, higher clearance/bioavailability of pimozide is seen as compared to the EMs.[104] Studies indicate that concomitant use of paroxetine and azole antifungal agents may impair pimozide metabolism.[105]

Thioridazine

The CYP2D6 enzyme converts thioridazine to the active metabolite thioridazine 2-sulfoxide,[81] and CYP2D6 metabolizer status may alter the concentration of the drug and its metabolites.[106] Thioridazine-related cardiac abnormalities include dose-dependent QTc prolongation, torsade de pointes and sudden cardiac death.[81]

CYP2D6 PMs have high plasma concentrations of thioridazine and high thioridazine to thioridazine 2-sulfoxide ratio at standard doses.[81,107] Thus, PMs are at increased risk of cardiac side effects, such as prolonged QTc interval and arrhythmia.[108] IMs have reduced CYP2D6 activity and may also be at an increased risk of thioridazine-related cardiac side effects, such as prolonged QTc interval and arrhythmia. The drug label contraindicates thioridazine in patients with reduced CYP2D6 activity.[109]

CYP2D6 EMs,[110,111,112,113] and possibly IMs[110,112,113] are at risk of conversion to PM status due to dose-dependent inhibition of CYP2D6 metabolism by thioridazine. UMs have low thioridazine to thioridazine 2-sulfoxide ratios at standard doses.[107] UMs have low thioridazine to thioridazine 2-sulfoxide ratios at standard doses,[107] but there are no data on adverse effects for UMs.

Zuclopenthixol

The CYP2D6 enzyme metabolizes zuclopenthixol to inactive metabolites,[114,115,116] and CYP2D6 variants are implicated in zuclopenthixol pharmacokinetics.[96,115,116,117,118] There is also evidence in the literature that CYP2D6 PMs and IMs may be at an increased risk of zuclopenthixol related adverse effects.[118,119] However, there is not enough evidence linking CYP2D6 gene polymorphism to zuclopenthixol efficacy.

CYP2D6 PMs, defined by debrisoquine hydroxylation assay, display increased plasma elimination half-life, reduced oral plasma clearance and increased dose-corrected bioavailability for zuclopenthixol compared to EMs.[115] In a study of PM psychiatry patients, median steady-state serum concentration-to-dose ratio of zuclopenthixol was 60% higher than EM

patients.[117] Moreover, a study of schizophrenic patients receiving zuclopenthixol found that the median plasma concentration was 1.6 fold and 1.4 fold higher in PMs and heterozygous EMs, respectively, than in homozygous EMs.[118] In Swedish schizophrenic patients, zuclopenthixol oral clearance rates were approximately two-fold higher in homozygous EMs than PMs.[96]

Individuals with CYP2D6 *3 and *4 alleles tended to be at increased risk of neurological adverse effects with an odds ratio of 2.3 for development of parkinsonism and 1.7 for tardive dyskinesia, but these findings did not reach statistical significance.[118] In Swedish schizophrenic patients, zuclopenthixol oral clearance rates were approximately two-fold higher in homozygous EMs than PMs.[96] In a case report, CYP2D6 inhibition by fluoxetine followed by co-administration of zuclopenthixol resulted in dangerous extra-pyramidal side effects, most likely, due to significantly increased plasma concentration of zuclopenthixol.[119]

The concurrent use of CYP2D6 or CYP3A4 inhibitors with zuclopenthixol may increase plasma concentrations of zuclopenthixol.

The Royal Dutch Association for the Advancement of Pharmacy's Pharmacogenetics Working Group (PWG) recommends reducing zuclopenthixol dose by 50% in PMs. A dose reduction of 25% is recommended for IMs, and being alert to low zuclopenthixol plasma concentrations is recommended for UMs. The use of an alternative medication is a recommended option for EMs, IMs and UMs.[17]

Markers and Alleles Tested

CYP2D6 gene

CYP2D6 alleles are classified as non-functional, reduced-function, normal-function and increased-function.

Non-functional alleles: *3, *4, *5, *6, *7, *8, *11, *12, *14A, *15, *36, *4xN, and *36xN
Reduced-function alleles: *9, *10, *17, *29, *41, *9xN, *10xN, *17xN, *41xN and *36-*10
Normal-function alleles: *1, *2 and *35
Increased-function alleles: *1xN, *2xN and *35xN

Predicted CYP2D6 Metabolizer Status

Metabolizer Status	CYP2D6 Genotype
Poor metabolizer	Two non-functional alleles
Intermediate metabolizer	One non-functional allele and one reduced-function allele OR Two reduced-function alleles
Extensive metabolizer	One or two normal-function copies of the CYP2D6 gene
Ultrarapid metabolizer	Three or more normal-function copies of the CYP2D6 gene

Ethnic Distribution of Alleles or Phenotypes

CYP2D6 Phenotypes[72,73,74]

Metabolizer Status	African American	Caucasian	East Asian	Hispanic
Poor Metabolizer	2-8%	5-10%	<2%	3-10%
Intermediate Metabolizer	~30%	10-17%	50-60%	No data
Extensive Metabolizer	60-70%	70-80%	40-50%	No data
Ultrarapid Metabolizer	~5%	3-10%	<1%	0-5%

Limitations and Warnings: Many rare CYP2D6 variants have been identified but are not part of this test. It is possible that the patient may have a variant that is not included in this test.

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Mood stabilizers and Benzodiazepines

Mood stabilizers

Report Type: Pharmacogenetics

Reported Medications: carbamazepine, divalproex, lamotrigine, oxcarbazepine, phenytoin, valproic acid

About

Carbamazepine, divalproex, lamotrigine, oxcarbazepine, phenytoin and valproic acid are used to treat epilepsy, mania/ bipolar disorder and neuropathic pain.[1,2,3,4,5,6] Valproic acid (VPA) is recommended for the treatment of epilepsy, seizures migraine, chronic headache, bipolar, mood, anxiety and psychiatric disorders.[5,6] The most serious side effects associated with carbamazepine, lamotrigine, oxcarbazepine and phenytoin are dangerous hypersensitivity reactions, also known as Stevens Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN).[7,8] SJS and TEN are serious blistering reactions of the skin and mucous membranes that can be permanently disabling or fatal.

Valproic acid and divalproex are reported to increase the risk of liver damage and resultant death in patients with hereditary neurometabolic disorder caused due to inherited POLG mutations.[6,9,10,11]

Lamotrigine is metabolized to an inactive form by the UGT1A4 enzyme.[12] UGT1A4 variants are associated with plasma concentrations of latmotrigine.[13]

Genetics

Carbamazepine

HLA-B gene

The human leukocyte antigen (HLA) system is a region on chromosome 6 that contains a large number of genes related to immune system function in humans. The strong genetic association of the HLA-B*1502 allele with carbamazepine hypersensitivity suggests a direct involvement of HLA in the pathogenesis of carbamazepine hypersensitivity, but the exact mechanism is still unknown. Oxcarbazepine- and lamotrigine-related adverse effects have also been reported in HLA-B*1502-positive patients. Anticonvulsant drugs, such as lamotrigine and phenytoin, share a common binding site in neuronal voltage-gated Na^+^ channels.[14]

In 2007, FDA issued an alert that carbamazepine-associated SJS and TEN are significantly more common in patients with the HLA-B*1502 allele.[15,16] A corresponding boxed warning was added to the label for carbamazepine drugs. The HLA-B*1502 allele occurs almost exclusively in the Asian population, consistent with the increased incidence of SJS/TEN in some Asian countries compared to countries with mainly Caucasian populations. In 2004, a small study in Han Chinese patients was the first to describe an association between HLA-B*1502 and carbamazepine-induced SJS;[17] a follow-up study

indicated HLA-B*1502 was not associated with other carbamazepine-induced adverse reactions, namely maculo-papular exanthema or drug hypersensitivity syndrome.[18] The association of HLA-B*1502 and carbamazepine-induced SJS/TEN has been replicated in studies from Taiwan,[18] Hong Kong,[19] Malaysia[20] and Thailand.[3] A recent study from Taiwan showed clinical utility of prescreening patients for HLA-B*1502 before prescribing carbamazepine.[21] The avoidance of carbamazepine in HLA-B*1502 positive patients was associated with a decrease in incidence of carbamazepine induced SJS/TEN.

The HLA-B*1502 allele has also been shown to be associated with increased risk of SJS/TEN for antiepileptic drugs that are related to carbamazepine, such as phenytoin and oxcarbazepine.[3,4,22,23]

FDA's boxed warning on Carbatrol, Epitol, Equetro and Tegretol drug labels recommends HLA-B*1502 screening for patients of Asian ancestry prior to carbamazepine therapy; patients who test positive for the HLA-B*1502 allele should not be treated with carbamazepine unless the benefits clearly outweigh the risks.[24,25,26,27] FDA's alert on carbamazepine hypersensitivity notes that patients who have been taking carbamazepine for more than a few months without developing skin reactions are at low risk of ever developing these events from carbamazepine, even if the patient is positive for the HLA-B*1502 allele. FDA further states that patients who test positive for HLA-B*1502 may also be at increased risk of SJS/TEN from other antiepileptic drugs that have been associated with SJS/TEN.[15] Healthcare professionals who prescribe carbamazepine products should be aware of the difficulty in ascertaining ethnic ancestry, as well as the possibility of mixed ancestry.

HLA-A gene

Individuals carrying the HLA-A*3101 allele have an increased risk of SJS/TEN, maculopapular eruptions and drug reaction with eosinophilia and systemic symptoms when treated with carbamazepine.[28,29,30,31]

Divalproex

POLG gene

Divalproex sodium (Depakote) is a stable coordination compound comprised of valproic acid and sodium valproate. It is on the WHO's list of essential medicines, a list of the most important medications needed in the basic health system. Individuals homozygous or compound heterozygous for the three SNPs are at an increased risk of divalproex-induced acute liver failure and resultant death.[6,9,10,11] Based on the FDA approved drug label, divalproex is contraindicated in the patients over 2 years of age who are clinically suspected to have a hereditary mitochondrial disease and should only be used after other anticonvulsants have failed.[32]

Lamotrigine

HLA-B gene

Multiple studies have examined the relationship between the HLA-B*1502 allele and lamotrigine-induced maculopapular eruption (MPE), a mild form of cutaneous side effect, and SJS/TEN.[4,8,19,33] Though none of these studies reported a significant association, the population sizes of these studies were relatively small. Additionally, two studies concluded that

the possibility of HLA-B*1502 being associated with lamotrigine-induced SJS/TEN cannot be ruled out.[8,33] One study recommended that caution should be exercised when administering lamotrigine to individuals who have HLA-B*1502 based on the fact that one of two patients with lamotrigine-induced SJS/TEN tested HLA-B*1502-positive.[4] There is consensus in the literature that caution should be exercised when administering lamotrigine to patients with the HLA-B*1502 allele.

UGT1A4 gene

Studies suggest that the L48V allele of the UGT1A4 gene increases lamotrigine metabolism, leading to decreased plasma concentrations. In a study of Turkish patients with epilepsy, non-smoking lamotrigine monotherapy patients with the L48V allele had approximately half the plasma concentrations of patients with wild-type alleles.[13] This study did not estimate lamotrigine glucuronidation levels, but based on the results, it appeared that L48V facilitates increased lamotrigine clearance, suggesting it leads to increased enzyme activity.[13] Indeed, multiple studies have demonstrated that the UGT1A4 L48V allele results in increased glucuronidation of olanzapine and lamotrigine.[13,34,35,36,37]

Although lamotrigine does not affect metabolism of other antiepileptic drugs, lamotrigine serum levels significantly increase with co-administration of valproic acid[13,38,39] or decrease with drugs such as phenytoin, carbamazepine, phenobarbital or oral contraceptive agents that are hepatic enzyme inducers.[13,38,40,41]

Oxcarbazepine

HLA-B gene

Oxcarbazepine-related adverse reactions, which range from mild maculopapular eruption to severe reactions such as SJS and TEN, have been reported in five to nine percent of patients.[2] Preliminary evidence suggests that oxcarbazepine-related SJS/TEN is associated with the HLA-B*1502 allele.[4,42] A study of Han Chinese patients found that three out of three individuals who displayed oxcarbazepine-related SJS/TEN had HLA-B*1502. There was a significant association of HLA-B*1502 with oxcarbazepine-induced SJS/TEN compared to normal healthy volunteers. A limitation of this study is that the authors did not compare the association of HLA-B*1502 allele between SJS/TEN patients and patients tolerant to oxcarbazepine.[4] Case studies report oxcarbazepine-induced SJS in Chinese and Taiwanese patients with HLA-B*1502.[42,43]

The described studies are consistent with oxcarbazepine being an analog of carbamazepine. The two drugs are metabolized via different biochemical pathways, which may explain why the evidence is presently limited for the association of HLA-B*1502 with oxcarbazepine-induced SJS/TEN. Carbamazepine 10,11-epoxide is regarded as the most common cause of adverse reactions associated with carbamazepine,[44,45] but it is not generated during oxcarbazepine metabolism.[43]

Phenytoin

HLA-B gene

Two studies have demonstrated an increased risk for phenytoin-induced SJS/TEN in patients with a variant of HLA-B allele, HLA-B*1502.[3,4] The HLA-B*1502 allele occurs almost exclusively in the Asian population, consistent with the increased incidence of SJS/TEN in some Asian countries compared to countries with mainly Caucasian populations.[16] A Han Chinese study of 139 individuals (26 with phenytoin (PHT)-induced SJS and 113 phenytoin tolerant controls), HLA-B*1502 allele was

present in 8 (30.8%) out of 26 PHT-SJS/TEN patients.[4] By comparison, HLA-B*1502 was present in 9 (8%) out of 113 PHT-tolerant controls. When comparing the allele frequencies between cases and tolerant controls, the odds ratio for patients carrying the HLA-B*1502 allele to develop phenytoin-induced SJS/TEN was 5.1 (95% CI: 1.8-15.1, p=0.0041). The other study of 49 Thai individuals (4 with phenytoin-induced SJS and 45 phenytoin tolerant controls), when the frequencies of HLA-B*1502 in the phenytoin-SJS patients (4 of 4) and the phenytoin-tolerant groups (8 of 45) were compared, significant associations were found (p=0.005, OR=18.5, 95% CI=1.82-188.40).[3]

CYP2C9 gene

CYP2C9 poor and intermediate metabolizers may associate with decreased clearance and increased plasma concentrations of phenytoin, which may increase the risk of phenytoin toxicity.[46,47,48,49,50,51,52,53] In addition, individuals of African descent carrying a nonfunctional allele of CYP2C9 (CYP2C9*6) have been reported to have decreased phenytoin clearance and increased phenytoin toxicity.[54,55]

Valproic acid

POLG gene

In some studies, heterozygous, homozygous or compound heterozygous POLG variations were associated with VPA induced liver toxicity;[6,9,11] while one study showed VPA induced liver toxicity, and subsequent death in homozygous or compound heterozygous individuals with POLG variation.[10] The US FDA approved drug label and the health Canada Santé Canada (HCSC) suggest that valproic acid is contraindicated in the patients over 2 years of age who are clinically suspected to have a hereditary mitochondrial disease and should only be used after other anticonvulsants have failed.[56] Valproic acid is also contraindicated in the patients with known urea cycle disorders, particularly ornithine transcarbamylase (OTC) deficiency. The label further reports that the A467T and W748S mutations are present in approximately 2/3 of patients with autosomal recessive POLG-related disorders. This drug has a black box warning for several adverse events including pancreatitis, liver failure and death, and major congenital malformations such as neural tube defects from exposure in utero.

Markers or Alleles Tested

HLA-B gene

This test includes two markers rs3909184 and rs2844682, that are highly linked to the HLA-B*1502 allele status in Han Chinese.[57] However, for patients with a particular genotype (rs3909184 (G/C), rs2844682 (C/T)), the HLA-B*1502 status cannot be determined, and thus these patients are assigned an “Unable to Report” result. These patients may require further evaluation.

HLA-A gene

This test includes the rs1061235 marker in the HLA-A gene, a proxy SNP of HLA-A*3101.

CYP2C9 gene

CYP2C9 alleles tested: [CYP2C9 *2, CYP2C9 *3, CYP2C9*6]

Predicted CYP2C9 Metabolizer Status

Metabolizer Status	CYP2C9 Diplotype
Poor Metabolizer	*2/*2, *2/*3, *3/*3, *2/*6, *3/*6, *6/*6
Intermediate Metabolizer	*1/*2, *1/*3, *1/*6
Extensive Metabolizer	*1/*1

POLG gene

This test includes the rs113994097, rs113994095 and rs113994098 in the POLG gene. Patient's carrying one or more copies of any of the three markers may have an increased risk of valproic acid (VPA)-induced acute liver failure and resultant death.[6,9,10,11]

UGT1A4 gene

This test includes the rs2011425 marker in the UGT1A4 gene.

Ethnic Distribution of Tested Alleles

HLA-B gene

The HLA-B*1502 allele is more prevalent in individuals of Asian ancestry.[16] The HLA-B*1502 allele has been observed in about 10% to 15% of patients in parts of China, Thailand, Malaysia, Indonesia, the Philippines and Taiwan. The frequency of this allele in South Asian individuals, such as Indians, is about 2% to 4%, but the frequency may be higher in some groups. The frequency of HLA-B*1502 is much lower (less than 1%) in Japan and Korea.[58] The HLA-B*1502 allele is also less frequently found (less than 1%) in those of African, European, Hispanic or Native American descent.[16]

HLA-A gene

Frequency of the rs1061235 marker for HLA-A*3101 allele is about 3-7% in Caucasians, 9% in Africans, and 11-12% in Asians (data: 1000 Genomes).

CYP2C9 gene

Allele	Enzyme activity	CYP2C9 marker	Caucasian	African	South Asian	Latino
*2	Reduced	rs1799853	24%	2%	5%	7%
*3	Reduced	rs1057910	12%	1%	11%	4%
*6	None	rs9332131	0.003%	1%	0%	0.03%

(data: Exome Aggregation Consortium-ExAC)

POLG gene

Frequency of these POLG markers (rs113994097, rs113994095 and rs113994098) is about 0.5% in European (Finnish) population as reported by Exome Aggregation Consortium (ExAC). The POLG rs113994098 SNP is also reported in people from American, European and African ancestry at a very low frequency. Although POLG variations are rare, they represent about 2/3 of the patients with autosomal recessive POLG-related disorders.[32,56]

UGT1A4 gene

The UGT1A4*3 (L48V) allele frequency was reported to be approximately 8% in Caucasians, and 12% in Asians.[59]

Limitations and Warnings

The markers tested for HLA-B*1502 are most applicable to patients of Han Chinese descent.[57] If clinically indicated, patients of other Asian ethnicities could be advised to undergo HLA sequencing to assess their risk of carbamazepine hypersensitivity. Other HLA alleles have been shown to be associated with carbamazepine hypersensitivity in people of Caucasian and Japanese descent, in whom HLA-B*1502 is largely absent.[60] Many HLA-B*1502-positive Asian patients treated with carbamazepine will not develop SJS/TEN. Conversely, these reactions can still occur infrequently in HLA-B*1502-negative patients of any ethnicity. Therefore, healthcare professionals are advised to watch for symptoms in all patients.

Some of the polymorphisms not reported in the test also result in altered UGT1A4 activity. Therefore, a negative result for the reported UGT1A4 variants does not rule out the presence of additional polymorphisms that can cause altered UGT1A4 activity.

This test detects three SNPs (rs113994097, rs113994095 and rs113994098) in the POLG gene. Many other POLG variants have been identified, but are not part of this test. It is possible that the patient may have a variant that is not included in this test.

Benzodiazepines

Report Type: Pharmacogenetics

Reported Medications: alprazolam, clobazam, diazepam

About

Benzodiazepines (BDZ) are a class of drugs primarily used for treating anxiety, but they also are effective in treating epilepsy, panic disorders and various other disorders.[61] The exact mechanism of action of BDZs is not known, but they appear to work by affecting neurotransmitters like gamma-aminobutryic acid (GABA) in the brain. Benzodiazepines are metabolized through cytochrome P450 family of enzymes, namely CYP2C19, CYP3A4, CYP3A5 and CYP2B6.

Alprazolam

Alprazolam is a triazolo analog of the 1,4 benzodiazepine compound that is indicated by FDA for the management of anxiety disorder or the short-term relief of symptoms of anxiety, as well as for the treatment of panic disorder. Agents of the 1,4 benzodiazepine class presumably exert their effects by binding at stereo specific receptors at several sites within the central nervous system. Their exact mechanism of action is unknown. Clinically, all benzodiazepines cause a dose-related central nervous system depressant activity varying from mild impairment of task performance to hypnosis.

Alprazolam is metabolized primarily by hepatic microsomal oxidation, yielding 4-hydroxyalprazolam and alpha-hydroxyalprazolam as its principal metabolic products.[62] In vitro studies show that cytochrome P450 3A4 (CYP3A4) is the main isoform to catalyze the 4-hydroxylation of alprazolam, whereas the alpha-hydroxylation is catalyzed predominantly by CYP3A5.[63,64] The most common nonfunctional variant of CYP3A5 is CYP3A5*3. Individuals with the CYP3A5*3/*3 genotype are considered to be CYP3A5 non-expressors.[65]

Clobazam

Clobazam (CLB) is used to reduce the frequency of seizures in epileptic patients who do not respond to treatment with other drugs.[66] CLB has a long history as an anxiolytic and anticonvulsant, and FDA recently approved it for use in the U.S. as adjunctive therapy for the treatment of seizures associated with Lennox-Gastaut syndrome in patients aged 2 years and older.[67]

CLB acts through allosteric activation of gamma-aminobutyric acid type A receptors.[67] In the liver, clobazam is demethylated by CYP3A4, CYP2C19 and CYP2B6 to yield an active metabolite called N-desmethylclobazam (N-CLB). N-CLB is inactivated by hydroxylation by CYP2C19. Variants in CYP2C19 gene are associated with metabolism of clobazam. In CYP2C19 PMs, increased plasma concentrations of the active metabolite of the drug are observed. Majority of these studies were carried out in Japanese individuals.[66,68,69,70] According to the FDA approved drug label, dose adjustment is recommended for the individuals who are CYP2C19 PMs.[66,68,69,70,71]

Diazepam

Diazepam, commonly known as Valium, a medication of the benzodiazepine family, is one of the most prescribed drugs in the US. Effects of BDZs include sedation, decreased anxiety, hypnosis, anti-convulsant activity, and muscle relaxation. Diazepam is N-demethylated by CYP3A4 and CYP2C19 to the active metabolite N-desmethyldiazepam, and is hydroxylated by CYP3A4 to the active metabolite temazepam. N-desmethyldiazepam and temazepam are both further metabolized to oxazepam. Temazepam and oxazepam are largely eliminated by glucuronidation.[72,73,74]

Variants in CYP2C19 gene are associated with metabolism of clobazam. In CYP2C19 PMs increased plasma concentrations of the active metabolite and slower clearance of diazepam are observed as compared to individuals who are CYP2C19 EMs.[75,76] Variants in CYP3A5 gene are associated with metabolism of alprazolam.[77]

Markers or Alleles Tested

CYP2C19

CYP2C19 alleles tested: [CYP2C19 *2, CYP2C19 *3, CYP2C19 *4, CYP2C19 *5, CYP2C19 *6, CYP2C19 *7, CYP2C19 *8, CYP2C19 *17]

Predicted CYP2C19 Metabolizer Status

Metabolizer Status	CYP2C19 Diplotype
Poor Metabolizer	*2-*8/*2-*8
Intermediate Metabolizer	*1/*2-*8, *17/*2-*8
Extensive Metabolizer	*1/*1
Ultrarapid Metabolizer	*1/*17, *17/*17

CYP3A5

CYP3A5 non-function allele tested: CYP3A5*3 (rs776746)

Predicted CYP3A5 Expressor Status

Expressor Status	CYP3A5 Diplotype
Non-expressor	Two *3 alleles
Expressor, heterozygous	One *3 allele
Expressor, homozygous	No *3 allele

Ethnic Distribution of Alleles or Phenotypes

CYP2C19 gene

The frequency of CYP2C19 PMs is distinctly higher in Asians (13-23%) compared to Caucasians (2-5%). Combinations of CYP2C19 *2 and CYP2C19 *3 alleles can account for 100% of Asian PMs.[78] In Caucasians, the homozygous CYP2C19 *2 carriers represent 75-93% of the PMs.[79]

The CYP2C19 panel detects alleles that have a combined frequency of over 99% in major ethnic groups.[80]

Allele	Enzyme activity	CYP2C19 marker	Caucasian	African	East Asian	Middle Eastern
*1	Normal	Wild-type	63%	68%	60%	87%
*2	None	rs4244285	15%	15%	29%	12%
*3	None	rs4986893	0.42%	0.52%	8.9%	1.1%
*4	None	rs28399504	0.25%	0.093%	0.049%	ND[a]
*5	Reduced	rs56337013	0.0073%	ND	0.062%	ND
*6	None	rs72552267	0.017%	0%	0%	ND
*7	None	rs72558186	ND	ND	0%	ND
*8	Reduced	rs41291556	0.35%	0%	0%	ND
*17	Increased	rs12248560	21%	16%	2.7%	ND

[a]Not Determined

CYP3A5

We test for CYP3A5*3 allele (rs776746) at Pathway Genomics. Its frequency varies widely across human populations. In White populations, the estimated allele frequency of CYP3A5*3 is 82 – 95%. The allele frequency in other ethnic groups is as follows: African American, 33%; Japanese, 85%; Chinese, 65%; Mexicans, 75%; Southeast Asians (excluding Japanese and Chinese), 67%; Pacific Islanders, 65%; and Southwest American Indians, 40%.[65]

Limitations and Warnings

Many rare CYP2C19 and CYP3A5 variants have been identified, but are not part of this test. It is possible that the patient may have a variant that is not included in this test.

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Medications for ADHD and other neurological disorders

Norepinephrine reuptake inhibitor

Report Type: Pharmacogenetics

Reported Medications: atomoxetine

Genetics

Introduction

Metabolism of atomoxetine is carried by the cytochrome P450 (CYP) enzyme family, primarily by CYP2D6 and CYP1A2. Correlation between genotype and drug plasma concentrations or adverse effects is most compelling for CYP2D6, while CYP2C19 and other CYPs act when the individual is a poor metabolizer of CYP2D6.[1] Therefore, outcomes of atomoxetine included in this test are based on genotypes for CYP2D6 alleles that fall into one of four categories: non-functional, reduced function, normal function or increased function. Based on the combination of alleles, patients are classified by metabolizer type: poor metabolizer (PM, low or no enzyme activity), intermediate metabolizer (IM, intermediate enzyme activity), extensive metabolizer (EM, normal enzyme activity) or ultrarapid metabolizer (UM, higher than normal enzyme activity).

Atomoxetine

CYP2D6 gene

Atomoxetine is a FDA approved drug indicated for attention deficit/hyperactivity disorder (ADHD) among children, adolescents and adults. It is a potent and selective inhibitor of the pre-synaptic norepinephrine transporter with minor affinity for serotonin and dopamine transporters.[1] Atomoxetine is primarily metabolized by CYP2D6 to 4-hydroxyatomoxetine, an active compound. However in CYP2D6 PMs, atomoxetine is metabolized slowly by CYP2C19 and other cytochrome P450 enzymes.[2] Studies carried out on the Asian populations suggest that CYP2D6 PM individuals are likely to have better response to atomoxetine, show more frequent adverse effects[3] and slower excretion of the drug.[1] Based on the current information, FDA approved drug label recommends dose adjustments for the CYP2D6 PMs as well as for the individuals who are prescribed CYP2D6 inhibitors concomitantly.[4]

Markers and Alleles Tested

CYP2D6 gene

CYP2D6 alleles are classified as non-functional, reduced-function, normal-function and increased-function.

Non-functional alleles: *3, *4, *5, *6, *7, *8, *11, *12, *14A, *15, *36, *4xN, and *36xN
Reduced-function alleles: *9, *10, *17, *29, *41, *9xN, *10xN, *17xN, *41xN and *36-*10

Normal-function alleles: *1, *2 and *35
Increased-function alleles: *1xN, *2xN and *35xN

Predicted CYP2D6 Metabolizer Status

Metabolizer Status	CYP2D6 Genotype
Poor metabolizer	Two non-functional alleles
Intermediate metabolizer	One non-functional allele and one reduced-function allele OR Two reduced-function alleles
Extensive metabolizer	One or two normal-function copies of the CYP2D6 gene
Ultrarapid metabolizer	Three or more normal-function copies of the CYP2D6 gene

Ethnic Distribution of Alleles or Phenotypes

CYP2D6 Phenotypes[5,6,7]

Metabolizer Status	African American	Caucasian	East Asian	Hispanic
Poor Metabolizer	2-8%	5-10%	<2%	3-10%
Intermediate Metabolizer	~30%	10-17%	50-60%	No data
Extensive Metabolizer	60-70%	70-80%	40-50%	No data
Ultrarapid Metabolizer	~5%	3-10%	<1%	0-5%

Limitations and Warnings

Many rare CYP2D6 variants have been identified but are not part of this test. It is possible that the patient may have a variant that is not included in this test.

Other neurological medications

Report type: Pharmacogenetics

Reported Medications: dextromethorphan and quinidine, galantamine, modafinil, tetrabenazine

Genetics

Dextromethorphan and Quinidine

Dextromethorphan and quinidine sulfate combination is an oral formulation used to treat pseudo bulbar effect. CYP2D6 is the key enzyme involved in the biotransformation of dextromethorphan to the active component dextrorphan. The quinidine component of Nuedexta competitively inhibits the CYP2D6 to increase the bioavailability of the dextromethorphan[8] that may increase risk of adverse effects in the CYP2D6 PMs[8].

Galantamine

Galantamine is a cholinesterase inhibitor indicated for the treatment of mild to moderate Alzheimer's disease.[9,10,11,12] CYP2D6 and CYP3A4 enzymes metabolize approximately 75% of the galantamine while the remaining is excreted unchanged in the urine.[13] Variants in CYP2D6 affect the plasma concentrations of galantamine.[14,15] In CYP2D6 PMs higher plasma levels of the drug are observed at standard doses.[14,15]

Modafinil

Modafinil is a wakefulness-promoting agent used to treat excessive daytime sleepiness associated with narcolepsy.[16] Modafinil is often used in combination with tricyclic antidepressant medication.[17] In CYP2D6 PMs, higher plasma concentration of TCAs and SSRI drugs are observed when modafinil is concomitantly used with these drugs.[17,18]

Tetrabenazine

Tetrabenazine (XENAZINE) is a vesicular monoamine transporter 2 (VMAT) inhibitor indicated for the treatment of chorea associated with Huntington's disease.[19] Tetrabenazine (TBZ) is primarily metabolized in liver into the pharmacologically active metabolites, alpha dihydro-tetrabenazine (α-HTBZ) and beta-dihydro-tetrabenazine (β-HTBZ).[20] In one study, CYP2D6 PMS had higher plasma concentrations of the primary active metabolites of the drug, α-HTBZ and β-HTBZ than then EMs.[21,22]

Markers and Alleles Tested

CYP2D6 gene

CYP2D6 alleles are classified as non-functional, reduced-function, normal-function and increased-function.

Non-functional alleles: *3, *4, *5, *6, *7, *8, *11, *12, *14A, *15, *36, *4xN, and *36xN
Reduced-function alleles: *9, *10, *17, *29, *41, *9xN, *10xN, *17xN, *41xN and *36-*10
Normal-function alleles: *1, *2 and *35
Increased-function alleles: *1xN, *2xN and *35xN

Predicted CYP2D6 Metabolizer Status

Metabolizer Status	CYP2D6 Genotype
Poor metabolizer	Two non-functional alleles
Intermediate metabolizer	One non-functional allele and one reduced-function allele OR Two reduced-function alleles
Extensive metabolizer	One or two normal-function copies of the CYP2D6 gene
Ultrarapid metabolizer	Three or more normal-function copies of the CYP2D6 gene

Ethnic Distribution of Alleles or Phenotypes

CYP2D6 Phenotypes[5,6,7]

Metabolizer Status	African American	Caucasian	East Asian	Hispanic
Poor Metabolizer	2-8%	5-10%	<2%	3-10%
Intermediate Metabolizer	~30%	10-17%	50-60%	No data
Extensive Metabolizer	60-70%	70-80%	40-50%	No data
Ultrarapid Metabolizer	~5%	3-10%	<1%	0-5%

Limitations and Warnings

Many rare CYP2D6 variants have been identified but are not part of this test. It is possible that the patient may have a variant that is not included in this test.

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