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Aripiprazole Therapy and *CYP2D6* Genotype

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Introduction

Aripiprazole is an atypical antipsychotic used in the management of schizophrenia, bipolar disorder, major depressive disorder, irritability associated with autistic disorder, and treatment of Tourette's disorder.

The metabolism and elimination of aripiprazole is mainly mediated through two enzymes, CYP2D6 and CYP3A4. Approximately 8% of Caucasians, 3–8% of Black/African Americans and up to 2% of Asians cannot metabolize CYP2D6 substrates and are classified as "poor metabolizers" (1).

The FDA-approved drug label for aripiprazole states that in CYP2D6 poor metabolizers, half of the usual dose should be administered. In CYP2D6 poor metabolizers who are taking concomitant strong CYP3A4 inhibitors (e.g., itraconazole, clarithromycin), a quarter of the usual dose should be used (Table 1) (2).

Table 1. The FDA-recommended dose adjustments for aripiprazole in patients who are known CYP2D6 poor metabolizers and patients taking concomitant CYP2D6 inhibitors, CYP3A4 inhibitors, and/or CYP3A4 inducers (2016)

Factors	Dosage Adjustments for ABILIFY
Known CYP2D6 Poor Metabolizers	Administer half of usual dose
Known CYP2D6 Poor Metabolizers taking concomitant strong CYP3A4 inhibitors (e.g., itraconazole, clarithromycin)	Administer a quarter of usual dose
Strong CYP2D6 (e.g., quinidine, fluoxetine, paroxetine) or CYP3A4 inhibitors (e.g., itraconazole, clarithromycin)	Administer half of usual dose
Strong CYP2D6 and CYP3A4 inhibitors	Administer a quarter of usual dose
Strong CYP3A4 inducers (e.g., carbamazepine, rifampin)	Double usual dose over 1 to 2 weeks

Table is adapted from a FDA-approved drug label for aripiprazole (2).

Drug: Aripiprazole

Aripiprazole is an atypical antipsychotic primarily used in the treatment of schizophrenia and bipolar disorder. Aripiprazole may also be used as part of the management of major depressive disorder, irritability associated with autism, and treatment of Tourette's disorder (2).

The first antipsychotics to be discovered in the 1950s were haloperidol and chlorpromazine. Known as "first-generation" or "typical" antipsychotics, these drugs are used to treat psychosis (regardless of the cause), chronic psychotic disorders (e.g., schizophrenia), and other psychiatric conditions. However, prominent adverse effects

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included extrapyramidal side effects such as tardive dyskinesia, muscle rigidity, tremors, and Parkinsonian-like symptoms.

Newer antipsychotics, known as "second generation" or "atypical" antipsychotics, have a lower risk of extrapyramidal side effects such as tardive dyskinesia. However, many have serious metabolic effects. Aripiprazole is an atypical antipsychotic that is noted for having fewer metabolic side effects than other atypicals, such as clozapine, olanzapine, risperidone, and quetiapine. Other atypicals currently approved by the FDA include asenapine, brexpiprazole, cariprazine, lurasidone, paliperidone, and ziprasidone.

The main action of both first-generation and second-generation antipsychotics is thought to be the post-synaptic blockade of D2 dopamine receptors. All antipsychotics, with the exception of aripiprazole, are D2 antagonists.

Aripiprazole is a partial D2 agonist. Aripiprazole binds to the D2 receptor with a high affinity similar to dopamine. However, because it has low intrinsic activity, it causes much lower activation of the receptor compared to dopamine.

The combination of a high affinity for the D2 receptor and its partial agonist activity may result in aripiprazole reducing the high-frequency firing of dopamine neurons in the brain's mesolimbic system. Overactivity in this region is thought to underlie psychosis and other positive symptoms of schizophrenia. In addition, the preservation of some D2 receptor activity in other dopamine-rich pathways in the brain (mesocortical and nigrostriatal areas) may provide more protection against extrapyramidal side effects (3, 4).

Aripiprazole also has a high affinity for the serotonin 5-HT_{2A} receptors, where it acts as an antagonist and it moderately blocks the alpha 1 adrenergic and histamine H1 receptors, which may account for the lower incidence of orthostatic hypotension and sedation compared to other antipsychotics (5).

Adverse events to aripiprazole include increased mortality in elderly patients with psychosis caused by dementia, suicidal thoughts and behavior in children and young adults, neuroleptic malignant syndrome, and tardive dyskinesia (2).

Aripiprazole is extensively metabolized in the liver by CYP450 enzymes, mainly CYP2D6 and CYP3A4. Aripiprazole activity is thought to be primarily due to the parent drug, and to a lesser extent its major metabolite, dehydro-aripiprazole. The mean elimination half-life is about 75 hours for aripiprazole, but in individuals who have no appreciable CYP2D6 activity (poor metabolizers), the mean elimination half-life for aripiprazole is about 146 hours.

Genetic variations in the *CYP2D6* gene have been found to impact serum levels of aripiprazole (6, 7). Because standard doses of aripiprazole lead to higher plasma levels of aripiprazole and dehydro-aripiprazole, the dose of aripiprazole should be adjusted in subjects carrying two nofunction alleles causing poor metabolizer status.

The FDA recommends that patients who are known to be CYP2D6 poor metabolizers should receive half the standard dose of aripiprazole, or a quarter of the standard dose if they are also taking medicines that strongly inhibit CYP3A4 (e.g., itraconazole, clarithromycin) (See Table 1).

A recent study substantiates the FDA recommendations by concluding that poor metabolizers should receive a reduced dose of aripiprazole (30–50% reduction). This study also suggested that individuals with increased CYP2D6 activity (ultrarapid metabolizers) may need to take an alternative antipsychotic not metabolized by CYP2D6 because of reduced drug levels (8).

The cytochrome P450 superfamily

The cytochrome P450 superfamily (CYP450) is a large and diverse group of enzymes that form the major system for metabolizing lipids, hormones, toxins, and drugs. The CYP450 genes are highly polymorphic and can result in no, decreased, normal or increased enzyme activity.

Gene: *CYP2D6*

CYP2D6 is highly polymorphic, with over 100 star (*) alleles described (9). *CYP2D6*1* is the reference (or wild-type) allele encoding enzyme with normal activity. The *CYP2D6*2*, **33*, and **35* alleles are also considered to confer normal activity (Table 2).

Table 2. Activity status of selected *CYP2D6* alleles

Allele type	*CYP2D6* Alleles
Increased	**1xN, *2xN* (*xN* denoting gene duplication or multiplication)
Normal	**1, *2, *35*
Decreased activity	**9, *10, *17, *29, *36, *41*
Inactive	**3-*8, *11-*16, *18-*21, *38, *40, *42*

For a detailed list of *CYP2D6* alleles, please see (9).

Individuals who have more than two normal function copies of the *CYP2D6* gene are "ultrarapid metabolizers," whereas individuals who carry two normal or one normal and one decreased function allele are classified as "normal metabolizers." Subjects with one normal and one no function allele or two decreased function alleles are categorized as "normal metabolizers" by CPIC guidelines, but have also been categorized as "intermediate metabolizers" in the literature. Subjects with one decreased and one no function allele are predicted to be intermediate metabolizers and those with two no function alleles, as mentioned above, are poor metabolizers.

The most common no function alleles include *CYP2D6*3*, **4*, **5*, and **6* (10, 11), and the most common decreased function alleles include *CYP2D6*9, *10, *17, *29* and **41* (Table 2). There are large inter-ethnic differences in the frequency of these alleles. For example, *CYP2D6*4* is the most common no function allele in Caucasians, but less abundant in subjects with African ancestry, and rare in Asians. In contrast, the decreased function allele *CYP2D6*10* is the most common allele in Asians, and *CYP2D6*17* is almost exclusively found in individuals with African ancestry (1). Consequently, the phenotype frequencies also vary substantially among the major ethnicities and may vary among populations. Approximately 6-10% of European Caucasians and their descendants are poor metabolizers, mainly due to the prevalent no function *CYP2D6*4* and **5* alleles (12, 13).

Gene: *CYP3A4*

In contrast to *CYP2D6*, genetic variation cannot explain *CYP3A4* variability. Although 26 allelic variants are currently described, the majority have not been shown to alter CYP3A4 activity (14, 15). To date, only three no function *CYP3A4* alleles, all being rare, have been identified (*CYP3A4*6, CYP3A4*20* and *CYP3A4*26*) (16, 17). The *CYP3A4*20* allele, for example, has been reported to have a frequency of about 0.2% in European Americans and 0.05% in African Americans, while it was observed at a frequency of 1.2% in Spain; notably, it reached up to 3.8% in specific Spanish regions (16). Although a decreased function allele, *CYP3A4*22*, has been associated with tacrolimus dose requirements (18), its clinical utility warrants further investigation.

Genetic Testing

Genetic testing for *CYP2D6* and *CYP3A4* is available. Test panels may include tests for additional genes involved in drug metabolism including aripiprazole. For tests available to predict CYP2D6 activity to optimize aripiprazole therapy (i.e., adjust dosage or opt for an alternative drug) please see the Genetic Testing Registry.

Results are typically reported as a diplotype, such as *CYP2D6 *1/*1*. A result for copy number, if available, is also important when interpreting *CYP2D6* results (19).

Therapeutic Recommendations based on Genotype

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

2016 Statement from the US Food and Drug Administration (FDA): Dosage adjustments are recommended in patients who are known CYP2D6 poor metabolizers and in patients taking concomitant CYP3A4 inhibitors or CYP2D6 inhibitors or strong CYP3A4 inducers (see Table 1). When the coadministered drug is withdrawn from the combination therapy, aripiprazole dosage should then be adjusted to its original level. When the coadministered CYP3A4 inducer is withdrawn, aripiprazole dosage should be reduced to the original level over 1 to 2 weeks. Patients who may be receiving a combination of strong, moderate, and weak inhibitors of CYP3A4 and CYP2D6 (e.g., a strong CYP3A4 inhibitor and a moderate CYP2D6 inhibitor or a moderate CYP3A4 inhibitor with a moderate CYP2D6 inhibitor), the dosing may be reduced to one-quarter (25%) of the usual dose initially and then adjusted to achieve a favorable clinical response.

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

2011 Summary of recommendations from the Pharmacogenetics Working Group of the Royal Dutch Association for the Advancement of Pharmacy (KNMP): In CYP2D6 poor metabolizers, reduce the maximum dose of aripiprazole to 10 mg/day (67% of the maximum recommended daily dose).

Please review the complete therapeutic recommendations that are located here: (20).

Nomenclature

Nomenclature of selected *CYP2D6* alleles

Common allele name	Alternative names	HGVS reference sequence		dbSNP reference identifier for allele location
		Coding	Protein	
*CYP2D6*4*	1846G>A	NM_000106.5:c.506-1G>A	Variant occurs in a non-coding region (splice variant causes a frameshift)	rs3892097
*CYP2D6*5*	Variant results in a whole gene deletion			
*CYP2D6*6*	1707 del T Trp152Gly • CYP2D6T	NM_000106.5:c.454delT	NP_000097.3:p.Trp152Glyfs	rs5030655
*CYP2D6*10*	100C>T (Pro34Ser)	NM_000106.5:c.100C>T	NP_000097.3:p.Pro34Ser	rs1065852
*CYP2D6*17*	1023C>T[1] (Thr107Ile)	NM_000106.5:c.320C>T	NP_000097.3:p.Thr107Ile	rs28371706
	2850C>T[1] (Cys296Arg)	NM_000106.5:c.886T>C	NP_000097.3:p.Cys296Arg	rs16947

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

Nomenclature of selected continued from previous page.

Common allele name	Alternative names	HGVS reference sequence		dbSNP reference identifier for allele location
		Coding	Protein	
*CYP2D6*41*	2850C>T[2] (Cys296Arg)	NM_000106.5:c.886T>C	NP_000097.3:p.Cys296Arg	rs16947
	2988G>A	NM_000106.5:c.985+39 G>	Variant occurs in a non-coding region (impacts slicing).	rs28371725

[1] In the literature, 1023C>T is also referred to as 1111C>T, and 2850C>T is also referred to 2938C>T.
[2] In the literature, 2850C>T is also referred to as 2938C>.

Nomenclature of selected *CYP3A4* alleles

Common allele name	Alternative names	HGVS reference sequence		dbSNP reference identifier for allele location
		Coding	Protein	
*CYP3A4*6*	17661_17662insA 277Frameshift	NM_017460.5:c.830_831i nsA	NP_059488.2:p.Asp277Glufs	rs4646438
*CYP3A4*20*	1461_1462insA 488Frameshift	NM_017460.5:c.1461_14 62insA	NP_001189784.1:p.Pro487Thrfs	rs67666821
*CYP3A4*26*	17633C>T R268Stop			

Guidelines for the description and nomenclature of gene variations are available from the Human Genome Variation Society (HGVS): http://www.hgvs.org/content/guidelines
Nomenclature for Cytochrome P450 enzymes is available from the Pharmacogene Variation Consortium database: https://www.pharmvar.org/

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