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Risperidone Therapy and *CYP2D6* Genotype

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Introduction

Risperidone is the most commonly prescribed antipsychotic medication in the US. It is an atypical (second generation) antipsychotic used in the treatment of schizophrenia, bipolar disorder, severe dementia, and irritability associated with autism.

Risperidone is metabolized to the active metabolite 9-hydroxyrisperidone by the enzyme CYP2D6 and to a lesser extent by CYP3A4. Individuals who carry two inactive copies of the *CYP2D6* gene are termed "poor metabolizers" and may have a decreased capacity to metabolize risperidone. These individuals may be at a higher risk of adverse effects because of increased exposure to plasma risperidone, compared to normal metabolizers, who carry two active copies of *CYP2D6*. Individuals who are CYP2D6 ultrarapid metabolizers (who carry more than two functional copies of *CYP2D6*) may have a decreased response to therapy, resulting from lower steady-state risperidone concentrations.

The FDA-approved drug label states that analysis of clinical studies involving a modest number of poor metabolizers (n=70) does not suggest that poor and extensive (normal) metabolizers have different rates of adverse effects (1). In addition, the Dutch Pharmacogenetics Working Group (DPWG) recently changed its dosing recommendations to "no action is needed" for CYP2D6 poor metabolizers taking risperidone (2).

Drug: Risperidone

Risperidone is an atypical antipsychotic primarily used in the treatment of schizophrenia and manic or mixed episodes in bipolar disorder. Risperidone may also be used as part of the management of aggression and/or psychosis in severe dementia and irritability associated with autistic disorder in children and adolescents (1).

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 underlying cause), chronic psychotic disorders (e.g., schizophrenia), and other psychiatric conditions.

All antipsychotics, with the exception of aripiprazole, are dopamine receptor antagonists. Blockade of the D2 dopamine receptor in the brain's limbic system is thought to improve the "positive" symptoms of schizophrenia, such as delusions and hallucinations, which are signs of psychosis.

However, typical antipsychotics also block dopamine receptors in the nigrostriatal pathway. This can cause movement disorders known as extrapyramidal side effects. These disorders include akathisia (motor restlessness), dystonia (abnormal muscle tone), and tardive dyskinesia (involuntary and repetitive movements).

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Newer antipsychotics, known as "second generation" or "atypical" antipsychotics, have a lower risk of extrapyramidal side effects. Risperidone is an atypical antipsychotic. The most common side effects of risperidone therapy are sedation and dry mouth, but the rates of both appear to be low, at around 5% (3). Other atypical antipsychotics approved by the FDA include aripiprazole, asenapine, brexpiprazole, cariprazine, clozapine, lurasidone, olanzapine, quetiapine, and ziprasidone.

Atypical antipsychotics, such as risperidone, are thought to transiently occupy D2 receptors and then rapidly dissociate, to allow for normal dopamine neurotransmission (4). Because risperidone has high affinity for the D2 receptor but binds it "loosely", it does not block dopamine receptors in the nigrostriatal pathway and extrapyramidal side effects are less likely (5).

Risperidone also blocks serotonin receptors, alpha 1 adrenergic receptors, and, to a lesser extent, histamine H1 and alpha 2 adrenergic receptors.

The main route of risperidone metabolism is in the liver by the enzyme CYP2D6. The major active metabolite, 9-hydroxyrisperidone, contributes to the pharmacological effects of this drug (5). While risperidone and 9-hydroxyrisperidone are often regarded as equipotent, they display different affinities towards the two target receptors (D2 and 5HT2A), where risperidone appears to be approximately 2-fold more potent than 9-hydroxyrisperidone. There is also a difference in brain distribution; risperidone is distributed more to the CNS (6).

Genetic variations in the *CYP2D6* gene may contribute to an increased risk of adverse events associated with risperidone therapy (7). Individuals who are "CYP2D6 poor metabolizers" carry two no function copies of the *CYP2D6* gene. In these individuals, standard doses of risperidone may lead to increased plasma levels of risperidone and decreased levels of 9-hydoxyrisperidone.

However, it is unclear to the extent to which *CYP2D6* genotype influences the efficacy and safety of risperidone therapy. One small study of 76 patients with schizophrenia reported that CYP2D6 poor metabolism was associated with greater clinical improvement in the total Positive and Negative Syndrome Scale (PANSS) (8). Other studies have reported a higher rate of adverse reactions and drug discontinuations in CYP2D6 poor metabolizers compared to normal metabolizers (5, 9, 10).

The ratio of risperidone to 9-hdroxyrisperidone, which largely reflects CYP2D6 phenotype, may be a risk factor for different side effects (11). Because prolactin levels mainly correlate with 9-hydroxyrisperidone levels, CYP2D6 ultrarapid metabolizers may experience different side effects than normal metabolizers (12). In addition, because elderly patients accumulate 9-hydroxyrisperidone due to reduced renal function, older patients who are CYP2D6 poor metabolizers (and others with reduced renal function) are at particular risk of side effects during risperidone treatment (5).

Individuals who are "CYP2D6 ultrarapid metabolizers" may have decreased plasma levels of risperidone, due to increased CYP2D6 activity—these individuals carry more than two functional copies of the *CYP2D6* gene. A small study of 85 patients taking long-lasting risperidone showed that the plasma concentrations of risperidone and its active metabolite were subtherapeutic in three individuals who were CYP2D6 ultrarapid metabolizers. The study, however, did not report whether these changes affected the effectiveness or tolerability of the drug in these patients (13).

Overall, it remains unclear whether the accurate determination of an individual's *CYP2D6* genotype, together with therapeutic drug monitoring, has the potential to optimize the response of CYP2D6 poor metabolizers and ultrarapid metabolizers to antipsychotic therapy (9, 14).

The Cytochrome P450 Superfamily

The cytochrome P450 superfamily (CYP450) is a large and diverse group of enzymes that form the major system for metabolizing or detoxifying lipids, hormones, toxins, and drugs. The *CYP450* genes are very polymorphic and can result in reduced, absent, or increased enzyme activity.

Gene: *CYP2D6*

CYP2D6 is highly polymorphic, with over 100 star (*) alleles described (15). *CYP2D6*1* is the reference (or wild-type) allele encoding an enzyme with normal activity. The *CYP2D6*2*, **33*, and **35* alleles are also considered to confer normal enzyme activity (Table 1).

Table 1. Activity status of selected *CYP2D6* alleles

Allele type	*CYP2D6* Alleles
Normal function	**1, *2, *33, *35*
Decreased function	**9, *10, *17, *29, *36, *41*
No function	**3, *4, *5, *6, *7, *8, *11, *12, *13, *14, *15, *16, *19, *20, *21, *38, *40, *42*

For a detailed list of *CYP2D6* alleles, please see (15).

Individuals who have more than two normal function copies of the *CYP2D6* gene are classified as "ultrarapid metabolizers," whereas individuals who carry two normal or one normal and one decreased function allele are classified as "normal metabolizers" (also referred to as "extensive metabolizers").

Individuals with one normal and one no function allele or two decreased function alleles are also categorized as "normal metabolizers" by recent nomenclature guidelines (16), but have also been categorized as "intermediate metabolizers" elsewhere 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 are considered to be "poor metabolizers" (Table 2).

Table 2: 2016 Assignment of CYP2D6 phenotypes by CPIC

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

Table 2 continued from previous page.

Phenotype	Activity Score	Genotypes	Examples of diplotypes
CYP2D6 poor metabolizer (approximately 1–10% of patients)	0	An individual carrying two no function alleles	**4/*4* **4/*4xN* **3/*4* **5/*5* **5/*6*

[a] For population-specific allele and phenotype frequencies, please see (17).
[b] Where *xN* represents the number of *CYP2D6* gene copies (N is 2 or more).
[c] Patients with an activity core of 1.0 may be classified as intermediate metabolizers by some reference laboratories.
For more information about activity scores, please see the Genetic Testing section.
This table has been adapted from Hicks J.K., Sangkuhl K., Swen J.J., Ellingrod V.L., Müller D.J., Shimoda K., Bishop J.R., Kharasch E.D., Skaar T.C., Gaedigk A., Dunnenberger H.M., Klein T.E., Caudle K.E. Clinical Pharmacogenetics Implementation Consortium Guideline (CPIC®) for *CYP2D6* and *CYP2C19* Genotypes and Dosing of Tricyclic Antidepressants: 2016 Update. Clinical pharmacology and therapeutics. 2016 Dec 20 [Epub ahead of print] (17).

The most common no function alleles include *CYP2D6*3*, **4*, **5*, and **6* (18, 19, 20, 21), and the most common decreased function alleles include *CYP2D6*9, *10, *17, *29* and **41* (19, 21, 22, 23, 24). 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 is less abundant in subjects with African ancestry and is 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 (25).

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 (26, 27).

Genetic Testing

The NIH's Genetic Testing Registry provides examples of the genetic tests that are currently available for risperidone response and for the *CYP2D6* gene.

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* genotyping results (28). However, it is important to note that the number of variants tested can vary among laboratories, which can result in diplotype result discrepancies between testing platforms and laboratories (29).

If the test results include an interpretation of the patient's predicted metabolizer phenotype, this should be confirmed by checking the diplotype and assigning an activity score to each allele (e.g., 0 for no function, 0.5 for decreased function, and 1 for each copy of a normal function allele). The phenotype is defined by the sum of the two scores:

- A normal (previously referred to as "extensive") metabolizer phenotype has an activity score of 1 to 2
- An intermediate metabolizer has an activity score of 0.5
- A poor metabolizer has an activity score of 0
- An ultrarapid metabolizer has an activity score greater than 2 (17, 30)

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): Risperidone is extensively metabolized in the liver. The main metabolic pathway is through hydroxylation of risperidone to 9-hydroxyrisperidone by the enzyme, CYP 2D6. A minor metabolic pathway is through N-dealkylation. The main metabolite, 9-hydroxyrisperidone, has similar pharmacological activity as risperidone. Consequently, the clinical effect of the drug results from the combined concentrations of risperidone plus 9-hydroxyrisperidone.

CYP 2D6, also called debrisoquin hydroxylase, is the enzyme responsible for metabolism of many neuroleptics, antidepressants, antiarrhythmics, and other drugs. CYP 2D6 is subject to genetic polymorphism (about 6%–8% of Caucasians, and a very low percentage of Asians, have little or no activity and are "poor metabolizers") and to inhibition by a variety of substrates and some non-substrates, notably quinidine. Extensive[2] CYP 2D6 metabolizers convert risperidone rapidly into 9-hydroxyrisperidone, whereas poor CYP 2D6 metabolizers convert it much more slowly. Although extensive metabolizers have lower risperidone and higher 9-hydroxyrisperidone concentrations than poor metabolizers, the pharmacokinetics of risperidone and 9-hydroxyrisperidone combined, after single and multiple doses, are similar in extensive and poor metabolizers.

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

2017 Summary of recommendations from the Dutch Pharmacogenetics Working Group (DPWG) of the Royal Dutch Association for the Advancement of Pharmacy (KNMP):

CYP2D6 Poor metabolizers:

No action is needed for this gene-drug interaction.

The genetic variation can result in both an increase in side effects and a stronger decrease in schizophrenia symptoms. In addition to this, the genetic variation may lead to a decrease in the required maintenance dose. However, as the effect on the dose is smaller than that of the normal biological variation, action is not useful.

CYP2D6 intermediate metabolizers:

No action is needed for this gene-drug interaction.

There is little evidence to support an increase in side effects caused by the genetic variation. The genetic variation may lead to a decrease in the required maintenance dose. However, as the effect on the dose is smaller than that of the normal biological variation, action is not useful.

CYP2D6 ultrarapid metabolizers:

No action is needed for this gene-drug interaction.

Genetic variation may lead to an increase in the required maintenance dose. However, as the effect is smaller than that of the normal biological variation, action is not useful.

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

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[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.

[2] The FDA statement uses the term "extensive metabolizer." CPIC recently introduced standardized nomenclature for pharmacogenetic terms, which included replacing the term "extensive metabolizer" with the term "normal metabolizer." More details can be found in the 2016 paper, "Standardizing terms for clinical pharmacogenetic test results: consensus terms from the Clinical Pharmacogenetics Implementation Consortium (CPIC)" 16. Caudle, K.E., H.M. Dunnenberger, R.R. Freimuth, J.F. Peterson, et al., *Standardizing terms for clinical pharmacogenetic test results: consensus terms from the Clinical Pharmacogenetics Implementation Consortium (CPIC).* Genet Med, 2016.

Nomenclature

Nomenclature for selected *CYP2D6* alleles

Common allele name	Alternative names / Major SNP	HGVS reference sequence		dbSNP reference identifier for allele location
		Coding	Protein	
*CYP2D6*4*	1846G>A	NM_000106.5:c.506-1G>A	Not applicable - variant occurs in a non-coding region	rs3892097
*CYP2D6*5*	Not applicable - variant results in a whole gene deletion			
*CYP2D6*6*	1707 del T Trp152Gly	NM_000106.5:c.454delT	NP_000097.3:p.Trp152Glyfs	rs5030655
*CYP2D6*10*	100C>T Pro34Ser	NM_000106.5:c.100C>T	NP_000097.3:p.Pro34Ser	rs1065852
*CYP2D6*17*	Includes at least two functional variants*: 1023C>T (Thr107Ile) 2850C>T (Cys296Arg)	NM_000106.5:c.320C>T NM_000106.5:c.886T>C	NP_000097.3:p.Thr107Ile NP_000097.3:p.Cys296Arg	rs28371706 rs16947
*CYP2D6*41*	2988G>A	NM_000106.5:c.985+39G>A	Not applicable – variant occurs in a non-coding region	rs28371725

SNP= Single Nucleotide Polymorphism
*In the literature, 1023C>T is also referred to as 1111C>T, and 2850C>T is also referred to 2938C>T.

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

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

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