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Thioridazine Therapy and *CYP2D6* Genotypes

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Introduction

Thioridazine is an antipsychotic used in the treatment of schizophrenia and psychosis. Its use is reserved for patients who have failed to respond to or cannot tolerate other antipsychotics.

Thioridazine has been shown to prolong the QT interval (the time taken for the heart ventricles to depolarize and repolarize) in a dose related manner. Drugs with this potential have been associated with the life-threatening ventricular tachycardia, "torsades de pointes".

The CYP2D6 enzyme is involved in metabolizing thioridazine. About 7% of the population has reduced enzyme activity because of variants in the *CYP2D6* gene. In individuals with low CYP2D6 activity, standard doses of thioridazine may lead to higher drug levels in the plasma, and increase the risk of cardiac arrhythmias.

The FDA-approved drug label for thioridazine states that thioridazine is contraindicated in individuals who are known to have reduced levels of CYP2D6 activity. The label also states it is contraindicated to coadminister thioridazine with drugs that inhibit CYP2D6 (e.g., fluoxetine, paroxetine) or inhibit the metabolism of thioridazine (e.g., fluvoxamine, propranolol, and pindolol) (1).

Drug Class: Antipsychotics

The first antipsychotics to be discovered in the 1950s were haloperidol and chlorpromazine, followed by other agents, including fluphenazine, loxapine, pherphenazine, pimozide, thioridazine, thiothixene, and trifluoperazine.

Known as "first generation" or "typical" antipsychotics, these drugs were used to treat psychosis (regardless of the cause), chronic psychotic disorders (e.g., schizophrenia), and other psychiatric conditions. However, prominent adverse effects included extrapyramidal side effects such as tardive dyskinesia, muscle rigidity, and tremors, i.e., Parkinsonian-like symptoms.

Newer antipsychotics, known as "second generation" or "atypical" antipsychotics, have a lower risk of extrapyramidal side effects. However, many have serious metabolic effects. These antipsychotics include aripiprazole, clozapine, iloperidone, olanzapine, and risperidone.

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Drug: Thioridazine

Thioridazine is a first generation "typical" antipsychotic used in the treatment of schizophrenia. Schizophrenia is a severe neurodevelopmental disorder with a worldwide prevalence of around 0.3–0.7% (2). The etiology of schizophrenia is unknown, but it is thought to result from a combination of complex genetic and environmental factors. Before the discovery of the first antipsychotics in the 1950s, the management of schizophrenia relied heavily upon sedation, electroconvulsive therapy, and institutionalization.

The symptoms of schizophrenia fall into three main categories: positive, negative, and cognitive. Positive symptoms are generally not found in healthy individuals, but may come and go or persist in individuals with schizophrenia. Positive symptoms include reality distortion (e.g., delusions, hallucinations), and thought disorders. These symptoms often respond well to treatment.

Negative symptoms are deficits in normal emotions and behavior, and may be mistaken for depression. Symptoms divide into reduced expression of emotion (e.g., speaking without moving or with a monotonous voice) and avolition (a lack of motivation to start or continue with a task). No treatment has established efficacy for these pathologies.

Cognitive symptoms may also be difficult to recognize. They include poor executive functioning (understanding information and using it to make decisions) and trouble focusing or paying attention. And again, no treatment has established efficacy.

The use of thioridazine is reserved for patients who have failed to respond to or cannot tolerate the side effects of other antipsychotics. The FDA-approved drug label for thioridazine strongly recommends that prior to starting thioridazine, a patient should be given at least two trials, each with a different antipsychotic drug product, at an adequate dose, for an adequate duration of time. The label also states that for patients who do require chronic treatment with thioridazine, the smallest dose and the shortest duration of treatment should be sought and the need for continued treatment should be reassessed periodically; and cautions that the efficacy of thioridazine in treating patients with refractory schizophrenia is unknown (1).

The main action of both first-generation and second-generation antipsychotics appears to be the post-synaptic blockade of D2 dopamine receptors in the brain. (An exception is aripiprazole, which is a D2 partial agonist.) Blockade of the D2 receptor in the brain's limbic system is thought to improve the "positive" symptoms of schizophrenia (3).

However, because the first-generation antipsychotics also block dopamine receptors in the nigrostriatal pathway, they 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).

Compared to other first generation antipsychotics, thioridazine shares a similar efficacy, but has a lower risk of extrapyramidal side effects (4-6). However, a higher level of EKG changes is associated with thioridazine therapy (6).

Antipsychotics, and thioridazine in particular, can inhibit cardiac ion channels. Most first generation antipsychotics block the cardiac potassium channel KCNH2, previously known as the human ether-a-go-go-related gene (hERG) (7, 8). Blockade of this channel reduces inward potassium current, resulting in longer cardiac repolarization times. On the EKG, this manifests as a prolonged QT interval. In extreme cases, this can lead to a life-threatening ventricular tachycardia known as torsades de pointes ("twisting of the points") (9-11).

At one point, thioridazine was one of the most commonly used medications for major mental health disorders. However, numerous case reports of sudden, unexpected death led to label changes in 2000, which recommended that thioridazine be used as a last resort (12). In 2005, the manufacturer Novartis discontinued the branded form

of thioridazine because of its association with QT prolongation, but generic forms are still available in the US (13, 14).

Thioridazine is metabolized by CYP2D6 to the active metabolite mesoridazine, which is further metabolized to sulforidazine, both of which are more potent than thioridazine. In addition, both thioridazine and mesoridazine have similar effects on the QT interval (15, 16).

Recent research has found that thioridazine is active against multidrug resistant tuberculosis, when used in combination with other antituberculosis drugs. Thioridazine increases the permeability of the cell-envelope, enabling the enhanced uptake of antibiotics (17).

The FDA drug label states that no teratogenic effect has been shown with thioridazine to date. However, all drugs should be kept to a minimum during pregnancy, so thioridazine should be given only when the benefits exceed the possible risks to mother and fetus. Of note, neonates exposed to antipsychotic drugs during the third trimester are at risk for extrapyramidal and/or withdrawal symptoms following delivery which vary in severity; while in some cases symptoms have been self-limited, in other cases neonates have required intensive care unit support and prolonged hospitalization.

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 very polymorphic and can result in reduced, absent, or increased enzyme activity.

Gene: *CYP2D6*

CYP2D6 is highly polymorphic; over 100 star (*) alleles are described and currently catalogued at the Human Cytochrome P450 (CYP) Allele Nomenclature Database (18). *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 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, *41*
No function	**3-*8, *11-*16, *19-*21, *38, *40, *42*

For a detailed list of *CYP2D6* alleles, please see (18).

An activity score can be assigned to each *CYP2D6* allele, e.g., 1 for each functional allele, 0.5 for a decreased function allele, and 0 for a no function allele. Individuals who carry more than two normal function copies (e.g., multiple copies) of the *CYP2D6* gene are "ultrarapid metabolizers", whereas individuals who are "normal metabolizers" either carry two normal function copies of *CYP2D6*, or a combination of normal/decreased/no function alleles that result in an activity score between 1.0 and 2.0. Individuals who are intermediate or poor metabolizers carry copies of decreased or no function *CYP2D6* alleles, respectively (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]

Table 2. continued from previous page.

Phenotype	Activity Score	Genotypes	Examples of diplotypes
CYP2D6 Normal metabolizer (approximately 72-88% of patients)	1.0 – 2.0[c]	An individual carrying two normal function alleles or two decreased function alleles or one normal and no function allele or one normal function and decreased function allele or combinations of duplicated alleles that result in an activity score of 1.0 to 2.0	**1/*1* **1/*2* **2/*2* **1/*9* **1/*41* **41/*41* **1/*5* **1/*4*
CYP2D6 Intermediate metabolizer (approximately 1-13% of patients)	0.5	An individual carrying one decreased function and one no function allele	**4/*41* **5/*9* **4/*10*
CYP2D6 Poor metabolizer (approximately 1-10% of patients)	0	An individual carrying two no function alleles	**4/*4* **4/*4xN* **3/*4* **5/*5* **5/*6*

[a] For population-specific allele and phenotype frequencies, please see
[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] (19).

The most common no function alleles include *CYP2D6*3*, **4*, **5*, and **6* (20-23), and the most common decreased function alleles include *CYP2D6*9, *10, *17, *29* and **41* (24-28) .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 (29).

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 (30, 31).

In individuals who are *CYP2D6* poor metabolizers, standard doses of thioridazine may lead to the drug accumulating in the plasma. Since a dose-related side effect of thioridazine is prolongation of the QTc interval, which is a potentially life threatening event, the FDA has stated that the use of thioridazine is contraindicated in individuals who are known to have reduced CYP2D6 activity (1, 32). In addition, the label also states it is contraindicated to coadminister thioridazine with other drugs that inhibit CYP2D6 activity (e.g., the antidepressants fluoxetine and paroxetine) or inhibit the metabolism of thioridazine (e.g., the beta-blockers propranolol and pindolol, and the antidepressant fluvoxamine) (1).

Genetic Testing

The NIH's Genetic Testing Registry, GTR, provides examples of the genetic tests that are currently available for the thioridazine response and 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* results (33). However, it needs to be noted that the number of variants tested varies substantially among laboratories and there is no standardized way to report results (34).

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:

- An extensive (normal) 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 of greater than 2 (19, 35)

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): Reduced cytochrome P450 2D6 isozyme activity drugs that inhibit this isozyme (e.g., fluoxetine and paroxetine) and certain other drugs (e.g., fluvoxamine, propranolol, and pindolol) appear to appreciably inhibit the metabolism of thioridazine. The resulting elevated levels of thioridazine would be expected to augment the prolongation of the QTc interval associated with thioridazine and may increase the risk of serious, potentially fatal, cardiac arrhythmias, such as Torsades de pointes type arrhythmias. Such an increased risk may result also from the additive effect of coadministering thioridazine with other agents that prolong the QTc interval. Therefore, thioridazine is contraindicated with these drugs as well as in patients, comprising about 7% of the normal population, who are known to have a genetic defect leading to reduced levels of activity of P450 2D6.

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

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[2] (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>A	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>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 Human Cytochrome P450 (CYP) Allele Nomenclature Database: http://www.cypalleles.ki.se/

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