



Deutetrabenazine Therapy and CYP2D6 Genotype

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Introduction

Deutetrabenazine (brand name Austedo) is used to treat chorea associated with Huntington disease (HD) and tardive dyskinesia (TD). Both HD and TD are types of involuntary movement disorders.

The recommended starting dose is 6 mg once daily for individuals with HD and 12 mg per day (6 mg twice daily) for individuals with TD. The maximum recommended daily dosage for both conditions is 48 mg (24 mg, twice daily).

The active metabolites of deutetrabenazine are reversible inhibitors of vesicular monoamine transporter 2 (VMAT2). The VMAT2 protein transports the uptake of monoamines, such as dopamine, into the nerve terminal. The inhibition of VMAT2 leads to a depletion of pre-synaptic dopamine and reduces the amount of dopamine realized when that neuron fires. This is thought to lead to fewer abnormal, involuntary movements.

The CYP2D6 enzyme converts the active metabolites of deutetrabenazine to minor, reduced activity metabolites. Individuals who have no CYP2D6 activity (“CYP2D6 poor metabolizers”) are likely to have a 3- to 4-fold increased exposure to active metabolites, compared with normal metabolizers, following the recommended standard doses of deutetrabenazine.

The 2018 FDA-approved drug label for deutetrabenazine states that the daily dose of deutetrabenazine should not exceed 36 mg (maximum single dose of 18 mg) for individuals who are CYP2D6 poor metabolizers or concurrently taking a strong CYP2D6 inhibitor (e.g., quinidine, antidepressants such as paroxetine, fluoxetine, and bupropion) (Table 1).

In addition, the drug label cautions that tetrabenazine, a closely related VMAT2 inhibitor, causes QT prolongation. Therefore, a clinically relevant QT prolongation may occur in some individuals treated with deutetrabenazine who are CYP2D6 poor metabolizers or are co-administered a strong CYP2D6 inhibitor (1).

Table 1. The FDA (2017) Deutetrabenazine Dosage and Administration.

Disorder	Maximum dose of deutetrabenazine	
	Standard recommendation	Recommendation for CYP2D6 poor metabolizers
Chorea association with Huntington disease	48 mg (24 mg twice daily)	36 mg per day (18 mg twice daily)
Tardive dyskinesia	48 mg (24 mg twice daily)	36 mg per day (18 mg twice daily)

Please see Therapeutic Recommendations based on Genotype for more information from the FDA. This FDA table is adapted from (1).

Drug: Deutetrabenazine

Deutetrabenazine (brand name Austedo) is used in the management of involuntary movement disorders: chorea associated with HD, and TD in adults. The use of deutetrabenazine is also being investigated for the management of tics associated with Tourette syndrome (2, 3).

Deutetrabenazine belongs to the drug class of VMAT2 inhibitors. These agents act centrally by depleting dopamine storage in presynaptic vesicles in the central nervous system. This reduces the amount of dopamine released when neurons fire, which may result in fewer abnormal, involuntary movements. Other drugs in this class include valbenazine (brand name Ingrezza) and tetrabenazine (brand name Xenazine).

The recommended initial dose of deutetrabenazine is 6 mg/day for chorea associated with HD, and 12 mg/day for TD. The dose should be titrated up by weekly increments of 6 mg/day, based on tolerability and the reduction of chorea or TD, until the individual optimal and tolerated dose is established in both conditions. The standard maximum dose is 48 mg/day (24 mg, twice daily) (1). However, in the Aim to Reduce Movements in Tardive Dyskinesia study, the maximum allowable dose was 72 mg/day (4).

Tetrabenazine was the first drug to be licensed for the treatment of chorea associated with HD, but its use was limited by frequent dosing (at least 3 times daily) and dose-related adverse events (e.g., somnolence, anxiety, and depression).

Deutetrabenazine is a modified (deuterated) form of tetrabenazine. In deuterated drugs, key hydrogen atoms have been replaced with the heavier hydrogen isotope, deuterium, while preserving pharmacological activity. Because deuterium-carbon bonds are stronger than hydrogen-carbon bonds, these drugs tend to be more resistant than non-deuterated drugs to metabolizing enzymes (e.g., CYP2D6), resulting in a longer half-life that allows less frequent dosing. In addition, peak drug concentrations are reduced, potentially reducing any side effects that are associated with peak concentrations. The maximum daily dose of tetrabenazine is 100 mg, compared with 48 mg for deutetrabenazine; and deutetrabenazine is dosed less frequently (twice daily, compared with at least 3 times daily for tetrabenazine) (5-11).

The exact mechanism of action of deutetrabenazine is unknown, but it is thought to involve the reversible depletion of monoamines (such as dopamine, serotonin, norepinephrine, and histamine) from nerve terminals. Deutetrabenazine's active alpha and beta metabolites (α -HTBZ and β -HTBZ) are reversible inhibitors of VMAT2, a transporter protein that is localized in the presynaptic neurons in the central nervous system.

Dopamine and other monoamine transmitters are transported by VMAT2 from the neuronal cell cytoplasm into the neuronal synaptic vesicle. Dopamine that is not taken up into the presynaptic vesicle as a result of VMAT2

blockade by deutetrabenazine is rapidly degraded by monoamine oxidase, resulting in presynaptic depletion of dopamine (7, 11-14).

Huntington Disease

Huntington disease is primarily an adult-onset hereditary autosomal dominant progressive neurodegenerative disorder, which is characterized by involuntary movements (“chorea”), psychiatric symptoms, and cognitive dysfunction that can lead to dementia. More than 35,000 people in the US have HD. There is a juvenile form of HD that is characterized by onset of signs and symptoms before 20 years of age.

The prevalence of HD varies across regions of the world. For individuals of European ancestry, the prevalence of HD is estimated to be 3–10 per 100,000. Individuals from the US, Europe, and Australia generally fall within this range. Huntington disease is less common in Japan, China, Korea, Finland, Africa, and South Africa, with estimated prevalence values ranging from 0.1–2 per 100,000 (15, 16).

In the US, more than 35,000 people have HD, and, in Caucasians, the prevalence of HD is estimated to be 4.8 per 100,000. Interestingly, the prevalence of HD is higher for Black Americans (6.4 per 100,000). This suggests that HD is far more common in Blacks living in the US compared with Blacks living in Africa. For example, for Blacks living in South Africa the prevalence of HD is 0.02 per 100,000, and for those living in Zimbabwe it is 1.00 per 100,000 (15).

Huntington disease is caused by an unstable expanded repeat of the cytosine-adenine-guanine (CAG) trinucleotide coding for polyglutamine in the *huntingtin* (*HTT*) gene on chromosome 4. A repeat of 39 or more repeats invariably causes HD. The pathogenesis of HD is not understood, but the mutated huntingtin protein is thought to become toxic, which is accompanied by selective loss of neurons in the caudate and putamen (striatum).

Electron microscopy reveals aggregates of mutated huntingtin protein, which may form because the mutated protein is less soluble, or because it is likelier to form bonds with other proteins, or both of these mechanisms may contribute. The MRI scans of the brain reveal early progressive atrophy of the striatum, with the caudate often more severely affected than the putamen.

Chorea is a defining motor symptom, occurring in approximately 90% of individuals with HD, and is characterized by sudden, random, jerky, involuntary movements that can affect any part of the body. Initially, these movements may be mild and misinterpreted as restlessness, but as HD progresses, the movements increasingly interfere with daily functioning, causing social isolation, and increasing the risk of injury from instability and falls. Chorea tends to stabilize and dissipate during the later stages of HD when other movement impairments such as rigidity and dystonia (involuntary twisting movements) become more prominent (11, 13, 17).

Currently, the mainstay of treatment for HD is symptomatic and supportive care -- no drugs are available to stop or prevent the progression of HD. Deutetrabenazine therapy has been shown to effectively control chorea symptoms compared with placebo and is generally well tolerated. However, comparison data with other VMAT2 inhibitors is limited due to a lack of reported head-to-head trials (6, 9-11, 13, 14, 17, 18).

Tardive Dyskinesia

Tardive dyskinesia (TD) is a medication-induced movement disorder. These movements are involuntary and repetitive, and most commonly affect the tongue, mouth, jaw, and face, but can also affect limbs and trunk. Severe cases are associated with difficulty speaking and swallowing. The condition can be disfiguring and stigmatizing, severely negatively impacting the individual’s quality of life (19).

Tardive dyskinesia is caused by medicines that block dopamine receptors -- these include antipsychotic medications (e.g., [aripiprazole](#), [clozapine](#), [risperidone](#), [thioridazine](#)) and antiemetic drugs used to treat nausea and vomiting (e.g., metoclopramide and prochlorperazine). Tardive dyskinesia is irreversible and life long, persisting after the causative medicine has been stopped.

Approximately one-third of individuals with schizophrenia treated with antipsychotics have TD (20). Initially, it was thought that the prevalence of TD would decrease as newer antipsychotics were developed that are less likely to cause TD; however, TD remains prevalent. This is partly because the newer antipsychotics are indicated to treat conditions other than schizophrenia, such as depression, bipolar disorder, personality disorder, irritability in autism spectrum disorder, as well as off-label uses including insomnia and anxiety. Therefore, the population exposed to the risk of TD has increased (21-24).

Because TD is irreversible, prevention is crucial -- requiring both the limited use of drugs that cause TD and early diagnosis (25, 26). While not a cure, deutetrabenazine has been shown to reduce the abnormal movements associated with TD and is generally well tolerated. However, there are no head-to-head comparisons between VMAT2 inhibitors, and TD returns approximately 4 weeks after treatment is discontinued (4, 12, 20, 22, 25, 27-29).

Gene: **CYP2D6**

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

The CYP2D6 enzyme is responsible for the metabolism of many commonly prescribed drugs, including antidepressants, antipsychotics, analgesics, and beta-blockers. Importantly, CYP2D6 is also the main enzyme that metabolizes the active metabolites of deutetrabenazine (1).

CYP2D6 Alleles

The *CYP2D6* gene is highly polymorphic, as over 100 star (*) alleles have been described and cataloged at the Pharmacogene Variation ([PharmVar](#)) Consortium, and each allele is associated with either normal, decreased, or absent enzyme function (Table 2).

The combination of *CYP2D6* alleles that a person has is used to determine their diplotype (e.g., CYP2D6 *4/*4). Based on function, each allele can be assigned an activity score from 0 to 1, which in turn is often used to assign a phenotype (e.g., CYP2D6 poor metabolizer). However, the activity score system is not standardized across clinical laboratories or *CYP2D6* genotyping platforms.

Table 2. Activity Status of Selected *CYP2D6* Alleles

Allele type	<i>CYP2D6</i> 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 comprehensive list of *CYP2D6* alleles, please see [PharmVar](#).

*CYP2D6**1 is assigned when no variant is detected and is assumed to have normal enzyme activity (CYP2D6 normal metabolizer phenotype). The *CYP2D6* alleles *2, *33, and *35 are also considered to have near-normal activity.

Alleles that encode an enzyme with decreased activity include *10, *17, and *41, and alleles that encode a nonfunctional enzyme include *3, *4, *5, and *6. There are large inter-ethnic differences in the frequency of these alleles, with *3, *4, *5, *6, and *41 being more common in Caucasians, *10 more common in Asians, and *17 more common in Africans (30).

Additional variant alleles and their multi-ethnic population frequencies have previously been reported (31). Moreover, given the structural variability of the CYP2D6 region at chromosome 22q13.2, full gene deletion and duplication alleles, as well as complex tandem alleles with CYP2D6's pseudogene, CYP2D7, also occur in some individuals, and populations (32).

CYP2D6 Phenotypes

In the US and globally, most individuals, around 70-80%, are classified as “normal metabolizers” (also referred to as “extensive metabolizers”). They either have 2 normal function alleles (e.g., *1/*1) or one normal and one decreased function allele (e.g., *1/*41).

Individuals who have one normal function and one no function allele (e.g., *1/*4) or 2 decreased function alleles (e.g., *41/*41) are also categorized as “normal metabolizers” by recent nomenclature guidelines (33), but have also been categorized as “intermediate metabolizers” (34).

Individuals who have more than 2 normal function copies of the CYP2D6 gene are classified as “ultrarapid metabolizers,” which accounts for 1–10% of Caucasian individuals. For individuals of North African, Ethiopian and Saudi ancestry, the frequency is 16–28% (Table 3) (35).

Individuals who do not have any fully functional alleles are either intermediate metabolizers (one decreased function and one no function allele, e.g., *4/*41) or poor metabolizers (2 no function alleles, e.g., *4/*4).

Approximately 6–10% of European Caucasians and their descendants are poor metabolizers, mainly due to the prevalent nonfunctional *4 and *5 alleles. Compared with Europeans, individuals of Asian descent are likelier to be intermediate metabolizers because of increased prevalence of decreased function alleles, such as *10. Approximately 30% of Asians and individuals of Asian descent are intermediate metabolizers. Similarly, Africans and African Americans are likelier to be intermediate metabolizers than Europeans because of the prevalence of a wide range of decreased function variants (30, 36-38).

Table 3. CPIC (2017). Assignment of likely CYP2D6 Phenotype based on Genotype

Phenotype ^a		Genotype	Examples of CYP2D6 diplotypes ^b
Metabolizer status	Activity score		
CYP2D6 ultrarapid metabolizer	>2.0	An individual with duplications of functional alleles	*1/*1xN, *1/*2xN, *2/*2xN ^c
CYP2D6 normal metabolizer	1.5–2.0	An individual with 2 normal function alleles or one normal function and one decreased function allele	*1/*1, *1/*2, *1/*9, *1/*41, *2/*2
CYP2D6 normal metabolizer or intermediate metabolizer (controversy remains) ^b	1.0	An individual with 2 decreased function alleles or one normal function and one no function allele	*1/*4, *1/*5, *41/*41
CYP2D6 intermediate metabolizer	0.5	An individual with one decreased function and one no function allele	*4/*10, *4/*41, *5/*9

Table 3. continued from previous page.

Phenotype ^a		Genotype	Examples of <i>CYP2D6</i> diplotypes ^b
Metabolizer status	Activity score		
CYP2D6 poor metabolizer	0	An individual with only no functional alleles	*3/*4, *4/*4, *5/*5, *5/*6

^a See the *CYP2D6* frequency table in (35) for race-specific allele and phenotype frequencies.

^b For a complete list of *CYP2D6* diplotypes and resulting phenotypes, see the *CYP2D6* genotype to phenotype table in (35). Note that genotypes with an activity score of 1 are classified as normal metabolizers in the *CYP2D6* genotype to phenotype table on the CPIC website (35).

^c Where xN represents the number of *CYP2D6* gene copies. For individuals with *CYP2D6* duplications or multiplications, see supplemental data for additional information on how to translate diplotypes into phenotypes.

^d Individuals with an activity score of 1.0 may be classified as intermediate metabolizers by some reference laboratories. A group of *CYP2D6* experts are currently working to standardize the *CYP2D6* genotype to phenotype translation system. This Clinical Pharmacogenetics Implementation Consortium (CPIC) table is adapted from (35)

Linking Gene Variation with Treatment Response

The *CYP2D6* enzyme is responsible for converting deutetrabenazine active metabolites to minor, reduced activity metabolites. Individuals who are taking a strong *CYP2D6* inhibitor (e.g., quinidine, antidepressants such as paroxetine, fluoxetine, and bupropion) have an approximately 3–4 fold higher exposure to active deutetrabenazine metabolites after standard dosing. Therefore, it is likely that individuals who are *CYP2D6* poor metabolizers will have a similarly increased exposure to deutetrabenazine.

The FDA-approved drug label for deutetrabenazine cautions that a clinically relevant QT prolongation may occur in *CYP2D6* poor metabolizers or individuals who are taking a strong *CYP2D6* inhibitor. The drug label also states that a closely related VMAT2 inhibitor, tetrabenazine, has been shown to prolong the QT interval (the time taken for the heart ventricles to depolarize and repolarize). Other drugs with this potential have been associated with life-threatening ventricular tachycardia.

The FDA states that the total daily dosage of deutetrabenazine should be reduced in *CYP2D6* poor metabolizers or individuals who are taking a strong *CYP2D6* inhibitor. The total daily dose of deutetrabenazine should not exceed 36 mg, with a maximum single dose of 18 mg taken twice daily (the standard recommended total daily dose is 48 mg) (1).

Genetic Testing

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

The *CYP2D6* gene is a particularly complex gene that is difficult to genotype because of the large number of variants and the presence of gene deletions, duplications, multiplications, and pseudogenes. The complexity of genetic variation complicates the correct determination of *CYP2D6* genotype.

Targeted genotyping typically includes up to 30 variant *CYP2D6* alleles (of the more than 100 alleles that have been identified so far). Test results are reported as a diplotype, such as *CYP2D6* *1/*1. However, it is important to note that the number of variants tested can vary between laboratories, which can result in diplotype result discrepancies between testing platforms and laboratories (35).

A result for copy number, if available, is also important when interpreting *CYP2D6* genotyping results. Gene duplications and multiplications are denoted by “xN”; e.g., *CYP2D6**1xN with xN representing the number of *CYP2D6* gene copies.

If the test results include an interpretation of the individual's predicted metabolizer phenotype, such as "CYP2D6 *1/*1, normal metabolizer", this can be confirmed by checking the diplotype and assigning an activity score assigned to each allele (e.g., 0 for no function, 0.5 for decreased function, and 1.0 for each copy of a normal function allele, Table 3).

The CYP2D6 phenotype is defined by the sum of the 2 activity scores, which is usually in the range of 0–3.0:

- An ultrarapid metabolizer has an activity score greater than 2
- A normal metabolizer phenotype has an activity score of 1.5–2.0
- A normal metabolizer or intermediate metabolizer has a score of 1.0
- An intermediate metabolizer has an activity score of 0.5
- A poor metabolizer has an activity score of 0 (35)

A standardized CYP2D6 genotype to phenotype assignment logic is currently being developed by an [international working group](#) of CYP2D6 experts and both the CPIC and the Dutch Pharmacogenetics Working Group (DPWG).

Therapeutic Recommendations based on Genotype

This section contains excerpted¹ information on gene-based dosing recommendations. Neither this section nor other parts of this review contain the complete recommendations from the sources.

2017 Statement from the US Food and Drug Administration (FDA)

2.4 Dosage Adjustment in Poor CYP2D6 Metabolizers

In patients who are poor CYP2D6 metabolizers, the total daily dosage of deutetrabenazine should not exceed 36 mg (maximum single dose of 18 mg).

[...]

5.3 QTc Prolongation

Tetrabenazine, a closely related VMAT2 inhibitor, causes an increase (about 8 msec) in the corrected QT (QTc) interval. A clinically relevant QT prolongation may occur in some patients treated with deutetrabenazine who are CYP2D6 poor metabolizers or are co-administered a strong CYP2D6 inhibitor.

For patients who are CYP2D6 poor metabolizers or are taking a strong CYP2D6 inhibitor, dose reduction may be necessary. The use of deutetrabenazine in combination with other drugs that are known to prolong QTc may result in clinically significant QT prolongations.

[...]

8.7 Poor CYP2D6 Metabolizers

Although the pharmacokinetics of deutetrabenazine and its metabolites have not been systematically evaluated in patients who do not express the drug metabolizing enzyme, it is likely that the exposure to α -HTBZ and β -HTBZ would be increased similarly to taking a strong CYP2D6 inhibitor (approximately 3-fold).

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

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. Certain terms, genes and genetic variants may be corrected in accordance to nomenclature standards, where necessary. We have given the full name of abbreviations, shown in square brackets, where necessary.

Nomenclature

Nomenclature for Selected *CYP2D6* Alleles

Common allele name	Alternative names / major SNP	HGVS reference sequence		dbSNP reference identifier for allele location
		Coding	Protein	
<i>CYP2D6</i> *4	1846G>A	NM_000106.5:c.506-1G>A	Not applicable - variant occurs in a non-coding region	rs3892097
<i>CYP2D6</i> *5	Not applicable - variant results in a whole gene deletion			
<i>CYP2D6</i> *6	1707 del T Trp152Gly	NM_000106.5:c.454delT	NP_000097.3:p.Trp152Glyfs	rs5030655
<i>CYP2D6</i> *10	100C>T Pro34Ser	NM_000106.5:c.100C>T	NP_000097.3:p.Pro34Ser	rs1065852
<i>CYP2D6</i> *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
<i>CYP2D6</i> *41	2988G>A	NM_000106.5:c.985+39G>A	Not applicable – variant occurs in a non-coding region	rs28371725

SNP= Single Nucleotide Polymorphism

Note: In the literature, 1023C>T is also referred to as 1111C>T, and 2850C>T is also referred to 2938C>T.

Note: The variant 1846G>A often occurs with both 4180G>C and 100C>T; and the variant 988G>A occurs with 2850C>T (Cys296Arg).

Pharmacogenetic Allele Nomenclature: International Workgroup Recommendations for Test Result Reporting (39).

Guidelines for the description and nomenclature of gene variations are available from the Human Genome Variation Society (HGVS).

Nomenclature for Cytochrome P450 enzymes is available from Pharmacogene Variation (PharmVar) Consortium.

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