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Brivaracetam Therapy and CYP2C19 Genotype

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Introduction

Brivaracetam (brand name Briviact) is an antiseizure drug used in the treatment of partial-onset (focal) epilepsy in adults. It is thought to act by binding to a synaptic vesicle glycoprotein, SV2A, and reducing the release of neurotransmitters.

Brivaracetam is primarily metabolized by hydrolysis, via amidase enzymes, to an inactive metabolite. To a lesser extent, it is also metabolized by a minor metabolic pathway via CYP2C19-dependent hydroxylation.

Individuals who have no CYP2C19 enzyme activity, "CYP2C19 poor metabolizers", will have a greater exposure to standard doses of brivaracetam. Because they are less able to metabolize the drug to its inactive form for excretion, they may have an increased risk of adverse effects. The most common adverse effects of brivaracetam therapy include sedation, fatigue, dizziness, and nausea.

The recommended starting dosage for brivaracetam monotherapy or adjunctive therapy is 50 mg twice daily (100 mg per day). Based on how the individual responds, the dose of brivaracetam may be decreased to 25 mg twice daily (50 mg per day) or increased up to 100 mg twice daily (200 mg per day) (1).

The FDA-approved drug label for brivaracetam states that patients who are CYPC19 poor metabolizers, or are taking medicines that inhibit CYP2C19, may require a dose reduction (Table 1). Approximately 2% of Caucasians, 4% of African Americans, and 14% of Chinese are CYP2C19 poor metabolizers (1).

Table 1. FDA (2017) Drug Label for Brivaracetam. Recommendations for CYP2C19 Phenotype: Pharmacokinetics.

Phenotype	Recommendations
CYP2C19 poor metabolizer	CYP2C19 poor metabolizers and patients using inhibitors of CYP2C19 may require dose reduction.

This table is adapted from (1).

Drug: Brivaracetam

Brivaracetam is an antiseizure drug that is used in the treatment of partial-onset (focal) seizures in patients aged 16 years or older. Brivaracetam can be used as monotherapy, or more commonly, is used in combination with other antiseizure drugs (1). There is also some evidence to suggest that brivaracetam may be useful in the treatment of generalized seizures (2).

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Brivaracetam displays a high and selective affinity for SV2A in the brain, which is thought to contribute to the antiseizure effect (3).

In a neuron, at the synapse, vesicles store various neurotransmitters. The neurotransmitters are released and then refilled in a process regulated by voltage-dependent calcium channels. These synaptic vesicles are essential for propagating nerve impulses between neurons, and the SV2A protein is a major component of the vesicle (4).

Levetiracetam was the first antiseizure drug that was found to bind to SV2A, among other targets. Brivaracetam is an analogue of levetiracetam and was designed to selectively target SV2A with a much higher affinity (5-7).

Over 50 million people worldwide suffer from epilepsy. Epilepsy is characterized by spontaneous recurrent epileptic seizures, which may be classified as focal or generalized. Generalized seizures appear to originate in all regions of the cortex simultaneously and include absence seizures (sudden impaired consciousness and staring) and general tonic-clonic seizures (loss of consciousness, stiffening of limbs in the tonic phase, and twitching or jerking muscles in the clonic phase). In contrast, symptoms of focal seizures depend upon where the focus of the seizure originates in the brain; e.g., jerking of a limb indicates a focus in the contralateral motor cortex.

Most antiseizure drugs currently available target sodium channels (e.g., carbamazepine, phenytoin), calcium channels (e.g., ethosuximide), or the GABA pathway (e.g., clobazam). However, up to one-third of patients may not achieve seizure control or they may not be able to tolerate the side effects. Newer antiseizure drugs have unconventional targets, such as SV2A (8-10).

Brivaracetam was licensed in 2016, and in phase III trials and with long term follow up, brivaracetam was reported to be well tolerated with good efficacy (11, 12). Compared with the addition of placebo to a treatment regime, the addition of brivaracetam reduced the frequency of focal seizures by approximately half (13-16).

The most common side effects associated with brivaracetam therapy include dizziness, fatigue, somnolence, nausea and vomiting. Psychiatric symptoms such as irritability, insomnia and depression, and behavioral effects have also been reported, but some studies suggest these may be less likely to occur with brivaracetam compared with levetiracetam (17-20).

Brivaracetam is primarily metabolized (approximately 60%) by cytochrome P450 (CYP)-independent hydrolysis (via amidase) to inactive metabolites. Minor metabolic pathways include hydroxylation by CYP2C19.

One study found that co-administration of rifampin (a strong enzyme inducer) decreased exposure to brivaracetam by 45%, this is probably through an induction of the CYP2C19 pathway which clears brivaracetam metabolites from the blood (21). One small study (n=79) found that individuals who lacked CYP2C19 activity had increased exposure to brivaracetam (22). It is therefore possible that genetic variations associated with a loss of CYP2C19 function may reduce brivaracetam metabolism leading to increased levels of active drug levels in the plasma, and possibly increases the probability of side effects. However, the recommended therapeutic dose is 50–200 mg/day, and patients are individually titrated to optimal efficacy, safety, and tolerability.

Gene: CYP2C19

The CYP superfamily is a large and diverse group of enzymes that form the major system for metabolizing lipids, hormones, toxins, and drugs. The CYP genes are very polymorphic and can result in reduced, absent, or increased drug metabolism.

The CYP2C19 enzyme contributes to the metabolism of a range of clinically important drugs, such as antidepressants (23), benzodiazepines, several proton pump inhibitors, the antifungal agent voriconazole (24), the antiplatelet agent clopidogrel (25), and antiseizure drugs such as brivaracetam, clobazam, diazepam, lacosamide, phenytoin, and phenobarbital.

The *CYP2C19* gene is highly polymorphic—35 variant star (*) alleles are cataloged at the Pharmacogene Variation (PharmVar) Consortium. The *CYP2C19*1* is the wild type allele and is associated with normal enzyme activity and the "normal metabolizer" phenotype.

The *CYP2C19*17* allele is associated with increased enzyme activity and, depending on the number of alleles present, is associated with the "rapid" (one **17* allele) and "ultrarapid" (two **17* alleles) metabolizer phenotypes.

Nonfunctional alleles include *CYP2C19*2* and **3*. The *CYP2C19* "intermediate" metabolizers carry one copy of an allele that encodes a nonfunctional allele (e.g., **1/*2*), whereas "poor" metabolizers carry 2 nonfunctional alleles (e.g., **2/*2*, **2/*3*) (Table 2).

Table 2. CPIC (2016) *CYP2C19* Functional Status and Phenotypes

Phenotype	Genotype	Examples of diplotypes
CYP2C19 ultrarapid metabolizer (~2–5% of patients)[a]	An individual carrying 2 increased function alleles.	**17/*17*
CYP2C19 rapid metabolizer (~2–30% of patients)	An individual carrying one normal function allele and one increased function allele.	**1/*17*
CYP2C19 normal metabolizer (~35–50% of patients)	An individual carrying 2 normal function alleles.	**1/*1*
CYP2C19 intermediate metabolizer (~18–45% of patients)	An individual carrying one normal function allele and one no function allele, or one no function allele and one increased function allele.	**1/*2* **1/*3* **2/*17*[b]
CYP2C19 poor metabolizer (~2–15% of patients)	An individual carrying 2 no function alleles.	**2/*2* **2/*3* **3/*3*

[a] CYP2C19 metabolizer status frequencies are based on average multiethnic frequencies. See the *CYP2C19* Frequency Tables for population-specific allele and phenotype frequencies (23).
[b] The predicted metabolizer phenotype for the **2/*17* genotype is a provisional classification. The currently available evidence indicates that the *CYP2C19*17* increased function allele is unable to completely compensate for the *CYP2C19*2* nonfunctional allele.
This table is adapted from (23).

Approximately 2% of Caucasians, 4% of African Americans, and 14% of Chinese are CYP2C19 poor metabolizers; and up to 45% of patients are CYP2C19 intermediate metabolizers.

The most common nonfunctional variant is *CYP2C19*2*, which contains a NM_000769.1:c.681G>A variant in exon 5 that results in an aberrant splice site that produces a truncated and nonfunctioning protein. The *CYP2C19*2* allele frequencies are ~15% in Caucasians and Africans, and ~29–35% in Asians.

Another commonly tested nonfunctional variant is *CYP2C19*3*, which contains a NM_000769.1:c.636G>A variant in exon 4 that causes a premature stop codon. The *CYP2C19*3* allele frequencies are ~2-9% in Asian populations, but rare in other racial groups. Other nonfunctional variants occur in less than 1% of the general population and include *CYP2C19*4-*8* (25).

Linking Gene Variation with Treatment Response

One small study (n=79) reports that *CYP2C19* allele status influences the pharmacokinetics of brivaracetam, but that this is unlikely to be clinically relevant because of the minor role of CYP-dependent hydroxylation in the metabolism of brivaracetam (22). However, the FDA does state that CYP2C19 poor metabolizers may require a reduction in the dose of brivaracetam (1).

Genetic Testing

Clinical genotyping tests are available for several *CYP2C19* alleles. The NIH's Genetic Testing Registry (GTR) provides examples of the genetic tests that are currently available for the *CYP2C19* gene.

Usually a patient's result is reported as a diplotype, such as *CYP2C19 *1/*1*, and may also include an interpretation of the patient's predicted metabolizer phenotype (ultrarapid, rapid, normal, intermediate, or poor).

The *CYP2C19*2* and **3* alleles are most commonly tested for, and Table 2 summarizes common CYP2C19 phenotypes. Less common nonfunctional alleles (e.g., *CYP2C19*4-*8*) may also influence drug response similarly to **2* and **3* but they may not be tested for, and data are lacking on their effects on the brivaracetam drug response.

To facilitate *CYP2C19* genetic testing and improve genotyping concordance across laboratories, the Pharmacogenetics Working Group of the Association for Molecular Pathology Clinical Practice Committee (AMP PGx) has recommended a minimum set of *CYP2C19* alleles, referred to as "tier 1", which should be included in clinical *CYP2C19* pharmacogenomic tests. As of 2018, the tier 1 alleles are *CYP2C19*2*, *CYP2C19*3*, and *CYP2C19*17* (Table 3) (26).

In addition, AMP PGx have defined a list of tier 2 *CYP2C19* alleles that do not meet the criteria for inclusion in tier 1 and are thus considered optional (Table 4) (26).

Table 3. AMP PGx (2018) *CYP2C19* Tier 1 Variant Alleles.

Allele	Allele functional status[a]	Defining functional variant	Multiethnic allele frequency, %
*CYP2C19*2*	No function	rs4244285	12-54
*CYP2C19*3*	No function	rs4986893	0.3-15
*CYP2C19*17*	Increased function	rs12248560	4-21

[a] Citations for assignment of function can be found at PharmGKB Gene-specific Information for *CYP2C19*.
Note that the defining **2* variant (rs4244285) is most likely linked with the defining variant of the **35* allele (rs12769205); however, the **35* definition includes rs12769205 without rs4244285.

Table 4. AMP PGx (2018) *CYP2C19* Tier 2 Variant Alleles.

Genotype	Allele functional status*	Defining functional variant	*Multiethnic allele frequency, %
*CYP2C19*4*	No function	rs28399504	0.1-0.3
*CYP2C19*4B*	No function	rs28399504; rs12248560	0-0.2
*CYP2C19*5*	No function	rs56337013	0
*CYP2C19*6*	No function	rs72552267	0-0.1
*CYP2C19*7*	No function	rs72558186	0
*CYP2C19*8*	No function	rs41291556	0.1-0.3
*CYP2C19*9*	Decreased function	rs17884712	0.1-4.2
*CYP2C19*10*	Decreased function	rs6413438	0.1-6
*CYP2C19*35*	No function	rs12769205	0.8-3.1

* Multiethnic allele frequency from PharmVar.org (last accessed June 20, 2017.)
Both Table 3 and Table 4 are adapted from (26).

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.

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

Brivaracetam is primarily metabolized by hydrolysis of the amide moiety to form the corresponding carboxylic acid metabolite, and secondarily by hydroxylation on the propyl side chain to form the hydroxy metabolite. The hydrolysis reaction is mediated by hepatic and extra-hepatic amidase. The hydroxylation pathway is mediated primarily by CYP2C19. In human subjects possessing genetic variations in CYP2C19, production of the hydroxy metabolite is decreased 2-fold or 10-fold, while the blood level of brivaracetam itself is increased by 22% or 42%, respectively, in individuals with one or both mutated alleles. CYP2C19 poor metabolizers and patients using inhibitors of CYP2C19 may require dose reduction. An additional hydroxy acid metabolite is created by hydrolysis of the amide moiety on the hydroxy metabolite or hydroxylation of the propyl side chain on the carboxylic acid metabolite (mainly by CYP2C9). None of the 3 metabolites are pharmacologically active.

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

Nomenclature of selected *CYP2C19* alleles

Common allele name	Alternative names	HGVS reference sequence		dbSNP reference identifier for allele location
		Coding	Protein	
*CYP2C19*2*	681G>A Pro227Pro	NM_000769.1:c.681G>A	NP_000760.1:p.Pro227=	rs4244285
*CYP2C19*3*	636G>A Trp212Ter	NM_000769.1:c.636G>A	NP_000760.1:p.Trp212Ter	rs4986893
*CYP2C19*17*	-806C>T	NM_000769.1:c.-806C>T	Not applicable - variant occurs in a non-coding region	rs12248560

Note: the normal "wild type" allele is *CYP2C19*1*.
Pharmacogenetic Allele Nomenclature: International Workgroup Recommendations for Test Result Reporting (27).
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 the Pharmacogene Variation (PharmVar) Consortium.

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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.

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