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NLM Citation: Dean L. Clobazam Therapy and *CYP2C19* Genotype. 2019 Sep 23. In: Pratt VM, McLeod HL, Rubinstein WS, et al., editors. Medical Genetics Summaries [Internet]. Bethesda (MD): National Center for Biotechnology Information (US); 2012-.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Clobazam Therapy and *CYP2C19* Genotype

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Created: September 23, 2019.

Introduction

Clobazam (brand names Onfi, Sympazan) is approved by the FDA to treat seizures associated with Lennox-Gastaut syndrome (LGS) in patients aged 2 years and older (1). The drug is widely used in the chronic treatment of focal and generalized seizures, and has application in the treatment of diverse epilepsy syndromes, including epileptic encephalopathies other than LGS, such as Dravet syndrome (2-6).

Lennox-Gastaut syndrome is characterized by different types of seizures that typically begin in early childhood and may be associated with intellectual disability. Clobazam has been shown in controlled clinical trials to reduce drop (atonic) seizures in children with LGS, but there is evidence that it is effective for other seizure types as well.

Clobazam is a 1,5-benzodiazepine that acts as a positive allosteric modulator of $GABA_A$ receptors. It is often used in combination with other drugs, including stiripentol, cannabidiol, and many others.

Clobazam is extensively metabolized in the liver by cytochrome P450 (CYP) and non-CYP transformations. The major metabolite is N-desmethylclobazam (norclobazam), which has similar activity to clobazam on $GABA_A$ receptors and is an active antiseizure agent. During chronic treatment, levels of norclobazam are 8–20 times higher than those of the parent drug so that seizure protection during chronic therapy is mainly due to this metabolite.

Norclobazam is principally metabolized by CYP2C19. Individuals who lack CYP2C19 activity ("CYP2C19 poor metabolizers") have higher plasma levels of norclobazam and are at an increased risk of adverse effects.

The FDA-approved drug label states that for patients known to be CYP2C19 poor metabolizers, the starting dose of clobazam should be 5 mg/day. Dose titration should proceed slowly according to weight, but to half the standard recommended doses, as tolerated. If necessary and based upon clinical response, an additional titration to the maximum dose (20 mg/day or 40 mg/day, depending on the weight group) may be started on day 21 (Table 1) (1).

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Table 1. The FDA (2019) Drug Label for Clobazam: Recommended Total Daily Dosing by Weight Group

	Less than or equal to 30 kg body weight	Greater than 30 kg body weight	CYP2C19 poor metabolizers
Starting dose	5 mg	10 mg	In patients known to be CYP2C19 poor metabolizers, the starting dose should be 5 mg/day and dose titration should proceed slowly according to weight, but to half the recommended total daily doses presented in this table, as tolerated. If necessary, and based upon clinical response, an additional titration to the maximum dose (20 mg/day or 40 mg/day, depending on the weight group) may be started on day 21.
Starting day 7	10 mg	20 mg	
Starting day 14	20 mg	40 mg	

This FDA table is adapted from (1).

Drug: Clobazam

Clobazam is a 1,5-benzodiazepine that is an adjunct treatment of seizures associated with LGS. Clobazam is used in patients aged 2 years and above, and is dosed according to body weight (1). Clobazam was licensed for use in the United States in 2011.

Lennox-Gastaut syndrome is characterized by severe seizures in childhood. Typically, seizures begin between 3–5 years of age, and there may be different seizure types (e.g., absent, tonic, atonic, myoclonic). In addition, there may be signs of mental retardation.

Over half of all cases of LGS are associated with another condition, such as tuberous sclerosis, meningitis, or head injuries. For approximately 40% of cases, the cause is not known, but increasingly, genetic disorders are being identified, such as de novo mutations or chromosomal syndromes.

The seizures associated with LGS are often difficult to treat. Therapy is influenced by the underlying cause of the syndrome, and certain antiseizure drugs, such as clobazam, have been found to be helpful. Previously, 2 studies reported that clobazam was effective at reducing drop seizures in children with LGS (5, 7). Other treatment options include a ketogenic diet, as well as surgical options (8).

The FDA-approved drug label for clobazam contains a boxed warning regarding the risks of the concomitant use of benzodiazepines (such as clobazam) with opioids. The warning states that this may result in profound sedation, respiratory depression, coma, and death. Other adverse effects of clobazam therapy include sedation, lethargy, drooling, severe dermatological reactions, and dependence (1).

Clobazam may cause fetal harm. There are no adequate studies in pregnant women, but in animal studies, the administration of clobazam during pregnancy resulted in fetal toxicity, including an increased incidence of fetal malformations. Therefore, clobazam should only be used during pregnancy if the potential benefit to the mother justifies the potential risk to the fetus. Infants born to mothers who have taken benzodiazepines in later stages of pregnancy can develop dependence and subsequently undergo withdrawal in the postnatal period.

Clobazam is primarily metabolized by CYP3A4, and to a lesser extent, by CYP2C19 and CYP2B6. The active metabolite, N-desmethylclobazam (norclobazam) is an antiseizure agent that is less potent than clobazam, but during chronic clobazam therapy, the circulating levels of norclobazam are 8–20 times higher than clobazam levels. Therefore, seizure protection during chronic therapy is mainly due to norclobazam.

With long-term exposure, tolerance to clobazam does occur in some patients; however, many patients exhibit continued efficacy. Therefore, the propensity for tolerance maybe less than with some other benzodiazepines (1, 9–11).

In individuals who lack CYP2C19 activity ("CYP2C19 poor metabolizers"), standard doses of clobazam lead to higher levels of norclobazam. Compared with individuals with normal CYP2C19 activity, poor metabolizers have up to 5 fold higher plasma levels of norclobazam, increasing the risk of adverse effects.

The recommended total daily doses of clobazam, by weight, are provided in the drug label (Table 1). The label states that each dose should be individualized within each body weight group based on clinical efficacy and tolerability. Any dose greater than 5 mg should be divided into a twice daily dose, and increases in doses should not be increased more rapidly than weekly, because the serum concentrations of clobazam and its active metabolite requires 5 and 9 days, respectively, to reach steady-state (1). Steady-state levels of clobazam are typically reached in under 3 weeks in normal metabolizers, but may take several months in CYP2C19 poor metabolizers (12).

Determining a patient's CYP2C19 status may be helpful in preventing an overdose when starting clobazam therapy, because levels of norclobazam will be increased in CYP2C19 poor metabolizers (13–15). The drug label states that in patients known to be CYP2C19 poor metabolizers, the starting dose should be 5 mg/day (1). A 2015 study recommends a lower starting dose of 2.5 mg/day (16).

In CYP2C19 poor metabolizers, the drug label states that dose titration should proceed slowly, as tolerated, and according to weight, but to half the dose presented in Table 1. If necessary and based upon clinical response, an additional titration to the maximum dose (20 mg/day or 40 mg/day, depending on the weight group) may be started on day 21 (1).

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, antiplatelet agents, some proton pump inhibitors, and benzodiazepines such as clobazam.

The *CYP2C19* gene is highly polymorphic as there currently are 35 variant star (*) alleles catalogued by the Pharmacogene Variation (PharmVar) Consortium. The *CYP2C19*1* is considered the wild-type allele when no variants are detected and is associated with normal enzyme activity and the "normal metabolizer" phenotype.

The *CYP2C19*17* allele is associated with increased enzyme activity and is found among individuals with "rapid" (**1/*17*) and "ultrarapid" (**17/*17*) metabolizer phenotypes. Heterozygous carriers of non-functional alleles (e.g., **2* and **3*) are classified as "intermediate metabolizers" (e.g., **1/*2*), and individuals who have 2 non-functional alleles are classified as "poor metabolizers" (e.g., **2/*2*, **2/*3*) (Table 2).

Table 2. CPIC (2016). Assignment of *CYP2C19* Phenotypes.

Phenotype	Genotype	Examples of diplotypes
CYP2C19 ultrarapid metabolizer (approximately 2–5% of individuals)[a]	An individual who has 2 increased function alleles	**17/*17*
CYP2C19 rapid metabolizer (approximately 2–30% of individuals)	An individual who has one normal function allele and one increased function allele	**1/*17*
CYP2C19 normal metabolizer (approximately 35–50% of individuals)	An individual who has 2 normal function alleles	**1/*1*
CYP2C19 intermediate metabolizer (approximately 18–45% of individuals)	An individual who has 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]

Table 2. continued from previous page.

Phenotype	Genotype	Examples of diplotypes
CYP2C19 poor metabolizer (approximately 2–15% of individuals)	An individual who has 2 no function alleles	**2/*2* **2/*3* **3/*3*

[a] CYP2C19 metabolizer status frequencies are based on average multi-ethnic frequencies. See the *CYP2C19* Frequency Tables for population-specific allele and phenotype frequencies (17).
[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* no function allele.
This CPIC table is adapted from (17).

Approximately 2% of Caucasians, 4% of African Americans, and 15–25% in East Asians are *CYP2C19* poor metabolizers; and up to 45% of patients are CYP2C19 intermediate metabolizers (17–19).

The most common no function allele is *CYP2C19*2*, which is defined by a c.681G>A variant in exon 5 that creates an aberrant splice site that translates a truncated and nonfunctioning protein. The *CYP2C19*2* allele frequencies are ~15% in Caucasians and Africans, and ~29–35% in Asians (20).

For CYP2C19, another commonly tested no function variant is *CYP2C19*3*, which contains a 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 no function variants occur in less than 1% of the general population, and include *CYP2C19*4–*8* (20).

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 clobazam response and the *CYP2C19* gene. In addition, variant *CYP2C19* alleles to be included in clinical genotyping assays have been recommended by the Association for Molecular Pathology (21).

Usually an individual's result is reported as a diplotype, such as *CYP2C19 *1/*1*, and may also include an interpretation of the individual's predicted metabolizer phenotype (ultrarapid, normal, intermediate, or poor). Table 2 summarizes common *CYP2C19* phenotypes.

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.

2019 Statement from the US Food and Drug Administration (FDA)

2.5 Dosage Adjustments in CYP2C19 Poor Metabolizers

In CYP2C19 poor metabolizers, levels of N-desmethylclobazam, clobazam's active metabolite, will be increased. Therefore, in patients known to be CYP2C19 poor metabolizers, the starting dose should be 5 mg/day and dose titration should proceed slowly according to weight, but to half the dose presented in Table 1, as tolerated. If necessary and based upon clinical response, an additional titration to the maximum dose (20 mg/day or 40 mg/day, depending on the weight group) may be started on day 21.

[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.

[…]

8.6 CYP2C19 Poor Metabolizers

Concentrations of clobazam's active metabolite, N-desmethylclobazam, are higher in CYP2C19 poor metabolizers than in normal metabolizers. For this reason, dosage modification is recommended

[…]

12.5 Pharmacogenomics

The polymorphic CYP2C19 is the main enzyme that metabolizes the pharmacologically active N-desmethylclobazam. Compared with CYP2C19 normal metabolizers, N-desmethylclobazam AUC and Cmax are approximately 3–5 times higher in poor metabolizers (e.g., subjects with *2/*2 genotype) and 2 times higher in intermediate metabolizers (e.g., subjects with *1/*2 genotype). The prevalence of CYP2C19 poor metabolism differs depending on racial/ethnic background. Dosage in patients who are known CYP2C19 poor metabolizers may need to be adjusted.

The systemic exposure of clobazam is similar for both CYP2C19 poor and normal metabolizers.

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

Nomenclature for 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

dbSNP: The Single Nucleotide Polymorphism Database
Note: the normal "wild-type" allele is *CYP2C19*1*.
Pharmacogenetic Allele Nomenclature: International Workgroup Recommendations for Test Result Reporting (22).
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.

Acknowledgments

The author would like to thank Michael A. Rogawski, Professor of Neurology, University of California, Davis, Davis, (CA), USA; and Junji Saruwatari, PhD, Associate Professor, Division of Pharmacology & Therapeutics, Kumamoto University, Kumamoto, Japan, for reviewing this summary.

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