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Carisoprodol Therapy and *CYP2C19* Genotype

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Introduction

Carisoprodol is a centrally acting muscle relaxant used to relieve acute back pain. Due to its potential for dependence and abuse, it should only be used for treatment periods of up to 2–3 weeks. Carisoprodolol is classified as a Schedule IV controlled substance, and overdose may result in central nervous system respiratory depression, seizures, or even death.

Carisoprodol is metabolized by the enzyme CYP2C19 into meprobamate, a sedative used for anxiety disorders. In individuals with low or absent CYP2C19 activity (termed "CYP2C19 poor metabolizers"), standard doses of carisoprodol can lead to a 4-fold increase in exposure to carisoprodol and a concurrent 50% decrease in meprobamate exposure compared to normal metabolizers. Approximately 3–5% of Caucasians and Africans, and 15–20% of Asians, are CYP2C19 poor metabolizers (1).

The FDA-approved drug label advises caution when prescribing carisoprodol to individuals with reduced CYP2C19 activity (Table 1) and when co-administering drugs that inhibit or induce CYP2C19 (1). The efficacy, safety, and pharmacokinetics of carisoprodol have not been established in pediatric individuals (under 16 years) or individuals over 65 years.(1). Decades of clinical use have not identified a risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes associated with carisoprodol (1).

Table 1: Clinical Management Recommendations for Carisoprodol Based on CYP2C19 Status from the US Food and Drug Administration (2024)

CYP2C19 status	Impact	Clinical action
Poor metabolizers (reduced activity)	Higher exposure (4-fold increase) to carisoprodol; 50% reduced exposure to meprobamate	Caution in administration of carisoprodol

Table adapted from (1).

Drug: Carisoprodol

Carisoprodol, also known by the brand name Soma, is a centrally acting muscle relaxant used to treat acute musculoskeletal pain, especially acute low back pain. It provides pain relief and aids in mobilization but has a high potential for abuse, classifying it as a Schedule IV controlled substance (see Alphabetical listing of Controlled Substances from (2)). Additionally, it can be toxic in overdose, which may be fatal. Carisoprodol is

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contraindicated in individuals with acute intermittent porphyria or hypersensitivity to carbamate medications (1).

The mechanism of action of carisoprodol is not fully understood but it acts as an indirect $GABA_A$ receptor agonist, impacting neuronal communication in the brainstem's reticular formation and spinal cord. In addition to skeletal muscle relaxation, it has weak anticholinergic, antipyretic, and analgesic properties. Adverse effects include sedation, tachycardia, shortness of breath, and dizziness (1, 3, 4).

Carisoprodol is metabolized by CYP2C19 into meprobamate, an active metabolite used to treat anxiety. Although its exact mechanism of action remains unclear, it has barbiturate-like properties and can be toxic in overdose (5).

Individuals with reduced or absent CYP2C19 activity have higher plasma levels of carisoprodol, and an increased ratio of carisoprodol:meprobamate compared to those with normal CYP2C19 activity. Carisoprodol's narrow therapeutic index implies there may be increased risk of toxicity in CYP2C19 poor metabolizers. However, available data are limited, and small studies have not found evidence linking *CYP2C19* genotype status with increased mortality risk or adverse effects after a single dose of carisoprodol (5, 6, 7).

The FDA-approved drug label for carisoprodol recommends caution when administering carisoprodol to individuals with reduced CYP2C19 activity. Co-administration with CYP2C19 inhibitors, such as omeprazole or fluvoxamine, could result in increased carisoprodol levels and decreased meprobamate exposure. CYP2C19 inducers, such as rifampin or St. John's Wort, could result in decreased exposure of carisoprodol and increased exposure of meprobamate. Low dose aspirin may also induce CYP2C19. The full pharmacological impact of these potential exposure alterations on the efficacy or safety of carisoprodol is unknown (1).

Carisoprodol's safety, efficacy, and pharmacokinetics are not established in pediatric (under 16) or geriatric (over 65) individuals (1). There is no clinical evidence suggesting increased risks of major birth defects, miscarriage, or other adverse maternal or fetal outcomes (1). Carisoprodol therapy does necessarily required discontinuing breastfeeding, though other agents may be preferred for mothers nursing a newborn or preterm infant (8). Carisoprodol and meprobamate are present in breastmilk, and there is one reported case of sedation in a breastfed infant whose mother was taking the medication. Therefore, the FDA advises monitoring infants exposed through breastfeeding for sedation (1).

Gene: *CYP2C19*

The CYP2C19 enzyme contributes to the metabolism of various clinically important drugs, including several proton pump inhibitors, clopidogrel, benzodiazepines, and certain tricyclic antidepressants like imipramine.

The *CYP2C19* gene is highly polymorphic, with over 35 variant star (*) alleles catalogued by the Pharmacogene Variation Consortium (PharmVar) (9). Allele functionality is assigned by the Clinical Pharmacogenetic Implementation Consortium (CPIC) (10). The *CYP2C19*1* wild-type allele is associated with normal enzyme activity and the "normal metabolizer" phenotype, while the *CYP2C19*17* allele is linked to increased enzyme activity, leading to "rapid" and "ultrarapid" metabolizer phenotypes (11).

The most common loss-of-function variant is *CYP2C19*2*, which contains a c.681G>A variant in exon 5 that results in an aberrant splice site, producing a truncated, non-functional protein. The *CYP2C19*2* allele frequencies are ~15% in Caucasians and Africans and ~29–35% in Asians (11, 12).

Another commonly tested loss-of-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. Additional loss-of-function variants, such as *CYP2C19*4-*8,* occur in less than 1% of the general population (11, 12). Individuals classified as *CYP2C19* intermediate metabolizers have one allele that encodes reduced or absent function (for example, **1/*2*), whereas poor metabolizers are either homozygous or

compound heterozygous for 2 loss-of-function alleles (for example, **2/*2*, **2/*3*) (Table 2). Estimates of the poor metabolizer phenotype frequency in the Oceanian population are notably higher than other global populations (13).

Table 2. Functional Status and Phenotypes of *CYP2C19*

Phenotype (frequency)	Genotype	Examples of diplotype
CYP2C19 ultrarapid metabolizer (0.3–4.6% of individuals)[a]	An individual with 2 increased-function alleles.	**17/*17*
CYP2C19 rapid metabolizer (2.1–27.1% of individuals)	An individual with one normal-function allele and one increased-function allele.	**1/*17*
CYP2C19 normal metabolizer (3.5–62.7% of individuals)	An individual with 2 normal-function alleles.	**1/*1*
CYP2C19 intermediate metabolizer (19–45.9% of individuals)	An individual with 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*
CYP2C19 poor metabolizer (1.4–57.1% of individuals)	An individual with 2 no-function alleles.	**2/*2* **2/*3* **3/*3*

[a] CYP2C19 metabolizer status frequencies are based on the range of multi-ethnic frequencies. See the *CYP2C19* Frequency Tables for population-specific allele and phenotype frequencies (14).
Table is 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., and Stingl J.C. Clinical Pharmacogenetics Implementation Consortium Guideline (CPIC®) for CYP2D6 and CYP2C19 Genotypes and Dosing of Tricyclic Antidepressants: 2016 Update. 2016 Dec 20; doi: 10.1002/cpt.597. [Epub ahead of print] (15) and updated *CYP2C19* Frequency Tables allele frequency ranges.
Note: The nomenclature used in this table reflects the standardized nomenclature for pharmacogenetic terms proposed by CPIC in a 2016 paper, "Standardizing terms for clinical pharmacogenetic test results: consensus terms from the Clinical Pharmacogenetics Implementation Consortium (CPIC)" (16).

Genetic Testing

Clinical genotyping tests are available for several *CYP2C19* alleles. The NIH's Genetic Testing Registry (GTR) provides examples of genetic tests available for carisoprodol response, CYP2C19-related poor drug metabolism, and variations in the CYP2C19 gene.

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.

2024 Statement from the US Food and Drug Administration (FDA):

Carisoprodol is metabolized in the liver by CYP2C19 to form meprobamate. Co-administration of CYP2C19 inhibitors, such as omeprazole or fluvoxamine, with carisoprodol could result in increased exposure of carisoprodol and decreased exposure of meprobamate. Co-administration of CYP2C19 inducers, such as rifampin or St. John's Wort, with carisoprodol could result in decreased exposure of carisoprodol and increased exposure of meprobamate. Low dose aspirin also showed induction effect on CYP2C19. The full pharmacological impact of these potential alterations of exposures in terms of either efficacy or safety of carisoprodol is unknown.

[1] The FDA assigns labels to 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.

[...]

Patients with Reduced CYP2C19 Activity: Patients with reduced CYP2C19 activity have higher exposure to carisoprodol. Therefore, caution should be exercised in administration of carisoprodol to these patients.

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	NG_008384.3:g.4220C>T (NM_000769.2:c.-806C>T)[a]	Not applicable—variant occurs in a non-coding region	rs12248560

[a] The *CYP2C19*17* allele has increased expression due to an upstream, non-coding variant. The legacy HGVS expression for the change relative to the coding sequence is provided, but the correct RefSeq genomic sequence is provided as well.
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 PharmVar database (9) https://www.pharmvar.org/

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Version History

Version 1.0 was published on April 4, 2017.

Version 1.1 was published on October 21, 2024. This revision includes an updated citation for a more recent FDA-approved drug label, updated *CYP2C19* allele references including definitions of haplotypes, frequencies of metabolizer phentoypes, and additional citations for regarding carisoprodol use during pregnancy and lactation. Relative to version 1.0, there is no change to the prescribing recommendations from FDA or any other cited source regarding the utility of CYP2C19 phenotype and carisoprodol therapy.

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