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# Diazepam Therapy and *CYP2C19* Genotype

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## Introduction

Diazepam is a benzodiazepine with several clinical uses, including managing anxiety, insomnia, muscle spasms, seizures, and alcohol withdrawal (1). Brand names include Valium, Diastat Acudial, Diastat, and Diazepam Intensol.

Diazepam is primarily metabolized by CYP3A4 and CYP2C19 to the major active metabolite, desmethyldiazepam. Approximately 2% of Europeans, 13% of East Asians, and as much as 57% of Oceanians have reduced or absent CYP2C19 enzyme activity ("poor metabolizers") (2).

The FDA-approved drug label for diazepam gel states that "the marked inter-individual variability in the clearance of diazepam reported in the literature is probably attributable to variability of CYP2C19"(3). However, the most recent drug label for oral formulations (tablet and liquid) only briefly discusses CYP2C19 in the context of potential drug interactions (Table 1)(1). Diazepam is available in multiple formulations including tablets (1), rectal gel (3), injectable solution (4), and oral solutions (5). The injectable solution does not discuss potential pharmacogenetic interactions with CYP2C19.

**Table 1.** The FDA Diazepam Statements on Metabolism and Drug Interactions (2020, 2017)

| Drug (formulation) | Metabolism and pharmacogenetic interactions |
|---|---|
| Diazepam (tablet, oral solution)[a] | Diazepam is N-demethylated by CYP3A4 and 2C19 to the active metabolite N-desmethyldiazepam, and is hydroxylated by CYP3A4 to the active metabolite temazepam.<br>[…]<br>There is a potentially relevant interaction between diazepam and compounds that inhibit certain hepatic enzymes (particularly CYP3A and CYP2C19). Data indicate that these compounds influence the pharmacokinetics of diazepam and may lead to increased and prolonged sedation. At present, this reaction is known to occur with cimetidine, ketoconazole, fluvoxamine, fluoxetine, and omeprazole. |

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*Table 1. continued from previous page.*

| Drug (formulation) | Metabolism and pharmacogenetic interactions |
|---|---|
| Diazepam (gel)[b] | The marked inter-individual variability in the clearance of diazepam reported in the literature is probably attributable to variability of *CYP2C19* (which is known to exhibit genetic polymorphism; approximately 3–5% of Caucasians have little or no activity and are "poor metabolizers") and *CYP3A4*.<br>[…]<br>… Potential interactions may occur when diazepam is given concurrently with agents that affect CYP2C19 and CYP3A4 activity. Potential inhibitors of CYP2C19 and CYP3A4 could decrease the rate of diazepam elimination, while inducers of CYP2C19 and CYP3A4 could increase the rate of elimination of diazepam. Effect of diazepam on the metabolism of other drugs: There are no reports as to which isozymes could be inhibited or induced by diazepam. But, based on the fact that diazepam is a substrate for CYP2C19 and CYP3A4, it is possible that diazepam may interfere with the metabolism of drugs that are substrates for CYP2C19, (for example, omeprazole, propranolol, and imipramine) and CYP3A4 (for example, cyclosporine, paclitaxel, terfenadine, theophylline, and warfarin) leading to a potential drug-drug interaction. |

[a] Information adapted from (1, 5).
[b] Information adapted from (3).

# Drug: Diazepam

Diazepam is used to manage anxiety disorders or for the short-term relief of the symptoms of anxiety. In acute alcohol withdrawal, diazepam may provide symptomatic relief from agitation, tremor, delirium tremens, and hallucinations. Diazepam is also useful as an adjunct treatment for the relief of acute skeletal muscle spasms, as well as spasticity caused by upper motor neuron disorders (1, 6).

There are 16 benzodiazepines licensed by the FDA. Diazepam was the second benzodiazepine to be used clinically (after chlordiazepoxide), after being approved for use in 1963. It remains a commonly used drug today, and is included in the World Health Organization's core list of essential medicines needed for a basic healthcare system (7).

The use of benzodiazepines has replaced the use of barbiturates. Although these drug classes share similar therapeutic effects, barbiturates have a narrower therapeutic index, they are more sedative at therapeutic doses, and a barbiturate overdose is more likely to be fatal (8).

Like all benzodiazepines, diazepam is a controlled substance. Chronic use, either at standard therapeutic doses or through recreational abuse, can lead to tolerance and physical dependence. If diazepam treatment is abruptly discontinued, withdrawal symptoms can arise that can be severe and include seizures. Therefore, a gradual tapering of dose is recommended after chronic therapy.

Diazepam has several therapeutic effects—it is a sedative, anxiolytic, anticonvulsant muscle relaxant, and has amnesic effects. Diazepam is thought to exert these effects through an interaction with gamma-aminobutyric acid (GABA) A-type receptors ($GABA_A$), and GABA is the major inhibitory neurotransmitter in the central nervous system. When GABA binds to the $GABA_A$ receptor, the receptor opens, allowing the influx of chloride ions into neurons. This reduces the ability of neurons to depolarize and produce action potentials (excessive action potentials are implicated in seizures). It is thought that diazepam enhances the effects of GABA by increasing the affinity between GABA and its receptor, causing GABA to bind more tightly to the $GABA_A$ receptor (1, 3).

Diazepam is primarily metabolized via CYP2C19 and CYP3A4 to the major active metabolite (desmethyldiazepam), which is found in the plasma at concentrations equivalent to diazepam. Two minor active metabolites include temazepam and oxazaepam, which are usually not detectable. Other cytochrome P450 (CYP) enzymes involved in diazepam metabolism include CYP2C9, CYP2B6, and CYP3A5 (9).

Safe and effective use of oral diazepam in pediatric individuals below the age of 6 months has not been established. Pharmacokinetics indicate that the mean half-life of diazepam in children aged 3–8 years old is less than 18 hours, with elimination half-lives in full-term infants closer to 30 hours. Diazepam rectal gel has been studied and shown to be effective in children 2 years or older; safety and efficacy has not been established in children under 2 (3). Diazepam can be transmitted in breast milk to nursing infants, thus breastfeeding is not recommended for individuals receiving oral diazepam (1). Diazepam and desmethyldiazepam have long half-lives, thus there is little to no benefit to timing of breastfeeding with respect to the dose of diazepam (10). Breastfeeding after acute use of diazepam gel is possible, though "an appropriate period of time" should pass between dosage and nursing (3).

The FDA-approved label for diazepam tablets states that there is a suggested increased risk of congenital malformations and other developmental abnormalities associated with benzodiazepine drug use during pregnancy. Neonatal flaccidity, respiratory and feeding difficulties, and hypothermia have been reported in children born to mothers who have received benzodiazapines late in pregnancy or during labor and delivery. (1)

Both gel and tablet formulations of diazepam have reduced clearance and increased elimination half-lives in geriatric populations. This can alter the peak and trough concentrations for oral diazepam as well as the time to achieve steady state concentrations (1) and leads to a higher risk of ataxia or overdose in the gel formulation (3). Diazepam gel should be used with caution in individuals with compromised respiratory function (3). Similarly, individuals with renal or hepatic impairment should be administered oral or gel formulations of diazepam with caution, as these individuals have reduced clearance of diazepam and their metabolites (1, 3).

## Gene: *CYP2C19*

The CYP superfamily is a large and diverse group of hepatic 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, including antidepressants, antiplatelet agents, antifungal agents, some proton pump inhibitors, and benzodiazepines such as diazepam.

The *CYP2C19* gene is highly polymorphic, as there are over 35 variant star (*) alleles cataloged 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 (for example, **2* and **3*) are classified as 'intermediate metabolizers' (for example, **1/*2*), and individuals who have 2 non-functional alleles are classified as "poor metabolizers" (for example, **2/*2*, **2/*3*) (Table 2).

**Table 2.** The CPIC Assignment of CYP2C19 Phenotype based on Genotype (2017)

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

*Table 2. continued from previous page.*

| Phenotype | Genotype | Examples of diplotypes |
|---|---|---|
| CYP2C19 intermediate metabolizer (approximately 18–45% 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*<br>**1/*3*<br>**2/*17*[b] |
| CYP2C19 poor metabolizer (approximately 2–15% of individuals) | An individual with 2 no function alleles | **2/*2*<br>**2/*3*<br>**3/*3* |

CPIC: Clinical Pharmacogenetics Implementation Consortium
[a] CYP2C19 metabolizer status frequencies are based on average multi-ethnic frequencies. See the *CYP2C19* Frequency Tables for population-specific allele and phenotype frequencies (11).
[b] The predicted metabolizer phenotype for the**2/*17* genotype is a provisional classification. The 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 (11).

## Linking Gene Variation with Treatment Response

It is well documented that wide inter-individual variation in the metabolism of benzodiazepines occurs, which includes diazepam metabolism. This can result in marked differences in drug levels when standard dosing is used and may potentially influence both therapeutic and adverse effects. It is thought that the variability in clearance of many benzodiazepines, including diazepam, is due to the variability in *CYP2C19* and *CYP3A4* genotypes (1, 9, 12-14).

## 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 available for the diazepam 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 (15).

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

**2020 Statement from the US Food and Drug Administration (FDA):** [Diazepam tablets, oral solution] Diazepam is N-demethylated by CYP3A4 and 2C19 to the active metabolite N-desmethyldiazepam, and is hydroxylated by CYP3A4 to the active metabolite temazepam.

[…]

There is a potentially relevant interaction between diazepam and compounds which inhibit certain hepatic enzymes (particularly CYP3A and CYP2C19). Data indicate that these compounds influence the

[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.

pharmacokinetics of diazepam and may lead to increased and prolonged sedation. At present, this reaction is known to occur with cimetidine, ketoconazole, fluvoxamine, fluoxetine, and omeprazole.

**Please review the complete therapeutic recommendations that are located here: ( 1 , 5 ).**

**2017 Statement from the US Food and Drug Administration (FDA):** [Diazepam gel] The metabolism of diazepam is primarily hepatic and involves demethylation (involving primarily CYP2C19 and CYP3A4) and 3-hydroxylation (involving primarily CYP3A4), followed by glucuronidation. The marked inter-individual variability in the clearance of diazepam reported in the literature is probably attributable to variability of CYP2C19 (which is known to exhibit genetic polymorphism; about 3-5% of Caucasians have little or no activity and are "poor metabolizers") and CYP3A4.

[…]

Effect of Other Drugs on Diazepam Metabolism: *In vitro* studies using human liver preparations suggest that CYP2C19 and CYP3A4 are the principal isozymes involved in the initial oxidative metabolism of diazepam. Therefore, potential interactions may occur when diazepam is given concurrently with agents that affect CYP2C19 and CYP3A4 activity. Potential inhibitors of CYP2C19 (for example, cimetidine, quinidine, and tranylcypromine) and CYP3A4 (for example, ketoconazole, troleandomycin, and clotrimazole) could decrease the rate of diazepam elimination, while inducers of CYP2C19 (for example, rifampin) and CYP3A4 (for example, carbamazepine, phenytoin, dexamethasone and phenobarbital) could increase the rate of elimination of diazepam.

Effect of Diazepam on the Metabolism of Other Drugs: There are no reports as to which isozymes could be inhibited or induced by diazepam. But, based on the fact that diazepam is a substrate for CYP2C19 and CYP3A4, it is possible that diazepam may interfere with the metabolism of drugs which are substrates for CYP2C19, (for example omeprazole, propranolol, and imipramine) and CYP3A4 (for example cyclosporine, paclitaxel, terfenadine, theophylline, and warfarin) leading to a potential drug-drug interaction.

**Please review the complete therapeutic recommendations that are located here: ( 3 ).**

## 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 (16).
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.
Please note that the *CYP2C19*2* defining variant (rs4244285) has recently been reported to be in high linkage disequilibrium with an intronic variant implicated in aberrant slicing (rs12769205) (17).

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## Version history

To view the 2016 version of this summary (created on 25 August 2016) please click here.

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