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NLM Citation: Dean L. Diazepam Therapy and *CYP2C19* Genotype. 2016 Aug 25. 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/

Diazepam Therapy and *CYP2C19* Genotype

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Created: August 25, 2016.

Introduction

Diazepam is a benzodiazepine with several clinical uses, including the management of anxiety, insomnia, muscle spasms, seizures, and alcohol withdrawal. The clinical response to benzodiazepines, such as diazepam, varies widely between individuals (1, 2).

Diazepam is primarily metabolized by CY2C19 and CYP3A4 to the major active metabolite, desmethyldiazepam. Approximately 3% of Caucasians and 15 to 20% of Asians have reduced or absent CYP2C19 enzyme activity ("poor metabolizers"). In these individuals, standard doses of diazepam may lead to a higher exposure to diazepam.

The FDA-approved drug label for diazepam states that "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" (1).

Drug: Diazepam

Diazepam is used in the management of 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 (3).

There are currently 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 (4).

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 (5).

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 which can be severe and include seizures. Therefore, a gradual tapering of dose is recommended after chronic therapy.

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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 GABA A-type receptors ($GABA_A$). 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).

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 CYP enzymes involved in diazepam metabolism include CYP2C9, CYP2B, and CYP3A5 (2).

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 (2, 3, 6, 7).

Gene: *CYP2C19*

The cytochrome P450 superfamily (CYP) 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, several proton pump inhibitors, clopidogrel, and benzodiazepines, including diazepam.

The *CYP2C19* gene is highly polymorphic, as 35 variant star (*) alleles are currently catalogued at the Human Cytochrome P450 (CYP) Allele Nomenclature Database (http://www.cypalleles.ki.se/cyp2c19.htm). The *CYP2C19*1* wild-type allele is associated with normal enzyme activity and the "normal metabolizer" phenotype, whereas the *CYP2C19*17* allele is associated with increased enzyme activity and the "ultrarapid metabolizer" phenotype (8).

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. This leads to the production of a truncated and non-functioning protein. The *CYP2C19*2* allele frequencies are ~15% in Caucasians and Africans, and ~29–35% in Asians (8, 9).

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. Other loss-of-function variants occur in less than 1% of the general population, and include *CYP2C19*4-*8* (8, 9).

"Intermediate *CYP2C19* metabolizers" carry one copy of an allele that encodes reduced or absent function (e.g., **1/*2*), whereas "poor metabolizers" are homozygous or compound heterozygous for two loss-of-function alleles (e.g., **2/*2*, **2/*3*) (table 1).

Table 1: *CYP2C19* phenotypes

Phenotype	Phenotype Definition	Genetic Definition	Diplotype Examples
CYP2C19 Ultrarapid metabolizer	Increased enzyme activity compared to rapid metabolizers	Two increased function alleles	**17/*17*

Table 1 continued from previous page.

Phenotype	Phenotype Definition	Genetic Definition	Diplotype Examples
CYP2C19 Rapid metabolizer	Increased enzyme activity compared to normal metabolizers, but less than ultrarapid metabolizers	Combinations of normal function and increased function alleles	**1/*17*
CYP2C19 Normal metabolizer	Fully functional enzyme activity	Two normal function alleles	**1/*1*
CYP2C19 Intermediate metabolizer	Decreased enzyme activity (activity between normal and poor metabolizer)	Combinations of normal function, decreased function, and/or no function alleles	**1/*2* **1/*3* **2/*17* **3/*17*
CYP2C19 Poor metabolizer	Little or no enzyme activity	Combination of no function alleles, and/or decreased function alleles	**2/*2* **2/*3* **3/*3*

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)" (10).

Studies have found that individuals who are poor metabolizers have a lower plasma clearance of diazepam compared to normal metabolizers, and that diazepam had a longer plasma half-life (7, 11-13). However, currently, the FDA does not recommend a reduced dose of diazepam in *CYP2C19* poor metabolizers.

One common use of diazepam is to relieve preoperative anxiety in patients. One study found that *CYP2C19* poor metabolizers took a longer period of time to emerge from general anesthesia than normal metabolizers. This study also found that the "slow emergers" had lower levels of CYP3A4 mRNA (14).

Although CYP3A4 is also involved in diazepam metabolism, there have been conflicting results from studies of the impact of *CYP3A4* and *CYP3A5* variants on benzodiazepine metabolism (15-18).

Genetic Testing

Clinical genotyping tests are available for several *CYP2C19* alleles, and a list of test providers is available at the Genetic Testing Registry (GTR) of the National Institutes of Health.

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 (see table 1).

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.

Statement from the US Food and Drug Administration (FDA): It has been reported in the literature that diazepam is extensively metabolized to one major active metabolite (desmethyldiazepam) and two minor active metabolites, 3- hydroxydiazepam (temazepam) and 3-hydroxy-N-diazepam (oxazepam) in plasma. At therapeutic doses, desmethyldiazepam is found in plasma at concentrations equivalent to those of diazepam while oxazepam and temazepam are not usually detectable. The metabolism of diazepam is primarily hepatic

[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.

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. No inhibition was demonstrated in the presence of inhibitors selective for CYP2A6, CYP2C9, CYP2D6, CYP2E1, or CYP1A2, indicating that these enzymes are not significantly involved in metabolism of diazepam.

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

Nomenclature

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

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 Human Cytochrome P450 (CYP) Allele Nomenclature Database: http://www.cypalleles.ki.se/

Acknowledgments

The author would like to thank Stuart Scott, Assistant Professor of Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai; Jitesh Kawedia, Pharmaceutical/Pharmacy Research Specialist at the University of Texas MD Anderson Cancer Center; Chakradhara Rao S. Uppugunduri, Maître-assistant at the CANSEARCH Laboratory, University of Geneva, Switzerland; and Megan J. Ehret, PharmD, MS, BCPP Behavioral Health Clinical Pharmacy Specialist, Fort Belvoir Community Hospital, Virginia, for reviewing this summary.

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