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Clozapine Therapy and *CYP2D6*, *CYP1A2*, and *CYP3A4* Genotypes

Laura Dean, MD[1]

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Introduction

Clozapine is one of the most effective antipsychotics available in the treatment of schizophrenia and the only antipsychotic found to be effective in treatment-resistant schizophrenia. Clozapine is also used to reduce the risk of recurrent suicidal behavior in patients with schizophrenia or schizoaffective disorder (1, 2).

Compared to typical antipsychotics, clozapine is far less likely to cause movement disorders, known as extrapyramidal side effects, which include dystonia, akathisia, parkinsonism, and tardive dyskinesia. However, there are significant risks associated with clozapine therapy that limits its use to only the most severely ill patients who have not responded adequately to standard drug therapy. Most notably, because of the risk of clozapine-induced agranulocytosis, clozapine treatment requires monitoring of white blood counts and absolute neutrophil counts, and in the US, the FDA requires that patients receiving clozapine be enrolled in a computer-based registry (3).

Clozapine is metabolized in the liver by the cytochrome P450 (CYP) system of enzymes. CYP1A2 is the main CYP isoform in clozapine metabolism and CYP1A2 activity is an important determinant of clozapine dose (4). Other CYP enzymes involved in clozapine metabolism include CYP2D6 and CYP3A4.

Approximately 6-10% of Caucasians have reduced activity of CYP2D6 ("poor metabolizers"). These individuals may develop higher than expected plasma concentrations of clozapine with usual doses. The FDA-approved drug label for clozapine states that a dose reduction may be necessary in patients who are CYP2D6 poor metabolizers (1).

Drug: Clozapine

Clozapine is an antipsychotic used in the treatment of schizophrenia. Schizophrenia is a severe neurodevelopmental disorder with a worldwide prevalence of around 1%. The etiology of schizophrenia is unknown, but it is thought to result from a combination of complex genetic and environmental factors. Before the discovery of the first antipsychotics in the 1950s, the management of schizophrenia relied heavily upon sedation, electroconvulsive therapy, and institutionalization.

The symptoms of schizophrenia fall in to three main categories: positive, negative, and cognitive. Positive symptoms are generally not found in healthy individuals, but may come and go or persist in individuals with schizophrenia. Positive symptoms include reality distortion (e.g., delusions, hallucinations), and thought disorders. These symptoms often respond well to treatment.

Author Affiliation: 1 NCBI; Email: mgs@ncbi.nlm.nih.gov.

Negative symptoms are deficits in normal emotions and behavior, and may be mistaken for depression. Symptoms divide into reduced expression of emotion (e.g., speaking without moving or with a monotonous voice), and avolition (a lack of motivation to start or continue with a task). No treatment has established efficacy for these pathologies.

Cognitive symptoms may also be difficult to recognize. They include poor executive functioning (understanding information and using it to make decisions) and trouble focusing or paying attention. And again, no treatment has established efficacy.

Clozapine is unique among the antipsychotics because it effectively treats positive symptoms, and appears to be more effective in treating negative symptoms, and some cognitive symptoms when compared with other antipsychotics that cause negative symptoms or impair cognition (5-7).

Clozapine has also been shown to reduce aggression and reduce the risk of suicide, and is the only antipsychotic found to be effective in treatment-resistant schizophrenia (2, 8-10). More than one third of patients are thought to have schizophrenia that only partially responds or is resistant to standard drugs; these patients may then be treated with clozapine (2, 10, 11).

The first antipsychotics to be discovered in the 1950s were haloperidol and chlorpromazine. Known as "first generation" or "typical" antipsychotics, these drugs are used to treat psychosis (regardless of the cause), chronic psychotic disorders (e.g., schizophrenia), and other psychiatric conditions. However, prominent adverse effects included extrapyramidal side effects such as tardive dyskinesia, muscle rigidity, tremors, and Parkinsonian-like symptoms.

Newer antipsychotics, known as "second generation" or "atypical" antipsychotics, have a lower risk of extrapyramidal side effects such as tardive dyskinesia. However, many have serious metabolic effects. These antipsychotics include aripiprazole, clozapine, iloperidone, olanzapine, and risperidone.

Clozapine was introduced in 1971 as the first atypical antipsychotic, but the manufacturer (Novartis, formerly Sandoz) voluntarily withdrew the drug in 1975 because of safety concerns (7). One of the most dangerous risks reported was that of clozapine-induced neutropenia—a severely low level of neutrophils (a type of white blood cell), which places patients at high risk of infection. However, because it was later shown that clozapine was the most effective antipsychotic in the management of treatment-resistant schizophrenia, in 1989 the FDA reapproved clozapine for that use (5, 7, 9).

The main action of both first-generation and second-generation antipsychotics appears to be the post-synaptic blockade of D2 dopamine receptors in the brain. (An exception is aripiprazole, which is a D2 partial agonist.) Blockade of the D2 receptor in the brain's limbic system are thought to improve the "positive" symptoms of schizophrenia (12).

However, because the first-generation antipsychotics also block dopamine receptors in the nigrostriatal pathway, they cause movement disorders known as extrapyramidal side effects. These disorders include akathisia (motor restlessness), dystonia (abnormal muscle tone), and tardive dyskinesia (involuntary and repetitive movements).

Clozapine only transiently occupies D2 receptors and then rapidly dissociates to allow normal dopamine neurotransmission. It is thought that because clozapine has a relatively low affinity for the D2 receptor and binds "loosely," extrapyramidal side effects are less likely (11, 13).

In addition to binding the D2 receptor, clozapine has a high affinity for the serotonin 5-HT_{2A} receptors. Blockade of 5-HT_{2A} in the mesocortical tract may also provide some protection against extrapyramidal side effects by increasing amounts of dopamine. Clozapine and its major metabolite (N-desmethylclozapine) have been shown to indirectly activate NMDA receptors, and may also modulate GABA and cholinergic pathways.

However, despite these findings, it remains unclear what gives clozapine its superior efficacy to other antipsychotics (7).

One of the most prominent side effects of clozapine therapy is weight gain. The most severe side effects are included in five boxed warnings on the drug label: 1) severe neutropenia, 2) seizures (more likely at higher doses), 3) myocarditis (inflammation of the heart muscle induced by clozapine, that can be fatal), 4) increased mortality in elderly patients with dementia-related psychosis, and 5) an increased risk of orthostatic hypotension, bradycardia, and syncope (1).

Because of the risk of neutropenia, clozapine can only be prescribed according to a schedule that monitors the patient's white blood cell count (WBC) and absolute neutrophil count (ANC). Neutropenia, defined as an ANC of less than 500/mm^3, is estimated to occur in around 1% of patients, and could prove fatal if not detected early by regular monitoring (14).

Genetic risk factors for clozapine-induced neutropenia have been identified, consisting of two independent amino acid changes in *HLA-DQB1* (126Q) and *HLA-B* (158T). *HLA-DQB1* is associated with autoimmune disease and *HLA-B* is an important component of severe drug reactions, including carbamazepine-induced Stevens-Johnson syndrome and abacavir hypersensitivity. Despite this genetic insight, a genetic test based solely on *HLA-DQB1* and *HLA-B* would not be able to adequately identify if all the patients are truly at low risk of clozapine-induced neutropenia (15).

The Cytochrome P450 Superfamily

The cytochrome P450 superfamily (CYP450) is a large and diverse group of enzymes that form the major system for metabolizing lipids, hormones, toxins, and drugs. The *CYP450* genes are very polymorphic and can result in reduced, absent, or increased enzyme activity.

Clozapine is extensively metabolized in the liver by CYP450 enzymes, especially by CYP1A2, CYP3A4, and CYP2D6. Most of the metabolites are inactive, but N-desmethylclozapine has been found to have limited activity (7, 16).

The dose of clozapine may need to be adjusted when clozapine is given with medications that inhibit or induce the enzymes responsible for metabolizing clozapine. Inhibitors of CYP enzymes include the antibiotic ciprofloxacin (CYP1A2 inhibitor) and the antidepressant fluvoxamine (CYP3A4 and CYP2D6 inhibitor). Inducers include the antiseizure drug carbamazepine (strong CYP3A4 inducer). In addition, other agents can influence CYP enzymes—caffeine and oral contraceptives are weak or moderate CYP1A2 inhibitors, and tobacco smoke is a moderate inducer of CYP1A2 (and smoking is common among patients with schizophrenia).

Gene: CYP2D6

CYP2D6 is highly polymorphic, with more than 100 star (*) alleles described (17). *CYP2D6*1* is the wild-type allele and is associated with normal enzyme activity and the "extensive metabolizer" phenotype. The *CYP2D6* alleles **2*, **33*, and **35* are also considered to have near-normal activity (Table 1).

Table 1. Activity status of *CYP2D6* alleles

Allele type	*CYP2D6* Alleles
Active	**1, *2, *33, *35*
Decreased activity	**9, *10, *17, *29, *36, *41*
Inactive	**3-*8, *11-*16, *19-*21, *38, *40, *42*

For a detailed list of *CYP2D6* alleles, please see (18).

Individuals who have multiple functional copies of the *CYP2D6* gene are known as "ultrarapid metabolizers," whereas individuals who carry one or two copies of reduced-activity or non-functioning *CYP2D6* alleles are known as "intermediate" or "poor metabolizers."

The most common non-functional alleles include **3*, **4*, **5*, and **6* (19-22), and the most common reduced activity alleles include **10*, **17*, and **41* (23-25). There are large inter-ethnic differences in the frequency of these alleles, with **3*, **4*, **5*, **6*, and **41* being more common in Caucasians, **17* more common in Africans, and **10* more common in Asians (26-29).

Approximately 6-10% of European Caucasians and their descendants are poor metabolizers, mainly due to the more prevalent nonfunctional **4* and **5* alleles (26, 30). These individuals may develop higher than expected plasma concentrations of clozapine when given in usual doses. Therefore, the FDA-approved drug label for clozapine states that in poor metabolizers, a lower dose of clozapine may be necessary (1).

However, although in theory poor metabolizers may require lower doses of clozapine to achieve the desired therapeutic effects, evidence for this is lacking. Several studies investigating the association between *CYP2D6* genotypes and response to antipsychotic therapy did not report significant findings (31, 32).

Gene: CYP1A2

CYP1A2 alleles influence the treatment response of several antipsychotics (4). However, understanding the pharmacogenomic effects of *CYP1A2* variation is still at an early stage compared with that of other CYP2D6 and other CYP enzymes (33).

CYP1A2 comprises around 13% of all CYP protein in the liver, whereas CYP2D6 comprises around 2%. Approximately 25 variant alleles of *CYP1A2* have been reported, some of which have been shown to alter the activity of CYP1A2. For example, the **1C* allele is associated with decreased enzyme activity (by altering the binding site of an unknown transcription factor in the gene promoter), and the **1F* allele is associated with increased enzyme activity (by increasing the induction of expression) (33, 34).

CYP1A2 is the main CYP isoform in clozapine metabolism (35). Case studies have found that patients with one or more copies of *CYP1A2*1F* (ultrarapid metabolizers) respond poorly to clozapine therapy. However, the treatment response is improved by increasing the dose of clozapine, and also co-administering fluvoxamine, a CYP1A2 inhibitor (36, 37).

The frequency of *CYP1A2*1F* (defined by a C > A polymorphism in intron 1) exists at similar frequencies in all populations (starting at around 0.29) with the highest frequency among Africans (up to 0.51) (38). Environmental factors also strongly influence CYP1A2 activity, such as oral contraceptive use (inhibition) and smoking (induction). Indeed, the sudden cessation of smoking during clozapine therapy may trigger side effects, because of sudden increase in drug levels (39).

Gene: CYP3A4

In contrast to *CYP2D6, CYP1A2,* and other genes that encode drug-metabolizing enzymes, *CYP3A4* shows little genetic variation. Although around 40 variant alleles of *CYP3A4* have been reported, most have not been shown to alter the activity of CYP3A4 (40, 41). To date, only three loss-of-function *CYP3A4* alleles have been identified (*CYP3A4*6, CYP3A4*20* and *CYP3A4*26*) (42, 43).

The *CYP3A4*20* allele contains a premature stop codon which results in a loss-of-function of *CYP3A*. It appears to be the most common *CYP3A4*-defective allele but is still relatively rare, with about 0.2% of European Americans and 0.05% African Americans being carriers. However in Spain, the *CYP3A4*20* allele is present in 1.2% of the population, and up to 3.8% in specific Spanish regions (42).

Genetic Testing

Genetic testing is available for common *CYP2D6, CYP3A4,* and *CYP1A2* alleles. Often a panel of tests is performed. These panels test for variants in multiple genes, which are involved in the metabolism of many drugs, including clozapine. For examples of the tests available for the clozapine drug response, please see the Genetic Testing Registry.

Results are typically reported as a diplotype, such as *CYP2D6 *1/*1*. A result for copy number, if available, is also important when interpreting *CYP2D6* results (44).

If the test results include an interpretation of the patient's predicted metabolizer phenotype, this should be confirmed by checking the diplotype and assigning an activity score to each allele (e.g., 0 for nonfunctional, 0.5 for reduced function, and 1 for each copy of a functional allele). The phenotype is defined by the sum of the two scores:

- An extensive (normal) metabolizer phenotype has an activity score of 1 to 2
- An intermediate metabolizer has an activity score of 0.5
- A poor metabolizer has an activity score of 0
- An ultrarapid metabolizer has an activity score greater than 2

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.

2014 Statement from the US Food and Drug Administration (FDA): Dose reduction may be necessary in patients who are CYP2D6 poor metabolizers. Clozapine concentrations may be increased in these patients, because clozapine is almost completely metabolized and then excreted.
Please review the complete therapeutic recommendations that are located here: (1).

Nomenclature

***CYP2D6* Nomenclature**

Common allele name	Alternative names	HGVS reference sequence		dbSNP reference identifier for allele location
		Coding	Protein	
*CYP2D6*4*	1846G>A	NM_000106.5:c.506-1G>A	Not applicable - variant occurs in a non-coding region	rs3892097
*CYP2D6*5*	Not applicable - variant results in a whole gene deletion			
*CYP2D6*6*	1707 del T Trp152Gly	NM_000106.5:c.454delT	NP_000097.3:p.Trp152Glyfs	rs5030655
*CYP2D6*10*	100C>T Pro34Ser	NM_000106.5:c.100C>T	NP_000097.3:p.Pro34Ser	rs1065852
*CYP2D6*17*	Includes at least two functional variants*: 1023C>T (Thr107Ile) 2850C>T (Cys296Arg)	NM_000106.5:c.320C>T NM_000106.5:c.886T>C	NP_000097.3:p.Thr107Ile NP_000097.3:p.Cys296Arg	rs28371706 rs16947

[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.

CYP2D6 Nomenclature continued from previous page.

Common allele name	Alternative names	HGVS reference sequence		dbSNP reference identifier for allele location
		Coding	Protein	
*CYP2D6*41*	2988G>A	NM_000106.5:c.985+39 G>A	Not applicable – variant occurs in a non-coding region	rs28371725

* In the literature, 1023C>T is also referred to as 1111C>T, and 2850C>T is also referred to 2938C>T.

***CYP1A2* Nomenclature**

Common allele name	Alternative names	HGVS reference sequence		dbSNP reference identifier for allele location
		Coding	Protein	
*CYP1A2*1C*	-3860G>A -2964G>A	Unknown	Not applicable—variant occurs in a non-coding region	rs2069514
*CYP1A2*1F*	-	NM_000761.4:c.-9-154C>A	Not applicable—variant occurs in a non-coding region	rs762551

***CYP3A4* Nomenclature**

Common allele name	Alternative names	HGVS reference sequence		dbSNP reference identifier for allele location
		Coding	Protein	
*CYP3A4*6*	17661_17662insA 277Frameshift	NM_017460.5:c.830_831i nsA	NP_059488.2:p.Asp277Glufs	rs4646438
*CYP3A4*20*	1461_1462insA 488Frameshift	NM_017460.5:c.1461_146 2insA	NP_001189784.1:p.Pro487Thrfs	rs67666821
*CYP3A4*26*	17633C>T R268Stop			

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 Pharmacogene Variation Consortium database: https://www.pharmvar.org/

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