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Clozapine Therapy and *CYP* Genotype

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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 (TRS). Clozapine is also used to reduce the risk of recurrent suicidal behavior in individuals with schizophrenia or schizoaffective disorder (1, 2).

Compared with 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 individuals 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 cell counts (WBC) and absolute neutrophil counts (ANC), and in the US, the FDA requires that individuals receiving clozapine be enrolled in a computer-based registry (3). There is also a propensity for clozapine use to induce metabolic effects, resulting in substantial weight gain (1).

Clozapine is metabolized in the liver by the cytochrome P450 (CYP450) superfamily of enzymes. The CYP1A2 enzyme is the main CYP enzyme involved in clozapine metabolism, and CYP1A2 activity is a potential determinant of clozapine dose requirements (4). Other CYP enzymes involved in clozapine metabolism include CYP2D6, CYP3A4, and CYP2C19 (5).

The FDA-approved drug label states that a subset of the population (2–10%) have reduced activity of CYP2D6 ("poor metabolizers"[PMs]) and these individuals may develop higher than expected plasma concentrations of clozapine with typical standard doses. Therefore, the FDA states that a dose reduction may be necessary in individuals who are CYP2D6 PMs (Table 1) (1). However, the Dutch Pharmacogenetics Working Group (DPWG, Table 2) does not recommend dose alterations based on *CYP2D6* genotype, though the gene-drug interaction is acknowledged (6). The DPWG further states that there is not a gene-drug interaction between *CYP1A2* and clozapine due to the limited effect of known genetic variants on CYP1A2 function (6). Consequently, neither the FDA nor the DPWG recommend dose alterations based on *CYP1A2* genotype.

Additionally, clozapine clearance is affected by gender, tobacco use, and ethnicity, with further contributions from pharmacologic interactions. Females have lower CYP1A2 enzyme activity than males. Non-smokers have lower CYP1A2 activity than smokers and Asians and Amerindians have lower activity than Caucasians.

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Clozapine clearance can also be affected by co-medications that induce or inhibit CYP1A2 and the presence of inflammation or obesity (7, 8).

Table 1. The FDA Clozapine Dosage and CYP2D6 Poor Metabolizers (2020)

Phenotype	Dosing considerations
CYP2D6 poor metabolizers	Dose reduction may be necessary in individuals who are CYP2D6 poor metabolizers. Clozapine concentrations may be increased in these individuals, because clozapine is almost completely metabolized and then excreted.

This FDA table is adapted from (1).

Table 2. The DPWG Recommendations for Clozapine and CYP2D6 (2016)

Phenotype	Dosing considerations
CYP2D6 poor metabolizer	No action is required for this gene-drug interaction.
CYP2D6 intermediate metabolizer	No action is required for this gene-drug interaction.
CYP2D6 ultrarapid metabolizer	No action is required for this gene-drug interaction.

This DPWG table is adapted from (6).

Drug: Clozapine

Clozapine is an antipsychotic used in the treatment of schizophrenia. Schizophrenia is a severe psychiatric disorder with a worldwide prevalence of around 1%. The specific etiology of schizophrenia is unknown; however, it is largely considered to result from a combination of complex genetic, immunologic, and environmental factors.

The symptoms of schizophrenia fall into 3 main categories: positive, negative, and cognitive. Positive symptoms include reality distortion (for example, delusions, hallucinations) and thought disorders, which both can respond well to treatment. Negative symptoms are deficits in normal emotions and behavior and may be mistaken for depression. Symptoms divide into reduced expression of emotion (for example, 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 symptoms. 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. Similarly, no treatment has major established efficacy.

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 (for example, 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. These medications include aripiprazole, clozapine, olanzapine, and risperidone. Apart from aripiprazole, atypical antipsychotics can have serious metabolic side effects.

Clozapine is unique among the antipsychotics as 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 (9, 10, 11). Clozapine has also been shown to reduce aggression and reduce the risk of suicide, and is the only antipsychotic found to be effective in TRS (2, 12, 13, 14). More than one third of individuals are thought to have schizophrenia that only partially responds or is resistant to standard drugs; these individuals may then be treated with clozapine (2, 14, 15).

Clozapine was introduced in 1971; however, it was withdrawn in 1975 due to safety concerns, including severe neutropenia induced by the drug (11). This severely low level of neutrophils (a type of white blood cell) places individuals at high risk of potentially lethal infections. Given that clozapine was the most effective antipsychotic used to treat TRS, in 1989 the FDA reapproved clozapine for that use (9, 11, 13). The FDA defines TRS as severe schizophrenia that does not respond adequately to standard antipsychotic treatment (1).

The main action of both first- 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 (16). 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 (15, 17). 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, also called norclozapine) have been shown to indirectly activate N-methyl-D-aspartate receptors and may also modulate gamma-aminobutyric acid and cholinergic pathways. However, despite these findings, it remains unclear what gives clozapine its superior efficacy to other antipsychotics (11).

Clozapine is primarily metabolized in the liver by the CYP450 superfamily of enzymes. The primary metabolic steps are demethylation to form norclozapine and oxidation to clozapine n-oxide. The major enzymes involved in clozapine demethylation are CYP3A4 and CYP1A2, with CYP2D6 playing a minor role. Oxidation is primarily catalyzed by CYP1A2 (18). Clozapine is almost completely metabolized before excretion. Norclozapine has limited activity in some brain receptors, while the clozapine n-oxide metabolite is inactive (1, 11, 19). Norclozapine is not an effective antipsychotic and may contribute to some of the clozapine adverse drug reactions (20, 21).

The most severe side effects of clozapine therapy are included in 5 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 individuals with dementia-related psychosis, and 5) an increased risk of orthostatic hypotension, bradycardia, and syncope (1). Additional side effects include weight gain and metabolic changes, QT interval prolongation, gastrointestinal hypomobility with severe complications, eosinophilia, hepatotoxicity, neuroleptic malignant syndrome and pulmonary embolism (1).

Additionally, there is a high risk that individuals with TRS taking clozapine may develop pneumonia, with a population attributable risk of pneumonia in clozapine-medicated individuals with TRS of 64%. Individuals with TRS in the absence of clozapine therapy had an estimated population attributable risk of pneumonia of 45%, which has been attributed to smoking, medication issues, and obesity prevalence in the TRS population. Clozapine use may decrease immunoglobulin levels and increase the interleukin-1 receptor antagonist, putting individuals at a higher risk for community-acquired pneumonia. Many medications used for TRS, clozapine included, can also negatively affect swallowing, increase salivation and sedation, contributing to the risk of aspiration pneumonia (22, 23, 24)

Because of the risk of neutropenia, clozapine can only be prescribed according to a schedule that monitors the patient's WBC and ANC. A severe neutropenia termed agranulocytosis is defined as an ANC of less than $500/mm^3$, is estimated to occur in around 1% of individuals, and could prove fatal if not detected early by regular monitoring (1, 25, 26). Before initiating clozapine therapy, baseline ANC must be obtained and

monitored regularly during treatment. Clozapine therapy should be suspended if the ANC falls below 1500 and monitoring of ANC should be performed before reinitiating clozapine therapy (1).

Genetic risk factors for clozapine-induced neutropenia have been identified, consisting of 2 independent amino acid changes in *HLA-DQB1* (126Q) and *HLA-B* (158T). The *HLA-DQB1* gene is associated with autoimmune disease and *HLA-B* is an important component of severe drug reactions. Despite this genetic insight, a genetic test based solely on *HLA-DQB1* and *HLA-B* would not be able to adequately identify if individuals are truly at low risk of clozapine-induced neutropenia (27). More recent studies have confirmed these risk-associated loci and suggested the *SLCO1B3/SLCO1B7* locus as contributing to additional risk; however, these data do not support these loci having sufficient predictive power to recommend genetic testing (28).

A genetic variant in the *ACKR1* gene, commonly referred to as the Duffy-null genotype, causes a benign form of neutropenia usually called benign ethnic neutropenia (BEN) that can be mistaken for clozapine-induced neutropenia. This allele is common in individuals with African ancestry, but has also been reported in Middle Eastern, south west Asian and Oceania genetic backgrounds (28). For individuals known to have BEN, the FDA label indicates that a lower ANC is acceptable as compared with individuals without the Duffy-null genotype (1).

Therapeutic drug monitoring (TDM) may be employed in conjunction with the FDA-required ANC testing during treatment (29). A consensus guideline recommends a therapeutic range of 350–600 ng/ml for trough steady-state concentrations (30). The concentration to dose ratio is a useful clinical measure of clozapine clearance rates when determining appropriate dosage for individuals with altered CYP metabolic profiles, either due to genetic variation or comedication (29, 31). Moreover, the consensus guidelines strongly recommend clozapine TDM due to the narrow therapeutic range for this medication (30, 31). The importance of TDM in clozapine use is underscored by the observation that it was the third most toxic US medication between 1998-2005, when it was associated with 3277 deaths or serious non-fatal outcomes, lower than only oxycodone and fentanyl (32).

The use of clozapine in pregnancy has not been well-studied in humans, thus the FDA advises that clozapine tablets should only be used during pregnancy if clearly indicated. The increase of estrogen in the second and third trimester is associated with a decrease in the metabolism of CYP1A2 drugs. Thus, it is possible that clozapine levels may increase at the end of the pregnancy, though studies have been very limited (31). The FDA also states that clozapine is present in human breast milk and this poses a potential for serious adverse reactions in the nursing infants. A decision should be made whether to discontinue nursing or discontinue taking the drug. Additionally, safety and effectiveness in pediatric individuals has not been established (1).

The Cytochrome P450 Family

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

Other factors can affect CYP enzyme activity in addition to genetic variation, including concomitant medications. Inhibitors of CYP enzymes include the antibiotic ciprofloxacin (CYP1A2 inhibitor) and the antidepressant fluvoxamine (potent CYP1A2 and CYP2C19 inhibitor, moderate or weak inhibitor for CYP3A4, CYP2C9, and CYP2D6) (33). Inducers of the CYP enzymes include the antiseizure drug carbamazepine (CYP3A and CYP1A2 inducer), rifampin, phenytoin, phenobarbital, and St. John's wort (all CYP3A4 inducers) (1, 34, 35).

In addition, other agents can influence CYP enzymes—caffeine and oral contraceptives are weak or moderate CYP1A2 inhibitors (36). Tobacco smoke has polycyclic aromatic hydrocarbons that bind the aryl hydrocarbon receptor, thereby increasing the expression of CYP1A2 (37). Thus, it is a weak inducer of CYP1A2 (1). Omeprazole has similar weak inducer properties and by binding the aryl hydrocarbon receptor, omeprazole

increases the expression of CYP1A2. Thus, omeprazole has clinically relevant inducer effects on non-smokers (38).

Physiologic conditions can also alter CYP enzyme expression and activity. Studies have proposed that obesity may be associated with decreased clearance of clozapine, as well as other CYP1A2 substrates (39, 40, 41). Inflammation releases cytokines that inhibit CYPs including CYP1A2 (42). One study of post-surgery inflammation suggests that inflammation decreases CYP1A2 activity by half (43).

The phenomenon by which non-genetic factors alter the enzymatic phenotype typically associated with a particular genotype is termed phenoconversion. As discussed above, medications, other ingested substances, and physiologic conditions can alter the enzymatic activity of CYP proteins. For example, an individual with a genotype-predicted intermediate metabolizer (IM) status may have a clinical presentation more akin to a PM due to comedication with a known CYP enzyme inhibitor, such as ciprofloxacin.

Gene: *CYP1A2*

Altered function of CYP1A2 influences the clearance of the clozapine (4). Understanding the full pharmacogenomic effects of *CYP1A2* variation is still at an early stage compared with that of CYP2D6 and other CYP enzymes (44). The CYP1A2 enzyme is the main CYP enzyme involved in clozapine metabolism (4, 45).

The CYP1A2 enzyme comprises around 13% of all CYP protein in the liver, whereas CYP2D6 comprises around 2%. Approximately 25 variant *CYP1A2* alleles have been reported, some of which have been shown to alter the activity of CYP1A2 (Table 3). 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) (44, 46).

The frequency of *CYP1A2*1F* (g.5732C>A in intron 1, rs762551) varies across populations. Studies have reported the frequency of the *CYP1A2*1F* allele to range from 54.9% in Africans to ~60% in Chinese and 68.2% in Caucasians (47, 48). The frequency of individuals who are heterozygous or homozygous for the *CYP1A2*1F* allele ranges from 57–69% in Czech and Hungarian populations and up to 73% in Turkish populations (49). The global average allele frequency of rs762551 (agnostic to potential other variants in *cis*) is 69.2%, but this ranges from 57% in South Asian populations up to 92% in other areas of Asia (50).

Additional rare alleles associated with decreased CYP1A2 activity include *CYP1A2*7* and *CYP1A2*6,* both of which have been reported primarily in individuals of European ancestry, with the *CYP1A2*7* allele being notably absent in a study of Chinese Han PMs (51, 52, 53). Other *CYP1A2* alleles with low activity (**8*, **15*, **16*, and **11*) have been found in low numbers in East Asians (54). A study of 250 Japanese individuals found allele frequencies of 0.4% for *CYP1A2*8*, 0.2% for *CYP1A2*15*, and 0.2% for *CYP1A2*16* (55).

As previously discussed, additional factors beyond genetic variation can influence CYP1A2 activity, resulting in phenoconversion.

Table 3. Activity Status of Selected *CYP1A2* Alleles

Allele type	*CYP1A2* alleles
Normal function	**1A*
Decreased function	**1C, *1K, *3, *4, *7, *8, *11, *15, *16*
No function	**6*
Increased function (inducible)	**1F*

For a comprehensive list of *CYP1A2* alleles, please see PharmVar.

Gene: *CYP2D6*

The CYP2D6 enzyme is responsible for the metabolism of many commonly prescribed drugs, including antidepressants, antipsychotics, analgesics, and beta-blockers.

CYP2D6 Alleles

The *CYP2D6* gene on chromosome 22q13.2 is highly polymorphic. Over 140 star (*) alleles have been described and catalogued at the Pharmacogene Variation (PharmVar) Consortium, and each allele is associated with either normal, decreased, absent, or unknown enzyme function (Table 4) (56).

The combination of *CYP2D6* alleles that a person has is used to determine their diplotype (for example, *CYP2D6 *4/*4*). Based on function, each allele can be assigned an activity score from 0 to 1, which in turn is often used to assign a phenotype (for example, CYP2D6 PMs). When duplicated alleles are detected, both copies are assigned an activity score for phenotyping. However, the activity score system is not standardized across clinical laboratories or *CYP2D6* genotyping platforms. The CPIC revised their activity scoring guidelines in October 2019 to promote harmonization. The CYP2D6 phenotype is defined by the sum of the 2 allele activity scores, which is most commonly in the range of 0 to 3.0 (57).

- Ultrarapid metabolizer (UM) has an activity score greater than 2.25
- Normal metabolizer phenotype (NM) has an activity score of 1.25 to 2.25
- Intermediate metabolizer (IM) has an activity score of >0 to <1.25
- Poor metabolizer (PM) has an activity score of 0 (14)

Table 4. Activity Status of Selected *CYP2D6* Alleles

Allele type	*CYP2D6* alleles	Activity score
Normal function	**1, *2, *27, *33*	1
Decreased function	**17, *41, *49*	0.5
Strongly decreased function	**10*	0.25
No function	**3, *4, *5, *6, *36*	0

For a comprehensive list of *CYP2D6* alleles, please See PharmVar.

The *CYP2D6*1* allele is considered the wild-type allele when no variants are detected, which is associated with normal enzyme activity and the "normal metabolizer" phenotype. In addition, the *CYP2D6*2*, **27*, and **33* alleles are also considered to have near-normal activity.

Other *CYP2D6* alleles include variants that produce a non-functioning enzyme (for example, **3*, **4*, **5*, and **6*) (58, 59, 60, 61) or an enzyme with decreased activity (for example, **10*, **17*, and **41*) (62, 63, 64) (see Table 4). 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 (65).

Allele Frequencies Vary between Populations

Among Asians and in individuals of Asian descent, only approximately 50% of *CYPD6* alleles are normal function, and the frequency of *CYP2D6* duplications is as high as 45%, although this may have been overestimated by not accounting for tandem hybrid alleles (for example, **36+*10*) (66). Other studies of a US individual population suggested less than 50% of alleles detected within Asian-descent individuals are normal-function alleles in a single copy, with 30% of alleles arising from structural variants (duplications or deletions) (67). Common no-function variants are *CYP2D6*36* and *CYP2D6*4* (67). Both these alleles contain the variant "c.100C>T," which is the defining variant in *CYP2D6*10* (see Allele Nomenclature table) (65, 66, 68, 69). The

*CYP2D6*36* allele is the result of a gene conversion event with the pseudogene *CYP2D7* (70). This no-function allele is most commonly found in individuals of Asian ancestry (67).

Among Africans and African Americans, approximately 50% of *CYP2D6* alleles are normal function (58, 64, 65, 71). African Americans also have been found to have a higher frequency of no-function structural variants or decreased-function single-copy variant alleles versus Caucasian or Hispanic-Americans (67). Intermediate and NM alleles are present in approximately 80% of the population of individuals of African descent (72).

Middle Eastern countries show a great diversity in phenotypic and allelic distribution for *CYP2D6* (73), though on average, these individuals show a lower frequency of PM phenotypes (0.91%) and higher UM phenotypes than other ethnicities (74). The highest frequencies of CYP2D6 UM reported to date are 20% in Oceanians and 9.5% Near Easterners (72, 75).

Among European countries, there is diversity of allelic distribution (76). Gene duplications were more common in the south-eastern countries (Greece, Turkey: 6%) and less common in north-western countries (Sweden and Denmark, <1%). Meanwhile, *CYP2D6*4* and **5* alleles were generally more common in the north and less common in the south (76). Worldwide *CYP2D6* genotype and phenotype frequencies have been catalogued and recently published (74).

Gene: *CYP3A4*

In contrast to *CYP2D6, CYP1A2,* and other genes that encode drug-metabolizing enzymes, *CYP3A4* shows little genetic variation with known functional consequences (Table 5). Although around 40 variant *CYP3A4* alleles have been reported, most have not been shown to alter the activity of CYP3A4 (77, 78). To date, only 3 loss-of-function *CYP3A4* alleles have been identified (*CYP3A4*6, CYP3A4*20* and *CYP3A4*26*) (79, 80).

The *CYP3A4*22* allele has decreased function and explains 12% of the variation in CYP3A4 activity (81). This variant that is present in 3.2–10.6% of the Dutch population and 5.2–8.3% of the population in America (82). The Allele Frequency Aggregator project reports this reduced-function allele to be present in approximately 5% of the global population, with the lowest prevalence in Asian and African populations (83). The 1000 Genomes Project phase 3 data release estimates global prevalence to be slightly lower (~1%); a minor allele frequency of 5% is reported for the European average (84).

The *CYP3A4*20* allele contains a premature stop codon that results in a loss-of-function of *CYP3A4*. It appears to be the most common *CYP3A4*-defective allele but is still relatively rare, with approximately 0.2% of European Americans and 0.05% African Americans who are heterozygous. However, in Spain, the *CYP3A4*20* allele is present in 1.2% of the population, and up to 3.8% in specific Spanish regions (79).

Table 5. Activity Status of Selected *CYP3A4* Alleles

Allele type	*CYP3A4* alleles
Normal function	**1A*
Decreased function	**16A, *16B, *22*
No function	**6, *20, *26*

For a comprehensive list of *CYP3A4* alleles, please see PharmVar.

Gene: *CYP2C19*

Another CYP enzyme with a minor contribution to clozapine metabolism is CYP2C19. The CYP2C19 enzyme contributes to the metabolism of a range of clinically important drugs, including antidepressants, antiplatelet agents, anti-fungal agents, some proton pump inhibitors, and benzodiazepines such as diazepam.

The *CYP2C19* gene is highly polymorphic, as there are over 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. Individuals who have one copy 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 6).

Table 6. The CPIC Assignment of *CYP2C19* Phenotype based on Genotype (2017)

Phenotype	Genotype	Examples of diplotype
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*
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* **1/*3* **2/*17*[b]
CYP2C19 poor metabolizer (approximately 2–15% of individuals)	An individual with 2 no-function alleles	**2/*2* **2/*3* **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 (85).
[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 (85).

It has been reported that approximately 2% of Caucasians, 4% of African Americans, and 14% of Chinese are CYP2C19 PMs; and up to 45% of individuals are CYP2C19 IMs (86). Other studies have found PM phenotypes to range between 10.8–16.4% in Asian populations, 3% in African descendants, and 1.6% in Middle Eastern populations (87, 88). Pacific Islanders have been reported to have higher frequencies of PMs—11.8% (88). The frequency of IMs is similarly distributed, higher in East and South Asian and Pacific Islander, lower in African or Middle Eastern populations (87).

The FDA-approved drug label for omeprazole, a CYP2C19 substrate, states that approximately 15–20% of Asians are CYP2C19 PMs, compared with 3% of Caucasians (89). The most common no-function allele 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 of European descent and Africans, and ~27–36% in Asians (87, 90).

The *CYP2C19*3* allele is another commonly identified no-function variant, which contains a c.636G>A variant in exon 4 that causes a premature stop codon. The *CYP2C19*3* allele frequencies are ~2–7% in Asian populations (90), but rare in other racial groups. Other no-function variants occur in less than 1% of the general population and include *CYP2C19*4-*8* (91, 92).

The *CYP2C19*17* allele, which results in rapid and UMs, has frequencies of only 1.3–4% among Asian populations compared with approximately 20–33.7% of African, European, and Near-Eastern populations (87, 88).

Linking Gene Variation with Treatment Response

There is growing evidence to support that genetic factors, such as *CYP2D6*, play a role in determining the clinical outcome of antipsychotic treatment. However, there is no definitive evidence for clozapine treatment with regard to *CYP1A2*, *CYP2D6, CYP3A4* or *CYP2C19*, with the latter 3 playing a minor role in clozapine metabolism. Although pharmacogenetic testing is available, its use in personalizing antipsychotic treatment is minimal (93). While the FDA recommends adjusting dosage only for CYP2D6 PMs, studies investigating the potential benefit of pharmacogenomic-guided dosing have studied CYP1A2, CYP2C19, and CYP3A status (93, 94).

There is no consensus on the effect of various *CYP1A2* alleles on clozapine treatment, however, mounting evidence exists to suggest that changes in CYP1A2 activity can significantly affect clozapine plasma levels. Increased CYP1A2 activity is predicted to result in a more rapid metabolism of clozapine and lower clozapine half-life; conversely, reduced CYP1A2 activity would lead to reduced clozapine metabolism and a longer clozapine half-life (1, 18, 29). Cessation of smoking or co-medication with CYP1A2 inhibitors (for example, ciprofloxacin, fluvoxamine, or enoxacin) have led to an increase in clozapine exposure (95). Differences in gender and smoking status influence clozapine plasma levels. At least one case has been documented where high caffeine consumption was associated with an UM phenotype (40). Given that smoking is more common among individuals with schizophrenia than in the general population, the effect of tobacco use on CYP1A2 metabolism is particularly important for clozapine therapy (96). Multiple reports have found that infections, particularly pneumonia, are associated with risk of clozapine intoxication due to the release of cytokines (97, 98, 99). The decrease of clozapine clearance during infections is not specific; any inflammation with systemic manifestations, such as fever or serum C-reactive protein (CRP) elevations, can cause elevated clozapine serum concentrations. Thus, CRP elevations can help identify inflammation as a cause of clozapine concentration elevations (100). In one study, only 11% of individuals with concurrent infections during clozapine therapy were able to continue their medication without dose alteration (101).

Studies suggest that the required dose to maintain therapeutic plasma concentrations in individuals with Asian Indian and Southeast Asian ancestry is half of the dose of an individual with European ancestry, though the exact mechanism remains to be elucidated (29, 102). Several reports have documented that clozapine is used at lower doses in Asian individuals and that east Asians have a lower clozapine clearance as compared with Caucasians (53, 103, 104, 105). Similarly, studies of CYP1A2 activity have found Caucasians to have higher average enzyme activity than Asians (106). Typical clozapine doses in Asians range from 150–300 mg/day (40). Native Americans and other Amerindians may have clozapine metabolism similar to Asians and need similar lower doses as compared with Caucasians (107). A recent case of myocarditis in a Canadian of South Asian ancestry indicates that this dosing difference may be clinically relevant since the individual developed a clozapine-induced myocarditis when started with a Canadian typical titration with an initial dose of 25 mg/day and 100 mg/day was reached in the 11 day. On the other hand, a slower titration (initial dose 6.5 mg/day and final dose 81.25 mg/day) was tolerated without myocarditis (108). Furthermore, an analysis of 6 combined studies of European Caucasians established that the minimal therapeutic doses ranged from 236 (female non-smokers) to 368 mg/d (male smokers). These dosages are much lower than the ones proposed by the US clozapine package insert, which recommends targeting doses from 300-450 mg/day and then consider increases by 100 mg/day, up to 900 mg/day in rare situations (109). Thus, determination of CYP1A2 metabolizer status should account for not only genotype, but gender, obesity, inflammation, smoking or comedication, and ethnic background as potential confounding factors leading to phenoconversion (8).

Case studies have reported individuals with one or more copies of the increased-function allele *CYP1A2*1F* who responded poorly to clozapine therapy. However, evidence for a universal, clinically significant effect of *CYP1A2*1F* alleles on CYP1A2 is lacking. Out of the 7 kinetic studies, ranging in size from 58–185 individuals, only one medium-sized study (95 individuals) found a significant effect of the **1F* allele on clozapine pharmacokinetics (110, 111, 112, 113, 114, 115, 116).

The FDA drug label indicates that individuals taking strong CYP1A2 inhibitors should take a significantly reduced dose of clozapine, due to reduced clearance via CYP1A2 metabolism (1). However, experts strongly caution against co-prescribing CYP1A2 inhibitors such as fluvoxamine or ciprofloxacin with clozapine due to potentially fatal drug-drug interactions (117, 118).

While the FDA-approved drug label states that dose adjustments may be required for CYP2D6 PMs, there are no specific guidelines from any pharmacogenomic authority to pre-emptively adjust an individual's clozapine dosage based on *CYP2D6* genotype. Case studies have reported altered pharmacodynamics in CYP2D6 PMs and UMs, however, further analysis suggests that phenoconversion due to comedication has a larger effect on CYP2D6-mediated clozapine metabolism than genotype alone (119, 120, 121, 122). Indeed, in vitro analysis suggests the CYP2D6 enzyme is responsible for approximately 6% of clozapine metabolism, further supporting a modest role for this enzyme in clinical management (5). Similarly, *CYP3A4* genotypes have not been definitively shown to be associated with a specific response or altered dosage of clozapine, likely due to the primary role of CYP1A2 in clozapine metabolism (94, 114). However, one study suggests that CYP3A4 activity may play a role in metabolic side effects from clozapine therapy (123).

Multiple studies have examined the effect of CYP2C19 genotypes on the response to antipsychotics, including clozapine, with variable conclusions being reached to determine genotype-based guidance for clozapine. Genotypes studied include *CYP2C19*2* and *CYP2C19*17* (53, 124, 125).

Genetic Testing

Genetic testing is available for common *CYP2D6*, *CYP1A2*, *CYP3A4* and *CYP2C19* 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 NIH 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 (126). Gene duplications and multiplications can be denoted by "xN", for example: *CYP2D6*1xN* with *xN* representing the number of *CYP2D6* gene copies. Note: representation of duplications is also not standardized among laboratories.

In 2018, the Association for Molecular Pathology (AMP) published recommendations for *CYP2C19* genotyping allele selection. The recommendations determined varying tiers of alleles, based on the strength of evidence supporting drug response, minor allele frequencies and availability of reference materials. The AMP's tier one group represent the core alleles recommended for genotyping panels: **2, *3,* and **17* (127). These guidelines provide information for laboratories performing *CYP2C19* genotype testing and are a useful complement to CPIC prescribing recommendations.

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.

[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 with nomenclature standards, where necessary. We have given the full name of abbreviations, shown in square brackets, where necessary.

2020 Statement from the US Food and Drug Administration (FDA)

Dosage Adjustments with Concomitant use of CYP1A2, CYP2D6, CYP3A4 Inhibitors or CYP1A2, CYP3A4 Inducers

Clozapine is a substrate for many cytochrome P450 isozymes, in particular CYP1A2, CYP3A4, and CYP2D6. Use caution when administering clozapine tablets concomitantly with drugs that are inducers or inhibitors of these enzymes.

[…]

Dose adjustments may be necessary in patients with concomitant use of:

- strong CYP1A2 inhibitors (e.g., fluvoxamine, ciprofloxacin, or enoxacin);
- moderate or weak CYP1A2 inhibitors (e.g., oral contraceptives, or caffeine);
- CYP2D6 or CYP3A4 inhibitors (e.g., cimetidine, escitalopram, erythromycin, paroxetine, bupropion, fluoxetine, quinidine, duloxetine, terbinafine, or sertraline);
- CYP3A4 inducers (e.g., phenytoin, carbamazepine, St. John's wort, and rifampin);
- or CYP1A2 inducers (e.g., tobacco smoking)

[…]

Concomitant use of Strong CYP1A2 Inhibitors: Reduce clozapine tablets dose to one-third when coadministered with strong CYP1A2 inhibitors (e.g., fluvoxamine, ciprofloxacin, enoxacin).

Concomitant use of Strong CYP3A4 Inducers is not recommended.

Discontinuation of CYP1A2 or CYP3A4 Inducers: Consider reducing clozapine tablets dose when CYP1A2 inducers (e.g., tobacco smoke) or CYP3A4 inducers (e.g., carbamazepine) are discontinued.

Anticholinergic drugs: Concomitant use may increase the risk for anticholinergic toxicity.

[…]

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.

[…]

A subset (3%–10%) of the population has reduced activity of CYP2D6 (CYP2D6 poor metabolizers). These individuals may develop higher than expected plasma concentrations of clozapine when given usual doses.

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

Summary of recommendations from the Dutch Pharmacogenetics Working Group (DPWG) of the Royal Dutch Association for the Advancement of Pharmacy (KNMP) (2016, 2020)

CYP2D6 Poor, Intermediate or Ultrarapid Metabolizer-Clozapine [December 2020]

NO action is required for this gene-drug interaction.

The genetic variation results in a slightly elevated plasma concentration of clozapine, but there are no clinical consequences.

CYP1A2 [2016]

This is NOT a drug-gene interaction.

Please review the complete therapeutic recommendations that are located here: (6).

Nomenclature for selected alleles

***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*1K*	-739T>G -729C>T -163C>A	NM_000761.5:c.-10+103T>G NM_000761.5:c.-10+113C>T NM_000761.5:c.-9-154C>A	Not applicable—variant occurs in a non-coding region	rs2069526 rs12720461 rs762551
*CYP1A2*1F*	-164C >A	NM_000761.4:c.-9-154C>A	Not applicable—variant occurs in a non-coding region	rs762551
*CYP1A2*3*	2116G>A; 5347T>C	NM_000761.5:c.1042G>A	NP_000752.2:p.Asp348Asn	rs56276455
*CYP1A2*4*	2499A>T; I386F	NM_000761.5:c.1156A>T	NP_000752.2:p.Ile386Phe	rs72547516
*CYP1A2*6*	5090C>T; R431W	NM_000761.5:c.1291C>T	NP_000752.2:p.Arg431Trp	rs28399424
*CYP1A2*7*	3533G>A	NM_000761.5:c.1253+1G>A	Splicing defect	rs56107638
*CYP1A2*8*	5347T>C; 5166G>A; R456H	NM_000761.5:c.1367G>A	NP_000752.2:p.Arg456His	rs72547517
*CYP1A2*11*	558C>A; F186L	NM_000761.5:c.558C>A	NP_000752.2:p.Phe186Leu	rs72547513

*CYP1A2*1A* is the wild-type allele and is determined to be present with no variants are detected.

***CYP2D6* Nomenclature**

Common allele name	Alternative names	HGVS reference sequence		dbSNP reference identifier for allele location
		Coding	Protein	
*CYP2D6*2*	2851C>T (Arg296Cys)	NM_000106.6:c.457G>C	NP_000097.3:p.Arg296Cys	rs16947
	4181G>C (Ser486Thr)	NM_000106.6:c.886C>T	NP_000097.3:p.Ser486Thr	rs1135840
*CYP2D6*3*	2550delA (Arg259fs)	NM_000106.6:c.775delA	NP_000097.3:p.Arg259fs	rs35742686
*CYP2D6*4*	1846G>A	NM_000106.6:c.506-1G>A	Variant occurs in a non-coding region (splice variant causes a frameshift)	rs3892097
*CYP2D6*5*	Variant results in a whole gene deletion			
*CYP2D6*6*	1707 del T (Trp152Glyfs) CYP2D6T	NM_000106.6:c.454delT	NP_000097.3:p.Trp152Glyfs	rs5030655
*CYP2D6*10*	100C>T (Pro34Ser)	NM_000106.6:c.886T>C	NP_000097.3:p.Pro34Ser	rs1065852

CYP2D6 Nomenclature continued from previous page.

Common allele name	Alternative names	HGVS reference sequence		dbSNP reference identifier for allele location
		Coding	Protein	
*CYP2D6*17*	1023C>T[1] (Thr107Ile)	NM_000106.6:c.1457G>C	NP_000097.3:p.Thr107Ile	rs28371706
	2851C>T[2] (Arg296Cys)	NM_000106.6:c.457G>C	NP_000097.3:p.Arg296Cys	rs16947
	4181G>C (Ser486Thr)	NM_000106.6:c.886C>T	NP_000097.3:p.Ser486Thr	rs1135840
*CYP2D6*27*	3854G>A (Glu410Lys)	NM_000106.6:c.1319G>A	NP_000097.3:p.Glu410Lys	rs769157652
*CYP2D6*31*	2851C>T (Arg296Cys)	NM_000106.6:c.1457G>C	NP_000097.3:p.Arg296Cys	rs16947
	4043G>A (Arg440His)	NM_000106.6:c.454delT	NP_000097.3:p.Arg440His	rs267608319
	4181G>C (Ser486Thr)	NM_000106.6:c.100C>T	NP_000097.3:p.Ser486Thr	rs1135840
*CYP2D6*36*[3]	100C>T (Pro34Ser)	NM_000106.6:c.320C>T	NP_000097.3:p.Pro34Ser	rs1065852
	4129C>G (Pro469Ala)	NM_000106.6:c.1405C>G	NP_000097.3:p.Pro469Ala	rs1135833
	4132A>G (Thr470Ala)	NM_000106.6:c.1408A>G	NP_000097.3:p.Thr470Ala	rs1135835
	4156C>T+4157A>C (His478Ser)	NM_000106.6:c.1432C>T + NM_000106.6:c.1433A>C	NP_000097.3:p.His47Ser	rs28371735 + rs766507177
	4159G>C (Gly479Arg)	NM_000106.6:c.1435G>C	NP_00097.3:p.Gly479Arg	
	4165T>G (Phe481Val)	NM_000106.6:c.1441T>G	NP_00097.3:p.Phe481Val	
	4168G>A+4169C>G (Ala482Ser)	NM_000106.6:c.1444G>A + NM_000106.6:c.1445C>G	NP_000097.3:p.Ala482Ser	rs74478221 + rs75467367
	4181G>C (Ser486Thr)	NM_000106.6:c.1457G>C	NP_000097.3:p.Ser486Thr	rs1135840
*CYP2D6*41*	2851C>T (Arg296Cys)	NM_000106.6:c.457G>C	NP_000097.3:p.Arg296Cys	rs16947
	2988G>A	NM_000106.6:c.985+39G>A	Variant occurs in a non-coding region (impacts splicing).	rs28371725
*CYP2D6*49*	100C>T (Pro34Ser)	NM_000106.6:c.100C>T	NP_000097.3:p.Pro34Ser	rs1065852
	1612T>A (Phe120Ile)	NM_00106.6:c.358T>A	NP_000097.3:p.Phe120Ile	rs1135822
	4181G>C (Ser486Thr)	NM_000106.6:c.1457G>C	NP_000097.3:p.Ser486Thr	rs1135840

[1] In the literature, 1023C>T is also referred to as 1111C>T
[2] In the literature, 2851C>T is also referred to as 2938C>T
[3] *CYP2D6*36* is a gene conversion with *CYP2D7;* variants provided here are from the Pharmacogene Variation Consortium. *CYP2D6*1* is the wild-type allele and is presumed to be present with no variants are detected.

***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_831insA	NP_059488.2:p.Asp277Glufs	rs4646438
*CYP3A4*16A*	554C>G, T185S	NM_017460.6:c.554C>G	NP_059488.2:p.Thr185Ser	rs12721627
*CY P3A4*16B*	554C>G, T185S	NM_017460.6:c.554C>G	NP_059488.2:p.Thr185Ser	rs12721627
	20230G>A (gDNA)	NM_017460.6:c.1026+12G>A	Not applicable—variant occurs in a non-coding region	rs2242480
*CYP3A4*20*	1461_1462insA 488Frameshift	NM_017460.5:c.1461dup	NP_059488.2:p.Pro488Thrfs	rs67666821
*CYP3A4*22*	15389C>T	NM_017460.6:c.522-191C>T	Not applicable—variant occurs in a non-coding region	rs35599367
*CYP3A4*26*	17633C>T R268Stop	NM_017460.6:c.802C>T	NP_059488.2:p.Arg268Ter	rs138105638

*CYP3A4*1A* is the wild-type allele and is determined to be present with no variants are detected.

***CYP2C19* Nomenclature**

Common allele name	Alternative names	HGVS reference sequence		dbSNP reference identifier for allele location
		Coding	Protein	
*CYP2C19*2*	681G>A Pro227Pro	NM_000769.4:c.681G>A	NP_000760.1:p.Pro227=	rs4244285
*CYP2C19*3*	636G>A Trp212Ter	NM_000769.4:c.636G>A	NP_000760.1:p.Trp212Ter	rs4986893
*CYP2C19*4*	1A>G Met1Val	NM_000769.4:c.1A>G	NP_000760.1:p.Met1Val	rs28399504
*CYP2C19*5*	90033C>T Arg433Trp	NM_000769.4:c.1297C>T	NP_000760.1:p.Arg433Trp	rs56337013
*CYP2C19*6*	12748G>A Arg132Gln	NM_000769.4:c.395G>A	NP_000760.1:p.Arg132Gln	rs72552267
*CYP2C19*7*	19294T>A	NM_000769.4:c.819+2T>A	(Splice donor variant)	rs72558186
*CYP2C19*8*	12711T>C Trp120Arg	NM_000769.4:c.358T>C	NP_000760.1:p.Trp120Arg	rs41291556
*CYP2C19*9*	12784G>A Arg144His	NM_000769.4:c.431G>A	NP_000760.1:p.Arg144His	rs17884712
*CYP2C19*17*	-806C>T	NM_000769.4:c.-806C>T	Not applicable - variant occurs in a non-coding region	rs12248560

Note: when no variants are detected the genotype is designated as *CYP2C19*1* and is considered the normal "wild-type" allele.
Pharmacogenetic Allele Nomenclature: International Workgroup Recommendations for Test Result Reporting (128).
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 the Pharmacogene Variation (PharmVar) Consortium.

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