

## Genetic polymorphisms associated with antiepileptic metabolism

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## 1. ABSTRACT

Several factors, including pharmacogenetics, contribute to inter-individual variability in drug response. Many antiepileptic drugs (AEDs) are metabolized by a variety of enzymatic reactions, and the cytochrome P450 (CYP) family has attracted considerable attention. Some of the CYPs exist as genetic (allelic) variants, which may also affect the plasma concentrations or drug exposure. Regarding the metabolism of AEDs, the polymorphic CYP2C9 and CYP2C19 are of particular interest. There have been recent advances in discovering factors such as these, especially those underlying the risk of medication toxicity. This review summarizes the evidence about whether such polymorphisms affect the clinical action of AEDs to facilitate future studies on the pharmacogenetics of epilepsy. We performed Key Words searches in the public databases PubMed, Medscape, and Rxlisty, Pharm GKB for genetic polymorphisms and the NCBI website for the nomenclature of alleles of CYP450, finding that CYP2D6, CYP2C9, CYP3A4, and CYP2D19 were involved in the metabolism of most antiepileptic drugs, given the allele frequency in the population and the associated variability in the clinical response.

## 2. INTRODUCTION

Epilepsy is one of the most common neurological disorders (1), affecting 1-2% of the world population (2). The main treatment of choice in chronic epilepsy is antiepileptic drugs (AEDs), but until now approximately one-third of epileptic patients have been resistant to drug treatment, despite advances in antiepileptic drug therapy. The consequences of uncontrolled epilepsy can be severe and include shortened lifespan, bodily injury, neuropsychological and psychiatric impairment, and social disability. Most patients with refractory epilepsy (RE) are resistant to several, if not all, AEDs, even though these drugs act via different mechanisms (3,4,5,6). In order to find an explanation for refractoriness, several hypotheses have been suggested. Among them, the pharmacokinetics theory suggests that intervention of different proteins decrease or prevents the entry of AEDs in the brain (7). These proteins are involved in active transport of xenobiotics like the ABC carrier proteins found in the blood-brain barrier and whose over-expression is observed in resected tissue from patients with focal epilepsy (8); also, proteins with enzymatic activity are able to transform compounds intrinsically and exogenously, as with the

**Table 1.** Enzymes involved in the metabolism of the most commonly prescribed antiepileptic drugs, adapted from (29)

Antiepileptic drug	CYP 450 Metabolizing family member
Carbamazepine	CYP3A4, CYP1A2, CYP2A6, CYP2C8, CYP2C19, CYP2D6, UGT1A6, UBG2B
Valproic Acid	50% by UGT, CYP2C9, CYP2C19
Phenytoin	CYP2C9, CYP2C19, UGT
Phenobarbital	CYP2C9, CYP2C19
Primidone	CYP2C9, CYP2C19
Gabapentin	95% is excreted by the kidneys without changes
Tiagabine	CYP3A4, UGT
Topiramate	80% excreted by kidney, the rest by CYP2C9, CYP2C19
Felbamate	CYP2E1, CYP3A4, CYP2C19
Lamotrigine	Over 70% UGT1A4, 10% excreted unchanged
Levetiracetam	60% excreted unchanged, 24% hydrolysis of acetamide and 2.5.% via P450 enzymes

superfamily of cytochrome P450 (CYP450) found in different cell membranes and tissues (9). On other hand, pharmacogenomics is a discipline that studies genetic factors of proteins involved on drug metabolism, in order to determine individual differences to drug therapy and their adverse reactions (10). Historically, the variability in drug response has been attributed to the presence of enzyme isoforms that each individual has in his genes, because each isoform contributes to individual differences in bioavailability, transport, metabolism and action of drugs, therefore the importance of drug monitoring when drugs are substrates of CYP450 (11). Genetic variants associated with variability in the metabolism of AEDs in different ethnic groups are described in this article.

### 3. GENETICS OF DRUG RESPONSE

Genetic polymorphisms, meanwhile, are variations in the genome that initially appear as mutations in some individuals but are compatible with life, are transmitted to offspring and gain a population frequency of 1 in 1000 (12). Relevant polymorphisms may potentially alter drug absorption and disposition and its action sites of drugs. The most frequent polymorphisms in the human genome and for variations in response to drug treatment are single nucleotide polymorphisms (SNPs). These changes can occur in coding regions (exons) or in non-coding regions (introns, promoters, UTRs, etc.), and they are currently used in the identification of genetic patterns, in identification or in association with disease. The genetic studies on drug response may prove to be more amenable to analysis than other aspects of genetics in epilepsy because the proteins that are drug targets, drug transporters, and drug metabolizes are, to varying extents, already known. For example, individuals possessing certain alleles of the CYP2C9 gene, which encodes the major metabolizing enzyme of phenytoin (PHT), have significantly reduced rates of PHT metabolism and require a low maintenance dose, although prospective genotyping is not yet undertaken in clinical practice. Whether variants in the ABCB1 gene, which encodes the broad-spectrum multidrug transporter P-glycoprotein (P-gp), influencing resistance to AEDs remains widely debated. There are numerous studies supporting the genetic variability in the ABCB1 gene. One report showed that English refractory patients were more

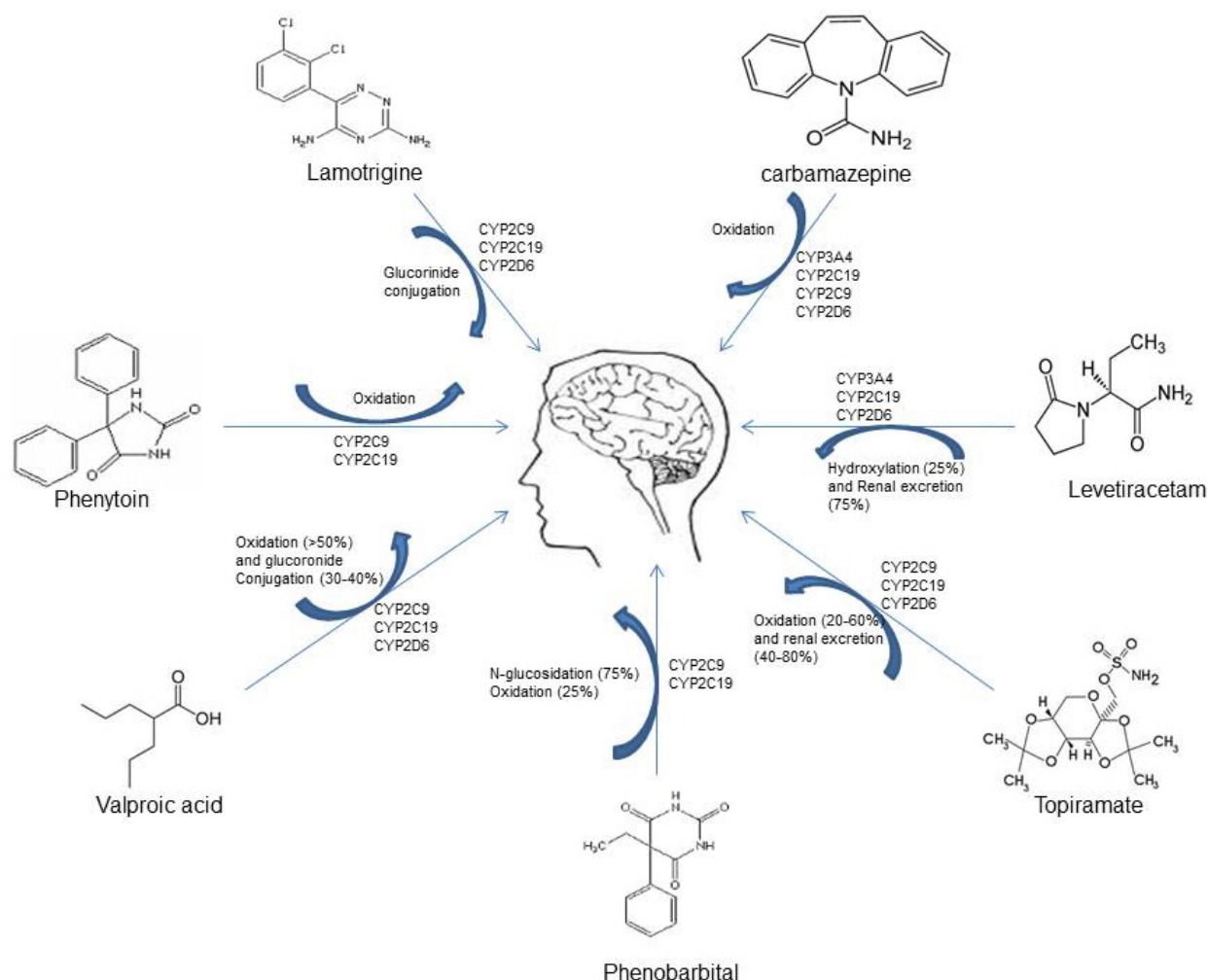
likely to possess the CC genotype at the C3435T region of the ABCB1 gene and be resistant to multiple antiepileptic drugs; in another study, 210 European patients with temporal lobe epilepsy, clustered by seizures/year, exhibited a relationship between the CGC haplotype at the regions C1236T, G2677T and C3435T, showing resistance to several antiepileptic drugs, and they also showed an increase in drug resistance of up to 6 times in homozygous CGC patients with mesial temporal lobe epilepsy (MTLE) (13,14). In another report, of 210 Japanese epileptic patients with two years of treatment with carbamazepine, 126 displayed RE. Patients (stratified by gender, age, weight, age of onset of epilepsy, duration of therapy, F72.1. or F73.1. classification according to the International Classification of Diseases, seizure type, etiology, number of drugs in use and history of drug used) showed a tendency to the T-allele in the region C3435T, the TT genotype at the G2677T/A and/or C3435T regions and haplotype of TTT in regions C1236T, G2677T/A and C3435T, when the drug was employed (15).

Genetic variants influencing the sensitivity of targets to AEDs are also being uncovered, for example, the presence of rs3812718 polymorphism in the 1A subunit of the sodium channel (SCN1A) has been observed in association with high doses of carbamazepine in epileptic patients (16). Similarly, in Holland *et al.*, a mutation was detected in channel 3A subunit of sodium (SCN3A-K354Q) in pediatric patients with partial epilepsy who were refractory to monotherapy with carbamazepine and oxcarbazepine (17).

#### 3.1. Genetics of drug metabolism

Although monotherapy remains the mainstay in the treatment of epilepsy, combinations of AEDs are frequently used in patients who do not respond to a single drug. When combination therapy is used in patients, drug interactions become clinically relevant for a variety of reasons: (i) AEDs are administered for extended periods, often for a lifetime, so the possibility of interactions with the prescribed drug is increased; (ii) most AEDs have a narrow therapeutic index, and even modest alterations in pharmacokinetics may result in loss of response or toxicity; (iii) the most commonly used AEDs (carbamazepine, valproic acid, phenytoin and phenobarbital) have significant effects on the activity of enzymes that metabolize most existing drugs; and (iv) most of the old and new generations of AEDs are substrates of cytochrome P450 (CYP450), including CYP1A2, CYP2C9, CYP2C19 and CYP3A4, and glucuronyl transferase and epoxide hydrolase (Table 1) (18,19).

Furthermore, most (AEDs) are lipophilic compounds with high capacities for crossing biological membranes, including the blood-brain barrier. This allows the inference that the access of antiepileptic drugs to the central nervous system (CNS) is directly related to their plasma concentrations. It is expected that the higher the circulating concentration of the drug, the higher the amount of the compound that will enter the CNS. However, there are individual genetic variations that change patients' ability to metabolize AEDs in some during and disposition



**Figure 1.** Biotransformation reactions produced by CYP isoenzymes in antiepileptic drugs, adapted from (76)

phase, excretion and dissemination. Therefore, there can be different relationships between plasma concentrations and access to the central nervous system, which affects the therapeutic response. This fact has been connected to different genetic polymorphisms that are associated with all phases of the dose/response system (20). The first association between epilepsy and pharmacogenetics was made in the cytochrome P450 system because of previous experience with other conditions that showed resistance or drug intoxication (21,22).

### 3.2. CYP450 overview

The CYP450 superfamily consists of 57 active genes with high gene variability whose products are hemoprotein isoenzymes that can be isolated from liver microsomes (23,24). These enzymes catalyze biotransformation reactions aimed at increasing the hydrophilicity of xenobiotics and facilitating their fast excretion from the body. These reactions can be distinguished in reactions of Phase I and Phase II. In Phase I, enzymes increase the polarity of the lipophilic compounds by oxidation, reduction or hydrolysis, leading

to the occurrence of polar groups in the molecule, which results in increasing its water solubility and thus its of excretion (Figure 1). In Phase II, the substrate may either be xenobiotic as a metabolite from a phase I reaction or be conjugated with an endogenous substance to facilitate transport into the body and subsequent excretion (25). CYP450 and other enzymes may also activate pro-drugs or other chemical substances that produce reactive products and damage to the cell (26).

In most people, the pharmacokinetic pattern of a given drug maintains its therapeutic effect in the desired range for a given dose of medicine. These patients are called extensive metabolizers (EM) and conventionally assigned to the first allele of each sub-family (e.g., CYP2D6\*1, CYP2C9\*1, CYP2C19\*1 and CYP3A4\*1). However, there is a group of patients who do not respond to regular doses or can form toxic metabolites or have excessive amounts of active drug when treated with drug precursors. This may be due to the large number of active copies of the gene in the same allele, and these patients are called ultrafast metabolizers (UM); when the duplication or

**Table 2.** Phenotypes and cytochrome P450 polymorphisms and alleles and functional importance of drugs, adapted from (24,52]

Phenotype	Genotype	alleles causing of the phenotype	Clinical consequences
Fast metabolizers	More than two active gene copies	<i>CYP2C19*17 (CYP2D6*1/*2XN</i>	Absence of response to drugs, likelihood of adverse reactions
Extensive metabolizers	Two functional alleles	<i>CYP2C9*1, CYP2C19*1, CYP2D6*1</i>	Good therapeutic response
Intermediate metabolizers	One or two defective alleles	<i>CYP2C9*2, CYP2D6*10, CYP2D6*41</i>	Increase in drug concentration
Poor metabolizers	Two defective alleles	<i>CYP2C9*3, CYP2C19*2, CYP2C19*3, CYP2D6*4, CYP2D6*5</i>	High levels of drug, increased likelihood of adverse reactions

multiplication of genes occurs in 13 tandem copies, they are considered fast metabolizers (FM). In contrast, there are patients with increased likelihood of adverse reactions in whom the desired effect of the drug is present, and these patients are called poor metabolizers (PM). Finally, there is a phenotype of less efficient metabolism than normal, fast or ultrafast but more efficient than slow metabolizers, and these patients are called intermediate metabolizers (IM) (27). Patients with increased possibilities of adverse reactions without the desired effect of the drug belong to the PM group. Thus, the pharmacological action of a drug is determined by the genetic polymorphisms that influence the pharmacokinetic and pharmacodynamic processes.

#### 4. CYP450 PHARMACOGENETICS

Pharmacokinetics is the branch of pharmacology that studies the processes to which a drug is submitted by its passage through the body, and this field of knowledge allowed the identification of variations in drug responses during the early 1950s (28). Pharmacogenetics, meanwhile, is the study of the association between genetic variations and response to a drug, both in terms of effectiveness and possible side effects, even before administration. Pharmacogenetic studies were initiated when it was observed that there were differences in drug concentrations in serum and its drug metabolites distribution in patients with identical diagnosis. These studies subsequently include the increased or decreased expression of the associated genes, genetic variations between individuals and the effects in clinical practice (29). Genetic differences between populations result in different chemical reactions to drugs. For each AED, there are several CYP enzyme polymorphisms. Although not all are relevant to the phenotypic level, some are crucial in drug metabolism, making such studies relevant. In humans, the families involved in the metabolism of xenobiotics are CYP1, CYP2 and CYP3. Almost 50% of CYP450 alleles in humans belong to one of three subfamilies, although there are still many catalytic functions that remain to be identified (29). The presence of a genetic polymorphism may have some relevance to function, either through changes in, a) the expression of messenger RNA or b) in protein expression, c) substrate selectivity, or d) enzymatic activity (30).

Among the polymorphic enzymes that metabolize xenobiotics, class I enzymes are well preserved and show unimportant polymorphisms but are active in the metabolism of drugs and pre-carcinogens, and they include CYP1A1, CYP1A2, CYP2E1 and CYP3A4. The class II enzymes are highly polymorphic and active in the metabolism of no pre-carcinogenic drugs; this group includes CYP2B6, CYP2C9, CYP2C19 and CYP2D6 (31).

Pharmacogenetics has achieved favorable results of between 40 and 50% for the control of seizures and/or the identification of adverse reactions to drug treatment (32). Thus, the study of genetic variability in genes associated with drug metabolism is related to pharmacological responses to antiepileptic drugs (Table 2).

##### 4.1. Genetic biomarkers for efficient therapy

Pharmacogenetic biomarkers proposed by the FDA are classified into three groups by their reliability, scientific validation and clinical significance: "probably valid", "definitely valid" and "exploratory" or "research" (33).

From 1945 to 2005, 1200 drugs were reviewed, 121 of which had pharmacogenetic importance, but only 69 were associated with polymorphisms in cytochromes *CYP2D6*, *CYP2C9*, *CYP2C19* and *CYP3A4*. These genetic biomarkers are excellent molecular tools to predict the outcome of drug treatment.

##### 4.2. Genetic variability of CYP450 in different populations

###### 4.2.1. CYP2D6

This enzyme is also called debrisoquine hydroxylase, and its variants are characterized by the metabolism of antidepressants, including selective serotonin reuptake inhibitors, antipsychotic drugs, antiarrhythmics, beta-blockers, analgesics, antiemetics, and antihistamines (34). In 1967, Hammer and F Sjoqvist (35) from the Karolinska Institute were the first to observe variations in the metabolism of carbamazepine, debrisoquine and desipramine/nortriptyline by the enzyme CYP2D6.

The allelic variants associated with poor or slow metabolism are CYP2D6\*3, \*4, \*5 and \*6, and these variants represent 97% of the non-functional variants in Caucasian people (36). Studies of allele frequencies in the Mexican mestizo population determined that *CYP2D6*\*2, \*3, \*4, \*5, \*10 and \*17 are present in 19.34%, 1.44%, 11.21%, 2.67%, 12.4.5% and 1.6.5%, respectively (37, 38). Similar research demonstrated that *CYP2D6*\*4 has a frequency of 17.2% in the European population; *CYP2D6*\*10 occurs with a frequency of 45% in the Chinese population, 42% in the Japanese population, 49.5% in the Malaya population, and less than 3% in the South African Caucasian population; *CYP2D6*\*17 has a frequency of 19.1% in African Americans and of 28.3% in North African populations (39,40,23). Furthermore, pharmacological tests (e.g., dextromethorphan test) have identified the PM phenotype in different populations. Therefore, it is observed that 10% of mestizo Mexicans

have a slow metabolism for this class of drugs, similar to that observed in Caucasian Spaniards (3,37). This phenotype is reported to occur at 3.2% in Mexican Americans (41), at 6.6% in the Colombian population, at 4.4% among *Ngobe* natives of Panama, and at 2.2% among Colombia's Embera (42).

However, variants of CYP2D6 are not associated only with poor or slow metabolism. In 1985, Bertilsson *et al.* described the case of a patient with a surprisingly rapid metabolism of nortriptyline; this patient carried three copies of the CYP2D6 gene (43). This genetic alteration suppressed the pharmacological effect of antidepressants and later was associated with suicide attempts (44,21). In the Mexican mestizo population, duplication of this gene was found in 12.76% of the study sample. Conversely, the variant CYP2D6\*2 in Mexican Amerindian Tepehuanos had a low frequency, reported as 0.20. In addition, a limited range variation had been reported among Mexican Amerindian Purepechas, Tojolobales, Tzotziles and Tzeltles (45).

### 4.2.2. CYP2C9

This enzyme and its variants represent 20% of the members of the superfamily of CYP450. They metabolize coumarin anticoagulants, sulfonylureas, angiotensin II blockers, nonsteroidal anti-inflammatory drugs and the anticonvulsant phenytoin (36,43). CYP2C9\*2 and CYP2C9\*3 are low-metabolism allelic variants, representing approximately 85% of the polymorphisms of this gene and occurring at a frequency of 2-6% in the Caucasian population (43). CYP2C9\*2 has a population frequency of less than 0.5% in East Asians and African Americans, significantly lower than in Caucasians. CYP2C9\*3 has a low frequency of 0.6% in the Mongolian, Japanese, and Chinese populations compared to Caucasians and Africans (44).

### 4.2.3. CYP2C19

CYP2C19 and its variants metabolize inhibitors of the potassium pump, benzodiazepines, tricyclic antidepressants, selective serotonin reuptake inhibitors, barbiturates, antimalarial proguanil, the antiepileptic phenytoin and the antianxiety drug moclobemide (36). Various mutations generate inactive enzymes and are related to the phenotype present in the PM allelic variant CYP2C19\*2 (46). CYP2C19\*2 occurs at 2-5% in Caucasians and Africans and at 6-8% in Asian, European and African populations, corroborating the results of Goldstein *et al.* in populations of Japan and Africa (47,48,49). However, these findings differ from those of Zhou *et al.*, who reported a frequency of 28.9 -31.2 % in an Asian population, significantly higher than the 12.7% in Caucasians and the 18.2% in African Americans (22). Finally, among Brazilians, one of the most genetically heterogeneous populations in the world, the reported frequency was 9.8 % (23). Furthermore, the frequency of CYP2C19\*3 was found to be 10-23% of the Asian population 4.5 and 6.7 % in Caucasians and Africans; as in the previous case, there is a discrepancy with other studies reporting a frequency for this allelic variant of 5.7 -9.6 % in Asian populations and of 0.9 % in Caucasians (23).

In the Mongolian population, the genotypes CYP2C19\*2/\*2, CYP2C19\*2/\*3 and CYP2C19\*3/\*3 have a frequency of 8%, similar to that reported in Asian populations but high compared to Caucasians and Africans, who present a frequency of 2% (43). Interestingly, the CYP2C19\*1 allele, CYP2C19\*2 and the genotype CYP2C19\*1/\*3 are identified as EM in the Chinese population but behave as PM in the Taiwanese population (50). Furthermore, polymorphisms at the CYP2C19\*17 allele (-806C>T and -3402C>T) are identified as FM (23). In particular, the polymorphism -806C>T occurs at a frequency of 22% in the Caucasian population but at 18% in a Dutch-Ethiopian population, and the polymorphism -3402C>T is present at 22% in Caucasians but at only 4% in the Chinese population. The latter polymorphism acts as a fast metabolizer when either the mRNA or the enzyme is overexpressed *in vitro* (50).

### 4.2.4. CYP3A4

The CYP3A family is associated with the metabolism of more than 50% of antiepileptic drugs, as well as steroids, antidepressants, antibiotics, and immunosuppressive agents; the most notable member is CYP3A4 (51,52). In Europe, this isoform is most common in the population of Greece, in which it is expressed at 94.35%, followed by frequencies of 94% in England, 91.7% in the Netherlands, 82% in France, 7% in Portugal, and 5.5% in Spain (25,47). The CYP3A4\*1B allele is the only variant detected in Amerindians of Tepehuano origin from Mexico, with a frequency of 0.08, similar to that observed in Mexican Mestizos (0.088) and Hispanic Americans (0.093 – 0.11) (45).

## 4.3. Metabolism of antiepileptic drugs by CYP

80% of phenytoin ingested by humans is removed through 4'-hydroxylation, mediated primarily by CYP2C9 and to a lesser extent by CYP2C19 (53). However, when the concentration of the anticonvulsant increases, the metabolic contribution of CYP2C19 also increases, suggesting that CYP2C19 is particularly important when the metabolism of phenytoin via CYP2C9 saturates, at therapeutic concentrations of 10-20 mg/L (40-80 mmol/L) (54). However, a recent study showed that CYP3A4 is induced by phenytoin when allelic variants CYP2C9\*2, CYP2C9\*3, and CYP2C19\*2 are present in the individual, with either homozygous or heterozygous, at the fifth day of intake, when therapeutic levels are reached (55). This drug exhibits nonlinear pharmacokinetics, a narrow therapeutic index, and concentration-dependent toxicity, and the rate of elimination of the drug is also age-dependent. Thus, small changes in the activity of CYP2C9 are clinically relevant, including the presence of allelic variants CYP2C9\*2 to CYP2C9\*6, which are related to PM (56,57,58). In clinical practice, it is important to identify these subjects and reduce their average dose to decrease the incidence of adverse effects (48).

Unlike phenytoin, the antiepileptic mephenytoin (specifically the enantiomer (S)-) is only metabolized by CYP2C19. This property characterizes the PM phenotype of CYP2C19 in multiple populations and pharmacological studies because the toxicity of this drug means that it is

now rarely used as an antiepileptic (59). Another antiepileptic whose metabolism depends on CYP2C19 is phenobarbital. Mamiya *et al.* demonstrated that patients with homozygous LM genotypes in CYP2C19 (\*2/\*2 or \*2/\*3) have a lower rate of elimination of phenobarbital than heterozygous patients (\*1/\*2 or \*1/\*3) and, in turn, the latter show a tendency toward lower clearance than EM homozygotes (\*1/\*1) (60). To limit the involvement of CYP2C19, patients with PM genotypes in CYP2C9 (\*2 or \*3) were excluded in this study also participate as ML phenobarbital and if administered in combination with valproic acid because it inhibits p-hydroxylation and N-glycosylation of the drug (61). Valproic acid within the therapeutic range induces the expression of CYP3A4 by the direct activation of constitutive androstane receptor (CAR). Some authors reported the expression of CYP3A4 and its enzyme activity via the activity of the nuclear receptor PXR (pregnane X receptor) (62). Other antiepileptic drugs metabolized by this enzyme are ethosuximide, tiagabine, zonisamide and carbamazepine. Carbamazepine (CBZ) undergoes first-pass metabolism in the gut wall mucosa and the liver with the initial pathways being catalyzed by the enzymes CYP3A4 and CYP2C9/19, respectively, with minor participation of CYP2C8 and CYP3A5 (63,64). Maekawa *et al.* showed that the variant CYP3A4\*16 has a carbamazepine removal rate of 50% less than the reference variant in an *in vitro* system, but the involvement of CYP3A5 is controversial (65). The authors discuss the possibility that other CYP3A family enzymes are involved in carbamazepine metabolism or are induced by the concomitant administration of other drugs (66,67). They also found lowered catalytic activities of the two alleles found in East Asians, CYP3A4\*16 (Thr185Ser) and CYP3A4\*18 (Leu293Pro), for metabolism of some drug substrates, including CBZ compared with wild type allele, CYP3A4\*1 (68). In another study, no association of the CYP3A4\*1B (rs2740574; A > G) with CBZ pharmacokinetics phenotypes within racial groups (African Americans vs. Caucasians) was found. However, the combined cohort patients with the CYP3A4\*1/\*1 genotype had significantly higher CBZ clearance values as compared with patients with at least one CYP3A4\*1B allele (69). The high sequence similarity between the CYP3A4 and CYP3A5 isoforms (> 85% sequence identity) leads to highly similar substrate selectivity between the isoforms (63). A total of 784 genetic variants have been described for CYP3A5; the CYP3A5\*3 allele is the most common of them, causing loss of activity. The CYP3A5\*3/\*3 genotype was associated with a greater CBZ half-life in African Americans; no significant association was observed in Caucasians (67).

### 4.4. Interaction of CYP with new antiepileptic drugs

Pharmacokinetic studies are important for revealing interactions between drugs. The best example is valproic acid, a first-generation antiepileptic drug characterized by inhibition of metabolic enzymes involved in the oxidation of phenobarbital, lamotrigine glucuronidation and conversion of carbamazepine 10,11-epoxide to the corresponding diol (18, 19). In the case of topiramate, a first study evaluating its concomitant use with carbamazepine, phenytoin, and valproate demonstrated that

plasma levels of carbamazepine or its epoxide are not altered, unlike the plasma levels of phenytoin, which increased modestly, and plasma levels of valproate, which decreased slightly. When patients switched from concomitant therapy with phenytoin or carbamazepine to topiramate monotherapy, the rate of elimination of the antiepileptic was reduced by approximately 50%, an adjustment in the dose of topiramate was required (70). Years later, Contin *et al.* studied patients undergoing concomitant therapy with CYP450 inducers (carbamazepine and phenytoin) and noninducing drugs (valproic acid and lamotrigine); their results showed that the rate of elimination of topiramate was 1.5 times higher in conjunction with CYP450 inducers than with noninducing antiepileptic drugs (70,71). Later, the same group performed a similar study with levetiracetam; in this case, the rate of removal of this antiepileptic drug was 1.3 times higher in conjunction with CYP450 inducers than with noninducing antiepileptic drugs (71,72). Furthermore, a recent study by Walzer *et al.* determined the types of interaction between clobazam and antiepileptic phenobarbital, phenytoin, carbamazepine, valproic acid, lamotrigine, oxcarbazepine, and felbamate through a pharmacological study of different CYP isozymes in volunteers and patients diagnosed with Lennox-Gastaut syndrome (73). Their results showed no clinically significant drug interactions between clobazam and drugs metabolized by CYP3A4, CYP2C19, CYP1A2 and CYP2C9, but disputed whether dose adjustment is necessary when drugs metabolized by CYP2D6 are used concomitantly, and, finally, that this drug can be safely used as adjuvant therapy in patients with Lennox-Gastaut syndrome (74). In addition to its connection with drug metabolism CYP2D6 has been associated with certain diseases. Soundararajan *et al.*, in a study of epileptic patients and controls, found a significant association between the 2850C>T polymorphism and the presence of generalized tonic-clonic seizures (68,75).

## 5. SUMMARY AND PERSPECTIVE

Enzymes of the cytochrome P450 superfamily play a fundamental role in the pharmacokinetics of antiepileptic drugs, and the presence of CYP450 polymorphisms in patients with epilepsy is therefore critical in the response to monotherapy, or combined therapy. Understanding the pharmacokinetics of these drugs requires monitoring blood. However, few studies have corroborated the effects, whether therapeutic or toxicological, making them invalid in patients with different metabolic types. Epileptic patients are segmented groups within the population, and although they have the same frequencies of CYP variants as most of the population, this must be corroborated in practice to explain why the participation or induction of unknown CYP isozymes affects antiepileptic treatment.

Given this controversy, we face the quandary of whether to publicize individual studies of polymorphisms, as the type of response will depend on the patient, or to continue the search for new polymorphisms in independent and segmented groups, as their validation requires

correlation with treatment. In either case, the information presented to the patient and the physician should aim to counter the morbidity that occurs during the course of the disease, improve the patients' quality of life, and control the high prevalence of this neurological disorder.

## 6. ACKNOWLEDGMENTS

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**Abbreviations:** CYP: Cytochrome P450, AEDs: antiepileptic drugs, RE: refractory epilepsy, BBB: blood-brain barrier, SNPs: single nucleotide polymorphisms, PHT: phenytoin, MTLE: mesial temporal lobe epilepsy, EM: extensive metabolizers, UM: ultrafast metabolizers, FM: fast metabolizers, PM poor metabolizers, IM: intermediate metabolizers.

**Key Words:** Epilepsy, Pharmacogenetics, CYP450 genes, DNA polymorphism, Alleles, Anticonvulsants, Drug metabolism, Review

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