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Review Article

Carbamazepine Resistance in Epileptic Patients & Its Association with Genetic Polymorphism

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Abstract

Epilepsy is a brain disorder with a lasting tendency to produce epileptic episodes. It carries neurological, cognitive, psychological, and social consequences. Carbamazepine (CBZ) is one of the most widely prescribed antiepileptic drugs. It is first-line therapy to treat partial tonic-clonic seizures, trigeminal, glossopharyngeal neuralgias, and bipolar disorder. The main goal of epilepsy treatment is to avoid seizures without detrimental side effects. Unfortunately, despite appropriate and adequate medication, one-third of the patients do not respond to antiepileptic drugs. Individuals with drug-resistant epilepsy have a higher risk of neurological damage, psychiatric dysfunction, lower quality of life, and even death. For a long time, genetic factors have been known to play a role in the pathophysiology of epilepsy. In parallel, pharmacogenetic factors are also hypothesized to induce drug-resistant epilepsy, with gene polymorphism being one of the most investigated. This review is a collection of studies aimed at investigating resistance to CBZ in epilepsy patients influenced by the polymorphism of genes encoding metabolic enzymes and drug transporters. Pharmacogenetic intervention is likely to improve treatment strategies and pave the way toward personalized medicine for epileptic patients.

Keywords: Epilepsy, carbamazepine resistance, genetic polymorphism, pharmacogenomics

1. Introduction

Acute coronary syndrome Epilepsy is disabling chronic neurologic impairment that has affected over 70 million individuals globally (Thijs et al. 2019). Since the introduction of bromide as an anti-seizure medication in 1857, there has been a significant increase in therapeutic agents for reducing seizures in epileptic patients. Currently, available treatments can help most people to manage epilepsy with fewer side effects and, in some cases, even achieve seizure freedom (Thijs et al. 2019). Treatment decisions are made on the basis of drug safety profile, type of seizure as well as age, sex, genotype, comorbidities, childbearing potential, and collateral use of drugs (Thijs et al. 2019). Of several available antiepileptic drugs, carbamazepine (CBZ) is prescribed most frequently. It is used to treat partial tonic-clonic seizures, trigeminal, glossopharyngeal neuralgias, and bipolar disorder as first-line therapy(Puranik et al. 2013). CBZ is used to treat several seizure disorders and nerve pain. It can be given in combination with an antipsychotic in the case of schizophrenia, which has proven to be a successful medication strategy for bipolar disorder. On the other hand, one-third of epilepsy patients worldwide do not respond to this drug.

Several factors, including genetics, have been proposed to account for this resistance, with single nucleotide polymorphisms (SNPs) being one of the most important. Individual reactions to epilepsy medicines may differ due to modest changes in the structure of ion channels due to genetic diversity in the population (Abe et al. 2008). Patients with drug-resistant epilepsy (DRE) are at higher risk of injury, psychological dysfunction, lower quality of life, and mortality (Löscher et al. 2020).

Several different patterns of resistance can be observed in treatment-refractory patients 1) de novo (or ab initio) anti-seizure resistance (ASD), in which the patient never enters a useful period of seizure-freedom from the onset of epilepsy; 2) delayed resistance, in which the patient initially becomes seizure-free, but seizures recur and become uncontrollable; 3) a waxing-and-waning (or fluctuating) pattern, in which the epilepsy alternates between being controlled and uncontrolled (Löscher et al. 2020). Pharmacoresistance is a major problem associated with antiepileptic drugs (Franco and Perucca 2015). This review article highlights the studies investigating CBZ resistance in epileptic patients and its association with genetic polymorphisms.

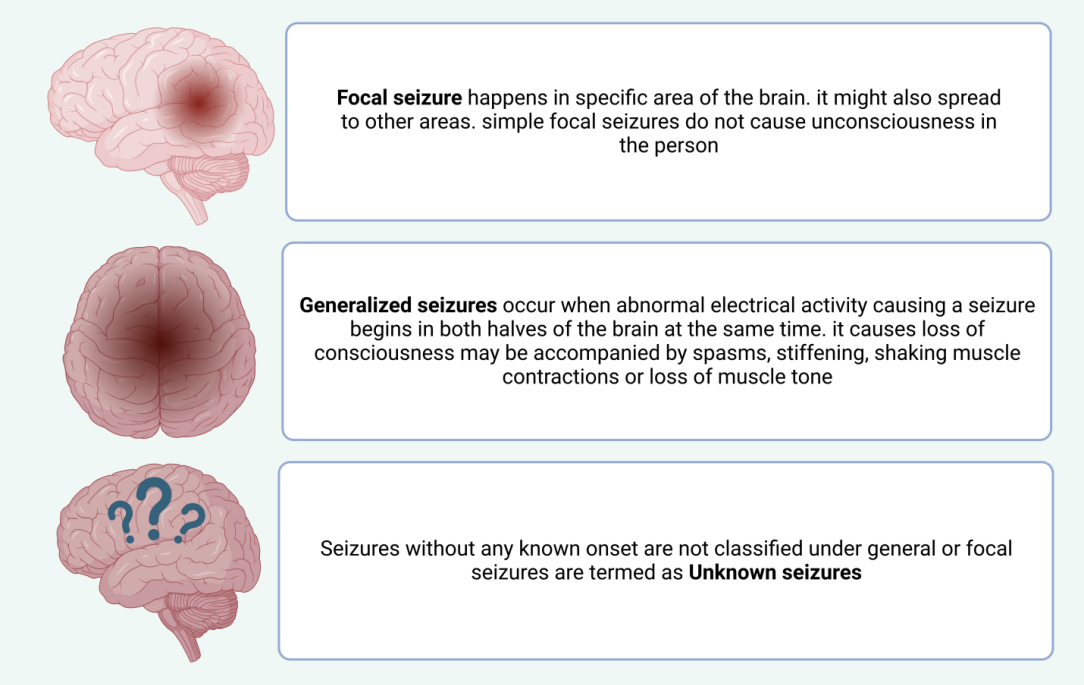

Figure 1 Types of seizures in epilepsy patients (Thijs et al. 2019)

Seizures are classified according to their onset(Falco-Walter, Scheffer, and Fisher 2018). The classification applies to seizures in adults as well as children, except for neonatal seizures (Thijs et al. 2019). Focal seizure is a consequence of abnormal electrical activity originating from one side of the cerebral cortex and proceeding to the other side (Sarmast, Abdullahi, and Jahan 2020). According to an electroencephalogram (EEG), a generalized onset seizure occurs when both hemispheres (possibly asymmetrically) are active simultaneously at the outset of the seizure. When the onset is unknown but other manifestations are recognized, this is referred to as "unknown" onset (figure 1). 'Unclassified' is also a category in seizure classification.

2. Epidemiology

Epilepsy is a chronic neurological illness that affects both sexes and people of all ages,

accounting for around 0.5-1% of the global population. According to studies, the prevalence is greater in low-income nations than in high-income countries, with rates exceeding 80-100 per 100,000 persons each year, while high-income nations have an annual incidence of 50 (range 40-70) per 100,000 people. The distribution is bimodal. About 65-70 million people around the world are affected by this neurological brain disorder. The annual incidence of epilepsy is 67.77 per 100.000, while the incidence rate is 61.44 per 100.000 person-years (Boughrara and Chentouf 2022). The incidence rises with age and peaks around 70 years. Additionally, the occurrence of epilepsy is more frequent in males than females. It primarily affects the elderly and increases the risk of stroke, neurological illness, and malignancies. However, focused seizures are more common in youngsters. A focal impaired awareness seizure is the most prevalent form of the focal seizure (accounting for around 36% of all seizures) (Beghi 2020).

3. Risk Factors for Epilepsy

Most patients have non-genetic epilepsy; the source of the condition is unknown, although genetics are thought to play a role. Common risk factors include any brain damage due to a stroke or brain injury, which may increase the chance of epilepsy. Geographic location is also significant since parasitic diseases such as falciparum malaria, neurocysticercosis, and onchocerciasis are among the most frequent but avoidable risk factors for epilepsy globally(Thijs et al. 2019). A poor healthcare system, poor cleanliness, inadequate basic sanitation, an increased risk of infection, and traumatic brain damage may all play important roles in developing epilepsy (Thijs et al. 2019).

4. Risk Factors for Drug-Resistant Epilepsy

Recurrent seizures, regardless of the cause, expose patients to a variety of physical, psychological, and social morbidities. By completely controlling seizures, these disadvantages can be prevented to a significant extent. The ultimate objective of antiepileptic medication is to eliminate seizures. As a result, while the majority of patients diagnosed with epilepsy are likely to achieve good seizure control with antiepileptic drugs (AEDs), a subset of them continues to have seizures despite taking a variety of AEDs in adequate doses either singly or in combination, and their seizures are also more frequently associated with intractability(Xue-Ping et al. 2019).

5. Carbamazepine Pharmacodynamics and Pharmacokinetics

CBZ inhibits action potentials and reduces synaptic transmission by modulating voltage-gated sodium channels (VGSC). CBZ, like many other anticonvulsants, is thought to bind to the alpha subunit of VGSC, specifically at a binding pocket created by the external pore loop and the pore-lining section of domain IV. Researchers hypothesized that CBZ keeps sodium channels inactive, causing fewer channels to open, thereby inhibiting the production of action potentials (figure 2). CBZ also binds to other voltage-gated ion channels, such as the voltage-gated calcium channel.

About 80 % of CBZ is absorbed after oral ingestion, while 85-75 % binds to plasma protein. It undergoes metabolism by activating hepatic enzymes cytochrome P450. CBZ is primarily metabolized to carbamazepine 10-11 (CBZ-E) epoxide via hepatic CYP3A4 and CYP2C8 metabolism. CBZ -E is further metabolized to inactive carbamazepine -10,11-trans dihydrodiol by EPHX1, which is ultimately secreted in the urine(Puranik et al. 2013). Since it is an enzyme inducer, CBZ interacts with several medicines that are processed by the liver(Sankaraneni and Lachhwani 2015).

6. Indications of CBZ

CBZ and oxcarbazepine are prescribed as the first drug of choice for partial seizures, while absence seizures are not treated with CBZ. Moreover, FDA has approved CBZ as a first-line therapy for trigeminal neuralgia or tic douloureux. A systematic study demonstrated the effectiveness of CBZ extended-release in individuals with acute manic or mixed episodes of bipolar I mania (Maan and Saadabadi 2021). CBZ is sometimes used off-label to treat bipolar disorder. In a comparative trial with CBZ, lithium, and valproic acid, patients using CBZ had increased incidences of recurrence, although not to a significant level (Maan and Saadabadi 2021).

7. Therapeutic Drug Monitoring

CBZ plasma level is directly correlated with dose, therapeutic effect, and side effects. CBZ monotherapy is one of the most frequently prescribed antiepileptic drug therapies. It is especially preferred for well-tolerability regarding weight gain and adverse metabolic concerns. The efficiency of learning new information and memory-scanning rate displays a concentration-dependent relationship with CBZ level. Poor performance is significantly associated with higher plasma concentrations; therefore, plasma level monitoring may help prevent unnecessary concentration-dependent cognitive decline by keeping plasma levels at the lower therapeutic range. Once seizures are controlled, plasma levels of the drug should be measured to establish optimum levels for patients being treated(Panday et al. 2017).

8. Carbamazepine Resistance

Drug-resistant or refractory epilepsy is defined as the inability of a patient to experience persistent seizure independence, following treatment with two antiepileptic medications that have been properly selected and used (Zybina et al. 2018). Antiepileptic medication CBZ is prescribed as the first-line medication for focal or generalized tonic-clonic epileptic seizures all over the world (Zhao et al. 2021, Zhao et al. 2019). Most patients can effectively manage their seizures with AEDs, while up to 20–25% of individuals do not respond to antiepileptic therapy (Zhao et al. 2019). Medication resistance occurring in epileptic patients is deteriorating epileptic patterns. There could be many reasons for resistance to therapy, as illness, inflammatory processes, pharmacokinetic periphery, and morphological abnormalities all play a role in drug resistance while treating an epileptic patient. Moreover, AEDs do not penetrate the brain as effectively as they should. Other explanations could include that ion channels and neurotransmitter receptors—which serve as the primary targets of AEDs—have acquired structural and/or functional changes, or there is an innate resistance brought on by genetic variations in proteins involved in the pharmacokinetics and pharmacodynamics of AEDs action (Zybina et al. 2018).

9. Genetic Polymorphism & CBZ Resistance

As discussed earlier, environmental factors, concurrent medications, and genetic variation may contribute to the inter-individual variability of CBZ treatment response. Genetic variation of drug-metabolizing enzymes has gathered much attention recently and has been hypothesized to have a significant impact on drug therapy for epilepsy (Zhao et al. 2019). Pharmacokinetics and pharmacodynamics of therapeutic drugs, pollutants, and toxins primarily depend on phase I and phase II metabolizing enzymes and drug transporters. Consequently, any variation in genes encoding these enzymes and transporter could alter the efficacy and therapeutic response to drugs processed by them, making them interesting avenues for investigating inter-individual variability (Table 1).

Table 1: Pharmacogenetics studies showing influence of genetic variation on the efficacy of carbamazepine.

Gene	SNP	Association	Reference
ABCB1	rs*1045642*	*ABCB1* or *P-gp* activity was found to be responsible for the altered response of CBZ	(Taur et al. 2014)
ABCG2	rs2231137	*ABCG2* polymorphism is associated with drug resistance	(Mousavi et al. 2022)
CYP3A5	rs776746	Poorly metabolizes CBZ, thus elevating the drug's toxicity level and adverse effects.	(Ganesapandian et al. 2019, Al-Gahtany, Karunakaran, and Munisamy 2014, Meng et al. 2011)
	rs15524-rs776746	A significant association was present	(Wang et al. 2015)
	rs776746	A significant association was present	(Zhao et al. 2021)
CYP3A4	rs2242480	Association is present	(Zhao et al. 2021)
	rs35599367	Positive association is observed	(Chbili et al. 2016)
CYP2C9	rs1799853, rs1057910	May be responsible for drug resistance	(Maqbool et al. 2022)
EPHX1	rs1051740, rs35599367	Association is present	(Makmor-Bakry et al. 2009)
	rs1051740	Required higher maintenance dos as compared to wild type	(Hung et al. 2012)
	rs1051740	Association is present	(He et al. 2014)
	rs1051740, rs35599367	Association is present	(Chbili et al. 2016)
	rs1051740	Association is present	(Daci et al. 2015)
	rs1051740, rs35599367	No association was observed	(Caruso et al. 2014)
SCN1A	rs3812718	association between resistance to CBZ therapy and the *SCN1A* polymorphism	(Abe et al. 2008)
	rs3812718, rs2298771	*SCN1A* rs2298771 polymorphism showed no association with CBZ metabolism or resistance	(Zhao et al. 2021)
	rs2298771, rs17183814	Associated with carbamazepine resistance	(Nazish, Ali, and Ullah 2018)
	rs3812718	Carriers required higher CBZ maintenance dosage than non-carriers	(Hung et al. 2012)
	rs3812718	No association was observed	(Namazi et al. 2015)
UGT2B7	rs7439366	Steady-state concentration of CBZ was significantly associated	(Lu et al. 2018)
	rs12233719	No association	(Lu et al. 2018)

9.1 ABCB1

Inter-individual variability in drug response can be attributed to genetic polymorphism in genes encoding different drug transporters. Therefore, (Taur et al. 2014) conducted a study to find the impact of genetic variation in the ATP binding cassette subfamily B member 1 (*ABCB 1*) gene that encodes transporter protein. Patients on antiepileptic therapy, including CBZ, were grouped as responders and non-responder as per criteria mentioned by International League against Epilepsy. High-performance liquid chromatography (HPLC) was used to determine plasma concentration. Flow cytometry using rhodamine efflux was used to measure the activity of P-glycoprotein. Polymorphism of *ABCB1* (C3435T) was studied using the polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP). The presence of C3435T in *ABCB1* or P-gp activity was found to be responsible for the altered response of CBZ.

9.2 ABCG2

As mentioned earlier, the ABC transporter family is critically implicated in transporting therapeutic agents across the blood-brain barrier (BBB) throughout the CNS. ABCG2 transporter encoded by the *ABCG2* gene having locus on chromosome 4q22 belongs to the ABC superfamily. The variation in genes encoding this transporter could alter the penetration of drugs and bioavailability in CNS (Vasiliou, Vasiliou, and Nebert 2009). Ninety-three Iranian patients aged between 1.5 to 14 years were enrolled in a study to evaluate the association between *ABCG2* gene polymorphs and resistance to antiepileptic therapy. Forty-six children with drug-resistant epilepsy were genotyped for *ABCG2* (rs2231137) polymorphisms using high-resolution melting (HRM) method. A positive association between *ABCG2* polymorphism and resistance to antiepileptic therapy in children was observed (Mousavi et al. 2022).

9.3 CYP3A5

Various enzymes metabolize antiepileptic drugs, among which the CYP P450 family has garnered significant attention. Some of the CYPs exist as genetic (allelic) variants, which may also affect plasma concentrations or drug exposure (Garcia et al. 2014). CBZ metabolism depends largely on CYP3A5. Therefore, *CYP3A5* genetic polymorphism is found to significantly impact the therapeutic outcome of CBZ. Frequently reported nonfunctional variant, *CYP3A5*3* (6986A>G rs776746) allele poorly metabolizes CBZ, thus elevating the toxicity level and adverse effects of the drug (Ganesapandian et al. 2019, Al-Gahtany, Karunakaran, and Munisamy 2014, Meng et al. 2011). Similarly, 88 epileptic patients in China were recruited from Xiangya Hospital Central South University and genotyped to evaluate the association between the genetic polymorphisms of rs15524 and rs776746 in the *CYP3A5* gene and concentrations of CBZ in plasma. They found a significant association of rs15524-rs776746 GT, AC haplotype, with dose-adjusted CBZ plasma concentration (Wang et al. 2015). These studies are supported by a meta-analysis, which shows evidence of association between gene polymorphs of *CYP3A5* (rs776746) , and efficacy of CBZ (Zhao et al. 2021). Such findings could be beneficial in improving the individualized treatment of epileptic patients in clinical settings.

9.4 CYP3A4

According to a meta-analysis that included 18 studies and 2574 patients, significant associations are present between *CYP3A4* (rs2242480) and plasma concentrations of CBZ (Zhao et al. 2021). (Chbili et al. 2016) investigated the impact of polymorphisms in the *CYP3A4*22* (rs35599367) genes involved in CBZ metabolism. They found a significant association of the *CYP3A4*22* variant allele with a lower CBZ-D: CBZ-E ratio.

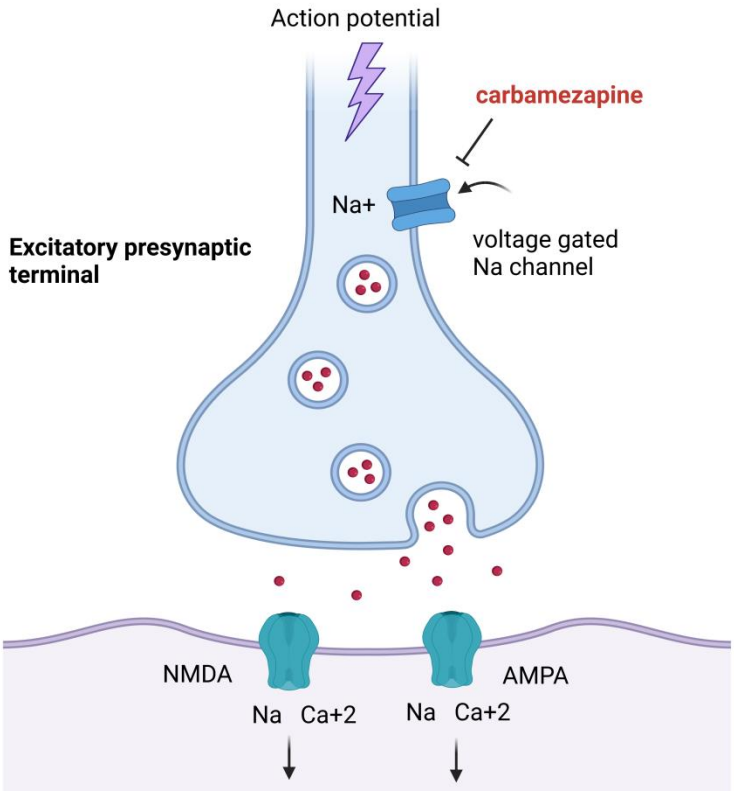

Figure 2 Mechanism of action of carbamazepine.

9.5 CYP2C9

(Maqbool et al. 2022) designed a study comprising 337 subjects from the Pakistani population, of which 100 were control subjects. One hundred twenty-seven responded to antiepileptic drug therapy, while 110 subjects showed drug resistance. The study aimed to investigate the *CYP2C9* gene polymorphism associated with AEDs resistance. Blood was collected for genomic DNA isolation, and PCR was utilized to amplify rs1799853 (430C > T) and rs1057910. Sanger's sequencing was used for genotyping of *CYP2C9*. The researchers concluded that rs1799853 and rs1057910 may be involved in drug resistance in the Pakistani population.

9.6 EPHX1

Human microsomal epoxide hydrolase *(mEH)* is encoded by Human Epoxide Hydrolase1 (*EPHX1*) gene located on chromosome 1 at q42.1, containing nine exons spanning approximately 35.471 kbps. The expression of the *EPHX1* gene is highly polymorphic and may change the catalytic activity and expression level of mEH (Hu et al. 2021). (Makmor-Bakry et al. 2009) found a significant association of (c.337T>C, c.416A>G) of the *EPHX1* gene with the maintenance dose of CBZ in a study conducted on 70 epileptic patients. However, the sample size was too small and needs further investigation to be carried out on a larger sample size. (Hung et al. 2012) conducted a study in which patients with the variant EPHX1 (c.337T>C rs1051740) compared to wild-types required higher maintenance dose, and the same trend was observed in homozygous variant carriers.

Moreover, (He et al. 2014) found a significant association between *EPHX1* c.337T>C polymorphisms and the development of CBZ-related adverse effects such as Steven Johnson syndrome and toxic epidermal necrolysis in Han ethnicity living in northeastern China. They concluded that *EPHX1* c.337T>C polymorphisms are responsible for increased CBZ metabolite concentration and may be

linked to the development of adverse effects in epileptic patients on CBZ therapy. In addition, (Chbili et al. 2016) evaluated the impact of polymorphisms in the *EPHX1* genes (c.416A > G, c.337T > C) and CBZ metabolism in 118 Tunisian patients with epilepsy under the maintenance dose of CBZ. Both variants of *EPHX1 c.416A > G* and *c.337T > C* are significantly associated with a higher metabolic ratio CBZ-D: CBZ-E and seem to decrease the epoxide hydrolase activity. The above findings are further corroborated by (Daci et al. 2015), who evaluated the effects of gene variants in the *EPHX1* gene influencing the pharmacodynamics and pharmacokinetics of CBZ and the response in patients with epilepsy. They recruited 145 epileptic patients on CBZ monotherapy. When compared to common alleles *EPHX1* c.337T>C rs1051740) variant presented a significantly lower plasma level of CBZ.

On the other hand, (Caruso et al. 2014) showed conflicting results. They investigated the association between two genetic polymorphisms in the coding regions (exon 3 and exon 4) of the *EPHX1* gene, i.e., 337T>C and 416A>G, and the metabolism of CBZ 10, 11-epoxide by monitoring the variation in CBZ 10.11 epoxide in serum after 4 hours of administration. They deduced a lack of association between the *EPHX1* gene polymorphism and metabolism of CBZ.

9.7 SCN1A

Activation of VGSC leads to the initiation of depolarization in the neuronal cells. Therefore, these channels are ideal targets for AEDs like CBZ (Remy and Beck 2006). The α-subunit of VGSC targeted by CBZ is encoded by *SCN1A* and *SCN2A* genes (Abe et al. 2008). To find interdependence of *SCN1A* IVS5-91 G > A polymorphism of the *SCN1A* gene on effectiveness of CBZ, blood samples were taken for genotyping from 228 Japanese epileptic patients. AA genotype frequency was significantly higher in epileptic patients resistant to CBZ therapy. This pinpoints a significant association between resistance to CBZ therapy and *SCN1A* polymorphism (Abe et al. 2008).

(Zhao et al. 2021*) found SCN1A* rs3812718 A allele was significantly associated with decreased CBZ plasma concentration and increased CBZ resistance. However, *SCN1A* rs2298771 polymorphism showed no association with CBZ metabolism or resistance.

In Pakistan, 93 epileptic patients who were poor responders to CBZ therapy but without any other comorbidity were enrolled in a study. The aim was to find any connection between *SCN1A* and *SCN2A* gene polymorphisms and response to CBZ treatment. HPLC was used to monitor CBZ plasma levels. *SCN1A* and *SCN2A* genes were genotyped using restriction fragment length polymorphism (RFLP*)*. The researchers found a significant association between the *SCN1A (3184 AG* and *GG)* and *SCN2A (56GA* and *AA)* genotypes with CBZ treatment resistance (Nazish, Ali, and Ullah 2018).

In line with this, (Hung et al. 2012) stated that carriers of the variant SCN1A IVS5–91 G>A (rs3812718) allele tended to require higher CBZ maintenance dosage than non-carriers and the homozygous variant carriers showed the same trend.

Conversely, results obtained from another study conducted in Iran that recruited 70 epileptic patients treated with CBZ for at least six months showed no association between *SCN1A* gene polymorphisms and plasma levels of CBZ and its active metabolite (Namazi et al. 2015).

9.8 ***UGT2B7***

UGT2B7 enzyme is responsible for the glucuronidation of CBZ and its active metabolite CBZ 10.11 epoxide. A known polymorph of this enzyme, *UGT2B7**2 (802C>T; rs7439366), that arises from a C to T trans version at nucleotide 802 of the *UGT2B7* coding region can alter drug response. To investigate this polymorphism's possible association with CBZ therapy's response, 62 epileptic patients were recruited. The results indicated that steady-state concentration of CBZ was significantly

associated with *UGT2B7**2 SNP. *UGT2B7**1/*2 and *2*/2 patients exhibited lower normalized CBZ concentrations and larger CBZ dose requirements than the wild-type subjects. Moreover, they found that the steady-state concentration remains unaffected by *UGT2B7**3 (211G>T; rs12233719) gene polymorphism. On the contrary, other studies did not find any association between drug levels and *UGT2B7* polymorphisms (Lu et al. 2018).

10 Conclusions & Recommendations

Numerous studies have been carried out to evaluate the influence of polymorphism in genes. These studies investigated genes implicated in the metabolic pathway of CBZ, its response, and adverse effects and are compiled in this review. More than 40 anti-seizure drugs are approved to treat epilepsy, either alone or in various combinations. However, about one-third of epilepsy patients are unable to gain benefit from pharmacotherapy. A number of ideas have explained the drug-resistant phenotype, pharmacogenomics being one of them. By exploring the effect of genetic polymorphisms on the pharmacokinetics and pharmacodynamics of CBZ, individualized therapy based on the unique genetic makeup of epileptic patients could be practiced in clinics. This approach would aid in avoiding the adverse effects of drugs along with improved drug response. Our comprehensive study suggests that implementing individualized medicine in clinical settings is a major challenge. There is a massive knowledge gap that should be filled by designing studies with large sample sizes, correct interpretation of the associations, improving the predictive tools for *in-silico* and *in-vitro* studies, and developing of large bio-bank containing information for researchers to study the relationship between genotype and phenotype.

Conflict of Interest

The authors declare that they have no competing interests.

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Study Approval

NA

Consent Forms

NA

Authors Contribution

JM conceptualized the study and wrote the final manuscript, HHB and ZZ helped in the analysis and writing the first draft, ZBM did the literature review, and JM supervised the whole project.

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References

Abe, T., T. Seo, T. Ishitsu, T. Nakagawa, M. Hori, and K. Nakagawa. 2008. "Association between SCN1A polymorphism and carbamazepine-resistant epilepsy." *Br J Clin Pharmacol* no. 66 (2):304-7. doi: 10.1111/j.1365-2125.2008.03203.x.

Al-Gahtany, Mubarak, Gauthaman Karunakaran, and Murali Munisamy. 2014. "Pharmacogenetics of CYP3A5 on Carbamazepine pharmacokinetics in epileptic patients developing toxicity." *BMC Genomics* no. 15 (2):P2. doi: 10.1186/1471-2164-15-S2-P2.

Beghi, Ettore. 2020. "The epidemiology of epilepsy." *Neuroepidemiology* no. 54 (2):185-191.

Boughrara, Wefa, and Amina Chentouf. 2022. "The ABCB1, ABCC2 and RALBP1 polymorphisms are associated with

carbamazepine response in epileptic patient: a systematic review." *Acta Neurologica Belgica* no. 122 (4):871-880.

Caruso, A., C. Bellia, A. Pivetti, L. Agnello, F. Bazza, C. Scazzone, G. Bivona, B. Lo Sasso, and M. Ciaccio. 2014. "Effects of EPHX1 and CYP3A4 polymorphisms on carbamazepine metabolism in epileptic patients." *Pharmgenomics Pers Med* no. 7:117-20. doi: 10.2147/pgpm.s55548.

Chbili, C., N. Fathallah, A. Laouani, M. Nouira, A. Hassine, S. Ben Amor, S. Ben Ammou, C. Ben Salem, and S. Saguem. 2016. "Effects of EPHX1 and CYP3A4*22 genetic polymorphisms on carbamazepine metabolism and drug response among Tunisian epileptic patients." *J Neurogenet* no. 30 (1):16-21. doi: 10.3109/01677063.2016.1155571.

Daci, Armond, Giangiacomo Beretta, Driton Vllasaliu, Aida Shala, Valbona Govori, Giuseppe Danilo Norata, and Shaip Krasniqi. 2015. "Polymorphic variants of SCN1A and EPHX1 influence plasma carbamazepine concentration, metabolism and pharmacoresistance in a population of Kosovar Albanian epileptic patients." *PLoS One* no. 10 (11):e0142408.

Falco-Walter, Jessica J, Ingrid E Scheffer, and Robert S Fisher. 2018. "The new definition and classification of seizures and epilepsy." *Epilepsy research* no. 139:73-79.

Franco, Valentina, and Emilio Perucca. 2015. "The pharmacogenomics of epilepsy." *Expert review of neurotherapeutics* no. 15 (10):1161-1170.

Ganesapandian, M., K. Ramasamy, S. Adithan, and S. K. Narayan. 2019. "Influence of cytochrome P450 3A5 (CYP3A5) genetic polymorphism on dose-adjusted plasma levels of carbamazepine in epileptic patients in South Indian population." *Indian J Pharmacol* no. 51 (6):384-388. doi: 10.4103/ijp.IJP_122_19.

Garcia, Miguel, Iris Feria-Romero, Hector Serrano, David Escalante-Santiago, Israel Grijalva, and Sandra Orozco-Suárez. 2014. "Genetic polymorphisms associated with antiepileptic metabolism." *Frontiers in bioscience (Elite edition)* no. 6:377-386.

He, X. J., L. Y. Jian, X. L. He, M. Tang, Y. Wu, Y. Y. Xu, X. J. Sun, and L. M. Zhao. 2014. "Association of ABCB1, CYP3A4, EPHX1, FAS, SCN1A, MICA, and BAG6 polymorphisms with the risk of carbamazepine-induced Stevens-Johnson syndrome/toxic epidermal necrolysis in Chinese Han patients with epilepsy." *Epilepsia* no. 55 (8):1301-6. doi: 10.1111/epi.12655.

Hu, Ting, Xiaoxi Zeng, Tian Tian, and Jinping Liu. 2021. "Association of EPHX1 polymorphisms with plasma concentration of carbamazepine in epileptic patients: Systematic review and meta-analysis." *Journal of Clinical Neuroscience* no. 91:159-171. doi: https://doi.org/10.1016/j.jocn.2021.07.009 .

Hung, C. C., W. L. Chang, J. L. Ho, J. J. Tai, T. J. Hsieh, H. C. Huang, Y. W. Hsieh, and H. H. Liou. 2012. "Association of polymorphisms in EPHX1, UGT2B7, ABCB1, ABCC2, SCN1A and SCN2A genes with carbamazepine therapy optimization." *Pharmacogenomics* no. 13 (2):159-69. doi: 10.2217/pgs.11.141.

Löscher, Wolfgang, Heidrun Potschka, Sanjay M Sisodiya, and Annamaria Vezzani. 2020. "Drug resistance in epilepsy: clinical impact, potential mechanisms, and new innovative treatment options." *Pharmacological reviews* no. 72 (3):606-638.

Lu, Q., Y. T. Huang, Y. Shu, P. Xu, D. X. Xiang, Q. Qu, and J. Qu. 2018. "Effects of CYP3A5 and UGT2B7 variants on

steady-state carbamazepine concentrations in Chinese epileptic patients." *Medicine (Baltimore)* no. 97 (30):e11662. doi: 10.1097/md.0000000000011662.

Maan, Jasdave S, and Abdolreza Saadabadi. 2021. "Carbamazepine." In *StatPearls [Internet]*. StatPearls Publishing.

Makmor-Bakry, M., G. J. Sills, N. Hitiris, E. Butler, E. A. Wilson, and M. J. Brodie. 2009. "Genetic variants in microsomal epoxide hydrolase influence carbamazepine dosing." *Clin Neuropharmacol* no. 32 (4):205-12. doi: 10.1097/WNF.0b013e318187972a.

Maqbool, Hafsa, Tayyaba Saleem, Nadeem Sheikh, and Aqsa Ashfaq. 2022. "Genetic Analysis of CYP2C9 with Reference to Drug Response in Epilepsy Patients of Pakistan." *Genetics Research* no. 2022:1451007. doi: 10.1155/2022/1451007.

Meng, Hongmei, Jinyan Ren, Yudan Lv, Weihong Lin, and Yingjie Guo. 2011. "Association study of CYP3A5 genetic polymorphism with serum concentrations of carbamazepine in Chinese epilepsy patients." *Neurology Asia* no. 16 (1):39-45.

Mousavi, Seyedeh Farnaz, Kazem Hasanpour, Milad Nazarzadeh, Abolfazl Adli, Malihe Sadat Bazghandi, Alireza Asadi, Abolfazl Rad, and Omid Gholami. 2022. "ABCG2, SCN1A and CYP3A5 genes polymorphism and drug-resistant epilepsy in children: A case-control study." *Seizure - European Journal of Epilepsy* no. 97:58-62. doi: 10.1016/j.seizure.2022.03.009.

Namazi, Soha, Negar Azarpira, Katayoon Javidnia, Mehrdad Emami, Rahimeh Rahjoo, Razieh Berahmand, and Afshin Borhani-Haghighi. 2015. "SCN1A and SCN1B gene polymorphisms and their association with plasma concentrations of carbamazepine and carbamazepine 10, 11 epoxide in Iranian epileptic patients." *Iranian Journal of Basic Medical Sciences* no. 18 (12):1215.

Nazish, H. R., N. Ali, and S. Ullah. 2018. "The possible effect of SCN1A and SCN2A genetic variants on carbamazepine response among Khyber Pakhtunkhwa epileptic patients, Pakistan." *Ther Clin Risk Manag* no. 14:2305-2313. doi: 10.2147/tcrm.s180827.

Panday, D Raj, KR Panday, M Basnet, S Kafle, B Shah, and GP Rauniar. 2017. "Therapeutic drug monitoring of carbamazepine." *Int J Neurorehabilitation Eng* no. 4 (245):2376-0281.

Puranik, Yogita Ghodke, Angela K Birnbaum, Susan E Marino, Ghada Ahmed, James C Cloyd, Rory P Remmel, Ilo E Leppik, and Jatinder K Lamba. 2013. "Association of carbamazepine major metabolism and transport pathway gene polymorphisms and pharmacokinetics in patients with epilepsy." *Pharmacogenomics* no. 14 (1):35-45.

Remy, Stefan, and Heinz Beck. 2006. "Molecular and cellular mechanisms of pharmacoresistance in epilepsy." *Brain* no. 129 (1):18-35.

Sankaraneni, Ram, and Deepak Lachhwani. 2015. "Antiepileptic drugs—a review." *Pediatric annals* no. 44 (2):e36-e42.

Sarmast, S. T., A. M. Abdullahi, and N. Jahan. 2020. "Current Classification of Seizures and Epilepsies: Scope, Limitations and Recommendations for Future Action." *Cureus* no. 12 (9):e10549. doi: 10.7759/cureus.10549.

Taur, SR, NB Kulkarni, PP Gandhe, BK Thelma, SH Ravat, NJ Gogtay, and UM Thatte. 2014. "Association of polymorphisms of CYP2C9, CYP2C19, and ABCB1, and activity of P-glycoprotein with response to antiepileptic drugs." *Journal of Postgraduate Medicine* no. 60 (3):265.

Thijs, Roland D., Rainer Surges, Terence J. O'Brien, and Josemir W. Sander. 2019. "Epilepsy in adults." *The Lancet* no. 393 (10172):689-701. doi: 10.1016/S0140-6736(18)32596-0.

Vasiliou, V., K. Vasiliou, and D. W. Nebert. 2009. "Human ATP-binding cassette (ABC) transporter family." *Hum Genomics* no. 3 (3):281-90. doi: 10.1186/1479-7364-3-3-281.

Wang, Ping, Tao Yin, Hong-Ying Ma, Dan-Qi Liu, Yang-Hao Sheng, Can Wang, and Bo-Ting Zhou. 2015. "Effects of CYP3A4/5 and ABCB1 genetic polymorphisms on carbamazepine metabolism and transport in Chinese patients with epilepsy treated with carbamazepine in monotherapy and bitherapy." *Epilepsy Research* no. 117:52-57. doi: https://doi.org/10.1016/j.eplepsyres.2015.09.001.

Xue-Ping, Wang, Wang Hai-Jiao, Zhu Li-Na, Da Xu, and Liu Ling. 2019. "Risk factors for drug-resistant epilepsy: A systematic review and meta-analysis." *Medicine* no. 98 (30).

Zhao, Gui-Xin, Ming-Li Shen, Zheng Zhang, Ping Wang, Chun-Xiang Xie, and Gong-Hao He. 2019. "Association between EPHX1 polymorphisms and carbamazepine metabolism in epilepsy: a meta-analysis." *International journal of clinical pharmacy* no. 41 (6):1414-1428.

Zhao, Gui-Xin, Zheng Zhang, Wen-Ke Cai, Ming-Li Shen, Ping Wang, and Gong-Hao He. 2021. "Associations between CYP3A4, CYP3A5 and SCN1A polymorphisms and carbamazepine metabolism in epilepsy: a meta-analysis." *Epilepsy Research* no. 173:106615.

Zybina, Anna, Anastasiya Anshakova, Julia Malinovskaya, Pavel Melnikov, Vladimir Baklaushev, Vladimir Chekhonin, Olga Maksimenko, Sergey Titov, Vadim Balabanyan, and Jörg Kreuter. 2018. "Nanoparticle-based delivery of carbamazepine: A promising approach for the treatment of refractory epilepsy." *International Journal of Pharmaceutics* no. 547 (1-2):10-23.