Pharmacogenomics and personalization of Epilepsy treatment

Giovanna Leal Cruz Santos

Marcelle de Castro Baraky

Rafaianne Santos Veloso,

Fernanda de Souza Matos

Amanda Torres de Freitas

ABSTRACT
Epilepsy is a chronic neurological condition that affects millions of people worldwide. Conventional treatment of epilepsy involves the prescription of antiepileptic drugs (MAEs), but the response to these drugs varies considerably between individuals. Pharmacogenomics, which focuses on the study of the genetic variations that influence drug response, has emerged as a powerful tool in personalizing epilepsy treatment. This article reviews the advances and challenges of pharmacogenomics applied to epilepsy. First, the identification of genetic markers associated with response to MAEs is discussed, highlighting the importance of genetic polymorphisms in genes related to MAE metabolism and transport. These genetic markers allow doctors to more accurately predict how a patient will respond to a specific MAE. Next, the development of personalized dosing strategies based on the patient's genetic profile is addressed. These strategies have the potential to optimize treatment efficacy and minimize side effects by ensuring that each patient receives the appropriate dose of MAEs according to their individual metabolic capacity. In addition, the role of genetic-based clinical decision support tools, such as algorithms and artificial intelligence systems, in translating genetic information into practical recommendations for physicians is highlighted. However, the path to full implementation of pharmacogenomics in epilepsy faces challenges, such as the need for affordable genetic testing and continuing medical education on pharmacogenomics. Ethical and privacy issues related to the use of genetic information also require careful attention. In summary, pharmacogenomics offers the promise of more effective and personalized therapies for patients with epilepsy. As research advances and tools become more accessible, pharmacogenomics are expected to play a crucial role in improving the quality of life for patients with epilepsy and optimizing the clinical management of this complex condition.

Keywords: Epilepsy, Pharmacogenomics, Antiepileptic drugs, Genetic markers, Personalized dosing.

1 INTRODUCTION

Epilepsy, a chronic neurological disease characterized by recurrent epileptic seizures, affects millions of people worldwide. Conventional treatment of epilepsy often involves the prescription of antiepileptic drugs (AEMs), which aim to control seizures and improve patients' quality of life. However, the response to MAEs can vary substantially from one individual to another, leading to significant challenges in clinical management. The quest for personalization of epilepsy treatment has become a priority, and this is where pharmacogenomics plays a crucial role.

Pharmacogenomics is a discipline that focuses on the study of how individual genetic variations influence the response to drugs. In a clinical setting, this means that pharmacological treatment can be tailored to the genetic characteristics of each patient, allowing for a more precise and effective approach. Pharmacogenomics applied to epilepsy offers the promise of identifying genetic markers that can predict response to specific MAEs and aid in the choice of the most appropriate treatment.

Research in this area has led to significant discoveries, such as the identification of polymorphisms in genes related to the metabolism and transport of MAEs that may affect the efficacy and safety of these drugs. Studies, such as those conducted by Kwan and Brodie (2000) and Tate et al. (2005), have highlighted the importance of these genetic markers in the prescription of MAEs and demonstrated how considering the patient's genetics can improve therapeutic outcomes.

In addition, personalized dosing strategies based on the patient's genetic profile have been explored in studies such as those by Cavalleri et al. (2007) and Kasperavičiūtė et al. (2010). These strategies have the potential to optimize treatment effectiveness, reduce side effects, and minimize risks by ensuring that each patient receives the appropriate dose of MAEs based on their individual metabolic capacity.

Technological evolution and ongoing research have also led to the development of genetics-based clinical decision support tools, such as algorithms and AI systems, that can translate complex genetic information into practical recommendations for clinicians. Research by Higgs et al. (2014) and Dubois et al. (2021) exemplifies progress in this area, demonstrating how these tools can assist healthcare providers in choosing and appropriate dosing of MAEs.

Therefore, this review will comprehensively address pharmacogenomics applied to the treatment of epilepsy, exploring the main advances, challenges, and clinical implications of this personalized approach. The goal is to provide a detailed look at how genetics can transform the way we approach the treatment of epilepsy, promoting more effective therapy and improving patients' quality of life.

2 METHOD

2.1 SEARCH STRATEGY

To understand the impact of pharmacogenomics on personalizing epilepsy treatment, we conducted an extensive review of the literature. The search included the PubMed, Scopus and Web of Science databases, using search terms such as "pharmacogenomics", "epilepsy", "personalized treatment" and other related terms. Studies published up to September 2021, focusing on human research and articles in Portuguese and English, were considered.

3 RESULTS

The review revealed a number of studies exploring the relationship between pharmacogenomics and the treatment of epilepsy. These studies cover a variety of areas, from identifying genetic markers associated with response to MAEs to implementing personalized dosing strategies based on the patient's genetic profile. Below, we highlight the main findings grouped by type of intervention, target population, and outcome.

3.1 IDENTIFICATION OF GENETIC MARKERS ASSOCIATED WITH RESPONSE TO MAES IN EPILEPSY

Pharmacogenomics has revolutionized the approach to the treatment of epilepsy, allowing for a deeper understanding of individual variations in response to antiepileptic drugs (MAEs). The identification of genetic markers associated with response to MAEs has emerged as a crucial area of research. These markers are specific genetic variants that may influence the efficacy and safety of MAEs in patients with epilepsy. In this context, several studies have played a key role in identifying these markers, providing valuable insights for treatment personalization.

Remarkable research by Kwan and Brodie (2000) revealed the role of polymorphism in the CYP2C9 gene in the metabolization of phenytoin, a widely used MAE. This discovery demonstrated that patients with certain genetic variants of this gene may experience slower metabolization of phenytoin, leading to elevated levels of the drug in the blood and increasing the risk of side effects (Kwan & Brodie, 2000). This is just one of many findings underscoring the importance of pharmacogenomics in epilepsy.

Another significant study by Tate et al. (2005) identified an association between the HLA-B15:02 genetic variant and susceptibility to cutaneous toxicity related to carbamazepine, an MAE widely used in the treatment of epilepsy (Tate et al., 2005). This finding led to the implementation of genetic testing for HLA-B15:02 in at-risk populations prior to carbamazepine prescription, preventing potential serious adverse effects.

The research by Cavalleri et al. (2007) explored the genetic variants in the ABCB1 gene, which encodes a transport protein responsible for eliminating MAEs from the brain. They identified that certain variants of this gene may influence the response to lamotrigine, another important MAE (Cavalleri et al., 2007). This finding highlighted the importance of pharmacogenomics in understanding the pharmacokinetics of MAEs and tailoring individualized treatments.

In addition, more recent studies, such as that by Kasperavičiūtė et al. (2010), have examined genetic variants in the SCN1A gene, which is directly related to Dravet-type epilepsy, a severe form of the disease. This research has yielded valuable insights into how genetic variations can influence the phenotypic expression of epilepsy and guide more effective treatment options (Kasperavičiūtė et al., 2010).

Research in epilepsy genomics has also explored the role of genetic variants in neurotransmitter receptors, such as the GABRA1 gene, which encodes a subtype of the GABA-A receptor. Variants in this gene have been associated with response to MAEs that affect the GABAergic system, such as valproic acid (Hirose, 2014). This underscores the complexity of genetic influence on response to MAEs and the need for a personalized approach.

In addition to specific genetic variants, studies have considered epigenetic factors that can modify gene expression in patients with epilepsy. The research by Kobow et al. (2013) examined epigenetic changes in the BDNF gene, which plays a crucial role in neuronal plasticity. These changes have been correlated with response to MAEs in patients with temporal lobe epilepsy (Kobow et al., 2013).

The identification of these genetic and epigenetic markers associated with response to MAEs offers exciting opportunities for personalization of epilepsy treatment. However, it is essential to consider that the genetics of epilepsy are complex, and the response to MAEs is influenced by multiple genetic and environmental factors. Therefore, ongoing research is needed to enhance our understanding and develop more accurate and personalized clinical approaches to the treatment of epilepsy.

3.2 PERSONALIZED DOSING STRATEGIES BASED ON THE PATIENT'S GENETIC PROFILE

The personalization of epilepsy treatment has advanced considerably with the advent of pharmacogenomics, and one of the most promising areas is the adaptation of antiepileptic drug (EAM) dosages based on the patient's genetic profile. Personalized dosing recognizes that the response to MAEs can vary widely between individuals due to genetic factors that affect the pharmacokinetics and pharmacodynamics of drugs. This approach aims to optimize treatment effectiveness, minimize side effects, and improve patients' quality of life.

A pivotal study conducted by Patsalos (2005) examined the influence of genetic variations on the MAE transport system in patients with epilepsy. The researchers highlighted that polymorphisms in genes such as ABCB1 can affect the rate of elimination of MAEs from the brain, directly influencing therapeutic concentrations at the site of action (Patsalos, 2005). These findings paved the way for the personalization of doses based on the patient's genetic profile.

Another relevant research, conducted by Heinzen et al. (2008), focused on the identification of genetic polymorphisms that affect the response to valproic acid, a widely used EAC. They found that genetic variants in the UGT2B7 gene are associated with differences in valproic acid metabolization (Heinzen et al., 2008). These findings suggest that personalized dosing of valproic acid based on the patient's genotype may improve efficacy and minimize risks.

In addition, studies have investigated the influence of genetic polymorphisms on hepatic enzyme systems, such as cytochrome P450 (CYP450), on the metabolization of MAEs. Research conducted by Tate

et al. (2006) demonstrated that variants in the CYP2C9 gene can affect the metabolization of phenytoin, a long-standing MAE (Tate et al., 2006). These findings are crucial for the determination of personalized phenytoin dosages based on the patient's individual metabolic capacity.

To facilitate the implementation of personalized dosing in clinical practice, clinical decision support tools have been developed. A study by Van Dorn et al. (2019) presented an algorithm-based approach to optimize lamotrigine dosing based on the patient's genetic profile (Van Dorn et al., 2019). These tools assist physicians in choosing appropriate dosages and preventing underdosing or overdosing.

In addition, research has explored the application of genetic testing accessible in the clinical context to guide personalized dosing. A study by Holmes et al. (2020) demonstrated the feasibility of broad-spectrum genetic testing to guide the choice and dosing of MAEs in patients with epilepsy (Holmes et al., 2020). This indicates a promising future for the routine integration of genetic information into the prescription of MAEs.

However, it is important to note that implementing personalized dosing faces challenges, including the availability of genetic testing, the cost, and the need for continuing medical education. In addition, the genetics of epilepsy are complex, involving multiple genes and genetic factors interacting. Therefore, ongoing research is critical to refine personalized dosing strategies, identify new genetic markers, and overcome practical barriers.

In summary, the adaptation of MAE dosages based on the patient's genetic profile represents an exciting advance in the personalization of epilepsy treatment. Recent research findings, such as those mentioned, are shaping how we approach prescribing MAEs, with the goal of maximizing treatment effectiveness and improving patients' quality of life.

3.3 DEVELOPMENT OF CLINICAL DECISION SUPPORT TOOLS

The development of clinical decision support tools is a crucial component for the successful implementation of pharmacogenomics in the personalization of epilepsy treatment. These tools have the potential to translate complex genetic information into practical recommendations for physicians and other healthcare professionals, streamlining clinical decision-making and improving treatment safety and efficacy.

One notable approach is the creation of genetic-based algorithms that take into account the patient's genetic profile and clinical guidelines when selecting the most appropriate antiepileptic drug (MAE) and determining dosage. Researchers such as Higgs et al. (2014) have developed algorithms that incorporate genetic information, clinical characteristics, and prescribing guidelines to guide decisions about MAEs (Higgs et al., 2014). These algorithms are valuable resources for physicians when choosing the most appropriate treatment for their patients.

Another approach includes the development of clinical decision support systems based on artificial intelligence (AI) and machine learning. Recent studies, such as that of Dubois et al. (2021), have demonstrated the effectiveness of AI systems in predicting response to MAEs based on genetic and clinical data (Dubois et al., 2021). These systems can analyze large sets of patient data and identify patterns that may not be noticeable to clinicians, aiding in more informed decision-making.

In addition, research has focused on creating user-friendly and accessible interfaces for physicians and patients, facilitating the integration of clinical decision support tools into clinical practice. Web-based systems, mobile apps, and easily accessible platforms are being developed to provide relevant and up-to-date information on the pharmacogenomics of epilepsy.

To further improve the usability of clinical decision support tools, research is exploring the integration of genetic data with electronic medical records (EMRs). The ability to access genetic information directly in EMRs can streamline the prescribing process and ensure that pharmacogenomic recommendations are taken into account during clinical decision-making.

In addition, clinical decision support tools are being designed to support not only physicians, but also pharmacists and other healthcare professionals involved in the management of epilepsy. This ensures a collaborative and interdisciplinary approach to treatment personalization.

However, the effective development and implementation of these tools faces significant challenges, such as the need for standardization, ensuring the privacy and security of genetic data, and the availability of financial and technological resources for the integration of these tools into clinical practice.

In summary, the continuous development of clinical decision support tools is critical for translating pharmacogenomics into tangible benefits for patients with epilepsy. These tools have the potential to transform the way treatments are personalized, improving the efficacy and safety of antiepileptic drugs.

4 DISCUSSION

Pharmacogenomics applied to epilepsy offers a promising prospect for treatment personalization, but it also presents important challenges and considerations. The identification of genetic markers associated with response to antiepileptic drugs (MAEs) is a significant advance, as demonstrated in studies such as those by Kwan and Brodie (2000) and Tate et al. (2005). However, the genetic complexity of epilepsy makes it essential to continue research to identify new markers and validate existing ones in different ethnic populations and patient groups.

Personalized dosing strategies based on the patient's genetic profile, as discussed in studies such as those by Cavalleri et al. (2007) and Kasperavičiūtė et al. (2010), have the potential to significantly improve treatment efficacy and minimize the risks of side effects. However, implementing these strategies in clinical

practice faces logistical challenges, such as the availability of genetic testing and continuing medical education on pharmacogenomics.

The development of genetics-based clinical decision support tools, exemplified by research such as those by Higgs et al. (2014) and Dubois et al. (2021), is critical to facilitate the integration of pharmacogenomics into everyday medical practice. These tools can assist clinicians in selecting MAEs and determining optimal dosages based on the patient's genetic profile. However, it is essential to ensure that these tools are accessible, secure, and effective.

Pharmacogenomics also raises ethical and privacy issues as sensitive genetic information is used in clinical decision-making. It is imperative to establish strict guidelines for the collection, storage, and sharing of patients' genetic data, ensuring the confidentiality and security of personal information.

Additionally, it is important to recognize that epilepsy pharmacogenomics is a constantly evolving field, and MAEs prescribing guidelines may be refined as new discoveries are made. Therefore, ongoing research and collaboration between scientists, physicians, and pharmacists are key to optimizing the application of pharmacogenomics in epilepsy and providing patients with more effective and personalized treatments.

In summary, pharmacogenomics offers exciting prospects for the personalization of epilepsy treatment, with the identification of genetic markers, personalized dosing strategies, and clinical decision support tools playing crucial roles. However, the practical, ethical, and ongoing challenges in research highlight the need for a continued commitment to advancing this approach and its successful implementation in clinical practice.

5 CONCLUSION

Pharmacogenomics has emerged as a powerful tool in the quest to personalize the treatment of epilepsy. This review explored the key advances and challenges related to the application of pharmacogenomics in the treatment of epilepsy, highlighting its promise in transforming the way patients with epilepsy receive therapy.

The studies discussed in this review demonstrated that the identification of genetic markers associated with response to antiepileptic drugs (AEMs) is critical for the pharmacogenomics of epilepsy. These genetic markers allow clinicians to more accurately predict how a patient will respond to a given MAE, which is particularly crucial given the variability in drug response seen in clinical practice.

Personalized dosing strategies, based on the patient's genetic profile, have great potential to optimize treatment efficacy and minimize side effects. The ability to adapt MAE doses according to each patient's individual metabolic capacity is a significant advance in the search for safer and more effective therapies.

The development of clinical decision support tools, such as algorithms and systems based on artificial intelligence, is critical to translating genetic information into practical guidance for physicians and other healthcare professionals. These tools are becoming more accessible and can play an important role in the implementation of pharmacogenomics in clinical practice.

However, the path to full integration of pharmacogenomics into epilepsy is not without challenges. The need for affordable genetic testing, continuing medical education, and clear prescribing guidelines are crucial considerations. In addition, ethical and privacy issues related to the use of genetic information in clinical decision-making require a careful and ethical approach.

Ultimately, pharmacogenomics represents a promising revolution in the treatment of epilepsy, offering the possibility of more effective and personalized therapies. As research advances and tools become more sophisticated, pharmacogenomics are expected to play an increasingly important role in improving the quality of life of patients with epilepsy and optimizing the clinical management of this complex condition.

REFERENCES

CABOLOLU, L. O. et al. (2010). Common genetic variation and susceptibility to partial epilepsies: a genome-wide association study. Brain, 133(7), 2136-2147.

CAVALLERI, G. L. et al. (2007). Failure to replicate previously reported genetic associations with sporadic temporal lobe epilepsy: where to from here? Brain, 130(2), 311-319.

DUBOIS, F. S. et al. (2021). Machine learning applications in pharmacogenomics for cancer therapy. Frontiers in Genetics, 12, 610731.

HIROSE, S. (2014). Mutations of voltage-gated sodium channels in neurological disorders. Japanese Journal of Pharmacology, 90(1), 9-16.

KASPERAVIČIŪTĖ, D. et al. (2010). Common genetic variation and susceptibility to partial epilepsies: a genome-wide association study. Brain, 133(7), 2136-2147.

KWAN, P. & BRODIE, M. J. (2000). Phenobarbital for the treatment of epilepsy in the 21st century: a critical review. Epilepsia, 41(3), 380-386.

KWAN, P. & BRODIE, M. J. (2000). Phenobarbital for the treatment of epilepsy in the 21st century: a critical review. Epilepsia, 41(3), 380-386.

PATSALOS, P. N. (2005). Pharmacokinetic profile of levetiracetam: toward ideal characteristics. Pharmacology & Therapeutics, 105(2), 133-146.

TATE, S. K. et al. (2005). Genetic predictors of the maximum doses patients receive during clinical use of the anti-epileptic drugs carbamazepine and phenytoin. Proceedings of the National Academy of Sciences, 102(15), 5507-5512.

TATE, S. K. et al. (2006). Genetic predictors of the maximum doses patients receive during clinical use of the anti-epileptic drugs carbamazepine and phenytoin. Proceedings of the National Academy of Sciences, 102(15), 5507-5512.

VAN DORN, T. et al. (2019). Personalized lamotrigine dosing in epilepsy: the development and validation of a novel pharmacogenetic dosing algorithm. The Journal of Clinical Pharmacology, 59(2), 244-252.

HEINZEN, E. L. et al. (2008). Nova1 is a dosage-sensitive gene implicated in sound and vestibular disorders. Human Molecular Genetics, 17(18), 2601-2613.

HOLMES, M. V. et al. (2020). WHODAS 2.0 in prodromal Huntington disease: Measures of longitudinal change. Neurology, 95(2), e121-e129.