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REVISÃO DA EVIDÊNCIA ATUAL SOBRE A TERAPIA FARMACOLÓGICA DA EPILEPSIA

REVIEW OF THE CURRENT EVIDENCE ON THE PHARMACOLOGICAL THERAPY OF EPILEPSY

Lucas Bezerra de Aguiar*[I], Pedro Fernandes Mariz[II], Cláudia Barros Gonçalves Cunha[III]

Resumo. A epilepsia é um distúrbio neurológico comum que afeta cerca de 50 milhões de pessoas, mas, se tratada adequadamente, os pacientes podem alcançar remissão a longo prazo. No entanto, a escolha do tratamento adequado ainda é um desafio, uma vez que muitas drogas antiepilépticas estão disponíveis e as respostas dos pacientes a essas drogas são variáveis. Nosso objetivo é comparar vários estudos sobre monoterapia e terapia combinada para dar uma melhor perspectiva ao profissional médico sobre as opções disponíveis até o momento para o tratamento farmacológico da epilepsia. Trata-se de uma revisão de literatura baseada na base de dados PubMed. A busca feita foi "epilepsy" AND "treatment" AND "clinical", e os filtros utilizados foram "meta-analysis" e 2019-2020 para o período de publicação. De acordo com os resultados de todas as revisões sistemáticas e meta-análises consideradas neste estudo, fica claro que há grande heterogeneidade e nenhum consenso sobre as melhores formas de tratamento clínico dos vários tipos de epilepsia. As evidências científicas apresentadas nos estudos têm baixa relevância estatística e dificultam a escolha do tratamento com baixo risco ao paciente e desempenho satisfatório. Mais ensaios clínicos randomizados são necessários para a avaliação comparativa de medicamentos isolados, incluindo uma amostra populacional expressiva. Só assim será possível chegar a conclusões mais assertivas.

PALAVRAS-CHAVE: Anticonvulsivantes. Epilepsia. Prática Baseada em Evidências. Neurologia. Farmacologia. Terapêutica.

Abstract. Epilepsy is a common neurological disorder that affects around 50 million people but if treated properly, patients can achieve long-term remission. However, choosing the appropriate treatment is still a challenge, since many antiepileptic drugs are available and patient responses to these drugs are variable. We aim to compare various studies about monotherapy and combined therapy to give a better perspective to the medical professional about the options available to this date for pharmacological epilepsy treatment. This is a literature review based on the PubMed database. The search made was "epilepsy" AND "treatment" AND "clinical", and the used filters were "meta-analysis" and 2019-2020 for the period of publication. According to the results of all the systematic reviews and meta-analyses considered in this study, it is clear that there is great heterogeneity and no consensus about the best forms of clinical treatment of the various types of epilepsy. Scientific evidence presented in the studies has low statistical relevance and impairs the choice of treatment with low risk to the patient and satisfactory performance. More randomized clinical trials are necessary for the comparative evaluation of isolated drugs, including an expressive populational sample. Only then it will be possible to come to more assertive conclusions.

KEYWORDS: Anticonvulsants. Epilepsy. Evidence-Based Practice. Neurology. Pharmacology. Therapeutics.

[I]Graduando (a). Faculdade de Medicina Nova Esperança - FAMENE. CEP: 58067-695, João Pessoa, Paraíba, Brasil.
*Autor correspondente: aguiar.b.lucas@gmail.com
ORCID ID: 0000-0003-3385-3563

[II]Graduando (a). Faculdade de Medicina Nova Esperança - FAMENE. CEP: 58067-695, João Pessoa, Paraíba, Brasil.
ORCID ID: 0000-0002-8854-3397

[III]Neurologista. Mestre, Faculdade de Medicina Nova Esperança – FAMENE. Prog. Pós-graduação: Mestrado Profissional em Saúde da Família. CEP: 58067-695, João Pessoa, Paraíba, Brasil.
ORCID ID: 0000-0002-9412-9096

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INTRODUCTION

Epilepsy is one of the most common neurological disorders on the planet, affecting about 50 million people. It is characterized by the brain's propensity to generate spontaneous and recurrent epileptic seizures, linked to neurobiological, cognitive, and social consequences. According to Nevitt et al[1], up to 70% of patients with epilepsy can go into remission and remain without epileptic events shortly after starting drug therapy and most of these patients achieve therapeutic success with only one drug. Nevertheless, the study by Chen et al2 considers that approximately one-third of patients with epilepsy do not respond well to monotherapy and require more drugs to achieve better therapeutic efficacy.

Given these divergences, in this review, meta-analyses were selected that seek to elucidate the perspectives of pharmacological therapy for epileptic seizures, so that the medical professional can offer the treatment with the best perspective for the health of people suffering from epilepsy, always respecting the heterogeneity and peculiarities of each individual.

MATERIALS AND METHODS

A qualitative study made from a literature review in the PubMed database using the searchers "epilepsy" AND "treatment" AND "clinical", and the filters "meta-analysis", for study type, in the period 2019-2020. Seven out of 47 publications were selected considering the methodological quality of the content as an inclusion criterion, and papers that did not have pharmacological treatment as the main approach were excluded.

RESULTS AND DISCUSSION

A Canadian meta-analysis that comparatively studied the use of antiepileptic drugs in monotherapy revealed that Carbamazepine (CBZ) was more likely to have its use discontinued when compared to Lamotrigine (LTG) due to the adverse effects caused, being, therefore, less tolerated by the elderly population. It is worth noting that this meta-analysis did not differentiate controlled release Carbamazepine (CBZ-LC) from immediate-release Carbamazepine (CBZ-LI), so the studies that established this relationship were those that compared LTG with CBZ-LI, so there is a chance that taking the comparison between LTG and CBZ-LC as a reference, there is no significantly important difference in tolerability. Furthermore, there is a limitation in proving that Lamotrigine was more effective than Carbamazepine due to the heterogeneity found in the results of the studies, with only the one that demonstrated this relationship as true and with statistical

significance being included. Another comparison made between Lamotrigine and Levetiracetam (LEV) showed that the latter was more effective in stopping seizures in relative terms, which was not verified by the absolute quantitative, since these results did not present statistical relevance.[3]

Another meta-analysis showed better tolerability in elderly patients at one year, in descending order, for valproic acid (AVP), LEV, LTG, CBZ-LC, and CBZ-LI. Importantly, the confidence interval for the OR value between CBZ-LI and the other drugs had the largest range of variation in the comparison with AVP, which corresponds to more than double the variation that occurred in the comparison with LEV, the second largest. It was also seen in this study that AVP offered less risk of promoting adverse effects than CBZ-LC or LTG. An important point of this review is that no significant difference was found between the results obtained in the six-month and one-year periods concerning the efficacy of the comparative monotherapies.[4]

A systematic review published by Brigo et al5 regarding the comparison between monotherapy with Clonazepam or Ethosuximide in individuals newly diagnosed with epilepsy revealed a higher risk of treatment abandonment when Clonazepam was the drug of choice. Therefore, it was concluded that there is still not enough evidence to indicate monotherapy with Clonazepam for individuals with epilepsy.

The study published by Nevitt et al1 aimed to compare the efficacy of two drugs widely used in the monotherapy treatment of epilepsy, Topiramate, and Carbamazepine. A review of data on the time to therapeutic failure for both drugs, the time to recurrence of an epileptic seizure after initiation of treatment, and the time to 6- and 12-month remission of episodes was performed, including groups of patients with focal and generalized epileptic seizures. The review results suggested that Carbamazepine may be a more effective drug for individuals with recent focal seizures in terms of treatment maintenance (treatment failure due to lack of efficacy, adverse events, or both, occurred later with Carbamazepine) and that these individuals may achieve one year of seizure remission sooner with Carbamazepine than with Topiramate. However, for individuals with generalized tonic-clonic seizures of recent onset, the results are indeterminate due to the small number of patients with this condition included in the selected trials.

The meta-analysis published by Charokopou et al6 sought to elucidate the efficacy and safety of using Brivaracetam as an adjuvant in the treatment of epilepsy. Its results showed relatively equivalent efficacy among the antiepileptic drugs included in the research (Brivaracetam, Eslicarbazepine, Gabapentin, Lacosamide, Lamotrigine, Levetiracetam, Oxcarbazepine, Perampanel, Phenytoin, Pregabalin, Retigabine/Ezogabine, Tiagabine, Topiramate, Zonisamide.). However, the study warns that the assessment of patient heterogeneity during clinical practice is critical to achieving optimal treatment for each individual.

In the study that analyzed Levetiracetam as an adjuvant in the treatment of focal epilepsy in the pediatric age group was observed an increased occurrence of drowsiness and hostility about two times compared to the placebo group. The results on adverse effects, response rate, and

remission in the studies analyzed by the group are heterogeneous. In comparison with six other drugs, LEV had the best performance, although it was surpassed by Lamotrigine concerning remission; however, the latter presented more adverse effects.

Brivaracetam (BRV), a derivative of LEV with greater synaptic affinity, can be used in late adolescence as an alternative for patients with adverse effects caused by LEV. Other drugs not considered within the group of antiepileptic drugs, but that have action in this pathology were superficially approached in this work. The group considered that VLE may be a better adjuvant in treating these patients, but larger and better studies are needed to consolidate this statement. It is noteworthy that this meta-analysis has a series of limitations and considered studies with different designs, compromising to a certain degree the relevance of its results.[7]

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In the study that evaluated Losigamone for focal epilepsy, an improvement in seizure frequency was observed at the expense of lower tolerability, more adverse effects, and discontinuation of the medication when compared to the placebo group, with dizziness being the only adverse effect with statistically significant increase in those groups. The improvement in the condition was only relevantly observed in the subgroup that took the highest dose analyzed, although it was also the subgroup that most reported adverse effects and discontinuation of treatment. The meta-analysis in question only included two randomized clinical trials and does not provide information for children under eighteen years of age nor for long-term effects, so the observations pointed out were not considered relevant in our analysis.[2]

CONCLUSION

Given the results expressed by all systematic reviews and meta-analyses considered in this study, the great heterogeneity in the results of current publications for the clinical treatment of various types of epilepsy is noted. The scientific evidence provided showed to have, in general, low statistical relevance and make it difficult to justify the choice of drugs with superior performance and safety profiles considering the various age groups since the numerous limitations of all studies conferred a low degree of reliability in the results obtained. More randomized clinical trials are needed for the evaluation of drugs in isolation and comparatively and with a sufficient population sample, to allow more assertive conclusions.significance being included. Another comparison made between Lamotrigine and Levetiracetam (LEV) showed that the latter was more effective in stopping seizures in relative terms, which was not verified by the absolute quantitative, since these results did not present statistical relevance.3

CONFLICT OF INTEREST DISCLOSURE

None of the authors has any conflict of interest to disclose.

CONFLICT OF INTEREST DISCLOSURE

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