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Modern pharmacological strategies in the treatment of Drug-Resistant Epilepsy: evaluation of efficacy and safety: a review

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Abstract

Introduction: Drug-resistant epilepsy (DRE) is a neurological condition, defined as a failure to make the patient seizure free, after the use of two tolerated, appropriately chosen antiepileptic drugs (AED). Although there is an increasing number of available antiepileptic drugs, it is estimated that pharmacotherapy remains ineffective in approximately 30% of patients. Drug-resistant epilepsy is considered as one of the greatest challenges in modern neurology that affects millions of patients worldwide, who do not respond to standard treatments. Even though epilepsy is one of the most common neurological diseases, with a global total of 50 million people suffering from the condition, treatment of its resistant forms remains complicated and often ineffective. Chronic epileptic seizures can cause serious health problems, limiting patients' mobility, affecting quality of life and increasing the risk of emotional disorders such as depression and anxiety. In response to this challenge, the development of modern drugs for drug-resistant epilepsy has become a medical priority. In recent years, there has been growing interest in new medications such as Cenobamate, Fenfluramine and Cannabidiol, which have different mechanisms of action and promising results in reducing the seizure frequency. Before diagnosing DRE, it is essential to exclude the pseudo-resistance, which may result from different factors such as inadequate doses of medicine, choosing the incorrect medications, or patient-related errors (poor compliance).

Aim: Our aim was to review the efficacy of modern pharmacological therapies in drug-resistant epilepsy and evaluate their safety. For these analyses, we pointed out the new drugs that have entered the marketplace in the past several years and attempted to review and describe medications such as cenobamate, fenfluramine, and cannabidiol. We wanted to assess the available data to see if these drugs can help to control seizures, how they affect patients' quality of life, and what risks or side effects they may cause.

Review methods : We have done a detailed review of a current medical literature, analysing the treatments for patients suffering from drug-resistant epilepsy. We focused on using the databases such as PubMed and Google Scholar. We reviewed articles concerning efficacy and safety of cenobamate, fenfluramine and cannabidiol and assessed how they affect the quality of patients' life. Inclusion criteria were as follows: available clinical trials from the last 10 years, the efficacy and safety of cenobamate, fenfluramine and cannabidiol in drug-resistant epilepsy, full texts available in English. Exclusion criteria included: studies that focused on the pediatric population for therapies that are not approved for adults, animal-only studies and articles without clear outcome measures.

Conclusions: There are few, promising anti-epileptic drugs that can be helpful to reduce the amount of seizures. We can point out drugs such as cenobamate, fenfluramine or cannabidiol. Despite their side effects, those drugs are considered to be safe for DRE patients in combination therapy with other most common anti-epileptic drugs. This review has several limitations. The analysis was limited to only three drugs, potentially overlooking other promising treatments for drug-resistant epilepsy. Finally, while long-term safety is being studied, there is limited experience with these therapies in specific patient populations.

Key words: Epilepsy, Drug-resistant epilepsy, Cenobamate, Fenfluramine, Cannabidiol, Dravet Syndrome, Lennox-Gastaut Syndrome

Introduction

Epilepsy is one of the most common neurological conditions - around 50 million people worldwide suffer from epilepsy [1], with one-third of them having drug-resistant epilepsy (DRE) [2]. According to the World Health Organization (WHO), approximately 5 million new cases of epilepsy are diagnosed globally each year. This condition has various mechanisms and causes, which can further complicate effective pharmacological treatment. Few patients can benefit from surgical treatment, while the majority of them still relies on pharmacological treatment [4]. The only way to improve their quality of life is to be seizure free. That is why it is essential to analyze the efficacy of different antiepileptic drugs (AEDs). Initiation of the right treatment is one of the most crucial issues concerning epilepsy. Uncontrolled seizures can negatively affect life and be the cause of psychiatric disorders such as depression and anxiety or cause a difficulty in finding a certain job. Patients may avoid forming new friendships, travelling, in fear of having a seizure [5]. Another problematic issue is the fact that 30 % of patients diagnosed with epilepsy are considered drug-resistant, as they don't respond to at least 3 AEDs [6]. DRE can either occur from the onset of the condition or, in some patients, develop as "tolerance" to the previously used antiepileptic medication [7]. It is crucial to rule out pseudo-resistance, before we diagnose DRE. Initiation of the right treatment is one of the most crucial issues concerning epilepsy. Pseudo-resistance may result from medical errors (incorrect diagnosis, improper medication choice) or from non-compliance with the doctor's instructions including drug dosage or missing doses. It may occur while treating younger patients, as well as those who misuse alcohol or drugs. There is also noticeable pseudo-resistance among patients with higher impulsivity [8]. New hope for drug-resistant epilepsy treatment comes from recent reports on drugs, such as cenobamate and fenfluramine [9]. In recent years, there has also been increasing interest in the use of cannabidiol [10]. The aim of our article is to explore the efficacy and safety of these drugs in combination with the currently available antiepileptic drug (AED). We reviewed numerous articles related to these medications on PubMed.

Cenobamate - efficacy evaluation

Cenobamate was FDA and EMA approved in 2019–2021 for treatment of focal seizures in adults. This drug is from the alkyl-carbamate drug class. Other alkyl-carbamates are

meprobamate (previously used for the treatment of anxiety disorders) and felbamate [11]. In the United States of America, felbamate is also used to manage some of the most severe forms of epilepsy (e.g., Lennox-Gastaut Syndrome) [12]. The reason why felbamate, relatively to cenobamate, did not evolve to the revolutionary drug for drug-resistant epilepsy therapy in Europe, is due to its side effects (the risk of aplastic anemia, liver toxicity) [13] outweigh the benefits of its use. Cenobamate has a dual mechanism of action, including positive allosteric modulators' mechanism of synaptic and extrasynaptic γ-aminobutyric acid (GABAA) ionotropic receptors and a voltage gated sodium channels inhibitor. Topiramate and phenytoin are said to have similar mechanisms to that of cenobamate, whereas cenobamate appears to have a greater effect in lowering the amount of seizures. However, the exact mechanism of its effect in patients with drug-resistant epilepsy remains to be fully understood [4].

Important studies on cenobamate were performed appropriately and there were several conclusions made by the researchers. The Study C013 (Chung et al., 2020) [14] was a study of adjunctive cenobamate at a dose of 200 mg/day in patients with uncontrolled seizures. The placebo-adjusted reduction in seizures was approximately 55.6% with cenobamate, compared with 21.5% with placebo. The responder rate for a ≥50% reduction in seizures was 50.4% for cenobamate and 22.2% for placebo. Seizures were completely controlled in 28.3% of patients during maintenance treatment with cenobamate. The other published study by Krauss et al.[15] assessed the effects of cenobamate as an adjunctive treatment. Doses of cenobamate were 100, 200 and 400 mg/day, respectively. Reduction in seizures was 35.5%, 55%, and 55% for the cenobamate doses, compared to 24% reduction in the placebo group. The rates of therapeutic response were 40% (100 mg), 56% (200 mg), and 64% (400 mg). At a dose of 400 mg in patients treated with cenobamate, 21% were seizure-free. Finally, in the performed study in 2022 by Klein et al. [16] , patients at the age of 18–70 years and diagnosed with focal seizures, have been treated by cenobamate to determine the long-lasting seizure reduction and response to the treatment. The average seizure reduction at 48 months was 76.1%. Full seizure control was achieved in 16.4% of patients, while a ≥90% reduction in seizures was seen in 39.1% of patients.

Cenobamate - safety profile

Recent studies looking at real-world data show that cenobamate is generally safe for patients. The most frequent side effects affect the nervous system - patients most often reported feeling fatigue, sleepy, or dizzy. The FAERS database reported rarer adverse effects experienced by

patients, such as gait and balance disturbances, hypersomnia, and vision problems [18]. The prospective study of cenobamate in drug-resistant epilepsy did not find significant negative changes in cognitive performance, negative affectivity (anxiety and depression), or quality of life after 3 and 6 months of treatment. The conclusions suggest that cenobamate is a generally safe antiseizure medication in terms of these aspects, with most patients remaining stable throughout the therapy. After 3 months of treatment the majority of patients (78.1%) showed no reliable change in depressive symptoms. There was also improvement in depressive symptoms, as it was noted in 6.3% of patients, however worsening of depressive symptoms was noted in 15.6% of patients. The level of anxiety decreased in 12.5% of patients. [17]

Mar Carreño et al. [19] created guidelines on adjusting the doses of patients' existing anti-seizure medications (ASMs). The goal was to make adjunctive cenobamate treatment safer and more effective for people with drug-resistant epilepsy. Cenobamate should be added with other antiepileptic drugs in combination therapy, however the correct dose of this drug is essential for patients' health. We need to evaluate different AEDs, blood levels of medications, tolerance, severity of epilepsy, types and frequency of epileptic seizures, side effects. When the dose of cenobamate is ≥ 150 mg daily, patients treated with sodium channel blocker (SCB) should be given a reduced dose of it. For people taking some GABAergic drugs, the dose of cenobamate should be lower, when cenobamate dose is about 50-100 mg/day; the people taking both medicines should have more drowsiness. Based on the data, phenytoin dose reduction is advisable in combination therapy with cenobamate, when the blood level of phenytoin is 15 μg/ml, and the dose of cenobamate is approximately 25 mg/day. Likewise, in the situation when blood level of phenobarbital is more than 30 μg/ml and the daily dose of cenobamate is approximately 25 mg, the administration of phenobarbital must be lowered.

In the 12-week randomized phase 2 study conducted by Chung et al., [14] patients reported more frequent side effects with cenobamate compared to placebo. In the cenobamate group, 76.1% of patients had adverse reactions versus 63.3% in the placebo group. Patients who were treated with cenobamate, most frequently reported symptoms such as drowsiness, dizziness, headache, nausea, and fatigue. The most common symptoms for the placebo group were dizziness, headache and drowsiness. Most importantly, the majority of side effects were mild or moderate, with very few cases of severe symptoms. There were significant differences between the groups: Urinary tract infections and nasopharyngitis happened more often in the patients who were given cenobamate. Although suicidal thoughts happened in both groups, they did not become any worse.

In a multicenter, double-blind, randomized, placebo-regulated, dose response trial [15], patients who took cenobamate at different doses had different rates of side effects. The group taking the maximum dose of cenobamate (400 mg) experienced the highest rate of side effects, with 90% of patients reporting at least one symptom. This rate was lower in the other dosage groups: 76% for the 200 mg group and 65% for the 100 mg group. Notably, 70% of patients in the placebo group (who received a sugar pill) also reported side effects.The most common adverse events observed were drowsiness, headaches, fatigue and double vision. It was clear that the frequency of these side effects increased as the cenobamate dose got higher. Most of these symptoms were mild to medium, but some of severe side effects happened as well, including seizures, difficulties with coordination, episodes of dizziness, abnormal eye movements, and suicidal thoughts. No deaths were documented in the research. Most patients stopped taking the drug because of coordination issues, dizziness, and drowsiness. Despite the mentioned side effects of this drug, it's important to remember that for patients dealing with drug-resistant forms of epilepsy, the benefits of cenobamate may outweigh the risks.

Fenfluramine - efficacy evaluation

Drug resistant epilepsy occurs in rare childhood epileptic encephalopathies, for example Dravet Syndrome [20][21]. This disorder is very rare and the reduction of the seizures in this case may be very complicated. Dravet Syndrome has been treated with numerous medications for years, such as valproate sodium, clobazam, stiripentol or topiramate. Despite using several antiepileptic medications, approximately 45% of patients experience more than three epileptic seizures per month [9]. Fenfluramine inhibits the reuptake of serotonin and stimulates the release of serotonin into extracellular space. The higher level of serotonin causes the stimulation of several 5-HT receptors. Through this mechanism, fenfluramine reduces the amount of seizures. Fenfluramine used to be an anorectic drug, but due to its dangerous side effects such as pulmonary arterial hypertension or valvular heart disease, it is not used for this purpose anymore.

For treating epileptic seizures, the dose of fenfluramine should be maximum 26 mg per day [25]. The efficacy of fenfluramine in Dravet syndrome was assessed in three randomized, double-blind, placebo-controlled, multinational, phase III trials [22]. In the first conducted clinical trial [23] 119 patients (aged 2 to 18 years) were divided randomly into 2 groups with different doses of fenfluramine, respectively - 0.2 mg per kg, 0.7 mg per kg and placebo. Patients included in this study didn’t receive stiripentol. The double-blind clinical study drew

significant conclusions after half a year's observations. Those administered 0.7 mg/kg of fenfluramine witnessed their typical seizure frequency decrease by nearly 75 %, while the much smaller 0.2 mg/kg dosage still reduced occurrences by over 40 %. Comparatively, the placebo control average seizures were reduced by slightly less than 20 %. Given these outcomes, fenfluramine unambiguously turned out more effective than placebo at minimizing convulsions among this specific cohort of patients. In a separate randomized controlled trial [24], all participants had Dravet syndrome and had previously taken stiripentol with inadequate control of their seizures. These subjects were randomly assigned into two arms - one group received placebo whereas the alternate cohort was administered 0.4 mg/kg daily of fenfluramine, not to surpass 17 mg per day. In this study, fenfluramine successfully reduced a seizure frequency by 50 % in 54 % of patients, compared to 5 % of seizures reduced by placebo, which implies that this medication may be crucial for treating Dravet Syndrome. In the third randomized, placebo-controlled clinical trial [25], 143 patients were randomly assigned either to placebo or 0.2 to 0.7 mg/kg per day of fenfluramine treatment. Individuals were involved in the study on the condition that they did not receive stiripentol. In 72.9 % of patients the seizure frequency was reduced by ≥ 50 %, while in the placebo the seizure frequency was reduced by 6.3 %. This proves the efficacy of fenfluramine, considering the antiepileptic mechanism of it.

Fenfluramine - safety profile

According to randomized controlled trials [23] [24] [25] , fenfluramine was deemed safe for patients diagnosed with Dravet Syndrome, though not without noticeable side effects. The first trial [23] found that while those treated with fenfluramine reported loss of appetite, diarrhea, nasopharyngitis, lethargy, drowsiness and fever, the placebo group saw milder symptoms. Higher doses often caused weight loss in individuals. During the trial, some patients experienced uncontrolled seizures requiring hospitalization; fortunately, no deaths were reported. However, not all reacted the same - where others found relief, a few suffered burdensome side effects or saw their condition further deteriorate. The trials aimed to help those suffering, but determining ideal treatment in the complex world of neurology remains an ongoing challenge. There weren't any serious cardiovascular side effects (especially pulmonary arterial hypertension) and the echocardiography results among the patients were normal. Moreover, after 14 weeks of fenfluramine treatment (0.7 mg/kg per day) there were noticeable improvements in behavioral functions.

In the other randomized, controlled trial [24] side effects of fenfluramine were similar to the first trial, except for appearing in a few cases of mitral valve regurgitation, which might be a physiological phenomenon, common in healthy children.

During the third randomized, placebo controlled trial [25], apart from typical side effects noticed in previous trials, there were tremors and reductions in blood glucose levels. Regarding the issue of serious adverse effects (SAE), 8 patients experienced SAE such as infections, injuries, status epilepticus and elevated liver enzymes. There was one sudden unexpected death in epilepsy reported in the placebo group, so it wasn't caused by the fenfluramine. Taking into consideration all of the aforementioned results, fenfluramine may be regarded as the new, promising drug for epileptic seizures in Dravet Syndrome, despite its few mild side effects.

Cannabidiol - efficacy evaluation

Cannabidiol (CBD) has various molecular mechanisms. This medication is a partial agonist and a negative allosteric modulator of CB2 receptors. Increased activity of CB2 receptors can reduce neuronal excitability. Furthermore, CBD acts as a positive allosteric modulator of GABA-A receptors (particularly the beta subunit), enhancing their inhibitory effects. This mechanism enables the suppression of seizure activity [26]. The most common diagnoses where cannabidiol is effective in treating drug resistant epilepsy are Dravet Syndrome, Lennox-Gastaut Syndrome and epilepsy related to tuberous sclerosis complex [27]. This medication was approved by the US Food and Drug Administration (FDA; 2018), the European Medicines Agency (EMA; 2018), and DCGI/CDSCO (April 2023) as an adjunctive therapy in those disorders.

In a certain retrospective study (which lasted a year) [28] researchers assessed the efficacy of cannabidiol as an adjunctive therapy, dividing 91 patients into two groups. The first one, included Dravet, Lennox-Gastaut Syndrome and Tuberous Sclerosis Complex and second one with ,,off-label'' diagnosis. The ,,off-label" group featured genetic and chromosomal abnormalities, Rett syndrome, brain abnormalities and other unclassified disorders such as perinatal asphyxia, post-infectious encephalitis, Febrile Infection Related Epilepsy Syndrome (FIRES), Lance-Adams syndrome, hemiplegia/convulsion. The reduction of seizures was noticeable in both of the groups - 31.3 % in the authorized group and 35.6 % in the second one. It proved that cannabidiol is not only effective in treating epilepsy in authorized disorders

(DS, LGS, TSC) but also positively affects the seizure control in off-label disorders. Additionally it was proven that cannabidiol and clobazam have a potential synergistic effect.

During the recent randomized clinical study conducted in 2022 [29], 198 patients diagnosed with Dravet syndrome participated in a trial that assessed cannabidiol oral solution as an adjunctive therapy. The double-blind, placebo-controlled investigation compared cannabidiol treatment administered at either 10 or 20 mg per kg daily to a control group receiving the placebo. For the lower cannabidiol dose of 10 mg per kg daily, seizure frequency was reduced roughly 48.7%, a substantially greater decrease than the placebo group's 29.8% reduction. However, patients with prescribed higher cannabidiol amounts of 20 mg per kg daily, experienced a slightly more modest yet still significant 45.7% reduction in seizures. Both evaluated cannabidiol doses effectively curbed seizure occurrences in children suffering from Dravet Syndrome, though the lesser 10 mg per kg daily quantity proved better tolerated with fewer side effects reported.

The long-term OLE trial [30] evaluated the long-term efficacy and safety of cannabidiol in patients with Lennox Gastaut Syndrome. Lennox Gastaut Syndrome is a severe pediatric epileptic encephalopathy in which chronic control of epileptic seizures is a challenge for pediatric neurologists. Patients experience different types of seizures and are intellectually disabled. Those individuals are most often treated with valproic acid, although it is not the first-line drug of choice. Approved drugs for treating the condition to date have been: felbamate, lamotrigine, topiramate, rufinamide, clobazam, clonazepam, and most recently a purified plant-based formulation of cannabidiol (CBD). Patients who had previously undergone two double randomized, double-blind, placebo-controlled trials (GWPCARE3 and GWPCARE4) participated in the mentioned before, long-term OLE trial. In the group of 366 patients, a daily average of 24 milligrams of Cannabidiol per kilogram of body weight was administered. After ongoing treatment for 156 weeks, seizure frequency saw a considerable decline with a median decrease in epileptic seizures of 48 to 71 % and 48 to 68 % for all seizure types. During repeated follow-ups at twelve week intervals, more than 87 percent of patients or their caretakers noted improvements extending beyond seizure control into the person's overall wellness. Based on these promising outcomes, long-term cannabidiol therapy resulted in a significant lessening of seizures. Those providing care and the individuals themselves witnessed clear benefits to functioning and quality of life. The treatment demonstrated effectiveness both in reducing seizure occurrence and in the perspective of patients and their families.

Cannabidiol - safety evaluation

In a retrospective analysis conducted by Quentin Calonge et al. [28] , the researchers found that drowsiness was one of the more regularly documented side effects of cannabidiol. While this side effect is typical of this medication, it rarely results in termination of therapy. Fatigue was another frequently reported side effect.

During a randomized clinical trial conducted by Ian Miller et al. [29], adverse effects manifested in approximately 89% of all groups. Cannabidiol side effects were prevalent, though most were mild or moderate in nature. Most common unwanted symptoms were decreased appetite, diarrhea, fever and fatigue. A few patients experienced nasopharyngitis as well. It is certainly true that higher doses of cannabidiol were more likely to cause serious side effects, such as much worse epileptic seizures and greatly increased liver enzyme levels.The increase in liver enzymes occurred only in the group that was also taking valproate sodium. The analysis highlighted that combining CBD with clobazam increases the likelihood of specific side effects, indicating that these patients require more careful follow-up. In the group taking clobazam and cannabidiol at the same time, side effects such as increased sleepiness, rashes, or pneumonia were more common. Cannabidiol showed little interaction with the other antiepileptic drugs used, suggesting that it is relatively safe as an add-on treatment. No participants died during the study. In the long-term OLE study [30], about 42% of the group experienced serious side effects including pneumonia, seizures or status epilepticus as well. A total 12% of patients stopped taking cannabidiol because of unpleasant side effects like diarrhea or extra seizures. Children were more likely than adults to experience serious side effects. There were 11 deaths in total, but none of them were caused by cannabidiol use.

Conclusions

Managing drug-resistant epilepsy is very challenging, as it affects patients who do not respond adequately to standard treatments. Patients who suffer from drug-resistant epilepsy often experience a worsening of quality of life, causing not only seizures but also psychosocial problems such as depression, anxiety, and job-related difficulties. The main goal of treatment is to reduce seizures and improve patients' quality of life. It requires a personalized approach, including applying the right dosage and monitoring for drug interactions. With new treatments, including recently approved drugs like cenobamate, cannabidiol, and fenfluramine, there is hope for better control of drug-resistant epilepsy.

Although they can cause some mild side effects, drugs like cenobamate, fenfluramine, and cannabidiol have been shown to be very effective in reducing seizures. Since these drugs act differently from standard anti-seizure medications, these treatments offer people with drug-resistant epilepsy an opportunity to manage their condition more effectively. These developments bring patients closer to living with fewer seizures and a better quality of life.

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