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Innovations in epilepsy treatment: pharmacological strategies and machine learning applications

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ABSTRACT

Epilepsy remains a significant global health challenge, with a substantial portion of patients experiencing inadequate seizure control despite existing therapeutic options. This review aimed at exploring recent advances in critical areas that, in the authors' opinion, hold promise for improving epilepsy treatment outcomes.

Our paper briefly discusses issues related to gene therapy, including recently initiated clinical trials using this technique. Additionally, we explore the utility of machine learning techniques in diagnostics and predicting responses to antiseizure treatment. Next, we present novel drug delivery routes, such as intranasal and transdermal systems, which provide alternative methods to enhance drug efficacy and minimise side effects. Finally, we briefly characterise new antiseizure medication (ASMs) introduced within the European Union in the last five years, as well as ASMs currently in phase III clinical trials. In summary, this review highlights the potential impact of innovative treatments and technologies on epilepsy management.

Keywords: gene therapy, machine learning, new delivery routes for antiseizure medications, new antiseizure medications

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Introduction

Epilepsy accounts for a significant burden of global disease, affecting nearly 50 million people worldwide, with five million new diagnoses every year. It is estimated that 4–10 in every 1,000 people are affected by active epilepsy requiring pharmacological intervention [1].

Despite being one of the oldest recorded diseases, with documented cases dating back 6,000 years, epilepsy is still associated with significant psycho-social disturbances such as fear, misunderstanding, discrimination, and stigma. The unpredictability of seizures can destroy self-confidence, cause stress and contributes to social withdrawal. In many cases, the long-term prognosis of epilepsy is poor. Patients with epilepsy have a higher likelihood of morbidity, which refers to the physical consequences of uncontrolled seizures, such as fractures, scalding, and bruising, as well as comorbidity with other disorders, either systemic or psychiatric, and an increased risk of mortality [2]. Additionally, antiepileptic treatment, which typically improves patients' quality of life by reducing the frequency of seizures, can unfortunately actually worsen it due to the occurrence of drug side effects, both in paediatric and adult populations.

Therefore, achieving seizure freedom remains the main goal in the treatment of epilepsy. However, for nearly 30% of patients suffering epilepsy, despite the availability of many antiseizure medications (ASMs) with various target molecular mechanisms, proper control of seizures is unsatisfactory and patients are diagnosed as drug resistant [3].

This paper reviews significant advances in epilepsy research, with a focus on gene therapy, machine learning, and novel drug delivery methods for ASMs. Additionally, we briefly discuss new ASMs introduced in the European Union over the past five years and currently in phase III clinical trials.

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Gene therapy in treatment of epilepsy

Gene therapy represents an important new frontier in epilepsy treatment because of its concept of addressing genetic determinants, rather than mere symptom alleviation. The approach involves the direct delivery of therapeutic genes into neuronal cells to achieve a modification in neural circuitry, and hence a reduction in seizure frequency. Currently used techniques include a range of delivery techniques, such as viruses (the most frequently used are adeno-associated viruses (AAVs), lentiviruses, and herpes simplex viruses), ribonucleoprotein complexes, and nanoparticles [4]. It is worthy of note that to date viral vectors have been the most frequently used [5]. The use of genetic techniques in the treatment of epilepsy is currently undergoing very intensive development. So far, most research using genetic techniques has been preclinical, but the first clinical trials are under way. Genetic methods attempted in the treatment of seizures focus either on correcting the genetic dysfunction that leads to seizures (e.g. sodium voltage-gated channel alpha subunit 1 (SCN1A) mutations), or on influencing known seizure-generating mechanisms.

A vector containing the genetic material, after crossing the blood-brain barrier or spreading through the brain following intracerebral administration, leads to the correction of the existing genetic defect [4, 6]. Techniques are also employed to target genes to specific cell types (e.g. ETX101, which is directed primarily toward interneurons, as discussed below). In contrast, there have been attempts to correct the activity of epileptic *foci* involving delivering genes directly to the epileptic focus, the products of which affect the function of ion channels, receptors, or the release of neurotransmitters or neurotrophins [7, 8]. One specific method focuses on altering neurotransmitter pathways with the use of genes that enhance inhibitory neurotransmitters such as GABA. Alternative approaches aim to restore the functionality of impaired ion channels, which are usually linked to genetic causes of epilepsy [9].

Another important aspect is that the concept of gene therapy is not limited to introducing 'healthy' gene variants into cells, but also involves influencing gene activity as well as gene editing, by which is meant the correction of genetic material by inserting, replacing, or deleting specific DNA sequences to cure or to alleviate the symptoms of a genetic disease.

It is important to note that, unlike early genetic techniques, which randomly inserted genetic material into a host genome, modern genome editing technologies aim at targeting insertions to specific *loci*. To achieve proper gene modulation, various techniques are used, including antisense oligonucleotides, CRISPR-Cas9, and microRNAs [4].

Gene therapy in its current form remains an approach that is indicated only for those patients who have no other treatment option, including surgical treatment. Most importantly, this is due to the lack of a clearly identifiable epileptic focus, or because the epileptic focus resides in an eloquent cortex. Nevertheless, recent developments in viral vector technology, especially concerning AAV, have significantly enhanced the efficiency and safety of gene delivery to the brain. These vectors possess the ability to selectively target neurons and facilitate prolonged expression of therapeutic genes.

Animal model epilepsy research has shown that gene therapy can even reduce the frequency and severity of seizures. One recent, very interesting, study has examined the potential application of gene therapy in a mouse model of frontal lobe focal cortical dysplasia (FCD) [10]. This study evaluated a gene therapy targeting overexpression of the Kv1.1 potassium channel. The therapy used an engineered potassium channel under a human neuron-specific promoter (calcium/calmodulin dependent protein kinase II alpha) delivered using an AAV9. In this model, gene therapy reduced seizures by 64% without affecting behaviour related to frontal lobe function. This is therefore a promising prospect for the treatment of mTOR-related epilepsy. Preclinical studies have also demonstrated the effectiveness of other therapeutic strategies, including the antiseizure effect of single vector gene therapy for neuropeptide Y and neuropeptide Y2 receptors, dynorphins, GDNF, NaV1.1, Kv1.1, and many others [5, 11–15]. A detailed review of the application of gene therapy in epilepsy models has been carried out by Zhang and Wang [5].

In 2024, several clinical trials evaluating the utility of gene therapy in clinical settings for the treatment of epilepsy got under way. In September, a Phase I/II clinical trial (NCT04601974) was started, investigating the safety of a lentiviral epilepsy gene therapy using an engineered potassium channel in patients with refractory epilepsy. Patients with drug-resistant epilepsy (DRE), qualified for removal of the epileptic focus, are included in the study. The lentiviral vector will be administered via intracerebral infusion to the epileptic focus. The aim of this study is primarily to assess the safety of the lentiviral gene therapy (early and late adverse events) as well as treatment efficacy indicators. The trial's estimated completion date is 2032.

In addition, three clinical trials (NCT06112275, NCT06283212, NCT05419492) were initiated in the first half of 2024 to assess the efficacy and safety of ETX101, an AAV9-delivered gene therapy in children with SCN1A+ Dravet syndrome. ETX101 is administered as an intracerebroventricular infusion using the neurosurgical technique. ETX101 consists of a non-replicating recombinant AAV9 vector, and a transgene coding for an engineered SCN1A-specific transcription factor (eTF^{SCN1A}). Expression of the transgene is controlled by a GABAergic inhibitory neuron-selective regulatory element (RE^{GABA}). This approach is believed to increase the production of $Na_V1.1$ at endogenous levels, while restoring inhibitory function and minimising potential off-target effects [16]. The primary measure of the success of the intervention will be the percentage change from baseline in the monthly seizure frequency at Week 52, post-ETX101 administration. Countable seizures are generalised tonic-clonic or clonic seizures, focal motor seizures with clearly observable clinical

manifestations, tonic bilateral seizures, and atonic seizures. Another parameter to be looked at is the number of participants remaining free from prolonged seizures and/or status epilepticus by Week 52. The estimated completion dates for these trials are 2029 for two of them and 2031 for the third (ClinicalTrial.gov, accessed 18/10/2024).

Human clinical trials for gene therapy are still in their early stages, but have shown promise for selected forms of genetic epilepsy. Despite this progress, significant hurdles remain to delivering gene therapies safely. An example could be the issue of neuroinflammation induction as a result of using viral vectors, which is a significant factor that increases the risk of exacerbating seizures. Moreover, relatively little is known about long-term toxicity or about interactions of gene therapies with the human immune system. The issue of gene therapy safety is very broad, and goes beyond the scope of this paper.

Machine learning

An accurate seizure and epilepsy diagnosis presents difficulties, and setting the most suitable treatment with a high prediction of response is also demanding. One of the significant challenges in accurately diagnosing and personalising treatment for patients is the issue of precise and timely analysis of diagnostic tests, both morphological, e.g. MRI, and functional, e.g. EEG or video EEG. Therefore, in recent years, artificial intelligence (AI) and machine learning (ML) have garnered significant attention as offering hope of interpretation of complex and ambiguous clinical epilepsy data [17]. AI simulates human intelligence processes using computer systems, while ML is a subtype of AI with the ability to learn on the basis of data provided rather than making decisions following predefined routines.

ML in interpretation of EEG data

Several ML models has been developed for EEG spike detection [17]. SpikeNet was trained using 9,571 scalp EEG recordings for detection of interictal epileptiform discharges (IEDs) and has been found to classify EEGs recording as IED-positive and IED-negative with an accuracy of 65%, sensitivity of 67%, and specificity of 63% [18, 19]. Another study has also reported the validation of an ML model for the detection of epileptiform discharges, but using a small amount of labelled EEG data for training (n = 100) [20]. The model had a sensitivity of 89%, specificity of 70%, and accuracy of 80%. Moreover, a comprehensive, fully automated AI-based interpretation model has been developed and validated — SCORE-AI (Standardised Computer-based Organised Reporting of EEG-Artificial Intelligence). SCORE-AI was found not only to distinguish normal from abnormal recordings, but also to be able to categorise EEG recordings as epileptiform-focal, epileptiform-generalised, non-epileptiform-focal, or non-epileptiform-diffuse. SCORE-AI achieved efficacy comparable to that of human experts in the interpretation and categorisation of EEGs [21]. In another study, SCORE-AI was found to achieve human expert performance in interpreting EEGs in a geographically distinct patient population and obtained from different equipment and settings than those used for model development [22]. Thus, it has a strong potency for broad clinical implementation.

ML in interpretation of neuroimaging results

AI has also been considered for neuroimaging analysis. In epilepsy, AI tools have been used in patients with established epilepsy to help detect and localise seizure focus for further management and prediction of disease progression [23]. Proper neuroimaging analysis is particularly important, as brain malformations are a leading cause of DRE. It has been found that early detection and resection of epilepsy lesions favour postoperative seizure freedom. However, despite the development of neuroimaging techniques, detecting malformations is still challenging, as they sometimes blend into surrounding tissues.

Multicentre validated deep learning algorithms has been developed to detect FCD using MRI from 148 patients. It has been found that the developed model accurately indicated patients with FCD who were initially diagnosed as MRI-negative. Generalisability across patient ages and MRI equipment was found [24]. A 3D convolutional neural network (CNN) using MRI data from 158 patients for training was also developed for FCD detection. This model presented high sensitivity and low specificity; however, it still favoured automated detection, as the number of false-positive lesions was lower compared to morphometric analysis [25]. A CNN algorithm for examiner-independent FCD detection and segmentation using MRI data from 180 patients was learned and exhibited high sensitivity and specificity (sensitivity of 90%, specificity of 70%) [26]. In one study, PET results were used alongside MRI for training. It was found that without PET data, the sensitivity of the model decreased from 90% to 80% [27].

Developed algorithms has been shown to indicate epilepsy lesions with high sensitivity and specificity and are believed to be used in everyday clinical practice. This is particularly important as some patients suffer from misdiagnosis regarding the presence of malformation, which in turn delays the decision to undergo neurosurgical treatment and impacts upon the overall outcomes for the patients.

Predicting results of pharmacological treatment

Despite advances in non-pharmacological treatments, including resective surgery, neuromodulation, and dietary therapies, drug therapy remains the primary and first-line approach for epilepsy management. However, selecting the appropriate pharmacotherapy still largely relies on trial and error, with nearly 30% of patients experiencing DRE, meaning a poor response to ASMs. Although general guidelines exist based on

seizure types, there is currently no reliable way to predict the most effective drug for each individual patient. Consequently, in recent years, an increasing number of studies have focused on using ML models to predict treatment responses in epilepsy.

Based on clinical data collected from 786 patients with epilepsy, seven classical ML algorithms have been trained to predict the response to ASMs. Two models — Extreme Gradient Boost (EGB) and Support Vector Classifier (SVC) — demonstrated superior predictive value for ASMs treatment outcomes [28]. Prediction of ASMs treatment response using EGB and SVC models may be valuable in optimising treatment strategies, particularly in the context of personalised medicine. In a study involving children (aged 1–24 months), 11 models were compared to identify the best model for predicting treatment outcomes. The Support Vector Machine algorithm was found to be the best fitted for detection of drug resistance, with accuracy of 97% and AUC of 0.9934, suggesting its potential as a supportive tool for paediatric neurologists in epilepsy management [29]. Using the quantitative EEG features and ML, an algorithm was developed to predict therapeutic effects of valproic acid patients with childhood absence seizure. Responders had higher alpha band power and lower delta band power compared to non-responders. Among the models tested, K-nearest Neighbour had the best performance with sensitivity of 92.31%, specificity of 76.92%, accuracy of 84.62%, and area under the curve of 88.46% [30].

Using ML in the field of epilepsy treatment and management is rapidly evolving and may yield significant benefits. AI can identify patterns and correlations that are not easily detectable by traditional methods and contribute to the better prediction of pharmacological treatment and faster reaching of alternative options, optimising drug selection based on individual patient profiles, but also continuous monitoring and adjustment of treatment. However, while AI holds significant promise in predicting pharmacological treatment responses, it still faces challenges related to data quality, model transparency, ethical considerations, and real-world applicability. Overcoming these limitations will be crucial for realising the full potential of AI in personalised medicine.

New delivery routes for ASMs

One strategy of seeking alternative options for drug-resistant seizure treatment is to develop new delivery routes for ASMs, which can improve efficacy, enhance patient compliance, and address various clinical scenarios such as rapid seizure control in emergencies or challenges with oral administration (Tab. 1).

Intranasal administration

The primary rationale for intranasal ASMs development lies in fast absorption through the nasal mucosa, which allows efficient systemic drug circulation and provides fast seizure control, especially for seizure emergencies like status epilepticus. Additionally, intranasal administration is non-invasive and can be administered by caregivers or in emergency situations without requiring IV access. Two intranasal products for the acute treatment of cluster seizures have been approved by the US Food and Drug Administration (FDA): midazolam (Nayzilam®) for patients aged 12 and older in 2019, and diazepam (Valtoco®) for patients aged 6 and older in 2020. The European Medicines Agency (EMA) also granted marketing authorisation for intranasal midazolam (Nasolam®) in 2022 in

Table 1. Advantages and challenges for intranasal, inhaled and transdermal delivery of antiseizure medications (ASMs)

Delivery route	Advantages	Challenges
Intranasal administration	– Fast absorption – Rapid seizure control – Non invasive – Can be administered by caregivers or in emergency situations – Direct path to brain – Improved patient compliance (avoiding gastrointestinal absorption) – Avoidance of first-pass metabolism	– Limited surface area of nasal cavity – Individual anatomical and physiological differences of nasal cavity – Short-term effect – Challenges in self-administration – Not all ASMs are suitable for intranasal delivery
Inhaled delivery	– Rapid absorption through lungs – Non invasive – Easy self-administration in cases of a seizure aura – Improved patient compliance (avoiding gastrointestinal absorption) – Avoidance of first-pass metabolism	– Individual anatomical and physiological differences, e.g. respiratory rate, lung capacity, that affect drug absorption – Requires specialised training for effective device use – Not all ASMs are suitable for inhalation
Transdermal delivery	– Continuous drug delivery (chronic treatment) – Easy to use – Non invasive – Reduced risk of gastrointestinal side effects – Discreet administration – Avoidance of first-pass metabolism	– Limited skin penetration for most of ASMs – Variable absorption due to individual differences in skin thickness, hydration levels, and skin integrity – Potential skin irritation

ASMs — antiseizure medications

the Netherlands, Denmark, Germany, Finland, Ireland, Sweden, Norway, and the United Kingdom (Northern Ireland) [31].

Treatment success was achieved in 53.7% of patients treated with intranasal midazolam compared to 34.4% of placebo-treated patients (P = 0.0109). Also, fewer patients receiving intranasal midazolam had seizure recurrence (38.1% vs 59.7%; P = 0.0043). Sixteen patients (5%) discontinued due to a treatment-emergent adverse event during test dose phase, and none during outpatient comparative phase. During comparative phase, 27.6% of midazolam treated compared to 22.4% of placebo patients experienced ≥ 1 treatment emergent adverse event (TEAE). The most frequently reported adverse reactions to intranasal midazolam include somnolence, headache, nasal discomfort, throat irritation, and rhinorrhoea [32]. For intranasal diazepam, the most commonly observed adverse events were somnolence, headache, and nasal discomfort, reported by nearly 4% of patients [33]. Available intranasal ASMs were designed to reach similar systemic exposure as earlier applied formulations, for example rectal and intravenous. However, a second approach to intranasal ASM administration involves its potential for chronic treatment. In recent years, there has been an increase in research on the potential use of intranasal administration of medications intended for long-term (chronic) treatment, such as lamotrigine and carbamazepine [34, 35]. This approach raises hope for reducing systemic exposure while simultaneously targeting brain tissue more effectively.

Inhaled delivery

In recent years, an inhaled formulation of alprazolam — Staccato® alprazolam — has been under development. This formulation is designed for rapid absorption and quick onset of action. Inhaled alprazolam bypasses first-pass metabolism in the liver, leading to increased bioavailability and more effective dosing. Additionally, due to its direct delivery into the bloodstream through the lungs, a reduction in side effects associated with gastrointestinal absorption is anticipated (Tab. 1).

According to clinicaltrial.gov, three clinical studies on Staccato® alprazolam have been completed: one Phase I study for dose selection (NCT04857307; [36]) and two Phase II studies assessing efficacy and safety (NCT03478982; NCT02351115). All doses of staccato alprazolam reduced the standardised photosensitivity range within 2 minutes, with effects lasting 4 hours for the 0.5 mg dose and 6 hours for the 1 and 2 mg doses [37] . For the 1 and 2 mg doses, the proportion of responders was 65.8% (P = 0.0392), compared to 42.5% (P = 0.0392) for placebo in patients with stereotypic seizure episodes involving prolonged or repetitive seizures [38]. The most common adverse events were cough, somnolence, and dysgeusia, generally of mild to moderate intensity. Staccato® alprazolam effectively terminated seizures and was well-tolerated. The next step will be a Phase III confirmatory study to establish the efficacy and safety of Staccato® alprazolam for rapid seizure cessation.

Transdermal delivery

Transdermal delivery of ASMs offers a novel, non-invasive method of medication administration for patients with epilepsy, particularly for those who may have difficulties with oral intake or require chronic treatment. While transdermal ASMs are not yet available, they are under investigation. The effectiveness and tolerability of two drugs — cannabidiol and fosphenytoin — are being studied for potential use in transdermal formulations. However, for fosphenytoin, clinical trials have so far focused only on neuropathic pain management.

In an open-label trial, cannabidiol transdermal gel achieved a ≥ 44% median reduction in focal impaired awareness, focal to bilateral tonic-clonic, and generalized tonic-clonic seizures in children and adolescents with developmental and epileptic encephalopathies. Additionally, 58% of participants reported improvements in alertness, awareness, and energy [39]. In a nonrandomised controlled trial, transdermal cannabidiol treatment led to a 58% reduction in monthly seizures at 5 months and a 43.5% reduction over the entire 6.5-month study period for focal impaired awareness seizures and tonic-clonic seizures. The cannabidiol transdermal gel was generally well-tolerated, with mild to moderate side effects observed in a minority of participants. Further studies are recommended to determine optimal dosing and evaluate efficacy [40].

Transdermal delivery of antiseizure medications is a promising area, especially for chronic seizure control and patient convenience. Transdermal delivery of ASMs requires drugs that can effectively penetrate the skin. Further clinical trials are underway to determine the full efficacy, safety, and scope of these treatments in epilepsy management.

New ASMs

Despite advances in epilepsy treatment methods, including those described above, pharmacotherapy remains the main tool for managing seizures. In this review, we have presented the most important data about drugs that have received authorisation from the EMA over the past five years. The drugs that have emerged during this period include (in order of their appearance) cannabidiol (Epidyolex — date of authorisation: 19 September 2019), fenfluramine (Fintepla — date of authorisation: 18 December 2020), cenobamate (Ontozry — date of authorisation: 26 March 2021), and ganaxolone (Ztalmy — date of authorisation: 26 July 2023).

Cannabidiol

Cannabidiol (Epidyolex) is a drug that has been registered for use in patients aged two and older as adjunctive therapy for seizures associated with tuberous sclerosis complex (TSC) as well as with Lennox-Gastaut syndrome and Dravet syndrome (in conjunction with clobazam). The proposed mechanism of action responsible

for cannabidiol's effectiveness in treating seizures involves reducing neuronal hyper-excitability through its influence on GPR55 receptors (G protein-coupled receptor 55) and TRPV-1 (transient receptor potential vanilloid 1 channels), as well as inhibition of adenosine cellular uptake via the nucleoside transporter 1 (ENT-1).

The efficacy of cannabidiol in adjunctive therapy for patients with TSC (patients simultaneously used at least one antiseizure medication) was evaluated in a double-blind, placebo-controlled randomised clinical trial. It was shown that using cannabidiol at doses of 25 and 50 mg/kg/day leads to almost identical reductions in seizure frequency by 48.6% ($P < 0.001$) and 47.5% ($P < 0.002$), respectively. Given the identical efficacy of both doses, the maximum recommended dose of the drug for TSC is 25 mg/kg/day. In the group receiving 25 mg/kg/day of cannabidiol, a reduction in seizure frequency by 50% or more was achieved in 36% of patients ($P < 0.07$). The study also confirmed the additive antiseizure effect of using cannabidiol with clobazam. The safety profile was acceptable, with the most common adverse effects being diarrhoea and drowsiness. Additionally, increased liver enzyme levels were observed in the cannabidiol groups [41].

Cannabidiol has also proven to be effective in preventing seizures in Dravet syndrome. In one of the key randomised, placebo-controlled trials conducted on children and young adults, it was shown that patients receiving cannabidiol had a 39% median reduction in seizure frequency [from 12.4 to 5.9 seizures per month; ($P < 0.01$)] compared to a 13% reduction in the placebo group (from 14.9 to 14.1 seizures per month). Additionally, 43% of cannabidiol-treated patients achieved a ≥ 50% reduction in seizures, compared to 27% in the placebo group ($P = 0.03$). The safety profile, similar to that in studies with TSC patients, was acceptable, with the most common adverse events being diarrhoea, vomiting, fatigue, fever, drowsiness, and abnormal liver-function test results [42].

Similar results were obtained in another randomised, double-blind, placebo-controlled study conducted on a group of 198 patients. It was found that administering cannabidiol at a dose of 10 mg/kg/day compared to placebo resulted in a reduction in seizure frequency by 29.8% (95% CI, 8.4%–46.2%; $P = 0.01$), while for the 20 mg/kg/day dose, the reduction was 25.7% (95% CI, 2.9%–43.2%; $P = 0.03$). At least a 50% reduction in seizure frequency compared to baseline was observed in 43.9% of patients receiving cannabidiol at a dose of 10 mg/kg/day ($P = 0.03$) and in 49.3% for the 20 mg/kg/day dose ($P = 0.007$). As in the previous study, the most common adverse events were decreased appetite, diarrhoea, drowsiness, fever, and fatigue [43].

Besides the previously mentioned Dravet syndrome and TSC, cannabidiol is also registered for the treatment of seizures associated with Lennox-Gastaut syndrome. The key study that evaluated and confirmed the drug's efficacy and safety in this indication was a multicentre, double-blind, placebo-controlled trial involving 225 patients. It was shown that using cannabidiol at doses of 10 and 20 mg/kg/day led to a significant reduction in seizure frequency by 41.9% ($P = 0.005$) and 37.2% ($P = 0.002$), respectively, compared to placebo. Additionally, a 50% reduction in seizure frequency was observed in 39% ($P < 0.001$) of patients in the 20-mg/kg/day cannabidiol group and in 36% ($P = 0.003$) in the 10-mg/kg/day cannabidiol group compared to placebo. The most common adverse events among patients in the cannabidiol groups were drowsiness, decreased appetite, and diarrhoea, with these events occurring more frequently in the higher-dose group [44].

Fenfluramine

Fenfluramine (Fintepla) is a drug that, similarly to cannabidiol, has been approved as an add-on therapy to other antiseizure medications for the treatment of seizures associated with Dravet syndrome and Lennox-Gastaut syndrome in patients aged two and older. The mechanism of action of fenfluramine is based on stimulating the release of serotonin, leading to the activation of serotonin receptors 5-HT1D, 5-HT2A, 5-HT2C, and sigma-1 receptors. It is believed that this action restores the balance between excitatory and inhibitory systems, thereby reducing the frequency of seizures. The drug's efficacy in Dravet syndrome was verified in randomised, placebo-controlled clinical trials, where fenfluramine was administered at doses of 0.2 mg/kg/day and 0.7 mg/kg/day in patients who had not responded to at least one prior treatment (the most commonly used drugs being valproate, clobazam, topiramate, or levetiracetam). In patients treated with fenfluramine at a dose of 0.7 mg/kg/day, the reduction in seizure frequency reached 62.3% ($P < 0.001$) compared to placebo. Simultaneously, the percentage of patients with a 50% reduction in seizure frequency reached 68%, and in patients with a 75% reduction in seizures reached 50% [45]. The combination of fenfluramine at a dose of 0.4 mg/kg/day with stiripentol was also effective, with the percentage of patients achieving a more than 50% reduction in seizure frequency being 54.9% ($P < 0.001$) [46].

The efficacy of fenfluramine in patients with Lennox-Gastaut syndrome, administered at doses of 0.2 mg/kg/day and 0.7 mg/kg/day, was evaluated in a randomised, double-blind, placebo-controlled study. A 26.5% reduction in the median seizure frequency was observed in the group treated with the higher dose of fenfluramine, and 25% of patients achieved a 50% or greater reduction in seizure frequency [47].

The safety profile of the drug in patients with Dravet or Lennox-Gastaut syndromes is satisfactory. However, due to the risk of valvular heart disease, which was identified during the use of fenfluramine for obesity treatment (at doses much higher than those recommended for the treatment of seizures), it is recommended to perform regular ECHO exams both before starting the drug and during treatment (every six months during the first two years of therapy, and then annually). Additionally, it should be noted that patients

with pulmonary hypertension and valvular heart disease were excluded from the conducted clinical trials. An important advantage of fenfluramine also appears to be its positive impact on quality of life, sleep quality, cognitive functions, attention span, and reaction speed. Moreover, it seems that this effect may be independent of the reduction in seizure frequency [48, 49].

Cenobamate

Cenobamate (Ontozry) is a drug indicated for adjunctive therapy in adult patients with focal-onset seizures, with or without secondary generalisation, who have not achieved adequate disease control with at least two antiseizure drugs. It is important to note that this indication applies in Europe, whereas in the US it is not limited to patients with insufficient response to standard treatment. Cenobamate combines two primary mechanisms of action. Firstly, it affects sodium channels by inhibiting the late sodium current, and secondly it enhances GABAergic activity by influencing GABA-A receptors. Unlike many classic GABAergic antiseizure medications, which primarily affect GABA receptors responsible for phasic inhibition (containing the γ2 subunit), cenobamate also enhances tonic inhibition by acting on extrasynaptic GABA-A receptors, containing the δ subunit, which are generally insensitive to benzodiazepines. This mixed mechanism of action appears to contribute to its effectiveness across various types of seizures.

The drug's efficacy has been confirmed in phase II and III studies in adult patients with focal seizures who failed to achieve seizure control with 1–3 antiseizure medications, and these results formed the basis for the drug's approval [50, 51]. In the first study, the percentage of patients who achieved a 50% or greater reduction in seizure frequency while on cenobamate was 50.4% (placebo 22.2%) [50]. In the second study, the percentage of patients on cenobamate who became seizure-free reached 4%, 11%, and 21% (placebo 1%) after using the drug at 100, 200, and 400 mg, respectively [51]. It has been shown that cenobamate is effective regardless of baseline seizure frequency, disease duration, the number of previous treatment lines, or even in patients for whom epilepsy surgery had failed [52]. Also, it has been shown that crushed cenobamate, administered orally or via a nasogastric tube, demonstrates comparable bioavailability to the intact tablet, suggesting its suitability for alternative administration methods [53].

The drug's safety profile is acceptable, with typical adverse events including ataxia, balance disorders, dizziness, drowsiness, double vision, and gastrointestinal issues (constipation and diarrhoea). Cenobamate continues to be the subject of many clinical trials, and the amount of data available on its efficacy and safety is growing rapidly. In particular, results are awaited from studies on the use of cenobamate in the paediatric and adolescent population (aged 2–18 years) with drug-resistant focal seizures.

Ganaxolone

Ganaxolone (ZTALMY) is a drug approved for the adjunctive treatment of epileptic seizures associated with cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder (CDD) in patients aged 2–17 years, with the possibility of continuing treatment beyond 18 years of age. CDD is an ultra-rare disease, with an estimated frequency of 2.36 cases per 100,000 live births, which, besides intellectual disability and cortical visual impairment, is characterised by various types of epileptic seizures that are typically resistant to pharmacological treatment. Until recently, CDD was considered an atypical form of Rett syndrome (the Hanefeld variant), but it is now recognised as an independent disorder.

Ganaxolone is a neurosteroid, an analogue of allopregnanolone, belonging to the GABAergic class of drugs. Structural modifications to ganaxolone ensure its acceptable bioavailability, which was a significant obstacle to the clinical use of allopregnanolone. Ganaxolone's mechanism of action is based on the positive allosteric modulation of GABA-A receptors, located both synaptically and extrasynaptically. This feature is crucial for the drug's efficacy, as extrasynaptic GABA-A receptors do not undergo internalisation and do not become functionally inactive following prolonged seizures [54]. No other targets for ganaxolone related to its antiseizure action are known. It is important to note that ganaxolone's bioavailability increases several times when taken with food; therefore, it should always be administered with or shortly after a meal.

In the randomised phase III MARIGOLD trial, it was shown that adjunctive therapy with ganaxolone in patients with CDD and drug-resistant seizures, who had previously failed up to four lines of treatment, led to a 30.7% reduction in seizure frequency (compared to a 6.9% reduction in the placebo group, $P = 0.004$). The responder rate, defined as the percentage of patients achieving a 50% or greater reduction in seizure frequency, was 24% in the ganaxolone group vs. 10% in the placebo group ($P = 0.064$) [55]. The drug's safety profile is acceptable, with the most common adverse events being drowsiness, dizziness, and fatigue. Ganaxolone's effectiveness has also been evaluated in drug-resistant focal epilepsy, drug-resistant status epilepticus, and in the treatment of seizures associated with tuberous sclerosis and protocadherin 19 (PCDH19) clustering epilepsy, with promising results, although these indications require further research. However, in certain conditions, such as infantile spasms or drug-resistant partial-onset seizures, ganaxolone did not demonstrate efficacy. Ganaxolone is also being investigated for potential use in other conditions such as postpartum depression, post-traumatic stress disorder (PTSD), and in reducing the behavioural symptoms of Fragile X syndrome.

Drugs in development

In addition to the described drugs, several substances with antiseizure properties are currently being evaluated in ongoing

phase II and III clinical trials. A brief overview of the most promising substances is presented below.

SPN-817 is a new synthetic form of huperzine A. Huperzine A is a sesquiterpene alkaloid derived from Huperzia serrata. Its antiseizure mechanism of action is not fully understood. It is postulated that the reduction in neuronal hyperexcitability results from its dual activity as an acetylcholinesterase (AChE) inhibitor and NMDA receptor antagonist. In addition, it possesses neuroprotective properties, including the modulation of neurotrophin signalling, suppression of neuroinflammation, and protection of the blood-brain barrier, which helps prevent neurovascular damage. No evidence supports its influence on GABA release or receptor activation. In preclinical studies, it has demonstrated effectiveness in partial seizures and Dravet syndrome. SPN-817 has received Orphan Drug designation for both Dravet syndrome and Lennox-Gastaut syndrome from the FDA. A multicentre clinical trial (NCT05518578) evaluating the safety and tolerability of SPN-817 in adult patients with DRE has now begun.

An interesting drug currently in development is BHV--7000, which is a selective activator of Kv7.2/7.3 potassium channels. Potential indications include psychiatric disorders (depression and bipolar disorder) as well as epilepsy. Currently, the drug's efficacy and safety are being evaluated in three multicentre clinical trials for the treatment of adult patients with treatment-resistant partial seizures, as well as patients with generalised tonic-clonic seizures (NCT06309966, NCT06132893, NCT06425159).

Other drugs in the sodium channel group include NBI-921352 and PRAX-562. NBI-921352 is an inhibitor of NaV1.6 sodium channels. In preclinical studies, the drug demonstrated efficacy in preventing seizures in Scn8a gain-of-function mice, and wild-type mice and rats. Currently, there is a trial evaluating the efficacy and safety of NBI-921352 as an add-on therapy for treating seizures in patients with SCN8A Developmental and Epileptic Encephalopathy Syndrome (SCN8A-DEE) (NCT04873869). A Phase II randomised trial evaluating the pharmacokinetics, efficacy, safety, and tolerability of the drug as an add-on therapy in patients with focal onset seizures has been completed, but the results are not yet available (NCT05159908).

On the other hand, PRAX-562's mechanism of action involves inhibiting the persistent sodium current. Preclinical studies have shown that the drug is similarly effective to carbamazepine and somewhat more effective than lamotrigine, with a noticeably better safety profile [56]. A Phase II double-blind, randomised trial (NCT05818553) evaluating the safety, tolerability, efficacy, and pharmacokinetics of PRAX-562 in children with seizures associated with SCN2A-DEE and SCN8A-DEE is currently ongoing.

ES-481 acts by targeting transmembrane AMPA receptor regulatory proteins (TARP)-gamma 8-dependent AMPA receptor, which regulates fast excitatory transmission. Currently, its efficacy in treating epileptic seizures is being evaluated in a Phase II randomised, double-blind, placebo-controlled study in adult patients with drug resistant epilepsy (NCT04714996).

A very interesting drug currently being evaluated for its antiseizure effects in clinical trials is soticlestat. Its mechanism of action is distinct from currently available drugs and involves inhibiting the brain-specific enzyme cholesterol 24-hydroxylase (CH24H), which is responsible for converting cholesterol into 24S-hydroxycholesterol (24HC), thereby lowering its level. The reduction of 24HC leads to decreased TNF-α levels and is associated with increased functional EAAT2 in peri-synaptic astrocytes. These processes result in a reduction of extracellular glutamate levels and decreased neuronal hyperexcitability [57]. A multicentre, open-label, pilot study of soticlestat (TAK-935/OV935) in participants with 15Q Duplication Syndrome (Dup15q) or Cyclin-Dependent Kinase-Like 5 (CDKL5) Deficiency Disorder (the ARCADE study) found that adjunctive soticlestat treatment was associated with a decrease in motor seizure frequency from baseline in patients with CDD and a reduction in all seizure frequency in both patient groups. However, soticlestat treatment was associated with an increase in motor seizure frequency in patients with Dup15q syndrome [58]. The efficacy, safety, and tolerability of the drug were also evaluated in a randomised, placebo-controlled trial in paediatric and adult subjects with Lennox-Gastaut syndrome. Preliminary results, however, do not indicate efficacy in this patient population (ClinicalTrial.Gov, accessed 16 October 2024). The results of a completed randomised, controlled trial that evaluated the efficacy, safety, and tolerability of soticlestat as adjunctive therapy in paediatric and young adult subjects with Dravet syndrome (NCT04940624) are not yet available. Another open-label Phase III trial, which is an extension of the above studies in the population, is ongoing as adjunctive therapy in subjects with Dravet syndrome or Lennox-Gastaut syndrome (ENDYMION 2).

The last promising drug in development is AMT-260. This is an AAV9 gene therapy product that locally delivers miRNA silencing technology to target the GRIK2 gene and suppress aberrantly expressed GluK2-containing kainate receptors. Currently, a first-in-human Phase I/IIa study is being conducted in the US (NCT06063850). The trial will evaluate the safety, tolerability, and efficacy of AMT-260 in 12 patients with refractory unilateral mesial temporal lobe epilepsy administered via MRI-guided convection-enhanced delivery. The study is expected to be completed by 2027. The therapeutic goal is to reduce the expression of GluK2-containing kainate receptors, which play a crucial role in neuronal hyperactivity within the hippocampal structures.

Conclusions and future directions

The treatment of epilepsy remains one of the biggest challenges for modern medicine. In spite of obvious progress in the efficacy of current methods, they still seem to be insufficient

for a considerable group of patients. On the other hand, there is a dynamic development of therapeutic strategies with the introduction of new ASMs, new routes of administration, and gene therapy, which is increasingly used in the treatment of epilepsy.

It is also worth noting the broader application of different methods to predict response to treatment using machine learning and artificial intelligence which is bringing the idea of personalised medicine closer to reality. As personalised treatment becomes increasingly available, we can expect a significant improvement in the quality of life for patients who have previously been resistant to conventional therapies.

Over the next few years, we are likely to witness major advances in the treatment of epilepsy, awaited by neurologists, and most importantly, by patients. The increasing amount of research and clinical trials will most probably result in these advances becoming the standard of care in the not-so-distant future.

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