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The Evolving Epilepsy Treatment Spectrum: A Review of Antiepileptic Drugs in Late Development

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Epilepsy is a condition that causes seizures and has a significant impact on quality of life (QOL).¹ The goal of treatment is to eliminate seizures with minimal or no adverse events, and many options are available to help achieve this goal, ranging from surgery to diet to devices.² Antiepileptic drugs (AEDs) are often the first treatment measure.³ Despite the availability of more than 20 FDA-approved AEDs for the treatment of epilepsy, treatment outcomes have remained relatively unchanged for the past 20 years.⁴ Roughly 45% of patients achieve seizure freedom via AED monotherapy, but subsequent regimens are associated with much less success (11.6% and 4.4% of patients achieve seizure freedom on their second and third regimens, respectively).⁴

Given the relatively static rate of seizure freedom with the current AED armamentarium, a need remains for the development of new compounds to help enable more patients to achieve seizure freedom (zero seizures). Fortunately, several investigational therapeutic agents and delivery systems are in phase 3 development, which are being investigated for the treatment of orphan diseases (rare forms of epilepsy), focal (partial-onset) seizures, and generalized tonic-clonic seizures. This article provides a pipeline update on investigational AEDs and delivery systems in phase 3 trials.

DRUG PIPELINE UPDATE

Cenobamate

Cenobamate has been developed for the treatment of focal (partial-onset) seizures in adults.⁵ It is believed to work through 2 mechanisms: enhancing inhibitory currents through positive modulation of γ -aminobutyric acid type A (GABA_A) receptors and decreasing excitatory currents by inhibiting the persistent sodium current.⁶ In February 2019, the FDA accepted a New Drug Application (NDA) based on the results from 2 phase 2 trials and a long-term phase 3 safety trial.^{5,6}

In one of phase 2 trials, a randomized, double-blind, dose-response study, 437 patients were split into different arms to receive cenobamate 100 mg/d (n = 108), 200 mg/d (n = 110), 400 mg/d (n = 111), or placebo (n = 108) for 18 weeks.⁷ Presented at the 2018 American Academy of Neurology annual meeting, results showed that median seizure frequencies decreased for all doses of cenobamate: Patients who received 100 mg/d experienced a 35.5% reduction, those who were administered 200 mg/d

had a 55.0% reduction, and the 400 mg/d group saw a 55.0% drop. In comparison, the placebo group experienced a 24.0% reduction in median seizure frequency. For patients with simple partial seizures, median frequencies decreased by 48.0% in the 100 mg/d group, 63.0% in the 200 mg/d group, 58.5% in the 400 mg/d group, and 7.0% in the placebo group.⁷ For patients with complex partial seizures, median frequencies decreased by 55.0% in the 200 mg/d group, 60.0% in the 400 mg/d group, and 28.5% in the placebo group.⁷ For patients with secondary generalized tonic-clonic seizures, median frequencies decreased by 91.0% in the 200 mg/d group, 78.0% in the 400 mg/d group, and 33.0% in the placebo group.⁷

In the early clinical development of cenobamate, 3 patients were confirmed to have experienced a drug reaction with eosinophilia and systemic symptoms (DRESS). A large phase 3 safety trial is assessing whether a titration rate slower than the rates used in the earlier phase 2 studies would reduce incidence of DRESS in patients receiving cenobamate. Results from an interim study report were presented at the 2018 American Epilepsy Society Annual Meeting and showed no cases of DRESS with a slower titration schedule.⁸ Additional ongoing trials include a phase 3 trial evaluating the efficacy and safety of cenobamate as adjunctive therapy for primary generalized tonic-clonic seizures.⁹

Fenfluramine

Another AED in phase 3 development for the treatment of epilepsy is fenfluramine, which affects serotonin levels in the brain. Preliminary data show that fenfluramine reduces convulsive seizure frequency and may be a highly effective, well-tolerated treatment for patients with Dravet syndrome, a rare form of epilepsy that affects 1 in 15,700 individuals.^{10,11} In a phase 3 study, patients aged 2 to 18 years were randomized to fenfluramine or placebo twice daily for 14 weeks.¹⁰ Patients who were given fenfluramine 0.8 mg/kg/d had a 63.9% greater reduction in monthly frequency in major motor seizures, and those who received 0.2 mg/kg/d also experienced a seizure reduction of 33.7% compared with placebo.¹²

In April 2019, the FDA denied a review of the marketing application for the drug due to a lack of submission of certain nonclinical studies to allow for examination of the chronic administration of fenfluramine.¹³ Zogenix, manufacturer of fenfluramine, plans to resubmit its NDA in the third quarter of 2019.

Ganaxolone

Ganaxolone, another AED that recently initiated phase 3 trials, is a positive allosteric modulator of synaptic and extrasynaptic GABA_A receptors.¹⁴ The phase 3 Violet study is investigating ganaxolone for the treatment of children with PCDH19-related epilepsy (PCDH19-RE), a rare genetic form of epilepsy.¹⁵ The study will involve up to 70 patients with PCDH19-RE aged 1 to 17 years.¹⁴

Ganaxolone is being developed in intravenous, capsule, and liquid formulations to achieve maximum therapeutic reach.¹⁴ In a previous open-label phase 2 trial involving 11 patients with PCDH19-RE, ganaxolone led to a 25% decrease in median seizure frequency compared with baseline.¹⁴

ENHANCED DRUG DELIVERY SYSTEMS IN PHASE 3 TRIALS

In addition to new AEDs in development, new delivery systems with potential to enhance the efficacy and reduce the toxicity of AEDs are under investigation. For example, the safety and efficacy of long-term treatment with a diazepam auto-injector (AI) was studied in a phase 3 open-label study for the treatment of acute repetitive seizures. A total of 129 subjects were administered 1380 diazepam AI treatments in which 1071 (77.6%) were effective, with no subsequent seizure or rescue during the 12-hour follow-up period.¹⁶

Another delivery system for diazepam in development is NRL-1, an intranasal solution. NRL-1 is being evaluated for the management of patients with epilepsy who are on a stable regimen of AEDs but require intermittent use of diazepam to control cluster or acute repetitive seizures.¹⁷ A phase 3 trial of NRL-1 currently underway is assessing various doses of NRL-1 administered over 12 months: 5, 10, 15, or 20 mg. Dose selection will be based on the patient's weight.¹⁸

CONCLUSIONS AND FUTURE DIRECTIONS

Other monotherapies, adjunctive therapies, and delivery systems for the treatment of epilepsy are in active development and investigation. The availability of new AEDs will offer patients and health care providers more options as they strive to achieve and maintain seizure freedom.

The possibility of increased rates of seizure freedom may be getting closer, as the mechanisms of seizure disorders are increasingly elucidated and newer and more innovative approaches are refined. With unmet needs in the treatment spectrum well established, it is important for pharmacists to understand the evolving epilepsy landscape in order to provide appropriate guidance to patients. Education and awareness regarding new treatments and burden of disease are critical. Moreover, collaboration among health care providers is needed to ensure adherence to medication regimens, attain effective outcomes, and ultimately improve patients' QOL. ♦

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