EPILEPSY

Perampanel—new promise for refractory epilepsy?

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Three recent phase III trials have shown that adjunctive treatment with perampanel—a first-in-class, noncompetitive AMPA antagonist—decreases seizure frequency in patients with refractory focal epilepsy. Although the introduction of perampanel offers more treatment choice for epilepsy, whether it brings urgently needed clinical benefit over existing drugs remains to be addressed.

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Over the past 30 years, 16 new compounds have been approved in the USA or Europe for the treatment of epilepsy, but seizure outcome has not improved substantially. One in three patients with new-onset epilepsy experiences uncontrolled seizures.[1] For patients with uncontrolled focal seizures who are treated with adjunctive modern antiepileptic drugs, less than 10% achieve remission above those who are given placebo.[2] More-efficacious and better-tolerated antiepileptic drugs are clearly a major unmet need in the treatment of uncontrolled focal seizures. With that in mind, perampanel—a drug that has a highly selective mechanism of antiglutamatergic action (Figure 1)—raises hope for better treatment of refractory epilepsy. Indeed, the results of three phase III trials have recently been published, and all report efficacy, safety and acceptable tolerability of perampanel as an adjunctive antiepileptic treatment in patients with uncontrolled seizures.[3–5]

Glutamate, the main excitatory neurotransmitter in the brain, is thought to have a central role in the generation of seizures. Consequently, glutamate receptors, particularly ionotropic *N*-methyl-D-aspartate (NMDA) receptors and α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors, have long been investigated as therapeutic targets in epilepsy.[6] Disappointing clinical results with NMDA antagonists in the 1990s, however, dampened enthusiasm for this approach.[7] Subsequent development and testing of competitive and noncompetitive AMPA antagonists indicated that such drugs may be more effective and tolerable than NMDA antagonists for the treatment of epilepsy, and led to the development of the AMPA antagonist perampanel.[6,8]

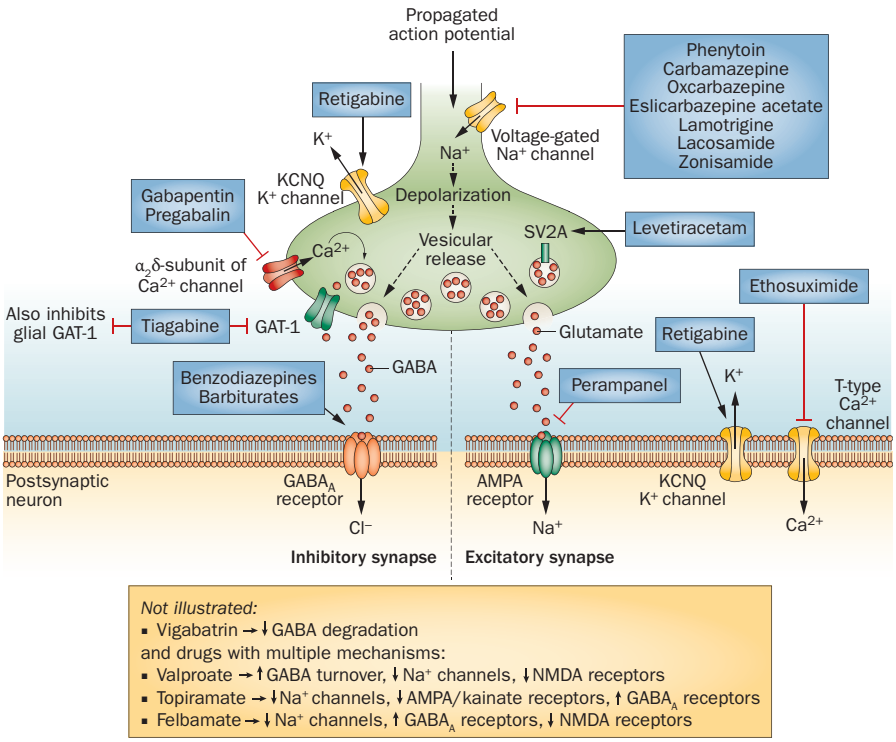

Figure 1 | Mechanisms of action of antiepileptic drugs. Clinically approved antiepileptic drugs such as perampanel display a spectrum of mechanisms of action, with effects on both inhibitory (left-hand side) and excitatory (right-hand side) nerve terminals. Abbreviations: AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid; GABA, γ-aminobutyric acid; GAT-1, sodium- and chloride-dependent GABA transporter 1; SV2A, synaptic vesicle glycoprotein 2A. Modified with permission from Macmillan Publishers Ltd © Bialer, M. & White, H. S. *Nat. Rev. Drug Discov.* **9**, 68–82 (2010).

The AMPA receptor is the predominant mediator of excitatory neurotransmission in the brain, being critical to the generation and spread of epileptic activity.[6] Furthermore, AMPA receptors may have a role in epileptogenesis and seizure-induced brain damage.[6] The development of AMPA antagonists is only the second rational strategy (after the development of γ-aminobutyric acid-mimetic drugs such as vigabatrin or tiagabine in the 1980s and 1990s[7]) that has led to approval of a new antiepileptic drug. Specifically, and unlike the majority of current antiepileptic drugs, which were found or developed after random drug screening, via structural variations of known drugs, or through serendipity, the AMPA antagonist drug

design strategy was based on the basic mechanisms that underlie the generation and propagation of seizures.[1,7]

In July 2012, perampanel was granted market authorization by the European Commission as an adjunctive treatment for partial-onset seizures with or without secondarily generalized seizures in patients with epilepsy who are aged 12 years and older.[9] Three recent phase III trials (designated studies 304, 305 and 306), involving a total of 1,480 patients with uncontrolled partial-onset seizures, reported the efficacy, safety and acceptable tolerability of once-daily 4–12 mg perampanel when added to approved antiepileptic drugs.[3–5] The trials included a 6-week baseline phase and a 19-week double-blind phase, the latter stage involving a 6-week dose titration to reach the target dose followed by a 13-week maintenance period.

> “...one in three patients with new-onset epilepsy experiences uncontrolled seizures”

The investigators found that patients treated with adjunctive perampanel had reduced seizure frequencies and, with one exception,[3] higher responder rates than patients given placebo. Interestingly, in study 304,[3] the lack of difference in outcome between the perampanel and placebo groups was attributable to a substantial placebo response in patients from Central and South America compared with patients from North America, but the basis for such regional differences in response remained unexplained. This observation reminds us that, in patients with epilepsy, we have very little insight into which factors, if any, affect the magnitude of placebo response —a standard control in regulatory trials. For patients who received 12 mg per day perampanel, seizure-free rates corrected on the basis of the maintenance period (excluding patient dropout during titration) were less than 7%, whereas placebo-corrected values indicate that only 5% of patients achieved freedom from seizures.[3,5]

Perampanel was safe and its tolerability was acceptable. Treatment-emergent adverse events occurred in up to 86% of those receiving 12 mg perampanel,[3,4] and led to discontinuation of treatment in 19% of participants in study 304.[3] The most frequent treatment-emergent adverse effects of perampanel were dizziness, somnolence, headache, fatigue and, although infrequent, falls.[3–5] Enzyme-inducing antiepileptic drugs may increase the clearance of perampanel: the responder rate achieved with 12 mg perampanel dropped from 50% to 30% in the presence of perampanel metabolism-inducing antiepileptic drugs such as carbamazepine, oxcarbazepine and phenytoin, whereas co-medication with non-enzyme-inducing antiepileptic drugs did not produce this drop in responder rate. At doses of 12 mg per day, perampanel may decrease the effectiveness of progestative hormonal contraceptives.[9]

The long-term clinical effects of perampanel were assessed in an open-label extension study of 1,218 patients who participated the phase III trials.[10] At the interim analysis, 840 (71%) patients remained on perampanel treatment, with treatment-emergent adverse events reported in 88% of these individuals. No new adverse events emerged during the extension period. In patients for whom 1 year of data was available, the seizure-free rate for the 12-month period was 7%. Although the overall group efficacy of all perampanel-treated patients was maintained over the duration, the extension study did not examine loss of initial efficacy or tolerance in same-patient follow-up, nor did it include a placebo comparison. In addition, the extension study protocol allowed for changes in concomitant therapies that may have contributed to seizure control.

In conclusion, adjunctive perampanel is safe and has acceptable tolerability. This drug reduces the frequency of refractory partial-onset seizures, but only single-digit percentages of patients became seizure free for the duration of the trials.[3–5] Although the study design of these perampanel trials precludes their direct comparison with studies of other antiepileptic drugs, and with the caveat that the study population was restricted to only patients with highly treatment-resistant partial-onset seizures, it seems that perampanel offers no dramatic benefit in efficacy over other modern adjunctive antiepileptic drugs for refractory partial epilepsy.[2] One possible explanation is that single-mechanism drugs are not optimal to address the complex nature of seizure generation. Surprisingly, however, various clinically established antiepileptic drugs that act via diverse mechanisms (Figure 1) seem to have a similar magnitude of clinical efficacy in the treatment of focal seizures as do single-mechanism drugs. The phase III trials[3–5] also raise questions about the validity of placebo controls in such trials. Given the role of AMPA receptors in epileptogenesis and glutamate-induced brain damage, AMPA antagonists such as perampanel may provide more than anti-seizure effects in the treatment of epilepsy, and further investigation into such effects are warranted.

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Competing interests
The authors declare no competing interests.

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