EXPERT REVIEWS

AMPA receptor inhibitors for the treatment of epilepsy: the role of perampanel

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α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors in the postsynaptic membrane are involved in fast excitatory signaling in the brain and their activation may lead to the firing of action potentials. Talampanel and perampanel were the first noncompetitive AMPA receptor antagonists to be tested as add-on drugs in patients with refractory partial seizures, and were found to be effective in improving seizure control. Due to an unfavorable kinetic and tolerability profile, talampanel clinical development in the field of epilepsy was discontinued early while perampanel has been recently approved in Europe and the USA as adjunctive therapy for adults with partial seizures with or without secondary generalization. The recommended perampanel starting dose is 2 mg/day once daily, which can be increased up to the recommended maintenance dose of 4–8 mg/day. Increments should be of 2 mg/day and based on clinical response and tolerability. Titration should be performed at 1-week intervals or at lower speed and a 12-mg daily dose should be considered after careful evaluation. To date, no serious and/or idiosyncratic adverse effects have been associated with this agent. Most frequently reported adverse effects are dizziness, ataxia, aggression, irritability, vertigo, somnolence, fatigue, headache and gait disturbance. Weight increase is the only non-neurological adverse effects associated with perampanel.

KEYWORDS: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors • antiepileptic drugs • drug therapy • epilepsy • partial-onset seizures • perampanel

All antiepileptic drugs (AEDs) have in common the ability to decrease neuronal excitation or increase neuronal inhibition by one or multiple pharmacological processes, including modulation of voltage-gated cation channels, potentiation of GABA-ergic activity, inhibition of glutamatergic processes and/or modification of neurotransmitter release [1,2].

Most frequently, drugs acting on neurotransmitters potentiate inhibition by acting at the $GABA_A$ receptor, either by enhancing the response to synaptically released $GABA_A$ (barbiturates, benzodiazepines) or by altering its synthesis (sodium valproate), metabolism (vigabatrin) or reuptake (tiagabine) at the synapse [3]. AEDs with multiple mechanisms of actions may also decrease neuronal excitability. Felbamate, topiramate and zonisamide block specific subtypes of glutamate receptors leading to a reduction in fast excitatory neurotransmission [4,5].

However, to date, no drug has been developed to specifically target excitatory mechanisms as its main mechanism of action. Perampanel, which is an orally active, noncompetitive antagonist of the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor, is the first agent developed as an AED and has recently received marketing approval in Europe and the USA as adjunctive therapy for adults with focal seizures with or without secondary generalization.

This review will discuss the characteristics of excitatory neurotransmission and will subsequently focus on the mechanism of action, pharmacokinetic and clinical characteristics of this new agent entering the market.

Mechanisms of excitatory neurotransmission

Ionotropic glutamate receptors

In excitatory neurons, action potentials induce the release of glutamate from presynaptic terminals to postsynaptic excitatory and inhibitory neurons. Glutamate is the major excitatory neurotransmitter in the CNS [6] and affects multiple receptors that are also selectively activated by

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a variety of synthetic and naturally occurring neuroexcitatory amino acids. These receptors are classified as NMDA, kainate and AMPA.

AMPA receptors are involved in fast excitatory signaling in the brain and are a critical component of all neuronal networks, and their activation may lead to the firing of action potentials by the postsynaptic neuron. Excitatory synapses generally express both AMPA and NMDA receptors. While AMPA receptors mediate the major component of the synaptic response, NMDA receptors, which are permeable to calcium as well as sodium and potassium and are blocked by magnesium at resting potential, can only be activated after prolonged depolarization of cellular membrane, induced by repetitive activation of AMPA receptors. The NMDA receptor mediates the component of the response that is associated with calcium influx into the postsynaptic neuron and triggers various forms of synaptic plasticity, including long-term potentiation that is of strategic importance in the process of epileptogenesis [7]. Although the role of kainate receptors in the pathophysiology of seizures has not yet been completely understood, it is known that these receptors are located presynaptically at both excitatory and inhibitory synapses where they regulate neurotransmitter release; by contrast, AMPA and NMDA receptors are largely postsynaptic [8].

The structure of AMPA receptors is characterized by tetrameric combinations of four different subunits designated GluA1–GluA4, each encoded by a separate gene [6]. Between these subunits, GluA2 has a critical function. In fact, when this subunit is present in the AMPA receptor, the channel is calcium impermeable; when the subunit is absent AMPA receptors are calcium permeable. In addition, the subunits modulate the sensitivity of AMPA receptors to pharmacological agents, including antagonists [9]. These receptors have an ion-selective central pore that, at resting, is closed to ion flow. Binding of glutamate causes the opening of the pore, which allows cations to flux across the postsynaptic membrane and results in membrane depolarization. Although AMPA receptors are permeable to sodium, potassium and in some cases also calcium, at resting potential sodium is the main carrier of the depolarizing current. The physiology of cation channels associated with AMPA receptors is different from that of voltage-gated sodium channels. While the opening of the first are controlled by a neurotransmitter and are largely insensitive to membrane potential, voltage-gated sodium channels are responsible for neuron's intrinsic excitability [10].

Experimental studies with NMDA & AMPA receptor antagonists

Although NMDA antagonists exert seizure protection in some animal seizure models, most notably the maximal electroshock test and reflex seizure models and also in some chemoconvulsant models, such as pentylenetetrazol-induced clonic seizures, they are not effective against fully kindled seizures and fail to suppress or eliminate epileptiform activity in most *in vitro* seizure models [11]. Furthermore, NMDA antagonists cause toxic symptoms in animal models [10].

AMPA receptor antagonists have a broader spectrum of anticonvulsant activity since they are also effective against fully kindled seizures [10,12] and do not produce the side effects seen with NMDA antagonists in kindled animals [13]. These findings from experimental studies suggest that, while selective NMDA receptor antagonists are unlikely to be useful for the treatment of epilepsy, AMPA receptor antagonists might be useful in the treatment of partial seizures [12,13].

Noncompetitive AMPA receptor antagonists

AMPA receptor antagonists can be competitive and noncompetitive and have similar profiles of efficacy in animal seizure models. However, in the majority of animal models, noncompetitive antagonists have stronger anticonvulsant activity, which may be due to the inability of high glutamate levels to overcome their blocking action, as it occurs during prolonged seizures [14]. These experimental data have encouraged clinical studies of AMPA receptor noncompetitive antagonists in epileptic patients.

Talampanel was the first noncompetitive AMPA receptor antagonist to be tested as add-on drug in patients with refractory partial seizures and it was found of a certain clinical efficacy [15]. However, even though larger trials with this agent were completed [10], clinical development of this agent in the field of epilepsy has been terminated, probably because of an unfavorable ratio between efficacy and tolerability (drowsiness, ataxia and dizziness were the adverse effects most frequently reported). This may be, at least in part, due to its short half-life and an even faster drug metabolism, which is observed when the experimental drug is coadministered with enzyme inducer AEDs (mean talampanel half-life is 5 h in noninduced subjects and approximately 3 h in induced epileptic patients) [16]. It is by far known that large daily fluctuations of blood levels may worsen tolerability of several AEDs [17,18].

Perampanel, a potent and highly selective AMPA receptor noncompetitive antagonist, has been found to be active in several animal models of epilepsy, has not been associated with the behavioral adverse effects of NMDA receptor antagonists [19] and has better pharmacokinetic characteristics than talampanel.

Perampanel

This agent has been tested in some neurologic diseases in which a pathogenetic role is supposed to be played by an increase of excitatory neurotransmission. Since it is known that enhancement of glutamatergic activity in the striatum may modify basal ganglia output and generate treatment-related motor complications [20], perampanel has been studied in patients with Parkinson's disease who are already being treated with levodopa and experienced wearing-off motor fluctuations [21–23]. This was administered with the assumption that inhibition of AMPA-mediated excitatory neurotransmission might improve motor symptoms [24,25]. Results of these studies failed to demonstrate a statistically significant effect of this drug over placebo. Further studies in the field of epilepsy had more favorable results and will be discussed in detail.

Pharmacokinetics

Absorption

After administration of a single oral dose, perampanel is rapidly and almost completely absorbed. This is consistent with a low first-pass metabolism due to a low hepatic extraction ratio. Fasting conditions do not affect the extent of absorption, but slow the drug absorption. With once-daily multiple-dose administration (1–6 mg) under fasting conditions, peak to trough ratios ($C_{min}/C_{max} \times 100\%$) range from 57 to 82% [101].

Distribution

In humans, perampanel is 95.3–95.8% bound to plasma proteins and *in vitro* studies demonstrated that in human plasma, albumin is the principal binding protein, followed by α-1-acid glycoprotein and globulins [101].

Elimination

Perampanel is primarily eliminated by oxidative metabolism (mainly CYP3A4) followed by glucuronidation and fecal and urinary excretion of perampanel metabolites. Approximately 30% of radiolabeled, orally administered dose is found in the urine and 70% in the feces, primarily as a mixture of oxidative and conjugated metabolites.

The mean terminal elimination half-life of perampanel ranges from 53 to 136 h across studies and dose-dependent pharmacokinetic parameters (C_{max} and area under the curve [AUC]) increase proportionally over the dose range studied (0.25–12 mg).

Special populations

No effect of age on perampanel clearance has been detected in a population pharmacokinetic analysis of patients ranging in age from 12 to 74 years, while impaired hepatic function determines a reduction of drug clearance. In mildly and moderately liver-impaired subjects, the unbound perampanel clearance was in fact consistently decreased (from 30 to 70%, respectively) compared with age-matched normal subjects, with a clear increase of drug half-life, which reached 300 h (more than double that of the people with normal liver function). No data are available so far on the pharmacokinetics of perampanel in subjects with renal impairment [101].

Drug interactions

Drug–drug interactions were evaluated in healthy volunteers and in a population pharmacokinetic analysis based on the pooled double-blind studies. The effect of drugs with inducing or inhibiting properties on CYP3A4, the main perampanel metabolizing enzyme, have been tested. Treatment with the inducer carbamazepine, has a clear effect on perampanel kinetic with a threefold increase of clearance and a reduction of half-life up to 25 h. A less evident effect was observed after phenytoin treatment which increased perampanel clearance approximately twofold. Topiramate slightly increased perampanel clearance by 20–30%. On the other hand, treatment with the CYP3A4 inhibitor ketoconazole increased perampanel AUC by 20%. It is suggested that a higher extent of interaction could result from coadministration of itraconazole, a CYPP3A4 inhibitor with a longer half-life. In population studies, no effect was identified of lamotrigine, valproate, levetiracetam, clobazam, zonisamide, clonazepam, phenobarbital and primidone on perampanel clearance [101,102].

Possible drug–drug interaction between perampanel and components of oral contraceptive have been explored and it has been found that perampanel exposure at daily dose of 4 and 8 mg does not affect ethinylestradiol and levonorgestrel clearance; at high doses (12 mg), perampanel induces clearance of levonorgestrel by approximately 40%, although this induction does not appear to be CYP3A4-dependent. The effect on ethinylestradiol was negligible. Perampanel kinetic was not influenced by oral contraceptives. No detailed information is available on possible drug–drug interactions between perampanel and other drugs.

With regard to the effect of perampanel on other drugs, in clinical studies the clearance of almost all the associated AEDs (clonazepam, levetiracetam, phenobarbital, phenytoin, topiramate, zonisamide, carbamazepine, clobazam, lamotrigine and valproic acid) was not changed in a clinically relevant manner by perampanel administration even at high doses. Oxcarbazepine showed a 26% decrease of its clearance and midazolam AUC was decreased by 13% after exposure to a perampanel dose of 6 mg for 20 days (Table 1). Finally, perampanel does not significantly influence levodopa AUC and C_{max} [101].

Therapeutic efficacy

Double-blind studies

Four Phase III, double-blind, parallel, multicenter studies, in which more than 2000 elderly patients were recruited, have assessed the efficacy of perampanel in patients with Parkinson's disease already being treated with levodopa and with motor fluctuations [21–23]. In all studies, perampanel was administered once-daily in add-on fixed daily doses of 0.5, 1, 2 and 4 mg. Slight improvements were observed in primary (comparison of 'off' time during treatment with a baseline) and also in secondary (e.g., changes in motor function during 'on' and 'off' time) efficacy end points. However, no statistically significant differences emerged with respect to placebo-treated patients. In one study,

Table 1. Perampanel: pharmacokinetics and metabolism.

T_{max}	0.5–4.0 h
Bioavailability	Close to 100%
$T_{1/2}$	105 h (up to 25 h in induced subjects and up to 300 h in patients with impaired hepatic function)
Pharmacokinetics	Linear over the dose range studied (0.25–12 mg)
Protein binding	95%
Metabolism	P450 (CYP3A4) and glucuronide derivatives
Excretion	Fecal and urinary excretion of drug metabolites

Data taken from [101].

Table 2. Baseline characteristics of patient included in Phase III epilepsy studies.

	Study 304 [27]	Study 305 [28]	Study 306 [29]
Patients enrolled (n)	534	496	878
Mean age (years, range)†	35.6–36.7	34.4–36.7	33.4–34.6
Female gender (%)	48.5–55.4	47.8–58.7	48.6–54.4
Median seizure frequency (range)†	12–14.3	11.8–13.7	9.3–10.9
Baseline treatment (range)†			
– 1 AED (%)	12.4–19.5	7–12.5	11–16.7
– 2 AEDs (%)	52.6–61.2	47.1–52.7	44.4–51.2
– 3 AEDs (%)	24.6–34.7	34.9–40.5	35.5–38.9
Mean duration of epilepsy (years, range)†	23–24	21–22	19.1‡
Patients with secondarily generalized seizures (%, range)†	68.4–75.4	63.6–69.9	63.9–73.5

†Range of values in patients randomized to placebo and various perampanel doses.
‡Median seizure frequency.
AED: Antiepileptic drug.

which was terminated early, patients were randomized to placebo, perampanel and entacapone. Results showed that, whereas perampanel was not superior to placebo on any efficacy end points, entacapone was superior to placebo on the primary end point and most secondary outcomes [21]. Even though these studies failed to demonstrate a significant clinical advantage of perampanel in patients with Parkinson's disease, they showed a generally good drug tolerability profile in this population of elderly patients.

Five studies, two Phase II [26] and three Phase III studies [27–29], which recruited approximately 1700 patients with drug-resistant partial epilepsies, have subsequently demonstrated efficacy of this agent in this field and as such will be reported here more in detail.

In the two Phase II dose-finding, placebo-controlled studies that preceded larger Phase III studies, patients who experienced uncontrolled partial-onset seizures despite taking stable doses of 1–3 approved AEDs were recruited. In the first study (study 206), 153 adult patients aged 18–70 years were randomized to a once-daily (n = 51) or twice-daily regimen (n = 51) of 4 mg/day of perampanel with a starting dose of 1 mg/day, or to placebo (n = 51), while in the second study (study 208), placebo (n = 10) or the experimental drug (n = 38) was administered at the initial dose of 2 mg and slowly titrated up to 12 mg/day. In both studies, therapy was tolerated by substantial proportions of patients randomized to all doses without any significant differences between placebo and perampanel in any safety variables, and no differences in tolerability or efficacy were noted between patients randomized to once daily or twice daily. These studies showed preliminary evidence of efficacy and identified the range of doses and drug regimens that were subsequently evaluated in larger trials [26–28]. It should be stressed that drug doses that were found to be effective in patients with epilepsy were consistently higher than that previously used in patients with Parkinson's disease.

Three randomized, double-blind, placebo-controlled, parallel-group, fixed-dose, multicenter Phase III trials with a similar design subsequently investigated efficacy and tolerability of perampanel as adjunctive treatment in subjects aged 12 years or older with partial-onset seizures with or without secondary generalization [27–29]. All studies had identical duration with a pre-randomization period of 6 weeks, a double-blind phase of 19 weeks (6-week titration + 13-week maintenance) and a follow-up of 4 weeks.

All patients received perampanel once daily at the initial dose of 2 mg/day and titration speed was identical. Treatment was increased by increments of 2 mg/day each week up to the randomized doses or to the highest tolerable dose and this treatment was continued for the duration of the study. Dose reductions were permitted for intolerability. The most important difference between these trials was that in the Krauss *et al*. study [29], patients treated with active drug were randomized to 2, 4 or 8 mg/day, while in the French *et al*. studies [27,28], patients were randomized to 8 or 12 mg/day. Baseline characteristics of patients included in these studies are shown in Table 2.

Results of all studies are summarized in Table 3. The most relevant information was that at the 2 mg/day dose, analysis of both outcome measures failed to demonstrate a significant difference between patients treated with the active drug or placebo; at doses of 4, 8 and 12 mg/day, the experimental drug was significantly more efficacious in the outcome measure 50% responder rate in two studies [28,29] and in the measure median percent change in seizure frequency in all the three studies. It is interesting to note that the outcome 50% responder rate failed to show a significant difference both at a dose of 8 mg/day and at a dose of 12 mg/day in study 304 [27]. However, as this multicenter study was conducted in several countries of America, a subanalysis of responder rates by region showed that, in North America, responder rates for perampanel significantly differed from placebo either at the dose of 8 mg and at 12 mg dose, whereas in the remaining subpopulation of patients (from South America), this outcome measure showed no difference versus placebo at both doses. It has been suggested that differences in patient selection or study conduct may have contributed to these discrepant findings [27]. Table 3 shows that there is a slight or no difference in both efficacy measures between patients treated with 8 and 12 mg/day, while the percentage of patients withdrawing because of intolerable adverse effects is consistently worse at the 12 mg/day dose, being more than doubled compared with the patients randomized to 8 mg/day.

Open-label extension trials

Open extension studies were performed as part of the perampanel clinical development program in patients who completed Phase II studies [30] and pivotal Phase III trials [31]. The primary

Table 3. Efficacy and tolerability of perampanel as add-on therapy in drug-resistant patients with partial-onset seizures. Results of three randomized, double-blind, placebo-controlled multicenter trials.

Study	Randomized patients (n)	Responder rate (%)†	Median percent change in seizure frequency (%)‡	Patients withdrawing because of adverse events (%)	Ref.
Study 306	Placebo: 185	17.90	-10.69	3.90	[29]
	Perampanel 2 mg: 180	20.6§	-13.63§	6.70	
	Perampanel 4 mg: 172	28.5#	-23.33††	3	
	Perampanel 8 mg: 169	34.9‡‡	-30.80‡‡	7.1	
Study 304	Placebo: 121	26.4	-20.95	6.6	[27]
	Perampanel 8 mg: 133	37.6§	-26.34#	6.80	
	Perampanel 12 mg: 134	36.1§	-34.49#	19.40	
Study 305	Placebo: 136	14.70	-9.72	4.40	[28]
	Perampanel 8 mg: 129	33.3††	-30.52‡‡	9.3	
	Perampanel 12 mg: 121	33.9‡‡	-17.57#	19	

†Percentage of patients who had at least a 50% reduction in seizure frequency in the maintenance period relative to baseline.
‡Median percentage change in seizure frequency during the double-blind phase compared with baseline.
§p = nonsignificant.
#p < 0.05.
††p < 0.005.
‡‡p < 0.001.

objective of these studies was to evaluate the long-term tolerability and safety of once-daily adjunctive perampanel and a secondary objective was to assess whether the efficacy of perampanel was maintained with long-term use.

The design of these open studies comprised a 12- or 16-week titration period to 12 mg/day and a maintenance period of up to 424 or 256 weeks for extension studies 207 [30] or 307 [31], respectively. A description of characteristics of patients included in open studies is reported in Table 4.

In these studies, all perampanel doses were given once daily at bedtime with food. Patient entered the study on the same concomitant AED regimens and perampanel daily dose received during the double-blind studies. Perampanel doses were increased (during a 16-week blind conversion period in study 307) by 2 mg every 2 weeks to a maximum tolerated dose (up to 12 mg/day). In both studies, concomitant AEDs could be reduced in dose, discontinued or changed. In Table 5, the most relevant findings of these open studies are reported.

In these open-label studies, mean exposure to perampanel, at doses of 7 or 10 mg/day, was >2 years (mean values: 116.4 weeks ± 74.9 SD) for Rektor *et al.* study [30] and approximately 1 year (mean values: 52.5 weeks ± 25.6) in the Krauss *et al.* study [31], respectively. Percentages of patients discontinuing were similar in the two studies and were relatively low.

Percentages of responders and median percent change in seizure frequency versus baseline, which are the two outcome measures most often used also in key clinical studies, were generally higher than that reported in previous double-blind studies. For a correct interpretation of these findings, it should be noted that in post-double-blind continuation studies, those patients who did not respond to, or did not tolerate the experimental drug, were excluded. However, these findings can be interpreted as evidence of a persistent clinical effect and also of a relative lack of new adverse events appearing during chronic treatment.

Tolerability

Clinical tolerability of perampanel was assessed by analysis of treatment emergent adverse events observed in approximately 4000 patients, who were recruited in controlled studies on drug resistant epilepsies and on Parkinson's disease (2627 randomized to perampanel and 1320 to placebo) and by patients recruited in open extension studies that followed epilepsy trials.

Perampanel tolerability was excellent up to doses of 8 mg/day with very low percentages of patients discontinuing for adverse events at these doses, while at 12 mg/day dose, the percentages of patients withdrawing was approximately 20% (Table 3). At a drug dose of 4 mg/day, the percentage of patients with epilepsy discontinuing the active drug was 3%, which seems to be consistently lower than that observed in patients with Parkinson's disease treated with same daily dose level (~10%) [21].

Most frequently reported adverse effects were dizziness, ataxia, aggression, irritability, vertigo, somnolence, fatigue, headache and gait disturbance. Some of these adverse effects, most of which are usually dose-dependent and often observed during treatment with several AEDs [32], were also those most frequently leading to drug discontinuation. Serious adverse effects appeared in a relatively small percentage of patients both in double-blind and in long-term studies, and no single serious adverse effect was considered drug related.

Rash, which is the most common idiosyncratic reaction associated with several AEDs [33], was reported only in a small number of patients (18 patients randomized to perampanel and four patients randomized to placebo). This is important because it has been shown that perampanel metabolism may lead to formation of reactive metabolites [101,102] that, in some cases, may induce idiosyncratic immune-mediated adverse drug reactions [33].

No adverse effects directly related to cognition were observed during perampanel treatment. This is noteworthy because, in experimental studies, dysfunction of excitatory neurotransmission,

Table 4. Population of patients selected for inclusion and characteristics of patients included in the two open-label studies with perampanel.

	Study 207 [30]	Study 307 [31]
Patients recruited in double-blind studies (n)	201†	1480‡
Patients who completed double-blind studies (n)	180	1264
Patients included in open studies (n) Previously randomized to placebo (n) Previously randomized to perampanel (n)	138 43 95§	1218 380 838#
Patients included in safety analysis (n)	138	1186
Patients included in the ITT analysis (n)	138	1207
Duration of exposure (weeks)††	>26; n = 119 (86.2%); >52; n = 96 (69.6%); >104; n = 70 (50.7%); >156; n = 57 (41.3%); >208; n = 18 (13%)	>16; n = 1089 (91.8%); >52; n = 580 (48.9%); >76; n = 250 (21.1%)
Exposure (weeks)	116.4 ± 74.9‡‡	51.4 (1.1–128.1)§§
AEDs at baseline (n):		
– 2 AEDs (%)	68.1	50.3
– 3 AEDs (%)	9.4	36.3
Mean ± SD final perampanel dose	7.3 ± 3.3 mg/day##	10.1 ± 2.3 mg/day†††

†n = 153 in study 206; n = 48 in study 208.
‡n = 388 in study 304; n = 386 in study 305; n = 706 in study 306.
§Approximately 80.0% of patients had been exposed to a maximum dose of 4 mg or had no prior exposure to perampanel.
#n = 147 given 2 mg/day; n = 154 given 4 mg/day; n = 356 given 8 mg/day; n = 181 given 12 mg/day.
††Number of patients exposed to the experimental drug at various times. In parentheses are reported percentages of patients recruited in the study who were exposed for the corresponding time.
‡‡Mean ± standard deviation.
§§Median (range).
##Open-label maintenance period.
†††Entire extension treatment phase.
AED: Antiepileptic drug; ITT: Intention to treat; SD: Standard deviation.

as determined by AMPA receptor inhibition, may affect cognition [34]. It is known that, among AEDs, topiramate, which affects excitatory neurotransmission, may cause several cognitive effects [35].

Some psychiatric disorders such as aggression, irritability, insomnia and also a few cases of psychosis were observed in perampanel clinical studies. This has led to a warning related to the use of perampanel in patients with history of psychotic disorders [101].

In double-blind studies, the adverse effect of weight gain, defined as >7% increase in bodyweight, was observed in 154 of 1038 patients randomized to perampanel and 31 of 442 patients randomized to placebo. This effect of perampanel on weight has been confirmed in open-label studies where it also appeared to be related with the administered dose. It is known that several other AEDs, with different mechanisms of actions and metabolic effects, such as gabapentin, pregabalin, valproic acid, vigabatrin, carbamazepine and levetiracetam, have a similar effect on weight [36]. Finally, no clinically significant differences between placebo and perampanel were detected in clinical laboratory values, ECG, or any other safety variables both in randomized and in open-label studies.

Expert commentary

Perampanel has been approved in Europe and the USA as adjunctive therapy for adults with focal seizures with or without secondary generalization. The recommended starting dose is 2 mg/day and drug doses may be increased up to the recommended maintenance dose of 4–8 mg/day [37]. As elimination half-life of perampanel is approximately 105 h in noninduced subjects, once a day administration is suitable, with small fluctuations of drug plasma levels. This is an advantage in terms of ease of use and neurological tolerability. By contrast, titration of this drug must be slow (no faster than 2 mg/day weekly increments) because of the long time required to achieve a stationary state. Possible unexpected tolerability problems may result from dosage adjustments that are too frequent relative to the half-life of the drug in patients with longer half-lives. A potential disadvantage in the kinetic of perampanel is its high binding to plasma proteins, which, in some circumstances, might determine, as yet unknown, kinetic interactions.

Efficacy has been satisfactorily demonstrated at doses of 4, 8 and 12 mg/day. Even though a clear dose response between the 8- and 12-mg daily dose did not emerge from double-blind studies, open studies have demonstrated that those patients who do not achieve a satisfactory seizure control with an 8-mg dose but tolerate this dose, may benefit from a 12-mg/daily dose. However, approximately 20% of the subjects randomized to 12 mg/day in controlled studies did not tolerate this dose in respect to less than 10% of the patients treated with 8 mg/day. For all these reasons, it may be wise to titrate perampanel at a 4- or 8-mg/daily dose, and then carefully proceed to further dose increments in subjects whose response to treatment is not satisfactory and tolerability is good.

As far as safety is concerned, up to now, perampanel has not been associated with idiosyncratic reactions and cutaneous rush was only reported in a few subjects. However, some metabolites have been identified after perampanel administration that are thought to result from a reactive epoxide intermediate [101]. The formation of reactive metabolites deserves particular attention since several idiosyncratic immune-mediated adverse drug reactions occur with AEDs that are mediated through the formation of reactive metabolites [33].

No drug-related serious adverse effects emerged throughout the perampanel clinical development program. Cognitive problems associated with the drug are not reported. Psychiatric disorders and weight gain are two adverse effects that should be better characterized in future Phase IV studies. To date, a warning on

the risk of aggression has been added in the summary of product characteristics [101].

Tolerability of this new AED in fragile populations (elderly patients, patients with cognitive disorders) will be better clarified in future studies. However, studies conducted in patients with Parkinson's disease, whose mean ages were approximately 65 years, did not show any particular adverse effects, even though, at 4-mg/daily dose, intolerable adverse effects were more frequent in this population compared with younger epileptic patients (mean age in double-blind studies was ~35 years) treated with the same drug dose level. The better tolerability observed in patients with epilepsy may be related to the fact that perampanel metabolism is induced by enzymatic inducers AEDs [101]. Namely, epileptic patients concomitantly treated with these drugs might have had lower perampanel levels and hence a better drug tolerability than patients with Parkinson's disease. Some disease- or age-specific neurobiologic characteristics might contribute to perampanel's AE profile, although it has been demonstrated that drug kinetics are not consistently modified in elderly populations [101].

Table 5. Results of open-label studies.

	Study 207 [30]	Study 307 [31]
Tolerability		
Any TEAE	93.50%	87.40%
Any serious TEAE	15.20%	13.20%
Any TEAE leading to discontinuation	12.30%	13.20%
Long-term efficacy		
Responder rate		
Open-label treatment†	37.00%	
Maintenance period	45.80%	
End of the blinded conversion period		
Patients previously treated with perampanel‡		43.30%
Patients previously treated with placebo‡		44.20%
1 year of exposure (n = 588)		47.60%
Median percent change in seizure frequency		
Open-label treatment (range)†	-31.5% (-99.2–512.2)	
Maintenance period, patients (n = 120; range)	-39.4% (-99.2–542.4)	
Patients previously treated with perampanel‡ (n = 817)		-41.5%
Patients previously treated with placebo‡ (n = 369)		-42.40%
1 year exposure (n = 588)		-47.20%

Median percentage change in seizure frequency during the open phase was compared with a 6-week prerandomization period for those patients who were randomized to perampanel during double-blind study and prerandomization period plus a double-blind phase for patients randomized to placebo.
†Including the titration period.
‡Patients who had been previously treated with perampanel or placebo during double-blind, Phase III studies were titrated to perampanel 12 mg/day during the blinded conversion period.
TEAE: Treatment-emergent adverse events (with respect to baseline).

Expert commentary

Who is the ideal patient to benefit from perampanel treatment?

Perampanel is a new AED with an innovative mechanism of action, inhibition of AMPA mediated excitatory neurotransmission. Even though there is not experimental evidence, we can hypothesize that drugs with new mechanisms of actions have more chances of an effective result in patients who did not satisfactory respond to AEDs with more traditional mechanisms of actions as, for example, drugs acting on voltage-gated sodium channels. For this reason, in a near future, AEDs with innovative mechanisms of actions, such as perampanel or retigabine [38,39] should be tried in patients with uncontrolled partial seizures who do not respond to combination of AEDs acting through a stabilization of ionic membranes or potentiation of GABAergic inhibition.

Perampanel has a favorable kinetic and tolerability profile. Therefore, no limitations are expected in the use of this AED in special populations at higher risk for specific adverse effects, that is, elderly patients or patients taking multiple AEDs. Attention should be given to patients with a history of psychiatric disturbances, and the drug should be avoided in patients with severe hepatic impairment or used at lower doses in patients with mild and moderate hepatic impairment. Future studies aimed towards a better identification of epileptic patients who can experience advantages from perampanel add-on treatment are needed.

Five-year view

Several unresolved questions will have to be answered in the next years. Will new AMPA receptor antagonists be studied in the field of epilepsy and other neurological diseases? As regards perampanel, further long-term and observational studies should try to better define the efficacy and tolerability spectrum of this drug and its place in the treatment of epilepsy. Finally, will this new AED only be available as an add-on treatment for drug resistant epilepsies? Will new studies demonstrate efficacy and a possible role of perampanel also as monotherapy in newly diagnosed epilepsy patients?

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Key issues

- α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors in the postsynaptic membrane that are activated by glutamate released from the excitatory neuron axon terminals are involved in fast excitatory signaling in the brain. Their activation may lead to the firing of action potentials by the postsynaptic neuron, which may facilitate the appearance of epileptic discharges.
- Perampanel is the first noncompetitive AMPA receptor antagonist approved as adjunctive therapy for adults with focal seizures with or without secondary generalization.
- The recommended perampanel starting dose is 2 mg/day once daily, which can be increased weekly up to the recommended maintenance dose of 4–8 mg/day. A 12-mg daily dose should be considered after careful evaluation.
- The safety spectrum of perampanel is favorable with approximately 20% of patients withdrawing because of adverse effects at the highest dose of 12 mg/day.
- Most frequently reported adverse effects are dizziness, ataxia, aggression, irritability, vertigo, somnolence, fatigue, headache, gait disturbance and weight increase.

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