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The AMPA receptor antagonist perampanel in the adjunctive treatment of partial-onset seizures: clinical trial evidence and experience

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***Abstract*:** More than 20 antiepileptic drugs (AEDs) are currently available for the medical treatment of epilepsies. However, still about 30% of all epilepsies have a drug-resistant course. Even worse, in the case of some epilepsy syndromes, freedom from seizures is almost never achieved. Therefore, new treatment options are still necessary, especially if theoretical concepts such as a new mode of action offer new horizons. Perampanel is the first-in-class orally active, selective, noncompetitive antagonist of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors. The pharmacokinetic profile offers once-daily dosing in the evening as the best route of administration.
According to the results of three pivotal placebo-controlled, double-blind phase III trials that investigated perampanel as an adjunctive AED in adult and adolescent patients from age 12 years who had ongoing focal epileptic seizures despite receiving one to three AEDs, perampanel has been widely licensed and introduced. Phase III trials showed superiority of adjunctive perampanel over placebo consistently in the range between 4 and 12 mg. Dizziness and somnolence were by far the leading adverse events. This review covers the clinical trial evidence but also clinical experience with perampanel after launch according to observational studies.

Keywords: drug therapy, epilepsy, glutamate, perampanel

Introduction

Chronic antiepileptic drug (AED) therapy, i.e. the sustained prevention of epileptic seizures, is still the standard of epilepsy treatment [Steinhoff, 2013]. Meanwhile, a variety of new AEDs have broadened the range of available anticonvulsant compounds. Other than in other neurological indications such as Parkinson's disease or migraine, new drugs in epileptology do not represent a class of compounds that all offer the same new mode of action like dopamine agonists or triptans. Indeed the only principle that characterizes new AEDs is their introduction after the 1990s. New AEDs comprise a rather heterogeneous group of drugs with varying profiles and modes of action [Steinhoff, 2013].

Only few new AEDs offer new selective modes of action such as vigabatrin that blocks gamma-butyric acid (GABA) aminotransferase or tiagabine via the blockade of GABA reuptake from the synaptic cleft. Gabapentin, pregabalin and levetiracetam are also defined by specific mechanisms of action, at least in part: gabapentin and pregabalin modulate calcium channels by specific receptor site binding; levetiracetam acts via the binding to the presynaptic SV2A receptor site. Both new AEDs that were introduced prior to perampanel, lacosamide and retigabine also act by a new mode of action that had not been described for other AEDs, namely the slow inactivation of sodium channels and the opening of inhibitory potassium channels [Brodie *et al*. 2011; Steinhoff, 2013, 2014a].

It is tempting to speculate that the approximately 20–30% of AED-resistant epilepsy patients [Schmidt and Schachter, 2014] might be treated

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more effectively by those new AEDs that offer a new mechanisms that is different from the modes of action covered by more established compounds. Beyond the modes of action that have been mentioned in this paper already, the leading modes of action of first- and second-generation AEDs and of newer substances such as lamotrigine, oxcarbazepine and eslicarbazepine acetate comprise the voltage-gated and use-dependent blockade of sodium channels, additional effects on other voltage-gated ion channels especially on calcium channels and the activation of GABA as the main inhibitory neurotransmitter [Steinhoff, 2013].

Another apparent potential mode of action is certainly the inhibitory impact on excitatory neurotransmitters. Interestingly, the postsynaptic glutamatergic excitatory neurotransmission that is thought to play a major role in the generation of epleptogenesis [Rogawski, 2011] has been barely addressed by the available AEDs. Topiramate and felbamate are examples of such drugs that offer some antiglutamatergic efficacy as a minor part of their anticonvulsant efficacy [Steinhoff, 2013, 2014a].

Glutamatergic transmission is mediated mainly by three receptor types, N-methyl-D-Aspartate (NMDA), kainate and alpha-amino-3-hydroxy-5-methyl-4-isoxazolproprionic acid (AMPA) receptors. AMPA receptors are found mainly at the postsynaptic membrane of excitatory synapses in the brain. They have a glutamate binding site and mediate glutamate-related signals [Rogawski, 2011]. It is suggested that in human hippocampal and neocortical tissue hypersensitive AMPA receptors and an augmented number of glutamate binding sites occur [Zilles *et al*. 1999; Vollmar *et al*. 2004]. Therefore, therapeutic potential is expected if AMPA receptor antagonists are applied [Meldrum and Rogawski, 2007; Rogawski, 2011].

With perampanel the first-in-class selective non-competitive AMPA receptor antagonist has been clinically tested and finally approved for add-on treatment of patients with focal seizures with and without secondary generalization.

After a short summary of the mode of action and pharmacological profile, this review reports the clinical trial data of the pivotal phase II and III trials and adds clinical experience after the introduction of perampanel.

Compound and mode of action

Perampanel is an orally active noncompetitive and highly selective antagonist at the AMPA receptor that underwent extensive clinical research over recent years [Hanada *et al*. 2011]. AMPA receptors are mainly located at the postsynaptic membrane of excitatory synapses in the mammalian brain. They contain a glutamate binding site and mediate glutamatergic postsynaptic signals [Rogawski, 2011]. It is assumed that human hippocampal and neocortical tissue in the brain of patients with epilepsy shows hypersensitivity of AMPA receptors and an increased density of glutamate binding sites [Zilles *et al*. 1999; Vollmar *et al*. 2004]. Therefore, one expects that AMPA receptor antagonists such as perampanel should have a promising therapeutic anticonvulsant potential [Meldrum and Rogawski, 2007; Rogawski, 2011].

There is evidence that perampanel probably inhibits the AMPA-induced increase of the intracellular calcium concentration which results in reduced neuronal excitability [Krauss *et al*. 2012]. It has been shown that perampanel does not interact with NMDA or kainate binding sites to a relevant level [Hanada *et al*. 2011; Rogawski, 2011]. Other AMPA receptors have been investigated as potential AEDs, the outcome of which is currently not published [Chappell *et al*. 2002; Faught, 2014].

Preclinical anticonvulsant profile

Perampanel was investigated in several preclinical seizure models [Hanada *et al*. 2012]. It was highly effective in the maximum electroshock seizure (MES) test in mice [Hanada *et al*. 2012] which is sought to reflect efficacy against generalized tonic–clonic seizures in humans [Löscher, 2011]. The audiogenic seizure model in mice is also assumed to reflect potential therapeutic efficacy in generalized tonic–clonic seizures of humans. Perampanel was also highly effective in this model as it was against pentylene tetrazole-induced seizures of mice [Hanada *et al*. 2012]. In all of these classical preclinical seizure models the effective doses were lower than for the traditional AEDs carbamazepine and valproic acid. In the amygdala kindling model of the rat which is sought to resemble mesial temporal epileptogenesis [Löscher, 2002] perampanel increased the afterdischarge threshold, the duration of the motor seizure phase duration and the duration of afterdischarges [Hanada *et al*. 2012]. In contrast to many AEDs perampanel was highly

effective in the 6 Hz electroshock seizure model in mice. No efficacy was seen in the classical absence model of the Strasbourg rat [Hanada *et al.* 2012].

Clinical pharmacology

Perampanel is absorbed from the gastrointestinal tract rapidly and completely. In healthy volunteers maximum serum concentration was measured 1 hour after oral intake with a range between 15 minutes and 2 hours. Food reduces the maximum serum concentration by 40%. Under these circumstances maximum serum concentrations are reached 2 hours after intake. The total absorption, the concentration over 24 hours and the elimination half-life are not altered by food. Absolute bioavailability approaches 100%. Pharmacokinetics are linear. Between doses of 2 and 12 mg, dose proportionality was shown.

Plasma protein binding rate is 95%. Elimination half-life is 105 hours. Plasma steady state is reached after 14 days [Bialer *et al.* 2010; Patsalos, 2014].

Perampanel undergoes extensive metabolization with involvement of cytochromes CYP3A4 and/or CYP3A5. Under the influence of carbamazepine there is a threefold increase of clearance whereas phenytoin and oxcarbazepine induce a double increase of the clearance. Elimination half-life is reduced from 105 to 25 hours under the influence of carbamazepine. Ketoconazole acts as a potent inhibitor of CYP3A and leads to an increase of the elimination half-life of perampanel of 15%. A total of 70% are eliminated by feces and 30% in the urine [Bialer *et al.* 2010; Patsalos, 2014].

Perampanel has no significant influence on the clearance of clonazepam, levetiracetam, phenobarbital, phenytoin, topiramate and zonisamide. The clearance of oxcarbazepine is reduced by 26%. The highest investigated dose of perampanel was 12 mg per day. This dose has a significant impact on the clearance of carbamazepine, clobazam, lamotrigine and valproic acid. However, the total amount of this impact lies below 10% [Bialer *et al.* 2010; Patsalos, 2014]. Recently, single cases have been reported in which serum concentrations of phenytoin, phenobarbital and rufinamide were reduced with adjunctive perampanel with severe clinical consequences (worsening of epilepsy and status epilepticus) [Novy *et al.* 2014] so that in individual cases careful watching of the clinical course and serum concentrations of concomitant AEDs may be helpful.

With doses of 4 and 8 mg no effect of perampanel on the concentration of levonorgestrel and ethinylestradiol was measured. However, 12 mg of perampanel led to a reduction of the maximum serum level and the concentration over 24 hours of levonorgestrel by 40% [Bialer *et al.* 2010; Patsalos, 2014].

Clinical trials

Adjunctive perampanel has been evaluated in an extensive clinical development program across a large, multinational population of patients with refractory partial-onset seizures. Key studies included two randomized, double-blind, placebo-controlled phase II dose-finding trials, in which the perampanel dose was titrated up to 4 mg once or twice daily or 12 mg once daily [Krauss *et al.* 2012], and three randomized, double-blind, placebo-controlled phase III registration trials, in which the perampanel dose was titrated up to 8 or 12 mg once daily [French *et al.* 2012, 2013; Krauss *et al.* 2012]. In all studies, patients were also receiving one to three concomitant AEDs.

Phase II studies

Two clinical phase II trials were performed with perampanel [Krauss *et al.* 2012]. Both were double-blind placebo-controlled trials in adults with partial-onset epileptic seizures and intended to define the maximum tolerated daily dose of perampanel. Patients were between 18 and 70 years of age.

During the first trial patients were treated with adjunctive perampanel or placebo for 12 weeks, 8 of which were used for titration and 4 for the maintenance period. In this study 4 mg of perampanel per day were applied either once daily or according to a bid regimen. During the second trial perampanel was increased to 12 mg per day once daily during 12 weeks followed by a maintenance period of 4 weeks.

For the low-dose trial 153 patients were randomized (51 patients each for perampanel twice daily, perampanel once daily and placebo, respectively). The second study comprised 49 patients on perampanel and 10 on placebo.

Tolerability was not different between placebo and 4 mg of perampanel, independently of once- or

twice-daily dosing. Most patients tolerated more than 6 mg of perampanel in the second trial. In both studies most adverse events were related to the central nervous system (CNS) and of moderate intensity. From these two trials it was concluded that the expected and practicable maintenance dose would range between 4 and 12 mg once daily. The following pivotal phase III trials were conceptualized accordingly.

Phase III trials

Three randomized multicenter prospective placebo-controlled phase III trials investigated efficacy and tolerability of perampanel as adjunctive AED in patients with difficult-to-treat epilepsies with partial-onset seizures from age 12 years on [French *et al.* 2012, 2013; Krauss *et al.* 2012]. Pooled analysis data of these three trials have been published additionally [Steinhoff *et al.* 2013; Kramer *et al.* 2014].

Two studies [French *et al.* 2012, 2013] compared maintenance doses of 8 and 12 mg, respectively, with placebo. The third trial [Krauss *et al.* 2012] addressed 2, 4 and 8 mg. All three studies led into the possibility of an extended open-label study that allowed a dose increase up to 12 mg. The interim results of this open-label extension have been published also [Krauss *et al.* 2013, 2014].

Perampanel was always started at 2 mg once daily and increased by 2 mg per week. Maintenance phases lasted 13 weeks. Thereafter patients were offered to enter a long-term open follow up with the possibility of a titration up to 12 mg perampanel per day. The transition phase to this open follow up lasted 4 weeks.

In all three studies, the primary endpoint for the intent to treat (ITT) analysis set (all randomized and treated patients with any seizure data) was median percentage change in the frequency of all partial seizures per 28 days (baseline *versus* double-blind phase). For EU registration, the primary endpoint was the percentage of patients achieving a 50% reduction in the frequency of all partial seizures per 28 days (50% responder rate; baseline *versus* maintenance). The median percentage changes in the frequencies of complex partial (CP) plus secondary generalized (SG) (CP + SG) seizures and SG seizures only (baseline *versus* double-blind phase) were also assessed as secondary and exploratory endpoints, respectively. Other exploratory endpoints included 50% responder rates for CP + SG and SG (baseline *versus* maintenance); 75% responder rates for all partial seizures (baseline *versus* maintenance); seizure-freedom rates for all partial seizures (percentage of patients with no seizures during the entire maintenance period); and the proportion of patients with a >50% increase in seizure frequency (baseline *versus* maintenance) [Steinhoff *et al.* 2013].

Study 306

In Study 306 [Krauss *et al.* 2012], target maintenance dosages were 2, 4 and 8 mg. The trial was performed in Europe, Asia and Australia. A total of 878 patients were recruited, and 712 were randomized. Treatment groups comprised $n = 185$ in the placebo, $n = 180$ in the 2 mg, $n = 172$ in the 4 mg and $n = 169$ in the 8 mg group. Demographic characteristics were similar in all four treatment groups. Mean epilepsy duration was 19.1 years. A total of 14.7% of patients were on one AED, 85.3% on two or three AEDs. Median seizure frequency during baseline in the treatment groups varied between 9.3 and 10.9 seizures per 28 days.

Study completer percentages in these groups were 89.7%, 85.6%, 91.9% and 85.8%, respectively. Study discontinuation due to an adverse event happened in 3.2% of patients on adjunctive placebo, 5.6% of patients with 2 mg perampanel, in 2.9% with 4 mg of perampanel, and in 6.5% with 8 mg of perampanel.

Median percentage change rates per 28 days were 10.7% with placebo, 13.6% for 2 mg of perampanel, 23% for 4 mg of perampanel and 30.8% with 8 mg of perampanel. Adjunctive treatment with 4 and 8 mg was statistically significantly superior to adjunctive placebo ($p = 0.003$ and $p < 0.001$, respectively). Responder rates were 17.9% for placebo and 20.6% with 2 mg, 28.5% with 4 mg and 34.9% for 8 mg perampanel. Again, these differences were statistically significant for 4 and 8 mg of perampanel ($p = 0.013$ and $p < 0.001$). The numbers needed to treat in order to achieve a responder were 37 with 2 mg, 8 with 4 mg and 6 with 8 mg.

Freedom of seizures was observed in 1.2% of patients with placebo, 1.9% with 2 mg of perampanel, 4.4% with 4 mg and in 4.8% with 8 mg of perampanel.

Dizziness and somnolence were the adverse events that most often led to dose reductions. In

general, dizziness, somnolence, fatigue and gait disturbances occurred more than twice as often as with placebo. Headache was reported in 9–11% of patients under perampanel, but also in 8.6% of patients with placebo. Treatment-emergent adverse events that led to a discontinuation of the trial were reported in 3.8% under placebo, in 6.7% with 2 mg of perampanel, in 2.9% under 4 mg of perampanel and in 7.1% under 8 mg with adjunctive perampanel. The leading adverse events that were associated with treatment discontinuation were dizziness, seizures and fatigue. A more than 50% increase of seizures during the maintenance period occurred in 15% with placebo, in 11% with 2 mg of perampanel and in 8% with both 4 and 8 mg of perampanel.

Study 305

In the multicenter trial Study 305 [French *et al.* 2013], the maintenance dosages of perampanel were 8 and 12 mg. A total of 496 participants were recruited and 389 finally randomized. In the placebo group there were 136 patients, 129 were randomized to a maintenance dose of 8 mg perampanel and 121 to 12 mg. Study completers were 88.2% (placebo), 83.7% (8 mg of perampanel) and 76.9% (12 mg of perampanel). Thus discontinuation rates were 11.8%, 16.3% and 23.1%, respectively. Discontinuations due to treatment-emergent adverse events occurred in 2.9% with placebo, in 8.5% with 8 mg of perampanel and in 19% with 12 mg of perampanel.

Median percentage change of seizure frequency was 9.7% under placebo, 30.5% under 8 mg of perampanel and 17.6% with 12 mg of perampanel. These differences *versus* placebo were both statistically significant ($p=0.0008$ and $p=0.0105$, respectively). Responder rates also differed significantly and accounted for 14.7% (placebo), 33.3% (8 mg of perampanel) and 33.9% (12 mg of perampanel) ($p = 0.0018$ and $p = 0.0006$, respectively). Seizure freedom was observed in 1.7% of patients with placebo, whereas 2.8% and 6.5% became seizure-free with 8 and 12 mg of add-on perampanel.

The rate of adverse events was 68.4-% with placebo, 86.8 % with 8 mg of perampanel and 86.0% with 12 mg of perampanel. Severe adverse events occurred in 5.1%, 7.8% and 9.9%. The most frequently reported adverse events with a frequency of more than 10% were dizziness, somnolence, fatigue and headache. Again, the frequency of headache did not differ between the placebo and perampanel patients. Most frequent adverse events that led to dose reduction or study discontinuation were dizziness, somnolence, headache, fatigue, ataxia and asthenia.

Study 304

Study 304 [French *et al.* 2012] was the second multicenter, double-blind, placebo-controlled study on adjunctive perampanel that addressed maintenance dosages of 8 and 12 mg. Patients were randomized according to a 1:1:1 ratio. A total of 534 patients were recruited and 390 randomized. The placebo group comprised 121, the perampanel 8 mg group comprised 133 and the perampanel 12 mg group comprised 134 patients. Study completer percentage in these groups was 87.6%, 85.7% and 74.6%. Corresponding discontinuation rates were therefore 12.4%, 14.3% and 25.4%. Treatment-emergent adverse events led to discontinuations in 5.8% of patients in the placebo group, in 6.8% of the patients with 8 mg of add-on perampanel and in 17.9% of patients under 12 mg of adjunctive perampanel.

In this trial the rather high percentage of successful courses under placebo was quite remarkable and had some impact on part of the results. Median percentage change of seizures was 21.0%, with placebo, 26.3% with 8 mg of perampanel and 34.5% with 12 mg of perampanel. For this outcome variable, the differences were statistically significant ($p=0.0261$ and $p=0.0158$, respectively). However, for the criterion of responder rate only a trend and not statistical superiority was observed in favor of perampanel: responder rates were 26.4% for placebo, 37.6% for 8 mg of perampanel and 36.1% for 12 mg of perampanel ($p=0.076$ and $p=0.091$, respectively). Numbers needed to treat for a responder were 9 and 10 for 8 and 12 mg of perampanel. Seizure freedom rates were 0% for placebo, 2.6% for 8 mg and 2.0% for 12 mg of perampanel. The main reason for the high placebo response rate was the great impact of few centers with high recruitment and placebo response rates [Steinhoff, 2014b].

The rate of adverse events was 82.6% under placebo, 88.0% under perampanel 8 mg and 91.8% under perampanel 12 mg. Adverse events that led to dose reduction or discontinuation were observed in 5.0% with placebo, in 22.6 % with perampanel 8 mg and in 33.6% with perampanel 12 mg. Severe adverse events were reported in 5.0%, 6.0% and 6.7%. Most frequently reported adverse events with a frequency >10% comprised dizziness,

Table 1. Efficacy of perampanel in phase III trials.

Median percentage change of seizure frequency.

	Placebo	2 mg	4 mg	8 mg	12 mg
Krauss *et al.* [2012]	–10.7%	–13.6	–23.3%	–30.8%	-
p	-	n.s.	0.003	< 0.001	
French *et al.* [2012]	–9.7%	-	-	–30.5%	–17.6%
p	-	-	-	0.0008	0.0105
French *et al.* [2012]	–21.0%	-	-	–26.3%	–34.5%
p	-	-	-	0.0261	0.0158

Responder rate.

	Placebo	2 mg	4 mg	8 mg	12 mg
Krauss *et al.* [2012]	17.9%	20.6%	28.5%	34.9%	-
p	-	n.s.	0.013	< 0.001	
French *et al.* [2012]	14.7%	-	-	33.3%	33.9%
p	-	-	-	0.0018	0.0006
French *et al.* [2012]	26.4%	-	-	37.6%	36.1%
p	-	-	-	0.076, n.s.	0.091, n.s.

somnolence, headache (again with a similarly high rate under placebo), falls, irritability and ataxia.

Table 1 shows the summarized results for efficacy

Pooled intent to treat results of the randomized and treated patients with available seizure data include 1478 patients [Steinhoff *et al.* 2013].

The median percentage of seizure frequency of partial-onset seizures was significantly higher for perampanel 4, 8 and 12 mg ($p < 0.01$ for each dose *versus* placebo). The reduction rates were 23.3% for perampanel 4 mg, 28.8% for 8 mg, 27.2% for 12 mg and 12.8% for placebo [Steinhoff *et al.* 2013]. Similarly, responder rates were statistically significantly higher for each investigated dose compared with placebo (19.3%) and added up to 28.5% with perampanel 4 mg, 35.3% for perampanel 8 mg and 35.0% for perampanel 12 mg (for each dose $p < 0.05$). Median percentage change of CP and SG was also significantly different from placebo (perampanel 4 mg 31.2%, 8 mg 35.6%, 12 mg 28.6%, placebo 13.9%).

It was an interesting finding that efficacy data of perampanel were worse in patients with carbamazepine as comedication, although even in these patients still significant superiority over placebo could be shown [Steinhoff *et al.* 2013]. This may indicate that due to lower serum concentrations caused by the potent enzyme induction of carbamazepine at least in some of the patients who are treated with enzyme inducing AEDs higher doses of perampanel may be necessary to achieve a better therapeutic effect.

Efficacy data of the phase III trials showed an efficacy plateau reached at 8 mg. With perampanel 12 mg pooled data did not indicate a further dose-dependent improvement for the primary outcome variables median percentage seizure reduction or responder rates [Steinhoff *et al.* 2013]. However, considering differing patient characteristics and especially differing baseline medication at least a part of those patients who did not benefit from adjunctive perampanel 8 mg may still have a major benefit when they are uptitrated. Open-label follow-up data indicate this clearly [Kramer *et al.* 2014; Krauss *et al.* 2013, 2014].

The results of the three pivotal phase III trials clearly proved that the efficacy of perampanel was significantly higher than adjunctive placebo in patients with partial-onset seizures. Therefore, perampanel received approval from the US Food and Drug Administration and the European Medicines Agency as an adjunctive treatment for partial-onset seizures, with or without secondary generalization, in patients aged 12 years and older [Steinhoff *et al.* 2014c].

As the first-in-class selective, noncompetitive AMPA receptor antagonist perampanel proved to

be efficacious in difficult-to-treat epilepsies with partial-onset seizures. It is justified to hope that it might be a promising therapeutic additional option in such patients in clinical practice.

No treatment-related deaths or clinically significant effects, in terms of clinical laboratory values, vital signs or electrocardiogram data, were reported. The most frequently reported adverse events in the phase II and III trials were dizziness and somnolence [Steinhoff *et al.* 2013]. This is supported by a meta-analysis of the phase II and III data, which has indicated that, compared with placebo, perampanel 8 and 12 mg were associated with greater incidences of dizziness (significant at both doses: 8 mg, risk ratio 3.44, 95% confidence interval [CI] 2.48–4.77; 12 mg, risk ratio 4.94, 95% CI 3.27–7.48) and somnolence (significant at 8 mg only: 8 mg, risk ratio 2.17, 95% CI 1.19–3.93; 12 mg, risk ratio 3.11, 95% CI 0.81–11.97) [Hsu *et al.* 2013]. Other adverse drug reactions reported in ⩾5% of patients treated with perampanel 4–12 mg in the phase III trials were fatigue, irritability, nausea and falls [Steinhoff *et al.* 2013]. The warnings and precautions section of the prescription information also recommends monitoring for gait disturbance, as well as falls and injuries [Steinhoff *et al.* 2014c], since an increased incidence of falls was reported with perampanel compared with placebo in the phase III trials [Steinhoff *et al.* 2013]. This risk of falls has been suggested to be associated with dizziness and somnolence [Steinhoff *et al.* 2014c].

While headache was the third most frequently reported adverse events with perampanel across the pooled phase III trials, incidence rates were similar to those observed with placebo (perampanel 2–12 mg, 8.9–13.3%; placebo, 11.3%) [Steinhoff *et al.* 2013].

Across the pooled phase III data, adverse events necessitated withdrawal of perampanel (at doses of 2–12 mg) in 9.5% of patients and placebo in 4.8% of patients. The adverse events most commonly leading to withdrawal were dizziness and somnolence. The adverse events typically resolved upon perampanel discontinuation [Steinhoff *et al.* 2013].

The rate of allergic skin reactions was low and added up to 1.1% with perampanel 2 mg, 2.3% with 4 mg, 2.8% with 8 mg and 2.0% with 12 mg. Placebo rate was 1.6% [Steinhoff *et al.* 2013].

Psychiatric adverse events may be of special interest due to the mode of action of perampanel. The incidence of aggression, suicidal ideation and other psychiatric events with perampanel is also highlighted in the perampanel summary of product characteristics (SPC) and the prescribing information (PI) [Steinhoff *et al.* 2014]. Specifically, the PI states that serious or life-threatening psychiatric and behavioral adverse reactions, including aggression, hostility, irritability, anger, and homicidal ideation and threats, have been reported in patients taking perampanel.

Of note, serious psychiatric adverse events were reported to have affected 1.2% of patients treated with any dose of perampanel across the phase III trials (*versus* 0.9% of placebo-treated patients [Steinhoff *et al.* 2013].

Sleeplessness was observed in 3.6% of patients with placebo and occurred with perampanel 2, 4, 8 and 12 mg in 1.1%, 1.2%, 3.5% and 4.3%, respectively. For fear these rates (placebo, 2, 4, 8 and 12 mg of perampanel, respectively) were 1.1%, 2.2%, 1.7%, 3.0% and 3.5%, for aggression 0.5%, 0.6%, 0.6%, 1.6% and 3.1%, for depression 1.6%, 0.6%, 0.6%, 0.7% and 2.4%. Impaired memory was described in 1.1% of patients under add-on placebo and in 1.1% with perampanel 2 mg, 0% with 4 mg, 1.2% with 8 mg and in 2.0% with 12 mg [Steinhoff, 2014b].

In addition, psychiatric and behavioral adverse events were analyzed across the three phase III trials of perampanel using a broad and narrow Medical Dictionary for Regulatory Activities (MedDRA) Standardised Medical Query (SMQ) for events suggestive of hostility/aggression, including broadly related terms such as fall and contusion [Steinhoff *et al.* 2013]. The analysis found that events within this SMQ were more frequently reported in patients treated with higher doses of perampanel (8 mg, 12%; 12 mg, 20%) than in those treated with placebo (6%), with aggression and irritability being the most common. Most reported cases of aggression, anger or irritability were either mild or moderate in intensity, and patients recovered either spontaneously or with dose adjustment. In addition, thoughts of harming others, physical assault or threatening behavior were also observed in some patients (<1%). Homicidal ideation and/or threat were exhibited in 0.1% of 4368 perampanel-treated patients in controlled and open-label studies, including nonepilepsy studies [Steinhoff *et al.* 2014c].

Table 2 summarizes the adverse events.

Table 2. Pooled incidence rates of adverse events occurring in ⩾5% of patients in any treatment group across the perampanel phase III trials [Steinhoff *et al.* 2013, 2014c].

		Perampanel			
Adverse event, *n* (%)	Placebo (*n* = 442)	2 mg (*n* = 180)	4 mg (*n* = 172)	8 mg (*n* = 431)	12 mg (*n* = 255)
Any adverse event	294 (66.5)	111 (61.7)	111 (64.5)	350 (81.2)	227 (89.0)
Dizziness	40 (9.0)	18 (10.0)	28 (16.3)	137 (31.8)	109 (42.7)
Somnolence	32 (7.2)	22 (12.2)	16 (9.3)	67 (15.5)	45 (17.6)
Headache	50 (11.3)	16 (8.9)	19 (11.0)	49 (11.4)	34 (13.3)
Fatigue	21 (4.8)	8 (4.4)	13 (7.6)	36 (8.4)	31 (12.2)
Irritability	13 (2.9)	7 (3.9)	7 (4.1)	29 (6.7)	30 (11.8)
Nausea	20 (4.5)	4 (2.2)	5 (2.9)	25 (5.8)	20 (7.8)
Fall	15 (3.4)	2 (1.1)	3 (1.7)	22 (5.1)	26 (10.2)
Nasopharyngitis	18 (4.1)	7 (3.9)	9 (5.2)	23 (5.3)	11 (4.3)
Upper respiratory tract Infection	12 (2.7)	11 (6.1)	6 (3.5)	14 (3.2)	10 (3.9)
Ataxia	0 (0.0)	0 (0.0)	1 (0.6)	14 (3.2)	21 (8.2)
Balance disorder	2 (0.5)	0 (0.0)	0 (0.0)	22 (5.1)	8 (3.1)

Results from open-label extension study

During the transition to the open-label extension perampanel was increased by 2 mg fortnightly and thus slower than in the phase III trials. Central nervous adverse events occurred less frequent with this regimen. During the conversion to the open-label extension 91% of the patients who remained in the study reached doses of 10 or 12 mg [Krauss *et al.* 2012]. Treatment-emergent adverse events that led to the discontinuation occurred in 11.7%. The median percentage seizure reduction in patients on perampanel during the double-blind maintenance phase and those patients who had been in the placebo arm and were treated thereafter with perampanel during the open-label study phase was almost identical. After 1 year of open-label treatment it was 48.8% in the former and 49.2% in the latter group [Krauss *et al.* 2012].

Long-term results after an observation period of 3 years have been published recently [Krauss *et al.* 2014]. Median treatment duration was 1.5 years (range 1 week to 3.3 years) in 1216 patients who had been followed during this study. More than 300 patients had been treated for more than 2 years. Retention rate was 58.5%. The most frequently reported adverse events with a frequency >10% were dizziness, somnolence, headache, fatigue, irritability and weight gain. Only dizziness and irritability led to the discontinuation of perampanel in more than 1% of all patients. Clinically relevant abnormal findings concerning vital signs, electrocardiographic assessments, or laboratory findings were not observed. Responder rate and median percentage of seizure reduction remained stable. They amounted to 46% each after 9 months (980 patients) 58% and 60%, respectively, after 2 years (337 patients). Median percentage seizure reduction of SG was 77% after 9 months and 90% after 2 years. A total of 5.3% of those patients who had been followed for more than 1 year remained seizure-free.

Practical clinical experiences after introduction

Monocenter study at the Kork Epilepsy Center

Self-evidently, in a tertiary center like the Kork Epilepsy Center with nationwide and partly international referrals, many patients suffer from difficult-to-treat epilepsies and the burden of ongoing seizures. Only a minority of these patients are suitable for AED trials because appropriate patients for such trials need to meet several requirements that are not met in many instances of our patients with ongoing seizures: of course there must be an unequivocal diagnosis of difficult-to-treat epilepsy. Furthermore additional comorbidities such as a recent history of status epilepticus, severe psychiatric or medical disorders or certain abnormal laboratory values are defined as exclusion criteria. These exclusion criteria often prevent recruitment so that many of our patients have to wait with us until a new AED option is introduced to the market.

It is relatively easy to collect such patients consecutively, to assess their experiences concerning efficacy and tolerability and thus to gain data from quite large patient groups within a short period of time after the launch of a new AED.

In a monocentric observational study [Steinhoff *et al.* 2014a] we gathered the clinical course of the first patients who were treated with adjunctive perampanel after the launch of perampanel in Germany in 2012. Perampanel was initiated in these patients between September and December of 2012. At the cutoff in June of 2013, we identified a group of 74 patients with a minimum observational period of 6 months.

In every case we dosed once daily at bedtime, started with 2 mg of perampanel once daily and increased by 2 mg fortnightly. After having reached 4 mg we asked patients to wait for 4 weeks because we noted in single cases that a dose of 4 mg could have a beneficial effect already. Therefore we opted for a longer observational period at that dosage in order to prevent unnecessary further increases of perampanel. Efficacy data were evaluated for the period of the last 3 months. Retention rate was assessed monthly during the first 6 months of observation. In the case of discontinuation the reason was stated.

Mean age was 38.4 years with a range between 15 and 71 years. A total of 43 (58%) participants were female. Etiology was distributed as follows: structural/metabolic epilepsies comprised 52 patients (70%), epilepsies of unknown etiology 18 patients (24%) and Lennox–Gastaut syndrome four patients (5%). Eight patients (11%) were on one baseline AED, 35 (47%) were on two AEDs, 25 (34%) were on three AEDs and the remaining six patients (8%) had four baseline AEDs. At cutoff maintenance dosages varied widely. Mean dosage was 8.8 mg (range 4–14 mg). Ten patients (14%) were on 4 mg, 13 (18%) were on 6 mg, 16 (22%) were on 8 mg, eight (11%) were on 10 mg, 25 (34%) on 12 mg and one patient (1%) was on 14 mg.

Considering the last 3 months of observations compared with baseline, 34 patients (46%) were responders with a reduction of seizure frequency by at least 50%. Ten patients out of these (14% of all) were seizure-free.

A total of 43 patients (58%) were on enzyme inducers. In this group the responder rate was 42% ($n = 18$) as compared with 48% ($n = 15$) in patients with adjunctive perampanel together with nonenzyme inducing AEDs. This difference was statistically not significant.

Adverse events were reported in 40 patients (54%). Leading side effects were somnolence ($n = 31$; 42%) and dizziness ($n = 13$; 18%) followed by ataxia, irritability, falls, cognitive slowing and depression in single cases.

Retention rate after 6 months was 70%. A total of 22 patients had discontinued perampanel, most of them due to a lack of efficacy ($n = 17$; 77% of all discontinuers). Mean dosage of perampanel was 8.9 mg (4–12 mg) in those patients. It was 8 mg in a patient with irritability, 4 mg in patients with somnolence, 4 mg in the only patient who discontinued perampanel due to depression and 12 mg in a patients who stopped medication with adjunctive perampanel because she planned pregnancy.

Multicenter study at nine epilepsy centers in Germany and Austria

This was an observational study at nine sites in Germany and Austria with identical design as the monocentric study reported above [Steinhoff *et al.* 2014b]. The study comprised 281 patients who were treated with adjunctive perampanel. Mean age was 39 years (range 12–84 years). Mean perampanel daily dosage was 7.7 mg (range 4–15 mg). A total of 44 patients were on a monotherapy when perampanel was added (16%). Baseline medication consisted of two AEDs in 124 cases (43%), of three AEDs in 62 patients (22%) and in the remaining 51 cases (18%) of four baseline AEDs.

After 6 months 169 patients were still on perampanel so that a retention rate of 60% resulted. The 50% responder rate for CP was 48%, 14.5% were seizure-free from CP. A total of 57% were responders concerning SG, 32% remained free from SG. Considering all seizures, the 50% responder rate was 50%. We observed complete seizure freedom in 15% of patients. Mean perampanel dosage was 8.7 mg in seizure-free patients with a range between 2 and 15 mg. Most patients were on 8 mg (45%). Adjunctive perampanel had a statistically significant impact on seizure reduction of all seizure types. Overall incidence of adverse events was 52.0%.

The leading adverse events were somnolence (24.6%) and dizziness (19.6%) followed by ataxia

(3.9%), aggression (2.8%), nausea (2.5%) and irritability (2.1%). The probability of adverse events did not clearly correlate with the dosage. Tolerability was better in patients with one or two baseline AEDs.

Other observational studies

A recent publication from Manchester, UK, reported on a series of 47 patients treated with adjunctive perampanel. Median dose was 8 mg. Results were worse than in our series because no patient became seizure-free and 28% were responders. Retention rate was 55%. The authors watched psychiatric adverse events more often than we did, namely suicidal ideation in two, aggressive behavior also in two and both adverse events together in one further patient [Coyle *et al.* 2014].

Conclusions

Perampanel is a completely new therapeutic option with a mode of action that has not yet been addressed by previous AEDs. After many years of experience with many new AEDs it is tempting and fascinating to use and study an almost purely antiglutamatergic AED.

The pharmacological profile is special and offers the possibility of once daily dosing due to the long half-life. In the major group of patients, higher dosages around 10 and 12 mg may be necessary in order to achieve the best possible therapeutic effect. Due to the impact of enzyme inducing AEDs it is almost always necessary to increase the dose of perampanel. It could be shown that a variety of patients still clearly benefit from such a dose increase. However, in some patients efficacy or adverse events may become apparent at relatively low dosages already. One has to keep in mind that after alterations of the dose it needs 14 days until plasma steady state is reached again. Open-label observational studies showed that more than 1% of patients with hitherto intractable epilepsy syndromes may achieve a period of freedom of seizures for at least 3 months. These figures contradict the recently published statement that adjunctive perampanel means no progress in AED therapy [Prescrire New Products, 2014].

Dizziness and somnolence were the leading adverse events both in phase II and III trials and in observational studies. Psychiatric and neurocognitive adverse events have been considered as a potential hazard. In our hands they were of minor relevance. However, a recent observational study [Coyle *et al.* 2014] should provide motivation to watch such potential adverse events carefully.

Conflict of interest statement

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