Review Article

Perampanel for focal epilepsy: insights from early clinical experience

Perampanel is approved for adjunctive therapy of focal epilepsy with or without secondarily generalized seizures in patients aged >12 years. This narrative review uses real-world and clinical trial data to elucidate perampanel's role in the clinic. Audit data show good tolerability with perampanel and higher freedom-from-seizure rates in elderly vs younger patients. When using perampanel in elderly patients, special attention should be given to comorbidities and co-medication to avoid potential interactions or adverse events. Slower titration is generally recommended, and seizure control should be reassessed at a dose of 4 mg before further dose increases. Perampanel efficacy is similar in adolescents and adults; however, somnolence, nasopharyngitis, and aggression are more frequent in adolescents vs the overall population. Individualized and slow-dose titration can minimize adverse events. Low serum concentrations of perampanel may occur in patients also receiving some enzyme-inducing anti-epileptic drugs; a perampanel dose increase may be required. Adverse events of importance with perampanel include dizziness; anger, aggression, and hostile behavior (particularly in adolescents); and falls (particularly in patients >65 years). An individualized approach to dosing, including slower up-titration and bedtime dosing, reduces dizziness risk. Other drugs may cause or aggravate dizziness; reducing concomitant drugs may be necessary when up-titrating perampanel. It would seem clinically appropriate to give due consideration to avoiding use in patients with a history of anger or hostile/aggressive behavior. The possibility of such behaviors should be discussed with patients before starting perampanel, with monitoring during up-titration. Slower up-titration of perampanel in older patients helps reduce fall risk.

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Introduction

Importance of real-world data

The armamentarium of anti-epileptic drugs (AEDs) has increased exponentially over the past 20 years, with the introduction of 15 new compounds (1). However, despite the plethora of novel agents for the adjunctive treatment of uncontrolled focal seizures, this common type of seizure remains uncontrolled in more than 30% of patients (2). Furthermore, resistance to AEDs makes it improbable that a single agent could eradicate refractory epilepsy, increasing the role of combination therapy. However, there is a higher risk of neurotoxicity with polytherapy using drugs that have a similar mechanism of action (3). Thus, AEDs with novel mechanisms of action offer an opportunity to improve both seizure control and treatment tolerability (1). Such AEDs may also allow for better individualization of treatment to patient characteristics, such as age, sex, side effects, comorbidities, and the potential for drug–drug interactions (1–4).

It is important for clinicians to understand how these AEDs might be best used in real-world clinical settings. However, clinical trials of AEDs, which are required for regulatory purposes, often do not reflect drug use in everyday clinical practice (5, 6). For example, they are based on fixed doses compared with placebo in patients using up to three AEDs, the dosage range tends to be higher, and the titration schedule is often more rapid than in clinical practice (7). Furthermore, tolerability data generated in clinical trials may overestimate drug toxicity in less severely affected patients taking fewer AEDs (8). Thus, there is a need for real-world data that reflect the use of AEDs in everyday clinical practice to supplement the clinical trial data (9).

Real-world data often come from observational studies; that is, studies in which participants are not randomized or otherwise pre-assigned to a treatment, but rather the choice of treatment is decided upon by physicians (often in consultation with patients) (9). In a prospective observational study, outcomes of interest are studied after the study commences and the patient is exposed to the interventions, whereas in a retrospective observational study existing secondary data sources in which both exposure and outcomes have already occurred are used (9). Retrospective studies have the advantages of low cost and fast execution; however, the datasets used may not contain all the information required. Prospective observational studies offer the potential for a fuller dataset (although this may not be as complete as in a randomized controlled trial), but are more costly and slower than retrospective studies. Ultimately, the choice of design will depend on the question being asked, but will also involve trade-offs between speed and cost, and the quality and relevance of data collected (9).

Perampanel clinical profile

Perampanel is a selective non-competitive AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptor antagonist used as adjunctive therapy for focal seizures with or without secondarily generalized seizures in patients >12 years with epilepsy. The efficacy and tolerability of perampanel has been evaluated in an extensive clinical trial program, which included three randomized, double-blind, placebo-controlled phase 3 studies in patients experiencing focal seizures despite treatment with up to three AEDs (E2007-304, -305, -306) and one extension study (E2007-307) (10–13). In the first three trials,

patients were randomized to an initial daily dose of perampanel 2, 4, 8, or 12 mg or placebo for 19 weeks in the 'core' phase; subsequently, the perampanel dose could be titrated upwards to a tolerable level. At the conclusion of the core phase, participants were eligible to participate in an open-label extension phase, during which those randomized to perampanel continued on their core dosage, while those randomized to placebo were given perampanel at a 2 mg initial daily dose, titrated upwards to a tolerable dose over 19 weeks. In total, 1218 patients entered the open-label maintenance period (planned duration 5 years).

In all placebo-controlled studies, perampanel 4, 8, and 12 mg/day consistently and significantly reduced the frequency of focal seizures compared with placebo. Responder rates and freedom-from-seizure rates were also improved (10–12). A *post hoc* analysis of pooled data from 1480 patients in these randomized trials supported the individual study data (14). During up to 3 years' follow-up in the open-label extension study, seizure responses remained stable, with marked reductions, particularly in secondarily generalized seizures (13).

Perampanel was associated with a predictable and acceptable adverse-event profile, with most adverse events being mild or moderate in intensity (10–12, 15). The most common adverse events with perampanel occurred in the central nervous system [dizziness (10.0–47.9%) and somnolence (9.3–18.2%)] and were dose dependent. Headache, fall, irritability, ataxia, and fatigue also occurred in ≥10% of patients in any treatment group. Aggression, ataxia, blurred vision, convulsion, dizziness, dysarthria, fatigue, headache, hypersomnia, somnolence, and vertigo most frequently resulted in the discontinuation, reduction, or interruption of perampanel dosing. There were no drug-related serious adverse events and no cases of sudden unexpected death in epilepsy. The adverse-event profile with long-term use of perampanel reflected that seen in placebo-controlled trials (13).

Perampanel has also been evaluated in real-world clinical settings. Here we use real-world cohort data, supplemented with clinical trial data, to further elucidate the role of perampanel in the clinic, providing practical insights into optimizing perampanel use, including managing common side effects, key considerations for add-on use with other AEDs, and the use of perampanel in specific patient groups, such as the elderly and adolescents.

Effectiveness of perampanel in real-world clinical settings

While clinical trials constitute the gold standard for assessing the efficacy and short-term tolerability of any new medication, they do not provide information on longer-term safety, nor can they predict how well the drug will work in clinical practice. Therefore, real-world experience is of great importance because it complements clinical data, provides valuable insight into how epilepsy treatment impacts different patient populations, and helps to inform on the use of newer AEDs.

Perampanel has been available since 2012 in Europe and real-world experience with this agent is now accumulating. Much of the data below have been recently presented in preliminary form, but some of the first results are now fully published (16, 17). Study design and patient baseline characteristics for these studies are presented in Table 1. With the exception of the one multicenter study from Germany and Austria ($N = 281$) (17), most studies have included only small patient populations ($N = 9–74$) (16, 18–27). Studies varied in length, but most had observation periods of 6 months or more (Table 1). Patients tended to have severe refractory epilepsy, having failed between 1 and 17 previous AEDs before starting perampanel, which was administered at doses of 2–15 mg/day.

Efficacy and safety of perampanel

Real-world data from a wide range of clinical settings and representing up to 3 years' continuous experience with perampanel have shown an

Table 1 Study design and baseline data for prospective and retrospective studies of perampanel in real-life clinical settings

Country	N	Age, mean (range)	Dose, mean (range)	Design	Duration of observation, months	Duration of epilepsy, years, mean (range)	Previous AEDs, n	Baseline AEDs
Germany and Austria (17)	281	39 (12–84)	7.7 mg (4–15 mg)	Cross-sectional, observational study across 9 centers	6*	–	–	1 AED, 16%; 2 AEDs, 43%; 3 AEDs, 22%, 4 AEDs, 18%
Germany (Kork) (16)	74	38.4 (15–71)	8.8 mg (4–14 mg) 4 mg: 14% 6 mg: 18% 8 mg: 22% 10 mg: 11% 12 mg: 34% 14 mg: 1%	Prospective observational study	6*	–	–	1 AED, 11%; 2 AEDs, 47%; 3 AEDs, 34%, 4 AEDs, 8%
Denmark (18)	22	32 (20–64)	(2–8 mg) 2 mg: 1/22 4 mg: 9/22 6 mg: 6/22 8 mg: 6/22	–	8 mean (range: 3–13)	17 (2–54)	–	1–3 AEDs
Scotland (19)	22	48 median (23–65)	Median 4 mg (4–12 mg)	Prospective observation study	6	–	1–15 schedules (median 3 schedules)	1–4 AEDs (median 2)
Canada (20)	9	37.4	4 mg: 1/9 6 mg: 1/9 12 mg: 7/9	Prospective SAP	3 years	–	–	2 AEDs: 88.8% 3 AEDs: 11.2%
England, Bristol (21)	60	40 median (18–77)	6 mg median (2–12 mg)	Retrospective observation study	14	24 (3–76)	5 median (range: 2–12)	3 median (range 1–5)
England, Cornwall (22)	24	(22–61)	(2–6 mg)	Retrospective observation study	16	–	8 mean (range: 1–12)	(range 1–3)
England, Leads (23)	39	–	–	Prospective observation study	–	–	9 mean (range: 5–11)	–
England, Birmingham (24)	16	42 median (24–59)	(4–12 mg)	Retrospective audit	7–285 days	30 (7–53)	11 (range: 3–16)	Range: 2–3
England, Manchester (25)	30	30.5 median (19–50)	8 mg median (2–12 mg)	Retrospective observation study	–	–	–	–
Wales (26)	36	–	–	3 epilepsy centers	134 days (6–431 days)	22	5.8 mean	2.1 mean
Ireland (27)	20	31.3 median (28–63)	–	Retrospective observation study	3–12	–	10 median (range: 5–17)	–

AED, anti-epileptic drug; SAP, Special Access Programme.
*Patients had been on treatment for at least 6 months, and the assessment period for efficacy was 3 months.

efficacy and safety profile that is consistent with that demonstrated in the phase 3 studies and their extension (11–14). Clinical response, defined as a reduction of seizure frequency of at least 50%, occurred in up to 89% of patients, although there was considerable variation [ranging from 9% in Denmark to 89% (for secondarily generalized seizures) in Cornwall, England],

which may relate to the perampanel doses administered and the small sample sizes in some studies (Table 2). In the large, multicenter audit conducted in Germany and Austria, response rates were 46% in 281 patients receiving a mean perampanel dosage of 7.7 mg/day (17). Similar response rates of 50% were reported in another German study, where 74 patients received peram-

Table 2 Efficacy and tolerability data for prospective and retrospective studies of perampanel in real-life clinical settings

Cohort	Responder rate	Seizure free	Retention rate	Adverse events
Germany and Austria (17)	50%	15%	60%	All AEs: 52.0% Somnolence: 24.6% Dizziness: 19.6% Ataxia: 3.9% Aggression: 2.8% Nausea: 2.5% Irritability: 2.1%
Germany (Kork) (16)	34/74 (46%)	10/74 (14%)	52/74 (70%)	All AEs: 40/74 (54%) Somnolence: 31/74 (42%) Dizziness: 13/74 (18%) Ataxia, irritability, falls, cognitive slowing, and depression in single cases
Denmark (18)	9%	2/22 (9.1%)	68%	Fatigue: 8/22 (33.3%) Aggressiveness: 5/22 (22.7%) Dizziness: 4/22 (18.1%) No AEs: 9/22 (40.9%)
Scotland (19)	4/22 (18.2%)	1/22 (4.5%)	24/41 (58.5%)	All AEs: 15/22 (68.2%) Depression: 3/22 (13.6%) Weight gain: 3/22 (13.6%) Irritability: 2/22 (9.0%) Aggression: 1/22 (4.5%) Paranoia: 1/22 (4.5%)
Canada (20)	–	2/9 (22%)	8/9 (88.9%)	Dizziness: 1/9 Falls/injury: 1/9 Weight loss: 1/9 Prolonged QTc interval: 1/9
England, Bristol (21)	16/60 (27%) 27% (SG) 27% (CP)	10/60 (17%)	75%	All AEs: 37% Dizziness: 27% Unsteadiness: 17% Behavioral disturbance: 8%
England, Cornwall (22)	89% (SG); 75% (CP)	2/24 (8.3%)	75%	Unsteadiness: 6/24 (25%) Dizziness: 4/24 (17%) Behavior disturbances: 4/24 (17%)
England, Leeds (23)	50% (GTC) 45% (CP)	1/39 (2.6%)	27/39 (70%)	Sedation: 46% Dizziness: 18% Unsteadiness: 15% Headache: 10% Anger/aggression: 10%
England, Birmingham (24)	3/16 (18.8%)	0%	7/16 (43.8%)	Behavioral disturbance: 37% Sedation: 18.8% Dizziness: 18.8% Unsteadiness: 12.5%
England, Manchester (25)	5/19 (26%)	–	19/30 (63.3%)	Dizziness: 8/30 (26.6%) Sedation: 7/30 (23.3%) Behavioral disturbance: 6/30 (20%) Unsteadiness: 5/30 (16.7%) Confusion/mental slowing: 4/30 (13.3%) Depersonalization/abnormal thoughts: 3/30 (10%)
Wales (26)	66.7%	–	75%	All AEs: 16/36 (44%)
Ireland (27)	7/20 (35%)	0%	10/20 (50%)	All AEs: 11/20 (55%) Fatigue: 7/11 Mood/behavioral alteration: 6/11 Dizziness: 2/11

panel at a mean dosage of 8.8 mg/day (16). Across all real-life studies, up to 22% of patients were seizure free (Table 2), with 14% of patients being seizure free in the single-center German study, and 15% being seizure free in the multi-center study in Germany and Austria (16, 17). Retention rates were relatively high across all studies, ranging from 44% to 89% (Table 2), with highest retention in patients receiving slow titration (<2 mg every 2 weeks) (26).

Perampanel was well tolerated across all available observational studies, with approximately 37–68% of patients experiencing any adverse events (Table 2). The most common adverse events were somnolence and dizziness (Table 2) as would be expected based on data from clinical trials (11–14). Ataxia, behavior disturbances (aggression, irritability), nausea, falls, unsteadiness, cognitive slowing, and depression were also often reported (Table 2). In the largest observational study (from Austria and Germany), the probability of adverse events did not clearly correlate with perampanel dosage (17). In this study, tolerability was better in patients receiving one or two baseline AEDs than in those on more than two AEDs (17). Psychiatric adverse events in this study were in the range that would be expected in these difficult-to-treat patients (17). Unexpected serious adverse events (e.g., dermatological, cardiologic, or laboratory findings) were not found (16, 17).

Perampanel in different patient types

Perampanel and the elderly

Background – The management of epilepsy in the elderly is complicated and challenging, particularly as comorbidity and co-medication rates are high (28, 29). Physiological changes associated with aging, including impairment of hepatic and renal function and age-related changes in receptor numbers and function, affect the pharmacokinetic and pharmacodynamic properties of agents and increase the likelihood of side effects (28, 29). In addition, high levels of polypharmacy increase the chances of drug–drug interactions and associated toxicity (28). For these reasons, AED trials in elderly patients are particularly challenging and to date, only four randomized, double-blind, comparative clinical trials in older patients have been published, all of them in newly diagnosed epilepsies (30–33). Other published reports of the use of AEDs in elderly patients are scarce (34–37). In general, there has been an increasing trend away from the use of older AEDs in elderly

patients, for reasons including high levels of protein binding and unfavorable pharmacokinetics.

Salzburg prospective audit – In the Salzburg prospective audit, the efficacy and tolerability of perampanel in 20 elderly patients (7 female; mean age 69.8 years, SD 7.8) and 65 younger patients (39 female; mean age 36.8 years; SD 11.5) were compared (38). Elderly patients had numerically fewer seizures than younger patients in the last month before baseline (mean 2.0 vs 8.4). The mean number of concomitant medications was 1.74 (range 1–3) for elderly patients compared with 1.91 (range 0–4) for younger patients. Perampanel dosages were 2–8 mg/day in elderly patients and 2–12 mg/day in younger patients. Over 57 months, 75% (15/20) elderly patients and 53.8% [35/65] younger patients were still taking perampanel, and 35% (7/20) elderly patients were seizure free compared with 13.8% (9/65) younger patients ($P = 0.009$). In the elderly group, 5% (1/20) experienced seizure reduction 50–75%, and 20% (4/20) experienced seizure reduction <50%, with data missing for 3 patients at follow-up. This compared with 3.1% (2/65) seizure reduction >75%; 15.4% (10/65) seizure reduction 50–75%; and 56.9% (37/65) seizure reduction <50% in younger patients. Thirty-five percent (7/20) of elderly patients experienced adverse events, compared with 55.4% (36/65) of the younger patients ($P = 0.563$). Fatigue (20%) and vertigo (15%) were the most common adverse effects in the elderly group, while vertigo (40%) and psychiatric effects (9.2%) were most common in younger patients. Overall, the efficacy and tolerability in elderly patients was good with higher freedom-from-seizure rates observed in elderly vs younger patients.

Although the clinical profile of perampanel looks encouraging, prospective studies are needed to explore the full potential of this drug in the elderly. In addition, the adverse-event profile may be found to differ in the elderly vs younger patients, once data from real-world studies accumulate or prospective studies are performed in the elderly.

Practice points – In elderly patients, special attention has to be given to the high rate of comorbid illnesses and co-medications. A careful look for potential interactions and a critical review of the current medication regimen in these patients can help avoid potential adverse events. Based on our clinical practice and personal experience, we recommend slower titration rates (e.g., <2 mg per 2 weeks). Also, patients may respond to lower doses, and seizure control should be reassessed

when they reach 4 mg perampanel, before increasing the dose, if required.

Perampanel and adolescents

Efficacy – The efficacy of add-on treatment with perampanel in adolescents has been evaluated in three pivotal, double-blind, placebo-controlled, phase 3 studies (studies 304, 305, and 306) (39). In total, 145 patients aged 12–17 years with focal seizures were randomized either to placebo or perampanel 2, 4, 8, and 12 mg daily (Table 3).

The treatment period comprised a 6-week titration and 13-week maintenance period. The primary efficacy endpoint was the percent change in seizure frequency over 28 days during double-blind treatment phase vs baseline; secondary endpoints included 50% responder rate, and the percent change in the frequency of complex partial and secondarily generalized seizures over 28 days during the double-blind treatment phase vs placebo. For pooled data from studies 304 and 305, the 50% responder rates in perampanel 8 and 12 mg/day groups were double that of the placebo group. In study 306, perampanel doses 4 and 8 mg/day were most efficacious in terms of 50% responder rates compared with placebo (note that the 12 mg dose was not included in study 306) (Table 4).

In patients with complex partial seizures with or without secondary generalization, all perampanel doses ≥4 mg/day resulted in marked mean percent change from baseline compared with placebo: −42.9, −40.3, and −39.2 vs −4.4%, respectively, for the 4, 8, and 12 mg doses vs placebo (39).

Table 3 Patient randomization in studies 304, 305, and 306 (39)

Category	Randomized (*n*)	Treated (*n*)	Completed (*n*)*
Placebo	45	45	37
Perampanel 2 mg	21	21	20
Perampanel 4 mg	13	13	13
Perampanel 8 mg	45	44	41
Perampanel 12 mg	21	20	18

*Some patients did not complete the study either due to adverse events or choice.

Table 4 50% responder rate in adolescents with focal seizures (39)

Study	Placebo (%)	Perampanel (%)			
		2 mg/day	4 mg/day	8 mg/day	12 mg/day
304 and 305	22.2	DNS	DNS	40.9	45.0
306	7.1	4.8	15.4	33.3	DNS

DNS, dose not studied in this trial.

Overall, 124 of 129 adolescent patients who completed the 'core' phase 3 trials were enrolled into an extension study (40) with an initial 16-week blinded conversion period. Patients receiving placebo in the core studies were started on perampanel 2 mg/day and titrated every 2 weeks to the individualized maximum tolerated dose, up to 12 mg/day. Patients receiving perampanel during the core trials continued to receive the drug on the blinded basis during the conversion period. At an interim cutoff date, 87 adolescent patients reached ≥1 year of perampanel exposure, and 44 reached ≥2 years (40). The results showed improvement in seizure control following initiation of perampanel for patients taking placebo in the core studies and sustained improvement for patients who received perampanel in a double-blind study (40). The decrease in seizure frequency was maintained up to 52 weeks (Tables 5 and 6).

Of interest, perampanel was most effective in patients with secondarily generalized seizures. These patients also had the highest 50% responder rate during the entire treatment period. At the interim cutoff, >50% reduction of seizure frequency was observed in 59% patients with secondarily generalized seizures compared with 46% of patients with complex partial seizures and 46% in the overall patient population (≥1 year of

Table 5 Median percent reduction in seizure frequency/28 days in adolescent patients exposed to perampanel ≥1 year (40)

Weeks of treatment	Overall, % (*n* = 87)	CP and SG, % (*n* = 77)	SG only, % (*n* = 44)
1–13	34	39	53
14–26	46	47	64
27–39	55	52	73
40–52	47	45	65

CP, complex partial seizures; SG, secondarily generalized seizures.

Table 6 Median percent reduction in seizure frequency/28 days in adolescent patients exposed to perampanel ≥2 years (40)

Weeks of treatment	Overall, % (*n* = 44)	CP and SG, % (*n* = 37)	SG only, % (*n* = 19)
1–13	23	39	60
14–26	32	47	65
27–39	57	57	71
40–52	50	50	65
53–65	54	62	88
66–78	67	68	80
79–91	58	77	85
92–104	61	62	90

CP, complex partial seizures; SG, secondarily generalized seizures.

perampanel exposure). In the group exposed to perampanel ≥2 years, the corresponding figures comprised 74% patient with secondarily generalized seizures, 60% patient with complex partial seizures, and 57% in the overall population (40).

Thus, the efficacy of adjunctive therapy with perampanel in adolescents with focal seizures has been demonstrated in phase 3 trials and extension study. These results appear similar to those in adult patients with focal epilepsy (39, 41).

Safety – The safety of perampanel in adolescent patients with focal epilepsy has been demonstrated in several studies (39–41). In phase 3 core trials, the overall incidence of treatment-emergent adverse events (TEAEs) was similar in placebo group and all doses of perampanel (Table 7).

Discontinuation rate was the highest in placebo group and in patients exposed to perampanel 12 mg/day (Table 5) (39). The most common adverse events, occurring in more than 5% of patients, included dizziness (20%), somnolence (15%), aggression (8.2%), decreased appetite (6%), and rhinitis (5%). Aggression rates were higher in adolescent patients (18.2%) compared with the overall population (4.5%) (41).

In the extension study, the overall incidence of TEAEs was 88.4%, and the most commonly observed adverse events included dizziness (30.6%), somnolence (24%), nasopharyngitis (19%), and aggression (18.2%) (40, 41). Of the 22 adolescent patients with treatment-emergent aggression in the extension phase, 21 received higher doses of perampanel (<8–12 mg), 17 were male (77.3%), and the majority experience a single episode of aggression (*n* = 16, 72.7%) (42).

In adolescent patients, the overall incidence of TEAEs was similar between the placebo group and all doses of perampanel (39). TEAEs of somnolence, nasopharyngitis, and aggression occurred more frequently in adolescents than in the overall population (41).

Practical recommendations – Although real-world data for perampanel are accumulating, these data

Table 7 Overall incidence of treatment-emergent adverse events (TEAEs) and discontinuation rates for adolescents during the double-blind phase in studies 304, 305, and 306 (39)

Patient groups	Incidence of TEAEs (%)	Discontinuation (%)
Placebo (*n* = 45)	68.9	6.7
Perampanel 2 mg (*n* = 21)	71.4	0
Perampanel 4 mg (*n* = 13)	61.5	0
Perampanel 8 mg (*n* = 44)	75.0	2.3
Perampanel 12 mg (*n* = 20)	70.0	5.0

are currently limited in adolescent patients. Obtaining further data will be especially important for this patient group because information on drug safety and effectiveness in children and adolescents from clinical trials is always less prominent than that for adult patients. Based on currently available clinical trial data, few recommendations specific to adolescent patients can be made. A similar efficacy of perampanel can be expected in adolescents with focal epilepsy refractory to other AEDs. To avoid the potential adverse events in adolescent patients, dose titration should be slow (every third to fourth week) and individualized for each patient. As our knowledge advances, real-world data will have a key role in further clarifying practical recommendations on the use of perampanel in adolescent patients, particularly regarding behavioral problems.

Patients taking concomitant enzyme-inducing anti-epileptic drugs

Enzyme-inducing (EI) AEDs may interfere with the metabolism of perampanel and reduce the serum concentrations of perampanel considerably (14). An analysis of the phase 3 pharmacokinetic and pharmacodynamic data showed that three EI AEDs – carbamazepine, oxcarbazepine, and phenytoin – increased perampanel clearance leading to a reduction of serum levels of up to 30% (43).

Carbamazepine reduces mean exposure to perampanel to approximately 70% of that observed in the overall population (43, 44). It may therefore be expected to affect not only efficacy, but also the rates of dose-related adverse events in patients receiving perampanel. However, a recent analysis of the pooled phase 3 data has indicated little variation in the incidences of dizziness, somnolence, or headache in patients who were or were not receiving the non-EI AEDs, valproic acid, lamotrigine, or levetiracetam (45). Nonetheless, the efficacy of perampanel was reduced, although still significantly superior to placebo, if carbamazepine was among the AEDs to which perampanel had been added (14). Physicians should be aware that low serum concentrations of perampanel may occur in some patients receiving perampanel in combination with EI AEDs; a dosage increase in perampanel may be required in these patients (14). However, variation in response exists, with some patients on EI AEDs and adjunctive perampanel showing a good response, and others experiencing adverse events at low dosages and serum concentrations of perampanel in real-life clinical settings (16, 17). In

the prospective observational study from Kork (Germany), 43 patients (58%) were taking EI AEDs. The responder rate in this group was 42% ($n = 18$) compared with 48% ($n = 15$) in patients taking non-EI AEDs; the difference was not statistically significant (16).

Managing common side effects

To prevent the common adverse events with perampanel, dosing should be individualized and a slow-dose titration schedule initiated, particularly in at risk individuals, such as the elderly and adolescent patients. Adolescent patients, and those with learning difficulties or dementia, should be monitored closely during treatment initiation. In addition, psychiatric comorbidity and family history of psychiatric disorders should be considered when prescribing perampanel and may suggest the need to consider slower dose titration and close monitoring. The potential for some adverse events, such as dizziness and somnolence during the day, may be minimized by bedtime dosing of perampanel because pharmacokinetic data show that the peak plasma concentration of perampanel is reached at about 0.5–2.5 h after dosing (46). If dizziness or other dose-related adverse events do occur, a dose reduction should be considered. Note that it takes approximately 2 weeks to reach steady state levels of perampanel in plasma (down to 1 week for perampanel plus EI AEDs); titration is therefore generally recommended every 2 weeks (or every 1 week in conjunction with an EI-AED) (46). Therefore, if a patient is on perampanel and an EI-AED, then titration every 2 weeks is slower than normal.

Dizziness

Background – Dizziness refers to 'a disorienting sensation such as faintness, light-headedness, or unsteadiness' (47). Without doubt dizziness is one of the most often reported complaints in patients taking central nervous active drugs, especially in the elderly population. It occurs usually during up-titration or under high doses, but decreases after some time or with dose reduction. Due to this dose dependency, dizziness is classified as classic Type A adverse effect, which is often accompanied by unsteadiness, vertigo, imbalance, ataxia, diplopia, and tremor (48, 49). Dizziness is one of the characteristic adverse events of first generation AEDs (carbamazepine, phenytoin, phenobarbital, primidone). In the Veterans Administration Affair Monotherapy study, 44–

68% of the patients had treatment failures almost exclusively due to and dizziness, sedation, and coordination difficulties (50). In a meta-analysis of randomized, placebo-controlled, add-on trials of second-generation AEDs (gabapentin, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, tiagabine, topiramate, and zonisamide), any dose was associated with an almost threefold increase in risk of coordination difficulties (51). The risk was highest for oxcarbazepine (RR 4.70, 95% CI 2.61–8.45), lamotrigine (3.50, 2.06–5.96), topiramate (3.26, 2.1–5.03), and pregabalin (3.14, 1.37–7.19), whereas it was not elevated for gabapentin and levetiracetam at any dose (51).

Perampanel data – In pooled data from the phase 3 studies using perampanel as adjunctive treatment, dizziness, somnolence, and headache were the most frequent adverse events. In patients receiving perampanel, dizziness was reported in 16%, 32%, and 43% for 4, 8, and 12 mg, respectively, vs 9% for placebo (14). Although dizziness was mild in most patients, it was also the adverse event most frequently necessitating treatment withdrawal, which was 0.6% with 2 mg, 0.6% with 4 mg, 2.1% with 8 mg, and 4.3% with 12 mg, compared with 0.9% with placebo (14). In a meta-analysis including 1178 patients treated with perampanel and 503 treated with placebo, the risk ratio for dizziness was 2.86 (95% CI 2.16–3.79) for any dose (52). A similar frequency of dizziness was also found in open real-world studies, in which somnolence and dizziness were the most commonly reported adverse event. In a study from Germany and Austria, 52% of patients experienced adverse events, the most common of which were somnolence (24.6%), dizziness (19.6%), ataxia (3.9%), aggression (2.8%), nausea (2.5%), and irritability (2.1%) (53). In the Salzburg prospective audit, 125 patients with drug-resistant epilepsy received perampanel as adjunctive treatment and were observed over more than 20 months. Dizziness was the most common adverse event (32%), followed by fatigue (12%), psychiatric symptoms (7%), cognitive deficits (6%), speech problems (5%), nausea (4%), and gait problems (4%). Most adverse events were mild, and dizziness disappeared when dose was reduced by 2 mg and patients were instructed to take perampanel at bedtime. By doing this, the peak of dose effect with a C_{max} of about 1 h was not experienced by the patients during sleep. Also a slower titration rate (<2 mg per 2 weeks) resulted in decreased dizziness and increased tolerability, which was also found in another real-world study (26).

Management of patients with dizziness – As dizziness is a multifactorial symptom, an individualized approach is necessary to minimize its occurrence. Although dizziness is a classic Type A adverse effect, which is clearly dose related, there are also patient related factors, such as age, comorbid polyneuropathy, structural brain lesions, visual problems, or hypoacusis. In these patients, a slower titration rate is mandatory (e.g., <2 mg per 2 weeks). Special attention should be drawn to the co-medication, which is very common in the elderly population due to the high comorbidity (28). Virtually any centrally active drug, but also antihypertensives or diuretics, may cause or aggravate dizziness. In patients with drug-resistant epilepsy, the total drug load has to be taken into consideration when dizziness occurs. Sometimes a reduction of concomitant drugs is necessary when up-titrating perampanel. Due to the specific pharmacokinetic profile with high C_{max} after 0.5–2.5 h (46), it is advisable to take the medication immediately before bedtime.

Behavioral change and aggression

Background – Aggression can be defined as an apparent unprovoked assault, verbal or physical or both, resulting from irritability, impulsivity, anger, and hostility. These behavioral changes in response to the addition of some AEDs are exacerbated by the high incidence of neurophysiological and psychiatric comorbidities occurring particularly in the drug-resistant epilepsy population (54). The major neurotransmitter systems implicated in the pathogenesis of aggression include serotonin, glutamate, norepinephrine, dopamine, and δ-aminobutyric acid together with their respective receptors (55). Levetiracetam stands out as the AED most likely to produce or worsen hostility and aggression across of a range of epilepsy patient populations (56–63). Other AEDs implicated in producing behavioral changes include topiramate (64) and zonisamide (62). Associated factors have included fast titration rates, previous aggression, a psychiatric history, a history of febrile seizures, and a family history of psychiatric disorders (58, 64, 65). The possibility of physical violence in this setting is always a concern (57).

Perampanel data – Aggression is listed as a 'common' psychiatric disorder in the Fycompa [perampanel] Summary of Product Characteristics (66). Anger, aggression, and hostile behavior have been reported in patients taking adjunctive perampanel, particularly at higher dosage. Most events were mild or moderate, and some patients recovered spontaneously or with dosage adjustment. However, thoughts of harming others, physical assault or threatening behavior were observed in <1% patients in clinical trials with perampanel.

Serious psychiatric TEAEs – most commonly aggression – were reported in 12/1480 (1.2%) patients with partial-onset seizures receiving perampanel in a pooled analysis of three phase 3 studies [vs 4 patients (0.9%) receiving placebo] (12). Further analysis of TEAEs suggestive of hostility or aggression showed that irritability (4 mg, 4%; 8 mg, 7%; 12 mg, 12%; vs placebo, 3%) and aggression (4 mg, 1%; 8 mg, 2%; 12 mg 3%; vs placebo, 1%) were the most common (14).

In the core phase 3 perampanel studies, 143 adolescent patients (aged 12–17 years) received at least one dose of perampanel ($n = 98$ vs $n = 45$ placebo) (39). Aggression was reported as a TEAE by eight adolescents (8%) in the perampanel group vs none randomized to placebo. In the extension study, aggression occurred more frequently as a TEAE in adolescents (18.5%) than in adults (3.6%) (41). A randomized, double-blind, placebo-controlled study of the short-term effect of adjunctive perampanel (2–12 mg/day) on cognition in adolescents (12–17 years) with inadequately controlled partial-onset seizures found that 15 patients (17.6%) taking perampanel experienced at least one adverse event relating to hostility or aggression (vs placebo, $n = 2$; 4.2%) (67). TEAEs were considered serious in two of those patients on perampanel (daily dose 8 and 12 mg); however, both completed the study and continued into the extension phase.

Glasgow perampanel audit – Seven of 41 patients enrolled in the ongoing prospective audit of adjunctive perampanel in patients with refractory epilepsy (Western Infirmary Epilepsy Unit, Glasgow) withdrew due to neuropsychiatric side effects (three depression, two irritability, one each aggression, and paranoia) (19). Patients with overt anger issues and major psychiatric problems were specifically excluded from the audit. The patient exhibiting aggression had focal refractory epilepsy and was taking high-dose oxcarbazepine and zonisamide when perampanel was introduced in January 2013. The dose was titrated up to 8 mg nocte without problem until mid-June 2013, when his general practitioner stopped perampanel after the patient developed uncharacteristic aggressive behavior. The problem rapidly resolved spontaneously thereafter.

Management of aggression with perampanel – Many patients with epilepsy, particularly those taking levetiracetam, self-report feelings of anger toward others (68). The situation is made more complicated by the high prevalence of comorbid psychiatric and behavioral disorders in patients with refractory epilepsy (54). Conversely, no patients with parkinsonism, neuropathic pain, multiple sclerosis, or migraine receiving perampanel in doses up to 8 mg daily in clinical trials reported aggression or hostility (69). Arguably, from a clinician's perspective, it would seem appropriate to consider avoiding use in patients with a history of serious anger management issues and/or hostile or aggressive behavior. In all other patients, the possibility of irritability, impulsivity anger, and aggression should be sensitively discussed with the patient and their close family when prescription of perampanel is being considered. Some patients do not notice their own behavior change, so family input is essential; providing a contact number for patients and their family to report any inappropriate behavior to their physician can be useful. All such problems should be monitored while the perampanel dose is titrated to the optimum amount for each individual patient. Documentation of any personal or family history of psychiatric disorders will alert the prescriber to consider slower introduction of the drug.

Particular care should be taken when prescribing perampanel for patients with learning disability or dementia. Adolescents, too, are particularly susceptible to developing behavioral side effects with perampanel (41, 67), and hence, its introduction should be closely monitored in this population. There is some evidence that alcohol may exacerbate levels of anger in some patients; this issue should be explored in patients reporting behavioral problems with perampanel (66). To the authors' knowledge, there are no data to suggest that behavioral problems with perampanel are likely to be any worse in patients who were already taking levetiracetam. Aggression and hostility have the potential for serious medico-legal implications, and so, accurate documentation in the case notes and in the correspondence to the patient's general practitioner of any behavioral problems should be an essential accompaniment to each consultation, particularly if a problem with impulsivity, anger, or aggression is reported. These symptoms can be managed in many patients without necessarily withdrawing the perampanel. The patient and family are normally in a good position to decide whether or not to discontinue the drug should a behavioral problem arise.

Falls, fatigue, and somnolence

Falls are among the more frequently reported adverse events in the randomized controlled phase 3 trials with adjunctive perampanel. In these three pivotal trials (10–12), adverse drug reactions occurring in more than 5% of patients receiving perampanel 4–12 mg were dizziness (16%, 32%, and 43% for 4, 8, and 12 mg, respectively, vs 9% for placebo), somnolence (9%, 16%, and 18% vs 7%), fatigue (8%, 8%, and 12% vs 5%), irritability (4%, 7%, and 12% vs 3%), nausea (3%, 6%, and 8% vs 5%), and falls (2%, 5%, and 10% vs 3%) (14). Falls were more frequent with perampanel 8 or 12 mg than with placebo, although only one fall was considered a serious TEAE (14). Accordingly, the potential for increased risks of falls (along with aggression and suicidal ideation) is noted in the European and US licenses (14).

Falls may occur more frequently in individuals older than 65 years than in younger patients. Although overall adverse-event rates were similar in perampanel-treated patients aged ≥65 years ($n = 20$) and those aged ≥18 to <65 years ($n = 920$) in a subanalysis of pooled phase 3 data by age, some individual adverse events were reported more frequently in patients aged ≥65 years. These included dizziness (45.0% vs 28.6% for placebo), fatigue (25.0% vs 8.7%), and falls (25.0% vs 4.9%) (53). While these data represent a relatively small elderly population, the increased likelihood of these adverse events may warrant slower up-titration of the perampanel dose in patients aged ≥65 years (53). The 'warnings and precautions' section of the prescribing information also recommends monitoring for gait disturbance, as well as falls and injuries. It has been suggested that the risk of falls may be associated with dizziness and somnolence (53).

As mentioned above, fatigue and somnolence together with dizziness belong to the most frequent adverse events reported under adjunctive perampanel in the pivotal trials (10–12, 14, 70). This is supported by a meta-analysis of the phase 2 and phase 3 data, which has indicated that, compared with placebo, perampanel 8 and 12 mg were associated with greater incidences of 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). Other adverse drug reactions reported in ≥5% of patients treated with

Table 8 Pooled incidence rates of adverse events occurring in ≥5% patients in any treatment group across the perampanel phase III trials (14, 53)

Adverse event, n (%)	Perampanel				
	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)
Falls	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)

perampanel 4–12 mg in the phase 3 trials were fatigue, irritability, nausea, and falls (14, 53).

The dose-dependent incidences of fatigue and somnolence are shown in Table 8. This was confirmed by the open-label, follow-up study after the pivotal trials (13, 16, 17, 53). In the phase 3 extension study that comprised 1216 patients, fatigue and somnolence were among the five adverse events that were reported in ≥10% of patients. Somnolence was reported in 21.2% and fatigue in 13.1%. Other side effects than somnolence and fatigue, namely dizziness and irritability, were responsible for discontinuations of perampanel in 1% or more of the patients (13).

The increased incidence of somnolence and fatigue in clinical trials is reflected in real-world data. In the single-center, post-launch observational trial in 84 patients treated at the Kork Epilepsy Centre (16), somnolence and fatigue (summarized as somnolence) were reported in 42% of patients. However, only one patient discontinued perampanel due to somnolence. Other leading side effects were dizziness (*n* = 13, 18%), followed by ataxia, irritability, falls, cognitive slowing, and depression in single cases (16). Physicians found that somnolence and dizziness generally could be prevented or reduced with the strategy of using perampanel at bedtime (16). Furthermore, the multicenter survey of nine epilepsy centers in Germany and Austria (17) revealed somnolence in 24.6% of patients.

Conclusions

Perampanel has shown high rates of efficacy and good tolerability in real-world settings, with most adverse events being mild and no severe adverse events reported to date. The safety profile of perampanel in the elderly and adolescents is similar to that for adults. The most frequently reported adverse events are dizziness, fatigue, and somnolence. The risk of these adverse events can be reduced by dosing of perampanel at bedtime. Adverse events can also be managed with slow-dose titration and dose adjustments.

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