Update on Perampanel: A Novel Antiepileptic Drug for Partial-Onset Seizures

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Abstract  Perampanel, a drug with a unique mechanism of action, was approved by the US Food and Drug Administration (FDA) in October 2012 for adjunctive treatment of partial-onset seizures with or without secondarily generalized seizures. During the 66th Annual Meeting of the American Epilepsy Society, held in San Diego, California, researchers presented data from three core studies that led to FDA approval of this novel antiepileptic drug (AED). At the 67th Annual Meeting of the American Epilepsy Society, held in Washington, DC, many of the same research teams and others presented results of post hoc analyses of the pooled perampanel phase 3 pivotal studies and 14 phase 1 studies. This research addressed such subjects as the effect of food on the drug’s absorption, its complementary mechanism of action when combined with other AEDs, the efficacy and safety of the drug in different populations, and factors that might affect its long-term use.

Perampanel is a selective, orally active, noncompetitive α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) glutamate receptor antagonist. In three multicenter, double-blind, randomized, parallel-group, placebo-controlled, phase 3 trials known as studies 304, 305, and 306, perampanel therapy was both effective and well tolerated. In more than 30 countries—including the United States, Canada, and the European Union—perampanel has been approved for adjunctive treatment of partial-onset seizures, with or without secondarily generalized seizures. In the United States and the European Union, the drug is approved for use in adult and adolescent patients ≥ 12 years of age; in Canada, it is approved for those ≥ 18 years of age.

PHARMACOKINETICS OF PERAM PANEL

Gidal and colleagues analyzed data from 14 phase 1 studies in which either single doses of 0.2–12 mg or once-daily doses ranging from 1 to 6 mg of perampanel were given by mouth to healthy male and female volunteers. Following dosing, plasma drug concentrations were obtained via validated methods.

As shown in Table 1, perampanel was quickly and completely absorbed following oral administration (median time to maximum plasma concentration [tmax], 0.75 hour; range, 0.5–1 hour). Administration of perampanel with food consistently slowed its absorption, When ingested with a high-fat meal, tmax was delayed by 2–3 hours, and the maximum plasma concentration (Cmax) fell by 28%–39%, depending on the dose administered. However, the overall extent of perampanel absorption, based on the area under the concentration-time (AUC) curve, was not affected by food. In the same studies, perampanel’s mean terminal elimination half-life (t1/2) ranged from 53 to 136 hours; plasma binding capacity was about 95%.

Perampanel is extensively metabolized via cytochrome P3A4; the main metabolic pathway is oxidation at the pyridine, benzene, or benzonitrile rings, followed by glucuronide conjugation. Forty-one days after oral and intravenous administration of 14C-perampanel, 70.1% of the radioactivity was recovered, with 22.3% in urine and 47.8% in feces. In addition, the rate of renal excretion of unchanged perampanel was low (< 0.12%) when compared with its metabolic clearance.

These findings continue to support the safe and effective use of perampanel in patients with partial-onset seizures, with no new concerns. Still, caution might be recommended in patients with hepatic disease. Although food slows the absorption of perampanel and reduces the Cmax of the drug, it does not affect its overall absorption.

POST HOC ANALYSES OF POOLED PHASE 3 STUDIES

In the core phase 3 studies, patients ≥ 12 years of age with refractory partial-onset seizures were being treated concomitantly with up to three other antiepileptic drugs (AEDs). After a 6-week baseline period, patients were randomized in double-blind fashion to receive once-daily
doses of 8 or 12 mg of perampanel or placebo (studies 304 and 305)\textsuperscript{1,2} or 2, 4, or 8 mg of perampanel or placebo (study 306).\textsuperscript{3} If patients did not tolerate the assigned randomized dose levels, down-titration was permitted, so the actual (last) dose could have differed from the assigned randomized dose.

Using data from these studies, various research teams evaluated the efficacy and safety of perampanel under different scenarios. Study endpoints for most of these analyses included: (1) primary efficacy, defined as the median percent change from baseline in seizure frequency over 28 days; (2) secondary efficacy (responder rates), defined as the percentage of patients achieving a 50% reduction in seizure frequency over 28 days in the 13-week maintenance period, compared with the seizure frequency at baseline, with the last observation carried forward; and (3) safety, defined as the frequency of treatment-emergent adverse events (TEAEs) reported in patients receiving perampanel or placebo.

**Adjunctive Use of Perampanel with Concomitant AEDs**

One of the questions these post hoc analyses was designed to address was whether the number of AEDs used concomitantly by patients at baseline in the three core phase 3 trials\textsuperscript{1-3} impacted the safety and efficacy of adjunctive perampanel therapy. Glauser and colleagues\textsuperscript{5} pooled data from all three trials. A total of 1,480 patients were included in the safety analysis, and 1,478 patients were included in the efficacy analysis. In all, 206 (13.9%), 749 (50.7%), and 523 (35.4%) patients were taking one, two, or three AEDs concomitantly at baseline. Although age, gender, and seizure type were similar across all three groups, time elapsed since diagnosis was significantly less among patients taking one AED (18.8 years) than either two AEDs (21.1 years) or three AEDs (21.9 years). The median rate of seizures at baseline was also significantly higher in patients taking three AEDs (14.0) compared with those taking one (9.7) or two AEDs (10.8).

Patients on one AED at baseline were significantly more likely to respond to adjunctive perampanel therapy than patients on three AEDs (odds ratio, 1.55; 95% confidence interval, 1.07–2.24; \( P < 0.02 \)). The incidence of TEAEs in patients who received the highest dose of perampanel (12 mg/d) was similar regardless of the number of AEDs being taken concomitantly at baseline (92.9%, 88.3%, and 89.0% for one, two, and three AEDs, respectively). The most common TEAEs were dizziness, somnolence, and headache, occurring in 10% or more of all patients treated with perampanel. Consequently, in this post hoc analysis, fewer AEDs being taken concomitantly at baseline was associated with higher response rates to perampanel, and the number of AEDs being taken did not affect the incidence of TEAEs.

Most AEDs either inhibit neuronal excitation via a non-\( \gamma \)-aminobutyric acid (GABA) mechanism of action, such as ion-channel blockers, glutamate antagonists, and SV2A-binding agents, or augment neuronal inhibition, such as GABA(A) agonists, GABA-uptake inhibitors, and GABA transaminase inhibitors. AEDs that have a non-GABA mechanism of action include acetazolamide, carbamazepine, eslicarbazepine, ethosuximide, felbamate, gabapentin, lamotrigine, levetiracetam, mesuximide, oxcarbazepine, phenytoin, pregabalin, rufinamide, sulthiame, topiramate, valproic acid, and zonisamide. Those possessing a GABA mechanism include alprazolam, bromazepam, clonazepam, clorazepic acid, diazepam, eszolam, gizdazepam, lorazepam, lombezepam, nitrazepam, oxazepam, phenazepam, phentobarbital primidone, temezepam, and tiagabine.

**TABLE 1**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Perampanel 1-mg dose</th>
<th>Perampanel 2-mg dose</th>
<th>Perampanel 4-mg dose</th>
<th>Perampanel 6-mg dose</th>
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<tbody>
<tr>
<td></td>
<td>Day 1 (n = 6)</td>
<td>Day 14 (n = 6)</td>
<td>Day 1 (n = 6)</td>
<td>Day 14 (n = 6)</td>
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<tr>
<td></td>
<td>Day 1 (n = 12)</td>
<td>Day 14 (n = 6)</td>
<td>Day 1 (n = 6)</td>
<td>Day 14 (n = 6)</td>
</tr>
<tr>
<td></td>
<td>Day 1 (n = 4)</td>
<td>Day 14 (n = 4)</td>
<td>Day 1 (n = 4)</td>
<td>Day 14 (n = 4)</td>
</tr>
<tr>
<td>( C_{\text{max}} ) (ng/mL)</td>
<td>42.3 ± 13.2</td>
<td>92.3 ± 22.5</td>
<td>79.2 ± 14.6</td>
<td>150 ± 28.5</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>79.2 ± 14.6</td>
<td>150 ± 28.5</td>
<td>131 ± 38.2</td>
<td>365 ± 78.7</td>
</tr>
<tr>
<td>( C_{\text{min}} ) (ng/mL)</td>
<td>–</td>
<td>76.3 ± 26.9</td>
<td>–</td>
<td>221 ± 70.7</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>–</td>
<td>76.3 ± 26.9</td>
<td>–</td>
<td>221 ± 70.7</td>
</tr>
<tr>
<td>( t_{\text{max}} ) (h)</td>
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<td>0.77</td>
<td>0.55</td>
<td>1.00</td>
</tr>
<tr>
<td>Median</td>
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<td>0.77</td>
<td>0.55</td>
<td>1.00</td>
</tr>
<tr>
<td>Minimum</td>
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<td>0.77</td>
<td>0.55</td>
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</tr>
<tr>
<td>Maximum</td>
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<td>2.00</td>
<td>2.00</td>
<td>2.00</td>
</tr>
<tr>
<td>AUC(_{\text{p.f.}}) (ng·h/mL)</td>
<td>370 ± 109</td>
<td>1,461 ± 327</td>
<td>696 ± 141</td>
<td>2,365 ± 786</td>
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<tr>
<td>Mean ± SD</td>
<td>370 ± 109</td>
<td>1,461 ± 327</td>
<td>696 ± 141</td>
<td>2,365 ± 786</td>
</tr>
<tr>
<td>( t_{\text{p.f.}} ) (h)</td>
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<td>72.1 ± 21.3</td>
<td>–</td>
<td>129 ± 146</td>
</tr>
<tr>
<td>Mean ± SD</td>
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<td>72.1 ± 21.3</td>
<td>–</td>
<td>129 ± 146</td>
</tr>
<tr>
<td>PTF (%)</td>
<td>68.1 ± 13.7</td>
<td>82.0 ± 30.6</td>
<td>58.7 ± 16.5</td>
<td>56.9 ± 6.66</td>
</tr>
</tbody>
</table>

\(_{AUC_{\text{p.f.}}} = \) area under plasma concentration-time curve during 24-h dosing interval; \(_{C_{\text{max}}} = \) maximum plasma concentration; \(_{C_{\text{min}}} = \) minimum plasma concentration at steady state; \(_{PTF} = \) peak-to-trough fluctuation in plasma concentration (\(|C_{\text{max}} - C_{\text{min}}|/C_{\text{average}} \times 100\%); \(_{SD} = \) standard deviation; \(_{t_{\text{max}}} = \) terminal half-life; \(_{t_{\text{max}}} = \) time to \(_{C_{\text{max}}}^{*}\)

Source: Gidal et al\textsuperscript{a}
Muller and others analyzed data from the three core phase 3 studies (304, 305, and 306) to compare the efficacy and safety of perampanel therapy in patients using GABA-enhancing AEDs versus non-GABA-acting AEDs. The full intent-to-treat population included a GABA group (placebo, 136 patients; perampanel, 262 patients) and a non-GABA group (placebo, 306 patients; perampanel, 776 patients). TEAEs were reported in 93 (68.4%) of the placebo-treated patients and 210 (80.2%) of the perampanel-treated patients in the GABA subgroup and in 201 (65.7%) of the placebo-treated patients and 589 (75.9%) of the perampanel-treated patients in the non-GABA subgroup. The most common TEAEs reported in both groups were dizziness, somnolence, and headache.

More TEAEs were reported in the perampanel-treated groups than in the placebo-treated groups. However, no significant difference was observed among those taking non-GABA or GABA AEDs concomitantly. Therefore, perampanel therapy generally was safe when used concomitantly with GABA or non-GABA AEDs.

In the same study, the completer population for the GABA group (placebo, 100 patients; perampanel, 180 patients) and non-GABA group (placebo, 248 patients; perampanel, 601 patients) was used to analyze the median percent change in seizure frequency from baseline to 28 days. As shown in Figure 1, efficacy was comparable between the GABA and non-GABA subgroups. However, this research was limited by treatment groups reporting by last dose instead of randomized dose; in addition, the GABA group had a smaller sample size, especially among patients using 6 and 10 mg of perampanel.

Safety and Efficacy in Lesional vs Nonlesional Partial Epilepsy

Besag and Patsalos reported that 65% of adults with partial-onset seizures have structural lesions, 31% of cases are nonlesional, and 52% of patients have refractory seizures. In a post hoc analysis of the pivotal phase 3 studies 304, 305, and 306, Marsh and colleagues studied the safety and efficacy of perampanel therapy in patients with partial-onset seizures who had or did not have structural epileptogenic lesions. Patients underwent magnetic resonance imaging (MRI) of the brain before joining the trials to help classification.

The epilepsy-specific medical history was similar for both lesional and nonlesional patients, with the exception of lesion etiology. Structural lesions included structural brain anomalies/malformations (39.2%), head injury/cranial trauma (27.3%), central nervous system infection (25.2%), vascular brain anomalies (5.5%), and stroke (2.9%). Most patients (79.4%) in the nonlesional subgroup had seizures of unknown etiology. Partial seizures with altered awareness were the most common seizure type experienced by patients in the lesional and nonlesional groups (85.3% and 85.7%, respectively), and no significant difference was observed in the location of the epileptogenic zone (temporal lobe, 54.9% and 56.5%; extratemporal lobe, 41.8% and 34.6%; uncertain, 12.4% and 17.9%).

The completer population for the lesional group (37.3%; placebo, 133 patients; perampanel, 288 patients) and nonlesional group (62.7%; placebo, 215 patients; perampanel, 493 patients) was used to analyze efficacy. Responder rates for placebo and perampanel were comparable between the lesional and nonlesional groups. Patients with structural lesions had a lower response rate to 2–8 mg of perampanel than patients without lesions but had a higher response rate than did nonlesional patients at 10 and 12 mg of the drug. This finding may have been due to concomitant use of enzyme-inducing AEDs (eg, carbamazepine, phenytoin) in the lesional group, which reduces perampanel’s effect on seizure rates. In the group given 12 mg of perampanel, the lesional group had a smaller percentage of patients (48.5%) on inducers than did the nonlesional group (77.8%).

The safety analysis included the full intent-to-treat population for the lesional group (placebo, 161 patients; perampanel, 398 patients) and the nonlesional group (placebo, 281 patients; perampanel, 640 patients). TEAEs were reported in 398 patients) and the nonlesional group (77.8%) of patients receiving perampanel. As in other studies of patients taking perampanel, the
most common TEAEs reported in both the lesional and nonlesional groups were dizziness, somnolence, and headache.

Both subgroups showed improved seizure control with perampanel therapy relative to placebo administration. Furthermore, perampanel was effective and well tolerated regardless of the presence or absence of structural lesions. However, as previously reported by Stephen et al and Kwan and Brodie, patients with structural lesions were more likely to develop refractory seizures and presented more of a treatment challenge.

Assessment of Liver Toxicity
Liver metabolism is vital in the elimination of AEDs. Perampanel is extensively metabolized via primary oxidation and glucuronidation. Hepatic toxicity is a concern with some AEDs.

Laurenza et al assessed potential hepatotoxicity and injury in patients with refractory partial-onset seizures taking part in studies 304, 305, and 306. Altogether, 442 patients received placebo, and 1,038 patients received perampanel. At baseline and at the end of treatment, patients had clinical laboratory tests for hepatobiliary function, including quantification of alkaline aminotransferase (ALT), alkaline phosphatase, aspartate aminotransferase (AST), γ-glutamyltranspeptidase (GGT), and total bilirubin. Values obtained were summarized via descriptive statistics, shift tables relative to laboratory normal range, and treatment-emergent markedly abnormal values (increase from baseline to a National Cancer Institute Common Toxicity Criteria grade 2 or higher).

None of the patients had ALT, alkaline phosphatase, or AST levels greater than five times the upper limit of normal (ULN); however, up to 1.5% of patients in both the group receiving placebo and the group treated with perampanel had values greater than three times the ULN but not greater than five times the ULN. No relationship was found between these elevations and the dose of perampanel. In all, 2.1% and 1.8% of patients in the placebo and perampanel groups, respectively, had GGT values over five times the ULN, whereas < 5% in both groups had values that were over three times but up to five times the ULN, with no dose-related trends. None of the patients had values that met the criteria for Hy’s Law (ie, AST or ALT > three times the ULN; total bilirubin > two times the ULN, and alkaline phosphatase < two times the ULN). However, one patient receiving placebo (0.2%) and three patients on perampanel (0.3%) met the criteria for Temple’s Corollary (ALT > three times the ULN but not satisfying Hy’s Law).

Mean values of hepatobiliary function tests were within normal ranges at baseline and at the end of treatment in both the placebo and perampanel groups. Very small mean changes from baseline to end of therapy were not clinically significant or related to the perampanel dose, suggesting that perampanel has a low hepatotoxic potential despite its extensive hepatic metabolism.

Effect on QT Interval Duration
The International Conference on Harmonization (ICH) E14 guidance recommends that a thorough clinical study assess the potential of a drug to prolong cardiac repolarization (QT prolongation). Yang and others performed a thorough analysis of the QT interval in 264 healthy male and female subjects receiving perampanel or placebo in a double-blind, parallel-group study.

Subjects in the first group were given 6 mg of perampanel in a single daily dose on days 1–7, followed by 8 mg on day 8, 10 mg on day 9, and 12 mg on days 10–16 and then a single moxifloxacin placebo capsule on day 16. The second study group was given placebo on days 1–16, followed by a single moxifloxacin placebo capsule or 400 mg of moxifloxacin on day 16. QT intervals corrected for heart rate (QTc) recorded on 12-lead electrocardiograms (ECGs) were obtained 2 days before the study began and again on days 7 and 16. In addition, several blood samples were taken on days 6 and 17 following evaluation of the QTc interval.

Of 264 subjects enrolled, 261 were randomized (placebo, 75 patients; perampanel, 111 patients; moxifloxacin, 75 patients). Researchers used Fridericia’s correction formula (QTcF) as the primary parameter for statistical analysis. Statistical comparisons were made between placebo and 12 mg of perampanel (highest dose), 6 mg of perampanel (midtherapeutic dose), and 400 mg of moxifloxacin.

Administration of a single 400-mg dose of moxifloxacin resulted in an increase in QTc interval as compared with placebo, validating the assay sensitivity. The greatest time-matched mean difference in baseline-adjusted QTcF from placebo (ΔΔQTcF) observed for 6 mg of perampanel was 2.34 ms at 1.5 hours post dose; for the 12-mg dose, it was 3.92 ms at 0.5 hours post dose. The one-sided upper 95% confidence level of ΔΔQTcF for 6 mg and 12 mg of perampanel was < 10 ms for all time points, showing that perampanel did not cause a clinically relevant prolongation in the QT interval. In addition, blood samples taken on days 7 and 16 showed no relationship between perampanel plasma concentrations and QT interval duration. Cardiac repolarization in healthy subjects was not affected by either the “midtherapeutic” (6 mg) or “high-therapeutic” (12 mg) dose of perampanel.

A total of 24 healthy subjects (21.6%) in the perampanel group discontinued therapy, primarily due to adverse events (12.6%); further, 5.3% of moxifloxacin-treated subjects stopped therapy as a result of adverse events, consent withdrawal, or abnormal laboratory values. This finding raised concerns of tolerability and adequate duration for monitoring perampanel’s effect on cardiac repolarization, prompting the post hoc analysis of pooled data from the three phase 3 trials (304, 305, and 306) to evaluate the potential of perampanel to prolong cardiac repolarization in patients with epilepsy.

A total of 1,480 patients with partial-onset seizures made up the safety population, including 442 receiving placebo and 1,038 patients receiving perampanel. ECG parameters were analyzed from baseline to the end of the 19-week treatment study period, allowing adequate assessment of perampanel’s safety.

No QTc values calculated using Barrett’s formula (QTcB) or QTcF exceeded
500 ms in any of the patients. In addition, there was no clinically significant difference between the placebo and perampanel groups in the percentage of patients with QTcB intervals > 450 ms (1.4% and 1.3%, respectively) or QTcF intervals > 450 ms (0.5% and 0.8%). Finally, the percentages of patients showing prolongation of the QT interval > 60 ms from baseline were low and comparable between the placebo and perampanel groups (QTcB, 0.2% and 0.2%, respectively; QTcF, 0.5% and 0.2%).

In summary, there was no evidence in healthy volunteers or in patients enrolled in the three core phase 3 studies that perampanel in doses up to and including 12 mg/d prolong the duration of the QT interval.

Efficacy and Safety in the Elderly

Few clinical trials of epilepsy have been performed in the elderly because of difficulties in recruiting subjects, distinguishing seizures in older patients, and dealing with differences in the characteristics of epilepsy in this age group. Nevertheless, Williams et al performed a pooled subgroup analysis of studies 304, 305, and 306 to obtain data on the efficacy and safety of perampanel given to patients ≥ 65 years of age. This subpopulation made up 1.9% of the total population in the pooled studies.

In all, 28 patients were included in the analysis; eight received placebo, three received 2 mg of perampanel, one received 4 mg of perampanel, nine received 8 mg of perampanel, and seven received 12 mg of perampanel. This subgroup was compared with 1,307 adults in the three studies who were between 18 and 64 years of age (placebo, n = 388; 2 mg of perampanel, n = 156; 4 mg of perampanel, n = 158; 8 mg of perampanel, n = 378 patients; and 12 mg of perampanel, n = 227).

Baseline characteristics were similar between the elderly and the adult cohorts, including some etiologies for seizures. However, stroke was more common in the elderly (7.1%) than in the younger adults (1.1%). Partial seizures with altered awareness were the most common seizure type experienced (younger adults, 85.5%; elderly patients, 89.3%); 51.3% of the younger adults and 42.9% of the elderly were using two AEDs concomitantly at baseline.

Elderly patients generally were responsive to perampanel therapy, particularly in regard to the median percent change in seizure frequency at 28 days among patients taking 8 or 12 mg of the drug daily and in regard to responder rates among those receiving 12 mg/d when compared with placebo. However, no meaningful comparisons at lower doses were feasible because of the small numbers of elderly patients receiving 2 or 4 mg/d of perampanel.

Falls and headaches were more common among the elderly than among the younger adult group, and falls were more frequently seen in those using 8 and 12 mg of perampanel. The elderly subgroup also had a higher percentage of balance and gait disturbance adverse events (10% and 15%, respectively) when compared with the younger adults (2.9% and 2.8%).

Serious adverse events were reported in five elderly patients. One case of subdural hemorrhage was reported in a patient using placebo. One case of aortic hemorrhage occurred in a patient using 8 mg/d of perampanel. At 12 mg/d, one patient taking perampanel experienced a grand mal convolution, fell, and suffered a wrist fracture. A second patient experienced head injury, hypotension, and convulsion with disorientation, and a third patient experienced status epilepticus with urinary incontinence.

In all, 57.1% of the elderly and 18.4% of the younger adults discontinued therapy. Discontinuation was highest among those using 12 mg/d of perampanel and was attributed mainly to adverse events (ie, fall, grand mal convolution, ataxia/dizziness/gait disturbance, feeling drunk, status epilepticus).

Due to the increased likelihood for certain adverse events (eg, falls) in the elderly, dosing titration should proceed cautiously in patients ≥ 65 years of age, especially when higher dose levels of perampanel are used.

Analysis by Gender

Population pharmacokinetic analysis has shown that perampanel exposure is higher among females than in males. Vazquez and others used a fixed-dose randomization study design to perform a gender subgroup analysis of studies 304, 305, and 306 to evaluate differences in the efficacy and safety of perampanel therapy given to males and females.

In these studies, data from 719 males (placebo, n = 220; perampanel, n = 499) and 759 females (placebo, n = 221; perampanel, n = 538) were analyzed. Baseline demographic characteristics and epilepsy-specific medical histories were similar in both groups. For males and females, the mean age was 34.1 and 35.5 years and the mean weight, 75.4 and 64.9 kg, respectively. Focal seizures with altered awareness occurred in 83.2% of males and 87.7% of females, and two concomitant AEDs were used by 51.9% of the males and 49.5% of the females at baseline. Oral contraceptives were taken concomitantly by 21 (9.5%) of the females on placebo and 38 (7.1%) of those taking perampanel. Hormones were taken concomitantly in 17 females (7.7%) on placebo and 36 females (6.7%) on perampanel. In both males and females, seizure control improved among patients taking 4, 8, or 12 mg/d of perampanel compared with those on placebo. Reduction in seizure frequency and responder rates were higher among females (statistical significance was not determined).

The apparent clearance of perampanel was lower (17%) in a typical woman than in a man, assuming the same fatty body mass at 0.665 L/h and 0.730 L/h, respectively. However, the population pharmacokinetic/pharmacodynamic model showed no difference in perampanel concentration response as a function of gender.

TEAEs occurred in ≥ 10% of males and females and were not significantly influenced by gender, although dizziness and headache were slightly more frequent in women than in males taking perampanel (dizziness, 31.5% and 24.4%, respectively; headache, 13.2% and 9.4%). Adverse events were the primary reason for treatment discontinuation in both males and females and were more frequent, in general, among patients taking perampanel than among those receiving placebo.

Males experienced improved seizure
control when using perampanel than when given placebo. Females experienced more seizure reduction and dizziness than did males. Although the gender-related differences seen in these phase 3 trials may have been due to the fixed-dose randomization study design, individualized dosing of perampanel, as with any AED, should be based on clinical response and tolerability.

**Efficacy and Safety in Patients with Neurologic and Psychiatric Comorbidities**

Epilepsy can be complicated by certain neurologic and psychiatric comorbidities.²¹ Squillacote and others²² performed a post hoc analysis of the three core phase 3 trials¹⁻³ to evaluate the efficacy and safety of perampanel in patients with neurologic and psychiatric comorbidities. Preexisting neurologic and psychiatric comorbidities were grouped using Medical Dictionary for Regulatory Activities (MedDRA) terminology.

Baseline characteristics were similar among patients with neurologic comorbidities, psychiatric comorbidities, and any comorbidity. Partial seizures with altered awareness were the most common seizure type experienced; partial seizures without altered awareness or motor signs were more frequently seen among patients with comorbidities, and most patients were taking two concomitant AEDs at baseline.

Efficacy analysis was limited to the completer population for the neurologic (n = 264) and psychiatric (n = 185) comorbidity groups, exclusion of patients from Latin American sites, and analysis of the actual (last) dose reached by completers. The findings are summarized in Figure 2.²²

Efficacy was evaluated by the median percent reduction from baseline in seizure frequency per 28 days and 50% responder rate. Although perampanel therapy was more effective than placebo in patients with neurologic and/or psychiatric comorbidities, results were variable for responder rate depending on dose. Among those with psychiatric comorbidities, there was no difference between 4 mg/d and 10 mg/d of perampanel.

TEAEs were seen in ≥ 10% of the perampanel patients in each comorbidity subgroup when compared with patients without comorbidities, regardless of treatment dose. The most common TEAEs reported by patients with neurologic and/or psychiatric comorbidities on perampanel were dizziness, somnolence, and fatigue.

Thus, perampanel’s efficacy and safety in patients with partial-onset seizures who had neurologic or psychiatric comorbidities were similar to its efficacy and safety in the overall study population of patients with partial-onset seizures. However, patients with neurologic or psychiatric comorbidities had a higher risk of TEAEs on either perampanel or placebo than did patients who did not have these comorbidities.

**Time to Onset and Duration for Most Common Adverse Events**

Perampanel has a long half-life of 25–105 hours, depending on the presence or
absence of cytochrome P enzyme-inducing AEDs. In the presence of cytochrome P inducers, plasma levels of perampanel may decline as much as 50%–60%. Ko and others evaluated the frequency, severity, time of onset, and duration of the three most common adverse effects related to perampanel therapy in a post hoc analysis of pooled data from the three pivotal phase 3 trials. The investigators identified pivotal phase 3 trials.1–3

The safety population included 1,480 patients. Adverse events were more prevalent among the perampanel group than among those taking placebo, with patients experiencing a first adverse event during week 1 (somnolence, 4%; fatigue, 2.8%). First onset for these events was seen even at the end of the 19-week study. The duration of dizziness, somnolence, and fatigue was variable, ranging from 1 day to more than 3 months, although the median duration for fatigue was shorter in the perampanel group than in the placebo group (55 and 77 days, respectively) and longer for dizziness (28 and 13 days) and somnolence (55 and 34 days).

Dizziness (placebo, 9%; perampanel, 28%), somnolence (placebo, 7.2%; perampanel, 14.5%), and fatigue (placebo, 4.8%; perampanel, 8.5%) were mild or moderate and were not dose-dependent. These TEAEs did, however, lead to drug discontinuation in 39 patients (3.8%) in the perampanel group and 5 patients (1.1%) in the placebo group; they also led to treatment interruption or dose reduction in 127 patients (12.2%) in the perampanel group and 7 patients (1.6%) in the placebo group. The incidence of headache in the total perampanel group, however, was not different from that of the placebo group. Most TEAEs were either mild or moderate in intensity. To prevent adverse events, the dosage of perampanel should be titrated more slowly than the rapidity with which doses were titrated in the phase 3 studies.

**Psychiatric and Behavioral Events**

The package labeling for perampanel includes a boxed warning about serious psychiatric and behavioral reactions, including aggression, hostility, irritability, anger, and homicidal ideation and threats. Ettinger and colleagues used data from subjects with partial-onset epilepsy, non-epilepsy, and healthy volunteers populations from the three pooled phase 3 studies to review psychiatric and behavioral safety concerns related to perampanel use. Serious and non-serious TEAEs were evaluated using MedDRA search terms for psychiatric disorders and standard MedDRA queries (SMQs) for hostility and aggression-related events.

In the epilepsy group, the percentage of patients with any psychiatry TEAEs was similar among the placebo and perampanel groups (12.4% and 15.3%, respectively). A dose relationship was observed for anxiety, aggression, anger, and sleep disorder; incidence rates were almost twice as high among those using 8 and 12 mg of perampanel as for those using placebo, with a greater percentage of those using the higher dose reporting TEAEs. Further, 1.2% of perampanel patients and 0.9% of placebo patients developed psychiatric disorders that were treatment-emergent serious adverse events (SAEs). Aggression was the most common SAE reported among those using 12 mg of perampanel, whereas depression was most common among the placebo group. In addition, 1.6% of the placebo group and 2.5% of the perampanel group experienced psychiatric TEAEs leading to discontinuation. Aggression, anger, and anxiety were the main events leading to discontinuation among those using 12 mg of the drug.

Overall, 11.8% of patients on perampanel versus 5.7% of those on placebo reported hostility/aggression TEAEs. SAEs for hostility/aggression were noted in 0.2% and 0.7% of the placebo and perampanel groups, respectively, with aggression, irritability, and anger being the main TEAEs leading to adjustment or discontinuation of the study drug. In fact, the need to adjust the dose or discontinue perampanel was most notable in the group using 12 mg of the drug.

In the non-epilepsy double-blinded trials that included patients with Parkinson’s disease, neuropathic pain, multiple sclerosis, and migraines, patients received placebo or up to 8 mg of perampanel. The percentage of subjects with TEAEs related to psychiatry disorders and treatment-emergent SAEs were similar in the placebo (10.5% and 0.6%, respectively) and the perampanel group (11.4% and 0.8%). The incidence of psychiatric TEAEs leading to discontinuation of the study drug was higher among those using perampanel (2.9%) than for those given placebo (1.1%).

In both the epilepsy and non-epilepsy patients, there were 2,279 subject years for exposure to perampanel for all treated partial-onset seizure patients (n = 1,651) and 1,651.5 subject-years for the nonepilepsy population (n = 2,717). TEAEs for psychiatric disorders occurred in 28.8% of the epilepsy treated group and 18.4% of all treated nonepilepsy patients; the most common TEAEs for both populations were insomnia (epilepsy, 4.9%; nonepilepsy, 5.3%). Homicidal ideation and/or threats were exhibited in 0.1% of the 4,368 perampanel-treated patients, including epilepsy and nonepilepsy populations.

Among all healthy subjects, all TEAEs related to psychiatric disorders were mild to moderate in severity. No SAEs and no TEAEs led to treatment discontinuation. Psychiatric and/or behavioral changes may occur in patients taking perampanel, especially if the drug is used at higher doses and during the initial titration period. These findings support the boxed warning for serious psychiatric and behavioral reactions that appears on the package insert for perampanel.

**Analysis of Aggression**

LoPresti et al performed a post hoc analysis of aggression-related safety data from the three pooled perampanel double-blind, placebo-controlled, phase 3 trials. The investigators identified TEAEs and SAEs using MedDRA search terms and SMQs for hostility- and aggression-related events.

A subgroup analysis of 100 adolescents 12 to 16 years of age and 1,342 adults 17 to 64 years of age was performed for aggression-related events. Among the safety population, there were 1,038 adults in the perampanel group and 442 in the placebo group; in addition, there were 72
and 38 adolescents, respectively.

Hostility/aggression-related TEAEs were seen in 3.0% of perampanel-treated patients and 0.7% of the placebo group; 1.6% and 1.2% of perampanel-treated patients reported aggression and anger, respectively. A dose-response relationship between both of these TEAEs and most TEAEs seen in the 8- and 12-mg perampanel groups was noted. TEAEs leading to treatment discontinuation in the perampanel group included aggression, anger, and belligerence, with the majority of treatment discontinuations occurring in the group taking the highest dose of perampanel (12 mg/d).

Among adolescents, aggression-related TEAEs were reported in 9.7% of those given perampanel and in none of the placebo group; in adults, they were noted in 1.1% of all patients given perampanel and 0.5% of the placebo group.

Patients should be monitored for hostility/aggression-related adverse events during perampanel treatment, particularly during dose titration, with higher doses, and when the drug is given to adolescents, who tend to have a higher incidence of hostility/aggression-related adverse events than adults.

Exploration of Adverse Events by Region

The long-term safety and tolerability of new therapies for epilepsy need to be followed for several years in regions with different ethnicities, practice styles, and antiepileptic use. Ben-Menachem and colleagues investigated the regional incidence of adverse events, focusing on psychiatric adverse events. Patients with refractory partial-onset seizures had up to 3 years of perampanel exposure and were involved in the core phase 3 studies 304, 305, and 306. In an extension trial with a cut-off of December 2010 (307 study), information on 1,216 patients from 249 centers across 39 countries was included in the safety analysis dataset; 711 of these patients (58.5%) were continuing with the trial at the time of cut-off.

Patients were evaluated for adverse events, seizure outcome, and duration of drug exposure. Adverse-event incidence was based on the entire duration of perampanel exposure (starting from either the core or extension) and was reported for all patients and by geographic region. Duration of exposure began at first exposure to perampanel, starting from the core study for patients who had previously taken perampanel and from visit 1 of the extension study for patients in the core studies who were given placebo. For patients taking perampanel with a 14-day gap between the study and extension trial, duration was calculated from visit 1 of the extension trial.

Findings were primarily determined by geography, socioeconomic factors, ethnicity, practice patterns, and treatment patterns. The five key geographic locations were North America (including the United States and Canada); Latin America (including Argentina, Chile, and Mexico); Europe, the Middle East, and Africa (EMEA); the Indo-Pacific region (including Australia, India, Malaysia, Philippines, and Thailand); and the China-Pacific region (including China, Hong Kong, South Korea, and Taiwan).

Perampanel was well tolerated across geographic regions as adjunctive therapy for pharmacoresistant partial-onset seizures.
acid (33.3%), lamotrigine (31.3%), and levetiracetam (29.2%). Use of carbamazepine and valproic acid was lowest in North America and highest in Latin America and the China-Pacific region, whereas use of lamotrigine and levetiracetam was highest in North America and EMEA.

The total exposure was 1,803 patient-years (range, 1 week to 3.3 years); 1,122 patients (92.3%) took either 10 or 12 mg/d of perampanel (mean daily dose, 10.6 mg/d). Following the blinded conversion period, the probability of remaining on the study drug was similar between patients receiving perampanel in the core studies and those who converted from administration of placebo in the core studies.

At the extension-study cut-off, 505 of the 1,216 patients (41.5%) had discontinued perampanel therapy, primarily due to subject choice (13.8%), adverse events (12.9%), and inadequate seizure control (11.6%). Most treatment discontinuations due to adverse events were seen after the blinded conversion period (4.3% overall) but dropped at 2 years of perampanel treatment. Dizziness (3.9%) was the most commonly reported adverse event that led to discontinuation, followed by irritability (1.3%). Discontinuation rates were lowest in the Indo-Pacific region (28.9%) and highest in North America (48.3%). This finding may have been related to the differences in culture, healthcare systems, attitudes, and availability of other treatment options.

A safety assessment included 1,216 patients given at least one dose of perampanel in the extension trial and who participated in at least one post-dose safety assessment in the extension trial. At least one adverse event was reported by 91.3% of patients during the entire duration of adjunctive perampanel therapy for partial-onset seizures. Adverse events in 80.2% of patients were mild or moderate. More than 10% of patients reported dizziness, somnolence, headache, fatigue, irritability, or weight increase. A total of 18.7% experienced SAEs. The five reportable events were considered to be unrelated to the study medication; they included death due to a motor-vehicle accident as a passenger, intracranial hemorrhage, head injury (caused by a seizure), sudden unexpected death in epilepsy, and sudden death of unknown etiology in a patient with cardiac disease.

Seizure outcome was analyzed by the median percent change in seizure frequency from baseline in 1,217 patients. The median percent change in seizure frequency from baseline was −45.7% among 980 patients exposed to perampanel for more than 9 months and −59.6% among 336 patients exposed for more than 24 months; 5.3% of 37 patients were free of seizures for at least 1 year.

Participants in this study, including 300 patients with partial-onset seizures who continued taking perampanel for up to 24 months, did not show any new safety signals, and seizure control remained stable.

**CONCLUSION**

The results of these analyses provide some reassurance about the safety and efficacy of perampanel. No new, clinically significant pharmacokinetic, efficacy, or safety information was reported that would alter the use of perampanel as an adjunctive therapy for partial-onset seizures. Adjunctive perampanel can be used safely and effectively with either concomitant GABA or non-GABA AEDs and in lesional or nonlesional partial-onset epilepsy. Negative results for hepatotoxicity and cardiac repolarization changes due perampanel also were presented. Certain types of adverse events, such as falls, are more likely to occur in elderly patients than in younger patients; thus, drug doses should be titrated cautiously in older patients. These results also support the boxed warning included in the full prescribing information for perampanel about possible psychiatric/behavioral changes that may occur at higher doses and during initial titration of the drug.

**REFERENCES**

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Update on Perampanel: A Novel Antiepileptic Drug for Partial-Onset Seizures


