FULL-LENGTH ORIGINAL RESEARCH

Psychiatric and behavioral adverse events in randomized clinical studies of the noncompetitive AMPA receptor antagonist perampanel

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Summary

Objective: Perampanel, a selective, noncompetitive α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) glutamate receptor antagonist, is indicated for adjunctive treatment of partial seizures in patients ≥12 years based on three phase III clinical studies. The perampanel U.S. Prescribing Information includes a boxed warning for serious psychiatric and behavioral adverse reactions. To provide context for this warning, detail on psychiatric and behavioral safety data from perampanel clinical studies is presented.

Methods: An analysis of pooled safety data from three phase III studies in patients with partial seizures is presented. Data from phase I and phase II studies in patients with and without epilepsy were also analyzed. Psychiatric and behavioral treatment-emergent adverse events (TEAEs) were evaluated according to Medical Dictionary for Regulatory Activities (MedDRA) terms, using "narrow" and "narrow-and-broad" standardized MedDRA queries (SMQs) for TEAEs suggestive of hostility/aggression.

Results: From the three phase III partial-seizure studies, the overall rate of psychiatric TEAEs was higher in the 8 mg (17.2%) and 12 mg (22.4%) perampanel groups versus placebo (12.4%). In the "narrow" SMQ, hostility/aggression TEAEs were observed in 2.8% for 8 mg and 6.3% for 12 mg perampanel groups, versus 0.7% of placebo patients. "Narrow-and-broad" SMQs for hostility/aggression TEAE rates were 12.3% for 8 mg and 20.4% for 12 mg perampanel groups, versus 5.7% for placebo; rates for events resulting in discontinuation were perampanel = 1.6% versus placebo = 0.7%. For events reported as serious AEs (SAEs), rates were perampanel = 0.7% versus placebo = 0.2%. In nonepilepsy patients, psychiatric TEAEs were similar between patients receiving perampanel and placebo. In phase I subjects/volunteers, all psychiatric TEAEs were mild or moderate. These analyses suggest that psychiatric adverse effects are associated with use of perampanel.

Significance: Patients and caregivers should be counseled regarding the potential risk of psychiatric and behavioral events with perampanel in patients with partial seizures; patients should be monitored for these events during treatment, especially during titration and at higher doses.

KEY WORDS: Antiepileptic drugs, Partial seizures, Epilepsy, Perampanel, Safety, Behavioral symptoms, Psychiatric adverse events.

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Key Points

- A dose-related increase in psychiatric TEAEs was observed in patients with partial seizures treated with perampanel at doses up to 12 mg.
- Perampanel showed higher incidence of hostility/aggression TEAEs versus placebo using either "narrow" SMQs (3.0 vs. 0.7%) or "narrow-and-broad" (11.8 vs. 5.7%).
- Risk of anger and aggression was not increased with perampanel treatment compared to placebo in the nonepilepsy (≤8 mg) or phase I (>12 mg) studies.
- In subjects with psychiatric/behavioral events, TEAEs were manageable, although perampanel dose may need to be adjusted or discontinued if symptoms persist.

Perampanel is a noncompetitive, selective α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid AMPA glutamate receptor antagonist that is administered orally, once daily, at an initial dose of 2 mg in patients not on enzyme-inducing antiepileptic drugs (AEDs) and 4 mg in patients on enzyme-inducing AEDs. The recommended therapeutic dose range is 4–12 mg per day.[1] Perampanel is indicated in both the United States and the European Union for adjunctive treatment of partial seizures with or without secondarily generalized seizures in patients with epilepsy who are ≥12 years old, and in Canada for adult patients with epilepsy ≥18 years old. To date, perampanel has been approved for use in >40 countries.[1–3]

U.S. approval of perampanel was based on the outcomes of three multicenter, double-blind, randomized, parallel-group, placebo-controlled phase III studies in patients with drug-resistant partial seizures, at doses of 2, 4, 8, and 12 mg.[4–6] Perampanel treatment was generally well tolerated, with dizziness, somnolence, headache, and fatigue being the most common treatment-emergent adverse events (TEAEs).[4–7] Pooled data from the three phase III studies also showed elevated rates of TEAEs suggestive of hostility/aggression among patients receiving perampanel compared to those receiving placebo. The most common of these TEAEs were 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%).[7] Serious psychiatric TEAEs were reported in 12 patients (1.2%) treated with perampanel and in 4 (0.9%) patients receiving placebo from the pooled phase III studies.

This post hoc analysis reviews available psychiatric and behavioral safety data from the existing double-blind and open-label extension (OLE) partial-seizure studies with perampanel, along with safety data from perampanel clinical studies in nonepilepsy patients.

Methods

The total perampanel safety database was derived from three populations in multiple phase I, II, and III (with OLE) clinical studies. Populations included epilepsy (partial seizures), nonepilepsy (Parkinson's disease, neuropathic pain, multiple sclerosis, and migraine headache), and phase I subject or volunteer populations, as shown in Table 1.

In the all-treated partial-seizure populations, patients were asked at the screening visit about past medical and psychiatric history. Date of diagnosis or onset of disease symptoms and available end dates of these symptoms were recorded by investigators. Concomitant medications with doses and start and available end dates were also recorded. Exclusion criteria have been previously published for the phase III double-blind partial-seizure studies.[4–6] Although patients with more severe psychosis and psychiatric disorders were excluded, a heterogeneous group of patients with prior psychiatric history and who were on stable medica-

Table 1. Number of patients in populations used for safety analyses

Population	Population description	N
Phase III DB partial seizures	Perampanel-treated patients with partial seizures from three phase III DB studies	1,038
Nonepilepsy	Patients from nonepilepsy DB studies, including in Parkinson's disease, neuropathic pain, multiple sclerosis, and migraine headache	3,092
	1 2,013 patients receiving perampanel	
	2 1,079 receiving placebo	
All-treated patients	Perampanel-treated patients with partial seizures and nonepilepsy patients from phase II and III DB and OLE studies, which includes the following:	4,368
	1 1,651 patients with partial seizures from three phase III and three phase II DB and OLE studies	
	2 2,717 patients from nonepilepsy DB and OLE trials, including in Parkinson's disease, neuropathic pain, multiple sclerosis, and migraine headache	
Phase I subjects/ volunteers	Phase I subjects/volunteers from 27 clinical studies[a]:	
	1 Single-dose studies	579
	2 Multiple-dose studies	343

[a]Subjects/volunteers from phase I studies were healthy subjects or volunteers in 27 clinical studies; two of these phase I studies were Drug Dependency and Drug Abuse Liability studies that evaluated recreational drug users.
DB, double-blind; OLE, open-label extension.

tions with nonclinically significant disorders were still included in the studies.

This post hoc analysis of TEAEs suggestive of hostility/aggression is based on a classification of events reported in the clinical studies, which were not designed to specifically target behavioral abnormalities and did not use validated measures or specific scales or assessments for this purpose. Investigators recorded TEAEs using the verbatim term during study conduct; these events were then coded using the Medical Dictionary for Regulatory Activities (MedDRA). Serious and nonserious TEAEs were evaluated using MedDRA search terms for psychiatric disorders and standard MedDRA queries (SMQs) for AEs suggestive of hostility/aggression (Table S1). Whereas "narrow" SMQ identifies cases likely to represent the condition of interest (e.g., aggression, anger, belligerence, and physical assault), broad SMQ identifies all possible cases, including some that may be of little or no interest under closer scrutiny (e.g., skin laceration due to fall following a seizure).[8,9] "Narrow-and-broad" SMQs include both categories of terms. The definition of a TEAE employed for this study was an AE that began on or after the first dose date and up to 30 days after the last dose date of the study drug, or began before the first dose date and increased in severity during the treatment period. Statistical significance was not determined in this analysis.

The presentation of the perampanel safety data is divided into four subsections in Results: (1) pooled data from phase III double-blind partial-seizure studies; (2) pooled data from double-blind nonepilepsy studies; (3) pooled data from the all-treated populations (patients with partial seizures and nonepilepsy patients from phase III double-blind and OLE studies as well as phase II double-blind and OLE studies); and (4) pooled data for subjects/volunteers who had received perampanel in phase I studies.

Study Designs

The study designs of the three phase III studies (clinicaltrials.gov: Study 304, NCT00699972; Study 305, NCT00699582; and Study 306, NCT00700310) have been previously described.[4–6] The three double-blind phase II studies were randomized and placebo-controlled (clinicaltrials.gov: Study 206, NCT00144690; Study 208, NCT00416195; and Study E2007-E049-203). The designs of other studies included in this analysis were heterogeneous. A subgroup analysis of adolescents, defined as individuals aged 12 to <18 years, compared to adults, aged 18 to <65 years, was performed for aggression TEAEs.

All studies were conducted in accordance with the provisions of the World Medical Association Declaration of Helsinki and its amendments concerning medical research in humans and in conformance with all local laws and regulations, whichever afforded the greater protection to the individual. Documentation procedures complied with International Conference on Harmonisation guidelines. Study procedures were designed to ensure adherence to Good Clinical Practice and the 21 Code of Federal Regulations. All patients provided written informed consent prior to screening.[7,10]

Results

Phase III double-blind partial-seizure studies

Psychiatric disorder TEAEs

Table 2 displays the incidence of psychiatric disorder TEAEs occurring in at least three patients in any treatment group in the phase III partial-seizure studies. The percent of patients with any psychiatric TEAE was similar in the perampanel group (15.3%) compared to the placebo group (12.4%). However, the rate of overall psychiatric TEAEs was higher in the 8 mg perampanel group and the 12 mg group than in the 4 mg group or the placebo group. Much of this difference is attributed to higher rates of anxiety, aggression, anger, and sleep disorder in the perampanel-treated patients, and there was a dose–response relationship for all of these TEAEs, with the exception of sleep disorder. Thus, the incidence rates for anxiety, aggression, and anger were higher in the 8 and 12 mg perampanel groups than in the placebo group. All other psychiatric disorder preferred terms, including suicidal ideation, occurred in similar percentages of patients in the perampanel and placebo groups.

Psychiatric treatment-emergent serious adverse events (SAEs) were observed in 12 (1.2%) of the perampanel-treated patients, compared to 4 patients (0.9%) in the placebo group. Aggression was the most common psychiatric SAE reported among 12 mg perampanel-treated patients (two patients; 0.8%), whereas depression was the most common psychiatric SAE in the placebo group (two patients; 0.5%). TEAEs for psychiatric disorders leading to discontinuation were reported in 26 perampanel patients (2.5%), compared to seven placebo patients (1.6%). Aggression, anger, and anxiety were the main events leading to discontinuation in the 12 mg perampanel group (1.6, 1.6, and 0.8%, respectively), whereas no patient in the placebo group discontinued due to these events. No deaths related to study treatment were reported in the phase III studies.

"Narrow" SMQ for TEAEs suggestive of hostility/aggression

TEAEs suggestive of hostility/aggression from the "narrow" SMQ were more common among patients receiving perampanel, compared to those receiving placebo, as shown in Table 3. Incidence of these events was higher during the titration phase for perampanel (2.0%) and placebo patients (0.5%) versus the maintenance phase (perampanel = 1.2% and placebo = 0.2%). In all, 1.6% of perampanel patients reported aggression and 1.2% reported anger, compared to 0.5 and 0.2%, respectively, in the placebo group. A dose–

Table 2. TEAEs for psychiatric disorders occurring in ≥3 patients in any treatment group[a]: double-blind phase III partial-seizure studies

		Perampanel[c]				
TEAE (MedDRA preferred term[b])	Placebo[c] (N = 442) n (%)	2 mg/day (N = 180) n (%)	4 mg/day (N = 172) n (%)	8 mg/day (N = 431) n (%)	12 mg/day (N = 255) n (%)	Total (N = 1,038) n (%)
Patients with any TEAE	55 (12.4)	17 (9.4)	11 (6.4)	74 (17.2)	57 (22.4)	159 (15.3)
Insomnia	16 (3.6)	2 (1.1)	2 (1.2)	15 (3.5)	11 (4.3)	30 (2.9)
Anxiety	5 (1.1)	4 (2.2)	3 (1.7)	13 (3.0)	9 (3.5)	29 (2.8)
Aggression	2 (0.5)	1 (0.6)	1 (0.6)	7 (1.6)	8 (3.1)	17 (1.6)
Anger	1 (0.2)	0	0	5 (1.2)	7 (2.7)	12 (1.2)
Depression	7 (1.6)	1 (0.6)	1 (0.6)	3 (0.7)	6 (2.4)	11 (1.1)
Sleep disorder	1 (0.2)	2 (1.1)	1 (0.6)	6 (1.4)	2 (0.8)	11 (1.1)
Nervousness	3 (0.7)	1 (0.6)	0	6 (1.4)	2 (0.8)	9 (0.9)
Confusional state	2 (0.5)	1 (0.6)	1 (0.6)	3 (0.7)	4 (1.6)	9 (0.9)
Mood swings	3 (0.7)	1 (0.6)	0	5 (1.2)	2 (0.8)	8 (0.8)
Depressed mood	4 (0.9)	2 (1.1)	0	4 (0.9)	1 (0.4)	7 (0.7)
Mood altered	2 (0.5)	0	1 (0.6)	2 (0.5)	4 (1.6)	7 (0.7)
Euphoric mood	0	0	0	1 (0.2)	4 (1.6)	5 (0.5)
Agitation	2 (0.5)	0	0	3 (0.7)	1 (0.4)	4 (0.4)
Apathy	2 (0.5)	0	0	3 (0.7)	0	3 (0.3)

[a]A patient with ≥2 adverse events with the same preferred term is counted only once for that preferred term.
[b]MedDRA preferred terms are sorted in descending order of frequency in the total perampanel column.
[c]Patients treated during the double-blind study. Dose groups are based on the actual treatment groups.
MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse event.

Table 3. TEAEs, SAEs, and TEAEs leading to discontinuation (Narrow SMQs for Hostility/Aggression)[a]: double-blind phase III partial-seizure studies

		Perampanel[c]				
TEAE Category (MedDRA preferred term[b])	Placebo[c] (N = 442) n (%)	2 mg/day (N = 180) n (%)	4 mg/day (N = 172) n (%)	8 mg/day (N = 431) n (%)	12 mg/day (N = 255) n (%)	Total (N = 1,038) n (%)
Any TEAE	3 (0.7)	1 (0.6)	2 (1.2)	12 (2.8)	16 (6.3)	31 (3.0)
Aggression	2 (0.5)	1 (0.6)	1 (0.6)	7 (1.6)	8 (3.1)	17 (1.6)
Anger	1 (0.2)	0	0	5 (1.2)	7 (2.7)	12 (1.2)
Belligerence	0	0	0	0	1 (0.4)	1 (0.1)
Physical assault	0	0	1 (0.6)	0	0	1 (0.1)
Any treatment-emergent SAEs	0	1 (0.6)	0	0	3 (1.2)	4 (0.4)
Aggression	0	1 (0.6)	0	0	2 (0.8)	3 (0.3)
Belligerence	0	0	0	0	1 (0.4)	1 (0.1)
Any TEAEs leading to discontinuation	0	0	0	1 (0.2)	9 (3.5)	10 (1.0)
Aggression	0	0	0	1 (0.2)	4 (1.6)	5 (0.5)
Anger	0	0	0	0	4 (1.6)	4 (0.4)
Belligerence	0	0	0	0	1 (0.4)	1 (0.1)
Any TEAEs leading to dose reduction	0	0	0	5 (1.2)	3 (1.2)	8 (0.8)
Aggression	0	0	0	4 (0.9)	2 (0.8)	6 (0.6)
Anger	0	0	0	1 (0.2)	1 (0.4)	2 (0.2)

[a]A patient with ≥2 adverse events with the same preferred term is counted only once for that preferred term.
[b]MedDRA preferred terms are sorted in descending order of frequency in the total perampanel column.
[c]Patients treated during the double-blind study. Dose groups are based on the actual treatment groups.
MedDRA, Medical Dictionary for Regulatory Activities; SAE, serious adverse event; SMQ, standardized MedDRA query; TEAE, treatment-emergent adverse event.

response relationship was observed for both aggression and anger. No patients captured in the "narrow" hostility/aggression SMQ experienced recurrence of these TEAEs, meaning that no subsequent TEAE started after the first TEAE resolved. Treatment-emergent SAEs suggestive of hostility/aggression were observed in four (0.4%) of the perampanel patients compared to no patients in the placebo group. Three perampanel patients (0.3%) experienced aggression SAEs,

whereas no aggression SAEs occurred in the placebo group. Ten perampanel-treated patients (1.0%) who discontinued from phase III partial-seizure studies experienced TEAEs suggestive of hostility/aggression. Aggression TEAEs leading to discontinuation in the double-blind phase all resolved at the time of the last follow-up, while two patients in the perampanel 12 mg group who discontinued due to anger TEAEs did not achieve resolution. Dose reduction due to hostility/aggression TEAEs occurred in 8 perampanel-treated patients (0.8%).

"Narrow-and-broad" SMQs for TEAEs suggestive of hostility/aggression

As noted in the Methods section, "broad" SMQ events were captured in addition to the above-described "narrow" SMQ of TEAEs suggestive of hostility/aggression. When these are combined, 11.8% of perampanel and 5.7% of placebo patients were identified using the relevant "narrow-and-broad" SMQs for AEs suggestive of hostility/aggression (Table 4). There appeared to be a dose-related increase, with 12.3% and 20.4% of these events being seen in the 8 mg and 12 mg groups, respectively. Along with aggression and anger (discussed under "narrow" SMQ), irritability and skin laceration were the other most frequently reported TEAEs suggestive of hostility/aggression. Irritability accounted for more than half of the perampanel patients in the "narrow-and-broad" SMQs (7.0%).

Table 4 also shows all treatment-emergent SAEs as well as TEAEs leading to discontinuation or dose reduction using the "narrow-and-broad" SMQs for AEs suggestive of hostility/aggression. SAEs were reported in seven perampanel patients (0.7%) compared to one placebo patient (0.2%). Although irritability was not reported as an SAE, there were four discontinuations (0.4%) from the study due to irritability in perampanel patients versus one discontinuation (0.2%) in the placebo group. A dose–response relationship was seen for discontinuations among patients receiving perampanel. The majority of the main TEAEs resulting in discontinuation (aggression and anger, discussed under "narrow" SMQ, and irritability) resolved after perampanel withdrawal. Two patients in the perampanel 12 mg group who discontinued due to an irritability TEAE did not have resolution at the time of last follow-up. Dose reductions due to irritability occurred in nine perampanel patients (0.9%).

Prior psychiatric history and history of aggression were determined for patients included in the relevant "narrow-and-broad" SMQs for AEs suggestive of hostility/aggression. For this select population of patients, prior psychiatric history, as categorized according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR)[11] axes I–III or unknown (those with psychiatric history not categorized into axes I–III), was reported to exist in 40.7% of perampanel patients and 60% of placebo patients [relative risk (RR): 0.6775, 95% confidence interval (CI): 0.4611–0.9954], whereas prior hostility/aggressive behavior was found to exist in 12.2% of perampanel patients and 12.0% of placebo patients (RR 1.0163, 95% CI 0.3177–3.2503). Specific assessments on levels of hostility, aggression, or psychiatric behavior were not performed at baseline or during the study. Concomitant use of medications that have been associated with AEs suggestive of hostility/aggression within the "narrow-and-broad" SMQs was also calculated and did not show any notable differences between perampanel- and placebo-treated subjects. Antipsychotic use in the perampanel group occurred at a rate of 8.9%, compared to 12.0% in the placebo group (RR 0.7453, 95% CI 0.2240–2.4793). Antidepressants were used by 17.9% and 20.0% of the perampanel and placebo groups, respectively (RR 0.8943, 95% CI 0.3744–2.1360), whereas benzodiazepines were used at approximately twice that rate (perampanel 34.1%, placebo 40.0%; RR 0.8537, 95% CI 0.4979–1.4637). Psychostimulants were used by 0.8% of the perampanel group and no patients in the placebo group. Concomitant use of individual AEDs for patients included in the relevant "narrow-and-broad" SMQs for AEs suggestive of hostility/aggression also showed no notable differences between perampanel- and placebo-treated subjects (Table S2). In addition, combinations of AEDs and perampanel also had no notable effect on the probability of experiencing any of the AEs analyzed.

Aggression in adolescents versus adults from phase III double-blind partial-seizure studies

A subgroup analysis of the three phase III studies in partial seizures compared psychiatric AEs in adolescent patients (12 to <18 years; n = 143) versus adult patients (≥18 to <65 years; n = 1,309). Psychiatric AEs were observed in 21 (21.4%) perampanel-treated adolescent patients and 5 (11.1%) placebo-treated adolescent patients. Aggression was the most common psychiatric-related TEAE in perampanel-treated adolescents, seen in 8 (8.2%) patients (1 [4.8%], 1 [7.7%], 3 [6.8%], and 3 [15.0%] in the 2, 4, 8, and 12 mg groups, respectively) versus no patients in the placebo group. Among adults, nine (1.0%) perampanel-treated patients (4 [1.1%] and 5 [2.2%] in the 8 mg and 12 mg groups, respectively) and two (0.5%) placebo patients experienced aggression as a TEAE. Of a total of three reported aggression SAEs, one was experienced by an adolescent. Of the five reported aggression TEAEs leading to discontinuation, one occurred in an adolescent.

Double-blind studies in nonepilepsy patients

The pool of 3,092 patients without epilepsy, 2,013 of whom received perampanel and 1,079 of whom received placebo, included patients in clinical trials of Parkinson's disease, neuropathic pain, multiple sclerosis, and migraine headache. None of these patients received doses >8 mg daily. Table 5 displays psychiatric disorder TEAEs occurring in three or more of these patients. Overall, the rate of

Table 4. TEAEs, SAEs, and TEAEs leading to discontinuation (narrow & broad SMQs for hostility/aggression)[a]: double-blind phase III partial-seizure studies

		Perampanel[c]				
TEAE (MedDRA preferred term[b])	Placebo[c] (N = 442) n (%)	2 mg/day (N = 180) n (%)	4 mg/day (N = 172) n (%)	8 mg/day (N = 431) n (%)	12 mg/day (N = 255) n (%)	Total (N = 1,038) n (%)
Any TEAE	25 (5.7)	9 (5.0)	9 (5.2)	53 (12.3)	52 (20.4)	123 (11.8)
Irritability	13 (2.9)	7 (3.9)	7 (4.1)	29 (6.7)	30 (11.8)	73 (7.0)
Aggression[d]	2 (0.5)	1 (0.6)	1 (0.6)	7 (1.6)	8 (3.1)	17 (1.6)
Skin laceration	7 (1.6)	1 (0.6)	0	7 (1.6)	6 (2.4)	14 (1.3)
Anger[d]	1 (0.2)	0	0	5 (1.2)	7 (2.7)	12 (1.2)
Agitation	2 (0.5)	0	0	3 (0.7)	1 (0.4)	4 (0.4)
Abnormal behavior	0	0	0	2 (0.5)	2 (0.8)	4 (0.4)
Laceration	0	0	0	2 (0.5)	1 (0.4)	3 (0.3)
Affect lability	0	0	0	0	2 (0.8)	2 (0.2)
Personality change	1 (0.2)	0	0	1 (0.2)	0	1 (0.1)
Psychotic disorder	1 (0.2)	0	0	1 (0.2)	0	1 (0.1)
Belligerence[d]	0	0	0	0	1 (0.4)	1 (0.1)
Disinhibition	0	0	0	1 (0.2)	0	1 (0.1)
Hypomania	0	0	0	1 (0.2)	0	1 (0.1)
Impulse-control disorder	0	0	0	0	1 (0.4)	1 (0.1)
Injury	0	0	0	0	1 (0.4)	1 (0.1)
Personality disorder	0	0	0	1 (0.2)	0	1 (0.1)
Physical assault[d]	0	0	1 (0.6)	0	0	1 (0.1)
Psychomotor hyperactivity	0	0	0	1 (0.2)	0	1 (0.1)
Any treatment-emergent SAE	1 (0.2)	1 (0.6)	0	2 (0.5)	4 (1.6)	7 (0.7)
Aggression	0	1 (0.6)	0	0	2 (0.8)	3 (0.3)
Psychotic disorder	1 (0.2)	0	0	1 (0.2)	0	1 (0.1)
Belligerence	0	0	0	0	1 (0.4)	1 (0.1)
Impulse-control disorder	0	0	0	0	1 (0.4)	1 (0.1)
Skin laceration	0	0	0	1 (0.2)	0	1 (0.1)
Any TEAE leading to discontinuation	3 (0.7)	0	0	4 (0.9)	13 (5.1)	17 (1.6)
Aggression	0	0	0	1 (0.2)	4 (1.6)	5 (0.5)
Irritability	1 (0.2)	0	0	1 (0.2)	3 (1.2)	4 (0.4)
Anger	0	0	0	0	4 (1.6)	4 (0.4)
Personality change	1 (0.2)	0	0	1 (0.2)	0	1 (0.1)
Psychotic disorder	1 (0.2)	0	0	1 (0.2)	0	1 (0.1)
Belligerence	0	0	0	0	1 (0.4)	1 (0.1)
Impulse-control disorder	0	0	0	0	1 (0.4)	1 (0.1)
Skin laceration	0	0	0	0	1 (0.4)	1 (0.1)
Any TEAE leading to dose reduction	0	0	0	6 (1.4)	12 (4.7)	18 (1.7)
Irritability	0	0	0	1 (0.2)	8 (3.1)	9 (0.9)
Aggression	0	0	0	4 (0.9)	2 (0.8)	6 (0.6)
Abnormal behavior	0	0	0	1 (0.2)	1 (0.4)	2 (0.2)
Anger	0	0	0	1 (0.2)	1 (0.4)	2 (0.2)
Psychomotor hyperactivity	0	0	0	1 (0.2)	0	1 (0.1)

[a]A patient with ≥2 adverse events with the same preferred term is counted only once for that preferred term.
[b]MedDRA preferred terms are sorted in descending order of frequency in the total perampanel column.
[c]Patients treated during the double-blind study. Dose groups are based on the actual treatment groups.
[d]Narrow SMQ term for hostility/aggression.
MedDRA, Medical Dictionary for Regulatory Activities; SAE, serious adverse event; SMQ, standardized MedDRA query; TEAE, treatment-emergent adverse event.

psychiatric TEAEs in nonepilepsy patients was similar between those receiving perampanel and those in the placebo group (11.4% vs. 10.5%). Confusional state was the only event that: (1) occurred in ≥1% of perampanel-treated, nonepilepsy patients; (2) had an incidence rate higher than placebo; and (3) exhibited a dose–response relationship. As stated in the U.S. Prescribing Information for perampanel, a larger proportion of perampanel-treated nonepilepsy patients than placebo-treated nonepilepsy patients experienced disorientation, delusion, and paranoia. In total, 18 of 2,013 nonepilepsy perampanel-treated patients experienced these three TEAEs combined.[1] The risk of anger and aggression was not increased with perampanel treatment in the nonepilepsy studies.

Table 5. TEAEs for psychiatric disorders occurring in ≥3 patients in any treatment group[a]: nonepilepsy double-blind studies

TEAE (MedDRA preferred term[b])	Placebo[c] (N = 1,079) n (%)	Perampanel[c] 2 mg/day (N = 908) n (%)	Perampanel[c] 4 mg/day (N = 814) n (%)	Perampanel[c] 8 mg/day (N = 291) n (%)	Perampanel[c] Total (N = 2,013) n (%)
Any TEAE	113 (10.5)	100 (11.0)	98 (12.0)	31 (10.7)	229 (11.4)
Insomnia	39 (3.6)	25 (2.8)	35 (4.3)	9 (3.1)	69 (3.4)
Depression	18 (1.7)	18 (2.0)	16 (2.0)	5 (1.7)	39 (1.9)
Anxiety	21 (1.9)	20 (2.2)	14 (1.7)	3 (1.0)	37 (1.8)
Confusional state	6 (0.6)	6 (0.7)	11 (1.4)	7 (2.4)	24 (1.2)
Hallucination	13 (1.2)	11 (1.2)	10 (1.2)	0	21 (1.0)
Abnormal dreams	7 (0.6)	3 (0.3)	8 (1.0)	0	11 (0.5)
Hallucination, visual	7 (0.6)	4 (0.4)	3 (0.4)	2 (0.7)	9 (0.4)
Delusion	1 (0.1)	3 (0.3)	2 (0.2)	2 (0.7)	7 (0.3)
Disorientation	1 (0.1)	1 (0.1)	3 (0.4)	2 (0.7)	6 (0.3)
Nightmare	4 (0.4)	2 (0.2)	1 (0.1)	2 (0.7)	5 (0.2)
Panic attack	1 (0.1)	3 (0.3)	0	1 (0.3)	4 (0.2)
Psychotic disorder	2 (0.2)	3 (0.3)	0	0	3 (0.1)
Sleep disorder	3 (0.3)	2 (0.2)	0	0	2 (0.1)
Initial insomnia	3 (0.3)	1 (0.1)	0	0	1 (0.0)
Pathological gambling	3 (0.3)	1 (0.1)	0	0	1 (0.0)
Delirium	3 (0.3)	0	0	0	0

[a]A patient with ≥2 adverse events with the same preferred term is counted only once for that preferred term.
[b]MedDRA preferred terms are sorted in descending order of frequency in the total perampanel column.
[c]Patients treated during the double-blind study. The 8 mg/day perampanel group includes doses of 6–8 mg/day.
MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse event.

For treatment-emergent psychiatric SAEs, the incidence rate was similar between perampanel-treated (0.8%) and placebo-treated (0.6%) nonepilepsy patients. The most common SAE was confusional state, which occurred in 0.2% of patients in the perampanel group and 0.1% of placebo patients. Psychiatric TEAEs leading to discontinuation in the nonepilepsy patients were more common in the perampanel group (2.9%) compared to the placebo group (1.1%), with confusional state being the main TEAE leading to discontinuation (0.7% for perampanel-treated patients vs. 0.1% for placebo).

All-treated population (patients with partial seizures and nonepilepsy patients)

Additional analysis was conducted to describe TEAEs among an "all-treated" population, which included all patients with partial seizures and nonepilepsy patients who had participated in the following: (1) phase III double-blind studies and their OLEs and (2) phase II double-blind studies and their OLEs. These two pooled groups included 4,368 patients: 1,651 patients who had participated in all partial-seizure studies and 2,717 patients from nonepilepsy studies (Table 1). The overall extent of exposure to perampanel was 2,281 patient-years (vs. 165 patient-years for placebo exposure) for the all-treated partial-seizure population and 1,653 patient-years (vs. 364 patient-years for placebo exposure) for the nonepilepsy patients. TEAEs for psychiatric disorders in the all-treated partial-seizure group were reported in 475 (28.8%) of 1,651 patients, whereas 501 (18.4%) of 2,717 patients from the nonepilepsy group reported TEAEs. The most common TEAE for both populations was insomnia, reported in 4.9% and 5.3% of the partial-seizure and nonepilepsy groups, respectively. SAEs of psychiatric disorders were reported in 59 patients (3.6%) from the all-treated partial-seizure group and 43 (1.6%) from the nonepilepsy group. Discontinuations due to psychiatric disorders were reported in 99 patients (6.0%) from the all-treated partial-seizure group and 118 (4.3%) from the nonepilepsy group.

Homicidal ideation and/or threat were exhibited in 6 (0.1%) of 4,368 perampanel-treated patients from the partial seizure and nonepilepsy patient groups.[1] Patients categorized as exhibiting homicidal ideation and/or threat were described as having worsening of intermittent aggressive behavior disorder, aggressive behavior, and anger outburst as well as homicidal ideation (Table 6). Of the six cases of homicidal ideation and/or threat, one patient was from a phase III double-blind partial-seizure study, one was from the double-blind nonepilepsy studies, and four were from the phase III partial-seizure OLE; all were considered SAEs in the relevant "narrow-and-broad" SMQs for TEAEs suggestive of hostility/aggression.

Phase I subjects/volunteers

An analysis of safety data from 922 phase I subjects/volunteers participating in 27 clinical studies in which they were treated with perampanel included 579 subjects from

Table 6. Summary of patients with homicidal ideation and/or threat by study

Patient Group	Gender, Age at Time of Event (years)	Region	Previous Psychiatric History	Concomitant Medications	Dose at Time of Event	Study Drug Action Taken/Other Action Taken	Verbatim Term for Event	Latency[a]	Outcome
Phase III partial seizures study (double-blind)	Male, 32	North America	Depression; personality disorder; intermittent aggressive behavioral disorder	Thomapyrin N, Ibuprofen, Cetirizine, Naproxen, Felbamate, Esomeprazole, Pregabalin, Venlafaxine, Lisinopril, Diphenhydramine, Haloperidol, Lorazepam, Zolpidem	12 mg	Drug withdrawn/ Withdrawn from study	Worsening of intermittent aggressive behavior disorder	41 days	Recovered
Nonepilepsy study (double-blind)	Male, 57	North America	Situational anxiety	Glibenclamide, Metformin, Procet, Rizatriptan, Nortriptyline, Phenolphthalein, Prinzide, Tadalafil, Acetylsalicylic Acid, Lovastatin, Omeprazole	6 mg	Drug withdrawn	Homicidal ideation	45 days	Recovered
Phase III OLE - partial seizures	Female, 34	North America	Depression; anxiety; irritability	Clonazepam, Quetiapine, Nortriptyline, Esomeprazole, Carbamazepine, Propranolol, Triaminic-DM, Paracetamol, Demazin, Ibuprofen, Sertraline	12 mg	Dose not changed	Anger outburst	88 days	Recovered
Phase III OLE - partial seizures	Female, 24	Asia	Not reported	Phenobarbital, Valproic acid	6 mg	Dose reduced	Aggressive behavior	159 days	Recovered
Phase III OLE - partial seizures	Female, 43	North America	Depression; anxiety disorder; intermittent insomnia	Loperamide, Narine, Promethazine, Di-Gesic, Ibuprofen, Rhamnus Purshiana, Trazodone,	10 mg	Dose reduced	Homicidal ideation	393 days	Recovered

Continued

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Table 6. Continued.

Patient Group	Gender, Age at Time of Event (years)	Region	Previous Psychiatric History	Concomitant Medications	Dose at Time of Event	Study Drug Action Taken/Other Action Taken	Verbatim Term for Event	Latency[a]	Outcome
				Zonisamide, Duloxetine, Eszopiclone, Propacet, Alprazolam, Estrogen Nos, Aripiprazole					
Phase III OLE - partial seizures	Male, 13	North America	Aggression; behavioral outbursts	Valproic acid, Folic acid, Guanfacine, Risperidone, Buspirone	10 mg	Dose not changed	Aggressive behavior	617 days	Recovered

[a]Defined as time to onset from first perampanel dose.
OLE, open-label extension.

single-dose studies and 343 from multidose studies (Table 1).

Within the single-dose cohort, at least one psychiatric TEAE was observed in 73 (7.9%) of those receiving perampanel and 7 (4.8%) of the placebo subjects. Euphoric mood was the most common TEAE among single-dose study participants, occurring in 54 (5.9%) of perampanel-treated subjects and 4 (2.8%) of placebo-treated subjects. It should be noted, however, that 36 of the 54 euphoric events occurred in subjects receiving perampanel doses in excess of 12 mg, and occurred in 2 (of the 27) phase I studies in which the safety and tolerability of perampanel at single supratherapeutic doses was evaluated in recreational drug users (Drug Dependency and Drug Abuse Liability studies). Euphoric mood was not a common TEAE reported in the multidose group that did not include any studies evaluating recreational drug users. A dose-related trend was observed for all TEAEs, including euphoric mood, across all perampanel dose groups. All other TEAEs apart from euphoric mood occurred in ≤0.7% of patients in both the perampanel and placebo groups. All TEAEs related to psychiatric disorders were mild or moderate, and neither psychiatric SAEs nor deaths related to psychiatric disorders occurred. No patient discontinued treatment due to a psychiatric TEAE.

Discussion

An analysis of the safety data from the entire perampanel clinical program, including phase II and III studies in patients with partial seizures, nonepilepsy patients, and phase I subjects/volunteers, was initiated to better understand psychiatric and behavioral TEAEs related to perampanel treatment for patients with partial seizures.[1] We present a "narrow" SMQ for AEs suggestive of hostility/aggression to distinguish those TEAEs in phase III partial-seizure studies that might be more revealing about psychiatric and behavioral risk, and present "narrow-and-broad" SMQs for AEs suggestive of hostility/aggression including those that might be less specific in nature.[9]

The warning in the perampanel U.S. Prescribing Information states that "hostility- and aggression-related adverse reactions occurred in 12% and 20% of patients randomized to receive perampanel at doses of 8 mg and 12 mg/day, respectively, compared to 6% of patients in the placebo group."[1] This statement corresponds to the combined "narrow-and-broad" SMQs in the phase III double-blind partial-seizure studies (Table 4). In contrast, the "narrow" terms revealed TEAE rates of 2.8% for perampanel 8 mg, 6.3% for perampanel 12 mg, and 0.7% for placebo (Table 3). In patients with partial seizures, treatment with perampanel up to 12 mg caused a dose-related increase in psychiatric TEAEs.[1] Prior studies have shown that past psychiatric history or family psychiatric history is associated with a higher risk of adverse psychotropic effects.[12,13] In the phase III double-blind partial-seizure studies, fewer than half the

patients with TEAEs suggestive of hostility/aggression ("narrow-and-broad" SMQs) had a prior psychiatric history or a history of aggression. Patients taking perampanel were less likely to have prior psychiatric history (RR = 0.6775) compared to patients on placebo, whereas risk of history of hostility/aggression is relatively unchanged for perampanel versus placebo (RR = 1.0163); therefore, these reactions can occur in patients with and without a prior psychiatric history. A large proportion of patients also had antipsychotic, antidepressant, and benzodiazepine use. Physicians should be aware of patients' preexisting psychiatric conditions and monitor them closely when treating with perampanel.

Our analysis in patients with partial seizures treated with perampanel up to 12 mg also showed that these psychiatric events generally appeared within the first 6 weeks of treatment, corresponding to the higher incidence observed during titration in the phase III studies. Thus, patients should be monitored during the initial few weeks of drug therapy and when taking higher doses, although patients could experience new psychiatric events after the initial titration period. A majority of subjects who experienced psychiatric events and/or TEAEs suggestive of hostility/aggression continued the study, although some at reduced doses. These data support the notion that these psychiatric TEAEs are manageable; nonetheless, perampanel dose should be reduced if these symptoms persist.

In the all-treated population analysis, homicidal ideation was reported in one patient from the phase III partial-seizure studies and one patient from the nonepilepsy studies during the double-blind phase, and in four patients from the phase III partial-seizure OLE. In the OLE, it is important to note the longer treatment exposure and that adjustments were permitted in perampanel dose, number of concomitant AEDs, and other concomitant medications.[14] It is possible that these factors may play a role in the emergence of events associated with homicidal ideation and/or threat.

Understanding the significance of psychiatric and behavioral TEAE rates associated with perampanel treatment requires taking into consideration the occurrence of these types of TEAEs associated with other AEDs. A post hoc analysis of phase III partial-seizure studies for hostility/aggression-related AEs based on concomitant administration of perampanel and levetiracetam (previously presented at the 68th Annual Meeting of the American Epilepsy Society) showed no additional liability for hostility/aggression TEAEs with perampanel concomitant with levetiracetam.[15] Although no direct comparison between perampanel and other AEDs with regard to psychiatric and behavioral TEAEs is possible with the available data, it is also worth noting the incidence of psychiatric and behavioral TEAEs from epilepsy trials with other agents. One recently published study compared rates of self-reported anger and aggression in patients with epilepsy taking levetiracetam (n = 158) to those taking other AEDs (n = 260), including those most commonly used, such as carbamazepine, valproate, lamotrigine, and topiramate. The authors found that 49% of patients taking levetiracetam reported anger as a problem sometimes or always (with a dose-related trend), whereas 39% of patients taking a different AED reported experiencing anger sometimes or always.[16] An earlier study of self-reported symptoms associated with the most commonly used AEDs in 119 patients with epilepsy found that "feeling of anger" occurred at the following rates: levetiracetam 33%, valproate 19%, carbamazepine 16%, and lamotrigine 15%.[17]

A 2012 survey of adverse effects in clinical studies of AEDs describes a highly varied set of outcomes in which psychiatric and behavioral AEs were measured.[18] For example, a randomized, double-blind study of phenobarbital reported aggression in 21.6% of the 51 study patients.[18] Aggression outcomes in a levetiracetam study included a reduction from baseline, although an elevation in irritability was observed in the same study. Another levetiracetam study reported a 12.5% incidence of aggression.[18] One double-blind study in 41 patients with epilepsy treated with topiramate observed a 24.4% incidence of aggression, whereas another double-blind study observed behavioral problems occurring in 43.8% of 48 patients.[18] Overall, aggression or irritability have been associated with levetiracetam, gabapentin, lamotrigine, phenobarbital, tiagabine, topiramate, and zonisamide.[18] Regarding the issue of homicidal ideation and/or threat, currently no systematic review on homicidal ideation and AEDs has been published, and it is therefore difficult to compare the results presented here with those of other AEDs.

U.S. Prescribing Information for all AEDs includes the following language: "AEDs increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. Patients treated with any AED for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior."[1,19,20] Thus, it is expected that all AEDs may have some level of psychiatric and/or behavioral effect. Furthermore, behavioral effects common to all AEDs have also been shown to be more common in the epilepsy population than in other groups, including populations with cognitive and anxiety disorders.[21] This is consistent with the effects seen with perampanel in patients with partial seizures, relative to the nonepilepsy patients and phase I subjects/volunteers. It is important to also consider that epilepsy-related variables may contribute to treatment-emergent psychiatric events with AED treatment. For example, location of the seizure focus, presence of brain damage, or neurochemical changes related to neuronal excitation and seizure inhibition may predispose patients to psychiatric phenomena.[22] Additional studies have shown that variables related to epilepsy implicated in treatment-emergent psychiatric events of AEDs can include limbic system dysfunction, hippocampal sclerosis, neuronal

channel dysfunction, or forced normalization.[23] Ultimately, several factors may be implicated in treatment-emergent psychiatric AEs in patients with epilepsy. The data presented here were unable to assess such epilepsy-related variables, and thus further studies investigating these variables and individual AEDs are needed.

Because statistical significance was not determined in this analysis, data can only indicate trends seen in the population with partial seizures and compare them with those seen in the other populations examined. Another limitation of this analysis is that the safety data collected through AE reporting are pooled from randomized, controlled trials. As previously stated, formal neuropsychiatric assessments were not performed at baseline or during the study. In addition, such controlled trials are stringent with regard to drug doses, titration schedules, and inclusion/exclusion criteria —resulting in the exclusion of patients with more severe and complex psychiatric comorbidities—and thus may not be representative of real-world clinical practice.[23] The prevalence rates of psychiatric and behavioral symptoms reported in these studies may be an underrepresentation of their true prevalence and reflect the most serious events, as the recording of adverse reactions in these trials is based on "spontaneous" reports by patients or family. Patients with a chronic history of irritability (seen in a significant percentage of patients with drug-resistant epilepsy), for example, may not report such symptoms even if perampanel yielded an exacerbation in severity of these symptoms. Nonetheless, use of randomized, controlled trials to review treatment-emergent psychiatric events lends valuable insight into possible psychiatric symptoms, and this work provides useful additional data on treatment-emergent psychiatric adverse events with AEDs.[12] Data presented here exhibited a dose-related increase in psychiatric AEs seen in patients with partial seizures following perampanel treatment. Clinicians should monitor patients for these events when treating with perampanel.

Conclusions

The additional safety data presented here provide further understanding and context for psychiatric and behavioral events observed with perampanel treatment. "Narrow" versus "narrow-and-broad" SMQs produced markedly different rates of TEAEs suggestive of hostility/aggression in subjects treated with perampanel compared to placebo, although few resulted in discontinuation from the study or were reported as SAEs. A dose-related increase in psychiatric TEAEs was observed in patients with partial seizures treated with perampanel at doses up to 12 mg. However, an increase in aggression or anger was not observed in the nonepilepsy subjects who were treated with perampanel up to 8 mg, or in the phase I subjects/volunteers who were treated with greater than 12 mg of perampanel. In phase III partial-seizure studies, a higher incidence of aggression was observed for the adolescent population compared with the adult population. Patients, caregivers, and families should be informed of potential psychiatric/behavioral risks associated with taking perampanel, especially at higher doses and during the initial titration period. The dose of perampanel should be reduced if these symptoms persist.

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Disclosure of Conflicts of Interest

Alan Ettinger has served on advisory boards for Eisai Inc. and UCB Pharma. Antonia LoPresti, Haichen Yang, Betsy Williams, Sharon Zhou, Randi Fain, and Antonio Laurenza are employees of Eisai Inc. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

References

1. *FYCOMPA (perampanel) US prescribing information*. Woodcliff Lake, NJ: Eisai Inc; 2014.
2. *FYCOMPA (perampanel) summary of product characteristics*. Hatfield, Hertfordshire, UK: Eisai Europe Limited; 2012.
3. *FYCOMPA (perampanel) product monograph*. Mississauga, ON, Canada: Eisai Limited; 2013.
4. French JA, Krauss GL, Biton V, et al. Adjunctive perampanel for refractory partial-onset seizures: randomized phase III study 304. *Neurology* 2012;79:589–596.
5. French JA, Krauss GL, Steinhoff BJ, et al. Evaluation of adjunctive perampanel in patients with refractory partial-onset seizures: results of randomized global phase III study 305. *Epilepsia* 2013;54:117–125.
6. Krauss GL, Serratosa JM, Villanueva V, et al. Randomized phase III study 306: adjunctive perampanel for refractory partial-onset seizures. *Neurology* 2012;78:1408–1415.
7. Steinhoff BJ, Ben-Menachem E, Ryvlin P, et al. Efficacy and safety of adjunctive perampanel for the treatment of refractory partial seizures: a pooled analysis of three phase III studies. *Epilepsia* 2013;54:1481–1489.
8. MedDRA Maintenance and Support Services Organization. *Introductory guide to standardised MedDRA queries (SMQs): version 15.0*. Chantilly, VA: 2012.
9. *Standardised MedDRA queries. MedDRA website*. MacLean, VA: Medical Dictionary for Regulatory Activities (MedDRA); 2014.
10. Krauss GL, Bar M, Biton V, et al. Tolerability and safety of perampanel: two randomized dose-escalation studies. *Acta Neurol Scand* 2012;125:8–15.
11. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders*, 4th ed. Text Revision. Washington, DC: American Psychiatric Association; 2000.
12. Mula M, Kanner AM, Schmitz B, et al. Antiepileptic drugs and suicidality: an expert consensus statement from the Task Force on Therapeutic Strategies of the ILAE Commission on Neuropsychobiology. *Epilepsia* 2013;54:199–203.
13. Kanner AM, Wuu J, Faught E, et al. A past psychiatric history may be a risk factor for topiramate-related psychiatric and cognitive adverse events. *Epilepsy Behav* 2003;4:548–552.
14. Krauss GL, Perucca E, Ben-Menachem E, et al. Perampanel, a selective, noncompetitive α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor antagonist, as adjunctive therapy for refractory partial-onset seizures: interim results from phase III, extension study 307. *Epilepsia* 2013;54:126–134.

15. Fain R, Chung S, Yang H, et al. Aggression adverse events with concomitant levetiracetam use in perampanel phase III partial seizure clinical studies. Poster presented at the 68th Annual Meeting of the American Epilepsy Society, Seattle, WA, USA, December 5–9, 2014. *Epilepsy Curr* 2015; 15(S1): Abstract No 2.288.
16. Wieshmann UC, Baker GA. Self-reported feelings of anger and aggression towards others in patients on levetiracetam: data from the UK antiepileptic drug register. *BMJ Open* 2013;3(3).
17. Wieshmann UC, Tan GM, Baker G. Self-reported symptoms in patients on antiepileptic drugs in monotherapy. *Acta Neurol Scand* 2011;124:355–358.
18. Piedad J, Rickards H, Besag FM, et al. Beneficial and adverse psychotropic effects of antiepileptic drugs in patients with epilepsy: a summary of prevalence, underlying mechanisms and data limitations. *CNS Drugs* 2012;26:319–335.
19. *Keppra (levetiracetam) prescribing information*. Smyrna, GA: UCB Inc; 2013.
20. *Lamictal (lamotrigine) prescribing information*. Research Triangle Park, NC: GlaxoSmithKline; 2013.
21. Cramer JA, Blum D, Reed M, et al. The influence of comorbid depression on seizure severity. *Epilepsia* 2003;44:1578–1584.
22. Schwartz JM, Marsh L. The psychiatric perspectives of epilepsy. *Psychosomatics* 2000;41:31–38.
23. Mula M. Treatment-emergent psychiatric adverse events of antiepileptic drugs in epilepsy: how can we avoid them? *Neuropsychiatry* 2011;1:371–376.
24. MedDRA Maintenance and Support Services Organization. *Introductory guide for standardised MedDRA queries (SMQs) version 13.1*. Chantilly, VA; 2010.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Complete List of "Narrow" and "Broad" Standardized Medical Dictionary for Regulatory Activities (MedDRA) Queries (SMQs) for TEAEs Suggestive of Hostility/Aggression.[24]

Table S2. Concomitant Medications in Double-Blind Phase III Subjects with TEAEs in the Hostility/Aggression "Narrow-and-Broad" SMQ.