doi:10.1111/ene.12170

The adverse event profile of perampanel: meta-analysis of randomized controlled trials

G. Zaccara[a], F. Giovannelli[a], M. Cincotta[a], A. Verrotti[b] and E. Grillo[c]

[a]*Unit of Neurology, Department of Medicine, Florence Health Authority, Firenze;* [b]*Department of Pediatrics, University of Chieti, Chieti; and* [c]*Medical School, University of Milan, Milan, Italy*

Keywords:
adverse effects, antiepileptic drugs, epilepsy, meta-analysis, perampanel, side effects

Received 20 January 2013
Accepted 11 March 2013

Background and purpose: To identify adverse events (AEs) significantly associated with perampanel treatment in double-blind clinical studies (RCTs). Serious AEs, study withdrawals due to AEs and dose–effect responses of individual AEs were also investigated.

Methods: All placebo controlled, double-blind RCTs investigating therapeutic effects of oral perampanel were searched. AEs were assessed for their association with perampanel after exclusion of synonyms, rare AEs and non-assessable AEs. Risk difference (RD) was used to evaluate the association of any AE (99% confidence intervals) and withdrawals or serious AEs (95% confidence intervals) with perampanel.

Results: Nine RCTs (five in pharmacoresistant epilepsy and four in Parkinson's disease) were included in our study. Almost 4000 patients had been recruited, 2627 of whom were randomized to perampanel and treated with drug doses of 0.5 mg/day (n = 68), 1 mg/day (n = 65), 2 mg/day (n = 753), 4 mg/day (n = 1017), 8 mg/day (n = 431) or 12 mg/day (n = 293). Serious AEs were not significantly associated with perampanel treatment. The experimental drug was significantly associated with an increased risk of AE-related study withdrawals at 4 mg/day [RD (95% confidence interval) 0.03 (0.00, 0.06)] and 12 mg/day [RD (95% confidence interval) 0.13 (0.07, 0.18)]. Of 15 identified AEs, five (dizziness, ataxia, somnolence, irritability and weight increase) were found to be significantly associated with perampanel and one (seizure worsening) was significantly associated with placebo.

Conclusions: Vestibulocerebellar AEs (dizziness, ataxia), sedative effects (somnolence), irritability and weight increase were significantly associated with perampanel treatment.

Introduction

Information on tolerability of a new antiepileptic drug (AED) which is entering the market can only be obtained from key clinical studies. Although meta-analyses of placebo-controlled RCTs have attempted to answer the question, inclusion of studies limited to a specific disorder have reduced the statistical power of the assessments. To overcome these limitations, two systematic reviews and meta-analyses of all available RCTs with two new AEDs were recently conducted, also including studies performed in different areas than epilepsy, and several AEs significantly associated with pregabalin [1] and lacosamide [2] were identified.

Correspondence: G. Zaccara, Unit of Neurology, San Giovanni di Dio Hospital, Via Di Torregalli n 3, 50143 Firenze, Italy (tel.: +39 055 719 2476; fax: +39 055 719 2280; e-mail: gaetano.zaccara@asf.toscana.it).

Perampanel, which has recently been approved in Europe for the treatment of drug-resistant epilepsies, is a non-competitive selective antagonist of the ionotropic α-amino-3-hydroxy-5-methyl-4-isoxazoleproprionic acid (AMPA) glutamate receptors, and exerts a direct influence on post-synaptic glutamatergic transmission [3]. The AMPA receptors are the predominant mediators of excitatory transmission in the central nervous system and are critical to the generation and spread of epileptic activity. However, inhibition of excitatory neurotransmission may determine dysfunction in some areas of the central nervous system associated with cognitive and/or motor function impairment [4]. Indeed, experimental studies show that glutamate antagonists may produce several characteristic and apparently dose-dependent AEs in kindled animals [5].

So far, this agent has been investigated in two different populations of neurological patients. Several

phase 3 studies which recruited more than 2000 subjects assessed the efficacy of perampanel in patients with Parkinson's disease (PD) already being treated with levodopa and with motor fluctuations [6–8]. The hypothesized mechanism of action for an effect of this agent in this condition was that, since enhancement of glutamatergic activity in the striatum may modify basal ganglia output and generate treatment-related motor complications [9], inhibition of AMPA-mediated excitatory neurotransmission could alleviate these motor symptoms [10]. Drug development in this field has probably been discontinued due to lack of efficacy.

A little fewer than 1700 patients with drug-resistant partial-onset epilepsies (POS) were recruited in phase 2 [11] and 3 [12–14] studies designed to assess the efficacy of the drug in this area.

In this meta-analysis, with the purpose of identifying those AEs associated with perampanel, all studies in which this agent had been used were included. It was thought that different ranges of ages (around 35 years for epileptic patients and around 65 for PD patients) between the populations studied may offer a unique opportunity to assess drug effect also in fragile geriatric subjects, who are often excluded by epilepsy trials [15].

Doses of perampanel used in these conditions were different (up to 4 mg/day for PD patients, and between 4 and 12 mg/day for patients with POS). To identify as many AEs as possible, also not dose-dependent AEs, in a first analysis all doses used were merged. A second analysis was focused on the identification of dose-dependent AEs and therefore doses were separately evaluated, with the exception of very low doses. Several other aspects of perampanel tolerability and safety were also investigated, including serious AEs, study withdrawals due to AEs, dose–effect responses of individual AEs and the effect of disease-specific neurobiological characteristics on drug tolerability.

Methods

Types of studies

Randomized, placebo-controlled, double-blind trials investigating the therapeutic effects of oral perampanel in adults with different neurological disorders were included. Full journal publication or summary clinical trial reports were required. Moreover, abstracts containing more detailed safety and tolerability data from key clinical trials were included. All other study types, including non-randomized trials, case reports or observational trials, were excluded.

Search methods for identification of studies

RCTs of perampanel were identified using MEDLINE via PubMed, EMBASE and the Cochrane Central Register of Controlled Trials. The search term 'perampanel' was used. Additional studies were sought in reference lists of retrieved papers and by searching the Internet for summary clinical trial reports not available as full publications.

All studies were read independently and considered eligible by two authors (GZ, EG) and agreement was reached after discussion.

Exclusions from the list of AEs were synonyms, AEs reported in no more than five subjects amongst those randomized to perampanel and subjects for whom it was not possible to calculate risk difference (RD).

Statistical analysis

All analyses were performed using RevMan version 5.1 [16]. Statistical heterogeneity was assessed using the I^2 test, with an $I^2 > 70\%$ indicating heterogeneity. The chi-squared test for heterogeneity was also used. Provided no significant clinical or statistical heterogeneity was present, the analyses used a fixed-effect model. In cases where I^2 was >70%, a random-effect model was used. In all cases, RD values were calculated. When assessing the association of any AE with perampanel treatment, the confidence intervals (CIs) of RD values were set at 99%. This conservative approach was aimed at minimizing the error rate. For all other analyses, 95% CIs were used. An inverse variance-weighted meta-regression model was used to test the relationship between perampanel dose and RD for all AEs.

Results

Results of the search

Our search, performed in November 2012, yielded 25 papers in Pubmed, 126 in EMBASE and eight in Cochrane Central. From this initial screening, non-double-blind studies, open studies and studies performed on healthy volunteers were excluded. Seven papers were identified which reported nine RCTs (four RCTs reported in two studies [7,11]). Five RCTs in which perampanel had been administered to subjects of more than 12 years and affected by drug-resistant POS and four in which it had been administered to PD patients were evaluated and included in our analysis. One conference abstract containing adjunctive data on safety and tolerability from one of the included clinical trials [17] was also included. The main clinical characteristics of the selected studies,

Table 1 Characteristics of the studies included in our analysis

Author	Disease	Study duration (weeks)[a]	Placebo (*n*)	0.5 mg/day (*n*)	1.0 mg/day (*n*)	2.0 mg/day (*n*)	4.0 mg/day (*n*)	8.00 mg/day (*n*)	12 mg/day (*n*)
Study 206 (Krauss, 2011) [11]	Drug-resistant partial epilepsy	12	51	–	–	–	102[b]	–	–
Study 208 (Krauss, 2011) [11]	Drug-resistant partial epilepsy	16	10	–	–	–	–	–	38
Study 304 (French, 2012) [12]	Drug-resistant partial epilepsy	19	121	–	–	–	–	133	134
Study 305 (French, 2013) [13]	Drug-resistant partial epilepsy	19	136	–	–	–	–	129	121
Study 306 (Krauss, 2012) [14]	Drug-resistant partial epilepsy	19	185	–	–	180	172	169	–
Eggert, 2010 [8]	Parkinson's disease	12	66	68	65	64			
Study 301 (Lees, 2011) [7]	Parkinson's disease	30	254			258	251		
Study 302 (Lees, 2011) [7]	Parkinson's disease	20	250	–	–	251	250	–	–
Rascol, 2012 [6]	Parkinson's disease	18	247	–	–	–	242	–	–
Total			1320	68	65	753	1017	431	293

Details on titration are given in the text. [a]The length of the double-blind phase (titration plus maintenance) not including the final transition period was considered as study duration; [b]drug administered twice daily in 51 patients.

which in all cases were sponsored by EISAI, are reported in Table 1.

The nine studies included a total of 3947 subjects, 2627 of whom were randomized to perampanel and 1320 to placebo. In all studies but one (study 206) [11] in which the drug daily regimen was twice a day for some patients, drug was administered once a day in the evening. No titration was performed up to a dose of 2 mg/day. In patients randomized to higher doses, titration was low for PD patients (4 weeks to achieve a 4 mg/day dose) and for epileptic patients included in the two phase 2 studies (increments of 1 or 2 mg/day every 2 weeks). Patients with drug-resistant POS included in phase 3 studies [12–14] had a weekly 2 mg/day increase of perampanel up to the final dose. The duration of studies was between 12 and 30 weeks.

Patients with serious adverse events

The number of serious AEs, reported in all studies, was 152/2627 (5.7%) for subjects randomized to perampanel and 81/1320 (6.1%) for subjects randomized to placebo. In POS studies they were mainly related to epilepsy (convulsion or status epilepticus) and in PD studies they were injuries or their consequences (fractures). No evidence of heterogeneity (I^2 = 15%) was found; therefore a fixed-effect model was used. The risk of experiencing a serious AE did not differ between the perampanel and placebo groups [RD (95% CI), −0.00 (−0.02, 0.01); P = 0.65].

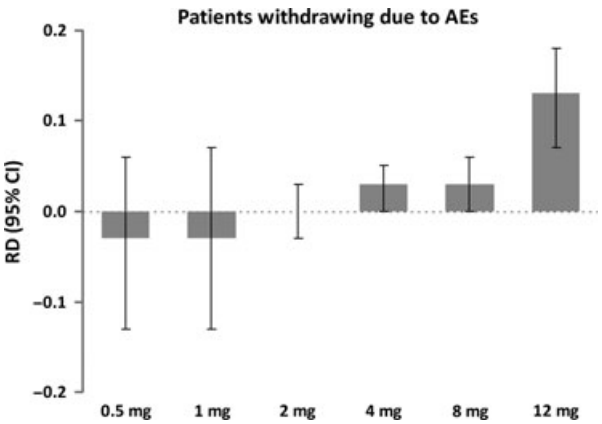

Figure 1 Number of patients discontinuing perampanel treatment because of adverse effects at the different doses used in clinical trials.

Study withdrawals due to adverse events and comparison across the two different neurological conditions

As no evidence of heterogeneity emerged (I^2 between 0% and 55%) a fixed-effect model was used. Perampanel was significantly associated with an increased risk of AE-related study withdrawals at 4 mg/day [RD (95%) 0.03 (0.00, 0.05), P = 0.05] and 12 mg/day [RD (95%) 0.13 (0.07, 0.18), P < 0.01; Fig. 1]. At 4 mg/day, a comparison of withdrawals due to AEs between PD patients and patients with POS was possible. PD patients treated with the experimental drug

were more likely to withdraw from the study with respect to placebo-treated patients [RD (95%) 0.04 (0.00, 0.07), $P = 0.03$]. In contrast, at this dose level patients with drug-resistant POS had similar chances of withdrawing compared with patients treated with placebo [RD (95%) = −0.01 (−0.04, 0.03), $P = 0.72$].

Adverse events identified in included studies

In the nine studies included in our analysis, 34 AEs occurred during perampanel treatment. Of these AEs, five (16%) were considered to be synonyms of another AE (nasopharyngitis and bronchitis = respiratory infection, asthenia = fatigue, gait disturbance = ataxia, and aggression = irritability). These synonyms were merged with their corresponding AEs in all analyses. Thirteen AEs (anger, anxiety, confusional state, constipation, dyspnea, edema, hallucination, hypertension, nausea, vomiting, suicidal ideation, sleep disorder, rhinitis) were reported in no more than five subjects amongst those treated with perampanel. They were therefore considered to be rare and excluded by our analysis.

Dyskinesia was reported in 7.2% and 12.8% of patients treated with the active drug in studies 301 and 302, respectively [7], but the number of patients with this AE in the placebo group was not reported and the AE was excluded from our analysis.

The 15 remaining AEs were included in our meta-analysis. In all studies, weight increase was defined as a gain >7% of baseline weight and seizure worsening was defined as a >50% increase in seizure frequency with respect to baseline. Data on both these AEs were reported as a single data item for all perampanel doses.

Meta-analysis results

Treatment-emergent adverse effects associated with perampanel: all doses merged

Evidence of heterogeneity ($I^2 > 70\%$), due to a lower reporting in one study [14], was found for dizziness, somnolence, respiratory infection and ataxia and in these cases a random-effect model was used. In all other cases, a fixed-effect model was used.

Dizziness [RD (99% CI) = 0.21 (0.02, 0.40), $P < 0.01$], somnolence [RD (99% CI) = 0.08 (−0.00, 0.16), $P = 0.01$] and weight increase [RD (99% CI) = 0.08 (0.03, 0.12), $P < 0.01$] were significantly associated with perampanel. The AE seizure worsening observed in epilepsy patients was significantly more frequent in placebo-treated patients [RD (99% CI) = −0.05 (−0.09, 0.00), $P = 0.01$]. RD values (99% CI) are reported in Appendix 1for all 15 AEs included in this analysis.

Treatment-emergent adverse events associated with perampanel at various doses

Analysis of the AE observed at each dose was calculated only at doses of 2, 4, 8 and 12 mg/day. A random-effect model was used for somnolence at the 12 mg/day dose and respiratory infection at the 4 mg/day dose ($I^2 > 70\%$). In all other cases, a fixed-effect model was used.

No AEs were significantly associated with the experimental drug at low doses (2 and 4 mg/day). Dizziness [RD (99% CI) = 0.23 (0.16, 0.29), $P < 0.001$], ataxia [RD (99% CI) = 0.05 (0.01, 0.09), $P < 0.001$] and somnolence [RD (99% CI) = 0.08 (0.03, 0.14), $P < 0.001$] were significantly associated with perampanel at 8 mg/day. Dizziness [RD (99% CI) = 0.35 (0.26, 0.44), $P < 0.001$], ataxia [RD (99% CI) = 0.12 (0.07, 0.17), $P < 0.001$] and irritability [RD (99% CI) = 0.09 (0.02, 0.16), $P < 0.001$] were associated with a drug dose of 12 mg/day.

AEs significantly associated with perampanel treatment (all doses merged and all doses tested individually) are reported in Fig. 2. In Appendix 2 are reported all RD (99% CI) data of these AEs.

Analysis of dose–event relationships

A significant dose–event relationship emerged for dizziness ($P < 0.001$) and ataxia ($P = 0.007$). For these AEs, RD values increased with increasing dose.

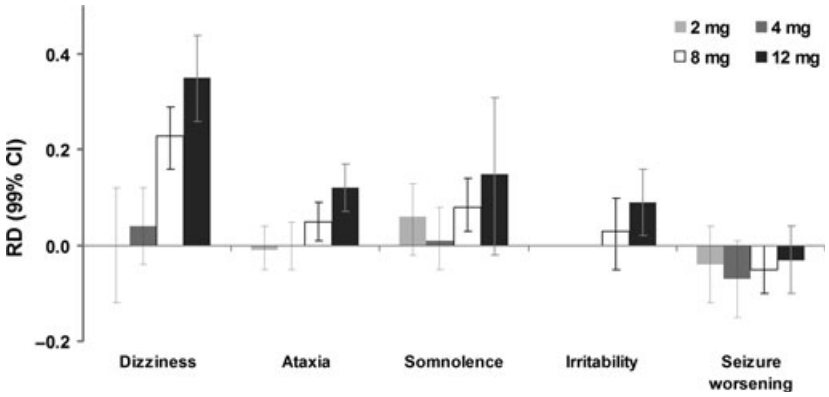

Figure 2 RD (99% CI) of a selection of the analyzed adverse effects. All adverse events explored are reported in Appendix 2.

Discussion

In this meta-analysis perampanel was significantly associated with intolerable AEs (those leading to drug discontinuation) at daily doses of 4 and 12 mg. Findings at 4 mg/day doses were due to an apparently worse tolerability in PD patients whilst drug-resistant epileptic patients treated with this drug dose level had almost identical probabilities of withdrawing as placebo-treated patients. At a dose of 8 mg/day, which is a recommended daily dose in the CHMP assessment report [4], the percentage of patients discontinuing because of intolerable AEs did not significantly differ from placebo-treated patients. In a previous meta-analysis with lacosamide [2], a new AED for which double-blind trials were available for drug-resistant epilepsy and neuropathic pain, a significant association between drug discontinuation due to AEs and the experimental drug was found both at recommended (400 mg/day) and high (600 mg/day) doses. As with other new AEDs, a good tolerability profile of perampanel also emerges from the analysis of serious AEs which were not significantly more frequently reported during perampanel treatment than with placebo.

Of the five AEs significantly associated with perampanel, two AEs, dizziness and ataxia, are considered as due to cerebellar/brainstem dysfunction. In routine clinical practice these AEs are commonly observed in subjects treated with AEDs acting on voltage-gated sodium channels, such as phenytoin, carbamazepine, lamotrigine and oxcarbazepine, and are clearly dose dependent [18]. In two previous meta-analyses aimed at evaluating the AE profile of other AEDs, pregabalin [1], which inhibits the depolarization-dependent calcium influx at P-, Q- and N-type voltage-gated calcium channels [19], and lacosamide [2], which selectively enhances slow inactivation of sodium channels [20], were studied. Both drugs were associated with several AEs either directly or indirectly caused by vestibulocerebellar/brainstem involvement. It is interesting to note that perampanel, which inhibits excitatory neurotransmission and hence has a different mechanism of action, has a similar effect, although perhaps less pronounced, on cerebellovestibular structures.

Somnolence is another characteristic AE associated with perampanel treatment. Vigilance and alertness are commonly impaired in individuals taking traditional AEDs [21]. Some of the new AEDs, e.g. lacosamide [2], may have a less sedative effect.

It is noteworthy that no AEs obviously related to cognition were associated with perampanel treatment. This is particularly important since in the experimental studies dysfunction of excitatory neurotransmission, also that determined by AMPA receptor inhibition, may affect cognition whilst AMPA receptor potentiation is believed to have an opposite effect [22]. Among AEDs, topiramate, which affects excitatory neurotransmission, is associated with several cognitive effects [23]. Although in one study on PD patients [8] some neuropsychological tests showed that there was no evidence of any alteration of working memory performance and accuracy, further studies aimed at evaluating the effects of perampanel on cognitive abilities are required.

Irritability is a psychiatric AE significantly associated with perampanel. In this meta-analysis, aggression was considered synonymous with irritability and was merged with this AE. Other AEDs may have similar effects [24]. This aspect of perampanel tolerability should be considered and studied in more detail in further long-term studies, particularly in children and in special populations of patients.

The only non-neurological AE of perampanel is weight gain. An increase in weight has been associated with treatment with several AEDs with very different mechanisms of action, i.e. gabapentin, pregabalin, valproic acid, vigabatrin, carbamazepine and levetiracetam [25]. It is not known whether, in the case of perampanel, this effect may be mediated by AMPA receptor inhibition or may be caused by another, as yet unknown, mechanism.

As far as idiosyncratic AEs are concerned, it should be noted that a rash, which is the most common idiosyncratic reaction associated with several AEDs [26], was reported only in a small number of patients (four receiving placebo versus 18 receiving perampanel) and was non-significantly associated with perampanel. This is important because perampanel is partly metabolized to reactive metabolites and it is known that idiosyncratic immune-mediated adverse drug reactions may be mediated through the formation of reactive metabolites [4]. Although these findings seem to be reassuring, it should be borne in mind that the number of patients included in RCTs is insufficient to detect rare idiosyncratic AEs [26].

In this meta-analysis RCTs performed with elderly PD patients treated with levodopa and RCTs on drug-resistant epilepsy patients already being treated with 1–3 AEDs were included. It is known that disease-specific neurobiological characteristics, concomitant treatments and age may all affect tolerability of a drug. In similar studies on pregabalin [1,27] and lacosamide [2], it was found that placebo-corrected incidences of AEs across different disorders can be affected or not by concomitant diseases or associated drugs, according to the characteristics of the experimental drug [28–30]. In this meta-analysis, doses used in PD patients (up to 4 mg/day) and epileptic patients (between 4 and 12 mg/day) were different, and this

has precluded comparison between all doses used. However, at 4 mg/day, assessment of patients withdrawing because of intolerable AEs showed that there was an apparently better tolerability in epileptic patients than PD patients. It can be speculated that, since perampanel metabolism is induced by enzymatic inducer AEDs [4], epileptic patients treated with these drugs might have had lower perampanel levels and hence improved drug tolerability compared with PD patients. A further possible explanation is that PD patients, who were older than patients with epilepsy, were more prone to perampanel AEs.

In conclusion, perampanel data from double-blind clinical trials display a relatively good tolerability profile with vestibulocerebellar AEs being in the first line, followed by sedative effects (somnolence) and hence by irritability and weight increase. Further studies, mainly long-term phase 4 studies, are needed to fully clarify the perampanel tolerability profile.

Acknowledgement

The authors received no funding for this study.

Disclosure of conflict of interest

GZ has received speakers' or consultancy fees from EISAI, GSK, Jansen-Cilag, Novartis, Sanofi-Aventis and UCB Pharma. AV has received speakers' or consultancy fees from Jansen-Cilag. EG is an employee of EISAI s.r.l. FG and MC have nothing to disclose.

References

1. Zaccara G, Gangemi P, Perucca P, Specchio L. The adverse event profile of pregabalin: a systematic review and meta-analysis of randomized controlled trials. *Epilepsia* 2011; **52:** 826–836.
2. Zaccara G, Perucca P, Loiacono G, Giovannelli F, Verrotti A. The adverse event profile of lacosamide: a systematic review and meta-analysis of randomized controlled trials. *Epilepsia* 2013; **54:** 66–74.
3. Rogawski MA. Revisiting AMPA receptors as an antiepileptic drug target. *Epilepsy Curr* 2011; **11:** 56–63.
4. Fycompa. EPAR. Public assessment report [online]. Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002434/human_med_001572.jsp&mid=WC0b01ac058001d124.
5. Dziki M, Hönack D, Löscher W. Kindled rats are more sensitive than non-kindled rats to the behavioural effects of combined treatment with MK-801 and valproate. *Eur J Pharmacol* 1992; **222:** 273–278.
6. Rascol O, Barone P, Behari M, *et al*. Perampanel in Parkinson disease fluctuations: a double-blind randomized trial with placebo and entacapone. *Clin Neuropharmacol* 2012; **35:** 15–20.
7. Lees A, Fahn S, Eggert KM, *et al*. Perampanel, an AMPA antagonist, found to have no benefit in reducing 'off' time in Parkinson's disease. *Mov Disord* 2012; **27:** 284–288.
8. Eggert K, Squillacote D, Barone P, *et al*. Safety and efficacy of perampanel in advanced Parkinson's disease: a randomized, placebo-controlled study. *Mov Disord* 2010; **25:** 896–905.
9. Fox SH, Brotchie JM, Lang AE. Non-dopaminergic treatments in development for Parkinson's disease. *Lancet Neurol* 2008; **7:** 927–938.
10. Konitsiotis S, Blanchet PJ, Verhagen L, Lamers E, Chase TN. AMPA receptor blockade improves levodopa-induced dyskinesia in MPTP monkeys. *Neurology* 2000; **54:** 1589–1595.
11. 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.
12. 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.
13. 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.
14. 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.
15. Rheims S, Perucca E, Cucherat M, Ryvlin P. Factors determining response to antiepileptic drugs in randomized controlled trials. A systematic review and meta-analysis. *Epilepsia* 2011; **52:** 219–233.
16. RevMan. *Review Manager (RevMan)* [Computer program]. Version 5.1. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011.
17. Ryvlin P, Lagae L, Unterberger I, *et al*. Perampanel as adjunctive therapy in patients with refractory partial-onset seizures: safety and tolerability analysis from a phase III trial. *Epilepsy Curr* 2012; **12**(Suppl. 1)**:** 1.
18. Zaccara G, Cincotta M, Borgheresi A, Balestrieri F. Adverse motor effects induced by antiepileptic drugs. *Epileptic Disord* 2004; **6:** 153–168.
19. Ben-Menachem E. Pregabalin pharmacology and its relevance to clinical practice. *Epilepsia* 2004; **45**(Suppl. 6)**:** 13–18.
20. Errington AC, Stchr T, Heers C, Lees G. The investigational anticonvulsant lacosamide selectively enhances slow inactivation of voltage-gated sodium channels. *Mol Pharmacol* 2008; **73:** 157–169.
21. Beghi E, Di Mascio R, Tognoni G. Adverse effects of anticonvulsant drugs – a critical review. *Adverse Drug React Acute Poisoning Rev* 1986; **5:** 63–86.
22. Bannerman DM, Deacon RM, Brady S, *et al*. Cognitive enhancing effects of an AMPA receptor positive modulator on place learning in mice. *Behav Brain Res* 2012; **226:** 18–25.
23. Loring DW, Williamson DJ, Meador KJ, Wiegand F, Hulihan J. Topiramate dose effects on cognition: a randomized double-blind study. *Neurology* 2011; **76:** 131–137.
24. Loring DW, Marino S, Meador KJ. Neuropsychological and behavioral effects of antiepilepsy drugs. *Neuropsychol Rev* 2007; **17:** 413–425.

25. Ben-Menachem E. Weight issues for people with epilepsy – a review. *Epilepsia* 2007; **48**(Suppl. 9)**:** 42–45.
26. Zaccara G, Franciotta D, Perucca E. Idiosyncratic adverse reactions to antiepileptic drugs. *Epilepsia* 2007; **48:** 1223–1244.
27. Zaccara G, Perucca P, Gangemi PF. The adverse event profile of pregabalin across different disorders: a meta-analysis. *Eur J Clin Pharmacol* 2012; **68:** 903–912.
28. Novy J, Patsalos PN, Sander JW, Sisodiya SM. Lacosamide neurotoxicity associated with concomitant use of sodium channel-blocking antiepileptic drugs: a pharmacodynamic interaction? *Epilepsy Behav* 2011; **20:** 20–23.
29. Stephen LJ, Kelly K, Parker P, Brodie MJ. Adjunctive lacosamide in clinical practice: sodium blockade with a difference? *Epilepsy Behav* 2011; **22:** 499–504.
30. Ryvlin P, Perucca E, Rheims S. Pregabalin for the management of partial epilepsy. *Neuropsychiatr Dis Treat* 2008; **4:** 1211–1224.

Appendix 1

Adverse events included in the meta-analysis in order of their frequency in subjects treated with the active drug (all doses)

Adverse event	No. of studies	Patients with the AE/patients treated with the active drug	Patients with the AE/ patients treated with placebo	RD (99%) and I^2
Dizziness	5	328/1178	49/503	**0.21 [0.02, 0.40], $P = 0.004$** I^2 = 92% random
Ataxia	2	36/788	2/306	0.05 [−0.06, 0.16], $P = 0.023$ I^2 = 93% random
Fall	3	52/714	13/323	0.03 [−0.00, 0.07], $P = 0.02$ I^2 = 0% fixed
Somnolence	5	170/1178	37/503	**0.08 [−0.00, 0.16], $P = 0.01$** I^2 = 72% random
Fatigue	4	77/911	21/382	0.04 [−0.0, 0.07], $P = 0.02$ I^2 = 0% fixed
Irritability	1	29/267	6/121	0.06 [−0.01, 0.13], $P = 0.03$
Headache	5	135/1178	58/503	0.00 [−0.04, 0.04], $P = 0.99$ I^2 = 0% fixed
Seizure worsening	3	93/1038	59/442	**−0.05 [−0.09, 0.00], $P = 0.01$** I^2 = 0% fixed
Akinesia	1	13/197	2/66	0.04 [−0.05, 0.12], $P = 0.29$
Weight increase	3	150/1038	31/442	**0.08 [0.03, 0.12], $P < 0.001$** I^2 = 0% fixed
Rash	2	18/771	4/321	0.01 [−0.01, 0.03], $P = 0.15$ I^2 = 0% Fixed
Diarrhea	2	9/235	2/76	0.01 [−0.05, 0.07], $P = 0.66$ I^2 = 0% fixed
Respiratory infection	4	56/858	14/312	0.02 [−0.06, 0.10], $P = 0.49$ I^2 = 73% random
Urinary infection	1	6/197	4/66	−0.03 [−0.13, 0.06], $P = 0.36$
Contusion	1	7/102	2/51	0.03 [−0.07, 0.12], $P = 0.43$

Significant results are in bold.

Appendix 2

Adverse events included in the meta-analysis at each daily dose

	2 mg/day	4 mg/day	8 mg/day	12 mg/day
Dizziness	0.00 [−0.12, 0.12][a]	0.04 [−0.04, 0.12] I^2 = 31%	**0.23 [0.16, 0.29]** $\boldsymbol{I^2 = 40\%}$	**0.35 [0.26, 0.44]** I^2 = 52%
Ataxia	−0.01 [−0.05, 0.04][a]	0.00 [−0.05, 0.05][a]	**0.05 [0.01, 0.09]** I^2 = 0%	**0.12 [0.07, 0.17]**[a]
Fall	0.02 [−0.05, 0.08][b]	na	0.03 [−0.03, 0.10][a]	0.06 [−0.01, 0.11][a]
Somnolence	0.06 [−0.02, 0.13][a]	0.01 [−0.05, 0.08] I^2 = 0	**0.08 [0.03, 0.14]** I^2 = 0%	0.15 [−0.02, 0.31] $\boldsymbol{I^2 = 76\%}$
Fatigue	0.02 [−0.33, 0.37][a]	0.04 [−0.02, 0.09] I^2 = 8%	0.04 [−0.02, 0.09] I^2 = 0%	0.06 [−0.04, 0.17] I^2 = 38%
Irritability	na	na	0.03 [−0.05, 0.10][a]	**0.09 [0.02, 0.16]**[a]
Headache	0.00 [−0.08, 0.08][a]	0.01 [−0.06, 0.08] I^2 = 0%	−0.00 [−0.06, 0.05] I^2 = 5%	0.01 [−0.07, 0.08] I^2 = 0%
Seizure worsening	−0.04 [−0.12, 0.04][a]	−0.07 [−0.15, 0.01][a]	−0.05 [−0.10, 0.00] I^2 = 0%	−0.03 [−0.10, 0.04] I^2 = 0%
Akinesia	0.02 [−0.07, 0.10][b]	na	na	na
Weight increase	na	na	na	na
Rash	na	na	0.03 [−0.02, 0.09][a]	0.01 [−0.01, 0.03][a]
Diarrhea	0.03 [−0.02, 0.08][b]	na	na	0.01 [−0.04, 0.05][a]
Respiratory infection	0.05 [−0.00, 0.11] I^2 = 0%	−0.02 [−0.20, 0.16] I^2 = 86%	−0.01 [−0.06, 0.05][a]	0.01 [−0.03, 0.06][a]
Urinary infection	−0.04 [−0.15, 0.06][b]	na	na	na
Contusion	na	0.03 [−0.07, 0.12][a]	na	na

Significant results are in bold; na, not available. [a]One study in epileptic patients; [b]Parkinson's.