Article:
Shah, E., Reuber, M., Goulding, P. et al. (3 more authors) (2016) Clinical experience with adjunctive perampanel in adult patients with uncontrolled epilepsy: A UK and Ireland multicentre study. Seizure - European Journal of Epilepsy , 34. pp. 1-5. ISSN 1059-1311

https://doi.org/10.1016/j.seizure.2015.10.017

Clinical experience with adjunctive perampanel in adult patients with uncontrolled epilepsy: A UK and Ireland multicentre study.

Authors: Emily Shah[a], Markus Reuber[b], Peter Goulding[c], Cora Flynn[d], Norman Delanty[d], Steven Kemp[a].

[a] Department of Clinical and Health Psychology, St James's University Hospital, Leeds, LS9 7TF

[b] Department of Neurology, Royal Hallamshire Hospital, Sheffield, S10 2JF

[c] Department of Neurology, Leeds General Infirmary, Leeds, LS1 3EX

[d] Department of Neurology, Beaumont Hospital, Dublin, Dublin 9

Corresponding author: Emily Shah, Department of Clinical and Health Psychology, St James's University Hospital, Leeds Teaching Hospitals NHS Trust, Beckett Street, Leeds, LS9 7TF, UK. Telephone +44 113 206 5897

E-mail address: emilyshah@nhs.net

Abstract

Purpose: To derive clinically useful information about the efficacy and tolerability of adjunctive treatment with perampanel for refractory epilepsy in an outpatient setting.

Methods: We pooled retrospective data from the case notes of adult patients with refractory epilepsy that had been prescribed perampanel from 18 hospitals throughout the UK and Ireland.

Results: Three hundred and ten patients were included (mean age 40.9 [SD= 12.0], 50% women, 27.7% with learning disability). The mean duration of epilepsy for these patients was 26.7 years (range 2 – 67 years, SD= 13.5) and 91.9% were taking two or more anti-epileptic drugs at the time of perampanel initiation. Mean retention time was 6.9 months (range 1 day- 22.3 months, SD= 4.5). The retention rates were 86% at 3 months, 71% at 6 months, 47.6% at 12 months and 27% at 18 months. At the final follow-up a >50% reduction in seizure frequency was reached in 57.5% of those with tonic-clonic seizures, 57.4% of those with complex partial seizures and 43.8% of those with simple partial seizures. Eleven patients (3.5%) became seizure free. Two hundred and nine patients (67.4%) experienced adverse effects and of these 67% withdrew treatment due to their effects. The most common were sedation, behaviour/mood disturbance, dizziness, and unsteadiness.

Conclusion
Perampanel appears to be a safe and effective antiepileptic drug when used as adjunctive therapy in patients with uncontrolled partial epilepsy although few patients in the refractory population described achieved complete seizure control. Long-term retention rates were slightly lower than reported rates for other anti-epileptic drugs, although this may be partially explained by the highly refractory nature of this study's population. It seems similarly safe and effective in the subgroup of these patients with learning disability. Monitoring for adverse effects on energy levels, mood and behaviour is recommended.

Keywords
Epilepsy; Perampanel; Antiepileptic drug; Responder rate; Tolerability; Efficacy

Introduction

Perampanel is a new first-in-class non-competitive AMPA (a-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) antagonist licensed as an adjunctive treatment for partial-onset seizures in patients with refractory epilepsy aged twelve or above. It was licensed for use in the UK in September 2012 and in the US in October 2012.

Three randomised, multi-centre, double-blind, placebo-controlled trials of perampanel have demonstrated a major reduction in seizure frequency at four different doses, with >50% responder rates varying from 20.6% at 2mg/day, 28.5% at 4mg/day, 33.3%-37.6% at 8mg/day and 33.9%-36.1% at 12mg/day. In these studies, the placebo responder rates varied from 14.7%-26.4% (French et al., 2012; 2013; Krauss et al, 2012). Two post-marketing studies have been published, also showing high response rate and good tolerability (Steinhoff et al., 2014a; 2014b). Here, we present the clinical experience with perampanel in a large patient cohort from fifteen centres around the UK and Ireland.

Method

Data were obtained from case notes from eighteen secondary and tertiary epilepsy centres in the UK and Ireland between February 2014 and December 2014. Cases were identified from the electronic medical and pharmacy records of patients who had been prescribed perampanel. Those included were adults attending their usual epilepsy clinic and the decision to use perampanel was based upon the treating clinician's recommendation. Data were obtained by reviewing medical notes and clinic letters, then entered on to an electronic database.

All adult patients who had been prescribed perampanel were included, irrespective of the length of time they took the drug. The only exclusion criterion was a lack of follow-up. Data included: patient demographics, clinical features, history and treatment details; such as concomitant antiepileptic drugs (AEDs), maximum dosage of perampanel, length of exposure to perampanel, adverse effects and withdrawal rates.

Patients were typically seen in clinic every three to six months. Frequencies of seizures were obtained from medical notes or seizure diaries when available. Clinicians usually documented the number of seizures each month or provided a monthly average since their previous review of the patient. If numerical recordings of seizure frequency were not provided yet the clinician felt improvement had been achieved, patients were recorded as demonstrating a less than 50% reduction in seizure frequency.

Outcomes following treatment were defined as follows:

- Seizure free: a terminal remission of seizures for three months or more.
- 50% or more reduction: a reduction in seizure frequency of 50% or more in the last three months of follow-up compared with a pre-treatment three month baseline. Only cases where seizure frequency was accurately recorded were placed in this group.

- Less than 50% reduction: a reduction of between 1% and 49% in seizure frequency in the last three months of follow-up compared to the three month baseline period. A minority of cases deemed to show improvement but lacking accurate frequency data were also placed in this group.
- No reduction or worsening of seizures: this was based either on numerically recorded frequencies or on qualitative clinical impression.

Two response rates were determined, the first based upon the seizure frequency in the first three months after commencing perampanel and the second upon the three months prior to last follow-up. Those with less than three months exposure were excluded from the first response rate. The second response rate was only determined for patients with a minimum of six months follow-up. Inferential statistical tests were used to describe the dataset. Retention time on perampanel was estimated using Kaplan-Meier survival curves and compared using a Tarone-West test.

Results

Case notes were reviewed for 522 patients. A total of 310 patients (155 female) undergoing perampanel treatment who had at least one follow-up were included in analysis. 230 patients were classified as having symptomatic or cryptogenic partial epilepsy, 15 symptomatic generalised epilepsy, 8 idiopathic generalised epilepsy and 57 patients were either unclassified or their form of epilepsy was unknown. The following analyses were ran separately for those patients with partial epilepsy, however, as no differences were apparent between these patients and the sample as whole, data for the overall cohort have been reported here (table 1).

Ages of the patients ranged between 18 and 75 years old (mean 40.9, SD=12.0). The mean duration of epilepsy for this patient group was 26.7 years (range 2-67 years, SD=13.4) and mean number of concomitant anti-epileptic drugs was 2.6 (range 0-6, SD= 0.9). 91.9% of these patients were taking two or more AEDs at the time of perampanel initiation.

Table 1. Clinical features of all 310 patients that underwent perampanel treatment

Characteristic		Total number/ Number with ≥6 months FU
Age	18-30	74/33
	31-50	166/87
	51-75	70/41
Learning Disability	Yes	86/40
	No	177/96
Gender	Male	155/81
	Female	155/80
Syndrome	SPE/CPE	230/122
	IGE	8/6
	SGE	15/7
	U	57/14
Concomitant AEDS	1	22/13
	2	131/66
	>3	154/80
Length of treatment (months)	<3.0	60
	3.0-5.9	87

	6.0-8.9	71
	9.0-11.9	47
	>12.0	40

Titration

The initial starting dose was typically 2mg. This was then titrated up by a further 2mg/2 weeks in 64.2% of patients without LD, although these increments varied between 2mg/1 week - 2mg/6 week according to the judgement of the clinician (table 2). The mean maximum dose reached was 7.12mg (SD= 2.9), ranging between 2mg and 16mg. There was a trend towards a significant difference between the length of treatment in the fast and slow titration groups; t(150)=1.68, p= 0.09, 95% CI [-0.30,3.60]. Fisher's exact test revealed a significant difference in the prevalence of dizziness in the fast and slow groups; p= 0.025.

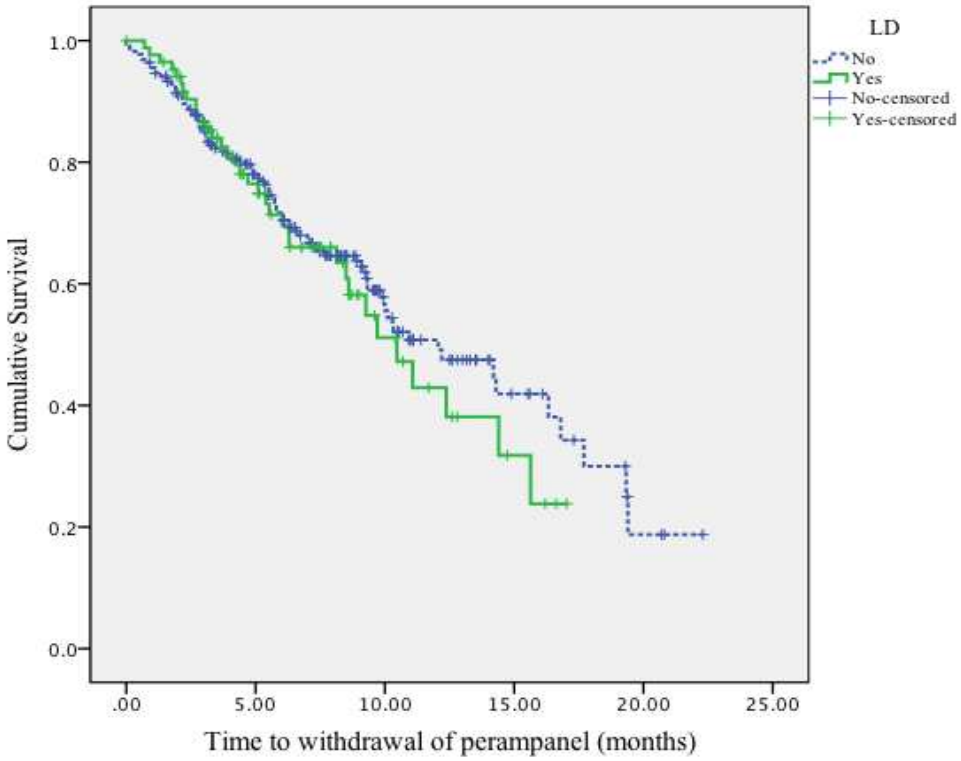
Table 2. Impact of titration rate on patients without learning disability (LD)

	≤2mg/2 weeks	>2mg/2 weeks
No. of patients	131	22
Mean max dose (range, SD)	7.1 (2-12, 2.9)	6.6 (2-12, 2.8)
No. experienced AEs (%[95%CI])	94 (75[66.9-82.0])	13 (61.9[40.8-79.3])
Sedation (%[CI])	34 (27[20.3-35.9])	6 (30[14.3-52.1])
Behavioural/Mood disturbance (%[CI])	26 (21[14.7-29.0])	3 (15[4.1-35.5])
Unsteadiness (%[CI])	21 (16.9[11.3-24.6])	1 (5[<0.1-25.4])
Dizziness (%[CI])	25 (20.1[14.0-28.1])	0
Mean length of treatment (range, SD)	7.1 (0.1-19.4, 4.0)	5.5 (0.9-13, 4.4)
No. withdrew (%[CI])	55 (42[33.6-50.2])	4 (18[6.7-39.1]
No. withdrew due to adverse effects (%[CI])	37 (29.1[22.0-37.6])	3 (13.6[3.9-34.2])
Seizure free	7	1
>50% reduction TCS at final FU (%[CI])	25 (56.8[39.2-66.7])	4 (50[21.5-78.5])
>50% reduction CPS at final FU (%[CI])	39 (47[36.6-57.6])	4 (28.5[1.5-12.1])

Follow-up and Outcome

The duration of perampanel treatment ranged from one day to 22.3 months with a mean of 6.9 months (SD= 4.6). The probability of remaining on treatment with perampanel was assessed using Kaplan-Meier graphs (figure 1). The probability of remaining on perampanel treatment was 86% at three months, 71% at six months, 47.6% at twelve months and 27% at eighteen months.

Figure 1. Kaplan-Meier survival curve of perampanel retention times for all patients with partial onset epilepsy



The first outcome measure was taken at three months following commencement of perampanel. Of the total 310 patients that were initiated on the drug, 42 (13.5%) had already discontinued treatment, predominantly due to adverse effects (AEs) (81%). Twenty three patients were still on the treatment regime, but had less than three months of exposure by the end of the study. This left 250 patients able to be included in analysis of the first follow-up (table 3).

Table 3. Seizure frequency responses at three month follow-up

Seizure Type (N)	Patients with at least 3 months of follow up data, N (%, [95% CI])			
	≥50% seizure reduction	<50% seizure reduction	No response	Increase in seizure frequency
TCS (77)	28 (36.4[26.5-47.5])	4 (5.2[1.6-13.0])	27 (35.1[25.3-46.2])	18 (23.4[15.3-34.0])
CPS (101)	48 (52.2[38.1-57.2])	24 (24.0[16.5-33.0])	14 (13.9[8.3-22.1])	15 (14.9[9.1-23.2])
SPS (28)	11 (45.8[23.5-57.6])	8 (28.6[15.1-47.2])	7 (25[12.4-43.6])	2 (7.1[0.9-23.7])

Tonic-clonic seizures (TCS), Complex partial seizures (CPS), Simple partial seizures (SPS)

The second outcome was based upon seizure frequency during the last three months of follow-up as compared to frequency during the three month baseline period. One hundred and sixty one patients were recorded with six months or longer duration of treatment (table 4). Of these, 45 had discontinued treatment mostly due to lack of efficacy (62.2%) or intolerable AEs (57.8%). The mean duration of treatment at final

follow-up was 10.2 months (range 6-22.3 months, SD= 4.2). Nine patients (5.6%) were seizure free for a minimum of three months at final follow up.

Table 4. Seizure frequency responses during the three months before last follow-up

Seizure Type	Patients with at least 6 months of follow up data, N (%[95%CI])			
	≥50% seizure reduction	<50% seizure reduction	No response	Increase in seizure frequency
TCS (73)	42 (57.5[46.1-68.2])	3 (4.1[0.9-11.9])	17 (23.3[15.0-34.3])	11 (15.1[8.5-25.2])
CPS (129)	74 (57.4[48.7-65.6])	14 (10.1[6.5-17.5])	26 (20.2[14.1-28.0])	15 (11.6[7.1-18.4])
SPS (32)	14 (43.8[28.2-60.7])	5 (15.6[6.4-32.2])	11 (34.4[20.3-51.8])	2 (6.3[0.7-21.2])

Adverse Effects

Adverse effects were experienced by 209 (67.4%) of all 310 patients (table 5). The mean retention in these patients was 6.6 months (SD= 4.4). Of those 209 patients that experienced AEs, 83 (39.7%) withdrew perampanel predominantly due to intolerable AEs, 26 (12.4%) withdrew due to lack of treatment efficacy and fourteen (6.7%) due to an increase in seizure frequency. In eleven (5.3%) of these patients, the reason for withdrawal was not stated. Amongst those 83 patients that withdrew treatment due to intolerable side effects, fourteen also experienced a lack of efficacy and eight experienced increased seizure frequency.

The most common AEs experienced by patients were sedation (23.8%), behavioural/mood disturbance (22.6%), dizziness (13.5%), unsteadiness (11.3%) and increase in seizure frequency (7.1%). When the behavioural/mood disturbance category was explored further, 18.1% of patients were found to have experienced irritability/aggression and 7.7% experienced mood change/anxiety. Four patients reported suicidal ideation; two of these patients went on to attempt and one patient died by suicide.

Table 5. Incidence and nature of adverse effects

Adverse Effect	Number of patients (%)
Sedation	74 (23.8)
Behaviour/Mood disturbance	70 (22.6)
Dizziness	42 (13.6)
Unsteadiness	35 (11.3)
Increase in seizure frequency	22 (7.1)
Weight change	16 (5.2)
Headache	13 (4.2)
Nausea	12 (3.9)
Sleep disturbance	9 (2.9)
Confusion/Mental slowing	8 (2.6)
Double vision	7 (2.3)
Limb/Joint pain	7 (2.3)
Slurred speech	5 (1.6)

Gastrointestinal disturbance	5 (1.6)
Memory problems	4 (1.3)
Skin irritation	3 (1.0)
Depersonalisation	3 (1.0)
Breathlessness	3 (1.0)
Tremor	1 (0.3)
Hallucinations	1 (0.3)

Learning Disability

Learning disability was present in 86 patients (27.7%), 47 of whom were male. These patients had epilepsy for a mean of 27.4 years (range 3-53 years, SD= 13.5). They were taking a mean of 2.9 other AEDs (range 1-6, SD= 2.8). Length of perampanel treatment for those with LD ranged from 0.1 – 17 months (mean 6.3 months, SD= 4.1). Patients with LD tended to be titrated up more slowly than those without; 28.5% of those with LD increased their dose by 2mg/3 weeks or longer whereas only 14.3% of patient without LD had the same schedule.

A similar prevalence of AEs was recorded in patients with LD (63%) as in those without LD (67.4%). The most commonly reported AEs were behaviour/mood disturbance (29.1%), sedation (23.3%) and dizziness (8.1%). The likelihood of discontinuing treatment was similar for both groups (40% of those with LD/ 39.5% of those without LD).

The probability of LD patients remaining on perampanel treatment was 85.3% at three months, 69.6% at six months and 38.1% at twelve months (figure 1). A Tarone-Ware test was selected due to the mildly crossing survival curves. This showed that there was no difference between the survival curves for those with and those without LD ($p = 0.741$).

In terms of efficacy, perampanel appeared to be broadly similar in patients with LD as without. Of those whom experienced generalised seizures 42.3% had a ≥50% seizure reduction and 43.6% of those with complex partial seizures experienced a ≥50% reduction in seizure frequency. Given the difficulties in accurate reporting of simple partial seizures in this patient group, data for this seizure type have not been included. Two patients with LD became completely seizure free.

Idiopathic generalised epilepsy

Eight patients in the sample had idiopathic generalised epilepsy (three males). These patients had epilepsy for a mean of 28 years (range 17-48 years, SD= 13.7) and were taking a mean of 2.9 concomitant AEDs (range 2-4, SD= 0.9). The duration of perampanel treatment for this group of patients ranged from 1.97 to 11.1 months. No patients withdrew from treatment, although one patient died due to SUDEP. Two patients reported AEs, these being sedation and dizziness. Two patients reported a ≥50% reduction in seizure frequency, four reported <50% response, one patient did not respond to treatment and one patient had an increase in seizure frequency.

Discussion

This study is reflective of the experience of perampanel treatment in 310 patients with uncontrolled epilepsy. As data were collated from eighteen outpatient centres throughout the UK and Ireland, it provides a good representation of the use of perampanel throughout these countries, and is the largest observational study of perampanel in hospital-based clinics to date. The sample of patients reported here are a highly refractory group, as can be seen by the long durations of epilepsy, high usage of concomitant AEDs and large proportion of patients with LD. Given the highly refractory nature of many of the patients included, this study also provided an opportunity to review the effectiveness of perampanel for non-licensed indications. There was no major difference in efficacy, tolerability or safety in the partial-onset sub-group as opposed to the population as a whole. Whilst more detailed investigation of these groups is recommended, initial appearances suggest that perampanel may be effective in groups broader than its licensed indications.

This study differs from other reports of perampanel in that outcomes were assessed using retention time and that all adult patients were included, regardless of seizure type. As this study was a retrospective chart review, it was not always possible to determine seizure frequency outcome from numerical data. Only those with recorded frequency figures were included as >50% responders; those felt by their clinicians to have shown qualitative improvement were categorised with the <50% responders. It is also possible that this study underestimates the adverse effects of perampanel, however, as all patients were monitored by specialist epilepsy services it is unlikely that major events were unrecorded. Whilst these patients likely benefitted from a close degree of monitoring, it is a limitation of this study that all patients were sourced from hospital-based clinics as this may restrict the generalisability of findings from patients in different settings.

There are obvious difficulties in comparison of retention rates between different drugs, not least given that the population studied here was highly refractory. Here, the one year retention rate of 47.6% is broadly in keeping with that of other newer AEDs. The one-year retention rate for lacosamide is 68% (Flores et al., 2012), for topiramate 60%, for lamotrigine 75% and for gabapentin 53% (Marson et al., 2007). There is, thus far, little long-term retention data available from clinical samples for perampanel. However, marketing studies have reported 38.4% remained on perampanel after 4 years (Rektor et al., 2012), which sits concordantly with long-term retention of other newer AEDs; 30% topiramate, 29% lamotrigine and <10% gabapentin (Lhatoo et al, 2000).

Here, it was found that 67.4% of patients experienced AEs, which lies between levels reported in both pooled analysis of the three phase III studies (77%) (Steinhoff et al., 2013) and the other clinical sample (52.0%) (Steinhoff et al., 2014b). It is likely that much of this discrepancy can be ascribed to the differences between the prospective and retrospective designs used. Data from the phase III trials describes how 12.4% of those that experienced AEs withdrew perampanel treatment because of this. The present study found this figure to be considerably higher, with 39.7% of patients experiencing AEs subsequently withdrawing treatment. The present study found that the most common AEs reported were sedation (23.8%), behaviour/mood disturbance (22.6%), dizziness (13.6%), and unsteadiness (11.3%). It is difficult directly to compare the prevalence of individual AEs to those reported in the marketing studies

as the current study does not differentiate between AEs reported at each dosage level, although the majority of the more common AEs are the same. Certainly, looking at the clinical study, levels of sedation (24.6%) and dizziness (19.6%) were very similar to those reported here.

A notable exception to this is that considerably higher levels of behaviour/mood disturbance were reported in this study than others. Steinhoff's (2014b) clinical study found aggression and irritability in 4.9% of patients and a pooled analysis of phase III studies reported aggression in just 1.6% (LoPresti et al., 2014), which stands in contrast to the irritability/aggression reported in the present sample (18.1%). Four patients in the study experience suicidal ideation, with one patient later dying due to suicide; details of two of these patients are available elsewhere in the literature (Coyle et al., 2014). Limitations of retrospective design make it difficult assess reasons for the higher incidence of behaviour and mood related AEs in this sample, nonetheless, it would seem appropriate to monitor patients for neuropsychiatric AEs.

From comparing the impact of different titration rates on patient experience, it would seem that by titrating up at a faster rate patients were only slightly more likely to experience AEs, however, they were considerably more likely to withdraw treatment because of them. Whilst inferences can be drawn from this are limited, a likely explanation would be that faster titration increased the intensity of AEs.

There is little in the current literature regarding perampanel use in those with LD, bar a case report concerning challenging behaviour (Dolton and Choudry, 2014). In the present sample, patients with LD were no more likely to withdraw from perampanel treatment than those without; the incidence of AEs was also broadly similar between the two groups. There was no difference in the likelihood of remaining of perampanel between those with and without LD. Thus, whilst further investigation within this sub-population would be beneficial, initial appearances are that perampanel is well tolerated in those with LD.

Conclusion

Adjunctive therapy with perampanel appears to be well-tolerated and effective for treating partial and generalised seizures in patients with difficult-to-treat epilepsy. Long-term retention rates were slightly lower than reported rates for other AEDs, although this may be partially explained by the highly refractory nature of this study's population. It seems similarly safe and effective in the subgroup of these patients with LD. Monitoring for adverse effects on energy levels, mood and behaviour is recommended.

Acknowledgements

The authors would like to express their gratitude to the following for facilitating collection of patient data:
Dr Dougall McCorry, Birmingham; Dr Stefan Schumacher/Dr Ayse Turan, Bolton; Dr Julia Aram, Brighton; Niamh Colleran/Dr Michael Hennessy, Galway; Lucy Murena/Dr Mark Lawden, Leicester; Dr Udo Weishmann, Liverpool; Hannah Worthington/ Dr Andrew Kelso, St Bart's, London; Dr Simon Taggart, Middlesbrough; Dr Margaret Jackson, Newcastle; Melesina Goodwin/Dr Paul Davies,

Northampton; Dr Martin Sadler, Plymouth; Lesley North/ Dr Hedley Emsley, Preston; Helen Coyle/Dr Rajiv Mohanraj/Dr Paul Cooper, Salford; Phil Tittensor/Dr Beatrice Summers, Stafford; Mary Parrett/Dr Brendan McLean, Truro.

Conflict of Interest Statement

Eisai provided an educational grant to fund the broad-ranging post of a psychology graduate (ES) who worked on this and other non-medical projects. SK, MR, PG, CF and ND have received educational grants from Eisai and other pharmaceutical companies. MR has received speaker and advisory board payments by Eisai and other pharmaceutical companies. This study was led by non-prescribers.

References

Coyle, H., Clough, P., Cooper, P., & Mohanraj, R. (2014). Clinical experience with perampanel: Focus on psychiatric adverse effects. *Epilepsy & Behavior : E&B*, *41*, 193–6. doi:10.1016/j.yebeh.2014.09.072

Dolton, E., & Choudry, A. (2014). Case Report Perampanel and Challenging Behaviour in Intellectual Disability and Epilepsy : A Management Dilemma, *2014*, 3–6.

Flores, L., Kemp, S., Colbeck, K., Moran, N., Quirk, J., Ramkolea, P., von Oertzen, T., Nashef, L., Richardson, M., Goulding, P. & Elwes, R. (2012). Clinical experience with oral lacosamide as adjunctive therapy in adult patients with uncontrolled epilepsy: a multicentre study in epilepsy clinics in the United Kingdom (UK). *Seizure*, *21*(7), 512–7. doi:10.1016/j.seizure.2012.05.005

French, J. A., Krauss, G. L., Biton, V., Squillacote, D., Yang, H., Laurenza, A., Kumar, D. & Rogawski, M. A. (2012). Adjunctive perampanel for refractory partial-onset seizures: Randomized phase III study 304 . *Neurology* , *79* (6), 589–596. doi:10.1212/WNL.0b013e3182635735

French, J. A., Krauss, G. L., Steinhoff, B. J., Squillacote, D., Yang, H., Kumar, D., & Laurenza, A. (2013). Evaluation of adjunctive perampanel in patients with refractory partial-onset seizures: Results of randomized global phase III study 305. *Epilepsia*, *54*(1), 117–125. doi:10.1111/j.1528-1167.2012.03638.x

Krauss, G. L., Serratosa, J. M., Villanueva, V., Endziniene, M., Hong, Z., French, J., Yang, H., Squillacote, D., Edwards, H., Zhu, J. & Laurenza, A. (2012). Randomized phase III study 306: Adjunctive perampanel for refractory partial-onset seizures . *Neurology* , *78* (18), 1408–1415. doi:10.1212/WNL.0b013e318254473a

Lhatoo, S. D.; Wong, I. C. K; Polizzi, G.; Sander, J. W. A. S. (2000). Long-Term Retention Rates of Lamotrigine, Gabapentin, and Topiramate in Chronic Epilepsy. *Epilepsia*, *41*(12), 1592–1596. doi:10.1111/j.1499-1654.2000.001592.x

LoPresti, A., Ettinger, A., Yang, H., Williams, B., Zhou, S., Fain, R., & Laurenza, A. (2014). Review of Aggression in Adults and Adolescents in Perampanel Phase III Epilepsy Clinical Trials (P3.009). *Neurology* , *82* (10 Supplement), P3.009–P3.009. Retrieved from http://www.neurology.org/content/82/10_Supplement/P3.009.abstract

Marson, A. G., Al-Kharusi, A. M., Alwaidh, M., Appleton, R., Baker, G. A., Chadwick, D. W., ... & SANAD Study Group. (2007). The SANAD study of effectiveness of carbamazepine, gabapentin, lamotrigine, oxcarbazepine, or topiramate for treatment of partial epilepsy: an unblinded randomised controlled trial. The Lancet, 369(9566), 1000-1015.

Rektor, I., Krauss, G. L., Bar, M., Biton, V., Klapper, J. A., Vaiciene-Magistris, N., Kuba, R., Squillacote, D., Gee, M. & Kumar, D. (2012). Perampanel Study 207: long-term open-label evaluation in patients with epilepsy. *Acta Neurologica Scandinavica*, *126*(4), 263–269. doi:10.1111/ane.12001

Steinhoff, B. J., Bacher, M., Bast, T., Kornmeier, R., Kurth, C., Scholly, J., Staack, M. & Wisniewski, I. (2014a). First clinical experiences with perampanel—The Kork experience in 74 patients. *Epilepsia*, *55*, 16–18. doi:10.1111/epi.12492

Steinhoff, B. J., Ben-Menachem, E., Ryvlin, P., Shorvon, S., Kramer, L., Satlin, A., Squillacote, D., Yang, H., Zhu, J. & Laurenza, A. (2013). Efficacy and safety of adjunctive perampanel for the treatment of refractory partial seizures: A pooled analysis of three phase III studies. *Epilepsia*, *54*(8), 1481–1489. doi:10.1111/epi.12212

Steinhoff, B. J., Hamer, H., Trinka, E., Schulze-Bonhage, A., Bien, C., Mayer, T., Baumgartner, C., Lerche, H. & Noachtar, S. (2014b). A multicenter survey of clinical experiences with perampanel in real life in Germany and Austria. *Epilepsy Research*, *108*(5), 986–8. doi:10.1016/j.eplepsyres.2014.03.015