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Add-on treatment with pregabalin for partial seizures with or without generalisation: Pooled data analysis of four randomised placebo-controlled trials

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ABSTRACT

Pooled data analysis was performed on individual data from 807 pregabalin- and 367 placebo-treated patients with treatment-resistant partial seizures with or without generalization from four placebo-controlled studies evaluating the short-term efficacy, safety and tolerability of add-on pregabalin 150–600 mg/day. Short-term add-on treatment with pregabalin resulted in statistically significant reductions from baseline in seizure frequency and statistically significantly higher responder rates over placebo (OR 5.93 [95% CI 4.10, 8.57]). Its overall tolerability was good, with an OR of withdrawing from the study due to any reason of 1.71 (95% CIs 1.24, 2.35). The most commonly reported AEs were dizziness and somnolence, however, they were most pronounced during the first week of treatment, followed by a sharp fall in incidences across all dosing groups to <5% from Week 2 and onwards. Weight gain, reported by 5.4–17.1% of patients across pregabalin dosing groups, appeared to be dose-related, but it led to study withdrawal in only 0.74% (6 out of 810) pregabalin-treated subjects. Our analysis suggests that pregabalin has a robust efficacy and good tolerability demonstrated in a study population more treatment-refractory compared to the one enrolled into short-term studies of other new antiepileptic drugs.

Introduction

Pregabalin is an alfa-2-delta (α_2-δ) ligand with anticonvulsant, analgesic and antianxiety properties. It is thought that pregabalin binds to the $\alpha_2\delta$ protein subunit, consequently producing allosteric modulation of p and Q-type voltage gated calcium channels that results in reduced excitatory neurotransmitter release.[1,2] Pregabalin does not affect GABAergic neurotransmission: unlike benzodiazepines and barbiturates, it does not augment GABAergic neurotransmission, nor has any GABA-reuptake inhibiting effects like tiagabine, or GABA-transaminase inhibiting effects like vigabatrin. Furthermore, pregabalin treatment, at concentrations that are therapeutically relevant, subtly but significantly reduced the emptying of neurotransmitter vesicles from presynaptic sites in living neurons in the rat hippocampus.[3]

This apparently occurs by binding of pregabalin to $\alpha_2\delta$ subunits, and possibly accounting for its actions *in vivo* to reduce neuronal excitability and seizures.[4] Several studies indicate that the pharmacology of pregabalin requires binding to $\alpha_2\delta$ subunits, including structure–activity analyses of compounds binding to $\alpha_2\delta$ subunits and pharmacology in mice deficient in binding at the $\alpha_2\delta$ Type 1 protein (for review, see Taylor et al.).[4] The preclinical findings to date are consistent with a proposed mechanism that may entail reduction of abnormal neuronal excitability through reduced neurotransmitter release.[4] Pregabalin was found to be effective against seizures in a wide range of experimental animal models, as well as in preventing seizures in kindled rats or genetically susceptible mice.[2,4–6] A recent study in mutant mice containing a single-point mutation within the gene encoding a specific auxiliary subunit protein (α_2-∂-1) of voltage-dependent calcium channels conclusively demonstrated that analgesic effects of pregabalin are mediated through this subunit, while establishing it as a therapeutic target for pain control.[7]

Across the dosing range of 150–600 mg/day, pregabalin has a linear pharmacokinetic profile with predictable oral absorption and ≥90% bioavailability.[8] In addition, it does not bind to plasma proteins, is not hepatically metabolised, is excreted virtually

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unchanged by the kidneys, and consequently has a low potential for drug–drug interactions.[2,9]

The efficacy of pregabalin as an add-on therapy for partial seizures with or without partial generalisation was evaluated in 4 short-term, randomised, placebo-controlled trials. The aim of the present analysis was to evaluate the overall efficacy, safety and tolerability of fixed-dose pregabalin (150–600 mg/day) as add-on therapy in partial seizures with or without generalisation in a large patient cohort formed by pooling individual patient data from 4 randomised placebo-controlled trials.

Materials and methods

Included studies

This analysis was based on pooled individual patient data from 3 fixed-dose, 12 week, multicenter, randomised, placebo-controlled trials,[10–12] one of which assessed efficacy and safety of b.i.d. and t.i.d. dosing regimens.[12] The fourth study was a placebo-controlled study with a fixed-dose 600 mg/day arm and flexible-dose arm.[13] Because the flexible-dose arm did not match with any arms in the other three trials (both in dose and conduct) it could not be included in the pooled data analyses but results from that individual study are described herein, and included in the seizure freedom calculations. The 50 mg/day b.i.d. arm of the French et al. study[10] was also excluded because it was not considered clinically effective. An overview of study details such as the numbers of participating centres and countries, dosages, subject numbers in the intent-to-treat (ITT) population, and dosing periods across included studies are presented in Table 1.[10–13] Results of all four studies included in this analysis are published in full.

Inclusion and exclusion criteria

Outpatients of either gender aged ≥18 years[11–13] or ≥12–70 years[10] with a history of being refractory to treatment with ≥2 marketed antiepileptic drugs at maximum tolerated dosages and inadequate seizure control while on 1–3 standard antiepileptic drugs were eligible for participation in the studies. The subjects had to have ≥6 partial seizures in the 8-week baseline period[10–12] or ≥4 partial seizures in the 6-week baseline period[13] prior to treatment, with no 4-week seizure free interval. Subjects with evidence or history of haematological, cardiovascular, renal, or hepatic disease, or significant psychiatric disorders were not eligible for participation in the studies. History of absence of seizures, treatable causes of seizures, diagnosis of Lennox Gastaut Syndrome or generalised tonic–clonic status epilepticus within the previous year also precluded participation. Usage of CNS active drugs was prohibited during the study, except for the current antiepileptic therapy or stable doses of antidepressant monotherapy for mild depression.

Other considerations

Protocols for all studies were approved by local ethical boards prior to commencement of any study-related activities. The studies were conducted in compliance with the Declaration of Helsinki and its later revisions, as well as Good Clinical Practice Guidelines. Randomisation was by computer generated code stratified by center using a block size of 6.[10–12] The Elger et al.[13] study used 1:2 randomisation and a block size of 5. All medication was prepared as identical looking capsules.

Assessments and outcome variables

The patients were required to maintain a daily seizure diary during the baseline and double-blind periods, with or without assistance. The frequency and types of seizures according to the International Classification of Epileptic Seizures[14] were determined by study personnel on the basis of diary entries, and from these the data percentage change in seizure frequency and responder rates were calculated. The percentage change was defined as the percentage change in seizure frequency during treatment compared with baseline over the last 28-day period, and was calculated using the following equation: percent change = $[(T - B)/B] \times 100$, where B is the baseline seizure frequency and T is the seizure frequency during treatment. However, seizure frequency data can be difficult to analyse because of high intra- and inter-subject variability, and the data's non-parametric nature.[15] Non-parametric analyses, such as the response ratio (RRatio) used as a primary outcome variable in placebo-controlled pregabalin trials, can be used to address this problem. The RRatio allows for percentage change in seizure rate from baseline that is normalised or symmetrised; its values always fall between −100 and +100, making it compatible with the parametric statistical data analysis.[16] RRatio was calculated using the equation $[(T - B)/(T + B)] \times 100$, where B is the patient's 28-day baseline seizure frequency and T is the seizure frequency during treatment. Negative RRatio values indicate a reduction in the seizure frequency from baseline. The RRatio range is between −100 (representing seizure freedom), via 0 (indicating no change), to +100 (indicating an approximately 6-fold increase in seizure frequency). The direct monotonic transformation of percent

Table 1
Overview of pooled clinical trials

Study	Number of patients in the ITT group					Data acquisition period (weeks)		
	Placebo	Pregabalin dose (mg/day)			Dosing schedule	Baseline	Titration period	Fixed-dose period
		150	300	600				
French[a] et al.[10]: 76 centers—USA, Canada	100	86	90	89	b.i.d.	8	–	12
Arroyo et al.[11]: 45 centers—Australia, Austria, Belgium, Finland, France, Germany, Italy, The Netherlands, UK, South Africa, Spain, Switzerland	96	99	–	92	t.i.d.	8	1	11
Elger et al.[13]: 53 centers—Austria, France, Germany, Italy, Lithuania, Spain, UK[b]	73	–	–	137	b.i.d.	6	–	12
Beydoun et al.[12]: 43 centers—USA, Canada	98	–	–	214	b.i.d./t.i.d.	8	1	11
Total	367	185	90	532				

Total pregabalin-treated subjects across three dosing groups 807; total subjects included in the analysis 1174.
[a] The subjects participating in the 50 mg/day b.i.d. arm were excluded from the analysis.
[b] Only subjects participating in the fixed-dose arm were included in the pooled data analysis.

Table 2
Group characteristics at baseline

Category	Overall groups[a]		Arroyo et al. (2004)		French et al. (2003)		Beydoun et al. (2005)		Elger et al. (2005)	
	Placebo, *n* = 367	All pregabalin, *n* = 807	Placebo, *n* = 96	All pregabalin, *n* = 191	Placebo, *n* = 100	All pregabalin, *n* = 265	Placebo, *n* = 98	All pregabalin, *n* = 214	Placebo, *n* = 73	All pregabalin, *n* = 137
Gender, *N* (%)										
Male	193 (52.6)	393 (48.7)	54 (56.3)	91 (47.6)	52 (52.0)	127 (47.9)	50 (51.0)	106 (49.5)	37 (50.7)	69 (50.4)
Female	174 (47.4)	414 (51.3)	42 (43.8)	100 (52.4)	48 (48.0)	138 (52.1)	48 (49.0)	108 (50.5)	36 (49.3)	68 (49.6)
Race, *N* (%)										
White	331 (90.2)	714 (88.5)	89 (92.7)	177 (92.7)	84 (84.0)	225 (84.9)	87 (88.8)	179 (83.6)	71 (97.3)	133 (97.1)
Black	12 (3.3)	33 (4.1)	1 (1.0)	4 (2.1)	7 (7.0)	19 (7.2)	4 (4.1)	9 (4.2)	0 (0.0)	1 (0.7)
Hispanic	13 (3.5)	41 (5.1)	2 (2.1)	3 (1.6)	7 (7.0)	16 (6.0)	3 (3.1)	20 (9.3)	1 (1.4)	2 (1.5)
Asian or Pacific islander	2 (0.5)	11 (1.4)	1 (1.0)	3 (1.6)	1 (1.0)	4 (1.5)	0 (0.0)	4 (1.9)	0 (0.0)	0 (0.0)
American Indian or Alaskan native	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)
Other	9 (2.5)	7 (0.9)	3 (3.1)	4 (2.1)	1 (1.0)	1 (0.4)	4 (4.1)	1 (0.5)	1 (1.4)	1 (0.7)
Age (years)										
Mean (S.D.)	39.3 (12.3)	38.3 (11.8)	38.1 (12.4)	36.5 (10.9)	39.5 (12.6)	37.7 (11.9)	39.6 (11.8)	38.8 (11.9)	40.3 (12.5)	41.1 (12.2)
Range	16–82	12–75	17–73[b]	18–70	16–73	12–75	17–82	18–75	18–65	18–71
Seizure aetiology, *N* (%)										
Birth compl.	22 (6.0)	57 (7.1)	13 (13.5)	14 (7.3)	3 (3.0)	18 (6.8)	4 (4.1)	13 (6.1)	2 (2.7)	12 (8.8)
Infections	32 (8.7)	99 (12.3)	8 (8.3)	19 (9.9)	8 (8.0)	35 (13.2)	11 (11.2)	35 (16.4)	5 (6.8)	10 (7.3)
Trauma	49 (13.4)	114 (14.1)	8 (8.3)	19 (9.9)	21 (21.0)	49 (18.5)	16 (16.3)	39 (18.2)	4 (5.5)	7 (5.1)
Family history	23 (6.3)	25 (6.4)	7 (7.3)	14 (7.3)	9 (9.0)	21 (7.9)	5 (5.1)	13 (6.1)	2 (2.7)	4 (2.9)
Structural abn.	16 (4.4)	26 (3.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	16 (21.9)	26 (19.0)
Unknown	177 (48.2)	395 (48.9)	45 (46.9)	101 (52.9)	43 (43.0)	126 (47.5)	54 (55.1)	101 (47.2)	35 (47.9)	67 (48.9)
Other	64 (17.4)	114 (14.1)	21 (21.9)	35 (18.3)	19 (19.0)	35 (13.2)	13 (13.3)	28 (13.1)	11 (15.1)	16 (11.7)
Duration of epilepsy (years)										
Mean (S.D.)	23.5 (13.6)	25.7 (12.9)	22.8 (13.6)	25.0 (12.1)	28.7 (14.0)	25.3 (13.3)	23.6 (11.9)	26.8 (13.0)	24.1 (15.6)	25.6 (13.3)
Median	22.1	25.1	21.3	24.1	22.7	25.3	22.6	26.2	24.0	26.0
Range	0.6–63.2	0.6–71.3	2.3–58.3	2.3–53.4	0.8–63.2	1.1–71.3	0.6–53.6	0.6–66.6	1.0–55.0	2.0–60.0
28-day seizure rate at baseline										
Mean (S.D.)	32.3 (178.7)	21.2 (34.8)	23.5 (41.1)	22.8 (34.0)	22.3 (42.1)	20.2 (30.2)	25.1 (37.8)	21.4 (40.1)	67.2 (392.7)	20.7 (35.5)
Median	9.5	10.0	9.3	12.0	9.5	9.0	11.0	10.0	8.7	10.0
Range	1.5–3356.7	2.00–435.8	1.5–327.5	2.0–219.0	2.69–311.0	2.00–253.5	2.5–245.0	2.00–435.7	2.67–3365.0	2.00–305.13
Concurrent AEDs, *N* (%)										
1 AED	97 (26.6)	205 (25.5)	23 (24.0)	30 (15.7)	26 (26.0)	79 (29.8)	30 (31.3)	61 (28.8)	18 (24.7)	35 (25.5)
2 AEDs	179 (49.0)	409 (50.8)	42 (43.8)	105 (55.0)	48 (48.0)	139 (52.5)	50 (52.2)	100 (47.2)	39 (53.4)	65 (47.4)
3 AEDs	85 (23.3)	184 (22.9)	30 (31.3)	55 (28.8)	24 (24.0)	47 (17.7)	16 (16.7)	48 (22.6)	15 (20.5)	34 (24.8)
4 AEDs	4 (1.1)	6 (0.7)	1 (1.0)	1 (0.5)	2 (2.0)	0 (0.0)	0 (0.0)	3 (1.4)	1 (1.4)	2 (1.5)
5 AEDs	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)

[a] ITT group.
[b] Two patients were aged 17 years; both patient and their legal representatives gave consent.

change from baseline to RRatio is demonstrated using the following equation:

$$\text{RRatio} = \frac{100 \times \text{percentage change}}{\text{percentage change} + 200}.$$

In addition, responder rates according to the regulatory requirement (i.e. the proportion of patients with ≥50% reduction in seizure frequency during treatment compared with baseline) and seizure freedom for the last 28 days in the study were calculated as well.[17] Incidences (overall and per reason) of patients prematurely withdrawing from the studies were calculated for each treatment group. Spontaneously reported or observed treatment-emergent adverse events (AEs) were recorded and classified using the COSTART IV dictionary.[18] Laboratory variables and vital signs were also measured during the studies.

Statistical analysis

All analyses were performed on the ITT group, which comprised randomised subjects who took at least one dose of blinded study medication. Group baseline characteristics, drop-out rates and incidences of AEs were tabulated and compared using descriptive statistics. The primary efficacy variable, the RRatios, were compared by using an analysis of variance (ANOVA) model with treatment and centre as the main effects and the rank of the RRatio as the dependent variable. The difference in unadjusted means on unranked raw RRatio data were summarised for each pairwise group overall, and by centres. A 95% CI for each difference in means was also computed. Generalisabity of the ANOVA model was examined. Consistency of treatment effects across centers was explored by adding a treatment-by-centre (interaction term) to the ANOVA model. To examine generalisability, the interaction term was tested at a significance level of 0.15. Seizure reduction based on percentage change from baseline was derived by transformation of the mean RRatio using the equation:

$$\frac{200 \times \text{RRatio}}{100 - \text{RRatio}}$$

Pairwise comparisons were performed by using a step-down procedure to maintain an overall 5% Type 1 error, and the pregabalin dose–response relationship was analysed by testing the linear contrasts from the main ANOVA model. The responder rates were compared using the Cochran–Mantel–Haenszel test adjusting for cluster. Odds ratios and corresponding 95% CIs for response with 150, 300, 600 mg/day and all doses of pregabalin were calculated. Odds ratios and 95% CIs for withdrawal from pregabalin vs. placebo treatment were also calculated. Percentages of AEs were tabulated per treatment group.

Results

Patients' disposition

There were 1206 randomised subjects (pregabalin, $n = 810$; placebo, $n = 396$), with a total of 1174 subjects comprised the ITT populations (pregabalin, $n = 807$; placebo, $n = 367$) used for efficacy analyses. The percentage of patients completing the 12-week treatment period was slightly higher in the placebo group (308/368, 83.7%) than in the overall pregabalin group (606/810, $n = 74.8\%$). The most frequent reasons for premature discontinuation were AEs in both groups (pregabalin, 155/810, 19.1% and placebo, 23/368, 6.3%; OR 3.55, 95% CI 2.25, 5.61).

Group characteristics at baseline

Baseline group and disease characteristics were similar across treatment groups and across studies (Table 2), with approximately half of the patients being male, and their age across studies ranging between 12 and 82 years. On average, participating patients experienced epileptic seizures for 26 years (S.D.: 12.7–14.1), with a median seizure rate between 9 and 12 seizures/28 days, and 74% of patients were receiving ≥2 concomitant antiepileptic drugs.

There were no relevant differences among the overall treatment groups regarding seizure etiology, though there were some differences between studies (Table 2).

Efficacy

Reduction in seizure frequency

Pregabalin-treated patients consistently experienced significantly greater reductions in seizure frequency across the 150–600 mg effective dose range than those on placebo, across the individual trials as well as in the overall analysis. In the individual trials, statistically significant frequency reductions were registered with pregabalin across all doses studied vs. placebo (reduction ranges across studies: pregabalin, −16.5 to 50.9% vs. placebo, −7 to +1.3%). In the pooled data analysis, significant reductions in seizure frequency were demonstrated for all pregabalin doses studied vs. placebo (Fig. 1), with a positive linear dose–response relationship ($p < 0.0001$; based on the main ANOVA model).

Derived by transformation of the main RRatio using the formula

$$: \frac{200 \times \text{mean RRatio}}{1 - \text{mean RRatio}}$$

Responder rates

Significantly greater proportions of pregabalin- than placebo-treated patients were classified as responders (i.e. patients who had ≥50% reduction in seizure frequency during treatment compared with baseline). In the individual trials, responder rates were between 14–31% with pregabalin 150 mg/day, 40% with 300 mg/day and from 43–51% with 600 mg/day compared to 6–14% with placebo ($p \leq 0.0001$; Cochran–Mantel–Haenszel test adjusted for cluster). Similarly, in the pooled data analysis, statistically significantly more pregabalin- than placebo-treated patients were classified as responders (Fig. 2).

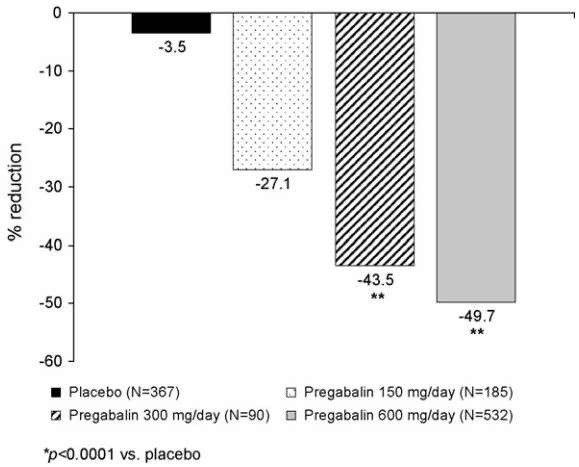

Fig. 1. Percentages reduction in seizure frequency across all treatment groups; $^{*}p < 0.0001$ vs. placebo.

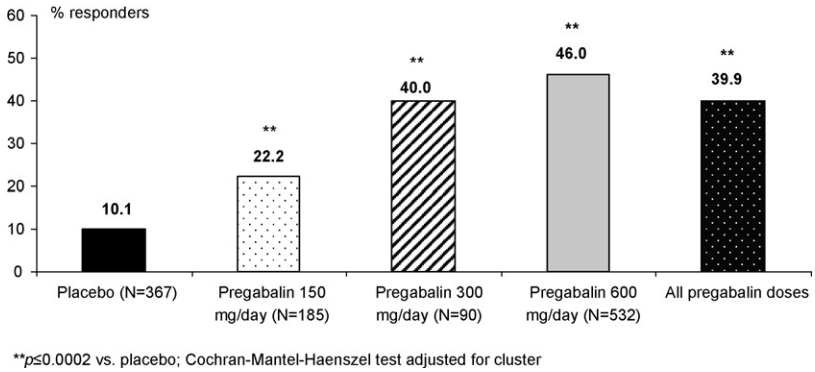

Fig. 2. Percentages of responders (patients with ≥50% reduction in seizure frequency vs. baseline): $^{**}p \leq 0.0002$ vs. placebo; Cochran–Mantel–Haenszel test adjusted for cluster.

Moreover, the subjects treated with pregabalin had a statistically significantly greater likelihood of becoming a responder than the subjects treated with placebo, in each dose group studied as well as in the overall pregabalin group (Fig. 3).

RRatio

Response rate ratios were calculated for each pregabalin dose as well as for all doses together, and compared with placebo (Table 3). All pregabalin doses studied as well as the overall pregabalin group produced a reduction in seizure frequency, with all differences vs. placebo being statistically significant.

Seizure freedom

The seizure-free period was calculated for the last 28 days in all the studies. During the last 28 days of treatment, 16 (12.2%) patients in the pregabalin flexible-dose group, 66 (12.4%) in the pregabalin 600 mg group, 11 (12.2%) in the pregabalin 300 mg group, 12 (6.5%) in the pregabalin 150 mg group and 20 (5.4%) in the placebo group were completely free of seizures. The flexible group in the Elger study, pooled 300 mg and pooled 600 mg were statistically significant vs. placebo for seizure freedom during the last 28 days (Table 4).

Tolerability and safety

The overall tolerability of pregabalin was good, with low percentages of study discontinuations, and with the majority of AEs of mild to moderate severity. During the first week of treatment, a total of 0.0, 5.1, 8.9, 18.2 and 7.4% receiving pregabalin 150 (b.i.d.), 150 (t.i.d.), 300 (b.i.d.), 600 (b.i.d.) and 600 (t.i.d.) mg/day discontinued treatment vs. 1.5% of patients receiving placebo. The rates of pregabalin-treated patients who discontinued the studies during weeks 2–12 were similar to the rates in the placebo group (0.9, 1.2, 2.1, 2.5 and 2.8% in the pregabalin groups vs. 2.3% patients on placebo (mean/week).

The most common AEs (with ≥5% frequency in either treatment group) are presented in Table 5. The most frequent AEs were dizziness and somnolence that were typically mild and tended to resolve with continued treatment, affecting <5% of subjects across all dosing groups from Week 2 and onwards (Fig. 4).

Weight gain was reported as an AE (via both spontaneous and solicited reports) across the dose range studied in 4.9–17.1% pregabalin- vs. 2.5% placebo-treated patients. Clinically significant weight change (i.e. increase or decrease of ≥7% from baseline weight) was registered in 20.6% of pregabalin and 5.2% of placebo-treated patients ($p < 0.0001$, Chi-square test). The median endpoint weight gain was 2.0 kg in pregabalin and 0.0 in placebo treated patients, and it was dose-related in affected patients. Nevertheless, weight gain led to discontinuation in only 6/807 (0.74%) of pregabalin-treated subjects, 4 of whom were in the 600 mg/day b.i.d. dosing group.

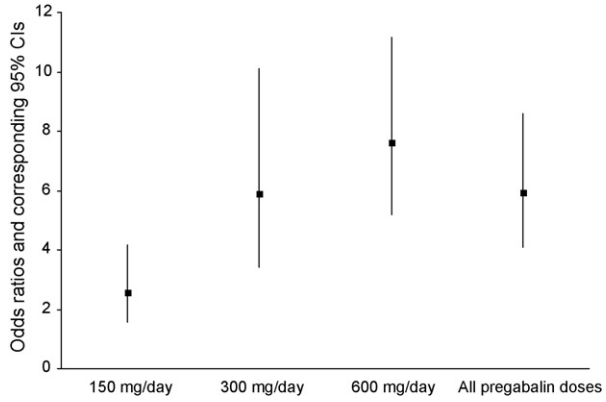

Fig. 3. Odds ratios and corresponding 95% CI for response with 150, 300, 600 mg/day and all doses of pregabalin (ITT population): p value for testing the difference between each dose regimen and placebo is derived from an ANCOVA model with treatment and cluster of centres as main effects and baseline seizure frequency as covariate: 150 mg/day, $p = 0.0002$; 300 mg/day, $p < 0.0001$; 600 mg/day, $p < 0.0001$; all pregabalin doses, $p < 0.0001$.

Discussion

Results of this pooled data analysis in a cohort of 1174 patients with treatment-resistant partial seizures with or without generalization confirm the short-term efficacy, safety and tolerability of add-on pregabalin 150–600 mg/day. Short-term add-on treatment with pregabalin resulted in statistically significant reductions from baseline in seizure frequency and statistically significantly higher responder rates over placebo. Its overall tolerability was good, with an OR of withdrawing from the study due to any reason of 1.71 (95% CIs 1.24, 2.35). The most frequent reasons for premature

Table 3
RRatios (ITT population)

Treatment group	*n*	Mean (S.D.)	RRatio range	*p* value[a]
Placebo	367	−1.78 (27.01)	−100; 88.23	–
150 mg/day	185	−15.69 (26.50)	−100; 53.07	<0.0001
300 mg/day	90	−27.80 (36.46)	−100; 72.04	<0.0001
600 mg/day	532	−33.12 (41.42)	−100; 99.47	<0.0001
All pregabalin doses	807	−28.53 (38.59)	−100; 99.47	<0.0001

[a] p value for testing the difference between each dose regimen and placebo is derived from an ANCOVA model with treatment and cluster of centres as main effects and baseline seizure frequency as covariate.

Table 4
Seizure freedom last 28 days (ITT population)

	Placebo, $N = 367$	150 mg/ day, $N = 185$	300 mg/day, $N = 90$	600 mg/day, $N = 532$	Flexible 150–600 mg/ day, $N = 131$	All pregabalin doses, $N = 938$
N (%)	20 (5.4%)	12 (6.5%)	11 (12.2%)	66 (12.4%)	16 (12.2%)	105 (11.2%)
p value[a]		0.7003	0.0310[b]	0.005[b]	0.0170[b]	0.0011[b]

[a] p value for testing the difference between each dose regimen and placebo.
[b] Statistically different vs. placebo.

discontinuation were AEs in both the overall pregabalin as well as in the placebo group (155/810, 19.1% and 23/368, 6.0%, respectively). The most commonly reported AEs were dizziness and somnolence, however, they were most pronounced during the first week of treatment, followed by a sharp fall in incidences across all dosing groups to <5% from Week 2 and onwards. Although pregabalin 600 mg/day b.i.d. and t.i.d. dosing regimens have been demonstrated to have superior efficacy over placebo, some advantages in pharmacodynamics of the t.i.d. regimen may suggest it would be better tolerated by some patients. Weight gain, reported by 5.4–17.1% of patients across pregabalin dosing groups, appeared to be dose-related, but it led to study withdrawal in only 0.74% (6 out of 810) pregabalin-treated subjects. Weight gain seen during pregabalin treatment appears to be particularly pronounced with pregabalin 600 mg/day b.i.d., with 4 (66.6%) of all weight gain related withdrawals occurring with this dosage regimen. Currently there are no data regarding possible weight changes during slow up-titration of pregabalin.

Additional data on weight change associated with placebo and pregabalin were yielded in a mathematical model which described the weight change data observed in 36 efficacy/safety studies, placebo-controlled studies of pregabalin across different indications (3 healthy volunteer studies and 33 double blind studies), the relationship between placebo or pregabalin exposure, and identified factors affecting this relationship.[19,20] Predicted fractional change (i.e. change in weight expressed as a percentage of baseline weight) reached steady state in 85 days, and was 0.7% for placebo; 1.6% for pregabalin 150 mg/day; 2.5% for 300 mg/day and 4.2% for 600 mg/day (Fig. 5).

In addition, efficacy and tolerability results of this fixed-dose studies pooled data analysis compare favourably with the results of the flexible-dose arm of the Elger et al. study[13] ($n = 131$, 150–600 mg/day; 2005). Flexible-dose regimen significantly reduced seizure frequency compared to placebo (35.4% vs. 10.6%, $p = 0.0001$). Although the flexible dosing regimen was less efficacious than the fixed-dose regimen (49.3%, $p = 0.0337$ vs. flexible regimen), it was superior in terms of tolerability, with less study withdrawals due to AEs (12.2% vs. 32.8%) and a lower incidence of reported AEs.

In their meta-analysis, Otoul et al.[21] calculated the odds ratios for response and withdrawal rates with levetiracetam, and indirectly compared them with the published results for other new antiepileptic drugs (lamotrigine, tiagabine, topiramate, oxcarabazepine and zonisamide)[22–30] (Table 6). Felbamate and vigabatrin were not included due to their limited use resulting from the associated serious AEs (i.e. aplastic anaemia/hepatic failure and visual field defects, respectively). The odds ratio calculations were based on data from registration trials of new

Table 5
The most common AEs with ≥5% frequency in either treatment group[a]

AEs (%)	Placebo ($n = 367$)	Pregabalin 150 mg/ day ($n = 185$)	Pregabalin 300 mg/ day ($n = 90$)	Pregabalin 600 mg/ day ($n = 532$)
Dizziness	10.1	17.8	31.1	39.3
Somnolence	10.4	11.4	17.8	25.6
Ataxia	4.1	5.9	10.0	19.9
Weight gain	2.5	4.9	6.7	17.1
Asthenia	9.3	10.8	12.2	13.9
Diplopia	3.3	5.4	6.7	11.8
Amblyopia	3.8	5.4	7.8	11.8

[a] AEs are presented by decreasing frequency.

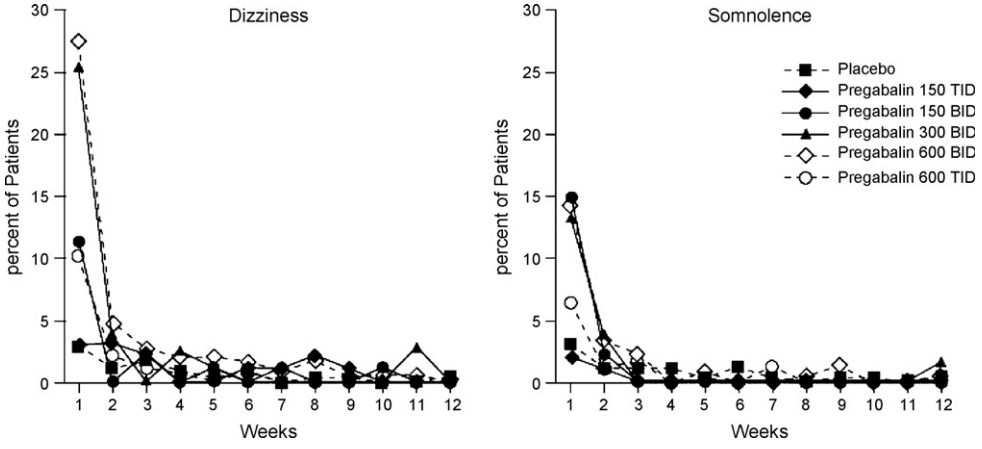

Fig. 4. Resolution of dizziness and somnolence with continued pregabalin treatment.

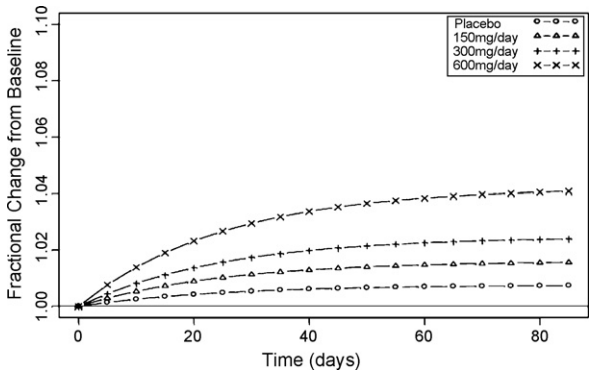

Fig. 5. Predicted fractional weight change with placebo or pregabalin.

antiepileptic drugs using the Mantel–Haenszel method (Table 6). The trials were all add-on, randomised, placebo-controlled trials available in the public domain, evaluating efficacy, tolerability and safety of new antiepileptic drugs in treatment-resistant partial seizure epilepsy with or without generalization, using a design with ≥4 weeks of baseline and ≥8 weeks of treatment period. The results of the Otoul meta-analysis extend previously reported results of a meta-analysis of antiepileptic drugs and vagal nerve stimulation, based on a smaller number of trials.[31] When our results are added to the Otoul et al. data, in this indirect comparison among all new antiepileptic drugs, pregabalin was associated with the highest odds ratio for achieving response to treatment compared to placebo [5.93 (4.10, 8.57)], and was in the group of new antiepileptic drugs with OR of <2 for withdrawal compared to placebo.

However, it should be noted that the results of the Otoul et al. meta-analysis[21] were based on registration trials of antiepileptic drugs available in the public domain. In some of them, dosages differing from those currently used in clinical practice were used. For example, the dosages of topiramate and oxcarbazepine used in registration trials were higher than those currently used in clinical practice.[21] It is, however, unlikely that changes in dosage would have yielded more favourable ORs for both response and withdrawal. Another meta-analysis,[6] based on all randomised controlled trials of currently available antiepileptic drugs in adult patients with drug resistant epilepsy, obtained through literature searches and from pharmaceutical companies, yielded similar results. In the all-dose analysis, among 10 antiepileptic drugs analysed pregabalin had the second highest odds ratios for 50% responder rates (3.44, 95% CI 2.51–4.71), while in the effective doses analysis based on data from 9 antiepileptic drugs, pregabalin had the highest odd ratios (3.68; 95% CI 2.88–5.04). In the odds ratio withdrawal analysis based on data from 10 antiepileptic drugs, pregabalin was in the group of 4 antiepileptic drugs with ORs <1.5. It should be noted that the efficacy measure used in the above meta-analyses of antiepileptic drugs were response rates, with response defined as ≥50% reduction from baseline seizure frequency, however, it was not possible to take into account important clinical variables such as seizure duration and severity. Although seizure freedom represents the ultimate efficacy outcome measure, low seizure freedom rates obtained in add-on trials for partial seizures of all new antiepileptic drugs and differences in methodologies used to yield these data, currently represent a methodological obstacle for using seizure data in meta analyses and indirect comparisons between antiepileptic drugs.[32]

Efficacy and tolerability data from our pooled data analysis are similar to an analysis performed on a levetiracetam registration studies data set.[33,34] Levetiracetam was the last antiepileptic drug to become available prior to the introduction of pregabalin in 2005/2006. However, there are some important differences in the design of levetiracetam and pregabalin studies that should be taken into account when interpreting the results of the respective analyses, such as differences in cohort size, duration of the baseline period, baseline number of seizures, duration of the up-titration period, study exclusion criteria and level of refractoriness of the study population. The levetiracetam analysis was based on a smaller cohort of patients (levetiracetam, $n = 589$; placebo, $n = 310$)[33]; compared with our analysis (pregabalin, $n = 810$; placebo, $n = 396$). All three levetiracetam fixed-dose, placebo-controlled studies included in the analysis had a 12-week baseline period.[35–37] By contrast, the baseline period in the included pregabalin studies was 8 weeks in 3 studies and 6 weeks in one study.[13] Although the median baseline number of seizures calculations were performed using different approaches [i.e. levetiracetam data were presented as a median number of seizures per week,[34] and pregabalin data as a median number of seizures over a 28-day period], the numbers are similar (levetiracetam = 2.3, placebo = 1.9,[34] pregabalin = 2.5, placebo, $n = 2.4$, recalculated from 28-day data). In the levetiracetam studies, the baseline period was followed by a 4-week up-titration,[35–37] while only 2 pregabalin studies were followed by a 1-week up-titration.[11,12] It is therefore conceivable that using the identical, prolonged up-titration period in the pregabalin studies may have improved tolerability, and resulted in a lower rate of study withdrawals due to AEs. This is also supported by the AEs

Table 6
Mantel-Haenszel odds ratios for response and withdrawal rates with new antiepileptic drugs vs. placebo (presented in alphabetical order; adapted from Otoul et al.[21]

Antiepileptic drug	Response rate Odds ratio (95% CI)	Withdrawal rate Odds ratio (95% CI)
Lamotrigine [24]	2.87 (1.92, 4.29)	1.16 (0.81, 1.66)
Levetiracetam [25]	5.35 (3.51, 8.16)	1.26 (0.86, 1.84)
Oxcarbazepine [26]	3.49 (2.49, 4.98)	2.27 (1.62, 3.17)
PREGABALIN [27]	5.93 (4.10, 8.57)	1.71 (1.24, 2.35)
Tiagabine [28]	3.82 (2.27, 6.43)	2.02 (1.30, 3.12)
Topiramate [29]	5.22 (3.68, 7.40)	2.42 (1.56, 3.74)
Zonisamide [30]	2.98 (1.81, 4.89)	1.78 (1.03, 3.08)

analysis in the pregabalin studies, with high incidences of dizziness and somnolence observed during the first week of treatment (see above) and subsequently decreasing to an incidence of ≤5% during the latter course of the studies.

It also appears that the pregabalin and levetiracetam cohorts differed in treatment-refractoriness of the seizure disorder. While the subjects who were seizure free for at least a 28-day period during the baseline period where not eligible for participation in the pregabalin studies, the same or similar exclusion criterion was not used in the levetiracetam studies. Consequently, the subjects who were more treatment refractory could have been recruited into the pregabalin studies. Furthermore, the pregabalin studies included in this analysis comprised substantially higher percentages of patients who were using ≥3 antiepileptic drugs concomitantly than the levetiracetam studies (pregabalin: 23.7%, placebo: 24.4%; levetiracetam: 3–5.2%, placebo: 3–5%).[35–37] Usage of more antiepileptic drugs has been identified as an indicator of treatment refractoriness,[38] and also increases the risk of cognitive and other central nervous system AEs. As the existing differences between the registration study designs preclude any extensive indirect comparisons between tolerability profiles of new antiepileptic drugs, it is possible that data yielded in large scale, simple naturalistic trials using different up titration strategies, may shed more light onto this issue. Finally, in contrast to levetiracetam, pregabalin is licensed in the EU for the treatment of Generalised Anxiety Disorder (GAD), and also showed favourable effect on depressive symptoms associated with GAD.[39] These characteristics may make pregabalin particularly suitable for treating subjects with epilepsy and comorbid anxiety and/or depressive symptoms, frequently encountered in clinical practice.[40,41]

Conclusions

In conclusion, the data from analysis of pooled patient data from four short-term placebo studies of pregabalin (150–600 mg/day) demonstrate that pregabalin is an effective and well tolerated add-on treatment for partial seizure with or without secondary generalization. Our analysis suggests that pregabalin has a robust efficacy demonstrated in a study population more treatment-refractory compared to the one enrolled into short-term studies of other new antiepileptic drugs. Because of its proven efficacy on anxiety and associated depressive symptoms, pregabalin may be particularly suitable for treating subjects with epilepsy and comorbid anxiety/depressive symptoms, frequently encountered in everyday clinical practice.

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