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An open-label, add-on study of pregabalin in patients with partial seizures: A multicenter trial in Greece

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ABSTRACT

Introduction: Pregabalin efficacy and safety as an adjunctive treatment for partial seizures was evaluated using an open-label, flexible-dose.
Study design: In 98 adults with refractory partial epilepsy taking 1–3 anti-epileptic drugs with ≥2 seizures during an 8-week baseline period.
Methods: Pregabalin was increased to ≤600 mg/day during a 9-week dose optimization period with dosage maintained for 12 additional weeks. Primary endpoint was the percentage change in partial seizure frequency between the 8-week baseline and 12-week observation period.
Results: Pregabalin treatment was associated with a significant reduction in partial seizure frequency: median percent change in partial seizure frequency from baseline to 12 weeks was −33% and −22% in patients with a baseline seizure frequency of ≤3 and >3 per 28 days, respectively. The 50% and 75% responder rates were 41.94% (95% CI: 31.91–51.96) and 30.11% (95% CI: 20.78–39.43), respectively. Nineteen percent of subjects were seizure-free throughout the last 12 weeks. Pregabalin administration resulted in a significant reduction in anxiety (mean reduction in Hospital Anxiety and Depression Scale scores of 1.68 units, 95% CI: −2.60 to −0.76). Most patients were much improved or very much improved on Patient Global Impression of Change (53.8%) and Clinical Global Impression of Change (53.8%). The most frequently self-reported adverse events (AEs) were mild or moderate somnolence (20.4%) and dizziness (5.1%) with a low AE discontinuation rate (5.1%).
Conclusions: The efficacy and side-effect profile of pregabalin were similar to previous pregabalin double-blind, controlled studies. Additionally, pregabalin, as an add-on treatment for partial epilepsy, exhibits significant anti-anxiety properties.

1. Introduction

Epilepsy affects about 50 million people worldwide,[1] and partial-onset seizures (including simple partial, complex partial and secondarily generalized) are the most common. The management of patients with partial epilepsies is currently considered suboptimal, despite the availability of many anti-epileptic drugs (AEDs). Only 50–75% of patients achieve complete remission from seizure activity within the first 5 years after diagnosis. Among

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patients with partial epilepsy, more than 30% have seizures refractory to AEDs administered either alone or in combination and continue to require an additional anti-epileptic treatment.[2,3]

Pregabalin is a selective α2δ ligand of the presynaptic voltage-gated calcium channels. Binding at this site reduces calcium influx at hyperexcitable nerve terminals and decreases the release of neurotransmitters including glutamate, norepinephrine and substance P. This activity is thought to impart the analgesic, anxiolytic and anti-epileptic properties of pregabalin.[4]

Controlled clinical trials have demonstrated that pregabalin is effective in the treatment of peripheral[5] and central[6] neuropathic pain, and in the treatment of generalized anxiety disorder.[7] Pregabalin has a favorable pharmacokinetic profile with linear elimination and is predictable with low intra-subject variability. It is cleared renally and does not undergo hepatic metabolism.[8] Additionally, pregabalin does not interact with other AEDs,[9] providing ease of use in the clinic.

Pregabalin was first licensed as an adjunctive treatment for adults with partial seizures, with or without secondary generalization, in Europe and the United States in 2004 based on data from several double-blind, placebo-controlled, parallel-group, multicenter studies in patients with refractory partial seizures.[10–13] Most clinical trials of pregabalin have been conducted according to set protocols and using fixed dosages. The objective of this study was to explore the use of pregabalin in real-world treatment situations and everyday clinical practice including dose optimization and inclusion of a broader range of subjects in the study population.

2. Methods

2.1. Study population

Patients were males or females, aged 18 years or older, with a diagnosis of epilepsy with partial seizures not adequately controlled by one to three AEDs administered as monotherapy or in combination, within 1 year of study screening. All patients had a minimum of two partial seizures within 2 months of the baseline visit. Additionally, eligible patients had no evidence of progressive neurological disorders, no absence seizures or status epilepticus within 1 year prior to screening, and no record of vigabatrin use. Patients using any medication, or with any medical condition or abnormality that may have increased the risk associated with study participation, were excluded.

2.2. Study design

This was an open-label, uncontrolled, add-on treatment, multicenter study in which subjects took pregabalin orally BID as an add-on treatment for partial seizures. All seizures were recorded in a detailed seizure diary by the patient, a trained observer or a legal guardian. The study was conducted at eight study centers in Greece and comprised three main phases with a total treatment duration of 21 weeks: baseline phase of 8 weeks (historical baseline allowed if medical history could be verified), treatment dose-optimization phase of 9 weeks, and treatment observation phase of 12 weeks (Fig. 1). For patients who discontinued, pregabalin was withdrawn gradually over a minimum of 1 week; patients returned for a follow-up visit 1 or 2 weeks after the last dose of pregabalin.

Pregabalin (75 mg and 150 mg capsules) was initiated at 150 mg/day given as BID and increased based on individual response and tolerability. 75-mg capsules were available up to visit 3 (week 9), and 150-mg capsules were available thereafter. The maximum dose was 600 mg/day given as BID during the 9-week dose-optimization period. Dosage changes were separated by 1 week, and 9 weeks were allowed to reach an optimal pregabalin dosage, which was maintained for 3 months. However, at any time during the study, patients could have adjustments to dosages between 150 and 600 mg/day at the discretion of the investigator. Concomitant AEDs had to remain unchanged throughout the whole study period.

The study was conducted in compliance with the Declaration of Helsinki, Good Clinical Practice guidelines, and local laws and regulations, and received local ethics board approval. The final protocol and informed consent documentation were reviewed and approved by the Institutional Review Boards and/or Independent Ethics Committees at each of the investigational centers participating in the study. Patients or their legal guardian gave written informed consent. The study was conducted between December 2005 and December 2007.

2.3. Analyses

Efficacy analyses were based on the full analysis set (FAS)/intent-to-treat (ITT) population (all subjects who received at least one dose of study treatment and had a minimum of two partial seizures during the baseline period). For the primary efficacy endpoint, supportive sensitivity analysis using the per-protocol population (all subjects in the ITT who completed a minimum of 19 weeks treatment and did not have major protocol deviations) was performed to assess the robustness of the conclusions.

Seizure rate during the treatment period was calculated on a last observation carried forward (LOCF) basis. Seizure frequency was based on the 12 weeks prior to the last dose and was calculated as total number of partial seizures per 28-day period. To accommodate the skewed character of seizure frequencies, the mean 28-day seizure frequency was calculated using a Response Ratio (RRatio).[14] The RRatio is defined as the ratio $[(T-B)/(T+B)] \times 100$, where B = Baseline Seizure Rate and T = Treatment

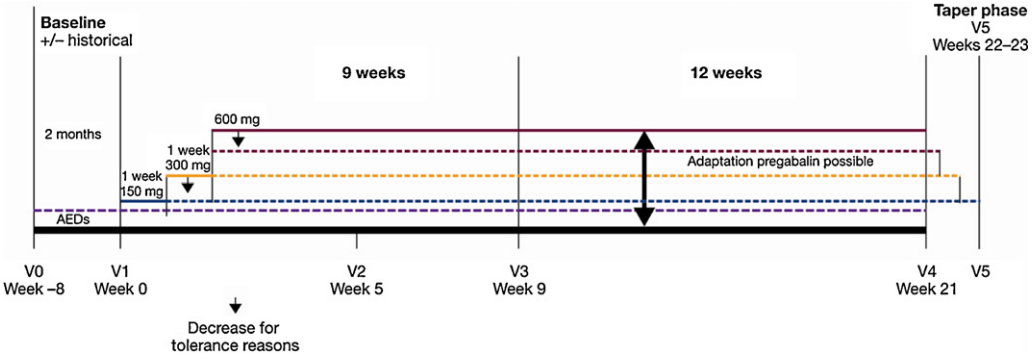

Fig. 1. Study protocol timeline and organization. V: visit; AEDs: anti-epileptic drugs.

Seizure Rate. The RRatio allows for a "symmetrized" percent change with a range of −100 to 100. Negative values of the RRatio represent an improvement in seizure rate and positive values indicate a worsening of seizure rate. The median change from baseline was also calculated.

The primary endpoint was the percentage change in partial seizure frequency between the 8-week baseline and the 12-week observation period. Seizure activity for efficacy assessments was recorded by the subject or caregiver in the subject's seizure diary from Day 1 through the end of the study. Secondary endpoints included the following: change in partial seizure frequency, seizure-free patients during the last 4 and 12 weeks of the observation period, 50% and 75% responder rates, sleep quality using the Medical Outcomes Study (MOS) – Sleep Scale, Hospital Anxiety and Depression Scale (HADS) between baseline and visit 4, Patient Global Impression of Change (PGIC), and Clinical Global Impression of Change (CGIC). The HADS, which comprises an anxiety and a depression subscale, was used to investigate various dimensions of mood.[15] The anxiety subscale (HADS-A) assesses features of a generalized anxiety state, such as restlessness, panic attacks, anxious thoughts and anxious mood, whereas the depression subscale (HADS-D) identifies a state of lost interest and reduced pleasure. Each subscale includes seven items and has a total score ranging from 0 to 21 with higher scores reflecting poorer psychological well being. On both subscales, a score of 0–7 is considered normal whereas scores ≥8 represent levels of pathological anxiety and depression. The PGIC and CGIC are 7-point scales on which patients and clinicians, respectively, rate changes from baseline as "much improved" to "much worse."[16] Symptoms of depression and anxiety were assessed using the HADS at visits 1 and 4. Impression of change was assessed by the subject using the PGIC and by the clinician using the CGIC at visit 4. All observed or volunteered AEs, regardless of causal relationship to the study drug, were recorded from the time the subject took his/her first dose through the last subject visit.

3. Results

3.1. Patients

In total, 102 patients were screened and 98 patients received treatment with pregabalin. Patient mean age was 38.2 years; 70.4% were 18–44 years and 25.5% were 45–64 years. All patients were white and equally distributed between males and females. The mean duration of epilepsy since first diagnosis was 21.2 years (range, 0.6–60.4 years). Patients were receiving the following primary AEDs at the time of study entry: carbamazepine (33.0%), levetiracetam (32.0%) and oxcarbazepine (32.0%).

All 98 patients who received treatment were analyzed for safety, and 93 FAS/ITT patients were assessed for efficacy. A total of 12 patients (12.2%) discontinued treatment including five (5.1%) discontinuations due to AEs, four (4.1%) due to lack of efficacy, and three (3.0%) due to reasons unrelated to treatment.

Table 1
Patient and Clinical Global Impression of Change.

	Patient Global Impression of Change, *n* (%)	Clinical Global Impression of Change, *n* (%)
Subjects in the FAS/ITT	93	93
Very much improved	14 (15.1)	15 (16.1)
Much improved	36 (38.7)	35 (37.6)
Minimally improved	17 (18.3)	24 (25.8)
No change	9 (9.7)	11 (11.8)
Minimally worse	3 (3.2)	4 (4.3)
Much worse	1 (1.1)	2 (2.2)
Very much worse	0	0
Missing/not done	13 (14.0)	2 (2.2)

FAS: full analysis set; ITT: intent-to-treat.

3.2. Efficacy

The median percent change from baseline to the last 12 weeks was −33% in the FAS/ITT population in patients with baseline seizure frequency 3 or less in 28 days, and the mean RRatio in the FAS/ITT population was −24.93 (95% CI: −43.66 to −6.20). In patients with baseline seizure frequency more than 3 seizures in 28 days, the median percent change from baseline to the last 12 weeks was −22%, and the mean RRatio was −20.78 (95% CI: −35.24 to −6.33). When both seizure frequency groups were analyzed together, the mean RRatio was −22.72 (95% CI: −34.16 to −11.28), which corresponded to a 37% reduction in seizure frequency from baseline for all ITT patients. When analyzed over the entire 21-week, open-label period, the mean RRatio of −17.26 (95% CI: −27.36 to −7.15) for both seizure groups (≤3 and >3 seizures/28 days) again showed a significant reduction in partial seizure frequency.

Overall, 41.94% (95% CI: 31.91–51.96) of patients experienced at least a 50% reduction in partial seizure frequency between baseline and the last 12 weeks of treatment (excluding the first 3 weeks of treatment) of the observation period; 30.11% (95% CI: 20.78–39.43) experienced a seizure reduction of at least 75%. The percentage of subjects who were seizure-free throughout the last 12-week observation period was 19%.

The majority of subjects reported improvements in the PGIC and CGIC by the end of the 21-week observation period. In both PGIC and CGIC, 54% of scores showed steady improvement during the course of pregabalin treatment with most patients and clinicians reporting "much improved" or "very much improvement." Among the ITT population, 39% of patients and 38% of clinicians reported that the overall status of patients had much improved after 21 weeks (Table 1).

Scores on the MOS-sleep scale did not significantly improve from baseline to week 21. HADS anxiety symptoms were significantly reduced by a mean of 1.68 units (95% CI: −2.60 to −0.76) between baseline and the week 21/early termination visit (Table 2). Symptoms of depression did not significantly improve.

Table 2
Summary of HADS depression and anxiety symptoms subscales.

Pregabalin (*n* = 93)		Baseline	Week 21/early termination	Change from baseline to week 21/early termination
HADS-D score	*n*	88	77	76
	Mean (SD)	5.35 (3.639)	4.87 (4.131)	−0.59 (3.442)
	95% CI	4.58, 6.12	3.93, 5.81	−1.38, 0.19
HADS-A score	*n*	89	77	76
	Mean (SD)	7.44 (4.445)	5.91 (4.425)	−1.68 (4.037)
	95% CI	6.50, 8.38	4.91, 6.92	−2.60, −0.76

CI: confidence interval; HADS-A: Hospital Anxiety and Depression Scale-Anxiety subscale; HADS-D: Hospital Anxiety and Depression Scale-depression subscale; SD: standard deviation.

Table 3
Incidence and severity of treatment-emergent adverse events occurring in ≥2 subjects (all causalities).

System organ class MedDRA preferred term	Total, *n* (%)	Severity		
		Mild, *n*	Moderate, *n*	Severe, *n*
Subjects evaluable for adverse event	98 (100)			
Gastrointestinal disorders				
Constipation	2 (2.0)	1	1	0
General disorders and administration-site conditions				
Asthenia	2 (2.0)	1	1	0
Gait disturbance	3 (3.1)	1	2	0
Edema peripheral	2 (2.0)	2	0	0
Investigations				
Weight increased	3 (3.1)	1	1	1
Nervous system disorders				
Ataxia	2 (2.0)	1	0	1
Convulsions	4 (4.1)	0	4	0
Disturbance in attention	2 (2.0)	1	1	0
Dizziness	5 (5.1)	4	1	0
Headache	2 (2.0)	2	0	0
Somnolence	20 (20.4)	14	6	0
Psychiatric disorders				
Agitation	4 (4.1)	3	1	0

MedDRA: Medical Dictionary for Regulatory Activities.

3.3. Safety and tolerability

The most common (>3% incidence) self-reported treatment-emergent adverse events (AEs) with pregabalin were: somnolence (20.4%), dizziness (5.1%), convulsions (4.1%), agitation (4.1%) and gait disturbance/weight gain (both 3.1%) (Table 3). A weight gain of 7% or more was seen in 13 patients (13.3%) with the majority (8 patients, 8.2%) gaining between 7% and 10%. All treatment-emergent AEs were of mild or moderate intensity. Discontinuations owing to treatment-emergent AEs in the ITT population were low (5.1%). In total, 3 patients experienced serious AEs during the study, but 2 were unrelated to use of study drug and 1 was related to non-compliance with medication. There were no deaths during the study. Clinically meaningful changes from baseline to last observation in systolic or diastolic blood pressure, heart rate or respiration rate were not observed.

4. Discussion

This study underscores the safety and efficacy of pregabalin as an adjunctive anti-convulsant treatment in typical daily practice settings. Flexible dosing, which allows clinicians to titrate dose to efficacy and tolerability, is more relevant to "real world" practice than fixed-dose regimens commonly used in clinical trials.

Research in this population of Greek subjects supports the findings of earlier researchers on the safety and efficacy of pregabalin as an adjunctive anti-convulsant treatment when used in an open-label, flexible-dose paradigm for the treatment of patients with partial seizures.[10–13] For all ITT patients, pregabalin treatment yielded a significant reduction of 37% in partial seizure frequency between baseline and the last 12 weeks of treatment. Pregabalin treatment also yielded a significant reduction from baseline in partial seizure frequency throughout the 21-week treatment period. The majority of patients reported improvements in PGIC and CGIC by the end of the 21-week observation period, indicating satisfaction with treatment.

Adverse effects of anti-epileptic drugs are a particular concern in patients with epilepsy, due to their high frequency and strong association with poor health-related quality of life (HRQOL).[17] It is clear, therefore, that AEDs with a favorable side-effect profile are of utmost importance to the optimal management of epilepsy particularly in an add-on setting as multidrug treatment increases the risk of toxicity. In the present study, most side effects were mild to moderate in intensity leading to discontinuation in 5.1% of patients. This discontinuation rate related to adverse effects was lower than in controlled studies, as expected in daily clinical practice, but similar to that of flexible dose studies.[4,13] On the other hand, it should be acknowledged that AEs in the present study were either observed by caregivers or were volunteered by the patients themselves. Therefore, the absence of a structured questionnaire for AEs, which has been previously shown to detect increased rates of AEs compared to spontaneous reporting,[18] may have contributed, to some extent, to the favorable AE profile.

The observed reduction in the levels of anxiety after the administration of pregabalin merits further discussion. Anxiety is a common emotional problem in patients with epilepsy, occurring in 25% of epileptic subjects in a community setting,[19] whereas in secondary care and specialist centers its prevalence exceeds 50%.[20,21] In our cohort, 49% of subjects suffered from anxiety (HADS-A scores ≥8). Of particular clinical importance is the recent finding that anxiety exerts a profound negative effect on the HRQOL in patients with epilepsy. A number of studies[22,23] demonstrated that anxiety and depression explain more variance in HRQOL than any other seizure-related or demographic variable. It is conceivable, therefore that AEDs with anti-anxiety properties may be particularly beneficial for patients with epilepsy. Currently, there is no clear, evidence-based therapeutic strategy for treating anxiety in patients with epilepsy. Over the years, the mainstay of treatment has been the use of benzodiazepines, due to their potent anti-convulsant and anti-anxiety properties. Their use, however, should be avoided over prolonged periods due to the danger of dependence and potential of withdrawal seizures.[24] Alternatively, selective serotonin re-uptake inhibitors may be used; however, these agents have a delayed onset of action and are associated with a small risk of seizure exacerbation. Our data suggest that pregabalin as an add-on treatment is a reasonable choice for patients with partial epilepsy who have concomitant symptoms of an anxiety disorder.

Our research is limited by the short observation period and, most importantly, by the lack of a control group, which limits the extent to which the results can be generalized. "Real world" studies such as this provide useful insight into the use of pregabalin in typical clinical situations; however, comparisons of the results of this study with earlier controlled trials of pregabalin should be made with caution.

5. Conclusions

This 21-week, open label study adds to the accumulating evidence of the efficacy and safety of pregabalin as an adjunctive treatment for partial seizures.[10–13,25–30] As demonstrated by this research in everyday clinical practice, seizure frequency was reduced by 37% with more than half of patients and clinicians reporting "much improved" or "very much improvement." Additionally, pregabalin, as an add-on treatment in patients with partial epilepsy, exhibited significant anti-anxiety properties.

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