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FULL-LENGTH ORIGINAL RESEARCH

Long-term add-on pregabalin treatment in patients with partial-onset epilepsy: Pooled analysis of open-label clinical trials

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Summary

Purpose: To evaluate the safety, tolerability, and efficacy of long-term pregabalin as add-on therapy for patients with poorly controlled partial seizures.

Methods: Analysis of data from six long-term clinical trials involving 2,061 patients receiving open-label pregabalin 75–600 mg/day adjunctive therapy for partial onset epilepsy refractory to multiple antiepileptic drugs.

Results: Total pregabalin exposure was 3,877 person-years. The mean duration of pregabalin treatment was 534 days (range 0.3–8 years) and 59% completed 1 year. One-third of patients discontinued for lack of efficacy. The most common dose was ≥300 mg/day; over half took ≥450 mg/day. There was a mean reduction in the 28-day seizure rate of 25–40%, and more than 40% of all patients had a ≥50% reduction in seizures from baseline during the last 3 months of treatment. Twelve percent of all patients had a 6-month period continuously free of seizures. In the last year, 6% were seizure-free for the entire year. Pregabalin was generally well-tolerated and the safety profile favorable in patients treated for up to several years, with an adverse event (AE) profile similar to short-term placebo-controlled trials. Common AEs included CNS symptoms (dizziness, somnolence, headache, and asthenia), accidental injury, and weight gain. CNS AEs tended to be mild and transient. Rates of sudden unexpected death in epilepsy (SUDEP), mortality, cancer, and status epilepticus were within the expected range for this population.

Conclusions: Adjunctive pregabalin was effective, generally well tolerated, and safe in the long-term treatment of partial seizures, and provided clinically meaningful seizure reduction and freedom without evidence of tolerance over 2 years of follow-up.

KEY WORDS: Pregabalin, Epilepsy, Antiepileptic drugs, Long-term therapy, Clinical trials, Open-label.

Pregabalin is a novel anticonvulsant, which has also demonstrated analgesic and anxiolytic effects in preclinical animal models (Ben-Menachem, 2004) and in randomized controlled clinical trials (Brodie, 2004). These actions may be due to potent binding of pregabalin to the auxiliary alpha$_2$-delta subunit of voltage-gated calcium channels (Taylor et al., 1993; Dooley et al., 2002; Fink et al., 2002; Ben-Menachem, 2004) in the peripheral and central nervous system (CNS). A series of four well-designed, 12-week clinical trials have already demonstrated that pregabalin (150–600 mg/day) is effective, safe, and well-tolerated when administered as adjunctive therapy in patients with treatment-refractory partial-onset epilepsy (French et al., 2003; Arroyo et al., 2004; Beydoun et al., 2005; Elger et al., 2005). Furthermore, a dose–response effect was observed, which has also been confirmed by an exposure–response analysis of the data (Miller et al., 2003). Moreover, pregabalin has a low potential for drug interactions, as indicated by the absence of metabolism by the cytochrome P450 system, its lack of protein binding (Ben-Menachem, 2004), and its lack of pharmacokinetic interaction with concomitantly administered antiepileptic drugs (AEDs) (Bockbrader et al., 2001; Ben-Menachem, 2004; Brodie et al., 2005).

Epilepsy is largely a chronic, debilitating condition (Baker, 2002), and approximately one-third of patients with partial epilepsy will continue to experience seizures despite ongoing use of AED treatment (Brodie & Kwan, 2002). Such treatment-refractory patients are often treated with AED polytherapy (Landmark et al., 2007). There is a continuing need for well-tolerated and safe treatments that

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may provide additional seizure control. Most patients with epilepsy take AEDs for several years, if not for life. Such long-term exposure will require the management of drug interactions, tolerability issues, and safety concerns that can affect patient adherence to long-term treatment. In addition, rare potential adverse events (AEs) will not always be apparent in short-term clinical trials required for marketing approval. It is vital that prescribing clinicians are aware of potential long-term AEs, particularly those that could have serious consequences for affected patients.

It is commonplace in the clinical development of drugs for chronic illnesses such as epilepsy to offer patients who take part in randomized, placebo-controlled, double-blind trials the opportunity to receive treatment with the experimental agent in extension studies, which are usually open-label. Such studies tend to run until the agent being studied receives a license and is brought to market. Therefore, some patients might be treated with a new agent under such circumstances for several years during which time data on efficacy, tolerability, and safety are routinely collected. Such data provide useful insight into the behavior of a new drug when it is used long-term under conditions that are more akin to clinical practice than controlled trials.

To determine what physicians might expect during long-term treatment with pregabalin, six open-label extension studies evaluated the long-term efficacy, safety, and tolerability of pregabalin (dose range 75–600 mg/day) administered two or three times daily as adjunctive therapy in partial epilepsy. This report examines the long-term effects of pregabalin on seizure control, as well as tolerability and safety, by evaluating data pooled from the six studies that have very similar designs.

Methods

This report includes data from six open-label studies, all of which allowed pregabalin adjunctive therapy with marketed AEDs. Investigators at 252 centers throughout 19 countries worldwide conducted these studies between November 1997 and February 2006. The studies ranged in duration from 3.5 years to almost 8 years (Table 1). Each study was approved by institutional review boards and ethics committees and was conducted in accordance with the International Conference on Harmonisation Guidelines for Good Clinical Practice and the Declaration of Helsinki. Patients or their authorized representatives gave written informed consent.

Studies

These were six long-term, open-label, adjunctive therapy studies conducted in patients with partial-onset seizures refractory to AED treatment. Patients who had taken part in six preceding randomized, double-blind clinical trials (French et al., 2003; Arroyo et al., 2004; Beydoun et al., 2005; Elger et al., 2005; Data on file, Pfizer Inc., New York, NY, U.S.A.) had the option to enter the open-label extension studies (Table 1). All but one of the preceding double-blind clinical trials evaluated adjunctive treatment. The other was a small 1-week study of monotherapy in inpatients who were hospitalized for seizure monitoring and had existing AED treatment discontinued as a standard procedure in seizure presurgical workup (Abou-Khalil et al., 1999). Patients voluntarily extended their hospitalization beyond the presurgical workup requirements without resuming existing AEDs prior to randomization to pregabalin 600 mg/day or gabapentin 300 mg/day (n = 93) (Data on file, Pfizer Inc., New York, NY, U.S.A.). In addition, three

Table 1. Summary of six open-label extension studies

Study no.	Pregabalin dose (mg/day)	Dosing frequency	Target dose[a] (mg/day)	Study duration (months)	Total N (ITT)	De novo entered	Location
008	150–600	TID	450	95	82	No	U.S.A.
010	225–600	TID or BID	450	86	454	Yes (n = 195)	Canada U.S.A.
012	75–600	TID or BID	450	85	321	Yes (n = 89)	Australia Europe South Africa
035	100–600	BID	400	70	623	Yes (n = 228)	Canada U.S.A.
114	150–600	BID	300	44	333	No	Australia Canada Europe
164	150–600	BID	300	53	248	No	Canada Europe

ITT, intent to treat; TID, three times daily dosing; BID, twice daily dosing.

[a]In each of the studies patients received a target dose in the initial phase of the study irrespective of previous double-blind treatment assignment, which was unknown by the investigator at the time of entry to the open-label study. Target doses were attained either within 1–7 days of entry, depending on the study. Dosing was fully flexible from 75–600 mg/day after the target dose had been reached (or an attempt had been made to reach).

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of the studies allowed the entry of de novo patients. The dosing regimens, duration of the studies, and numbers of patients in each of the studies are summarized in Table 1.

Patients

Patients were male or female (pregnant or lactating women excluded), with a diagnosis of epilepsy with partial-onset seizures with or without secondary generalization, as defined in the International League Against Epilepsy (ILEA) Classification of Seizures (Commission on Classification and Terminology of the International League against Epilepsy, 1981). In most studies the minimum age was 18 years, except for two studies with U.S. sites in which a few patients aged 12–18 were allowed to enter. Patients in the five adjunctive double-blind pregabalin studies that preceded open-label treatment were on one to three other AEDs; had no longer than a 4-week period free of seizures during the pretreatment, baseline assessment phase; and had at least six partial seizures during the 8-week pretreatment, baseline period (French et al., 2003; Arroyo et al., 2004; Beydoun et al., 2005) or at least four in the 6-week prestudy, baseline period (Elger et al., 2005; Data on file, Pfizer Inc., New York, NY, U.S.A.). De novo patients with partial seizures who had not taken part in the preceding double-blind trials and entered the long-term open-label study had at least four seizures in the preceding 2 months based on retrospective assessment, were not adequately controlled on current AED treatment, and investigators thought they could possibly benefit from adjunctive pregabalin treatment.

At the request of the U.S. Food and Drug Administration (FDA) in March 2001, approximately 2 to 3.5 years after the studies started, the 431 U.S. patients remaining in the studies at that time were required to meet requalification criteria to continue, at both an initial requalification visit and at every subsequent study visit. Only those U.S. patients who were refractory to other AEDs (defined as failing three AEDs from two different mechanistic AED classes in the past and with an epilepsy diagnosis ≥2 years), and who were responding to pregabalin (defined as ≥30% reduction in all-type seizure frequency compared to baseline) were allowed to continue in these studies. It is worth noting that under these response criteria a patient presenting at any follow-up visit with an average of five simple partial seizures per 28 days during the most recent 12 weeks compared to a 28-day average baseline frequency of one simple partial seizure, four complex partial seizures, and two secondarily generalized seizures would not requalify by protocol and would be discontinued from the study despite having a marked reduction in the actual severity of seizures.

Assessments

Patients maintained a daily seizure diary. The clinic visit schedule varied across studies but was generally monthly for the first 4 months and then 3-monthly thereafter. In addition to the collecting of seizure diaries, AEs were recorded at each clinic visit. All treatment-emergent, spontaneously reported, or observed AEs were recorded by the investigator or designee and classified using the COSTART IV dictionary (Department of Health and Human Services, 1996). For the open-label extension studies, treatment emergent was defined as any AE that was not evident during double-blind treatment, or that was previously observed but increased in intensity or frequency, or changed in character during open-label treatment. Prolongations of seizure duration, or increase in seizure intensity or frequency, were considered to indicate lack of efficacy and were not recorded as AEs. Status epilepticus was classified separately from AEs and lack of efficacy. A central laboratory performed clinical laboratory tests on blood and urine samples collected at each study visit, and upon discontinuation. Physical and neurologic examinations were conducted at each visit, and electrocardiography(ECG) was conducted at study entry, after 1–2 months, and at 6-month intervals thereafter.

Data analyses

Two populations were analyzed for efficacy: all patients enrolled in the extension studies who took at least one dose of pregabalin treatment, and the cohort of patients who completed 2 years of treatment. No inferential testing was undertaken. The baseline 28-day seizure rate was that derived from diaries before patients were exposed to active study treatment, that is, before entry to double-blind studies for patients originally randomized to active AED treatment, and the last month of the double-blind phase for patients who had been on placebo before entering the open-label extension. Prospective assessments of baseline seizure rates were not available for de novo patients or those who had originally taken part in the small monotherapy study. The mean percentage reduction in seizures from baseline was calculated for each 3-month treatment interval. The percentage of patients with ≥50% reduction from baseline in seizures was calculated. For the 2-year cohort the percentages with ≥25% and ≥75% reductions were also determined. The percentages of patients free of seizures for specified intervals were calculated. The cumulative frequency of discontinuation by month for any reason was calculated.

The time to pregabalin discontinuation was evaluated using Kaplan-Meier survival analysis. The most common pregabalin dose was determined for each patient, and averages were calculated. The mean pregabalin dose was also determined by month for the cohorts who remained on treatment for 1, 2, and 3 years.

All patients who received at least one dose of study medication were included in the evaluation of safety data. The frequency of AEs and discontinuations due to AEs were calculated. The median times to onset and duration of the most common treatment-emergent AEs were also determined. For patients who had received placebo, fixed-dose pregabalin 600 mg/day, and semiflexible pregabalin

150–600 mg/day in preceding 12-week double-blind trials, the frequency of treatment-emergent AEs during double-blind treatment and the first 12 weeks of open-label pregabalin treatment were compared.

The number of concomitant AEDs taken during open-label pregabalin treatment was also recorded and compared with the number of concomitant AEDs at baseline. In this analysis, any patients from the double-blind, adjunctive studies who switched between different concomitant AED medications were counted as an increase in the number of concomitant AEDs during open-label. Hence, only patients who did not switch or reduce/increase the number of concomitant AED medications were counted as "no change."

An exploratory analysis of weight changes occurring during the first year of open-label-treatment with pregabalin was conducted using patients who were randomized to placebo in the double-blind trials, or who entered the open-label trials de novo (i.e., pregabalin-naive). In order to examine weight change over time in a homogeneous population exposed to pregabalin, patients previously randomized to double-blind pregabalin were not included in this analysis, since they had already received 12 weeks treatment before the start of open-label. Because each study had a different schedule for patient visits, weight change during open-label pregabalin treatment was analyzed and reported as a continuum rather than at discrete time points. Estimates at selected time points were then derived from the fitted nonparametric weight-change-by-time curve. Similar estimates were also determined for pregabalin-naive patients who entered the open-label studies and discontinued pregabalin prior to 1 year of open-label treatment.

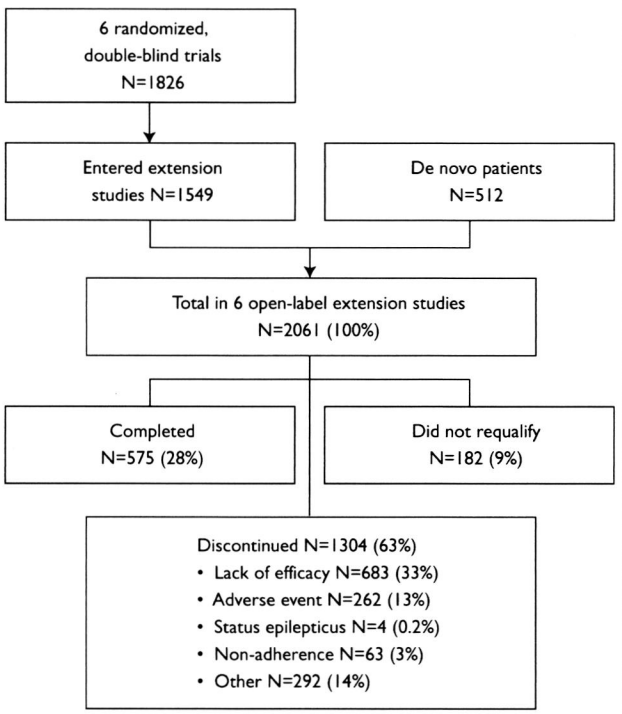

Figure 1.
Disposition of patients who entered open-label extension studies. Other includes lost to follow-up and administrative reasons. In March 2001 patients in the United States had to meet the following requalification criteria at each clinic visit to remain on pregabalin treatment: Had history of failing ≥3 antiepileptic drugs (AEDs) from ≥2 different mechanistic classes and had ≥30% reduction from pretreatment baseline. Of the patients who entered from randomized, double-blind trials, 82 were from the monotherapy trial; the remainder were from adjunctive trials. Patients were classified as completed if they remained in the study until it ended (i.e., when pregabalin was approved and made available on prescription).
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Results

Patients and disposition

In total 2,061 patients were treated with open-label pregabalin (Fig. 1). On entry to the open-label studies 50% of patients were women and the mean age was 38.6 years (range 12–82 years). Concomitant AED use before entry was as follows: zero = 2.1%, one = 26.4%, two = 47.3%, three = 22.3%, and more than three = 1.9%. The median baseline seizure rate before patients were treated in the original double-blind adjunctive studies was 9.5/28 days (mean 21/28 days, range 0–356/28 days,). Before entering the open-label extension studies, 47% had previously been treated with pregabalin, 21% with placebo, and 7% had previously been randomized to other AEDs (45 patients on gabapentin, 103 on lamotrigine), whereas the remaining 25% were de novo. The patients who had previously been exposed to pregabalin 2% had been taking <150 mg/day. Patient characteristics for the double-blind cohort were similar to those of the de novo cohort, and these combined patient characteristics were similar to those in each of the six open-label studies (Table S1, supplemental material appendix). The proportions of patients who were classified as double-blind responders (≥50% seizure reduction from baseline) were similar among those who did (29%) and did not (30%) choose to enter the open-label extension studies.

Of the 1,979 patients who had not been in the preceding monotherapy study, 57% did not change concomitant AEDs during open-label treatment and 43% changed concomitant AEDs. Of the 82 patients who entered from the monotherapy study, 71 added concomitant AEDs during open-label treatment. In general, the most frequently used concomitant AEDs in each of the six trials were similar. Overall, the most commonly used AEDS (>10% of all patients) were carbamazepine (56.7%), topiramate (26.7%), phenytoin (25.9%), lamotrigine (25.8%), levetiracetam (20.1%), lorazepam (10.2%), and clobazam (10.2%).

Epilepsia, 51(6):968–978, 2010
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Pregabalin exposure and dosing

A total of 575 patients [28% of the total intent-to-treat (ITT) population] completed one of the six open-label studies (i.e., remained on treatment until the study ended; Fig. 1). Overall, at the completion date, 79% of patients had been exposed to pregabalin for ≥6 months, 61% for ≥1 year, 34% for ≥2 years, and 14% for ≥3 years. The total exposure to pregabalin was 3,877 person-years. The percentage of patients completing at least 1 year was similar in each of the six open-label studies. Of the 795 patients who were on treatment for <1 year, 779 discontinued, one failed to requalify, and for 15 patients the study they were in ended before they had the opportunity to complete 1 year of treatment. Of the 1,364 patients who were on treatment for <2 years, 1,195 discontinued, one failed to requalify, and for 168 patients the study ended before they could complete 2 years of treatment. Therefore, of the patients who had the opportunity to complete 1 and 2 years of treatment, 38.1% and 63.1% discontinued, respectively. In the Kaplan-Meier analysis of time to pregabalin discontinuation, the probability of remaining on pregabalin treatment was 59% at 1 year and 37% at 2 years.

The mean duration of open-label pregabalin treatment was 534 days and the median was 450 days (range 1–1,764 days). The distribution of patients according to their most common pregabalin dose is shown in Fig. 2A. In the analysis of pregabalin dosing in cohorts who were on pregabalin treatment for at least 1, 2, and 3 years, the dose tended to stabilize at approximately 500 mg/day by 6 months of treatment (Fig. 2B). The mean dose among patients who discontinued pregabalin in the first year, when the majority of discontinuations occurred, tended to be lower than in those who stayed on treatment and across quarters ranged from 311–315 mg/day.

Efficacy

The mean percentage reductions in seizures from baseline in those patients who had taken part in the preceding double-blind trials, for all patients, and for the 2-year cohort are shown in Fig. 3. In the analysis of responder rates in all patients, overall 43% had a ≥50% reduction in the 28-day seizure frequency from baseline during their last 3 months of pregabalin treatment. The percentage of patients who were 50% responders in the first 3 months of pregabalin treatment and in their last 3 months of treatment, irrespective of the duration between these periods, was 24%. In the analysis of the 2-year cohort in which different levels of response were evaluated, response rates were consistent over time (Fig. 4).

The percentages of patients who achieved seizure freedom continuously at any time on treatment and during the last period on treatment are shown in Table 2. In the all patient group, 27.3% reached seizure freedom for any 3 months and 6.2% for any year. Rates of seizure freedom in the 2-year cohort were greater than in the all patient group in the analysis of seizure freedom continuously. The rates of seizure freedom in the last periods on treatment were similar in the all patient analysis, the 2-year cohort (Table 2), and in de novo patients alone (data not shown).

Tolerability and safety

Of the 2,061 patients in total who received open-label pregabalin, 1,891 (91.7%) experienced at least one AE and 262 patients (12.7%) discontinued because of AEs. Most AEs were mild or moderate in intensity; only 386 patients (18.7%) experienced AEs that were rated as severe in intensity. The most common AEs generally affected the CNS (Table 3). The AE coded as "thinking abnormal" was reported in 9.8% of patients, but this was not deemed to be suggestive of psychosis or other psychiatric AEs. Peripheral edema was observed in 7.6% of patients. There was only a

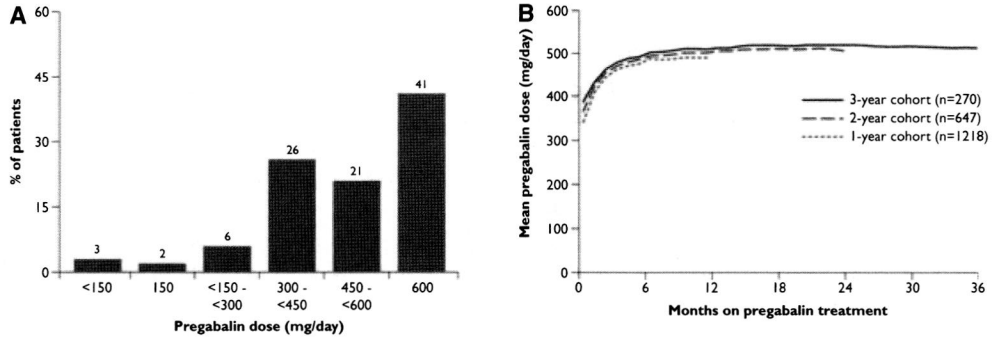

Figure 2.

(**A**) Pregabalin most common dose distribution during open-label treatment and (**B**) mean pregabalin dose in patient cohorts treated for at least 1, 2, and 3 years. The pregabalin dose range varied across the six open-label studies. Across all studies the dose range was 75–600 mg/day. The target dose also varied across studies and ranged between 300 and 400 mg/day.

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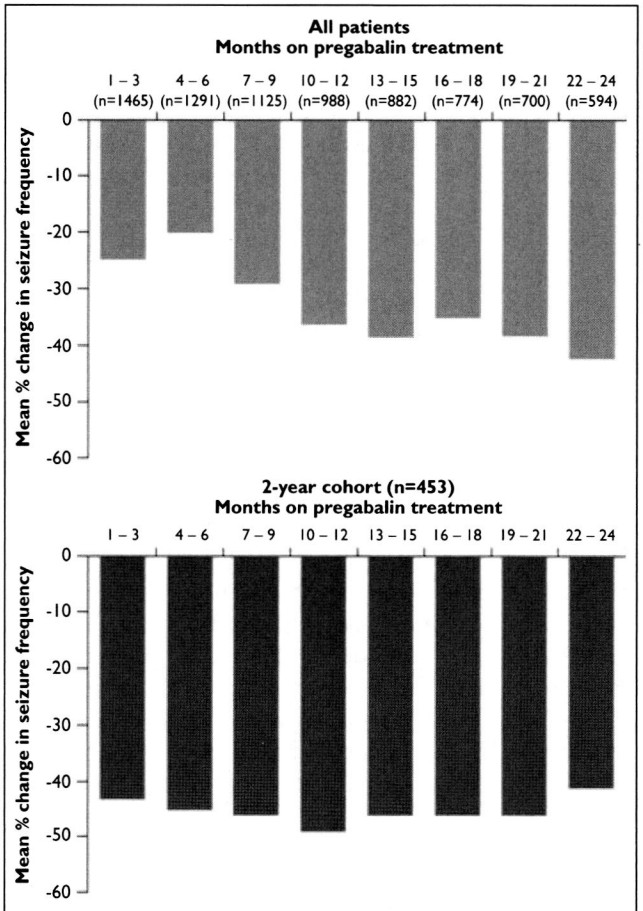

Figure 3.

Mean percentage reduction in 28-day seizure frequency from baseline in all patients and the 2-year efficacy cohort. Mean % change from back-transformed Response ratio (RRatio). Only patients with prospective baseline diary data collected before entry into double-blind studies could be included in this analysis. The baseline 28-day seizure rate was that preceding exposure to active study treatment.

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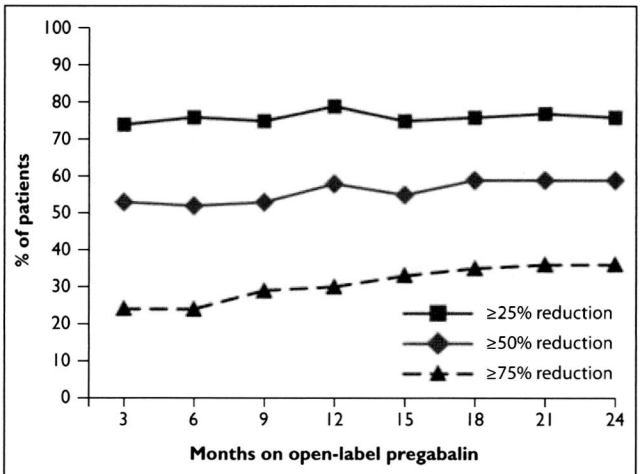

Figure 4.

Percentages of patients with ≥25%, ≥50%, and ≥75% reductions in 28-day seizure frequency from baseline (assessment immediately before initial pregabalin exposure) in the 2-year cohort. The 2-year efficacy analysis cohort includes 453 patients who were treated with pregabalin for at least 2 years and who had complete efficacy assessment data.

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Table 2. Percentages of patients free of seizures in the all-patient group and the 2-year efficacy cohort

	All patients (n = 2,061) (%)	2-year cohort (n = 453) (%)
Any 3 months continuously	27.3	35.8
Any 6 months continuously	11.6	15.7
Any 12 months continuously	6.2	9.3
Last 3 months	19.3	18.1
Last 6 months	8.4	9.5
Last 12 months	5.2	6.0

De novo patients were not included in the 2-year efficacy cohort.

low incidence of AEs that have been associated with certain other AEDs (Wong & Lhatoo, 2000), such as hyponatremia (29 patients, 1.41%.), and glaucoma (one patient). Only in 4 of the 29 patients was hyponatremia considered a serious adverse event, and in none of these four cases was the AE related to pregabalin; two patients were on carbamazepine or oxcarbazepine at the time. Examination of the median onset and duration of the most common AEs (Table 3) indicates that they were mainly observed within the first few weeks of open-label pregabalin treatment and that they tended to be transient in nature. Additional data on AEs are provided in Table S2 of supplemental material appendix.

In patients who had taken part in the preceding double-blind trials, the frequency of some common AEs occurring during the 12 weeks of double-blind treatment was compared with the first 12 weeks of open-label treatment (Table 4). The frequency of these AEs increased when patients switched from double-blind placebo to open-label pregabalin, and decreased when patients switched from double-blind, high-dose pregabalin (600 mg) to open-label flexible pregabalin, when target pregabalin doses were lower. A lower frequency of these AEs was also observed when patients were switched from the semiflexible pregabalin 150–600 mg/day dosing to the truly flexible dosing of the open-label study.

Serious AEs were reported in 309 patients (15.0%); however, in only 21 patients (1.0%) were these considered to be related to treatment with study drug. The most frequent serious AEs experienced were accidental injury (68 patients, 3.3%), pneumonia (21 patients, 1.02%), overdose (14 patients, 0.68%), depression (12 patients, 0.58%), psychosis (10 patients, 0.48%), and cancer (11 patients, 0.53%). Most (20) of the 21 patients experiencing treatment-related

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Table 3. Summary of incidence, time to onset, and duration of most common treatment-emergent adverse events (AEs)[a] (experienced by ≥10% of patients) for all patients[b] in the open-label studies (n = 2,061) and their contributions to discontinuation of treatment

AE	Frequency of AE (%)	Discontinuation due to AE (%)	Median time to onset (days)	Median duration (days)
Dizziness	**30.0**	**1.6**	**19 (9, 28)**	**19 (15, 27)**
Accidental injury	25.3	0.3	215 (174, 251)	20 (16, 28)
Somnolence	**22.8**	**2.0**	**26 (16, 32)**	**57 (44, 67)**
Weight gain	**20.8**	**1.6**	**69 (60, 92)**	**564 (472, 652)**
Infection	20.2	0	243 (212, 293)	10 (8, 11)
Headache	18.2	0.5	159 (122, 192)	30 (15, 43)
Asthenia	17.6	1.3	52 (32, 78)	93 (79, 119)
Pain	14.6	0.1	214 (177, 257)	42 (30, 62)
Ataxia	**12.1**	**0.9**	**42 (28, 69)**	**39 (31, 55)**
Amblyopia	**11.0**	**0.5**	**53 (29, 81)**	**41 (30, 58)**
Diplopia	10.0	0.3	79 (63, 98)	24 (15, 40)

[a]All-causality adverse events under treatment with study drug.
[b]53% of patients were pregabalin naive before entering the open-label studies.
The five most common adverse events as listed in the U.S.A. prescribing information for pregabalin are highlighted in bold text.

Table 4. Comparison of treatment-emergent adverse events observed during the previous 12-week double-blind treatment period and during the first 12 weeks of open-label pregabalin treatment

	DB placebo to OL flexible pregabalin (n = 427)		DB pregabalin 600 mg to OL flexible pregabalin (n = 402)		DB semiflexible pregabalin (150–600 mg)[a] to OL flexible pregabalin (n = 103)	
Adverse event	DB (%)	OL (%)	DB (%)	OL (%)	DB (%)	OL (%)
Dizziness	9.6	23.9	38.8	9.2	22.3	15.5
Somnolence	9.1	15.0	24.6	8.2	18.4	3.9
Ataxia	3.0	10.3	18.9	2.5	9.7	0.9
Weight gain	1.9	10.5	17.4	6.7	21.4	4.9
Amblyopia	3.5	6.6	12.2	2.0	1.9	1.9

Data are given for the five most common adverse events as listed in the U.S. prescribing information for pregabalin. DB, double-blind; OL, open-label.
[a]The average daily dose of flexible-dose pregabalin was 588 mg/day during the final month.

serious AEs recovered from them, with approximately half of these continuing on the same dose of pregabalin and the remainder withdrawing from the study, except for one patient with a visual field defect. This patient developed loss of peripheral vision 2 years after commencing open-label treatment, and this persisted for an additional 8 months, at which point study medication was discontinued. Although the patient had not yet fully recovered at the time of writing, vision was now almost back to baseline levels.

A listing of serious AEs occurring in two or more patients during open-label pregabalin treatment that were not observed during the double-blind or baseline period of one of the six preceding controlled trials is provided in Table S3 of supplemental material appendix. There were 12 cases of carcinoma among 11 patients in these studies. None of these cancers was considered to be related to pregabalin. There were no cases of aplastic anemia, liver failure, or Stevens-Johnson syndrome reported in these studies. There were only four cases of status epilepticus.

A total of 28 patients died in these studies. None of these deaths was considered to be related to pregabalin. Eleven deaths were related to seizures: Three patients died due to aspiration following a seizure, one died due to an obstructed airway caused by vomiting during a seizure, and two died due to grand mal convulsions. Only four of these deaths were actually coded as sudden unexpected death in epilepsy patient (SUDEP), giving a SUDEP incidence of 1.03 per 1,000 person-years. Other causes of death included four deaths related to cardiovascular events, four to intracranial hemorrhage, three to cancer, two to sepsis, one to a fall, one to drowning, and one to pulmonary embolism; in one case the cause of death was unknown.

Nine patients became pregnant during open-label treatment. Five of these pregnancies resulted in live births (following discontinuation of pregabalin when pregnancy had been detected) with healthy offspring at birth and up to 2 years follow-up. Two of the remaining patients experienced spontaneous abortions, and two received elective abortions; three of these patients remained in the study.

An exploratory analysis of weight changes occurring during the first year of open-label pregabalin in the placebo/de novo patients who had not previously received double-

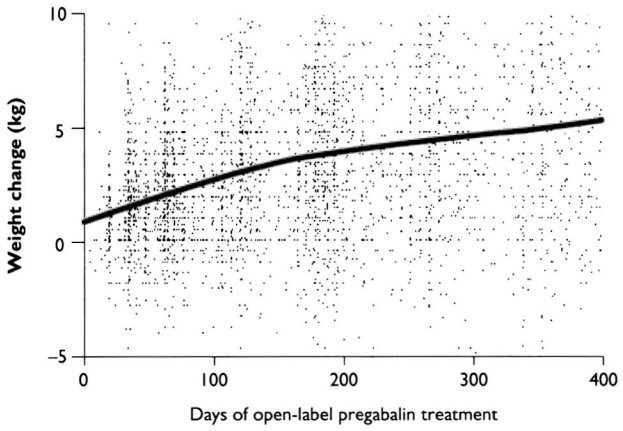

Figure 5.
Weight change (kg) over the first year of open-label pregabalin treatment in patients entering de novo or who received double-blind placebo during the corresponding double-blind trial. Weight measurement was available for 332 patients at 100 days, 183 patients at 200 days, and 87 patients at 300 days.
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blind pregabalin or active comparator revealed a trend toward weight increase (Fig. 5). Typically this weight increase was first evident by the end of 1 month of open-label treatment, and the rate of increase diminished, starting at 4 months. The nonparametric curve estimates of weight change at 1, 2, 4, 6, 9, and 12 months, respectively, were 1.5, 2.1, 3.2, 3.9, 4.6, and 5.2 kg for the placebo/de novo patients. For placebo/de novo patients with no data beyond the first year of open-label treatment, the estimates at 1, 2, 4, 6, 9, and 12 months, respectively ,were 1.4, 2.0, 3.1, 3.7, 4.2, and 4.0 kg. The discontinuation rate attributable to weight changes as an AE was 1.4% in this placebo/de novo population.

There was no pattern of clinically meaningful changes in any laboratory measures. There were no clinically important changes in heart rate or blood pressure during open-label treatment. Twenty three patients were reported to develop a new clinically significant electrocardiography (ECG) abnormality (such as rhythm conduction abnormalities, axis deviation, myocardial infarction, or QRS or ST-T changes). There were no neurologic examination findings of clinical concern noted.

Discussion

The findings presented here are drawn from a large database collected during six open-label studies involving a total of 2,061 patients with treatment-refractory partial onset epilepsy. Patients in these studies were followed for up to several years (14% for ≥3 years), resulting in a total pregabalin exposure of 3,877 person-years and a mean duration of treatment of almost 1.5 years. On entry to these open-label studies, 53% of patients had never previously been exposed to pregabalin. The large sample size combined with the long duration of exposure probably makes pregabalin the most studied AED in a clinical trial setting to date. The combined results from these six open-label studies indicate that adjunctive pregabalin is effective in the long-term, providing clinically relevant seizure control without evidence of tolerance and is generally well-tolerated as for treatment of partial onset seizures in patients with or without secondary generalization, thus confirming data from an earlier analysis of interim data for four of these studies (Ryvlin, 2005).

Over the entire period of follow-up, one-third of patients discontinued because of lack of efficacy, which is not unexpected given the refractory nature of the patients' conditions. We noted that the average pregabalin dose in all patients who discontinued was lower (approximately 300 mg/day) than the average in patients who remained on treatment (approximately 500 mg/day). It is possible that those who discontinued due to lack of efficacy may not have received a sufficient dose and that tolerability may have been a limiting factor for dose escalation.

Among patients who remained on treatment and had prospective baseline seizure assessments, the mean seizure frequency was reduced by 30–50% over the course of the extension trials at each 3-monthly assessment, and 43% were considered responders (i.e., ≥50% seizure reduction from baseline) during their last 3 months of treatment. This magnitude of seizure reduction and the response rate are similar to those observed in the 3-month, double-blind trials (French et al., 2003; Arroyo et al. 2004, Beydoun et al. 2005; Elger et al., 2005). Furthermore, 24% of patients were responders both in the first 3 months and last 3 months of pregabalin treatment, indicating that in a meaningful proportion of patients there was a robust initial response that was sustained. This, along with the finding that the average pregabalin dose tended to stabilize at approximately 500 mg/day by 6 months, indicates that in those patients in whom pregabalin was effective, tolerance did not develop. This is corroborated by the finding that in the cohort of patients treated for at least 2 years who had complete efficacy assessment data the reduction in seizures remained fairly constant at approximately 40–50% at the 3-monthly assessment over the 2 years.

Notable were the rates of seizure freedom observed in this refractory sample. More than one-fourth of all patients treated had a 3-month period continuously free of seizures at some time on treatment; 12% had a 6-month period seizure-free and 6% were free of seizures for a year. Therefore, adjunctive pregabalin treatment enabled meaningful proportions of patients to attain seizure freedom for long periods of time. The finding that 12% of all patients on pregabalin had a 6-month period continuously free of seizures is comparable to the rates of seizure freedom reported for levetiracetam and topiramate in an extensive review of long-term open-label studies of other newer AEDs (Zaccara et al., 2006).

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When interpreting the findings of efficacy analyses such as those presented here, it is important to be cognizant of limitations. One possible limitation is that the patients who actually chose to enter the open-label trials following the double-blind trials might have been different from those who did not, even though they were not aware of double-blind treatment assignment at the time. This does not appear to be the case as previous treatment assignment and response rates were similar among those who did and did not choose to enter the extension trials. Another consideration is that such studies retain only those patients who continue to respond to and tolerate treatment. Although this is undoubtedly true for some patients, it should be noted that retention rates in such trials are influenced by multiple factors different from treatment efficacy and tolerability issues such as patients moving, patients being recruited into new clinical trials, and nonadherence with the study protocol. Nonetheless, over time the sample is likely to be enriched with those who tend to do well, which largely mimics clinical practice. By evaluating seizure reduction in the 2-year cohort, as well as the all-patient group, over time, we observed that patients who stayed on treatment had an initial robust response that was maintained over time, indicating that the robust response in the all-patient group was not just a function of sample enrichment. A further consideration is that concomitant AED treatment was also flexible, and at the last observation 43% of patients had changed concomitant AEDs. The reduction in seizures observed in the entire sample may have been confounded by the change in concomitant AEDs.

In the evaluation of tolerability, the types of AEs were consistent with those previously observed in the short-term, double-blind, placebo-controlled studies. As expected for a CNS-active drug, and taken in combination with other AEDs, CNS symptoms such as dizziness and somnolence were common. Nonetheless, dizziness and somnolence tended to be transient, resolving in a few to several weeks, and infrequently resulted in discontinuation. Accidental injury and weight gain were also among the most frequent non-CNS AEs. Although most patients did experience at least one AE during their long exposure to pregabalin, these were mostly mild or moderate in intensity, and were transient in nature. It is also important to note that some of the AEs observed in these pregabalin studies could actually have been due to addition or changes in concomitant AEDs rather than to pregabalin itself. Approximately 40% of patients had their concomitant AED medication changed over the course of open-label treatment.

Comparison of the frequency of AEs experienced by patients during double-blind and open-label treatment with pregabalin suggests that fewer patients experience common AEs such as dizziness, somnolence, ataxia, weight gain, and amblyopia when pregabalin is administered in a real-world setting with truly flexible dosing. As would be expected, patients who had previously received double-blind placebo did report a higher frequency of these treatment-emergent AEs when they switched to open-label pregabalin. Another predictable observation was that for patients who switched from high-dose double-blind pregabalin (600 mg/day), the frequency of treatment-emergent AEs during open-label treatment was lower than in those previously taking placebo, as these patients mostly moved to a lower dose at the start of open-label (although this could then be increased as necessary for optimum efficacy and tolerability). This is expected, as dosing could be tailored to optimize tolerability (and efficacy) for individual patients. Indeed, in the earlier flexible dosing study, patients in the flexible dosing group experienced fewer AEs than those in the fixed-dose 600 mg/day group (Elger et al., 2005).

The rate of discontinuation due to AEs (13%) compares favorably to those reported for other AEDs in a retrospective clinic-based study involving add-on therapy in treatment-refractory patients with localization-related epilepsy (Datta & Crawford, 2000). In this long-term study in which patients were followed for up to 9 years, withdrawal rates due to AEs for various AEDs were topiramate (42%), tiagabine (11%), gabapentin (16%), vigabatrin (16%), and lamotrigine (15%). The retention rate of 59% at 1 year in the pregabalin open-label extension studies is comparable to long-term studies of other new AEDs (lamotrigine, levetiracetam, and topiramate) that were evaluated in an extensive review (Zaccara et al., 2006). This indicates that the efficacy of pregabalin in reducing seizures, along with the fact that it is generally well tolerated with long-term treatment translates into meaningful clinical benefit in a substantial proportion of patients who voluntarily continued with long-term treatment.

An exploratory analysis of weight changes occurring during the first year of open-label pregabalin in those patients who had not previously received double-blind pregabalin or active comparator indicated that there was a trend toward weight increase. Importantly, however, the rate of weight gain had diminished quite considerably by 4 months of open-label treatment, and few patients discontinued as a direct result of weight gain (1.6% overall). Indeed, estimates of weight change in patients discontinuing during the first year indicate little gain after the first 6 months, suggesting that for most patients, weight change was not a reason for discontinuation.

Overall, the incidence of serious AEs was similar to those in another report in patients with uncontrolled seizures (Baker et al., 1997). Very few patients (21) on pregabalin experienced serious AEs that were considered to be related to treatment. Reassuringly, all except one of the 21 patients experiencing treatment-related serious AEs have fully recovered from them, and the one remaining patient, who developed a visual field defect, has almost recovered at the time of writing. It is also

encouraging, given the high number of patient-years of exposure, that there was no case of aplastic anemia, liver failure, or Stevens-Johnson syndrome in these studies. Therefore, if these events do occur with prolonged pregabalin exposure, they are likely to be extremely rare. An encouraging observation is the low number of cases of status epilepticus reported during these studies. There were only four cases of status epilepticus, giving an overall frequency of 0.19%, which is certainly well within the expected range for this type of refractory population. For example, retrospective analysis of National Society for Epilepsy records for patients with refractory localization-related epilepsy has found frequencies of nonconvulsive status epilepticus of 2.7% and 7.8% for non-tiagabine and tiagabine-treated patients, respectively (Koepp et al., 2005). There were no laboratory or ECG findings of clinical concern.

During these open-label studies, cancer was reported in 11 patients, giving an overall incidence of cancer in the study population of 534 cases per 100,000. Therefore, long-term pregabalin treatment does not appear to be associated with any increased risk of cancer development, as this incidence is comparable to recent estimates of cancer incidence in the general U.S. population of around 490 cases per 100,000 (National Cancer Institute, NIH, DHHS, 2005).

Published studies report that the incidence of SUDEP in the general epilepsy population ranges from around 0.35 to 10 cases per 1,000 person-years and may be as high as 3–9 cases per 1,000 person-years in patients with severe refractory seizures, such as those included in the present studies (Tellez-Zenteno et al., 2005; Tomson et al., 2005). Therefore, in the current studies involving 3,877 person-years of treatment in subjects who were highly refractory to treatment, one would have expected at least 11.6 cases of SUDEP. Four epilepsy-related deaths were actually classified as SUDEP, and there were only 11 epilepsy-related deaths overall, meaning that the incidence of SUDEP in these studies (1.03/1,000 patient-years) was similar to that reported in medically intractable patients with epilepsy (Nashef et al., 1995; Shorvon, 1996). This may be the result of the additional seizure control provided by long-term pregabalin treatment or due to more careful care as part of being in a study.

In conclusion, add-on pregabalin offers promise in achieving significant and sustained seizure control among patients with poorly controlled partial-onset epilepsy. Overall, add-on pregabalin was well tolerated in these open-label studies over several years of treatment and no new safety concerns were identified with long-term treatment.

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We, the authors, confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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Supporting Information

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

Table S1. Summary of patient characteristics before entry to the lead-in double-blind study (double-blind patients) or before entry to the open-label trial (de novo patients) (ITT population).

Table S2. Summary of most common treatment-emergent adverse events (experienced by at least 5% of patients for all patients entering an open-label trial; n = 2,061). Data given for onset and duration are the median with 95% confidence limits. The five most common adverse events as listed in the U.S. prescribing information for pregabalin are highlighted in bold text.

Table S3. Serious adverse events occurring in ≥2 patients during open-label pregabalin treatment that were not observed during the double-blind or baseline period of one of the six preceding controlled trials.

Data S1. Investigators.

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