

Pregabalin in the management of partial epilepsy

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Abstract: Pregabalin is a new antiepileptic medication that works by binding to alpha 2 delta subunit of the voltage-dependent calcium channels present in presynaptic neurons. Its pharmacokinetic advantages include rapid and almost complete absorption, lack of protein binding, linear kinetics, absence of enzyme induction, and absence of interactions with other drugs. Pregabalin was found effective as adjunctive therapy for refractory partial-onset seizures, with up to 51% responder at a dose of 600 mg/day. The lowest effective dose was 150 mg/day. Pregabalin is also approved for treatment of painful diabetic polyneuropathy, postherpetic neuralgia and pain with fibromyalgia. Studies also suggest a beneficial effect on sleep and generalized anxiety disorders. Its main adverse effects in randomized adjunctive trials in adults have been mild to moderate. Most common side effects were dizziness, ataxia, somnolence and diplopia. Weight gain was not prominent in pivotal pregabalin trials, but was more problematic in long-term postmarketing analyses in epilepsy patients. Pregabalin, with its potent antiseizure effect, favorable pharmacokinetic profile, and effectiveness in common co-morbidities is an important addition to the treatment of epilepsy.

Keywords: epilepsy, seizures, pregabalin, pharmacology, antiepileptic drugs, tolerability

Epilepsy is a common chronic neurological disorder that affects 0.5% to 1% of the population,¹ and presents with recurrent unprovoked epileptic seizures. Surgical treatment may be curative in selected patients but overall there is no curative therapy for all epilepsy patients, and therapy is usually directed to prevention of seizures with antiepileptic drugs (AEDs). The management of epilepsy should be geared towards complete control of seizures while minimizing the occurrence of adverse events and improving the patient's quality of life.² Approximately two thirds of patients become seizure-free with AED therapy, leaving the remaining third with persistent seizures.³ Patients may have to take AEDs for the rest of their life. Thus there is a need for newer and better-tolerated AEDs.

Before 1993 a limited number of AEDs were available. A variety of antiepileptic drugs have been introduced over the last 15 years. All of the newer AEDs have been shown to be effective as adjunctive agents in partial epilepsy. Marson et al's meta-analysis has shown that the response and tolerability of new AEDs in patients with refractory epilepsy are similar. Each drug was significantly better than placebo at preventing seizures.⁴

Pregabalin is the latest addition in the antiepileptic medication regimen in the United States. It was approved by Food and Drug Administration in 2005 as an add-on therapy for partial epilepsy, for painful diabetic polyneuropathy, postherpetic neuralgia, and fibromyalgia.

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Mechanism of action

Pregabalin was designed to be an analogue of GABA, but it does not act at GABA receptors.⁵ Pregabalin does not act on sodium channels, potassium channels, or glutamate receptors. Like gabapentin it works by binding to alpha 2 delta subunit of the P/Q-type voltage-sensitive Ca²⁺ channels (VSCC) which are present in presynaptic neurons.^{6,7} It does not block calcium channels rather it modulates calcium channels.⁶ In various animal models pregabalin exhibits anticonvulsant, anxiolytic and analgesic properties.⁵

Pharmacology

Pregabalin is rapidly and completely absorbed after oral dosing in the fasting state (bioavailability is >90%). Its absorption is not dose-dependent. Maximal plasma concentrations are reached in 1 hour after single or multiple doses, and steady state is achieved within 24 to 48 hours after repeated administration. Therefore, pregabalin can be taken with or without food. The pharmacokinetics of pregabalin is linear and predictable across the therapeutic dosage range (150 to 600 mg/day). Pregabalin has a plasma half-life of 6.3 hours. It has to be given in 2 or 3 divided doses. It reaches steady-state plasma levels within 1 or 2 days of dosing.

Pregabalin is not protein bound and is excreted virtually unchanged by the kidneys. AEDs by the virtue of their protein binding and hepatic metabolism commonly results in important drug interactions that can have life-threatening clinical consequences.⁸ Pregabalin does not go through any significant hepatic metabolism. Pregabalin does not inhibit or induce hepatic enzymes. These properties enable it to cause no significant interactions with concomitant medications, eg, oral contraceptives.^{9,10} As was evident in a study of patients with refractory partial seizures in open-label, multiple-dose study with pregabalin 600 mg/day, given as 200 mg 3 times a day for 7 days, in addition to maintenance monotherapy with valproate (VPA), phenytoin (PHT), lamotrigine (LTG), or carbamazepine (CBZ). The baseline antiepileptic medications were unaffected by concomitant pregabalin administration.¹¹ However in another study

pregabalin level decreased by 20% to 30% in the presence of enzyme-inducing antiepileptic drugs (eg, carbamazepine).¹² Because pregabalin is excreted mostly unchanged through kidney, there is less need for therapeutic drug monitoring. However drug monitoring may be useful based on intra-individual comparisons of drug serum concentrations.¹³ Its excretion is proportional to creatinine clearance. In patients with renal insufficiency pregabalin dose has to be adjusted according to the creatinine clearance if lower than 60 mL/min. A 50% reduction in pregabalin daily dose is recommended for patients with creatinine clearance between 30 and 60 mL/min. Pregabalin daily doses should be further reduced by approximately 50% for each additional 50% decrease in creatinine clearance, as noted by Randinitis et al.¹⁴

Pregabalin clinical trials

Pregabalin's efficacy and safety have been studied in patient with partial epilepsy, with or without secondary generalization as an add-on therapy. Pregabalin was studied in 4 randomized, double-blind, placebo-controlled trials (Table 1).

French et al studied pregabalin's efficacy, safety, and tolerability in patients with partial seizures and to confirm the dose-response relationship. In this multicenter, double-blind, randomized, placebo-controlled, parallel-group study, patients were given pregabalin in 2 divided doses over a 12-week double-blind phase.¹⁵

Patients with refractory partial seizures on 1 to 3 antiepileptic drugs were randomized to one of the five treatment groups (placebo or 50, 150, 300, and 600 mg/day pregabalin, all administered twice daily). The intent-to-treat analysis included 453 patients. Seizure frequency reductions from baseline analyses showed 7% in the placebo group, 12% in the 50 mg/day arm, 34% in the 150 mg/day arm, 44% in the 300 mg/day arm, and 54% in 600 mg/day arm.¹⁵

Seizure responder rates (50% or more reduction in seizure frequency) were 14% in placebo group, 15% in the 50 mg/day arm, 31% in the 150 mg/day arm, 40% in the 300 mg/day arm and 51% in the 600 mg/day arm. There was trend of better

Table 1 Summary of randomized, double-blind, placebo-controlled trials with pregabalin

Author	Doses used (mg/day)	Seizure responder rate (%)	Discontinuation rate (%)	Most common side effects
French ¹⁵	50, 150, 300, 600 in BID doses	15, 31, 40, 51	7, 1.2, 14, 24	Somnolence, dizziness
Arroyo ¹⁶	150, 600 in TID doses	14.1, 43.5	10, 18.5	Dizziness, somnolence
Beydoun ¹⁷	600 in BID vs TID doses	43, 49	26, 19	Dizziness, somnolence
Elger ¹⁸	600 in BID vs 150–600 flexible dose	45.3, 31.3	33, 12	Dizziness, ataxia

Abbreviations: BID, given in two divided doses; TID, given in three divided doses.

efficacy with higher doses. The 150 to 600 mg/day pregabalin groups were associated with greater reductions in seizures ($P \leq 0.0001$) and greater responder rates compared with the placebo group ($P \leq 0.006$). However the discontinuation rate due to side effects was also higher with higher dosages (5% in placebo, 7% in the 50 mg/day group, 1.2% in the 150 mg/day group, 14% in the 300 mg/day group, and 24% in the 600 mg/day group). Most adverse events were of mild or moderate intensity, tended to occur sooner after initiation of pregabalin and resolved while patients remained on study treatment. Most common side effects were dizziness and somnolence.

Arroyo et al did a dose response study with pregabalin. In a multicenter 12-week, double-blind, randomized study in refractory partial epilepsy patients they evaluated pregabalin 150 mg/day vs 600 mg/day given in three divided dose.¹⁶ Pregabalin was significantly more effective than placebo in reducing the risk ratio (RR, a simple transformation of the seizure data and allows for the use of parametric statistics) in both 150 mg/day and 600 mg/day groups (-11.5 [$P = 0.0007$] and -31.4 [$P \leq 0.0001$], respectively).¹⁶

The RR values corresponded to seizure-frequency reductions from baseline of 1.8%, 20.6%, and 47.8% for placebo, 150 mg/day, and 600 mg/day, respectively. They found that pregabalin efficacy was dose-related and more patients on pregabalin were responders compared to placebo ($P < 0.0001$). Responder rate for the 600 mg/day pregabalin group was statistically superior to that of the 150 mg/day pregabalin group ($P \leq 0.001$).

Pregabalin was well tolerated in this study. Adverse events were mostly mild or moderate in intensity. Most common side effects reported were somnolence, dizziness, ataxia, diplopia, and weight gain. The median duration of any adverse events was similar among the 600 mg/day pregabalin group (54 days) and the placebo group (55 days) and was shortest in the 150 mg/day pregabalin group (28 days). The withdrawal rate because of adverse events was higher in the 600 mg/day group (18.5% at 600 mg/day vs 10% at 150 mg/day; 6.2% in the placebo group).

Bejdoun et al studied pregabalin given in two vs. three divided doses in a multicenter, double-blind, randomized, parallel-group, placebo-controlled 12 weeks trial of refractory partial epilepsy patients.¹⁷ Pregabalin 600 mg/day dose was administered in two or three divided doses. Pregabalin resulted in significant seizure frequency reductions compared to placebo ($P < 0.0001$) (53% for three times a day group vs 44% for twice daily group vs 1% increase for placebo). Fifty percent responder rates were 49% for three times a day group vs 43% for twice daily group compared with 9% for placebo ($P < 0.001$).¹⁷

The majority of side effects were mild to moderate in intensity in this study. Overall, dizziness was most frequently occurring side effects in all three treatment groups and it was dose dependent (38% for three times a day and 42% for twice daily) than in placebo-treated patients (12%). Other adverse events (AEs), eg, somnolence, ataxia, weight gain, amblyopia, asthenia, diplopia, and abnormal thinking occurred more frequently in patients randomized to the pregabalin groups. The withdrawal rate owing to adverse events was higher in the twice daily group than the three times a day group (26% vs 19%).¹⁷

Elger et al studied pregabalin in fixed vs flexible dosing in randomized, double-blind, placebo-controlled 12 week study of patients with partial seizures refractory to AED treatment.¹⁸ Pregabalin was given either in fixed dose of 600 mg/day given twice daily, or flexible dose of 150 to 600 mg/day given twice daily. Pregabalin resulted in a reduction in seizure frequency of 35.4% for the pregabalin flexible-dose group, and 49.3% for the pregabalin fixed-dose group compared with 10.6% for the placebo group.¹⁸ Most adverse events were mild to moderate. Overall, dizziness was the most frequent side effect in all three treatment groups and was dose-dependent (5.3% for the flexible dose group and 13.9% for the fixed dose group; placebo 0%). Other side effects seen more frequently in the pregabalin-treated group were ataxia, asthenia, somnolence, vertigo, and diplopia. The withdrawal rate owing to adverse events was higher in the fixed- than the flexible-dose group (32.8% vs 12.2%).¹⁸

In all these four randomized placebo-controlled parallel trials of pregabalin as an add on therapy for partial epilepsy, the odds ratio for a $\geq 50\%$ reduction in seizure frequency was 3.56 (CI 2.60 to 4.87) for pregabalin (all doses pooled) relative to placebo.¹⁹

The long-term efficacy of pregabalin as add on therapy in partial epilepsy was studied in four long term open label extension studies of 1480 patients. Majority of patients received pregabalin ≥ 450 mg/day. Over the last 6 and 12 months of pregabalin across these studies, proportion of seizure freedom ranged from 7.4% to 24.2% and from 4.5% to 18.4%. Seizure responder rates were 41% to 60% during the subsequent 6, 12, or 24 months.^{20,21}

Postmarketing epilepsy studies

Since the marketing of pregabalin a number of published open-label and placebo controlled studies have confirmed the efficacy of pregabalin. Selected studies are presented in relation to specific aspects of pregabalin.

In a placebo-controlled randomized study of pregabalin in refractory epilepsy, patients were randomized to adjunctive

pregabalin fixed dose (600 mg/day twice daily), or pregabalin flexible dose (150 and 300 mg/day for 2 weeks each; 450 and 600 mg/day for 4 weeks each, twice daily) or placebo for 12 weeks.²² Dosage was adjusted based on tolerability and maintained when a 4-week seizure-free period was achieved. Both pregabalin regimens significantly reduced seizure frequency compared with placebo, by 35.4%, for flexible dose ($P = 0.0091$) and 49.3% for fixed dose ($P = 0.0001$) vs 10.6% for placebo, and the fixed-dose group was superior to the flexible-dose group ($P = 0.0337$). Most adverse events were mild or moderate and incidence of adverse events and discontinuations were lower in patients when dosing was individualized to optimize efficacy and tolerability. Discontinuation rates due to adverse events were higher in fixed dose group and discontinuation was earlier than other groups (32.8% fixed vs 12.2% flexible group).²²

In another trial evaluating cost effectiveness of pregabalin to other antiepileptic medications, the cost-effectiveness of pregabalin therapy in terms of cost per seizure-free day gained or cost per quality-adjusted life-years gained compares favorably with published estimates for other add-on antiepileptic medications.²³

In analysis of pooled patient data from four short-term placebo studies of pregabalin (150 to 600 mg/day) demonstrates that pregabalin is an effective and well tolerated add-on treatment for partial seizure with or without secondary generalization.²⁴ Weight gain, reported by 5.4% to 17.1% of patients across pregabalin dosing groups, was dose-related (highest in the 600 mg/day group) and resulted in withdrawal from study in only 0.74% (6/810, 4 of whom were in 600 mg/day group) pregabalin-treated subjects. Weight gain reached steady state in 85 days.²⁴

Weight gain has been a significant adverse effect with pregabalin. In another study evaluating the utility of short counseling program to prevent weight gain, showed the mean bodyweight increase, compared to baseline, of 2.5 kg (SD \pm 3.7 kg; median: 2.0 kg) and 4.0 kg (SD \pm 4.1 kg; median: 4.0 kg; N = 60) at the 3- and 6-month follow-up, respectively.²⁵ The body mass index increment was 0.9 (SD \pm 1.3; median: 0.6) and 1.4 (SD \pm 1.4; median: 1.3) for the 3- and 6-month follow-up, respectively.²⁵

Pregabalin in epilepsy patients with intellectual and developmental disability

Epilepsy is common in patients with intellectual and developmental disability (I/DD) and they tend to have medically

refractory epilepsy, often with multiple seizure types.²⁶ Pregabalin efficacy and tolerability has been studied in institutionalized patients with epilepsy and intellectual and developmental disability (I/DD) mostly in a retrospective study design.^{27,28} Huber et al retrospective study of pregabalin in 32 institutionalized patients with therapy-resistant epilepsy and intellectual disability showed modest efficacy.²⁸ The retention rate was 75% after 6 months. Six patients (18.75%) were responders (50% seizure reduction). No patient was seizure free. Eight patients had side effects that were essentially impairing. Weight gain, somnolence, asthenia, and ataxia were the most frequent adverse effects. Rare adverse events were severe mental slowing and loss of daily life capacities on a low dose of pregabalin in one patient and increase in auto-aggression in another patient. After 12 months, the retention rate dropped to 40.6%, the responder rate was 25%, and one patient was seizure free.

Modur et al studied efficacy and tolerability of pregabalin in a retrospective study of seven institutionalized patients with I/DD.²⁷ The primary efficacy measure was the change in the median frequency of seizure days per week between the baseline (8 weeks prior to initiating pregabalin) and treatment (12 weeks of titration and maintenance) periods. The mean dose of pregabalin was 293 mg/day (range 150 to 350 mg/day). Pregabalin was efficacious, resulting in a significant reduction in the median frequency of seizure days/week between baseline and treatment (1.38 vs 0.50, $P = 0.018$). The 50% responder rate was 71%. The adverse effects at last follow-up (mean 13 months) included weight gain, myoclonus, and sedation. Though Modur et al study had a smaller sample size but their responder rate was better than Huber study. The reason for the discrepancy may be that these studies had different dosages – mean dose 390 mg/day in Huber vs 293 mg/day in Modur. Modur et al studied efficacy at the end of 12 weeks of treatment while Huber evaluated efficacy at 6 months and 12 months of treatment; thus Huber et al had a longer study duration that may account for the relatively low responder rate.

In a postmarketing retrospective analysis, efficacy and tolerability of pregabalin was studied over 15 months, in 119 patients from two epilepsy clinics. Forty-six (38.6%) patients had discontinued pregabalin, 33% (15/46) of patients discontinued pregabalin for lack of efficacy, while 66% stopped pregabalin for adverse effects.²⁹ The most common adverse effect causing discontinuation was behavioral and psychiatric adverse effects, including agitation, irritability, and depression (9 patients – 20% of those discontinuing). Weight gain was the second most common reason for

discontinuation (7 patients, 15%). The average weight change was +12 lb (5.5 kg) (range -8 to +71 lb; 3.6 to 32.3 kg) and average weight change per month was 1.1 lb (0.5 kg).²⁹ Twenty-nine (33%) patients had a >10% increase in weight. The median reduction in seizure frequency was 41%. Pregabalin efficacy postmarketing was similar to that in clinical trials. However, behavioral adverse effects and weight gain were the most important reasons for discontinuation.

Pregabalin is the latest addition to the armamentarium against epilepsy. Its pharmacological and pharmacokinetic properties make it favorable for its use in clinical practice. Pregabalin's potent anticonvulsant activity (seizure responder rate of 51%) is helpful in its clinical use. In clinical trials pregabalin has been found to be highly effective and well tolerated as adjunctive therapy for the treatment of patients with partial onset seizures with or without secondary generalization. Pregabalin's predictable oral absorption, lack of interaction, lack of protein binding, lack of hepatic metabolism, and linear pharmacokinetics are favorable. However weight gain, behavioral adverse effects, and myoclonus have to be carefully monitored by the clinicians while using pregabalin.

Effect on sleep in epilepsy patients

Sleep problems are a common issue with epilepsy patients and lack of sleep can worsen seizures. Pregabalin has been reported to enhance NREM sleep and reduces REM sleep in rats.³⁰ Similarly in humans it improves sleep quality. In a trial of adult patients with partial epilepsy treated with pregabalin underwent 24-hour ambulatory polysomnography. Sleep quality was assessed with Epworth Sleepiness Scale (ESS) before and after 3 months treatment with pregabalin.³¹ A significant increase in REM sleep and a decrease of stage 2 NREM sleep was noted with pregabalin use. Epworth Sleepiness Scale showed a significant increase in the score but did not reach the pathological cut-off value (mean ESS score <10). The increase in REM sleep may indicate an improvement in nocturnal sleep quality while the increase of ESS score indicates that daytime somnolence is a minor adverse effect of pregabalin.³¹

Pregabalin in other neurological/psychiatric disorders

Comorbidities are important considerations in epilepsy patients in choosing the AED. AEDs are now often used to treat other disorders besides epilepsy and their efficacy is established in some non-epilepsy disorders both in neurology and psychiatry.³² In a randomized controlled 5-week trial of

pregabalin in diabetic peripheral neuropathic pain, patients on doses of 300 or 600 mg/day showed significant improvements in endpoint mean pain score vs placebo ($P = 0.0001$).³³ Sustained improvements in pain and sleep quality were seen as early as week 1. A dose-related response was seen as a 50% reduction in pain compared to baseline at 46% in the 300 mg/day arm and 48% in the 600 mg/day arm. Pregabalin was well tolerated with a low discontinuation rate.³³ This trial showed pregabalin's efficacy in the treatment of diabetic peripheral neuropathic pain.

In another randomized controlled 8-week trial of pregabalin in the treatment of postherpetic neuralgia, pregabalin-treated patients had significantly greater decreases in pain score than placebo (3.60 vs 5.29, $P = 0.0001$).³⁴ Pain was significantly reduced very early in the trial. Similar to the trial in diabetic peripheral neuropathy, sleep also improved in patients treated with pregabalin compared to placebo ($P = 0.0001$). The side effects were generally mild to moderate.³⁴

More recently pregabalin was studied in fibromyalgia in a randomized, controlled 13-week trial.³⁵ Patients in all pregabalin groups (300, 450 and 600 mg/day) showed statistically significant improvement in endpoint mean pain score. Similarly, all patients showed statistically significant improvement in assessments of sleep.³⁵ Dizziness and somnolence were the most frequently reported adverse events.

Pregabalin has been evaluated for generalized anxiety disorder in 4 placebo-controlled clinical trials. Patients were randomized to 6 weeks of double-blind treatment with pregabalin 400 or 600 mg/day, venlafaxine 75 mg/day, or placebo.³⁶ Pregabalin showed significantly greater improvement in anxiety score even at week 1. Pregabalin was concluded to be safe, well tolerated, and rapidly efficacious across the physical-somatic as well as the emotional symptoms of anxiety in primary care and psychiatric settings. Pregabalin has been approved in the European Union for generalized anxiety disorder.

Pregabalin tolerability

Pregabalin was found to be very well tolerated in the initial placebo-controlled adjunctive trials in partial epilepsy. The treatment-related adverse events were mild to moderate, appeared in the beginning of treatment, and resolved while patients remained on study treatment. Most common side effects were dizziness, ataxia, somnolence, and diplopia. Weight gain and behavioral side effects were not prominent in pivotal pregabalin trials. However in postmarketing analysis of pregabalin in epilepsy patients, the most common adverse effects causing discontinuation were behavioral

adverse effects (agitation, irritability, and depression) and weight gain. Of note, no systemic side effects have been seen with pregabalin but myoclonus has been reported in 4 patients who developed new onset myoclonus at a dose of 50 to 600 mg/day.³⁷ Patients had focal or multifocal myoclonus without any EEG changes. Myoclonic jerks significantly decreased after dose reduction of pregabalin.³⁷

Place of pregabalin in epilepsy therapy

Pregabalin is effective in partial epilepsy, but its efficacy in generalized epilepsy is not established. It should be considered as an early adjunctive therapy in partial epilepsy because of its ease of use, linear kinetics and lack of drug–drug interactions.^{19–21,24,38} Pregabalin's lack of drug–drug interaction makes it a particularly good choice in elderly patients who commonly are on multiple medications. In patients with hepatic insufficiency pregabalin along with levetiracetam and gabapentin are a good choice because of the absence of hepatic metabolism. Pregabalin's efficacy in multiple conditions makes it an earlier choice in epilepsy patients who suffer from such conditions. Since anxiety is a common comorbidity in epilepsy patients,³⁹ patients with epilepsy and anxiety may benefit from pregabalin. Similarly in epilepsy patients with diabetic polyneuropathy and fibromyalgia, pregabalin would be a very appropriate add-on therapy.

Because of the potential side effect of weight gain patients should be counseled about routine exercise and their weight should be closely monitored when they are started on pregabalin. Similarly patients started on pregabalin should also be monitored for behavioral adverse effects, especially in epilepsy patients with intellectual and developmental disability.

The prescribing information recommends an adult starting dose of 50 mg three times a day or 75 mg twice a day, with subsequent escalation by 100 to 150 mg every week up to a maximum of 300 mg twice daily. These recommendations are based on the dose used in pivotal trials. However because of clinical experience and evidence from postmarketing analyses, the author favors a lower starting dose of 50 mg twice daily or 75 mg at bedtime because of excessive sedation especially in elderly patients, with escalation to 75 mg twice daily after 1 week if the starting dose is well tolerated. In patients at higher risk for behavioral–psychiatric adverse effects, the starting dose can even be smaller, at 50 mg at bedtime. In patients who tolerate pregabalin but still have uncontrolled seizures on 300 mg twice a day, the author recommends splitting the dose to 200 mg three times

a day for better efficacy. However three times a day dosing may decrease compliance and hence benefits and risks have to be weighed.

Overall pregabalin is a good addition to the armamentarium against epilepsy. Its reliable absorption, linear kinetics, better efficacy, lack of drug–drug interaction, and lack of hepatic metabolism make it an attractive adjunctive therapy in controlling seizures. Pregabalin monotherapy trials will be needed to evaluate it as first-line therapy in new onset epilepsy or for conversion monotherapy in less refractory partial epilepsy.

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