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REVIEW

Pregabalin: A new antiepileptic drug for refractory epilepsy

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Summary Pregabalin is a recently licensed and marketed antiepileptic drug for use as adjunctive treatment of partial epilepsy. It acts at presynaptic calcium channels, modulating neurotransmitter release in the CNS, properties it shares with gabapentin. Its clinical development over the past decade has included its use in the treatment of neuropathic pain, and generalized anxiety disorder, in addition to epilepsy. Three multi-centre randomised, double-blind, placebo-controlled trials enrolling patients with refractory partial epilepsy have demonstrated an antiepileptic effect of pregabalin against placebo, as adjunctive therapy, with 31—51% of patients showing a 50% reduction in seizure frequency. Adverse effects were dose related, the commonest being somnolence, dizziness, and ataxia. Weight gain was seen in 14% of patients on the highest dose of 600 mg/day. Around 9000 people have been exposed to pregabalin in its development for all indications. No idiosyncratic reactions have been described to date. Pregabalin may be a useful addition in the treatment of refractory partial epilepsy. As with all new AEDs long-term follow up and post marketing surveillance is required.

Contents

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Introduction

Up to 70% of people diagnosed with epilepsy become seizure free with single or combination antiepileptic drug (AED) therapy.[1] The remaining continue to have seizures despite optimal AED therapy. Depending on the seizure substrate a small number of these may benefit from epilepsy surgery.[2] AEDs, however, remain the mainstay of treatment. Those in whom seizure control remains elusive are subject to higher doses and combinations of AEDs with subsequent increased risk of side effects and drug–drug interactions. Lifestyle implications of treatment are therefore as important as seizure control, the primary goal of therapy being seizure reduction with minimal side effects.

Since 1989 nine new anti epileptic drugs (AEDs) have been licensed for the treatment of epilepsy in the UK. These include vigabatrin, lamotrigine, gabapentin, topiramate, tiagabine, oxcarbazepine, levetiracetam and most recently pregabalin and zonisamide. Vigabatrin has now restricted use due to the development of visual field defects as a chronic side effect.

Studies of any new AED are required to satisfy regulatory authorities with regards efficacy and safety prior to licensing.[3] Ethical considerations require that study design maintains patients on established treatments with new AEDs as add on therapy, hence their initial licensed use as adjunctive therapy. Subsequent monotherapy licensing is achieved after a period of post marketing surveillance and recognized efficacy in clinical use. Of the 'new' AEDs, lamotrigine, topiramate and oxcarbazapine are licensed in the UK for monotherapy use. A number of further AEDs are in the developmental phase. These include amongst others carabersat, lacosemide, rufinamide, safinamide, talampanel and valrocemide.[4] Therapeutic options in epilepsy are therefore increasing rapidly and detailed knowledge of the new drugs is necessary for appropriate treatment recommendations.

Pregabalin has been in the development pipeline for just over a decade. Its role in the treatment of two other common conditions: neuropathic pain,[5] and generalized anxiety disorder[6] in addition to epilepsy has been evaluated simultaneously. This is timely in view of the widespread "off label" use of other antiepileptic drugs, for these conditions. As a consequence around 9000 people have received the drug during the clinical development programme for all indications, totaling about 6500 patient/years exposure.

Pregabalin like gabapentin is a structural, but not functional analogue of the neurotransmitter gamma-aminobutyric acid (GABA). Pregabalin has shown greater potency than gabapentin in preclinical models of epilepsy and pain[7] in addition to anxiolytic properties.[8] It is hydrophilic but readily crosses the blood brain barrier. Pregabalin binds potently to the α_2-δ subunit, an auxiliary protein associated with voltage-gated calcium channels in the CNS, attenuating depolarization-induced Ca^{2+} influx in nerve terminals (Fig. 1).[9] This results in reduction of glutamate,[10] noradrenaline[11] and substance P[12] release. Pregabalin is inactive at $GABA_A$ and $GABA_B$ receptors and it has no effect on GABA uptake or degradation.

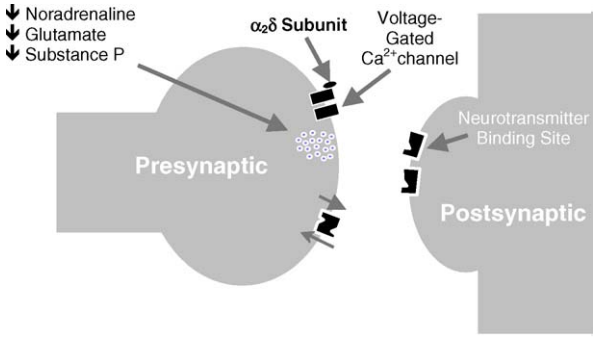

Figure 1 Schematic of pregabalin mode of action. Binding to the α_2-δ subunit of voltage-gated calcium channels to modulate calcium influx and hence neurotransmitter release.

Pregabalin is active in a number of animal models of epileptic seizures including maximal electroshock-induced tonic extensor seizures in mice and rats,[13] hippocampal kindled rats[14] and threshold clonic seizures from the convulsive agent pentylenetetrazol and genetic mouse models, with a greater potency than gabapentin.[7] In animal models of spontaneous absence seizures (i.e. Wistar rats), spike wave activity was not blocked by pregabalin[7] suggesting that like gabapentin, pregabalin should be avoided in the treatment of idiopathic generalized epilepsy.

Pregabalin exhibits linear pharmakokinetics. There is no protein binding or hepatic metabolism. It is renally excreted. No drug–drug interactions have been identified during its development, but pregabalin is additive in the impairment of cognitive and motor function when taken with oxycodone (an opiate analgesic) and may potentiate the effects of lorazepam and alcohol.[15]

Review of randomised-controlled trials

The efficacy and tolerability of pregabalin in the treatment of epilepsy has been investigated in three multi centre randomised, double-blind, placebo-controlled trials, as adjunctive therapy in patients

Table 1 Outline of the three double-blind randomised placebo-controlled trials of pregabalin in the treatment of patients with refractory partial epilepsy

Trial	Total daily dose (mg/day)	Dose regime	Titration	Treatment	*N*(ITT)	Location
French et al.[16]	50	25 mg BD	None	12 weeks	453	USA
	150	75 mg BD				Canada
	300	150 mg BD				
	600	300 mg BD				
Arroyo et al.[17]	150	50 mg TDS	None	12 weeks	287	Europe
	600	200 mg TDS	None			Australia
						South Africa
Beydoun et al.[18]	600	200 mg TDS	None	12 weeks	312	USA
	600	300 mg BD				Canada

with refractory focal epilepsy (Table 1).[16–18] A total of 1052 patients were entered into these studies, 758 randomized to the treatment arms and 294 to placebo arms. Study protocols were similar to those of other second generation AEDs developed over the past 10 years. Patients recruited had refractory partial seizures. An 8-week baseline monitoring period was followed by a 0–1-week titration phase and 12-week treatment phase with placebo or drug, with the option to continue with an open label phase. Inclusion criteria included partial seizures refractory to medical therapy, greater than six partial seizures in the 8-week baseline monitoring period and no 4-week period free of seizures during baseline. Patients were taking at least one but not more than three AEDs. Baseline AEDs were continued throughout the trial period. Exclusion criteria included significant medical or psychiatric illness; seizures caused by an underlying medical illness, absence seizures, Lennox Gestaut syndrome or status epilepticus in the year prior to entry (see Table 2 for baseline characteristics).

Table 2 Baseline characteristics patients recruited in the three randomized placebo-controlled trial of pregabalin[16–18]

Age (mean (range))	38 (12–82) years
Age at diagnosis (mean (range))	13.7 (0–73.5) years
Duration of epilepsy (mean (range))	25 (0.5–71.2) years
No. of seizures in baseline period 28 days (mean/median)	24.4/11.2
Number of concomitant AEDs	
1	27%
2	50%
3	23%

The primary end point of the trials was seizure reduction measured by the Response Ratio (RRatio), a new measure in AED trials. The RRatio = $[(T - B)/(T + B)] \times 100$, where B is the patients seizure frequency during the baseline period and T the seizure frequency during the treatment period. The RRatio is a transformation from baseline in seizure frequency that allowed the use of parametric statistical methods in subgroup analyses, e.g. for different seizure types. It ranges from −100 and approaches +100, an RRatio of zero means no change, −100 complete elimination of seizures, and −33 corresponds to a 50% reduction in seizure frequency. To obtain more clinically meaningful units, seizure reduction on the percent change scale were obtained by back transforming the mean RRatio using the following formula, per cent change = $[(200 \times \text{RRatio})/(100 - \text{RRatio})]$. The utility of these measures to clinical practice have not been formally assessed, nor do they allow comparisons to be made with other AEDs.

The more traditional Responder Rate (percentage of patients with 50% reduction on seizures during treatment versus baseline) was a secondary endpoint, but provides an easier comparison with outcomes in trials of other new AEDs. The results of the studies are summarized in Figs. 2 and 3, Table 3, and outlined below.

Study 1. Dose response study[16]

This multi-centre study was conducted in the US and Canada. Four hundred and fifty-three patients (eligibility 12–70 years), were randomised to one of five treatment groups 50, 150, 300 or 600 mg/day or placebo administered twice daily with no titration period.[16] The mean age at onset of epilepsy was 14 years, and mean duration 25 years. The baseline seizure rate was 10 in 28 days. 49.9% of patients were taking 2 AEDs and 19.6 taking 3. No significant difference in seizure frequency was seen between

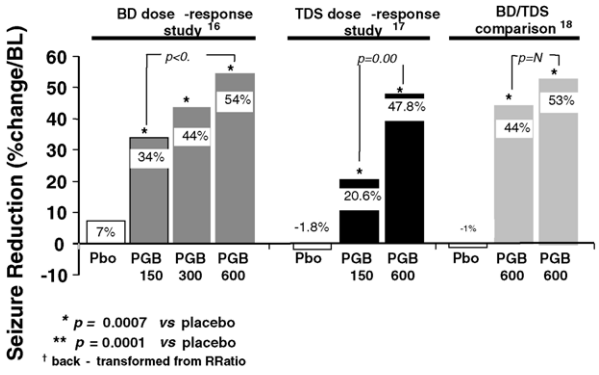

Figure 2 Seizure reduction—percentage change from baseline† in the three randomized placebo-controlled trials of pregabalin in the treatment of patients with refractory partial epilepsy. PGB, pregabalin; BD, twice day; TDS, three times day; Pbo, placebo.

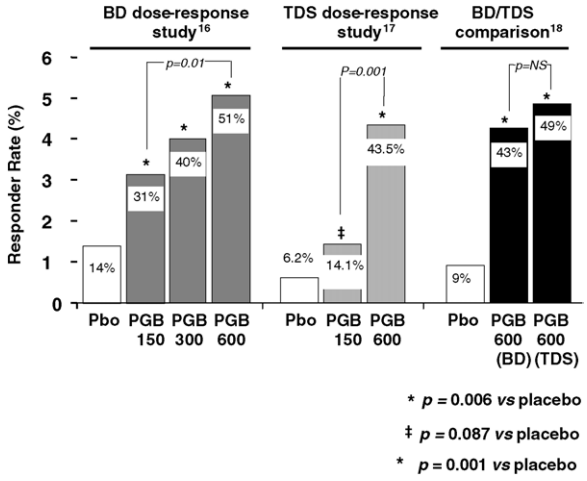

Figure 3 Responder rate: percentage of patients with ≥50% reduction in seizures vs. baseline. PGB, pregabalin; BD, twice day; TDS, three times day, Pbo, placebo.

placebo and 50 mg/day, 7% and 12%. Thereafter, there was a dose related reduction in seizure frequency 34% at 150 mg/day, 44% at 300 mg/day and 54% at 600 mg/day. This was reflected in the responder rates. At 50 mg a day responder rates were similar to placebo, 14% (placebo) versus 15% (50 mg/day). Subsequently, the percentage of patients experiencing a 50% reduction in seizure frequency reduction were, 31% at 150 mg/day, 40% at 300 mg/day, and 51% at 600 mg/day.[16] Withdrawal rates due to lack of efficacy were less than 5%.[16] There was also a dose related effect in discontinuation rates due to adverse events, significant in the 300 mg and 600 group but not the 50 mg group. Five patients (5.0%) withdrew from the placebo group, six (6.8%) from the 50 mg/day group, one (1.2%) from the 150 mg/day group, 13 (14.4%) from the 300 mg/day group, and 21 (23.6%) from the 600 mg/day group. Seventy-three percent of patients who withdrew due to adverse events did so in the fist two weeks of therapy. The most frequent adverse effects were CNS related: ''dizziness'', somnolence and ataxia. Dose related weight gain was reported, 1.1% in the 50 mg group versus 12.4% in the 600 mg/day, with a mean weight gain of 0.5 kg in the placebo group compared to 2.28 kg in the 600 mg/day group, however, only one patient withdrew due to weight gain.

Study 2. Dose response study[17]

This study was carried out in Europe, South Africa and Australia, and 287 patients were randomised to treatment with either 50 mg, 600 mg/day or placebo [17]. The median duration of epilepsy was 23 years and the median seizure frequency during the 8-week baseline period was 11 seizures/28 days. There was a short titration phase, patients randomised to 150 mg/day were titrated to full dose by day 4, and those randomised to 600 mg/day were

Table 3 The most common adverse effects and associated withdrawals in trials of pregabalin and placebo in treatment of patients with refractory partial epilepsy

Adverse event (AE) (preferred term)	Frequency (%)		Discontinuation due to AE (%)	
	Pregabalin	Placebo	Pregabalin	Placebo
Dizziness	28.9	10.5	5.3	0.3
Somnolence	20.8	10.9	3.3	0.0
Ataxia	13.2	4.1	3.0	0.3
Asthenia	11.2	8.2	1.8	0.3
Weight gain	10.4	1.4	0.4	0.0
Accidental injury	9.9	5.4	0.9	0.0
Headache	9.1	11.6	1.2	0.0
Amblyobia	9.0	4.4	1.6	0.0
Diplopia	8.4	3.7	1.6	0.7
Tremor	7.5	3.7	1.5	0.0
Thinking abnormal	7.0	2.0	1.3	0.0

titrated to full dose by day 8. Pregabalin at 150 and 600 mg/day were both significantly more effective in reducing seizures compared to placebo, with seizure reductions of −1.8% placebo, 20.6% for 150 mg/day and 47.8% for 600 mg/day. This was reflected in the responder rates (number of patients with ≥50% reduction in seizure frequency) with 43.5% in the 600 mg/day group and 6.2% in the placebo group. The responder rate for the 150 mg/day was 14.1% which was not statistically significant. Again CNS adverse effects were the most commonly reported, with somnolence, dizziness and ataxia. The withdrawal rates due to adverse effects were 6.2% for the placebo group, 10% for the 150 mg/day group, and 18.5% for the 600 mg/day group. Weight gain was reported in 2.1% of patients taking placebo, 7.1% on 150 mg/day and 14.1 percent taking 600 mg/day; one patient withdrew due to weight gain.

Study 3. Twice day and three day dosing comparison[18]

A third study compared the effects of twice day and three times a day dosing of pregabalin against placebo.[18] In this study carried out in the US and Canada, 312 patients were randomised to receive either one of two regimens of 600 mg/day (two divided doses (BD), or three divided doses (TDS)) or placebo. Seventy-six percent of patients completed the 12-week study. Both dosage regimens were significantly more effective than placebo with a seizure reduction of 44% for the BD group and 53% for the TDS group and −1% for the placebo group. The corresponding responder rates were 43% for the BD group and 49% for the TDS group and 9% for the placebo group. Again dizziness, somnolence, and ataxia were the most frequent adverse events. Dizziness was reported in 38% of patients for TDS, 42% of patients for BD and 9% for placebo.

The incidence of withdrawals due to adverse events was 26, 19 and 7% with pregabalin BD, TDS or placebo, respectively.

A separate report noted myoclonus in 4 of 19 patients enrolled into one of the studies.[19] There appeared a dose dependency with jerks being most severe in the patient taking 600 mg of pregabalin a day and jerks subsided with reduction of the drug; EEG recoding in this patient with the highest frequency of myoclonic jerks did not show any change. All patients were also taking carbemazepine at a dose that was slightly higher than those taking this combination who did not develop jerks. It is not clear whether the combination of pregabalin and carbemazapine was responsible, but the finding is in keeping with the known association of the related gabapentin and myoclonic jerks. The mechanism is unclear.

Discussion

The results of these controlled studies suggest that pregabalin may be effective in the treatment of partial epilepsy. A key question is how it compares with currently available AEDs. There are recognised difficulties in making such comparisons with currently available evidence.[20] Differences in study design and study populations cannot be formally accounted for. Nevertheless the design of studies for new AEDs over the past decade has been broadly similar. The responder rates for pregabalin (600 mg/day) is similar than those seen in trials of other new AEDs, levetiracetam (2000—3000 mg/day) and topiramate (300—800 mg).[21]

Adverse effects were similar to other AEDs, CNS related side effects predominated. High starting doses or rapid titration are likely to have influenced these. Similarly around a quarter of patients were taking three concomitant AEDs that could increase the likelihood of adverse symptoms. Eighty three percent of patients from the treatment arm and 87% from the placebo arm of those who completed the randomized phase entered into the open label extension. The reported weight gain again shows similarities in the behaviour of pregabalin to gabapentin. The mechanism remains unclear.

Pregabalin is available in 25, 50, 75, 100, 150, 200 and 300 mg capsules. The initial recommended starting dose is 150 mg/day, a level at which significant therapeutic benefit was seen in one trial.[16] Nevertheless high starting doses and rapid titration have lead to increased adverse effects with other new AEDs and we feel that a lower stating dose than the recommended 150 mg/day, and slow titration would be preferable.

In conclusion, pregabalin is a CNS acting drug structurally and functionally related to gabapentin with greater potency than gabapentin in animal models of partial epilepsy and other neurological and psychiatric conditions, namely peripheral neuropathic pain and anxiety. Its efficacy and tolerability against placebo has been demonstrated in three randomised-controlled trials in partial epilepsy. Clinicians are likely to first use pregabalin in their patients with refractory seizures in whom other ''established'' add on AEDs lack efficacy or are not tolerated due to side effects. The absence of pharmacokinetic interactions facilitate its use in those already on multiple AEDs. Early indications are that this is not a broad spectrum drug for

epilepsy, and it should be avoided or used with caution in idiopathic generalized epilepsy and possibly Lennox Gastaut syndrome. How its greater potency in animal models, compared to gabapentin translates in clinical practice remains to be seen. The next important step in assessing the place of pregabalin in the antiepileptic armemantarium will be post marketing surveillance and case reporting as well as longer term retention studies.

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