Pregabalin – a New Treatment for Partial Epilepsy and Neuropathic Pain

In July 2004, pregabalin (Lyrica®), a new therapy was introduced to the UK with a licence covering both epilepsy (adults with partial seizures, with or without secondary generalisation), and peripheral neuropathic pain. Unlike some other compounds used to treat these conditions, pregabalin has a well defined mode of action, binding to the alpha2delta subunit of voltage-gated calcium channels to modulate calcium influx (see Figure 1). This is believed to reduce the release of excitatory neurotransmitters, thus resulting in anti-epileptic, analgesic and anxiolytic effects.1,3,2

Both neuropathic pain and epilepsy are notoriously complex and challenging conditions to treat. Epilepsy remains one of the major disabling neurological disorders, affecting two percent of the population. In the UK, 15 anti-epileptic drugs (AEDs) are already available, yet even in the best centres, up to 30% of patients with epilepsy remain uncontrolled,4 a figure which rises to around 50% in the community.1

The key question is whether pregabalin offers new possibilities and additional benefits over and above the existing therapies, and whether it can help improve the lives of patients with epilepsy. This article discusses the key clinical data for pregabalin in epilepsy and the potential place for the drug in a therapy area where therapy uptake is heavily influenced by clinicians’ evolving experience.

Clinical evidence for pregabalin in epilepsy
Pregabalin’s effectiveness as an adjunctive therapy has been studied in three double-blind, placebo-controlled trials of 12 weeks duration and including 1,052 highly refractory adult patients (Table 1).6,7,8 All patients included in these trials had at least six partial seizures over the 8-week baseline period prior to the trial; and no 4-week seizure free period. In addition, patients were required to be receiving 1-3 AEDs. These cohorts comprised a highly refractory patient population, with 73% of patients on at least two AEDs at baseline and a mean baseline 28-day seizure rate of 24 (a median of 11 and a range of 1 to 436) seizures across the studies.

These studies demonstrated that the addition of pregabalin to existing treatment regimens delivered significant efficacy compared with placebo across the recommended dose range 150-600mg daily (given in either two or three divided doses) both in terms of seizure reduction (% change from baseline) and ‘responder rate’ (50% reduction in seizures). Pregabalin’s onset of efficacy was seen as early as week 1.9

In the dose-response study by French et al,6 both seizure frequency (p<0.0001) and responder rates (p<0.001) showed significant dose response: 150mg/day reduced seizures by 34%; 300mg/day by 44%; and 600mg/day by 54% compared with placebo at 7%. In addition, the study showed significantly more patients were responders in the 600mg group than in the placebo group (51% vs. 14%).6 These findings are consistent with those of the other two studies of similar design that evaluated similar patient populations with refractory partial seizures.7,8 Seizure freedom (defined as the last 28 days of double-blind treatment), was achieved in up to 12% of previously refractory patients (p=0.002).1 Pregabalin’s efficacy was similar regardless of whether patients were on 1, 2 or 3 baseline AEDs10 and both BD and TDS regimens showed similar efficacy.8

Table 1: Adjunctive Placebo-Controlled Trials (n=1052)

<table>
<thead>
<tr>
<th>Study</th>
<th>Total daily dose</th>
<th>Dose Regime</th>
<th>Titration</th>
<th>Double blind treatment</th>
<th>N (ITT)</th>
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After training in Neurology and Clinical Neurophysiology at the Walton Centre in Liverpool, Dr John Paul Leach took up a consultant post at the Neurology Department in his home town of Glasgow. He continues his research interest into the diagnosis and treatment of epilepsy.

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Drugs in Neurology

Figure 1: Pregabalin binds to the alpha2delta subunit of voltage-gated calcium channels to modulate calcium influx.

Figure 2: Effect of pregabalin on hyperexcited neuron.
As expected, the majority of adverse events reported on pregabalin treatment were CNS-related with somnolence and dizziness the most common. Both were generally mild or moderate, dose-related, and somnolence was shown to be more common in patients receiving three concomitant AEDs. Dizziness ranged from 19.2% of patients at 150mg/day up to 26.1% at 600mg/day (compared to 8.3% on placebo) and somnolence 6.1% at 150mg/day up to 29.3% at 600mg/day (7.3% on placebo).

When 600mg/day was initiated on day 1 without titration, as might be expected, the reported incidence of dizziness was higher (42.7% compared to 9% on placebo). Between 2.3% (150 mg/dose) and 14.1% (600 mg/dose) of patients reported weight gain but this, and adverse events generally, resulted in few discontinuations of the treatment. In individuals where weight gain may be a concern, physicians should be aware of this possibility so they can manage it appropriately.

Pregabalin has a predictable and linear pharmacokinetic profile, as well as a lack of pharmacokinetic drug interactions. Pregabalin benefits from renal excretion, minimal hepatic metabolism (<2%) and lack of protein binding. Significantly it has no interactions with the contraceptive pill or with other AEDs.

Pregabalin’s recommended starting dose is 150mg/day, with efficacy demonstrated across the dose range of 150–600mg/day. It is available in 25mg, 50mg, 75mg, 100mg, 150mg, 200mg and 300mg capsules (the lower doses available for patients with renal impairment who require dose reduction).

The cost of treating a patient with pregabalin (bd dosing) compares favourably with other newer AEDs at about £840 per year, with a flat price structure across the dose range.

**Implications for clinical practice**

As monotherapy fails to bring seizure freedom in a significant number of patients, polypharmacy in epilepsy is often unavoidable. A sizeable minority of patients with partial seizures will benefit from a new AED option to improve seizure control. The clinical trial results with pregabalin are promising and offer hope to refractory patients with partial seizures.

The efficacy of pregabalin in terms of responder rate (50% reduction in seizures) demonstrated in clinical trials compares favourably with other available AEDs; future meta-analysis should help confirm this. The incidence of seizure freedom in reported studies also compares well with newer AEDs. An examination of pregabalin’s list of reported adverse events shows they are similar to those seen with commonly prescribed AEDs.

With any new add-on therapy, the ease of use in clinics arises from a lack of pharmacokinetic interactions, and a toxicity profile which differs from that of existing AEDs. Pregabalin’s lack of pharmacokinetic drug interactions and different mode of action compared with the commonly used monotherapies (carbamazepine, valproate and lamotrigine) potentially make it a rational and sensible choice for early use as add-on therapy. As none of the other commonly used AED monotherapies possess the same mode of action, this would suggest that pregabalin may be easily added in to most treatment regimens with theoretically less risk of producing neurotoxic side effects.

Clinical practice is much more complex than that of clinical trials, so widespread use of pregabalin in the real world will be determined by the initial experiences of clinicians using it to treat their most refractory patients. The traditional pattern of use with new antiepileptic drugs involves first usage as adjunctive therapy in refractory patients. In the coming years, if pregabalin lives up to its early promise, we can expect to see an expansion in its use.

**References**


**Figure 2:** Responder rate: percentage of patients with ≥50% reduction in seizures vs. baseline.