

NEW DRUG EVALUATION

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PREGABALIN FOR NEUROPATHIC PAIN

Pregabalin is an antiepileptic agent licensed for adjunctive therapy in the treatment of partial seizures and for peripheral neuropathic pain. Common adverse effects include somnolence and dizziness. It has not been compared directly with any other treatment for neuropathic pain and there is no evidence to suggest that it is more effective or has fewer adverse effects than other established therapies. Its use is therefore not currently recommended.

What is it?

Pregabalin (Lyrica®, Pfizer) is licensed for the treatment of peripheral neuropathic pain in adults and as adjunctive therapy in adults with partial seizures with or without secondary generalisation.¹ It has also been investigated for the treatment of fibromyalgia and generalised anxiety disorder, but a licence has not yet been approved for these indications. It is recommended that the dose for neuropathic pain be titrated, according to response and tolerability, from 150 mg/day to 300 mg/day after 3-7 days and then to 600 mg a day after an additional 7 days.¹ Pregabalin is structurally and pharmacologically related to gabapentin, although there are differences in pharmacokinetics. Preclinical (in vitro and animal) studies have demonstrated an increased binding affinity for receptors associated with pain relief compared with gabapentin; however, it is unclear whether this is translated into a clinical advantage.^{2,3} The launch of pregabalin follows gabapentin's (Neurontin®, Pfizer) availability as a generic.

How effective is it?

Efficacy has been studied in 12 double-blind, placebo-controlled, randomised trials in patients with diabetic neuropathy (DPN) or post-herpetic neuralgia (PHN).⁴ Efficacy has not been studied in other types of neuropathic pain, although for an indication in peripheral neuropathic pain to be approved, efficacy needs only to be demonstrated in two different peripheral neuropathic pain models. Currently, only three studies have been fully published.^{3,5,6}

The primary aim in each of the 12 studies (total n=3124) was to assess the efficacy of pregabalin on neuropathic pain compared with placebo. The primary efficacy parameter was the mean pain score at the end of the study, using an 11-point numerical rating scale (0, no pain; 10, worst possible pain). The main differences between the trials concerned dosage and duration of treatment (from 5-13 weeks). Pregabalin at a dose of 300 or 600 mg/day was shown to give significant pain relief compared with placebo, whereas doses of 150 mg daily were of questionable efficacy and 75 mg daily was not effective.⁴ Effective doses provided pain relief as early as 1 week after treatment and this was sustained to study-end (up to 13 weeks).⁴ Mean differences in pain score between placebo

and pregabalin ranged from -0.18 to -1.57 for 300 mg/day and -0.64 to -2.02 points for 600 mg/day.⁴ In controlled clinical trials 35% of the pregabalin treated patients and 18% of the patients on placebo had a 50% improvement in their pain score.⁴ The difference in pain scores between twice-daily dosing (BID) and thrice-daily dosing (TID) regimens were not judged to be clinically relevant.⁴

In the published studies patients who had previously failed to respond to ≥ 1200 mg/day of gabapentin were excluded and two studies excluded prior use of pregabalin.^{3,5,6} This is expected to bias the results in favour of pregabalin, especially considering that in randomised trials doses of 1800 mg/day of gabapentin have been needed to treat neuropathic pain effectively.⁷ The manufacturer states that later, unpublished studies have not excluded patients who failed to respond to gabapentin and that these studies demonstrate similar efficacy to the published studies.⁸ However, these studies cannot be evaluated and no specific analysis of gabapentin-treated patients has been carried out.

In an unpublished study, 256 patients with DPN were randomised into three groups: placebo (n=81), pregabalin titrated to 600 mg/day (n=87) and amitriptyline 75 mg/day (n=88) as a positive control.⁴ Reductions in mean pain scores were not significant for pregabalin 600 mg/day (6.9 to 4.0, $p=0.08$) but were significant for amitriptyline (6.4 to 3.7, $p=0.01$) compared with placebo (6.3 to 4.6). Responder analysis (responders are patients with >50% reduction in pain score as compared to baseline values) was significant for amitriptyline ($p=0.03$) but not pregabalin ($p=0.24$) compared with placebo. The study was not powered to detect differences between amitriptyline and pregabalin. There is no direct evidence to suggest pregabalin has a faster onset of action than amitriptyline. No trials have been undertaken comparing pregabalin with gabapentin or carbamazepine.

How safe is it?

Adverse events reported in clinical trials were generally dose-dependent and of mild to moderate intensity.^{1,4} In all controlled studies 65% and 80% of placebo- and pregabalin-treated patients respectively experienced adverse events.⁴ The most common adverse reactions were dizziness and somnolence.^{1,4} The discontinuation rate due

to adverse events was 7% and 13% for placebo- and pregabalin-treated patients respectively; dizziness and somnolence the most common reason for discontinuation.¹ Significant weight gain was noted in 5.6% of pregabalin-treated patients across all trials; diabetic patients who gain weight on pregabalin treatment may need to adjust their hypoglycaemic medication.^{1,4} Patients with compromised renal function should have their dose of pregabalin reduced.¹

What other options are there?

Tricyclic antidepressants (TCAs), in particular amitriptyline (25–75 mg/day), are widely used for neuropathic pain (although none are licensed in the UK for this indication).⁹ If patients fail to respond to low dose amitriptyline the dose should be titrated to the maximum tolerated dose (maximum 150 mg/day) before alternative treatment options are considered.¹⁰ A systematic review showed that for every 100 patients given TCAs compared with placebo, approximately 30 will obtain more than 50% pain relief.¹⁰ Carbamazepine and phenytoin are both licensed for the treatment of trigeminal neuralgia.⁹ Phenytoin, due to its adverse effects, should be reserved for patients with trigeminal neuralgia who fail to respond to carbamazepine or TCAs. A systematic review found that gabapentin was not superior to carbamazepine.¹¹ Our recent review on gabapentin concluded that it should be reserved for

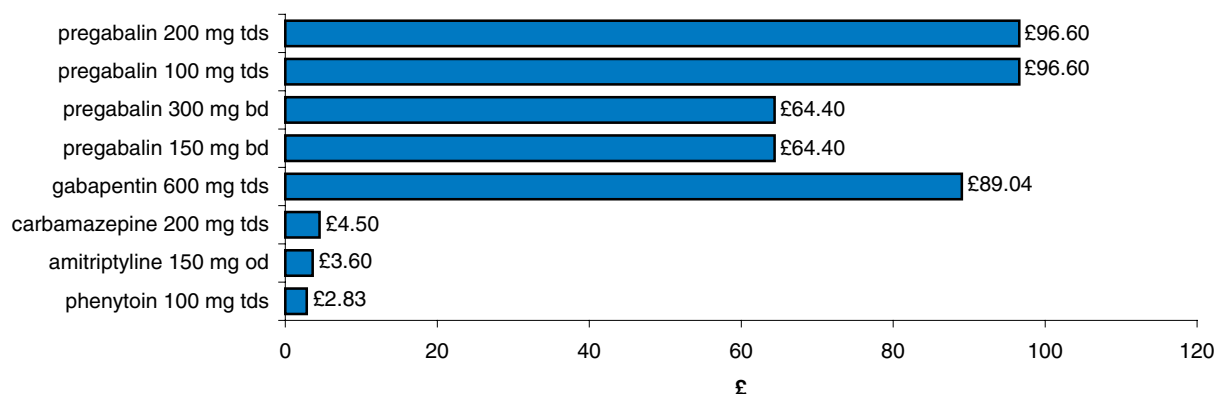
patients, in whom other agents are contra-indicated, not tolerated or ineffective and continued only if an objective benefit is observed.⁷ Other treatment options were discussed.⁷

When should it be used?

Amitriptyline and carbamazepine remain the first-line choices for the treatment of neuropathic pain. There is no direct evidence to suggest pregabalin is more effective or has fewer adverse effects than other established therapies for neuropathic pain and controlled trials comparing pregabalin with other treatments are currently lacking. There is currently no evidence that patients who fail to respond to gabapentin respond to pregabalin – the two treatments are of similar structure and pharmacology. Pregabalin is expensive, particularly when prescribed as a thrice-daily regimen, while the cost of gabapentin is likely to fall following its recent availability as a generic. Pregabalin is therefore not currently recommended for treating neuropathic pain.

How much does it cost?

Cost for 28 days treatment (prices from MIMS/Drug Tariff November 2004)



NB. Doses shown are for general comparison only and do not imply therapeutic equivalence.

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KEY RCT - randomised controlled trial, CT-controlled trial, G-guideline, O-open study, MA-meta analysis, R-review, U-unpublished, Abs- abstract, E-editorial

Wolfson Unit, Claremont Place, Newcastle upon Tyne NE2 4HH
Tel: 0191 232 1525 Fax 0191 260 6192 E-mail: nyrdtc.di@ncl.ac.uk
www.nyrdtc.nhs.uk
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