

# DRUG UPDATE

No. 30

April 2004

## GABAPENTIN FOR NEUROPATHIC PAIN

Gabapentin is an antiepileptic agent licensed for adjunctive therapy in the treatment of partial seizures and for neuropathic pain. Common adverse effects include somnolence and dizziness. With the exception of amitriptyline, 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 than other therapies. It cannot therefore be recommended as a first-line agent. A therapeutic trial of gabapentin should be reserved for patients, in whom other agents (amitriptyline and carbamazepine) are contra-indicated, not tolerated or ineffective and continued only if an objective benefit is observed.

### What is it?

Gabapentin (Neurontin®, Parke-Davis/Pfizer) was launched in 1993 for use as adjunctive therapy in the treatment of partial seizures with or without secondary generalisation.<sup>1,2</sup> In 2000 it was approved for the treatment of neuropathic pain.<sup>2</sup> Gabapentin's mechanism of action is currently unclear.<sup>1</sup> It is recommended that the dose be titrated, according to response, by 300 mg daily to the maximum tolerated dose (maximum 1800 mg/day).<sup>3</sup> Gabapentin is now available generically.

### How effective is it?

#### Mixed Neuropathies

In an 8 week randomised double-blind study of 305 patients with a wide range of neuropathic pain syndromes gabapentin (titrated over 5 weeks up to 2400 mg/day – greater than the maximum licensed dose) reduced the average daily pain score on a Likert scale (0, no pain; 10, worst possible pain) by 1.5 points (7.1 to 5.6) compared with 1.0 points (7.3 to 6.3) for placebo.<sup>4</sup> Although statistically significant ( $p=0.048$ ) this effect is of questionable clinical importance, especially as patients who previously failed to respond to or were intolerant of gabapentin were excluded from the study.

#### Post Herpetic Neuralgia (PHN)

Two randomised, double-blind studies have evaluated the efficacy of gabapentin in PHN.<sup>5,6</sup>

In the first study ( $n=229$ ), treatment with gabapentin for 8 weeks (titrated over 4 weeks to a maximum of 3600 mg/day – twice the maximum licensed dose) reduced the average daily pain score on a Likert scale by 2.1 points (6.3 to 4.2) compared with 0.5 points (6.5 to 6.0) for placebo ( $p<0.001$ ).<sup>5</sup> In a second study 334 patients were randomised into three groups: placebo ( $n=111$ ), gabapentin titrated over 16 days to 1800 mg/day ( $n=115$ ) or 2400 mg/day ( $n=108$ ).<sup>6</sup> Reductions in average daily pain score on a Likert scale at study end (week 7) were significantly larger for gabapentin 1800 mg/day (6.5 to 4.3,  $p<0.01$ ) and 2400 mg/day (6.5 to 4.2,  $p<0.01$ ) compared with placebo (6.4 to 5.3).

### Diabetic Peripheral Neuropathy (DPN)

In an 8 week randomised double-blind study ( $n=165$ ) gabapentin (up to 3600 mg/day) decreased the mean daily pain score by 2.5 points (6.4 to 3.9) compared with 1.4 points (6.5 to 5.1) for placebo ( $p<0.001$ ).<sup>7</sup> In a smaller randomised, double-blind crossover trial (each arm lasting 6 weeks) gabapentin 900 mg/day was probably ineffective or only minimally effective ( $n=40$ ),<sup>8</sup> however the dose of gabapentin used may have been inadequate.

A number of small randomised controlled trials have been conducted in patients with various neuropathic pain syndromes.<sup>9-12</sup> In a comparative double-blind crossover study (each arm lasting 6 weeks) gabapentin 900-1800 mg/day was no more effective at relieving pain than amitriptyline 25-75 mg/day ( $p=0.26$ ) ( $n=25$ ).<sup>9</sup> However, due to the lack of power in these trials it is difficult to draw any firm conclusions from the results.

### How safe is it?

Adverse events reported in the four large clinical trials were generally mild to moderate in intensity and often subsided on dose reduction.<sup>4-7</sup> Withdrawal rates due to adverse events in the gabapentin and placebo groups were generally similar.<sup>4,5,7</sup> In one study withdrawal rates due to adverse events were more common in both gabapentin groups than the placebo group.<sup>6</sup> The most common adverse-effects associated with gabapentin are dizziness and somnolence.<sup>1</sup>

Gabapentin can cause mood and behavioural disturbance and caution is recommended in patients with a history of psychotic illness.<sup>1</sup> Patients with compromised renal function should have their dose of gabapentin reduced.<sup>1</sup>

### 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).<sup>3</sup> If patients fail to respond to amitriptyline the dose should be titrated to the maximum tolerated dose (maximum 150

mg/day) before alternative treatment options are considered. A systematic review showed that for every 100 patients given TCAs compared with placebo, approximately 30 will obtain more than 50% pain relief.<sup>13</sup>

Carbamazepine and phenytoin are both licensed for the treatment of trigeminal neuralgia.<sup>3</sup> Phenytoin, due to its adverse-effects, should be reserved for patients with trigeminal neuralgia who fail to respond to carbamazepine. In a systematic review of 20 randomised controlled trials, 70% of patients with trigeminal neuralgia benefited from treatment with carbamazepine.<sup>14</sup> There was also a significant effect in patients with DPN treated with carbamazepine or phenytoin compared with placebo.<sup>14</sup> Another systematic review concluded that gabapentin is not superior to carbamazepine.<sup>15</sup>

Opioid analgesics can be moderately effective against neuropathic pain.<sup>16</sup>

Capsaicin 0.075% cream is licensed for use in PHN but may only be used under the supervision of a hospital consultant in DPN.<sup>3</sup>

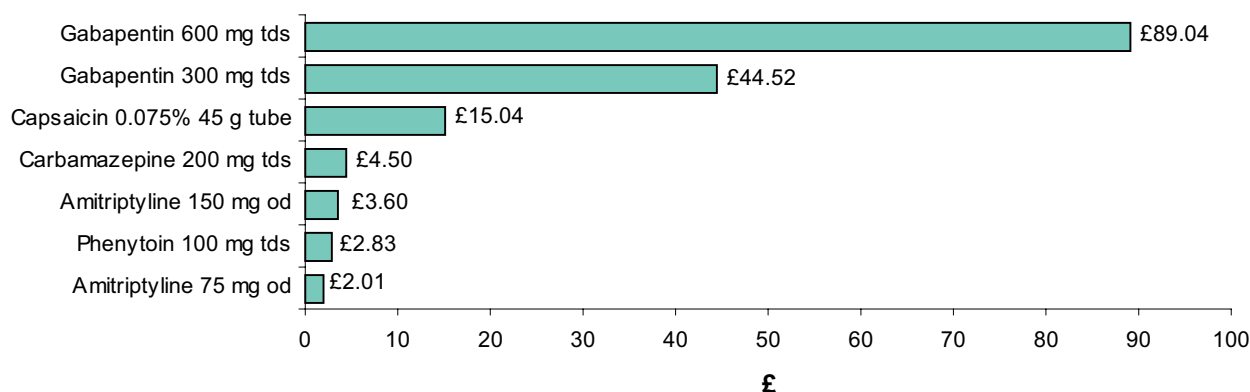
The use of sodium valproate, lamotrigine ketamine, lidocaine intravenous infusion or mexiletine for neuropathic pain is unlicensed and should only be used on the advice of a consultant and when other treatments have failed.

### When should it be used?

There is no evidence to suggest gabapentin is more effective than other therapies for neuropathic pain and controlled trials comparing gabapentin with other treatments are currently lacking. Therefore, gabapentin cannot be recommended as a first-line agent. A therapeutic trial of gabapentin should be reserved for patients, in whom other agents (TCAs and carbamazepine) are contra-indicated, not tolerated or ineffective and continued only if an objective benefit is observed.

### How much does it cost?

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



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

### REFERENCES

1. Parke Davis/Pfizer. Neurontin® Summary of Product Characteristics. <http://emc.medicines.org.uk/emc/assets/c/html/displayDocPrinterFriendly.asp?documentid=1428> (last accessed 23/01/2004).
2. Personal communication. Pfizer January 2004.
3. British National Formulary No.46 September 2003.
4. Serpell MG et al. Gabapentin in neuropathic pain syndromes: a randomised, double-blind, placebo controlled study. *Pain* 2002;99:557-66. (RCT)
5. Rowbotham M et al. Gabapentin for the treatment of postherpetic neuralgia. A randomised controlled trial. *JAMA* 1998;280:1837-42. (RCT)
6. Rice ASC et al. Gabapentin in postherpetic neuralgia: a randomised, double-blind, placebo controlled study. *Pain* 2001;94:215-24. (RCT)
7. Backonja M et al. Gabapentin for the symptomatic treatment of painful neuropathy in patients with diabetes mellitus. *JAMA* 1998;280:1831-6. (RCT)
8. Gorson KC et al. Gabapentin in the treatment of painful diabetic neuropathy: a placebo controlled, double-blind, crossover trial. *J Neurol Neurosurg Psychiatry* 1999;66:251-2. (RCT)
9. Morello CM et al. Randomised double-blind study comparing the efficacy of gabapentin with amitriptyline on diabetic peripheral neuropathy pain. *Arch Intern Med* 1999;159:1931-7. (RCT)
10. Bone M et al. Gabapentin in postamputation phantom limb pain: a randomised double-blind placebo controlled crossover study. *Reg Anesth Pain Med* 2002;27:481-6. (RCT)
11. Pandey CK et al. Gabapentin for the treatment of pain in Guillain-Barre syndrome: a double-blinded placebo controlled crossover study. *Anesth Analg* 2002;95:1719-23. (RCT)
12. Tai Q et al. Gabapentin for the treatment of neuropathic pain after spinal cord injury: a prospective randomised double-blind crossover trial. *J Spinal Cord Med* 2002;25:100-5. (RCT)
13. McQuay HJ et al. A systematic review of antidepressants in neuropathic pain. *Pain* 1996;68:217-27. (MA)
14. McQuay H et al. Anticonvulsant drugs for management of pain: a systematic review. *BMJ* 1995;311:1047-52. (MA)
15. Wiffen P et al. Anticonvulsant drugs for acute and chronic pain. *The Cochrane Library*, Issue 4 2003. (MA)
16. Sindrup SH et al. Efficacy of pharmacological treatments of neuropathic pain: an update and effect related to mechanism of drug action. *Pain* 1999;83:389-400. (MA)

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

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