PREGABALIN OR GABAPENTIN FOR NEUROPATHIC PAIN

KEY MESSAGES

• Pregabalin is structurally related to gabapentin and has a similar pharmacologically action and adverse event profile. There are no comparative studies between pregabalin and gabapentin for post-herpetic neuralgia or diabetic neuropathy.

• NICE clinical guidelines included pregabalin or amitriptyline as options for neuropathic pain. The exclusion of gabapentin has been questioned and the guideline is currently under review.

• Pregabalin can be given twice daily compared with three times daily for gabapentin. This may be beneficial for a small proportion of patients. Prescribing pregabalin as a three time daily dose is very expensive.

• If a GABA analogue is required, gabapentin is still a suitable first-line option for peripheral neuropathic pain in preference to pregabalin.

WHAT IS THE PROBLEM?

• In 2011-12 the NHS in the East Midlands spent nearly £11 million on pregabalin at an average of £65.42 per prescription. Anecdotally, the vast majority of this prescribing was for neuropathic pain.

In a survey of practice pharmacists and PCT/CCG prescribing advisers in the E Midlands, their perception was that about 90% of prescribing is for neuropathic pain. Those who had conducted reviews and audits of pregabalin prescribing in GP practices in their localities reported all prescribing was for neuropathic pain.

• If this had all been prescribed as gabapentin, which had an average prescription cost of £11.53 per prescription, the equivalent cost would be £1.9 million; a saving of nearly £9 million. Even if half is prescribed as gabapentin at maximal licensed dose, this would free up £3.1 million to spend on other services.

East Midlands prescribing data April 2011-March 2012

<table>
<thead>
<tr>
<th></th>
<th>Total items</th>
<th>Total cost</th>
<th>Average cost per item</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gabapentin</td>
<td>288,957</td>
<td>£3,330,403.22</td>
<td>£11.53</td>
</tr>
<tr>
<td>Pregabalin</td>
<td>164,843</td>
<td>£10,784,756.50</td>
<td>£65.42</td>
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<tr>
<td></td>
<td>453,800</td>
<td>£14,115,159.72</td>
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</table>

Difference £53.90

Using average cost per item, if all prescriptions for pregabalin had been prescribed as gabapentin, the equivalent cost would have been £1,900,640 (164,843 x £11.53). This would be a saving of £8,884,117.

If 50% of pregabalin prescribing was switched to gabapentin 1200mg tds, assuming a 28-day prescription:

- Gabapentin cost £2,290,493 (82,422 x £27.79)
- Pregabalin cost £5,392,047 (82,422 x £65.42)
- Total cost £7,682,540

This would equate to a saving of £3,102,216 on 2011-12 prescribing costs.
WHAT IS THE EVIDENCE?

- The GABA analogues pregabalin and gabapentin are structurally and pharmacologically related. Both agents are licensed for epilepsy and peripheral neuropathic pain. Pregabalin is additionally licensed for central neuropathic pain and generalised anxiety disorders.

- NICE clinical guidelines on the management of neuropathic pain (2010) recommended amitriptyline or pregabalin as cost-effective options. The exclusion of gabapentin was subsequently criticised; the Drug and Therapeutic Bulletin questioned whether switching away from gabapentin was a justifiable and affordable option. NICE agreed to review their decision and are currently updating the guideline.

The NICE Clinical Guideline (CG96, 2010) on the management of neuropathic pain in adults in non-specialist settings recommended amitriptyline or pregabalin (or duloxetine for painful diabetic neuropathy (PDN)) as first-line treatment options.

Health economic modelling data was taken from a health technology assessment (HTA) in development, of trials in post-herpetic neuralgia (PHN) and PDN, to which the Guideline Development Group (GDG) had been given access. To date, this has not been published in full although details of the methodology are included in the NICE guideline. The GDG noted that there is evidence (of high to moderate quality) for the efficacy of pregabalin and gabapentin for the treatment of neuropathic pain. They concluded that pregabalin is a better treatment than gabapentin for neuropathic pain for the following reasons:

Evidence from indirect comparisons of meta-analyses of the two treatments showed that pregabalin has lower NNT values for at least 30% and at least 50% pain reduction compared with gabapentin, with a similar adverse-effect profile.

Pregabalin has simple dosing and titration compared with gabapentin. Cost-effectiveness modelling showed that pregabalin is more cost effective than gabapentin.

The Drug and Therapeutic Bulletin published an editorial questioning the affordability of this decision. They highlighted the choice available to the NHS; treating more patients with a cheaper but (on indirect evidence) slightly less effective drug, or fewer patients with a more expensive, seemingly more effective drug.

NICE subsequently agreed to review this recommendation. However, the review process has subsequently been changed to a full review of the clinical guideline. The draft document does include gabapentin as an option but there is no anticipated date of publication of the revised guideline.

- There are no published prospective comparative studies between pregabalin and gabapentin for post-herpetic neuralgia, diabetic neuropathy or other neuropathies apart from one small trial in neuropathic cancer pain. This did not use maximal doses of both agents.

The study was a 4-week prospective randomised trial conducted in India which enrolled 120 patients with severe neuropathic cancer pain. Patients were randomised to amitriptyline 50mg daily increasing weekly to 100mg daily by week 3, gabapentin 300mg tds increasing to 600mg tds by week 3, pregabalin 75mg bd increasing to 300mg bd by week 3 or placebo. Thus patients were titrated to the maximal licensed dose of pregabalin but a sub-maximal dose of gabapentin. The primary outcome measure was efficacy as measured on a 100mm visual analogue scale (VAS, 0mm no pain, 100mm unbearable pain). However baseline VAS scores were 7.47-7.77, suggesting a 10-point scale was used. In addition, oral morphine was given for rescue analgesia at any time if the VAS was >3, again suggesting a 10 point scale and potentially affecting the resultant pain scores. The mean VAS score reductions from baseline to week 4 were 7.77 to 3.23 for amitriptyline; 7.5 to 3.07 for gabapentin; 7.77 to 2.5 for pregabalin and 7.47 to 3.4 for placebo.

There is no mention of whether all patients completed the study. Given the issues with trial design and inconsistencies in presentation of results, this trial cannot be relied upon.

- The majority of trials of these agents in neuropathic pain involve 100-200 patients in short-term placebo-controlled trials. Using these data, NICE concluded that pregabalin has lower number needed to treat (NNT) values for at least 30% and 50% pain reduction compared with gabapentin, with a similar adverse-effect profile. NNTs for a 50% pain reduction were 7.3 for gabapentin (2 studies) and 4.6 for pregabalin (10 studies).

The full guidelines from NICE included two trials of gabapentin with a primary outcome of patient-reported 50% pain reduction; one in PHN and one in mixed neuropathic pain. Overall 27.5% of patients taking gabapentin showed a 50% reduction in pain compared with 13.8% taking placebo giving a NNT of 7.3 (95% CI 5.0, 14.2).

For pregabalin, 10 trials were included (four in PHN, four in PDN, one in PHN or PDN and one in spinal cord injury). Overall 38.8% of patients taking pregabalin showed a 50% reduction in pain compared with 16.8% taking placebo giving a NNT of 4.6 (95% CI 3.9, 5.5).
A further meta-analysis included randomised, placebo-controlled trials of any pharmacological agent in neuropathic pain identified from Medline and Embase up to April 2010. Additional papers were identified from reference lists and review papers. The main results for gabapentin, pregabalin and tricyclic antidepressants are as follows:

<table>
<thead>
<tr>
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<th>Painful polyneuropathy</th>
<th>Postherpetic neuralgia</th>
<th>Number needed to harm (NNH, for one withdrawal due to adverse effects)</th>
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<tbody>
<tr>
<td><strong>Gabapentin</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of trials</td>
<td>4</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>NNT (95% CI)</td>
<td>6.4 (4.3-12)</td>
<td>4.3 (3.3-6.1)</td>
<td>32.5 (18-222)</td>
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<td><strong>Pregabalin</strong></td>
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<tr>
<td>Number of trials</td>
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<td>4</td>
<td></td>
</tr>
<tr>
<td>NNT (95% CI)</td>
<td>4.5 (3.6-5.9)</td>
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<td>10.6 (8.7-14)</td>
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<td><strong>TCAs</strong></td>
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<tr>
<td>Number of trials</td>
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<tr>
<td>NNT (95% CI)</td>
<td>2.1 (1.9-2.6)</td>
<td>2.8 (2.2-3.8)</td>
<td>15.9 (11-26)</td>
</tr>
</tbody>
</table>

**WHAT ARE THE COSTS?**

Costs for 28 days supply. Taken from Drug Tariff August 2012

Doses are a guide and are based on licensed doses

**References:**

Date of preparation August 2012
Trent Medicines Information Service, Leicester Royal Infirmary, LE1 5WW.
The information in this review is believed to be true and accurate. It is issued on the understanding that it is the best available from the resources at our disposal at the time of issue.