

## Gabapentin or Pregabalin for neuropathic pain?

### Executive Summary

- Pregabalin is structurally related to gabapentin and has a similar pharmacological action and adverse event profile.
- In 2014, NHS North Central London spent nearly £3.2 million on pregabalin at an average of approximately £60 per prescription. This is an increase from 2013 when £2.7 million was spent representing a 20.2% year-on-year increase. Anecdotally, the vast majority of this prescribing was for neuropathic pain
- If all the pregabalin prescribed in the North Central London in 2014 had been prescribed as gabapentin, the equivalent cost would have been £345k which would provide a saving of over £2.8 million to spend on other services within the NHS.
- There are no comparative studies between pregabalin and gabapentin for neuropathic pain (including post-herpetic neuralgia, diabetic neuropathy, and spinal cord injury related neuropathic pain), however indirect comparisons show a similar efficacy and tolerability profile.
- Both drugs have the propensity for misuse.
- NICE clinical guidelines recommend amitriptyline (off-label), duloxetine, gabapentin, or pregabalin as safe and cost-effective options for neuropathic pain. There is no evidence that one is clinically superior to another.
- Pregabalin can be given twice daily compared with three times daily for gabapentin. This should make little difference to the majority of patients. Prescribing pregabalin as a three time daily dose is very expensive.
- If a GABA analogue is required and considered clinically appropriate for peripheral neuropathic pain, gabapentin should be prescribed first-line with pregabalin reserved only in cases where gabapentin has resulted in clinical effect but off-target adverse effects.

### 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. Although generic pregabalin is now available, branded pregabalin (Lyrica®) still retains patent protection for its pain indication.
- NICE clinical guideline (CG 173) on the management of neuropathic pain recommends amitriptyline (off-label), duloxetine, gabapentin or pregabalin as safe and cost effective options.<sup>1</sup> NICE does not recommend one drug as clearly superior to the others and advised that the choice of treatment should be made on an individual basis.
- As with all NICE guidance, where more than one option is recommended, the order should be based on least to most expensive. The guideline development group (GDG) for CG 173 found that gabapentin had the highest net benefit per QALY, although amitriptyline had lower net costs. Pregabalin and duloxetine were recommended due to their wider licenses; however the GDG acknowledged that both of these treatments represented poor value for money.
- 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.<sup>2</sup> This did not use maximal doses of both agents.
- A systematic review and meta-analysis concluded that tricyclic antidepressants, duloxetine, gabapentin or pregabalin could all be recommended as first-line treatments in neuropathic pain.<sup>2</sup> NNTs (numbers needed to treat for 50% pain relief) were 7.7 for pregabalin and 7.2 for gabapentin.
- A Canadian (CADTH) review stated that the benefits and harms of pregabalin are similar to gabapentin but at a higher cost.<sup>3</sup>
- An Australian (RADAR) review stated that there was currently a lack of robust data in the form of head-to-head randomised controlled trials directly comparing the efficacy of pregabalin with other drugs for neuropathic pain.<sup>4</sup>
- Further to the above NICE clinical guideline, Public Health England have published advice for prescribers stating that both gabapentin and pregabalin have propensity for dependence and misuse.<sup>5</sup> Both drugs have known psychiatric side effects including euphoria and hallucinations.<sup>6,7</sup> The document suggests that alternative drugs should be preferentially offered and includes information on tapering and discontinuing gabapentin / pregabalin.

## Cost

- Table 1 below shows the costs for gabapentin and pregabalin
- Pregabalin may be prescribed as either a twice daily or three times each day regime, however the three times each day regime is considerably more expensive.

**Table 1: Costs for gabapentin and pregabalin.**<sup>8,9</sup>

Product	Price for 28 capsules	Dose: ONE capsule twice daily (28-day cost)	Dose: ONE capsule three times each day (28-day cost)
Gabapentin 100mg capsules	£0.72	n/a	£2.16
Gabapentin 300mg capsules	£0.99	n/a	£2.97
Pregabalin 75mg capsules	£32.20	£64.40	£96.60
Pregabalin 100mg capsules	£32.20	£64.40	£96.60
Pregabalin 150mg capsules	£32.20	£64.40	£96.60
Pregabalin 200mg capsules	£32.20	£64.40	£96.60
Pregabalin 225mg capsules	£32.20	£64.40	Above max licensed dose
Pregabalin 300mg capsules	£32.20	£64.40	Above max licensed dose

## Switching from pregabalin to gabapentin

- There have been no studies looking at a switch from pregabalin to gabapentin, however, there have been a few studies looking at a switch from gabapentin to pregabalin which have used various strategies and dosing regimens to undertake the switch – some strategies including direct switch and dose-tapering switch are discussed below.
- The manufacturer of both pregabalin and gabapentin advises that if they are to be discontinued, or the dose reduced or substituted with an alternative medicine, the dose should be tapered gradually over a minimum of one week.<sup>8,9</sup> This withdrawal is however to minimise the risk of increased seizure frequency where they are being used for patients with seizure disorders. The clinical importance of a slow withdrawal in patients with neuropathic pain remains unknown.<sup>10</sup>
- A pharmacokinetic simulation study looked at two different transition designs.<sup>11</sup> The first involved immediate discontinuation of gabapentin and initiation of pregabalin; the second involved gradual transition (50% gabapentin dose and 50% pregabalin dose) for four days followed by gabapentin discontinuation and full dose of pregabalin. The simulation showed that for both transition designs, predicted pregabalin concentrations did not depart from those calculated during periods of steady state monotherapy; therefore changing patient's therapy could be achieved by either of the two approaches.
- An open-label study substituted gabapentin with pregabalin overnight in patients with neuropathic pain.<sup>12</sup> No serious adverse effects were noted as part of the switch. Patients who had not responded to gabapentin therapy appeared to have a higher likelihood of adverse effects such as sedation and dizziness, although these did not lead to treatment discontinuation. Table 2 below shows the dose conversions used.

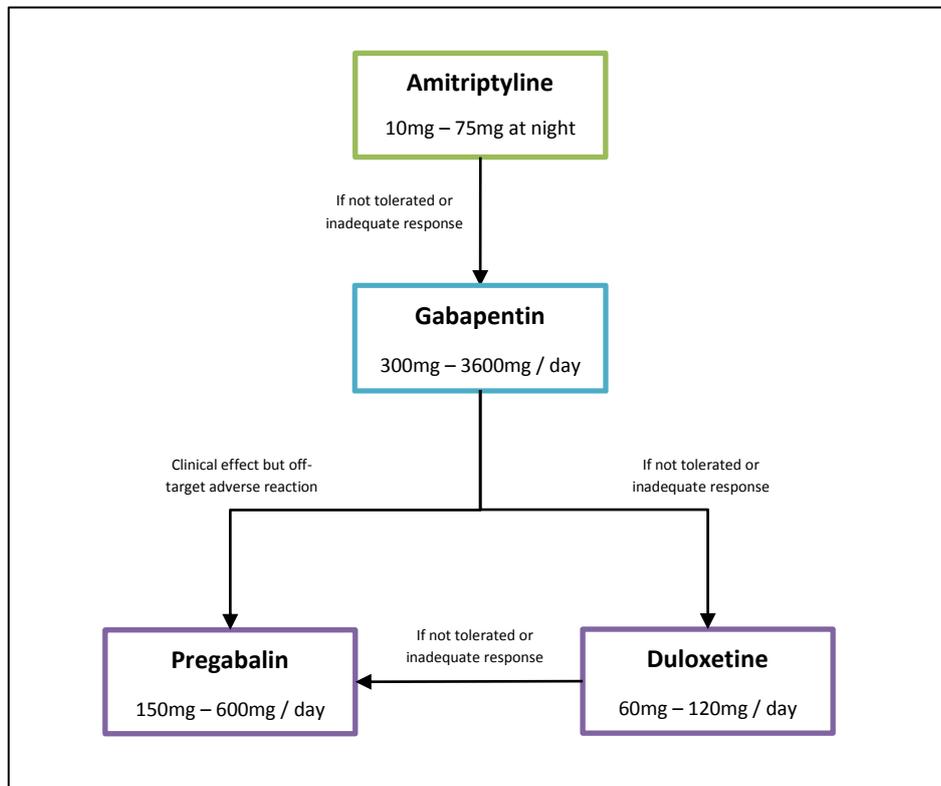
**Table 2: Dose conversion of gabapentin to pregabalin.**<sup>12</sup>

Daily dose of gabapentin (pre-switch)	Dosing schedule for pregabalin
0 – 900	75mg twice daily
901 – 1500	75mg morning + 150mg evening
1501 – 2100	150mg twice daily
2101 – 2700	150mg morning + 300mg evening
2700 or higher	300mg twice daily

## Prescribing Pathway

- Figure 1 below shows the proposed place in therapy for each agent
- Acute review: all treatments should be reviewed on an 8 week basis (minimum frequency) up until the dose is titrated to a clinically adequate dose. Discontinue treatments that are ineffective
- Ongoing review: all treatment should be reviewed regularly to determine continued need

Figure 1: Neuropathic pain treatment algorithm



## References:

1. NICE Clinical Guideline CG173 2013 Neuropathic pain: The pharmacological management of neuropathic pain in adults in non-specialist settings Available from [www.nice.org.uk](http://www.nice.org.uk)
2. Finnerup NB et al Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis Lancet Neurology 2015; 14: 162-173
3. Hadj Tahar, A. Pregabalin for peripheral neuropathic pain [Issues in Emerging Health TechnologiesP issue 67]. Ottawa: Canadian Coordinating Office for Health Technology Assessment; 2005. [www.cadth.ca/media/pdf/351\\_pregabalin\\_cetap\\_e.pdf](http://www.cadth.ca/media/pdf/351_pregabalin_cetap_e.pdf)
4. National Prescribing Service Pregabalin for Neuropathic Pain. April 2013. Available at: [http://www.nps.org.au/\\_data/assets/pdf\\_file/0004/219217/Pregabalin.pdf](http://www.nps.org.au/_data/assets/pdf_file/0004/219217/Pregabalin.pdf)
5. Public Health England Advice for prescribers on the risk of the misuse of pregabalin and gabapentin Dec 2014. Available from [www.evidence.nhs.uk](http://www.evidence.nhs.uk)
6. Summary of Product Characteristics Neurontin 300mg Hard Capsules. Pfizer Ltd. last updated on the eMC: 26/06/2013 accessed 12/03/2015. <http://www.medicines.org.uk/emc/medicine/17095>
7. Summary of Product Characteristics Lyrica Capsules. Pfizer Ltd. last updated on the eMC: 29/04/2013 accessed 12/03/2015. <http://www.medicines.org.uk/emc/medicine/14651>
8. Drug Tariff, March 2015. [http://www.ppa.org.uk/edt/March\\_2015/mindex.htm](http://www.ppa.org.uk/edt/March_2015/mindex.htm)
9. Martin J, editor. British National Formulary No 68; September 2014
10. Johnson H. How do you switch between pregabalin and gabapentin for neuropathic pain and vice versa? UKMi QA 408.1 November 2012
11. Bockbrader H et al. Gabapentin to Pregabalin therapy transition: a pharmacokinetic simulation. American Journal of Therapeutics 2013; 20: 32-36
12. Toth C. Substitution of gabapentin therapy with pregabalin therapy in neuropathic pain due to peripheral neuropathy. Pain Medicine 2010; 11: 456-465