

# DRUG UPDATE

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## NEUROPATHIC PAIN

Established pharmacological treatments such as amitriptyline and carbamazepine should remain as first-line treatment options for neuropathic pain, with gabapentin reserved for patients in whom these agents are ineffective or contraindicated. These drugs have an established evidence base and safety profile supporting their use compared with newer and more expensive alternatives such as pregabalin and transdermal lidocaine.

### What is it?

Neuropathic pain is often described as a numbing pain with associated shooting, tingling, or burning painful sensations, often worse at night. <sup>1</sup> It can be triggered by numerous different identifiable or spontaneous stimuli. The causes of neuropathic pain are many but common examples are diabetes, lower back injury, neuropathic damage following herpes viral infection, and cancer. <sup>1</sup>

Many drugs and drug combinations are used to manage neuropathic pain but not all treatments are specifically licensed for this indication. This review focuses on the principal drug treatments used in practice and some newer therapies.

### How effective are they?

Comparisons are made using a number needed to treat (NNT) value which has the advantage of comparing drugs from different trials often with different outcome measures and duration. However using a pooled NNT value may obscure important trial findings and does not take into account inclusion and exclusion criteria, and definitions of pain and response, therefore caution should be used in making direct comparisons. <sup>2</sup>

### Tricyclic antidepressants

None of the agents within this class are licensed for the management of neuropathic pain but they have been used for many years for this indication. <sup>3</sup> Amitriptyline and nortriptyline are the most common agents used, typically at daily doses of up to 75 mg with higher doses reserved for specialist supervision. <sup>3</sup> Doses should be titrated to the maximum tolerated or recommended dose before treatment failure is confirmed. Amitriptyline represents an effective and low cost first-line agent with a large evidence base. It is associated with a NNT of two relating to at least moderate pain relief. There is less evidence supporting the use of other antidepressants, however imipramine and nortriptyline appear to be as effective as amitriptyline. <sup>4</sup>

### Anticonvulsants

Several anticonvulsants have been studied and are used for the management of neuropathic pain, for example carbamazepine, gabapentin, lamotrigine, phenytoin, and valproate. <sup>3,5-7</sup> Neither lamotrigine nor valproate are licensed for the management of neuropathic pain and carbamazepine and phenytoin are only licensed for

trigeminal neuralgia. <sup>8</sup> Gabapentin is licensed at doses up to 3.6 g/day, <sup>8</sup> and it is associated with a NNT of five (improvement in neuropathic pain). <sup>5</sup> The NNT for any pain relief for carbamazepine in trigeminal neuralgia is two, although this result is derived from a small patient sample (n=47). <sup>6</sup> There is less evidence for lamotrigine, phenytoin, and valproate and they often demonstrate variable or little effect. <sup>7</sup>

### Opioid analgesics

Although there are no opioid analgesics specifically licensed for neuropathic pain they are a useful treatment option. The most robustly studied are morphine (NNT of three relating to > 50% pain relief in post-herpetic neuralgia [PHN], diabetic neuropathy, and phantom limb pain), oxycodone (NNT of three relating to > 50% pain relief in PHN and diabetic neuropathy), and tramadol (NNT of four relating to > 50% pain relief in PHN and polyneuropathy). <sup>2</sup> An enhanced effect for the combination of gabapentin and morphine compared to either alone was observed in a small cross-over study (n = 41). <sup>9</sup> However this is insufficient evidence upon which to recommend the combination except within the confines of a clinical study.

### Newer treatments

Pregabalin (Lyrica<sup>®</sup>▼) is licensed for peripheral and central neuropathic pain in adults. <sup>8</sup> It is a GABA analogue, believed to exert its effects through the same mechanism as gabapentin with a site of action in the central nervous system. <sup>8,10</sup> All published studies of pregabalin were placebo-controlled comparisons rather than comparisons to another accepted treatment. <sup>10</sup> It is associated with a NNT of five relating to > 50% pain relief in PHN and diabetic neuropathy. <sup>2</sup> Pregabalin is associated with a relatively high withdrawal rate of about 1 in 8 to 1 in 12. <sup>2,8</sup> Pregabalin should be reserved for third-line therapy and specialist initiation only, due to the relative lack of prescribing experience and increased cost compared with gabapentin.

The most recently licensed therapy for neuropathic pain, specifically PHN, is a transdermal lidocaine patch (Versatis<sup>®</sup>). <sup>8</sup> The only published controlled studies evaluating lidocaine patches were short-term studies ( $\leq 3$  weeks), which all demonstrated significantly greater efficacy of the patch compared to placebo patch or no patch. <sup>11</sup>

Lidocaine 5% patches are associated with a NNT of five relating to  $\geq 50\%$  response in various peripheral neuropathic pain syndromes including PHN. This result is derived from a small population sample ( $n = 40$  of whom 22 had PHN).<sup>11</sup> The patches are associated with a high frequency of adverse reactions, particularly dermatological.<sup>8,11</sup> Each patch must be worn for only 12 hours per day and a maximum of three patches can be applied at any time.<sup>8</sup> Lidocaine patches are costly compared to standard daily doses of other treatments for PHN and should therefore be reserved as an option for treatment-resistant patients only.

Capsaicin 0.075% cream (Axsain®) is licensed for PHN and diabetic neuropathy.<sup>8</sup> It is associated with a NNT of seven relating to  $> 50\%$  pain relief in PHN, nerve injury, mixed neuropathic pain, and diabetic neuropathy.<sup>2</sup> Topical capsaicin is associated with a high frequency of local dermatological adverse reactions, although a low incidence of systemic reactions.<sup>8</sup> This comparatively low efficacy and high incidence of adverse effects have resulted in relatively little use of topical capsaicin for neuropathic pain.

### How safe are they?

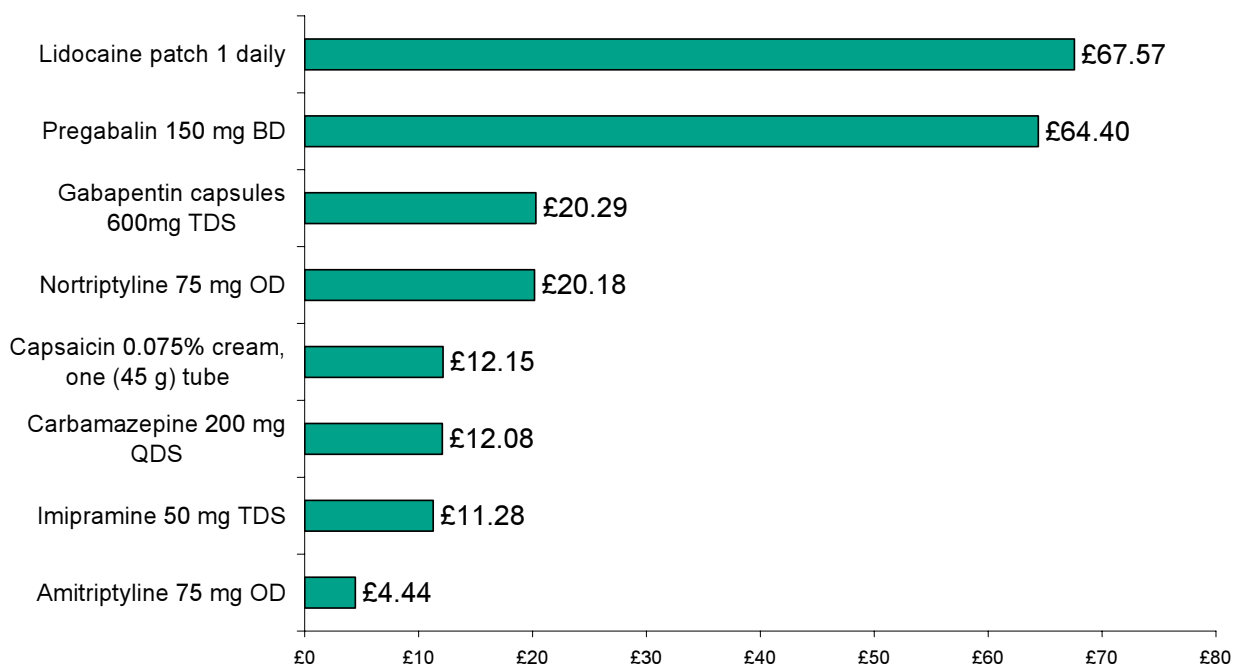
There is no evidence to indicate that the incidence or nature of adverse effects associated with oral drugs when used for neuropathic pain are any different from those when the drugs are used at similar doses for other indications. Pregabalin is a black triangle drug subject to close safety surveillance; it should be prescribed with caution and all suspected adverse reactions reported via the Yellow Card scheme.

### When should they be used?

Established pharmacological treatments such as amitriptyline and carbamazepine should remain as first-line treatment options for neuropathic pain. These drugs have a greater evidence base supporting their use, known adverse effect profiles, lower acquisition costs compared to newer alternatives, and they demonstrate high levels of efficacy. Gabapentin can be used as a second-line treatment option for patients in whom these first-line agents are ineffective or contraindicated.

### How much do they cost?

Cost for 28 days treatment (Drug Tariff and NHS dm+d, August 2007)



N.B. Doses are for comparison and do not imply therapeutic equivalence. Individual responses and prescribed doses vary substantially in the management of neuropathic pain.

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KEY E - editorial, G - guideline, R - review, RCT - randomised controlled trial

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