

# National Institute for Health and Care Excellence

## Surveillance programme

### Surveillance proposal consultation document

#### Neuropathic pain in adults: pharmacological management in non-specialist settings NICE guideline CG173 – 4-year surveillance review

### Background information

Guideline issue date: November 2013

### Surveillance proposal for consultation

We propose to not update the guideline on [neuropathic pain in adults](#) at this time.

We also propose to remove the following NICE research recommendations from the NICE version of the guideline and the NICE research recommendations database:

RR–02 Is response to pharmacological treatment predicted more reliably by underlying aetiology or by symptom characteristics?

RR–04 What are the key factors, including additional care and support that influence participation and quality of life in people with neuropathic pain?

RR–05 What is the impact of drug-related adverse effects on health economics and quality of life in neuropathic pain?

RR–06 Is there a potential for dependence associated with pharmacological agents for neuropathic pain?

## ***Reason for the proposal***

### **Assessing the evidence**

We found 84 relevant studies in a search for randomised controlled trials and systematic reviews published between 31 July 2012 and 24 January 2017. No additional studies were identified by members of the guideline committee who originally worked on this guideline.

This included evidence on pharmacological treatment for all neuropathic pain, peripheral neuropathic pain, central neuropathic pain and trigeminal neuralgia that supports current recommendations.

We found evidence on combination pharmacological therapy, which was not covered in the guideline. This evidence was considered to be insufficient to add new recommendations in this area at this time.

### **Research recommendations**

At 4-year and 8-year surveillance reviews of guidelines published after 2011, we assess progress made against prioritised research recommendations. See the [research recommendations](#) section of appendix A for further information.

For this surveillance review we assessed 6 prioritised research recommendations, and proposed that 4 should be removed from the NICE version of the guideline and the [NICE research recommendations database](#).

### **Equalities**

No equalities issues were identified during the surveillance process.

### **Overall proposed decision**

After considering all the evidence and views of topic experts, we propose to not update this guideline.

We also propose to remove 4 NICE research recommendations from the NICE version of the guideline and the NICE research recommendations database.

### ***Further information***

See [appendix A](#): summary of evidence from surveillance below for further information.

For details of the process and update decisions that are available, see [ensuring that published guidelines are current and accurate](#) in developing NICE guidelines: the manual.

## Appendix A: Summary of evidence from surveillance

### 4-year surveillance (2017) – [Neuropathic pain – pharmacological management \(2013\) NICE guideline CG173](#)

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### Summary of evidence from surveillance

#### *Treatment*

**Q – 01 What is the clinical effectiveness of different pharmacological treatments as monotherapy compared with each other or placebo for the management of neuropathic pain in adults, outside of specialist pain management services?**

#### Recommendations derived from this question

##### *All neuropathic pain (except trigeminal neuralgia)*

- 1.1.8 Offer a choice of amitriptyline, duloxetine, gabapentin or pregabalin as initial treatment for neuropathic pain (except trigeminal neuralgia)\*.
- 1.1.9 If the initial treatment is not effective or is not tolerated, offer one of the remaining 3 drugs, and consider switching again if the second and third drugs tried are also not effective or not tolerated.
- 1.1.10 Consider tramadol only if acute rescue therapy is needed (see recommendation 1.1.12 about long-term use).
- 1.1.10 Consider capsaicin cream\*\*for people with localised neuropathic pain who wish to avoid, or who cannot tolerate, oral treatments.

##### *Treatments that should not be used*

- 1.1.12 Do not start the following to treat neuropathic pain in non-specialist settings, unless advised by a specialist to do so:
- cannabis sativa extract
  - capsaicin patch
  - lacosamide
  - lamotrigine
  - levetiracetam
  - morphine
  - oxcarbazepine

- topiramate
- tramadol (this is referring to long-term use; see recommendation 1.1.10 for short-term use)
- venlafaxine.

### Trigeminal neuralgia

- 1.1.13 Offer carbamazepine as initial treatment for trigeminal neuralgia.
- 1.1.14 If initial treatment with carbamazepine is not effective, is not tolerated or is contraindicated, consider seeking expert advice from a specialist and consider early referral to a specialist pain service or a condition-specific service.

\* At the time of publication (November 2013), amitriptyline did not have a UK marketing authorisation for this indication, duloxetine is licensed for diabetic peripheral neuropathic pain only, and gabapentin is licensed for peripheral neuropathic pain only, so use for other conditions would be off-label. In addition, the Lyrica (Pfizer) brand of pregabalin has patent protection until July 2017 for its licensed indication of treatment of peripheral and central neuropathic pain; until such time as this patent expires generic pregabalin products will not be licensed for specific indications and their use may be off-label and may infringe the patent, see summaries of product characteristics of pregabalin products for details. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's [Good practice in prescribing and managing medicines and devices](#) for further information.

\*\*At the time of publication (November 2013), capsaicin cream (Axsain) had a UK marketing authorisation for post-herpetic neuralgia and painful diabetic peripheral polyneuropathy, so use for other conditions would be off-label. The SPC states that this should only be used for painful diabetic peripheral polyneuropathy 'under the direct supervision of a hospital consultant who has access to specialist resources'. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's [Good practice in prescribing and managing medicines and devices](#) for further information.

### Surveillance decision

This review question should not be updated.

### Evidence summary

#### 4-year surveillance summary

##### Diabetic neuropathy - Antiepileptics (anticonvulsants) - Pregabalin

A meta-analysis<sup>1</sup> (11 RCTs) evaluated the efficacy of pregabalin in patients with painful diabetic peripheral neuropathy. Pregabalin significantly reduced pain scores compared with placebo when patients with all pain levels were combined. In the moderate and severe pain cohorts, pregabalin treatment significantly reduced mean pain scores at endpoint compared with placebo. Patients with severe pain showed greater improvements in pain and pain-related sleep interference than patients with moderate pain.

A systematic review<sup>2</sup> (9 studies n=2,056) assessed the efficacy and safety of pregabalin for managing pain associated with diabetic polyneuropathy. Pooled analysis showed that pregabalin was significantly superior to placebo for improving mean pain scores. Pregabalin

reduced pain below baseline by at least 50% in a significantly greater proportion of patients compared with placebo. Patients were significantly more likely to self-report their status as 'improved' after taking pregabalin than placebo. Pregabalin also improved sleep quality more than placebo.

A meta-analysis<sup>3</sup> (11 RCTs) examined whether pregabalin has a direct independent effect on patient function/quality of life (QoL). Pregabalin treatment showed moderate-to-substantial pain relief (a >30% decrease in pain) and significant improvement in QoL assessed by 36-Item Short Form Health Survey (SF-36) compared with placebo.

An RCT<sup>4</sup> compared the analgesic efficacy of pregabalin, amitriptyline, and duloxetine, and their effect on sleep, daytime functioning, and QoL in patients with chronic diabetic peripheral neuropathic pain. Pregabalin improved sleep continuity significantly, whereas duloxetine increased wake and reduced total sleep time significantly. There was a significantly higher

number of adverse events in the pregabalin treatment group.

A cross-over RCT<sup>5</sup> (n=45) evaluated the efficacy of pregabalin in the treatment of pre-diabetic neuropathic pain. There was 36% pain reduction in the Numeric Rating Scale from baseline after 1 month of single-blind pregabalin. Twenty-six participants were eligible for the double-blind phase. There was a statistically significant pain reduction in the double-blind pregabalin than the placebo.

A multicentre, cross-over RCT<sup>6</sup> (n=284) evaluated the efficacy and safety of pregabalin (150 to 300 mg/day) for treatment of pain in patients with diabetic peripheral neuropathy. There was no statistically significant treatment difference for pregabalin versus placebo in the mean pain on walking. Adverse events and discontinuation were more frequent with pregabalin than with placebo.

A cross-over RCT<sup>7</sup> (n=665) evaluated the efficacy of pregabalin versus placebo for pain relief in patients with diabetic peripheral neuropathy inadequately treated by other therapies. Patients received pregabalin in a 6-week single-blind phase. Two hundred ninety-four patients who achieved a >30% pain response were randomised to receive pregabalin or placebo in a double-blind phase for a further 13 weeks. Pregabalin improved all measures assessed during the single-blind phase. At the end of the double-blind withdrawal phase, there was no significant difference in the primary endpoint of mean pain score between pregabalin and placebo. Pregabalin was associated with a significantly longer time to loss of pain response versus placebo, and some aspects of sleep and QoL also showed significant improvements with pregabalin.

A cross-over RCT<sup>8</sup> (n=301) examined pregabalin's efficacy and safety for pain improvement in patients with diabetic peripheral neuropathy pain. Patients with diabetic polyneuropathy using a nonsteroidal anti-inflammatory drug were randomised to receive 150 to 300 mg/day pregabalin-placebo (n=154) or placebo-pregabalin (n=147). The findings showed no statistically significant difference between pregabalin and placebo in mean weekly pain. However, greater pain score reductions was observed with pregabalin than placebo at weeks 2 to 4 and overall. The mean

treatment difference in diabetic polyneuropathy related sleep interference, favoured significantly pregabalin over placebo.

A post-hoc analysis of data<sup>9</sup> pooled from 16 trials of pregabalin (n=4,527) evaluated the ability of pregabalin to reduce pain associated with diabetic peripheral neuropathy and postherpetic neuralgia. Pregabalin significantly reduced mean pain scores in the diabetic polyneuropathy (n=3,056) and postherpetic neuralgia (n=1,471) cohorts.

An RCT<sup>10</sup> (n=257) evaluated the efficacy and safety of carbamazepine, pregabalin, and venlafaxine in patients with painful diabetic neuropathy. Mean visual analogue scale (VAS) scores for carbamazepine, pregabalin, and venlafaxine treatment groups at the baseline (74.5, 82.3, and 74.5) and endpoint (39.6, 33.4, and 46.6) showed significant reduction. Pregabalin was more effective than carbamazepine, and venlafaxine. Mean scores of sleep, mood, and work interferences were improved in all treatment groups.

An RCT<sup>11</sup> (n=147) examined the efficacy and safety of a gastroretentive formulation of gabapentin (G-GR) in treating painful diabetic peripheral neuropathy. Patients received G-GR 3000 mg, as a single evening daily dose or a divided dose (1200 mg AM/1800 mg PM), or placebo for 4 weeks. A significantly larger decrease in average daily pain score was observed in the single dose group compared with placebo (-2.50 versus -1.30). A >50% reduction in average daily pain score was achieved in 34.8% of single dose recipients compared with 7.8% of placebo recipients.

A post hoc analysis of an RCT<sup>12</sup> examined the efficacy of duloxetine versus pregabalin in the treatment for diabetic peripheral neuropathic pain, comparing patient subgroups with and without antidepressant use. Seventy nine patients were concomitantly treated with antidepressants and 328 without antidepressants. Among patients without antidepressants. Among patients without antidepressant use, patients treated with duloxetine had significantly greater pain reduction than pregabalin at week 4 and at each successive week up to the 12-week endpoint. Patients treated with duloxetine plus gabapentin had also greater pain reduction than pregabalin at weeks 2, 3, 5, and 7 to 9.

*Diabetic neuropathy - Antiepileptics (anticonvulsants) - Gabapentin*

A systematic review<sup>13</sup> (37 RCTs n= 5633), reviewed the effects of oral gabapentin (1200 mg or more daily) in patients with painful diabetic neuropathy. A statistically significant increase in the proportion of patients reporting at least a 50% reduction in pain, was observed in those who received gabapentin compared with placebo.

#### Diabetic neuropathy - Tricyclic antidepressants - Imipramine

A Cochrane systematic review<sup>14</sup> (5 RCTs n=168) examined the analgesic efficacy of imipramine for chronic neuropathic pain in adults. The authors indicated that no data were available on the proportion of people with at least 50% or 30% reduction in pain or equivalent. They also indicated that no pooling of data was possible, but evidence in individual studies indicated some improvement in pain relief with imipramine compared with placebo. Limited information about adverse events was reported.

#### Diabetic neuropathy - Selective serotonin reuptake inhibitors - Duloxetine

A systematic review<sup>15</sup> (18 RCTs n= 6,407), investigated the efficacy of duloxetine for reducing pain (60 mg daily for 12 weeks). A statistically significant increase in the proportion of patients with painful diabetic neuropathy, reporting at least a 50% reduction in pain, was observed. One included study reported no significant reduction in pain in patients with central neuropathic pain.

An RCT<sup>16</sup> (n=258) examined the long-term efficacy and safety of duloxetine in the treatment of patients with diabetic neuropathic pain. Significant improvements were observed in Brief Pain Inventory severity and in Brief Pain Inventory interference and Patient's Global Impression of Improvement scores. The authors indicated that none of reported adverse events (somnolence, constipation, nausea) were clinically meaningful and there were no clinically significant safety concerns.

A multicentre RCT<sup>17</sup> (n=405) assessed the efficacy and safety of duloxetine (60 mg once daily) compared with placebo in patients with diabetic peripheral neuropathic pain. Patients were assigned to duloxetine 60 mg once daily (n=203) and to placebo (n=202). At 12 weeks, patients treated with duloxetine showed significantly greater pain relief on 24-h average

pain ratings compared with placebo-treated patients. Compared with placebo, patients treated with duloxetine experienced higher rates of nausea, somnolence and asthenia.

#### Diabetic neuropathy - Opioid analgesics - Oxycodone

An updated Cochrane systematic review<sup>18</sup> assessed the analgesic efficacy and adverse events of oxycodone for chronic neuropathic pain in adults. Five studies with 687 participants (637 had painful diabetic neuropathy and 50 had postherpetic neuralgia) were included. Three studies (n=537) in painful diabetic neuropathy reported outcomes equivalent to 'moderate benefit', which was experienced by 44% of participants with oxycodone and 27% with placebo. Three studies reported a greater pain intensity reduction and better patient satisfaction with modified-release oxycodone (oxycodone MR) alone than with placebo. More participants experienced adverse events with oxycodone MR alone (86%) than with placebo (63%). Serious adverse events and adverse event withdrawals were not significantly different between groups. The authors indicated that evidence from this systematic review was based on poor quality studies.

#### Diabetic neuropathy - Opioid analgesics - Tapentadol

An RCT<sup>19</sup> (n=318) evaluated the efficacy and tolerability of tapentadol extended release (ER) for the management of chronic pain associated with diabetic peripheral neuropathy. Patients were randomised and received one or more doses of double-blind placebo (n=152) or tapentadol ER (n=166). The mean change in pain intensity was significantly higher at tapentadol ER, compared with placebo. Treatment-emergent adverse events in the tapentadol ER group were nausea (21.1%) and vomiting (12.7%).

#### Diabetic neuropathy - Opioid analgesics - Buprenorphine

A multicentre RCT<sup>20</sup> (n=186) evaluated the efficacy and safety of transdermal buprenorphine in patients with diabetic peripheral neuropathic pain. Patients were randomly assigned to receive buprenorphine (n= 93) or placebo patches (n=93). A high proportion of patients did not complete the study due to untreated nausea and/or vomiting

(buprenorphine 37/93, placebo 24/93). At per-protocol analysis significantly more patients in the buprenorphine group (86.3%) experienced a 30% reduction in average versus baseline pain at week 12 than those in the placebo group (56.6%). A nonsignificant trend favoured the buprenorphine group within the intention-to-treat analysis of the same end point.

#### Diabetic neuropathy - Non-opioid analgesics - Ketamine

An RCT<sup>21</sup> (n=17) examined the efficacy of topical 5% ketamine cream in reducing the pain of diabetic neuropathy. Patients applied 1 mL of either ketamine cream or placebo cream for 1 month. Pain improved significantly over time in both groups. There was no statistical interaction effect (treatment x time) in any of the pain characteristics, indicating that pain improved in the two treatment groups similarly with time.

#### Diabetic neuropathy - Cannabinoids

An enriched enrolment randomised withdrawal design trial<sup>22</sup> (n=26) assessed efficacy of oral cannabinoid, nabilone, in the treatment of diabetic peripheral neuropathic pain. Patients with regular pain medications were randomised to receive either flexible-dose nabilone 1-4 mg/day (n=13) or placebo (n=13) for 5-weeks. For nabilone there was an improvement in the change in mean end-point neuropathic pain versus placebo. Flexible-dose nabilone 1-4 mg/day was effective in relieving diabetic polyneuropathy symptoms, improving disturbed sleep, quality of life, and overall patient status.

A systematic review and mixed treatment comparison<sup>23</sup> (58 studies n=11,883, 28 interventions) assessed pharmacological treatments including sativex for painful diabetic peripheral neuropathy. Pain reduction over that of placebo on the 11-point numeric rating scale ranged from -3.29 for sodium valproate to 1.67 for sativex. Pregabalin was the most effective pain reduction on VAS; topiramate was the least. Relative risks (RRs) of 30% pain reduction ranged from 0.78 (sativex) to 1.84 (lidocaine 5% plaster). Fluoxetine had the lowest risk of adverse events; oxycodone had the highest.

#### Diabetic Neuropathy - Topical analgesics – Capsaicin, Lidocaine

An RCT<sup>24</sup> (n=122) assessed tolerability of the capsaicin patch following topical lidocaine (4%)

or oral tramadol (50 mg) pre-treatment in patients with peripheral neuropathic pain. Tolerability of the capsaicin patch was similar following pre-treatment with lidocaine and tramadol. Following patch application, pain levels increased and after patch removal, tramadol-treated patients experienced greater pain relief up to the end of day 1; in the evening, mean changes in Numeric Pain Rating Scale scores from baseline were 0 for lidocaine and -1 for tramadol. Proportions of patients reporting pain increase on the day of treatment were similar between arms. Adverse event incidence was similar between arms.

An RCT<sup>25</sup> (n=102) compared the effect of amitriptyline and capsaicin cream in relieving pain in patients with diabetic neuropathy. Patients either received amitriptyline 2% or capsaicin 0.75% creams 3 times daily for 12 weeks on the feet. Both drugs significantly relieved pain in 12 weeks compared with baseline values. Treatment responders were similar in both groups. Intention-to-treat analysis showed no significant difference in the efficacy between the two treatments. Adverse events were significantly more common in the capsaicin group.

An RCT<sup>26</sup> (n=139) compared the effect of clonidine gel and capsaicin cream in relieving pain associated with diabetic polyneuropathy. Patients were randomised to receive clonidine (n=69) or capsaicin (n=70). Both drugs significantly relieved pain at 12 weeks (assessed by VAS) but no significant difference in the efficacy between the two treatments was observed. Dermatologic complications were more common in the capsaicin group.

An RCT<sup>27</sup> (n=369) evaluated the efficacy and safety of capsaicin 8% patch versus placebo patch in diabetic peripheral neuropathy. Patients with painful diabetic peripheral neuropathy were randomised to one 30-minute treatment with capsaicin 8% patch (n=186) or placebo patch (n=183) to painful areas of the feet. Percentage reduction in average daily pain score from baseline was statistically significant for capsaicin 8% patch versus placebo; improvements in pain were observed from week 2 onward. Patients treated with capsaicin 8% patch had a shorter median time to treatment response and modest improvements in sleep interference scores than placebo.



### Diabetic neuropathy - All drugs

A systematic review and network meta-analysis<sup>28</sup> (65 studies n=12,632, 27 pharmacological interventions) evaluated the comparative effectiveness of oral and topical analgesics for diabetic neuropathy. Nine head-to-head trials showed greater pain reduction associated with serotonin-norepinephrine reuptake inhibitors (SNRIs) than anticonvulsants and with tricyclic antidepressants than topical capsaicin. SNRIs, topical capsaicin, tricyclic antidepressants and anticonvulsants were better than placebo for short-term pain control. Specifically, carbamazepine, venlafaxine, duloxetine, and amitriptyline were more effective than placebo in management of the pain.

### Diabetic neuropathy - Other drugs - Rosuvastatin

A Phase II RCT<sup>29</sup> evaluated the effect of rosuvastatin in diabetic polyneuropathy in patients with type 2 diabetes and diabetic polyneuropathy. Participants were randomised to two parallel groups that received rosuvastatin 20 mg or placebo for 12 weeks. There was greater improvement of diabetic polyneuropathy and neuropathic symptom score in the rosuvastatin group compared with placebo.

### Postherpetic neuralgia - Antiepileptics (anticonvulsants) - Pregabalin

A systematic review<sup>30</sup> of 5 RCTs (n=1,625) examined efficacy of pregabalin for postherpetic neuralgia pain treatment. Pregabalin was effective in reducing the mean pain score and sleep interference score and increasing the percentage of 30% and 50% pain responders in comparison with placebo.

An RCT<sup>31</sup> (n=220) assessed the efficacy of pregabalin in patients with postherpetic neuralgia. Participants were randomised to receive pregabalin 300 mg/day or placebo. Improvement in mean pain score with pregabalin was significantly greater than placebo. Improvements in VAS and sleep interference score at endpoint were significantly greater with pregabalin than placebo.

### Postherpetic neuralgia - Antiepileptics (anticonvulsants) - Gabapentin

A systematic review<sup>32</sup> (7 RCTs n=2,039) evaluated the efficacy and safety of gabapentin

for management of postherpetic neuralgia. Gabapentin reduced postherpetic neuralgia-related pain significantly more than placebo. Gabapentin reduced pain below baseline by at least 50% significantly more than placebo. Gabapentin also improved sleep quality significantly more than placebo. Patients given gabapentin were significantly more likely to experience dizziness, somnolence, peripheral oedema, ataxia or gait disturbance and diarrhoea.

An RCT<sup>33</sup> (n=80) evaluated the long-term safety and tolerability of a gastroretentive formulation of gabapentin (G-GR) and its effect on weight gain in postherpetic neuralgia. The incidence of adverse events (dizziness, somnolence) with gabapentin was low and the frequency, intensity, and severity of adverse events did not change with long-term treatment. The mean weight change from baseline was +0.76 kg. Weight increase was reported for 2 (2.5%) patients.

A systematic review<sup>34</sup> (7 RCTs n=2,041) assessed the different doses of gabapentin formulations (gabapentin ER), and gabapentin enacarbil (GEN) for improving postherpetic neuralgia. Gabapentin ER 1800 mg/day once daily treatment was significantly effective in pain relief and had high incidence of adverse events, but twice daily treatment showed no significant differences in both efficacy and side effects compared with placebo. Gabapentin GEN 1200 mg/day and 2400 mg/day doses were more effective in treating postherpetic neuralgia.

A systematic review<sup>35</sup> (6 RCTs) assessed the efficacy and safety of gabapentin 1800 mg/day in post-herpetic neuralgia patients. RCTs that compared gabapentin 1800 mg/day to placebo for postherpetic neuralgia were included. Gabapentin 1800 mg/day reduced the 24-h average pain intensity scores and average daily sleep rating scores. Gabapentin treatment improved post-herpetic neuralgia significantly but increased mild to moderate somnolence, peripheral oedema, total adverse effects and withdrawal due to adverse events.

### Postherpetic neuralgia - All drugs

A systematic review and mixed treatment comparison<sup>36</sup> (28 studies n=4,317 patients, 21 interventions) assessed the relative efficacy of pharmacological therapies for treatment of postherpetic neuralgia MS-related pain,

posttraumatic pain, central poststroke pain and human immunodeficiency virus (HIV)-related neuropathic pain. Of treatments studied in >50 patients, opioids had the greatest mean pain reduction versus placebo. Pregabalin >300 mg/day was most effective for >30% and >50% pain reduction. Adverse events and discontinuations for most treatments were not significantly greater than placebo except in postherpetic neuralgia, where 8 of 12 treatments had higher risks of adverse events compared with placebo and tricyclic antidepressants and opioids had higher risk of discontinuation compared with placebo.

An RCT<sup>37</sup> (n=50) examined the clinical efficacy of amitriptyline and pregabalin. Participants were randomised to receive either amitriptyline or pregabalin. Satisfactory significant improvements in pain perception was observed at the end of 2 months (36% versus 8%) and 4 months (61.9% versus 27.8%) in pregabalin group compared with amitriptyline group. However, this difference diminished after 6 months. None of the patients stopped treatment due to adverse reactions.

#### Postherpetic neuralgia - Topical analgesics - Lidocaine

A crossover RCT<sup>38</sup> (n=46) compared the effect of lidocaine in patients with and without irritable nociceptor phenotype defined by hypersensitivity and preserved small-fibre function. Patients with neuropathic pain due to nerve injury or postherpetic neuralgia were randomised to 4-week treatment periods of lidocaine 5% patch or placebo. Lidocaine reduced pain and sleep disturbance significantly more than placebo. There was no significant interaction between treatment and phenotype, but there was a significant interaction for pain paroxysms and deep aching pain.

#### Postherpetic neuralgia - Opioid analgesics - Methadone

A cross-over proof of concept RCT<sup>39</sup> (n=10) evaluated the use of low-dose methadone in postherpetic neuralgia patients. Patients received either methadone (5 mg twice daily) or placebo for three weeks, followed by a 15-day washout period and a second three-week treatment with either methadone or placebo. The intensity of spontaneous pain was significantly decreased after the methadone treatment compared to placebo on the category

verbal scale. Evoked pain was reduced under methadone compared to placebo. Findings showed sleep improvement during the methadone treatment. Side effects were similar between both treatments.

#### Postherpetic neuralgia - Non-steroidal anti-inflammatory drugs (NSAIDs)

A cross-over randomised trial<sup>40</sup> (n=28) examined the effect of 1.5% topical diclofenac on neuropathic pain. Participants with postherpetic neuralgia and complex regional pain syndrome were recruited. After 2 weeks of topical application, participants in topical diclofenac group showed lower overall pain score compared with placebo group as well as decreased burning pain. There were no differences in constant pain, shooting pain, or hypersensitivity over the painful area between the groups. There were no statistically significant changes in functional status in patients.

#### Neuropathic pain following spinal cord injury - Antiepileptics (anticonvulsants) - Pregabalin, Gabapentin

An RCT<sup>41</sup> (n=220) assessed the efficacy and tolerability of pregabalin for the treatment of central neuropathic pain after spinal cord injury. Patients were randomised to receive 150 to 600 mg/day pregabalin (n=108) or matching placebo (n=112) for 17 weeks. Significant pain improvement was observed as early as week 1 at pregabalin group and was sustained throughout the treatment period. Pregabalin treatment resulted in significant improvements in the change in mean pain score, patient global impression of change scores, and the change in mean pain-related sleep interference score from baseline to end point.

A systematic review<sup>42</sup> (8 RCTs) examined the effectiveness of gabapentin and pregabalin compared with placebo in improving neuropathic pain in individuals with spinal cord injury. There was a significant reduction in the intensity of neuropathic pain at <3 months and between 3 and 6 months with use of gabapentin and pregabalin. Sleep interference, and depression, were significantly improved in gabapentin and pregabalin groups.

A cross over RCT<sup>43</sup> (n=28) compared the efficacy and side effects of gabapentin and pregabalin for the treatment of neuropathic pain in spinal cord injury. Patients were randomised

to receive pregabalin or gabapentin. At the first 4 weeks the pain improved significantly in pregabalin group assessed with VAS compared to gabapentin group. But after 8 weeks of treatments the significance disappeared between the two groups. In neuropathic pain scale, and Lattinen test parameters, no difference was present between the two study groups before or after the treatment. Frequency of side effects and withdrawal from the study due to side effects were higher for the pregabalin group but there was no significant difference between the groups.

Neuropathic pain following spinal cord injury  
Antiepileptics (anticonvulsants) -  
Carbamazepine

An RCT<sup>44</sup> (n=21) evaluated whether early treatment with carbamazepine decreases the incidence of neuropathic pain or its intensity in patients with spinal cord injury who developed neuropathic pain. At 1, 3, and 6 month follow-up assessments, neuropathic pain was present in 4, 11, and 10 patients of the carbamazepine group and in 8, 9, and 8 patients of the placebo group, respectively. At 1 month, 2 patients in the carbamazepine group versus 8 patients in the placebo group reported moderate/intense pain. At the 3 and 6 month follow-up, there was no significant difference in moderate/intense pain reported by patients in carbamazepine and placebo group.

Neuropathic pain following spinal cord injury -  
All drugs

A systematic review<sup>45</sup> (9 studies of which 8 had <100 participants) assessed the efficacy and safety of pharmacological therapies for treating neuropathic pain associated with spinal cord injury. The estimated 11-point numeric rating scale (NRS) pain reduction relative to placebo was -1.72 for pregabalin, -1.65 for amitriptyline, -1.0 for duloxetine, -1 for levetiracetam, -0.27 for gabapentin, 1 for lamotrigine, and 2 for dronabinol. Meta-analytic comparisons showed significantly more adverse events with pregabalin and tramadol compared with placebo, and no differences in discontinuation was observed between placebo and any treatment.

A systematic review<sup>46</sup> (4 RCTs) assessed the effectiveness and safety of antidepressants for neuropathic pain among individuals with spinal cord injury. Of the 4 RCTs, 2 studies assessed

amitriptyline, 1 trazadone, and 1 duloxetine among individuals with neuropathic spinal cord injury pain. Effectiveness of antidepressants in reducing pain was small. Significantly higher risk of experiencing constipation and dry mouth was found amongst individuals receiving antidepressant treatment compared to those in the control group.

Neuropathic pain following cancer or cancer -  
Opioid analgesics

An RCT<sup>47</sup> (n=52) assessed the efficacy of strong opioids in patients with head-and-neck cancer and pain with a neuropathic pain component. Twenty-six patients were treated with methadone and 26 with fentanyl. Patients were evaluated at 1, 3 and 5 weeks. Reduction in pain numerical rating scale was higher with the use of methadone at 1, 3 and 5 weeks compared to fentanyl. This difference was significant at 1 and at 3 weeks. Clinical success (>50% improvement) was significantly higher with methadone at 1 week. The change in pain and side-effect profile were not significantly different between the groups.

Trigeminal neuralgia - Antiepileptics  
(anticonvulsants) - Gabapentin

A meta-analysis<sup>48</sup> (16 RCTs n=1,331) examined the safety and efficacy of gabapentin compared with carbamazepine in the treatment of trigeminal neuralgia. The findings showed that the total effective rate of gabapentin therapy group was similar with carbamazepine therapy group. While the effective rate of gabapentin therapy for 4 weeks was higher than that of carbamazepine therapy, the QoL improvement was also better in the gabapentin therapy group after a 4-week treatment. The adverse events in gabapentin group was significantly lower than the carbamazepine group.

Trigeminal neuralgia - Antiepileptics  
(anticonvulsants) - Carbamazepine

A Cochrane systematic review<sup>49</sup> (4 RCTs n=139) examined the efficacy and tolerability of anticonvulsants including carbamazepine for trigeminal neuralgia treatment. Three trials compared one of the oral non-antiepileptic drugs tizanidine and pimozone with carbamazepine. In a trial of tizanidine involving 12 participants, pain improved in one of five participants treated with tizanidine and four of six treated with carbamazepine. For pimozone,

at six weeks, there was greater analgesic efficacy than carbamazepine.

#### Fabry disease

A systematic review<sup>50</sup> of 26 observational studies (n=55, group-sizes ranging from 1 to 8) evaluated the pain management strategies for neuropathic pain in Fabry disease.

Carbamazepine showed complete pain relief in 5/25, partial relief in 17/25, and no benefit in 3/25 patients. Phenytoin resulted in complete relief in 1/27, partial relief in 12/27 and no benefit in 6/27 patients. In 8/55 patients, a significant reduction in the frequency of pain attacks was reported. Gabapentin caused partial relief in 6/7 and no relief in 1/7 patients.

#### Central neuropathic pain - Selective serotonin reuptake inhibitors - Duloxetine

An RCT<sup>51</sup> (n=38) examined the efficacy of duloxetine for central pain in patients with multiple sclerosis. Participants were randomised to receive duloxetine (n=18) or matched placebo (n=20). Among those who completed treatment, worst pain at 6 weeks was reduced by 29% for duloxetine versus 12% for placebo. At 6 weeks, average daily pain was reduced significantly in the duloxetine group compared to the placebo group (39% versus 10%).

#### Central neuropathic pain - Antiepileptics (anticonvulsants) - Levetiracetam

An RCT<sup>52</sup> (n=42) examined the efficacy and tolerability of levetiracetam in patients with central post-stroke pain. Patients with central post-stroke pain lasting at least 3 months were treated over two 8-week periods with a maximum dose up to 3000 mg levetiracetam or placebo. Side effects and withdrawals were more frequent in the levetiracetam group (n=5) than in the placebo group (n=1). Patients treated with levetiracetam did not show any improvement of pain compared with placebo.

#### Sciatica neuropathic pain - Non-steroidal anti-inflammatory drugs (NSAIDs)

An updated Cochrane systematic review<sup>53</sup> (10 RCTs n=1,651) examined the efficacy of NSAIDs in pain reduction, overall improvement, and reported side effects in people with sciatica. Three trials (n=918) compared the effects of NSAIDs to those of placebo on pain reduction. The pooled mean difference showed comparable pain reduction in the NSAIDs and placebo groups. NSAIDs showed a better

global improvement compared to placebo (3 RCTs n=753). NSAIDs were no more effective than placebo on reducing disability (1 RCT n=214). Higher incidence of adverse effects were reported in the NSAIDs group than in the placebo group (4 RCTs n=967).

#### Sciatica neuropathic pain - Opioid analgesics - Morphine

An RCT<sup>54</sup> (n=300) examined the efficacy of intravenous morphine and intravenous acetaminophen (paracetamol) for pain treatment in patients presenting to the emergency department with sciatica. Participants were assigned to one of three intravenous interventions: morphine (0.1 mg/kg), paracetamol (1 g), or placebo. Rescue drug (fentanyl) use and adverse effects were also recorded. The median change in pain intensity based on visual analogue scale between treatment arms at 30 minutes were as follows: morphine versus paracetamol 25 mm, morphine versus placebo 41 mm, and paracetamol versus placebo 16 mm. Eighty percent of the patients in the placebo group, 18% of the patients in the paracetamol group, and 6% of those in the morphine group required a rescue drug. Incidence of adverse effects were similar between the morphine and paracetamol groups.

#### All neuropathic pain - Antiepileptics (anticonvulsants) - Pregabalin

A systematic review<sup>55</sup> (12 RCTs) evaluated the efficacy, safety and tolerability of pregabalin for neuropathic pain management. Compared with the placebo group, the pregabalin group improved pain assessed by VAS. There was significant reduction in the pregabalin group at both 'anxiety' and 'depression' assessed by the Hospital Anxiety and Depression Scale.

Patient-level data<sup>56</sup> (31 studies n=7,510) of pregabalin versus placebo in peripheral neuropathic pain were analysed and assessed the incidence of adverse events. The risk analysis identified 9 adverse events: dizziness, somnolence, peripheral oedema, weight increase, dry mouth, constipation, blurred vision, balance disorder, and euphoric mood.

An RCT<sup>57</sup> (n=30) compared the effectiveness of gabapentin and pregabalin in the treatment of neuropathic pain due to peripheral nerve injury. Patients were randomised to receive gabapentin (n=15) or pregabalin (n=15). The

mean reduction in VAS pain and the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) scores from baseline to after the first week, first month, and third month of treatment was statistically significant in both groups; however, there were no significant differences in mean changes in VAS pain and LANSS scores between the two groups. The mean reduction in sleep interference score from baseline to after three months of treatment was significantly greater in pregabalin group than in gabapentin group.

An RCT<sup>58</sup> (n=50) investigated the effects of gabapentin and pregabalin on uraemic pruritus along with neuropathic pain in patients receiving haemodialysis. Patients were randomly assigned to gabapentin 300 mg after each haemodialysis session and pregabalin 75 mg daily. After 6 weeks of treatment, cross-over was performed and patients received the other drug for another 6 weeks. Gabapentin and pregabalin improved both neuropathic pain and pruritus significantly. There was no difference between the study drugs in terms of efficacy against pain and pruritus.

All neuropathic pain - Antiepileptics (anticonvulsants) - Carbamazepine

A Cochrane systematic review<sup>59</sup> (10 studies, n=480) assessed the analgesic efficacy of carbamazepine in the treatment of chronic neuropathic pain and fibromyalgia. Participants with trigeminal neuralgia, diabetic neuropathy, and post stroke pain were included. The authors indicated that limited and low quality evidence showed that carbamazepine generally provided better pain relief than placebo. In four studies 65% (113/173) of participants experienced at least one adverse event with carbamazepine, and 27% (47/173) with placebo; authors calculated that for every five participants treated, two experienced an adverse event who would not have done so with placebo. In eight studies 3% (8/268) of participants withdrew due to adverse events with carbamazepine, and none (0/255) with placebo. Serious adverse events were not reported; rashes were associated with carbamazepine. Four deaths occurred in patients on carbamazepine, with no obvious drug association.

All neuropathic pain - Antiepileptic (Clonazepam, Phenytoin)

An overview of 10 Cochrane systematic reviews<sup>60</sup> examined the efficacy of antiepileptic drugs compared with placebo in neuropathic pain. The findings indicated that for pregabalin, point estimates of numbers needed to treat (NNT) for an additional beneficial effect were in the range of 4 to 10 for the pain intensity reduction over baseline of 50% or more. There was no evidence for other antiepileptic drugs (clonazepam, phenytoin), and very little and inconclusive evidence about valproic acid. Evidence indicated little or no effect for lamotrigine, oxcarbazepine, topiramate on pain intensity reduction. Serious adverse events were not reported, except with oxcarbazepine.

All neuropathic pain - Antiepileptics (anticonvulsants) - Oxcarbazepine

An RCT<sup>61</sup> examined the effect of oxcarbazepine compared with placebo in patients with peripheral neuropathic pain. Ninety-seven patients with peripheral neuropathic pain due to polyneuropathy, surgical or traumatic nerve injury, or postherpetic neuralgia were randomised to two 6-week treatment periods of oxcarbazepine (1800-2400 mg) or placebo. Oxcarbazepine relieved pain significantly more than placebo.

All neuropathic pain - Antiepileptics (anticonvulsants) - Lamotrigine

An updated Cochrane review<sup>62</sup> (12 RCTs n=1,511) assessed the analgesic efficacy of lamotrigine in the treatment of chronic neuropathic pain and fibromyalgia. RCTs investigating the use of lamotrigine (any dose, by any route, and for any study duration) for the treatment of chronic neuropathic pain or fibromyalgia were included. Lamotrigine was not effective in treating neuropathic pain and fibromyalgia at doses of 200 mg to 400 mg daily. Almost 10% of participants taking lamotrigine reported a skin rash.

All neuropathic pain - Antiepileptics (anticonvulsants) - Topiramate

A Cochrane systematic review<sup>63</sup> (4 studies n=1,684) assessed the analgesic efficacy and associated adverse events of topiramate for chronic neuropathic pain and fibromyalgia in adults. There was no difference in analgesic efficacy for topiramate at 200 to 400 mg/day over placebo. Eighty-two per cent in topiramate

group and 71% in placebo group experienced at least one adverse event. There was no difference in serious adverse events reported (6.6% versus 7.5%). Adverse event withdrawals with 400 mg daily were much more common with topiramate (27%) than with placebo (8%).

All neuropathic pain - Antiepileptics (anticonvulsants) - Levetiracetam

A Cochrane systematic review<sup>64</sup> assessed the analgesic efficacy and adverse events of levetiracetam in chronic neuropathic pain conditions in adults. Six studies including five small, cross-over studies with 174 participants, and one parallel group study with 170 participants were included. Participants were treated with levetiracetam (2000 mg to 3000 mg daily) or placebo for between four and 14 weeks. Each study included participants with a different type of neuropathic pain. The authors indicated that there were insufficient data for a pooled efficacy analysis in particular neuropathic pain conditions, but individual studies did not show any analgesic effect of levetiracetam compared with placebo. Significantly more participants experienced an adverse event with levetiracetam than with placebo. There were significantly more adverse event withdrawals with levetiracetam.

All neuropathic pain - Tricyclic antidepressants - Amitriptyline

A Cochrane systematic review<sup>65</sup> (n=17 RCTs n=1342), investigated the effects of at least 4 weeks treatment of amitriptyline compared with placebo or other active medications, on chronic neuropathic pain. Only in 2/17 studies amitriptyline was significantly better than placebo for pain improvement. A statistically significant increase in adverse events was observed in those receiving amitriptyline compared with placebo.

All neuropathic pain - Opioid analgesics - Fentanyl

A Cochrane systematic review<sup>66</sup> (1 RCT) assessed the analgesic effectiveness and safety of fentanyl for chronic neuropathic pain in adults. The number of participants completing the study without an increase of pain was 47/84 (56%) with fentanyl and 28/79 (35%) with placebo. Almost 60% of participants taking fentanyl were 'satisfied' and 'very

satisfied' with their treatment at the end of the study, compared with about 40% with placebo.

All neuropathic pain - Opioid analgesics - Morphine

An update of a Cochrane systematic review<sup>67</sup> assessed the analgesic efficacy of hydromorphone for chronic neuropathic pain in adults. One *post hoc* analysis of a randomised withdrawal trial with 94 participants was included. Findings showed slightly larger increase in average pain intensity for placebo in the randomised withdrawal phase than for continuing with hydromorphone. Adverse events occurred in about half of participants with hydromorphone, the most common being constipation and nausea. A similar proportion of participants experienced adverse events with placebo.

All neuropathic pain - Topical analgesics - Capsaicin

An updated systematic review<sup>68</sup> (6 RCTs n=2,073) examined the efficacy and tolerability of topically applied low-concentration (<1%) capsaicin in chronic neuropathic pain in adults. Studies compared regular application of low dose (0.075%) capsaicin cream with placebo cream. Only 2 studies reported data for the preferred primary outcome of at least 50% pain relief, and there were too few data for pooled analysis. Local skin reactions were more common with capsaicin, usually tolerable, the number need to harm for repeated low-dose application was 2.5.

An updated Cochrane review<sup>69</sup> (8 RCTs n=2,488) examined the efficacy and tolerability of topically applied high-concentration (8%) capsaicin in chronic neuropathic pain in adults. Result from four studies (n=1,272) on patients with postherpetic neuralgia indicated that at both 8 and 12 weeks about 10% more participants reported themselves much or very much improved with high-concentration capsaicin than with placebo. More participants had average 2 to 8-week and 2 to 12-week pain intensity reductions over baseline of at least 30% and at least 50% with capsaicin than control. Findings from 2 studies that reported the result for painful HIV-neuropathy (n=801), indicated that more participants (about 10%) had average 2 to 12-week pain intensity reductions over baseline of at least 30% with capsaicin than control. Findings from one small study of 46 participants with persistent pain

following inguinal herniorrhaphy did not show a difference between capsaicin and placebo for pain reduction.

#### All neuropathic pain - Topical analgesics - Lidocaine

A Cochrane systematic review<sup>70</sup> (12 RCTs n=508) assessed the analgesic efficacy of topical lidocaine for chronic neuropathic pain in adults, and its association with adverse events. Six studies enrolled participants with moderate or severe postherpetic neuralgia, and the remaining studies enrolled different, or mixed, neuropathic pain conditions, including trigeminal neuralgia and postsurgical or post-traumatic neuralgia. Four different formulations were used: 5% medicated patch, 5% cream, 5% gel, and 8% spray. In all but one study, evidence indicated that lidocaine was better than placebo for some measure of pain relief. The authors indicated that pooling multiple-dose studies across conditions demonstrated no clear evidence of an effect of lidocaine on the incidence of adverse events or withdrawals.

#### All neuropathic pain - Other drugs - Clonidine

A Cochrane systematic review<sup>71</sup> (2 RCTs n=344) assessed the analgesic efficacy of topical clonidine for chronic neuropathic pain and its association with frequency of adverse events in adults with neuropathic pain. A greater number of participants in the topical clonidine group had at least 30% reduction in pain compared with placebo. Topical clonidine was no better than placebo for achieving at least 50% reduction in pain intensity and on the Patient Global Impression of Change Scale. The rate of adverse events did not differ between groups.

#### **Topic expert feedback**

Topic experts commented that there has not been any large scale study of any interventions that show a consistent superior benefit. They also noted that newer antiepileptic drugs (i.e. zonisamide) or other antidepressants (i.e. venlafaxine), had not shown consistent benefit.

Topic experts also highlighted [PrescQIPP Bulletin 119: Neuropathic pain: Pregabalin and gabapentin prescribing \(January 2016\)](#). This bulletin details and gives guidance on prescribing gabapentin and pregabalin for the management of neuropathic pain. Topic experts felt that the bulletin was consistent with the issues raised in section 2.5: 'Impact of drug

related adverse effects on quality of life' and, section 2.6: 'Potential for abuse'. Topic experts noted that there has been an increase in the reporting of abuse on some of the medications discussed in CG173. Topic experts commented that the potential for abuse of these medicines, may cause patients and clinicians to hesitate in initiating treatments that would otherwise improve their function and overall quality of life. However, the topic experts noted that this increasing concern of the abuse potential may not be evidence based. In addition to this, topic experts noted an increase of illegal procurement of gabapentinoids, fuelled by precautionous prescribing. It was noted that there are also concerns of tramadol leading to opioid dependence, and thus negatively reflecting in prescribing patterns in non-specialist care settings.

One topic expert noted that there may be inequality issues in regards to 'postcode prescribing' and prescribing within prisons. They were concerned that drugs recommended for neuropathic pain may be prescribed as an alternative to opioids.

Topic experts indicated that pregabalin (Lyrica®) is due to come off of patent this year, whilst duloxetine has now come off patent since the publication of the guideline. Topic experts noted that there may now be significant changes to the costings of these medications, and hence their cost-effectiveness.

#### **Impact statement**

##### Diabetic neuropathy: Antiepileptics (anticonvulsants)

This evidence is unlikely to impact on recommendations in CG173.

There is a large body of evidence suggesting that anticonvulsants, in particular pregabalin, is effective medication for managing diabetic neuropathy associated pain.

This is in line with current CG173 recommendation that indicates 'Offer a choice of amitriptyline, duloxetine, gabapentin or pregabalin as initial treatment for neuropathic pain (except trigeminal neuralgia) (1.1.8).

Topic experts noted that there has been an increase in the reporting of abuse on some of the medications discussed in CG173. Concerns also raised on the risk of addiction in '[Advice for prescribers on the risk of the misuse of pregabalin and gabapentin](#)' published by Public

Health England. However we have not found any evidence in the literature supporting this.

Diabetic neuropathy: Antidepressants (imipramine) - SSRIs (duloxetine)

This evidence is unlikely to impact on recommendations in CG173.

There was little evidence to support the use of imipramine to treat diabetic neuropathy.

The new evidence suggests that duloxetine may be effective for managing diabetic neuropathy pain. This is in line with current CG173 recommendation that indicates 'Offer a choice of amitriptyline, duloxetine, gabapentin or pregabalin as initial treatment for neuropathic pain (except trigeminal neuralgia) (1.1.8).

Diabetic neuropathy: Opioid analgesics (oxycodone, tapentadol, buprenorphine)

This evidence is unlikely to impact on recommendations in CG173.

The evidence on opioid analgesics (oxycodone, tapentadol, buprenorphine) suggests that these opioids may provide greater pain reduction in diabetic neuropathic when compared with placebo.

These opioids were not considered in CG173 recommendations and current evidence is from poor quality studies and insufficient to trigger an update.

Topic experts commented that the potential for abuse of these medicines, may cause patients and clinicians to hesitate in initiating treatments that would otherwise improve their function and overall quality of life. However, the topic experts noted that this increasing concern of the abuse potential may be unreliable rather than evidence based.

Diabetic neuropathy: Non-opioid analgesics (ketamine)

This evidence is unlikely to impact on recommendations in CG173.

Ketamine was not considered in CG173 for treatment of neuropathic pain. The new evidence showed that it is unlikely that ketamine provides benefit to patients with diabetic neuropathy therefore no impact on current recommendations is anticipated.

Diabetic neuropathy: Cannabinoids (nabilone, sativex)

This evidence is unlikely to impact on recommendations in CG173.

New evidence from a small study showed that nabilone may improve diabetic neuropathic pain. However evidence from a mixed treatment comparison analysis of pharmacological therapies for painful diabetic peripheral neuropathy indicated that sativex ranked as slightly better than the worst treatment. Therefore the evidence is broadly in line with current recommendation that states not to start treatment with cannabis sativa extract in non-specialised setting unless advised by a specialist to do so (1.1.12).

Diabetic neuropathy: Topical analgesics (capsaicin)

This evidence is unlikely to impact on recommendations in CG173.

New evidence suggests that capsaicin cream was effective in relieving pain when compared with placebo but showed no significant difference when compared with topical amitriptyline or topical clonidine and adverse effects were more common in the capsaicin group. This is broadly in line with current CG173 recommendation that indicates 'Consider capsaicin cream for people with localised neuropathic pain who wish to avoid, or who cannot tolerate, oral treatments'. (1.1.10).

Evidence suggests that capsaicin patch may provide modest pain relief and sleep quality improvements in diabetic neuropathy. Current recommendation indicates do not start the cannabis capsaicin patch to treat neuropathic pain in non-specialised setting unless advised by a specialist to do so (1.1.12). The new evidence is limited and insufficient to trigger an update of this topic.

Diabetic neuropathy: All drugs

This evidence is unlikely to impact on recommendations in CG173.

Evidence from a network meta-analysis suggests that greater pain reduction was associated with SNRIs (class of antidepressant drugs) compared with anticonvulsants and with tricyclic antidepressants compared with topical capsaicin. This is in line with current recommendation (1.1.8).

Diabetic neuropathy: Other drugs (rosuvastatin)



This evidence is unlikely to impact on recommendations in CG173.

New evidence suggests that rosuvastatin may improve diabetic polyneuropathy. There are currently no recommendations on use of rosuvastatin in the guideline and new evidence is insufficient to trigger an update of this topic and the addition of new recommendations.

#### Postherpetic neuralgia

This evidence is unlikely to impact on recommendations in CG173.

The evidence indicated that pregabalin, gabapentin, amitriptyline and opioids are all effective in managing pain in postherpetic neuralgia. This is in line with current recommendation (1.1.8) in CG173 that suggests offering a choice of amitriptyline, duloxetine, gabapentin or pregabalin as initial treatment for neuropathic pain.

#### Neuropathic pain following spinal cord injury

This evidence is unlikely to impact on recommendations in CG173.

Pregabalin was associated with better efficacy for pain reduction when compared with amitriptyline, duloxetine, levetiracetam, gabapentin, lamotrigine and dronabinol. This is broadly in line with recommendation 1.1.8.

#### Neuropathic pain following cancer

This evidence is unlikely to impact on recommendations in CG173.

Evidence from one small study suggests that methadone may be effective in the treatment of oncological pain with a neuropathic component. There are currently no recommendations on use of methadone in neuropathic pain and new evidence is insufficient to trigger an update of this topic and the addition of new recommendations.

#### Trigeminal neuralgia

This evidence is unlikely to impact on recommendations in CG173.

Evidence from a systematic review comparing gabapentin with carbamazepine in the treatment of trigeminal neuralgia showed no significant difference in efficacy and side effect between the two treatments. This is broadly in line with the current recommendation that indicates 'Offer carbamazepine as initial treatment for trigeminal neuralgia' (1.1.13).

#### Fabry disease

This evidence is unlikely to impact on recommendations in CG173.

Evidence suggests that carbamazepine, phenytoin and gabapentin are effective in reducing neuropathic pain in Fabry disease. This is generally in line with current recommendations (1.1.8, 1.1.14).

#### Central neuropathic pain

This evidence is unlikely to impact on recommendations in CG173.

New evidence suggests that levetiracetam may not be effective in treatment of central post-stroke pain. The evidence is consistent with CG173 recommendation that indicates do not start the levetiracetam to treat neuropathic pain in non-specialised setting unless advised by a specialist to do so (1.1.12).

#### Sciatica neuropathy pain

This evidence is unlikely to impact on recommendations in CG173.

The evidence about efficacy of NSAIDs for pain reduction in sciatica is uncertain. The new evidence suggest that morphine and paracetamol may be effective for treating sciatica with morphine being superior to paracetamol. The evidence does not provide a basis for updating this topic.

#### All neuropathic pain: Antiepileptics (pregabalin, carbamazepine, oxcarbazepine, lamotrigine, topiramate, levetiracetam, clonazepam, phenytoin)

This evidence is unlikely to impact on recommendations in CG173.

The new evidence generally suggests that pregabalin may be an effective medication for managing neuropathic pain.

This is in line with current recommendation 1.1.8.

The new evidence also suggests that carbamazepine is probably effective in some people with chronic neuropathic pain.

Recommendation 1.1.14 states 'Offer carbamazepine as initial treatment for trigeminal neuralgia'.

The new evidence suggests that oxcarbazepine may be effective for relief of peripheral neuropathic pain. The evidence is inconsistent with recommendation 1.1.12 that indicates do not start the oxcarbazepine to treat neuropathic pain in non-specialised setting

unless advised by a specialist to do so. However, the evidence is from one single study which is insufficient for changing the recommendation.

There was no convincing evidence that lamotrigine, topiramate and levetiracetam are effective in treating neuropathic pain. The evidence is consistent with 1.1.12 recommendation that indicates do not start the lamotrigine, topiramate and levetiracetam to treat neuropathic pain in non-specialised setting unless advised by a specialist to do so. There was not sufficient evidence for clonazepam, phenytoin to assess their efficacy for improving neuropathic pain, therefore no impact on the current recommendation is anticipated.

All neuropathic pain: Tricyclic antidepressants (amitriptyline)

Evidence from a systematic review showed uncertainty around the efficacy of amitriptyline for management of neuropathic pain. Recommendation 1.1.8 indicates 'Offer a choice of amitriptyline, duloxetine, gabapentin or pregabalin as initial treatment for neuropathic pain (except trigeminal neuralgia)'. The evidence was based on poor quality studies that did not report long term experience and efficacy of amitriptyline treatment. The evidence is insufficient for changing the current recommendation. Therefore no impact on the current recommendation is anticipated.

All neuropathic pain: Opioid analgesics (Fentanyl, Morphine)

There was insufficient evidence to confirm whether fentanyl and hydromorphone are effective in neuropathic pain. Therefore no impact on current recommendations is anticipated.

All neuropathic pain: Topical analgesics (capsaicin)

Evidence for efficacy of topical capsaicin as a low concentration (<1%) in improving neuropathic pain was limited and inconclusive. Evidence from one systematic review suggests that the high-concentration (8%) topical capsaicin used to treat postherpetic neuralgia, HIV-neuropathy, and painful diabetic neuropathy provided moderate or substantial levels of pain relief than control treatment. However the authors indicated that the results should be interpreted with caution as it was based on the moderate or very low evidence.

The evidence is broadly in line with recommendation 1.1.10:

'Consider capsaicin cream for people with localised neuropathic pain who wish to avoid, or who cannot tolerate, oral treatments'.

All neuropathic pain: Topical analgesics (lidocaine)

There was no convincing evidence that topical lidocaine is effective for treating neuropathic pain.

There are currently no recommendations on use of lidocaine in neuropathic pain and new evidence is insufficient to trigger an update of this topic and the addition of new recommendations.

All neuropathic pain: Other drugs (clonidine)

Limited evidence from a systematic review with 2 included studies suggests that topical clonidine may provide some benefits in decreasing neuropathic pain. There are currently no recommendations on use of clonidine in neuropathic pain and new evidence is insufficient to trigger an update of this topic and the addition of new recommendations.

New evidence is unlikely to change guideline recommendations.

**Q – 02 What is the clinical effectiveness of different pharmacological treatments as combination therapy compared with other combination therapies, monotherapy or placebo for the management of neuropathic pain in adults, outside of specialist pain management services? (No recommendations made)**

### Recommendations derived from this question

The same recommendations were derived from this question as in Q - 01

### Surveillance decision

This review question should not be updated.

### Evidence summary

#### 4-year surveillance summary

##### Diabetic neuropathy - Anticonvulsants plus antidepressants

A parallel-group RCT<sup>72</sup> (n=804 initial therapy, n=339 combination/high-dose) assessed whether, in patients with diabetic neuropathy, not responding to standard doses of duloxetine or pregabalin, combining both medications is superior to increasing each drug to its maximum recommended dose. For initial 8-week therapy, patients received either 60 mg/day duloxetine (groups 1, 2) or 300 mg/day pregabalin (groups 3, 4). Then, in the 8-week combination/high-dose therapy period, only nonresponders received 120 mg/day duloxetine (group 1), a combination of 60 mg/day duloxetine and 300 mg/day pregabalin (groups 2, 3), or 600 mg/day pregabalin (group 4). There were no significant differences in pain between combination and high-dose monotherapy. In exploratory analyses of the initial 8-week therapy uncorrected for multiple comparisons, 60 mg/day duloxetine was found superior to 300 mg/day pregabalin for improving pain. Both drugs, alone and in combination were well tolerated.

##### Diabetic neuropathy - Various drug combinations

An RCT<sup>73</sup> (n=270) assessed the efficacy and safety of gabapentin plus complex B vitamins (B1, B12), compared with pregabalin in patients

with diabetic neuropathy. Patients were randomised to gabapentin/B1/B12 (n=147) or to pregabalin (n=123). At 12 weeks both drugs reduced pain intensity equally. Occurrence of vertigo was statistically significantly lower in the gabapentin/B1-B12 group.

##### Neuropathic pain following cancer - Anticonvulsants plus antidepressants

A systematic review<sup>74</sup> (8 RCTs n=1,359) investigated the efficacy of anticonvulsants or antidepressants in combination for treatment of neuropathic pain in cancer patients. RCTs that compared anticonvulsants or antidepressants in combination with treatments without anticonvulsants or antidepressants (control group) were included. The mean difference in change in global pain suggested greater improvement with anticonvulsants or antidepressants in combination compared with control groups.

An RCT<sup>75</sup> (n=88) assessed the efficacy and safety of gabapentin and amitriptyline in combination with opioids in patients suffering from neuropathic pain in malignancy. Participants were randomly assigned to receive oral tramadol and gabapentin (group A) or oral tramadol and amitriptyline (group B). The findings showed decline in VAS pain score from baseline in both groups in the early phase of the study. Six patients in group A and eight patients in group B required rescue medication. A total of 12 patients in the gabapentin group and 15 patients in the amitriptyline group

experienced adverse events of mild to moderate severity.

A cross-over RCT<sup>76</sup> (n=40) evaluated the efficacy and the safety of pregabalin-morphine combination for the treatment of neuropathic cancer pain. Compared with placebo, pregabalin plus morphine resulted in a significant sleep improvement as well as a Constipation Assessment Scale reduction. Pregabalin plus morphine resulted in a statistically significant higher frequency of dry mouth and somnolence than placebo.

A phase II RCT<sup>77</sup> (n=75) compared the efficacy and tolerability of two dose escalation strategies for oxycodone and pregabalin combination therapy. Patients with oncological neuropathic pain, were randomised to oxycodone at a fixed dose with increasing pregabalin doses (arm A; n=38) or pregabalin at a fixed dose with increasing oxycodone doses (arm B; n=37). More patients in arm A (76%) than arm B (64%) achieved >1/3 overall pain reduction. Arm A reported fewer side effects including constipation, nausea, drowsiness, confusion than arm B.

#### Neuropathic pain following Morton neuroma

An RCT<sup>78</sup> (n=131) assessed whether methylprednisolone injection is an effective treatment for Morton neuroma (injury to the nerve between the toes) compared with an anaesthetic injection as a control. Patients with Morton neuroma were randomised to receive either methylprednisolone plus anaesthetic or anaesthetic alone (lignocaine). Significant and nonsignificant improvements associated with the methylprednisolone injection plus anaesthetic were observed for measures of pain, function, and patient global assessment of general health at one and three months after injection.

#### Neuropathic pain following multiple sclerosis (MS)

An RCT<sup>79</sup> involving 15 patients with MS induced neuropathic pain evaluated the efficacy of nabilone combined with gabapentin. After adjustment for key patient-level covariates (e.g., age, sex, duration of MS, baseline pain), decrease in VAS pain and VAS impact score, was statistically greater in nabilone-gabapentin versus placebo study group. No significant difference in attrition rates was noted between groups.

#### All neuropathic pain - Antidepressants plus analgesics

A cross-over RCT<sup>80</sup> (n=52) evaluated a nortriptyline-morphine combination, compared with each monotherapy. Patients with neuropathic pain were randomised to receive oral nortriptyline, morphine, and their combination. Brief Pain Inventory scores for pain were significantly lower for combination versus each monotherapy. Combination treatment resulted in moderate-severe constipation in 43% versus 46% with morphine and 5% with nortriptyline. Combination treatment resulted in moderate-severe dry mouth in 58% versus 49% with nortriptyline and 13% with morphine.

#### All neuropathic pain - Various drug combinations

A systematic review<sup>81</sup> (21 RCTs) evaluated the efficacy, tolerability and safety of various drug combinations for the treatment of neuropathic pain. The authors indicated that the majority of combination therapies shared some element of sedation, cognitive dysfunction which resulted in higher dropout rates in patients. Meta-analysis was only possible for gabapentin + opioid versus gabapentin alone (2 studies n=386) that showed modest, yet statistically significant, superiority of a gabapentin + opioid combination over gabapentin alone.

A systematic review and meta-analysis (n=229 double-blinded RCTs)<sup>82</sup> investigated the combined use of oral and topical preparations for neuropathic pain. A combined number needed to treat (NNT) were 6.4 for serotonin-noradrenaline reuptake inhibitors, of which 14 studies included duloxetine; NNT= 7.2, for gabapentin; NNT= 7.7, for pregabalin; and NNT= 10.6 for capsaicin patches.

A cross-over, multicentre RCT<sup>83</sup> (n=73) examined whether the combination of imipramine and pregabalin in moderate doses would relieve pain more effectively than monotherapy in patients with polyneuropathy. Patients were randomised to either imipramine 75 mg/day versus pregabalin 300 mg/day or combination therapy or placebo for four 5-week treatment periods. Patients in the combination therapy had significantly lower pain scores than both monotherapies: combination versus imipramine, combination versus pregabalin. During combination therapy, the dropout rate was higher and the patients reported a higher rate and severity of side effects.

An RCT<sup>84</sup> compared the efficacy of lidocaine alone with a combination of depo-methylprednisolone plus lidocaine in the management of neuropathic pain caused by peripheral nerve damage. Participants were randomised to receive 0.5% lidocaine (n=44) or 80 mg depo-methylprednisolone + 0.5% lidocaine proximal (n=44). Pain scores for the methylprednisolone plus lidocaine group were significantly improved at 3-month compared to lidocaine alone.

#### **Topic expert feedback**

Topic experts noted that there was an absence of studies of combined therapies which demonstrated superior benefit. They noted that it remains unclear, as to which treatments should be combined for the management of neuropathic pain.

A topic expert noted an ongoing health technology appraisal (OPTION-DM), which aims to establish a treatment pathway for the management of painful diabetic neuropathy using: amitriptyline, duloxetine and, pregabalin, alone or in combination. The study is due to start in March 2017 and complete in 2019.

Topic experts commented that screening and assessment criteria should be discussed, as currently only management is dealt with. They suggested commenting on the grading and staging of neuropathic pain which may influence the choice of pharmacological intervention.

#### **Impact statement**

##### *Diabetic neuropathy: Anticonvulsants plus antidepressants*

The new evidence is unlikely to impact on CG173.

New evidence on combination therapy on combination of anticonvulsants and antidepressants for treatment of diabetic neuropathy reported lower pain scores but high rate and severity of side effects. Gabapentin plus complex B vitamins compared with pregabalin reduced pain intensity equally in patients with diabetic neuropathy. These combined treatments were not considered in CG173. New evidence is limited and insufficient to trigger an update of this question and addition of new recommendations.

##### *Neuropathic pain following cancer: Anticonvulsants plus analgesics*

The new evidence is unlikely to impact on CG173.

Limited new evidence suggests that following combination therapies are effective approach for controlling neuropathic cancer pain: oxycodone-pregabalin combination, pregabalin-morphine combination, imipramine-pregabalin combination, oral tramadol-gabapentin combination and oral tramadol-amitriptyline combination. However the evidence is limited and does not definitively establish the basis for recommending the combination treatment. The combination therapies generally resulted in higher rate and severity of side effects.

##### *Morton neuroma and multiple sclerosis*

The new evidence is unlikely to impact on CG173.

Limited new evidence suggests that methylprednisolone-anaesthetic combination and nabilone-gabapentin combination therapies may improve neuropathic pain in patients with morton neuroma and multiple sclerosis respectively. However, the evidence is from small studies and insufficient to trigger an update of this question and addition of new recommendations.

##### *All neuropathic pain: Antidepressants plus analgesics*

The new evidence is unlikely to impact on CG173.

New evidence suggests that nortriptyline-morphine combination is effective for improving neuropathic pain and has less side effect compared with mono therapy. However, the evidence is from one small study and insufficient to trigger an update of this question and addition of new recommendations.

##### *All neuropathic pain: Various drug combinations*

The new evidence is unlikely to impact on CG173.

Evidence was identified from 2 systematic reviews and 2 RCTs that assessed different pharmacological treatments of neuropathic pain. The number of available studies for any one specific combination, as well as the limited trial size, preclude the recommendation of any one specific drug combination for neuropathic

pain. This is consistent with topic experts' comments indicating that there is an absence of studies of combined therapies which demonstrated superior benefit for management of neuropathic pain.

New evidence is unlikely to change guideline recommendations.

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## Research recommendations

### *Prioritised research recommendations*

At 4-year and 8-year surveillance reviews of guidelines published after 2011, we assess progress made against prioritised research recommendations. We may then propose to remove research recommendations from the NICE version of the guideline and the [NICE database for research recommendations](#). The research recommendations will remain in the full versions of the guideline. See NICE's [research recommendations process and methods guide 2015](#) for more information.

These research recommendations were deemed priority areas for research by the Guideline Committee; therefore, at this 4-year surveillance review time point a decision will be taken on whether to retain the research recommendations or stand them down.

We applied the following approach:

- New evidence relevant to the research recommendation was found and an update of the related review question is planned.
  - The research recommendation will be removed from the NICE version of the guideline and the NICE research recommendations database. If needed, a new research recommendation may be made as part of the update process.
- New evidence relevant to the research recommendation was found but an update of the related review question is not planned because the new evidence is insufficient to trigger an update.
  - The research recommendation will be retained because there is evidence of research activity in this area.
- New evidence relevant to the research recommendation was found but an update of the related review question is not planned because evidence supports current recommendations.
  - The research recommendation will be removed from the NICE version of the guideline and the NICE research recommendations database because further research is unlikely to impact on the guideline.
- Ongoing research relevant to the research recommendation was found.
  - The research recommendation will be retained and evidence from the ongoing research will be considered when results are published.
- No new evidence relevant to the research recommendation was found and no ongoing studies were identified.
  - The research recommendation will be removed from the NICE version of guideline and the NICE research recommendations database because there is no evidence of research activity in this area.
- The research recommendation would be answered by a study design that was not included in the search (usually systematic reviews or randomised controlled trials).
  - The research recommendation will be retained in the NICE version of the guideline and the NICE research recommendations database.
- The new research recommendation was made during a recent update of the guideline.

- The research recommendation will be retained in the NICE version of the guideline and the NICE research recommendations database.

**RR – 01 What is the clinical effectiveness, cost effectiveness and tolerability of pharmacological monotherapy compared with combination therapy for treating neuropathic pain?**

Ongoing research relevant to the research recommendation was found. The OPTION-DM – Optimal pathway for treating neuropathic pain in diabetes mellitus trial is expected to due to start recruiting in March 2017.

**Surveillance decision**

The research recommendation will be retained and evidence from the ongoing research will be considered when results are published.

**RR – 02 Is response to pharmacological treatment predicted more reliably by underlying aetiology or by symptom characteristics?**

No new evidence relevant to the research recommendation was found and no ongoing studies were identified.

**Surveillance decision**

The research recommendation will be removed from the NICE version of guideline and the NICE research recommendations database because there is no evidence of research activity in this area.

**RR – 03 What is the clinical and cost effectiveness of carbamazepine as initial treatment for trigeminal neuralgia compared with other pharmacological treatments?**

[New evidence](#) relevant to the research recommendation was found but an update of the related review question is not planned because evidence supports current recommendations.

**Surveillance decision**

The research recommendation will be retained and evidence from the ongoing research will be considered when results are published.

**RR – 04 What are the key factors, including additional care and support that influence participation and quality of life in people with neuropathic pain?**

No new evidence relevant to the research recommendation was found and no ongoing studies were identified.

**Surveillance decision**

The research recommendation will be removed from the NICE version of guideline and the NICE research recommendations database because there is no evidence of research activity in this area.

**RR – 05 What is the impact of drug-related adverse effects on health economics and quality of life in neuropathic pain?**

No new evidence relevant to the research recommendation was found and no ongoing studies were identified.

### Surveillance decision

The research recommendation will be removed from the NICE version of guideline and the NICE research recommendations database because there is no evidence of research activity in this area.

#### **RR – 06 Is there a potential for dependence associated with pharmacological agents for neuropathic pain?**

No new evidence relevant to the research recommendation was found and no ongoing studies were identified.

### Surveillance decision

The research recommendation will be removed from the NICE version of guideline and the NICE research recommendations database because there is no evidence of research activity in this area.

### *Other research recommendations*

The following research recommendations were not deemed as priority areas for research by the guideline committee.

#### **RR – 07 How should the symptomatic treatment of neuropathic pain relate to its cause?**

### Surveillance decision

This research recommendation will be considered again at the next surveillance point.

#### **RR – 08 Does early intervention to treat neuropathic pain reduce the likelihood of chronic pain?**

### Surveillance decision

This research recommendation will be considered again at the next surveillance point.

#### **RR – 09 What is the clinical and cost effectiveness of lidocaine patches for localised peripheral pain?**

### Surveillance decision

This research recommendation will be considered again at the next surveillance point.

#### **RR – 10 What is the clinical and cost effectiveness of alternative treatments as first-line treatment for trigeminal neuralgia compared with other better-tolerated pharmacological treatments?**

### Surveillance decision

This research recommendation will be considered again at the next surveillance point.



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