Neuropathic pain: the pharmacological management of neuropathic pain in adults in non-specialist settings

Full guideline

Draft for consultation, October 2009

This guideline was developed following the NICE short clinical guideline process. This document includes all the recommendations, details of how they were developed and summaries of the evidence they were based on.
## Disclaimer

NICE clinical guidelines are recommendations about the treatment and care of people with specific diseases and conditions in the NHS in England and Wales.

This guidance represents the view of NICE, which was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement.

However, the guidance does not override the individual responsibility of Neuropathic pain: NICE clinical guideline DRAFT (October 2009) Page 2 of 136
healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their duties to avoid unlawful discrimination and to have regard to promoting equality of opportunity. Nothing in this guidance should be interpreted in a way that would be inconsistent with compliance with those duties.

How to read this guideline

The following sections introduce the guideline, including which pharmacological treatments (table 2) and which neuropathic pain conditions (table 3) are included. A summary of the characteristics of all included studies is presented in table 5.

The evidence statements (section 2.2) are the overall descriptive summary of the evidence. Each evidence statement is linked to the evidence review, which is presented as a relevant GRADE profile (section 2.3). Each GRADE profile consists of the characteristics of the evidence, the detailed results of the primary outcomes and a description of the quality of the evidence. The health economics evidence review and a summary of a relevant Health Technology Assessment (HTA) report are also included in section 2.3.

Section 2.4 (Evidence to recommendations) captures all the discussion by the Guideline Development Group (GDG) about the quality of the evidence, and how they came to decisions, based on the evidence or consensus, to make specific recommendations.

The recommendations are listed in both section 1 (at the start of the document) and again in section 2.4.7 (towards the end of the document).

1 Fox-Rushby JA, GL Griffith, JR Ross et al. NIHR Health Technology Assessment programme. The clinical and cost-effectiveness of different treatment pathways for neuropathic pain [NP]. HTA ref. 05/30/03. Unpublished. Project abstract available from www.hta.ac.uk/1527

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Introduction

Neuropathic pain develops as a result of damage to, or dysfunction of, the system that normally signals pain. It may arise from a heterogeneous group of disorders affecting the peripheral and central nervous systems. Common examples include painful diabetic neuropathy, post-herpetic neuralgia and trigeminal neuralgia. Neuropathic pain may present with altered pain sensation, areas of numbness or burning, and continuous or intermittent spontaneous pain. It is an unpleasant sensory and emotional experience that can have a significant impact on a person's quality of life.

Neuropathic pain is often difficult to treat, because it is resistant to many medications and/or because of the adverse events that the medications cause. A number of drugs are used to manage neuropathic pain, including antidepressants, anticonvulsant (antiepileptic) drugs, opioids and topical agents such as capsaicin or lidocaine. Many patients require treatment with more than one drug, but the correct choice of drug, and the optimal sequence for their use, is not known.

Clinicians may be guided by a number of published guidelines and algorithms for the management of neuropathic pain, but these are not consistent regarding the choice of drug treatment. This may lead to variation in practice in terms of which therapy is initiated, how this is done, whether therapeutic doses are achieved and whether the different types of drugs are used in the correct sequence. Guidelines rarely include considerations of cost effectiveness. An ongoing systematic review of different treatment pathways for neuropathic pain, commissioned by the NIHR HTA programme and due to report in 2009, was used to inform this guideline where appropriate.

This guideline covers adults with neuropathic pain conditions managed in primary care and secondary care, excluding specialist pain management clinics. In the main, neuropathic pain was viewed as a 'blanket condition',

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2 Fox-Rushby JA, GL Griffith, JR Ross et al. NIHR Health Technology Assessment programme. The clinical and cost-effectiveness of different treatment pathways for neuropathic pain [NP]. HTA ref. 05/30/03. Unpublished. Project abstract available from www.hta.ac.uk/1527

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irrespective of the underlying cause. Condition-specific recommendations are made only where there is clear underlying evidence for doing so. The guideline excludes pain arising directly from trauma and orthopaedic surgical procedures.

For all drugs, recommendations are based on clinical and cost effectiveness and reflect whether their use for neuropathic pain is a good use of NHS resources. This guideline should be used in conjunction with clinical judgment and decision-making appropriate for the individual patient.

The guideline will assume that prescribers will use a drug’s summary of product characteristics (SPC) and the British National Formulary (BNF) to inform decisions made with individual patients. However, the Guideline Development Group (GDG) agreed that having clear statements on drug dosage and titration in the actual recommendations is crucial for treatment in non-specialist settings, to emphasise the importance of titration to achieve maximum benefit.

This guideline recommends some drugs for indications for which they do not have a UK marketing authorisation at the date of publication, if there is good evidence to support that use. Unlicensed drugs are marked with an asterisk in recommendations.

Table 1 Licensed indications for recommended pharmacological treatments for neuropathic pain

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amitriptyline</td>
<td>Not licensed for neuropathic pain</td>
</tr>
<tr>
<td>Duloxetine</td>
<td>Licensed for painful diabetic neuropathy</td>
</tr>
<tr>
<td>Imipramine</td>
<td>Not licensed for neuropathic pain</td>
</tr>
<tr>
<td>Nortriptyline</td>
<td>Not licensed for neuropathic pain</td>
</tr>
<tr>
<td>Pregabalin</td>
<td>Licensed for central and peripheral neuropathic pain</td>
</tr>
<tr>
<td>Tramadol</td>
<td>Licensed for moderate and severe pain</td>
</tr>
</tbody>
</table>

Patient-centred care

This guideline offers best practice advice on the pharmacological management of neuropathic pain in adults in non-specialist settings.
Treatment and care should take into account patients’ needs and preferences. People with neuropathic pain should have the opportunity to make informed decisions about their care and treatment, in partnership with their healthcare professionals. If patients do not have the capacity to make decisions, healthcare professionals should follow the Department of Health guidelines – ‘Reference guide to consent for examination or treatment’ (2001) (available from www.dh.gov.uk). Healthcare professionals should also follow the code of practice that accompanies the Mental Capacity Act (summary available from www.publicguardian.gov.uk).

Good communication between healthcare professionals and patients is essential. It should be supported by evidence-based written information tailored to the patient’s needs. Treatment and care, and the information patients are given about it, should be culturally appropriate. It should also be accessible to people with additional needs such as physical, sensory or learning disabilities, and to people who do not speak or read English.

If the patient agrees, families and carers should have the opportunity to be involved in decisions about treatment and care. Families and carers should also be given the information and support they need.
1 Summary

The following definitions apply to this guideline.

- **Non-specialist settings** Primary and secondary care services that do not provide specialist pain services. Non-specialist settings include general practice, general community care and hospital care.

- **Specialist pain services** Services that provide comprehensive assessment and multi-model management of all types of pain, including neuropathic pain.

- **Condition-specific services** Specialist services that provide treatment for the underlying health condition that is causing neuropathic pain, such as neurology, diabetology and oncology services.

The recommendations in this clinical guideline are for the pharmacological management of neuropathic pain in non-specialist settings only. There are other pharmacological and non-pharmacological treatments for neuropathic pain, with different care pathways in different settings, but these are not covered here.

### 1.1 List of all recommendations

#### Key principles of care

1.1.1 Address the person’s concerns and expectations when agreeing which treatments to use by discussing:

- the benefits and possible adverse effects of each treatment
- coping strategies for pain and possible adverse effects.

1.1.2 Explain both the importance of dosage titration and the titration process, providing written information if possible.

1.1.3 If the person or the healthcare professional (during the regular clinical reviews; see section 1.1.8) identifies unsatisfactory pain reduction or deterioration in the underlying health condition, follow
the care pathway (see page 14) or refer the person to a specialist 
pain service and/or a condition-specific service.

1.1.4 When selecting pharmacological treatments, take into account:

- the person’s vulnerability to specific adverse effects because of 
  comorbidities or age (for example, vulnerability to falls)
- lifestyle factors (such as occupation)
- any mental health problems (such as depression and/or anxiety)
- patient preference
- current medication.

1.1.5 When withdrawing or switching treatment, taper the withdrawal 
regimen to take account of dosage and any discontinuation 
symptoms.

1.1.6 When introducing a new treatment, consider an overlap of 
treatments to avoid deterioration in pain control.

1.1.7 After starting or changing a treatment, perform an early clinical 
review of dosage titration, tolerability and adverse effects, to 
assess the suitability of the chosen treatment.

1.1.8 Perform regular clinical reviews to assess and monitor the 
effectiveness of the chosen treatment. Each review should include 
assessment of:

- pain reduction
- mood (in particular, whether the person may have depression 
  and/or anxiety)
- daily activities and participation\(^3\) (including ability to work)
- adverse events
- overall improvement as reported by the person.

\(^3\) The World Health Organization ICF (International Classification of Functioning, Disability 
and Health) (2001) defines participation as ‘A person’s involvement in a life situation.’ It 
includes the following domains: learning and applying knowledge, general tasks and 
demands, mobility, self-care, domestic life, interpersonal interactions and relationships, major 
life areas, community, and social and civil life.
If there is satisfactory improvement, consider continuing or stepping down the treatment.

1.1.9 Continue existing treatments for people whose neuropathic pain is already effectively managed.

**First-line treatment**

1.1.10 Offer oral pregabalin or amitriptyline* as first-line treatment (but see recommendation 1.1.11 for people with painful diabetic neuropathy).

- For pregabalin: start at 150 mg per day (divided into two or three equal doses), with upward titration to an effective dose or the person’s maximum tolerated dose of no higher than 600 mg per day (divided into two or three equal doses).
- For amitriptyline*: start at 10 mg per day, with gradual upward titration to an effective dose or the person’s maximum tolerated dose of no higher than 75 mg per day (higher doses could be considered in consultation with a specialist pain service).

1.1.11 For people with painful diabetic neuropathy, offer duloxetine as first-line treatment. Start at 60 mg per day (a lower starting dose may be appropriate for some patients), with upward titration to an effective dose or the person’s maximum tolerated dose of no higher than 120 mg per day.

1.1.12 Based on both the early and regular clinical reviews:

- if there is satisfactory improvement, consider continuing or stepping down first-line treatment
- if amitriptyline* as first-line treatment results in satisfactory pain reduction but the person cannot tolerate the adverse effects, consider offering oral nortriptyline* or imipramine* as an alternative
• if the person’s underlying health condition has deteriorated, or
  the pain significantly limits their daily activities and participation\(^4\),
  consider referring them to a specialist pain service and/or a
  condition-specific service.

**Second-line treatment**

1.1.13 If satisfactory pain reduction is not achieved with first-line treatment
at the maximum tolerated dose, offer treatment with another drug
class\(^5\) instead of or in combination with the original drug, after
informed discussion with the person.

- If first-line treatment was with amitriptyline\(^*\) (or nortriptyline\(^*\) or
  imipramine\(^*\)), switch to or combine with oral pregabalin.
- If first-line treatment was with duloxetine for people with painful
diabetic neuropathy, switch to or combine with oral pregabalin.
- If first-line treatment was with pregabalin, switch to or combine
  with oral amitriptyline\(^*\).

Dosage and titration should be same as in recommendation 1.1.10.

**Third-line treatment**

1.1.14 If satisfactory pain reduction is not achieved with second-line
treatment:

- refer the person to a specialist pain service and/or a condition-
specific service and
- consider offering oral tramadol as third-line treatment instead of
  or in combination with the second-line treatment while waiting for
  referral.

1.1.15 For tramadol as monotherapy, start at 50 to 100 mg per day, with
upward titration if required to an effective dose or the person’s

\(^4\) The World Health Organization ICF (International Classification of Functioning, Disability
and Health) (2001) defines participation as ‘A person’s involvement in a life situation.’ It
includes the following domains: learning and applying knowledge, general tasks and
demands, mobility, self-care, domestic life, interpersonal interactions and relationships, major
life areas, community, and social and civil life.

\(^5\) Drug classes are antidepressants and anticonvulsants.
maximum tolerated dose of no higher than 400 mg per day. If tramadol is used as combination therapy, more conservative titration may be required.

### Other treatments

1.1.16 Do not start treatment with opioids (such as oral morphine or oxycodone) other than tramadol without an assessment by a specialist pain service or a condition-specific service.

1.1.17 Pharmacological treatments other than those recommended in this guideline may be started after an assessment by a specialist pain service or a condition-specific service. If treatment results in satisfactory pain reduction, it may be continued in non-specialist settings, with a multidisciplinary care plan and careful management of adverse effects.
Neuropathic pain: pharmacological management for adults in non-specialist settings

### 1.2 Care pathway

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**Key principles of care**

- Address the person’s concern and expectations when agreeing which treatment to use by discussing:
  - the benefits and possible adverse effects of each treatment
  - coping strategies for pain and possible adverse effects
- Explain both the importance of dosage titration and the titration process, providing written information if possible.
- If the person or the healthcare professional (during the regular clinical reviews) identifies unsatisfactory pain reduction or deterioration in the underlying health condition, follow the care pathway or refer the person to a specialist pain service and/or a condition-specific service.
- When selecting pharmacological treatments, take into account:
  - the person’s vulnerability to specific adverse effects because of comorbidities or age (for example, vulnerability to falls)
  - any mental health problems (such as depression and/or anxiety)
  - lifestyle factors (such as occupation)
  - patient preference
  - current medication.
- When withdrawing or switching treatment, taper the withdrawal regimen to take account of dosage and any discontinuation symptoms.
- When introducing a new treatment, consider an overlap of treatments to avoid deterioration in pain control.
- After starting or changing a treatment, perform an early clinical review of dosage titration, tolerability and adverse effects, to assess the suitability of the chosen treatment.
- Continue existing treatments for people whose neuropathic pain is already effectively managed.

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**First-line Treatment:**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregabalin</td>
<td>Licensed for central and peripheral neuropathic pain</td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>Licensed for diabetic neuropathy</td>
</tr>
</tbody>
</table>

**Specific for people with painful diabetic neuropathy:**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duloxetine</td>
<td>Offered at 60mg/day (a lower starting dose may be appropriate for some patients), with upward titration to an effective dose or the person’s maximum tolerated dose of no higher than 120mg/day.</td>
</tr>
</tbody>
</table>

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**Second-line Treatment:**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duloxetine</td>
<td>For tramadol as monotherapy, start at 50 to 100mg/day, with upward titration to an effective dose or the person’s maximum tolerated dose of no higher than 400mg/day.</td>
</tr>
</tbody>
</table>

**Third-line treatment:**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tramadol</td>
<td>Do not start treatment with opioids other than tramadol (such as oral morphine or oxycodone) without an assessment by a specialist pain service and/or a condition-specific service.</td>
</tr>
</tbody>
</table>

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**Other treatments**

- Do not start treatment with opioids other than tramadol (such as oral morphine or oxycodone) without an assessment by a specialist pain service and/or a condition-specific service.
- Pharmacological treatments other than those recommended in this guideline may be started after an assessment by a specialist pain service and/or a condition-specific service. If treatment results in satisfactory pain reduction, it may be continued in non-specialist settings, with a multidisciplinary care plan and careful management of adverse effects.

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1. The World Health Organization ICF (International Classification of Functioning, Disability and Health) (2001) defines participation as ‘A person’s involvement in a life situation.’ It includes the following domains: learning and applying knowledge, general tasks and demands, mobility, self-care, domestic life, interpersonal interactions and relationships, major life areas, community, and social and civil life.

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Licensed indications for recommended pharmacological treatments for neuropathic pain:

- Pregabalin – licensed for central and peripheral neuropathic pain
- Duloxetine – licensed for diabetic neuropathy
- Tramadol – licensed for moderate and severe pain

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The image contains a visual representation of the care pathway for neuropathic pain management, including first-line, second-line, and third-line treatments, along with specific indications for pharmacological treatments. The text provides detailed guidance on key principles of care, assessment, and management strategies. The pathway is designed to provide a structured approach to managing neuropathic pain in non-specialist settings, highlighting the importance of titration, monitoring, and consideration of individual factors.
1.3 **Overview**

1.3.1 **Neuropathic pain**

Pain is an unpleasant sensory and emotional experience that can have a significant impact on a person’s quality of life, general health, psychological health, and social and economic well-being. The International Association for the Study of Pain (IASP; [www.iasp-pain.org/AM/Template.cfm?Section=Home&Template=/CM/HTMLDisplay.cfm&ContentID=3058#Neuropathic](http://www.iasp-pain.org/AM/Template.cfm?Section=Home&Template=/CM/HTMLDisplay.cfm&ContentID=3058#Neuropathic)) defines neuropathic pain as follows:

‘Pain initiated or caused by a primary lesion or dysfunction in the nervous system. Peripheral neuropathic pain occurs when the lesion or dysfunction affects the peripheral nervous system. Central pain may be retained as the term for when the lesion or dysfunction affects the central nervous system’.

Neuropathic pain is very challenging to manage because of the heterogeneity of its aetiologies, symptoms and underlying mechanisms (Beniczky et al. 2005). Examples of common conditions that have peripheral neuropathic pain as a symptom are painful diabetic neuropathy, post-herpetic neuralgia, trigeminal neuralgia, radicular pain, pain after surgery and neuropathic cancer pain (that is, chemotherapy-induced neuropathy and neuropathy secondary to tumour infiltration). Examples of conditions causing central neuropathic pain include stroke, spinal cord injury and multiple sclerosis. Neuropathic pain can be intermittent or constant, and spontaneous or provoked. Typical descriptions of the pain include terms such as shooting, stabbing, like an electric shock, burning, tingling, tight, numb, prickling, itching and a sensation of pins and needles. People may also describe symptoms of allodynia (pain caused by a stimulus that does not normally provoke pain) and hyperalgesia (an increased response to a stimulus that is normally painful) (McCarberg 2006).

A review of the epidemiology of chronic pain found that there is still no accurate estimate available for the population prevalence of neuropathic pain (Smith BH, Torrence N (2010, in press) Chronic pain epidemiology: from Neuropathic pain: NICE clinical guideline DRAFT (October 2009) Page 13 of 136
aetiology to public health (edited: Croft PR). Oxford University Press. ISBN 9780199235766). For example, the prevalence of neuropathic pain overall has been estimated at between 1% and 2%, based on summed estimates of the prevalence in the USA (Bennett 1997) and the UK (Bowsher et al. 1991). These estimates of population prevalence came from a number of heterogeneous studies of variable validity, are likely to be inaccurate and are inconsistent. Other condition-specific studies have also mirrored the heterogeneous nature of neuropathic pain. For example, painful diabetic neuropathy is estimated to affect between 16% and 26% of people with diabetes (Jensen et al. 2006; Ziegler 2008). Prevalence estimates for post-herpetic neuralgia range from 8% to 19% of people with herpes zoster when defined as pain at 1 month after rash onset, and 8% when defined as pain at 3 months after rash onset (Schmader 2002). The development of chronic pain after surgery is also fairly common, with prevalence estimates ranging from 10% to 50% after many common operations (Shipton 2008). This pain is severe in between 2% and 10% of this subgroup of patients, and many of the clinical features closely resemble neuropathic pain (Jung et al. 2003; Mikkelsen et al. 2004; Kehlet et al. 2006). Furthermore, a recent study of 362,693 computerised records in primary care from the Netherlands estimated the annual incidence of neuropathic pain in the general population to be almost 1% (Dieleman et al. 2008). This considerable variability in estimates of the prevalence and incidence of neuropathic pain and similar conditions from general population studies is likely to be because of differences in the definitions of neuropathic pain, methods of assessment and patient selection (Smith BH, Torrence N (2010, in press) Chronic pain epidemiology: from aetiology to public health (edited: Croft PR). Oxford University Press. ISBN 9780199235766).

Currently, a number of pharmacological treatments are commonly used in the UK to manage neuropathic pain in non-specialist settings. However, there is considerable variation in practice in terms of how treatment is initiated, whether therapeutic doses are achieved and whether there is correct sequencing of therapeutic classes. This may lead to inadequate pain control, with considerable morbidity. In the context of this guideline, non-specialist...
settings are defined as primary and secondary care services that do not
provide specialist pain services. These include general practice, general
community care and hospital care. The commonly used pharmacological
treatments include antidepressants (tricyclic antidepressants [TCAs], selective
serotonin reuptake inhibitors [SSRIs] and serotonin–norepinephrine reuptake
inhibitors [SNRIs]), anticonvulsants (for example, gabapentin, pregabalin and
carbamazepine), topical treatments (for example, capsaicin and lidocaine) and
opioid analgesics are also used. All of these drug classes are associated with
disadvantages, as well as potential benefits. A further issue is that a number
of commonly used treatments (such as amitriptyline) are unlicensed for
treatment of neuropathic pain, which may limit their use by practitioners.
There is also uncertainty about which drugs should be used initially (first line
treatment) for neuropathic pain, and in what order (sequence) the drugs
should be used.

This short clinical guideline aims to improve the care of adults with
neuropathic pain by making evidence-based recommendations on the
pharmacological management of neuropathic pain in non-specialist settings.
Better management of neuropathic pain in non-specialist settings will also
help to ensure that people who require specialist assessment and
interventions are referred appropriately and in a timely fashion to a specialist
pain service and/or other condition-specific services.

1.3.2 Who this guideline is for

This document is intended to be relevant to healthcare professionals in
primary and secondary care who manage neuropathic pain conditions in
adults. It does not cover adults with neuropathic pain conditions that are
managed in specialist pain services, or adults with neuropathic pain in the first
3 months after trauma or orthopaedic surgical procedures.
2 How this guideline was developed

‘Neuropathic pain: the pharmacological management of neuropathic pain in adults in non-specialist settings’ (NICE clinical guideline XX) is a NICE short clinical guideline. For a full explanation of how this type of guideline is developed, see 'The guidelines manual' (2009) at www.nice.org.uk/GuidelinesManual

2.1 Introduction

2.1.1 Pharmacological treatments, key outcomes and analysis

Based on the guideline scope, neuropathic pain is treated as a 'blanket condition' in this guideline regardless of its aetiologies, unless there is valid health economics evidence that shows the cost-effectiveness of particular treatment for specific neuropathic pain condition. A total of 34 different pharmacological treatments for neuropathic pain within the four main drug classes (antidepressants, anticonvulsants, opioid analgesics and topical treatments) were agreed during the scoping workshop, the scope consultation and by the Guideline Development Group (GDG). The 34 pharmacological treatments are listed in table 2. The different neuropathic pain conditions that were included in the searches are listed in table 3. Systematic searches were carried out to identify randomised placebo-controlled trials on these 34 different pharmacological treatments for neuropathic pain within the four main drug classes, as well as any head-to-head comparative trials and combination therapy trials.
### Table 2 Pharmacological treatments considered for the clinical guideline on neuropathic pain

<table>
<thead>
<tr>
<th>Drug class/subclass</th>
<th>Drug</th>
</tr>
</thead>
</table>
| Antidepressants – tricyclic antidepressants (TCAs) | Amitriptyline  
Clomipramine  
Desipramine  
Dosulepin (dothiepin)  
Doxepin  
Imipramine  
Lofepramine  
Nortriptyline  
Trimipramine |
| Antidepressants – selective serotonin reuptake inhibitors (SSRIs) | Citalopram  
Fluoxetine  
Paroxetine  
Sertraline |
| Antidepressants – serotonin–norepinephrine reuptake inhibitors (SNRIs) | Duloxetine  
Venlafaxine |
| Anticonvulsants | Carbamazepine  
Gabapentin  
Lamotrigine  
Oxcarbazepine  
Phenytoin  
Pregabalin  
Sodium valproate  
Topiramate |
| Opioid analgesics | Buprenorphine  
Codeine phosphate  
Co-codamol  
Co-dydramol  
Dihydrocodeine  
Fentanyl  
Morphine  
Oxycodone  
Tramadol |
| Topical treatments | Topical capsaicin  
Topical lidocaine |
Table 3 Neuropathic pain conditions (search terms) included in the searches

<table>
<thead>
<tr>
<th>Neuropathic pain condition (search terms) included in the searches</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atypical facial pain</td>
</tr>
<tr>
<td>Central neuropathic pain/central pain</td>
</tr>
<tr>
<td>Compression neuropathies/nerve compression syndromes</td>
</tr>
<tr>
<td>Painful diabetic neuropathy/diabetic neuropathy</td>
</tr>
<tr>
<td>Facial neuralgia</td>
</tr>
<tr>
<td>HIV-related neuropathy</td>
</tr>
<tr>
<td>Idiopathic neuropathies</td>
</tr>
<tr>
<td>Mixed neuropathic pain</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
</tr>
<tr>
<td>Neurogenic pain</td>
</tr>
<tr>
<td>Neuropathic cancer pain/cancer pain</td>
</tr>
<tr>
<td>Neuropathic pain</td>
</tr>
<tr>
<td>Peripheral nerve injury</td>
</tr>
<tr>
<td>Peripheral neuropathies</td>
</tr>
<tr>
<td>Phantom limb pain</td>
</tr>
<tr>
<td>Post-amputation pain</td>
</tr>
<tr>
<td>Post-herpetic neuralgia</td>
</tr>
<tr>
<td>Post-stroke pain</td>
</tr>
<tr>
<td>Post treatment/surgery/operative pain</td>
</tr>
<tr>
<td>Radiculopathies/radicular pain</td>
</tr>
<tr>
<td>Spinal cord injury</td>
</tr>
<tr>
<td>Trigeminal neuralgia</td>
</tr>
</tbody>
</table>

A total of 23,207 studies were retrieved by the systematic searches (antidepressants = 2781, anticonvulsants = 4757, opioid analgesics = 9612, topical capsaicin and topical lidocaine = 6057). From the 23,207 studies, 92 randomised placebo-controlled trials, 10 head-to-head comparative trials and three combination therapy trials were included, based on the inclusion and exclusion criteria suggested by the Guideline Development Group (GDG) through two short questionnaires. The searches did not identify placebo-controlled studies that met the inclusion and exclusion criteria for 15 of the pharmacological treatments (table 4). The 104 included studies are summarised in table 5.
Table 4 Pharmacological treatments for which no studies met the inclusion and exclusion criteria

<table>
<thead>
<tr>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lofepramine</td>
</tr>
<tr>
<td>Trimipramine</td>
</tr>
<tr>
<td>Dosulepin (dothiepin)</td>
</tr>
<tr>
<td>Doxepin</td>
</tr>
<tr>
<td>Citalopram</td>
</tr>
<tr>
<td>Fluoxetine</td>
</tr>
<tr>
<td>Paroxetine</td>
</tr>
<tr>
<td>Sertraline</td>
</tr>
<tr>
<td>Phenytoin</td>
</tr>
<tr>
<td>Co-codamol</td>
</tr>
<tr>
<td>Co-dydramol</td>
</tr>
<tr>
<td>Dihydrocodeine</td>
</tr>
<tr>
<td>Buprenorphine</td>
</tr>
<tr>
<td>Fentanyl</td>
</tr>
<tr>
<td>Codeine phosphate</td>
</tr>
</tbody>
</table>

Table 5 Summary of included randomised placebo-controlled trials on antidepressants, anticonvulsants, opioid analgesics and topical treatments, and head-to-head comparative and combination therapy trials, for the treatment of neuropathic pain

<table>
<thead>
<tr>
<th>Drug class</th>
<th>No. of studies included</th>
<th>Treatment</th>
<th>Key outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antidepressants (TCAs)</td>
<td>11</td>
<td>Amitriptyline</td>
<td>30%, global, mean pain intensity scores, mean pain relief scores, AEs</td>
</tr>
<tr>
<td>Antidepressants (TCAs)</td>
<td>2</td>
<td>Desipramine</td>
<td>Global, AEs</td>
</tr>
<tr>
<td>Antidepressants (TCAs)</td>
<td>1</td>
<td>Nortriptyline</td>
<td>Global</td>
</tr>
<tr>
<td>Antidepressants (TCAs)</td>
<td>1</td>
<td>Imipramine</td>
<td>Global, AEs</td>
</tr>
<tr>
<td>Antidepressants (SNRIs)</td>
<td>3</td>
<td>Duloxetine</td>
<td>30%, 50%, AEs</td>
</tr>
<tr>
<td>Antidepressants (SNRIs)</td>
<td>5</td>
<td>Venlafaxine</td>
<td>50%, global, mean pain intensity scores, AEs</td>
</tr>
<tr>
<td><strong>Subtotal</strong></td>
<td>23</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>2</td>
<td>Carbamazepine</td>
<td>Global</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>3</td>
<td>Oxcarbazepine</td>
<td>30%, 50%, global, mean pain relief scores, AEs</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>3</td>
<td>Sodium valproate</td>
<td>Mean pain relief scores, mean pain intensity scores, AEs</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>3</td>
<td>Topiramate</td>
<td>30%, 50%, global, AEs</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>10</td>
<td>Lamotrigine</td>
<td>30%, 50%, global, AEs</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>13</td>
<td>Gabapentin</td>
<td>30%, 50%, global, mean change pain intensity scores, mean pain relief scores, AEs</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>12</td>
<td>Pregabalin</td>
<td>30%, 50%, global, mean pain intensity scores, AEs</td>
</tr>
<tr>
<td><strong>Subtotal</strong></td>
<td>46</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Opioid analgesics</td>
<td>4</td>
<td>Tramadol</td>
<td>50%, mean pain intensity scores, AEs</td>
</tr>
<tr>
<td>Opioid analgesics</td>
<td>3</td>
<td>Morphine</td>
<td>30%, 50%, global, AEs</td>
</tr>
<tr>
<td>Opioid analgesics</td>
<td>1</td>
<td>Oxycodone</td>
<td>Mean change pain intensity scores, AEs</td>
</tr>
<tr>
<td><strong>Subtotal</strong></td>
<td>8</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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Topical treatments  | 9  | Topical capsaicin | 40%, 50%, global, mean pain relief scores, mean change pain intensity scores, mean change pain relief scores, AEs |

Topical treatments  | 5  | Topical lidocaine | Mean pain relief scores, mean pain intensity scores, mean change pain relief scores, mean change pain intensity, AEs |

| Subtotal | 14 |

TCAs vs anticonvulsants  | 3  | Amitriptyline vs gabapentin | Global, 30%, AEs, mean change pain intensity scores, mean change pain relief scores |

TCAs vs anticonvulsants  | 1  | Nortriptyline vs gabapentin | 50%, mean change pain relief scores, AEs |

TCAs vs anticonvulsants  | 1  | Amitriptyline vs carbamazepine | Global, AEs |

Anticonvulsants vs opioids  | 1  | Pregabalin vs oxycodone | Mean pain intensity scores, AEs |

TCAs vs topical capsaicin  | 1  | Amitriptyline vs topical capsaicin | Mean change pain relief scores, mean change pain intensity scores, AEs |

Anticonvulsants vs topical lidocaine  | 1  | Pregabalin vs topical lidocaine | 30%, 50%, global, AEs |

TCAs vs TCAs  | 1  | Amitriptyline vs nortriptyline | AEs |

TCAs vs SNRIs  | 1  | Imipramine vs venlafaxine | Global, AEs |

| Subtotal | 10 |

Anticonvulsants + opioids vs anticonvulsants  | 1  | Gabapentin + oxycodone vs gabapentin | Mean pain relief scores, AEs |

Anticonvulsants + opioids vs anticonvulsants  | 1  | Pregabalin + oxycodone vs pregabalin | Mean pain intensity scores, AEs |

Anticonvulsants + opioids vs opioids  | 1  | Pregabalin + oxycodone vs oxycodone | Mean pain intensity scores, AEs |

| Subtotal | 3 |

TOTAL  | 104 |

1. TCA = tricyclic antidepressant; SNRI = serotonin–norepinephrine reuptake inhibitor; global = patient-reported global improvement; 30% = at least 30% pain reduction; 50% = at least 50% pain reduction; 2. AEs = adverse effects. 3. 4.

Analysis and synthesis

The primary outcomes for meta-analysis, based on the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) recommendations (Dworkin et al. 2005; Dworkin et al. 2008), were: at least 30% pain reduction; at least 50% pain reduction; patient-reported global improvement; and adverse effects. Specific adverse effects for each drug class were selected by the GDG (see appendix 10.3), based on their expert knowledge and experience (including the experience of patient and carer).
members of the GDG). A fixed-effects model meta-analysis by subclass of the pharmacological treatment (for example, antidepressants: TCAs, SSRIs, SNRIs) or by individual drug of the pharmacological treatment (for example, anticonvulsants: pregabalin, gabapentin, oxcarbazepine, lamotrigine, carbamazepine, phenytoin, sodium valproate, topiramate) were carried out on the primary outcomes. Where there was significant heterogeneity, a random-effects model was adopted for the meta-analysis. All results from the meta-analyses (relative risk or risk ratio [RR], absolute risk reduction [ARR], absolute risk increase [ARI], number-needed-to-treat to benefit [NNTB] and number-needed-to-treat to harm [NNTH]) were presented in GRADE profiles (for GRADE methodology, please see appendix 10.9) and subsequent evidence statements. No studies were excluded on the basis of outcomes.

For the completeness of the evidence base, included studies that did not report the primary outcomes recommended by the IMMPACT recommendations (Dworkin et al. 2005; Dworkin et al. 2008) were also summarised and presented in GRADE profiles and evidence statements as ‘other reported pain outcomes’. The ‘other reported pain outcomes’ included mean pain relief scores, mean pain intensity scores, mean change in pain relief scores from baseline, and mean change in pain intensity scores from baseline. Only evidence from the primary outcomes was used to generate recommendations. However, where evidence on particular pharmacological treatments was scarce or limited, evidence from ‘other reported pain outcomes’ was used to assist and generate discussions among the GDG to reach consensus, but not as the sole basis for making recommendations. For included studies that did not report primary outcomes or ‘other reported pain outcomes’, study characteristics were summarised in the evidence tables for information.

2.1.2 Health economics

No health economic modeling was undertaken for this guideline as there was a relevant health technology assessment (HTA) monograph in development to which the GDG had been given access (Fox-Rushby JA, GL Griffith, JR Ross et al. NIHR Health Technology Assessment programme. The clinical and cost-
effectiveness of different treatment pathways for neuropathic pain [NP]. HTA ref. 05/30/03. Unpublished. Project abstract available from www.hta.ac.uk/1527). The GDG reviewed, appraised and summarised the HTA report, and the results of the economic analyses from the HTA report informed this guideline as appropriate.

The HTA report focused on two neuropathic pain populations, and a systematic review of economic evidence was performed as part of the evidence review for this guideline. A systematic search found a total of 2273 papers. Full details on the search strategy can be found in appendix 10.7.

For the purposes of this guideline, the GDG decided at the outset that neuropathic pain would be treated as a ‘blanket condition’ where possible or necessary. However, it was clear that the treatment of various subpopulations would differ considerably and that it would not be possible to extrapolate from one subgroup to all people with neuropathic pain. In addition, the GDG decided that the HTA report included thorough data on the cost effectiveness of treatment pathways (sequences) for the subpopulations with post-herpetic neuralgia (PHN) and painful diabetic PDN. On this basis, the economic evidence review for this guideline excluded papers on people with PHN or PDN.

### 2.1.3 Summaries of included studies

**Table 6 Characteristics of included studies: antidepressants (placebo-controlled trials)**

<table>
<thead>
<tr>
<th>Author</th>
<th>Study period</th>
<th>Condition</th>
<th>Treatment (oral)</th>
<th>Titration or fixed dosage (mg/day)</th>
<th>Mean dose (mg/day)</th>
<th>Key outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bowsher 1997</td>
<td>3 months</td>
<td>PHN</td>
<td>Amitriptyline</td>
<td>25</td>
<td>NR</td>
<td>N/A</td>
</tr>
<tr>
<td>Graff-Radford 2000</td>
<td>8 weeks</td>
<td>PHN</td>
<td>Amitriptyline</td>
<td>12.5–200</td>
<td>NR</td>
<td>Mean pain intensity score, AEs</td>
</tr>
<tr>
<td>Max 1988</td>
<td>6 weeks</td>
<td>PHN</td>
<td>Amitriptyline</td>
<td>12.5–150</td>
<td>65</td>
<td>Global, AEs</td>
</tr>
<tr>
<td>Cardenas 2002</td>
<td>6 weeks</td>
<td>SCI</td>
<td>Amitriptyline</td>
<td>10–125</td>
<td>**50</td>
<td>Mean pain intensity score, AEs</td>
</tr>
<tr>
<td>Rintala 2007</td>
<td>8 weeks</td>
<td>SCI</td>
<td>Amitriptyline</td>
<td>150</td>
<td>150</td>
<td>30%, AEs</td>
</tr>
<tr>
<td>Kalso 1995</td>
<td>4 weeks</td>
<td>NP cancer</td>
<td>Amitriptyline</td>
<td>5–100</td>
<td>93.3</td>
<td>AEs</td>
</tr>
<tr>
<td>Kautio 2008</td>
<td>8 weeks</td>
<td>NP cancer</td>
<td>Amitriptyline</td>
<td>10–50</td>
<td>46.2</td>
<td>Global, AEs</td>
</tr>
<tr>
<td>Kieburstz 1998</td>
<td>9 weeks</td>
<td>HIV-RN</td>
<td>Amitriptyline</td>
<td>25–100</td>
<td>NR</td>
<td>Global, AEs</td>
</tr>
<tr>
<td>Leijon 1989</td>
<td>4 weeks</td>
<td>PSP</td>
<td>Amitriptyline</td>
<td>25–75</td>
<td>75</td>
<td>Global</td>
</tr>
<tr>
<td>Robinson 2004</td>
<td>6 weeks</td>
<td>Phan LP</td>
<td>Amitriptyline</td>
<td>10–125</td>
<td>NR</td>
<td>Mean pain relief score, AEs</td>
</tr>
<tr>
<td>Vrethem 1997</td>
<td>4 weeks</td>
<td>Poly</td>
<td>Amitriptyline</td>
<td>25–75</td>
<td>NR</td>
<td>30%, global, AEs</td>
</tr>
</tbody>
</table>

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** = median; PHN = post-herpetic neuralgia; PDN = painful diabetic neuropathy; SCI = spinal cord injury; NP cancer = neuropathic cancer pain; HIV-RN = HIV-related neuropathy; PSP = post-stroke pain; Phan LP = phantom limb pain; Poly = polyneuropathy; Radi = radiculopathy; ** Mixed NP = mixed neuropathic pain; global = patient-reported global improvement; 30% = at least 30% pain reduction; 50% = at least 50% pain reduction; AEs = adverse effects; NR = not reported; N/A = not applicable.

### Table 7 Characteristics of included studies: anticonvulsants (placebo-controlled trials)

<table>
<thead>
<tr>
<th>Author</th>
<th>Study period</th>
<th>Condition</th>
<th>Treatment (oral)</th>
<th>Titration or fixed dosage (mg/day)</th>
<th>Key Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leijon 1989</td>
<td>4 weeks</td>
<td>PSP</td>
<td>Carbamazepine</td>
<td>200–800</td>
<td>Global</td>
</tr>
<tr>
<td>Nicol 1989</td>
<td>46 months</td>
<td>Mixed NP</td>
<td>Carbamazepine</td>
<td>100–2400</td>
<td>Global</td>
</tr>
<tr>
<td>Beydoun 2006</td>
<td>16 weeks</td>
<td>PDN</td>
<td>Oxcarbazepine</td>
<td>to 600</td>
<td>Global, AEs</td>
</tr>
<tr>
<td>Dogra 2005</td>
<td>16 weeks</td>
<td>PDN</td>
<td>Oxcarbazepine</td>
<td>300–1800</td>
<td>30%, 50%, Global, AEs</td>
</tr>
<tr>
<td>Grosskopf 2006</td>
<td>16 weeks</td>
<td>PDN</td>
<td>Oxcarbazepine</td>
<td>300–600</td>
<td>Mean pain relief score, AEs</td>
</tr>
<tr>
<td>Agrawal 2009</td>
<td>3 months</td>
<td>PDN</td>
<td>S. valproate</td>
<td>20 per kg</td>
<td>Mean pain intensity score, AEs</td>
</tr>
<tr>
<td>Kochar 2002</td>
<td>4 weeks</td>
<td>PDN</td>
<td>S. valproate</td>
<td>1200</td>
<td>AEs</td>
</tr>
<tr>
<td>Raskin 2004</td>
<td>3 months</td>
<td>PDN</td>
<td>S. valproate</td>
<td>500</td>
<td>Mean pr, AEs</td>
</tr>
<tr>
<td>Thienel 2004</td>
<td>22 weeks</td>
<td>PDN</td>
<td>Topiramate</td>
<td>25–400</td>
<td>30%, 50%, Global, AEs</td>
</tr>
<tr>
<td>Thienel 2004</td>
<td>22 weeks</td>
<td>PDN</td>
<td>Topiramate</td>
<td>100, 200, 400</td>
<td>AEs</td>
</tr>
<tr>
<td>Khoromi 2005</td>
<td>6 weeks</td>
<td>Radi</td>
<td>Topiramate</td>
<td>50–400</td>
<td>Global, AEs</td>
</tr>
<tr>
<td>Eisenberg 2005</td>
<td>8 weeks</td>
<td>PDN</td>
<td>Lamotrigine</td>
<td>25–400</td>
<td>50%, Global, AEs</td>
</tr>
<tr>
<td>Luria 2000</td>
<td>8 weeks</td>
<td>PDN</td>
<td>Lamotrigine</td>
<td>25–400</td>
<td>50%, AEs</td>
</tr>
<tr>
<td>Vinik 2007a, 2007b</td>
<td>19 weeks</td>
<td>PDN</td>
<td>Lamotrigine</td>
<td>200, 300, 400</td>
<td>30%, 50%, AEs</td>
</tr>
<tr>
<td>Simpson 2000</td>
<td>14 weeks</td>
<td>HIV-RN</td>
<td>Lamotrigine</td>
<td>50–300</td>
<td>AEs</td>
</tr>
<tr>
<td>Simpson 2003</td>
<td>12 weeks</td>
<td>HIV-RN</td>
<td>Lamotrigine</td>
<td>25–400</td>
<td>Global, AEs</td>
</tr>
<tr>
<td>Breuer 2007</td>
<td>11 weeks</td>
<td>MS-NP</td>
<td>Lamotrigine</td>
<td>25–400</td>
<td>30%, AEs</td>
</tr>
<tr>
<td>Finnnerup 2002</td>
<td>9 weeks</td>
<td>SCI</td>
<td>Lamotrigine</td>
<td>25–400</td>
<td>AEs</td>
</tr>
<tr>
<td>McCleane 1999</td>
<td>8 weeks</td>
<td>Mixed NP</td>
<td>Lamotrigine</td>
<td>25–200</td>
<td>AEs</td>
</tr>
<tr>
<td>Rao 2008</td>
<td>10 weeks</td>
<td>NP cancer</td>
<td>Lamotrigine</td>
<td>25–300</td>
<td>AEs</td>
</tr>
<tr>
<td>Vestergaard 2001</td>
<td>8 weeks</td>
<td>PSP</td>
<td>Lamotrigine</td>
<td>200</td>
<td>AEs</td>
</tr>
<tr>
<td>Backonja 1998</td>
<td>8 weeks</td>
<td>PSP</td>
<td>Gabapentin</td>
<td>to 3600</td>
<td>Global, AEs</td>
</tr>
<tr>
<td>Simpson 2001</td>
<td>8 weeks</td>
<td>PDN</td>
<td>Gabapentin</td>
<td>to 3600</td>
<td>Global, AEs</td>
</tr>
<tr>
<td>Rice 2001</td>
<td>7 weeks</td>
<td>PHN</td>
<td>Gabapentin</td>
<td>1800, 2400</td>
<td>50%, Global, AEs</td>
</tr>
<tr>
<td>Rowbotham 1998</td>
<td>8 weeks</td>
<td>PHN</td>
<td>Gabapentin</td>
<td>to 3600</td>
<td>Global, AEs</td>
</tr>
<tr>
<td>Bone 2002</td>
<td>6 weeks</td>
<td>Phan LP</td>
<td>Gabapentin</td>
<td>300–2400</td>
<td>Mean change pain intensity score from baseline, AEs</td>
</tr>
<tr>
<td>Nikolaisen 2006</td>
<td>30 days</td>
<td>Phan LP</td>
<td>Gabapentin</td>
<td>300–2400</td>
<td>AEs</td>
</tr>
</tbody>
</table>

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Smith 2005  6 weeks  Phan LP  Gabapentin  300–3600  Global
Levendoglu 2004  8 weeks  SCI  Gabapentin  900–3600  Mean pr, AEs
Rintala 2007  8 weeks  SCI  Gabapentin to 3600  30%, AEs
Gordh 2008  5 weeks  NP-NI  Gabapentin  300–2400  Global, AEs
Hahn 2004  4 weeks  HIV-RN  Gabapentin  400–2400  AEs
Rao 2007  6 weeks  NP cancer  Gabapentin  300–2700  AEs
Serpell 2002  8 weeks  Mixed NP  Gabapentin  900–2400  50%, Global, AEs

Arezzo 2008  13 weeks  PDN  Pregabalin to 600  Mean pain intensity score, AEs
Lesser 2004  5 weeks  PDN  Pregabalin to 75, 300, 600  30%, 50%, Global, AEs
Richter 2005  6 weeks  PDN  Pregabalin  25–150, 100–600  50%, AEs
Rosenstock 2004  8 weeks  PDN  Pregabalin  300  50%, AEs
Tolle 2008  12 weeks  PDN  Pregabalin  150, 300, 300/600  50%, Global, AEs
Dworkin 2003  8 weeks  PHN  Pregabalin  150–600  30%, 50%, AEs
Sabatowski 2004  8 weeks  PHN  Pregabalin  150, 300  50%, Global, AEs
Stacey 2008  4 weeks  PHN  Pregabalin  150–600, 600  30%, 50%, AEs
van Seventer 2006  13 weeks  PHN  Pregabalin  150, 300, 600  30%, 50%, Global, AEs
Freynhagen 2005  12 weeks  PDN, PHN  Pregabalin  150–600, 300–600  30%, 50%, Global, AEs
Siddall 2006  12 weeks  SCI  Pregabalin  150–600  30%, 50%, AEs
Vranken 2008  7 weeks  PDN  Pregabalin  150–600  AEs

S. valproate = sodium valproate; MS-NP = Multiple sclerosis (central pain); NP-NI = nerve injury neuropathic pain; PHN = post-herpetic neuralgia; CenP = Central pain; PDN = painful diabetic neuropathy; SCI = spinal cord injury; NP cancer = neuropathic cancer pain; HIV-RN = HIV-related neuropathy; PSP = post-stroke pain; Phan LP = phantom limb pain; Radi = radiculopathy; Mixed NP = mixed neuropathic pain; Global = patient-reported global improvement; 30% = at least 30% pain reduction; 50% = at least 50% pain reduction; AEs = adverse effects.

**mean mg/6 hours; PHN = post-herpetic neuralgia; PDN = painful diabetic neuropathy; NP cancer = neuropathic cancer pain; Phan LP = phantom limb pain; Poly = polyneuropathy; Radi = radiculopathy; Global = patient-reported global improvement; 30% = at least 30% pain reduction; 50% = at least 50% pain reduction; AEs = adverse effects.

Table 8 Characteristics of included studies: opioid analgesics (placebo-controlled trials)

<table>
<thead>
<tr>
<th>Author</th>
<th>Study period</th>
<th>Condition</th>
<th>Treatment (oral)</th>
<th>Titration or fixed dosage (mg/day)</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arbaiza</td>
<td>6 weeks</td>
<td>NP cancer</td>
<td>Tramadol</td>
<td><strong>98.75</strong></td>
<td>Mean pain intensity score, AEs</td>
</tr>
<tr>
<td>Boureau</td>
<td>6 weeks</td>
<td>PHN</td>
<td>Tramadol</td>
<td>100–400</td>
<td>50%</td>
</tr>
<tr>
<td>Sindrup</td>
<td>6 weeks</td>
<td>Poly</td>
<td>Tramadol</td>
<td>100–400</td>
<td>Mean pain intensity score, AEs</td>
</tr>
<tr>
<td>Harati</td>
<td>4 weeks</td>
<td>PDN</td>
<td>Tramadol</td>
<td>200–400</td>
<td>Mean pain intensity score, AEs</td>
</tr>
<tr>
<td>Huse</td>
<td>4 weeks</td>
<td>Phan LP</td>
<td>Morphine</td>
<td>70–300</td>
<td>50%</td>
</tr>
<tr>
<td>Khoromi</td>
<td>6 weeks</td>
<td>Radi</td>
<td>Morphine</td>
<td>15–180</td>
<td>Global, AEs</td>
</tr>
<tr>
<td>Wu</td>
<td>7 weeks</td>
<td>Phan LP</td>
<td>Morphine</td>
<td>15–90</td>
<td>30%, 50%, AEs</td>
</tr>
</tbody>
</table>

**mean mg/6 hours; PHN = post-herpetic neuralgia; PDN = painful diabetic neuropathy; NP cancer = neuropathic cancer pain; Phan LP = phantom limb pain; Poly = polyneuropathy; Radi = radiculopathy; Global = patient-reported global improvement; 30% = at least 30% pain reduction; 50% = at least 50% pain reduction; AEs = adverse effects.

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### Table 9 Characteristics of included studies: topical capsaicin and topical lidocaine (placebo-controlled trials)

<table>
<thead>
<tr>
<th>Author</th>
<th>Study period</th>
<th>Condition</th>
<th>Treatment</th>
<th>Titration or fixed dosage (times/day)</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bernstein</td>
<td>6 weeks</td>
<td>PHN</td>
<td>Topical capsaicin</td>
<td>0.075% cream, 3 to 4</td>
<td>40%, AEs</td>
</tr>
<tr>
<td>Watson 1993</td>
<td>6 weeks</td>
<td>PHN</td>
<td>Topical capsaicin</td>
<td>0.075% cream, 4</td>
<td>Mean change pain relief score from baseline, AEs</td>
</tr>
<tr>
<td>Donofrio 1992</td>
<td>8 weeks</td>
<td>PDN or Radi</td>
<td>Topical capsaicin</td>
<td>0.075% cream, 4</td>
<td>Mean pr, Mean change pain intensity score, AEs</td>
</tr>
<tr>
<td>Scheffler 1991</td>
<td>8 weeks</td>
<td>PDN</td>
<td>Topical capsaicin</td>
<td>0.075% cream, 4</td>
<td>Mean pain relief score, Mean change pain intensity score from baseline, AEs</td>
</tr>
<tr>
<td>Tandan 1992</td>
<td>8 weeks</td>
<td>PDN</td>
<td>Topical capsaicin</td>
<td>0.075% cream, 4</td>
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<tr>
<td>Low 1995</td>
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<td>McClean 2000</td>
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<tr>
<td>Paice 2000</td>
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<tr>
<td>Watson 1992</td>
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<td>NP cancer</td>
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<td>Galer 2002</td>
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<td>Topical lidocaine</td>
<td>5% patch, 1</td>
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<td>Meier 2003</td>
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<tr>
<td>Ho 2008</td>
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<td>Mean pain intensity score</td>
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<tr>
<td>Estanislao 2004</td>
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<td>HIV-RN</td>
<td>Topical lidocaine</td>
<td>5% gel, 1</td>
<td>Mean pain relief score</td>
</tr>
</tbody>
</table>

PHN = post-herpetic neuralgia; PDN = painful diabetic neuropathy; NP cancer = neuropathic cancer pain; Poly = polineuropathy; Radi = radiculopathy; HIV-RN = HIV-related neuropathy; PS-NP = postsurgical neuropathic pain; Peri NP = peripheral neuropathic pain; Mixed NP = mixed neuropathic pain; Global = global improvement; 40% = at least 40% pain reduction; 50% = at least 50% pain reduction; AEs = adverse effects.

### Table 10 Characteristics of included studies: comparative trials and combination therapy (randomised controlled trials)

<table>
<thead>
<tr>
<th>Author</th>
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<td>Morello 1999</td>
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<tr>
<th>Study</th>
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<td>Leijon 1989</td>
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<td>Gatti 2008</td>
<td>3 months</td>
<td>MixNP</td>
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<td>Pre: 85.6 to max Oxy: 24.1 to max</td>
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<td><strong>TCAs vs Topical Capsaicin</strong></td>
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<td>Biesbroeck 1995</td>
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<td>Mean change pain relief score from baseline, Mean change pain intensity score from baseline, AEs</td>
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<td>Baron 2009</td>
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<td>PDN</td>
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<td>Pre: 150-600 5% Lido: 3–4 patches up to 12 hours/day</td>
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<td><strong>Within-class head-to-head comparison</strong></td>
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<td><strong>TCAs vs TCAs</strong></td>
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<tr>
<td>Watson 1998</td>
<td>5 weeks</td>
<td>PHN</td>
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<tr>
<td><strong>TCAs vs SNRIs</strong></td>
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<td>Sindrup 2003</td>
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<td>Imipramine</td>
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<td>Imi: 50–150 Ven: 75–225</td>
<td>Global, AEs</td>
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<td><strong>Combination therapy</strong></td>
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<td>Hanna 2008</td>
<td>12 weeks</td>
<td>PDN</td>
<td>Gabapentin + Oxycodone</td>
<td>Gabapentin</td>
<td>Gaba: 600–1800 Oxy: 5–80</td>
<td>Mean pain relief score, AEs</td>
</tr>
<tr>
<td>Gatti 2008</td>
<td>3 months</td>
<td>MixNP</td>
<td>Pregabalin + Oxycodone</td>
<td>Pregabalin</td>
<td>Combination: Pre 108.1 + Oxy 19.4 Pre: 85.6 to max</td>
<td>Mean pain intensity score, AEs</td>
</tr>
<tr>
<td><strong>Anticonvulsants + Opioids vs Opioids</strong></td>
<td></td>
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<tr>
<td>Gatti 2008</td>
<td>3 months</td>
<td>MixNP</td>
<td>Pregabalin + Oxycodone</td>
<td>Oxycodone</td>
<td>Combination: Pre 108.1 + Oxy 19.4 Oxy: 24.1 to max</td>
<td>Mean pain intensity score, AEs</td>
</tr>
</tbody>
</table>

Con = condition; T1 = treatment 1; T2 = treatment 2; PHN = post-herpetic neuralgia; PDN = painful diabetic neuropathy; MixNP = mixed neuropathic pain; PostSt: post-stroke pain; Poly = painful polyneuropathy; SCI = spinal cord injury; AMI = amitriptyline; Gaba = gabapentin; Nort = nortriptyline; Carba = carbamazepine; Pre = pregabalin; Oxy = oxycodone; Cap = topical capsaicin; Lido = topical lidocaine; Imi = imipramine; Ven = venlafaxine; Global = patient-reported global improvement; 30% = at least 30% pain reduction; 50% = at least 50% pain reduction; AEs = adverse effects.
2.2 Evidence statements

2.2.1 Antidepressants

Primary outcomes

TCAs (as monotherapy – placebo-controlled trials) (for evidence related to the following evidence statements, see Table 11 GRADE profiles)

For the following evidence statements, the TCAs referred to are amitriptyline, nortriptyline, desipramine and imipramine.

Outcomes on pain

For patients with neuropathic pain:

- There was moderate quality evidence that patients receiving TCAs were significantly more likely to report at least 30% pain reduction and global improvement compared with patients receiving placebo.

Adverse effects

For patients with neuropathic pain:

- Patients receiving TCAs were significantly more likely to withdraw from treatment because of adverse effects compared with patients receiving placebo (low-quality evidence).

- Patients receiving TCAs were significantly more likely to report dry mouth (moderate quality evidence) and sedation (low quality evidence) compared with patients receiving placebo.

- For incidences of blurred vision, dizziness, vomiting and gastrointestinal disturbances, there were no significant differences between patients receiving TCAs and patients receiving placebo (low-quality evidence).

- Patients receiving TCAs were significantly more likely to report any adverse effects (non-specified) compared with patients receiving placebo (high-quality evidence).
Lofepramine, trimipramine, dothiepin and doxepin

- No studies on lofepramine, trimipramine, dosulepin (dothiepin) or doxepin were identified that met the inclusion and exclusion criteria. Therefore there was no appropriate evidence that lofepramine, trimipramine, dosulepin (dothiepin) or doxepin is clinically effective in treating neuropathic pain.

SSRIs (as monotherapy – placebo-controlled trials)

- No studies on SSRIs were identified that met the inclusion and exclusion criteria. Therefore there was no appropriate evidence that SSRIs are clinically effective in treating neuropathic pain.

SNRIs (as monotherapy – placebo-controlled trials) (for evidence related to the following evidence statements, see Table 12 GRADE profiles)

For the following evidence statements, the SNRIs referred to are duloxetine and venlafaxine.

Outcomes on pain
For patients with neuropathic pain:

- There was moderate-to-high-quality evidence that patients receiving SNRIs were significantly more likely to report at least 30% pain reduction (duloxetine), at least 50% pain reduction (duloxetine and venlafaxine) and global improvement (venlafaxine) compared with patients receiving placebo.

Adverse effects
For patients with neuropathic pain:

- Patients receiving SNRIs were significantly more likely to withdraw from treatment because of adverse effects compared with patients receiving placebo (moderate-quality evidence).

- For incidences of dry mouth and gastrointestinal disturbances, there were no significant differences between patients receiving SNRIs and patients receiving placebo (low-quality evidence).
• For incidences of blurred vision and vomiting, there were no significant differences between patients receiving SNRIs and patients receiving placebo (very-low-quality evidence).

• For the incidence of any adverse effects (non-specified), there was no significant difference between patients receiving SNRIs and patients receiving placebo (very-low-quality evidence).

**Other reported pain outcomes (for evidence related to the following evidence statements, see Table 13 GRADE profiles)**

For mean pain intensity scores:

• There was conflicting low-quality evidence on the efficacy of amitriptyline in reducing pain intensity.

• There was low-quality evidence that there was no significant difference in pain intensity scores between patients receiving venlafaxine and patients receiving placebo.

For mean pain relief scores:

• There was low-quality evidence that there was no significant difference in pain relief scores between patients receiving amitriptyline and patients receiving placebo.

### 2.2.2 Anticonvulsants

**Primary outcomes**

_Gabapentin (as monotherapy – placebo-controlled trials) (for evidence related to the following evidence statements, see Table 14 GRADE profiles)_

**Outcomes on pain**

For patients with neuropathic pain:

• There was moderate-to-high-quality evidence that patients receiving gabapentin were significantly more likely to report at least 50% pain reduction and global improvement compared with patients receiving placebo.
The number of patients achieving at least 30% pain reduction was not significantly different between patients receiving gabapentin and patients receiving placebo (moderate-quality evidence).

Adverse effects

For patients with neuropathic pain:

- Patients receiving gabapentin were significantly more likely to withdraw from treatment because of adverse effects compared with patients receiving placebo (moderate-quality evidence).

- Patients receiving gabapentin were significantly more likely to report dizziness, somnolence (moderate-quality evidence) and fatigue (low-quality evidence) compared with patients receiving placebo.

- For incidences of sedation and gait disturbances, there were no significant differences between patients receiving gabapentin and patients receiving placebo (very-low-quality evidence).

- Patients receiving gabapentin were significantly more likely to report any (non-specified) adverse effects compared with patients receiving placebo (high-quality evidence).

Pregabalin (as monotherapy – placebo-controlled trials) (for evidence related to the following evidence statements, see Table 15 GRADE profiles)

Outcomes on pain

For patients with neuropathic pain:

- There was high-quality evidence that patients receiving pregabalin were significantly more likely to report at least 30% pain reduction, at least 50% pain reduction and global improvement compared with patients receiving placebo.

Adverse effects

For patients with neuropathic pain:
• Patients receiving pregabalin were significantly more likely to withdraw from treatment because of adverse effects compared with patients receiving placebo (high-quality evidence).

• Patients receiving pregabalin were significantly more likely to report dizziness, somnolence (high-quality evidence), weight gain and gait disturbances (low-quality evidence) compared with patients receiving placebo.

• For the incidence of fatigue, there was no significant difference between patients receiving pregabalin and patients receiving placebo (very-low-quality evidence).

• Patients receiving pregabalin were significantly more likely to report any (non-specified) adverse effects compared with patients receiving placebo (moderate-quality evidence).

Lamotrigine (as monotherapy – placebo-controlled trials) (for evidence related to the following evidence statements, see Table 16 GRADE profiles)

Outcomes on pain

For patients with neuropathic pain:

• The numbers of patients achieving at least 30% pain reduction and at least 50% pain reduction were not significantly different between patients receiving lamotrigine and patients receiving placebo (moderate-quality evidence).

• There was moderate-quality evidence that patients receiving lamotrigine were significantly more likely to report global improvement compared with patients receiving placebo.

Adverse effects

For patients with neuropathic pain:
• Patients receiving lamotrigine were significantly more likely to withdraw from treatment because of adverse effects compared with patients receiving placebo (moderate-quality evidence).

• For incidences of dizziness, fatigue (low-quality evidence) and sedation (very-low-quality evidence), there were no significant differences between patients receiving lamotrigine and patients receiving placebo.

• For the incidence of any adverse effects (non-specified), there was no significant difference between patients receiving lamotrigine and patients receiving placebo.

Oxcarbazepine (as monotherapy – placebo-controlled trials) (for evidence related to the following evidence statements, see Table 17
GRADE profiles)

Outcomes on pain

For patients with neuropathic pain:

• There was moderate-quality evidence that patients receiving oxcarbazepine were significantly more likely to report at least 30% pain reduction and at least 50% pain reduction compared with patients receiving placebo.

• The number of patients achieving global improvement was not significantly different between patients receiving oxcarbazepine and patients receiving placebo (moderate-quality evidence).

Adverse effects

For patients with neuropathic pain:

• Patients receiving oxcarbazepine were significantly more likely to withdraw from treatment because of adverse effects compared with patients receiving placebo (moderate-quality evidence).

• Patients receiving oxcarbazepine were significantly more likely to report dizziness and somnolence compared with patients receiving placebo (low-quality evidence).
• For the incidence of fatigue, there was no significant difference between patients receiving oxcarbazepine and patients receiving placebo (low-quality evidence).

Topiramate (as monotherapy – placebo-controlled trials) (for evidence related to the following evidence statements, see Table 18 GRADE profiles)

Outcomes on pain

For patients with neuropathic pain:

• There was moderate-quality evidence that patients receiving topiramate were significantly more likely to report at least 30% pain reduction, at least 50% pain reduction and global improvement compared with patients receiving placebo.

Adverse effects

For patients with neuropathic pain:

• Patients receiving topiramate were significantly more likely to withdraw from treatment because of adverse effects compared with patients receiving placebo (high-quality evidence).

• Patients receiving topiramate were significantly more likely to report somnolence, fatigue (moderate-quality evidence) and sedation (very-low-quality evidence) compared with patients receiving placebo.

• For the incidence of dizziness, there was no significant difference between patients receiving topiramate and patients receiving placebo (very-low-quality evidence).

Carbamazepine (as monotherapy – placebo-controlled trials) (for evidence related to the following evidence statements, see Table 19 GRADE profiles)

Outcomes on pain

For patients with neuropathic pain:
• The number of patients reporting global improvement was not significantly different between patients receiving carbamazepine and patients receiving placebo (moderate-quality evidence).

Adverse effects
For patients with neuropathic pain:

• Patients receiving carbamazepine were significantly more likely to report any (non-specified) adverse effects compared with patients receiving placebo (very-low-quality evidence).

Sodium valproate (as monotherapy – placebo-controlled trials) (for evidence related to the following evidence statements, see Table 20 GRADE profiles)

Outcomes on pain
• No study on sodium valproate that reported the primary outcomes on pain met the inclusion and exclusion criteria.

Adverse effects
For patients with neuropathic pain:

• For the incidence of withdrawal from treatment because of adverse effects, there was no significant difference between patients receiving sodium valproate and patients receiving placebo (low-quality evidence).

• For the incidence of any adverse effects (non-specified), there was no significant difference between patients receiving sodium valproate and patients receiving placebo (high-quality evidence).

Phenytoin
• No study on phenytoin met the inclusion and exclusion criteria. Therefore there was no appropriate evidence that phenytoin is clinically effective in treating neuropathic pain.

Other reported pain outcomes (for evidence related to the following evidence statements, see Table 21 GRADE profiles)
For sodium valproate:
There was conflicting low-quality evidence on the efficacy of sodium valproate in relation to pain intensity scores and pain relief scores.

For pregabalin:

- There was low-quality evidence that pain intensity scores for patients receiving pregabalin were significantly lower than those for patients receiving placebo.

For gabapentin:

- There was low-quality evidence that the mean change in pain intensity scores from baseline for patients receiving gabapentin was significantly greater than for patients receiving placebo.

For oxcarbazepine:

- There was low-quality evidence that there was no significant difference in pain relief scores between patients receiving oxcarbazepine and patients receiving placebo.

### 2.2.3 Opioids

**Primary outcomes**

*Morphine (as monotherapy – placebo-controlled trials) (for evidence related to the following evidence statements, see Table 22 GRADE profiles)*

**Outcomes on pain**

For patients with neuropathic pain:

- There was moderate-quality evidence that patients receiving morphine were significantly more likely to report at least 30% pain reduction and at least 50% pain reduction compared with patients receiving placebo.

- The number of patients reporting global improvement was not significantly different between patients receiving morphine and patients receiving placebo (moderate-quality evidence).
Adverse effects

For patients with neuropathic pain:

- Patients receiving morphine were significantly more likely to withdraw from treatment because of adverse effects compared with patients receiving placebo (very-low-quality evidence).

- Patients receiving morphine were significantly more likely to report constipation and somnolence/drowsiness compared with patients receiving placebo (low-quality evidence).

- For incidences of nausea and dizziness, there were no significant differences between patients receiving morphine and patients receiving placebo (low-quality evidence).

Tramadol (as monotherapy – placebo-controlled trials) (for evidence related to the following evidence statements, see Table 23 GRADE profiles)

Outcomes on pain

For patients with neuropathic pain:

- There was moderate-quality evidence that patients receiving tramadol were significantly more likely to report at least 50% pain reduction compared with patients receiving placebo.

Adverse effects

For patients with neuropathic pain:

- Patients receiving tramadol were significantly more likely to withdraw from treatment because of adverse effects compared with patients receiving placebo (low-quality evidence).

- Patients receiving tramadol were significantly more likely to report constipation, nausea and dizziness compared with patients receiving placebo (low-quality evidence).
• For incidences of somnolence/drowsiness and vomiting, there were no significant differences between patients receiving tramadol and patients receiving placebo (very-low-quality evidence).

**Oxycodone (as monotherapy – placebo-controlled trials) (for evidence related to the following evidence statements, see Table 24 GRADE profiles)**

**Outcomes on pain**

For patients with neuropathic pain:

• No studies on oxycodone that reported the primary outcomes on pain met the inclusion and exclusion criteria.

**Adverse effects**

For patients with neuropathic pain:

• For the incidence of withdrawal from treatment because of adverse effects, there was no significant difference between patients receiving oxycodone and patients receiving placebo (low-quality evidence).

• Patients receiving oxycodone were significantly more likely to report somnolence/drowsiness, nausea, dizziness and vomiting compared with patients receiving placebo (very-low-quality evidence).

**Co-codamol, co-dydramol, dihydrocodeine, buprenorphine, fentanyl and codeine phosphate**

• None of the studies identified on co-codamol, co-dydramol, dihydrocodeine, buprenorphine, fentanyl or codeine phosphate met the inclusion and exclusion criteria. Therefore there was no appropriate evidence that co-codamol, co-dydramol, dihydrocodeine, buprenorphine, fentanyl or codeine phosphate is clinically effective in treating neuropathic pain.

**Other reported pain outcomes (for evidence related to the following evidence statements, see Table 25 GRADE profiles)**

For tramadol:
• There was low-quality evidence that the pain intensity scores and pain relief scores for patients receiving tramadol were significantly lower than those for patients receiving placebo.

For oxycodone:

• There was low-quality evidence that the mean change in pain intensity scores from baseline for patients receiving oxycodone was significantly greater than for patients receiving placebo.

2.2.4 Topical treatments

Primary outcomes

Topical capsaicin (as monotherapy – placebo-controlled trials) (for evidence related to the following evidence statements, see Table 26 GRADE profiles)

Outcomes on pain:

For patients with neuropathic pain:

• The numbers of patients reporting at least 40% pain reduction, at least 50% pain reduction and global improvement were not significantly different between patients receiving topical capsaicin and patients receiving placebo (moderate-quality evidence).

Adverse effects:

For patients with neuropathic pain:

• Patients receiving topical capsaicin were significantly more likely to withdraw from treatment because of adverse effects compared with patients receiving placebo (low-quality evidence).

• Patients receiving topical capsaicin were significantly more likely to report a burning sensation compared with patients receiving placebo (high-quality evidence).

• For the incidence of skin irritation, there was no significant difference between patients receiving topical capsaicin and patients receiving placebo (very-low-quality evidence).
Topical lidocaine (as monotherapy – placebo-controlled trials) (for evidence related to the following evidence statements, see Table 27 GRADE profiles)

Outcomes on pain:
For patients with neuropathic pain:

- No studies were identified that reported the primary outcomes of pain.

Adverse effects:
For patients with neuropathic pain:

- For the incidence of withdrawal from treatment because of adverse effects, there was no significant difference between patients receiving topical lidocaine and patients receiving placebo (low-quality evidence).

- For incidences of rash and skin irritation, there were no significant differences between patients receiving topical lidocaine and patients receiving placebo (very-low-quality evidence).

Other reported pain outcomes

Topical capsaicin (for evidence related to the following evidence statements, see Table 28 GRADE profiles)

- There was conflicting low-quality evidence on the efficacy of topical capsaicin in reducing mean pain intensity scores.

- There was low-quality evidence that the mean change in pain intensity scores from baseline for patients receiving topical capsaicin was significantly greater than for patients receiving placebo.

Topical lidocaine (for evidence related to the following evidence statements, see Table 29 GRADE profiles)

- There was low-quality evidence that there were no significant differences in the pain intensity scores and pain relief scores between patients receiving topical lidocaine and patients receiving placebo.

- There was conflicting low-quality evidence on the efficacy of topical lidocaine in reducing pain intensity scores from baseline.
• There was low-quality evidence that the mean change in pain relief scores from baseline for patients receiving topical lidocaine was significantly greater than for patients receiving placebo.

2.2.5 Comparative trials and combination therapy

2.2.5.1 Cross-class comparative trials

Amitriptyline (TCA) compared with gabapentin (anticonvulsant)

Primary outcomes (for evidence related to the following evidence statements, see Table 30 GRADE profiles)

Outcomes on pain

For patients with neuropathic pain:

• There was moderate-quality evidence that patients receiving amitriptyline were significantly more likely to report at least 30% pain reduction compared with patients receiving gabapentin.

• The number of patients reporting global improvement was not significantly different between patients receiving amitriptyline and patients receiving gabapentin (moderate-quality evidence).

Adverse effects

For patients with neuropathic pain:

• For the incidence of withdrawal from treatment because of adverse effects, there was no significant difference between patients receiving amitriptyline and patients receiving gabapentin (low-quality evidence).

• For incidences of dry mouth, dizziness, blurred vision, sedation, fatigue and weight gain, there were no significant differences between patients receiving amitriptyline and patients receiving gabapentin (very-low-quality evidence).

• For the incidence of any adverse effects (non-specified), there was no significant difference between patients receiving amitriptyline and patients receiving gabapentin (very-low-quality evidence).
**Other reported pain outcomes (for evidence related to the following evidence statements, see Table 31 GRADE profiles)**

- There was very-low-quality evidence that the mean change in pain relief scores for patients receiving gabapentin was significantly greater than for patients receiving amitriptyline.

**Nortriptyline (TCA) compared with gabapentin (anticonvulsant)**

**Primary outcomes (for evidence related to the following evidence statements, see Table 32 GRADE profiles)**

**Outcomes on pain**

For patients with neuropathic pain:

- The number of patients reporting at least 50% pain reduction was not significantly different between patients receiving nortriptyline and patients receiving gabapentin (moderate-quality evidence).

**Adverse effects**

For patients with neuropathic pain:

- For incidences of somnolence, dry mouth and fatigue, there were no significant differences between patients receiving nortriptyline and patients receiving gabapentin (very-low-quality evidence).

**Amitriptyline (TCA) compared with carbamazepine (anticonvulsant)**

**Primary outcomes (for evidence related to the following evidence statements, see Table 33 GRADE profiles)**

**Outcomes on pain**

For patients with neuropathic pain:

- The number of patients reporting global improvement was not significantly different between patients receiving amitriptyline and patients receiving carbamazepine (moderate-quality evidence).

**Adverse effects**

For patients with neuropathic pain:

- For the incidence of any adverse effects (non-specified), there was no significant difference between patients receiving amitriptyline and patients receiving carbamazepine (very-low-quality evidence).

**Pregabalin (anticonvulsant) compared with oxycodone (opioid)**

Neuropathic pain: NICE clinical guideline DRAFT (October 2009) Page 41 of 136
analgesic)

Primary outcomes (for evidence related to the following evidence statements, see Table 34 GRADE profiles)

Outcomes on pain

For patients with neuropathic pain:

• No studies on pregabalin and oxycodone that reported the primary outcomes on pain met the inclusion and exclusion criteria.

Adverse effects

For patients with neuropathic pain:

• For the incidence of withdrawal from treatment because of adverse effects, there was no significant difference between patients receiving pregabalin and patients receiving oxycodone (very-low-quality evidence).

Pregabalin (anticonvulsant) compared with topical lidocaine

Primary outcomes (for evidence related to the following evidence statements, see Table 35 GRADE profiles)

Outcomes on pain

For patients with neuropathic pain:

• The numbers of patients reporting at least 30% pain reduction, at least 50% pain reduction and global improvement were not significantly different between patients receiving pregabalin and patients receiving topical lidocaine (very-low-quality evidence).

Adverse effects

For patients with neuropathic pain:

• Patients receiving pregabalin were significantly more likely to withdraw from treatment because of adverse effects compared with patients receiving topical lidocaine (very-low-quality evidence).

• Patients receiving pregabalin were significantly more likely to report any adverse effects (non-specified) compared with patients receiving topical lidocaine (very-low-quality evidence).
Amitriptyline (TCA) compared with topical capsaicin

Primary outcomes (for evidence related to the following evidence statements, see Table 36 GRADE profiles)

Outcomes on pain

For patients with neuropathic pain:

- No studies on amitriptyline and topical capsaicin that reported the primary outcomes on pain met the inclusion and exclusion criteria.

Adverse effects

For patients with neuropathic pain:

- Patients receiving amitriptyline were significantly more likely to report sedation compared with patients receiving topical capsaicin (very-low-quality evidence).

- Patients receiving topical capsaicin were significantly more likely to report a burning sensation compared with patients receiving amitriptyline (very-low-quality evidence).

Other reported pain outcomes (for evidence related to the following evidence statements, see Table 37 GRADE profiles)

- There were no significant differences in pain relief scores or mean change in pain intensity scores from baseline between patients receiving amitriptyline and patients receiving topical capsaicin (low-quality evidence).

2.2.5.2 Within-class comparative trials

Imipramine (TCA) compared with venlafaxine (SNRI)

Primary outcomes (for evidence related to the following evidence statements, see Table 38 GRADE profiles)

Outcomes on pain

For patients with neuropathic pain:

- The number of patients reporting global improvement was not significantly different between patients receiving imipramine and patients receiving venlafaxine (moderate-quality evidence).

Adverse effects

For patients with neuropathic pain:
- For incidences of dizziness, dry mouth, blurred vision and other (non-specified) adverse effects, there were no significant differences between patients receiving imipramine and patients receiving venlafaxine (very-low-quality evidence).

**Amitriptyline (TCA) compared with nortriptyline (TCA)**

*Primary outcomes (for evidence related to the following evidence statements, see Table 39 GRADE profiles)*

**Outcomes on pain**

For patients with neuropathic pain:

- No studies on amitriptyline and nortriptyline that reported the primary outcomes on pain met the inclusion and exclusion criteria.

**Adverse effects**

For patients with neuropathic pain:

- For incidences of dry mouth, dizziness, drowsiness and any (non-specified) adverse effects, there were no significant differences between patients receiving amitriptyline and patients receiving nortriptyline (very-low-quality evidence).

### 2.2.5.3 Combination therapy

**Pregabalin plus oxycodone (combination) compared with pregabalin alone (anticonvulsant)**

*Primary outcomes (for evidence related to the following evidence statements, see Table 40 GRADE profiles)*

**Outcomes on pain**

For patients with neuropathic pain:

- No studies on pregabalin plus oxycodone compared with pregabalin alone that reported the primary outcomes on pain met the inclusion and exclusion criteria.

**Adverse effects**

For patients with neuropathic pain:

- For the incidence of withdrawal from treatment because of adverse effects, there was no significant difference between patients receiving pregabalin

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plus oxycodone and patients receiving pregabalin alone (very-low-quality evidence).

**Gabapentin plus oxycodone (combination) compared with gabapentin alone (anticonvulsant)**

**Primary outcomes (for evidence related to the following evidence statements, see Table 41 GRADE profiles)**

**Outcomes on pain**

For patients with neuropathic pain:

- No studies on gabapentin plus oxycodone compared with gabapentin alone that reported the primary outcomes on pain met the inclusion and exclusion criteria.

**Adverse effects**

For patients with neuropathic pain:

- Patients receiving gabapentin plus oxycodone were significantly more likely to withdraw from treatment because of adverse effects compared with patients receiving gabapentin alone (very-low-quality evidence).
- Patients receiving gabapentin plus oxycodone were significantly more likely to report constipation, nausea, fatigue, dizziness, somnolence and other (non-specified) adverse effects compared with patients receiving gabapentin alone (very-low-quality evidence).
- For the incidence of vomiting, there was no significant difference between patients receiving gabapentin plus oxycodone and patients receiving gabapentin alone (very-low-quality evidence).

**Other reported pain outcomes (for evidence related to the following evidence statements, see Table 42 GRADE profiles)**

- There was low-quality evidence that the mean change in pain relief scores for patients receiving gabapentin and oxycodone was significantly greater than for patients receiving gabapentin alone.
Pregabalin plus oxycodone (combination) compared with oxycodone alone (opioid analgesic)

Primary outcomes (for evidence related to the following evidence statements, see Table 43 GRADE profiles)

Outcomes on pain

For patients with neuropathic pain:

- No studies on pregabalin plus oxycodone compared with oxycodone alone that reported the primary outcomes on pain met the inclusion and exclusion criteria.

Adverse effects

For patients with neuropathic pain:

- For the incidence of withdrawal from treatment because of adverse effects, there was no significant difference between patients receiving pregabalin plus oxycodone and patients receiving oxycodone alone (very-low-quality evidence).

2.2.6 Health economics

For patients with painful diabetic neuropathy:

- One high-quality study provided evidence that duloxetine, especially in dosages up to 60 mg per day, is the most cost-effective treatment.

- One high quality study concluded that amitriptyline is less cost effective than duloxetine, but has similar cost effectiveness to pregabalin at a WTP between £20,000 and £30,000 per QALY gained.

- One high quality study concluded that pregabalin is less cost effective than duloxetine, but has similar cost effectiveness to amitriptyline at a WTP between £20,000 and £30,000 per QALY gained.

For patients with painful diabetic neuropathy or post-herpetic neuralgia:

- There is strong evidence that pregabalin is more cost-effective than gabapentin
2.3 Evidence reviews

2.3.1 Antidepressants as monotherapy for neuropathic pain

Fifteen antidepressants (nine TCAs, four SSRIs and two SNRIs) were included in this review (see table 2) and a total of 2781 studies were retrieved by the systematic searches. From the 2781 studies, 23 randomised placebo-controlled trials on antidepressants were included, based on the inclusion and exclusion criteria suggested by the GDG through two short questionnaires.

No placebo-controlled studies on lofepramine, trimipramine, dosulepin (dothiepin), doxepin or SSRIs (citalopram, fluoxetine, paroxetine and sertraline) that were identified met the inclusion and exclusion criteria. The characteristics of the 23 included studies are summarised in table 6 (for detailed full evidence tables, see appendix 10.10):

### Primary outcomes

**Table 11 GRADE profiles – TCAs as monotherapy for neuropathic pain**

| TCAs (as monotherapy – placebo-controlled trials) for neuropathic pain | No. of studies | Design | Treatment | Placebo | Relative risk (95% CI) [ARR, 95% CI] | Limitations | Inconsistency | Indirectness | Imprecision | Other consideration | Quality |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **PRIMARY Outcome: Patient-reported 30% pain reduction** | 2 (Ami: 1, 2) | RCT | 33/55 (60.0%) | 13/55 (23.8%) | 2.54 (1.51, 4.28) | ARR = 36.4% NNTB = 2.8 (1.9, 5.5) | N | N | N | S (b) | N | Moderate |
| **PRIMARY Outcome: Patient-reported global improvement/impression of change** | 9 (5xAmi: 2 – 6) (1xNort: 13) (2xDesi: 11, 12) (1xImi: 14) | RCT | 123/248 (49.6%) | 58/245 (23.7%) | 2.47 (1.39, 4.41) | ARR = 25.9% NNTB = 3.9 (2.9, 5.7) | N | N | N | S (c) | N | Moderate |

For the full search strategies, see appendix 10.7; for the two GDG short questionnaires on inclusion and exclusion criteria, see appendix 10.3; for the full review protocol, see appendix 10.2; for study selection flowcharts and list of excluded studies, see appendix 10.4.

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## PRIMARY Outcome: Dry mouth (adverse effects)

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Treatment</th>
<th>Control</th>
<th>Pain reduction</th>
<th>ARI</th>
<th>NNTH</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>RCT</td>
<td>Ami: 2, 3, 8 – 10</td>
<td>Nort: 13</td>
<td>15.2% (4.3, 13.9)</td>
<td>N</td>
<td>N</td>
<td>S</td>
</tr>
<tr>
<td>2</td>
<td>RCT</td>
<td>Ami: 2, 3</td>
<td>Desi: 11, 12</td>
<td>15.2% (4.3, 13.9)</td>
<td>N</td>
<td>N</td>
<td>S</td>
</tr>
<tr>
<td>3</td>
<td>RCT</td>
<td>Ami: 2</td>
<td>Desi: 11, 12</td>
<td>15.2% (4.3, 13.9)</td>
<td>N</td>
<td>N</td>
<td>S</td>
</tr>
</tbody>
</table>

**Note:** No study reported the primary outcome of 'at least 50% pain reduction'.

1. N = No serious; S = Serious; VS = Very serious
2. Ami = amitriptyline; Nort = nortriptyline; Desi = desipramine; Imi = imipramine; N/A = not applicable.
3. Categorical scales for patient-reported global improvement/impression of change were dichotomised for analysis. For examples, ‘at least moderate improvement’ on a 6-item scale, ‘at least good improvement’ on a 5-item scale or ‘much or very much improved’ on the patients’ global impression of change (PGIC) scale were the cut-offs for dichotomisation.
4. Total number of events (positive outcomes) less than 300.
5. Total number of events (positive outcomes) less than 300 owing to small study sample.
6. GDG consensus: Total number of adverse effects less than 100, downgrade quality by 2 levels.
7. GDG consensus: Total number of adverse effects less than 300, downgrade 1 level.
15. Kalso (1995)
3. **GRADE profiles – SSRIs as monotherapy for neuropathic pain**

None of the placebo-controlled studies on SSRIs (citalopram, fluoxetine, paroxetine and sertraline) that were identified met the inclusion and exclusion criteria.

7. **Table 12 GRADE profiles – SNRIs as monotherapy for neuropathic pain**

<table>
<thead>
<tr>
<th>SNRIs (as monotherapy – placebo-controlled trials)</th>
<th><strong>for neuropathic pain</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No. of studies</strong></td>
<td><strong>Design</strong></td>
</tr>
<tr>
<td>PRIMARY Outcome: Patient-reported 30% pain reduction</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>RCT</td>
</tr>
<tr>
<td>PRIMARY Outcome: Patient-reported 50% pain reduction</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>RCT</td>
</tr>
<tr>
<td>PRIMARY Outcome: Patient-reported global improvement/impression of changea</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>RCT</td>
</tr>
<tr>
<td><strong>No. of studies</strong></td>
<td><strong>Design</strong></td>
</tr>
<tr>
<td>PRIMARY Outcome: No. of withdrawals owing to adverse effects</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>RCT</td>
</tr>
<tr>
<td>PRIMARY Outcome: Dry mouth (adverse effects)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>RCT</td>
</tr>
<tr>
<td>PRIMARY Outcome: Blurred vision (adverse effects)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>RCT</td>
</tr>
<tr>
<td>PRIMARY Outcome: Dizziness (adverse effects)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>RCT</td>
</tr>
<tr>
<td>PRIMARY Outcome: Vomiting (adverse effects)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>RCT</td>
</tr>
<tr>
<td>PRIMARY Outcome: gastrointestinal disturbances (adverse effects)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>RCT</td>
</tr>
</tbody>
</table>

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(1xDulo: 3)(1xVen: 5)(8.1%)(3.5%)ARI = 4.6%NNTH = N/A(f)

<table>
<thead>
<tr>
<th>PRIMARY Outcome: Any adverse effects: non-specified</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>4</td>
</tr>
<tr>
<td>5</td>
</tr>
<tr>
<td>6</td>
</tr>
<tr>
<td>7</td>
</tr>
<tr>
<td>8</td>
</tr>
</tbody>
</table>

Goldstein (2005)
Raskin (2005)
Wernicke (2006)
Rowbotham (2004)
Sindrup (2003)
Yucel (2005)
Forsell (2004)
Tasmuth (2002)

Other reported pain outcomes

Table 13 GRADE profiles – antidepressants for neuropathic pain

<table>
<thead>
<tr>
<th>Antidepressants (as monotherapy – placebo-controlled trials) for neuropathic pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of studies</td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>OTHER REPORTED PAIN OUTCOME: Pain intensity (Scale: VASpi-10cm)</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>OTHER REPORTED PAIN OUTCOME: Pain relief (Scale: NRS 11-point)</td>
</tr>
<tr>
<td>1</td>
</tr>
</tbody>
</table>

N = No serious; S = Serious; VS = Very serious
AMI = amitriptyline; SCI = spinal cord injury; AtyFacial = atypical facial pain; PHN = post-herpetic neuralgia; Phan LP = phantom limb pain; VASpi = visual analogue scale for pain intensity; NRS = numerical rating scale; NR = not reported.
2.3.2 Anticonvulsants as monotherapy for neuropathic pain

Eight anticonvulsants were included in this review (see table 2) and a total of 4757 studies were retrieved by the systematic searches. A total of 46 randomised placebo-controlled trials on anticonvulsants were included from the retrieved 4757 studies, based on the inclusion and exclusion criteria. None of the placebo-controlled studies identified on phenytoin met the inclusion and exclusion criteria. The characteristics of the 46 included studies are summarised in table 7 (for detailed full evidence tables, see appendix 10.10). Meta-analysis was carried out for individual anticonvulsants (gabapentin, pregabalin, lamotrigine, oxcarbazepine, topiramate, carbamazepine and sodium valproate) for primary outcomes and specific adverse effects. See section 2.1.1 for details of the analysis and synthesis of outcomes.

### Primary outcomes

**Table 14 GRADE profiles – gabapentin as monotherapy for neuropathic pain**

<table>
<thead>
<tr>
<th>No. of studies</th>
<th>Design</th>
<th>Treatment</th>
<th>Placebo</th>
<th>Relative risk (95% CI)</th>
<th>Limitations</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other consideration</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRIMARY Outcome: Patient-reported 30% pain reduction</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (SCI: 1)</td>
<td>RCT</td>
<td>5/22 (22.7%)</td>
<td>6/22 (27.3%)</td>
<td>0.83 (0.30, 2.33)</td>
<td>ARR = 4.6%</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>S (b)</td>
<td>N</td>
</tr>
<tr>
<td>PRIMARY Outcome: Patient-reported 50% pain reduction</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 (PHN: 2) (MixNP: 3)</td>
<td>RCT</td>
<td>91/331 (27.5%)</td>
<td>34/246 (13.8%)</td>
<td>1.91 (1.32, 2.76)</td>
<td>ARR = 13.7%</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>S (d)</td>
<td>N</td>
</tr>
</tbody>
</table>

---

8 For the full search strategies, see appendix 10.7; for the two GDG short questionnaires on inclusion and exclusion criteria, see appendix 10.3; for the full review protocol, see appendix 10.2; for study selection flowcharts and list of excluded studies, see appendix 10.4.
### PRIMARY Outcome: Patient-reported global improvement/impression of change

<table>
<thead>
<tr>
<th>No. of studies</th>
<th>Design</th>
<th>Treatment</th>
<th>Placebo</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>7 (2xPDN: 4, 5) (2xPHN: 2, 6) (NerP: 8) (MixNP: 3) (PhanLP: 7)</td>
<td>RCT</td>
<td>287/668 (43.0%)</td>
<td>111/569 (19.5%)</td>
<td>2.18 (1.81, 2.63) ARR = 23.5% NNTB = 4.2 (3.5, 5.4)</td>
</tr>
</tbody>
</table>

#### Limitations
- Inconsistency
- Imprecision

#### Quality
- High

### PRIMARY Outcome: No. of withdrawals owing to adverse effects

<table>
<thead>
<tr>
<th>No. of studies</th>
<th>Design</th>
<th>Treatment</th>
<th>Placebo</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>9 (2xPDN: 4, 5) (2xPHN: 2, 6) (NerP: 8) (MixNP: 3) (PhanLP: 13) (HIV: 11) (SCI: 1)</td>
<td>RCT</td>
<td>141/781 (18.1%)</td>
<td>66/676 (9.8%)</td>
<td>1.53 (1.17, 2.00) ARI = 8.3% NNT = 12.1 (8.5, 21.0)</td>
</tr>
</tbody>
</table>

#### Limitations
- Inconsistency
- Imprecision

#### Quality
- Moderate

### PRIMARY Outcome: Dizziness (adverse effects)

<table>
<thead>
<tr>
<th>No. of studies</th>
<th>Design</th>
<th>Treatment</th>
<th>Placebo</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>8 (2xPDN: 4, 5) (PhanLP: 9) (NerP: 8) (HIV: 11) (CanP: 12) (PHN: 2) (MixNP: 3)</td>
<td>RCT</td>
<td>187/732 (25.5%)</td>
<td>44/610 (7.2%)</td>
<td>3.04 (2.22, 4.17) ARI = 18.3% NNT = 5.5 (4.5, 6.9)</td>
</tr>
</tbody>
</table>

#### Limitations
- Inconsistency
- Indirectness

#### Quality
- Moderate

### PRIMARY Outcome: Somnolence (adverse effects)

<table>
<thead>
<tr>
<th>No. of studies</th>
<th>Design</th>
<th>Treatment</th>
<th>Placebo</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 (2xPDN: 4, 5) (PhanLP: 9) (HIV: 11) (PHN: 2) (MixNP: 3)</td>
<td>RCT</td>
<td>108/521 (20.7%)</td>
<td>25/401 (6.2%)</td>
<td>3.30 (2.18, 4.99) ARI = 14.5% NNT = 6.9 (5.3, 9.7)</td>
</tr>
</tbody>
</table>

#### Limitations
- Inconsistency
- Indirectness

#### Quality
- Moderate

### PRIMARY Outcome: Sedation (adverse effects)

<table>
<thead>
<tr>
<th>No. of studies</th>
<th>Design</th>
<th>Treatment</th>
<th>Placebo</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (SCI: 10)</td>
<td>RCT</td>
<td>0/20 (0.0%)</td>
<td>1/20 (5.0%)</td>
<td>0.33 (0.01, 7.72) ARI = −5.0% NNT = N/A</td>
</tr>
</tbody>
</table>

#### Limitations
- Indirectness

#### Quality
- Very low

### PRIMARY Outcome: Fatigue (adverse effects)

<table>
<thead>
<tr>
<th>No. of studies</th>
<th>Design</th>
<th>Treatment</th>
<th>Placebo</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 (NerP: 8) (CanP: 12)</td>
<td>RCT</td>
<td>32/211 (15.2%)</td>
<td>19/209 (9.1%)</td>
<td>1.68 (1.00, 2.82) ARI = 6.1% NNT = 16.5 (8.1, ∞)</td>
</tr>
</tbody>
</table>

#### Limitations
- Indirectness

#### Quality
- Low

### PRIMARY Outcome: Gait disturbances (adverse effects)

<table>
<thead>
<tr>
<th>No. of studies</th>
<th>Design</th>
<th>Treatment</th>
<th>Placebo</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (HIV: 11)</td>
<td>RCT</td>
<td>7/15 (46.7%)</td>
<td>3/11 (27.3%)</td>
<td>1.71 (0.57, 5.17) ARI = 19.4% NNT = N/A</td>
</tr>
</tbody>
</table>

#### Limitations
- Indirectness

#### Quality
- Very low

### PRIMARY Outcome: Any adverse effects: non-specified

<table>
<thead>
<tr>
<th>No. of studies</th>
<th>Design</th>
<th>Treatment</th>
<th>Placebo</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 (2xPHN: 2, 6) (SCI: 10) (PhanLP: 13) (MixNP: 3)</td>
<td>RCT</td>
<td>302/532 (56.8%)</td>
<td>132/422 (31.3%)</td>
<td>1.80 (1.50, 2.17) ARI = 25.5% NNT = 3.9 (3.2, 5.2)</td>
</tr>
</tbody>
</table>

#### Limitations
- Inconsistency
- Indirectness

#### Quality
- High

---

1. **N** = No serious; **S** = Serious; **VS** = Very serious
2. **N/A** = not applicable; **PDN** = painful diabetic neuropathy; **PHN** = post-herpetic neuralgia; **SCI** = spinal cord injury; **MixNP** = mixed neuropathic pain; **NerP** = nerve pain; **PhanLP** = phantom limb pain; **HIV** = HIV related neuropathy; **CanP** = cancer pain.
3. Categorical scales for patient-reported global improvement/impression of change were dichotomised for analysis. For examples, ‘at least moderate improvement’ on a 6-item scale, ‘at least good improvement’ on a 9-item scale.

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improvement’ on a 5-item scale or ‘much or very much improved’ on the patients’ global impression of change (PGIC) scale were the cut-offs for dichotomisation.

Total number of events (positive outcomes) less than 300 owing to small study sample.

Gait disturbances: outcome that needs specific consideration in relation to older people (> 65 years old) to prevent falls.

Total number of events (positive outcomes) less than 300.

GDG consensus: Total number of adverse effects less than 300, downgrade quality by 1 level.

GDG consensus: Total number of adverse effects less than 100, downgrade quality by 2 levels.

GDG consensus: if there is only one study with total number of adverse effects less than 100, the GDG decided that the quality should be graded as ‘very low’.

Rintala (2007)

Rice (2001)

Serpell (2002)

Backonja (1998)

Simpson (2001)

Rowbotham (1998)

Smith (2005)

Gordh (2008)

Bone (2002)

Levendoglu (2004)


Rao (2007)

Nikolajsen (2006)

Table 15 GRADE profiles – pregabalin as monotherapy for neuropathic pain

<table>
<thead>
<tr>
<th>No. of studies</th>
<th>Design</th>
<th>Treatment</th>
<th>Placebo</th>
<th>Relative risk (95% CI) [ARR] [NNTB, 95% CI]</th>
<th>Limitations</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other consideration</th>
<th>Quality</th>
</tr>
</thead>
</table>
| **PRIMARY Outcome: Patient-reported 30% pain reduction**
| 6 (3xPHN: 2–4) (PDN/PHN: 5) (PDN: 1) (SCI: 6) | RCT | 554/955 (58.0%) | 126/462 (27.3) | 2.08 (1.78, 2.44) ARR = 30.7% NNTB = 3.2 (2.8, 3.9) | N N N N N | High |
| **PRIMARY Outcome: Patient-reported 50% pain reduction**
| 10 (4xPHN: 2–4, 10) (4xPDN: 1, 7–9) (PDN/PHN: 5) (SCI: 6) | RCT | 612/1577 (38.8%) | 129/769 (16.8%) | 2.23 (1.89, 2.64) ARR = 22.0% NNTB = 4.6 (3.9, 5.5) | N N N N N | High |
| **PRIMARY Outcome: Patient-reported global improvement/impression of change**
| 5 (2xPHN: 4, 10) (2xPDN: 1, 9) (PDN/PHN: 5) | RCT | 459/1009 (45.5%) | 90/379 (23.7%) | 1.90 (1.57, 2.30) ARR = 21.8% NNTB = 4.6 (3.7, 6.1) | N N N N N | High |
| **No. of studies** | **Design** | **Treatment** | **Placebo** | **Relative risk (95% CI) [ARI] [NNTH, 95% CI]** | **Limitations** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other consideration** | **Quality** |
| 12 (4xPHN: 2–4, 10) (5xPDN: 1, 7–9, 12) (PDN/PHN: 5) | RCT | 259/1921 (13.5%) | 57/933 (6.1%) | 2.34 (1.76, 3.10) ARI = 7.4% NNTH = 13.6 (10.6, 19.5) | N N N N N | High |

Neuropathic pain: NICE clinical guideline DRAFT (October 2009)
### PRIMARY Outcome: Dizziness (adverse effects)

<table>
<thead>
<tr>
<th>N</th>
<th>(4xPHN: 2–4,10)</th>
<th>(5xPDN: 1, 7–9, 12)</th>
<th>(PDN/PHN: 5)</th>
<th>SCI: 6)</th>
<th>(CenP: 11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>RCT</td>
<td>444/1886</td>
<td>74/933</td>
<td>4.05 (2.18, 4.26)</td>
<td>N</td>
</tr>
</tbody>
</table>

### PRIMARY Outcome: Somnolence (adverse effects)

<table>
<thead>
<tr>
<th>N</th>
<th>(4xPHN: 2–4,10)</th>
<th>(5xPDN: 1, 7–9, 12)</th>
<th>(PDN/PHN: 5)</th>
<th>SCI: 6)</th>
<th>(CenP: 11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>RCT</td>
<td>298/1886</td>
<td>48/933</td>
<td>3.63 (2.69, 4.90)</td>
<td>N</td>
</tr>
</tbody>
</table>

### PRIMARY Outcome: Fatigue (adverse effects)

<table>
<thead>
<tr>
<th>N</th>
<th>(PHN: 3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>RCT</td>
</tr>
</tbody>
</table>

### PRIMARY Outcome: Weight gain (adverse effects)

<table>
<thead>
<tr>
<th>N</th>
<th>(3xPDN: 7,9,12)</th>
<th>(PHN: 3)</th>
<th>(PDN/PHN: 5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>RCT</td>
<td>82/959</td>
<td>3/421</td>
</tr>
</tbody>
</table>

### PRIMARY Outcome: Gait disturbances (adverse effects)

<table>
<thead>
<tr>
<th>N</th>
<th>(3xPHN: 2–4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>RCT</td>
</tr>
</tbody>
</table>

### PRIMARY Outcome: Any adverse effects: non-specified

<table>
<thead>
<tr>
<th>N</th>
<th>(2xPHN: 2, 3)</th>
<th>(PDN: 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>RCT</td>
<td>245/344</td>
</tr>
</tbody>
</table>

---

1 N = No serious; S = Serious; VS = Very serious
2 N/A = not applicable; PDN = painful diabetic neuropathy; PHN = post-herpetic neuralgia; SCI
3 = spinal cord injury; CenP = central pain
4 Categorical scales for patient-reported global improvement/impression of change were dichotomised for analysis. For examples, 'at least moderate improvement' on a 6-item scale, 'at least good improvement' on a 5-item scale or 'much or very much improved' on the patients' global impression of change (PGIC) scale were the cut-offs for dichotomisation.
5 Gait disturbances: outcome that needs specific consideration in relation to older people (> 65 years old) to prevent falls.
6 GDG consensus: if there is only 1 study with total number of adverse effects less than 100, the GDG decided that the quality should be graded as 'very low'.
7 GDG consensus: Total number of adverse effects less than 100, downgrade 2 levels.
8 GDG consensus: Total number of adverse effects less than 300, downgrade 1 level.
9 Freynhagen (2005)
10 Siddall (2006)
11 Richter (2005)
13 Tolle (2009)
14 Sabatowski (2004)
15 Vranken (2008)
16 Arezzo (2008)
Table 16 GRADE profiles – lamotrigine as monotherapy for neuropathic pain

| LAMOTRIGINE (as monotherapy – placebo-controlled trials) for neuropathic pain |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| No. of studies | Design | Treatment | Placebo | Relative risk (95% CI) | Limitations | Indirectness | Imprecision | Other consideration | Quality |
| PRIMARY Outcome: Patient-reported 30% pain reduction |
| 3 | (2xPDN: 1) (CenP: 2) | RCT | 115/335 (34.3%) | 43/131 (32.8%) | 1.04 (0.79, 1.39) ARR = 1.5% NNTB = N/A | N | N | N | S (b) | N | Moderate |
| PRIMARY Outcome: Patient-reported 50% pain reduction |
| 3 | (3xPDN: 1, 3) | RCT | 92/351 (26.2%) | 35/146 (24.0%) | 1.13 (0.81, 1.57) ARR = 2.2% NNTB = N/A | N | N | N | S (b) | N | Moderate |
| PRIMARY Outcome: Patient-reported global improvement/impression of change* |
| 2 | (PDN: 3) (HIV: 5) | RCT | 93/172 (54.1%) | 32/98 (32.7%) | 1.56 (1.15, 2.12) ARR = 21.4% NNTB = 4.7 (3.0, 10.9) | N | N | N | S (b) | N | Moderate |
| PRIMARY Outcome: No. of withdrawals owing to adverse effects |
| 11 | (4xPDN: 1, 3, 4) (2xHIV: 5, 6) (CenP: 2) (SCI: 7) (MixNP: 8) (CanP: 9) (PSP: 10) | RCT | 98/937 (10.5%) | 28/504 (5.6%) | 1.67 (1.12, 2.49) ARI = 4.9% NNTH = 20.4 (13.0, 47.5) | N | N | N | S (c) | N | Moderate |
| PRIMARY Outcome: Dizziness (adverse effects) |
| 5 | (3xPDN: 1, 3) (CenP: 2) (CanP: 9) | RCT | 45/637 (7.1%) | 14/277 (6.1%) | 1.21 (0.65, 2.26) ARI = 2.0% NNTH = N/A | N | N | N | VS (d) | N | Low |
| PRIMARY Outcome: Sedation (adverse effects) |
| 1 | (CenP: 2) | RCT | 1/15 (6.7%) | 0/15 (0.0%) | 3.00 (0.13, 68.26) ARI = 6.7% NNTH = N/A | N | N | N | VS (e) | N | Very low |
| PRIMARY Outcome: Fatigue (adverse effects) |
| 2 | (CenP: 2) (CanP: 9) | RCT | 4/78 (5.1%) | 4/77 (5.2%) | 0.99 (0.27, 3.68) ARI = −0.1% NNTH = N/A | N | N | N | VS (d) | N | Low |
| PRIMARY Outcome: Any adverse effects: non-specified |
| 5 | (3xPDN: 1, 3) (SCI: 7) (PSP: 10) | RCT | 446/617 (72.3%) | 158/258 (61.2%) | 1.07 (0.86, 1.33) ARI = 11.1% NNTH = N/A | N | N | N | N | N | High |

N = No serious; S = Serious; VS = Very serious
N/A = not applicable; PDN = painful diabetic neuropathy; PHN = post-herpetic neuralgia; SCI = spinal cord injury; MixNP = mixed neuropathic pain; CenP = central pain; PSP = post stroke pain; HIV = HIV related neuropathy; CanP = cancer pain.
* Categorical scales for patient-reported global improvement/impression of change were dichotomised for analysis. For examples, ‘at least moderate improvement’ on a 6-item scale, ‘at least good neuropathic pain: NICE clinical guideline DRAFT (October 2009) Page 55 of 136
improvement’ on a 5-item scale or ‘much or very much improved’ on the patients’ global impression of change (PGIC) scale were the cut-offs for dichotomisation.

Total number of events (positive outcomes) less than 300.

GDG consensus: Total number of adverse effects less than 300, downgrade quality by 1 level.

GDG consensus: Total number of adverse effects less than 100, downgrade quality by 2 levels.

GDG consensus: if there is only 1 study with total number of adverse effects less than 100, the GDG decided that the quality should be graded as ‘very low’.

1 Vinik (2007a, 2007b)
2 Breuer (2007)
3 Eisenberg (2001)
4 Luria (2000)
6 Simpson (2000)
7 Finnerup (2002)
8 McCleane (1999)
9 Rao (2008)
10 Vestergaard (2001)

Table 17 GRADE profiles – oxcarbazepine as monotherapy for neuropathic pain

**OXCARBAZEPINE (as monotherapy – placebo-controlled trials) for neuropathic pain**

<table>
<thead>
<tr>
<th>No. of studies</th>
<th>Design</th>
<th>Treatment</th>
<th>Placebo</th>
<th>Relative risk (95% CI)</th>
<th>Limitations</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other consideration</th>
<th>Quality</th>
</tr>
</thead>
</table>
| **PRIMARY Outcome: Patient-reported 30% pain reduction**
1 (PDN: 2) RCT | 31/69 (44.9%) | 22/77 (28.6%) | 1.57 (1.01, 2.44) | ARR = 16.3%, NNTB = 6.1 (3.2, 147.4) | N | N | N | S (b) | N | Moderate |
| **PRIMARY Outcome: Patient-reported 50% pain reduction**
1 (PDN: 2) RCT | 24/69 (34.8%) | 14/77 (18.2%) | 1.91 (1.08, 3.39) | ARR = 16.6%, NNTB = 6.0 (3.3, 43.2) | N | N | N | S (b) | N | Moderate |
| **PRIMARY Outcome: Patient-reported global improvement/impression of change**
2 (PDN: 1, 2) RCT | 97/229 (42.4%) | 52/149 (34.9%) | 1.16 (0.90, 1.49) | ARR = 7.5%, NNTB = N/A | N | N | N | S (b) | N | Moderate |
| **No. of studies** | **Design** | **Treatment** | **Placebo** | **Relative risk (95% CI)** | **Limitations** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other consideration** | **Quality** |
| **PRIMARY Outcome: No. of withdrawals owing to adverse effects**
3 (PDN: 1–3) RCT | 102/398 (25.6%) | 16/236 (6.8%) | 3.83 (2.29, 6.40) | ARR = 18.8%, NNTB = 5.3 (4.1, 7.4) | N | N | N | S (c) | N | Moderate |
| **PRIMARY Outcome: Dizziness (adverse effects)**
2 (PDN: 1, 2) RCT | 58/310 (18.7%) | 3/159 (1.9%) | 8.90 (2.81, 28.24) | ARR = 16.8%, NNTB = 5.9 (4.6, 8.3) | N | N | N | VS (d) | N | Low |
| **PRIMARY Outcome: Somnolence (adverse effects)**
2 (PDN: 1, 2) RCT | 21/310 (6.8%) | 3/159 (1.9%) | 2.95 (1.04, 8.35) | ARR = 4.9%, NNTB = 20.5 (11.9, 72.4) | N | N | N | VS (d) | N | Low |
| **PRIMARY Outcome: Fatigue (adverse effects)**
2 (PDN: 1, 2) RCT | 31/310 (10.0%) | 7/159 (4.4%) | 1.83 (0.83, 4.00) | ARR = 6.6% | N | N | N | VS (d) | N | Low |
Table 18 GRADE profiles – topiramate as monotherapy for neuropathic pain

<table>
<thead>
<tr>
<th>TOPIRAMATE (as monotherapy – placebo-controlled trials) for neuropathic pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of studies</td>
</tr>
<tr>
<td>PRIMARY Outcome: Patient-reported 30% pain reduction</td>
</tr>
<tr>
<td>1 (PDN: 1) RCT</td>
</tr>
<tr>
<td>PRIMARY Outcome: Patient-reported 50% pain reduction</td>
</tr>
<tr>
<td>1 (PDN: 1) RCT</td>
</tr>
<tr>
<td>PRIMARY Outcome: Patient-reported global improvement/impression of change</td>
</tr>
<tr>
<td>2 (PDN: 1) (Radi: 3) RCT</td>
</tr>
<tr>
<td>PRIMARY Outcome: No. of withdrawals owing to adverse effects</td>
</tr>
<tr>
<td>3 (2xPDN: 1,3) (Radi: 2) RCT</td>
</tr>
<tr>
<td>PRIMARY Outcome: Dizziness (adverse effects)</td>
</tr>
<tr>
<td>1 (PDN: 1) RCT</td>
</tr>
<tr>
<td>PRIMARY Outcome: Somnolence (adverse effects)</td>
</tr>
<tr>
<td>2 (2xPDN: 1,3) RCT</td>
</tr>
<tr>
<td>PRIMARY Outcome: Sedation (adverse effects)</td>
</tr>
<tr>
<td>1 (Radi: 2) RCT</td>
</tr>
<tr>
<td>PRIMARY Outcome: Fatigue (adverse effects)</td>
</tr>
<tr>
<td>3 RCT</td>
</tr>
</tbody>
</table>
Table 19 GRADE profiles – carbamazepine as monotherapy for neuropathic pain

| CARBAMAZEPINE (as monotherapy – placebo-controlled trials) for neuropathic pain |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| PRIMARY Outcome: Patient-reported global improvement/impression of change
<table>
<thead>
<tr>
<th>No. of studies</th>
<th>Design</th>
<th>Treatment</th>
<th>Placebo</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>(PSP: 1) (MixNP: 2)</td>
<td>RCT</td>
<td>20/34 (58.8%)</td>
<td>7/22 (31.8%)</td>
</tr>
</tbody>
</table>

ARR = 27.0%
NNTB = N/A

Limitations: Indirectness

Quality: Moderate

<p>| PRIMARY Outcome: Any adverse effects: non-specified |</p>
<table>
<thead>
<tr>
<th>No. of studies</th>
<th>Design</th>
<th>Treatment</th>
<th>Placebo</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(PSP: 1)</td>
<td>RCT</td>
<td>13/15 (86.7%)</td>
<td>7/15 (46.7%)</td>
</tr>
</tbody>
</table>

ARR = 40.0%
NNTB = 2.5 (1.4, 10.6)

Limitations: Indirectness

Quality: Very low

---

1 N = No serious; S = Serious; VS = Very serious
2 N/A = not applicable; PDN = painful diabetic neuropathy; Radi = radiculopathy
3 a Categorical scales for patient-reported global improvement/impression of change were dichotomised for analysis. For example, 'at least moderate improvement' on a 6-item scale, 'at least good improvement' on a 5-item scale or 'much or very much improved' on the patients' global impression of change (PGIC) scale were the cut-offs for dichotomisation.
4 b Total number of events (positive outcomes) less than 300.
5 c GDG consensus: if there is only 1 study with total number of adverse effects less than 100, the GDG decided that the quality should be graded as 'very low'.
6 d GDG consensus: Total number of adverse effects less than 300, downgrade 1 level.
7 1 Raskin (2004)
8 2 Khoromi (2005)
9 3 Thienel (2004)
**Table 20 GRADE profiles – sodium valproate as monotherapy for neuropathic pain**

No study on sodium valproate that reported the primary outcomes on pain met the inclusion and exclusion criteria.

<table>
<thead>
<tr>
<th>SODIUM VALPROATE (as monotherapy – placebo-controlled trials) for neuropathic pain</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No. of studies</strong></td>
</tr>
<tr>
<td>PRIMARY Outcome: No. of withdrawals owing to adverse effects</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>PRIMARY Outcome: Any adverse effects: non-specified</td>
</tr>
<tr>
<td>1</td>
</tr>
</tbody>
</table>

N = No serious; S = Serious; VS = Very serious
N/A = not applicable; PDN = painful diabetic neuropathy

* Total number of adverse effects less than 100.
* GDG consensus: if there is only 1 study with total number of adverse effects less than 100, the GDG decided that the quality should be graded as ‘very low’.

1 Agrawal (2009)
2 Kochar (2002)
3 Kochar (2004)

**Other reported pain outcomes**

**Table 21 GRADE profiles – anticonvulsants for neuropathic pain**

<table>
<thead>
<tr>
<th>ANTICONVULSANTS (as monotherapy – placebo-controlled trials) for neuropathic pain</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No. of studies</strong></td>
</tr>
<tr>
<td>OTHER REPORTED PAIN OUTCOME: Pain intensity (Scale: VASpi-10cm)</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>OTHER REPORTED PAIN OUTCOME: Pain intensity (Scale: NRS 11-point)</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>OTHER REPORTED PAIN OUTCOME: Pain relief (Scale: VASpr-100mm)</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>OTHER REPORTED PAIN OUTCOME: Percentage pain relief (NPS)</td>
</tr>
</tbody>
</table>

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2.3.3 Opioid analgesics as monotherapy for neuropathic pain

Nine opioid analgesics were included in this review (see table 2). A total of 9612 studies were retrieved by the systematic searches, and eight randomised placebo-controlled trials were included based on the inclusion and exclusion criteria. None of the placebo-controlled studies identified on co-codamol, co-dydramol, dihydrocodeine, buprenorphine, fentanyl or codeine phosphate met the inclusion and exclusion criteria. The eight studies that were included were on morphine, tramadol and oxycodone for adult patients with neuropathic pain. The characteristics of the eight included studies on opioid analgesics are summarised in table 8 (for detailed full evidence tables, see appendix 10.10). Meta-analysis was carried out for individual opioid analgesics (morphine, tramadol and oxycodone) for primary outcomes and adverse effects if there were sufficient data. See section 2.1.1 for details of the analysis and synthesis of outcomes.

---

For the full search strategies, see appendix 10.7; for the two GDG short questionnaires on inclusion and exclusion criteria, see appendix 10.3; for the full review protocol, see appendix 10.2; for study selection flowcharts and list of excluded studies, see appendix 10.4.

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## Table 22 GRADE profiles – morphine as monotherapy for neuropathic pain

<table>
<thead>
<tr>
<th>No. of studies</th>
<th>Design</th>
<th>Treatment</th>
<th>Placebo</th>
<th>Relative risk (95% CI) [ARR, 95% CI]</th>
<th>Limitations</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other consideration</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PRIMARY OUTCOME: Patient-reported 30% pain reduction</strong>&lt;sup&gt;1&lt;/sup&gt;</td>
<td>1 (Phan LP: 1)</td>
<td>RCT</td>
<td>33/50 (66.0%)</td>
<td>19/43 (44.2%)</td>
<td>1.49 (1.01, 2.21)</td>
<td>ARR = 21.8%</td>
<td>NNTB = 4.6 (2.5, 68.3)</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td><strong>PRIMARY OUTCOME: Patient-reported 50% pain reduction</strong>&lt;sup&gt;2&lt;/sup&gt;</td>
<td>2 (Phan LP: 1, 2)</td>
<td>RCT</td>
<td>28/62 (45.2%)</td>
<td>14/55 (25.5%)</td>
<td>1.75 (1.04, 2.96)</td>
<td>ARR = 19.7%</td>
<td>NNTB = 5.1 (2.8, 44.5)</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td><strong>PRIMARY OUTCOME: Patient-reported global improvement/impression of change”</strong>&lt;sup&gt;3&lt;/sup&gt;</td>
<td>1 (radicul: 3)</td>
<td>RCT</td>
<td>13/32 (40.6%)</td>
<td>11/33 (33.3%)</td>
<td>1.22 (0.64, 2.31)</td>
<td></td>
<td></td>
<td></td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td><strong>PRIMARY OUTCOME: Withdrawals owing to adverse effects</strong>&lt;sup&gt;4&lt;/sup&gt;</td>
<td>1 (radicul: 3)</td>
<td>RCT</td>
<td>9/55 (16.4%)</td>
<td>1/55 (1.8%)</td>
<td>9.00 (1.18, 68.66)</td>
<td></td>
<td></td>
<td></td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td><strong>PRIMARY OUTCOME: Constipation (adverse effects)”</strong>&lt;sup&gt;5&lt;/sup&gt;</td>
<td>2 (radicul: 3)</td>
<td>RCT</td>
<td>35/78 (44.9%)</td>
<td>4/71 (5.6%)</td>
<td>8.12 (3.05, 21.61)</td>
<td></td>
<td></td>
<td></td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td><strong>PRIMARY OUTCOME: Somnolence/drowsiness (adverse effects)”</strong>&lt;sup&gt;5&lt;/sup&gt;</td>
<td>2 (radicul: 3)</td>
<td>RCT</td>
<td>16/78 (20.5%)</td>
<td>4/71 (5.6%)</td>
<td>3.39 (1.17, 9.76)</td>
<td></td>
<td></td>
<td></td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td><strong>PRIMARY OUTCOME: Nausea (adverse effects)”</strong>&lt;sup&gt;5&lt;/sup&gt;</td>
<td>2 (radicul: 3)</td>
<td>RCT</td>
<td>6/78 (7.7%)</td>
<td>1/71 (1.4%)</td>
<td>3.94 (0.69, 22.46)</td>
<td></td>
<td></td>
<td></td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td><strong>PRIMARY OUTCOME: Dizziness (adverse effects)”</strong>&lt;sup&gt;5&lt;/sup&gt;</td>
<td>2 (radicul: 3)</td>
<td>RCT</td>
<td>6/78 (7.7%)</td>
<td>3/71 (4.2%)</td>
<td>1.86 (0.49, 7.04)</td>
<td></td>
<td></td>
<td></td>
<td>N</td>
<td>N</td>
</tr>
</tbody>
</table>

N = No serious; S = Serious; VS = Very serious

Phan LP = phantom limb pain; radicul = radiculopathy; N/A = not applicable.

Categorical scales for patient-reported global improvement/impression of change were dichotomised for analysis. For examples, ‘at least moderate improvement’ on a 6-item scale, ‘at least good improvement’ on a 5-item scale or ‘much or very much improved’ on the patients’ global impression of change (PGIC) scale were the cut-offs for dichotomisation.

Total number of events < 300 owing to small study sample.

GDG consensus: for adverse effects: serious (downgrade 1) if total events < 300; very serious (downgrade quality by 2 levels) if total events < 100.

GDG consensus: if there is only 1 study with total number of adverse effects less than 100, the GDG decided that the quality should be graded as ‘very low’.

Wu (2008)

Huse (2001)
Table 23 GRADE profiles – tramadol as monotherapy for neuropathic pain

| TRAMADOL (as monotherapy – placebo-controlled trials) for neuropathic pain |
|---|---|---|---|---|---|---|---|---|---|
| **No. of studies** | **Design** | **Treatment** | **Placebo** | **Relative risk (95% CI)** | **Limitations** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other consideration** | **Quality** |
| **PRIMARY OUTCOME: Patient-reported 50% pain reduction** |  
1 (PHN: 1) | RCT | 41/53 (77.4%) | 31/55 (56.4%) | 1.37 (1.04, 1.81) | ARR = 21.0% | NNTB = 4.8 (2.7, 31.5) | N | N | N | S (a) | N | Moderate |
| **No. of studies** | **Design** | **Treatment** | **Placebo** | **Relative risk (95% CI)** | **Limitations** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other consideration** | **Quality** |
| **PRIMARY OUTCOME: Withdrawals owing to adverse effects** |  
3 (NPCan: 2) (PDN: 4) (Polyneu: 3) | RCT | 19/128 (14.8%) | 3/129 (2.3%) | 5.60 (1.85, 17.00) | ARI = 12.5% | NNTH = 8.0 (5.0, 16.2) | N | N | N | VS (b) | N | Low |
| **PRIMARY OUTCOME: Constipation (adverse effects)** |  
2 (PDN: 4) (Polyneu: 3) | RCT | 24/110 (21.8%) | 4/111 (3.6%) | 6.05 (2.17, 16.86) | ARI = 18.2% | NNTH = 5.5 (3.7, 10.0) | N | N | N | VS (b) | N | Low |
| **PRIMARY OUTCOME: Somnolence/drowsiness (adverse effects)** |  
1 (PDN: 4) | RCT | 8/65 (12.3%) | 4/66 (6.1%) | 2.03 (0.64, 6.42) | ARI = 6.2% | NNH = N/A | N | N | N | VS (c) | N | Very low |
| **PRIMARY OUTCOME: Nausea (adverse effects)** |  
2 (PDN: 4) (Polyneu: 3) | RCT | 26/110 (23.6%) | 5/111 (4.5%) | 5.24 (2.09, 13.13) | ARI = 19.1% | NNTH = 5.2 (3.5, 9.5) | N | N | N | VS (b) | N | Low |
| **PRIMARY OUTCOME: Dizziness (adverse effects)** |  
2 (PDN: 4) (Polyneu: 3) | RCT | 18/110 (16.4%) | 1/111 (0.9%) | 7.42 (2.07, 26.60) | ARI = 15.5% | NNTH = 6.5 (4.2, 11.0) | N | N | N | VS (b) | N | Low |
| **PRIMARY OUTCOME: Vomiting (adverse effects)** |  
1 (PDN: 4) | RCT | 3/65 (4.6%) | 0/66 (0.0%) | 7.11 (0.37, 134.91) | ARI = 4.6% | NNTH = N/A | N | N | N | VS (c) | N | Very low |

N = No serious; S = Serious; VS = Very serious
PHN = post-herpetic neuralgia; NPCan = neuropathic cancer pain; PDN = painful diabetic neuropathy; Polyneu = polyneuropathy; N/A = not applicable.

a Total number of events < 300 owing to small study sample.

b GDG consensus: for adverse effects: serious (downgrade quality by 1 level) if total events < 300; very serious (downgrade 2) if total events < 100.

c GDG consensus: if there is only 1 study with total number of adverse effects less than 100, the GDG decided that the quality should be graded as ‘very low’.

1 Boureau (2003)
2 Arbaiza (2007)
3 Sindrup (1999)
4 Harati (1998)

Neuropathic pain: NICE clinical guideline DRAFT (October 2009)
Table 24 GRADE profiles – oxycodone as monotherapy for neuropathic pain

No study on oxycodone that reported the primary outcomes on pain met the inclusion criteria.

### OXYCODONE (as monotherapy – placebo-controlled trials) for neuropathic pain

<table>
<thead>
<tr>
<th>No. of studies</th>
<th>Design</th>
<th>Treatment</th>
<th>Placebo</th>
<th>Relative risk (95% CI) [ARI] [NNTH, 95% CI]</th>
<th>Limitations</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other consideration</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRIMARY OUTCOME: Withdrawals owing to adverse effects</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>1 (PDN: 1)</td>
<td>RCT</td>
<td>7/82 (8.5%)</td>
<td>4/77 (5.2%)</td>
<td>1.64 (0.50, 5.39) ARI = 3.3% NNTH = N/A</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>VS (a)</td>
<td>N</td>
<td>Very low</td>
</tr>
<tr>
<td>PRIMARY OUTCOME: Somnolence/drowsiness (adverse effects)</td>
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<td></td>
</tr>
<tr>
<td>1 (PDN: 1)</td>
<td>RCT</td>
<td>33/82 (40.2%)</td>
<td>1/77 (1.3%)</td>
<td>30.99 (4.34, 221.09) ARI = 38.9% NNH = 2.6 (2.0, 3.5)</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>VS (a)</td>
<td>N</td>
<td>Very low</td>
</tr>
<tr>
<td>PRIMARY OUTCOME: Nausea (adverse effects)</td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (PDN: 1)</td>
<td>RCT</td>
<td>30/82 (36.6%)</td>
<td>6/77 (7.8%)</td>
<td>4.70 (2.07, 10.65) ARI = 28.8% NNTH = 3.5 (2.5, 6.0)</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>VS (a)</td>
<td>N</td>
<td>Very low</td>
</tr>
<tr>
<td>PRIMARY OUTCOME: Dizziness (adverse effects)</td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (PDN: 1)</td>
<td>RCT</td>
<td>26/82 (31.7%)</td>
<td>8/77 (10.4%)</td>
<td>3.05 (1.47, 6.33) ARI = 21.3% NNTH = 4.7 (3.0, 11.2)</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>VS (a)</td>
<td>N</td>
<td>Very low</td>
</tr>
<tr>
<td>PRIMARY OUTCOME: Vomiting (adverse effects)</td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (PDN: 1)</td>
<td>RCT</td>
<td>17/82 (20.7%)</td>
<td>2/77 (2.6%)</td>
<td>7.98 (1.91, 33.41) ARI = 18.1% NNTH = 5.5 (3.5, 11.1)</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>VS (a)</td>
<td>N</td>
<td>Very low</td>
</tr>
</tbody>
</table>

N = No serious; S = Serious; VS = Very serious
PDN = painful diabetic neuropathy; N/A = not applicable.
GDG consensus: if there is only 1 study with total number of adverse effects less than 100, the GDG decided that the quality should be graded as ‘very low’.

1 N = No serious; S = Serious; VS = Very serious
2 PDN = painful diabetic neuropathy; N/A = not applicable.
3 GDG consensus: if there is only 1 study with total number of adverse effects less than 100, the GDG decided that the quality should be graded as ‘very low’.
4 Gimbel (2003)
Other reported pain outcomes

Table 25 GRADE profiles – opioid analgesics (overall) for neuropathic pain

| OPIOIDS (as monotherapy – placebo-controlled trials) for neuropathic pain |
|---|---|---|---|---|---|---|---|---|
| **No. of studies** | **Design** | **Treatment** | **Placebo** | **Mean (SD) at endpoint [p-value]** | **Limitations** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other consideration** | **Quality** |
| **OTHER REPORTED PAIN OUTCOME: Pain intensity (Scale: VASpi-10cm)** | | | | | | | | | | |
| 1 | (Trama) (NPcan: 1) | RCT | 18 | 18 | Treatment = 2.9 (NR) Placebo = 4.3 (NR) p < 0.001 | N | N | S (a) | S (b) | N | Low |
| 1 | (Trama) (PDN: 2) | RCT | 65 | 66 | Treatment = 1.4 (0.1) Placebo = 2.2 (0.1) p < 0.001 | N | N | S (a) | S (b) | N | Low |
| **OTHER REPORTED PAIN OUTCOME: Pain relief (Scale: NRS 11-point)** | | | | | | | | | | |
| 1 | (Trama) (Polyneu: 3) | RCT | 37 | 42 | Treatment = 4.5 (2.7) Placebo = 6.3 (2.4) p < 0.001 | N | N | S (a) | S (b) | N | Low |
| **OTHER REPORTED PAIN OUTCOME: Pain intensity (Scale: NRSpi 11-point)** | | | | | | | | | | |
| 1 | (Oxyco) (PDN: 4) | RCT | 82 | 77 | Treatment = −2.6 (2.54) Placebo = −1.5 (2.19) p < 0.001 | N | N | S (a) | S (b) | N | Low |

4 N = No serious; S = Serious; VS = Very serious
5 Trama = tramadol; NPcan = neuropathic cancer pain; PDN = painful diabetic neuropathy;
6 Polyneu = polyneuropathy; Oxyco = oxycodone; NR = Not reported
7 a Indirect outcome measure.
8 b Total number of events < 300 owing to small study sample.
9 1 Arbaiza (2007)
10 2 Harati (1998)
11 3 Sindrup (1999)

2.3.4 Topical capsaicin and topical lidocaine as monotherapy for neuropathic pain

Two topical treatments, capsaicin and lidocaine, were included in this review (see table 2). A total of 6057 studies were retrieved by the systematic searches and 14 randomised placebo-controlled trials were included based on the inclusion and exclusion criteria (nine studies for topical capsaicin and

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10 For the full search strategies, see appendix 10.7; for the two GDG short questionnaires on inclusion and exclusion criteria, see appendix 10.3; for the full review protocol, see appendix 10.2; for study selection flowcharts and list of excluded studies, see appendix 10.4.

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five studies for topical lidocaine). The characteristics of the 14 included
studies are summarised in table 9 (for detailed full evidence tables, see
appendix 10.10). Meta-analysis was carried out for both topical treatments for
primary outcomes and adverse effects if sufficient data were available. See
section 2.1.1 for details on analysis and synthesis of outcomes.

Primary outcomes

Table 26 GRADE profiles – topical capsaicin for neuropathic pain

| TOPICAL CAPSAICIN (as monotherapy – placebo-controlled trials) for neuropathic pain |
|----------------------------------|----------------------------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|
| No. of studies | Design | Treatment | Placebo | Relative risk (95% CI) | Limitations | Inconsistency | Indirectness | Imprecision | Other consideration | Quality |
| Primary outcome | (PHN: 1) | RCT | 7/16 (43.8%) | 1/16 (6.3%) | 7.00 (0.97, 50.57) | ARR = 37.5% | NNTB = N/A | N | N | N | S (b) | N | Moderate |
| Primary outcome | (CanP: 2) | RCT | 8/13 (61.5%) | 3/10 (30.0%) | 2.05 (0.73, 5.80) | ARR = 31.5% | NNTB = N/A | N | N | N | S (b) | N | Moderate |
| Primary outcome | (PDN: 3) | RCT | 23/40 (57.5%) | 26/40 (65.0%) | 0.88 (0.62, 1.26) | ARR = 7.5% | NNTB = N/A | N | N | N | S (b) | N | Moderate |

| No. of studies | Design | Treatment | Placebo | Relative risk (95% CI) | Limitations | Inconsistency | Indirectness | Imprecision | Other consideration | Quality |
| Primary outcome | Withdrawals owing to adverse effects | RCT | 40/280 (14.3%) | 6/267 (2.2%) | 4.97 (2.37, 10.44) | ARR = 12.1% | NNTH = 8.3 (5.9, 12.9) | N | N | N | VS (c) | N | Low |
| Primary outcome | Burning (adverse effects) | RCT | 228/354 (64.4%) | 94/353 (26.8%) | 2.35 (1.64, 3.35) | ARR = 37.8% | NNTH = 2.6 (2.3, 3.2) | N | N | N | N | N | High |
| Primary outcome | Skin irritation (adverse effects) | RCT | 1/40 (2.5%) | 0/40 (0.0%) | 3.00 (0.13, 71.51) | ARR = 2.5% | NNH = N/A | N | N | N | VS (c) | N | Very low |

N = No serious; S = Serious; VS = Very serious

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PHN = post-herpetic neuralgia; CanP = neuropathic cancer pain; PDN = painful diabetic neuropathy; polyne = polyneuropathy; HIV = HIV related neuropathy; N/A = not applicable.

a Categorical scales for patient-reported global improvement/impression of change were dichotomised for analysis. For examples, ‘at least moderate improvement’ on a 6-item scale, ‘at least good improvement’ on a 5-item scale or ‘much or very much improved’ on the patients’ global impression of change (PGIC) scale were the cut-offs for dichotomisation.

b Total number of events < 300 owing to small study sample.

c GDG consensus: if there is only 1 study with total number of adverse effects less than 100, the GDG decided that the quality should be graded as ‘very low’.

1 Bernstein (1989)
2 Watson (1992)
3 Tandan (1992)
4 Watson (1993)
5 Donofrio (1992)
6 Scheffler (1991)
7 Low (1995)
8 Paice (2000)

Table 27 GRADE profiles – topical lidocaine for neuropathic pain

No studies on topical lidocaine that reported the primary outcomes on pain met the inclusion and exclusion criteria.

<p>| TOPICAL LIDOCAINE (as monotherapy – placebo-controlled trials) for neuropathic pain |
|---------------------------------|---------------------------------|-------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>No. of studies</th>
<th>Design</th>
<th>Treatment</th>
<th>Placebo</th>
<th>Relative risk (95% CI) [ARI] [NNTH, 95% CI]</th>
<th>Limitations</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other consideration</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRIMARY OUTCOME: Withdrawals owing to adverse effects</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (PeriphNP: 1)</td>
<td>RCT</td>
<td>1/58 (1.7%)</td>
<td>0/58 (0.0%)</td>
<td>3.00 (0.12, 72.15) ARI = 1.7% NNTH = N/A</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>VS (a)</td>
<td>N</td>
</tr>
<tr>
<td>PRIMARY OUTCOME: Rash (adverse effects)</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>1 (PeriphNP: 1)</td>
<td>RCT</td>
<td>10/58 (17.2%)</td>
<td>11/58 (19.0%)</td>
<td>0.91 (0.42, 1.97) ARI = −1.8% NNTH = N/A</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>VS (a)</td>
<td>N</td>
</tr>
<tr>
<td>PRIMARY OUTCOME: Skin irritation (adverse effects)</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>1 (Mixed NP: 2)</td>
<td>RCT</td>
<td>5/35 (14.3%)</td>
<td>3/35 (8.6%)</td>
<td>1.67 (0.43, 6.45) ARI = 5.7% NNTH = N/A</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>VS (a)</td>
<td>N</td>
</tr>
</tbody>
</table>

N = No serious; S = Serious; VS = Very serious
PeriphNP = peripheral neuropathic pain; Mixed NP = mixed neuropathic pain; N/A = not applicable.

a GDG consensus: if there is only 1 study with total number of adverse effects less than 100, the GDG decided that the quality should be graded as ‘very low’.

1 Meier (2003)
2 Ho (2008)
Other reported pain outcomes

### Table 28 GRADE profiles – topical capsaicin for neuropathic pain

#### TOPICAL CAPSAICIN (as monotherapy – placebo-controlled trials) for neuropathic pain

<table>
<thead>
<tr>
<th>No. of studies</th>
<th>Design</th>
<th>Treatment</th>
<th>Placebo</th>
<th>Mean (SD) at endpoint [p-value]</th>
<th>Limitations</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other consideration</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>OTHER REPORTED PAIN OUTCOME: Pain intensity (Scale: VASpi-100mm)</strong></td>
<td></td>
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</tr>
<tr>
<td>1 (PDN/Radic: 1)</td>
<td>RCT</td>
<td>120</td>
<td>131</td>
<td>Treatment = 58.4 (NR) Placebo = 45.2 (NR) p = 0.004</td>
<td>N</td>
<td>N</td>
<td>S (a)</td>
<td>S (b)</td>
<td>N</td>
<td>Low</td>
</tr>
<tr>
<td>1 (Polyneuro: 2)</td>
<td>RCT</td>
<td>40</td>
<td>40</td>
<td>Treatment = 39.0 (NR) Placebo = 39.0 (NR) Not significant</td>
<td>N</td>
<td>N</td>
<td>S (a)</td>
<td>S (b)</td>
<td>N</td>
<td>Low</td>
</tr>
<tr>
<td>1 (PDN: 3)</td>
<td>RCT</td>
<td>24</td>
<td>25</td>
<td>Treatment = 65.7 (38.9) Placebo = 25.0 (38.6) p = 0.013</td>
<td>N</td>
<td>N</td>
<td>S (a)</td>
<td>S (b)</td>
<td>N</td>
<td>Low</td>
</tr>
<tr>
<td>1 (PHN: 4)</td>
<td>RCT</td>
<td>56</td>
<td>67</td>
<td>Treatment = 39.0 (NR) Placebo = 6.0 (NR) p = 0.006</td>
<td>N</td>
<td>N</td>
<td>S (a)</td>
<td>S (b)</td>
<td>N</td>
<td>Low</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>No. of studies</th>
<th>Design</th>
<th>Treatment</th>
<th>Placebo</th>
<th>Mean change (SD) from baseline [p-value]</th>
<th>Limitations</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other consideration</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>OTHER REPORTED PAIN OUTCOME: Pain intensity (Scale: VASpi-100mm)</strong></td>
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</tr>
<tr>
<td>1 (PDN/Radic: 1)</td>
<td>RCT</td>
<td>119</td>
<td>131</td>
<td>Treatment = −38.1 (NR) Placebo = −27.4 (NR) p = 0.037</td>
<td>N</td>
<td>N</td>
<td>S (a)</td>
<td>S (b)</td>
<td>N</td>
<td>Low</td>
</tr>
<tr>
<td>1 (Mixed NP: 5)</td>
<td>RCT</td>
<td>33</td>
<td>41</td>
<td>Treatment = −11.2 (NR) Placebo = 0.0 (NR) p &lt; 0.001</td>
<td>N</td>
<td>N</td>
<td>S (a)</td>
<td>S (b)</td>
<td>N</td>
<td>Low</td>
</tr>
<tr>
<td>1 (PDN: 3)</td>
<td>RCT</td>
<td>24</td>
<td>25</td>
<td>Treatment = −49.1 (44.5) Placebo = −16.5 (48.4) p = 0.02</td>
<td>N</td>
<td>N</td>
<td>S (a)</td>
<td>S (b)</td>
<td>N</td>
<td>Low</td>
</tr>
</tbody>
</table>

3 N = No serious; S = Serious; VS = Very serious.
4 PDN = painful diabetic neuropathy; Radic = radiculopathy; PHN = post-herpetic neuralgia;
5 Mixed NP = mixed neuropathic pain; NR = Not reported.
6 a Indirect outcome measure (non-primary outcome).
7 b Total number of events < 300 owing to small study sample.
8 1 Donofrio (1992)
9 2 Low (1995)
10 3 Scheffler (1991)
11 4 Watson (1993)
12 5 McCleane (2000)
13
### Table 29 GRADE profiles – topical lidocaine for neuropathic pain

<p>| TOPICAL LIDOCAINE (as monotherapy – placebo-controlled trials) for neuropathic pain |
|---------------------------------|---------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>No. of studies</th>
<th>Design</th>
<th>Treatment</th>
<th>Placebo</th>
<th>Mean (SD) at endpoint [p-value]</th>
<th>Limitations</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other consideration</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>OTHER REPORTED PAIN OUTCOME</strong></td>
<td>Pain intensity (Scale: NRSpi 11-point)</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>PostS NP: 1</td>
<td>RCT</td>
<td>8</td>
<td>13</td>
<td>Treatment = 4.4 (2.12) Placebo = 4.8 (1.71) p = 0.92</td>
<td>N</td>
<td>N</td>
<td>S (a)</td>
<td>S (b)</td>
<td>N</td>
</tr>
<tr>
<td><strong>OTHER REPORTED PAIN OUTCOME</strong></td>
<td>Pain relief (Scale: Global Pain Relief Scale)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>HIV-RN: 2</td>
<td>RCT</td>
<td>61</td>
<td>59</td>
<td>Treatment = 2.25 (5.94) Placebo = 2.23 (5.45) p = 0.715</td>
<td>N</td>
<td>N</td>
<td>S (a)</td>
<td>S (b)</td>
<td>N</td>
</tr>
<tr>
<td><strong>OTHER REPORTED PAIN OUTCOME</strong></td>
<td>Pain intensity (Scale: VASpi-100mm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Mixed NP: 3</td>
<td>RCT</td>
<td>30</td>
<td>31</td>
<td>Treatment = −5.7 (17.5) Placebo = −7.6 (23.9) p = 0.88</td>
<td>N</td>
<td>N</td>
<td>S (a)</td>
<td>S (b)</td>
<td>N</td>
</tr>
<tr>
<td>1</td>
<td>PeriphNP: 4</td>
<td>RCT</td>
<td>40</td>
<td>40</td>
<td>Treatment = NR Placebo = NR</td>
<td>N</td>
<td>N</td>
<td>S (a)</td>
<td>S (b)</td>
<td>N</td>
</tr>
<tr>
<td><strong>OTHER REPORTED PAIN OUTCOME</strong></td>
<td>Pain relief (Scale: Neuropathic Pain Scale)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>PHN: 5</td>
<td>RCT</td>
<td>67</td>
<td>29</td>
<td>Treatment = −15.3 (17.9) Placebo = −7.7 (14.2) p = 0.043</td>
<td>N</td>
<td>N</td>
<td>S (a)</td>
<td>S (b)</td>
<td>N</td>
</tr>
</tbody>
</table>

N = No serious; S = Serious; VS = Very serious
PostS NP = postsurgical neuropathic pain; HIV-RN, HIV-related neuropathy; Mixed NP = mixed neuropathic pain; PeriphNP = peripheral neuropathic pain; PHN = post-herpetic neuralgia; NR = Not reported

* Indirect outcome measure (non-primary outcome).
* Total number of events < 300 owing to small study sample.

### 2.3.5 Comparative trials on pharmacological treatments and combination therapy for neuropathic pain

Any head-to-head comparative trials and combination therapy trials that included the 34 pharmacological treatments were selected in this review (see table 2). Within the 23,207 studies that were retrieved by the systematic searches, 13 randomised trials were included based on the inclusion and exclusion criteria\(^{11}\) (head-to-head comparative = 10 studies, combination

\(^{11}\) For the full search strategies, see appendix 10.7; for the two GDG short questionnaires on inclusion and exclusion criteria, see appendix 10.3; for the full review protocol, see appendix 10.2; for study selection flowcharts and list of excluded studies, see appendix 10.4.

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therapy = 3 studies. The characteristics of the 13 included studies are summarised in table 10 (for detailed full evidence tables, see appendix 10.10). Meta-analysis was carried out for different comparisons or combinations for primary outcomes and specific adverse effects if sufficient data were available. See section 2.1.1 for details on analysis and synthesis of outcomes.

### 2.3.5.1 Cross-class comparative trials: antidepressants vs anticonvulsants

#### Primary outcomes for amitriptyline vs gabapentin

**Table 30 GRADE profiles**

| Amitriptyline vs gabapentin as monotherapy for neuropathic pain |
|---|---|---|---|---|---|---|---|---|
| No. of studies | Design | Ami (T1) | Gaba (T2) | Relative risk (95% CI) | [ARR] | [NNTB, 95% CI] | Limitations | Inconsistency | Indirectness | Imprecision | Other consideration | Quality |
| PRIMARY OUTCOME: Patient-reported 30% pain reduction |
| 1 (SCI: 1) | RCT | 13/22 (59.1%) | 5/22 (22.7%) | 2.60 (1.12, 6.05) | ARR = 36.4% | NNTB = 2.8 (1.7, 14.1) | N | N | N | N | S (b) | N | Moderate |
| PRIMARY OUTCOME: Patient-reported global improvement/impression of change |
| 1 (PDN: 2) | RCT | 14/21 (66.7%) | 11/21 (52.4%) | 1.27 (0.77, 2.11) | ARR = 14.3% | NNTB = N/A | N | N | N | S (b) | N | Moderate |

<table>
<thead>
<tr>
<th>No. of studies</th>
<th>Design</th>
<th>AMI</th>
<th>Gaba</th>
<th>Relative risk</th>
<th>[ARI]</th>
<th>[NNTH]</th>
<th>Limitations</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other consideration</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRIMARY OUTCOME: No. of withdrawals owing to adverse effects</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>2 (PDN: 2) (SCI: 1)</td>
<td>RCT</td>
<td>4/63 (6.3%)</td>
<td>3/63 (4.8%)</td>
<td>1.33 (0.31, 5.72)</td>
<td>ARI = 1.5%</td>
<td>NNTH = N/A</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>VS (c)</td>
<td>N</td>
<td>Low</td>
</tr>
<tr>
<td>PRIMARY OUTCOME: Dry mouth (adverse effects)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (PDN: 2)</td>
<td>RCT</td>
<td>8/25 (32.0%)</td>
<td>4/25 (16.0%)</td>
<td>2.00 (0.69, 5.80)</td>
<td>ARI = 16.0%</td>
<td>NNTH = N/A</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>VS (d)</td>
<td>N</td>
<td>Very low</td>
</tr>
<tr>
<td>PRIMARY OUTCOME: Dizziness (adverse effects)</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>1 (PDN: 2)</td>
<td>RCT</td>
<td>2/25 (8.0%)</td>
<td>7/25 (28.0%)</td>
<td>0.29 (0.07, 1.24)</td>
<td>ARI = −20.0%</td>
<td>NNTH = N/A</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>VS (d)</td>
<td>N</td>
<td>Very low</td>
</tr>
<tr>
<td>PRIMARY OUTCOME: Blurred vision (adverse effects)</td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (PDN: 2)</td>
<td>RCT</td>
<td>2/25 (8.0%)</td>
<td>1/25 (4.0%)</td>
<td>2.00 (0.19, 20.7)</td>
<td>ARI = 4.0%</td>
<td>NNTH = N/A</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>VS (d)</td>
<td>N</td>
<td>Very low</td>
</tr>
<tr>
<td>PRIMARY OUTCOME: Sedation (adverse effects)</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (PDN: 2)</td>
<td>RCT</td>
<td>8/25 (32.0%)</td>
<td>12/25 (48.0%)</td>
<td>0.67 (0.33, 1.35)</td>
<td>ARI = −6.0%</td>
<td>NNTH = N/A</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>VS (d)</td>
<td>N</td>
<td>Very low</td>
</tr>
<tr>
<td>PRIMARY OUTCOME: Fatigue (adverse effects)</td>
<td></td>
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<td></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>RCT</td>
<td>5/25</td>
<td>4/25</td>
<td>1.25 (0.38, 4.12)</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>VS</td>
<td>N</td>
<td>Very low</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Relative risks were calculated in the direction of T1 compared to T2.

T1 = treatment 1; T2 = treatment 2; N = No serious; S = Serious; VS = Very serious

Ami = amitriptyline; Gaba = gabapentin; PDN = painful diabetic neuropathy; SCI = spinal cord injury; N/A = not applicable.

a Categorical scales for patient-reported global improvement/impression of change were dichotomised for analysis. For examples, ‘at least moderate improvement’ on a 6-item scale, ‘at least good improvement’ on a 5-item scale or ‘much or very much improved’ on the patients’ global impression of change (PGIC) scale were the cut-offs for dichotomisation.

b Total number of events (positive outcome) less than 300.

c GDG consensus: Total number of adverse effects less than 100, downgrade 2 levels.

d GDG consensus: if there is only 1 study with total number of adverse effects less than 100, the GDG decided that the quality should be graded as ‘very low’.

e One of the 2 studies was an open-label study with no blinding; downgrade quality by 1 level.

TABLE 31 GRADE profiles

Amitriptyline vs gabapentin as monotherapy for neuropathic pain

<table>
<thead>
<tr>
<th>No. of studies</th>
<th>Design</th>
<th>Ami (T1)</th>
<th>Gaba (T2)</th>
<th>Mean change (SD) from baseline [p-value]</th>
<th>Limitations</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (PDN: *)</td>
<td>RCT</td>
<td>12</td>
<td>13</td>
<td>Ami = -1.3 (0.6) Gaba = -1.9 (0.8) p = 0.026</td>
<td>S (a)</td>
<td>N</td>
<td>S (b)</td>
<td>S (c)</td>
<td>N</td>
<td>Very Low</td>
</tr>
</tbody>
</table>

OTHER NON-PRIMARY OUTCOME: Pain relief (Scale: 5-point Pain Score)

T1 = treatment 1; T2 = treatment 2; N = No serious; S = Serious; VS = Very serious.

Ami = amitriptyline; Gaba = gabapentin; PDN = painful diabetic neuropathy.

a Open-label study with no blinding; subjective outcome on pain and global improvement; downgrade 1 level.

b Indirect outcome measure.

c Total number of events < 300 owing to small study sample.

d Dallocchio (2000)
### Table 32 GRADE profiles – nortriptyline vs gabapentin

<table>
<thead>
<tr>
<th>No. of studies</th>
<th>Design</th>
<th>Nortrip (T1)</th>
<th>Gabapentin (T2)</th>
<th>Relative risk (95% CI)</th>
<th>[ARR]</th>
<th>[NNTB, 95% CI]</th>
<th>Limitations</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other consideration</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRIMARY OUTCOME: Patient-reported 50% pain reduction</td>
<td>1 (PHN: *)</td>
<td>RCT</td>
<td>9/36 (25.0%)</td>
<td>7/34 (20.6%)</td>
<td>1.21 (0.51, 2.90)</td>
<td>ARR = 4.4%</td>
<td>NNTB = N/A</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>S</td>
<td>(a)</td>
</tr>
</tbody>
</table>

Relative risks were calculated in the direction of T1 compared to T2.

Nortrip = nortriptyline; Gabapentin = gabapentin; PHN = post-herpetic neuralgia; N/A = not applicable.

* Total number of events (positive outcome) less than 300.

Table 33 GRADE profiles – amitriptyline vs carbamazepine

<table>
<thead>
<tr>
<th>No. of studies</th>
<th>Design</th>
<th>Amitriptyline (T1)</th>
<th>Carbamazepine (T2)</th>
<th>Relative risk (95% CI)</th>
<th>[ARR]</th>
<th>[NNTB, 95% CI]</th>
<th>Limitations</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other consideration</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRIMARY OUTCOME: Patient-reported global improvement/impression of change*</td>
<td>1 (PostSt: *)</td>
<td>RCT</td>
<td>10/15 (66.7%)</td>
<td>5/14 (52.4%)</td>
<td>1.87 (0.85, 4.11)</td>
<td>ARR = 31.0%</td>
<td>NNTB = N/A</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>S</td>
<td>(b)</td>
</tr>
</tbody>
</table>
### Limitations

- Inconsistency
- Indirectness
- Imprecision
- Other consideration

**Quality**

<table>
<thead>
<tr>
<th>No. of studies</th>
<th>Design</th>
<th>AMI</th>
<th>Carba</th>
<th>Relative risk (95% CI)</th>
<th>Limitations</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other consideration</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (PostSt: *)</td>
<td>RCT</td>
<td>14/15 (93.3%)</td>
<td>13/14 (92.9%)</td>
<td>1.01 (0.82, 1.23) ARI = 0.4% NNTH = N/A</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>VS (c)</td>
<td>N</td>
<td>Very low</td>
</tr>
</tbody>
</table>

Relative risks were calculated in the direction of T1 compared to T2.

**Primary outcomes**

The only study identified that compared pregabalin with oxycodone did not report the primary outcomes of pain.

**Table 34 GRADE profiles – pregabalin vs oxycodone**

### Cross-class comparative trials: anticonvulsants vs opioid analgesics

**PRIMARY OUTCOME: No. of withdrawals owing to adverse effects**

<table>
<thead>
<tr>
<th>No. of studies</th>
<th>Design</th>
<th>Prega (T1)</th>
<th>Oxyco (T2)</th>
<th>Relative risk (95% CI)</th>
<th>Limitations</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other consideration</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (MixNP: *)</td>
<td>Open RCT</td>
<td>9/134 (6.7%)</td>
<td>11/106 (10.4%)</td>
<td>0.65 (0.28, 1.50) ARI = −3.7% NNTH = N/A</td>
<td>S (a)</td>
<td>N</td>
<td>N</td>
<td>VS (b)</td>
<td>N</td>
<td>Very low</td>
</tr>
</tbody>
</table>

Relative risks were calculated in the direction of T1 compared to T2.

**2.3.5.3 Cross-class comparative trials: anticonvulsants vs topical treatments**

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### Table 35 GRADE profiles – pregabalin vs topical lidocaine

<table>
<thead>
<tr>
<th>No. of studies</th>
<th>Design</th>
<th>Preg (T1)</th>
<th>T.Lido (T2)</th>
<th>Relative risk (95% CI) [ARR] [NNTB, 95% CI]</th>
<th>Limitations</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other consideration</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PRIMARY OUTCOME: Patient-reported 30% pain reduction</strong></td>
<td>1 (PDN+ PHN: *)</td>
<td>Open RCT</td>
<td>74/137 (54.0%)</td>
<td>85/144 (59.0%)</td>
<td>0.92 (0.74, 1.12) ARR = −5.0% NNTB = N/A</td>
<td>S (b)</td>
<td>N</td>
<td>N</td>
<td>S (c)</td>
<td>N</td>
</tr>
<tr>
<td><strong>PRIMARY OUTCOME: Patient-reported 50% pain reduction</strong></td>
<td>1 (PDN+ PHN: *)</td>
<td>Open RCT</td>
<td>44/137 (32.1%)</td>
<td>56/144 (38.9%)</td>
<td>0.83 (0.60, 1.14) ARR = −6.8% NNTB = N/A</td>
<td>S (b)</td>
<td>N</td>
<td>N</td>
<td>S (c)</td>
<td>N</td>
</tr>
<tr>
<td><strong>PRIMARY OUTCOME: Patient-reported global improvement/impression of change</strong></td>
<td>1 (PDN+ PHN: *)</td>
<td>Open RCT</td>
<td>65/137 (47.4%)</td>
<td>72/144 (50.0%)</td>
<td>0.95 (0.75, 1.21) ARR = −2.6% NNTB = N/A</td>
<td>S (b)</td>
<td>N</td>
<td>N</td>
<td>S (c)</td>
<td>N</td>
</tr>
</tbody>
</table>

#### No. of studies

- Relative risks were calculated in the direction of T1 compared to T2.
- T1 = treatment 1; T2 = treatment 2; N = No serious; S = Serious; VS = Very serious
- Prega = pregabalin; T.Lido = topical lidocaine; PDN = painful diabetic neuropathy; PHN = post-herpetic neuralgia; N/A = not applicable.
- Categorical scales for patient-reported global improvement/impression of change were dichotomised for analysis. For example, ‘at least moderate improvement’ on a 6-item scale, ‘at least good improvement’ on a 5-item scale or ‘much or very much improved’ on the patients’ global impression of change (PGIC) scale were the cut-offs for dichotomisation.
- Open-label study with no blinding; subjective outcome on pain and global improvement; downgrade 1 level.
- Total number of events (positive outcome) less than 300.
- Open-label study with no blinding; downgrade 1 level.
- GDG consensus: if there is only 1 study with total number of adverse effects less than 100, the GDG decided that the quality should be graded as ‘very low’.
- Baron (2009)
2.3.5.4 Cross-class comparative trials: antidepressants vs topical treatments

Primary outcomes

The only study identified that compared amitriptyline with topical capsaicin did not report the primary outcomes of pain.

Table 36 GRADE profiles – amitriptyline vs topical capsaicin

<table>
<thead>
<tr>
<th>No. of studies</th>
<th>Design</th>
<th>Ami (T1)</th>
<th>T.Cap (T2)</th>
<th>Relative risk (95% CI) [ARI] [NNTH, 95% CI]</th>
<th>Limitations</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other consideration</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRIMARY OUTCOME: Sedation (adverse effects)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (PDN: *)</td>
<td>RCT</td>
<td>69/117 (59.0%)</td>
<td>0/118 (0.0%)</td>
<td>∞ (∞) ARI = 59.0% NNTH = N/A</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>VS (a)</td>
<td>N</td>
<td>Very low</td>
</tr>
</tbody>
</table>

Relative risks were calculated in the direction of T1 compared to T2.

T1 = treatment 1; T2 = treatment 2; N = No serious; S = Serious; VS = Very serious

Other reported pain outcomes

Table 37 GRADE profiles – amitriptyline vs topical capsaicin

<table>
<thead>
<tr>
<th>No. of studies</th>
<th>Design</th>
<th>Ami (T1)</th>
<th>T.Cap (T2)</th>
<th>Mean (SD) at endpoint [p-value]</th>
<th>Limitations</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>OTHER REPORTED PAIN OUTCOME: Pain relief (Scale: VASpr-100mm)</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (PDN: *)</td>
<td>RCT</td>
<td>108</td>
<td>104</td>
<td>Ami = 57.0 (3.6) T.Cap = 55.1 (3.5) p &gt; 0.05</td>
<td>N</td>
<td>N</td>
<td>S (a)</td>
<td>S (b)</td>
<td>N</td>
<td>Low</td>
</tr>
</tbody>
</table>

Other reported pain outcomes

Table 37 GRADE profiles – amitriptyline vs topical capsaicin

<table>
<thead>
<tr>
<th>No. of studies</th>
<th>Design</th>
<th>Ami (T1)</th>
<th>T.Cap (T2)</th>
<th>Mean change (SD) from baseline [p-value]</th>
<th>Limitations</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>OTHER REPORTED PAIN OUTCOME: Pain intensity (Scale: VASpi-100mm)</td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (PDN: *)</td>
<td>RCT</td>
<td>108</td>
<td>104</td>
<td>Ami = −29.1 (2.9) T.Cap = −26.1 (2.9) p &gt; 0.05</td>
<td>N</td>
<td>N</td>
<td>S (a)</td>
<td>S (b)</td>
<td>N</td>
<td>Low</td>
</tr>
</tbody>
</table>

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2.3.5.5 Within-class comparative trials: antidepressants (TCAs) vs antidepressants (SNRIs)

Table 38 GRADE profiles – imipramine vs venlafaxine

<table>
<thead>
<tr>
<th>No. of studies</th>
<th>Design</th>
<th>Imipra (T1)</th>
<th>Venla (T2)</th>
<th>Relative risk (95% CI) [ARR] [NNTB, 95% CI]</th>
<th>Limitations</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other consideration</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRIMARY OUTCOME: Patient-reported global improvement/impression of change*</td>
<td>1 (Poly: *) RCT</td>
<td>14/33 (42.4%)</td>
<td>8/33 (24.2%)</td>
<td>1.75 (0.85, 3.60) ARR = 18.2% NNTB = N/A</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>S (b)</td>
<td>N</td>
<td>Moderate</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>No. of studies</th>
<th>Design</th>
<th>Imipra (T1)</th>
<th>Venla (T2)</th>
<th>Relative risk (95% CI) [ARR] [NNTB, 95% CI]</th>
<th>Limitations</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other consideration</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRIMARY OUTCOME: Dizziness (adverse effects)</td>
<td>1 (Poly: *) RCT</td>
<td>3/33 (9.1%)</td>
<td>2/33 (6.1%)</td>
<td>1.50 (0.27, 8.40) ARI = 3.0% NNTH = N/A</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>VS (c)</td>
<td>N</td>
<td>Very low</td>
</tr>
</tbody>
</table>

| PRIMARY OUTCOME: Dry mouth (adverse effects) | 1 (Poly: *) RCT | 12/33 (36.4%) | 4/33 (12.1%) | 3.00 (1.08, 8.35) ARI = 24.3% NNTH = 4.1 (2.3, 27.9) | N | N | N | VS (c) | N | Very low |

| PRIMARY OUTCOME: Blurred vision (adverse effects) | 1 (Poly: *) RCT | 1/33 (3.0%) | 1/33 (3.0%) | 1.00 (0.07, 15.3) ARI = 0.0% NNTH = N/A | N | N | N | VS (c) | N | Very low |

| PRIMARY OUTCOME: Any adverse effects: non-specified | 1 (Poly: *) RCT | 13/33 (39.4%) | 11/33 (33.3%) | 1.18 (0.62, 2.25) ARI = 6.1% NNTH = N/A | N | N | N | VS (c) | N | Very low |

Relative risks were calculated in the direction of T1 compared to T2.

T1 = treatment 1; T2 = treatment 2; N = No serious; S = Serious; VS = Very serious

Imipra = imipramine; Venla = venlafaxine; Poly = painful polyneuropathy; N/A = not applicable.

* Categorical scales for patient-reported global improvement/impression of change were dichotomised for analysis. For examples, ‘at least moderate improvement’ on a 6-item scale, ‘at least good improvement’ on a 5-item scale or ‘much or very much improved’ on the patients’ global impression of change (PGIC) scale were the cut-offs for dichotomisation.

b Total number of events (positive outcome) less than 300.

c GDG consensus: if there is only 1 study with total number of adverse effects less than 100, the GDG decided that the quality should be graded as ‘very low’.

Sindrup (2003)
2.3.5.6 Within-class comparative trials: antidepressants (TCAs) vs antidepressants (TCAs)

Primary outcomes

The only study identified that compared amitriptyline with nortriptyline did not report the primary outcomes of pain.

Table 39 GRADE profiles – amitriptyline vs nortriptyline

Amitriptyline vs nortriptyline as monotherapy for neuropathic pain

<table>
<thead>
<tr>
<th>No. of studies</th>
<th>Design</th>
<th>Ami (T1)</th>
<th>Nortrip (T2)</th>
<th>Relative risk (95% CI) [ARI, NNTH, 95% CI]</th>
<th>Limitations</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other Consideration</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRIMARY OUTCOME: Dry mouth (adverse effects)</td>
<td>1 (PHN: *)</td>
<td>RCT</td>
<td>28/33 (84.8%)</td>
<td>26/33 (78.8%)</td>
<td>1.06 (0.86, 1.35) [ARI = 6.0% NNTH = N/A]</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>VS (a)</td>
</tr>
<tr>
<td>PRIMARY OUTCOME: Dizziness (adverse effects)</td>
<td>1 (PHN: *)</td>
<td>RCT</td>
<td>3/33 (9.1%)</td>
<td>1/33 (3.0%)</td>
<td>3.00 (0.33, 27.4) [ARI = 6.1% NNTH = N/A]</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>VS (a)</td>
</tr>
<tr>
<td>PRIMARY OUTCOME: Drowsiness (adverse effects)</td>
<td>1 (PHN: *)</td>
<td>RCT</td>
<td>4/33 (12.1%)</td>
<td>6/33 (18.2%)</td>
<td>0.67 (0.21, 2.13) [ARI = −6.1% NNTH = N/A]</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>VS (a)</td>
</tr>
<tr>
<td>PRIMARY OUTCOME: Any adverse effects: non-specified</td>
<td>1 (PHN: *)</td>
<td>RCT</td>
<td>31/33 (93.9%)</td>
<td>31/33 (93.9%)</td>
<td>1.00 (0.88, 1.13) [ARI = 0.0% NNTH = N/A]</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>VS (a)</td>
</tr>
</tbody>
</table>

Relative risks were calculated in the direction of T1 compared to T2.

T1 = treatment 1; T2 = treatment 2; N = No serious; S = Serious; VS = Very serious

Amitriptyline; Nortriptyline; PHN = post-herpetic neuralgia; N/A = not applicable.

GDG consensus: if there is only 1 study with total number of adverse effects less than 100, the GDG decided that the quality should be graded as ‘very low’.

Watson (1998)

2.3.5.7 Combination therapy: anticonvulsants + opioid analgesics vs anticonvulsants alone

Primary outcomes

The only combination study identified that compared pregabalin plus oxycodone with pregabalin alone did not report the primary outcomes on pain.
### Table 40 GRADE profiles – pregabalin + oxycodone vs pregabalin alone

<table>
<thead>
<tr>
<th>No. of studies</th>
<th>Design</th>
<th>Preg + Oxyco (T1)</th>
<th>Prega (T2)</th>
<th>Relative risk (95% CI) [ARI] [NNTH, 95% CI]</th>
<th>Limitations</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other consideration</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (MixNP: *)</td>
<td>Open RCT</td>
<td>10/106 (9.4%)</td>
<td>9/134 (6.7%)</td>
<td>1.40 (0.59, 3.33) ARI = 2.7% NNTH = N/A</td>
<td>S (a)</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>VS (b)</td>
<td>Very low</td>
</tr>
</tbody>
</table>

Relative risks were calculated in the direction of T1 compared to T2.

T1 = treatment 1; T2 = treatment 2; N = No serious; S = Serious; VS = Very serious

Preg = pregabalin; Oxyco = oxycodone; MixNP = mixed neuropathic pain; N/A = not applicable.

* Open-label study with no blinding; downgrade 1 level.

GDG consensus: if there is only 1 study with total number of adverse effects less than 100, the GDG decided that the quality should be graded as ‘very low’.

The only combination study identified that compared gabapentin plus oxycodone with gabapentin alone did not report the primary outcomes on pain.

### Table 41 GRADE profiles – gabapentin + oxycodone vs gabapentin alone

<table>
<thead>
<tr>
<th>No. of studies</th>
<th>Design</th>
<th>Gaba + Oxyco (T1)</th>
<th>Gaba (T2)</th>
<th>Relative risk (95% CI) [ARI] [NNTH, 95% CI]</th>
<th>Limitations</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other consideration</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (PDN: *)</td>
<td>RCT</td>
<td>27/169 (16.0%)</td>
<td>9/169 (5.3%)</td>
<td>3.00 (1.45, 6.19) ARI = 10.7% NNTH = 9.4 (5.7, 23.5)</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>VS (a)</td>
<td>Very low</td>
</tr>
</tbody>
</table>

PRIMARY OUTCOME: No. of withdrawals owing to adverse effects

- Constipation (adverse effects)
- Nausea (adverse effects)
- Vomiting (adverse effects)
- Fatigue (adverse effects)
- Dizziness (adverse effects)
**PRIMARY OUTCOME: Somnolence (adverse effects)**

|   | PDN: * | RCT | 37/168 (22.0%) | 9/167 (5.4%) | 4.09 (2.04, 8.20) | ARI = 16.6%         | NNTH = 6.0 (4.1, 10.4) | N | N | N | VS (a) | N | Very low |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|

**Primary outcomes**

Relative risks were calculated in the direction of T1 compared T2.

T1 = treatment 1; T2 = treatment 2; N = No serious; S = Serious; VS = Very serious

Gaba = gabapentin; Oxyco = oxycodone; PDN = painful diabetic neuropathy; N/A = not applicable.

GDG consensus: if there is only 1 study with total number of adverse effects less than 100, the GDG decided that the quality should be graded as ‘very low’.

Hanna (2008)

**Other reported pain outcomes**

**Table 42 GRADE profiles – gabapentin + oxycodone vs gabapentin alone**

| Gabapentin + oxycodone (vs gabapentin alone) as combination therapy for neuropathic pain |
|---|---|---|---|---|---|---|---|
| No. of studies | Design | Gaba + Oxyco | Gaba | Mean (SD) at endpoint [p-value] | Limitations | Inconsistency | Indirectness | Imprecision | Other considerations | Quality |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 (PDN: *) | RCT | 169 | 169 | Gaba + Oxyco= 2.1 (2.51) Gaba = 1.5 (2.38) p = 0.007 | N | N | S | S | N | Low |

N = No serious; S = Serious; VS = Very serious

Gaba = gabapentin; Oxyco = oxycodone; PDN = painful diabetic neuropathy.

Indirect outcome measure.

Total number of positive events < 300.

Hanna (2008)

2.3.5.8 Combination therapy: anticonvulsants + opioid analgesics vs opioid analgesics alone

**Primary outcomes**

The only combination study identified that compared pregabalin plus oxycodone with oxycodone alone did not report the primary outcomes of pain.
Table 43 GRADE profiles – pregabalin + oxycodone vs oxycodone alone

<table>
<thead>
<tr>
<th>No. of studies</th>
<th>Design</th>
<th>Prega + Oxyco (T1)</th>
<th>Oxyco (T2)</th>
<th>Relative risk (95% CI) [ARI] [NNTH, 95% CI]</th>
<th>Limitations</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other consideration</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (MixNP: *)</td>
<td>Open RCT</td>
<td>10/106 (9.4%)</td>
<td>11/106 (10.4%)</td>
<td>0.91 (0.40, 2.05) ARI = −1.0% NNTH = N/A</td>
<td>S (a)</td>
<td>N</td>
<td>N</td>
<td>VS (b)</td>
<td>N</td>
<td>Very low</td>
</tr>
</tbody>
</table>

Relative risks were calculated in the direction of T1 compared to T2.

T1 = treatment 1; T2 = treatment 2; N = No serious; S = Serious; VS = Very serious
Prega = pregabalin; Oxyco = oxycodone; MixNP = mixed neuropathic pain; N/A = not applicable.

a Open-label study with no blinding; downgrade 1 level.
b GDG consensus: if there is only 1 study with total number of adverse effects less than 100, the GDG decided that the quality should be graded as 'very low'.

* Gatti (2008)

2.3.6 Health economic evidence review

In addition to the clinical effectiveness review, the evidence review for this guideline comprises a systematic review of economic evidence on the pharmacological management of neuropathic pain. A systematic search found a total of 2273 papers. Full details on the search strategy can be found in appendix 10.7.

There were 479 economic studies found on antidepressants, of which 39 were relevant based on title and abstract scanning. For anticonvulsants, 482 papers were retrieved, of which 40 were shortlisted. The search for opioids yielded 1125 hits, and a total of 140 papers were shortlisted for the review. Finally, 187 articles on topical treatments were found, of which 27 were shortlisted.

The GDG also had access to a relevant health technology assessment (HTA) report that had not been published during guideline development. This HTA report (Fox-Rushby JA, GL Griffith, JR Ross et al. NIHR Health Technology Assessment programme. The clinical and cost-effectiveness of different treatment pathways for neuropathic pain [NP]. HTA ref. 05/30/03. Unpublished. Project abstract available from www.hra.ac.uk/1527) reviewed the clinical and cost effectiveness of different treatment pathways for neuropathic pain. The initial review included all subpopulations for the various Neuropathic pain: NICE clinical guideline DRAFT (October 2009) Page 79 of 136
conditions associated with neuropathic pain. However, because of the availability of evidence, the HTA report focused on two distinct neuropathic pain populations: people with painful diabetic neuropathy (PDN) and people with post-herpetic neuralgia (PHN).

For our own review of the economic literature, 246 papers were shortlisted. Only 15 papers were ordered in full text because it was clear that the remaining papers either were studies of the wrong population or were not economic analyses. From the 15 papers ordered in full text, no study could be included. Reasons for exclusion included: study design (not an economic study); wrong patient population (no neuropathic pain; immediate post-surgery pain) and clinical indication (general anaesthetics); intervention (injection, infusion); and a follow-up period of less than 1 week. See appendix 10.4 for a table with the excluded studies and reasons for exclusion given in accordance with the economic profiles as set out in ‘The guidelines manual’ (2009).

For the purposes of this guideline, the GDG decided at the outset that neuropathic pain would be treated as a ‘blanket condition’ where possible or necessary. However, it was clear that the treatment of various subpopulations would differ considerably and that it would not be possible to extrapolate from one subgroup to all people with neuropathic pain.

No health economic modeling was undertaken for this guideline, because the GDG decided that the HTA report that was in development contained thorough data on the cost effectiveness of treatment pathways (sequences) for two common neuropathic pain conditions. The GDG reviewed, appraised and summarised the HTA report, and the results of the economic analyses from the HTA report informed this guideline as appropriate. The economic evidence search for the guideline excluded papers on people with PHN or PDN (which made up the bulk of the 246 retrieved papers) because these populations were covered by the HTA report.

2.3.6.1 HTA report: methods

Neuropathic pain: NICE clinical guideline DRAFT (October 2009)
The HTA report on the cost effectiveness of pharmacological treatments for painful diabetic neuropathy (PDN) and post-herpetic neuralgia (PHN) was included and appraised. Because of the nature of the data available in the HTA report, we decided to present the economic evidence review by subpopulation.

In order to present the best available evidence on the cost effectiveness of alternative pharmacological treatment pathways for people with PHN and PDN, the effectiveness evidence was searched and reviewed systematically for each subpopulation. Further searches for data on resource use, drug costs and utilities associated with health states were conducted. This information was synthesised in a meta-analysis as appropriate and entered into cost-effectiveness decision models of different treatment pathways.

Decision models represent a way to synthesise evidence currently available on the outcomes and costs of alternative healthcare interventions. Common examples of decision models are decision trees and Markov models. Markov models are frequently used to represent processes that evolve over time and are particularly suited to modelling the progression of chronic disease. Disease-specific health states are defined and transition probabilities assigned for movement between these states over a discrete time period (or Markov cycle). Once the model structure (health states, transitions) is set, associated estimates of resource use and health valuations are attached to each health state and transition in the model. By running the model over a large number of cycles (time horizon), it is possible to estimate the long-term costs and outcomes associated with a disease and a particular healthcare intervention. The use of incremental cost-effectiveness ratios (ICERs) and net benefits has been extensively discussed in the literature (for examples please see textbooks including those by Drummond et al. [2005] and Briggs et al. [2006], as well as articles such as Briggs and Sculpher [1998]). Markov models are able to account for second-order uncertainty in model parameters using probabilistic Monte Carlo simulation.

Markov models were developed for the evaluation of the cost effectiveness of pharmacological treatments for both PHN and PDN populations. For each...
population, four separate analyses were conducted. The efficacy review fed
data into a head-to-head comparison of all drugs for which useable data were
available. The head-to-head analysis showed a drug hierarchy in terms of net
benefit. Net benefit is another method to combine costs and outcomes from a
decision analysis. It has certain computational advantages over the ICER,
particularly when simulating large numbers of ICERs. For further details on
the use of ICERs and net benefits, please see Claxton (2008) and Hoch et al.
(2002), as well as the aforementioned textbooks. Based on this rank-ordered
list of drugs, a sequence was defined taking into account the clinical
convention to titrate individual, tolerated drugs upwards before switching to
another drug. This sequence was then compared with the International
Association for the Study of Pain Neuropathic Pain Special Interest Group
(IASP-NPSIG) prescription guidelines. Finally, a Bayesian value of information
(VOI) analysis estimated the value of future research, given the underlying
uncertainty.

**HTA post-herpetic neuralgia (PHN) model**

The model had a 10-year time horizon, with 6-week cycles in order to
represent the average expected interval between clinical consultations and to
capture side effects and relapses. A cohort of patients aged 70 years old was
modelled. The model included eight health states: pain relief and no adverse
events; pain relief and minor adverse events; no pain relief and no adverse
events; no pain relief and minor adverse events; severe adverse events
leading to withdrawal from treatment; spontaneous subsidence of pain; drug
terminated; and death.

For the model, effectiveness in terms of pain relief was defined as binary with
a ≥ 50% cut off for pain reduction. The HTA report states that this followed the
conventional, dichotomous representation of the natural history of pain relief.
They pooled the outcome, at least 50% pain reduction, with moderate and
greater improvement outcomes on global improvement scales. Pooled
estimates on pain relief from the meta-analysis were transformed to reflect 6-
week cycles and applied probabilistically by assigning a distribution to the
drug and placebo. From these, estimates could be sampled and relative risk
(RR) calculated. The same method was used to obtain estimates of RR of minor and major adverse events.

Data on spontaneous subsidence of pain were obtained from a separate, specific search that identified nine papers, four of which were included. Information on health state utilities was searched for in the literature. This search identified 12 papers, of which 11 were excluded. The one included paper was Europe-wide study that reported data on two neuropathic pain states and age-adjusted pain subsidence. There was a complete lack of adverse-event utility data in the published literature. A Google Scholar search found data on utility estimates where dizziness and drowsiness was experienced by patients receiving TCAs. Compliance was assumed to be 100% at base case, but this was lowered to 50% in sensitivity analysis to test uncertainty.

Cost data are relevant for a UK scenario and the model adopts an NHS perspective, accounting for health outcomes in terms of quality-adjusted life years (QALYs). Discounting is in line with NICE's reference case. As no published resource use data were available, a survey of healthcare professionals was undertaken. For the PHN model, three pathways were described: GP led, consultant led (by an anaesthetist/pain specialist, neurologist or ophthalmologist), and jointly led care by a GP and a consultant. Results were then incorporated into the model and a separate sensitivity analysis was undertaken to test the associated uncertainty. Unit costs were taken from established sources (Personal Social Services Research Unit [PSSRU] and ‘British National Formulary’ [BNF]).

As mentioned above, four separate analyses were conducted. The efficacy review informed a head-to-head comparison of all drugs where useable data were available. The head-to-head analysis showed a hierarchy of the drugs in terms of net benefit. For a description of the net benefit calculation, please see page 86 above and the glossary. From the head-to-head analysis, a sequence was defined that took into account the clinical convention to titrate dosages of one drug upwards before switching to another drug. This sequence was then compared with the IASP-NPSIG prescription guidelines.
Lastly a Bayesian VOI analysis estimated the value of future research, given the underlying uncertainty.

The head-to-head comparison involved probabilistic modelling of pregabalin (150 mg, 300 mg, 600 mg), gabapentin (1800 mg, 2400 mg, 3600 mg), oxycodone 60 mg and lidocaine 5% patch. Epidural methylprednisolone 60 mg and lidocaine intrathecal 90 mg were modelled deterministically.

Probabilistic modelling involves simultaneous random sampling from parameter distributions using data such as mean and standard error, whereas deterministic modelling uses a fixed base case estimate, such as a weighted mean difference. Probabilistic modelling is preferred providing that suitable data are available, since it allows an estimation of the overall uncertainty in the model and its parameters (second-order uncertainty) by repeated sampling of ICERs or net benefits.

The sequential analysis compared the recommended treatment lines from the IASP-NPSIG guidelines with the ‘optimal sequence’ identified in the head-to-head analysis. The head-to-head analysis allowed the prescription of the included treatments to be ranked in decreasing order of net benefit or cost effectiveness. Strict sequencing in terms of cost effectiveness was discarded and a pragmatic approach to titration that reflects clinical practice was adopted. The IASP recommendations separate treatment algorithms into first-line, second-line and third-line drugs. As first line, the IASP guideline recommends TCAs, SSNRIs, calcium channel ligands and topical lidocaine, with opioids in special circumstances. Second-line drugs are opioid analgesics, including tramadol. Third-line drugs are other antidepressants and antiepileptics (anticonvulsants), mexiletine, N-methyl-D-aspartate (NMDA) receptor antagonists and topical capsaicin. In the analysis this sequence of drugs is compared with the pragmatic, optimal strategy.

**Important assumptions for the PHN model**

These assumptions are adapted from those in the HTA report.

- Cycle length of 6 weeks within which a clinical change (pain relief or adverse event [AE]) would be expected in practice.
• Pain relief was assumed to reduce symptoms and not duration of pain.
• Beneficial effects and AEs were assumed to start from the second cycle, or after 6 weeks.
• Patients who did not achieve pain relief within the trial period were assumed to not respond to the drug. They were prescribed a new drug in the sequential analysis.
• Patients who experienced severe AEs leading to withdrawal had the drug terminated immediately and AEs were treated if necessary.
• Effectiveness period of trial: pain relief and AE data taken from trials with durations shorter than 6 weeks were assumed to result in no more pain relief or AEs than was found during the trial (that is, data were not extrapolated beyond the trial duration).
• Patients who experienced pain relief were assumed to remain on the drug and to receive pain relief until spontaneous subsidence of pain or death.
• Patients who experienced pain relief and minor AEs were assumed to have been titrated to the minimum dose that gives pain relief. They would continue to experience the AEs or require drugs to alleviate them until spontaneous subsidence of pain or death.
• Medication prescribed for minor AEs was assumed to be 100% effective.
• Less than 50% pain relief is considered insufficient pain relief that does not result in a change in health state utility or QALYs.
• Failure to respond to one drug was not assumed to affect the likelihood of responding to another.
• The trials of clinical effectiveness identified from the systematic review did not distinguish between patients experiencing pain relief and those who did not when reporting minor AEs. It was assumed that all patients randomised to the treatment arm had an equal probability of AEs regardless of whether or not they obtained pain relief.
• Because PHN has not been associated with increased mortality, all-cause mortality for the general public was applied in the model.
• In the base case, adherence to drug dose and frequency was assumed to be 100%, which reflects the trial conditions under which the clinical effectiveness data were collected.

HTA painful diabetic neuropathy (PDN) model
The model simulated a cohort of 2000 people aged 55 years until death, with a maximum of 360 cycles of 6 weeks’ duration (45 years) each. Similar to the PHN model, this model is based on two pain states (at least 50% pain relief or no pain relief) following conventional, dichotomous representation of natural history of pain relief in the literature. Because spontaneous pain resolution was deemed unlikely, this health state was omitted from the PDN model.

As in the PHN model, a 6-week cycle was selected to represent the average expected interval between clinical consultations and over which the symptoms would change. This cycle length was also described as suitable to represent direct death probabilities as a result of myocardial infarction (MI), which might be a clinically relevant endpoint for people receiving certain doses of medicines such as amitriptyline. Model assumptions differ slightly from those of the PHN model. Cost data are relevant for a UK scenario. The model adopts a NHS perspective, accounting for health outcomes in terms of QALYs. Discounting of costs and outcomes is in line with NICE methods.

For the model, effectiveness in terms of pain relief was defined as binary with a ≥ 50% cut off. Pooled estimates on pain relief from the meta-analysis were transformed to reflect 6-week cycles and applied probabilistically by assigning a distribution to the drug and placebo. From these, estimates could be sampled and RRs calculated. The same method was used to obtain estimates of RR of minor and major adverse events. In absence of PDN-specific mortality data, the model used age-adjusted all-cause mortality data for people with diabetes.

Spontaneous subsidence of pain was deemed not applicable to this model. Information on health state utilities was searched for in the literature. The search found 14 papers, 13 of which were excluded. One European study was included that had two pain states. There was a complete lack of adverse-
event utility data in the published literature. A Google Scholar search found
data on utility estimates where dizziness and drowsiness was experienced by
patients receiving TCAs. Compliance was assumed to be 100% at base case,
but was lowered to 50% in sensitivity analysis to test uncertainty.

Because of the complete lack of published data, resource use was estimated
via a survey to elicit expert opinion. For PDN, five main care pathways were
described: GP-led care; pain-specialist-led care; diabetologist-led care; jointly
led care by a GP and a pain specialist; and jointly led care by a GP and
diabetologist. At base case, resource use was consistent with patients being
under the care of a diabetologist. The model adopts an NHS perspective,
accounting for health outcomes in terms of QALYs. Unit costs were taken
from established sources (PSSRU, BNF). Discounting is in line with NICE
methods. Results were then incorporated into the model and a separate
sensitivity analysis was undertaken to test the associated uncertainty.

For the head-to-head modelling, some drugs could only be modelled
deterministically. As a result, only the drugs that could be modelled
probabilistically were included in the sequential analysis. Drugs modelled
probabilistically were pregabalin (150 mg, 300 mg, 600 mg), gabapentin
(900 mg, 3600 mg), oxcarbazepine (600 mg, 1200 mg, 1800 mg), zonisamide
(600 mg), topiramate (400 mg), amitriptyline (75 mg), duloxetine (20 mg,
60 mg, 120 mg) and venlafaxine (75 mg, 225 mg). Lamotrigine (400 mg) and
nortiptyline plus fluphenazine (60 mg + 3 mg) were modelled deterministically.

**Important assumptions for the PDN model**
Model assumptions are the same for PHN model as for the PDN model,
except for the following:

- Patients experiencing pain relief were assumed to remain on the drug and
  receive pain relief for the remainder of their lifetime.
- Patients who experienced pain relief and minor AEs were assumed to have
  been titrated to the minimum dose that gives pain relief. They will continue
to experience the AEs or require drugs to alleviate them for their lifetime.
• All-cause mortality for people with type 2 diabetes was applied in the model.

As was the case for the PHN model, the sequential analysis compared the recommended treatment lines from the IASP-NPSIG guideline with the ‘optimal sequence’ identified in the head-to-head analysis. The head-to-head analysis allowed the prescription of the included treatments to be ranked in decreasing order of net benefit or cost effectiveness. Strict sequencing in terms of cost effectiveness was discarded and a pragmatic approach to titration that reflected clinical practice adopted. The IASP recommendations separate treatment algorithms into first-line, second-line and third-line drugs. As first line, IASP recommends TCAs, SSNRIs, calcium channel ligands and topical lidocaine, with opioids in special circumstances. Second-line drugs are opioid analgesics, including tramadol. Third-line drugs are other antidepressants and antiepileptics (anticonvulsants), mexiletine, NMDA receptor antagonists and topical capsaicin. In the analysis this sequence of drugs is compared with the pragmatic optimal strategy.

For the sequential analysis, following the IASP-NPSIG guidelines with the pragmatic optimal strategy would require 373 individual drug models to be linked for the IASP-NPSIG sequence and 345 for the pragmatic optimal strategy. Given that the two strategies are identical in sequence from the first to the seventh drug prescribed (see table 44), the authors confined the sequential analysis to comparing the differences in the sequences and modelled both sequences from the eighth drug prescribed to the last.


Table 44 Prescription sequences for the IASP-NPSIG guidelines and the HTA report pragmatic strategy

<table>
<thead>
<tr>
<th>Prescription sequence</th>
<th>IASP-NPSIG</th>
<th>Pragmatic optimal strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st</td>
<td>Duloxetine 20 mg</td>
<td>Duloxetine 20 mg</td>
</tr>
<tr>
<td>2nd</td>
<td>Duloxetine 60 mg</td>
<td>Duloxetine 60 mg</td>
</tr>
<tr>
<td>3rd</td>
<td>Duloxetine 120 mg</td>
<td>Duloxetine 120 mg</td>
</tr>
<tr>
<td>4th</td>
<td>Pregabalin 150 mg</td>
<td>Pregabalin 150 mg</td>
</tr>
<tr>
<td>5th</td>
<td>Pregabalin 300 mg</td>
<td>Pregabalin 300 mg</td>
</tr>
<tr>
<td>6th</td>
<td>Pregabalin 600 mg</td>
<td>Pregabalin 600 mg</td>
</tr>
<tr>
<td>7th</td>
<td>Amitriptyline 75 mg</td>
<td>Amitriptyline 75 mg</td>
</tr>
<tr>
<td>8th</td>
<td>Venlafaxine 75 mg</td>
<td>Oxcarbazepine 600 mg</td>
</tr>
<tr>
<td>9th</td>
<td>Venlafaxine 225 mg</td>
<td>Oxcarbazepine 1200 mg</td>
</tr>
<tr>
<td>10th</td>
<td>Gabapentin 900 mg</td>
<td>Oxcarbazepine 1800 mg</td>
</tr>
<tr>
<td>11th</td>
<td>Gabapentin 3600 mg</td>
<td>Topiramate 400 mg</td>
</tr>
<tr>
<td>12th</td>
<td>Oxcarbazepine 600 mg</td>
<td>Venlafaxine 75 mg</td>
</tr>
<tr>
<td>13th</td>
<td>Oxcarbazepine 1200 mg</td>
<td>Venlafaxine 225 mg</td>
</tr>
<tr>
<td>14th</td>
<td>Oxcarbazepine 1800 mg</td>
<td>Gabapentin 900 mg</td>
</tr>
<tr>
<td>15th</td>
<td>Topiramate 400 mg</td>
<td>Gabapentin 3600 mg</td>
</tr>
<tr>
<td>16th</td>
<td>Zonisamide 600 mg</td>
<td>Zonisamide 600 mg</td>
</tr>
</tbody>
</table>

Value of information (VOI) analysis

VOI analysis estimates the potential value of conducting further research in this area, given the underlying uncertainty around parameter estimates. The modelling methods employed by the authors of the HTA report allow such analysis to be conducted. Their VOI analysis estimates the value of future investments in primary research in the field of neuropathic pain. For example, the uncertainty in some model parameters (such as utility when experiencing minor side effects) may not contribute to the decision rule about what is cost effective or not, but other parameters may do so. Thus these VOI estimates may provide useful information for the GDG when making research recommendations.

Further research is recommended to decrease the uncertainty around decisions on health technologies, which may impact on NHS resources. This uncertainty can be measured in terms of opportunity loss, which is defined as the probability that a wrong decision is made multiplied by the consequences of that wrong decision. VOI analysis can identify the reduction in opportunity

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loss associated with having perfect information about a parameter. The
reduction in opportunity loss can be obtained for all parameters (which would
mean there would be no uncertainty around parameter estimates) and is
referred to the expected value of perfect information (EVPI). The expected
value of perfect partial information (EVPPI) is obtained by estimating the value
of reducing opportunity loss associated with having perfect information for a
single parameter or group of parameters. In other words, parameter(s) that
contribute most to decision uncertainty will have the highest EVPPI.

The HTA conducted EVPI analyses for the overall model and EVPPI analyses
for individual parameters and groups of parameters for both populations. VOI
analysis incorporates the threshold in its calculation; a willingness to pay
(WTP) threshold of £30,000 per QALY gained was used as base case, and a
WTP threshold of £20,000 per QALY was used in sensitivity analysis. EVPI for
all parameters was also analysed for a wider range of WTP thresholds in
order to estimate the impact of the threshold on EVPI. A method that involved
sampling from the probability density function of the parameters of interest,
with all other parameters fixed at their expected value, was used (Single
Monte Carlo Simulation [MCS] method). See the HTA report and Coyle &
Oakley (2008), for further information.

2.3.6.2 HTA report: results

Head-to-head modelling: base-case results

The head-to-head analysis presents results in terms of decreasing mean net
benefit associated with each drug at a WTP threshold of £30,000 per QALY
gained. For the PHN model, the head-to-head analysis found that pregabalin
150 mg/day is the most cost effective. If this treatment does not provide
sufficient pain relief the next most cost effective is pregabalin 300 mg/day,
followed by pregabalin 600 mg/day, oxycodone 60 mg/day, gabapentin
1800 mg/day, 2400 mg/day and 3600 mg/day, and lidocaine 5% patch.

At base case for the PHN population, pregabalin 150 mg had a probability of
being most cost effective of 63%, followed by pregabalin 300 mg (32.3%) and
pregabalin 600 mg (4.6%). All other modelled drugs had zero probability of
being most cost effective, including gabapentin 1800 mg, 2400 mg and 3600 mg and oxycodone.

For the PDN model, the hierarchy of cost effectiveness from most to least cost effective in terms of mean net benefit was duloxetine 60 mg, duloxetine 20 mg, pregabalin 300 mg, amitriptyline 75 mg, duloxetine 120 mg, oxcarbazepine 1200 mg, pregabalin 600 mg, oxcarbazepine 600 mg, pregabalin 150 mg, oxcarbazepine 1800 mg, topiramate 400 mg, venlafaxine 225 mg, venlafaxine 75 mg, gabapentin 900 mg, gabapentin 3600 mg and zonisamide 600 mg.

At base case for the PDN population, duloxetine 60 mg had a 29.2% chance of being most cost effective, followed by duloxetine 20 mg (24.4%), pregabalin 300 mg (21.8%) and amitriptyline 75 mg (18.8%). The remaining 5.8% was distributed among a further five options, with seven options having a likelihood of being most cost effective of zero.

The authors of the HTA report were mindful of the convention in clinical practice to titrate drugs upwards. Therefore the sequence modelled differs from the head-to-head analysis results in that the drug sequence is retained, but each drug is titrated before moving on to the next drug. Therefore the most cost-effective pragmatic prescription strategy for PDN was duloxetine 20 mg, 60 mg and 120 mg, pregabalin 150 mg, 300 mg and 600 mg, amitriptyline 75 mg, oxcarbazepine 600 mg, 1200 mg and 1800 mg, topiramate 400 mg, venlafaxine 75 mg and 225 mg, gabapentin 900 mg, and 3600 mg and zonisamide 600 mg. The PHN model results already reflected increasing doses and so did not have to be changed.

Head–to-head modeling: sensitivity analysis and uncertainty

Uncertainty was accounted for in probabilistic sensitivity analysis. For this, the WTP threshold is varied and the probability that an option is most cost effective is plotted against the WTP. First, results were calculated for the base-case analysis with a WTP of £30,000 per QALY and then for a sensitivity value of £20,000 per QALY. Secondly, a wider range of thresholds was used and a cost-effectiveness acceptability curve (CEAC) constructed. CEACs are
constructed by recording the number of times each alternative has the highest net benefit (that is, is cost effective) from the simulated output of a model. The probability (% of times) that each is cost effective is plotted for a range of possible cost-effectiveness thresholds. It is important to note that the alternative with highest probability of being cost effective may not have the highest expected net benefit and thus may not be the cost-effective option. It is necessary to indicate which of the alternatives is expected to have the highest expected net benefit as well as its probability of being cost effective. For more details on CEAC and EVPI methods, see the NICE briefing paper for technology appraisals on exploring uncertainty by Claxton (2008), as well as Barton et al. (2008).

For the PHN model, the sensitivity analysis revealed little uncertainty at the £30,000 per QALY threshold, with various dosages of pregabalin (see the ‘Base-case results’ section above) having a combined probability of 100% of being most cost effective. At a lower threshold of £20,000 per QALY, this result did not change. This corresponds to pregabalin being expected to provide the highest net benefit compared with the other drugs included in the model.

Probabilistic sensitivity analysis for the PDN model showed that, at the £30,000 per QALY threshold, duloxetine at various dosages (see the ‘Base-case results’ section above for probabilities for individual dosages) has a 56% chance of being most cost effective, pregabalin a 21.8% chance and amitriptyline a 18.8% chance, with the remaining drugs having a negligible (less than 2%) chance of being most cost effective. Taking into account the sampling variability resulting from uncertainty around individual parameters, the order of drugs in terms of their likelihood of being the most cost effective at £20,000 per QALY changed to duloxetine 60 mg (26.6%), duloxetine 20 mg (26.1%; resulting in a combined probability for duloxetine of 52.7%), and amitriptyline 75 mg overtaking pregabalin 300 mg with a 28% and 16.9% chance respectively of being most cost effective. Oxcarbazepine in all three modelled doses had a low chance of less than 1.5%. The remaining drugs, including gabapentin, had a zero probability of being most cost effective.
Consequently, the CEAC for the PHN model shows that at a WTP threshold of between £20,000 and £30,000 per additional QALY, four drug treatments are highly likely to be cost effective compared with the remaining comparators evaluated: amitriptyline 75 mg, duloxetine 20 mg and 60 mg, and pregabalin 300 mg. At the lower threshold than £20,000, per QALY amitriptyline has the highest probability of being most cost effective. This changes at around £21,000 per QALY, presumably because of better effectiveness of duloxetine and pregabalin. Only when society is prepared to spend in excess of £21,000 per additional QALY is a more effective and more costly alternative to amitriptyline economically viable without making other people served by the health system worse off. The rank order in terms of probability of being most cost effective remained unchanged for higher WTP thresholds, albeit pregabalin became increasingly more likely to be cost effective, overtaking duloxetine 20 mg as the second most cost-effective option at a threshold of £27,000 per QALY.

In order to recommend the most cost-effective drug, we need to check the consistency of a drug being most cost effective and providing the highest expected net benefit. For the PDN model, the data show that this relationship is consistent at both thresholds. Duloxetine, particularly at the lower doses of 20 and 60 mg, provides the highest net benefit and has the highest probability of being most cost effective (with the same lower dosages again coming first and second in rank order). At the WTP threshold of £30,000 per QALY, pregabalin 300 mg has a higher expected net benefit as well as a higher chance of being cost effective than amitriptyline 75 mg. However, at the lower threshold £20,000 both relationships are reversed, thus favouring amitriptyline. It should be noted that this is true only for a specific, medium dose of pregabalin; however, since the sequence reflects the clinical practice of drug titration, it may be reasonable to generalise this result to say that pregabalin and amitriptyline both seem to be the most viable options after duloxetine within this WTP range.

For the drugs modelled deterministically, one-way and multiway sensitivity analyses did not change the hierarchy of cost effectiveness, with nortriptyline

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plus fluphenazine being consistently more cost effective than lamotrigine.

Nortriptyline was combined with fluphenazine in the trial to mask differences from placebo and strengthen the blinding, and hence was a single active treatment.

**Treatment sequence modelling results**

The sequential analysis compared the optimal, pragmatic strategy based on the head-to-head analysis with the sequence recommended by the IASP-NPSIG guidelines. A more sophisticated sequencing model was not possible because data to populate such a model were not available.

At base case, the sequences in both the PDN and PHN models provided a higher net benefit at a WTP threshold of £30,000 per QALY than the strategy in the IASP guidelines. When the WTP threshold was lowered to £20,000 per QALY, the optimal sequence remained more cost-effective than strategies based upon the IASP guidelines for the medications that could be modelled for both PHN and PDN.

For the PHN sequential analysis, a range of one-way and multi-way sensitivity analyses were undertaken to test the uncertainties around the threshold, care setting (GP-led care, consultant-led care and jointly led care), discounting and compliance.

When the WTP threshold was lowered to £20,000 per QALY, the optimal sequence remained more cost-effective than the IASP strategy for PHN, and the order of the six most cost-effective drugs in term of net benefit did not change. Changing from GP-led care to consultant-led care, changing to jointly care and changing the resource use associated with each clinical lead did not change the hierarchy of drugs in terms of net benefit, and nor did changing the discount rate to 0% or 10% and reducing adherence to 50%. Furthermore, the rank order of the drugs in terms of their probability of being cost effective did not change in any sensitivity analysis.

A range of one-way and multi-way sensitivity analyses were undertaken to test the uncertainty around some key parameters in the PDN sequential
DRAFT FOR CONSULTATION

analysis. These included the WTP threshold, care setting (GP-led care, consultant-led care and jointly led care), discounting and compliance.

Changing the care setting from specialist (diabetologist)-led to GP-led care or pain–specialist-led care, or applying a 0% discount rate, did not change the hierarchy of drugs in terms of net benefit. In a setting where care was under a GP and a pain specialist or a GP and a diabetes specialist, the rank changed for the seventh and eighth drugs in the sequence (oxcarbazepine 600 mg gave more net benefit than pregabalin 600 mg). When the discount rate was raised to 10% and adherence fell to 50%, the sixth and seventh drugs changed order, with pregabalin 600 mg providing more net benefit than oxcarbazepine 1200 mg.

In terms of the drugs’ probability of being the most cost-effective, changing to GP-led care or pain-specialist-led care did not change the hierarchy. When the clinical lead (GP, pain specialist, GP and pain specialist, and GP and diabetes specialist) was changed the net benefit by drug changed only marginally.

Value of information modelling results
Given the level of uncertainty, further research would be of value in this area. Global EVPI estimates the value of eliminating all uncertainty and thereby serves as an upper boundary on the cost of future research (Wailoo et al., 2008).

At an assumed value of a QALY of £30,000, the EVPI for the PHN model is £465.17 per patient, although this varies substantially as the threshold value of a QALY varies. The cost of conducting all additional research in this population conceptually must not exceed the EVPI per patient multiplied by the number of patients with the condition (the recipients of the added net benefit). For example, if there are 10,000 people with PHN in the general population, a trial to generate more certain estimates of treatment effects must not cost more than £4,651,700. If the costs of the trial (and hence the additional information) are greater than this ceiling value, the cost of the research is greater than the value of the gain in net benefit. Also, often it is
important to consider the time horizon within which the additional information
to reduce uncertainty is likely to be of greatest use. If, for example, the patent
for a costly and effective drug expires, the decision uncertainty may reduce
intrinsically, and further research conducted now may not benefit people for
longer than until that point in time.

The VOI modelling also found that parameters other than treatment effects did
not contribute to decision uncertainty, as their EVPPI values were £0.00. In
other words, research should focus on reducing uncertainty about the efficacy
and safety of treatments. There is likely to be considerable information value
from collecting further information on the drugs for which there was insufficient
information to allow their inclusion in the economic model – especially drugs
with lower cost such as amitriptyline which are recommended for the
treatment of neuropathic pain in this guideline.

For PDN, assuming a value of a QALY of £30,000, the EVPI for the overall
model is £3,347 per patient, although this varies substantially as the threshold
value of a QALY varies. The VOI analysis further found that investing in
research to ascertain more reliable estimates of treatment effects will yield the
highest gain in net benefit. Parameters other than the treatment effects
contributed relatively little to decision uncertainty, as their EVPPI values were
less than £2 per patient. The EVPPI for the treatment effects for all treatments
was £3,163.

The greatest contribution to decision uncertainty comes from the effects of
treatment and not from other parameters within both models. It is important to
bear in mind that these results are based only on the treatments included in
the analyses. There may be substantial information value in collecting further
information on the drugs for which there was insufficient information to allow
their inclusion in the economic model – especially lower-cost drugs that are
recommended for the treatment of PDN, such as amitriptyline at dosages
above and below 75 mg.

2.3.6.3 Discussion

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This discussion will contrast the two approaches used for the HTA report and the current clinical guideline and discuss their potential impact on interpretation and generalisability for this guideline. Then the remaining limitations of the model will be discussed. All limitations are listed continuously throughout this chapter to ease orientation. Finally, an evidence statement will summarise the (draft) findings from the HTA report.

Differences between the HTA report and the current guideline

It is recognised that the methodology adopted for the HTA report, in relation to both the efficacy review and health economic evaluation, was of high quality. Therefore the information provided below does not aim to appraise the validity of the HTA report, but to assess the generalisability of the HTA report in relation to the current guideline.

Efficacy review for HTA modelling – comments on generalisability

The current guideline addressed neuropathic pain as a blanket condition, while the HTA report reviewed only two conditions, namely PHN and PDN. This means that the health economic evidence base is better for these two subpopulations than other subgroups (please see section 2.3.6 for the health economic evidence review for this guideline). Conducting de novo economic modelling in the time frame of the current guideline would not have produced a different result than that reached by the HTA, as we would have had to base our models on the same evidence base. Other subpopulations would have been difficult to model because of lack of data availability, as shown by our effectiveness and economic reviews of the literature. As the information is presented in the HTA review, the GDG was able to appraise and discuss its generalisability. The results of the cost-effectiveness analysis for individual drugs may inform the recommended sequence for neuropathic pain as a blanket condition, and specific recommendations may be possible for subgroups.

The HTA report had no restrictions on which drugs to include in the reviews. On the other hand, the scope of the current guideline listed specific drugs to be covered by the guideline. Therefore a number of drugs in the HTA review were not covered by the current guideline scope. However, only three of these...
drugs were modelled, and none of them had a notable chance of being most
cost effective. Therefore this is unlikely to adversely affect the interpretability
of the decision modelling results.

Exclusion criteria differed for the current guideline compared with the HTA
report, after consultation with the GDG members based on their expertise and
experience. The exclusion criteria that were used for the current guideline but
not for the HTA reviews are listed in table 45.

**Table 45 Exclusion criteria used for the current guideline but not the
HTA report**

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Adults with neuropathic pain arising directly from trauma or orthopaedic surgical procedures.</td>
</tr>
<tr>
<td>2.</td>
<td>Studies on terminal pain, psychogenic pain, somatoform pain or musculoskeletal pain.</td>
</tr>
<tr>
<td>4.</td>
<td>Administration of drugs by an intravenous or epidural route (except opioid analgesics).</td>
</tr>
<tr>
<td>5.</td>
<td>For antidepressants and anticonvulsants, drug administration by topical application was excluded (but there was no restriction on the route of administration for opioid analgesics).</td>
</tr>
<tr>
<td>6.</td>
<td>Studies that measure spasticity or spasm, but not neuropathic pain.</td>
</tr>
<tr>
<td>7.</td>
<td>Studies on experimentally induced pain.</td>
</tr>
<tr>
<td>8.</td>
<td>Pre-emptive analgesia studies on acute pain with follow-up of less than 4 weeks (for example, pre-emptive analgesia studies on postoperative/post-surgical acute pain with 24 hours or 1 week after the operation as the end-point).</td>
</tr>
<tr>
<td>9.</td>
<td>Studies with a sample size of less than 10.</td>
</tr>
<tr>
<td>10.</td>
<td>Crossover studies with no washout and no analysis of carryover effects, or a washout period of less than 1 week.</td>
</tr>
<tr>
<td>11.</td>
<td>Studies with a treatment period of less than 4 weeks for antidepressants and anticonvulsants, less than 3 weeks for topical capsaicin or less than 1 week for opioids and topical lidocaine.</td>
</tr>
<tr>
<td>12.</td>
<td>Non-English papers.</td>
</tr>
</tbody>
</table>
Although the minimum trial duration (criteria 8 and 11 in table 10) was not specified in the inclusion criteria, the efficacy data used in the modelling was taken from RCTs with trial durations of at least 4 weeks. Limiting the route of drug administration (criteria 4 and 5) does not seem to make a lot of difference as only lidocaine was modelled. Washout periods (criterion 10) were not taken into consideration explicitly; however, a summary value for rate ratios has been taken from the meta-analysis, which gives some confidence in the used magnitude of effect. It seems reasonable to assume that any included studies with very few participants (criterion 9) and meeting the criteria for inclusion in meta-analysis and probabilistic modelling would have a notable impact on the overall findings.

In the HTA review, the primary pain outcomes for meta-analysis were: 50% response to pain (or 50% improvement in pain) and 30% response to pain (or 30% improvement in pain). The HTA review has dichotomised ‘global improvement’ measures to construct 50% pain improvement and 30% pain improvement, and then pooled them with the 50% and 30% pain reduction in meta-analysis and called it ‘50% response to pain’ and ‘30% response to pain’. The GDG agreed that pain reduction and global improvement are two distinct outcomes that measure different aspects in pain research, a notion supported by IMMPACT. The current guideline instead has pooled and presented pain reduction and global improvement separately. For the health economic modelling, pain relief has been used to define the health states, to which a global valuation of quality of life has been assigned – that is, a utility estimate. Pain and other outcome data are widely used to feed into these estimates, and pain is a dimension on the EQ-5D tool that is frequently used to measure quality of life for economic evaluations. However, from a purely conceptual viewpoint, more levels of pain states (such as 30% pain improvement) could have been modelled. It is unlikely that this would have altered the results of the analysis, especially for those drugs most likely to be cost effective. Currently, a drug that fails to provide less than 50% pain relief does not incur any health benefits in the model. But introducing a lower cut-off point may result in some benefit, albeit smaller than that obtained with a drug that reduces pain by at least 50%. Thus the differences between the more...
effective and less effective drugs may become smaller, but the rank order in
the head-to-head analysis will not change. In terms of the probability of a
treatment being the most cost effective, those treatments that currently have a
zero chance of being cost effective may achieve a marginally positive chance.
This would not alter the interpretation of the current findings.

**Health economic evaluation in the HTA report – comments on
generalisability**

A number of drugs were included in the probabilistic modelling (or
deterministic modelling) and sequential analysis that were not covered by the
current guideline scope, including epidural methylprednisolone and intrathecal
lidocaine in the PHN model, and venlafaxine and zonisamide in the PDN
model. None of these drugs were among those most likely to be cost effective.
Taking these drugs out of the modelling and the modelled sequence will not
change the rank order of the remaining drugs.

The HTA decision analysis for PDN modelled amitriptyline at a dose of 75 mg.
This is relatively high, and in practice a patient may start at a lower dose
followed by dose titration up to an effective dose that may still be lower than
75 mg. This is a limitation of the modelling, and the GDG carefully considered
this when making its recommendations.

As discussed above, both PHN and PDN models were based on two pain
states, which were ‘at least 50% pain relief’ or ‘no pain relief’, and the
assumption was that less than 50% pain relief is considered insufficient pain
relief that does not result in a change in health state utility or QALYs. In
addition to the assumptions and implications for the guideline discussed
above, basing the modelling on this meta-analysed outcome resulted in
numerous drugs not being evaluated in the modelling (especially TCAs for
PHN) because of a lack of data. This is a serious limitation to the
completeness and applicability of the analysis, and the GDG carefully
considered complementing the recommended drugs with others for the
treatment of all subgroups of the neuropathic pain population.
For both the PHN and PDN models, expert opinion supplemented the data where insufficient data were available. The experts were condition-specific, and six experts in PHN and four experts in PDN completed the questionnaire. The data obtained informed the costing in the model. The model was not sensitive to changing the three care settings for PHN and the five settings for PDN, and the rank order of the most cost effective drugs remained unchanged.

For both the PHN and PDN models, data on resource use of different care pathways was collected from experts (through questionnaires; see above). The care pathways used in the deterministic and probabilistic modelling do not appear match the definition of ‘non-specialist settings’ used in the current guideline. This has two possible implications: first, cost estimates may not reflect those relevant for the current guideline, and secondly, the drugs may not be suitable to be prescribed in a non-specialist setting. For example, healthcare professionals who are not pain specialists may have different levels of skills and confidence in prescribing and managing the long-term use of opioids. Moreover, some drugs which need specific monitoring, such as venlafaxine and epidural methylprednisolone, are not appropriate for the use in non-specialist settings, especially in general practice. Again, the GDG discussed the results and made their recommendations based on both the presented evidence and their own judgement. In terms of the model results, an example is that venlafaxine was modelled for PDN, but was ranked in 8th place in the sequence. The decision that venlafaxine is not an alternative for the decision problem for this particular guideline will not affect the results, since disregarding one option from the head-to-head findings will not alter the ranking of treatments.

The methods used in the HTA report are of high quality, although data synthesis techniques such as network meta-analysis might have enabled the analysts to evaluate a wider network of evidence. This may have resulted in the inclusion of more drugs in the models.
HTA model limitations resulting from the reliability of RCT data

The reliance of the model on data from clinical trials means that it is susceptible to the weaknesses associated with trials, such as failing to reflect real clinical practice.

The different drug doses used in the models were based on the efficacy trials. However, drug doses in trials do not necessarily reflect the doses prescribed in practice, and may be substantially higher than those prescribed outside trial conditions. This is an important issue and affects both clinical and cost effectiveness evidence. Making recommendations in an evidence-based way will require careful consideration of valid inferences. Deviations from the evidence will be made only where transparent reasoning allows.

In addition to the possible differences in dosages between trials and clinical practice, it is possible that the data on minor adverse events are unrepresentative. In a drug trial a patient experiencing minor adverse events may be asked to continue to take the drug for the short duration of the trial. In contrast, a member of the public under the care of their GP and/or a specialist may agree to try an alternative drug in the hope of obtaining pain relief without unpleasant adverse events.

Both the PHN and PDN models did not address combination therapy, which was a key question to be addressed by the current guideline. The limitations of the clinical evidence that informed the modelling did not allow combination therapies to be modelled. There may have been some crossover effect, as some trials allowed patients to take co-analgesics or did not report on this matter. It was not possible to estimate the implications for pain relief or adverse-event data recorded in the trials. Any recommendations relating to treatment combinations should, in the absence of reliable evidence, be made with caution. The deliberations and decision-making of the GDG have been recorded and are presented transparently.

The clinical trials did not report outcomes at titration stages and thus it was not possible to model movement between pain states and brief adverse events experienced during titration. Also, the clinical characteristics of pain...
may change over time, resulting in patients trying a medication that has been unsuccessful at relieving their pain in the past. Paucity of data on this topic prevented this practice from being modelled, and the GDG took this into consideration when making their recommendations.

Comorbidities associated with PDN and diabetes, such as cardiovascular disease and peripheral vascular disease, were not accounted for in the model, because the systematic review excluded efficacy trials that included patients with comorbidities.

Because the RCTs of PDN evaluated chronic neuropathic pain of moderate to severe intensity, the findings for such studies cannot be generalised to patients with mild PDN pain. This was considered by the GDG when making their recommendations.

Mortality rate imputation has been based on the best available evidence. However, there are a number of issues, including how similar or dissimilar the mortality rates of patients with type 2 diabetes and patients with PDN are. As a result the study may underestimate or overestimate the survival QALYs associated with the prescription of analgesic drugs to PDN patients. This was considered by the GDG when making their recommendations.

In conclusion, all of the items listed above have been discussed by the GDG, and consistency between the effectiveness review and the indirect cost-effectiveness evidence has been checked. The debate and reasoning behind recommendations is recorded in the next section.

2.4 Evidence to recommendations

2.4.1 Antidepressants

The GDG agreed that there is good evidence (of high to moderate quality) on the efficacy of antidepressants, namely TCAs and SNRIs, for the primary outcomes on pain.
TCAs

Amitriptyline: first-line and/or second-line treatment for neuropathic pain

The GDG acknowledged that the majority of the evidence on TCAs came from studies on amitriptyline, and that the evidence covered various study populations with different neuropathic pain conditions. Since amitriptyline is widely used for treating neuropathic pain in current practice, the GDG agreed that amitriptyline should be recommended as first-line and/or second-line treatment, depending on the patient’s condition, other lifestyle factors and current medication usage. Amitriptyline is not licensed for neuropathic pain. However, the evidence base for treatment efficacy was deemed sufficient to make this positive recommendation. Because amitriptyline is unlicensed for neuropathic pain, the GDG came to the consensus that its initial dosage and titration should be lower than is recommended in the ‘British National Formulary’ (BNF). The GDG agreed that clear statements on drug dosage and titration in the recommendations are crucial for non-specialist settings to emphasise the importance of titration to achieve maximum benefit. The GDG also agreed that the adverse effects of amitriptyline should be discussed with the patient and weighed against the benefit provided.

Nortriptyline and imipramine: alternatives for amitriptyline

The GDG was concerned that many patients would not tolerate the adverse effects of amitriptyline, even if they achieved satisfactory pain reduction. The GDG reached a consensus that in these cases other TCAs, namely nortriptyline and imipramine, should be recommended as alternatives to amitriptyline, because there is evidence on efficacy in relation to global improvement for these drugs. Both are relatively low-cost drugs, and for this patient population they are potentially good value for money, provided that they do not cause other adverse effects that would reduce the potential gain in quality of life obtained by switching from amitriptyline.

Desipramine

Although there was some evidence for the efficacy of desipramine, the GDG decided not to recommend desipramine because it is no longer in the BNF, and hence should not be used in clinical practice.
SNRIs

Duloxetine: first-line treatment for painful diabetic neuropathy

The GDG agreed that there is high-to-moderate-quality evidence for the efficacy of duloxetine and venlafaxine in treating neuropathic pain. However, all three studies on duloxetine were in patients with painful diabetic neuropathy, and cost-effectiveness evidence is specifically for the treatment of this condition (see section 2.3.6). Therefore the GDG decided that duloxetine should be recommended as first-line treatment specifically for painful diabetic neuropathy. The GDG also agreed that the adverse effects of duloxetine should be discussed with the patient and weighed against the benefit provided.

Venlafaxine

Based on information from the Medicines and Healthcare Products Regulatory Agency (MHRA), the GDG agreed that the use of venlafaxine for the treatment of neuropathic pain would need specialist care and regular monitoring, and so it should not be initiated in non-specialist settings.

Different drug class for second-line treatment

The GDG agreed that if satisfactory pain reduction was not achieved with an antidepressant as first-line treatment, a drug from another therapeutic class (namely an anticonvulsant – see section 2.4.2) should be recommended as second-line treatment or as combination therapy, instead of trying another antidepressant.

2.4.2 Anticonvulsants

The GDG agreed that there was insufficient evidence on the efficacy of lamotrigine, sodium valproate and phenytoin for the treatment of neuropathic pain.

Pregabalin as first-line and/or second-line treatment for neuropathic pain, in comparison with gabapentin

The GDG agreed that there is evidence (high to moderate quality) for the efficacy of pregabalin and gabapentin for the treatment of neuropathic pain. The evidence covered various study populations with different neuropathic...
pain conditions. The GDG discussed the evidence on these two drugs and agreed that pregabalin is a better treatment than gabapentin for neuropathic pain because:

- evidence showed that pregabalin has lower NNT values for at least 30% and at least 50% pain reduction compared with gabapentin, with a similar adverse-effect profile
- pregabalin has simple dosing and titration compared with gabapentin
- cost-effectiveness modelling showed that pregabalin is more cost effective than gabapentin (see section 2.3.6.3).

Since pregabalin and gabapentin have similar pharmacological profiles (that is, both have high affinity for the alpha-2-delta subunit of the voltage-dependent calcium channel in the central nervous system – therefore if a person had unsatisfactory pain reduction with one drug, it is highly unlikely that they will achieve pain reduction with the other), and the evidence showed that pregabalin is better than gabapentin, the GDG agreed that pregabalin should be recommended as first-line and/or second-line treatment (depending on the patient’s condition, other lifestyle factors and current medication usage). The GDG also agreed that clear statements on drug dosage and titration in the recommendations are crucial for non-specialist settings to emphasise the importance of titration to achieve maximum benefit. The GDG also agreed that the adverse effects of pregabalin should be discussed with the patient and weighed against the benefit provided.

**Different drug class for second-line treatment**

The GDG agreed that if satisfactory pain reduction was not achieved with an anticonvulsant as first-line treatment, a drug from another therapeutic class (namely an antidepressant – see section 2.4.1) should be recommended as second-line treatment or as combination therapy, instead of trying another anticonvulsant.

**Topiramate and oxcarbazepine**

There was only limited evidence (mainly from studies on patients with painful diabetic neuropathy) for the efficacy of topiramate and oxcarbazepine, and...
this evidence showed that patients on either of these drugs were more likely to withdraw because of adverse effects than patients on gabapentin and pregabalin (that is, the NNTH values were lower for topiramate and oxcarbazepine). The GDG therefore agreed that topiramate and oxcarbazepine should not be recommended for the treatment of neuropathic pain in non-specialist settings.

**Carbamazepine and trigeminal neuralgia**

The GDG recognised that the evidence on carbamazepine for the treatment of neuropathic pain overall is very limited and dated. Therefore the GDG agreed that carbamazepine should not be recommended for use across all neuropathic pain conditions. However, although only one study on carbamazepine and trigeminal neuralgia met the inclusion and exclusion criteria of this guideline, the GDG acknowledged that carbamazepine (within its licensed indication) has been the routine treatment for trigeminal neuralgia in clinical practice since the 1960s, and anecdotal evidence from clinical experience showed that carbamazepine may be effective for treating trigeminal neuralgia. As trigeminal neuralgia is an extremely painful condition, and currently there is no good-quality evidence on which to base specific recommendations for treating it, the GDG agreed that carbamazepine may have a specific role in treating trigeminal neuralgia, and expected that current routine practice will continue. Consequently, the GDG came to the consensus that a research recommendation should be made in order to further investigate the efficacy of carbamazepine for treating trigeminal neuralgia (see section 3.1).

### 2.4.3 Opioids

The GDG discussed the evidence on opioid analgesics, namely tramadol, morphine and oxycodone, and agreed that it was of moderate to low quality and lacked reliability. Hence the GDG recognised that the evidence does not fully reflect current clinical practice.

**Tramadol: third-line treatment for neuropathic pain**

The GDG acknowledged that, compared with other opioid analgesics, tramadol is commonly used in non-specialist settings. Hence the GDG felt that...
it is valid and appropriate to recommend tramadol for the treatment of neuropathic pain in non-specialist settings, either as third-line treatment (monotherapy) or as combination therapy with second-line treatment, to ensure that treatment is continued while a patient is waiting for referral to a condition-specific service and/or a specialist pain service. The GDG also agreed that clear statements on drug dosage and titration in the recommendations are crucial for non-specialist settings to emphasise the importance of titration to achieve maximum benefit.

The acquisition costs of tramadol are relatively low for 50 mg preparations (between approximately £30 and £40 per year), and higher for higher-dose, modified-release preparations (12-hour release preparations: 100 mg, £70 to £100 per year; 150 mg, £110 to £170 per year; 200 mg, £150 to £220 per year; 24-hour release preparations: 300 mg, £270 to £300 per year; 400 mg, £370 to £400 per year). If tramadol provides pain relief for patients for whom first-line and second-line treatments were ineffective and who are experiencing intolerable pain, this acquisition cost is likely to represent value for money. It may be partially offset by savings of further consultations or referrals to pain specialists (where the patient and clinician agree that referral is not required).

The adverse effects of tramadol should be discussed with the patient and weighed against the benefit provided. The GDG stressed that if tramadol is used as combination therapy, more conservative dosage and titration may be required.

**Morphine and oxycodone**

The GDG agreed that the evidence on morphine and oxycodone was limited and of only low or moderate quality. The GDG further agreed that the evidence showed that patients treated with morphine were more likely to withdraw because of adverse effects (that is, lower NNTH values) compared with patients treated with tramadol. There was insufficient evidence on the primary pain outcomes for oxycodone. Moreover, the GDG was concerned about the risk of long-term addiction or dependence, the severe adverse effects, and the potential fatality of overdose with morphine and oxycodone.
The GDG was also concerned that clinicians in non-specialist settings have very different levels of experience in prescribing and managing the long-term use of morphine and oxycodone. Therefore the GDG came to the consensus that morphine and oxycodone should not be initiated in non-specialist settings without an assessment by a specialist pain service and/or a condition-specific service. However, the GDG felt that if an assessment is carried out and an agreement to use morphine or oxycodone in non-specialist settings is obtained from the specialist pain service or condition-specific service, a multidisciplinary care plan is needed to ensure both appropriate management of adverse effects and continuing treatment in the non-specialist setting.

2.4.4 Topical treatments

Topical capsaicin

The GDG agreed that there is limited, moderate-quality evidence indicating that topical capsaicin has no efficacy for pain reduction or global improvement for neuropathic pain overall. However, the GDG (based on their clinical experience) acknowledged that a subgroup of patients with 'localised neuropathic pain' may benefit from topical capsaicin. Nevertheless, in view of the limited evidence available, the GDG felt that it could not recommend the use of topical capsaicin across all neuropathic pain conditions in non-specialist settings.

Topical lidocaine

Since none of the included studies on topical lidocaine reported the primary outcomes of pain, the GDG referred to the evidence statements for 'other reported pain outcomes' to generate discussion. The GDG agreed that there is a lack of evidence (especially placebo-controlled trials) for the efficacy of topical lidocaine in non-specialist settings. Moreover, in health-economic modelling, lidocaine was modelled for the patient population with painful diabetic neuropathy and provided the lowest mean net benefit at WTP thresholds between £20,000 and £30,000 per QALY, and had a zero probability of being the most cost-effective treatment when pregabalin is an option. However, as for topical capsaicin, the GDG (based on their clinical experience) acknowledged that a subgroup of patients with 'localised Neuropathic pain: NICE clinical guideline DRAFT (October 2009) Page 109 of 136
neuropathic pain’ may benefit from topical lidocaine. Nevertheless, in view of the limited evidence available, the GDG felt that it could not recommend the use of topical lidocaine across all neuropathic pain conditions in non-specialist settings.

2.4.5 Comparative and combination trials

The GDG acknowledged that there were few studies involving comparative trials and combination therapy trials, and that most evidence was of low or very low quality.

Amitriptyline or nortriptyline vs gabapentin

The GDG agreed that there was inconsistent, moderate-quality evidence on the efficacy of amitriptyline or nortriptyline compared with gabapentin. Moreover, as there is uncertainty in terms of the low-quality comparative evidence on adverse effects, the GDG agreed that both amitriptyline (with nortriptyline as an alternative) should be recommended as options for first-line and second-line treatment.

Pregabaline vs oxycodone and pregabalin vs topical lidocaine

The evidence from both comparisons was of very low quality. Therefore the GDG agreed that no comparative recommendations should be made.

Amitriptyline vs topical capsaicin

The comparative evidence was of low or very low quality. Therefore the GDG agreed that no comparative recommendations should be made.

Imipramine vs venlafaxine

Although the GDG agreed that there was moderate-quality evidence suggesting that there is no difference between the efficacy of imipramine and venlafaxine, the GDG concluded that safety information from the MHRA meant that venlafaxine should not be recommended for use in non-specialist settings.

Amitriptyline vs nortriptyline

The comparative evidence was of low or very low quality. Therefore the GDG agreed that no comparative recommendations should be made. However,
based on the limited evidence for the efficacy of nortriptyline (one placebo-controlled trial) and the GDG’s clinical experience, the GDG agreed that the recommendation that nortriptyline can be offered as an alternative to amitriptyline if the patient achieves satisfactory pain reduction with amitriptyline but cannot tolerate its adverse effects should remain.

**Pregabalin + oxycodone vs pregabalin**

The evidence on combination therapy was of very low quality. Therefore the GDG agreed that no recommendations should be made.

**Gabapentin + oxycodone vs gabapentin**

The evidence on combination therapy was of low or very low quality. Therefore the GDG agreed that no recommendations should be made.

**Pregabalin + oxycodone vs oxycodone**

The evidence on combination therapy was of very low quality. Therefore the GDG agreed that no recommendations should be made.

**Others**

Only limited studies on combination therapy were identified, and these provided insufficient evidence. However, based on current clinical practice and the experiences of patients and carers, the GDG came to the consensus that amitriptyline (or nortriptyline or imipramine as alternatives) with pregabalin, or duloxetine with pregabalin, should be an option for second-line treatment as combination therapy (see recommendation 1.1.13) where unsatisfactory pain reduction is achieved with a single drug, or where switching or stopping drugs is inappropriate for an individual patient. The same consensus was reached for tramadol (see recommendation 1.1.14).

**2.4.6 Key principles of care**

The GDG acknowledged that the low-quality evidence on adverse effects for both antidepressants and anticonvulsants was restricted by which, and how, data on particular adverse effects were collected in the trials. Based on the GDG’s knowledge and experience in clinical practice, the evidence did not fully reflect a complete picture of the adverse effects patients would
experience in real life. Issues such as contraindications, comorbidities, current medication usage, age (for example, vulnerability to falls), lifestyle factors, daily activities and participation, patient preference and patients' information needs should be taken into consideration when selecting pharmacological treatments. The GDG further discussed that extra caution is needed when switching or combining drugs.

The GDG also stressed that regular clinical reviews are important to assess and monitor drug titration, tolerability, adverse effects and the need to continue treatment. This principle should apply to all treatments throughout the care pathway to ensure that patients receive appropriate care.

As referral to specialist pain services is not an exit from non-specialist care, but the start of a collaborative, ongoing approach to management, the GDG felt that the gateway for referrals to pain specialist services, as well as other condition-specific services, should not be at the end of the care pathway. Clinicians or healthcare professionals in non-specialist settings should consider making referrals at any stage of the care pathway if their regular clinical reviews identify changes in or deterioration of the patient’s pain, health condition, mood (depression and/or anxiety), or daily activities and participation.

Finally, to ensure continuity of care, the GDG also came to a consensus that, for patients whose neuropathic pain is already effectively managed before the publication of this guideline, their existing treatments should be continued.

2.4.7 Recommendations

Key principles of care

1.1.1 Address the person’s concerns and expectations when agreeing which treatments to use by discussing:

- the benefits and possible adverse effects of each treatment
- coping strategies for pain and possible adverse effects.

1.1.2 Explain both the importance of dosage titration and the titration process, providing written information if possible.
1.1.3 If the person or the healthcare professional (during the regular clinical reviews; see section 1.1.8) identifies unsatisfactory pain reduction or deterioration in the underlying health condition, follow the care pathway (see page 14) or refer the person to a specialist pain service and/or a condition-specific service.

1.1.4 When selecting pharmacological treatments, take into account:

- the person’s vulnerability to specific adverse effects because of comorbidities or age (for example, vulnerability to falls)
- lifestyle factors (such as occupation)
- any mental health problems (such as depression and/or anxiety)
- patient preference
- current medication.

1.1.5 When withdrawing or switching treatment, taper the withdrawal regimen to take account of dosage and any discontinuation symptoms.

1.1.6 When introducing a new treatment, consider an overlap of treatments to avoid deterioration in pain control.

1.1.7 After starting or changing a treatment, perform an early clinical review of dosage titration, tolerability and adverse effects to assess the suitability of the chosen treatment.

1.1.8 Perform regular clinical reviews to assess and monitor the effectiveness of the chosen treatment. Each review should include assessment of:

- pain reduction
- mood (in particular, whether the person may have depression and/or anxiety)
- daily activities and participation12 (including ability to work)

• adverse events
• overall improvement as reported by the person.

If there is satisfactory improvement, consider continuing or stepping down the treatment.

1.1.9 Continue existing treatments for people whose neuropathic pain is already effectively managed.

**First-line treatment**

1.1.10 Offer oral pregabalin or amitriptyline* as first-line treatment (but see recommendation 1.1.11 for people with painful diabetic neuropathy).

• For pregabalin: start at 150 mg per day (divided into two or three equal doses), with upward titration to an effective dose or the person’s maximum tolerated dose of no higher than 600 mg per day (divided into two or three equal doses).
• For amitriptyline*: start at 10 mg per day, with gradual upward titration to an effective dose or the person’s maximum tolerated dose of no higher than 75 mg per day (higher doses could be considered in consultation with a specialist pain service).

1.1.11 For people with painful diabetic neuropathy, offer duloxetine as first-line treatment. Start at 60 mg per day (a lower starting dose may be appropriate for some patients), with upward titration to an effective dose or the person’s maximum tolerated dose of no higher than 120 mg per day.

1.1.12 Based on both the early and regular clinical reviews:

• if there is satisfactory improvement, consider continuing or stepping down first-line treatment
• if amitriptyline* as first-line treatment results in satisfactory pain reduction but the person cannot tolerate the adverse effects, consider offering oral nortriptyline* or imipramine* as an alternative.

• if the person’s underlying health condition has deteriorated, or the pain significantly limits their daily activities and participation\(^{13}\), consider referring them to a specialist pain service and/or a condition-specific service.

**Second-line treatment**

1.1.13 If satisfactory pain reduction is not achieved with first-line treatment at the maximum tolerated dose, offer treatment with another drug class\(^{14}\) instead of or in combination with the original drug, after informed discussion with the person.

- If first-line treatment was with amitriptyline* (or nortriptyline* or imipramine*), switch to or combine with oral pregabalin.
- If first-line treatment was with duloxetine for people with painful diabetic neuropathy, switch to or combine with oral pregabalin.
- If first-line treatment was with pregabalin, switch to or combine with oral amitriptyline*.

Dosage and titration should be same as in recommendation 1.1.10.

**Third-line treatment**

1.1.14 If satisfactory pain reduction is not achieved with second-line treatment:

- refer the person to a specialist pain service and/or a condition-specific service and

\(^{13}\) The World Health Organization ICF (International Classification of Functioning, Disability and Health) (2001) defines participation as ‘A person’s involvement in a life situation.’ It includes the following domains: learning and applying knowledge, general tasks and demands, mobility, self-care, domestic life, interpersonal interactions and relationships, major life areas, community, and social and civil life.

\(^{14}\) Drug classes are antidepressants and anticonvulsants.
• consider offering oral tramadol as third-line treatment instead of
  or in combination with the second-line treatment while waiting for
  referral.

1.1.15 For tramadol as monotherapy, start at 50 to 100 mg per day, with
  upward titration if required to an effective dose or the person's
  maximum tolerated dose of no higher than 400 mg per day. If
  tramadol is used as combination therapy, more conservative
  titration may be required.

Other treatments

1.1.16 Do not start treatment with opioids (such as oral morphine or
  oxycodone) other than tramadol without an assessment by a
  specialist pain service or a condition-specific service.

1.1.17 Pharmacological treatments other than those recommended in this
  guideline may be started after an assessment by a specialist pain
  service or a condition-specific service. If treatment results in
  satisfactory pain reduction, it may be continued in non-specialist
  settings, with a multidisciplinary care plan and careful management
  of adverse effects.

3 Research recommendations

The VOI analysis conducted for the HTA report revealed which parameters
have the highest potential to increase net benefit in the PDN and PHN
subpopulations through reducing uncertainty. The models for both populations
found that research should focus on the treatment effects of drugs providing
greatest net benefit, as well as on low-cost drugs that could not be modelled
at all relevant dosages.

In light of this and a wider discussion of all relevant evidence for this guideline,
we have made the following recommendations for research, based on our
review of evidence, to improve NICE guidance and patient care in the future.
3.1 Carbamazepine for trigeminal neuralgia

What is the clinical and cost effectiveness of carbamazepine as first-line treatment for trigeminal neuralgia compared with other better-tolerated pharmacological treatments?

Why this is important

Carbamazepine has been the standard treatment for trigeminal neuralgia since the 1960s. Although there is insufficient evidence, it is perceived by clinicians to be efficacious. There is evidence that antidepressants such as amitriptyline, and anticonvulsants such as pregabalin, are effective for treating peripheral neuropathic pain. However, the evidence is not specific to trigeminal neuralgia.

| Patient: | Adults (aged 18 or over) with trigeminal neuralgia. |
| Intervention: | Carbamazepine |
| Comparator: | Other pharmacological treatments such as amitriptyline, pregabalin, duloxetine and oxcarbazepine. |
| Outcome: | Patient-reported pain reduction (minimum reporting requirement of at least 30% and at least 50% pain reduction), patient-reported global improvement, minor and major adverse effects, mental health, function of daily activities, participation, health utilities and resource use. |
| Comment: | Trials on drug efficacy to relieve neuropathic pain should have a sufficiently long follow-up to assess the long-term effects of drugs. Minor and major adverse events should be reported separately for all trial arms, and data on failure to respond to other analgesics should be collected. Primary and secondary outcome definitions and data collection must be consistent for new research. Data on pain relief should be reported not only as a dichotomous outcome of pain relief at a threshold of 30% or 50%, but as a more clinically representative measure that better captures the degree of pain relief with a greater number of categories. |
3.2 Monotherapy versus combination therapy for neuropathic pain

What is the clinical effectiveness, cost effectiveness and tolerability of monotherapy versus combination therapy for neuropathic pain?

Why this is important

Combination therapy, such as antidepressants with anticonvulsants or antidepressants/anticonvulsants with opioid analgesics, is commonly prescribed for neuropathic pain. However, there is currently a lack of head-to-head comparative trials to assess the clinical effectiveness, cost effectiveness and tolerability of these combinations.

Patient: Adults (aged 18 or over) with neuropathic pain.

Intervention:
- Antidepressants as monotherapy including amitriptyline and duloxetine.
- Anticonvulsants such as pregabalin as monotherapy.
- Opioid analgesics such as tramadol as monotherapy.
- Combination therapy with the above.

Comparator: Compare amitriptyline, duloxetine, pregabalin and tramadol as monotherapy; as well as comparisons in different combination therapies.

Outcome: Patient-reported at least 30% and at least 50% pain reduction, patient-reported global improvement, and minor and major adverse effects, mental health, function of daily activities, participation, health utilities and resource use.

Comment: Trials on drug efficacy to relieve neuropathic pain should have a sufficiently long follow-up to assess the long-term effects of drugs. Minor and major adverse events should be reported separately for all trial arms, and data on failure to respond to other analgesics should be collected. Primary and secondary outcome definitions and data collection must be consistent for new research. Data on pain relief should be reported not only as a dichotomous

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outcome of pain relief at a threshold of 30% or 50%, but as a more clinically representative measure that better captures the degree of pain relief with a greater number of categories.

### 3.3 Non-pharmacological therapy

What is the clinical and cost effectiveness of non-pharmacological therapy in treating neuropathic pain in adults?

**Why this is important**

People with neuropathic pain are often offered non-pharmacological therapy, although there is limited robust evidence to support this. For example, electrical stimulation (transcutaneous electrical nerve stimulation [TENS] or dorsal column stimulation), transcranial magnetic stimulation, physiotherapy, psychological therapy and acupuncture are already in widespread use in the NHS but their evidence base is poor. Furthermore, little is known about their long-term efficacy or safety.

**Patient:** Adults (aged 18 or over) with neuropathic pain.

**Intervention:** Non-pharmacological treatments; for example, electrical stimulation (TENS or dorsal column stimulation), transcranial magnetic stimulation, physiotherapy, psychological therapy and acupuncture.

**Comparator:** Placebo/sham treatments, each other (??) or pharmacological treatments.

**Outcome:** Patient-reported at least 30% and at least 50% pain reduction, patient-reported global improvement, and minor and major adverse effects, mental health, function of daily activities, participation, health utilities and resource use.

**Comment:** Trials on drug efficacy to relieve neuropathic pain should have a sufficiently long follow-up to assess the long-term effects of drugs. Minor and major adverse events should be reported separately for all trial arms, and data
on failure to respond to other analgesics should be collected. Primary and secondary outcome definitions and data collection must be consistent for new research. Data on pain relief should be reported not only as a dichotomous outcome of pain relief at a threshold of 30% or 50%, but as a more clinically representative measure that better captures the degree of pain relief with a greater number of categories.

3.4  Factors influencing quality of life

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

Why this is important

There is evidence suggesting that people with neuropathic pain experience poorer physical and mental health than people with other forms of pain even when adjusted for pain intensity. The discrepancy between pain intensity and quality of life implies that other, unrecognised factors are important for people with neuropathic pain and that these factors may influence their daily activities and participation.

Patient: Adults (aged 18 or over) with neuropathic pain.

Intervention: Observational or qualitative study designed to identify key factors that may influence the daily activities and participation of people with neuropathic pain.

Comparator: N/A

Outcome: Improvement in overall quality of life.

15 The World Health Organization ICF (International Classification of Functioning, Disability and Health) (2001) defines participation as ‘A person’s involvement in a life situation.’ It includes the following domains: learning and applying knowledge, general tasks and demands, mobility, self-care, domestic life, interpersonal interactions and relationships, major life areas, community, and social and civil life.

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3.5 **Relationship between cause and treatment**

How should the symptomatic treatment of neuropathic pain relate to its cause?

**Why this is important**

It is often assumed that evidence for treating a particular neuropathic pain condition with a particular aetiology can be extrapolated to other neuropathic pain conditions with other aetiologies. There is currently little evidence for this assumption. More studies on how the aetiology of different neuropathic pain conditions influences treatment outcome are warranted in order to identify more effective, targeted treatments.

4 **Other versions of this guideline**

This is the full guideline. It contains details of the methods and evidence used to develop the guideline. It is available from our website (www.nice.org.uk/CGXXfullguideline). [Note: these details will apply to the published full guideline.]

**Quick reference guide**

A quick reference guide for healthcare professionals is available from www.nice.org.uk/CGXXquickrefguide

For printed copies, phone NICE publications on 0845 003 7783 or email publications@nice.org.uk (quote reference number N1XXX). [Note: these details will apply when the guideline is published.]

‘Understanding NICE guidance’

A summary for patients and carers (‘Understanding NICE guidance’) is available from www.nice.org.uk/CGXXpublicinfo

For printed copies, phone NICE publications on 0845 003 7783 or email publications@nice.org.uk (quote reference number N1XXX). [Note: these details will apply when the guideline is published.]
5 Related NICE guidance

Under development

NICE is developing the following guidance (details available from www.nice.org.uk):


6 Updating the guideline

NICE clinical guidelines are updated so that recommendations take into account important new information. New evidence is checked 3 years after publication, and healthcare professionals and patients are asked for their views; we use this information to decide whether all or part of a guideline needs updating. If important new evidence is published at other times, we may decide to do a more rapid update of some recommendations.

7 References, glossary and abbreviations

7.1 References


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7.2 Glossary

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Absolute risk reduction (risk difference)</td>
<td>The difference in event rates between two groups (one subtracted from the other) in a comparative study.</td>
</tr>
<tr>
<td>Absolute risk increase (risk difference)</td>
<td>The difference in event rates between two groups (one subtracted from the other) in a comparative study.</td>
</tr>
<tr>
<td>Bias</td>
<td>Systematic (as opposed to random) deviation of the results of a study from the ‘true’ results that is caused by the way the study is designed or conducted.</td>
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<tr>
<td>Clinical effectiveness</td>
<td>The extent to which an intervention produces an overall health benefit in routine clinical practice.</td>
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<tr>
<td>Comorbidity</td>
<td>Two or more diseases or conditions occurring at the same time, such as depression and anxiety.</td>
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<tr>
<td>Confidence interval</td>
<td>The range within which the ‘true’ values (for example, size of effect of an intervention) are expected to lie with a given degree of certainty (for example, 95% or 99%). (Note: confidence intervals</td>
</tr>
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Consensus methods
Techniques that aim to reach an agreement on a particular issue. Formal consensus methods include Delphi and nominal group techniques, and consensus development conferences. In the development of clinical guidelines, consensus methods may be used where there is a lack of strong research evidence on a particular topic. Expert consensus methods will aim to reach agreement between experts in a particular field.

Cost-effectiveness analysis
An economic evaluation that compares alternative options for a specific patient group looking at a single effectiveness dimension measured in a non-monetary (natural) unit. It expresses the result in the form of an incremental (or average or marginal) cost-effectiveness ratio.

Economic evaluation
Technique developed to assess both costs and consequences of alternative health strategies and to provide a decision making framework.

Guideline Development Group
A group of healthcare professionals, patients, carers and members of the Short Clinical Guidelines Technical Team who develop the recommendations for a clinical guideline. The group writes draft guidance, and then revises it after a consultation with organisations registered as stakeholders.

Generalisability
The degree to which the results of a study or systematic review can be extrapolated to other circumstances, particularly routine healthcare situations in the NHS in England and Wales.

Heterogeneity
A term used to illustrate the variability or differences between studies in the estimates of effects.

Number needed to treat to benefit (NNTB)
NNTB is an epidemiological measure used in assessing the effectiveness of a health-care intervention, typically a treatment with medication. The NNTB is the number of patients who need to be treated in order to prevent one additional bad outcome (i.e. the number of patients that need to be treated for one to benefit compared with a control in a clinical trial). It is defined as the inverse of the absolute risk reduction. The ideal NNTB is 1, where everyone improves with treatment and no-one improves with control. The higher the NNTB, the less effective is the treatment.

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Quality-adjusted life year (QALY)
A statistical measure, representing 1 year of life, with full quality of life.

Randomised controlled trial
A form of clinical trial to assess the effectiveness of medicines or procedures. Considered reliable because it tends not to be biased.

Relative risk
Also known as risk ratio; the ratio of risk in the intervention group to the risk in the control group. The risk (proportion, probability or rate) is the ratio of people with an event in a group to the total in the group. A relative risk (RR) of 1 indicates no difference between comparison groups. For undesirable outcomes, an RR that is less than 1 indicates that the intervention was effective in reducing the risk of that outcome.

Systematic review
Research that summarises the evidence on a clearly formulated question according to a pre-defined protocol using systematic and explicit methods to identify, select and appraise relevant studies, and
7.3 Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>ARI</td>
<td>Absolute risk increase</td>
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<tr>
<td>ARR</td>
<td>Absolute risk reduction</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>GRADE</td>
<td>Grading of Recommendations Assessment, Development and Evaluation</td>
</tr>
<tr>
<td>ICER</td>
<td>Incremental cost-effectiveness ratio</td>
</tr>
<tr>
<td>IMMPACT</td>
<td>Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials</td>
</tr>
<tr>
<td>NNTB</td>
<td>Number needed to treat to benefit</td>
</tr>
<tr>
<td>NNTH</td>
<td>Number needed to treat to harm</td>
</tr>
<tr>
<td>QALY</td>
<td>Quality-adjusted life year</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomised controlled trial</td>
</tr>
<tr>
<td>RR</td>
<td>Relative risk</td>
</tr>
<tr>
<td>SD</td>
<td>Standard deviation</td>
</tr>
<tr>
<td>SE</td>
<td>Standard error</td>
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8 Contributors

8.1 The Guideline Development Group

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8.1 Co-opted members

The following people were not full members of the Guideline Development Group but were co-opted onto the group as expert advisers:

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8.2 The short clinical guidelines technical team

A short clinical guidelines technical team was responsible for this guideline throughout its development. It prepared information for the Guideline}

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Development Group, drafted the guideline and responded to consultation comments. The following NICE employees made up the technical team for this guideline.

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### 8.3 The Guideline Review Panel

The Guideline Review Panel is an independent panel that oversees the development of the guideline and takes responsibility for monitoring adherence to NICE guideline development processes. In particular, the panel ensures that stakeholder comments have been adequately considered and responded to. The panel includes members from the following perspectives: primary care, secondary care, lay, public health and industry.

### 8.4 Declarations of interest

A full list of all declarations of interest made by this Guideline Development Group is available on the NICE website (www.nice.org.uk).
8.5 Authorship and citation

Authorship of this document is attributed to the NICE Short Clinical Guidelines Technical Team and members of the Guideline Development Group under group authorship.

The guideline should be cited as: [to be inserted for final version].

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National Institute for Health and Clinical Excellence. Available from:
www.nice.org.uk/CG[XX]