NICE National Institute for Health and Care Excellence

Neuropathic pain – pharmacological management

The pharmacological management of neuropathic pain in adults in non-specialist settings

This guideline updates and replaces NICE clinical guideline 96

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NICE clinical guideline 173
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NICE clinical guideline 173
Neuropathic pain – pharmacological management

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- The NICE guideline – all the recommendations.
- The NICE pathway – a set of online diagrams that brings together all NICE guidance and support tools.
- Information for the public – a summary for patients and carers.
- The full guideline (this document) – all the recommendations, details of how they were developed, and reviews of the evidence they were based on.

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Introduction

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 wellbeing. The International Association for the Study of Pain (IASP 2011) defines neuropathic pain as 'pain caused by a lesion or disease of the somatosensory nervous system'. Central neuropathic pain is defined as 'pain caused by a lesion or disease of the central somatosensory nervous system', and peripheral neuropathic pain is defined as 'pain caused by a lesion or disease of the peripheral somatosensory nervous system'.

Neuropathic pain is very challenging to manage because of the heterogeneity of its aetiologies, symptoms and underlying mechanisms (Beniczky et al. 2005). There is often uncertainty regarding the nature and exact location of a lesion or health condition associated with neuropathic pain, particularly in non-specialist settings. Examples of common conditions that have peripheral neuropathic pain as a symptom are painful diabetic neuropathy, post-herpetic neuralgia, trigeminal neuralgia, radicular pain, post-surgical chronic neuropathic pain, and neuropathic cancer pain (such as, chemotherapy-induced neuropathy, neuropathy secondary to tumour antigens, or caused by direct invasion or compression of neural structures). Examples of conditions that can cause 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), hyperalgesia (an increased response to a stimulus that is normally painful), anaesthesia dolorosa (pain felt in an anaesthetic [numb] area or region), and sensory gain or loss (IASP 2011).

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 et al. 2012). For example, the prevalence of neuropathic pain overall

has been estimated to be between 6% and 8%, from postal surveys in France (Bouhassira 2008) and the UK (Torrance 2006). However, these estimates came from studies using different questionnaires. 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 estimates of prevalence 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 those of neuropathic pain (Jung et al. 2004; Mikkelsen et al. 2004; Kehlet et al. 2006). Furthermore, a 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 and Torrance 2010, Smith et al. 2012).

A number of pharmacological treatments can be used to manage neuropathic pain outside of specialist pain management services. However, there is considerable variation in how treatment is initiated, the dosages used and the order in which drugs are introduced, whether therapeutic doses are achieved and whether there is correct sequencing of therapeutic classes. A further issue is that a number of commonly used treatments are unlicensed for treating neuropathic pain, which may limit their use. These factors may lead to inadequate pain control, with considerable morbidity.

Commonly used pharmacological treatments include antidepressants (tricyclic antidepressants [TCAs], selective serotonin reuptake inhibitors [SSRIs] and

serotonin–norepinephrine reuptake inhibitors [SNRIs]), antiepileptic (anticonvulsant) drugs, topical treatments and opioid analgesics. In addition to their potential benefits, all of these drug classes are associated with various adverse effects.

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 outside of specialist pain management services. A further aim is to ensure that people who require specialist assessment and interventions are referred appropriately and in a timely fashion to a specialist pain management service and/or other condition-specific services.

Drug recommendations

For all drugs, recommendations are based on evidence of clinical and cost effectiveness and reflect whether their use for the management of neuropathic pain is a good use of NHS resources. This guideline should be used in conjunction with clinical judgement 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 (this includes obtaining information on special warnings, precautions for use, contraindications and adverse effects of pharmacological treatments).

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. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. The patient (or those with authority to give consent on their behalf) should provide informed consent, which should be documented. See the General Medical Council's Good practice in prescribing and managing medicines and devices (2013). Where recommendations have been made for the use of drugs

outside their licensed indications (off-label use), these drugs are marked with a footnote in the recommendations.

Healthcare setting for this guideline

The recommendations in this clinical guideline are for the pharmacological management of neuropathic pain in non-specialist settings only. The Guideline Development Group acknowledged that there are other pharmacological and non-pharmacological treatments that will be of benefit to people with neuropathic pain, within different care pathways in different settings.

The following definitions apply to this guideline.

Non-specialist settings are 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 are those that that provide comprehensive assessment and multi-modal management of all types of pain, including neuropathic pain.

Patient-centred care

This guideline offers best practice advice on the care of adults with neuropathic pain who are treated outside specialist pain management services.

Patients and healthcare professionals have rights and responsibilities as set out in the NHS Constitution for England – all NICE guidance is written to reflect these. Treatment and care should take into account individual needs and preferences. Patients should have the opportunity to make informed decisions about their care and treatment, in partnership with their healthcare professionals. If the patient is under 16, their family or carers should also be given information and support to help the child or young person to make decisions about their treatment. Healthcare professionals should follow the Department of Health's advice on consent. If someone does not have capacity to make decisions, healthcare professionals should follow the code of practice that accompanies the Mental Capacity Act and the supplementary code of practice on deprivation of liberty safeguards. In Wales, healthcare professionals should follow advice on consent from the Welsh Government.

NICE has produced guidance on the components of good patient experience in adult NHS services. All healthcare professionals should follow the recommendations in Patient experience in adult NHS services.

Strength of recommendations

Some recommendations can be made with more certainty than others. The Guideline Development Group makes a recommendation based on the trade-off between the benefits and harms of an intervention, taking into account the quality of the underpinning evidence. For some interventions, the Guideline Development Group is confident that, given the information it has looked at, most patients would choose the intervention. The wording used in the recommendations in this guideline denotes the certainty with which the recommendation is made (the strength of the recommendation).

For all recommendations, NICE expects that there is discussion with the patient about the risks and benefits of the interventions, and their values and preferences. This discussion aims to help them to reach a fully informed decision (see also 'Patient-centred care').

Interventions that must (or must not) be used

We usually use 'must' or 'must not' only if there is a legal duty to apply the recommendation. Occasionally we use 'must' (or 'must not') if the consequences of not following the recommendation could be extremely serious or potentially life threatening.

Interventions that should (or should not) be used – a 'strong' recommendation

We use 'offer' (and similar words such as 'refer' or 'advise') when we are confident that, for the vast majority of patients, an intervention will do more good than harm, and be cost effective. We use similar forms of words (for example, 'Do not offer…') when we are confident that an intervention will not be of benefit for most patients.

Interventions that could be used

We use 'consider' when we are confident that an intervention will do more good than harm for most patients, and be cost effective, but other options may be similarly cost effective. The choice of intervention, and whether or not to have the intervention at all, is more likely to depend on the patient's values

and preferences than for a strong recommendation, and so the healthcare professional should spend more time considering and discussing the options with the patient.

Update information

This guidance is an update of NICE clinical guideline 96 (published March 2010) and will replace it.

The original NICE guideline and supporting documents are available here.

1 Recommendations

1.1 List of all recommendations

Key principles of care

1.1.1 When agreeing a treatment plan with the person, take into account their concerns and expectations, and discuss:

- the severity of the pain, and its impact on lifestyle, daily activities (including sleep disturbance) and participation[1]
- the underlying cause of the pain and whether this condition has deteriorated
- why a particular pharmacological treatment is being offered
- the benefits and possible adverse effects of pharmacological treatments, taking into account any physical or psychological problems, and concurrent medications
- the importance of dosage titration and the titration process, providing the person with individualised information and advice
- coping strategies for pain and for possible adverse effects of treatment
- non-pharmacological treatments, for example, physical and psychological therapies (which may be offered through a rehabilitation service) and surgery (which may be offered through specialist services).

For more information about involving people in decisions and supporting adherence, see Medicines adherence (NICE clinical guideline 76).

1.1.2 Consider referring the person to a specialist pain service and/or a condition-specific service[2] at any stage, including at initial

[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.

presentation and at the regular clinical reviews (see recommendation 1.1.6), if:

- they have severe pain **or**
- their pain significantly limits their lifestyle, daily activities (including sleep disturbance) and participation[3] **or**
- their underlying health condition has deteriorated.

1.1.3 Continue existing treatments for people whose neuropathic pain is already effectively managed, taking into account the need for regular clinical reviews (see recommendation 1.1.6).

1.1.4 When introducing a new treatment, take into account any overlap with the old treatments to avoid deterioration in pain control.

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

1.1.6 Carry out regular clinical reviews to assess and monitor the effectiveness of the treatment. Each review should include an assessment of:

- pain control
- impact on lifestyle, daily activities (including sleep disturbance) and participation[4]
- physical and psychological wellbeing
- adverse effects

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[2] A condition-specific service is a specialist service that provides treatment for the underlying health condition that is causing neuropathic pain. Examples include neurology, diabetology and oncology services.

[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.

[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.

- continued need for treatment.

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

Treatment

All neuropathic pain (except trigeminal neuralgia)

1.1.8 Offer a choice of amitriptyline, duloxetine, gabapentin or pregabalin as initial treatment for neuropathic pain (except trigeminal neuralgia)[5].

1.1.9 If the initial treatment is not effective or is not tolerated, offer one of the remaining 3 drugs, and consider switching again if the second and third drugs tried are also not effective or not tolerated.

1.1.10 Consider tramadol only if acute rescue therapy is needed (see recommendation 1.1.12 about long-term use).

1.1.11 Consider capsaicin cream[6] for people with localised neuropathic pain who wish to avoid, or who cannot tolerate, oral treatments.

Treatments that should not be used

1.1.12 Do not start the following to treat neuropathic pain in non-specialist settings, unless advised by a specialist to do so:

- cannabis sativa extract

[5] At the time of publication (November 2013), amitriptyline did not have a UK marketing authorisation for this indication, duloxetine is licensed for diabetic peripheral neuropathic pain only, and gabapentin is licensed for peripheral neuropathic pain only, so use for other conditions would be off-label. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing and managing medicines and devices for further information.

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

- capsaicin patch
- lacosamide
- lamotrigine
- levetiracetam
- morphine
- oxcarbazepine
- topiramate
- tramadol (this is referring to long-term use; see recommendation 1.1.10 for short-term use)
- venlafaxine.

Trigeminal neuralgia

1.1.13 Offer carbamazepine as initial treatment for trigeminal neuralgia.

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

2 Development of the guideline

2.1 Methodology

2.1.1 Rationale for presentation of data

The Guideline Development Group (GDG) recognised that neuropathic pain is very challenging to manage because of the heterogeneity of its causes, symptoms and underlying mechanisms. The GDG thought that presenting the evidence for each individual underlying condition may not be appropriate for non-specialist settings where the underlying cause is not always known. Consequently, the GDG decided to categorise neuropathic pain into 3 broad groups which they felt would have the most clinical value in these settings:

- central neuropathic pain,
- peripheral neuropathic pain and
- trigeminal neuralgia.

This decision was made before the results of the evidence were presented, and was based on the clinical perspective that similar underlying causes of neuropathic pain within these categories could be expected to respond to treatment similarly.

In addition, an overarching analysis of the evidence, described in this guideline as ‘all pain’, was conducted because:

- The underlying cause of neuropathic pain is not always known when a person presents in non-specialist settings.
- The type of neuropathic pain cannot always be identified in non-specialist settings, and it is important that treatment is not delayed unnecessarily for people with neuropathic pain.

Undertaking the analysis in this way enabled the GDG to consider as much valid clinical and health economic evidence as possible in their decision making.

The structure of this guideline, the categorisation of neuropathic pain conditions with relevant pharmacological treatments and analyses were based on this rationale.

The scope and protocols of studies included in this guideline, as well as the methods for analysis and synthesis, are briefly summarised below and in appendix D. These provide overall information and brief explanation for the characteristics of all evidence statements (except for the 'Key principles of care' section) in the guideline for the following sections.

2.1.2 Population and conditions

Adults with neuropathic pain. The different neuropathic pain conditions that were included in this guideline are listed in Table 1.

Table 1 Terms related to neuropathic pain that were used in the literature search

Central neuropathic pain/central pain
Complex regional pain syndromes
Compression neuropathies/nerve compression syndromes
Facial neuralgia
HIV-related neuropathy
Mixed neuropathic pain
Multiple sclerosis
Neurogenic pain
Neuropathic cancer pain/cancer pain
Neuropathic pain
Painful diabetic neuropathy/diabetic neuropathy
Peripheral nerve injury
Peripheral nervous system disease/neuropathies
Phantom limb pain
Polyneuropathies
Post-amputation pain
Post-herpetic neuralgia
Post-stroke pain
Post-treatment/post-surgery/post-operative pain
Radiculopathies/radicular pain
Spinal cord diseases
Spinal cord injury
Trigeminal neuralgia

2.1.3 Settings

Although the scope of this guideline is to provide recommendations for pharmacological treatment in non-specialist settings, studies conducted in specialist pain clinics were also included because it was felt that extrapolating the evidence to non-specialist settings is appropriate.

2.1.4 Treatments and comparators

Table 2 lists the 43 different pharmacological treatments that were considered for neuropathic pain. The guideline sought to investigate:

- the clinical effectiveness of the individually listed 43 pharmacological treatments as monotherapy compared with placebo
- the clinical effectiveness of individual pharmacological treatments compared with each other
- the clinical effectiveness of combination therapy against monotherapy or other combination therapy.

Only randomised controlled trials of the interventions listed in Table 2 (and which met the inclusion criteria specified in the review protocol in appendix D) were included in this guideline.

Table 2 Pharmacological treatments

Drug class: subclass	Drug
Antidepressants: tricyclic antidepressants (TCAs)	Amitriptyline Clomipramine Dosulepin (dothiepin) Doxepin Imipramine Lofepramine Nortriptyline Trimipramine
Antidepressants: selective serotonin reuptake inhibitors (SSRIs)	Citalopram Escitalopram Fluoxetine Paroxetine Sertraline
Antidepressants: others	Duloxetine Mirtazapine Reboxetine

	Trazodone Venlafaxine
Antiepileptics (anticonvulsants)	Carbamazepine Gabapentin Lacosamide Lamotrigine Levetiracetam Oxcarbazepine Phenytoin Pregabalin Valproate Topiramate
Opioid analgesics	Buprenorphine Co-codamol Co-dydramol Dihydrocodeine Fentanyl Morphine Oxycodone Oxycodone with naloxone Tapentadol Tramadol
Other treatments	Cannabis sativa extract Flecainide 5-HT_1-receptor agonists Topical capsaicin Topical lidocaine

Dosage

The GDG felt strongly that it would not be helpful to treat each dosage at which any given drug has been investigated as a separate comparator; rather, the GDG felt that the goal should be to provide guidance on the options that are most likely to provide benefit to patients across the variety of dosing regimens with which they may need to be prescribed. Therefore, in base-case syntheses, studies reporting different dosages of each agent were combined. However, it was recognised that dose could be an important confounder of treatment effect. Therefore, additional analyses were performed for some syntheses – in particular, those that were relied on in the health economic model – that sought to account for dose–response effects in the evidence (for details of methods, see appendix D, section 11). The results of these analyses

were considered by the GDG and used in sensitivity analyses on the health economic model (see section 3.1.3).

2.1.5 Critical and important outcomes for clinical evidence

The outcomes that were selected by the GDG as critical and important are listed below.

Table 3 Critical and important outcomes

Critical outcomes	Important outcomes
• Patient-reported global improvement • Patient-reported improvement in daily physical and emotional functioning, including sleep. • Major adverse effects (defined as leading to withdrawal from treatment)	• Patient-reported pain relief/intensity reduction • Individual adverse effects • Use of rescue medication
Please note that overall improvement in quality of life and treatment withdrawal were listed in the review protocol and this data were extracted into the evidence tables, but because they were not prioritised as the top critical and important outcomes, results were not pooled or presented in GRADE profiles	

Efficacy outcomes

Measuring pain alleviation alone would be insufficient to monitor the effect of treatment for neuropathic pain. The GDG considered that the outcome 'patient's global (or overall) experience of the pain and its impact on daily physical and emotional functioning (including sleep)' to be critical to their decision making.

Consequently, for the purposes of the GRADE assessment, pain alleviation outcomes were considered to be important (but not critical) to decision making. The GDG agreed that dichotomous outcomes of the proportion of patients achieving at least 30% and at least 50% pain relief should be presented, where reported in the evidence base. These are well-recognised levels of pain relief that are recommended by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) group and commonly used in the literature (Dworkin et al. 2005).The GDG was concerned that considering only mean changes in continuous outcomes would be inappropriate because decreases on a 10-point scale at different points

may have greater or lesser clinical significance (that is, a 2-point decrease from 8 to 6 may be valued more than a decrease from 4 to 2). However, the difficulty with using only dichotomous outcomes is that the reporting of these outcomes appears more frequently in the newer literature and in the studies on only some drugs. Because the use of dichotomous outcomes is not used in studies of all drugs of interest, the GDG asked for continuous as well as dichotomous outcome measures to be extracted from the literature where possible.

The efficacy outcomes may show that a drug appears to improve the patient experience, but this may be partly attributed to additional rescue medications. As a result, the use of rescue analgesia was also considered an important outcome.

Adverse effects

The GDG also considered the outcome 'withdrawal from treatment because of adverse effects' to be critical to decision making. The GDG acknowledged that assessing which individual adverse effects are tolerable would normally be made on an individual patient level and, therefore, considered individual adverse effects as important to decision making. Specific adverse effects for each drug class were selected and agreed by the GDG through survey questionnaires based on their expert knowledge and experience (including that of patient and carer members) (see appendix K for more details about the prioritisation of adverse effects).

2.1.6 Literature search for clinical evidence

Systematic literature searches were carried out to identify all randomised controlled trials on the 43 different pharmacological treatments (listed in Table2) for neuropathic pain conditions (listed in Table 1). For full search strategies, see appendix D.

2.1.7 Further details of methods

Evidence synthesis

For the synthesis of data, meta-analyses were conducted to combine the results of studies for each outcome, where this was possible.

When there were data available on more than 2 interventions, or where data were available on only 2 interventions that were not connected by head-to-head evidence, network meta-analyses (NMAs) were conducted. These allowed simultaneous comparison of multiple treatments in a single meta-analysis, preserving the randomisation of the randomised controlled trials included in the reviews. It also allowed all evidence to be combined in a single synthesis. A mixed/multiple treatment comparison (MTC) combines both direct and indirect evidence. This helps to reduce uncertainty where there are few head-to-head trials, but also provides coherence in the effect estimate producing a more robust estimate of the treatment effect. These were used when there were data available on more than 2 interventions. When there were data available on only 2 interventions that were not connected by head-to-head evidence, a simple type of network meta-analysis, an indirect treatment comparison (ITC), was used to provide an indirect estimate of the treatment effect between both interventions.

Presentation of results for network meta-analyses

Since network meta-analyses do not result in a single estimate of treatment effect like traditional pairwise meta-analyses, the results of the meta-analyses were presented in a number of ways.

- Relative effectiveness matrix, showing an estimate of effect for each treatment compared with each of its comparators; an estimate of effect based on direct evidence only (pairwise random-effects meta-analysis or the results from an individual study where only 1 study was available for a data point) is also presented for comparisons where data are available
- Caterpillar plot of the relative effectiveness of each drug compared with placebo (this includes any direct estimate and also the results of the NMA)

- Probability of each treatment being best
- Median rank with 95% credible interval
- Histograms demonstrating the probability of each treatment at each possible rank ('rankograms').

For the review protocol and further details of the methods for extraction, analysis and synthesis, see appendix D.

2.1.8 Literature search for cost-effectiveness evidence

Systematic literature searches were carried out to identify all relevant cost–utility analyses. Full details are provided in appendix F, and a summary of results is provided in section 3.1.3, below.

2.1.9 Undertaking health economic analysis

A de novo health economic model was built to inform the GDG's decision making. Full details are provided in appendix F, and a summary of methods and results is provided in section 3.1.3, below.

3 Evidence review and recommendations

Review questions

- What is the clinical effectiveness of different pharmacological treatments as monotherapy compared with each other or placebo for the management of neuropathic pain in adults, outside of specialist pain management services?
- What is the clinical effectiveness of different pharmacological treatments as combination therapy compared with other combination therapies, monotherapy or placebo for the management of neuropathic pain in adults, outside of specialist pain management services?

3.1 All neuropathic pain

3.1.1 Evidence review

Of 32,322 studies retrieved from searches, 585 studies were selected based on title and abstract and full papers were ordered. Of these, 470 studies were excluded (excluded studies are listed in appendix D). There were 115 studies with a total of 18,087 patients that met the inclusion criteria specified in the review protocol. These are summarised in Table 4.

Network meta-analyses were performed for all but 1 outcome, where a pairwise analysis was performed to pool 2 studies comparing gabapentin with placebo (sleep interference on normalised 10-point scale at 56±7 days).

For the outcome ‘patient-reported improvement in daily physical and emotional functioning, including sleep’, it was not possible to perform meta-analysis because the included studies reported this outcome across a variety of measurement tools with each measuring different aspects of functioning. It was also not possible to perform meta-analysis for the outcome ‘use of rescue medication’ because there was substantial variation in how this outcome was reported in the studies and many of the included studies did not report this outcome. Despite having acknowledged that these outcomes should be critical or important to decision-making, the GDG felt it was

inappropriate to use such varied data to inform their decisions, so did not consider these outcomes when writing recommendations.

Despite being unable to complete a meta-analysis for ‘patient-reported improvement in daily physical and emotional functioning, including sleep’, there were a proportion of studies that reported a continuous measure of sleep disturbance, and so a meta-analysis was performed on the results from these studies.

The GRADE summary table for each outcome where syntheses were performed is found in Table 5. GRADE tables were not completed for outcomes where it was not possible to pool results as they were not used in decision-making for the reasons stated above. A graphical representation of the results for each of these outcomes is presented in
Table 6 in the form of a summary graphics table (see an explanation of this table below). Full GRADE profiles and full results from the analyses are found in appendices G and J.

Figure 1 Number of studies included by type (total=115)

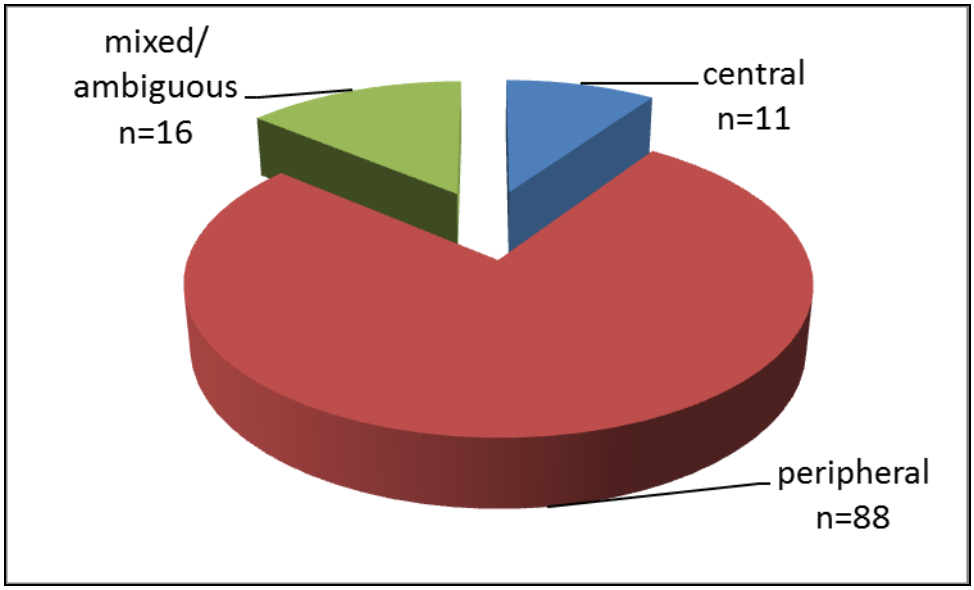


Figure 2 Proportion of patients in studies by pain type (total n=18,087)

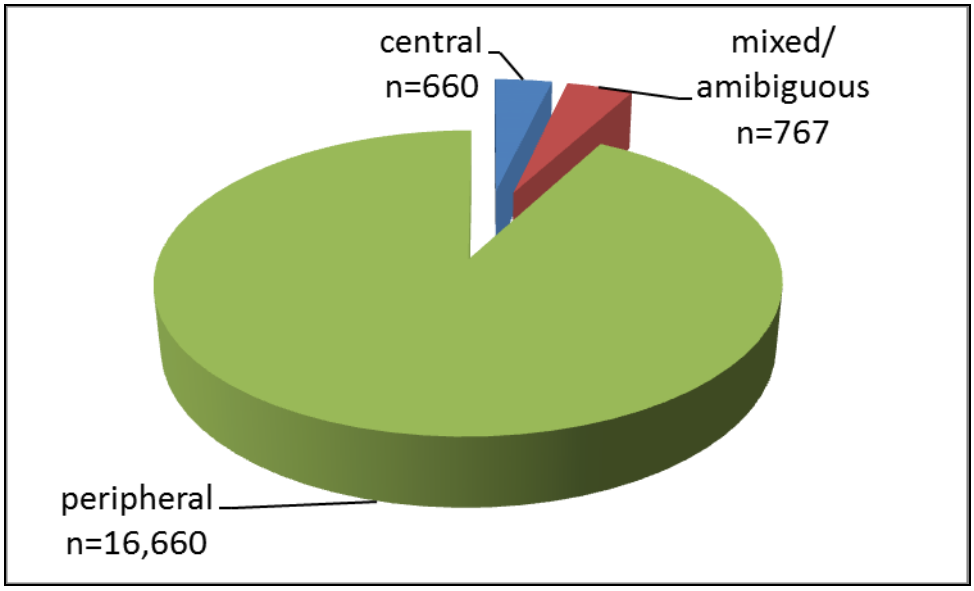


Table 4 Summary of included studies for 'all neuropathic pain'

Study / Country / N	Design / Duration / Baseline pain	Type of pain	Condition / Concomitant treatments	Treatments	Outcomes
Agrawal et al. (2009) India, N=83	Parallel 84d Base pain: 7.68	Peripheral	Painful diabetic neuropathy No concomitant pain meds allowed	(1) valproate fixed (1400 mg/d) (2) placebo	Pain intensity Study dropout Adverse effects
Arbaiza & Vidal (2007) Peru, N=36	Parallel 42d Base pain: 7.00	Peripheral	Mixed pain (including cancer & chemotherapy-induced) Concomitant pain meds allowed	(1) tramadol flexi (mean: 254 mg/d) (range: 240–360 mg/d) (2) placebo	Pain intensity Function (incl. sleep) Adverse effects
Arezzo et al. (2008) USA, N=167	Parallel 91d Base pain: 6.43	Peripheral	Painful diabetic neuropathy Concomitant pain meds allowed	(1) pregabalin fixed (600 mg/d) (2) placebo	Pain intensity Global improvement Function (incl. sleep) Study dropout Adverse effects
Backonja et al. (1998) USA, N=165	Parallel 56d Base pain: 6.45	Peripheral	Painful diabetic neuropathy Concomitant pain meds allowed	(1) gabapentin fixed (3600 mg/d) (2) placebo	Pain intensity Global improvement Function (incl. sleep) HRQoL Study dropout Adverse effects
Backonja et al. (2008) USA, N=402	Parallel 84d Base pain: 5.90	Peripheral	Post-herpetic neuralgia Concomitant pain meds allowed	(1) capsaicin patch fixed (60-min application) (2) placebo	Pain intensity Global improvement Study dropout Adverse effects
Bansal et al. (2009) India, N=51	Crossover 35d Base pain: 7.00	Peripheral	Painful diabetic neuropathy No concomitant pain meds allowed	(1) amitriptyline flexi (mean: 16 mg/d) (range: 10–50 mg/d) (2) pregabalin flexi (mean: 218 mg/d) (range: 150–600 mg/d)	Pain intensity Adverse effects
Bernstein et al. (1989) USA, N=32	Parallel 42d Base pain: 7.13	Peripheral	Post-herpetic neuralgia Concomitant pain meds allowed	(1) capsaicin cream flexi (3.5 applications/d) (2) placebo	Pain intensity Adverse effects
Beydoun et al. (2006) USA, N=347	Parallel 112d Base pain: 7.44	Peripheral	Painful diabetic neuropathy Concomitant pain meds allowed	(1) oxcarbazepine fixed (600 mg/d) (2) oxcarbazepine fixed (1200 mg/d) (3) oxcarbazepine fixed (1800 mg/d) (4) placebo	Pain intensity Global improvement Study dropout Adverse effects
Biesbroeck et al. (1995) USA, N=235	Parallel 56d Base pain: 6.31	Peripheral	Painful diabetic neuropathy Concomitant pain meds allowed	(1) amitriptyline flexi (range: 25–125 mg/d) (2) capsaicin cream fixed (4 applications/d)	Pain intensity Adverse effects

Study / Country / N	Design / Duration / Baseline pain	Type of pain	Condition / Concomitant treatments	Treatments	Outcomes
Bone et al. (2002) UK & Ireland, N=19	Crossover 42d Base pain: 6.40	Mixed / ambiguous	Phantom limb pain Concomitant pain meds allowed	(1) gabapentin flexi (range: 300–2400 mg/d) (2) placebo	Pain intensity Function (incl. sleep) Adverse effects
Boureau et al. (2003) France, N=127	Parallel 42d Base pain: 6.05	Peripheral	Post-herpetic neuralgia No concomitant pain meds allowed	(1) tramadol flexi (mean: 275.5 mg/d) (range: 100–400 mg/d) (2) placebo	Pain intensity Study dropout Adverse effects
Breuer et al. (2007) USA, N=18	Crossover 91d Base pain: NR	Central	MS neuropathic pain Concomitant pain meds allowed	(1) lamotrigine flexi (range: 25–400 mg/d) (2) placebo	Pain intensity Adverse effects
Cardenas et al. (2002) USA, N=84	Parallel 42d Base pain: 5.25	Mixed / ambiguous	Spinal cord injury pain Concomitant pain meds allowed	(1) amitriptyline flexi (median: 50 mg/d) (range: 10–125 mg/d) (2) placebo	Pain intensity Function (incl. sleep) Study dropout Adverse effects
Chandra et al. (2006) India, N=76	Parallel 63d Base pain: 5.70	Peripheral	Post-herpetic neuralgia Concomitant pain meds allowed	(1) nortriptyline flexi (range: ≤150 mg/d) (2) gabapentin flexi (range: ≤2700 mg/d)	Pain intensity Study dropout Adverse effects
Cheville et al. (2009) USA, N=28	Crossover 28d Base pain: 4.90	Peripheral	Post-surgical pain after surgery for cancer Concomitant pain meds allowed	(1) lidocaine (topical) flexi (range: ≤3 mg/d) (2) placebo	Pain intensity Function (incl. sleep) Study dropout Adverse event
Clifford et al. (2012) country not clear, N=494	Parallel 84d Base pain: 6.00	Peripheral	HIV-related neuropathy Concomitant pain meds allowed	(1) capsaicin patch fixed (60-min application) (2) capsaicin patch fixed (30-min application) (3) placebo	Pain intensity Global improvement HRQoL Study dropout Adverse effects
Davidoff et al. (1987) USA, N=18	Parallel 42d Base pain: 4.50	Mixed / ambiguous	Spinal cord injury pain Concomitant pain meds allowed	(1) trazodone fixed (150 mg/d) (2) placebo	Pain intensity Adverse effects
Dogra et al. (2005) USA, N=146	Parallel 112d Base pain: 7.29	Peripheral	Painful diabetic neuropathy Concomitant pain meds allowed	(1) oxcarbazepine flexi (mean: 1445 mg/d) (range: 300–1800 mg/d) (2) placebo	Pain intensity Global improvement Function (incl. sleep) Study dropout Adverse effects
Donofrio & Capsaicin study (1992), USA, N=277	Parallel 56d Base pain: 7.60	Peripheral	Painful diabetic neuropathy or radiculopathy Concomitant pain meds allowed	(1) capsaicin cream fixed (4 applications/d) (2) placebo	Pain intensity Study dropout Adverse effects

Study / Country / N	Design / Duration / Baseline pain	Type of pain	Condition / Concomitant treatments	Treatments	Outcomes
Dworkin et al. (2003) USA, N=173	Parallel 56d Base pain: 6.40	Peripheral	Post-herpetic neuralgia Concomitant pain meds allowed	(1) pregabalin fixed (600 mg/d) (2) placebo	Pain intensity Global improvement Function (incl. sleep) HRQoL Study dropout Adverse effects
Eisenberg et al. (2001) Israel, N=53	Parallel 56d Base pain: 6.50	Peripheral	Painful diabetic neuropathy No concomitant pain meds allowed	(1) lamotrigine fixed (400 mg/d) (2) placebo	Pain intensity Function (incl. sleep) Study dropout Adverse effects
Falah et al. (2012) Denmark, N=30	Crossover 42d Base pain: 5.80	Central	MS neuropathic pain No concomitant pain meds allowed	(1) levetiracetam flexi (range: 2000–3000 mg/d) (2) placebo	Pain intensity Function (incl. sleep) Study dropout Adverse effects
Finnerup et al. (2002) Denmark, N=30	Crossover 63d Base pain: 5.00	Mixed / ambiguous	Spinal cord injury pain Concomitant pain meds allowed	(1) lamotrigine flexi (range: 200–400 mg/d) (2) placebo	Pain intensity Function (incl. sleep) HRQoL Study dropout Adverse effects
Finnerup et al. (2009) Denmark, N=24	Crossover 35d Base pain: 6.00	Mixed / ambiguous	Spinal cord injury pain Concomitant pain meds allowed	(1) levetiracetam flexi (range: 2000–3000 mg/d) (2) placebo	Pain intensity Global improvement Function (incl. sleep) Study dropout Adverse effects
Freynhagen et al. (2005) USA, Germany, Poland, N=338	Parallel 84d Base pain: 6.85	Peripheral	Painful diabetic neuropathy or post-herpetic neuralgia Concomitant pain meds allowed	(1) pregabalin flexi (mean: 372.2 mg/d) (range: 150–600 mg/d) (2) pregabalin fixed (600 mg/d) (3) placebo	Pain intensity Global improvement Study dropout Adverse effects
Gao et al. (2010) China, N=215	Parallel 84d Base pain: 5.50	Peripheral	Painful diabetic neuropathy Concomitant pain meds allowed	(1) duloxetine flexi (range: 60–120 mg/d) (2) placebo	Pain intensity Global improvement Function (incl. sleep) HRQoL Study dropout Adverse effects

Study / Country / N	Design / Duration / Baseline pain	Type of pain	Condition / Concomitant treatments	Treatments	Outcomes
Gilron et al. (2012) Canada N=56	Crossover 35d Base pain: 5.40	Peripheral	Painful diabetic neuropathy or post-herpetic neuralgia Concomitant pain meds allowed	(1) gabapentin flexi (mean: 2433 mg/d) (range: ≤3600 mg/d) (2) nortriptyline flexi (mean: 61.6 mg/d) (range: ≤100 mg/d) (3) gabapentin+nortriptyline flexi (range: ≤999 mg/d)	Pain intensity Function (incl. sleep) HRQoL Study dropout Adverse effects
Gimbel et al. (2003) USA, N=159	Parallel 42d Base pain: 6.90	Peripheral	Painful diabetic neuropathy Concomitant pain meds allowed	(1) oxycodone flexi (mean: 37 mg/d) (range: 10–120 mg/d) (2) placebo	Pain intensity Function (incl. sleep) Study dropout Adverse effects
Goldstein et al. (2005) USA, N=457	Parallel 84d Base pain: 5.90	Peripheral	Painful diabetic neuropathy Concomitant pain meds allowed	(1) duloxetine fixed (20 mg/d) (2) duloxetine fixed (60 mg/d) (3) duloxetine fixed (120 mg/d) (4) placebo	Pain intensity Global improvement Function (incl. sleep) HRQoL Study dropout Adverse effects
Gordh et al. (2008) Denmark, Sweden, Finland, Norway, N=120	Crossover 35d Base pain: 5.32	Peripheral	Nerve injury neuropathic pain No concomitant pain meds allowed	(1) gabapentin flexi (mean: 2243 mg/d) (range: ≤2500 mg/d) (2) placebo	Pain intensity Function (incl. sleep) Study dropout Adverse effects
Graff-Radford et al. (2000) USA, N=50	Parallel 56d Base pain: 5.49	Peripheral	Post-herpetic neuralgia Concomitant pain meds allowed	(1) amitriptyline flexi (range: ≤200 mg/d) (2) placebo	Pain intensity Function (incl. sleep) Study dropout Adverse effects
Grosskopf et al. (2006) USA, Germany, UK N=141	Parallel 112d Base pain: 7.14	Peripheral	Painful diabetic neuropathy No concomitant pain meds allowed	(1) oxcarbazepine flexi (mean: 1091 mg/d) (range: 300–1200 mg/d) (2) placebo	Pain intensity Study dropout Adverse effects
Guan et al. (2011) China, N=309	Parallel 56d Base pain: 6.35	Peripheral	Painful diabetic neuropathy or post-herpetic neuralgia Concomitant pain meds allowed	(1) pregabalin flexi (range: 150–600 mg/d) (2) placebo	Pain intensity Study dropout Adverse effects
Hahn et al. (2004) Germany, N=26	Parallel 42d Base pain: 4.90	Peripheral	HIV-related neuropathy No concomitant pain meds allowed	(1) gabapentin flexi (range: 1200–2400 mg/d) (2) placebo	Pain intensity Function (incl. sleep) Study dropout Adverse effects

Study / Country / N	Design / Duration / Baseline pain	Type of pain	Condition / Concomitant treatments	Treatments	Outcomes
Hanna et al. (2008) Australia and Europe, N=338	Parallel 84d Base pain: NR	Peripheral	Painful diabetic neuropathy Concomitant pain meds allowed	(1) gabapentin flexi (mean: 1383.625731 mg/d) (range: 1384–1384 mg/d) (2) gabapentin+oxycodone flexi (range: ≤999 mg/d)	Pain intensity Study dropout Adverse effects
Harati et al. (1998) USA, N=131	Parallel 49d Base pain: 5.10	Peripheral	Painful diabetic neuropathy No concomitant pain meds allowed	(1) tramadol flexi (mean: 210 mg/d) (range: ≤400 mg/d) (2) placebo	Pain intensity Study dropout Adverse effects
Holbech et al. (2011) Denmark, N=92	Crossover 42d Base pain: 5.70	Peripheral	Polyneuropathy No concomitant pain meds allowed	(1) levetiracetam flexi (range: 2000–3000 mg/d) (2) placebo	Pain intensity Function (incl. sleep) Study dropout Adverse effects
Huse et al. (2001) Germany, N=12	Crossover 28d Base pain: 3.34	Mixed / ambiguous	Phantom limb pain Concomitant pain meds allowed	(1) morphine flexi (range: 70–300 mg/d) (2) placebo	Pain intensity Adverse effects
Irving et al. (2011) USA, N=416	Parallel 84d Base pain: 5.75	Peripheral	Post-herpetic neuralgia Concomitant pain meds allowed	(1) capsaicin patch fixed (60-min application) (2) placebo	Pain intensity Global improvement Study dropout Adverse effects
Kalso et al. (1995) Finland N=20	Crossover 28d Base pain: 4.15	Peripheral	Post-surgical pain after surgery for cancer Concomitant pain meds allowed	(1) amitriptyline flexi (range: 50–100 mg/d) (2) placebo	Pain intensity Function (incl. sleep) Adverse effects
Kautio et al. (2008) Finland N=42	Parallel 56d Base pain: NR	Peripheral	Chemotherapy-induced pain Concomitant pain meds allowed	(1) amitriptyline flexi (range: 10–50 mg/d) (2) placebo	Study dropout Adverse event
Khoromi et al. (2005) USA, N=42	Crossover 42d Base pain: 4.04	Peripheral	Radiculopathy Concomitant pain meds allowed	(1) topiramate flexi (range: 50–400 mg/d) (2) placebo	Pain intensity Adverse effects
Khoromi et al. (2007) USA N=55	Crossover 63d Base pain: 4.50	Peripheral	Radiculopathy Concomitant pain meds allowed	(1) morphine flexi (mean: 62 mg/d) (range: 15–90 mg/d) (2) nortriptyline flexi (mean: 84 mg/d) (range: 25–100 mg/d) (3) nortriptyline+morphine flexi (range: ≤999 mg/d) (4) placebo	Pain intensity Function (incl. sleep) HRQoL Study dropout Adverse effects
Kieburtz et al. (1998) USA, N=145	Parallel 70d Base pain: NR	Peripheral	HIV-related neuropathy Concomitant pain meds allowed	(1) amitriptyline flexi (range: 25–100 mg/d) (2) placebo	Pain intensity Study dropout Adverse event

Study / Country / N	Design / Duration / Baseline pain	Type of pain	Condition / Concomitant treatments	Treatments	Outcomes
Kim et al. (2011) Asia-pacific N=219	Parallel 91d Base pain: 6.40	Central	Post-stroke pain Concomitant pain meds allowed	(1) pregabalin flexi (mean: 356.8 mg/d) (range: 125–540 mg/d) (2) placebo	Pain intensity Global improvement Function (incl. sleep) HRQoL Study dropout Adverse effects
Kochar et al. (2002) India N=60	Parallel 28d Base pain: 4.95	Peripheral	Painful diabetic neuropathy Concomitant pain meds allowed	(1) valproate fixed (1200 mg/d) (2) placebo	Pain intensity Study dropout Adverse event
Kochar et al. (2004) India N=48	Parallel 84d Base pain: 5.86	Peripheral	Painful diabetic neuropathy Concomitant pain meds allowed	(1) valproate fixed (500 mg/d) (2) placebo	Pain intensity Study dropout Adverse effects
Kochar et al. (2005) India N=48	Parallel 56d Base pain: 6.55	Peripheral	Post-herpetic neuralgia No concomitant pain meds allowed	(1) valproate fixed (1000mg/d) (2) placebo	Pain intensity Global improvement Study dropout Adverse event
Leijon & Boivie (1989) Sweden N=15	Crossover 28d Base pain: NR	Central	Post-stroke pain Concomitant pain meds allowed	(1) amitriptyline fixed (75 mg/d) (2) carbamazepine flexi (range: 600–1200 mg/d) (3) placebo	Pain intensity Study dropout Adverse effects
Lesser et al. (2004) USA N=337	Parallel 245d Base pain: 6.40	Peripheral	Painful diabetic neuropathy Concomitant pain meds allowed	(1) pregabalin fixed (75 mg/d) (2) pregabalin fixed (300 mg/d) (3) pregabalin fixed (600 mg/d) (4) placebo	Pain intensity Global improvement Study dropout Adverse effects
Levendoglu et al. (2004) Turkey, N=20	Crossover 56d Base pain: 8.80	Mixed / ambiguous	Spinal cord injury pain No concomitant pain meds allowed	(1) gabapentin flexi (mean: 223.5 mg/d) (range: ≤2700 mg/d) (2) placebo	Pain intensity Adverse effects
Low et al. (1995) USA N=40	Parallel 56d Base pain: 8.40	Peripheral	Polyneuropathy Concomitant pain meds allowed	(1) capsaicin cream fixed (4 applications/d) (2) placebo	Pain intensity Adverse effects
Luria et al. (2000) Israel N=40	Parallel 56d Base pain: 6.55	Peripheral	Painful diabetic neuropathy No concomitant pain meds allowed	(1) lamotrigine fixed (400 mg/d) (2) placebo	Pain intensity Study dropout Adverse effects
Max et al. (1988) USA N=58	Crossover 42d Base pain: NR	Peripheral	Post-herpetic neuralgia Concomitant pain meds allowed	(1) amitriptyline flexi (mean: 65 mg/d) (range: 13–150 mg/d) (2) placebo	Pain intensity Adverse effects

Study / Country / N	Design / Duration / Baseline pain	Type of pain	Condition / Concomitant treatments	Treatments	Outcomes
McCleane (1999) UK N=100	Parallel 56d Base pain: 6.76	Mixed / ambiguous	Mixed neuropathic pain Concomitant pain meds allowed	(1) lamotrigine fixed (200 mg/d) (2) placebo	Pain intensity Function (incl. sleep) Study dropout Adverse event
McCleane (2000) Ireland N=100	Parallel 28d Base pain: 7.12	Mixed / ambiguous	Mixed neuropathic pain Concomitant pain meds allowed	(1) capsaicin cream fixed (3 applications/d) (2) placebo	Pain intensity Study dropout Adverse effects
Mishra et al. (2012) India N=120	Parallel 28d Base pain: 7.60	Mixed / ambiguous	Cancer pain Concomitant pain meds allowed	(1) amitriptyline fixed (100 mg/d) (2) gabapentin fixed (1800 mg/d) (3) pregabalin fixed (600 mg/d) (4) placebo	Pain intensity
Moon et al. (2010) Korea N=240	Parallel 56d Base pain: 6.30	Peripheral	Peripheral neuropathic pain Concomitant pain meds allowed	(1) pregabalin flexi (mean: 480 mg/d) (range: 150–600 mg/d) (2) placebo	Pain intensity Global improvement Study dropout Adverse effects
Morello et al. (1999) USA N=25	Crossover 42d Base pain: NR	Peripheral	Painful diabetic neuropathy No concomitant pain meds allowed	(1) amitriptyline flexi (mean: 59 mg/d) (range: 25–75 mg/d) (2) gabapentin flexi (mean: 1565 mg/d) (range: 900–1800 mg/d)	Pain intensity Study dropout Adverse effects
Norrbrink & Lundeberg (2009) Sweden N=35	Parallel 28d Base pain: 5.50	Mixed / ambiguous	Spinal cord injury pain Concomitant pain meds allowed	(1) tramadol flexi (mean: 326 mg/d) (range: 150–400 mg/d) (2) placebo	Pain intensity Global improvement Function (incl. sleep) Study dropout Adverse effects
Nurmikko et al. (2007) UK & Belgium N=125	Parallel 35d Base pain: 7.25	Peripheral	Peripheral neuropathic pain Concomitant pain meds allowed	(1) cannabis sativa extract flexi (mean: 29.43 mg/d) (range: ≤130 mg/d) (2) placebo	Pain intensity Function (incl. sleep) Study dropout Adverse effects
Otto et al. (2008) Denmark N=48	Crossover 35d Base pain: 5.60	Peripheral	Polyneuropathy No concomitant pain meds allowed	(1) escitalopram fixed (20 mg/d) (2) placebo	Pain intensity Function (incl. sleep) Study dropout Adverse effects
Paice et al. (2000) USA N=26	Parallel 28d Base pain: 4.70	Peripheral	HIV-related neuropathy Concomitant pain meds allowed	(1) capsaicin cream fixed (4 applications/d) (2) placebo	Pain intensity Study dropout Adverse event

Study / Country / N	Design / Duration / Baseline pain	Type of pain	Condition / Concomitant treatments	Treatments	Outcomes
Rao et al. (2007) USA N=115	Crossover 42d Base pain: 3.95	Peripheral	Chemotherapy-induced pain Concomitant pain meds allowed	(1) gabapentin flexi (median: 2700 mg/d) (range: ≤2700 mg/d) (2) placebo	Pain intensity Function (incl. sleep) Study dropout Adverse effects
Rao et al. (2008) USA N=125	Parallel 70d Base pain: 3.90	Peripheral	Chemotherapy-induced pain No concomitant pain meds allowed	(1) lamotrigine flexi (range: ≤300 mg/d) (2) placebo	Pain intensity Function (incl. sleep) Study dropout Adverse effects
Raskin et al. (2004) USA N=323	Parallel 84d Base pain: 6.86	Peripheral	Painful diabetic neuropathy Concomitant pain meds allowed	(1) topiramate flexi (mean: 161.2 mg/d) (range: ≤400 mg/d) (2) placebo	Pain intensity Function (incl. sleep) HRQoL Study dropout Adverse effects
Raskin et al. (2005) USA N=348	Parallel 84d Base pain: 5.60	Peripheral	Painful diabetic neuropathy No concomitant pain meds allowed	(1) duloxetine fixed (60 mg/d) (2) duloxetine fixed (120 mg/d) (3) placebo	Pain intensity Function (incl. sleep) Adverse event
Rauck et al. (2007) country not clear N=119	Parallel 70d Base pain: 6.55	Peripheral	Painful diabetic neuropathy Concomitant pain meds allowed	(1) lacosamide flexi (range: ≤400 mg/d) (2) placebo	Pain intensity Global improvement Function (incl. sleep) Study dropout Adverse effects
Rice & Maton (2001) UK N=344	Parallel 49d Base pain: 6.50	Peripheral	Post-herpetic neuralgia Concomitant pain meds allowed	(1) gabapentin fixed (1800 mg/d) (2) gabapentin fixed (2400 mg/d) (3) placebo	Pain intensity Global improvement Study dropout Adverse effects
Richter et al. (2005) USA N=246	Parallel 42d Base pain: 6.70	Peripheral	Painful diabetic neuropathy Concomitant pain meds allowed	(1) pregabalin fixed (150 mg/d) (2) pregabalin fixed (600 mg/d) (3) placebo	Pain intensity Global improvement Study dropout Adverse effects
Rintala et al. (2007) USA N=22	Crossover 56d Base pain: 5.60	Mixed / ambiguous	Spinal cord injury pain Concomitant pain meds allowed	(1) amitriptyline flexi (range: ≤150 mg/d) (2) gabapentin flexi (range: ≤3600 mg/d) (3) placebo	Pain intensity Study dropout Adverse effects
Robinson et al. (2004) USA, N=39	Parallel 42d Base pain: 3.40	Mixed / ambiguous	Phantom limb pain Concomitant pain meds allowed	(1) amitriptyline fixed (125 mg/d) (2) placebo	Pain intensity Function (incl. sleep) Adverse effects

Study / Country / N	Design / Duration / Baseline pain	Type of pain	Condition / Concomitant treatments	Treatments	Outcomes
Rog et al. (2005) UK N=66	Parallel 28d Base pain: 6.48	Central	MS neuropathic pain Concomitant pain meds allowed	(1) cannabis sativa extract flexi (mean: 25.9 mg/d) (range: ≤130 mg/d) (2) placebo	Pain intensity Global improvement Function (incl. sleep) Study dropout Adverse effects
Rosenstock et al. (2004) USA N=146	Parallel 56d Base pain: NR	Peripheral	Painful diabetic neuropathy Concomitant pain meds allowed	(1) pregabalin fixed (300 mg/d) (2) placebo	Pain intensity Global improvement Function (incl. sleep) HRQoL Study dropout Adverse effects
Rossi et al. (2009) Italy N=20	Parallel 84d Base pain: 6.97	Central	MS neuropathic pain No concomitant pain meds allowed	(1) levetiracetam fixed (500 mg/d) (2) placebo	Pain intensity HRQoL Study dropout Adverse effects
Rowbotham et al. (1998) USA N=229	Parallel 56d Base pain: 6.40	Peripheral	Post-herpetic neuralgia Concomitant pain meds allowed	(1) gabapentin flexi (range: ≤3600 mg/d) (2) placebo	Pain intensity Global improvement Function (incl. sleep) HRQoL Study dropout Adverse effects
Rowbotham et al. (2004) USA, N=244	Parallel 42d Base pain: 6.87	Peripheral	Painful diabetic neuropathy Concomitant pain meds allowed	(1) venlafaxine fixed (75 mg/d) (2) venlafaxine flexi (range: 150–225 mg/d) (3) placebo	Pain intensity Study dropout Adverse effects
Sabatowski et al. (2004) Europe and Australia N=238	Parallel 56d Base pain: 6.80	Peripheral	Post-herpetic neuralgia Concomitant pain meds allowed	(1) pregabalin fixed (150 mg/d) (2) pregabalin fixed (300 mg/d) (3) placebo	Pain intensity Global improvement Function (incl. sleep) Study dropout Adverse effects
Satoh et al. (2011) Japan N=317	Parallel 98d Base pain: 6.00	Peripheral	Painful diabetic neuropathy Concomitant pain meds allowed	(1) pregabalin fixed (300 mg/d) (2) pregabalin fixed (600 mg/d) (3) placebo	Pain intensity Study dropout Adverse effects
Scheffler et al. (1991) USA N=54	Parallel 56d Base pain: 7.48	Peripheral	Painful diabetic neuropathy Concomitant pain meds allowed	(1) capsaicin cream fixed (4 applications/d) (2) placebo	Pain intensity Study dropout Adverse effects

Study / Country / N	Design / Duration / Baseline pain	Type of pain	Condition / Concomitant treatments	Treatments	Outcomes
Selvarajah et al. (2010) UK, N=30	Parallel 84d Base pain: 6.54	Peripheral	Painful diabetic neuropathy Concomitant pain meds allowed	(1) cannabis sativa extract flexi (mean: 0.7 mg/d) (2) placebo	Pain intensity HRQoL
Shaibani et al. (2009) USA N=468	Parallel 126d Base pain: 6.30	Peripheral	Painful diabetic neuropathy Concomitant pain meds allowed	(1) lacosamide fixed (600 mg/d) (2) lacosamide fixed (400 mg/d) (3) lacosamide fixed (200 mg/d) (4) placebo	Pain intensity Global improvement Function (incl. sleep) Study dropout Adverse effects
Siddall et al. (2006) Australia N=137	Parallel 84d Base pain: 6.64	Central	Spinal cord injury pain Concomitant pain meds allowed	(1) pregabalin flexi (mean: 460 mg/d) (range: 150–600 mg/d) (2) placebo	Pain intensity Global improvement Function (incl. sleep) Study dropout Adverse effects
Simpson (2001) USA N=60	Parallel 56d Base pain: 6.45	Peripheral	Painful diabetic neuropathy No concomitant pain meds allowed	(1) gabapentin flexi (range: ≤3600 mg/d) (2) placebo	Pain intensity Global improvement Function (incl. sleep) HRQoL Study dropout Adverse effects
Simpson et al. (2000) USA, N=42	Parallel 98d Base pain: NR	Peripheral	HIV-related neuropathy Concomitant pain meds allowed	(1) lamotrigine fixed (300 mg/d) (2) placebo	Pain intensity Study dropout Adverse event
Simpson et al. (2003) USA N=227	Parallel 77d Base pain: 6.66	Peripheral	HIV-related neuropathy Concomitant pain meds allowed	(1) lamotrigine flexi (mean: 379.9 mg/d) (range: ≤600 mg/d) (2) placebo	Pain intensity Global improvement Study dropout Adverse effects
Simpson et al. (2008) USA N=307	Parallel 84d Base pain: 5.9	Peripheral	HIV-related neuropathy Concomitant pain meds allowed	(1) capsaicin patch fixed (30-min application) (2) capsaicin patch fixed (60-min application) (3) capsaicin patch fixed (90-min application) (4) placebo	Pain intensity Global improvement Study dropout Adverse effects
Simpson et al. (2010) USA N=302	Parallel 98d Base pain: 6.80	Peripheral	HIV-related neuropathy Concomitant pain meds allowed	(1) pregabalin flexi (mean: 385.7 mg/d) (range: 150–600 mg/d) (2) placebo	Pain intensity Global improvement Study dropout Adverse effects
Sindrup et al. (1999) Denmark, N=45	Crossover 28d Base pain: 6.66	Peripheral	Polyneuropathy Concomitant pain meds allowed	(1) tramadol flexi (range: 200–400 mg/d) (2) placebo	Pain intensity Study dropout Adverse effects

Study / Country / N	Design / Duration / Baseline pain	Type of pain	Condition / Concomitant treatments	Treatments	Outcomes
Sindrup et al. (2003) Denmark, N=40	Crossover 28d Base pain: 7.00	Peripheral	Polyneuropathy Concomitant pain meds allowed	(1) venlafaxine fixed (112.5 mg/d) (2) imipramine fixed (75 mg/d) (3) placebo	Pain intensity Study dropout Adverse effects
Smith et al. (2005) USA N=24	Crossover 42d Base pain: 4.38	Mixed / ambiguous	Phantom limb pain Concomitant pain meds allowed	(1) gabapentin flexi (median: 3600 mg/d) (range: 300–3600 mg/d) (2) placebo	Pain intensity Function (incl. sleep)
Stacey et al. (2008) USA, Germany, Italy, Spain, UK N=269	Parallel 28d Base pain: 6.50	Peripheral	Post-herpetic neuralgia Concomitant pain meds allowed	(1) pregabalin flexi (range: 150–600 mg/d) (2) pregabalin fixed (300 mg/d) (3) placebo	Pain intensity Study dropout Adverse effects
Tandan et al. (1992) USA N=22	Parallel 56d Base pain: 8.11	Peripheral	Painful diabetic neuropathy Concomitant pain meds allowed	(1) capsaicin cream fixed (4 applications/d) (2) placebo	Pain intensity Global improvement Study dropout Adverse effects
Tasmuth et al. (2002) Finland, N=15	Crossover 28d Base pain: 4.90	Peripheral	Post-surgical pain after surgery for cancer Concomitant pain meds allowed	(1) venlafaxine flexi (range: 19–75 mg/d) (2) placebo	Pain intensity Function (incl. sleep) Adverse effects
Thienel et al. (2004) USA N=1269	Parallel 140d Base pain: 5.80	Peripheral	Painful diabetic neuropathy No concomitant pain meds allowed	(1) topiramate fixed (100 mg/d) (2) topiramate fixed (200 mg/d) (3) topiramate fixed (400 mg/d) (4) placebo	Pain intensity Study dropout Adverse effects
Tolle et al. (2008) USA and Germany N=395	Parallel 84d Base pain: 6.43	Peripheral	Painful diabetic neuropathy Concomitant pain meds allowed	(1) pregabalin fixed (150 mg/d) (2) pregabalin fixed (300 mg/d) (3) pregabalin flexi (range: ≤600 mg/d) (4) placebo	Pain intensity Global improvement Study dropout Adverse effects
van Seventer et al. (2006) unclear N=370	Parallel 91d Base pain: 6.67	Peripheral	Post-herpetic neuralgia Concomitant pain meds allowed	(1) pregabalin fixed (150 mg/d) (2) pregabalin fixed (300 mg/d) (3) pregabalin fixed (600 mg/d) (4) placebo	Pain intensity Global improvement Function (incl. sleep) Study dropout Adverse effects
Vestergaard et al. (2001) Denmark, N=30	Crossover 56d Base pain: 6.00	Central	Post-stroke pain No concomitant pain meds allowed	(1) lamotrigine fixed (200 mg/d) (2) placebo	Pain intensity Study dropout Adverse effects
Vinik et al. (2007) USA N=360	Parallel 133d Base pain: 6.28	Peripheral	Painful diabetic neuropathy Concomitant pain meds allowed	(1) lamotrigine fixed (200 mg/d) (2) lamotrigine fixed (300 mg/d) (3) lamotrigine fixed (400 mg/d) (4) placebo	Pain intensity Study dropout Adverse effects

Study / Country / N	Design / Duration / Baseline pain	Type of pain	Condition / Concomitant treatments	Treatments	Outcomes
Vinik et al. (2007) USA N=360	Parallel 133d Base pain: 6.23	Peripheral	Painful diabetic neuropathy Concomitant pain meds allowed	(1) lamotrigine fixed (200 mg/d) (2) lamotrigine fixed (300 mg/d) (3) lamotrigine fixed (400 mg/d) (4) placebo	Pain intensity Study dropout Adverse effects
Vranken et al. (2008) Holland N=40	Parallel 28d Base pain: 7.50	Central	Central pain Concomitant pain meds allowed	(1) pregabalin flexi (range: 150–600 mg/d) (2) placebo	Pain intensity HRQoL Study dropout Adverse effects
Vranken et al. (2011) Holland N=48	Parallel 56d Base pain: 7.15	Central	Spinal cord injury pain Concomitant pain meds allowed	(1) duloxetine flexi (mean: 99.1 mg/d) (range: 60–120 mg/d) (2) placebo	Pain intensity Global improvement HRQoL Study dropout Adverse effects
Vrethem et al. (1997) Sweden, N=37	Crossover 28d Base pain: 4.55	Peripheral	Polyneuropathy Concomitant pain meds allowed	(1) amitriptyline fixed (75 mg/d) (2) placebo	Pain intensity Function (incl. sleep) Adverse effects
Wade et al. (2004) UK N=37	Parallel 42d Base pain: NR	Central	MS neuropathic pain Concomitant pain meds allowed	(1) cannabis sativa extract flexi (range: 3–120 mg/d) (2) placebo	Pain intensity
Watson & Evans (1992) Canada N=25	Parallel 42d Base pain: 6.00	Peripheral	Post-surgical pain after surgery for cancer Concomitant pain meds allowed	(1) capsaicin cream fixed (4 applications/d) (2) placebo	Pain intensity Global improvement Study dropout Adverse effects
Watson et al. (1993) USA & Canada N=143	Parallel 42d Base pain: NR	Peripheral	Post-herpetic neuralgia Concomitant pain meds allowed	(1) capsaicin cream fixed (4 applications/d) (2) placebo	Pain intensity Adverse effects
Watson et al. (1998) Canada N=33	Crossover 35d Base pain: NR	Peripheral	Post-herpetic neuralgia Concomitant pain meds allowed	(1) amitriptyline flexi (range: 10–160 mg/d) (2) nortriptyline flexi (range: 10–160 mg/d)	Adverse effects
Webster et al. (2010) USA N=155	Parallel 84d Base pain: 5.35	Peripheral	Post-herpetic neuralgia Concomitant pain meds allowed	(1) capsaicin patch fixed (60-min application) (2) placebo	Pain intensity Global improvement Study dropout Adverse effects

Study / Country / N	Design / Duration / Baseline pain	Type of pain	Condition / Concomitant treatments	Treatments	Outcomes
Webster et al. (2010) USA N=299	Parallel 84d Base pain: 5.60	Peripheral	Post-herpetic neuralgia Concomitant pain meds allowed	(1) capsaicin patch fixed (90-min application) (2) capsaicin patch fixed (60-min application) (3) capsaicin patch fixed (30-min application) (4) placebo	Pain intensity Global improvement Study dropout Adverse effects
Wernicke et al. (2006) Canada N=334	Parallel 84d Base pain: 6.10	Peripheral	Painful diabetic neuropathy No concomitant pain meds allowed	(1) duloxetine fixed (60 mg/d) (2) duloxetine fixed (120 mg/d) (3) placebo	Pain intensity Global improvement Function (incl. sleep) HRQoL Study dropout Adverse effects
Wu et al. (2008) USA N=60	Crossover 42d Base pain: 6.85	Mixed / ambiguous	Phantom limb pain Concomitant pain meds allowed	(1) morphine flexi (mean: 112 mg/d) (range: 15–180 mg/d) (2) placebo	Pain intensity Study dropout Adverse effects
Wymer et al. (2009) USA N=370	Parallel 126d Base pain: 6.55	Peripheral	Painful diabetic neuropathy Concomitant pain meds allowed	(1) lacosamide fixed (600 mg/d) (2) lacosamide fixed (400 mg/d) (3) lacosamide fixed (200 mg/d) (4) placebo	Pain intensity Global improvement Function (incl. sleep) Study dropout Adverse effects
Yasuda et al. (2011) Japan N=339	Parallel 84d Base pain: 5.78	Peripheral	Painful diabetic neuropathy No concomitant pain meds allowed	(1) duloxetine fixed (40 mg/d) (2) duloxetine fixed (60 mg/d) (3) placebo	Pain intensity Global improvement Function (incl. sleep) Study dropout Adverse effects
Yucel et al. (2005) Turkey N=60	Parallel 56d Base pain: 7.70	Mixed / ambiguous	Mixed neuropathic pain Concomitant pain meds allowed	(1) venlafaxine fixed (75 mg/d) (2) venlafaxine fixed (150 mg/d) (3) placebo	Pain intensity Adverse effects
Ziegler et al. (2010) Europe N=357	Parallel 126d Base pain: 6.47	Peripheral	Painful diabetic neuropathy No concomitant pain meds allowed	(1) lacosamide fixed (600 mg/d) (2) lacosamide fixed (400 mg/d) (3) placebo	Pain intensity Global improvement Function (incl. sleep) Study dropout Adverse effects

Table 5 GRADE table summary for 'all neuropathic pain'

Outcome (follow-up)	Number of studies	Number of patients	Interventions	Quality	Importance
Patient-reported global improvement – at least moderate improvement (28±7 days)[1]	4 RCTs[a]	412	cannabis sativa extract, levetiracetam, pregabalin, tramadol	Very low	Critical
Patient-reported global improvement – at least moderate improvement (56±7 days)	8 RCTs[b]	1525	capsaicin patch, duloxetine, gabapentin, pregabalin, valproate	Very low	Critical
Patient-reported global improvement – at least moderate improvement (84±14 days)	8 RCTs[c]	2337	capsaicin patch, lacosamide, lamotrigine, pregabalin	Low	Critical
Sleep interference normalised 10-point scale (28±7 days) [d]	4 RCTs[e]	489	cannabis sativa extract, escitalopram, gabapentin, gabapentin+nortriptyline, nortriptyline	Low	Critical
Sleep interference normalised 10-point scale (56±7 days) [d]	2 RCTs[f]	360	Gabapentin	Moderate	Critical
Sleep interference normalised 10-point scale (84±14 days) [d]	6 RCTs[g]	1650	duloxetine, pregabalin, topiramate	Low	Critical
Withdrawal due to adverse effects (all time points)	91 RCTs[h]	17274	23 (see appendix G)	Very low	Critical
Individual adverse events	97 RCTs[r] (3–67)	567–12190	See appendix J	Low to very low	Important
30% pain relief (28±7 days)	7 RCTs[i]	1087	cannabis sativa extract, capsaicin cream, gabapentin, levetiracetam, pregabalin, tramadol	Very low	Important
30% pain relief (56±7 days)	5 RCTs[j]	1234	amitriptyline, capsaicin patch, gabapentin, pregabalin	Very low	Important
30% pain relief (84±14 days)	18 RCTs[k]	4840	cannabis sativa extract, capsaicin patch, duloxetine, lacosamide, lamotrigine, pregabalin, topiramate	Very low	Important
50% pain relief (28±7 days)	8 RCTs[l]	1181	amitriptyline, cannabis sativa extract, gabapentin, levetiracetam, morphine, pregabalin, tramadol	Very low	Important
50% pain relief (56±7 days)	7 RCTs[m]	1120	gabapentin, lamotrigine, nortriptyline, pregabalin	Very low	Important
50% pain relief (84±14 days)	16 RCTs[n]	5866	capsaicin patch, duloxetine, pregabalin, topiramate	Very low	Important
30% and 50% pain relief (all time points)	49 RCTs[o]	20115	17 (see appendix G)	Low	Important
Pain relief (continuous) (28±7 days)	30 RCTs[p]	3546	21 (see appendix G)	Very low	Important
Pain relief (continuous) (56±7 days)	21 RCTs[q]	2923	13 (see appendix G)	Very low	Important
Pain relief (continuous) (84±14 days)	15 RCTs[r]	2987	10 (see appendix G)	Low	Important

[1] measured using the 7-point PGIC tool

[a] Finnerup et al. (2009), Lesser et al. (2004), Norrbrink & Lundeberg (2009), Rog et al. (2005); [b] Backonja et al. (1998), Irving et al. (2011), Kochar et al. (2005), Rice & Maton (2001), Rowbotham et al. (1998), Sabatowski et al. (2004), Simpson (2001), Vranken et al. (2011); [c] Arezzo et al. (2008), Freynhagen et al. (2005), Irving et al. (2011), Rauck et al. (2007), Simpson et al. (2003), Tolle et al. (2008), van Seventer et al. (2006); [d] this is the only synthesis possible for the outcome 'patient reported improvement

in daily physical and emotional functioning including sleep'; [e] Gilron et al. (2012), Gordh et al. (2008), Otto et al. (2008), Rog et al. (2005); [f] Backonja et al. (1998), Rowbotham et al. (1998); [g] Gao et al. (2010), Raskin et al. (2004), Raskin et al. (2005), Siddall et al. (2006), Wernicke et al. (2006), Yasuda et al. (2011); [h] Arbaiza & Vidal (2007), Arezzo et al. (2008), Backonja et al. (1998), Backonja et al. (2008), Bansal et al. (2009), Beydoun et al. (2006), Breuer et al. (2007), Cardenas et al. (2002), Cheville et al. (2009), Clifford et al. (2012), Dogra et al. (2005), Donofrio & Capsaicin study (1992), Dworkin et al. (2003), Eisenberg et al. (2001), Falah et al. (2012), Finnerup et al. (2002), Finnerup et al. (2009), Freynhagen et al. (2005), Gao et al. (2010), Gimbel et al. (2003), Goldstein et al. (2005), Gordh et al. (2008), Graff-Radford et al. (2000), Guan et al. (2011), Hahn et al. (2004), Hanna et al. (2008), Harati et al. (1998), Holbech et al. (2011), Irving et al. (2011), Kautio et al. (2008), Khoromi et al. (2005), Khoromi et al. (2007), Kim et al. (2011), Kochar et al. (2002), Kochar et al. (2004), Kochar et al. (2005), Lesser et al. (2004), Luria et al. (2000), Max et al. (1988), McCleane (1999), Moon et al. (2010), Morello et al. (1999), Norrbrink & Lundeberg (2009), Nurmikko et al. (2007), Otto et al. (2008), Paice et al. (2000), Rao et al. (2008), Raskin et al. (2004), Raskin et al. (2005), Rauck et al. (2007), Rice & Maton (2001), Richter et al. (2005), Rintala et al. (2007), Robinson et al. (2004), Rog et al. (2005), Rosenstock et al. (2004), Rossi et al. (2009), Rowbotham et al. (1998), Rowbotham et al. (2004), Sabatowski et al. (2004), Satoh et al. (2011), Scheffler et al. (1991), Shaibani et al. (2009), Siddall et al. (2006), Simpson (2001), Simpson et al. (2000), Simpson et al. (2003), Simpson et al. (2008), Simpson et al. (2010), Sindrup et al. (1999), Sindrup et al. (2003), Stacey et al. (2008), Tandan et al. (1992), Tasmuth et al. (2002), Thienel et al. (2004), Tolle et al. (2008), van Seventer et al. (2006), Vestergaard et al. (2001), Vinik et al. (2007), Vinik et al. (2007), Vranken et al. (2008), Vrethem et al. (1997), Watson & Evans (1992), Watson et al. (1993), Watson et al. (1998), Webster et al. (2010), Wernicke et al. (2006), Wymer et al. (2009), Yasuda et al. (2011), Yucel et al. (2005), Ziegler et al. (2010); [i] Bernstein et al. (1989), Finnerup et al. (2009), Lesser et al. (2004), Nurmikko et al. (2007), Sindrup et al. (1999), Stacey et al. (2008); [j] Backonja et al. (2008), Dworkin et al. (2003), Guan et al. (2011), Gordh et al. (2008), Moon et al. (2010), Rintala et al. (2007); [k] Backonja et al. (2008), Breuer et al. (2007), Clifford et al. (2012), Freynhagen et al. (2005), Gao et al. (2010), Irving et al. (2011), Raskin et al. (2004), Rauck et al. (2007), Selvarajah et al. (2010), Siddall et al. (2006), Simpson et al. (2003), Simpson et al. (2008), Simpson et al. (2010), van Seventer et al. (2006), Webster et al. (2010), Webster et al. (2010), Wernicke et al. (2006), Yasuda et al. (2011); [l] Bansal et al. (2009), Finnerup et al. (2009), Gordh et al. (2008), Huse et al. (2001), Lesser et al. (2004), Nurmikko et al. (2007), Sindrup et al. (1999), Stacey et al. (2008); [m] Chandra et al. (2006), Dworkin et al. (2003), Luria et al. (2000), Moon et al. (2010), Rice & Maton (2001), Rosenstock et al. (2004), Sabatowski et al. (2004); [n] Freynhagen et al. (2005), Gao et al. (2010), Goldstein et al. (2005), Irving et al. (2011), Raskin et al. (2004), Raskin et al. (2005), Satoh et al. (2011), Siddall et al. (2006), Simpson et al. (2010), Tolle et al. (2008), van Seventer et al. (2006), Webster et al. (2010), Webster et al. (2010), Wernicke et al. (2006), Yasuda et al. (2011); [o] Backonja et al. (2008), Bernstein et al. (1989), Gordh et al. (2008), Boureau et al. (2003), Webster et al. (2010), Chandra et al. (2006), Stacey et al. (2008), Clifford et al. (2012), Dogra et al. (2005), Dworkin et al. (2003), Eisenberg et al. (2001), Freynhagen et al. (2005), Gao et al. (2010), Goldstein et al. (2005), Guan et al. (2011), Irving et al. (2012), Irving et al. (2011), Lesser et al. (2004), Luria et al. (2000), Moon et al. (2010), Nurmikko et al. (2007), Raskin et al. (2005), Raskin et al. (2004), Rauck et al. (2007), Rice & Maton (2001), Richter et al. (2005), Rosenstock et al. (2004), Rowbotham et al. (2004), Sabatowski et al. (2004), Satoh et al. (2011), Wernicke et al. (2006), Simpson et al. (2010), Vinik et al. (2007), Webster et al. (2010), van Seventer et al. (2006), Simpson et al. (2003), Shaibani et al. (2009), Ziegler et al. (2010), Watson & Evans (1992), Yasuda et al. (2011), Tolle et al. (2008), Siddall et al. (2006), Vinik et al. (2007), Bansal et al. (2009), Breuer et al. (2007), Finnerup et al. (2009), Huse et al. (2001), Rintala et al. (2007), Sindrup et al. (1999), Wu et al. (2008) ; [p] Backonja et al. (1998), Bone et al. (2002), Boureau et al. (2003), Cheville et al. (2009), Dogra et al. (2005), Gilron et al. (2012), Gimbel et al. (2003), Gordh et al. (2008), Guan et al. (2011), Hanna et al. (2008), Huse et al. (2001), Kalso et al. (1995), Kochar et al. (2002), Kochar et al. (2004), Lesser et al. (2004), Levendoglu et al. (2004), Mishra et al. (2012), Nurmikko et al. (2007), Otto et al. (2008), Rao et al. (2007), Rao et al. (2008), Raskin et al. (2004), Rice & Maton (2001), Rog et al. (2005), Rossi et al. (2009), Sindrup et al. (1999), Sindrup et al. (2003), Vranken et al. (2008), Vranken et al. (2011), Vrethem et al. (1997); [q] Backonja et al. (1998), Biesbroeck et al. (1995), Chandra et al. (2006), Dogra et al. (2005), Eisenberg et al. (2001), Graff-Radford et al. (2000), Guan et al. (2011), Hanna et al. (2008), Kochar et al. (2005), Levendoglu et al. (2004), Luria et al. (2000), Moon et al. (2010), Rao et al. (2008), Raskin et al. (2004), Rice & Maton (2001), Rintala et al. (2007), Rossi et al. (2009), Rowbotham et al. (1998), Sabatowski et al. (2004), Tandan et al. (1992), Vranken et al. (2011); [r] Agrawal et al. (2009), Dogra et al. (2005), Goldstein et al. (2005), Kochar et al. (2004), Rao et al. (2008), Raskin et al. (2004), Raskin et al. (2005), Rauck et al. (2007), Rossi et al. (2009), Selvarajah et al. (2010), Siddall et al. (2006), Simpson et al. (2010), van Seventer et al. (2006), Wernicke et al. (2006), Yasuda et al. (2011); [r] see appendix J
Abbreviations: HRQoL, Health-related quality of life; NR, not reported; PGIC, patient-reported global impression of change; PICO, patient, intervention, comparator, outcome; RCT, randomised controlled trial; SSRI, selective serotonin reuptake inhibitor.

See appendix E for the evidence tables in full. For full results of all the network meta-analyses please see appendices G and J.

Summary graphics tables

The graphics in Table 6 (and subsequent tables for ‘peripheral neuropathic pain’ [Table 12] and ‘central neuropathic pain’ [Table 14]) summarise all the syntheses that have been performed for the effectiveness and safety review for this guideline. They present all the analyses on the same scale, providing an overview of all comparators across all outcomes.

The graphics contain exactly the same information as the rank probability histograms that appear in the detailed outputs of each individual analysis (see appendices G–J). That is, for each outcome, they indicate the probability that each treatment is the best option for which evidence is available, the worst available option, or any point in between. In this instance, the probabilities are indicated by intensity of colour (see key), rather than height of column.

All outcome rankings are presented on a standardised scale, from best (left) to worst (right). This means that, where the outcome in question is desirable – for example, pain relief – the treatment options with most intense colour in the left-hand part of the scale are those with the highest estimated probability of achieving that result. Those with more intense colour on the right are those that are least likely to do so. Conversely, where results are for an undesirable outcome – for example, nausea – a concentration of colour on the left-hand part of the scale implies a lower probability of the event. A concentration of colour on the right suggests higher event-rates. In either case, treatments with more intense colour on the left are those with a positive profile for that outcome.

Bars presenting a relatively pale colour across a broad spread of the scale are indicative of results that are subject to substantial uncertainty – that is, there is a probability that the treatment could be ranked anywhere along the continuum. A good example of this in Table 6 is the estimate of nortriptyline’s effectiveness on continuous measures of pain at 8 weeks. Here, there is insufficient evidence to say whether nortriptyline is better or worse than its comparators.

In contrast, bars in which all colour is intensely concentrated at one point on the scale reflect unambiguous results: we are relatively certain that the treatment is ranked at that point. An example of this in Table 6 comes with the estimate of the

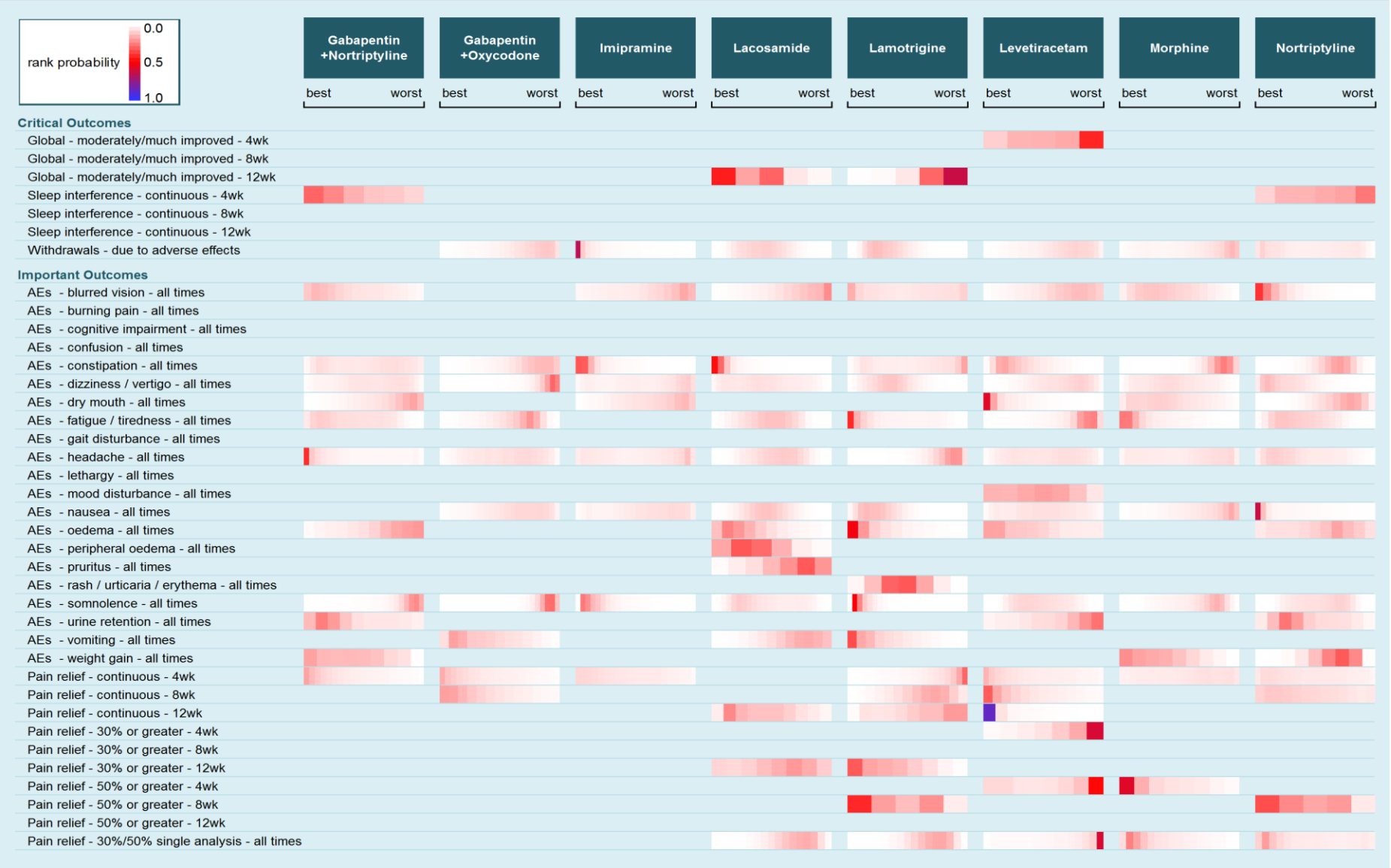
degree to which capsaicin cream causes somnolence: clearly, it is better than its comparators for this outcome, with a negligible probability that it is anything other than best.

Results for 3 treatments – carbamazepine, topical lidocaine and trazodone – are not shown in Table 6 because very few data were available for each, so they contributed to a small minority of analyses.

Table 6 Summary graphics table for ‘all neuropathic pain’ (page 1 of 3)

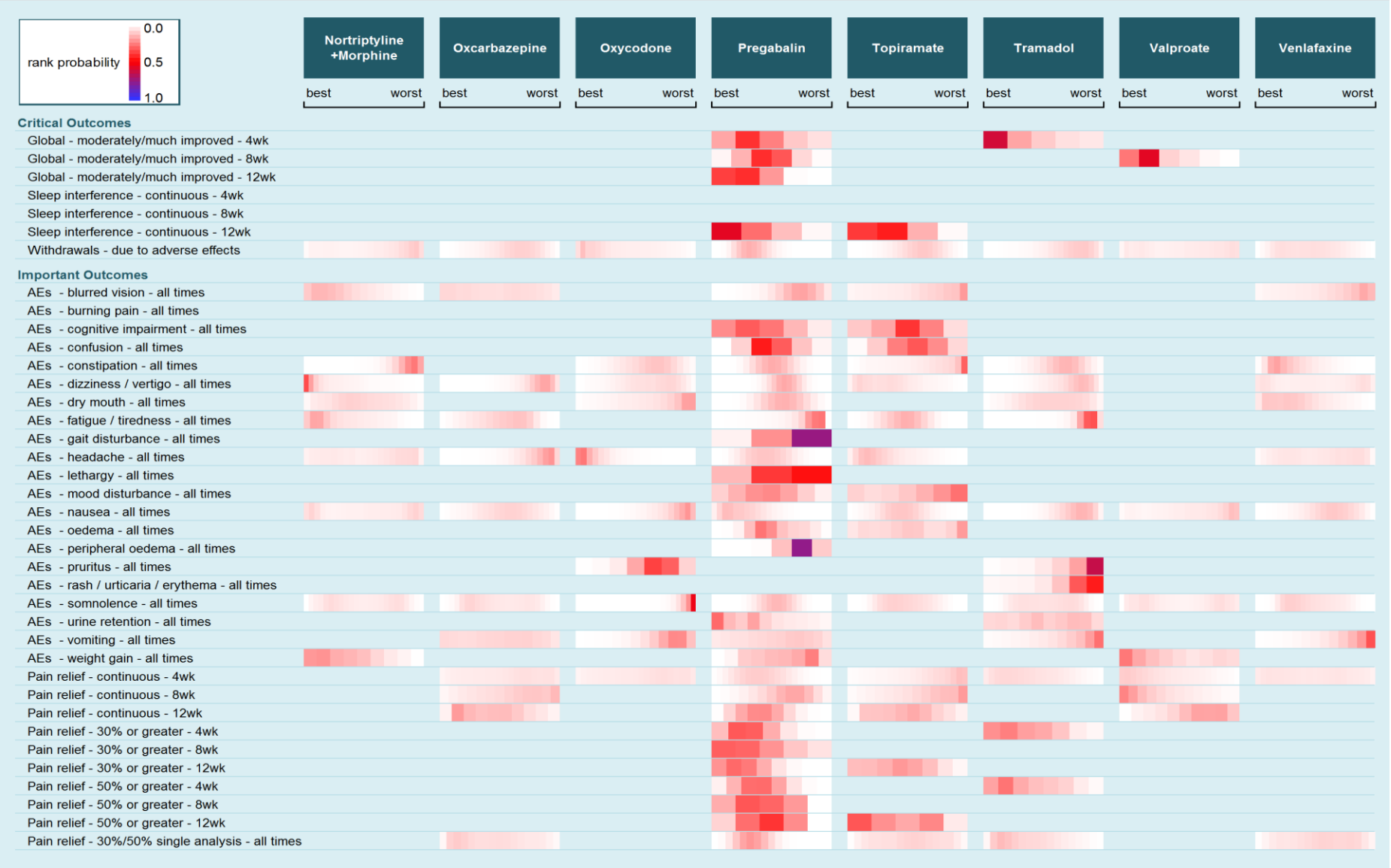
PLEASE NOTE THAT THIS TABLE IS BEST VIEWED IN COLOUR

Table 6 (continued; page 2 of 3)



PLEASE NOTE THAT THIS TABLE IS BEST VIEWED IN COLOUR

Table 6 (continued; page 3 of 3)



PLEASE NOTE THAT THIS TABLE IS BEST VIEWED IN COLOUR

3.1.2 Evidence statements

For details of how the evidence is graded, see The guidelines manual.

Critical outcomes

3.1.2.1 The evidence on patient-reported global improvement for all neuropathic pain conditions is available for only a limited number of drugs and at different follow-up periods. Network meta-analyses of 19 studies at 4, 8 and 12 weeks follow-up show uncertainty about which treatment is best at improving patient-reported global improvement. The evidence is low and very low quality.

3.1.2.2 The evidence on patient-reported improvement in daily physical and emotional functioning including sleep was reported across a wide variety of measurement tools with each measuring different aspects of functioning. As a result, it was not possible to synthesise the results from many of these studies in a meaningful way. Network meta-analyses and a pairwise meta-analysis of 12 studies at 4, 8 and 12 weeks follow-up show that a number of drugs may be better than placebo at improving sleep on a continuous scale. However, it is not clear if this is clinically significant and there is considerable uncertainty about which drugs were the best at improving sleep. Also, data were only available for a limited number of drugs. The evidence is moderate and low quality.

3.1.2.3 A network meta-analysis of 91 studies reporting withdrawal due to adverse effects at any follow-up showed that most drugs cause more drop-outs due to adverse effects than placebo, but there was considerable uncertainty about which drugs were least likely to cause drop-outs due to adverse effects. Accounting for the dosage at which drugs were delivered in the trials did not substantively explain heterogeneity or reduce uncertainty seen in the base-case analysis. The evidence was considered low quality.

Important outcomes

3.1.2.4 Network meta-analyses of 20 individual adverse effects from 97 studies (ranging from 3 studies for gait disturbance to 67 studies for dizziness or vertigo) show that some adverse effects were more frequent with particular drugs. However, it was difficult to draw conclusions on which particular drugs were best or worst for particular adverse effects. The evidence was considered low to very low quality.

3.1.2.5 Network meta-analyses of the proportion of patients achieving 30% or 50% pain relief (29 and 30 studies, respectively) at 4, 8 and 12 weeks follow-up and a combined network meta-analysis of 30% and 50% pain relief at all time-points (49 studies) show that most treatments are better than placebo. However, there is considerable uncertainty about which treatment is best at providing these levels of pain relief. These outcomes are available for only a limited number of drugs. Accounting for the dosage at which drugs were delivered in the trials did not substantively explain heterogeneity or reduce uncertainty seen in the base-case analysis. The evidence was considered low quality.

3.1.2.6 There was more evidence for continuous pain scores suggesting some improvement in pain. Network meta-analyses of 30 studies at 4 weeks, 21 studies at 8 weeks, and 15 studies at 12 weeks show that most treatments are better than placebo at improving mean pain scores but it is not clear if these differences are clinically significant. However, the confidence in these results and in the overall ratings of different drugs is low. The evidence was considered very low quality.

3.1.2.7 Overall, with regard to pain:

- *the results from the analyses showed that amitriptyline, duloxetine and pregabalin consistently reduce pain compared with placebo*

- *the majority of the results from the analyses showed that capsaicin cream, gabapentin, morphine, nortriptyline and tramadol consistently reduce pain compared with placebo*
- *the results from the analyses were inconsistent about whether levetiracetam and valproate reduce pain compared with placebo*
- *the results from the analyses were inconclusive about the effectiveness of gabapentin + nortriptyline, gabapentin + oxycodone, imipramine, lacosamide, lamotrigine, oxcarbazepine, oxycodone, topiramate or venlafaxine in reducing pain compared with placebo*
- *the results from the analyses showed that cannabis sativa and capsaicin patch may reduce pain compared with placebo, but both drugs appeared consistently worse at reducing pain than other drugs.*

3.1.2.8 Reporting on rescue medication use varied across the included studies, with some not reporting it at all, and those that reported it measuring usage in different ways (that is, proportion using rescue medications, number of tablets used, etc.). As a result, it was not possible to synthesise results meaningfully.

3.1.3 Health economics

Systematic review of published economic evaluations

Searches (see appendix D) for published cost–utility analyses (CUAs) yielded a total of 3353 unique citations; 3318 could be confidently excluded on review of title and abstract, 35 were reviewed as full text and 13 were included (Annemans et al., 2008; Armstrong et al., 2011; Beard et al., 2008; Bellows et al., 2012; Carlos et al., 2012; Cepeda 2006; Dakin et al., 2007; Gordon et al., 2012; O'Connor et al., 2007; O'Connor et al., 2008; Ritchie et al., 2010; Rodriguez et al., 2007; Tarride et al., 2006).

All 13 included studies addressed a population with peripheral neuropathic pain. No studies on central pain or trigeminal neuralgia were identified. The populations considered were: post-herpetic neuralgia (5 CUAs), painful

diabetic neuropathy (5), a mixed population of post-herpetic neuralgia and painful diabetic neuropathy (2), ‘refractory neuropathic pain’ (1) and non-specific peripheral neuropathic pain (1).

Each included study was judged to be partially applicable to the decision context, and each was considered to have potentially serious methodological limitations.

The range of comparators considered across the included studies was: amitriptyline (2 CUAs), capsaicin patch (1), carbamazepine (1), desipramine (2), duloxetine (5), gabapentin (10), lidocaine (3), nortriptyline (1), pregabalin (11), tramadol (2) and ‘usual care’ (2). However, the majority of the included studies (8) address a single pairwise comparison, and no more than 6 alternatives were examined in any one study.

Results for some of the treatments were inconsistent and occasionally contradictory between analyses. For full details of the design, quality and results of the included CUAs, see appendix F.

As none of the included studies assessed the range of comparators included in the scope of the guideline, and as it was not possible to draw robust conclusions from the heterogeneous evidence assembled, the GDG’s economic considerations were predominantly based on the de novo economic model developed for this guideline.

Original health economic model – methods

This is a summary of the modelling carried out for this review question. See appendix F for full details of the modelling carried out for the guideline.

The model assessed the costs and effects of all treatments in the assembled effectiveness and safety evidence base for which sufficient data were available. To be included in the model, at least 1 estimate of dichotomous pain relief (30% and/or 50% relief compared with baseline) and data on withdrawal due to adverse effects were required. In total, 17 treatments met these criteria:

- Placebo (that is, no treatment)
- Amitriptyline
- Cannabis sativa extract
- Capsaicin cream
- Capsaicin 8% patch
- Duloxetine
- Gabapentin
- Lacosamide
- Lamotrigine
- Levetiracetam
- Morphine
- Nortriptyline
- Oxcarbazepine
- Pregabalin
- Topiramate
- Tramadol
- Venlafaxine

Where multiple formulations of treatments were available, guidance was sought from the GDG as to the most appropriate formulation to be used in the model.

In line with the GDG's views on the appropriate subcategorisation of causes of neuropathic pain (see section 2.1.1), separate models for people with peripheral pain, central pain and trigeminal neuralgia were considered. Insufficient data were available to provide results for central pain and trigeminal neuralgia. It would have been possible to perform a dedicated analysis limited to people with peripheral pain; however, since the GDG concluded that there was insufficient evidence to distinguish between the peripheral-only group and the overall population (see section 3.2.4), a peripheral-only model was not pursued. Therefore, attention was focused on a single analysis including all types of neuropathic pain.

Time horizon, perspective, discount rates

A limited time horizon of 20 weeks was adopted. This was primarily because effectiveness data were only available up to this point. Extrapolation beyond this point in the absence of treatment-specific information would require making the same assumptions about the projected efficacy profiles for all drugs over time and so would, in any case, lead to the same conclusions as at 20 weeks. Additionally, no included studies suggested that any of the treatments considered in the model had an impact on mortality, which would be an important reason for a speculative extrapolation to a lifetime horizon.

The analysis was undertaken from the perspective of the NHS and personal social services, in accordance with NICE guidelines methodology. With a 20-week time horizon, there was no requirement to apply a discount rate to either costs or quality-adjusted life years (QALYs).

Model structure

With different scales used to measure pain, the GDG agreed that pain data should be modelled as a discrete variable with pain reductions of less than 30%, 30–49% or 50% or more. This approach to categorising pain relief is recommended by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) group and commonly used in the literature (Dworkin et al. 2005).

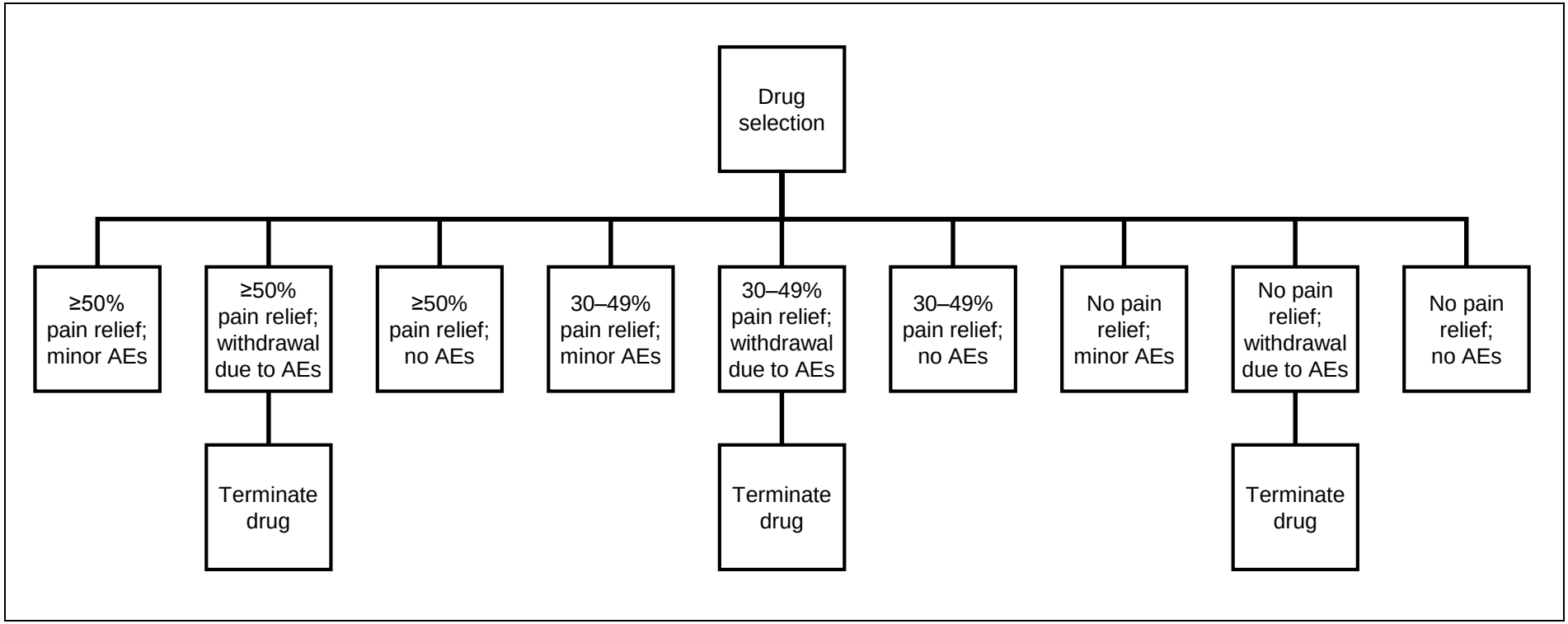
With a limited time horizon and with no data available on the independence of effect between different drugs (that is, we do not know how failure to achieve pain relief on one drug affects the likelihood of a patient achieving pain relief on another), a simple decision tree was adopted, rather than a more complicated approach, such as a Markov state-transition model. On starting treatment, patients can see pain relief of either 30–49% or of 50% or more. If pain relief is less than 30%, then no pain relief is assumed.

Data were available for all included comparators on 2 tolerable adverse effects: dizziness/vertigo and nausea. The quality of life impact and cost implications of these were included in the model. Data were also available on patients withdrawing due to intolerable adverse effects. When such

withdrawals are simulated in the model, they are assumed to occur after 4 weeks of treatment, with drug costs incurred up to that point and any efficacy benefits seen included in the analysis. In the base case, it was assumed that patients withdrawing from treatment due to adverse effects experienced no pain relief for the remaining 16 weeks of the model. The impact of this assumption was explored in a scenario analysis in which all simulated dropouts received the cheapest treatment considered (amitriptyline) for the remainder of the model.

A schematic of the model is shown in Figure 3.

Figure 3 Neuropathic pain model schematic



The model was not used to estimate the cost effectiveness of treatment strategies over more than 1 line. Because there are insufficient data on correlations between the effectiveness of different drugs, the efficacy of one drug for a patient would have to be assumed to be independent of likelihood of response to all other drugs. It was judged that this assumption is very unlikely to be true, since multiple class effects are expected to be present amongst the therapies under review (for example, a patient whose pain does not respond to pregabalin may be less likely than an unselected individual to derive benefit from gabapentin). In the absence of any evidence on these correlations, any explicit modelling of sequences would be extremely speculative and potentially unreliable. Therefore, the GDG agreed to make its recommendations on the basis that the sequential strategy with the highest probability of cost effectiveness for any individual patient is to try treatments in order of their individual probability of cost effectiveness.

Model inputs: efficacy and safety of treatments

Full details of the efficacy and safety data used in the health economic model are presented in appendix G and J.

Efficacy data were derived from an NMA of 30% and 50% pain relief probabilities from all available trials (see appendix D for methods and appendix G for results). Safety data were derived from separate NMAs estimating the likelihood that patients would experience nausea, dizziness/vertigo or an adverse effect of sufficient severity that the patient would withdraw from treatment.

An additional scenario analysis of the health economic model was performed using inputs from alternative NMAs that included extra terms that sought to account for dose–response effects in the underlying evidence.

Table 7 Health economic model – efficacy and safety parameters

	Probability (95% CrI) of pain relief after 20 weeks			Probability (95% CrI) of event within 20 weeks		
Drug	**<30%**	**30–49%**	**≥50%**	**Withdrawal due to AEs**	**Dizziness**	**Nausea**
Placebo	0.64 (0.49,0.77)	0.13 (0.10,0.16)	0.23 (0.13,0.36)	0.09 (0.08,0.11)	0.13 (0.10,0.17)	0.10 (0.08,0.14)
Amitriptyline	0.47 (0.25,0.70)	0.15 (0.12,0.17)	0.38 (0.18,0.60)	0.24 (0.12,0.41)	0.16 (0.07,0.30)	0.09 (0.01,0.30)
Cannabis extract	0.46 (0.20,0.73)	0.15 (0.11,0.17)	0.39 (0.16,0.66)	0.48 (0.10,0.98)	0.37 (0.13,0.73)	0.21 (0.07,0.47)
Capsaicin cream	0.20 (0.03,0.48)	0.12 (0.04,0.16)	0.68 (0.36,0.92)	0.46 (0.21,0.81)	0.57 (0.02,1.00)	0.60 (0.05,1.00)
Capsaicin patch	0.53 (0.37,0.70)	0.15 (0.12,0.16)	0.32 (0.18,0.48)	0.11 (0.03,0.27)	0.12 (0.04,0.25)	0.16 (0.08,0.30)
Duloxetine	0.43 (0.27,0.60)	0.15 (0.14,0.17)	0.41 (0.26,0.58)	0.24 (0.13,0.40)	0.27 (0.13,0.48)	0.34 (0.20,0.53)
Gabapentin	0.47 (0.28,0.66)	0.15 (0.13,0.17)	0.38 (0.21,0.57)	0.18 (0.10,0.30)	0.41 (0.24,0.63)	0.13 (0.05,0.26)
Lacosamide	0.55 (0.36,0.72)	0.15 (0.12,0.16)	0.31 (0.16,0.48)	0.23 (0.12,0.38)	0.28 (0.05,0.80)	0.18 (0.09,0.33)
Lamotrigine	0.55 (0.37,0.72)	0.15 (0.12,0.16)	0.31 (0.17,0.47)	0.18 (0.10,0.29)	0.20 (0.08,0.42)	0.12 (0.06,0.21)
Levetiracetam	0.68 (0.34,0.93)	0.12 (0.04,0.16)	0.20 (0.03,0.50)	0.41 (0.13,0.87)	0.46 (0.12,0.94)	0.25 (0.06,0.67)
Morphine	0.38 (0.16,0.62)	0.15 (0.12,0.17)	0.48 (0.24,0.72)	0.52 (0.07,1.00)	0.27 (0.05,0.75)	0.45 (0.08,0.99)
Nortriptyline	0.42 (0.13,0.74)	0.14 (0.09,0.16)	0.44 (0.15,0.77)	0.28 (0.03,0.92)	0.15 (0.03,0.42)	0.07 (0.00,0.34)
Oxcarbazepine	0.45 (0.22,0.71)	0.15 (0.12,0.17)	0.40 (0.17,0.65)	0.35 (0.14,0.65)	0.67 (0.29,0.99)	0.24 (0.09,0.50)
Pregabalin	0.43 (0.28,0.59)	0.16 (0.14,0.17)	0.41 (0.26,0.58)	0.19 (0.13,0.26)	0.36 (0.24,0.51)	0.12 (0.05,0.23)
Topiramate	0.49 (0.27,0.72)	0.15 (0.12,0.17)	0.36 (0.17,0.59)	0.32 (0.16,0.55)	0.20 (0.04,0.58)	0.18 (0.09,0.34)
Tramadol	0.43 (0.22,0.65)	0.15 (0.13,0.17)	0.42 (0.21,0.64)	0.45 (0.17,0.86)	0.55 (0.21,0.94)	0.39 (0.19,0.66)
Venlafaxine	0.50 (0.27,0.73)	0.15 (0.11,0.17)	0.35 (0.16,0.58)	0.24 (0.08,0.54)	0.40 (0.02,1.00)	0.29 (0.11,0.58)

Abbreviations: AE, adverse event; CrI, credible interval.

NB data shown do not reflect correlations between response probabilities as sampled in the model; therefore, credibility intervals for mutually exclusive outcomes can only be considered separately, and cannot be expected to sum to 1.

Costs

Costs of drugs

Drug prices were taken from the NHS Electronic Drug Tariff (March 2013) The model used a weighted average of dosages from the trials from which efficacy evidence was drawn. The dosage was rounded up to the nearest whole tablet (or spray or patch). The cost of the dosage was determined by the combination of tablets of different strengths that was the most cost efficient. For capsaicin cream, in the absence of any direct evidence, it was assumed that 1 g of cream would be applied in each application.

A full list of drugs, dosages and costs used in the modelling is shown in Table8.

Table 8 Health economic model – daily dosages and prices of drugs

Drug	Trial dosage[a]	Most efficient delivery[b]	140-day cost
Amitriptyline	95 mg/d	2×50mg	£8.20
Cannabis sativa	29.4 mgTHC/d	11 sprays/d	£2138.89
Capsaicin cream	3.7 applications	4×1 g applications	£177.96
Capsaicin patch	1 patch / 90 d	2 patches / 140 d	£420.00
Duloxetine	78 mg/d	1×60 mg + 1×30 mg	£250.60
Gabapentin	2572 mg/d	6×400 mg + 2×100 mg	£46.73
Lacosamide	422 mg/d	2×200 mg + 1×50 mg	£828.90
Lamotrigine	319 mg/d	1×200 mg + 1×100 mg + 1×50 mg	£25.50
Levetiracetam	2375 mg/d	4×750 mg	£61.69
Morphine	62 mg/d	1×60 + 1×10 mg	£51.08
Nortriptyline	122 mg/d	5×25 mg	£406.00
Oxcarbazepine	1261 mg/d	3×600 mg	£372.12
Pregabalin	398 mg/d	2×200 mg	£322.00
Topiramate	252 mg/d	3×100 mg	£23.94
Tramadol	298 mg/d	3×100 mg	£26.88
Venlafaxine	119 mg/d	4×37.5 mg	£25.30

Abbreviations: bd, twice daily; d, per day; od, once daily; qds, 4 times a day; tds, 3 times a day; THC, tetrahydrocannabinol.

[a] average of dosages delivered in all trials contributing to efficacy evidence, weighted according to number of participants in each arm.

[b] rounded up to nearest dose achievable using whole tablets.

Administration costs

The GDG advised that administration costs of the drugs would be equal in a primary care setting, and so were excluded from the analysis.

Costs of treating adverse effects

It was assumed that, for minor adverse effects, either 1 or 2 visits to a GP would be needed. For nausea, it was assumed that a course of antiemetics would be given for 7–14 days.

For adverse effects leading to withdrawal, it was assumed that there would be 2–4 visits to a GP before drug withdrawal. No treatment costs were assumed for the adverse effects.

Utilities

Measures of health benefit in the model are valued in QALYs. In view of the model structure adopted, the key health-state utility values needed were for pain relief of less than 30%, 30–49% and 50% or more. After a review of the utility values incorporated in previous cost–utility models identified in the systematic review of published economic analyses (see above), 2 studies appeared to provide appropriate evidence in a way that most closely matched the NICE reference case. However, 1 study (McCrink et al. 2006) was only available as a conference abstract. For this reason, the values reported by McDermott et al. (2006) were preferred. This pan-European survey of patients with various types of neuropathic pain used UK preference values for EQ-5D measured health states. The values for severe (0.16), moderate (0.46) and mild (0.67) pain were assumed to equate to less than 30%, 30–49% and 50% or more reductions in pain respectively.

For minor adverse effects, individual utility decrements were identified for nausea (−0.12; Revicki and Wood, 1998) and dizziness (−0.065; Sullivan et al., 2002). The disutility for people experiencing 1 or more episodes of these events was assumed to last for 7–14 days over the 20-week modelled period. For adverse effects leading to withdrawal, a relative utility of 0.9 (that is, a 10% reduction in health-related quality of life [HRQoL]) reported by Wilby et al. (2005) was chosen for ‘intolerable adverse effects’ (the same value was used by 4 of the identified cost-effectiveness studies).

Uncertainty

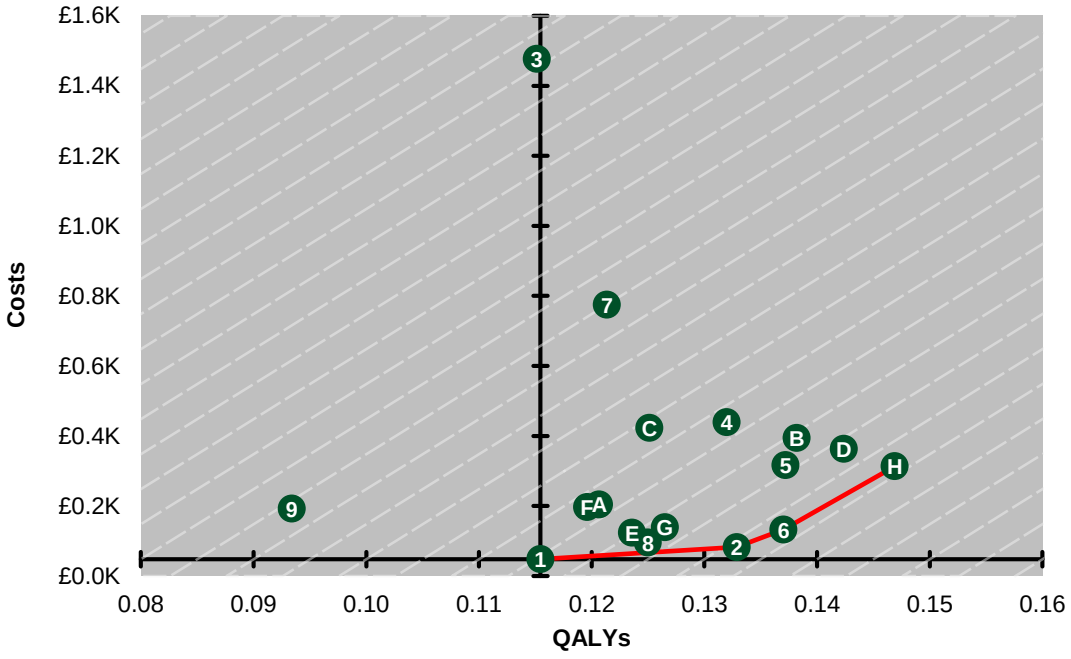
The model was built probabilistically to take account of the uncertainty surrounding each input parameter (for full details of distributions and parameters, please see appendix F). Because the effectiveness data were derived from a probabilistic process (Bayesian Markov-chain Monte-Carlo sampling), when the cost-effectiveness model was run, a value was chosen at random directly from the posterior distribution for the relevant parameter from the evidence synthesis model (WinBUGS CODA output). The model was run repeatedly (10,000 times) to obtain mean cost and QALY values.

Original health economic model – results

Incremental cost–utility results, representing the mean of 10,000 simulations, are presented in Table 9, with the efficiency frontier shown in Figure 4.

Table 9 Health economic model – incremental mean cost–utility results

	Absolute		Incremental		
Cohort	**Costs**	**QALYs**	**Costs**	**QALYs**	**ICER**
Placebo	£48.01	0.115			
Amitriptyline	£82.50	0.133	£34.49	0.017	£1980
Lamotrigine	£95.31	0.125	£12.81	−0.008	dominated
Topiramate	£123.80	0.124	£41.30	−0.009	dominated
Gabapentin	£132.73	0.137	£50.24	0.004	£12,091
Venlafaxine	£139.20	0.126	£6.47	−0.011	dominated
Levetiracetam	£192.65	0.093	£59.92	−0.044	dominated
Tramadol	£196.81	0.120	£64.08	−0.017	dominated
Morphine	£204.54	0.121	£71.81	−0.016	dominated
Capsaicin cream	£313.34	0.147	£180.60	0.010	£18,297
Duloxetine	£316.20	0.137	£2.86	−0.010	dominated
Pregabalin	£363.31	0.142	£49.97	−0.005	dominated
Nortriptyline	£394.41	0.138	£81.07	−0.009	dominated
Oxcarbazepine	£423.35	0.125	£110.01	−0.022	dominated
Capsaicin patch	£439.56	0.132	£126.22	−0.015	dominated
Lacosamide	£774.90	0.121	£461.56	−0.026	dominated
Cannabis extract	£1476.69	0.115	£1163.35	−0.032	dominated
Abbreviations: ext. dom., extendedly dominated; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.					



1=placebo; 2=amitriptyline; 3=cannabis sativa extract; 4=capsaicin patch; 5=duloxetine; 6=gabapentin; 7=lacosamide; 8=lamotrigine; 9=levetiracetam; A=morphine; B=nortriptyline; C=oxcarbazepine; D=pregabalin; E=topiramate; F=tramadol; G=venlafaxine; H=capsaicin cream

Figure 4 Health economic model – incremental mean cost–utility results (all neuropathic pain – dose-adjusted)

Probabilistic model outputs are tabulated in Table 10 and illustrated in Figure 5. These results indicate the probability that each treatment would be considered the most cost-effective option (that is, generate the greatest net benefit) as the assumed value of a QALY is altered.

Table 10 Health economic model – results of probabilistic sensitivity analysis

Treatment	QALYs valued at £20,000			QALYs valued at £30,000		
	NMB	Prob. of highest NMB	Prob. NMB > placebo	NMB	Prob. of highest NMB	Prob. NMB > placebo
Capsaicin cream	£2624.67	28.1%	75.4%	£4093.67	30.0%	80.4%
Gabapentin	£2607.86	9.5%	94.3%	£3978.16	7.6%	95.8%
Amitriptyline	£2575.01	13.3%	84.7%	£3908.42	10.7%	86.0%
Pregabalin	£2484.51	1.0%	98.3%	£3903.76	2.0%	100.0%
Duloxetine	£2427.91	1.3%	84.8%	£3799.97	2.1%	94.3%
Lamotrigine	£2404.57	1.2%	80.9%	£3751.60	0.8%	83.7%
Venlafaxine	£2390.80	6.5%	64.9%	£3655.80	5.6%	68.4%
Nortriptyline	£2369.60	16.9%	56.6%	£3654.51	20.1%	63.1%
Topiramate	£2348.01	4.1%	61.1%	£3583.92	3.5%	64.5%
Placebo	£2261.15	0.0%	–	£3519.76	0.0%	–
Morphine	£2208.58	12.4%	49.1%	£3415.72	11.6%	51.8%
Capsaicin patch	£2199.99	0.0%	33.3%	£3415.13	0.1%	68.5%
Tramadol	£2195.03	3.4%	44.2%	£3390.96	3.1%	48.9%
Oxcarbazepine	£2079.31	1.5%	30.3%	£3330.64	2.3%	43.0%
Levetiracetam	£1675.06	0.8%	10.0%	£2865.86	0.7%	11.2%
Lacosamide	£1652.27	0.0%	0.2%	£2608.91	0.0%	2.5%
Cannabis extract	£826.13	0.0%	0.0%	£1977.54	0.0%	0.6%
Abbreviations: NMB, net monetary benefit; QALY, quality-adjusted life year; prob., probability.						

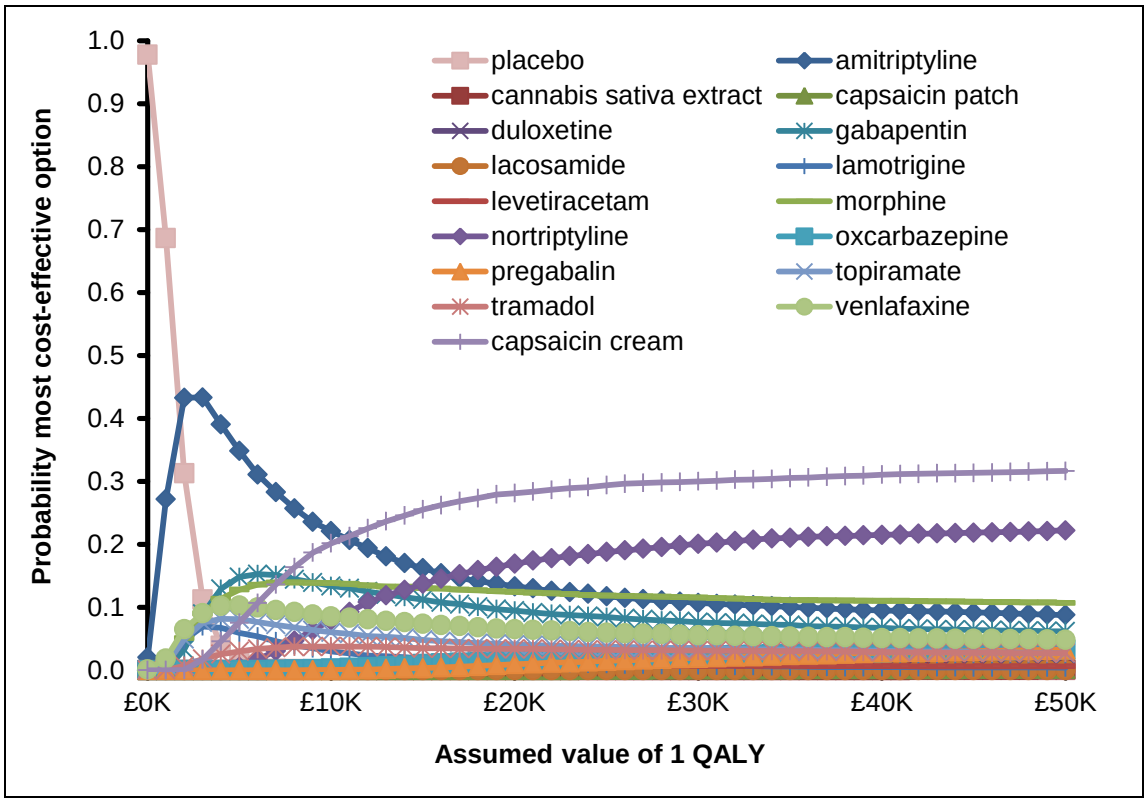


Figure 5 Health economic model – cost-effectiveness acceptability curve

Scenario analyses

Two additional analyses – one exploring the impact of second-line treatment following withdrawal due to adverse effects, and one using efficacy and safety inputs that sought to account for dose–response effects in the underlying dataset – produced results that were only subtly different from the base-case analysis (for details, see Appendix F). These findings demonstrated that model outputs are not particularly sensitive to assumptions that were thought to be critical.

3.1.4 Evidence to recommendations

Relative value of different outcomes	It was difficult to meaningfully compare the ability of different pharmacological treatments to improve the outcomes that were considered critical to decision making: patient-reported global improvement (using the 7-point patient-reported global impression of change [PGIC] tool) was not often reported and no tools were used consistently in measuring patient-reported improvement in daily physical and emotional functioning (including sleep). A meta-analysis of some studies that reported a continuous sleep interference measure was presented. The GDG found it difficult to interpret the results because only a few studies reported this outcome and there is no general consensus on what difference is clinically meaningful for sleep. More data were available on the adverse effects that the GDG felt were critical to decision making (including withdrawal due to adverse effects). However, the GDG felt that decisions about what individual adverse effects were acceptable to patients would vary from patient to patient, and certain adverse effects may be acceptable to some patients but not to others (for example, a patient whose job involves driving may find dizziness to be unacceptable). As a result, the GDG felt that judging the acceptability of different pharmacological treatments should be made at the individual patient level. Consequently, the frequency of individual adverse effects did not weigh heavily in the overall assessment of individual drugs. Please see the 'Key principles of care' section, which highlights the importance of discussing the possible adverse effects of pharmacological treatments with the person when agreeing on a treatment plan. Because of the overall lack of data on most critical outcomes, the GDG put more weighting on the evidence for pain relief which was considered alongside patient-reported global impression of change, where it was reported. However, this also presented difficulties. Firstly, some studies did not report 30% or 50% pain relief. Secondly, the GDG was wary of putting too much weight on the continuous pain measures because of the difficulty in using these tools for chronic pain. Generally, the GDG thought that a decrease of at least 2 points on a 10-point scale would be clinically meaningful, but the impact of such a decrease in pain would also depend on the baseline pain level. Comparing ‘mean change’ across all patients in a trial does not account for the difference from baseline pain for individual patients. Furthermore, many drugs did not appear to have a mean decrease in pain of at least 2 points compared with placebo, so it appeared that these results were not clinically significant (and many of those that showed a clinically significant mean decrease of pain compared with placebo were based on very small studies and hence lacked precision).
Trade-off between benefits and harms	There was considerable uncertainty in the results from the network meta-analyses and pairwise meta-analyses about the critical and important outcomes that should guide decision making on the best pharmacological treatment. As a result, the GDG was unable to recommend a single pharmacological treatment as clearly superior to all alternatives. Consequently, the GDG felt it was appropriate to

	assess the consistency of the evidence base overall for each individual drug at reducing pain compared with placebo. By doing this, it became clearer that the evidence on some drugs was very uncertain or even inconsistent, and that it would be difficult to justify recommending any such drugs. Consequently, some drugs listed in table 2 do not feature in the recommendations. The GDG took into account other factors, such as overall adverse effects and withdrawals due to adverse effects, as well as evidence on cost effectiveness. A summary of the GDG considerations for each pharmacological agent is below (a summary of the considerations regarding cost effectiveness is found below under 'Economic considerations'). **Amitriptyline** – the GDG felt that the analyses appeared consistent in demonstrating pain reduction compared with placebo. The group noted that side effects such as sedation may be considered intolerable by some patients, but conversely may be considered beneficial by patients who have problems with sleeping. **Cannabis sativa extract** – there is some evidence that cannabis sativa decreases pain compared with placebo, but in the analyses it appeared consistently worse than other treatments at reducing pain. **Capsaicin cream** – there is some evidence that capsaicin cream is better than placebo at reducing pain. The GDG acknowledged that it is an alternative treatment for patients with localised peripheral pain who are unable to, or prefer not to, use oral medications. The analyses appeared more consistent in showing that capsaicin cream is effective compared with placebo than other topical treatments. However, the GDG noted that it takes some time to learn how to apply the cream correctly (they noted that using gloves and/or avoiding particularly sensitive areas such as the eyes is often advised). **Capsaicin patch** – there is some evidence on the efficacy of capsaicin patch compared with placebo at reducing pain, but it appeared consistently worse in the analyses than other treatments at reducing pain; training in the use of the patch is also required in specialist centres. **Duloxetine** – the analyses appeared consistent that duloxetine reduces pain compared with placebo. **Gabapentin** – only 1 of the analyses showed that gabapentin did not have an effect on pain, but this analysis was based on 1 study. The GDG further discussed this and came to the conclusion that the study was of very poor quality and needed cautious interpretation. Apart from this study, the analyses were consistent that gabapentin reduced pain compared with placebo. **Lidocaine (topical)** – there was only 1 small crossover study on topical lidocaine, which showed no effect on pain reduction; however, the GDG felt that a research recommendation should be made to further investigate the use of this treatment for localised peripheral pain because it could be a potential alternative treatment for people who do not wish to, or are unable to, take oral medications. **Lamotrigine** – the analyses did not appear to consistently demonstrate that lamotrigine is effective compared with placebo. In addition, it appears to be associated with high withdrawals due to adverse effects. Specialist knowledge may be necessary because

	concurrent use of other medicines (especially valproate) is an important factor in using lamotrigine. **Morphine** – the majority of the analyses showed that morphine appears to reduce pain compared with placebo, but it is associated with significant adverse effects and higher rates of withdrawal due to adverse effects. The GDG also considered the potential risk of opioid dependency. As a result, the GDG agreed it was not appropriate to consider this in non-specialist settings. **Nortriptyline** –the analyses were generally consistent that nortriptyline reduces pain compared with placebo. However, there was much uncertainty around these estimates. **Oxcarbazepine** – the analyses were conflicting about whether oxcarbazepine is effective compared with placebo; it is also associated with many adverse effects. **Pregabalin** – the analyses appeared consistent that pregabalin reduces pain compared with placebo. **Topiramate** – the analyses appeared inconsistent about whether topiramate is effective compared with placebo. Also, the GDG advised that topiramate is associated with a range of adverse effects, some of which may be better understood in specialist settings. As a result, the GDG felt that it is not appropriate to be considered in non-specialist settings. **Tramadol** – the analyses were generally consistent that tramadol is effective at reducing pain compared with placebo. However, the effect estimates were imprecise because only small numbers of patients were involved in the included studies. Also, the included studies had very short study periods (up to 4 weeks), with higher rates of withdrawal due to adverse effects associated with the treatment. The GDG concluded that tramadol should only be considered as a rescue medication when people are awaiting referral to specialist pain services after initial treatment has failed. **Valproate** – the analyses appeared inconsistent about whether valproate was effective compared with placebo. Additionally, the evidence on valproate is from small studies, and valproate is associated with undesirable adverse effects. Hence, the GDG did not feel it was appropriate to consider valproate in non-specialist settings. **Gabapentin** + **nortriptyline**, **gabapentin** + **oxycodone**, **imipramine**, **lacosamide**, **levetiracetam**, **oxycodone**, **venlafaxine** – the analyses showed that these drugs either do not appear more effective than placebo or there is a lack of evidence and/or inconsistent evidence about whether they are better than placebo at reducing pain. The GDG also noted that the mean differences in continuous measures were not often clinically significant: even the most effective treatments were estimated to reduce pain by an average amount that tends to be less than the amount identified by the GDG as clinically meaningful (2 points on a 10-point scale). This could be due to the reporting of average change in pain across all patients in the study and the subsequent use of this in the syntheses. If the response to pain is bimodal (that is, patients either respond well or do not respond at all), the average change in pain score across all patients may not be the most appropriate measure of pain response. However, it was difficult to determine from the included studies whether this is the

	reason.
Economic considerations	A systematic review of published cost–utility analyses found inconsistent and, at times, contradictory results from a heterogeneous group of studies, each of which addressed a small subgroup of potentially relevant comparators. Therefore, the GDG's health economic considerations were predominantly based on the de novo health economic model devised for this guideline. Seventeen treatments were assessed in the model, which could be configured to rely on either dose-adjusted or non-dose-adjusted effectiveness evidence. The model suggested that **capsaicin cream** is likely to have the highest expected net benefit. However, the GDG was aware that this finding was based on effectiveness evidence from very small trials in highly selected populations in which there were concerns about adequate blinding. Consequently, although the GDG considered that the health economic evidence supported a recommendation for the use of capsaicin cream in appropriate cases, it would be misleading to suggest that it should be used in all cases as a primary strategy. Its recommendation therefore emphasises the importance of the patient's attitude to topical treatment in defining whether it is likely to be an acceptable, and therefore cost effective, form of treatment. Of the other options, **gabapentin** had the highest net benefit. This evidence, coupled with their own experience, persuaded the GDG to recommend it as an initial treatment option. For **amitriptyline**, the GDG was mindful that the health economic model relied on a relatively limited subset of the available efficacy data: of the 15 included studies investigating amitriptyline, only 2 reported a dichotomised measure of pain relief that could be used in the model. However, the GDG was also aware that excellent agreement had been demonstrated between this evidence and the broader evidence base analysing continuous data on pain relief with amitriptyline (see appendix L). Therefore, the GDG concluded that the efficacy of amitriptyline is unlikely to be overestimated in the subset of trials on which the health economic model relied. The GDG recognised that uncertainty around the effect estimate was greater than would be the case if it were possible to derive a robust and usable estimate of effect from all trials; however, it also understood that this uncertainty was appropriately reflected in the methods and results of the probabilistic decision model. The expected costs and QALYs for amitriptyline were closely comparable to those estimated for gabapentin. Although the model suggested that amitriptyline is associated with slightly poorer value for money than gabapentin, the difference is small. In addition, the GDG was mindful of guidance in the Guidelines Manual that stipulates that treatments should be made available to patients if those treatments are (a) associated with long-term health and personal social service costs that are lower than those of another recommended option, and (b) estimated to be below NICE's threshold for cost effectiveness. In this instance, treatment with amitriptyline was associated with lower net costs than treatment with gabapentin in 100% of model iterations, and it was found to have greater net benefit than placebo 85% of the time. Therefore, the GDG was satisfied that it was appropriate to recommend amitriptyline as an alternative first-line treatment.

	For 2 other treatments, **duloxetine** and **pregabalin**, mean cost-per-QALY estimates from the model suggested poor value for money in comparison with gabapentin and amitriptyline. Probabilistic sensitivity analysis showed a negligible probability that either of these options provides greatest net benefit at conventional QALY values. For these reasons, the GDG felt it would not be possible to support recommendations that suggested either option as an initial treatment for neuropathic pain. However, the GDG noted that, when compared with placebo alone (that is, no treatment), both drugs appeared to be viable options from a health economic point of view. Therefore, it would be appropriate to recommend these treatments in a context where other options were removed from the decision-space – that is, when they are contraindicated or when they have been tried and proved ineffective or were not tolerated. It was also the case that **nortriptyline**'s mean cost-per-QALY appeared to represent poor value for money compared with gabapentin and amitriptyline. However, the GDG was mindful that estimates of nortriptyline's effectiveness are highly uncertain (see 'Trade-off between benefits and harms' above). Because of this, it is not possible to exclude the possibility that it may be an extremely effective option and, as a direct consequence, probabilistic analysis showed that there is a greater than 15% probability that nortriptyline provides the most cost-effective option when QALYs are valued at between £20,000 and £30,000 (which, in the context of pervasive uncertainty, compares well with other options). The GDG also noted evidence that nortriptyline may be somewhat better tolerated than amitriptyline (to which it is closely related), with lower incidence of events in 7 of 10 safety network meta-analyses in which there was evidence for both drugs, with significant benefits estimated for fatigue and weight gain. The GDG was aware that this benefit may not be fully captured in the health economic model. However, the uncertainty inherent in the estimate of nortriptyline's effectiveness, coupled with its comparatively high acquisition cost, makes it difficult to exclude the possibility that it is a poor choice of treatment: it was no more cost effective than placebo in 43% of model iterations. Taking these considerations into account, the GDG felt it was not possible to make a positive recommendation in support of nortriptyline, either as an initial treatment option or at a later stage in the treatment pathway. However, it was also not convinced that sufficient evidence had been adduced to enable them to make a recommendation suggesting that nortriptyline should **not** be used. Therefore, the GDG agreed that this was a treatment for which it would not be helpful to make an explicit recommendation. The GDG considered that the health economic evidence may have been sufficient to support a positive recommendation for the use of 3 other drugs: **lamotrigine**, **topiramate** and **venlafaxine**. However, the GDG members noted that, in their experience, it can be challenging to establish an effective dosage and manage toxicity with these treatments. The GDG was aware that the effectiveness evidence underpinning the health economic model was predominantly drawn from specialist pain management settings and, because of the group's concerns about the challenges these treatments pose, it concluded that their cost effectiveness would be less positive in non-specialist settings. Therefore, the GDG concluded that the use of these drugs

	should only be considered in specialist settings. The mean cost-per-QALY of **morphine** and **tramadol** were greater than would normally be considered an effective use of NHS resources, although the probability that morphine might provide maximal net benefit was not trivial (over 10%). However, the GDG felt that caution should be exercised when generalising the results of the short-term trials underpinning the model to routine clinical practice (especially in view of the known potential for long-term adverse effects and dependency with opioids, which may not be fully captured in the health economic model). Therefore, the GDG did not consider it appropriate to make a positive recommendation for maintenance treatment using either drug. However, the GDG also believed opioids may fulfil an important role in temporarily managing acute pain in people who do not experience adequate pain relief with the maintenance therapy recommended in the initial treatment phase. To reflect this, the GDG recommended that this approach should be considered when awaiting referral to specialist care, with tramadol preferred to morphine on the basis of the GDG's belief that it is likely to prove safer in non-specialist settings. The health economic model provided no support for the use of **cannabis sativa extract**, **capsaicin patch**, **lacosamide**, **levetiracetam** or **oxcarbazepine**. In all analyses, these treatments were dominated by a number of other alternatives and, in some cases, they were dominated by placebo (that is, they were predicted to have higher costs and lower net health gains than treatment with placebo). Because of an absence of necessary effectiveness evidence, the health economic model was unable to assist the GDG's consideration of any combination therapy, or monotherapy with **imipramine, lidocaine patches**, **oxycodone** or **valproate**. The GDG recognised the limitations of the health economic model, including its reliance on a heterogeneous and uncertain evidence base, and its inability to extrapolate beyond a limited time horizon of 20 weeks. It also acknowledged that it had not been possible to explore the cost effectiveness of combination therapies and specified sequences of treatments. Because no evidence was available on the correlations between response probabilities, the GDG agreed to assume that the most cost-effective sequence of treatments is to try the options in order of their individual probability of cost effectiveness.
Quality of evidence	Overall, the quality of most of the evidence for different outcomes was low and very low. The evidence on patient-reported global improvement was of low and very low quality, the evidence on sleep was of moderate to low quality, and the evidence on adverse effects was of low to very low quality. The evidence on 30% and 50% pain relief was of low quality, whereas the evidence on mean continuous pain was considered very low quality. Most of the studies did not have sufficient follow-up periods to assess the long-term effect of different drugs, which is considered to be important for chronic conditions such as neuropathic pain. In addition, the included studies used different methods for dealing with missing data. Not all studies performed an intention-to-treat analysis so, at least for the dichotomous outcomes, the technical team performed their own intention-to-treat analysis using the number of

	patients randomised in the denominator. For continuous outcomes, dealing with this issue was more complex. Most of the studies that dealt with missing data used the last observation carried forward, which has been reported to produce bias in the results (please see the discussion on the approach to missing data in appendix D). The GDG acknowledged that it may be difficult to conduct trials in this area without allowing patients some concomitant medicines (and may be unethical not to give patients some treatment for their pain) but the use of concomitant drugs makes it more difficult to isolate the effects of the study drugs. A further complexity is that the included studies had differential allowances of concomitant medications, with some studies excluding some drugs but not others. As a result of the low-quality evidence (and high uncertainty of the results from the analyses referred to above), the GDG relied heavily on their experience and clinical opinion when making recommendations. The GDG also stated that better-quality research was needed (please see research recommendations).
Other considerations	The GDG had lengthy discussions about the most appropriate way to present the evidence (particularly, the appropriateness of grouping evidence on different conditions together). The GDG was particularly concerned about the risks of publication bias inherent in subdividing data into small condition-specific categories – that is, it was eager not to make recommendations that artefactually reproduced the subgroups in which research happens to have been undertaken and published, where there may be no compelling evidence of a genuinely different expectation of relative efficacy according to diagnosis. For this reason, the GDG felt it was most appropriate to focus on a broader evidence-base, and that further research was needed about how different aetiologies influence treatment outcomes, to inform future decision making. When it had reviewed evidence for peripheral neuropathic pain (see section 3.2) and central neuropathic pain (see section 3.3), the GDG concluded it was most appropriate to provide a single set of recommendations for all forms of neuropathic pain (except trigeminal neuralgia), based on the overall analysis combining all types of pain. The reasons for not providing separate recommendations for peripheral and central pain are provided in sections 3.2.4 and 3.3.4 respectively. The GDG also advised that combination therapies should be further explored, because the effect of adding a treatment onto another treatment may be more practical and effective than switching to a new treatment. The GDG also considered that the use of combination therapies could potentially reduce side effects of particular pharmacological agents through using a combination of lower dosages. However, current evidence is not sufficient to warrant any recommendation on combination therapies. As a result, the GDG recommended further research into combination therapies (please see research recommendations). The GDG discussed concerns that had been raised about people becoming dependent on drugs such as gabapentin and pregabalin. The GDG was not aware of any such issues, either in their clinical experience or in the evidence included in the guideline. The GDG further agreed that the potential for dependency was not limited to

	these drugs and is associated with a number of drugs, including opioids. The GDG was also concerned that people with a history of addiction or drug dependency could possibly be denied effective drugs. Based on this concern and the lack of evidence in the area, the GDG could not make a specific recommendation about the potential for dependency with certain drugs, but felt that the issue could be explored when assessing the risks and benefits for the individual person. The GDG was mindful that **amitriptyline** is off-label for treating neuropathic pain. However, the GDG noted that it is well established as a treatment for neuropathic pain (for example, advice on dosage is provided in the BNF), and there is extensive experience in prescribing it in non-specialist settings. Group members also noted that, in their experience, amitriptyline can be an effective treatment, and the adverse effects with which it is associated are well recognised and managed in non-specialist settings. As a result, the GDG was comfortable that it was appropriate to recommend amitriptyline for this indication.

NICE's considerations	Final approval prior to publication is required from NICE. NICE highlighted the following issues: • The uncertainty of the clinical evidence of efficacy included within the guideline and the consequent low reliability of the health economic model. • The requirement for the guideline to cover all types of neuropathic pain by a licensed or best available treatment. • The recommendation of an off-label preparation above a licensed preparation based on cost alone but in the absence of clear evidence of greater clinical efficacy in the outcomes identified as critical by the GDG. These issues have led NICE to the decision that we are unable to endorse a recommendation for an off-label pharmacological preparation ahead of a licensed pharmacological preparation in the absence of strong clinical evidence. For this reason, recommendation 1.1.8 includes duloxetine and pregabalin as initial treatment options for neuropathic pain alongside amitriptyline and gabapentin. Nortriptyline is no longer recommended in the guideline.

3.1.5 Recommendations and research recommendations for all neuropathic pain

Recommendations

Recommendation 1.1.8

Offer a choice of amitriptyline, duloxetine, gabapentin or pregabalin as initial treatment for neuropathic pain (except trigeminal neuralgia)[7].

Recommendation 1.1.9

If the initial treatment is not effective or is not tolerated, offer one of the remaining 3 drugs, and consider switching again if the second and third drugs tried are also not effective or not tolerated.

Recommendation 1.1.10

Consider tramadol only if acute rescue therapy is needed (see recommendation 1.1.12 about long-term use).

Recommendation 1.1.11

Consider capsaicin cream[8] for people with localised neuropathic pain who wish to avoid, or who cannot tolerate, oral treatments.

Recommendation 1.1.12

Do not start the following to treat neuropathic pain in non-specialist settings, unless advised by a specialist to do so:

[7] At the time of publication (November 2013), amitriptyline did not have a UK marketing authorisation for this indication, duloxetine is licensed for diabetic peripheral neuropathic pain only, and gabapentin is licensed for peripheral neuropathic pain only, so use for other conditions would be off-label. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing and managing medicines and devices for further information.

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

- cannabis sativa extract
- capsaicin patch
- lacosamide
- lamotrigine
- levetiracetam
- morphine
- oxcarbazepine
- topiramate
- tramadol (this is referring to long-term use; see recommendation 1.1.10 about short-term use)
- venlafaxine.

Research recommendations

See appendix B for full details of research recommendations.

Research recommendation B1

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

Research recommendation B2

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

Research recommendation B4

What are the key factors, including additional care and support, that influence participation[9] and quality of life in people with neuropathic pain?

Research recommendation B5

What is the impact of drug-related adverse effects on health economics and

[9] 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.

quality of life in neuropathic pain?

Research recommendation B6

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

3.2 Peripheral neuropathic pain

3.2.1 Evidence review

Of the 115 studies included for ‘all neuropathic pain’, 88 studies were on peripheral neuropathic pain, with a total of 16,660 patients. These are included in Table 4 above (studies where the ‘type of pain’ is listed as peripheral).

Network meta-analyses were performed for all but 3 outcomes: for 2 of these outcomes, data were only available on 1 drug compared with placebo (for at least moderate improvement in patient-reported global improvement at 28±7days and sleep interference on a normalised 10-point scale at 56±7 days) and the third had a pairwise analysis to pool 2 studies comparing gabapentin with placebo (sleep interference on normalised 10-point scale at 56±7 days).

As with ‘all neuropathic pain’, it was not possible to perform meta-analyses for the outcomes ‘patient-reported improvement in daily physical and emotional functioning, including sleep’ (except for a continuous measure of sleep disturbance) and ‘use of rescue medication’ because of the heterogeneity in the reporting of the outcomes across the literature. The GDG felt it was inappropriate to use such varied data to inform their decisions, so did not consider these outcomes when writing recommendations.

The GRADE summary table for each outcome where syntheses were performed is found in Table 11. GRADE tables were not completed for outcomes where it was not possible to pool results as they were not used in decision-making for the reasons stated above. Full GRADE profiles and full results from the analyses are found in appendix H. Results from the analyses of individual adverse effects were performed for ‘all neuropathic pain’ only and are included in appendix J (see the methods used in this guideline in appendix D for an explanation of why this was only performed for ‘all neuropathic pain’).

Table 11 GRADE table summary for peripheral neuropathic pain

Outcome (follow-up)	Number of Studies	Number of patients	Interventions	Quality	Importance
Patient-reported global improvement – at least moderate improvement (28±7 days)	1 RCT[a]	252	pregabalin	moderate	Critical
Patient-reported global improvement – at least moderate improvement (56±7 days)	7 RCTs[b]	1477	capsaicin patch, gabapentin, pregabalin, valproate	Very low	Critical
Patient-reported global improvement – at least moderate improvement (84±14 days)	8 RCTs[c]	2337	capsaicin patch, lacosamide, lamotrigine, pregabalin	low	Critical
Sleep interference normalised 10-point scale (28±7 days) [d]	3 RCTs[e]	326	escitalopram, gabapentin, gabapentin+nortriptyline, nortriptyline	Very low	Critical
Sleep interference normalised 10-point scale (56±7 days) [d]	2 RCTs[f]	360	gabapentin	moderate	Critical
Sleep interference normalised 10-point scale (84±14 days) [d]	5 RCTs[g]	1515	duloxetine, topiramate	low	Critical
Withdrawal due to AEs (all time points)	75 RCTs[h]	16072	23 (see appendix H)	Very low	Critical
Individual adverse events	97 RCTs[r] (3–67)	567–12190	See appendix J	Low to very low	Important
30% pain relief (28±7 days)	6 RCTs[i]	1015	cannabis sativa extract, capsaicin cream, gabapentin, pregabalin, tramadol	Very low	Important
30% pain relief (56±7 days)	4 RCTs[j]	1120	capsaicin patch, pregabalin	Very low	Important
30% pain relief (84±14 days)	16 RCTs[k]	4667	cannabis sativa extract, capsaicin patch, duloxetine, lacosamide, lamotrigine, pregabalin, topiramate	Very low	Important
50% pain relief (28±7 days)	6 RCTs[l]	1085	amitriptyline, cannabis sativa extract, gabapentin, pregabalin, tramadol	Very low	Important
50% pain relief (56±7 days)	7 RCTs[m]	1235	capsaicin patch, gabapentin, lamotrigine, nortriptyline, pregabalin	Very low	Important
50% pain relief (84±14 days)	14 RCTs[n]	4602	capsaicin patch, duloxetine, pregabalin, topiramate	Very low	Important
Pain (continuous) (28±7 days)	22 RCTs[o]	3152	18 (see appendix H)	Very low	Important
Pain (continuous) (56±7 days)	17 RCTs[p]	2750	11 (see appendix H)	Very low	Important
Pain (continuous) (84±14 days)	13 RCTs[q]	2833	90 (see appendix H)	Very low	Important

[a] Lesser et al. (2004); [b] Backonja et al. (1998), Irving et al. (2011), Kochar et al. (2005), Rice & Maton (2001), Rowbotham et al. (1998), Sabatowski et al. (2004), Simpson (2001); [c] Arezzo et al. (2008), Freynhagen et al. (2005), Irving et al. (2011), Rauck et al. (2007), Simpson et al. (2003), Simpson eta al. (2008), Tolle et al. (2008), van Seventer et al. (2006); [d] this is the only synthesis possible for the outcome 'patient reported improvement in daily physical and emotional functioning including sleep'; [e] Gilron et al. (2012), Gordh et al. (2008), Otto et al. (2008); [f] Backonja et al. (1998), Rowbotham et al. (1998); [g] Gao et al. (2010), Raskin et al. (2004), Raskin et al. (2005), Wernicke et al. (2006), Yasuda et al. (2011); [h] Arbaiza & Vidal (2007), Arezzo et al. (2008), Backonja et al. (1998), Backonja et al. (2008), Bansal et al. (2009), Beydoun et al. (2006), Cheville et al. (2009), Clifford et al. (2012), Dogra et al. (2005), Donofrio & Capsaicin study (1992), Dworkin et al. (2003), Eisenberg et al. (2001), Freynhagen et al. (2005), Gao et al. (2010), Gimbel et al. (2003), Goldstein et al. (2005), Gordh et al. (2008), Graff-Radford et al. (2000), Guan et al. (2011), Hahn et al. (2004), Hanna et al. (2008),

Harati et al. (1998), Holbech et al. (2011), Irving et al. (2011), Kautio et al. (2008), Khoromi et al. (2005), Khoromi et al. (2007), Kochar et al. (2002), Kochar et al. (2004), Kochar et al. (2005), Lesser et al. (2004), Luria et al. (2000), Max et al. (1988), Moon et al. (2010), Morello et al. (1999), Nurmikko et al. (2007), Otto et al. (2008), Paice et al. (2000), Rao et al. (2008), Raskin et al. (2004), Raskin et al. (2005), Rauck et al. (2007), Rice & Maton (2001), Richter et al. (2005), Rosenstock et al. (2004), Rowbotham et al. (1998), Rowbotham et al. (2004), Sabatowski et al. (2004), Satoh et al. (2011), Scheffler et al. (1991), Shaibani et al. (2009), Simpson (2001), Simpson et al. (2000), Simpson et al. (2003), Simpson et al. (2008), Simpson et al. (2010), Sindrup et al. (1999), Sindrup et al. (2003), Stacey et al. (2008), Tandan et al. (1992), Tasmuth et al. (2002), Thienel et al. (2004), Tolle et al. (2008), van Seventer et al. (2006), Vinik et al. (2007), Vinik et al. (2007), Vrethem et al. (1997), Watson & Evans (1992), Watson et al. (1993), Watson et al. (1998), Webster et al. (2010), Wernicke et al. (2006), Wymer et al. (2009), Yasuda et al. (2011), Ziegler et al. (2010); [i] Bernstein et al. (1989), Gordh et al. (2008), Lesser et al. (2004), Nurmikko et al. (2007), Sindrup et al. (1999), Stacey et al. (2008); [j] Backonja et al. (2008), Dworkin et al. (2003), Gordh et al. (2008), Guan et al. (2011), Moon et al. (2010); [k] Backonja et al. (2008), Clifford et al. (2012), Freynhagen et al. (2005), Gao et al. (2010), Irving et al. (2011), Raskin et al. (2004), Rauck et al. (2007), Selvarajah et al. (2010), Simpson et al. (2003), Simpson et al. (2008), Simpson et al. (2010), van Seventer et al. (2006), Webster et al. (2010), Webster et al. (2010), Wernicke et al. (2006), Yasuda et al. (2011); [l] Bansal et al. (2009), Lesser et al. (2004), Nurmikko et al. (2007), Sindrup et al. (1999), Stacey et al. (2008); [m] Chandra et al. (2006), Dworkin et al. (2003), Luria et al. (2000), Moon et al. (2010), Rice & Maton (2001), Rosenstock et al. (2004), Sabatowski et al. (2004); [n] Freynhagen et al. (2005), Gao et al. (2010), Goldstein et al. (2005), Irving et al. (2011), Raskin et al. (2004), Raskin et al. (2005), Satoh et al. (2011), Simpson et al. (2010), Tolle et al. (2008), van Seventer et al. (2006), Webster et al. (2010), Webster et al. (2010), Wernicke et al. (2006), Yasuda et al. (2011); [o] Backonja et al. (1998), Boureau et al. (2003), Cheville et al. (2009), Dogra et al. (2005), Gilron et al. (2012), Gimbel et al. (2003), Gordh et al. (2008), Guan et al. (2011), Hanna et al. (2008), Kalso et al. (1995), Kochar et al. (2002), Kochar et al. (2004), Lesser et al. (2004), Nurmikko et al. (2007), Otto et al. (2008), Rao et al. (2007), Rao et al. (2008), Raskin et al. (2004), Rice & Maton (2001), Sindrup et al. (1999), Sindrup et al. (2003), Vrethem et al. (1997); [p] Backonja et al. (1998), Biesbroeck et al. (1995), Chandra et al. (2006), Dogra et al. (2005), Eisenberg et al. (2001), Graff-Radford et al. (2000), Guan et al. (2011), Hanna et al. (2008), Kochar et al. (2005), Luria et al. (2000), Moon et al. (2010), Rao et al. (2008), Raskin et al. (2004), Rice & Maton (2001), Rowbotham et al. (1998), Sabatowski et al. (2004), Tandan et al. (1992); [q] Agrawal et al. (2009), Dogra et al. (2005), Goldstein et al. (2005), Kochar et al. (2004), Rao et al. (2008), Raskin et al. (2004), Raskin et al. (2005), Rauck et al. (2007), Selvarajah et al. (2010), Simpson et al. (2010), van Seventer et al. (2006), Wernicke et al. (2006), Yasuda et al. (2011); [r] see appendix J
Abbreviations: HRQoL, health-related quality of life; PICO, patient, intervention, comparator, outcome; RCT, randomised controlled trial; SSRI, selective serotonin reuptake inhibitor.

See appendix E for the evidence tables in full. For full results of all network meta-analyses see appendix H and J.

Summary graphics tables

The graphics in Table 12 summarise all the syntheses that have been performed using data reflecting people with peripheral neuropathic pain only. For notes on interpretation, please see the description in section 3.1.1.

Table 12 Summary graphics table for peripheral neuropathic pain (page 1 of 3)

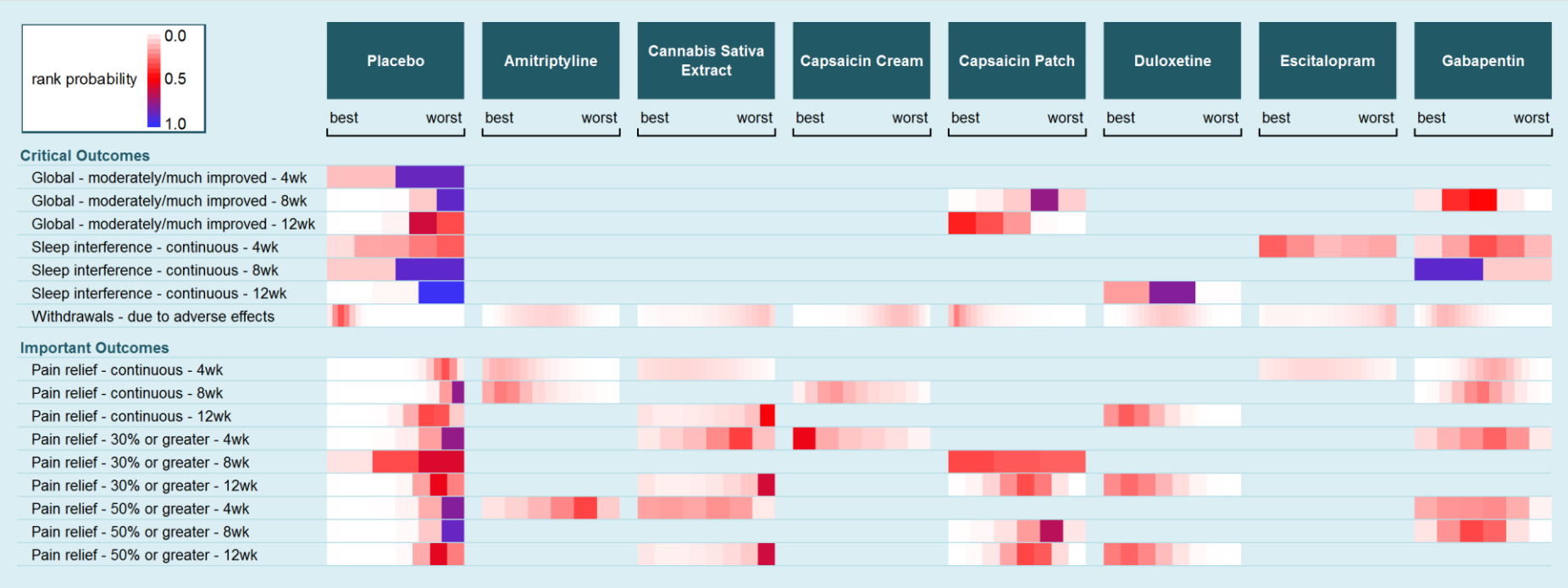


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Table 12 (continued; page 2 of 3)

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Table 12 (continued; page 3 of 3)

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3.2.2 Evidence statements

For details of how the evidence is graded, see The guidelines manual.

Critical outcomes

3.2.2.1 The evidence on patient-reported global improvement for peripheral neuropathic pain is available for only a limited number of drugs and at different follow-up periods. Network meta-analyses of 15 studies at 4, 8, and 12 weeks follow-up show uncertainty about which treatment is best at improving patient-reported global improvement. The evidence is low and very low quality.

3.2.2.2 The evidence on patient-reported improvement in daily physical and emotional functioning including sleep was reported across a wide variety of measurement tools with each measuring different aspects of functioning. As a result, it was not possible to synthesise the results from many of these studies in a meaningful way. Network analyses and a pairwise meta-analysis of 10 studies at 4, 8 and 12 weeks follow-up show that a number of drugs may be better than placebo at improving sleep on a continuous scale. However, it is not clear if this is clinically significant and there is considerable uncertainty about which drugs were the best at improving sleep. Also, data were only available for a limited number of drugs. The evidence is low to very low quality.

3.2.2.3 A network meta-analysis of 75 studies reporting withdrawal due to adverse effects at any follow-up showed that most drugs cause more drop-outs due to adverse effects than placebo, but there was considerable uncertainty about which drugs were least likely to cause drop-outs due to adverse effects. The evidence was considered low quality.

Important outcomes

3.2.2.4 Network meta-analyses of 20 individual adverse effects from 97 studies (ranging from 3 studies for gait disturbance to 67 studies for dizziness or vertigo) show that some adverse effects were more

frequent with particular drugs. However, it was difficult to draw conclusions on which particular drugs were best or worst for particular adverse effects. The evidence was considered low to very low quality.

3.2.2.5 Network meta-analyses of the proportion of patients achieving 30% or 50% pain relief (25 and 27 studies respectively) show that most treatments are better than placebo. However, there is considerable uncertainty about which treatment is best at providing these levels of pain relief. These outcomes are available for only a limited number of drugs and at different follow-up periods. The evidence was considered low quality.

3.2.2.6 There was more evidence for continuous pain scores suggesting some improvement in pain. However, network meta-analyses of 22 studies at 4 weeks, 17 studies at 8 weeks, and 13 studies at 12 weeks show improvement in mean pain but it is not clear if these differences are clinically significant. However, the confidence in these results and in the overall ratings of different drugs is low. The evidence was considered very low quality.

3.2.2.7 Overall with regard to pain:

- *the results from the analyses showed that duloxetine, gabapentin, and pregabalin reduce pain compared with placebo*
- *the majority of the results from the analyses showed that capsaicin cream, nortriptyline and tramadol consistently reduce pain compared with placebo*
- *the results from the analyses were inconsistent about whether valproate reduces pain compared with placebo*
- *the results from the analyses are inconclusive on the effectiveness of amitriptyline, gabapentin + nortriptyline, gabapentin + oxycodone, imipramine, lacosamide, lamotrigine, oxcarbazepine, oxycodone, topiramate or venlafaxine in reducing pain compared with placebo*

- *there is some evidence that cannabis sativa and capsaicin patch reduce pain compared with placebo but both drugs appeared consistently worse at reducing pain than other drugs .*

3.2.3 Health economic modelling

Data availability would have made it possible to perform a dedicated health economic analysis limited to people with peripheral neuropathic pain. However, since the GDG concluded that effectiveness results provided no conclusive evidence to distinguish between the peripheral-only group and the overall population (see section 3.2.4), a peripheral-only model was not pursued.

3.2.4 Evidence to recommendations

Relative value of different outcomes	As with 'all neuropathic pain', there was limited evidence on the critical and important outcomes. Please refer to the discussion in 'all neuropathic pain'.
Trade-off between benefits and harms	As with 'all neuropathic pain', there was considerable uncertainty in the results from the network meta-analyses and pairwise meta-analyses about the outcomes that should guide decision making on the best pharmacological treatment. As a result, the GDG was unable to consider a single pharmacological treatment as clearly superior to all alternatives. The GDG acknowledged that the clinical- and cost-effectiveness evidence for peripheral pain was similar to that of 'all neuropathic pain'. A reason could be that a large proportion of evidence on 'all neuropathic pain' came from studies on peripheral neuropathic pain. The main differences between pharmacological treatments for 'all neuropathic pain' and peripheral neuropathic pain were: **Amitriptyline** – there is slightly less evidence (2 studies) included in the analyses on the efficacy of amitriptyline in peripheral pain. **Gabapentin** – the analyses on the efficacy of gabapentin were consistent for peripheral pain because the very-low-quality study that showed negative effect of gabapentin was not on peripheral pain. **Levetiracetam and morphine** – there is no evidence on global improvement or pain relief for peripheral pain. **Nortriptyline** – although the evidence on nortriptyline that was included in the effectiveness analyses came from the same single trial that was included in the 'all neuropathic pain' analyses, greater effectiveness was estimated in the peripheral-only analyses. This is because nortriptyline is joined to the wider network via gabapentin, so it also benefits from the raised estimate of gabapentin's effectiveness. **Tramadol –** there is no evidence on global improvement but some efficacy evidence on 30% and 50% pain relief at 4 weeks. The GDG did not feel that it had seen persuasive evidence of systematically different patterns of response to treatment in people

	with peripheral neuropathic pain. Therefore, it felt that the recommendations on 'all neuropathic pain' should also apply to peripheral neuropathic pain.
Economic considerations	Since the GDG concluded that effectiveness results provided no conclusive evidence to distinguish between the peripheral-only group and the overall population, a peripheral-only model was not pursued.
Quality of evidence	As with 'all neuropathic pain', the quality of most of the evidence for different outcomes was low and very low. The evidence on patient-reported global improvement was of moderate, low and very low quality, the evidence on sleep was of moderate to very low quality, and the evidence on adverse effects was of low to very low quality. The evidence on 30% and 50% pain relief and mean continuous pain were both considered very low quality. As with 'all neuropathic pain', most of the studies did not have sufficient follow-up periods to assess the long-term effect of different drugs, which is considered to be important for a chronic condition such as neuropathic pain. There was also differential usage of concomitant medications among the included studies. See further discussion above in 'all neuropathic pain'.
Other considerations	See 'all neuropathic pain'.

NICE's considerations	See 'all neuropathic pain'.

3.2.5 Recommendations and research recommendations for peripheral neuropathic pain

Recommendations

See 'all neuropathic pain' (section 0).

Research recommendations

See 'all neuropathic pain' (section 0).

See appendix B for full details of research recommendations.

3.3 Central neuropathic pain

3.3.1 Evidence review

Of the 116 studies included for ‘all neuropathic pain’, 11 studies were on central neuropathic pain, with a total of 660 patients. These are included in Table 4 above (studies where the ‘type of pain’ is listed as central). There are some other studies that included patients with central pain, or that may have included a majority of patients with central pain, but we were unable to confidently say that all patients included in these studies had central pain.

Network meta-analyses were performed for withdrawal due to adverse effects, 30% pain relief at 84±14 days, and continuous pain outcomes at each follow-up. However, for 5 of the outcomes (patient-reported global improvement and sleep interference at all follow-up times, and 50% pain relief at 84±14 days) data on only 1 intervention compared with placebo were available.

As with ‘all neuropathic pain’, it was not possible to perform meta-analyses for the outcomes ‘patient-reported improvement in daily physical and emotional functioning, including sleep’ (except for a continuous measure of sleep disturbance) and ‘use of rescue medication’ because of the heterogeneity in the reporting of the outcomes across the literature. The GDG felt it was inappropriate to use such varied data to inform their decisions, and so did not consider these outcomes when writing recommendations.

The GRADE summary table for each outcome where syntheses were performed is found in Table 13. GRADE tables were not completed for outcomes where it was not possible to pool results as they were not used in decision-making for the reasons stated above. Full GRADE profiles and full results from the analyses are found in appendix I. Results from the analyses of individual adverse effects were performed for ‘all neuropathic pain’ only and are included in appendix J (see the methods used in this guideline in appendix D for an explanation of why this was only performed for ‘all neuropathic pain’).

Table 13 GRADE table summary for central neuropathic pain

Outcome (follow-up)	Number of Studies	Number of patients	Interventions	Quality	Importance
Patient-reported global improvement – at least moderate improvement (28±days)	1 RCT[a]	66	cannabis sativa extract	very low	Critical
Patient-reported global improvement – at least moderate improvement (56±7 days)	1 RCT[b]	48	duloxetine	low	Critical
Sleep interference normalised 10-point scale (28±7 days) [c]	1 RCT[d]	65	cannabis sativa extract	low	Critical
Sleep interference normalised 10-point scale (84±14 days) [c]	1 RCT[e]	135	pregabalin	low	Critical
Withdrawal due to AEs (all time points)	8 RCTs[f]	638	cannabis sativa extract, lamotrigine, levetiracetam, pregabalin	very low	Critical
Individual adverse events	97 RCTs[l] (3–67)	567–12190	See appendix J	Low to very low	Important
30% pain relief (84±14 days)	2 RCTs[g]	173	lamotrigine, pregabalin	very low	Important
50% pain relief (84±14 days)	1 RCT[h]	168	pregabalin	very low	Important
Pain (continuous) (28±7 days)	4 RCTs[i]	172	cannabis sativa extract, duloxetine, levetiracetam, pregabalin	very low	Important
Pain (continuous) (56±7 days)	2 RCTs[j]	67	duloxetine, levetiracetam	very low	Important
Pain (continuous) (84±14 days)	2 RCTs[k]	155	levetiracetam, pregabalin	very low	Important

[a] Rog et al. (2005); [b] Vranken et al. (2011); [c] this is the only synthesis possible for the outcome 'patient reported improvement in daily physical and emotional functioning including sleep'; [d] Rog et al. (2005); [e] Siddall et al. (2006); [f] Breuer et al. (2007), Falah et al. (2012), Kim et al. (2011), Rog et al. (2005), Rossi et al. (2009), Siddall et al. (2006), Vestergaard et al. (2001), Vranken et al. (2008); [g] Breuer et al. (2007), Siddall et al. (2006); [h] Siddall et al. (2006); [i] Rog et al. (2005), Rossi et al. (2009), Vranken et al. (2008), Vranken et al. (2011); [j] Rossi et al. (2009), Vranken et al. (2011); [k] Rossi et al. (2009), Siddall et al. (2006); [l] see appendix J

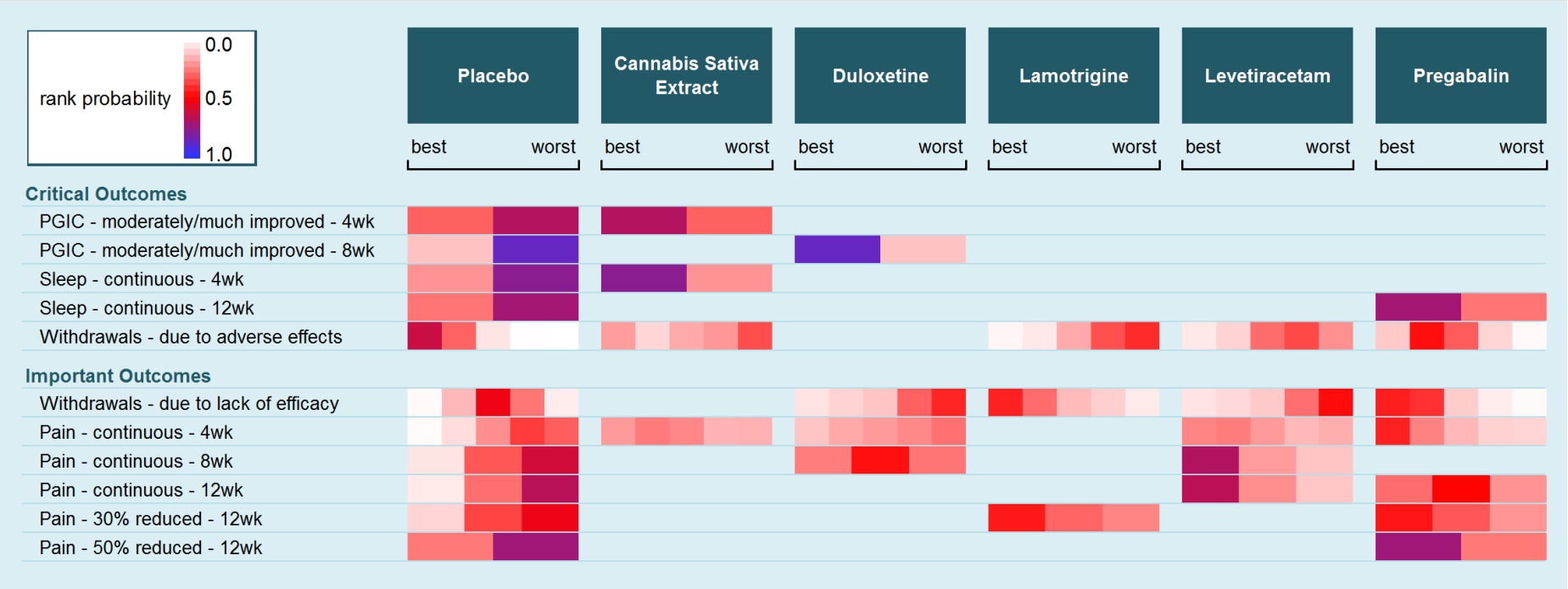
Abbreviations: NR, not reported; PICO, patient, intervention, comparator, outcome; RCT, randomised controlled trial; SSRI, selective serotonin reuptake inhibitor

See appendix E for the evidence tables in full. For full results of all network meta-analyses see appendix I and J.

Summary graphics tables

The graphics in Table 14 summarise all the syntheses that have been performed using data reflecting people with central neuropathic pain only. For notes on interpretation, please see description in section 3.1.1.

Table 14 Summary graphics table for central neuropathic pain



PLEASE NOTE THAT THIS TABLE IS BEST VIEWED IN COLOUR

3.3.2 Evidence statements

For details of how the evidence is graded, see The guidelines manual.

Critical outcomes

3.3.2.1 There was very little evidence reporting on patient-reported global improvement in central neuropathic pain. Low and very-low quality evidence from 2 small studies suggests that cannabis sativa and duloxetine may be better than placebo at follow-up periods of less than 12 weeks. However, confidence in the results is low and data were only available on a limited number of drugs.

3.3.2.2 The evidence on patient-reported improvement in daily physical and emotional functioning including sleep was reported across a wide variety of measurement tools with each measuring different aspects of functioning. As a result, it was not possible to synthesise the results from many of these studies in a meaningful way. Low-quality evidence from 2 studies shows that cannabis sativa may be better than placebo at improving sleep at 4 weeks and pregabalin may be better than placebo at improving sleep at 12 weeks, but it is not clear if this is clinically significant. However, data were only available on a limited number of drugs.

3.3.2.3 A network meta-analysis of 6 studies reporting withdrawal due to adverse effects at any follow-up show that lamotrigine may cause more drop-outs than placebo, and pregabalin caused the least drop-outs (next to placebo). However, there is little confidence in both these results and overall rankings, and the evidence was considered low quality. Also, data were only available on a limited number of drugs.

Important outcomes

3.3.2.4 Network meta-analyses of 20 individual adverse effects from 97 studies (ranging from 3 studies for gait disturbance to 67 studies for dizziness or vertigo) show that some adverse effects were more frequent with particular drugs. However, it was difficult to draw

conclusions on which particular drugs were best or worst for particular adverse effects. The evidence was considered low to very low quality.

3.3.2.5 There were very little data reporting on patients who had 30% and 50% improvement in pain. A network meta-analysis of 2 studies showed pregabalin was better at providing 30% relief than placebo and lamotrigine may be better at providing this pain relief at 12 weeks. However, there is uncertainty about which treatment is best and data were only available for a limited number of drugs. Only 1 study reported about 50% pain relief, showing that pregabalin was better than placebo at providing this level of relief at 12 weeks. There was more evidence on continuous pain scores suggesting some improvement in pain. However, the evidence was considered very low quality, the confidence in these results is low and data were only available for a limited number of drugs.

3.3.3 Health economic modelling

Health economic modelling was not performed for central neuropathic pain.

3.3.4 Evidence to recommendations

Relative value of different outcomes	It was particularly difficult to meaningfully compare the ability of different pharmacological treatments to improve the outcomes that were considered critical to decision making for central pain, the evidence review for which included only 11 studies. These studies only covered 6 drugs: cannabis sativa extract, carbamazepine, duloxetine, lamotrigine, levetiracetam, and pregabalin. Only 2 placebo-controlled trials reported patient-reported global improvement on 2 different drugs at different time-points. As with 'all neuropathic pain', patient-reported improvement in daily physical and emotional functioning (including sleep) had a lack of consistent tools used to report this outcome. Only 8 studies reported the proportion of patients who withdrew due to adverse effects, and this evidence only covered 4 pharmacological treatments. Unfortunately, unlike with 'all neuropathic pain' and peripheral neuropathic pain, the GDG could not make a meaningful judgement on other pain outcomes because only 2 studies reported 30% pain relief and only 1 study reported 50% pain relief. There were 8 placebo-controlled studies reported pain relief on continuous pain measures (4 studies at 4 weeks, and 2 at both 8 and 12 weeks) but the GDG felt uncomfortable in making a judgement solely based on this evidence, given the difficulties with the interpretation of continuous

	measures for pain relief (as highlighted earlier). Consequently, the GDG felt that there was not enough evidence to support recommendations for central neuropathic pain that were different than those made for ‘all neuropathic pain’.
Trade-off between benefits and harms	See the section on ‘all neuropathic pain’ for the discussion between benefits and harms that the GDG felt should also apply to central neuropathic pain. The GDG reflected on the lack of evidence and the existing low quality evidence for central neuropathic pain. The GDG agreed that central neuropathic pain is a complex condition that is difficult to treat, and acknowledged the difficulty in conducting research in this area. Despite these difficulties, the GDG stated the importance of further research to inform how best to treat people with central neuropathic pain.
Economic considerations	It was not possible to perform economic modelling for this population, because of inadequate availability of data. Therefore, the GDG's decision making was guided by the model that had been constructed for 'all neuropathic pain'.
Quality of evidence	The evidence on central neuropathic pain was either low or very low quality. In addition to the paucity of data, the GDG was concerned with the overall quality of the evidence. See ‘all neuropathic pain’ for a discussion of the overall quality of evidence that was used to make recommendations.
Other considerations	See ‘all neuropathic pain’.

NICE’s considerations	See ‘all neuropathic pain’.

3.3.5 Recommendations and research recommendations for central neuropathic pain

Recommendations

See ‘all neuropathic pain’ (section 0).

Research recommendations

See ‘all neuropathic pain’ (section 0).

See appendix B for full details of research recommendations.

3.4 Trigeminal neuralgia

3.4.1 Evidence review

No evidence was found that met the inclusion criteria specified in the review protocol.

3.4.2 Health economic modelling

Health economic modelling was not performed for trigeminal neuralgia.

3.4.3 Evidence to recommendations

Relative value of different outcomes	No evidence was identified for this condition that met the inclusion criteria.
Trade-off between benefits and harms	The GDG was concerned by the lack of robust evidence on trigeminal neuralgia but recognised that carbamazepine is the only drug currently licensed for this condition and it is widely used in current practice. The GDG was aware of other very poor quality studies on different off-label drugs for trigeminal neuralgia (which did not meet the inclusion criteria specified in the review protocol), such as oxcarbazepine or lacosamide, which could potentially have less side effects or be better tolerated than carbamazepine. However, in the absence of robust, good-quality evidence, the GDG felt unable to recommend the use of these off-label drugs. The GDG discussed the disabling nature of trigeminal neuralgia and the importance of making recommendations on its treatment. The GDG also agreed the importance of speed in starting treatment in order to prevent unnecessary suffering. The GDG decided that making recommendations based on the evidence from 'all neuropathic pain' would be inappropriate. The GDG viewed this condition to be particularly distinctive from other neuropathic pain conditions and felt that, based on their clinical experience, recommending anything other than treatment used in current practice (that is, carbamazepine) for trigeminal neuralgia would not be appropriate. Because of the disabling nature of the condition, the GDG also further considered the urgency of offering treatment and referring patients with trigeminal neuralgia to specialist pain services if the pain does not respond to carbamazepine, or if carbamazepine is not tolerated or is contraindicated. The GDG felt that pain specialists would have more experience in treating this specific group of patients. The group agreed that part of the reason why it may be difficult to conduct research in this area is that most patients in the UK with trigeminal neuralgia are already on carbamazepine and do not wish to risk not receiving the drug. The GDG also felt that, in the absence of robust evidence, this may show that there is at least some efficacy of this drug over no treatment for these patients. Consequently, despite the paucity of robust evidence and because treatment with carbamazepine is current practice, the GDG wanted to make a strong

	recommendation for carbamazepine. The GDG decided that there was insufficient evidence to make a recommendation to change current practice. However, despite its widespread use, the GDG urged that robust research to be undertaken into the clinical and cost effectiveness of carbamazepine for trigeminal neuralgia. The GDG also felt that it should strongly encourage that robust research to be done into the clinical and cost-effectiveness for alternative treatments for trigeminal neuralgia. As with initial treatment with carbamazepine, the GDG felt that expedient treatment should be a priority. Switching pain medications to the treatments recommended for 'all neuropathic pain' should be considered while patients are waiting referral to a specialist pain management service, so at least some intervention is attempted to alleviate the pain during this period.
Economic considerations	No health economic modelling was undertaken for this condition because no evidence was identified that met the inclusion criteria.
Quality of evidence	No evidence was identified for this condition that met the inclusion criteria.
Other considerations	The GDG also discussed and acknowledged that in some situations carbamazepine was not tolerated by patients because it was not titrated appropriately (that is, gradual, slow titration).

3.4.4 Recommendations and research recommendations for trigeminal neuralgia

Recommendations

Recommendation 1.1.13

Offer carbamazepine as initial treatment for trigeminal neuralgia.

Recommendation 1.1.14

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

Research recommendations

See appendix B for full details of research recommendations.

Research recommendation B3

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

3.5 *Key principles of care*

There was no specific review question regarding the key principles of care. However, the GDG agreed that patient care is particularly important in the treatment of neuropathic pain. The GDG decided that this should be further discussed to make recommendations for good principles of care based on informal consensus. No evidence was considered in this section and therefore there were no evidence statements. The recommendations were based on the expertise and experience of the GDG.

3.5.1 Evidence to recommendations

Relative value of different outcomes	The GDG agreed that elements of care other than pharmacological treatments, such as the person's experience, their information needs, individual preferences and different lifestyle factors, are also important to be considered in a person's care pathway.
Trade-off between benefits and harms	The GDG agreed that it was important to involve the person in their treatment plan. When selecting pharmacological treatments the GDG felt that it was important to discuss and take into account the pain severity and how it affects the person's daily activities (including sleep), the underlying cause of pain, any comorbidities that they might have and any concurrent medications for these comorbidities (or other conditions) and how they might affect the patient's vulnerability to specific adverse effects. The GDG also felt that it was important to discuss dosage titration and how the titration process works, different self-management strategies for pain and coping with the pain, rehabilitation (such as lifestyle changes or adaptations in work life), and that other non-pharmacological treatments are available. The GDG also agreed that the adverse effects of the recommended treatments (including any risk of dependence or misuse), as well as the special warnings and precautions for use as specified in the summary of product characteristics, should be discussed with the person and weighed for that particular person against the benefit provided. It is important to take into account the person's preferences about which adverse effects are acceptable or unacceptable. The GDG further discussed that extra caution is needed when switching or combining drugs, to ensure symptoms are adequately covered during this period. The GDG also highlighted that different titration periods can sometimes be confusing for some patients. The GDG agreed that it is crucial for drug dosage and titration to be done accurately in order to achieve maximum benefit and also to minimise dose-related adverse effects. This is found in the SPC for each drug and should be referred to when prescribing pharmacological treatments.
Economic considerations	The GDG agreed formal economic considerations are not necessary to support good principles of care.
Quality of evidence	No evidence was considered for these recommendations. The GDG's experience was used to develop the recommendations.

Other considerations	The GDG stressed that both early and regular clinical reviews are important. They felt that, in the limited time the person would have for a review with their GP, it is most important to assess the effectiveness of the treatment on pain symptom control and how this impacts on their daily activities and their participation, including their ability to sleep. The GDG also felt that this was the time to monitor drug titration, tolerability and any adverse effects, and how they affect the patient. The need to continue treatment should be assessed at each review, including the possibility of gradually reducing the dose if sustained improvement is observed. Because 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 specialist pain 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, including at initial presentation and at the regular clinical reviews, if the person has severe pain or there are changes in, or deterioration of, the person's pain, health condition and/or daily activities, and participation. The GDG felt that healthcare professionals in non-specialist settings should also consider seeking advice from specialist pain or condition-specific services when referral may not always be immediately necessary.

3.5.2 Recommendations and research recommendations for key principles of care

Recommendations

Recommendation 1.1.1

When agreeing a treatment plan with the person, take into account their concerns and expectations, and discuss:

- the severity of the pain and its impact on lifestyle, daily activities (including sleep disturbance) and participation[10]
- the underlying cause of the pain and whether this condition has deteriorated
- why a particular pharmacological treatment is being offered
- the benefits and possible adverse effects of pharmacological treatments,

[10] 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.

taking into account any physical or psychological problems and concurrent medications

- the importance of dosage titration and the titration process, providing the person with individualised information and advice
- coping strategies for pain and for possible adverse effects of treatment
- non-pharmacological treatments, for example, physical and psychological therapies (which may be offered through a rehabilitation service) and surgery (which may be offered through specialist pain services).

For more information about involving people in decisions and supporting adherence, see Medicines adherence (NICE clinical guideline 76).

Recommendation 1.1.2

Consider referring the person to a specialist pain service and/or a condition-specific service[11] at any stage, including at initial presentation and at the regular clinical reviews (see recommendation 1.1.6), if:

- they have severe pain **or**
- their pain significantly limits their lifestyle, daily activities (including sleep disturbance) and participation[12] **or**
- their underlying health condition has deteriorated.

Recommendation 1.1.3

Continue existing treatments for people whose neuropathic pain is already effectively managed, taking into account the need for regular clinical reviews (see recommendation 1.1.6).

Recommendation 1.1.4

When introducing a new treatment, take into account any overlap with the old

[11] A condition-specific service is a specialist service that provides treatment for the underlying health condition that is causing neuropathic pain. Examples include neurology, diabetology and oncology services.

[12] 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.

treatments to avoid deterioration in pain control.

Recommendation 1.1.5

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

Recommendation 1.1.6

Carry out regular clinical reviews to assess and monitor the effectiveness of the treatment. Each review should include an assessment of:

- pain control
- impact on lifestyle, daily activities (including sleep disturbance) and participation[13]
- physical and psychological wellbeing
- adverse effects
- continued need for treatment.

Recommendation 1.1.7

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

Research recommendations

See appendix B for full details of research recommendations.

[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.

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5 Glossary and abbreviations

The glossary terms and abbreviations in this list cover those in the guideline and appendices.

Glossary

Hazard ratio

Hazard is the chance that, at any given moment, the event will occur, given that it has not already done so; a hazard ratio is the hazard of one group exposed to a drug compared with a hazard in treatment compared with another drug or placebo

If both groups face the same chance that the event will occur, the hazard ratio is 1. If the first group had a hazard ratio of 2, subjects in that group would have twice the hazard of experiencing the event. A hazard ratio of less than one means the outcome is less likely in the first group.

Imprecision

This definition on imprecision relates to the use of the term within the GRADE methodology.

Within GRADE, on outcome may be downgraded for imprecision if the studies included have confidence intervals that cross the clinical decision threshold between recommending and not recommending a treatment. In addition, the outcome may be downgraded if the optimal information size is not met (see below).

Inconsistency

This definition on inconsistency relates to the use of the term within the GRADE methodology.

Within GRADE, an outcome may be downgraded for inconsistency if the difference in results between studies looking at the same or similar interventions are very different and the wide difference in results is unaccounted for. Criteria for evaluating consistency include similarity of point estimates, extent of overlap of confidence intervals, and statistical criteria including tests of heterogeneity. In network meta-analyses (see below), the extent to which direct and indirect evidence agrees is also a criterion for consistency.

Indirectness

This definition on indirectness relates to the use of the term within the GRADE methodology.

Within GRADE, an outcome may be downgraded for indirectness if there are substantial differences between the population, intervention, comparator, or outcome in relevant studies compared with those under consideration in a guideline or systematic review. The outcome may be downgraded if there are no head-to-head trials between interventions of interest (however, please see appendix D for how GRADE was assessed in this guideline).

Mean difference

A measure of statistical dispersion equal to the average absolute difference of two independent values drawn from a probability distribution.

Network meta-analysis

A statistical analysis of results in which multiple treatments (that is, 3 or more) are being compared using both direct comparisons of interventions within randomised controlled trials and indirect comparisons across trials based on a common comparator. This method of analysis leads to an estimate of the relative effectiveness of all treatment being compared. A ranking for each treatment can also be computed, reflecting the probability that each represents the best option available. This is known as a Rankogram.

Optimal information size

The total number of patients included in a systematic review which is considered adequate for the results of the review to be considered precise. This should be at least the number of patients generated by a conventional sample size calculation.

Please see the NICE glossary for an explanation of terms not described above.

Abbreviations

Abbreviation	Term
AE	Adverse effect
BPI	Brief pain inventory
CI	Confidence interval
CrI	Credible interval
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HR	Hazard ratio
HRQoL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
IMMPACT	Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials
MTC	Mixed or multiple treatment comparison
NPRS/NPS	Neuropathic pain rating scale/neuropathic pain scale

NRS	Numerical rating scale
PDN	Painful diabetic neuropathy
PHN	Post herpetic neuralgia
QALY	Quality-adjusted life year
OR	Odds ratio
PGIC	Patient-reported global impression of change (7-point)
RCT	Randomised controlled trial
SD	Standard deviation
SE	Standard error
SPC	Summary of product characteristics
VAS	Visual analogue scale
VRS	Verbal rating scale

6 Other information

6.1 Scope

NICE guidelines are developed in accordance with a scope that defines what the guideline will and will not cover. The scope of this guideline is given in appendix C.

6.2 Implementation

NICE has developed tools to help organisations implement this guidance.

6.3 Other versions of this guideline

6.3.1 NICE guideline

The NICE guideline contains all the recommendations, without the information on methods and evidence.

6.3.2 NICE pathway

The recommendations from this guideline have been incorporated into a NICE pathway.

6.3.3 Information for the public

NICE has produced information for the public explaining this guideline.

We encourage NHS and third sector, including voluntary, organisations to use text from this information in their own materials about neuropathic pain.

6.4 Related NICE guidance

Further information is available on the NICE website.

Published

General

- Patient experience in adult NHS services. NICE clinical guidance 138 (2012).
- Medicines adherence. NICE clinical guidance 136 (2011).

Condition-specific

- Opioids in palliative care. NICE clinical guideline 140 (2012)
- Low back pain. NICE clinical guideline 88 (2009).
- Multiple sclerosis. NICE clinical guideline 8 (2003).

Under development

NICE is developing the following guidance (details available from the NICE website):

- Type 1 diabetes (update). NICE clinical guideline. Publication date to be confirmed.
- Type 2 diabetes (update). NICE clinical guideline. Publication date to be confirmed.

Appendix A Contributors and declarations of interests

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An Internal Clinical Guidelines Programme technical team was responsible for this guideline throughout its development. It prepared information for the Guideline Development Group, drafted the guideline and responded to consultation comments.

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Declarations of interests

GDG Member	Interest Declared	Type of Interest	Decision Taken
Damien Longson (Chair)	None declared	N/A	N/A
Issak Bhojani	None declared	N/A	N/A
Brigitta Brandner	Chair of Specialists in Pain International Network (SPIN). The charity promotes good pain management overseas by educating health professionals in chronic pain management.	Personal non-pecuniary interest	Declare and participate
Karen Cavanagh	None declared	N/A	N/A
MunSeng Chong	In 2011 reimbursement was received from Astellas for giving a lecture and chairing a meeting. Medical Adviser to the Trigeminal Neuralgia Support Group (TNA UK) Medical Adviser to the Migraine Trust Member of SPIN which is a charity set up to promote good pain management overseas: for example in the West Bank and Gaza as well as Kenya and Rwanda, educating healthcare professionals in chronic pain	Specific personal pecuniary interest Personal non-pecuniary interests	Declare and participate as specific personal pecuniary interest occurred more than 12 months to prior to starting development of the guideline Declare and participate

	management. Member of BASH: British Association for Study of Headaches Member of the Association of British Neurologist subspeciality committee on headaches and chronic pain.		
Marie Fallon (participated on the GDG until April 2013)	Researched the potential role of pregabalin in cancer-induced bone pain. This RCT is predominantly CRUK-funded but was supplemented by Pfizer	Non-specific non-personal pecuniary interest	Declare and participate
Annette Gibb	Attended a training course on pain. Some funding support for the course was provided by Pfizer Presented at a conference on "patient experience how the NICE guidelines will improve patient care" hosted by Health Care Conferences UK.	Specific non-personal pecuniary interest Non-specific non-personal pecuniary	Declare and participate Declare and participate
Charles Lane (participated on the GDG until March 2013)	None declared	N/A	N/A
Ammy Pui-Chi LAM	None declared	N/A	N/A
Vera Neumann	None declared	N/A	N/A
Solomon Tesfaye (co-opted expert	Received reimbursement for delivering lectures in scientific meetings for Eli Lilly	N/A	N/A

	and Pfizer		
Sailesh Sankaranarayanan	None declared	N/A	N/A
Heather Wallace	Husband works with research institute that provides services to pharmacological industry.	Non-specific personal family interest	Declare and participate

Appendix B List of all research recommendations

The Guideline Development Group has made the following recommendations for research, based on its review of evidence, to improve NICE guidance and patient care in the future. The 6 key research recommendations are listed first with information about why they are important. Additional research recommendations are listed after those.

B1 Monotherapy versus combination therapy for treating neuropathic pain

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

Why this is important

Combination therapy is commonly prescribed for neuropathic pain. It may also be a helpful option as a stepwise approach if initially used drugs are insufficient at reducing pain. Combination therapy may also result in better tolerability because smaller doses of individual drugs are often used when combined with other drugs. However, there is a lack of trial evidence comparing the clinical and cost effectiveness and tolerability of different drug combinations. Further research should be conducted as described in the table below.

Criterion	Explanation
Population	Adults with a diagnosis of neuropathic pain. Neuropathic pain conditions include: • Central neuropathic pain/central pain • Complex regional pain syndromes • Compression neuropathies/nerve compression syndromes • Facial neuralgia • HIV-related neuropathy • Mixed neuropathic pain • Multiple sclerosis • Neurogenic pain • Neuropathic cancer pain/cancer pain • Neuropathic pain

	• Painful diabetic neuropathy/diabetic neuropathy • Peripheral nerve injury • Peripheral nervous system disease/neuropathies • Phantom limb pain • Polyneuropathies • Post-amputation pain • Post-herpetic neuralgia • Post-stroke pain • Post-treatment/post-surgery/post-operative pain • Radiculopathies/radicular pain • Spinal cord diseases • Spinal cord injury • Trigeminal neuralgia
Intervention(s)	Pharmacological agents as monotherapy or combination therapy. The pharmacological agents include: • Amitriptyline • Clomipramine • Dosulepin (dothiepin) • Doxepin • Imipramine • Lofepramine • Nortriptyline • Trimipramine • Citalopram • Escitalopram • Fluoxetine • Paroxetine • Sertraline • Duloxetine • Mirtazapine • Reboxetine • Trazodone • Venlafaxine • Carbamazepine • Gabapentin • Lacosamide • Lamotrigine • Levetiracetam • Oxcarbazepine • Phenytoin • Pregabalin • Valproate

	• Topiramate • Buprenorphine • Co-codamol • Co-dydramol • Dihydrocodeine • Fentanyl • Morphine • Oxycodone • Oxycodone with naloxone • Tapentadol • Tramadol • Cannabis sativa extract • Flecainide • 5-HT_1-receptor agonists • Topical capsaicin • Topical lidocaine
Comparator(s)	Any of the above listed pharmacological agents as monotherapy compared with any combinations of the above listed pharmacological agents as combination therapy.
Outcome(s)	Patient-reported global improvement (on a 7-point scale) Patient-reported improvement in daily physical and emotional functioning including sleep (on a 9-point scale) At least 30% and 50% pain reduction (on a 11-point Numerical rating scale [NRS] scale) Mean change from baseline pain scores (on a 11-NRS scale) Withdrawal due to adverse effects of the pharmacological agents Adverse effects of the pharmacological agents HRQoL (for example, EQ-5D, WHOQoL- BREF and London Handicap Scale)
Study design	Parallel triple-blinded randomised controlled trial of at least 12-weeks' study period (they should not have enriched enrolment). All participants should have a 'wash-out' period after assessment for inclusion in the study and before randomisation. Baseline pain scores between arms should be equal and clearly documented. Concomitant medications should not be allowed or should be restricted and maintained at a stable dose in the study. Difference in concomitant pain medication usage at baseline should be clearly described in each trial arm, including details of the number of patients on different drugs. Rescue pain medications should either not be allowed or, if used, their use should be accurately documented.

B2 Relationship between symptoms, cause of neuropathic pain and its treatment

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

Why this is important

There is little evidence about whether certain symptoms that present in healthcare settings, or whether different neuropathic pain conditions with different aetiologies, respond differently to different treatments. Current evidence is typically focused on particular conditions and is limited to particular drugs. Further research should be conducted as described in the table below.

Criterion	Explanation
Population	Adults with a diagnosis of neuropathic pain. Neuropathic pain conditions include: • Central neuropathic pain/central pain • Complex regional pain syndromes • Compression neuropathies/nerve compression syndromes • Facial neuralgia • HIV-related neuropathy • Mixed neuropathic pain • Multiple sclerosis • Neurogenic pain • Neuropathic cancer pain/cancer pain • Neuropathic pain • Painful diabetic neuropathy/diabetic neuropathy • Peripheral nerve injury • Peripheral nervous system disease/neuropathies • Phantom limb pain • Polyneuropathies • Post-amputation pain • Post-herpetic neuralgia • Post-stroke pain • Post-treatment/post-surgery/post-operative pain • Radiculopathies/radicular pain • Spinal cord diseases • Spinal cord injury • Trigeminal neuralgia

Intervention(s)	Any pharmacological agents as monotherapy or combination therapy (see research recommendation B1).
Comparator(s)	Same pharmacological agents chosen as the main treatments of interest but compare the treatment response across different groups of participants with different neuropathic pain conditions or underlying aetiology.
Outcome(s)	Patient-reported global improvement (on a 7-point scale) Patient-reported improvement in daily physical and emotional functioning including sleep (on a 9-point scale) At least 30% and 50% pain reduction (on a 11-NRS scale) Mean change from baseline pain scores (on a 11-NRS scale) Withdrawal due to adverse effects of the pharmacological agents Adverse effects of the pharmacological agents HRQoL (for example, EQ-5D, WHOQoL- BREF and London Handicap Scale)
Study design	Prospective cohort study All participants should have a 'wash-out' period before assessment for inclusion in the study. Baseline pain scores between arms should be equal and clearly documented. Concomitant medications should not be allowed, or should be restricted and maintained at stable dose during the study. Difference in concomitant pain medication usage at baseline should be clearly described in each trial arm, including details of the number of patients on different drugs. Rescue pain medications either not be allowed or, if used, their use should be accurately documented.

B3 Carbamazepine for treating trigeminal neuralgia

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

Why this is important

Carbamazepine has been the standard treatment for trigeminal neuralgia since the 1960s. Despite the lack of trial evidence, it is perceived by clinicians to be efficacious. Further research should be conducted as described in the table below.

Criterion	Explanation
Population	Adults with a diagnosis of trigeminal neuralgia.
Intervention(s)	Carbamazepine as monotherapy.
Comparator(s)	Any of the below listed pharmacological agents as monotherapy or combinations. The pharmacological agents include: • Amitriptyline • Clomipramine • Dosulepin (dothiepin) • Doxepin • Imipramine • Lofepramine • Nortriptyline • Trimipramine • Citalopram • Escitalopram • Fluoxetine • Paroxetine • Sertraline • Duloxetine • Mirtazapine • Reboxetine • Trazodone • Venlafaxine • Carbamazepine • Gabapentin • Lacosamide • Lamotrigine • Levetiracetam • Oxcarbazepine • Phenytoin • Pregabalin • Valproate • Topiramate • Buprenorphine • Co-codamol • Co-dydramol • Dihydrocodeine • Fentanyl • Morphine • Oxycodone

	• Oxycodone with naloxone • Tapentadol • Tramadol • Cannabis sativa extract • Flecainide • 5-HT_1-receptor agonists • Topical capsaicin • Topical lidocaine
Outcome(s)	Patient-reported global improvement (on a 7-point scale) Patient-reported improvement in daily physical and emotional functioning including sleep (on a 9-point scale) At least 30% and 50% pain reduction (on a 11-NRS scale) Mean change from baseline pain scores (on a 11-NRS scale) Withdrawal due to adverse effects of the pharmacological agents Adverse effects of the pharmacological agents HRQoL (for example, EQ-5D, WHOQoL- BREF and London Handicap Scale)
Study design	Parallel triple-blinded randomised controlled trial of at least 12 weeks' study period (they should not have enriched enrolment). All participants should have a 'wash-out' period after assessment for inclusion in the study and before randomisation. Baseline pain scores between arms should be equal and clearly documented. Concomitant medications should not be allowed or should be restricted and maintained at a stable dose during the study. Difference in concomitant pain medication usage at baseline should be clearly described in each trial arm, including details of the number of patients on different drugs. Rescue pain medications either not be allowed or, if used, their use should be accurately documented.

B4 Factors affecting participation and quality of life

What are the key factors, including additional care and support, that influence participation[14] and quality of life in people with neuropathic pain?

[14] 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.

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, unrecognisable factors are important for people with neuropathic pain and that these factors may influence their daily activities and participation. Further research should be conducted as described in the table below.

Criterion	Explanation
Population	Adults with a diagnosis of neuropathic pain. Neuropathic pain conditions include: • Central neuropathic pain/central pain • Complex regional pain syndromes • Compression neuropathies/nerve compression syndromes • Facial neuralgia • HIV-related neuropathy • Mixed neuropathic pain • Multiple sclerosis • Neurogenic pain • Neuropathic cancer pain/cancer pain • Neuropathic pain • Painful diabetic neuropathy/diabetic neuropathy • Peripheral nerve injury • Peripheral nervous system disease/neuropathies • Phantom limb pain • Polyneuropathies • Post-amputation pain • Post-herpetic neuralgia • Post-stroke pain • Post-treatment/post-surgery/post-operative pain • Radiculopathies/radicular pain • Spinal cord diseases • Spinal cord injury • Trigeminal neuralgia
Intervention(s)	Any important factors, including elements of additional care and support that are perceived as important by adults with neuropathic pain to improve their daily participation.
Comparator(s)	Non-applicable.
Outcome(s)	HRQoL (for example, EQ-5D, WHOQoL- BREF) Measurements of participation (for example, the London Handicap

	Scale) Satisfaction Patient experiences
Study design	Qualitative research or structured/semi-structured survey questionnaire.

B5 Impact of drug-related adverse effects on cost effectiveness and quality of life

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

Why this is important

Pharmacological agents for neuropathic pain are associated with various adverse effects. However, there is little evidence about how this affects cost of the quality of life of patients receiving treatment. Further research should be conducted as described in the table below.

Criterion	Explanation
Population	Adults with a diagnosis of neuropathic pain. Neuropathic pain conditions include: • Central neuropathic pain/central pain • Complex regional pain syndromes • Compression neuropathies/nerve compression syndromes • Facial neuralgia • HIV-related neuropathy • Mixed neuropathic pain • Multiple sclerosis • Neurogenic pain • Neuropathic cancer pain/cancer pain • Neuropathic pain • Painful diabetic neuropathy/diabetic neuropathy • Peripheral nerve injury • Peripheral nervous system disease/neuropathies • Phantom limb pain • Polyneuropathies • Post-amputation pain • Post-herpetic neuralgia • Post-stroke pain • Post-treatment/post-surgery/post-operative pain

	• Radiculopathies/radicular pain • Spinal cord diseases • Spinal cord injury • Trigeminal neuralgia
Intervention(s)	Any pharmacological treatment for neuropathic pain, alone or in combination (see research recommendation B1)
Comparator(s)	N/A
Outcome(s)	HRQoL (EQ-5D as well as any condition-specific instruments) in people experiencing adverse effects and people experiencing none Resource-use and costs in people experiencing adverse effects and people experiencing none
Study design	Case–control study This research should be performed in a cohort of people receiving a variety of pharmacological treatments for neuropathic pain. Those experiencing adverse effects should be matched with those experiencing none, and their HRQoL and resource-use/costs compared. Matching should be performed using as many modifiers of HRQoL as possible, including age, sex and underlying diagnosis. Analysis of single, named adverse events and also of people experiencing any serious adverse effect (those leading to discontinuation of the medication in question) would be valuable.

B6 Potential for dependence associated with pharmacological drugs for neuropathic pain

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

Why this is important

There has been some suggestion that some pharmacological agents for neuropathic pain are associated with increased potential for misuse. However, there had not been enough high-quality evidence to adequately explore this issue. Further research should be conducted as described in the table below.

Criterion	Explanation
Population	Adults with a diagnosis of neuropathic pain. Neuropathic pain conditions include: • Central neuropathic pain/central pain • Complex regional pain syndromes • Compression neuropathies/nerve compression syndromes • Facial neuralgia • HIV-related neuropathy

	• Mixed neuropathic pain • Multiple sclerosis • Neurogenic pain • Neuropathic cancer pain/cancer pain • Neuropathic pain • Painful diabetic neuropathy/diabetic neuropathy • Peripheral nerve injury • Peripheral nervous system disease/neuropathies • Phantom limb pain • Polyneuropathies • Post-amputation pain • Post-herpetic neuralgia • Post-stroke pain • Post-treatment/post-surgery/post-operative pain • Radiculopathies/radicular pain • Spinal cord diseases • Spinal cord injury • Trigeminal neuralgia
Intervention(s)	Any pharmacological treatment for neuropathic pain, alone or in combination (see research recommendation B1)
Comparator(s)	Any other pharmacological treatment for neuropathic pain, alone or in combination (see research recommendation B1)
Outcome(s)	Drug dependence (including withdrawal symptoms) Drug abuse or drug misuse
Study design	Long-term follow-up from a randomised controlled trial (minimum 6 months) or community-based observational studies. For trials: - Intention to observe dependency and misuse should be made in the study protocol and monitored throughout the study period. - All participants should have a 'wash-out' period after assessment for inclusion in the study and before randomisation. - Baseline pain scores between arms should be equal and clearly documented. - Concomitant medications should not be allowed or should be restricted and maintained at a stable dose in the study. Difference in concomitant pain medication usage at baseline should be clearly described in each trial arm, including details of the number of patients on different drugs. - Rescue pain medications should either not be allowed or, if used, their use should be accurately documented.

Additional research recommendations

Additional research recommendations that the GDG felt were important but which were not prioritised in the key 5 are:

- How should the symptomatic treatment of neuropathic pain relate to its cause?
- Does early intervention to treat neuropathic pain reduce the likelihood of chronic pain?
- What is the clinical and cost effectiveness of lidocaine patches for localised peripheral pain?
- What is the clinical and cost effectiveness of alternative treatments as first-line treatment for trigeminal neuralgia compared with other better-tolerated pharmacological treatments?

Appendix C Guideline scope

Please see separate file for appendix C.

Appendix D How this guideline was developed

Please see separate files for appendix D.

Appendix E Evidence tables

Please see separate file for Appendix E.

Appendix F Full health economic report

Please see separate file for Appendix F.

Appendix G GRADE profiles and results for 'all neuropathic pain'

Please see separate file for Appendix G

Appendix H GRADE profiles and results for 'peripheral neuropathic pain'

Please see separate file for Appendix H.

Appendix I GRADE profiles and results for 'central neuropathic pain'

Please see separate file for Appendix I.

Appendix J GRADE profiles and results for individual adverse effects for ‘all neuropathic pain’

Please see separate file for Appendix J.

Appendix K Specimen WinBUGS code

Please see separate file for Appendix K.

Appendix L Validation of efficacy dataset used in health economic model

Please see separate file for Appendix L.