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

NICE clinical guideline

Draft for consultation, June 2013

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

Contents

Appendices C, D, E, F, G, H, I, J, K and L are in separate files.

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). Examples of common conditions that have peripheral neuropathic pain as a symptom are painful diabetic neuropathy, post-herpetic neuralgia, trigeminal neuralgia, radicular pain, pain after surgery, and neuropathic cancer pain (that is, chemotherapy-induced neuropathy and neuropathy secondary to tumour antigens). 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) and hyperalgesia (an increased response to a stimulus that is normally painful) (McCarberg 2006).

A review of the epidemiology of chronic pain found that there is still no accurate estimate available for the population prevalence of neuropathic pain (Smith 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, which may contribute to the inconsistency. 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. Licensed indications are listed in table 1.

Table 1 Licensed indications for recommended pharmacological treatments for neuropathic pain (June 2013)

Amitriptyline	Not licensed for neuropathic pain
Duloxetine	Licensed for diabetic peripheral neuropathic pain
Gabapentin	Licensed for peripheral neuropathic pain
Nortriptyline	Not licensed for neuropathic pain
Pregabalin	Licensed for central and peripheral neuropathic pain

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 Consider referring the person to a specialist pain service and/or a condition-specific service[1] at any stage, including at initial presentation and at the regular clinical reviews (see recommendation 1.1.5), if:

- they have severe pain **or**
- their pain significantly limits their daily activities and participation[2] **or**
- their underlying health condition has deteriorated.

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

- the underlying causes of the pain
- why a particular pharmacological treatment is being offered
- the benefits and possible adverse effects of pharmacological treatments, taking into account any comorbidities and concurrent medications
- the importance of dosage titration and the titration process (and also provide written information)
- coping strategies for pain and for possible adverse effects of treatment

[1] 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.

[2] 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.

- non-pharmacological treatments (for example, physical and psychological therapies, which may be offered through a rehabilitation service, and surgery).

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

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

1.1.4 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.

1.1.5 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 daily activities and participation[3]
- adverse effects **and**
- continued need for treatment.

1.1.6 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)

1.1.7 Offer a choice of amitriptyline, gabapentin or nortriptyline as initial treatment for neuropathic pain (except trigeminal neuralgia)[4]. If the

[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.

initial treatment is not effective or not tolerated, offer another of these 3 treatments instead.

1.1.8 If initial treatment is not effective, is not tolerated or is contraindicated with all 3 of amitriptyline, gabapentin and nortriptyline, consider switching to duloxetine[5] or pregabalin.

1.1.9 Consider tramadol only if acute rescue therapy is needed while the person is waiting for a referral appointment.

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

Trigeminal neuralgia

1.1.11 Offer carbamazepine as initial treatment for trigeminal neuralgia.

1.1.12 If initial treatment with carbamazepine is not effective, not tolerated or is contraindicated, refer the person to a specialist. While waiting for the referral appointment, consider switching to a different neuropathic pain treatment (see recommendations 1.1.7–1.1.9).

Treatments that should not be used

1.1.13 Do not offer the following to treat neuropathic pain in non-specialist settings:

- cannabis sativa extract
- capsaicin patch
- lacosamide
- lamotrigine
- levetiracetam

[4] At the time of consultation (June 2013), amitriptyline and nortriptyline did not have a UK marketing authorisation for this indication, and gabapentin is licensed for peripheral neuropathic pain only. 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 medicines – guidance for doctors for further information.

[5] At the time of consultation (June 2013), duloxetine only had a UK marketing authorisation for diabetic peripheral neuropathic pain, 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 medicines – guidance for doctors for further information.

- oxcarbazepine
- topiramate
- venlafaxine.

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. Although the GDG felt that presenting the evidence for each individual underlying condition may not be appropriate for non-specialist settings, categorising neuropathic pain conditions into 3 broad groups would be of clinical value: central neuropathic pain, peripheral neuropathic pain and trigeminal neuralgia. This decision was made before the evidence was presented, and was based on the clinical perspective that similar underlying causes of neuropathic pain could be expected to respond to treatment analogously.

In addition, an overarching analysis of the evidence was conducted, which is described in this guideline as ‘all pain’. This was based on the rationales that:

- 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 appendices D and L. This will 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 2.

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 3 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 (placebo-controlled trials)
- the clinical effectiveness of individual pharmacological treatments against each other (head-to-head monotherapy comparative trials)
- the clinical effectiveness of combination therapy against monotherapy or other combination therapy (head-to-head combination therapy comparative trials).

Only randomised controlled trials of the interventions above were included in this guideline.

2.1.5 Critical and important outcomes for clinical evidence

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. 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). In addition, the reporting of dichotomous outcomes appears more frequently in the newer literature and in the studies on only some drugs. For this reason, the GDG asked for continuous 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 D 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 table 3) for neuropathic pain conditions (listed in table 2). For full search strategies, see appendix D.

2.1.7 Extraction, analysis and synthesis of clinical evidence

For further details of the methods used, see appendix L.

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.

Table 2 Neuropathic pain conditions (search terms) included in the searches

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

1 **Table 3 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 Sodium 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

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3 Evidence review and recommendations

For details of how this guideline was developed, see appendix L.

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

There were 116 studies with a total of 18,953 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 for pooling 2 studies comparing gabapentin with placebo (sleep interference on normalised 10-point scale at 56±7 days).

The GRADE summary table for each outcome where syntheses were performed is found in table 5. 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=116)

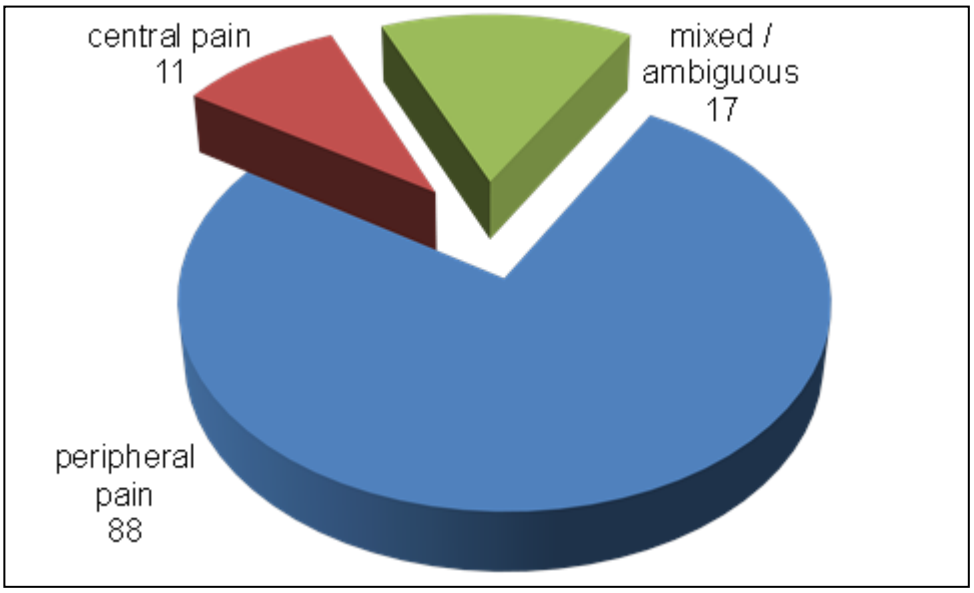


Figure 2 Proportion of patients in studies by pain type (total n=18,953)

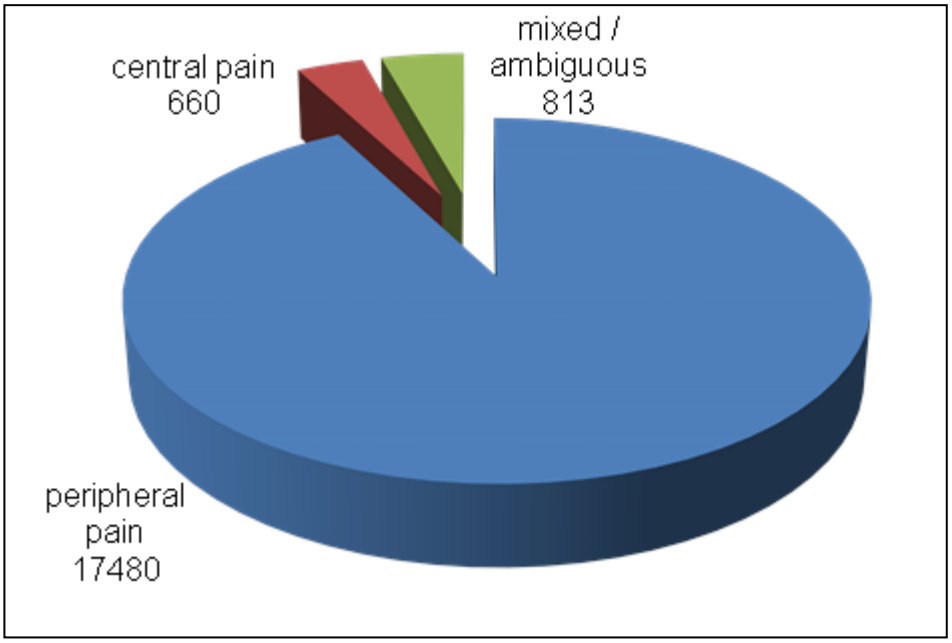


Table 4 Summary of included studies for 'all neuropathic pain'

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
Irving et al. (2012) USA, N=1127	Parallel 98d Base pain: 5.70	Peripheral	Post-herpetic neuralgia Concomitant pain meds allowed	(1) capsaicin patch flexi (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

Study / Country / N	Design / Duration / Baseline pain	Type of pain	Condition / Concomitant treatments	Treatments	Outcomes
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
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

Study / Country / N	Design / Duration / Baseline pain	Type of pain	Condition / Concomitant treatments	Treatments	Outcomes
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
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
Nikolajsen et al. (2006) Denmark, N=46	Parallel 28d Base pain: NR	Mixed / ambiguous	Phantom limb pain Concomitant pain meds allowed	(1) gabapentin flexi (median: 2100 mg/d) (range: 900–2400 mg/d) (2) placebo	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

Study / Country / N	Design / Duration / Baseline pain	Type of pain	Condition / Concomitant treatments	Treatments	Outcomes
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
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. (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
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

Study / Country / N	Design / Duration / Baseline pain	Type of pain	Condition / Concomitant treatments	Treatments	Outcomes
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
PGIC – at least moderate improvement (28±7 days)	4 RCTs[a]	412	cannabis sativa extract, levetiracetam, pregabalin, tramadol	Very low	Critical
PGIC – at least moderate improvement (56±7 days)	9 RCTs[b]	2652	capsaicin patch, duloxetine, gabapentin, pregabalin, valproate	Very low	Critical
PGIC – at least moderate improvement (84±14 days)	8 RCTs[c]	3157	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)	92 RCTs[h]	18140	23 (see appendix G)	Very low	Critical
Individual adverse events	97 RCTs[r] (3–72)	567–13838	See appendix J	Low to very low	Important
30% pain relief (28±7 days)	6 RCTs[I]	847	cannabis sativa extract, capsaicin cream, levetiracetam, pregabalin, tramadol	Very low	Important
30% pain relief (56±7 days)	6 RCTs[J]	2361	amitriptyline, capsaicin patch, gabapentin, pregabalin	Very low	Important
30% pain relief (84±14 days)	18 RCTs[k]	5660	cannabis sativa extract, capsaicin patch, duloxetine, lacosamide, lamotrigine, pregabalin, topiramate	Very low	Important
50% pain relief (28±7 days)	7 RCTs[l]	941	amitriptyline, cannabis sativa extract, levetiracetam, morphine, pregabalin, tramadol	Very low	Important
50% pain relief (56±7 days)	8 RCTs[m]	2362	capsaicin patch, 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
Pain (continuous) (28±7 days)	30 RCTs[o]	3546	21 (see appendix G)	Very low	Important
Pain (continuous) (56±7 days)	21 RCTs[p]	2923	13 (see appendix G)	Very low	Important
Pain (continuous) (84±14 days)	15 RCTs[q]	2987	10 (see appendix G)	Low	Important

[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), Irving et al. (2012), 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), Irving et al. (2012), 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), Irving et al. (2012), 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), Nikolajsen et al. (2006), 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. (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), Irving et al. (2012), 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), Irving et al. (2012), Raskin et al. (2004), Rauck et al. (2007), Selvarajah et al. (2010), Siddall et al. (2006), Simpson et al. (2003), 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), 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), Irving et al. (2012), 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), Irving et al. (2012), 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. (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); [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), 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); [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), 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 16] and 'central neuropathic pain' [table 24]) 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–K). 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.

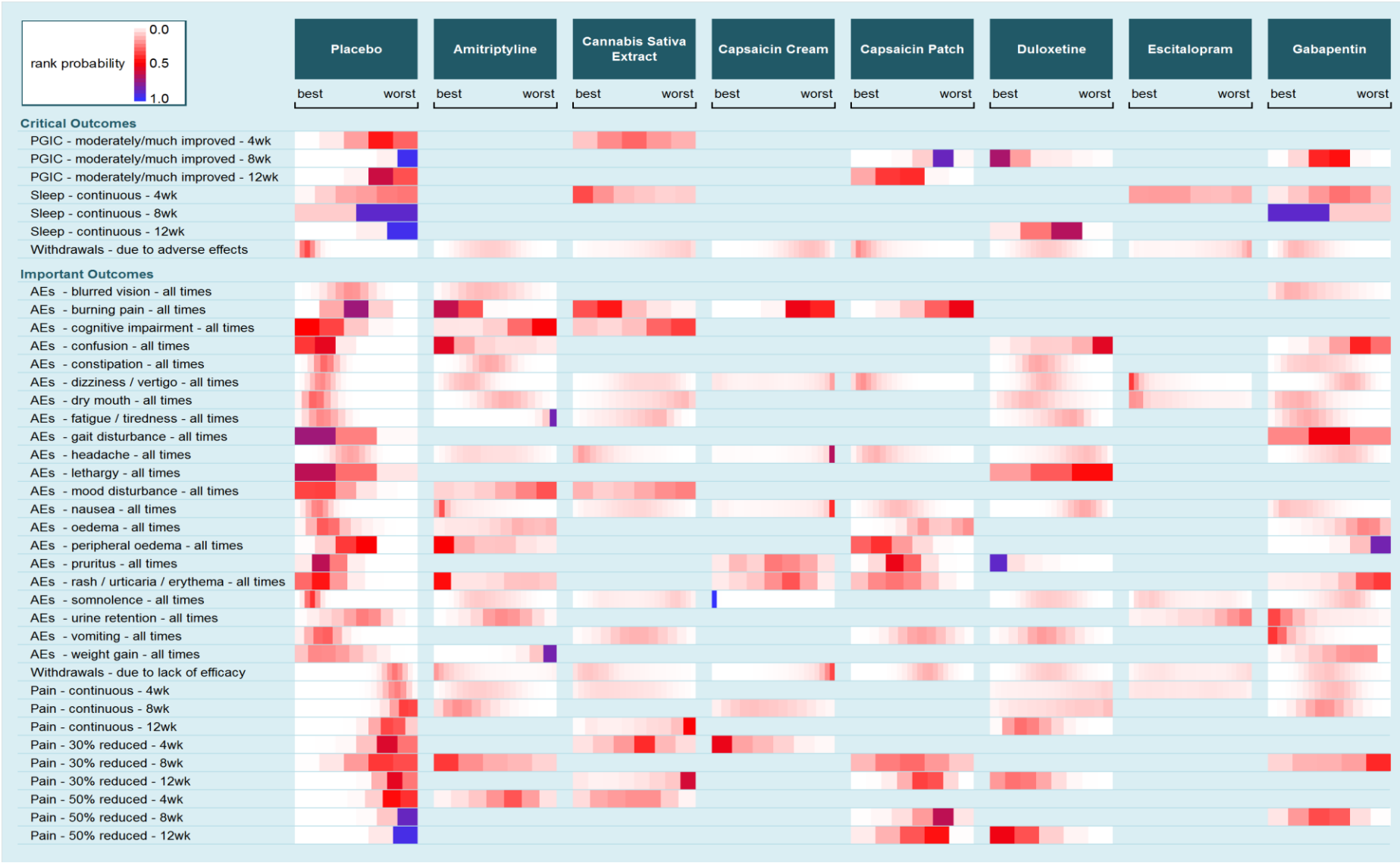
Bars presenting a relatively pale colour across a broad spread of the scale are indicative of results that are subject to substantial uncertainty – that is, there is a probability that the treatment could be ranked anywhere along the continuum. A good example of this in table 6 is the estimate of nortriptyline's 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 that

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.

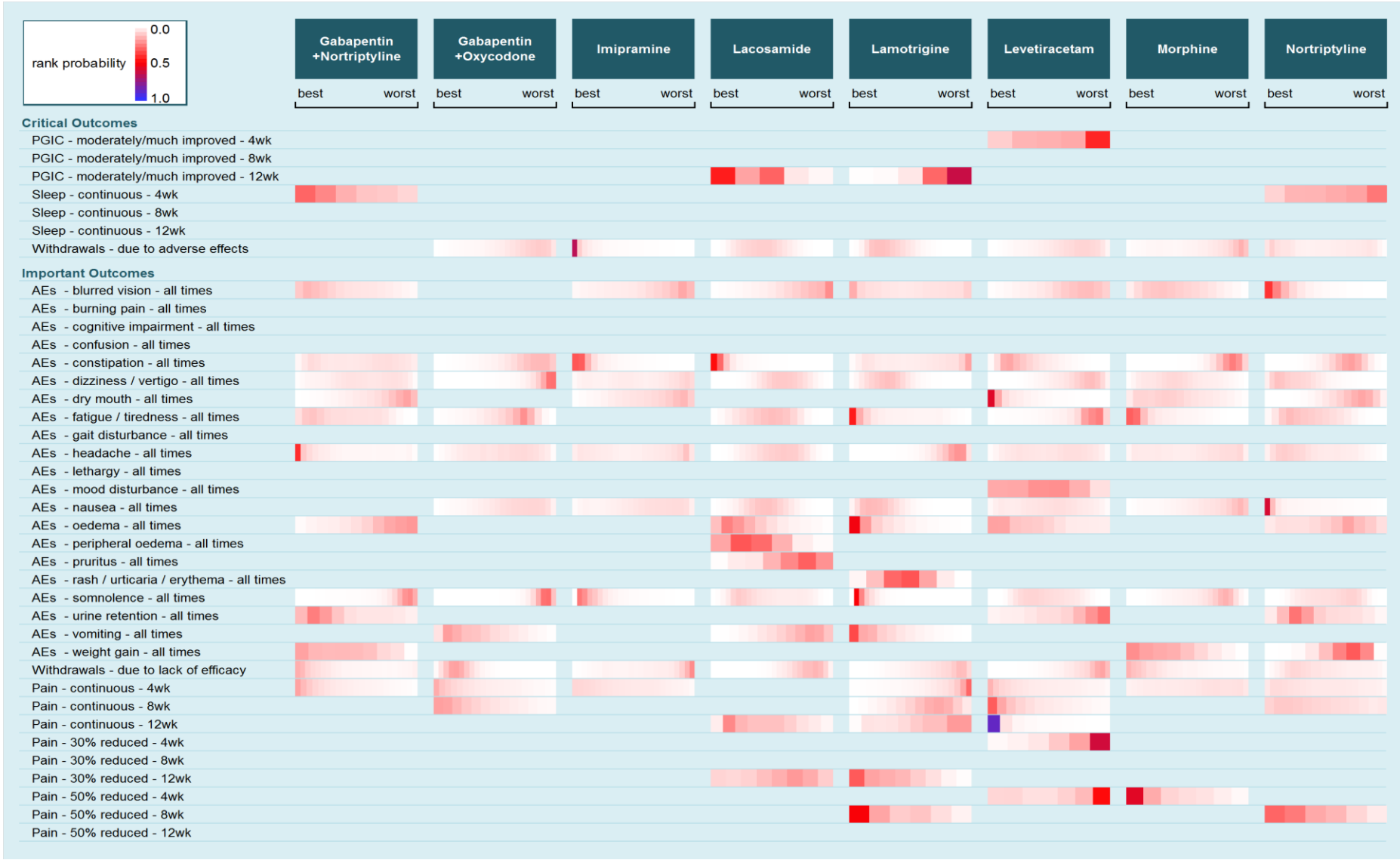
For reasons of space, 3 treatments for which very few data were available – carbamazepine, topical lidocaine and trazodone – are not shown in table 6.

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 92 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

3.1.2.4 *Network meta-analyses of 20 individual adverse effects from 97 studies (ranging from 3 studies for gait disturbance to 73 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 (28 and 30 studies, respectively) at 4, 8 and 12 weeks follow-up 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.*

3.1.2.6 *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 evidence showed consistent direction of effect estimates that amitriptyline, duloxetine and pregabalin reduce pain compared with placebo*
- *the majority of the evidence showed consistent direction of effect estimates that capsaicin cream, gabapentin, morphine, nortriptyline and tramadol reduce pain compared with placebo*
- *the evidence showed inconsistent directions of effect estimates on the effectiveness of levetiracetam and valproate in reducing pain compared with placebo*

- *there is inconclusive evidence on the effectiveness of capsaicin patch, gabapentin + nortriptyline, gabapentin + oxycodone, imipramine, lacosamide, lamotrigine, oxcarbazepine, oxycodone, topiramate or venlafaxine in reducing pain compared with placebo*
- *the evidence showed consistent direction of effect estimates that cannabis sativa does not reduce pain compared with placebo.*

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 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 0.075% 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. However, insufficient data were available to provide results for central pain and trigeminal neuralgia. Therefore, along with the analysis limited to people with peripheral pain, an additional analysis was performed including data from all types of neuropathic pain.

The GDG recognised the potential limitations on the model of assuming that efficacy data from a trial in one type of neuropathic pain is equally valid for all types of neuropathic pain. However, the GDG felt the efficacy networks were too sparse for any individual conditions or subgroups outside of peripheral pain to be able to produce informative models.

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

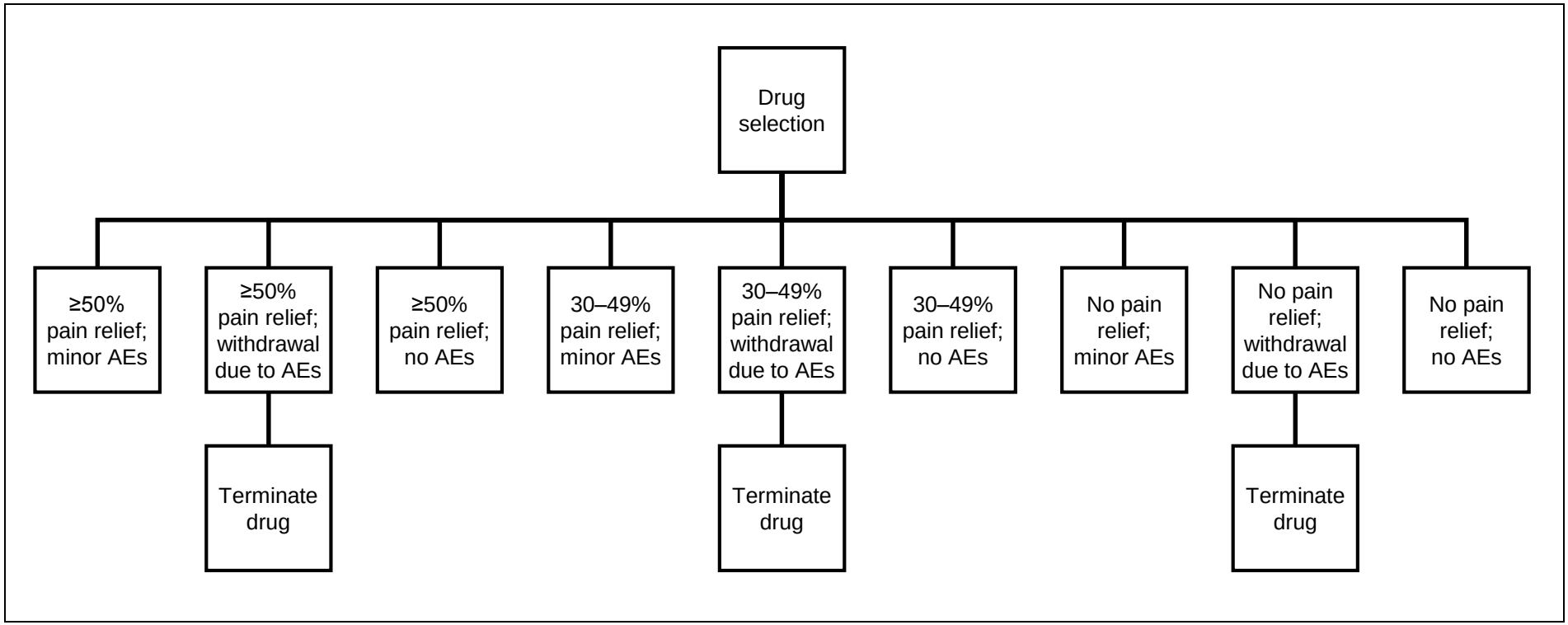
With different scales used to measure pain, the GDG agreed that pain data should be modelled as a discrete variable with pain reductions of less than 30%, 30–49% or 50% or more.

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 1 drug for a patient was assumed to be independent of all other drugs. This assumption of independence means that there would be no additional information gained by modelling different sequences of therapies: it can be assumed 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 K.

Two scenarios are presented, which use inputs from alternative synthesis models. Each synthesis is based on an identical dataset comprising response probabilities from all available trials. However, in recognition of heterogeneity of regimens investigated in the included trials, 1 model is dose-adjusted (it includes an additional term for each comparator, estimating the relationship between dose and response, which is incorporated as an additional coefficient in the linear model; see appendix K for details). Using this model, estimates of response probability can be computed for any specified dose level. The GDG was asked to estimate typical maintenance dosages for each drug in the decision-set, and these values were used as the expected dosage with which effects were calculated. For some less commonly used drugs, the GDG was not able to provide estimates of typical practice; in these instances, the mean value of dosages used in the trials was used instead.

For safety data, as for efficacy, models incorporating a coefficient reflecting dose–response were explored. However, because of limited data availability, it was only possible to estimate this relationship for withdrawal due to adverse effects. Therefore, individual adverse effects are estimated using models that do not adjust for dose.

Exploration of other potential covariates of outcome – including fixed versus flexible dose regimens, baseline pain status, age, sex and diagnosis – did not provide informative results or improve model fit for either efficacy or safety data.

1 **Table 7 Health economic model – efficacy and safety parameters (all neuropathic pain – dose-adjusted)**

Drug	Assumed dose	Probability (95% CrI) of pain relief after 20 weeks			Probability (95% CrI) of event within 20 weeks		
		<30%	30–49%	≥50%	Withdrawal due to AEs	Dizziness[a]	Nausea[a]
Placebo	-	0.64 (0.48,0.77)	0.14 (0.10,0.16)	0.22 (0.12,0.36)	0.09 (0.08,0.11)	0.12 (0.09,0.16)	0.10 (0.08,0.14)
Amitriptyline	50 mg/d[b]	0.54 (0.31,0.78)	0.15 (0.10,0.17)	0.30 (0.12,0.54)	0.23 (0.13,0.35)	0.12 (0.05,0.25)	0.09 (0.01,0.31)
Cannabis extract	4 sprays/d[b]	0.46 (0.18,0.76)	0.16 (0.10,0.17)	0.38 (0.13,0.70)	0.49 (0.14,0.98)	0.37 (0.13,0.75)	0.20 (0.08,0.41)
Capsaicin cream	4 apps/d[b]	0.19 (0.04,0.49)	0.13 (0.05,0.16)	0.68 (0.35,0.91)	0.43 (0.22,0.69)	0.58 (0.02,1.00)	0.47 (0.03,1.00)
Capsaicin patch	1×60-min	0.55 (0.37,0.74)	0.15 (0.11,0.17)	0.30 (0.15,0.47)	0.11 (0.04,0.25)	0.09 (0.03,0.21)	0.14 (0.07,0.23)
Duloxetine	60 mg/d[b]	0.44 (0.27,0.62)	0.16 (0.14,0.17)	0.40 (0.24,0.58)	0.21 (0.14,0.32)	0.26 (0.13,0.47)	0.28 (0.16,0.48)
Gabapentin	1800 mg/d[b]	0.41 (0.15,0.66)	0.16 (0.11,0.17)	0.43 (0.20,0.74)	0.18 (0.08,0.35)	0.40 (0.23,0.61)	0.11 (0.04,0.25)
Lacosamide	400 mg/d[b]	0.55 (0.36,0.71)	0.15 (0.12,0.17)	0.30 (0.17,0.48)	0.21 (0.13,0.32)	0.38 (0.18,0.66)	0.14 (0.06,0.27)
Lamotrigine	400 mg/d[b]	0.54 (0.36,0.72)	0.15 (0.12,0.17)	0.30 (0.16,0.48)	0.17 (0.11,0.27)	0.17 (0.06,0.35)	0.09 (0.05,0.16)
Levetiracetam	3000 mg/d[c]	0.70 (0.33,0.93)	0.12 (0.04,0.16)	0.18 (0.03,0.52)	0.44 (0.15,0.92)	0.57 (0.20,0.97)	0.25 (0.02,0.86)
Morphine	120 mg/d[b]	0.38 (0.15,0.60)	0.16 (0.11,0.17)	0.46 (0.25,0.74)	0.52 (0.09,1.00)	0.27 (0.05,0.74)	0.47 (0.11,0.99)
Nortriptyline	50 mg/d[b]	0.44 (0.13,0.80)	0.16 (0.08,0.17)	0.39 (0.10,0.77)	0.27 (0.03,0.83)	0.14 (0.03,0.40)	0.07 (0.00,0.34)
Oxcarbazepine	1800 mg/d[c]	0.45 (0.23,0.70)	0.16 (0.12,0.17)	0.39 (0.18,0.64)	0.30 (0.16,0.50)	0.65 (0.27,0.97)	0.18 (0.06,0.38)
Pregabalin	300 mg/d[b]	0.47 (0.34,0.68)	0.16 (0.13,0.17)	0.37 (0.19,0.50)	0.12 (0.08,0.17)	0.36 (0.24,0.50)	0.10 (0.04,0.17)
Topiramate	100 mg/d[b]	0.48 (0.09,0.89)	0.16 (0.05,0.17)	0.36 (0.05,0.82)	0.23 (0.15,0.34)	0.21 (0.04,0.59)	0.15 (0.07,0.25)
Tramadol	400 mg/d[b]	0.42 (0.23,0.69)	0.16 (0.12,0.17)	0.42 (0.19,0.63)	0.44 (0.20,0.81)	0.52 (0.18,0.93)	0.37 (0.20,0.65)
Venlafaxine	75 mg/d[b]	0.55 (0.32,0.77)	0.15 (0.10,0.17)	0.30 (0.13,0.52)	0.23 (0.09,0.48)	0.39 (0.01,1.00)	0.24 (0.11,0.45)

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

[a] not dose-adjusted

[b] estimate provided by GDG

[c] GDG felt unable to comment based on own experience; weighted mean of dosages in trials contributing to evidence base used instead

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.

2

Table 8 Health economic model – efficacy and safety parameters (all neuropathic pain – no dose adjustment)

	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)	0.14 (0.10,0.16)	0.22 (0.13,0.35)	0.09 (0.08,0.11)	0.12 (0.09,0.16)	0.10 (0.08,0.14)
Amitriptyline	0.48 (0.25,0.70)	0.16 (0.12,0.17)	0.37 (0.18,0.60)	0.24 (0.12,0.41)	0.12 (0.05,0.25)	0.09 (0.01,0.31)
Cannabis extract	0.44 (0.20,0.73)	0.16 (0.11,0.17)	0.40 (0.15,0.67)	0.48 (0.11,0.98)	0.37 (0.13,0.75)	0.20 (0.08,0.41)
Capsaicin cream	0.17 (0.04,0.43)	0.12 (0.05,0.16)	0.71 (0.41,0.92)	0.45 (0.22,0.78)	0.58 (0.02,1.00)	0.47 (0.03,1.00)
Capsaicin patch	0.54 (0.37,0.70)	0.15 (0.12,0.16)	0.30 (0.17,0.46)	0.11 (0.03,0.25)	0.09 (0.03,0.21)	0.14 (0.07,0.23)
Duloxetine	0.43 (0.27,0.60)	0.16 (0.14,0.17)	0.41 (0.25,0.58)	0.23 (0.13,0.37)	0.26 (0.13,0.47)	0.28 (0.16,0.48)
Gabapentin	0.49 (0.28,0.71)	0.16 (0.12,0.17)	0.35 (0.17,0.56)	0.17 (0.09,0.26)	0.40 (0.23,0.61)	0.11 (0.04,0.25)
Lacosamide	0.55 (0.36,0.71)	0.15 (0.12,0.17)	0.30 (0.17,0.49)	0.21 (0.11,0.36)	0.38 (0.18,0.66)	0.14 (0.06,0.27)
Lamotrigine	0.55 (0.37,0.72)	0.15 (0.12,0.17)	0.30 (0.17,0.47)	0.18 (0.10,0.29)	0.17 (0.06,0.35)	0.09 (0.05,0.16)
Levetiracetam	0.70 (0.32,0.94)	0.12 (0.04,0.16)	0.18 (0.03,0.53)	0.40 (0.12,0.84)	0.57 (0.20,0.97)	0.25 (0.02,0.86)
Morphine	0.36 (0.16,0.61)	0.16 (0.12,0.17)	0.48 (0.24,0.71)	0.58 (0.08,1.00)	0.27 (0.05,0.74)	0.47 (0.11,0.99)
Nortriptyline	0.44 (0.14,0.78)	0.16 (0.09,0.17)	0.40 (0.12,0.74)	0.33 (0.03,0.97)	0.14 (0.03,0.40)	0.07 (0.00,0.34)
Oxcarbazepine	0.45 (0.21,0.71)	0.16 (0.12,0.17)	0.39 (0.17,0.66)	0.34 (0.14,0.66)	0.65 (0.27,0.97)	0.18 (0.06,0.38)
Pregabalin	0.43 (0.27,0.59)	0.16 (0.14,0.17)	0.41 (0.27,0.58)	0.19 (0.12,0.26)	0.36 (0.24,0.50)	0.10 (0.04,0.17)
Topiramate	0.48 (0.26,0.71)	0.16 (0.12,0.17)	0.36 (0.17,0.59)	0.32 (0.16,0.53)	0.21 (0.04,0.59)	0.15 (0.07,0.25)
Tramadol	0.42 (0.22,0.64)	0.16 (0.13,0.17)	0.42 (0.22,0.65)	0.45 (0.17,0.88)	0.52 (0.18,0.93)	0.37 (0.20,0.65)
Venlafaxine	0.51 (0.27,0.73)	0.16 (0.11,0.17)	0.34 (0.15,0.59)	0.24 (0.08,0.55)	0.39 (0.01,1.00)	0.24 (0.11,0.45)

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; www.ppa.org.uk/edt/March_2013/mindex.htm). The GDG's estimate of typical maintenance dosage (see above) was used in the dose-adjusted model to determine drug cost as well as efficacy. The non-dose-adjusted model used a weighted average of dosages from the trials from which efficacy evidence was drawn.

In both models, 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 based on the frequency of dosage as advised by the GDG. 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 Table 9.

Table 9 Health economic model – daily dosages and prices of drugs

	Dose-adjusted model		Non-dose-adjusted model		
Drug	**GDG-advised dosage**	**140-day cost**	**Trial dosage[a]**	**Most efficient delivery[b]**	**140-day cost**
Amitriptyline	50 mg od	£4.10	95 mg/d	2×50mg	£8.20
Cannabis sativa extract	4 sprays/d	£777.78	29.4 mgTHC/d	11 sprays/d	£2138.89
Capsaicin cream	1 g qds	£177.96	3.7 applications	4×1 g applications	£177.96
Capsaicin patch	2 patches	£840.00	1 patch / 90 d	2 patches / 140 d	£420.00
Duloxetine	60 mg od	£138.60	78 mg/d	1×60 mg + 1×30 mg	£250.60
Gabapentin	600 mg tds	£54.60	2572 mg/d	6×400 mg + 2×100 mg	£46.73
Lacosamide	200 mg bd	£720.80	422 mg/d	2×200 mg + 1×50 mg	£828.90
Lamotrigine	200 mg bd	£24.90	319 mg/d	1×200 mg + 1×100 mg + 1×50 mg	£25.50
Levetiracetam	750 mg qds	£61.69	2375 mg/d	4×750 mg	£61.69
Morphine	60 mg bd	£75.60	62 mg/d	1×60 + 1×10 mg	£51.08
Nortriptyline	25 mg bd	£162.40	122 mg/d	5×25 mg	£406.00
Oxcarbazepine	600 mg tds	£372.12	1261 mg/d	3×600 mg	£372.12
Pregabalin	150 mg bd	£322.00	398 mg/d	2×200 mg	£322.00
Topiramate	50 mg bd	£17.13	252 mg/d	3×100 mg	£23.94
Tramadol	100 mg qds	£35.84	298 mg/d	3×100 mg	£26.88
Venlafaxine	37.5 mg bd	£12.65	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 required. 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 required 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 (5000 times) to obtain mean cost and QALY values.

Original health economic model – results

Results are presented separately for the model based on dose-adjusted estimates of efficacy and safety and on non-dose-adjusted inputs.

Dose-adjusted effect estimates

Incremental cost–utility results, representing the mean of 5000 simulations, are presented in Table 10, with the efficiency frontier shown in Figure 4.

Table 10 Health economic model – incremental mean cost–utility results (all neuropathic pain – dose-adjusted)

	Absolute		Incremental			Net monetary benefit	
Cohort	**Costs**	**QALYs**	**Costs**	**QALYs**	**ICER**	**@£20K/QALY**	**@£30K/QALY**
Placebo	£47.36	0.116	-	-	-	£2268.28	£3426.10
Amitriptyline	£73.75	0.123	£26.39	0.007	ext. dom.	£2381.32	£3608.86
Lamotrigine	£89.70	0.125	£42.34	0.010	ext. dom.	£2416.61	£3669.76
Topiramate	£99.01	0.132	£51.66	0.016	ext. dom.	£2531.79	£3847.20
Venlafaxine	£118.15	0.121	£70.79	0.005	dominated	£2302.38	£3512.64
Gabapentin	£136.66	0.146	£89.30	0.030	£2962	£2782.02	£4241.36
Tramadol	£197.54	0.121	£60.88	−0.025	dominated	£2230.98	£3445.24
Levetiracetam	£201.89	0.093	£65.23	−0.053	dominated	£1649.49	£2575.18
Nortriptyline	£205.51	0.133	£68.85	−0.013	dominated	£2453.71	£3783.32
Duloxetine	£218.37	0.139	£81.71	−0.007	dominated	£2557.61	£3945.61
Morphine	£222.17	0.118	£85.50	−0.028	dominated	£2139.52	£3320.37
Capsaicin cream	£300.19	0.150	£163.53	0.004	£43,304	£2694.02	£4191.12
Pregabalin	£363.97	0.139	£63.77	−0.011	dominated	£2407.72	£3793.56
Oxcarbazepine	£400.78	0.113	£100.59	−0.037	dominated	£1852.88	£2979.71
Cannabis extract	£631.59	0.115	£331.40	−0.035	dominated	£1661.47	£2807.99
Lacosamide	£703.05	0.123	£402.85	−0.027	dominated	£1753.75	£2982.15
Capsaicin patch	£818.09	0.130	£517.90	−0.019	dominated	£1786.74	£3089.16

Abbreviations: ext. dom., extendedly dominated; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

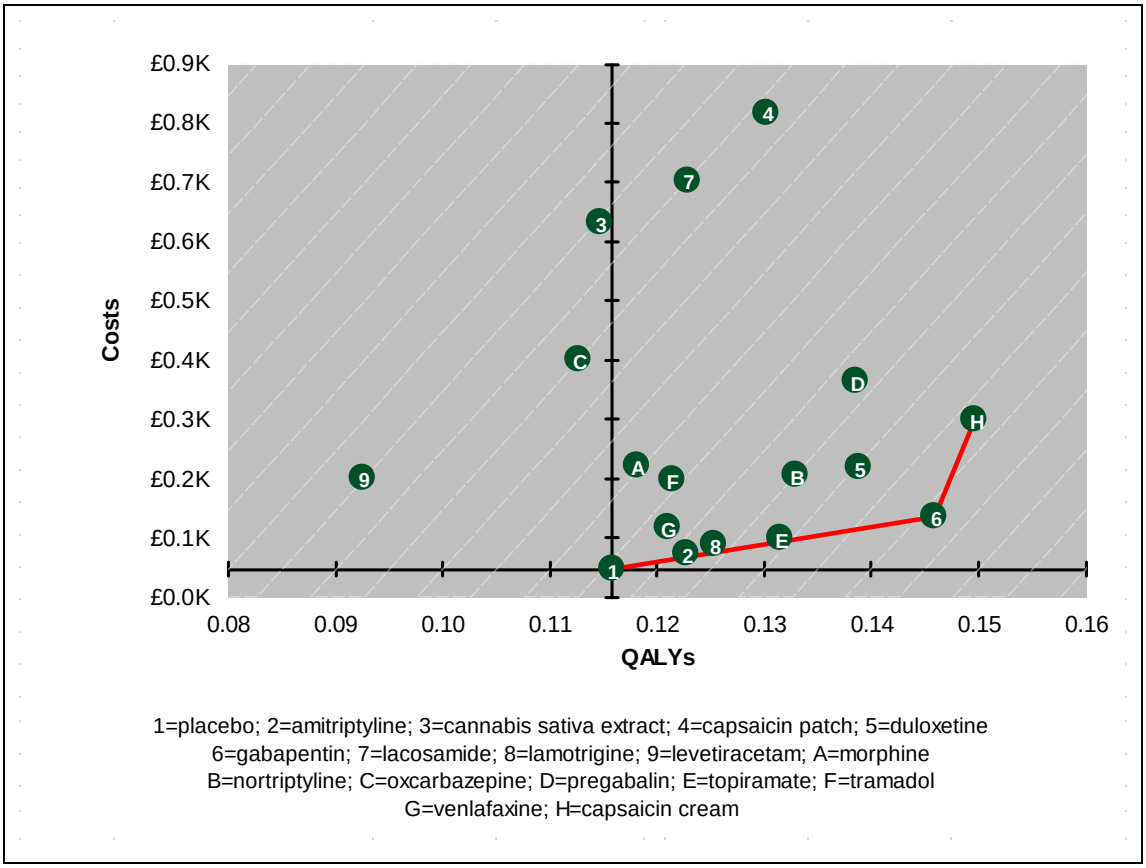


Figure 4 Health economic model – incremental mean cost–utility results (all neuropathic pain – dose-adjusted)

Probabilistic model outputs are tabulated in Table 11 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 11 Health economic model – results of probabilistic sensitivity analysis (all neuropathic pain – dose-adjusted)

Cohort	Probability of greatest net benefit	
	£20K/QALY	£30K/QALY
Topiramate	23.6%	22.5%
Capsaicin cream	22.8%	24.8%
Gabapentin	21.2%	19.9%
Nortriptyline	16.3%	16.9%
Morphine	5.6%	5.5%
Amitriptyline	2.8%	2.3%
Duloxetine	2.5%	2.6%
Venlafaxine	2.2%	1.7%
Tramadol	1.7%	1.6%
Lamotrigine	0.7%	0.3%
Cannabis sativa extract	0.4%	1.0%
Levetiracetam	0.3%	0.3%
Pregabalin	0.1%	0.3%
Capsaicin patch	0.0%	0.0%
Lacosamide	0.0%	0.0%
Oxcarbazepine	0.0%	0.0%
Placebo	0.0%	0.0%
Abbreviations: QALY, quality-adjusted life year.		

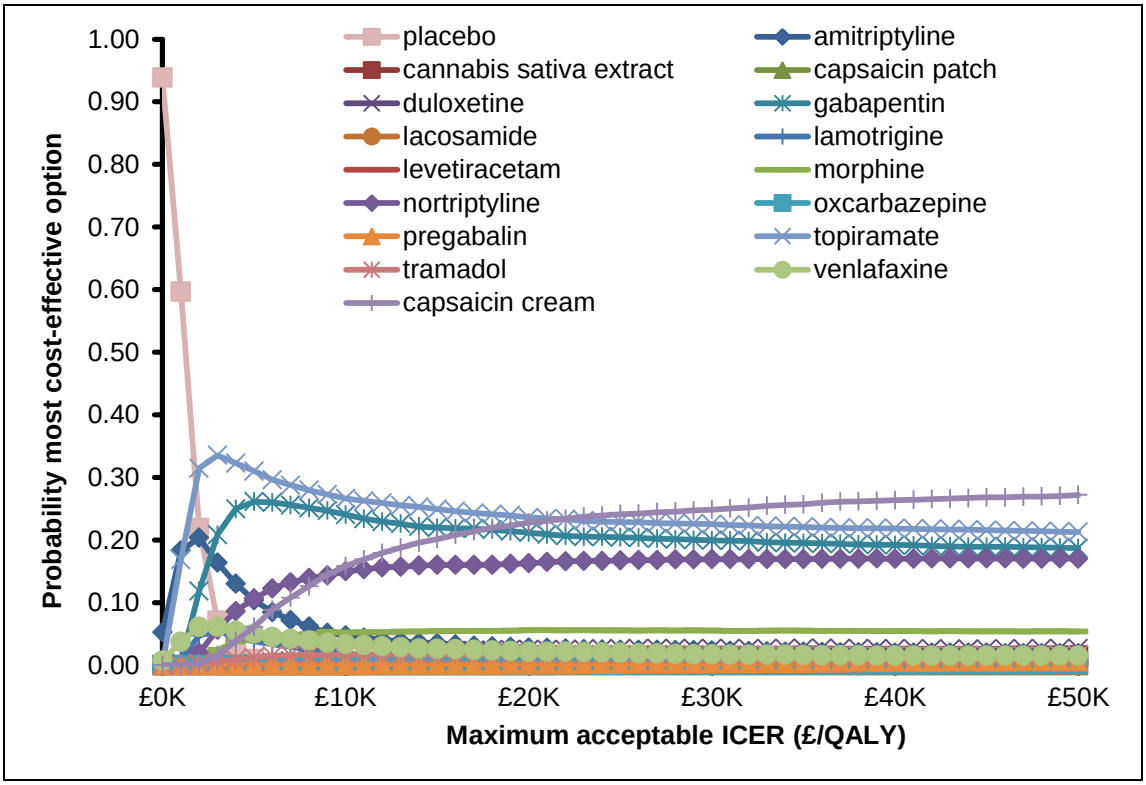


Figure 5 Health economic model – cost-effectiveness acceptability curve (all neuropathic pain – dose-adjusted)

Non-dose-adjusted effect estimates

Incremental cost–utility results, representing the mean of 5000 simulations, are presented in Table 12, with the efficiency frontier shown in Figure 6.

Table 12 Health economic model – incremental mean cost–utility results (all neuropathic pain – non-dose-adjusted)

	Absolute		Incremental			Net monetary benefit	
Cohort	**Costs**	**QALYs**	**Costs**	**QALYs**	**ICER**	**@£20K/QALY**	**@£30K/QALY**
Placebo	£46.80	0.117				£2284.40	£3450.00
Amitriptyline	£78.15	0.133	£31.35	0.017	£1887	£2585.30	£3917.02
Lamotrigine	£88.65	0.125	£10.50	−0.008	dominated	£2415.70	£3667.87
Topiramate	£118.81	0.126	£40.66	−0.008	dominated	£2391.97	£3647.36
Gabapentin	£128.32	0.134	£50.18	0.001	ext. dom.	£2556.95	£3899.59
Venlafaxine	£132.35	0.127	£54.20	−0.006	dominated	£2401.33	£3668.17
Tramadol	£193.51	0.121	£115.37	−0.013	dominated	£2217.55	£3423.09
Levetiracetam	£200.78	0.093	£122.63	−0.040	dominated	£1665.62	£2598.82
Morphine	£211.11	0.118	£132.96	−0.015	dominated	£2145.18	£3323.33
Capsaicin cream	£301.84	0.150	£223.69	0.016	£13,568	£2691.35	£4187.94
Duloxetine	£309.54	0.138	£7.70	−0.011	dominated	£2458.38	£3842.35
Pregabalin	£360.99	0.144	£59.15	−0.006	dominated	£2519.92	£3960.38
Nortriptyline	£388.84	0.131	£87.00	−0.018	dominated	£2234.49	£3546.16
Oxcarbazepine	£417.00	0.126	£115.16	−0.023	dominated	£2108.14	£3370.71
Capsaicin patch	£433.38	0.131	£131.55	−0.019	dominated	£2185.51	£3494.95
Lacosamide	£783.40	0.123	£481.56	−0.027	dominated	£1667.53	£2893.00
Cannabis extract	£1493.12	0.118	£1,191.28	−0.032	dominated	£865.29	£2044.49

Abbreviations: ext. dom., extendedly dominated; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

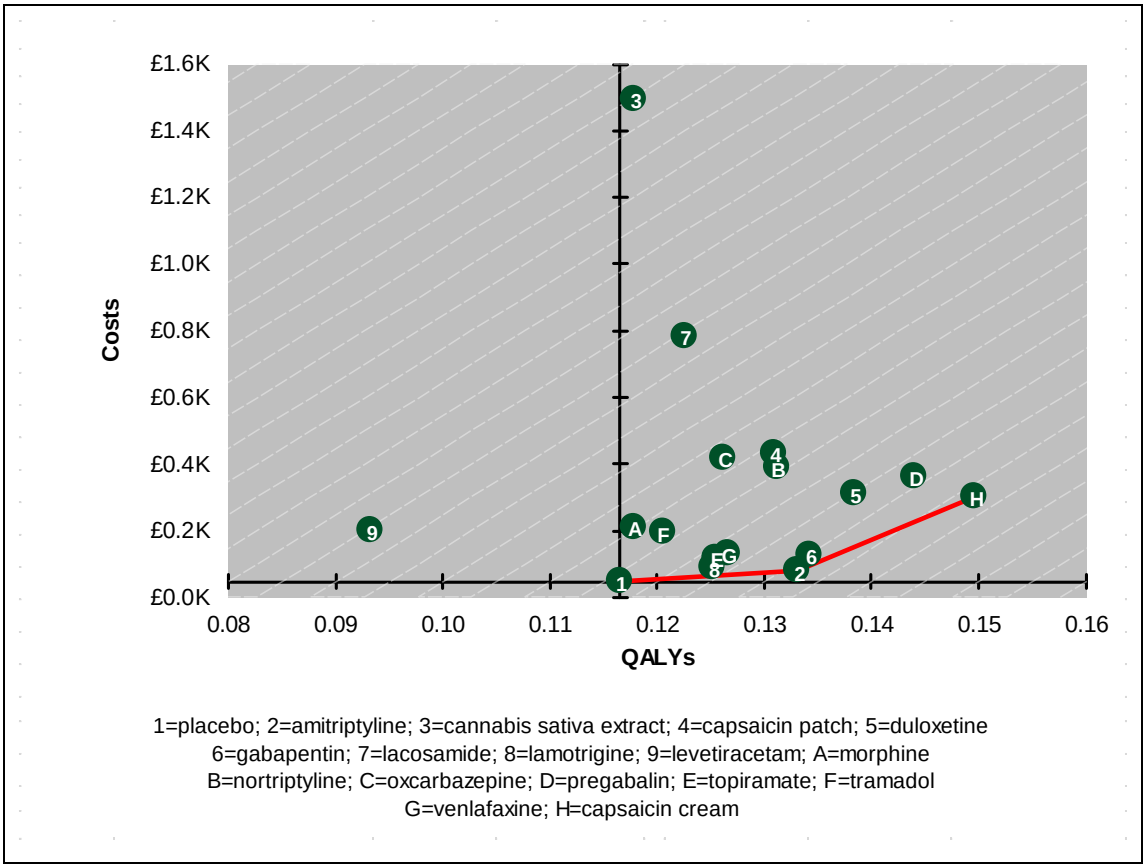


Figure 6 Health economic model – incremental mean cost–utility results (all neuropathic pain – non-dose-adjusted)

Probabilistic model outputs are tabulated in Table 13 and illustrated in Figure 7. 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 13 Health economic model – results of probabilistic sensitivity analysis (all neuropathic pain – non-dose-adjusted)

Cohort	Probability of greatest net benefit	
	£20K/QALY	£30K/QALY
Capsaicin cream	33.4%	35.4%
Amitriptyline	14.4%	11.5%
Morphine	10.9%	10.0%
Nortriptyline	10.3%	12.9%
Gabapentin	8.0%	6.7%
Venlafaxine	7.1%	6.1%
Topiramate	5.2%	4.2%
Tramadol	3.7%	3.3%
Duloxetine	2.1%	2.7%
Pregabalin	1.6%	3.5%
Oxcarbazepine	1.5%	2.5%
Lamotrigine	1.3%	0.8%
Levetiracetam	0.5%	0.4%
Placebo	0.0%	0.0%
Capsaicin patch	0.0%	0.0%
Lacosamide	0.0%	0.0%
Cannabis extract	0.0%	0.0%
Abbreviations: QALY, quality-adjusted life year.		

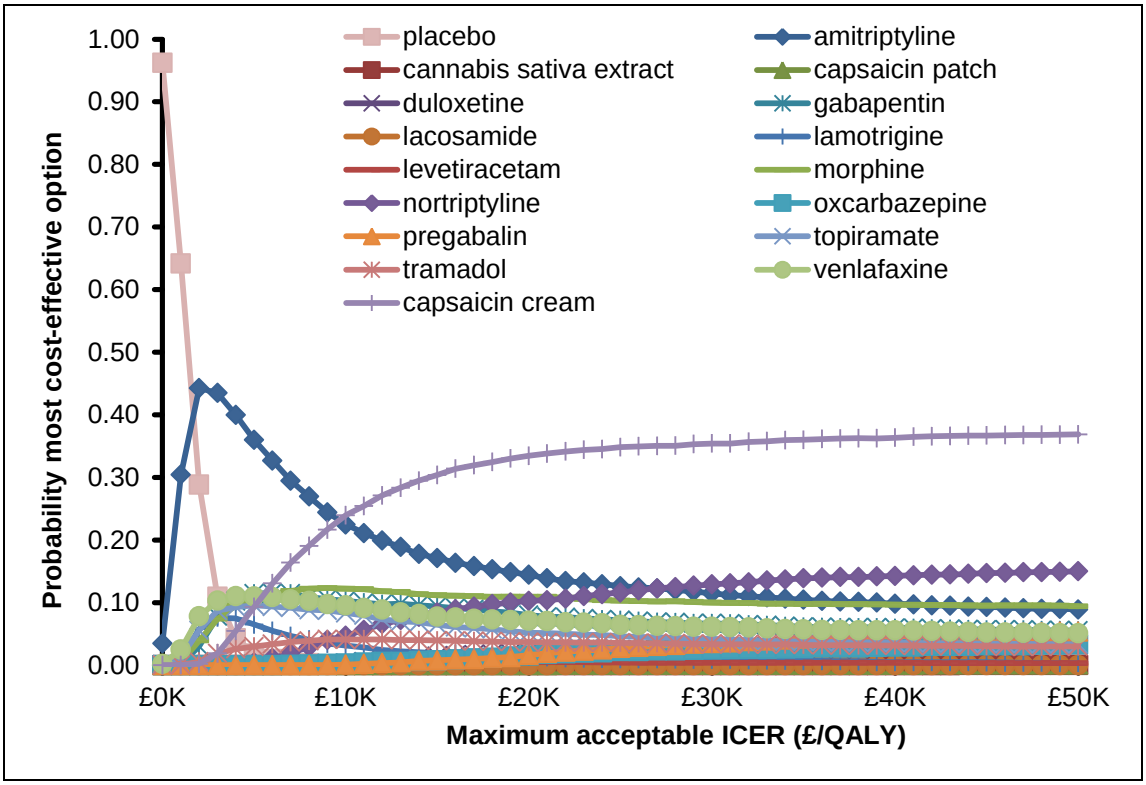


Figure 7 Health economic model – cost-effectiveness acceptability curve (all neuropathic pain – non-dose-adjusted)

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 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 a 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 they 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 3 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 clinical evidence appears consistent in demonstrating pain reduction compared with placebo. **Cannabis sativa extract** – the evidence showed that cannabis sativa does not appear to decrease pain compared with placebo. **Capsaicin cream** – there is some evidence that capsaicin cream is better than placebo at reducing pain, and 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 clinical evidence on its effectiveness appears to be more consistent than other topical treatments. **Capsaicin patch** – there is poor evidence on the efficacy of capsaicin patch at reducing pain; training in the use of the patch is also required in specialist centres. **Duloxetine** – the clinical evidence appears consistent in pain

	reduction compared with placebo. **Gabapentin** – results from 1 study showed that gabapentin did not have an effect on pain. 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 clinical evidence was 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** – there is poor evidence about the efficacy of lamotrigine and it appears to be associated with high withdrawals due to adverse effects. Specialist knowledge may be necessary as concurrent use of other medicines (especially valproate) is an important factor in using lamotrigine. **Morphine** – there is some evidence that morphine reduces pain 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** – there was some clinical evidence that showed nortriptyline is generally consistent in reducing pain compared with placebo. The GDG also commented that it is an alternative drug for people who cannot tolerate some of the adverse effects associated with amitriptyline. **Oxcarbazepine** – there is poor evidence on the efficacy of oxcarbazepine with some conflicting data; it is also associated with many adverse effects. **Pregabalin** – the clinical evidence appears consistent that pregabalin reduces pain compared with placebo. **Topiramate** – there is inconsistent evidence on the efficacy of topiramate and the GDG advised that it is also 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 clinical evidence showed that tramadol is generally consistent in reducing pain compared with placebo. However, the effect estimates were imprecise because of small numbers of patients 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** – there is inconsistent evidence on the efficacy of valproate from small studies, and it 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**, **lidocaine**, **levetiracetam**, **oxycodone**, **venlafaxine** –

	there is a lack of efficacy and/or inconsistent evidence showing that these drugs are better than placebo at reducing pain.
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. 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. **Amitriptyline** and **gabapentin** both appear to represent good value for money, with the relative cost effectiveness of the two depending on whether the model's efficacy and safety inputs are adjusted to reflect estimated dose–response effects in the underlying evidence. The GDG advised that in their experience both options can provide worthwhile pain relief depending on individual patient characteristics that are difficult to predict. As a result, the GDG recommended that either option should be offered as initial treatment. In both versions of the model, **nortriptyline**'s mean cost-per-QALY suggested it is likely to be dominated by other treatments, particularly gabapentin. However, probabilistic analysis showed that there is a greater than 10% 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. Therefore, the GDG decided that it would be helpful to add nortriptyline as an additional initial treatment option. For 2 other treatments, **duloxetine** and **pregabalin**, mean cost-per-QALY estimates from both versions of the model suggested poor value for money in comparison with less expensive treatments, particularly gabapentin (both dose-adjusted and non-dose-adjusted scenarios) and amitriptyline (non-dose-adjusted scenario only). 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. 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 models 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 5% and 10% in the dose-adjusted and non-dose-adjusted analyses respectively). 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 models 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 predicted to be more expensive and less effective than placebo (that is, no treatment). 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 had no option but 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. There was also differential usage of concomitant medications among the included studies. 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 also advised that **amitriptyline** and **nortriptyline** are off-label for treating neuropathic pain. 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 felt that further research was needed about how different aetiologies influence treatment outcomes, to inform future decision making. 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).

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3.1.5 Recommendations and research recommendations for all neuropathic pain

Recommendations

Recommendation 1.1.7

Offer a choice of amitriptyline, gabapentin or nortriptyline as initial treatment for neuropathic pain (except trigeminal neuralgia)[6]. If the initial treatment is not effective or not tolerated, offer another of these 3 treatments instead.

Recommendation 1.1.8

If initial treatment is not effective, is not tolerated or is contraindicated with all 3 of amitriptyline, gabapentin and nortriptyline, consider switching to duloxetine[7] or pregabalin.

Recommendation 1.1.9

Consider tramadol only if acute rescue therapy is needed while the person is waiting for a referral appointment.

Recommendation 1.1.10

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

Recommendation 1.1.13

Do not offer the following to treat neuropathic pain in non-specialist settings:

- cannabis sativa extract
- capsaicin patch
- lacosamide

[6] At the time of consultation (June 2013), amitriptyline and nortriptyline did not have a UK marketing authorisation for this indication, and gabapentin is licensed for peripheral neuropathic pain only. 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 medicines – guidance for doctors for further information.

[7] At the time of consultation (June 2013), duloxetine only had a UK marketing authorisation for diabetic peripheral neuropathic pain, 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 medicines – guidance for doctors for further information.

- lamotrigine
- levetiracetam
- oxcarbazepine
- topiramate
- 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

Do symptom characteristics or underlying aetiology better predict response to treatment with neuropathic agents?

Research recommendation B4

What are the key factors, including additional care and support, that influence participation[8] 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 quality of life in neuropathic pain?

[8] 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.

3.2 Peripheral neuropathic pain

3.2.1 Evidence review

Of the 116 studies included for 'all neuropathic pain', 88 studies were on peripheral neuropathic pain, with a total of 17,480 patients. These are summarised in table 14 below.

Network meta-analyses were performed for all but 2 outcomes where data were only available on 1 drug compared with placebo (for 'at least moderate improvement in patient-reported global impression of change [PGIC] at 28±7days and sleep interference on a normalised 10-point scale at 56±7 days).

The GRADE summary table for each outcome where syntheses were performed is found in table 15. 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 14 Summary of included studies for peripheral 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 (incl. 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

Study / Country / N	Design / Duration / Baseline pain	Type of pain	Condition / Concomitant treatments	Treatments	Outcomes
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
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
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) 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
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
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

Study / Country / N	Design / Duration / Baseline pain	Type of pain	Condition / Concomitant treatments	Treatments	Outcomes
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
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
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

Study / Country / N	Design / Duration / Baseline pain	Type of pain	Condition / Concomitant treatments	Treatments	Outcomes
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
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
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
Irving et al. (2012) USA N=1127	Parallel 98d Base pain: 5.70	Peripheral	Post-herpetic neuralgia Concomitant pain meds allowed	(1) capsaicin patch flexi (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

Study / Country / N	Design / Duration / Baseline pain	Type of pain	Condition / Concomitant treatments	Treatments	Outcomes
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: 84mg/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
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 (1000 mg/d) (2) placebo	Pain intensity Global improvement Study dropout Adverse event
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
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
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
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
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

Study / Country / N	Design / Duration / Baseline pain	Type of pain	Condition / Concomitant treatments	Treatments	Outcomes
Rauck et al. (2007) 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
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
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

Study / Country / N	Design / Duration / Baseline pain	Type of pain	Condition / Concomitant treatments	Treatments	Outcomes
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
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
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. (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
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
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
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

Study / Country / N	Design / Duration / Baseline pain	Type of pain	Condition / Concomitant treatments	Treatments	Outcomes
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
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
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
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

Study / Country / N	Design / Duration / Baseline pain	Type of pain	Condition / Concomitant treatments	Treatments	Outcomes
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
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 15 GRADE table summary for peripheral neuropathic pain

Outcome (follow-up)	Number of Studies	Number of patients	Interventions	Quality	Importance
PGIC – at least moderate improvement (28±7 days)	1 RCT[a]	252	pregabalin	moderate	Critical
PGIC – at least moderate improvement (56±7 days)	8 RCTs[b]	2604	capsaicin patch, gabapentin, pregabalin, valproate	Very low	Critical
PGIC – at least moderate improvement (84±14 days)	8 RCTs[c]	3157	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]	17063	23 (see appendix H)	Very low	Critical
Individual adverse events	97 RCTs[r] (3–72)	567–13838	See appendix J	Low to very low	Important
30% pain relief (28±7 days)	5 RCTs[i]	775	cannabis sativa extract, capsaicin cream, pregabalin, tramadol	Very low	Important
30% pain relief (56±7 days)	5 RCTs[j]	2247	capsaicin patch, pregabalin	Very low	Important
30% pain relief (84±14 days)	16 RCTs[k]	5487	cannabis sativa extract, capsaicin patch, duloxetine, lacosamide, lamotrigine, pregabalin, topiramate	Very low	Important
50% pain relief (28±7 days)	5 RCTs[l]	845	amitriptyline, cannabis sativa extract, pregabalin, tramadol	Very low	Important

50% pain relief (56±7 days)	8 RCTs[m]	2362	capsaicin patch, gabapentin, lamotrigine, nortriptyline, pregabalin	Very low	Important
50% pain relief (84±14 days)	15 RCTs[n]	5729	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), Irving et al. (2012), 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), Irving et al. (2012), 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); [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), Irving et al. (2012), 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. (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), 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), Irving et al. (2012), 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), Irving et al. (2012), Raskin et al. (2004), Rauck et al. (2007), Selvarajah et al. (2010), Simpson et al. (2003), 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), Irving et al. (2012), 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), Irving et al. (2012), 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; 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 network meta-analyses see appendix H and J.

Summary graphics tables

The graphics in table 16 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 on page 37.

Table 16 Summary graphics table for peripheral neuropathic pain (page 1 of 3)

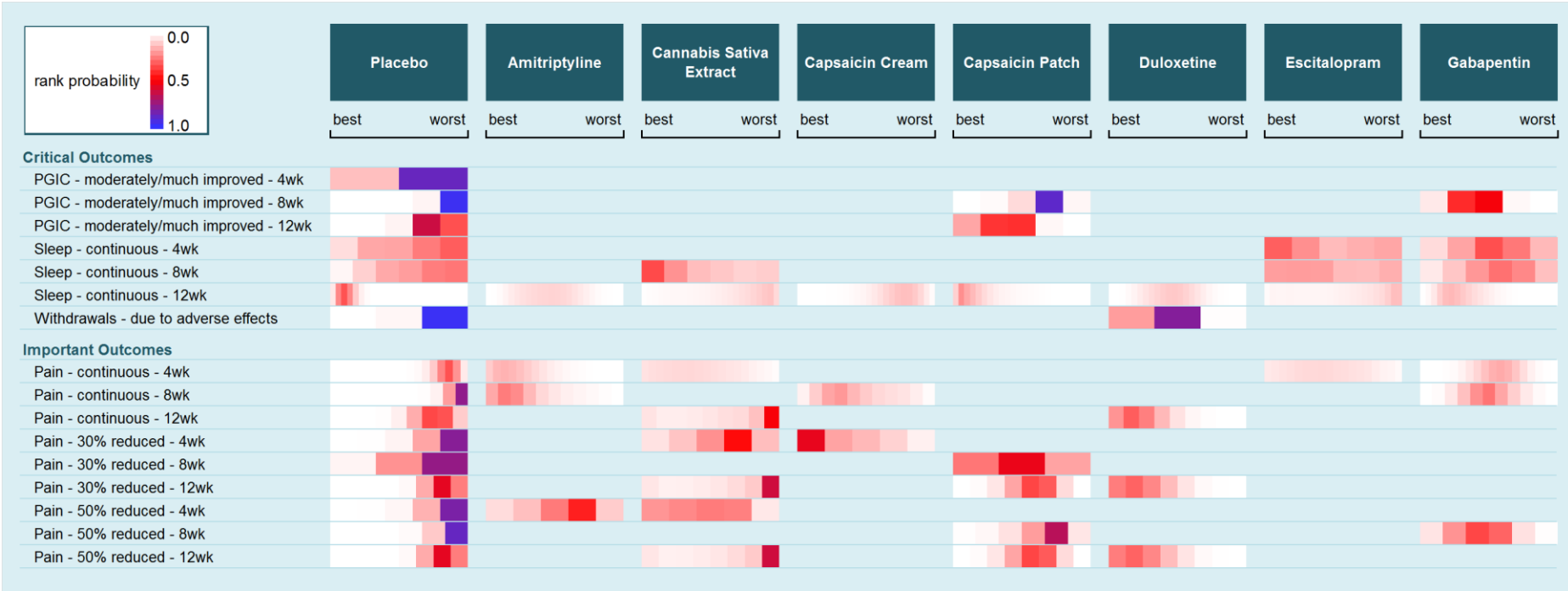

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Table 16 (continued; page 2 of 3)

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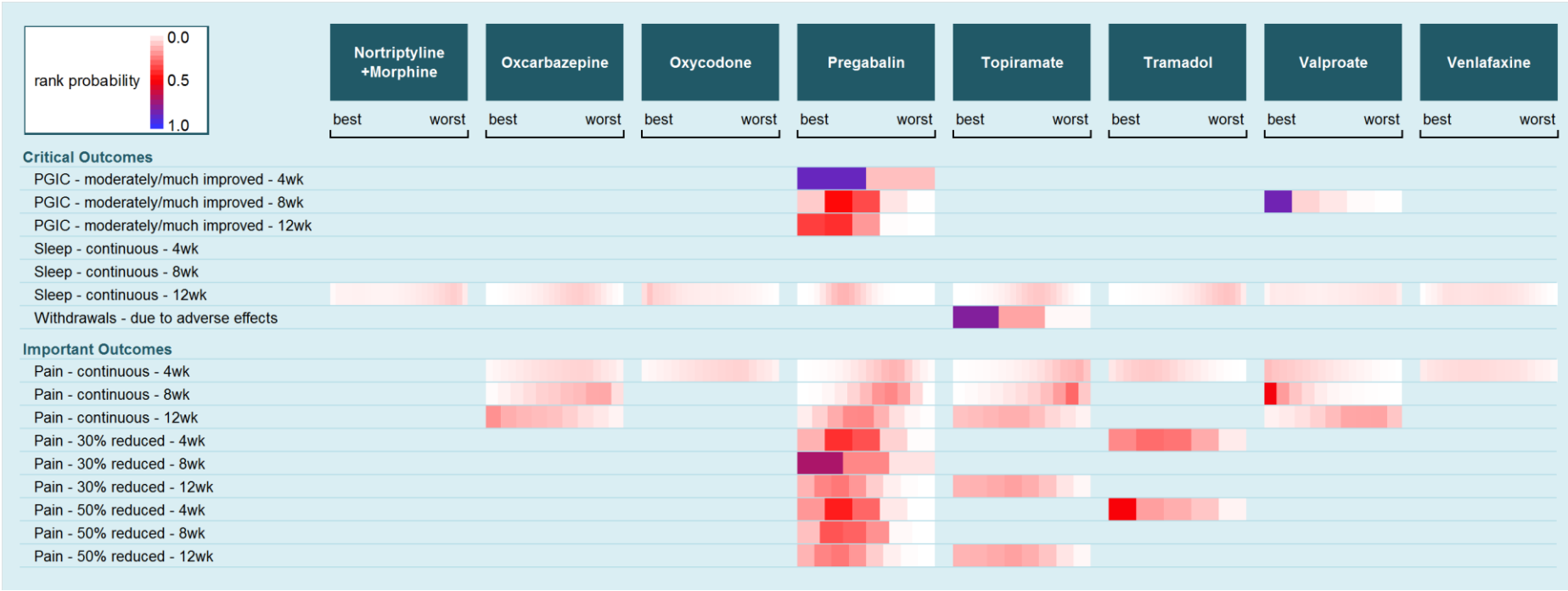
Table 16 (continued; page 3 of 3)



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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 73 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 (24 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 evidence showed consistent direction of effect estimates that duloxetine, gabapentin, and pregabalin reduce pain compared with placebo*
- *the majority of the evidence showed consistent direction of effect estimates that capsaicin cream, nortriptyline and tramadol reduce pain compared with placebo*
- *the evidence showed inconsistent directions of effect estimates on the effectiveness of valproate in reducing pain compared with placebo*
- *there is inconclusive evidence on the effectiveness of amitriptyline, capsaicin patch, gabapentin + nortriptyline, gabapentin + oxycodone, imipramine, lacosamide, lamotrigine,*

oxcarbazepine, oxycodone, topiramate or venlafaxine in reducing pain compared with placebo

- *the evidence showed consistent direction of effect estimates that cannabis sativa does not reduce pain compared with placebo.*

3.2.3 Health economic modelling

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.

Original health economic model – methods

Health economic modelling methods were identical to those described for the analysis of 'all neuropathic pain' (see section 3.1.3). Modelled treatments were also as in the model for 'all neuropathic pain', with the exception that data were not available for levetiracetam or morphine; therefore, these treatments were excluded from consideration in the peripheral-only model, leaving a total of 15 options assessed.

Model inputs: efficacy of treatments

The efficacy of the treatments was estimated in an identical manner, but on the basis of evidence derived from included randomised controlled trials in populations with solely peripheral neuropathic pain. Efficacy inputs are shown in Table 17. All other inputs (including estimates of safety parameters) were as in the full, generic evidence base.

Table 17 Health economic model – efficacy parameters (peripheral neuropathic pain)

Drug	Assumed dose	Probability (95% CrI) of pain relief after 20wk dose-adjusted			Probability (95% CrI) of pain relief after 20wk non-dose-adjusted		
		<30%	30–49%	≥50%	<30%	30–49%	≥50%
Placebo	-	0.64 (0.51,0.76)	0.14 (0.11,0.16)	0.22 (0.14,0.33)	0.64 (0.51,0.76)	0.14 (0.11,0.16)	0.22 (0.13,0.34)
Amitriptyline	50 mg/d[a]	0.61 (0.32,0.85)	0.14 (0.07,0.16)	0.24 (0.07,0.53)	0.56 (0.26,0.81)	0.15 (0.09,0.16)	0.29 (0.10,0.59)
Cannabis extract	4 sprays/d[a]	0.46 (0.18,0.77)	0.16 (0.10,0.17)	0.38 (0.12,0.69)	0.46 (0.22,0.72)	0.16 (0.11,0.17)	0.39 (0.16,0.64)
Capsaicin cream	4 apps/d[a]	0.18 (0.01,0.78)	0.12 (0.01,0.16)	0.70 (0.12,0.98)	0.18 (0.04,0.46)	0.12 (0.05,0.16)	0.69 (0.38,0.91)
Capsaicin patch	1×60-min	0.55 (0.39,0.71)	0.15 (0.12,0.16)	0.30 (0.17,0.46)	0.55 (0.39,0.69)	0.15 (0.12,0.16)	0.30 (0.18,0.44)
Duloxetine	60 mg/d[a]	0.44 (0.29,0.60)	0.16 (0.14,0.17)	0.40 (0.26,0.56)	0.43 (0.29,0.59)	0.16 (0.14,0.17)	0.41 (0.27,0.56)
Gabapentin	1800 mg/d[a]	0.42 (0.20,0.67)	0.16 (0.12,0.17)	0.42 (0.20,0.67)	0.42 (0.23,0.64)	0.16 (0.13,0.17)	0.42 (0.23,0.64)
Lacosamide	400 mg/d[a]	0.55 (0.37,0.70)	0.15 (0.12,0.17)	0.30 (0.18,0.47)	0.55 (0.38,0.71)	0.15 (0.12,0.16)	0.30 (0.17,0.46)
Lamotrigine	400 mg/d[a]	0.55 (0.39,0.72)	0.15 (0.12,0.16)	0.30 (0.16,0.45)	0.56 (0.40,0.72)	0.15 (0.12,0.17)	0.29 (0.16,0.44)
Nortriptyline	50 mg/d[a]	0.34 (0.00,1.00)	0.16 (0.00,0.16)	0.50 (0.00,1.00)	0.36 (0.10,0.71)	0.16 (0.09,0.17)	0.48 (0.17,0.81)
Oxcarbazepine	1800 mg/d[b]	0.45 (0.23,0.69)	0.16 (0.12,0.17)	0.39 (0.18,0.63)	0.45 (0.23,0.71)	0.16 (0.12,0.17)	0.39 (0.17,0.64)
Pregabalin	300 mg/d[a]	0.47 (0.31,0.58)	0.16 (0.14,0.17)	0.37 (0.27,0.53)	0.44 (0.30,0.59)	0.16 (0.14,0.17)	0.40 (0.27,0.55)
Topiramate	100 mg/d[a]	0.48 (0.00,1.00)	0.16 (0.00,0.16)	0.36 (0.00,1.00)	0.49 (0.28,0.72)	0.16 (0.12,0.17)	0.35 (0.16,0.57)
Tramadol	400 mg/d[a]	0.40 (0.23,0.71)	0.16 (0.12,0.17)	0.44 (0.17,0.64)	0.42 (0.23,0.65)	0.16 (0.13,0.17)	0.42 (0.22,0.63)
Venlafaxine	75 mg/d[a]	0.56 (0.38,0.94)	0.15 (0.03,0.16)	0.29 (0.02,0.46)	0.50 (0.29,0.71)	0.16 (0.12,0.17)	0.34 (0.17,0.56)

Abbreviations: CrI, credible interval.

[a] estimate provided by GDG

[b] GDG felt unable to comment based on own experience; weighted mean of dosages in trials contributing to evidence base used instead

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.

Original health economic model – results

Results are presented separately for the model based on dose-adjusted estimates of efficacy and safety and that based on non-dose-adjusted inputs.

Dose-adjusted effect estimates

Incremental cost–utility results, representing the mean of 5000 simulations, are presented in Table 18, with the efficiency frontier shown in Figure 8.

Table 18 Health economic model – incremental mean cost–utility results (peripheral neuropathic pain – dose-adjusted)

	Absolute		Incremental			Net monetary benefit	
Cohort	**Costs**	**QALYs**	**Costs**	**QALYs**	**ICER**	**@£20K/QALY**	**@£30K/QALY**
Placebo	£46.95	0.116				£2271.05	£3430.05
Amitriptyline	£72.98	0.114	£26.02	−0.002	dominated	£2198.16	£3333.73
Lamotrigine	£89.01	0.124	£42.05	0.008	ext. dom.	£2388.26	£3626.90
Topiramate	£98.76	0.133	£51.81	0.018	£2948	£2570.71	£3905.44
Venlafaxine	£118.37	0.120	£19.60	−0.013	dominated	£2287.68	£3490.71
Gabapentin	£136.01	0.144	£37.24	0.010	£3641	£2738.02	£4175.03
Tramadol	£196.34	0.118	£60.33	−0.026	dominated	£2165.93	£3347.06
Nortriptyline	£204.91	0.147	£68.90	0.004	ext. dom.	£2744.20	£4218.75
Duloxetine	£218.13	0.139	£82.12	−0.005	dominated	£2556.04	£3943.13
Capsaicin cream	£299.00	0.153	£162.99	0.009	£17,907	£2757.07	£4285.11
Pregabalin	£363.23	0.138	£64.23	−0.015	dominated	£2388.14	£3763.83
Oxcarbazepine	£399.74	0.113	£100.74	−0.040	dominated	£1855.60	£2983.27
Cannabis extract	£630.58	0.115	£331.59	−0.038	dominated	£1660.42	£2805.93
Lacosamide	£702.16	0.123	£403.16	−0.030	dominated	£1757.40	£2987.18
Capsaicin patch	£817.88	0.130	£518.89	−0.022	dominated	£1791.01	£3095.46

Abbreviations: ext. dom., extendedly dominated; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

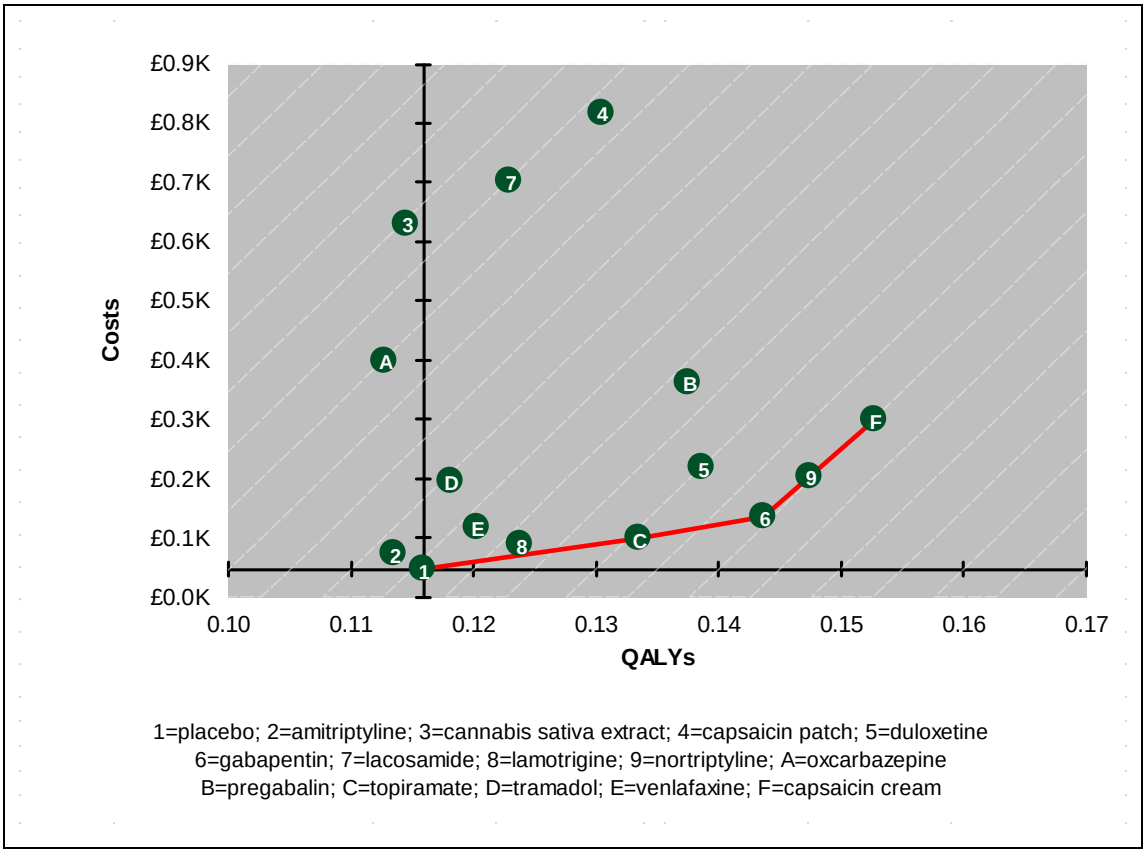


Figure 8 Health economic model – incremental mean cost–utility results (peripheral neuropathic pain – dose-adjusted)

Probabilistic model outputs are tabulated in Table 19 and illustrated in Figure 9. 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 19 Health economic model – results of probabilistic sensitivity analysis (peripheral neuropathic pain – dose-adjusted)

Cohort	Probability of greatest net benefit	
	£20K/QALY	£30K/QALY
Nortriptyline	31.7%	32.0%
Capsaicin cream	22.4%	24.8%
Topiramate	19.7%	18.6%
Gabapentin	18.9%	17.6%
Duloxetine	2.1%	2.1%
Amitriptyline	1.6%	1.3%
Venlafaxine	1.5%	1.2%
Tramadol	1.2%	1.2%
Lamotrigine	0.5%	0.3%
Cannabis sativa extract	0.2%	0.6%
Pregabalin	0.1%	0.2%
Placebo	0.0%	0.0%
Oxcarbazepine	0.0%	0.1%
Lacosamide	0.0%	0.0%
Capsaicin patch	0.0%	0.0%
Abbreviations: QALY, quality-adjusted life year.		

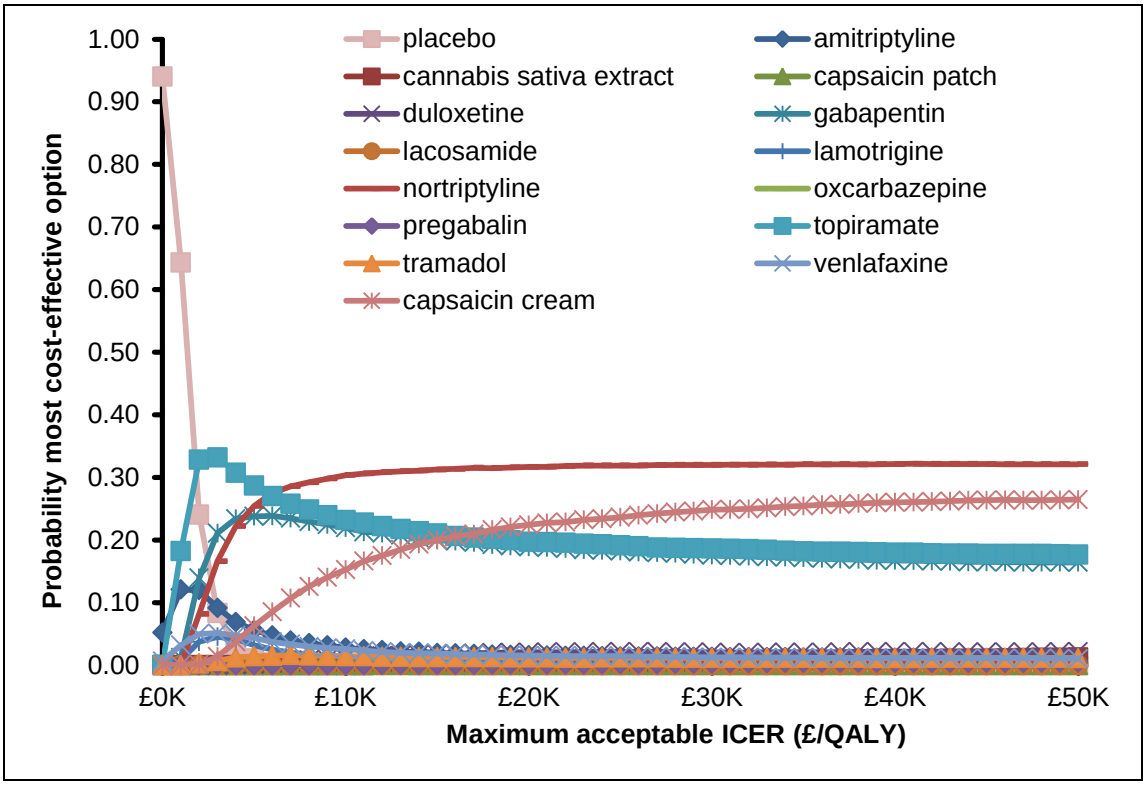


Figure 9 Health economic model – cost-effectiveness acceptability curve (peripheral neuropathic pain – dose-adjusted)

Non-dose-adjusted effect estimates

Incremental cost–utility results, representing the mean of 5000 simulations, are presented in Table 20, with the efficiency frontier shown in Figure 10.

Table 20 Health economic model – incremental mean cost–utility results (peripheral neuropathic pain – non-dose-adjusted)

	Absolute		Incremental			Net Monetary Benefit	
Cohort	**Costs**	**QALYs**	**Costs**	**QALYs**	**ICER**	**@£20K/QALY**	**@£30K/QALY**
Placebo	£46.77	0.116				£2266.03	£3422.43
Amitriptyline	£77.69	0.121	£30.91	0.005	ext. dom.	£2333.27	£3538.74
Lamotrigine	£88.63	0.124	£41.86	0.009	ext. dom.	£2394.34	£3635.83
Topiramate	£119.18	0.124	£72.41	0.009	ext. dom.	£2366.33	£3609.09
Gabapentin	£128.05	0.146	£81.27	0.030	£2684	£2790.34	£4249.54
Venlafaxine	£132.79	0.127	£4.74	−0.019	dominated	£2403.57	£3671.76
Tramadol	£193.34	0.120	£65.29	−0.026	dominated	£2201.95	£3399.59
Capsaicin cream	£300.85	0.148	£172.80	0.002	£71,291	£2666.02	£4149.45
Duloxetine	£309.69	0.138	£8.84	−0.011	dominated	£2447.04	£3825.40
Pregabalin	£360.91	0.142	£60.06	−0.007	dominated	£2474.07	£3891.55
Nortriptyline	£388.69	0.142	£87.85	−0.006	dominated	£2448.86	£3867.63
Oxcarbazepine	£418.14	0.126	£117.29	−0.022	dominated	£2106.63	£3369.02
Capsaicin patch	£433.08	0.130	£132.23	−0.019	dominated	£2162.92	£3460.91
Lacosamide	£784.06	0.122	£483.21	−0.026	dominated	£1656.16	£2876.27
Cannabis extract	£1501.00	0.117	£1200.15	−0.032	dominated	£834.71	£2002.56

Abbreviations: ext. dom., extendedly dominated; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

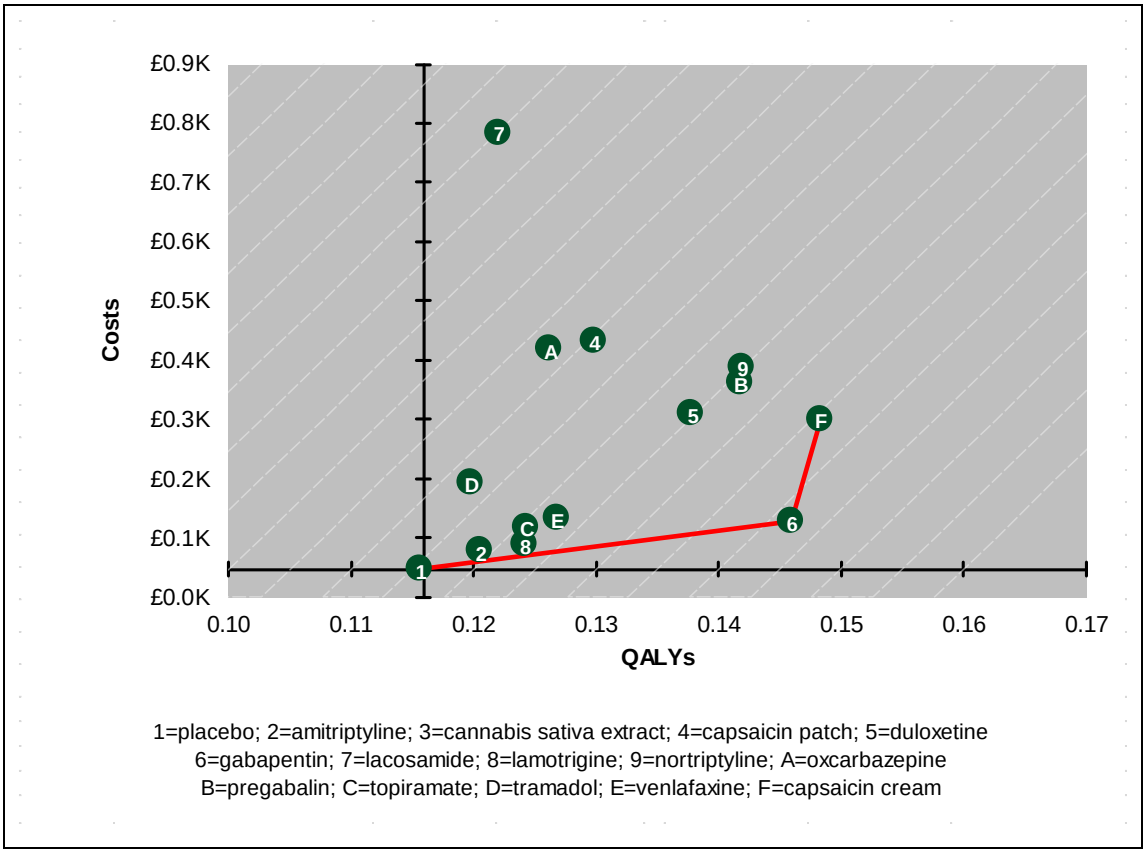


Figure 10 Health economic model – incremental mean cost–utility results (peripheral neuropathic pain – non-dose-adjusted)

Probabilistic model outputs are tabulated in Table 21 and illustrated in Figure 11. 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 21 Health economic model – results of probabilistic sensitivity analysis (peripheral neuropathic pain – non-dose-adjusted)

Cohort	Probability of greatest net benefit	
	£20K/QALY	£30K/QALY
Capsaicin cream	28.5%	30.7%
Gabapentin	28.0%	23.7%
Nortriptyline	19.9%	23.4%
Venlafaxine	6.1%	5.3%
Amitriptyline	5.9%	4.6%
Topiramate	3.9%	3.1%
Tramadol	2.9%	2.4%
Oxcarbazepine	1.5%	2.3%
Duloxetine	1.3%	2.0%
Lamotrigine	1.2%	0.7%
Pregabalin	0.9%	1.8%
Placebo	0.0%	0.0%
Capsaicin patch	0.0%	0.0%
Lacosamide	0.0%	0.0%
Cannabis sativa extract	0.0%	0.0%
Abbreviations: QALY, quality-adjusted life year.		

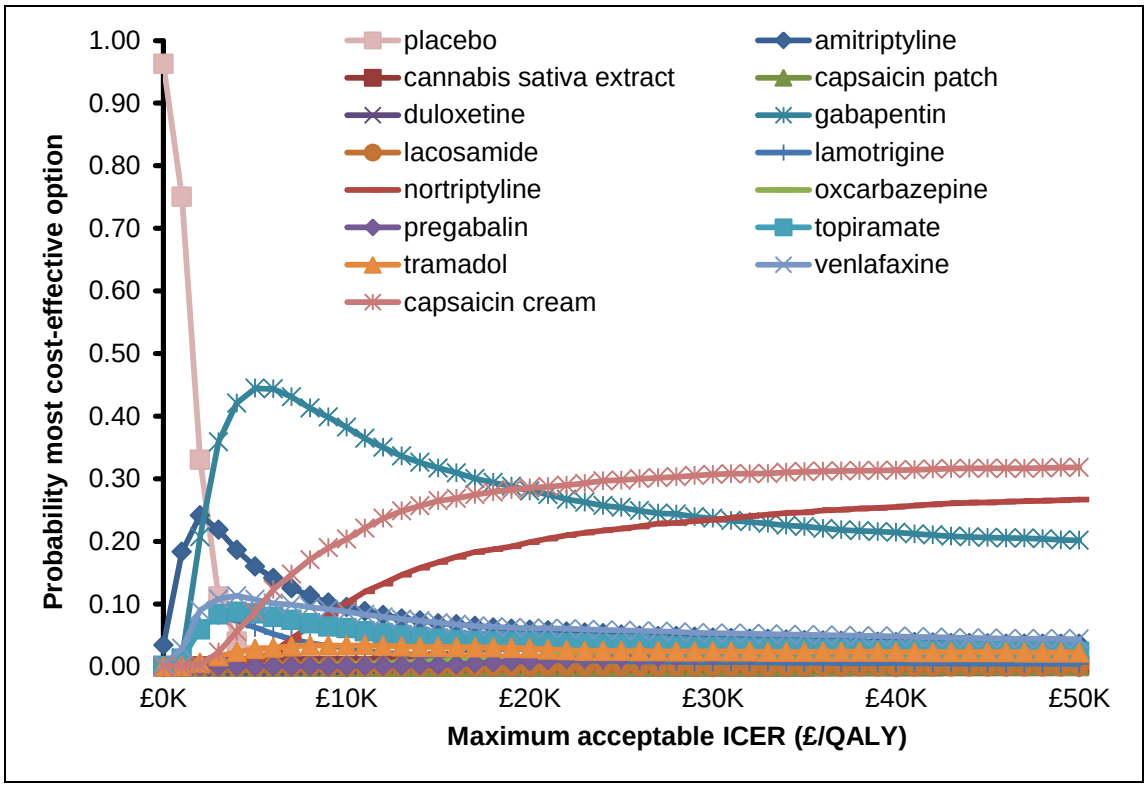


Figure 11 Health economic model – cost-effectiveness acceptability curve (peripheral neuropathic pain – non-dose-adjusted)

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 about the efficacy of amitriptyline in peripheral pain. **Gabapentin** – the evidence on its efficacy is consistent 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 evidence for the effectiveness of nortriptyline came from the same single trial that was used to inform the 'all neuropathic pain' synthesis, greater effectiveness was estimated in the peripheral-only synthesis. 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 felt that the recommendations on 'all neuropathic pain' should also apply to peripheral neuropathic pain.
Economic considerations	The health economic model for people with peripheral neuropathic pain produced results that were, on the whole, very similar to those from the model for the overarching patient population. Therefore, the GDG concluded that the recommendations on 'all neuropathic pain' should also apply to peripheral neuropathic pain. In making this decision, the GDG was mindful that the health economic model suggested that **amitriptyline** may provide poorer value for money in the peripheral-only population than in the wider 'all neuropathic pain' scenario. However, the GDG was hesitant to place too much weight on this result because it was aware that, with the exclusion of all data that did not relate to a peripheral-only patient group, the effectiveness evidence-base for amitriptyline was reduced to a single trial. The GDG also noted that, conversely, **nortriptyline** may appear more cost-effective in the peripheral-only subgroup. It understood that this result is an indirect consequence of differences in the evidence on gabapentin, the effectiveness of which is also estimated on the basis

	of a single trial, in this subpopulation. While there were concerns about the quantity and strength of evidence for amitriptyline and nortriptyline in the peripheral-only population, it was thought that any genuine subgroup effects would be unlikely to result in the cost-effectiveness of 2 structurally similar drugs moving in opposite directions: if 1 of the drugs really were better or worse in this population, it could be expected that the other would be, too. For these reasons, the GDG did not feel that cost–utility results in the peripheral-only subgroup were credibly different in a way that demanded separate recommendations.
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'.

3.2.5 Recommendations and research recommendations for peripheral neuropathic pain

Recommendations

See 'all neuropathic pain' (3.1.5).

Research recommendations

See 'all neuropathic pain' (3.1.5).

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 summarised in table 22 below. 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.

Pairwise meta-analyses were performed for most outcomes where data on only 1 intervention compared with placebo were available. 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.

The GRADE summary table for each outcome where syntheses was performed is found in table 23. 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 22 Summary of included studies for central neuropathic pain

Study / Country / N	Design / Duration / Baseline pain	Type of pain	Condition / Concomitant treatments	Treatments	Outcomes
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
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
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: 125–540mg/d) (2) placebo	Pain intensity Global improvement Function (incl. sleep) HRQoL Study dropout Adverse effects
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
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
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
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
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

Study / Country / N	Design / Duration / Baseline pain	Type of pain	Condition / Concomitant treatments	Treatments	Outcomes
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
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

1

2

Table 23 GRADE table summary for central neuropathic pain

Outcome (follow-up)	Number of Studies	Number of patients	Interventions	Quality	Importance
PGIC – at least moderate improvement (28±days)	1 RCT[a]	66	cannabis sativa extract	very low	Critical
PGIC – 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] (3–72)	567–13838	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] Backonja et al. (2008), Breuer et al. (2007), Clifford et al. (2012), Freynhagen et al. (2005), Gao et al. (2010), Irving et al. (2011), Irving et al. (2012), Raskin et al. (2004), Rauck et al. (2007), Selvarajah et al. (2010), Siddall et al. (2006), Simpson et al. (2003), 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); [h] Freynhagen et al. (2005), Gao et al. (2010), Goldstein et al. (2005), Irving et al. (2011), Irving et al. (2012), Raskin et al. (2004), Raskin et al. (2005), Satoh et al. (2011), Siddall et al. (2006); [i] Rog et al. (2005), Rossi et al. (2009), 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

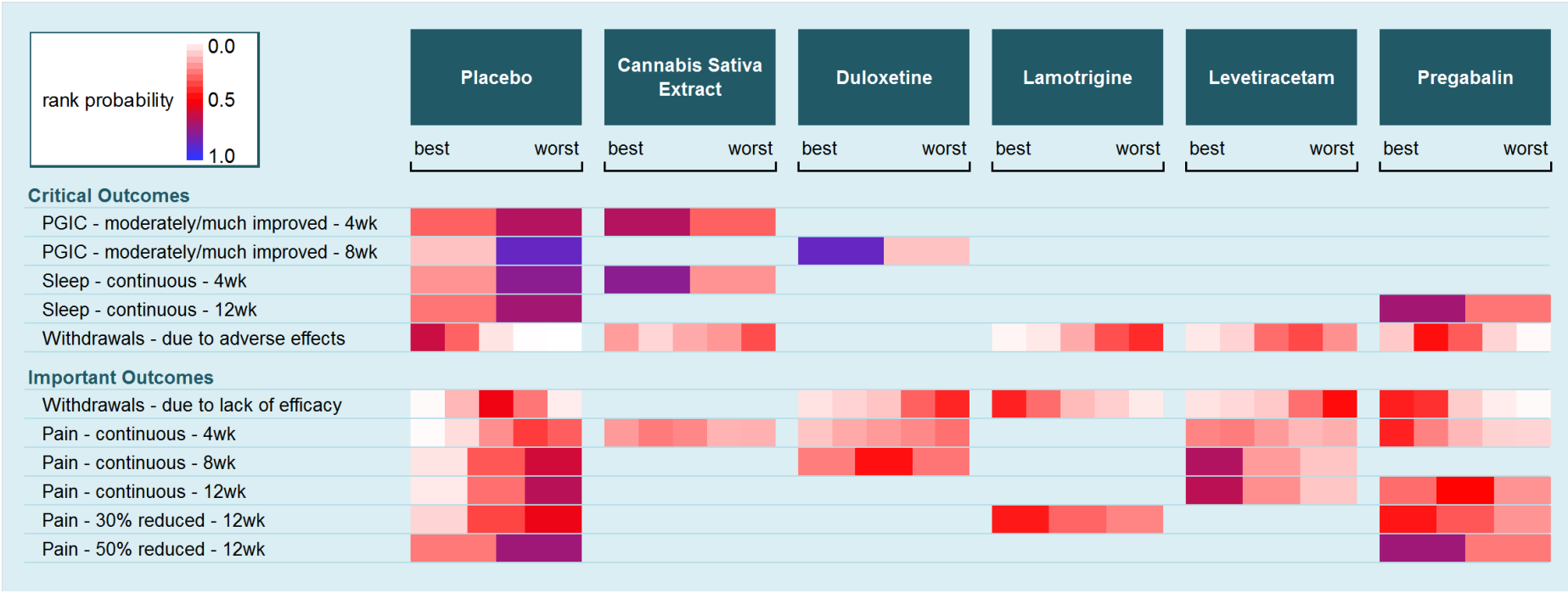
Abbreviations: NR, not reported; PGIC, patient-reported global impression of change; PICO, patient, intervention, comparator, outcome; RCT, randomised controlled trial; SSRI, selective serotonin reuptake inhibitor

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

Summary graphics tables

The graphics in table 24 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 on page 37.

Table 24 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 73 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. 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’.

3.3.5 Recommendations and research recommendations for central neuropathic pain

Recommendations

See ‘all neuropathic pain’ (3.1.5).

Research recommendations

See ‘all neuropathic pain’ (3.1.5).

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 about the lack of robust evidence on trigeminal neuralgia. The GDG 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 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 decided that there was

	insufficient evidence to make a recommendation to change current practice, and so recommended carbamazepine for trigeminal neuralgia. 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 they 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 1.1.11

Offer carbamazepine as initial treatment for trigeminal neuralgia.

Recommendation 1.1.12

If initial treatment with carbamazepine is not effective, not tolerated or is contraindicated, refer the person to a specialist. While waiting for the referral appointment, consider switching to a different neuropathic pain treatment (see recommendations 1.1.7–1.1.9).

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?

1

3.5 Key principles of care

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 felt that it was important to involve the person in agreeing a treatment plan. It is important when selecting pharmacological treatments to discuss and take into account the person's 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, self-management strategies for 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, 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 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 clear statements about drug dosage and titration in the recommendations are crucial for non-specialist settings, to emphasise the importance of titration to achieve maximum benefit and also to minimise dose-related adverse effects.
Economic considerations	The GDG agreed formal economic considerations are not necessary to support good principles of care.
Quality of evidence	The GDG agreed formal evidence review is not necessary to support good principles of care.
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.

1

3.5.2 Recommendations and research recommendations for key principles of care

Recommendations

Recommendation 1.1.1

Consider referring the person to a specialist pain service and/or a condition-specific service[9] at any stage, including at initial presentation and at the regular clinical reviews (see recommendation 1.1.5), if:

- they have severe pain **or**
- their pain significantly limits their daily activities and participation[10] **or**
- their underlying health condition has deteriorated.

Recommendation 1.1.2

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

- the underlying causes of the pain
- why a particular pharmacological treatment is being offered
- the benefits and possible adverse effects of pharmacological treatments, taking into account any comorbidities and concurrent medications
- the importance of dosage titration and the titration process (and also provide written information)
- 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).

For more information about involving people in decisions and supporting

[9] 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.

[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.

adherence, see Medicines adherence (NICE clinical guideline 76).

Recommendation 1.1.3

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

Recommendation 1.1.4

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 1.1.5

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 daily activities and participation[11]
- adverse effects **and**
- continued need for treatment.

Recommendation 1.1.6

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.

[11] 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 L 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
VAS	Visual analogue scale
VRS	Verbal rating scale

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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.

Note: these details will apply when the guideline is published.

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. Note: these details will apply when the guideline is published.

6.3.2 NICE pathway

The recommendations from this guideline have been incorporated into a NICE pathway. Note: these details will apply when the guideline is published.

6.3.3 Information for the public

NICE has produced information for the public explaining this guideline. Note: these details will apply when the guideline is published.

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

Details are correct at the time of consultation on the guideline (June 2013). 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

The Guideline Development Group

Damien Longson

Guideline Chair

Issak Bhojani

General Practitioner, Blackburn with Darwen

Brigitta Brandner

Consultant in Anaesthesia and Pain Management, University College London Hospital's Trust

Karen Cavanagh

Patient and carer member

MunSeng Chong

Consultant Neurologist, King's College Hospital's, London and The Medway Hospital, Gillingham

Marie Fallon

St Columba's Hospice Chair of Palliative Medicine, University of Edinburgh (until April 2013)

Annette Gibb

Nurse Consultant in Pain Management, Royal Berkshire NHS Foundation Trust

Paul Howard

Consultant in Palliative Medicine, Berkshire West Palliative Care Service

Charles Lane

General Practitioner, The Wirral (until March 2013)

Ammy Pui-Chi Lam

Clinical Pharmacist in Critical Care, Anaesthetics and Pain, Bart's and the London NHS Trust

Vera Neumann
Consultant and Honorary Senior Lecturer in Rehabilitation Medicine, Leeds Teaching Hospital NHS Trust and The University of Leeds

Sailesh Sankaranarayanan
Consultant Physician in Diabetes and Endocrinology, University Hospitals of Coventry and Warwickshire

Heather Wallace
Patient and carer member

Co-opted members

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

Solomon Tesfaye
Consultant Diabetologist, Royal Hallamshire Hospital, Sheffield

Internal Clinical Guidelines Programme technical team

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.

Susan Ellerby
Consultant Clinical Adviser

Nicole Elliott
Associate Director

Jasdeep Hayre
Health Economist

Michael Heath

Programme Manager

James Mahon

Health Economist (external contractor)

Stephanie Mills

Project Manager

Gabriel Rogers

Technical Adviser (Health Economics)

Heather Stegenga

Technical Analyst

Toni Tan

Technical Adviser

NICE Centre for Clinical Practice

Mark Baker

Director - Centre for Clinical Practice Director

Rachel Ryle

Guideline Commissioning Manager (until January 2013)

Clifford Middleton

Guideline Commissioning Manager (until May 2013)

Sarah Dunsdon

Guideline Commissioning Manager (from May 2013)

Laura Donegani

Guideline Coordinator (until March 2013)

Bhash Naidoo

Senior Technical Adviser (Health Economics)

Palida Teelucknavan

Guideline Coordinator (from March 2013)

Judith Thornton

Technical Lead

Sarah Palombella

Senior Medical Editor

Asma Khalik

Medical Editor

Erin Whittingham

Project Manager, Public Involvement Programme

Technical Support Unit (TSU)

Tony Ades

Professor of Public Health Science, University of Bristol

Sofia Dias

Research Fellow, University of Bristol

Sarah Davis

Senior Lecturer in Health Economics, School of Health and Related Research (ScHARR), University of Sheffield

Acknowledgements

Andrew Moore

Professor in Pain Research, Cochrane Pain, Palliative and Supportive Care Group

1 ***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	None declared	N/A	N/A
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 management. Member of BASH: British Association for Study of Headaches Member of the Association of	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

	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 and Pfizer	N/A	N/A
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 5 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 • Sodium 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
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 • Sodium 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.

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

Do symptom characteristics or underlying aetiology better predict response to treatment with neuropathic agents?

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.
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 • Sodium 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[12] and quality of life in people with neuropathic pain?

[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.

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.

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 appendices D and L for full details of how this guideline was developed.

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 Evidence syntheses for health economic model

Please see separate file for Appendix K.

Appendix L Additional details of methodology used

Please see separate file for Appendix L.