National Institute for Health and Clinical Excellence

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Neuropathic pain

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

NICE clinical guideline 96
Developed by the Centre for Clinical Practice at NICE

NICE clinical guideline 96
Neuropathic pain: the pharmacological management of neuropathic pain in adults in non-specialist settings

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National Institute for Health and Clinical Excellence

MidCity Place
71 High Holborn
London WC1V 6NA

www.nice.org.uk

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How to read this guideline

In this guideline, most of the information about the evidence is included in chapter 2. Details of which pharmacological treatments (table 2) and neuropathic pain conditions (table 3) were considered, as well as a summary of the characteristics of all included studies (table 5), are given in section 2.1.

The evidence statements (section 2.2) are the overall descriptive summary of the evidence. Each evidence statement is linked to an evidence review, which is presented as a GRADE profile (section 2.3). Each GRADE profile includes the characteristics of the evidence, the detailed results for the primary outcomes and a description of the quality of the evidence. Detailed evidence tables are included in appendix 10.9. The health economics evidence review, including a summary of a relevant Health Technology Assessment (HTA)[1] report, is described in section 2.4.

The evidence to recommendations section (section 2.5) captures all of the discussion by the Guideline Development Group (GDG) about the quality of the evidence, and outlines how the GDG reached decisions, based on the evidence or on consensus, to make specific recommendations.

The recommendations are listed both in section 1.1 (at the start of the guideline) and again in section 2.6 (towards the end of the guideline).

[1] Fox-Rushby JA, GL Griffith, JR Ross et al. (2010) The clinical and cost-effectiveness of different treatment pathways for neuropathic pain [NP]. NIHR Health Technology Assessment (HTA) programme, ref. 05/30/03. In press. Project abstract available from www.hta.ac.uk/1527

This clinical guideline updates and replaces the following recommendations on the drug treatment of painful diabetic neuropathy in previous NICE clinical guidelines:

- recommendations 1.11.5.2, 1.11.5.3, 1.11.5.4, 1.11.5.5 and 1.11.5.7 in 'Type 1 diabetes: diagnosis and management of type 1 diabetes in children, young people and adults' (NICE clinical guideline 15)
- recommendations 1.14.2.3, 1.14.2.4, 1.14.2.5 and 1.14.2.6 in 'Type 2 diabetes: the management of type 2 diabetes' (NICE clinical guideline 87).

Introduction

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

Neuropathic pain is often difficult to treat, because it is resistant to many medications and/or because of the adverse effects associated with effective medications. A number of drugs are used to manage neuropathic pain, including antidepressants, anti-epileptic (anticonvulsant) drugs, opioids and topical treatments such as capsaicin and lidocaine. Many people require treatment with more than one drug, but the correct choice of drugs, and the optimal sequence for their use, has been unclear.

Clinicians may be guided by a number of published guidelines and algorithms for the management of neuropathic pain, but these are not consistent regarding the choice of drug treatment. This may lead to variation in practice in terms of which therapy is started, how this is done, whether therapeutic doses are achieved and whether the different types of drugs are used in the

correct sequence. Furthermore, guidelines on the management of neuropathic pain rarely include considerations of cost effectiveness. An ongoing systematic review of different treatment pathways for neuropathic pain, commissioned by the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) programme and due to report in 2010[2], was used to inform this guideline where appropriate.

This clinical guideline covers the management of neuropathic pain conditions in adults (aged 18 or over) in primary care and secondary care, excluding specialist pain management clinics. The aim of the guideline is to provide clear recommendations to healthcare professionals in non-specialist settings on the treatment and management of neuropathic pain. This includes recommendations on appropriate and timely referral to specialist pain services and/or condition-specific services[3]. In general, regarding neuropathic pain as a 'blanket condition', irrespective of the underlying cause, is helpful and practical for both non-specialist healthcare professionals and patients. However, condition-specific recommendations and research recommendations have been made where robust evidence on clinical and cost effectiveness exists for specific conditions, or where the evidence is clearly uncertain. The guideline excludes acute pain arising directly (in the first 3 months) from trauma or orthopaedic surgical procedures.

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

[2] Fox-Rushby JA, GL Griffith, JR Ross et al. (2010) The clinical and cost-effectiveness of different treatment pathways for neuropathic pain [NP]. NIHR Health Technology Assessment (HTA) programme, ref. 05/30/03. In press. Project abstract available from www.hta.ac.uk/1527

[3] 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.

inform decisions made with individual patients (this includes obtaining information on special warnings, precautions for use, contraindications and adverse effects of pharmacological treatments). However, the Guideline Development Group (GDG) agreed that having clear statements on drug dosage and titration in the actual recommendations is crucial for treatment in non-specialist settings, to emphasise the importance of titration to achieve maximum benefit.

This guideline recommends some drugs for indications for which they do not have a UK marketing authorisation at the date of publication, if there is good evidence to support that use. When recommendations have been made for the use of drugs outside their licensed indications ('off-label' use), these drugs are marked with an asterisk in the recommendations. Licensed indications are listed in table 1.

Table 1 Licensed indications for recommended pharmacological treatments for neuropathic pain (March 2010)

Amitriptyline	Not licensed for neuropathic pain
Duloxetine	Licensed for painful diabetic neuropathy
Imipramine	Not licensed for neuropathic pain
Lidocaine (topical)	Licensed for post-herpetic neuralgia
Nortriptyline	Not licensed for neuropathic pain
Pregabalin	Licensed for central and peripheral neuropathic pain
Tramadol	Licensed for moderate and severe pain

Patient-centred care

This guideline offers best practice advice on the pharmacological management of neuropathic pain in adults in non-specialist settings.

Treatment and care should take into account patients' needs and preferences. People with neuropathic pain should have the opportunity to make informed decisions about their care and treatment, in partnership with their healthcare professionals. If patients do not have the capacity to make decisions, healthcare professionals should follow the Department of Health's advice on consent (available from www.dh.gov.uk/consent) and the code of practice that accompanies the Mental Capacity Act (summary available from www.publicguardian.gov.uk). In Wales, healthcare professionals should follow advice on consent from the Welsh Assembly Government (available from www.wales.nhs.uk/consent).

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

If the patient agrees, families and carers should have the opportunity to be involved in decisions about treatment and care.

Families and carers should also be given the information and support they need.

1 Summary

The 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. However, the purpose of this clinical guideline is to provide useful and practical recommendations on pharmacological management in non-specialist settings for both people with neuropathic pain and healthcare professionals.

The following definitions apply to this guideline.

- **Non-specialist settings** Primary and secondary care services that do not provide specialist pain services. Non-specialist settings include general practice, general community care and hospital care.
- **Specialist pain services** Services that provide comprehensive assessment and multi-modal management of all types of pain, including neuropathic pain.

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[4] at any stage, including at initial presentation and at the regular clinical reviews (see recommendation 1.1.9), if:

- they have severe pain **or**
- their pain significantly limits their daily activities and participation[5] **or**
- their underlying health condition has deteriorated.

1.1.2 Continue existing treatments for people whose neuropathic pain is already effectively managed[6].

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

- the benefits and possible adverse effects of each pharmacological treatment
- why a particular pharmacological treatment is being offered
- coping strategies for pain and for possible adverse effects of treatment
- that non-pharmacological treatments are also available in non-specialist settings and/or through referral to specialist services (for example, surgical treatments and psychological therapies).

[4] 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.

[5] 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.

[6] Note that there is currently no good-quality evidence on which to base specific recommendations for treating trigeminal neuralgia. The GDG expected that current routine practice will continue until new evidence is available (see also section 3.1).

1.1.4 When selecting pharmacological treatments, take into account:

- the person's vulnerability to specific adverse effects because of comorbidities
- safety considerations and contraindications as detailed in the SPC
- patient preference
- lifestyle factors (such as occupation)
- any mental health problems (such as depression and/or anxiety[7])
- any other medication the person is taking.

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

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

1.1.7 When introducing a new treatment, consider overlap with the old treatments to avoid deterioration in pain control.

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

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

- pain reduction
- adverse effects

[7] Refer if necessary to 'Anxiety' (NICE clinical guideline 22), 'Depression' (NICE clinical guideline 90) and/or 'Depression in adults with a chronic physical health problem' (NICE clinical guideline 91) (available at www.nice.org.uk).

- daily activities and participation[8] (such as ability to work and drive)
- mood (in particular, whether the person may have depression and/or anxiety[9])
- quality of sleep
- overall improvement as reported by the person.

First-line treatment

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

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

[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.

[9] Refer if necessary to 'Anxiety' (NICE clinical guideline 22), 'Depression' (NICE clinical guideline 90) and/or 'Depression in adults with a chronic physical health problem' (NICE clinical guideline 91) (available at www.nice.org.uk).

* In these recommendations, drug names are marked with an asterisk if they do not have UK marketing authorisation for the indication in question at the time of publication (March 2010). Informed consent should be obtained and documented.

1.1.11 For people with painful diabetic neuropathy, offer oral duloxetine as first-line treatment. If duloxetine is contraindicated, offer oral amitriptyline*.

- For duloxetine: start at 60 mg per day (a lower starting dose may be appropriate for some people), with upward titration to an effective dose or the person's maximum tolerated dose of no higher than 120 mg per day.
- For amitriptyline*: see recommendation 1.1.10.

1.1.12 Based on both the early and regular clinical reviews:

- if there is satisfactory improvement, continue the treatment; consider gradually reducing the dose over time if improvement is sustained
- if amitriptyline* as first-line treatment results in satisfactory pain reduction but the person cannot tolerate the adverse effects, consider oral imipramine* or nortriptyline* as an alternative.

Second-line treatment

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

- If first-line treatment was with amitriptyline* (or imipramine* or nortriptyline*), switch to or combine with oral pregabalin.
- If first-line treatment was with pregabalin, switch to or combine with oral amitriptyline* (or imipramine* or nortriptyline* as an alternative if amitriptyline* is effective but the person cannot tolerate the adverse effects; see recommendation 1.1.12).

- For people with painful diabetic neuropathy:
  - if first-line treatment was with duloxetine, switch to amitriptyline* or pregabalin, or combine with pregabalin
  - if first-line treatment was with amitriptyline*, switch to or combine with pregabalin.

Dosage and titration should be the same as in recommendation 1.1.10.

Third-line treatment

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

- refer the person to a specialist pain service and/or a condition-specific service[10] **and**
- while waiting for referral:
  - consider oral tramadol as third-line treatment instead of or in combination[11] with the second-line treatment
  - consider topical lidocaine[12] for treatment of localised pain for people who are unable to take oral medication because of medical conditions and/or disability.

1.1.15 For tramadol as monotherapy, start at 50 to 100 mg not more often than every 4 hours, with upward titration if required to an effective dose or the person's maximum tolerated dose of no higher than 400 mg per day. If tramadol is used as combination therapy, more conservative titration may be required.

[10] 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.
[11] The combination of tramadol with amitriptyline, nortriptyline, imipramine or duloxetine is associated with only a low risk of serotonin syndrome (the features of which include confusion, delirium, shivering, sweating, changes in blood pressure and myoclonus).
[12] Topical lidocaine is licensed for post-herpetic neuralgia, but not for other neuropathic pain conditions.

Other treatments

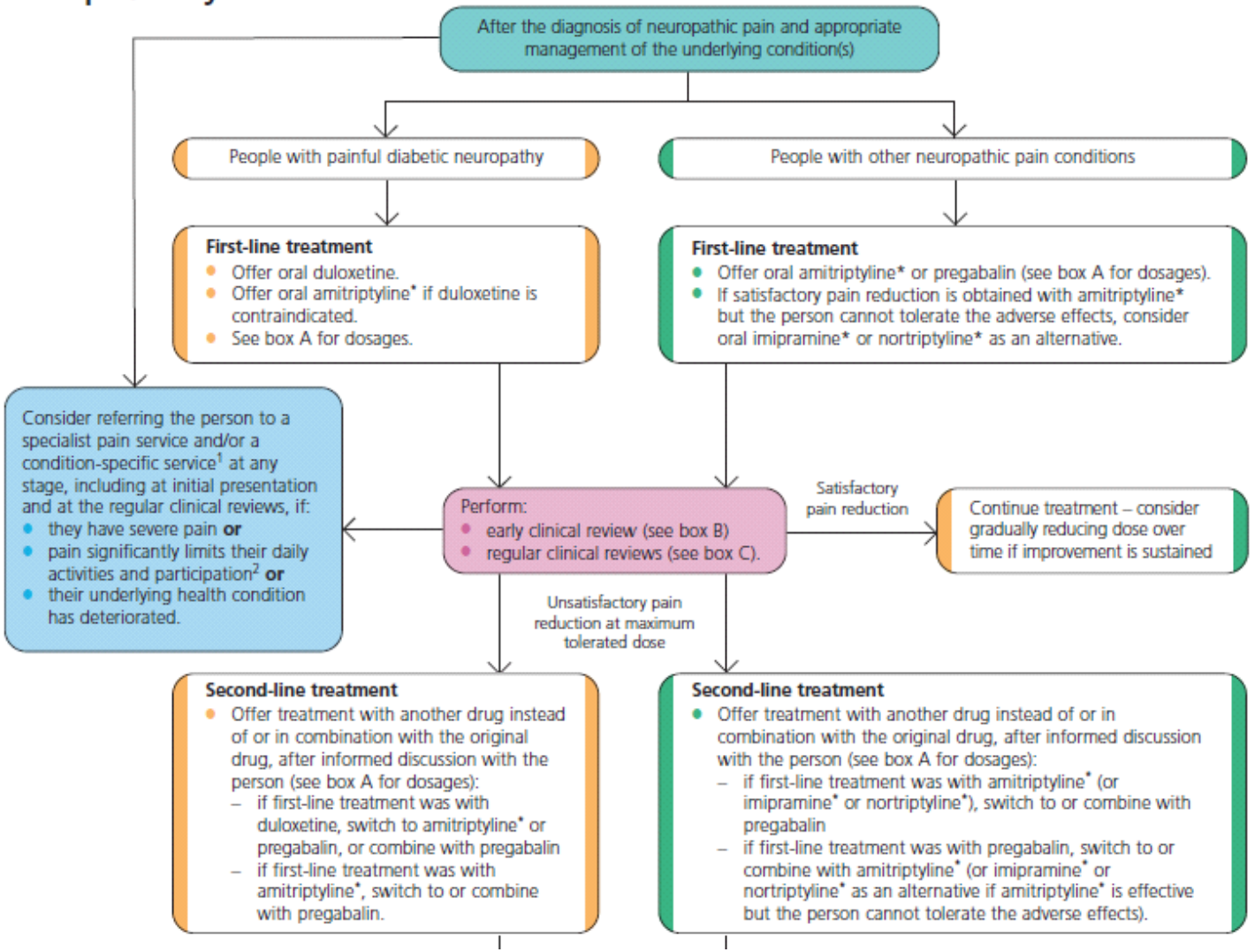
1.1.16 Do not start treatment with opioids (such as morphine or oxycodone) other than tramadol without an assessment by a specialist pain service or a condition-specific service[10].

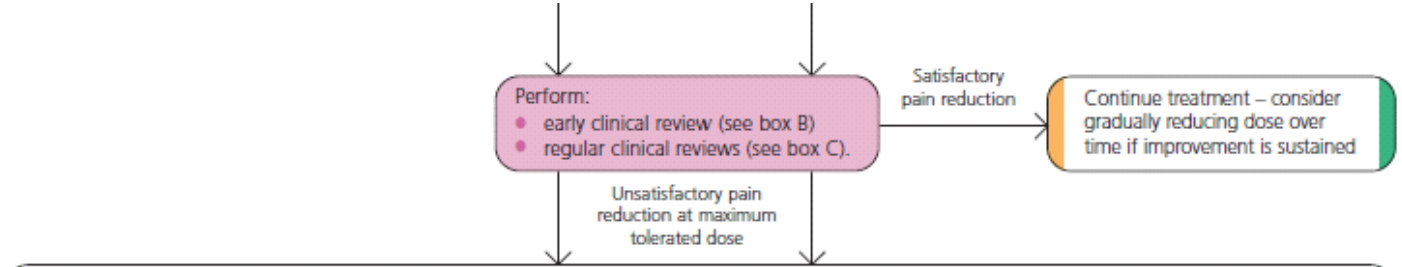
1.1.17 Pharmacological treatments other than those recommended in this guideline that are started by a specialist pain service or a condition-specific service[10] may continue to be prescribed in non-specialist settings, with a multidisciplinary care plan, local shared care agreements and careful management of adverse effects.

1.2 Care pathway

The care pathway (see next page) is reproduced from the quick reference guide for the guideline, which is available at http://www.nice.org.uk/guidance/CG96/QuickRefGuide

Care pathway





Third-line treatment

- Refer the person to a specialist pain service and/or a condition-specific service[1].
- While waiting for referral:
  - consider oral tramadol instead of or in combination[3] with second-line treatment (see box A for dosages)
  - consider topical lidocaine[4] for treatment of localised pain for people who are unable to take oral medication because of medical conditions and/or disability.

Other treatments

- Do not start treatment with opioids (such as morphine or oxycodone) other than tramadol without an assessment by a specialist pain service or a condition-specific service[1].
- Other pharmacological treatments that are started by a specialist pain service or a condition-specific service[1] may continue to be prescribed in non-specialist settings, with a multidisciplinary care plan, local shared care agreements and careful management of adverse effects.

Box A Drug dosages

- Start at a low dose, as indicated in the table.
- Titrate upwards to an effective dose or the person's maximum tolerated dose (no higher than the maximum dose listed in the table).

Drug	Starting dose	Maximum dose
Amitriptyline*	10 mg/day	75 mg/day[a]
Pregabalin	150 mg/day[b] (divided into 2 doses)	600 mg/day (divided into 2 doses)
Duloxetine	60 mg/day[b]	120 mg/day
Tramadol[c]	50–100 mg not more often than every 4 hours	400 mg/day

[a] Higher doses could be considered in consultation with a specialist pain service.
[b] A lower starting dose may be appropriate for some people.
[c] As monotherapy. More conservative titration may be required if used as combination therapy.

Box B Early clinical review

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

Box C Regular clinical reviews

Perform regular clinical reviews to assess and monitor effectiveness of chosen treatment. Include assessment of:

- pain reduction
- adverse effects
- daily activities and participation[2] (such as ability to work and drive)
- mood (in particular, possible depression and/or anxiety[5])
- quality of sleep
- overall improvement as reported by the person.

Key principles of care

- Address the person's concerns and expectations when agreeing which treatments to use by discussing:
  - benefits and possible adverse effects of each pharmacological treatment
  - why a particular pharmacological treatment is being offered
  - coping strategies for pain and for possible adverse effects of treatment
  - that non-pharmacological treatments are also available in non-specialist settings and/or through referral to specialist services (for example, surgical treatments and psychological therapies).
- When selecting pharmacological treatments, take into account:
  - the person's vulnerability to specific adverse effects because of comorbidities
  - safety considerations and contraindications as detailed in the summary of product characteristics (SPC)
  - patient preference
  - lifestyle factors (such as occupation)
  - any mental health problems (such as depression and/or anxiety[5])
  - any other medication the person is taking.
- Explain both the importance of dosage titration and the titration process – provide written information if possible.
- When withdrawing or switching treatment, taper the withdrawal regimen to take account of dosage and any discontinuation symptoms.
- When introducing a new treatment, consider overlap with old treatments to avoid deterioration in pain control.
- Continue existing treatments for people whose neuropathic pain is already effectively managed[6].

Key to terms

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

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

* Not licensed for this indication at time of publication (March 2010). Informed consent should be obtained and documented.

[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) 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] The combination of tramadol with amitriptyline, nortriptyline, imipramine or duloxetine is associated with only a low risk of serotonin syndrome (the features of which include confusion, delirium, shivering, sweating, changes in blood pressure and myoclonus).

[4] Topical lidocaine is licensed for post-herpetic neuralgia, but not for other neuropathic pain conditions (March 2010).

[5] Refer if necessary to the relevant NICE clinical guidelines (see 'Related NICE guidance' on back page).

[6] Note that there is currently no good-quality evidence on which to base specific recommendations for treating trigeminal neuralgia. The Guideline Development Group (GDG) expected that current routine practice will continue until new evidence is available.

1.3 Overview

1.3.1 Neuropathic pain

Pain is an unpleasant sensory and emotional experience that can have a significant impact on a person's quality of life, general health, psychological health, and social and economic well-being. The International Association for the Study of Pain (IASP 2007) defines neuropathic pain as follows:

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

Neuropathic pain is very challenging to manage because of the heterogeneity of its aetiologies, symptoms and underlying mechanisms (Beniczky et al. 2005). Examples of common conditions that have peripheral neuropathic pain as a symptom are painful diabetic neuropathy, post-herpetic neuralgia, trigeminal neuralgia, radicular pain, pain after surgery and neuropathic cancer pain (that is, chemotherapy-induced neuropathy and neuropathy secondary to tumour infiltration). Examples of conditions 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 and Torrance 2010). For example, the prevalence of neuropathic pain overall has been estimated at between 1% and 2%, based on summed

estimates of the prevalence in the USA (Bennett 1997) and the UK (Bowsher et al. 1991). These estimates of population prevalence came from a number of heterogeneous studies of variable validity, are likely to be inaccurate and are inconsistent. Other condition-specific studies have also mirrored the heterogeneous nature of neuropathic pain. For example, painful diabetic neuropathy is estimated to affect between 16% and 26% of people with diabetes (Jensen et al. 2006; Ziegler 2008). Prevalence estimates for post-herpetic neuralgia range from 8% to 19% of people with herpes zoster when defined as pain at 1 month after rash onset, and 8% when defined as pain at 3 months after rash onset (Schmader 2002). The development of chronic pain after surgery is also fairly common, with 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).

Currently, a number of pharmacological treatments are commonly used in the UK to manage neuropathic pain in non-specialist settings. However, there is considerable variation in practice in terms of how treatment is initiated, whether therapeutic doses are achieved and whether there is correct sequencing of therapeutic classes. This may lead to inadequate pain control, with considerable morbidity. In the context of this guideline, non-specialist settings are defined as primary and secondary care services that do not provide specialist pain services. These include general practice, general community care and hospital care. Commonly used pharmacological treatments include antidepressants (tricyclic antidepressants [TCAs], selective serotonin reuptake inhibitors [SSRIs] and serotonin–norepinephrine reuptake

inhibitors [SNRIs]), anti-epileptic (anticonvulsant) drugs (such as gabapentin, pregabalin and carbamazepine), topical treatments (such as capsaicin and lidocaine) and opioid analgesics. All of these drug classes are associated with disadvantages, as well as potential benefits. A further issue is that a number of commonly used treatments (such as amitriptyline) are unlicensed for treatment of neuropathic pain, which may limit their use by practitioners. There is also uncertainty about which drugs should be used initially (first-line treatment) for neuropathic pain, and the order (sequence) in which the drugs should be used.

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

1.3.2 Who this guideline is for

This document is intended to be relevant to healthcare professionals in non-specialist primary and secondary care settings. The target population is adults with neuropathic pain conditions. However, the guideline does not cover adults with neuropathic pain conditions who are treated in specialist pain services, or adults who have neuropathic pain in the first 3 months after trauma or orthopaedic surgical procedures.

2 How this guideline was developed

'Neuropathic pain: the pharmacological management of neuropathic pain in adults in non-specialist settings' (NICE clinical guideline 96) is a NICE short clinical guideline. For a full explanation of how this type of guideline is developed, see 'The guidelines manual' (2009) at www.nice.org.uk/GuidelinesManual

2.1 Introduction

2.1.1 Pharmacological treatments, key outcomes and analysis

Based on the guideline scope, neuropathic pain is treated as a 'blanket condition' in this guideline regardless of its aetiologies, unless there is valid and robust clinical and health economics evidence that shows the clinical efficacy and cost effectiveness of a particular treatment for a specific neuropathic pain condition.

It was agreed during the scoping workshop and consultation on the scope, and by the Guideline Development Group (GDG), to consider 34 different pharmacological treatments for neuropathic pain within the four main drug classes (antidepressants, anti-epileptics, opioid analgesics and topical treatments). These are listed in table 2. The different neuropathic pain conditions that were included in the searches are listed in table 3. Systematic literature searches were carried out to identify randomised placebo-controlled trials on these 34 different pharmacological treatments for neuropathic pain, as well as any head-to-head comparative trials and combination therapy trials.

Table 2 Pharmacological treatments considered for the clinical guideline on neuropathic pain

Drug class: subclass	Drug
Antidepressants: tricyclic antidepressants (TCAs)	Amitriptyline Clomipramine Desipramine Dosulepin (dothiepin) Doxepin Imipramine Lofepramine Nortriptyline Trimipramine
Antidepressants: selective serotonin reuptake inhibitors (SSRIs)	Citalopram Fluoxetine Paroxetine Sertraline
Antidepressants: serotonin–norepinephrine reuptake inhibitors (SNRIs)	Duloxetine Venlafaxine
Anti-epileptics (anticonvulsants)	Carbamazepine Gabapentin Lamotrigine Oxcarbazepine Phenytoin Pregabalin Sodium valproate Topiramate
Opioid analgesics	Buprenorphine Co-codamol Codeine phosphate Co-dydramol Dihydrocodeine Fentanyl Morphine Oxycodone Tramadol
Topical treatments	Topical capsaicin Topical lidocaine

Table 3 Neuropathic pain conditions (search terms) included in the searches

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

A total of 23,207 studies were retrieved by the systematic searches (antidepressants = 2781, anti-epileptics = 4757, opioid analgesics = 9612, topical capsaicin and topical lidocaine = 6057). From the 23,207 studies, 90 randomised placebo-controlled trials, 10 head-to-head comparative trials and four combination therapy trials were included, based on the inclusion and exclusion criteria suggested by the GDG through two short questionnaires[13]. The searches did not identify any placebo-controlled studies that met the inclusion and exclusion criteria for 15 of the pharmacological treatments (table 4). The 104 included studies are summarised in table 5.

[13] For the full search strategies, see appendix 10.7; for the two GDG short questionnaires on inclusion and exclusion criteria, see appendix 10.3; for the full review protocol, see appendix 10.2.

Table 4 Pharmacological treatments for which no studies met the inclusion and exclusion criteria

Drug class: subclass	Drug
Antidepressants: tricyclic antidepressants (TCAs)	Dosulepin (dothiepin) Doxepin Lofepramine Trimipramine
Antidepressants: selective serotonin reuptake inhibitors (SSRIs)	Citalopram Fluoxetine Paroxetine Sertraline
Anti-epileptics (anticonvulsants)	Phenytoin
Opioid analgesics	Buprenorphine Co-codamol Codeine phosphate Co-dydramol Dihydrocodeine Fentanyl

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

Drug class	No. of studies included	Treatment	Key outcomes
Antidepressants (TCAs)	11	Amitriptyline	30%, Global, mean pain intensity score, mean pain relief scores, AEs
Antidepressants (TCAs)	2	Desipramine	Global, AEs
Antidepressants (TCAs)	1	Nortriptyline	Global
Antidepressants (TCAs)	1	Imipramine	Global, AEs
Antidepressants (SNRIs)	3	Duloxetine	30%, 50%, AEs
Antidepressants (SNRIs)	4	Venlafaxine	50%, Global, mean pain intensity score, AEs
Subtotal	**22**		
Anti-epileptics	2	Carbamazepine	Global
Anti-epileptics	3	Oxcarbazepine	30%, 50%, Global, mean pain relief score, AEs
Anti-epileptics	3	Sodium valproate	Mean pain relief score, mean pain intensity score, AEs
Anti-epileptics	3	Topiramate	30%, 50%, Global, AEs
Anti-epileptics	10	Lamotrigine	30%, 50%, Global, AEs
Anti-epileptics	13	Gabapentin	30%, 50%, Global, mean change in pain intensity score, mean pain relief score, AEs
Anti-epileptics	12	Pregabalin	30%, 50%, Global, mean pain intensity score, AEs
Subtotal	**46**		
Opioid analgesics	4	Tramadol	50%, mean pain intensity score, AEs
Opioid analgesics	3	Morphine	30%, 50%, Global, AEs
Opioid analgesics	1	Oxycodone	Mean change in pain intensity score, AEs
Subtotal	**8**		
Topical treatments	9	Topical capsaicin	40%, 50%, Global, mean pain relief score, mean change in pain intensity score, mean change in pain relief score, AEs
Topical treatments	5	Topical lidocaine	Mean pain relief score, mean pain intensity score, mean change in pain relief score, mean change in pain intensity score, AEs

Subtotal	**14**		
TCAs vs anti-epileptics	3	Amitriptyline vs gabapentin	30%, Global, AEs, mean change in pain intensity score, mean change in pain relief score
TCAs vs anti-epileptics	1	Nortriptyline vs gabapentin	50%, mean change in pain relief score, AEs
TCAs vs anti-epileptics	1	Amitriptyline vs carbamazepine	Global, AEs
Anti-epileptics vs opioids	1	Pregabalin vs oxycodone	Mean pain intensity score, AEs
TCAs vs topical capsaicin	1	Amitriptyline vs topical capsaicin	Mean change in pain relief score, mean change in pain intensity score, AEs
Anti-epileptics vs topical lidocaine	1	Pregabalin vs topical lidocaine	30%, 50%, Global, AEs
TCAs vs TCAs	1	Amitriptyline vs nortriptyline	AEs
TCAs vs SNRIs	1	Imipramine vs venlafaxine	Global, AEs
Subtotal	**10**		
Anti-epileptics + opioids vs anti-epileptics	1	Gabapentin + oxycodone vs gabapentin	Mean pain relief score, AEs
Anti-epileptics + opioids vs anti-epileptics	1	Pregabalin + oxycodone vs pregabalin	Mean pain intensity score, AEs
Anti-epileptics + opioids vs opioids	1	Pregabalin + oxycodone vs oxycodone	Mean pain intensity score, AEs
Anti-epileptics + antidepressants vs anti-epileptics vs antidepressants	1	Gabapentin + nortriptyline vs gabapentin vs nortriptyline	Mean change in daily pain score
Subtotal	**4**		
TOTAL	**104**		

TCA = tricyclic antidepressant; SNRI = serotonin–norepinephrine reuptake inhibitor; 30% = at least 30% pain reduction; 40% = at least 40% pain reduction; 50% = at least 50% pain reduction; Global = patient-reported global improvement; AEs = adverse effects.

Analysis and synthesis

The primary outcomes for meta-analysis, based on the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) recommendations (Dworkin et al. 2005; Dworkin et al. 2008), were: at least 30% pain reduction; at least 50% pain reduction; patient-reported global improvement; and adverse effects. Specific adverse effects for each drug

class were selected by the GDG (see appendix 10.3), based on the expert knowledge and experience of GDG members (including that of patient and carer members). A fixed-effects model meta-analysis by subclass of the pharmacological treatment (for example, antidepressants: TCAs, SSRIs, SNRIs) or by individual drug of the pharmacological treatment (for example, anti-epileptics: pregabalin, gabapentin, oxcarbazepine, lamotrigine, carbamazepine, phenytoin, sodium valproate, topiramate) was carried out on the primary outcomes. Where there was significant heterogeneity, a random-effects model was adopted for the meta-analysis (for further information on methodology, see the review protocol in appendix 10.2). All results from the meta-analyses (relative risk or risk ratio [RR], absolute risk reduction [ARR], absolute risk increase [ARI], number-needed-to-treat to benefit [NNTB] and number-needed-to-treat to harm [NNTH]) are presented in GRADE profiles (for GRADE methodology, see appendix 10.9) and subsequent evidence statements. No studies were excluded on the basis of outcomes.

For the completeness of the evidence base, included studies that did not report the primary outcomes recommended by the IMMPACT recommendations (at least 30% pain reduction; at least 50% pain reduction; patient-reported global improvement; adverse effects) (Dworkin et al. 2005; Dworkin et al. 2008) were summarised in evidence tables (see appendix 10.9). Pain outcomes (other than the primary outcomes) reported in these studies are presented in GRADE profiles and evidence statements as ‘other reported pain outcomes’. The ‘other reported pain outcomes’ included mean pain relief score, mean pain intensity score, mean change in pain relief score from baseline, mean change in pain intensity score from baseline and mean change in daily pain score. Only evidence on the primary outcomes recommended by the IMMPACT recommendations (at least 30% pain reduction; at least 50% pain reduction; patient-reported global improvement; adverse effects) was used to generate recommendations. However, where evidence on the primary outcomes for particular pharmacological treatments was scarce or limited, evidence from ‘other reported pain outcomes’ was used to assist and generate discussion among the GDG to reach consensus, but not as the sole basis for making recommendations. For included studies that

did not report either primary outcomes or ‘other reported pain outcomes’, study characteristics were summarised in the evidence tables for information (see the evidence tables in appendix 10.9 for full information on each included study).

2.1.2 Health economics

No health economic modelling was undertaken for this guideline because there was a relevant health technology assessment (HTA) monograph in development to which the GDG had been given access (Fox-Rushby JA, Griffith GL, Ross JR et al. [2010] The clinical and cost-effectiveness of different treatment pathways for neuropathic pain [NP]. NIHR Health Technology Assessment [HTA] programme, ref. 05/30/03. In press. Project abstract available from www.hta.ac.uk/1527). The GDG reviewed, appraised and summarised the HTA report, and the results of the economic analyses from the HTA report informed this guideline as appropriate.

The HTA report focused on two neuropathic pain populations: people with post-herpetic neuralgia (PHN) and people with painful diabetic neuropathy (PDN). A systematic review of the economic evidence was also performed as part of the evidence review for this guideline. A systematic search found a total of 2273 papers. Full details on the search strategy can be found in appendix 10.7.

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

2.1.3 Summaries of included studies

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

Author	Study period	Condition	Treatment (oral)	Titration or fixed dosage (mg/day)	Mean dose (mg/day)	Key outcomes
Bowsher (1997)	3 months	PHN	Amitriptyline	25	NR	N/A
Graff-Radford et al. (2000)	8 weeks	PHN	Amitriptyline	12.5–200	NR	Mean pain intensity score, AEs
Max et al. (1988)	6 weeks	PHN	Amitriptyline	12.5–150	65	Global, AEs
Cardenas et al. (2002)	6 weeks	SCI	Amitriptyline	10–125	**50	Mean pain intensity score, AEs
Rintala et al. (2007)	8 weeks	SCI	Amitriptyline	150	150	30%, AEs
Kalso et al. (1996)	4 weeks	NP cancer	Amitriptyline	5–100	93.3	AEs
Kautio et al. (2008)	8 weeks	NP cancer	Amitriptyline	10–50	46.2	Global, AEs
Kieburtz et al. (1998)	9 weeks	HIV-RN	Amitriptyline	25–100	NR	Global, AEs
Leijon and Boivie (1989)	4 weeks	PSP	Amitriptyline	25–75	75	Global
Robinson et al. (2004)	6 weeks	PhanLP	Amitriptyline	10–125	NR	Mean pain relief score, AEs
Vrethem et al. (1997)	4 weeks	Poly	Amitriptyline	25–75	NR	30%, Global, AEs
Kishore-Kumar et al. (1990)	6 weeks	PHN	Desipramine	12.5–250	167	Global, AEs
Max et al. (1991)	6 weeks	PDN	Desipramine	12.5–250	201	Global, AEs
Khoromi et al. (2007)	7 weeks	Radi	Nortriptyline	25–100	84	Global
Sindrup et al. (2003)	4 weeks	Poly	Imipramine	50–150	NR	Global, AEs
Goldstein et al. (2005)	12 weeks	PDN	Duloxetine	20, 60, 120	N/A	50%, AEs
Raskin et al. (2005)	12 weeks	PDN	Duloxetine	60, 120	N/A	50%, AEs
Wernicke et al. (2006)	12 weeks	PDN	Duloxetine	60, 120	N/A	30%, 50%, AEs
Rowbotham et al. (2004)	6 weeks	PDN	Venlafaxine	75, 150–225	N/A	50%, AEs
Sindrup et al. (2003)	4 weeks	Poly	Venlafaxine	75–225	NR	Global, AEs
Tasmuth et al. (2002)	4 weeks	NP cancer	Venlafaxine	18.75–75	n/a	AEs
Yucel et al. (2005)	8 weeks	Mixed NP	Venlafaxine	75, 150	N/A	Global, AEs

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

Table 7 Characteristics of included studies: anti-epileptics (placebo-controlled trials)

Author	Study period	Condition	Treatment (oral)	Titration or fixed dosage (mg/day)	Key outcomes
Leijon and Boivie (1989)	4 weeks	PSP	Carbamazepine	200–800	Global
Nicol (1969)	46 months	Mixed NP	Carbamazepine	100–2400	Global
Beydoun et al. (2006)	16 weeks	PDN	Oxcarbazepine	to 600	Global, AEs
Dogra et al. (2005)	16 weeks	PDN	Oxcarbazepine	300–1800	30%, 50%, Global, AEs
Grosskopf et al. (2006)	16 weeks	PDN	Oxcarbazepine	300–600	Mean pain relief score, AEs
Agrawal et al. (2009)	3 months	PDN	Sodium valproate	20 per kg	Mean pain intensity score, AEs
Kochar et al.(2002)	4 weeks	PDN	Sodium valproate	1200	AEs
Kochar et al. (2004)	3 months	PDN	Sodium valproate	500	Mean pain relief score, AEs
Raskin et al. (2004)	12 weeks	PDN	Topiramate	25–400	30%, 50%, Global, AEs
Thienel et al. (2004)	22 weeks	PDN	Topiramate	100, 200, 400	AEs
Khoromi et al. (2005)	6 weeks	Radi	Topiramate	50–400	Global, AEs
Eisenberg et al. (2001)	8 weeks	PDN	Lamotrigine	25–400	50%, Global, AEs
Luria et al. (2000)	8 weeks	PDN	Lamotrigine	25–400	50%, AEs
Vinik et al. (2007)	19 weeks	PDN	Lamotrigine	200, 300, 400	30%, 50%, AEs
Simpson et al. (2000)	14 weeks	HIV-RN	Lamotrigine	50–300	AEs
Simpson et al. (2003)	12 weeks	HIV-RN	Lamotrigine	25–400	Global, AEs
Breuer et al. (2007)	11 weeks	MS-NP	Lamotrigine	25–400	30%, AEs
Finnerup et al. (2002)	9 weeks	SCI	Lamotrigine	25–400	AEs
McCleane (1999)	8 weeks	Mixed NP	Lamotrigine	25–200	AEs
Rao et al. (2008)	10 weeks	NP cancer	Lamotrigine	25–300	AEs
Vestergaard et al. (2001)	8 weeks	PSP	Lamotrigine	200	AEs

Author	Study period	Condition	Treatment (oral)	Titration or fixed dosage (mg/day)	Key outcomes
Backonja et al. (1998)	8 weeks	PDN	Gabapentin	to 3600	Global, AEs
Simpson (2001)	8 weeks	PDN	Gabapentin	to 3600	Global, AEs
Rice and Maton (2001)	7 weeks	PHN	Gabapentin	1800, 2400	50%, Global, AEs
Rowbotham et al. (1998)	8 weeks	PHN	Gabapentin	to 3600	Global, AEs
Bone et al. (2002)	6 weeks	PhanLP	Gabapentin	300–2400	Mean change in pain intensity score, AEs
Nikolajsen et al. (2006)	30 days	PhanLP	Gabapentin	300–2400	AEs
Smith et al. (2005)	6 weeks	PhanLP	Gabapentin	300–3600	Global
Levendoglu et al. (2004)	8 weeks	SCI	Gabapentin	900–3600	Mean pain relief score, AEs
Rintala et al. (2007)	8 weeks	SCI	Gabapentin	to 3600	30%, AEs
Gordh et al. (2008)	5 weeks	NP-NI	Gabapentin	300–2400	Global, AEs
Hahn et al. (2004)	4 weeks	HIV-RN	Gabapentin	400–2400	AEs
Rao et al. (2007)	6 weeks	NP cancer	Gabapentin	300–2700	AEs
Serpell (2002)	8 weeks	Mixed NP	Gabapentin	900–2400	50%, Global, AEs
Arezzo et al.(2008)	13 weeks	PDN	Pregabalin	to 600	Mean pain intensity score, AEs
Lesser et al. (2004)	5 weeks	PDN	Pregabalin	to 75, 300, 600	30%, 50%, Global, AEs
Richter et al. (2005)	6 weeks	PDN	Pregabalin	25–150, 100–600	50%, AEs
Rosenstock et al. (2004)	8 weeks	PDN	Pregabalin	300	50%, AEs
Tölle et al. (2008)	12 weeks	PDN	Pregabalin	150, 300, 300/600	50%, Global, AEs
Dworkin et al.(2003)	8 weeks	PHN	Pregabalin	150–600	30%, 50%, AEs
Sabatowski et al. (2004)	8 weeks	PHN	Pregabalin	150, 300	50%, Global, AEs
Stacey et al. (2008)	4 weeks	PHN	Pregabalin	150–600, 600	30%, 50%, AEs
van Seventer et al. (2006)	13 weeks	PHN	Pregabalin	150, 300, 600	30%, 50%, Global, AEs
Freynhagen et al. (2005)	12 weeks	PDN, PHN	Pregabalin	150–600, 300–600	30%, 50%, Global, AEs
Siddall et al. (2006)	12 weeks	SCI	Pregabalin	150–600	30%, 50%, AEs
Vranken et al.(2008)	4 weeks	CenP	Pregabalin	150–600	AEs

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

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

Author	Study period	Condition	Treatment (oral)	Titration or fixed dosage (mg/day)	Key outcomes
Arbaiza and Vidal (2007)	6 weeks	NP cancer	Tramadol	**68.75	Mean pain intensity score, AEs
Boureau et al. (2003)	6 weeks	PHN	Tramadol	100–400	50%
Sindrup et al. (2003)	6 weeks	Poly	Tramadol	100–400	Mean pain intensity score, AEs
Harati et al. (1998)	4 weeks	PDN	Tramadol	200–400	Mean pain intensity score, AEs
Huse et al. (2001)	4 weeks	PhanLP	Morphine	70–300	50%
Khoromi et al. (2007)	6 weeks	Radi	Morphine	15–180	Global, AEs
Wu et al. (2008)	7 weeks	PhanLP	Morphine	15–90	30%, 50%, AEs
Gimbel et al. (2003)	6 weeks	PDN	Oxycodone	10–120	Mean change in pain intensity score, AEs

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

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

Author	Study period	Condition	Treatment (topical)	Titration or fixed dosage (times/day)	Key outcomes
Bernstein et al. (1989)	6 weeks	PHN	Capsaicin	0.075% cream, 3 to 4	40%, AEs
Watson et al. (1993)	6 weeks	PHN	Capsaicin	0.075% cream, 4	Mean change in pain relief score, AEs
Donofrio et al. (1991)	8 weeks	PDN or Radi	Capsaicin	0.075% cream, 4	Mean pain relief score, mean change in pain intensity score, AEs
Scheffler et al. (1991)	8 weeks	PDN	Capsaicin	0.075% cream, 4	Mean pain relief score, mean change in pain intensity score, AEs
Tandan et al. (1992)	8 weeks	PDN	Capsaicin	0.075% cream, 4	Global, AEs
Low et al. (1995)	8 weeks	Poly	Capsaicin	0.075% cream, 4	Mean pain intensity score, AEs
McCleane (2000)	4 weeks	Mixed NP	Capsaicin	0.025% cream, 3	Mean change in pain intensity score
Paice et al. (2000)	4 weeks	HIV-RN	Capsaicin	0.075% cream, 4	AEs
Watson and Evans (1992)	6 weeks	NP cancer	Capsaicin	0.075% cream, 4	50%, AEs
Galer et al. (2002)	3 weeks	PHN	Lidocaine	5% patch, 1	Mean change in pain relief score
Meier et al. (2003)	1 week	Peri NP	Lidocaine	5% patch, up to 4 patches for 12 hours/day	Mean change in pain intensity score, AEs
Ho et al. (2008)	1 week	Mixed NP	Lidocaine	5% cream, 2	Mean change in pain intensity score, AEs
Cheville et al. (2009)	4 weeks	PS-NP	Lidocaine	5% patch, up to 3 patches for 18 hours/day	Mean pain intensity score
Estanislao et al. (2004)	2 weeks	HIV-RN	Lidocaine	5% gel, 1	Mean pain relief score

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

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

Author	Study period	Condition	T1	T2	Titration or fixed dosage (mg/day)	Key outcomes
Cross-class head-to-head comparison						
TCAs vs anti-epileptics						
Morello et al. (1999)	6 weeks	PDN	Amitriptyline	Gabapentin	Ami: 25–75 Gaba: 900–1800	Global, mean change in pain intensity score, AEs
Rintala et al. (2007)	8 weeks	SCI	Amitriptyline	Gabapentin	Ami: max 150 Gaba: max 3600	30%, AEs
Dallocchio et al. (2000)	12 weeks	PDN	Amitriptyline	Gabapentin	Ami: 10–90 Gaba: 400–2400	Mean change in pain relief score, AEs
Chandra et al. (2006)	9 weeks	PHN	Nortriptyline	Gabapentin	Nort: 50–100 Gaba: 900–2700	50%, Mean change in pain relief score, AEs
Leijon and Boivie (1989)	4 weeks	PSP	Amitriptyline	Carbamazepine	Ami: 25–75 Carba: 200–800	Global, AEs
Anti-epileptics vs opioids						
Gatti et al. (2009)	3 months	Mixed NP	Pregabalin	Oxycodone	Pre: 85.6 to max Oxy: 24.1 to max	Mean pain intensity score, AEs
TCAs vs topical capsaicin						
Biesbroeck et al. (1995)	8 weeks	PDN	Amitriptyline	Topical capsaicin	Ami: 25–125 Cap: 0.075% cream, 4 times/day	Mean change in pain relief score, mean change in pain intensity score, AEs
Anti-epileptics vs topical lidocaine						
Baron et al. (2009)	4 weeks	PDN PHN	Pregabalin	Topical lidocaine	Pre: 150-600 5% Lido: 3–4 patches up to 12 hours/day	30%, 50%, Global, AEs
Within-class head-to-head comparison						
TCAs vs TCAs						
Watson et al. (1998)	5 weeks	PHN	Amitriptyline	Nortriptyline	Ami: 20 to max Nort: 20 to max	AEs
TCAs vs SNRIs						
Sindrup et al. (2003)	4 weeks	Poly	Imipramine	Venlafaxine	Imi: 50–150 Ven: 75–225	Global, AEs
Combination therapy						
Anti-epileptics + opioids vs anti-epileptics						
Hanna et al.(2008)	12 weeks	PDN	Gabapentin + oxycodone	Gabapentin	Gaba: 600–1800 Oxy: 5–80	Mean pain relief score, AEs
Gatti et al. (2009)	3 months	Mixed NP	Pregabalin + oxycodone	Pregabalin	Combination: Pre 108.1 + Oxy 19.4 Pre: 85.6 to max	Mean pain intensity score, AEs
Anti-epileptics + opioids vs opioids						

Author	Study period	Condition	T1	T2	Titration or fixed dosage (mg/day)	Key outcomes
Gatti et al. (2009)	3 months	Mixed NP	Pregabalin + oxycodone	Oxycodone	Combination: Pre 108.1 + Oxy 19.4 Oxy: 24.1 to max	Mean pain intensity score, AEs
Anti-epileptics + antidepressants vs anti-epileptics vs antidepressants						
Gilron et al. (2009)	6 weeks	PDN, PHN	Gabapentin + nortriptyline	Gabapentin	Combination: Gaba 3600 + Nort 100 Gaba: 3600	Mean change in daily pain score
Gilron et al. (2009)	6 weeks	PDN, PHN	Gabapentin + nortriptyline	Nortriptyline	Combination: Gaba 3600 + Nort 100 Nort: 100	Mean change in daily pain score
T1 = treatment 1; T2 = treatment 2; PHN = post-herpetic neuralgia; PDN = painful diabetic neuropathy; Mixed NP = mixed neuropathic pain; PSP = post-stroke pain; Poly = polyneuropathy; SCI = spinal cord injury; Ami = amitriptyline; Gaba = gabapentin; Nort = nortriptyline; Carba = carbamazepine; Pre = pregabalin; Oxy = oxycodone; Cap = topical capsaicin; Lido = topical lidocaine; Imi = imipramine; Ven = venlafaxine; Global = patient-reported global improvement; 30% = at least 30% pain reduction; 50% = at least 50% pain reduction; AEs = adverse effects.						

2.2 Evidence statements

2.2.1 Antidepressants (see table 6)

Primary outcomes

TCAs (as monotherapy – placebo-controlled trials)

For evidence relating to the following evidence statements, see table 11 (GRADE profiles).

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

Outcomes on pain

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

Adverse effects

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

- Patients receiving TCAs were significantly more likely to report dry mouth (moderate-quality evidence) and sedation (low-quality evidence) compared with patients receiving placebo.
- For incidences of blurred vision, dizziness, vomiting and gastrointestinal disturbances, there were no significant differences between patients receiving TCAs and patients receiving placebo (low-quality evidence).
- Patients receiving TCAs were significantly more likely to report any adverse effects (non-specified) compared with patients receiving placebo (high-quality evidence).

Lofepramine, trimipramine, dothiepin and doxepin (as monotherapy – placebo-controlled trials)

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

SSRIs (as monotherapy – placebo-controlled trials)

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

SNRIs (as monotherapy – placebo-controlled trials)

For evidence relating to the following evidence statements, see table 12 (GRADE profiles).

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

Outcomes on pain

- Patients receiving SNRIs were significantly more likely to report at least 30% pain reduction (duloxetine) and at least 50% pain reduction (duloxetine and venlafaxine) (moderate-to-high-quality evidence).
- The number of patients reporting global improvement was not significantly different between patients receiving venlafaxine and patients receiving placebo (moderate-quality evidence).

Adverse effects

- Patients receiving SNRIs were significantly more likely to withdraw from treatment because of adverse effects compared with patients receiving placebo (moderate-quality evidence).
- For incidences of dry mouth and gastrointestinal disturbances, there were no significant differences between patients receiving SNRIs and patients receiving placebo (low-quality evidence).
- For incidences of blurred vision and vomiting, there were no significant differences between patients receiving SNRIs and patients receiving placebo (very-low-quality evidence).
- For the incidence of any adverse effects (non-specified), there was no significant difference between patients receiving SNRIs and patients receiving placebo (very-low-quality evidence).

Other reported pain outcomes

For evidence relating to the following evidence statements, see table 13 (GRADE profiles).

For mean pain intensity scores:

- There was conflicting low-quality evidence on the efficacy of amitriptyline in reducing pain intensity scores.
- There was no significant difference in pain intensity scores between patients receiving venlafaxine and patients receiving placebo (low-quality evidence).

For mean pain relief scores:

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

2.2.2 Anti-epileptics (see table 7)

Primary outcomes

Gabapentin (as monotherapy – placebo-controlled trials)

For evidence relating to the following evidence statements, see table 14 (GRADE profiles).

Outcomes on pain

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

Adverse effects

- Patients receiving gabapentin were significantly more likely to withdraw from treatment because of adverse effects compared with patients receiving placebo (moderate-quality evidence).
- Patients receiving gabapentin were significantly more likely to report dizziness, somnolence (moderate-quality evidence) and fatigue (low-quality evidence) compared with patients receiving placebo.
- For incidences of sedation and gait disturbances, there were no significant differences between patients receiving gabapentin and patients receiving placebo (very-low-quality evidence).
- Patients receiving gabapentin were significantly more likely to report any adverse effects (non-specified) compared with patients receiving placebo (high-quality evidence).

Pregabalin (as monotherapy – placebo-controlled trials)

For evidence relating to the following evidence statements, see table 15 (GRADE profiles).

Outcomes on pain

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

Adverse effects

- Patients receiving pregabalin were significantly more likely to withdraw from treatment because of adverse effects compared with patients receiving placebo (high-quality evidence).
- Patients receiving pregabalin were significantly more likely to report dizziness, somnolence (high-quality evidence), weight gain and gait disturbances (low-quality evidence) compared with patients receiving placebo.
- For the incidence of fatigue, there was no significant difference between patients receiving pregabalin and patients receiving placebo (very-low-quality evidence).
- Patients receiving pregabalin were significantly more likely to report any adverse effects (non-specified) compared with patients receiving placebo (moderate-quality evidence).

Lamotrigine (as monotherapy – placebo-controlled trials)

For evidence relating to the following evidence statements, see table 16 (GRADE profiles).

Outcomes on pain

- The numbers of patients reporting at least 30% pain reduction and at least 50% pain reduction were not significantly different between patients receiving lamotrigine and patients receiving placebo (moderate-quality evidence).
- Patients receiving lamotrigine were significantly more likely to report global improvement compared with patients receiving placebo (moderate-quality evidence).

Adverse effects

- Patients receiving lamotrigine were significantly more likely to withdraw from treatment because of adverse effects compared with patients receiving placebo (moderate-quality evidence).
- For incidences of dizziness, fatigue (low-quality evidence) and sedation (very-low-quality evidence), there were no significant differences between patients receiving lamotrigine and patients receiving placebo.
- For the incidence of any adverse effects (non-specified), there was no significant difference between patients receiving lamotrigine and patients receiving placebo (high-quality evidence).

Oxcarbazepine (as monotherapy – placebo-controlled trials)

For evidence relating to the following evidence statements, see table 17 (GRADE profiles).

Outcomes on pain

- Patients receiving oxcarbazepine were significantly more likely to report at least 30% pain reduction and at least 50% pain reduction compared with patients receiving placebo (moderate-quality evidence).
- The number of patients reporting global improvement was not significantly different between patients receiving oxcarbazepine and patients receiving placebo (moderate-quality evidence).

Adverse effects

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

Topiramate (as monotherapy – placebo-controlled trials)

For evidence relating to the following evidence statements, see table 18 (GRADE profiles).

Outcomes on pain

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

Adverse effects

- Patients receiving topiramate were significantly more likely to withdraw from treatment because of adverse effects compared with patients receiving placebo (high-quality evidence).
- Patients receiving topiramate were significantly more likely to report somnolence, fatigue (moderate-quality evidence) and sedation (very-low-quality evidence) compared with patients receiving placebo.
- For the incidence of dizziness, there was no significant difference between patients receiving topiramate and patients receiving placebo (very-low-quality evidence).

Carbamazepine (as monotherapy – placebo-controlled trials)

For evidence relating to the following evidence statements, see table 19 (GRADE profiles).

Outcomes on pain

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

Adverse effects

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

Sodium valproate (as monotherapy – placebo-controlled trials)

For evidence relating to the following evidence statements, see table 20 (GRADE profiles).

Outcomes on pain

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

Adverse effects

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

Phenytoin

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

Other reported pain outcomes

For evidence relating to the following evidence statements, see table 21 (GRADE profiles).

For sodium valproate:

- There was conflicting low-quality evidence on the efficacy of sodium valproate in relation to pain intensity scores and pain relief scores.

For pregabalin:

- Pain intensity scores for patients receiving pregabalin were significantly lower than those for patients receiving placebo (low-quality evidence).

For gabapentin:

- The mean change in pain intensity score from baseline was significantly greater for patients receiving gabapentin than for patients receiving placebo (low-quality evidence).

For oxcarbazepine:

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

2.2.3 Opioids (see table 8)

Primary outcomes

Morphine (as monotherapy – placebo-controlled trials)

For evidence relating to the following evidence statements, see table 22 (GRADE profiles).

Outcomes on pain

- Patients receiving morphine were significantly more likely to report at least 30% pain reduction and at least 50% pain reduction compared with patients receiving placebo (moderate-quality evidence).
- The number of patients reporting global improvement was not significantly different between patients receiving morphine and patients receiving placebo (moderate-quality evidence).

Adverse effects

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

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

Tramadol (as monotherapy – placebo-controlled trials)

For evidence relating to the following evidence statements, see table 23 (GRADE profiles).

Outcomes on pain

- Patients receiving tramadol were significantly more likely to report at least 50% pain reduction compared with patients receiving placebo (moderate-quality evidence).

Adverse effects

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

Oxycodone (as monotherapy – placebo-controlled trials)

For evidence relating to the following evidence statements, see table 24 (GRADE profiles).

Outcomes on pain

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

Adverse effects

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

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

Co-codamol, co-dydramol, dihydrocodeine, buprenorphine, fentanyl and codeine phosphate (as monotherapy – placebo-controlled trials)

- No studies on co-codamol, co-dydramol, dihydrocodeine, buprenorphine, fentanyl or codeine phosphate met the inclusion and exclusion criteria. Therefore there was no appropriate evidence that co-codamol, co-dydramol, dihydrocodeine, buprenorphine, fentanyl or codeine phosphate is clinically effective in treating neuropathic pain.

Other reported pain outcomes

For evidence relating to the following evidence statements, see table 25 (GRADE profiles).

For tramadol:

- Pain intensity scores and pain relief scores for patients receiving tramadol were significantly lower than those for patients receiving placebo (low-quality evidence).

For oxycodone:

- The mean change in pain intensity score from baseline for patients receiving oxycodone was significantly greater than that for patients receiving placebo (low-quality evidence).

2.2.4 Topical treatments (see table 9)

Primary outcomes

Topical capsaicin (as monotherapy – placebo-controlled trials)

For evidence relating to the following evidence statements, see table 26 (GRADE profiles).

Outcomes on pain

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

Adverse effects

- Patients receiving topical capsaicin were significantly more likely to withdraw from treatment because of adverse effects compared with patients receiving placebo (low-quality evidence).
- Patients receiving topical capsaicin were significantly more likely to report a burning sensation compared with patients receiving placebo (high-quality evidence).
- For the incidence of skin irritation, there was no significant difference between patients receiving topical capsaicin and patients receiving placebo (very-low-quality evidence).

Topical lidocaine (as monotherapy – placebo-controlled trials)

For evidence relating to the following evidence statements, see table 27 (GRADE profiles).

Outcomes on pain

- No studies on topical lidocaine were identified that reported the primary outcomes on pain.

Adverse effects

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

Other reported pain outcomes

Topical capsaicin (as monotherapy – placebo-controlled trials)

For evidence relating to the following evidence statements, see table 28 (GRADE profiles).

- There was conflicting low-quality evidence on the efficacy of topical capsaicin in reducing mean pain intensity scores.
- The mean change in pain intensity score from baseline was significantly greater for patients receiving topical capsaicin than for patients receiving placebo (low-quality evidence).

Topical lidocaine (as monotherapy – placebo-controlled trials)

For evidence relating to the following evidence statements, see table 29 (GRADE profiles).

- There were no significant differences in pain intensity scores and pain relief scores between patients receiving topical lidocaine and patients receiving placebo (low-quality evidence).
- There was conflicting low-quality evidence on the efficacy of topical lidocaine in reducing pain intensity scores from baseline.
- The mean change in pain relief score from baseline was significantly greater for patients receiving topical lidocaine than for patients receiving placebo (low-quality evidence).

2.2.5 Comparative trials and combination therapy (see table 10)

Cross-class comparative trials

Amitriptyline (TCA) compared with gabapentin (anti-epileptic)

Primary outcomes

For evidence relating to the following evidence statements, see table 30 (GRADE profiles).

Outcomes on pain

- Patients receiving amitriptyline were significantly more likely to report at least 30% pain reduction compared with patients receiving gabapentin (moderate-quality evidence).
- The number of patients reporting global improvement was not significantly different between patients receiving amitriptyline and patients receiving gabapentin (moderate-quality evidence).

Adverse effects

- For the incidence of withdrawal from treatment because of adverse effects, there was no significant difference between patients receiving amitriptyline and patients receiving gabapentin (low-quality evidence).
- For incidences of dry mouth, dizziness, blurred vision, sedation, fatigue and weight gain, there were no significant differences between patients receiving amitriptyline and patients receiving gabapentin (very-low-quality evidence).
- For the incidence of any adverse effects (non-specified), there was no significant difference between patients receiving amitriptyline and patients receiving gabapentin (very-low-quality evidence).

Other reported pain outcomes

For evidence relating to the following evidence statements, see table 31 (GRADE profiles).

- The mean change in pain relief score from baseline was significantly greater for patients receiving gabapentin than for patients receiving amitriptyline (very-low-quality evidence).

Nortriptyline (TCA) compared with gabapentin (anti-epileptic)

Primary outcomes

For evidence relating to the following evidence statements, see table 32 (GRADE profiles).

Outcomes on pain

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

Adverse effects

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

Amitriptyline (TCA) compared with carbamazepine (anti-epileptic)

Primary outcomes

For evidence relating to the following evidence statements, see table 33 (GRADE profiles).

Outcomes on pain

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

Adverse effects

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

Pregabalin (anti-epileptic) compared with oxycodone (opioid analgesic)

Primary outcomes

For evidence relating to the following evidence statements, see table 34 (GRADE profiles)

Outcomes on pain

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

Adverse effects

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

Pregabalin (anti-epileptic) compared with topical lidocaine

Primary outcomes

For evidence relating to the following evidence statements, see table 35 (GRADE profiles).

Outcomes on pain

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

Adverse effects

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

Amitriptyline (TCA) compared with topical capsaicin

Primary outcomes

For evidence relating to the following evidence statements, see table 36 (GRADE profiles).

Outcomes on pain

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

Adverse effects

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

Other reported pain outcomes

For evidence relating to the following evidence statements, see table 37 (GRADE profiles).

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

Within-class comparative trials

Imipramine (TCA) compared with venlafaxine (SNRI)

Primary outcomes

For evidence relating to the following evidence statements, see table 38 (GRADE profiles).

Outcomes on pain

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

Adverse effects

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

Amitriptyline (TCA) compared with nortriptyline (TCA)

Primary outcomes

For evidence relating to the following evidence statements, see table 39 (GRADE profiles).

Outcomes on pain

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

Adverse effects

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

Combination therapy

Pregabalin plus oxycodone (combination) compared with pregabalin alone (anti-epileptics)

Primary outcomes

For evidence relating to the following evidence statements, see table 40 (GRADE profiles).

Outcomes on pain

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

Adverse effects

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

Gabapentin plus oxycodone (combination) compared with gabapentin alone (anti-epileptics)

Primary outcomes

For evidence relating to the following evidence statements, see table 41 (GRADE profiles).

Outcomes on pain

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

Adverse effects

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

Other reported pain outcomes

For evidence relating to the following evidence statements, see table 42 (GRADE profiles).

- The mean change in pain relief score from baseline was significantly greater for patients receiving gabapentin plus oxycodone than for patients receiving gabapentin alone (low-quality evidence).

Pregabalin plus oxycodone (combination) compared with oxycodone alone (opioid analgesic)

Primary outcomes

For evidence relating to the following evidence statements, see table 43 (GRADE profiles).

Outcomes on pain

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

Adverse effects

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

Gabapentin plus nortriptyline (combination) compared with gabapentin alone and nortriptyline alone

Other reported pain outcomes

For evidence relating to the following evidence statements, see table 44 (GRADE profiles).

- The mean change in daily pain score was significantly greater for patients receiving gabapentin plus nortriptyline than for patients receiving gabapentin alone (low-quality evidence).
- The mean change in daily pain score was significantly greater for patients receiving gabapentin plus nortriptyline than for patients receiving nortriptyline alone (low-quality evidence).

2.2.6 Health economics evidence statements

For patients with painful diabetic neuropathy:

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

- One high-quality study concluded that amitriptyline is less cost effective than duloxetine, but its cost effectiveness is similar to that of pregabalin at a willingness to pay (WTP) threshold of between £20,000 and £30,000 per quality-adjusted life year (QALY) gained.
- One high-quality study concluded that pregabalin is less cost effective than duloxetine, but its cost effectiveness is similar to that of amitriptyline at a WTP threshold of between £20,000 and £30,000 per QALY gained.

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

- There is evidence from one high-quality HTA report that pregabalin is more cost effective than gabapentin.

See section 2.4 for a review of the health economics evidence.

2.3 Clinical evidence reviews

2.3.1 Antidepressants as monotherapy for neuropathic pain

Fifteen antidepressants (nine TCAs, four SSRIs and two SNRIs) were included in this review (see table 2) and a total of 2781 studies were retrieved by the systematic searches. From the 2781 studies, 23 randomised placebo-controlled trials on antidepressants were included, based on the inclusion and exclusion criteria suggested by the GDG through two short questionnaires[14]. No placebo-controlled studies on lofepramine, trimipramine, dosulepin (dothiepin), doxepin or SSRIs (citalopram, fluoxetine, paroxetine and sertraline) that were identified met the inclusion and exclusion criteria. The characteristics of the 23 included studies are summarised in table 6 (for detailed full evidence tables, see appendix 10.9).

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

Primary outcomes

Table 11 GRADE profiles – TCAs as monotherapy for neuropathic pain

No. of studies	Design	Treatment	Placebo	Relative risk (95% CI) [ARR] [NNTB, 95% CI]	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
PRIMARY Outcome: Patient-reported 30% pain reduction										
2 (Ami[1,2])	RCT	33/55 (60.0%)	13/55 (23.6%)	2.54 (1.51, 4.28) ARR = 36.4% NNTB = 2.8 (1.9, 5.5)	N	N	N	S[b]	N	Moderate
PRIMARY Outcome: Patient-reported global improvement/impression of change[a]										
9 (5xAmi[2–6)] (1xNort[7]) (2xDesi[8,9]) (1xImi[10])	RCT	123/248 (49.6%)	58/245 (23.7%)	2.47 (1.39, 4.41) ARR = 25.9% NNTB = 3.9 (2.9, 5.7)	N	N	N	S[c]	N	Moderate
No. of studies	**Design**	**Treatment**	**Placebo**	**Relative risk (95% CI) [ARI] [NNTH, 95% CI]**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Quality**
PRIMARY Outcome: No. of withdrawals owing to adverse effects										
11 (8xAmi [1–5,11–13]) (2xDesi [8,9]) (1xImi [10])	RCT	44/347 (12.7%)	20/348 (5.7%)	2.06 (1.29, 3.30) ARI = 7.0% NNTH = 14.4 (8.9, 37.6)	N	N	N	VS[d]	N	Low

PRIMARY Outcome: Dry mouth (adverse effects)										
9 (5xAmi [2,3,12–14]) (1xNort [7]) (2xDesi [8,9]) (1xImi [10])	RCT	123/272 (45.2%)	80/267 (30.0%)	1.52 (1.23, 1.88) ARI = 15.2% NNTH = 6.6 (4.3, 13.9)	N	N	N	S[e]	N	Moderate
PRIMARY Outcome: Blurred vision (adverse effects)										
4 (2xAmi[12,13]) (1xNort [7]) (1xImi [10])	RCT	5/123 (4.1%)	8/120 (6.7%)	0.68 (0.25, 1.82) ARI = −2.6% NNTH = N/A	N	N	N	VS[d]	N	Low
PRIMARY Outcome: Dizziness (adverse effects)										
5 (3xAmi [3,13,14]) (1xDesi [8]) (1xImi[10])	RCT	19/145 (13.1%)	21/146 (14.4%)	0.91 (0.52, 1.60) ARI = −1.3% NNTH = N/A	N	N	N	VS[d]	N	Low
PRIMARY Outcome: Sedation (adverse effects)										
4 (2xAmi [2,3]) (2xDesi [8,9])	RCT	51/136 (37.5%)	33/134 (24.6%)	1.53 (1.10, 2.13) ARI = 12.9% NNTH = 7.8 (4.2, 51.4)	N	N	N	VS[d]	N	Low
PRIMARY Outcome: Vomiting (adverse effects)										
2 (Ami [12,13])	RCT	2/62 (3.2%)	3/59 (5.1%)	0.82 (0.02, 30.99) ARI = −1.9% NNTH = N/A	N	N	N	VS[d]	N	Low
PRIMARY Outcome: gastrointestinal disturbances (adverse effects)										
3 (Ami [13]) (Nort [7]) (Imi [10])	RCT	2/79 (2.5%)	4/80 (5.0%)	0.61 (0.15, 2.48) ARI = −2.5% NNTH = N/A	N	N	N	VS[d]	N	Low

PRIMARY Outcome: Any adverse effects: non-specified										
7 (4xAmi [2,3,6,12]) (1xNort [7]) (2xDesi [8,9])	RCT	189/221 (85.5%)	140/217 (64.5%)	1.30 (1.06, 1.59) ARI = 21.0% NNTH = 4.8 (3.5, 7.6)	N	N	N	N	N	High
Note: No study reported the primary outcome of 'at least 50% pain reduction'.										
N = No serious; S = Serious; VS = Very serious Ami = amitriptyline; Nort = nortriptyline; Desi = desipramine; Imi = imipramine; N/A = not applicable. [a] Categorical scales for patient-reported global improvement/impression of change were dichotomised for analysis. For examples, 'at least moderate improvement' on a 6-item scale, 'at least good improvement' on a 5-item scale or 'much or very much improved' on the patients' global impression of change (PGIC) scale were the cut-offs for dichotomisation. [c] Total number of events (positive outcomes) less than 300. [b] Total number of events (positive outcomes) less than 300 owing to small study sample. [d] GDG consensus: Total number of adverse effects less than 100, downgrade quality by 2 levels. [e] GDG consensus: Total number of adverse effects less than 300, downgrade 1 level.										
[1] Rintala et al. (2007) [2] Vrethem et al. (1997) [3] Max et al. (1988) [4] Kautio et al. (2008) [5] Kieburtz et al. (1998) [6] Leijon and Boivie (1989) [7] Khoromi et al. (2007) [8] Kishore-Kumar et al. (1990) [9] Max et al. (1991) [10] Sindrup et al. (2003) [11] Graff-Radford et al. (2000) [12] Cardenas et al. (2002) [13] Robinson et al. (2004) [14] Kalso et al. (1996)										

Table 12 GRADE profiles – SNRIs as monotherapy for neuropathic pain

No. of studies	Design	Treatment	Placebo	Relative risk (95% CI) [ARR] [NNTB, 95% CI]	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
PRIMARY Outcome: Patient-reported 30% pain reduction										
1 (Dulo[1])	RCT	146/221 (66.1%)	44/106 (41.5%)	1.59 (1.25, 2.03) ARR = 24.6% NNTB = 4.1 (2.8, 7.6)	N	N	N	S[b]	N	Moderate
PRIMARY Outcome: Patient-reported 50% pain reduction										
4 (3xDulo [1–3]) (1xVen[4])	RCT	505/945 (53.4%)	136/411 (33.1%)	1.65 (1.42, 1.91) ARR = 20.3% NNTB = 4.9 (3.9, 6.8)	N	N	N	N	N	High
PRIMARY Outcome: Patient-reported global improvement/impression of change[a]										
2 (Ven [5,6])	RCT	28/69 (40.6%)	10/52 (19.2%)	1.89 (0.65, 5.52) ARR = 21.4% NNTB = N/A	N	N	N	S[c]	N	Moderate

No. of studies	Design	Treatment	Placebo	Relative risk [ARI] [NNTH]	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
PRIMARY Outcome: No. of withdrawals owing to adverse effects										
7 (3xDulo[1–3]) (4xVen[4,5,6,7])	RCT	132/1066 (12.4%)	29/524 (5.5%)	2.34 (1.59, 3.44) ARI = 6.9% NNTH = 14.6 (10.4, 24.6)	N	N	N	S[d]	N	Moderate
PRIMARY Outcome: Dry mouth (adverse effects)										
3 (1xDulo[2]) (2xVen[5,7])	RCT	55/406 (13.5%)	28/179 (15.6%)	1.26 (0.86, 1.85) ARI = −2.1% NNTH = N/A	N	N	N	VS[f]	N	Low
PRIMARY Outcome: Blurred vision (adverse effects)										
1 (Ven[5])	RCT	1/33 (3.0%)	0/33 (0.0%)	3.00 (0.13, 71.07) ARI = 3.0% NNTH = N/A	N	N	N	VS[e]	N	Very low
PRIMARY Outcome: Dizziness (adverse effects)										
3 (2xDulo[1,2]) (1xVen[5])	RCT	76/601 (12.6%)	15/256 (5.9%)	2.06 (1.21, 3.52) ARI = 6.7% NNTH = 14.7 (9.3, 34.8)	N	N	N	VS[f]	N	Low
PRIMARY Outcome: Vomiting (adverse effects)										
1 (Ven[4])	RCT	9/164 (5.5%)	0/81 (0.0%)	9.44 (0.56, 160.24) ARI = 5.5% NNTH = N/A	N	N	N	VS[e]	N	Very low
PRIMARY Outcome: gastrointestinal disturbances (adverse effects)										
2 (1xDulo[1]) (1xVen[5])	RCT	21/259 (8.1%)	5/141 (3.5%)	2.57 (0.93, 7.10) ARI = 4.6% NNTH = N/A	N	N	N	VS[f]	N	Low

PRIMARY Outcome: Any adverse effects: non-specified										
1 (Ven[7])	RCT	23/40 (57.5%)	11/20 (50.0%)	1.05 (0.65, 1.69) ARI = 7.5% NNTH = N/A	N	N	N	VS[e]	N	Very low

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

Dulo = duloxetine; Ven = venlafaxine; N/A = not applicable

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

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

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

[d] GDG consensus: Total number of adverse effects less than 300, downgrade 1 level.

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

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

[1] Wernicke et al. (2006)

[2] Goldstein et al. (2005)

[3] Raskin et al. (2005)

[4] Rowbotham et al. (2004)

[5] Sindrup et al. (2003)

[6] Yucel et al. (2005)

[7] Tasmuth et al. (2002)

Other reported pain outcomes

Table 13 GRADE profiles – antidepressants as monotherapy for neuropathic pain

No. of studies	Design	Treatment	Placebo	Mean (SD) at endpoint [p-value]	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
OTHER REPORTED PAIN OUTCOME: Pain intensity (Scale: VASpi-10cm)										
1 (Ami; SCI[1])	RCT	44	40	Treatment = 4.5 (1.9) Placebo = 4.0 (2.0) p > 0.05	N	N	S[a]	S[b]	N	Low
1 (Ami; PHN[2])	RCT	12	13	Treatment = 2.7 (1.7) Placebo = 4.9 (2.5) p < 0.05	N	N	S[a]	S[b]	N	Low
OTHER REPORTED PAIN OUTCOME: Pain relief (Scale: NRS 11-point)										
1 (Ami; PhanLP[3])	RCT	18	19	Treatment = 3.1 (2.7) Placebo = 3.1 (2.9) p > 0.05	N	N	S[a]	S[b]	N	Low

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

Ami = amitriptyline; SCI = spinal cord injury; PHN = post-herpetic neuralgia; PhanLP = phantom limb pain; VASpi = visual analogue scale for pain intensity; NRS = numerical rating scale; NR = not reported.

[a] Indirect outcome measure (non-primary).

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

[1] Cardenas et al. (2002)

[2] Graff-Radford et al. (2000)

[3] Robinson et al. (2004)

2.3.2 Anti-epileptics as monotherapy for neuropathic pain

Eight anti-epileptics were included in this review (see table 2) and a total of 4757 studies were retrieved by the systematic searches. A total of 46 randomised placebo-controlled trials on anti-epileptics were included from the retrieved 4757 studies, based on the inclusion and exclusion criteria[15]. None of the placebo-controlled studies identified on phenytoin met the inclusion and exclusion criteria. The characteristics of the 46 included studies are summarised in table 7 (for detailed full evidence tables, see appendix 10.9). Meta-analysis was carried out for individual anti-epileptics (gabapentin, pregabalin, lamotrigine, oxcarbazepine, topiramate, carbamazepine and sodium valproate) for primary outcomes and specific adverse effects. See section 2.1.1 for details of the analysis and synthesis of outcomes.

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

Primary outcomes

Table 14 GRADE profiles – gabapentin as monotherapy for neuropathic pain

No. of studies	Design	Treatment	Placebo	Relative risk (95% CI) [ARR] [NNTB, 95% CI]	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
PRIMARY Outcome: Patient-reported 30% pain reduction										
1 (SCI[1])	RCT	5/22 (22.7%)	6/22 (27.3%)	0.83 (0.30, 2.33) ARR = 4.6% NNTB = N/A	N	N	N	S[b]	N	Moderate
PRIMARY Outcome: Patient-reported 50% pain reduction										
2 (PHN[2]) (MixNP[3])	RCT	91/331 (27.5%)	34/246 (13.8%)	1.91 (1.32, 2.76) ARR = 13.7% NNTB = 7.3 (5.0, 14.2)	N	N	N	S[d]	N	Moderate
PRIMARY Outcome: Patient-reported global improvement/impression of change[a]										
7 (2xPDN [4,5]) (2xPHN [2,6]) (NerP[7]) (MixNP[3]) (PhanLP[8])	RCT	287/668 (43.0%)	111/569 (19.5%)	2.18 (1.81, 2.63) ARR = 23.5% NNTB = 4.2 (3.5, 5.4)	N	N	N	N	N	High
No. of studies	**Design**	**Treatment**	**Placebo**	**Relative risk (95% CI) [ARI] [NNTH, 95% CI]**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Quality**
PRIMARY Outcome: No. of withdrawals owing to adverse effects										
9 (2xPDN [4,5]) (2xPHN [2,6]) (NerP[7]) (MixNP[3]) (PhanLP[9]) (HIV[10]) (SCI[1])	RCT	141/781 (18.1%)	66/676 (9.8%)	1.53 (1.17, 2.00) ARI = 8.3% NNTH = 12.1 (8.5, 21.0)	N	N	N	S[e]	N	Moderate
PRIMARY Outcome: Dizziness (adverse effects)										
8 (2xPDN [4,5]) (PhanLP [11]) (NerP[7]) (HIV[10]) (CanP[12]) (PHN[2]) (MixNP[3])	RCT	187/732 (25.5%)	44/610 (7.2%)	3.04 (2.22, 4.17) ARI = 18.3% NNTH = 5.5 (4.5, 6.9)	N	N	N	S[e]	N	Moderate

PRIMARY Outcome: Somnolence (adverse effects)										
6 (2xPDN [4,5]) (PhanLP[11]) (HIV[10]) (PHN[2]) (MixNP[3])	RCT	108/521 (20.7%)	25/401 (6.2%)	3.30 (2.18, 4.99) ARI = 14.5% NNTH = 6.9 (5.3, 9.7)	N	N	N	S[e]	N	Moderate
PRIMARY Outcome: Sedation (adverse effects)										
1 (SCI[13])	RCT	0/20 (0.0%)	1/20 (5.0%)	0.33 (0.01, 7.72) ARI = −5.0% NNTH = N/A	N	N	N	VS[g]	N	Very low
PRIMARY Outcome: Fatigue (adverse effects)										
2 (NerP[7]) (CanP[12])	RCT	32/211 (15.2%)	19/209 (9.1%)	1.68 (1.00, 2.82) ARI = 6.1% NNTH = 16.5 (8.1, ∞)	N	N	N	VS[f]	N	Low
PRIMARY Outcome: Gait disturbances[c] (adverse effects)										
1 (HIV[10])	RCT	7/15 (46.7%)	3/11 (27.3%)	1.71 (0.57, 5.17) ARI = 19.4% NNTH = N/A	N	N	N	VS[g]	N	Very low
PRIMARY Outcome: Any adverse effects: non-specified										
5 (2xPHN [2,6]) (SCI[13]) (PhanLP[9]) (MixNP[3])	RCT	302/532 (56.8%)	132/422 (31.3%)	1.80 (1.50, 2.17) ARI = 25.5% NNTH = 3.9 (3.2, 5.2)	N	N	N	N	N	High

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

N/A = not applicable; PDN = painful diabetic neuropathy; PHN = post-herpetic neuralgia; SCI = spinal cord injury; MixNP = mixed neuropathic pain; NerP = nerve pain; PhanLP = phantom limb pain; HIV = HIV-related neuropathy; CanP = neuropathic cancer pain.

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

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

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

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

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

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

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

[1] Rintala et al. (2007)

[2] Rice and Maton (2001)

[3] Serpell (2002)

[4] Backonja et al. (1998)

[5] Simpson (2001)

[6] Rowbotham et al. (1998)

[7] Gordh et al. (2008)

[8] Smith et al. (2005)

[9] Nikolajsen et al. (2006)

[10] Hahn (2004)

[11] Bone et al. (2002)

[12] Rao et al. (2007)

[13] Levendoglu et al. (2004)

Table 15 GRADE profiles – pregabalin as monotherapy for neuropathic pain

No. of studies	Design	Treatment	Placebo	Relative risk (95% CI) [ARR] [NNTB, 95% CI]	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
PRIMARY Outcome: Patient-reported 30% pain reduction										
6 (3xPHN [1–3]) (PDN/PHN[4]) (PDN[5]) (SCI[6])	RCT	554/955 (58.0%)	126/462 (27.3)	2.08 (1.78, 2.44) ARR = 30.7% NNTB = 3.2 (2.8, 3.9)	N	N	N	N	N	High
PRIMARY Outcome: Patient-reported 50% pain reduction										
10 (4xPHN [1–3,7]) (4xPDN [5,8–10]) (PDN/PHN[4]) (SCI[6])	RCT	612/1577 (38.8%)	129/769 (16.8%)	2.23 (1.89, 2.64) ARR = 22.0% NNTB = 4.6 (3.9, 5.5)	N	N	N	N	N	High
PRIMARY Outcome: Patient-reported global improvement/impression of change[a]										
5 (2xPHN [3,7]) (2xPDN [5,10]) (PDN/PHN[4])	RCT	459/1009 (45.5%)	90/379 (23.7%)	1.90 (1.57, 2.30) ARR = 21.8% NNTB = 4.6 (3.7, 6.1)	N	N	N	N	N	High
No. of studies	**Design**	**Treatment**	**Placebo**	**Relative risk (95% CI) [ARI] [NNTH, 95% CI]**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Quality**
PRIMARY Outcome: No. of withdrawals owing to adverse effects										
12 (4xPHN [1–3,7]) (5xPDN [5,8–11]) (PDN/PHN[4]) (SCI[6]) (Cen[12])	RCT	259/1921 (13.5%)	57/933 (6.1%)	2.34 (1.76, 3.10) ARI = 7.4% NNTH = 13.6 (10.6, 19.5)	N	N	N	N	N	High
PRIMARY Outcome: Dizziness (adverse effects)										
12 (4xPHN [1–3,7]) (5xPDN [5,8–11]) (PDN/PHN[4]) (SCI[6]) (CenP[12])	RCT	444/1886 (23.5%)	74/933 (7.9%)	3.05 (2.18, 4.26) ARI = 15.6% NNTH = 6.4 (5.5, 7.7)	N	N	N	N	N	High

PRIMARY Outcome: Somnolence (adverse effects)										
12 (4xPHN [1–3,7]) (5xPDN [5,8–11]) (PDN/PHN[4]) (SCI[6]) (CenP[12])	RCT	298/1886 (15.8%)	48/933 (5.1%)	3.63 (2.69, 4.90) ARI = 10.7% NNTH = 9.4 (7.8, 11.8)	N	N	N	N	N	High
PRIMARY Outcome: Fatigue (adverse effects)										
1 (PHN[2])	RCT	13/179 (7.3%)	1/90 (1.1%)	6.54 (0.87, 49.18) ARI = 6.2% NNTH = N/A	N	N	N	VS [c]	N	Very low
PRIMARY Outcome: Weight gain (adverse effects)										
5 (3xPDN [8,10,11]) (PHN[2]) (PDN/PHN[4])	RCT	82/959 (8.6%)	3/421 (0.7%)	8.00 (3.17, 20.21) ARI = 7.9% NNTH = 12.8 (10.2, 17.0)	N	N	N	VS [d]	N	Low
PRIMARY Outcome: Gait disturbances[b] (adverse effects)										
3 (3xPHN [1–3])	RCT	17/543 (3.1%)	1/267 (0.4%)	5.31 (1.24, 22.74) ARI = 2.7% NNTH = 36.3 (22.8, 89.4)	N	N	N	VS [d]	N	Low
PRIMARY Outcome: Any adverse effects: non-specified										
3 (2xPHN [1,2]) (PDN[9])	RCT	245/344 (71.2%)	112/244 (45.9%)	1.58 (1.25, 1.99) ARI = 25.3% NNTH = 3.9 (3.0, 5.7)	N	N	N	S [e]	N	Moderate

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

N/A = not applicable; PDN = painful diabetic neuropathy; PHN = post-herpetic neuralgia; SCI = spinal cord injury; CenP = central pain

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

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

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

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

[e] GDG consensus: Total number of adverse effects less than 300, downgrade 1 level.

[1] Dworkin et al. (2003)

[2] Stacey et al. (2008)

[3] van Seventer et al. (2006)

[4] Freynhagen et al. (2005)

[5] Lesser et al. (2004)

[6] Siddall et al. (2006)

[7] Sabatowski et al. (2004)

[8] Richter et al. (2005)

[9] Rosenstock et al. (2004)

[10] Tölle et al. (2008)

[11] Arezzo et al. (2008)

[12] Vranken et al. (2008)

Table 16 GRADE profiles – lamotrigine as monotherapy for neuropathic pain

No. of studies	Design	Treatment	Placebo	Relative risk (95% CI) [ARR] [NNTB, 95% CI]	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Q
PRIMARY Outcome: Patient-reported 30% pain reduction										
3 (2xPDN[1]) (CenP[2])	RCT	115/335 (34.3%)	43/131 (32.8%)	1.04 (0.79, 1.39) ARR = 1.5% NNTB = N/A	N	N	N	S[b]	N	M
PRIMARY Outcome: Patient-reported 50% pain reduction										
3 (3xPDN [1,3])	RCT	92/351 (26.2%)	35/146 (24.0%)	1.13 (0.81, 1.57) ARR = 2.2% NNTB = N/A	N	N	N	S[b]	N	M
PRIMARY Outcome: Patient-reported global improvement/impression of change[a]										
2 (PDN[3]) (HIV[4])	RCT	93/172 (54.1%)	32/98 (32.7%)	1.56 (1.15, 2.12) ARR = 21.4% NNTB = 4.7 (3.0, 10.9)	N	N	N	S[b]	N	M
No. of studies	**Design**	**Treatment**	**Placebo**	**Relative risk (95% CI) [ARI] [NNTH, 95% CI]**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Q**
PRIMARY Outcome: No. of withdrawals owing to adverse effects										
11 (4xPDN [1,3,5]) (2xHIV [4,6]) (CenP[2]) (SCI[7]) (MixNP[8]) (CanP[9]) (PSP[10])	RCT	98/937 (10.5%)	28/504 (5.6%)	1.67 (1.12, 2.49) ARI = 4.9% NNTH = 20.4 (13.0, 47.5)	N	N	N	S[c]	N	M
PRIMARY Outcome: Dizziness (adverse effects)										
5 (3xPDN [1,3]) (CenP[2]) (CanP[9])	RCT	45/637 (7.1%)	14/277 (5.1%)	1.21 (0.65, 2.26) ARI = 2.0% NNTH = N/A	N	N	N	VS[d]	N	Lo

PRIMARY Outcome: Sedation (adverse effects)										
1 (CenP[2])	RCT	1/15 (6.7%)	0/15 (0.0%)	3.00 (0.13, 68.26) ARI = 6.7% NNTH = N/A	N	N	N	VS[e]	N	V
PRIMARY Outcome: Fatigue (adverse effects)										
2 (CenP[2]) (CanP[9])	RCT	4/78 (5.1%)	4/77 (5.2%)	0.99 (0.27, 3.68) ARI = −0.1% NNTH = N/A	N	N	N	VS[d]	N	L
PRIMARY Outcome: Any adverse effects: non-specified										
5 (3xPDN [1,3]) (SCI[7]) (PSP[10])	RCT	446/617 (72.3%)	158/258 (61.2%)	1.07 (0.86, 1.33) ARI = 11.1% NNTH = N/A	N	N	N	N	N	H

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

N/A = not applicable; PDN = painful diabetic neuropathy; PHN = post-herpetic neuralgia; SCI = spinal cord injury; MixNP = mixed neuropathic pain; CenP = central pain; PSP = post stroke pain; HIV = HIV-related neuropathy; CanP = neuropathic cancer pain.

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

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

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

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

[e] GDG consensus: if there is only 1 study with total number of adverse effects less than 100, the GDG decided that the quality sh graded as 'very low'.

[1] Vinik et al. (2007)

[2] Breuer et al. (2007)

[3] Eisenberg et al. (2001)

[4] Simpson et al. (2003)

[5] Luria et al. (2000)

[6] Simpson et al. (2000)

[7] Finnerup et al. (2002)

[8] McCleane (1999)

[9] Rao et al. (2008)

[10] Vestergaard et al. (2001)

Table 17 GRADE profiles – oxcarbazepine as monotherapy for neuropathic pain

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

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

N/A = not applicable; PDN = painful diabetic neuropathy

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

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

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

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

[1] Dogra et al. (2005)

[2] Beydoun et al. (2006)

[3] Grosskopf et al. (2006)

Table 18 GRADE profiles – topiramate as monotherapy for neuropathic pain

No. of studies	Design	Treatment	Placebo	Relative risk (95% CI) [ARR] [NNTB, 95% CI]	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
PRIMARY Outcome: Patient-reported 30% pain reduction										
1 (PDN[1])	RCT	103/208 (49.5%)	37/109 (33.9%)	1.46 (1.09, 1.96) ARR = 15.6% NNTB = 6.4 (3.8, 24.4)	N	N	N	S[b]	N	Moderate
PRIMARY Outcome: Patient-reported 50% pain reduction										
1 (PDN[1])	RCT	74/208 (36.3%)	23/109 (21.1%)	1.69 (1.12, 2.53) ARR = 15.2% NNTB = 6.9 (4.2, 25.4)	N	N	N	S[b]	N	Moderate
PRIMARY Outcome: Patient-reported global improvement/impression of change[a]										
2 (PDN[1]) (Radi[2])	RCT	127/237 (53.6%)	44/138 (31.9%)	1.66 (1.26, 2.17) ARR = 21.7% NNTB = 4.6 (3.2, 8.8)	N	N	N	S[b]	N	Moderate

No. of studies	Design	Treatment	Placebo	Relative risk (95% CI) [ARI] [NNTH, 95% CI]	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
PRIMARY Outcome: No. of withdrawals owing to adverse effects										
3 (2xPDN[1,2]) (Radi[3])	RCT	275/1140 (24.1%)	41/534 (7.7%)	3.06 (2.25, 4.16) ARI = 16.4% NNTH = 6.1 (5.1, 7.6)	N	N	N	N	N	High
PRIMARY Outcome: Dizziness (adverse effects)										
1 (PDN[1])	RCT	15/211 (7.1%)	6/109 (5.5%)	1.29 (0.52, 3.23) ARI = 1.6% NNTH = N/A	N	N	N	VS[c]	N	Very low
PRIMARY Outcome: Somnolence (adverse effects)										
2 (2xPDN[1,2])	RCT	108/1096 (9.9%)	19/493 (3.9%)	2.56 (1.59, 4.11) ARI = 6.0% NNTH = 16.7 (11.8, 28.2)	N	N	N	S[d]	N	Moderate
PRIMARY Outcome: Sedation (adverse effects)										
1 (Radi[3])	RCT	10/29 (34.5%)	1/29 (3.4%)	10.00 (1.37, 73.17) ARI = 31.1% NNTH = 3.2 (2.0, 8.0)	N	N	N	VS[c]	N	Very low
PRIMARY Outcome: Fatigue (adverse effects)										
3 (2xPDN[1,2]) (Radi[3])	RCT	168/1125 (14.9%)	53/522 (10.2%)	1.52 (1.14, 2.03) ARI = 4.7% NNTH = 20.9 (12.3, 68.7)	N	N	N	S[d]	N	Moderate
PRIMARY Outcome: Any adverse effects: non-specified										
2 (PDN[1]) (Radi[3])	RCT	195/243 (80.2%)	98/138 (71.0%)	1.14 (1.01, 1.29) ARI = 9.2% NNTH = 10.8 (5.5, 636.2)	N	N	N	S[d]	N	Moderate

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

N/A = not applicable; PDN = painful diabetic neuropathy; Radi = radiculopathy

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

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

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

[d] GDG consensus: Total number of adverse effects less than 300, downgrade 1 level.

[1] Raskin et al. (2004)

[2] Thienel et al. (2004)

[3] Khoromi et al. (2005)

Table 19 GRADE profiles – carbamazepine as monotherapy for neuropathic pain

No. of studies	Design	Treatment	Placebo	Relative risk (95% CI) [ARR] [NNTB, 95% CI)]	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
PRIMARY Outcome: Patient-reported global improvement/impression of change[a]										
2 (PSP[1]) (MixNP[2])	RCT	20/34 (58.8%)	7/22 (31.8%)	1.31 (0.80, 2.15) ARR = 27.0% NNTB = N/A	N	N	N	S[b]	N	Moderate
No. of studies	**Design**	**Treatment**	**Placebo**	**Relative risk (95% CI) [ARI] [NNTH, 95% CI]**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Quality**
PRIMARY Outcome: Any adverse effects: non-specified										
1 (PSP[1])	RCT	13/15 (86.7%)	7/15 (46.7%)	1.86 (1.04, 3.30) ARI = 40.0% NNTH = 2.5 (1.4, 10.6)	N	N	N	VS[c]	N	Very low

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

N/A = not applicable; PSP = post stroke pain; MixNP = mixed neuropathic pain.

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

[b] GDG consensus: Total number of events (positive trends) less than 300, downgrade quality by 1 level.

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

[1] Leijon and Boivie (1989)

[2] Nicol (1969)

Table 20 GRADE profiles – sodium valproate as monotherapy for neuropathic pain

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

No. of studies	Design	Treatment	Placebo	Relative risk (95% CI) [ARI] [NNTH, 95% CI]	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
PRIMARY Outcome: No. of withdrawals owing to adverse effects										
2 (PDN [1,2])	RCT	2/52 (3.8%)	0/51 (0.0%)	2.93 (0.32, 27.29) ARI = 3.8% NNTH = N/A	N	N	N	VS[a]	N	Low
PRIMARY Outcome: Any adverse effects: non-specified										
1 (PDN[3])	RCT	4/20 (20.0%)	1/20 (5.0%)	4.00 (0.49, 32.72) ARI = 15.0% NNTH = N/A	N	N	N	VS[b]	N	Very low

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

N/A = not applicable; PDN = painful diabetic neuropathy

[a] Total number of adverse effects less than 100.

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

[1] Kochar et al. (2002)

[2] Kochar et al. (2004)

[3] Agrawal et al. (2009)

Other reported pain outcomes

Table 21 GRADE profiles – anti-epileptics as monotherapy for neuropathic pain

No. of studies	Design	Treatment	Placebo	Mean (SD) at endpoint [p-value]	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
OTHER REPORTED PAIN OUTCOME: Pain intensity (Scale: VASpi-10cm)										
1 (SoV: PDN[1])	RCT	20	20	Treatment = 6.2 (1.4) Placebo = 6.9 (1.0) p > 0.05	N	N	S[a]	S[b]	N	Low
OTHER REPORTED PAIN OUTCOME: Pain intensity (Scale: NRS 11-point)										
1 (Preg: PDN[2])	RCT	82	85	Treatment = 3.54 (NR) Placebo = 4.82 (NR) p = 0.0003	N	N	S[a]	S[b]	N	Low
OTHER REPORTED PAIN OUTCOME: Pain relief (Scale: VASpr-100mm)										
1 (Oxcar: PDN[3])	RCT	71	70	Treatment = 27.9 (NR) Placebo = 31.1 (NR) p > 0.05	N	N	S[a]	S[b]	N	Low

1 (SoV: PDN[4])	RCT	22	21	Treatment = 30.0 (99.4) Placebo = 60.0 (84.2) p < 0.001	N	N	S[a]	S[b]	N	Low
OTHER REPORTED PAIN OUTCOME: Percentage pain relief (NPS)										
1 (Gaba: SCI[5])	RCT	20	20	Treatment = −69.9% Placebo = −13.2% p < 0.05	N	N	S[a]	S[b]	N	Low
No. of studies	**Design**	**Treatment**	**Placebo**	**Mean change (SD) from baseline [p-value]**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Quality**
OTHER REPORTED PAIN OUTCOME: Pain intensity (Scale: VASpi-10cm)										
1 (Gaba: PhanLP[6])	RCT	19	19	Treatment = −3.2 (2.1) Placebo = −1.6 (0.7) p < 0.03	N	N	S[a]	S[b]	N	Low

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

PDN = painful diabetic neuropathy; SCI = spinal cord injury; PhanLP = phantom limb pain.

SoV = sodium valproate; Preg = pregabalin; Oxcar = oxcarbazepine; Gaba= gabapentin; VASpi = visual analogue scale for pain intensity; NRS = numerical rating scale; VASpr = visual analogue scale for pain relief; NPS = Neuropathic Pain Scale; NR = Not reported

[a] Indirect outcome measure (non-primary).

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

[1] Agrawal et al. (2009)

[2] Arezzo et al. (2008)

[3] Grosskopf et al. (2006)

[4] Kocharet al. (2004)

[5] Levendoglu et al. (2004)

[6] Bone et al. (2002)

2.3.3 Opioid analgesics as monotherapy for neuropathic pain

Nine opioid analgesics were included in this review (see table 2). A total of 9612 studies were retrieved by the systematic searches, and eight randomised placebo-controlled trials were included based on the inclusion and exclusion criteria[16]. None of the placebo-controlled studies identified on co-codamol, co-dydramol, dihydrocodeine, buprenorphine, fentanyl or codeine phosphate met the inclusion and exclusion criteria. The eight studies that were included were on morphine, tramadol and oxycodone for adult patients with neuropathic pain. The characteristics of the eight included studies on opioid analgesics are summarised in table 8 (for detailed full evidence tables, see appendix 10.9). Meta-analysis was carried out for individual opioid analgesics (morphine, tramadol and oxycodone) for primary outcomes and

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

adverse effects if there were sufficient data. See section 2.1.1 for details of the analysis and synthesis of outcomes.

Primary outcomes

Table 22 GRADE profiles – morphine as monotherapy for neuropathic pain

No. of studies	Design	Treatment	Placebo	Relative risk (95% CI) [ARR] [NNTB, 95% CI]	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
PRIMARY OUTCOME: Patient-reported 30% pain reduction										
1 (PhanLP[1])	RCT	33/50 (66.0%)	19/43 (44.2%)	1.49 (1.01, 2.21) ARR = 21.8% NNTB = 4.6 (2.5, 68.3)	N	N	N	S[b]	N	Moderate
PRIMARY OUTCOME: Patient-reported 50% pain reduction										
2 (PhanLP [1,2])	RCT	28/62 (45.2%)	14/55 (25.5%)	1.75 (1.04, 2.96) ARR = 19.7% NNTB = 5.1 (2.8, 44.5)	N	N	N	S[b]	N	Moderate
PRIMARY OUTCOME: Patient-reported global improvement/impression of change[a]										
1 (radicul[3])	RCT	13/32 (40.6%)	11/33 (33.3%)	1.22 (0.64, 2.31) ARR = 7.3% NNTB = N/A	N	N	N	S[b]	N	Moderate
No. of studies	**Design**	**Treatment**	**Placebo**	**Relative risk (95% CI) [ARI] [NNTH, 95% CI]**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Quality**
PRIMARY OUTCOME: Withdrawals owing to adverse effects										
1 (radicul[3])	RCT	9/55 (16.4%)	1/55 (1.8%)	9.00 (1.18, 68.66) ARI = 14.6% NNTH = 6.9 (3.7, 22.0)	N	N	N	VS[d]	N	Very low
PRIMARY OUTCOME: Constipation (adverse effects)										
2 (radicul[3]) (PhanLP[1])	RCT	35/78 (44.9%)	4/71 (5.6%)	8.12 (3.05, 21.61) ARI = 39.3% NNTH = 2.5 (2.0, 3.8)	N	N	N	VS[c]	N	Low
PRIMARY OUTCOME: Somnolence/drowsiness (adverse effects)										
2 (radicul[3]) (PhanLP[1])	RCT	16/78 (20.5%)	4/71 (5.6%)	3.39 (1.17, 9.76) ARI = 14.9% NNTH = 6.7 (3.8, 23.5)	N	N	N	VS[c]	N	Low
PRIMARY OUTCOME: Nausea (adverse effects)										
2 (radicul[3]) (PhanLP1)	RCT	6/78 (7.7%)	1/71 (1.4%)	3.94 (0.69, 22.46) ARI = 6.3% NNTH = N/A	N	N	N	VS[c]	N	Low

PRIMARY OUTCOME: Dizziness (adverse effects)										
2 (radicul[3]) (PhanLP1)	RCT	6/78 (7.7%)	3/71 (4.2%)	1.86 (0.49, 7.04) ARI = 3.5% NNTH = N/A	N	N	N	VS[c]	N	Low

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

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

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

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

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

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

[1] Wu et al. (2008)

[2] Huse et al. (2001)

[3] Khoromi et al. (2007)

Table 23 GRADE profiles – tramadol as monotherapy for neuropathic pain

No. of studies	Design	Treatment	Placebo	Relative risk (95% CI) [ARR] [NNTB, 95% CI]	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
PRIMARY OUTCOME: Patient-reported 50% pain reduction										
1 (PHN[1])	RCT	41/53 (77.4%)	31/55 (56.4%)	1.37 (1.04, 1.81) ARR = 21.0% NNTB = 4.8 (2.7, 31.5)	N	N	N	S[a]	N	Moderate
No. of studies	**Design**	**Treatment**	**Placebo**	**Relative risk (95% CI) [ARI] [NNTH, 95% CI]**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Quality**
PRIMARY OUTCOME: Withdrawals owing to adverse effects										
3 (NPCan[2]) (PDN[3]) (Poly[4])	RCT	19/128 (14.8%)	3/129 (2.3%)	5.60 (1.85, 17.00) ARI = 12.5% NNTH = 8.0 (5.0, 16.2)	N	N	N	VS[b]	N	Low
PRIMARY OUTCOME: Constipation (adverse effects)										
2 (PDN[3]) (Poly[4])	RCT	24/110 (21.8%)	4/111 (3.6%)	6.05 (2.17, 16.86) ARI = 18.2% NNTH = 5.5 (3.7, 10.0)	N	N	N	VS[b]	N	Low

PRIMARY OUTCOME: Somnolence/drowsiness (adverse effects)										
1 (PDN[3])	RCT	8/65 (12.3%)	4/66 (6.1%)	2.03 (0.64, 6.42) ARI = 6.2% NNH = N/A	N	N	N	VS[c]	N	Very low
PRIMARY OUTCOME: Nausea (adverse effects)										
2 (PDN[3]) (Poly[4])	RCT	26/110 (23.6%)	5/111 (4.5%)	5.24 (2.09, 13.13) ARI = 19.1% NNTH = 5.2 (3.5, 9.5)	N	N	N	VS[b]	N	Low
PRIMARY OUTCOME: Dizziness (adverse effects)										
2 (PDN[3]) (Poly[4])	RCT	18/110 (16.4%)	1/111 (0.9%)	7.42 (2.07, 26.60) ARI = 15.5% NNTH = 6.5 (4.2, 11.0)	N	N	N	VS[b]	N	Low
PRIMARY OUTCOME: Vomiting (adverse effects)										
1 (PDN[3])	RCT	3/65 (4.6%)	0/66 (0.0%)	7.11 (0.37, 134.91) ARI = 4.6% NNTH = N/A	N	N	N	VS[c]	N	Very low

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

PHN = post-herpetic neuralgia; NPCan = neuropathic cancer pain; PDN = painful diabetic neuropathy; Poly = polyneuropathy; N/A = not applicable.

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

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

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

[1] Boureau et al. (2003)

[2] Arbaiza and Vidal (2007)

[3] Harati et al. (1998)

[4] Sindrup et al. (2003)

Table 24 GRADE profiles – oxycodone as monotherapy for neuropathic pain

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

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

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

PDN = painful diabetic neuropathy; N/A = not applicable.

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

[1] Gimbel et al. (2003)

Other reported pain outcomes

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

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

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

Trama = tramadol; NPcan = neuropathic cancer pain; PDN = painful diabetic neuropathy; Poly = polyneuropathy; Oxyco = oxycodone; NR = Not reported

[a] Indirect outcome measure.

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

[1] Arbaiza and Vidal (2007)

[2] Harati et al. (1998)

[3] Sindrup et al. (2003)

[4] Gimbel et al. (2003)

2.3.4 Topical capsaicin and topical lidocaine as monotherapy for neuropathic pain

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

the inclusion and exclusion criteria[17] (nine studies for topical capsaicin and five studies for topical lidocaine). The characteristics of the 14 included studies are summarised in table 9 (for detailed full evidence tables, see appendix 10.9). Meta-analysis was carried out for both topical treatments for primary outcomes and adverse effects if sufficient data were available. See section 2.1.1 for details of the analysis and synthesis of outcomes.

Primary outcomes

Table 26 GRADE profiles – topical capsaicin as monotherapy for neuropathic pain

No. of studies	Design	Treatment	Placebo	Relative risk (95% CI) [ARR] [NNTB, 95% CI]	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
PRIMARY OUTCOME: Patient-reported 40% pain reduction										
1 (PHN[1])	RCT	7/16 (43.8%)	1/16 (6.3%)	7.00 (0.97, 50.57) ARR = 37.5% NNTB = N/A	N	N	N	S[b]	N	Moderate
PRIMARY OUTCOME: Patient-reported 50% pain reduction										
1 (CanP[2])	RCT	8/13 (61.5%)	3/10 (30.0%)	2.05 (0.73, 5.80) ARR = 31.5% NNTB = N/A	N	N	N	S[b]	N	Moderate
PRIMARY OUTCOME: Patient-reported global improvement/impression of change[a]										
1 (PDN[3])	RCT	23/40 (57.5%)	26/40 (65.0%)	0.88 (0.62, 1.26) ARR = 7.5% NNTB = N/A	N	N	N	S[b]	N	Moderate

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

No. of studies	Design	Treatment	Placebo	Relative risk (95% CI) [ARI] [NNTH, 95% CI]	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
PRIMARY OUTCOME: Withdrawals owing to adverse effects										
6 (3xPDN [3–5]) (HIV[6]) (PHN[2]) (CanP[7])	RCT	40/280 (14.3%)	6/267 (2.2%)	4.97 (2.37, 10.44) ARI = 12.1% NNTH = 8.3 (5.9, 12.9)	N	N	N	VS [c]	N	Low
PRIMARY OUTCOME: Burning (adverse effects)										
8 (3xPDN [3–5]) (2xPHN [1,7]) (Poly[8]) (HIV[6]) (CanP[2])	RCT	228/354 (64.4%)	94/353 (26.6%)	2.35 (1.64, 3.35) ARI = 37.8% NNTH = 2.6 (2.3, 3.2)	N	N	N	N	N	High
PRIMARY OUTCOME: Skin irritation (adverse effects)										
1 (Poly[8])	RCT	1/40 (2.5%)	0/40 (0.0%)	3.00 (0.13, 71.51) ARI = 2.5% NNH = N/A	N	N	N	VS [c]	N	Very low

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

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

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

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

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

[1] Bernstein et al. (1989)

[2] Watson and Evans (1992)

[3] Tandan et al. (1992)

[4] Donofrio et al. (1991)

[5] Scheffler et al. (1991)

[6] Paice et al. (2000)

[7] Watson et al. (1993)

[8] Low et al. (1995)

Table 27 GRADE profiles – topical lidocaine as monotherapy for neuropathic pain

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

No. of studies	Design	Treatment	Placebo	Relative risk (95% CI) [ARI] [NNTH, 95% CI]	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
PRIMARY OUTCOME: Withdrawals owing to adverse effects										
1 (PeriphNP[1])	RCT	1/58 (1.7%)	0/58 (0.0%)	3.00 (0.12, 72.15) ARI = 1.7% NNTH = N/A	N	N	N	VS [a]	N	Very low
PRIMARY OUTCOME: Rash (adverse effects)										
1 (PeriphNP[1])	RCT	10/58 (17.2%)	11/58 (19.0%)	0.91 (0.42, 1.97) ARI = −1.8% NNTH = N/A	N	N	N	VS [a]	N	Very low
PRIMARY OUTCOME: Skin irritation (adverse effects)										
1 (Mixed NP[2])	RCT	5/35 (14.3%)	3/35 (8.6%)	1.67 (0.43, 6.45) ARI = 5.7% NNTH = N/A	N	N	N	VS [a]	N	Very low

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

PeriphNP = peripheral neuropathic pain; Mixed NP = mixed neuropathic pain; N/A = not applicable.

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

[1] Meier et al. (2003)

[2] Ho et al. (2008)

Other reported pain outcomes

Table 28 GRADE profiles – topical capsaicin as monotherapy for neuropathic pain

No. of studies	Design	Treatment	Placebo	Mean (SD) at endpoint [p-value]	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
OTHER REPORTED PAIN OUTCOME: Pain intensity (Scale: VASpi-100mm)										
1 (PDN/Radic[1])	RCT	120	131	Treatment = 58.4 (NR) Placebo = 45.2 (NR) p = 0.004	N	N	S[a]	S[b]	N	Low
1 (Poly[2])	RCT	40	40	Treatment = 39.0 (NR) Placebo = 39.0 (NR) Not significant	N	N	S[a]	S[b]	N	Low
1 (PDN[3])	RCT	24	25	Treatment = 65.7 (38.9) Placebo = 25.0 (38.6) p = 0.013	N	N	S[a]	S[b]	N	Low
1 (PHN[4])	RCT	56	67	Treatment = 39.0 (NR) Placebo = 6.0 (NR) p = 0.006	N	N	S[a]	S[b]	N	Low
No. of studies	**Design**	**Treatment**	**Placebo**	**Mean change (SD) from baseline [p-value]**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Quality**
OTHER REPORTED PAIN OUTCOME: Pain intensity (Scale: VASpi-100mm)										
1 (PDN/Radic[1])	RCT	119	131	Treatment = −38.1 (NR) Placebo = −27.4 (NR) p = 0.037	N	N	S[a]	S[b]	N	Low
1 (Mixed NP[5])	RCT	33	41	Treatment = −11.2 (NR) Placebo = 0.0 (NR) p < 0.001	N	N	S[a]	S[b]	N	Low
1 (PDN[3])	RCT	24	25	Treatment = −49.1 (44.5) Placebo = −16.5 (48.4) p = 0.02	N	N	S[a]	S[b]	N	Low

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

PDN = painful diabetic neuropathy; Radic = radiculopathy; PHN = post-herpetic neuralgia; Mixed NP = mixed neuropathic pain; NR = Not reported.

[a] Indirect outcome measure (non-primary outcome).

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

[1] Donofrio et al. (1991)

[2] Low et al. (1995)

[3] Scheffler (1991)

[4] Watson et al. (1993)

[5] McCleane (2000)

Table 29 GRADE profiles – topical lidocaine as monotherapy for neuropathic pain

No. of studies	Design	Treatment	Placebo	Mean (SD) at endpoint [p-value]	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
OTHER REPORTED PAIN OUTCOME: Pain intensity (Scale: NRSpi 11-point)										
1 (PostS NP[1])	RCT	8	13	Treatment = 4.4 (2.12) Placebo = 4.8 (1.71) p = 0.92	N	N	S[a]	S[b]	N	Low
OTHER REPORTED PAIN OUTCOME: Pain relief (Scale: Global Pain Relief Scale)										
1 (HIV- RN[2])	RCT	61	59	Treatment = 2.25 (5.94) Placebo = 2.23 (5.45) p = 0.715	N	N	S[a]	S[b]	N	Low
No. of studies	**Design**	**Treatment**	**Placebo**	**Mean change (SD) from baseline [p-value]**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Quality**
OTHER REPORTED PAIN OUTCOME: Pain intensity (Scale: VASpi-100mm)										
1 (Mixed NP[3])	RCT	30	31	Treatment = −5.7 (17.5) Placebo = −7.6 (23.9) p = 0.88	N	N	S[a]	S[b]	N	Low
1 (PeriphNP[4])	RCT	40	40	Treatment = NR Placebo = NR p = 0.002	N	N	S[a]	S[b]	N	Low
OTHER REPORTED PAIN OUTCOME: Pain relief (Scale: Neuropathic Pain Scale)										
1 (PHN[5])	RCT	67	29	Treatment = −15.3 (17.9) Placebo = −7.7 (14.2) p = 0.043	N	N	S[a]	S[b]	N	Low

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

PostS NP = postsurgical neuropathic pain; HIV-RN, HIV-related neuropathy; Mixed NP = mixed neuropathic pain; PeriphNP = peripheral neuropathic pain; PHN = post-herpetic neuralgia; NR = Not reported

[a] Indirect outcome measure (non-primary outcome).

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

[1] Cheville et al. (2009)

[2] Estanislao et al. (2004)

[3] Ho et al. (2008)

[4] Meier et al. (2003)

[5] Galer et al. (2002)

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

Any head-to-head comparative trials and combination therapy trials that included the 34 pharmacological treatments were selected in this review (see table 2). Within the 23,207 studies that were retrieved by the systematic

searches, 13 randomised trials were included based on the inclusion and exclusion criteria[18] (head-to-head comparative = 10 studies, combination therapy = 3 studies. The characteristics of the 13 included studies are summarised in table 10 (for detailed full evidence tables, see appendix 10.9). Meta-analysis was carried out for different comparisons or combinations for primary outcomes and specific adverse effects if sufficient data were available. See section 2.1.1 for details of the analysis and synthesis of outcomes.

Cross-class comparative trials: antidepressants vs anti-epileptics

Primary outcomes for amitriptyline vs gabapentin as monotherapy

Table 30 GRADE profiles

No. of studies	Design	Ami (T1)	Gaba (T2)	Relative risk (95% CI) [ARR] [NNTB, 95% CI]	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
PRIMARY OUTCOME: Patient-reported 30% pain reduction										
1 (SCI[1])	RCT	13/22 (59.1%)	5/22 (22.7%)	2.60 (1.12, 6.05) ARR = 36.4% NNTB = 2.8 (1.7, 14.1)	N	N	N	S[b]	N	Moderate
PRIMARY OUTCOME: Patient-reported global improvement/impression of changea										
1 (PDN[2])	RCT	14/21 (66.7%)	11/21 (52.4%)	1.27 (0.77, 2.11) ARR = 14.3% NNTB = N/A	N	N	N	S[b]	N	Moderate
No. of studies	**Design**	**Ami**	**Gaba**	**Relative risk [ARI] [NNTH]**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Quality**
PRIMARY OUTCOME: No. of withdrawals owing to adverse effects										
2 (PDN[2]) (SCI[1])	RCT	4/63 (6.3%)	3/63 (4.8%)	1.33 (0.31, 5.72) ARI = 1.5% NNTH = N/A	N	N	N	VS[c]	N	Low
PRIMARY OUTCOME: Dry mouth (adverse effects)										
1 (PDN[2])	RCT	8/25 (32.0%)	4/25 (16.0%)	2.00 (0.69, 5.80) ARI = 16.0% NNTH = N/A	N	N	N	VS[d]	N	Very low
PRIMARY OUTCOME: Dizziness (adverse effects)										
1 (PDN[2])	RCT	2/25 (8.0%)	7/25 (28.0%)	0.29 (0.07, 1.24) ARI = −20.0% NNTH = N/A	N	N	N	VS[d]	N	Very low

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

PRIMARY OUTCOME: Blurred vision (adverse effects)										
1 (PDN[2])	RCT	2/25 (8.0%)	1/25 (4.0%)	2.00 (0.19, 20.7) ARI = 4.0% NNTH = N/A	N	N	N	VS [d]	N	Very low
PRIMARY OUTCOME: Sedation (adverse effects)										
1 (PDN[2])	RCT	8/25 (32.0%)	12/25 (48.0%)	0.67 (0.33, 1.35) ARI = −6.0% NNTH = N/A	N	N	N	VS [d]	N	Very low
PRIMARY OUTCOME: Fatigue (adverse effects)										
1 (PDN[2])	RCT	5/25 (20.0%)	4/25 (16.0%)	1.25 (0.38, 4.12) ARI = 4.0% NNTH = N/A	N	N	N	VS [d]	N	Very low
PRIMARY OUTCOME: Weight gain (adverse effects)										
1 (PDN[2])	RCT	6/25 (24.0%)	0/25 (0.0%)	∞ (∞) ARI = 24.0% NNTH = N/A	N	N	N	VS [d]	N	Very low
PRIMARY OUTCOME: Any adverse effects: non-specified										
2 (PDN [2,3])	RCT	28/37 (75.7%)	22/38 (57.9%)	1.58 (0.49, 5.15) ARI = 17.8% NNTH = N/A	S[e]	N	N	VS [c]	N	Very Low

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

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

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

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

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

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

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

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

[1] Rintala et al. (2007)

[2] Morello et al. (1999)

[3] Dallocchio et al. (2000)

Other reported pain outcomes for amitriptyline vs gabapentin as monotherapy

Table 31 GRADE profiles

No. of studies	Design	Ami (T1)	Gaba (T2)	Mean change (SD) from baseline [p-value]	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
OTHER NON-PRIMARY OUTCOME: Pain relief (Scale: 5-point Pain Score)										
1 (PDN[1])	RCT	12	13	Ami = −1.3 (0.6) Gaba = −1.9 (0.8) p = 0.026	S[a]	N	S[b]	S[c]	N	Very Low

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

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

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

[b] Indirect outcome measure.

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

[1] Dallocchio et al. (2000)

Primary outcomes for other trials of antidepressants vs anti-epileptics

Table 32 GRADE profiles – nortriptyline vs gabapentin as monotherapy

No. of studies	Design	Nort (T1)	Gaba (T2)	Relative risk (95% CI) [ARR] [NNTB, 95% CI]	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
PRIMARY OUTCOME: Patient-reported 50% pain reduction										
1 (PHN[1])	RCT	9/36 (25.0%)	7/34 (20.6%)	1.21 (0.51, 2.90) ARR = 4.4% NNTB = N/A	N	N	N	S[a]	N	Moderate
No. of studies	**Design**	**Nortrip**	**Gaba**	**Relative risk (95% CI) [ARI] [NNTH, 95% CI]**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Quality**
PRIMARY OUTCOME: Somnolence (adverse effects)										
1 (PHN[1])	RCT	6/36 (16.7%)	4/34 (11.8%)	1.42 (0.44, 4.59) ARI = 4.9% NNTH = N/A	N	N	N	VS[b]	N	Very low
PRIMARY OUTCOME: Dry mouth (adverse effects)										
1 (PHN[1])	RCT	18/36 (50.0%)	0/34 (0.0%)	∞ (∞) ARI = 50.0% NNTH = N/A	N	N	N	VS[b]	N	Very low
PRIMARY OUTCOME: Fatigue (adverse effects)										
1 (PHN[1])	RCT	0/36 (0.0%)	1/34 (2.9%)	0.00 (0.00, ∞) ARI = −2.9% NNTH = N/A	N	N	N	VS[b]	N	Very low

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

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

Nort = nortriptyline; Gaba = gabapentin; PHN = post-herpetic neuralgia; N/A = not applicable.

[a] Total number of events (positive outcome) less than 300.

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

[1] Chandra et al. (2006)

Table 33 GRADE profiles – amitriptyline vs carbamazepine as monotherapy

No. of studies	Design	Ami (T1)	Carba (T2)	Relative risk (95% CI) [ARR] [NNTB, 95% CI]	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
PRIMARY OUTCOME: Patient-reported global improvement/impression of change[a]										
1 (PSP[1])	RCT	10/15 (66.7%)	5/14 (52.4%)	1.87 (0.85, 4.11) ARR = 31.0% NNTB = N/A	N	N	N	S[b]	N	Moderate
No. of studies	**Design**	**Ami**	**Carba**	**Relative risk (95% CI) [ARI] [NNTH, 95% CI]**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Quality**
PRIMARY OUTCOME: Any adverse effects: non-specified										
1 (PSP[1])	RCT	14/15 (93.3%)	13/14 (92.9%)	1.01 (0.82, 1.23) ARI = 0.4% NNTH = N/A	N	N	N	VS[c]	N	Very low

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

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

Ami = amitriptyline; Carba = carbamazepine; PSP = post-stroke pain; N/A = not applicable.

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

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

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

[1] Leijon and Boivie (1989)

Cross-class comparative trials: anti-epileptics vs opioid analgesics

Primary outcomes

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

Table 34 GRADE profiles – pregabalin vs oxycodone as monotherapy

No. of studies	Design	Prega (T1)	Oxyco (T2)	Relative risk (95% CI) [ARI] [NNTH, 95% CI]	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
PRIMARY OUTCOME: No. of withdrawals owing to adverse effects										
1 (MixNP[1])	Open RCT	9/134 (6.7%)	11/106 (10.4%)	0.65 (0.28, 1.50) ARI = −3.7% NNTH = N/A	S[a]	N	N	VS[b]	N	Very low
Relative risks were calculated in the direction of T1 compared with T2. T1 = treatment 1; T2 = treatment 2; N = No serious; S = Serious; VS = Very serious Prega = pregabalin; Oxyco = oxycodone; MixNP = mixed neuropathic pain; N/A = not applicable. [a] Open-label study with no blinding; subjective outcome on pain and global improvement; downgrade 1 level. [b] GDG consensus: if there is only 1 study with total number of adverse effects less than 100, the GDG decided that the quality should be graded as 'very low'.										
[1] Gatti et al. (2009)										

Cross-class comparative trials: anti-epileptics vs topical treatments

Primary outcomes

Table 35 GRADE profiles – pregabalin vs topical lidocaine as monotherapy

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

No. of studies	Design	Prega	T.Lido	Relative risk (95% CI) [ARI] [NNTH, 95% CI]	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
PRIMARY OUTCOME: No. of withdrawals owing to adverse effects										
1 (PDN+ PHN[1])	Open RCT	36/153 (23.5%)	4/155 (2.6%)	9.12 (3.33, 25.0) ARI = 20.9% NNTH = 4.8 (3.5, 7.1)	S[d]	N	N	VS[e]	N	Very low
PRIMARY OUTCOME: Any adverse effects: non-specified										
1 (PDN+ PHN[1])	Open RCT	63/153 (41.2%)	9/155 (5.8%)	7.09 (3.66, 13.7) ARI = 35.4% NNTH = 2.8 (2.3, 3.7)	S[d]	N	N	VS[e]	N	Very low

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

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

Prega = pregabalin; T.Lido = topical lidocaine; PDN = painful diabetic neuropathy; PHN = post-herpetic neuralgia; N/A = not applicable.

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

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

[c] Total number of events (positive outcome) less than 300.

[d] Open-label study with no blinding; downgrade 1 level.

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

[1] Baron et al. (2009)

Cross-class comparative trials: antidepressants vs topical treatments

Primary outcomes

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

Table 36 GRADE profiles – amitriptyline vs topical capsaicin as monotherapy

No. of studies	Design	Ami (T1)	T.Cap (T2)	Relative risk (95% CI) [ARI] [NNTH, 95% CI]	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
PRIMARY OUTCOME: Sedation (adverse effects)										
1 (PDN[1])	RCT	69/117 (59.0%)	0/118 (0.0%)	∞ (∞) ARI = 59.0% NNTH = N/A	N	N	N	VS [a]	N	Very low
PRIMARY OUTCOME: Burning (adverse effects)										
1 (PDN[1])	RCT	0/117 (0.0%)	68/118 (57.6%)	0.00 (0.00, ∞) ARI = −57.6% NNTH = N/A	N	N	N	VS [a]	N	Very low

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

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

Ami = amitriptyline; T.Cap = topical capsaicin; PDN = painful diabetic neuropathy; N/A = not applicable.

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

[1] Biesbroeck et al. (1995)

Other reported pain outcomes

Table 37 GRADE profiles – amitriptyline vs topical capsaicin as monotherapy

No. of studies	Design	Ami (T1)	T.Cap (T2)	Mean (SD) at endpoint [p-value]	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
OTHER REPORTED PAIN OUTCOME: Pain relief (Scale: VASpr-100mm)										
1 (PDN[1])	RCT	108	104	Ami = 57.0 (3.6) T.Cap = 55.1 (3.5) p > 0.05	N	N	S[a]	S[b]	N	Low
No. of studies	**Design**	**Ami**	**T.Cap**	**Mean change (SD) from baseline [p-value]**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Quality**
OTHER REPORTED PAIN OUTCOME: Pain intensity (Scale: VASpi-100mm)										
1 (PDN[1])	RCT	108	104	Ami = −29.1 (2.9) T.Cap = −26.1 (2.9) p > 0.05	N	N	S[a]	S[b]	N	Low

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

Ami = amitriptyline; T.Cap = topical capsaicin; PDN = painful diabetic neuropathy

[a] Indirect outcome measure.

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

[1] Biesbroeck et al. (1995)

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

Primary outcomes

Table 38 GRADE profiles – imipramine vs venlafaxine as monotherapy

No. of studies	Design	Imipra (T1)	Venla (T2)	Relative risk (95% CI) [ARR] [NNTB, 95% CI]	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
PRIMARY OUTCOME: Patient-reported global improvement/impression of change[a]										
1 (Poly[1])	RCT	14/33 (42.4%)	8/33 (24.2%)	1.75 (0.85, 3.60) ARR = 18.2% NNTB = N/A	N	N	N	S[b]	N	Moderate
No. of studies	**Design**	**Imipra**	**Venla**	**Relative risk (95% CI) [ARI] [NNTH, 95% CI]**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Quality**
PRIMARY OUTCOME: Dizziness (adverse effects)										
1 (Poly[1])	RCT	3/33 (9.1%)	2/33 (6.1%)	1.50 (0.27, 8.40) ARI = 3.0% NNTH = N/A	N	N	N	VS[c]	N	Very low
PRIMARY OUTCOME: Dry mouth (adverse effects)										
1 (Poly[1])	RCT	12/33 (36.4%)	4/33 (12.1%)	3.00 (1.08, 8.35) ARI = 24.3% NNTH = 4.1 (2.3, 27.9)	N	N	N	VS[c]	N	Very low
PRIMARY OUTCOME: Blurred vision (adverse effects)										
1 (Poly[1])	RCT	1/33 (3.0%)	1/33 (3.0%)	1.00 (0.07, 15.3) ARI = 0.0% NNTH = N/A	N	N	N	VS[c]	N	Very low
PRIMARY OUTCOME: Any adverse effects: non-specified										
1 (Poly[1])	RCT	13/33 (39.4%)	11/33 (33.3%)	1.18 (0.62, 2.25) ARI = 6.1% NNTH = N/A	N	N	N	VS[c]	N	Very low

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

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

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

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

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

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

[1] Sindrup et al. (2003)

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

Primary outcomes

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

Table 39 GRADE profiles – amitriptyline vs nortriptyline as monotherapy

No. of studies	Design	Ami (T1)	Nort (T2)	Relative risk (95% CI) [ARI] [NNTH, 95% CI]	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
PRIMARY OUTCOME: Dry mouth (adverse effects)										
1 (PHN[1])	RCT	28/33 (84.8%)	26/33 (78.8%)	1.08 (0.86, 1.35) ARI = 6.0% NNTH = N/A	N	N	N	VS[a]	N	Very low
PRIMARY OUTCOME: Dizziness (adverse effects)										
1 (PHN[1])	RCT	3/33 (9.1%)	1/33 (3.0%)	3.00 (0.33, 27.4) ARI = 6.1% NNTH = N/A	N	N	N	VS[a]	N	Very low
PRIMARY OUTCOME: Drowsiness (adverse effects)										
1 (PHN[1])	RCT	4/33 (12.1%)	6/33 (18.2%)	0.67 (0.21, 2.13) ARI = −6.1% NNTH = N/A	N	N	N	VS[a]	N	Very low
PRIMARY OUTCOME: Any adverse effects: non-specified										
1 (PHN[1])	RCT	31/33 (93.9%)	31/33 (93.9%)	1.00 (0.88, 1.13) ARI = 0.0% NNTH = N/A	N	N	N	VS[a]	N	Very low

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

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

Ami = amitriptyline; Nort = nortriptyline; PHN = post-herpetic neuralgia; N/A = not applicable.

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

[1] Watson et al. (1998)

Combination therapy: anti-epileptics + opioid analgesics vs anti-epileptics alone

Primary outcomes

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

Table 40 GRADE profiles – pregabalin + oxycodone vs pregabalin alone

No. of studies	Design	Prega + Oxyco (T1)	Prega (T2)	Relative risk (95% CI) [ARI] [NNTH, 95% CI]	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
PRIMARY OUTCOME: No. of withdrawals owing to adverse effects										
1 (MixNP[1])	Open RCT	10/106 (9.4%)	9/134 (6.7%)	1.40 (0.59, 3.33) ARI = 2.7% NNTH = N/A	S[a]	N	N	VS[b]	N	Very low

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

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

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

[a] Open-label study with no blinding; downgrade 1 level.

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

[1] Gatti et al. (2009)

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

Table 41 GRADE profiles – gabapentin + oxycodone vs gabapentin alone

No. of studies	Design	Gaba + Oxyco (T1)	Gaba (T2)	Relative risk (95% CI) [ARI] [NNTH, 95% CI]	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
PRIMARY OUTCOME: No. of withdrawals owing to adverse effects										
1 (PDN[1])	RCT	27/169 (16.0%)	9/169 (5.3%)	3.00 (1.45, 6.19) ARI = 10.7% NNTH = 9.4 (5.7, 23.5)	N	N	N	VS[a]	N	Very low
PRIMARY OUTCOME: Constipation (adverse effects)										
1 (PDN[1])	RCT	45/168 (26.8%)	10/167 (6.0%)	4.47 (2.33, 8.58) ARI = 20.8% NNTH = 4.8 (3.5, 7.5)	N	N	N	VS[a]	N	Very low
PRIMARY OUTCOME: Nausea (adverse effects)										
1 (PDN[1])	RCT	43/168 (25.6%)	18/167 (10.9%)	2.37 (1.43, 3.94) ARI = 14.7% NNTH = 6.7 (4.3, 15.0)	N	N	N	VS[a]	N	Very low
PRIMARY OUTCOME: Vomiting (adverse effects)										
1 (PDN[1])	RCT	16/168 (9.5%)	7/167 (4.2%)	2.27 (0.96, 5.38) ARI = 5.3% NNTH = N/A	N	N	N	VS[a]	N	Very low
PRIMARY OUTCOME: Fatigue (adverse effects)										
1 (PDN[1])	RCT	31/168 (18.5%)	14/167 (8.4%)	2.20 (1.21, 3.99) ARI = 10.1% NNTH = 9.9 (5.7, 35.2)	N	N	N	VS[a]	N	Very low
PRIMARY OUTCOME: Dizziness (adverse effects)										
1 (PDN[1])	RCT	25/168 (14.9%)	6/167 (3.6%)	4.14 (1.74, 9.84) ARI = 11.3% NNTH = 8.9 (5.6, 18.6)	N	N	N	VS[a]	N	Very low
PRIMARY OUTCOME: Somnolence (adverse effects)										
1 (PDN[1])	RCT	37/168 (22.0%)	9/167 (5.4%)	4.09 (2.04, 8.20) ARI = 16.6% NNTH = 6.0 (4.1, 10.4)	N	N	N	VS[a]	N	Very low
PRIMARY OUTCOME: Any adverse effects: non-specified										
1 (PDN[1])	RCT	147/168 (87.5%)	119/167 (71.3%)	1.23 (1.10, 1.37) ARI = 16.2% NNTH = 6.2 (4.0, 13.0)	N	N	N	VS[a]	N	Very low

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

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

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

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

[1] Hanna et al. (2008)

Other reported pain outcomes

Table 42 GRADE profiles – gabapentin + oxycodone vs gabapentin alone

No. of studies	Design	Gaba + Oxyco	Gaba	Mean (SD) at endpoint [p-value]	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
OTHER NON-PRIMARY OUTCOME: Pain relief (Scale: Box Scale-11)										
1 (PDN[1])	RCT	169	169	Gaba + Oxyco= 2.1 (2.61) Gaba = 1.5 (2.38) p = 0.007	N	N	S[a]	S[b]	N	Low

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

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

[a] Indirect outcome measure.

[b] Total number of positive events < 300.

[1] Hanna et al. (2008)

Combination therapy: anti-epileptics + opioid analgesics vs opioid analgesics alone

Primary outcomes

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

Table 43 GRADE profiles – pregabalin + oxycodone vs oxycodone alone

No. of studies	Design	Prega + Oxyco (T1)	Oxyco (T2)	Relative risk (95% CI) [ARI] [NNTH, 95% CI]	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
PRIMARY OUTCOME: No. of withdrawals owing to adverse effects										
1 (MixNP[1])	Open RCT	10/106 (9.4%)	11/106 (10.4%)	0.91 (0.40, 2.05) ARI = −1.0% NNTH = N/A	S[a]	N	N	VS[b]	N	Very low

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

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

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

[a] Open-label study with no blinding; downgrade 1 level.

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

[1] Gatti et al. (2009)

Combination therapy: anti-epileptics + antidepressants vs anti-epileptics alone and antidepressants alone

Primary outcomes

The only combination study identified that compared gabapentin plus nortriptyline with gabapentin alone and with nortriptyline alone did not report the primary outcomes of pain or adverse effects.

Other reported pain outcomes

Table 44 GRADE profiles – gabapentin + nortriptyline vs gabapentin alone vs nortriptyline alone

No. of studies	Design	Gaba + Nort	Gaba	Mean change from baseline at endpoint (95% CI)	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
OTHER REPORTED PAIN OUTCOME: Daily pain scores (numerical rating scale)										
1 (PDN/PHN [1])	RCT	45	45	Combination lower than gabapentin = −0.9 (−1.4 to −0.3)	N	N	S[a]	S[b]	N	Low
OTHER REPORTED PAIN OUTCOME: Daily pain scores (numerical rating scale)										
1 (PDN/PHN [1])	RCT	45	45	Combination lower than nortriptyline = −0.6 (−1.1 to −0.1)	N	N	S[a]	S[b]	N	Low

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

Gaba = gabapentin; Nort = nortriptyline; PDN = painful diabetic neuropathy; PHN = post-herpetic neuralgia

[a] Indirect outcome measure.

[b] Total number of positive events < 300.

[1] Gilron et al. (2009)

2.4 Health economics evidence review

A systematic review of economic evidence on the pharmacological management of neuropathic pain found a total of 2273 papers. Full details of the search strategy are given in appendix 10.7.

In addition, the GDG had access to a relevant health technology assessment (HTA) report that had not been published during guideline development. This HTA report (Fox-Rushby JA, Griffith GL, Ross JR et al. [2010] The clinical and cost-effectiveness of different treatment pathways for neuropathic pain [NP]. NIHR Health Technology Assessment [HTA] programme, ref. 05/30/03. In press. Project abstract available from www.hta.ac.uk/1527) reviewed the

clinical and cost effectiveness of different treatment pathways for neuropathic pain. The initial review included all subpopulations for the various conditions associated with neuropathic pain. However, because of the availability of evidence, the HTA report focused on two distinct neuropathic pain populations: people with painful diabetic neuropathy (PDN) and people with post-herpetic neuralgia (PHN).

In our own review of the economic literature, 479 economic studies were found on antidepressants, of which 39 were relevant based on title and abstract scanning. For anti-epileptic (anticonvulsant) drugs, 482 papers were retrieved, of which 40 were shortlisted. The search for opioids yielded 1125 hits, and a total of 140 papers were shortlisted for the review. Finally, 187 articles on topical treatments were found, of which 27 were shortlisted.

Of the 246 papers shortlisted, only 15 were ordered in full text because it was clear that the remaining papers either were studies of the wrong population or were not economic analyses. Papers on people with PHN or PDN (which made up the bulk of the 246 retrieved papers) were excluded because these populations were covered by the HTA report. Of the 15 papers ordered in full text, no study could be included. Reasons for exclusion included: study design (not an economic study); wrong patient population (no neuropathic pain; immediate post-surgery pain); wrong clinical indication (general anaesthetics); wrong route of administration (injection, infusion); and a follow-up period of less than 1 week. Appendix 10.4 lists the excluded studies and reasons for exclusion, in accordance with the economic profiles as set out in ‘The guidelines manual’ (NICE 2009).

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

No health economic modelling was undertaken for this guideline, because the GDG decided that the HTA report that was in development contained

thorough data on the cost effectiveness of treatment pathways (sequences) for two common neuropathic pain conditions. The GDG reviewed, appraised and summarised the HTA report, and the results of the economic analyses from the HTA report informed this guideline as appropriate.

2.4.1 HTA report: methods

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

Markov models were developed for the evaluation of the cost effectiveness of pharmacological treatments for both the PHN and PDN populations. For each population, four separate analyses were conducted. The efficacy review fed data into an indirect comparison of all drugs for which useable data were available. The indirect analysis produced a drug hierarchy in terms of net benefit. Two additional analyses were conducted which will not be fully reported here since they did not inform the GDG decisions: a sequential analysis based on clinical convention to titrate individual tolerated drugs upwards before switching to another drug, and a Bayesian value of information (VOI) analysis that estimated the value of future research, given the underlying uncertainty.

HTA post-herpetic neuralgia (PHN) model

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

leading to withdrawal from treatment; spontaneous subsidence of pain; drug terminated; and death.

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

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

Cost data were relevant for a UK scenario and the model adopted an NHS perspective, accounting for health outcomes in terms of quality-adjusted life years (QALYs). Discounting was in line with NICE's reference case (for details, see chapter 7 of 'The guidelines manual' (NICE 2009).

As no published resource use data were available, a survey of healthcare professionals was undertaken. For the PHN model, three pathways were described: GP-led, consultant-led (by an anaesthetist/pain specialist, neurologist or ophthalmologist), and jointly led care by a GP and a consultant. Results were then incorporated into the model and a separate sensitivity analysis was undertaken to test the associated uncertainty. Unit costs were taken from established sources (Personal Social Services Research Unit [PSSRU], 'British National Formulary' [BNF] and NHS drug tariff). Following

changes in pricing during stakeholder consultation on the guideline in November 2009, the unit costs of all drugs and adverse events were updated to be correct as of December 2009. The analyses were rerun using these up-to-date unit costs and reported in January 2010 (see the draft updated analysis report for details of unit costs – available from www.hta.ac.uk/1527). The dosing regimen of pregabalin was also adjusted in the rerun analyses, to reflect the GDG's recommendations (see recommendation 1.1.10).

The indirect comparison involved probabilistic modelling of pregabalin (150, 300 and 600 mg/day), gabapentin (1800, 2400 and 3600 mg/day), oxycodone 60 mg/day, lidocaine 5% patch, epidural methylprednisolone 60 mg and lidocaine intrathecal 90 mg.

Important assumptions for the PHN model

These assumptions are adapted from those in the HTA report.

- The cycle length was 6 weeks, within which period a clinical change (pain relief or adverse event) would be expected in practice.
- Pain relief was assumed to relate to a reduction in the symptoms, and not the duration, of pain.
- Beneficial effects and adverse events were assumed to start from the second cycle, or after 6 weeks.
- Patients who did not achieve pain relief within the period of time for which the trial data were available were assumed to not respond to the drug. These patients were prescribed a new drug in the sequential analysis.
- Patients who experienced severe adverse events leading to withdrawal had the drug terminated immediately. Adverse events were treated if necessary.
- Effectiveness period of trial: pain relief and adverse event data from trials with durations of less than 6 weeks were not extrapolated beyond the trial duration (that is, it was assumed that there was no more pain relief or adverse events than were found during the trial).
- Patients who experienced pain relief were assumed to remain on the drug and to continue to get pain relief until spontaneous subsidence of pain or death.

- Patients who experienced pain relief and minor adverse events were assumed to have been titrated to the minimum dose that gives pain relief. They would continue to experience the adverse events or require drugs to alleviate them until spontaneous subsidence of pain or death.
- Medication prescribed for minor adverse events was assumed to make the adverse events tolerable.
- Less than 50% pain reduction was considered insufficient pain relief that did not result in a change in health state utility or QALYs.
- Failure to respond to one drug was assumed not to affect the likelihood of responding to another.
- The trials of clinical effectiveness identified from the systematic review did not distinguish between patients who did and did not obtain pain relief when reporting minor adverse events. It was assumed that all patients randomised to the treatment arm had an equal probability of adverse events regardless of whether or not they obtained pain relief.
- Because PHN is not associated with increased mortality, all-cause mortality for the general public was applied in the model.
- In the base case, adherence to drug dose and frequency was assumed to be 100%, which reflects the trial conditions under which the clinical effectiveness data were collected.

HTA painful diabetic neuropathy (PDN) model

The model was described as simulating a cohort of 2000 people aged 55 years over a lifetime horizon, with a maximum of 360 cycles each of 6 weeks' duration. Similar to the PHN model, this model was based on two pain states (at least 50% pain reduction or no pain reduction), following the conventional, dichotomous representation of the natural history of pain relief in the literature. Because spontaneous pain resolution was deemed unlikely, this health state was omitted from the PDN model.

As in the PHN model, a 6-week cycle was selected to represent the average expected interval between clinical consultations and over which the symptoms would change. This cycle length was also described as being suitable to represent increased mortality as a result of myocardial infarction (MI), which

might be a relevant clinical endpoint for people receiving certain doses of drugs such as amitriptyline. Model assumptions differed slightly from those of the PHN model.

For the model, effectiveness in terms of pain relief was defined and implemented in the model using the same methods as in the PHN model. However, in the absence of PDN-specific mortality data, the PDN model used age-adjusted all-cause mortality data for people with diabetes. Spontaneous subsidence of pain was deemed not to be applicable to this model. Utilities for health states and adverse events were derived using the same methods as outlined for the PHN model. Compliance was assumed to be 100% at base case, but was lowered to 50% in sensitivity analysis to test uncertainty.

Because of a complete lack of published data, resource use was estimated via a survey to elicit expert opinion. For PDN, five main care pathways were described: GP-led care; pain-specialist-led care; diabetologist-led care; jointly led care by a GP and a pain specialist; and jointly led care by a GP and a diabetologist. At base case, resource use was consistent with patients being under the care of a diabetologist. The model adopted an NHS perspective, accounting for health outcomes in terms of QALYs. Unit costs were taken from established sources (PSSRU, BNF, NHS drug tariff). Following changes in pricing during stakeholder consultation on the guideline in November 2009, the unit costs of all drugs and adverse events were updated to be correct as of December 2009. The analyses were rerun using these up-to-date unit costs and reported in January 2010 (see the draft updated analysis report for details of unit costs – available from www.hta.ac.uk/1527). The dosing regimen of pregabalin was also adjusted in the rerun analyses, to reflect the GDG's recommendations (see recommendation 1.1.10). Discounting of costs and outcomes was in line with NICE methods (NICE 2009). Results were incorporated into the model and a separate sensitivity analysis was undertaken to test the associated uncertainty.

For the indirect modelling, some drugs could only be modelled deterministically – namely lamotrigine (400 mg/day) and nortriptyline plus fluphenazine (60 + 3 mg/day). Only the drugs that could be modelled

probabilistically were included in the sequential analysis. These were pregabalin (150, 300 and 600 mg/day), gabapentin (900 and 3600 mg/day), oxcarbazepine (600, 1200 and 1800 mg/day), zonisamide (600 mg/day), topiramate (400 mg/day), amitriptyline (75 mg/day), duloxetine (20, 60 and 120 mg/day) and venlafaxine (75 and 225 mg/day).

Important assumptions for the PDN model

Assumptions for the PDN model were the same as for PHN model, except for the following:

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

2.4.2 HTA report: results

Modelling indirect comparisons: base-case results

The indirect analysis presented results in terms of decreasing mean net benefit associated with each drug at a WTP threshold of £30,000 per QALY gained.

PHN model

For the PHN model, the indirect analysis found that pregabalin 150 mg/day is the most cost-effective treatment, as it provides the highest mean net benefit. If this treatment does not provide sufficient pain relief, the next most cost-effective option is pregabalin 300 mg/day, followed by pregabalin 600 mg/day, gabapentin 3600 mg/day, gabapentin 1800 mg/day, gabapentin 2400 mg/day, oxycodone 60 mg/day, lidocaine intrathecal 90 mg, lidocaine 5% patch and epidural methylprednisolone 60 mg.

At base case for the PHN population, pregabalin 150 mg/day had the highest probability of being most cost effective of 59.5%, followed by pregabalin 300 mg/day (30.2%) and pregabalin 600 mg/day (10.3%). All other modelled drugs, including gabapentin 1800, 2400 and 3600 mg/day and oxycodone, had zero probability of being the most cost-effective treatment option.

PDN model

For the PDN model, the hierarchy of cost effectiveness from most to least cost effective in terms of mean net benefit was duloxetine 60 mg/day, duloxetine 20 mg/day, amitriptyline 75 mg/day, duloxetine 120 mg/day, pregabalin 600 mg/day, oxcarbazepine 1200 mg/day, pregabalin 300 mg/day, oxcarbazepine 600 mg/day, gabapentin 3600 mg/day, oxcarbazepine 1800 mg/day, pregabalin 150 mg/day, topiramate 400 mg/day, venlafaxine 225 mg/day, venlafaxine 75 mg/day, gabapentin 900 mg/day and zonisamide 600 mg/day. When results for all doses of each drug were added together, oxcarbazepine appears more cost effective than pregabalin at a WTP threshold of £30,000 per QALY gained. However, this difference in net benefit was very small, although it increased slightly at the lower WTP threshold of £20,000 per QALY. The difference between pregabalin and the next best drug, gabapentin, was much greater, and so were the decrements in net benefit moving down the hierarchy to the least cost-effective drug, zonisamide.

At base case for the PDN population, duloxetine 60 mg/day had the highest probability of being most cost effective of 34.5%, followed by duloxetine 20 mg/day (33.2%), amitriptyline 75 mg/day (21.1%), pregabalin 300 mg/day (3.41%) and duloxetine 120 mg/day (3.37%).The remaining 4.42% was distributed among a further five treatment options, with seven options having a zero probability of being most cost effective.

Modelling indirect comparisons: sensitivity analysis and uncertainty

PHN model

For the PHN model, the sensitivity analysis revealed little uncertainty at the WTP threshold of £30,000 per QALY gained, with various dosages of pregabalin (see the ‘base-case results’ section above) having a combined

probability of 100% of being most cost effective. This result did not change at the lower WTP threshold of £20,000 per QALY. This corresponds to pregabalin being expected to provide the highest net benefit compared with the other drugs included in the model.

PDN model

Probabilistic sensitivity analysis for the PDN model showed that, at the WTP threshold of £30,000 per QALY gained, duloxetine at various dosages (see the 'base-case results' section above for probabilities for individual dosages) had a 70.8% probability of being most cost effective, followed by amitriptyline at 21.3%, pregabalin at 4.4% and oxcarbazepine at 3.6%, with the remaining drugs having a negligible (less than 2%) probability of being most cost effective.

At the WTP threshold of £20,000 per QALY, the order of drugs in terms of their probability of being the most cost effective changed to: duloxetine 20 mg/day (37.8%), duloxetine 60 mg/day (28.9%; resulting in a combined probability for duloxetine of 66.7%) and amitriptyline 75 mg/day (29.8%). Oxcarbazepine in all three modelled doses had a low probability of being most cost effective (2.7%), whereas pregabalin was very unlikely to be most cost effective (0.3% probability). All of the remaining drugs, including gabapentin, had a zero probability of being most cost effective.

The cost-effectiveness acceptability curve (CEAC) for the PDN model shows that at a WTP threshold of between £20,000 and £30,000 per additional QALY, two drug treatments are highly likely to be cost effective compared with the remaining comparators evaluated: duloxetine 20 mg/day and duloxetine 60 mg/day. Duloxetine 20 mg/day was most likely to be most cost effective at WTP thresholds between £14,000 and approximately £28,000 per additional QALY. Above a threshold of £28,000 per additional QALY, duloxetine 60 mg/day became most likely to be most cost effective. Below a threshold of £14,000 per additional QALY, amitriptyline had the highest probability of being most cost effective.

In order to recommend the most cost-effective drug, it is necessary to check the consistency of a drug being most cost effective and providing the highest expected net benefit. For the PDN model, the data show that this relationship is consistent at both WTP thresholds. Duloxetine, particularly at the lower doses of 20 and 60 mg/day, provides the highest net benefit and has the highest probability of being most cost effective (with the same dosages again coming first and second in rank order). Gabapentin has a zero probability of being most cost effective and provides a lower net benefit than similar drugs in its class, including pregabalin and oxcarbazepine. If duloxetine is not an option, amitriptyline provides the second highest net benefit, followed by pregabalin and oxcarbazepine. In the clinical context of this guideline, pregabalin and amitriptyline both seem to be viable options after duloxetine. (See section 2.5 for a discussion of the clinical interpretation.)

For the drugs modelled deterministically for the PDN model, one-way and multi-way sensitivity analyses did not change the hierarchy of cost effectiveness, with nortriptyline plus fluphenazine being consistently more cost effective than lamotrigine. Nortriptyline was combined with fluphenazine in the trial to mask differences from placebo and strengthen the blinding, and hence was a single active treatment.

2.4.3 Discussion

This discussion will contrast the approaches used for the HTA report and the current clinical guideline and discuss their potential impact on interpretation and generalisability for this guideline. Then the remaining limitations of the model will be discussed.

An evidence statement summarising the (draft) findings from the HTA report is given in section 2.2.6.

Differences between the HTA report and the current guideline

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

validity of the HTA report, but to assess the generalisability of the HTA report in relation to the current guideline.

Efficacy review for HTA modelling – comments on generalisability

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

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

The exclusion criteria for the current guideline, which were agreed by the GDG members based on their expertise and experience, differed from those of the HTA report. Exclusion criteria that were used for the current guideline but not for the HTA report are listed in table 45.

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

1	Adults with neuropathic pain arising directly from trauma or orthopaedic surgical procedures.
2	Studies on terminal pain, psychogenic pain, somatoform pain or musculoskeletal pain.
3	Concentration–response pharmacokinetic studies.
4	Administration of drugs by an intravenous or epidural route (except opioid analgesics).
5	For antidepressants and anti-epileptics, drug administration by topical application (but there was no restriction on the route of administration for opioid analgesics).
6	Studies that measure spasticity or spasm, but not neuropathic pain.
7	Studies on experimentally induced pain.
8	Pre-emptive analgesia studies on acute pain with follow-up of less than 4 weeks (for example, pre-emptive analgesia studies on postoperative/post-surgical acute pain with 24 hours or 1 week after the operation as the end-point).
9	Studies with a sample size of less than 10.
10	Crossover studies with no washout and no analysis of carryover effects, or a washout period of less than 1 week.
11	Studies with a treatment period of less than 4 weeks for antidepressants and anti-epileptics, less than 3 weeks for topical capsaicin or less than 1 week for opioids and topical lidocaine.
12	Papers in languages other than English.

Although the minimum trial duration (criteria 8 and 11 in table 45) was not specified in the inclusion criteria of the HTA report, the efficacy data used in the modelling were taken from RCTs with trial durations of at least 4 weeks. Limiting the route of drug administration (criteria 4 and 5) would not seem to make a lot of difference, as only lidocaine was modelled. Washout periods (criterion 10) were not taken into consideration explicitly in the HTA report; however, a summary value for rate ratios was taken from the meta-analysis, which gives some confidence in the magnitude of effect used. Applying the guideline's exclusion criterion (criterion 9) on study size (that is, excluding studies with very few participants) in the meta-analysis and probabilistic modelling would have no notable impact on the overall findings, as no studies in the probabilistic modelling in the HTA report had a sample size of below 10.

In the HTA review, the primary pain outcomes for meta-analysis were 50% response to pain (or 50% improvement in pain) and 30% response to pain (or

30% improvement in pain). The HTA review dichotomised ‘global improvement’ measures to construct 50% pain improvement and 30% pain improvement, and then pooled them with the 50% and 30% pain reduction in meta-analysis to give categories of ‘50% response to pain’ and ‘30% response to pain’. The GDG agreed that pain reduction and global improvement are two distinct outcomes that measure different aspects in pain research, a notion supported by IMMPACT. Therefore results for pain reduction and global improvement are pooled and presented separately in the current guideline.

For the health economic modelling in the HTA report, pain relief was used to define the health states, to which a global valuation of quality of life was assigned – that is, a utility estimate. Pain and other outcome data are used widely to feed into utility estimates, and pain is a dimension on the EQ-5D tool that is frequently used to measure quality of life for economic evaluations. Similar approaches to choosing and defining pain outcomes are taken in order to be as inclusive as possible and to avoid discarding data unnecessarily. From a purely conceptual viewpoint, more levels of pain states (such as 30% pain reduction) could have been modelled, but it is unlikely that this would have altered the results of the analysis, especially for those drugs most likely to be cost effective. However, it should be noted that most studies presented 50% pain reduction as the cut off, few studies used both 30% and 50% pain reduction, and fewer still provided data on 30–49% and 50% or more pain reduction.

A drug that fails to provide less than 50% pain reduction does not incur any health benefits in the model. However, introducing a lower cut-off point may result in some benefit, albeit smaller than that obtained with a drug that reduces pain by at least 50%. Thus the differences between the more effective and less effective drugs may become smaller with this approach, but the rank order in the indirect analysis would not change. In terms of the probability of a treatment being the most cost effective, those treatments that currently have a zero probability of being cost effective may achieve a small probability, but this would not alter the interpretation of the findings.

Health economic evaluation in the HTA report – comments on generalisability

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

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

As discussed above, both PHN and PDN models were based on two pain states, which were 'at least 50% pain reduction' and 'no pain reduction'. The assumption was that less than 50% pain reduction is considered insufficient and does not result in a change in health state utility or QALYs. In addition to the assumptions and implications for the guideline discussed above, basing the modelling on this meta-analysed outcome resulted in numerous drugs not being evaluated in the modelling (especially TCAs for PHN) because of a lack of data. This is a serious limitation to the completeness and applicability of the analysis, and the GDG carefully considered complementing the recommended drugs with others for the treatment of all subgroups of people with neuropathic pain.

For both the PHN and PDN models, expert opinion supplemented the data where insufficient data were available. Six experts in PHN and four experts in PDN completed a questionnaire, and the answers obtained informed the costing, as well as providing information on adverse events. The model was not sensitive to changing the three care settings for PHN or the five settings

for PDN, and the rank order of the most cost-effective drugs remained unchanged.

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

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

HTA model limitations resulting from the reliance on RCT data

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

The different drug doses used in the models were based on the efficacy trials. However, drug doses in trials do not necessarily reflect the doses prescribed

in practice, and may be substantially higher. This is an important issue and affects evidence of both clinical and cost effectiveness. Making recommendations in an evidence-based way requires careful consideration of valid inferences. Deviations from the evidence are possible only where transparent reasoning allows this.

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

Neither the PHN model nor the PDN model in the HTA report included combination therapy, which was a key question to be addressed by the current guideline. The limitations of the clinical evidence that informed the modelling did not allow combination therapies to be modelled. There may have been some crossover effect, as some trials allowed patients to take co-analgesics or did not report on this matter. It was not possible to estimate the implications for pain relief or adverse-event data recorded in the trials. In the absence of reliable evidence, any recommendations relating to treatment combinations should be made with caution. The deliberations and decision-making of the GDG have been recorded and are presented transparently.

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

Comorbidities associated with PDN and diabetes, such as cardiovascular disease and peripheral vascular disease, were not accounted for in the model,

because the systematic review excluded efficacy trials that included patients with comorbidities.

Because the RCTs for patients with PHN or PDN evaluated chronic neuropathic pain of moderate to severe intensity, the findings from such studies cannot be generalised to patients with mild PHN or PDN pain. This was taken into account by the GDG when making its recommendations.

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

In conclusion, all of the items listed above were discussed by the GDG, and consistency between the effectiveness review and the indirect cost-effectiveness evidence was checked. The debate and reasoning behind recommendations is recorded in section 2.5.

2.5 Evidence to recommendations

2.5.1 Antidepressants

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

TCAs

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

The GDG acknowledged that the majority of the evidence for TCAs is from studies on amitriptyline, and that the evidence covers various study populations with different neuropathic pain conditions. Since amitriptyline is widely used for treating neuropathic pain in current practice, the GDG agreed that amitriptyline should be recommended as either first-line or second-line treatment, depending on the person's condition, other lifestyle factors and current medication usage. Amitriptyline is not licensed for neuropathic pain,

but the evidence base for treatment efficacy was deemed sufficient to make this positive recommendation.

Because amitriptyline is not licensed for neuropathic pain, the GDG came to the consensus that its initial dosage and titration should be lower than is recommended in the 'British National Formulary' (BNF). The GDG agreed that clear statements on drug dosage and titration in the recommendations are crucial for non-specialist settings, to emphasise the importance of titration to achieve maximum benefit. The GDG also agreed that the adverse effects of amitriptyline, as well as the special warnings and precautions for its use as specified in the SPC (based on advice from the Medicines and Healthcare Products Regulatory Agency [MHRA]), should be discussed with the person and weighed against the benefit provided.

Amitriptyline for painful diabetic neuropathy

Based on the evidence of clinical and cost effectiveness, duloxetine was recommended as first-line treatment for people with painful diabetic neuropathy (see below). However, the GDG came to consensus that if duloxetine is contraindicated, amitriptyline should be offered as an alternative first-line treatment for people with this condition.

Nortriptyline and imipramine: alternatives to amitriptyline

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

Desipramine

Although there was some evidence for the efficacy of desipramine, it is no longer in the BNF, and so should not be used in clinical practice.

SNRIs

Duloxetine: first-line treatment for painful diabetic neuropathy

The GDG agreed that there is high-to-moderate-quality evidence for the efficacy of duloxetine in treating neuropathic pain. However, all three included studies on duloxetine were in patients with painful diabetic neuropathy, and evidence of cost effectiveness is specifically for the treatment of this condition (see section 2.4). Cost-effectiveness evidence demonstrated that duloxetine was the most cost-effective treatment for painful diabetic neuropathy. Therefore the GDG decided that duloxetine should be recommended as first-line treatment specifically for people with painful diabetic neuropathy. The GDG also agreed that the adverse effects of duloxetine, as well as the special warnings and precautions for its use as specified in the SPC (based on MHRA advice), should be discussed with the person and weighed against the benefit provided.

Venlafaxine

There is high-to-moderate-quality evidence for the efficacy of venlafaxine in treating neuropathic pain. However, based on information from the MHRA, the GDG agreed that the use of venlafaxine for the treatment of neuropathic pain would need specialist care and regular monitoring, and so it should not be initiated in non-specialist settings.

Second-line treatment after first-line treatment with an antidepressant

The GDG agreed that if satisfactory pain reduction was not achieved with amitriptyline (or nortriptyline and imipramine as alternatives) (that is, an antidepressant) as first-line treatment, a drug from another therapeutic class (namely an anti-epileptic – see section 2.5.2) should be recommended as second-line treatment, either as monotherapy or as combination therapy with first-line treatment, instead of trying another antidepressant. As described in section 2.5.2, the recommended anti-epileptic drug is pregabalin.

For people with painful diabetic neuropathy, the GDG concluded that if satisfactory pain reduction was not achieved with duloxetine as first-line treatment, it is possible that amitriptyline could be effective for a small subpopulation of people with this condition, even though both of these drugs are antidepressants. The economic model for the painful diabetic neuropathy population indicated that amitriptyline was more cost effective than duloxetine 120 mg/day, suggesting that amitriptyline is potentially cost effective for second-line treatment. The GDG was also concerned that a person may have a rapid escalation of treatment options in non-specialist settings if amitriptyline, which may be another effective option, was not offered. Therefore the GDG came to the consensus that if duloxetine is not effective as first-line treatment, people with painful diabetic neuropathy should be given the opportunity to switch to amitriptyline or pregabalin, or to combine duloxetine with pregabalin, as second-line treatment.

2.5.2 Anti-epileptics

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

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

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

- Evidence from indirect comparisons of meta-analyses of the two treatments showed that pregabalin has lower NNT values for at least 30% pain reduction and at least 50% pain reduction compared with gabapentin, with a similar adverse-effect profile.
- Pregabalin has simple dosing and titration compared with gabapentin.

- Cost-effectiveness modelling showed that pregabalin is more cost effective than gabapentin (see section 2.4.2).

Following changes in pricing during stakeholder consultation on the guideline in November 2009, the unit costs of all drugs and adverse events were updated and the cost-effectiveness analyses were rerun (see section 2.4.1). The results showed that pregabalin was still more cost effective than gabapentin, although the difference was slightly reduced. Overall, pregabalin provided more mean net benefit than gabapentin, and had a higher probability of being more cost effective. With the updated prices and an amended dosing regimen for pregabalin (to reflect the GDG's recommendations), gabapentin 3600 mg/day (at 9th place in hierarchy) was the only instance where gabapentin provided a marginally higher mean net benefit than pregabalin (at 150 mg/day) (11th place). This result was considered by the GDG in a clinical context. Pregabalin 150 mg/day is a comparatively low dose and most people would be titrated up to a higher dose. In contrast, gabapentin 3600 mg/day is a very high dose, which can be difficult to manage and titrate. The GDG concluded that these considerations, together with the clinical evidence, justified the decision to recommend pregabalin rather than gabapentin, despite the minor change in the modelling results. The evidence presented, especially the health economic evaluation, has shown the certainty of the treatment sequence, and therefore supports the recommendation.

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

The GDG further agreed that the adverse effects of pregabalin should be discussed with the person and weighed against the benefit provided.

Second-line treatment after first-line treatment with pregabalin

The GDG agreed that if satisfactory pain reduction was not achieved with pregabalin (an anti-epileptic) as first-line treatment, a drug from another therapeutic class (namely an antidepressant – see section 2.5.1) should be recommended as second-line treatment, either as monotherapy or as combination therapy with first-line treatment, instead of trying another anti-epileptic. As described above, the recommended antidepressant is amitriptyline, with imipramine or nortriptyline as an alternative if amitriptyline is effective but the person cannot tolerate the adverse effects.

Topiramate and oxcarbazepine

There was only limited evidence (mainly from studies on patients with painful diabetic neuropathy) for the efficacy of topiramate and oxcarbazepine, and this evidence showed that patients on either of these drugs were more likely to withdraw because of adverse effects than patients on gabapentin or pregabalin (that is, the NNTH values were lower for topiramate and oxcarbazepine).

The economic model for the painful diabetic neuropathy population included three doses of oxcarbazepine. Using prices that were correct at December 2009, the model showed only very small differences in net benefit between the various doses of oxcarbazepine and pregabalin at a WTP threshold of £30,000 per QALY gained. Despite the fact that the pragmatic sequence in the HTA report changed following the rerun of the cost-effectiveness analyses so that oxcarbazepine preceded pregabalin, it was felt that this evidence was not certain enough to balance the concern posed by the clinical evidence. Given the data on adverse effects and withdrawal, the GDG did not think that oxcarbazepine should be offered and managed routinely in a non-specialist setting. In addition, topiramate was unlikely to be cost effective when other drugs, such as pregabalin, are available. Therefore it was agreed that topiramate and oxcarbazepine should not be recommended for the treatment of neuropathic pain in non-specialist settings.

Carbamazepine for the treatment of trigeminal neuralgia

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

2.5.3 Opioids

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

Tramadol: third-line treatment for neuropathic pain

There was moderate-quality evidence on primary pain outcomes for both tramadol and morphine. However, the number of patients withdrawing from studies because of adverse effects and the incidence of constipation were both lower for patients on tramadol compared with those on morphine. The GDG also acknowledged that although tramadol may lead to dependence in some people, this drug is commonly used in non-specialist settings compared with other opioid analgesics. Hence the GDG felt that it is valid and appropriate to recommend tramadol as third-line treatment for neuropathic

pain in non-specialist settings, either as monotherapy or as combination therapy with second-line treatment (as rescue analgesics[19]). This will ensure that treatment can be continued while a person is waiting for referral to a specialist pain service and/or a condition-specific service. The GDG also agreed that clear statements on drug dosage and titration in the recommendations are crucial for non-specialist settings, to emphasise the importance of titration to achieve maximum benefit.

The acquisition costs of tramadol are relatively low for 50 mg preparations (between approximately £30 and £40 per year), and higher for higher-dose, modified-release preparations (12-hour release preparations: 100 mg, £70 to £100 per year; 150 mg, £110 to £170 per year; 200 mg, £150 to £220 per year; 24-hour release preparations: 300 mg, £270 to £300 per year; 400 mg, £370 to £400 per year). If tramadol provides pain relief for people for whom first-line and second-line treatments were ineffective and who are experiencing intolerable pain, this acquisition cost is likely to represent value for money

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

Morphine and oxycodone

The GDG agreed that the evidence on the efficacy of morphine and oxycodone for treating neuropathic pain was limited and of only low or moderate quality. In addition, as described above, the evidence showed that patients treated with morphine were more likely to withdraw because of adverse effects (that is, lower NNTH values) than patients treated with tramadol. There was insufficient evidence on the primary pain outcomes for oxycodone. Moreover, the GDG was concerned about the risk of long-term dependence, the severe adverse effects and the potential fatality of overdose

[19] Rescue analgesics are analgesics for breakthrough pain, which is pain that comes on suddenly for short periods of time and is not alleviated by the patient's normal pain suppression management.

with morphine and oxycodone. The GDG was also concerned that clinicians in non-specialist settings have very different levels of experience in prescribing and managing the long-term use of morphine and oxycodone. Therefore the GDG came to the consensus that morphine and oxycodone should not be started in non-specialist settings without an assessment by a specialist pain service or a condition-specific service. The GDG also concluded that if an assessment is carried out and treatment with morphine or oxycodone is started by a specialist pain service or condition-specific service, this treatment may be continued in a non-specialist setting provided that there is a multidisciplinary care plan, local shared care agreements and careful management of adverse effects.

2.5.4 Topical treatments

Topical capsaicin

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

Topical lidocaine

Because none of the included studies on topical lidocaine reported the primary outcomes of pain, the GDG referred to the evidence statements for 'other reported pain outcomes' to generate discussion. The GDG agreed that there is a lack of evidence (especially placebo-controlled trials) for the efficacy of topical lidocaine for treating neuropathic pain in non-specialist settings. Moreover, in health-economic modelling, lidocaine was modelled for the patient population with painful diabetic neuropathy and provided the lowest mean net benefit at WTP thresholds between £20,000 and £30,000 per QALY gained, and had a zero probability of being the most cost-effective treatment

when pregabalin is an option. However, based on the clinical experience of members, the GDG acknowledged that a subgroup of people with 'localised neuropathic pain' who are unable to take oral medication because of medical conditions and/or disability may benefit from topical lidocaine. In view of the limited evidence available, the GDG felt that it could not recommend the use of topical lidocaine as first-line or second-line treatment across all neuropathic pain conditions in non-specialist settings. However, topical lidocaine may play a role as a rescue analgesic (while waiting for a referral to a specialist pain service) in a very small subgroup of people with localised pain who are unable to take oral medication because of medical conditions and/or disability.

2.5.5 Comparative and combination trials

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

Amitriptyline or nortriptyline vs gabapentin

The GDG agreed that there was inconsistent, moderate-quality evidence on the efficacy of amitriptyline or nortriptyline compared with gabapentin. Moreover, as there is uncertainty in terms of the low-quality comparative evidence on adverse effects, and in the evidence from the cost-effectiveness analysis (see section 2.4.2), the GDG agreed that amitriptyline (with nortriptyline as an alternative) should be recommended as an option for first-line and second-line treatment.

Pregabalin vs oxycodone and pregabalin vs topical lidocaine

The evidence from both comparisons was of very low quality. In the economic modelling, topical lidocaine has virtually no probability of being a cost-effective treatment option when pregabalin is available. Therefore the GDG agreed that no recommendations should be made based on the comparative evidence.

Amitriptyline vs topical capsaicin

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

Imipramine vs venlafaxine

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

Amitriptyline vs nortriptyline

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

Combination therapy

Included studies on combination therapy compared pregabalin + oxycodone with pregabalin alone, gabapentin + oxycodone with gabapentin alone, pregabalin + oxycodone with oxycodone alone, and gabapentin + nortriptyline with gabapentin alone and nortriptyline alone. The evidence from these studies was of low or very low quality. Therefore the GDG agreed that no recommendations should be made based on these limited studies on specific combinations.

However, based on current clinical practice and the experiences of patients and carers, the GDG came to the consensus that amitriptyline (or nortriptyline or imipramine as alternatives) in combination with pregabalin, and duloxetine in combination with pregabalin, should be options for second-line treatment as combination therapy (see recommendation 1.1.13) where unsatisfactory pain reduction is achieved with a single drug, or where switching or stopping drugs is inappropriate for a particular person. A similar consensus was reached for tramadol in combination with second-line treatment (see recommendation 1.1.14).

2.5.6 Key principles of care

The GDG acknowledged that the low-quality evidence on adverse effects for both antidepressants and anti-epileptics was restricted by which, and how, data on particular adverse effects were collected in the trials. Based on the knowledge and experience of GDG members in clinical practice, the evidence did not fully reflect a complete picture of the adverse effects that people would experience in real life. Issues such as the person's vulnerability to specific adverse effects because of comorbidities, contraindications and safety considerations, current medication usage, mental health, lifestyle factors, daily activities and participation[20], patient preference and patients' information needs should all be taken into consideration when selecting pharmacological treatments. The GDG further discussed that extra caution is needed when switching or combining drugs.

The GDG stressed that both early and regular clinical reviews are important in order to assess the effectiveness of the treatment and to monitor drug titration, tolerability, adverse effects and the need to continue treatment (including the possibility of gradually reducing the dose if sustained improvement is observed). The GDG acknowledged that patient diaries may be a useful tool for recording progress and informing the clinical reviews. The principle of carrying out regular clinical reviews should apply to all treatments throughout the care pathway to ensure that people receive appropriate care.

As referral to specialist pain services is not an exit from non-specialist care, but the start of a collaborative, ongoing approach to management, the GDG felt that the gateway for referrals to 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

[20] 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.

or there are changes in, or deterioration of, the person's pain, health condition, and/or daily activities and participation.

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

2.6 Recommendations

Key principles of care

1.1.1 Consider referring the person to a specialist pain service and/or a condition-specific service[21] at any stage, including at initial presentation and at the regular clinical reviews (see recommendation 1.1.9), if:

- they have severe pain **or**
- their pain significantly limits their daily activities and participation[22] **or**
- their underlying health condition has deteriorated.

1.1.2 Continue existing treatments for people whose neuropathic pain is already effectively managed[23].

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

- the benefits and possible adverse effects of each pharmacological treatment
- why a particular pharmacological treatment is being offered
- coping strategies for pain and for possible adverse effects of treatment

[21] 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.

[22] 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.

[23] Note that there is currently no good-quality evidence on which to base specific recommendations for treating trigeminal neuralgia. The GDG expected that current routine practice will continue until new evidence is available (see also section 3.1).

- that non-pharmacological treatments are also available in non-specialist settings and/or through referral to specialist services (for example, surgical treatments and psychological therapies).

1.1.4 When selecting pharmacological treatments, take into account:

- the person's vulnerability to specific adverse effects because of comorbidities
- safety considerations and contraindications as detailed in the SPC
- patient preference
- lifestyle factors (such as occupation)
- mental health problems (such as depression and/or anxiety)
- any other medication the person is taking.

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

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

1.1.7 When introducing a new treatment, consider overlap with the old treatments to avoid deterioration in pain control.

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

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

- pain reduction
- adverse effects
- daily activities and participation[24] (such as ability to work and drive)

[24] 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

- mood (in particular, whether the person may have depression and/or anxiety[25])
- quality of sleep
- overall improvement as reported by the person.

First-line treatment

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

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

1.1.11 For people with painful diabetic neuropathy, offer oral duloxetine as first-line treatment. If duloxetine is contraindicated, offer oral amitriptyline*.

- For duloxetine: start at 60 mg per day (a lower starting dose may be appropriate for some people), with upward titration to an effective dose or the person's maximum tolerated dose of no higher than 120 mg per day.
- For amitriptyline*: see recommendation 1.1.10.

1.1.12 Based on both the early and regular clinical reviews:

- if there is satisfactory improvement, continue the treatment; consider gradually reducing the dose over time if improvement is sustained

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demands, mobility, self-care, domestic life, interpersonal interactions and relationships, major life areas, community, and social and civil life.

[25] Refer if necessary to 'Anxiety' (NICE clinical guideline 22), 'Depression' (NICE clinical guideline 90) and/or 'Depression in adults with a chronic physical health problem' (NICE clinical guideline 91) (available at www.nice.org.uk).

* In these recommendations, drug names are marked with an asterisk if they do not have UK marketing authorisation for the indication in question at the time of publication (March 2010). Informed consent should be obtained and documented.

- if amitriptyline* as first-line treatment results in satisfactory pain reduction but the person cannot tolerate the adverse effects, consider oral imipramine* or nortriptyline* as an alternative.

Second-line treatment

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

- If first-line treatment was with amitriptyline* (or imipramine* or nortriptyline*), switch to or combine with oral pregabalin.
- If first-line treatment was with pregabalin, switch to or combine with oral amitriptyline* (or imipramine* or nortriptyline* as an alternative if amitriptyline* is effective but the person cannot tolerate the adverse effects; see recommendation 1.1.12).
- For people with painful diabetic neuropathy:
  - if first-line treatment was with duloxetine, switch to amitriptyline* or pregabalin, or combine with pregabalin
  - if first-line treatment was with amitriptyline*, switch to or combine with pregabalin.

  Dosage and titration should be the same as in recommendation 1.1.10.

Third-line treatment

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

- refer the person to a specialist pain service and/or a condition-specific service[26] **and**
- while waiting for referral:
  - consider oral tramadol as third-line treatment instead of or in combination[27] with the second-line treatment
  - consider topical lidocaine[28] for treatment of localised pain for people who are unable to take oral medication because of medical conditions and/or disability.

1.1.15 For tramadol as monotherapy, start at 50 to 100 mg not more often than every 4 hours, with upward titration if required to an effective dose or the person's maximum tolerated dose of no higher than 400 mg per day. If tramadol is used as combination therapy, more conservative titration may be required.

Other treatments

1.1.16 Do not start treatment with opioids (such as morphine or oxycodone) other than tramadol without an assessment by a specialist pain service or a condition-specific service[26].

1.1.17 Pharmacological treatments other than those recommended in this guideline that are started by a specialist pain service or a condition-specific service[26] may continue to be prescribed in non-specialist settings, with a multidisciplinary care plan, local shared care agreements and careful management of adverse effects.

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[26] 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.

[27] The combination of tramadol with amitriptyline, nortriptyline, imipramine or duloxetine is associated with only a low risk of serotonin syndrome (the features of which include confusion, delirium, shivering, sweating, changes in blood pressure and myoclonus).

[28] Topical lidocaine is licensed for post-herpetic neuralgia, but not for other neuropathic pain conditions.

3 Research recommendations

The value of information (VOI) analysis conducted for the HTA report revealed which parameters have the highest potential to increase net benefit in the subpopulations of patients with painful diabetic neuropathy and post-herpetic neuralgia through reducing uncertainty. The models for both populations found that research should focus on the treatment effects of the drugs that provide the greatest net benefit, as well as on low-cost drugs that could not be modelled at all relevant dosages.

In light of this and a wider discussion of all relevant evidence for this guideline, the GDG has made the following recommendations for research, based on the review of evidence, to improve NICE guidance and patient care in the future.

For all of these research recommendations, trials on the efficacy of drugs in relieving neuropathic pain should have a sufficiently long follow-up to assess the long-term effects of the drugs. Minor and major adverse events should be reported separately for all trial arms, and data on failure to respond to other analgesics should be collected. Definitions of primary and secondary outcomes and data collection methods must be consistent for all neuropathic pain research. Data on pain reduction should be reported not only as a dichotomous outcome of pain reduction at a threshold of 30% or 50%, but also as a more clinically representative measure that better captures the degree of pain reduction with a greater number of categories.

3.1 Carbamazepine for treating trigeminal neuralgia

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

Why this is important

Carbamazepine has been the standard treatment for trigeminal neuralgia since the 1960s. Although there is a lack of trial evidence, it is perceived by clinicians to be efficacious. There is evidence that antidepressants such as amitriptyline, and anti-epileptics such as pregabalin, are effective in treating

peripheral neuropathic pain, but this evidence is not specific to trigeminal neuralgia. The research, such as clinical trials, should enrol adults (aged 18 or over) with trigeminal neuralgia. Comparators should include other pharmacological treatments for neuropathic pain, such as amitriptyline, pregabalin, duloxetine and oxcarbazepine. The primary outcomes should be patient-reported pain reduction (minimum reporting requirement of at least 30% and at least 50% pain reduction), patient-reported global improvement, and minor and major adverse effects. Other outcomes are mental health, ability to perform daily activities, participation, health utilities and resource use, and capacity to carry out paid work.

3.2 Monotherapy versus combination therapy for treating neuropathic pain

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

Why this is important

Combination therapy, such as an antidepressant with an anti-epileptic, or an antidepressant or anti-epileptic with an opioid analgesic, is commonly prescribed for neuropathic pain. However, there is currently a lack of head-to-head comparative trials assessing the clinical effectiveness, cost effectiveness and tolerability of these combinations. The research should enrol adults (aged 18 or over) with neuropathic pain. Treatments should include: (i) amitriptyline and duloxetine (antidepressants) each as monotherapy; (ii) pregabalin (anti-epileptic) as monotherapy; (iii) tramadol (opioid analgesic) as monotherapy; and (iv) combinations of two of the drugs (from different classes). These combination therapies should be compared with each of amitriptyline, duloxetine, pregabalin and tramadol as monotherapy, and comparisons between the various combination therapies should also be made. The primary outcomes for the research should be patient-reported pain reduction (minimum reporting requirement of at least 30% and and at least 50% pain reduction), patient-reported global improvement, and minor and major adverse effects. Other outcomes are mental health, ability to perform daily activities,

participation, health utilities and resource use, and capacity to carry out paid work.

3.3 Factors influencing quality of life of people with neuropathic pain

What are the key factors, including additional care and support, that influence participation[29] and quality of life in people with neuropathic pain?

Why this is important

There is evidence suggesting that people with neuropathic pain experience poorer physical and mental health than people with other forms of pain, even when adjusted for pain intensity. The discrepancy between pain intensity and quality of life implies that other, unrecognised factors are important for people with neuropathic pain and that these factors may influence their daily activities and participation. An observational or qualitative study should be carried out to identify the key factors that may influence the daily activities and participation of people with neuropathic pain. The study population should be adults (aged 18 or over) with neuropathic pain. The primary outcome of interest is the improvement in overall quality of life.

3.4 Relationship between cause of neuropathic pain and its treatment

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

Why this is important

It is often assumed that evidence for treating a particular neuropathic pain condition with a particular aetiology can be extrapolated to other neuropathic pain conditions with other aetiologies. There is currently little evidence for this assumption. More studies on how the aetiology of different neuropathic pain

[29] 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.

conditions influences treatment outcome are warranted in order to identify more effective, targeted treatments.

4 Other versions of this guideline

This is the full guideline. It contains details of the methods and evidence used to develop the guideline. It is available from our website (www.nice.org.uk/guidance/CG96/Guidance).

Quick reference guide

A quick reference guide for healthcare professionals is available from www.nice.org.uk/guidance/CG96/QuickRefGuide

For printed copies, phone NICE publications on 0845 003 7783 or email publications@nice.org.uk (quote reference number N2115).

'Understanding NICE guidance'

A summary for patients and carers ('Understanding NICE guidance') is available from www.nice.org.uk/guidance/CG96/PublicInfo

For printed copies, phone NICE publications on 0845 003 7783 or email publications@nice.org.uk (quote reference number N2116).

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

5 Related NICE guidance

Published

- Depression in adults with a chronic physical health problem. NICE clinical guideline 91 (2009). Available from www.nice.org.uk/guidance/CG91
- Depression. NICE clinical guideline 90 (2009). Available from www.nice.org.uk/guidance/CG90
- Type 2 diabetes. NICE clinical guideline 87 (2009). Available from www.nice.org.uk/guidance/CG87
- Medicines adherence. NICE clinical guideline 76 (2009). Available from www.nice.org.uk/guidance/CG76

- Spinal cord stimulation for chronic pain of neuropathic or ischaemic origin. NICE technology appraisal guidance 159 (2008). Available from www.nice.org.uk/guidance/TA159
- Anxiety (amended). NICE clinical guideline 22 (2004; amended 2007). Available from www.nice.org.uk/guidance/CG22
- Type 1 diabetes. NICE clinical guideline 15 (2004; amended 2009). Available from www.nice.org.uk/guidance/CG15

6 Updating the guideline

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

7 References, glossary and abbreviations

7.1 References

Agrawal RP, Goswami J, Jain S et al. (2009) Management of diabetic neuropathy by sodium valproate and glyceryl trinitrate spray: a prospective double-blind randomized placebo-controlled study. Diabetes Research and Clinical Practice 83: 371–8

Arbaiza D, Vidal O (2007) Tramadol in the treatment of neuropathic cancer pain: a double-blind, placebo-controlled study. Clinical Drug Investigation 27: 75–83

Arezzo JC, Rosenstock J, Lamoreaux L et al. (2008) Efficacy and safety of pregabalin 600 mg/d for treating painful diabetic peripheral neuropathy: a double-blind placebo-controlled trial. BMC Neurology 8: 33

Backonja M, Beydoun A, Edwards KR et al. (1998) Gabapentin for the symptomatic treatment of painful neuropathy in patients with diabetes mellitus. A randomized controlled trial. Journal of the American Medical Association 280: 1831–6

Baron R, Mayoral V, Leijon G et al. (2009) Efficacy and safety of 5% lidocaine (lignocaine) medicated plaster in comparison with pregabalin in patients with postherpetic neuralgia and diabetic polyneuropathy: interim analysis from an

open-label, two-stage adaptive, randomized, controlled trial. Clinical Drug Investigation 29: 231–41

Barton GR, Briggs AH, Fenwick EA (2008) Optimal cost-effectiveness decisions: the role of the cost-effectiveness acceptability curve (CEAC), the cost-effectiveness acceptability frontier (CEAF), and the expected value of perfection information (EVPI). Value Health 11: 886–97

Beniczky S, Tajti J, Timea VE et al. (2005) Evidence-based pharmacological treatment of neuropathic pain syndromes. Journal of Neural Transmission 112: 735–49

Bennett GJ (1997) Neuropathic pain: an overview. In: Borsook D, editor. Molecular Biology of Pain. Seattle: IASP Press; p109–13

Bernstein JE, Korman NJ, Bickers DR et al. (1989) Topical capsaicin treatment of chronic postherpetic neuralgia. Journal of the American Academy of Dermatology 21: 265–70.

Beydoun A, Shaibani A, Hopwood M et al. (2006) Oxcarbazepine in painful diabetic neuropathy: results of a dose-ranging study. Acta Neurologica Scandinavica 113: 395–404

Biesbroeck R, Bril V, Hollander P et al. (1995) A double-blind comparison of topical capsaicin and oral amitriptyline in painful diabetic neuropathy. Advances in Therapy 12: 111–20

Bone M, Critchley P, Buggy DJ (2002) Gabapentin in postamputation phantom limb pain: a randomized, double-blind, placebo-controlled, cross-over study. Regional Anesthesia and Pain Medicine 27: 481–6

Boureau F, Legallicier P, Kabir-Ahmadi M (2003) Tramadol in post-herpetic neuralgia: a randomized, double-blind, placebo-controlled trial. Pain 104: 323–31

Bowsher D, Rigge M, Sopp L (1991) Prevalence of chronic pain in the British population: a telephone survey of 1037 households. The Pain Clinic 4: 223–30

Bowsher D (1997) The effects of pre-emptive treatment of postherpetic neuralgia with amitriptyline: a randomized, double-blind, placebo-controlled trial. Journal of Pain & Symptom Management 13: 327–31

Breuer B, Pappagallo M, Knotkova H et al. (2007) A randomized, double-blind, placebo-controlled, two-period, crossover, pilot trial of lamotrigine in patients with central pain due to multiple sclerosis. Clinical Therapeutics 29: 2022–30

Briggs A, Sculpher M (1998) An introduction to Markov modelling for economic evaluation. Pharmacoeconomics 13: 397-–409

Briggs AH, Sculpher M, Claxton K (2006) Decision modelling for health economic evaluation. Oxford: Oxford University Press

Cardenas DD, Warms CA, Turner JA et al. (2002) Efficacy of amitriptyline for relief of pain in spinal cord injury: results of a randomized controlled trial. Pain 96: 365–73

Chandra K, Shafiq N, Pandhi P et al. (2006) Gabapentin versus nortriptyline in post-herpetic neuralgia patients: a randomized, double-blind clinical trial--the GONIP Trial. International Journal of Clinical Pharmacology and Therapeutics 44: 358–63

Cheville AL, Sloan JA, Northfelt DW et al. (2009) Use of a lidocaine patch in the management of postsurgical neuropathic pain in patients with cancer: a phase III double-blind crossover study (N01CB). Supportive Care in Cancer 17: 451–60

Claxton K (2008) Exploring uncertainty in cost-effectiveness analysis. Pharmacoeconomics 26: 781–98

Coyle D, Oakley J (2008) Estimating the expected value of partial perfect information: a review of methods. The European Journal of Health Economics 9: 251–9

Dallocchio C, Buffa C, Mazzarello P et al. (2000) Gabapentin vs. amitriptyline in painful diabetic neuropathy: an open-label pilot study. Journal of Pain & Symptom Management 20: 280–5

Dieleman JP, Kerklaan J, Huygen FJ et al. (2008) Incidence rates and treatment of neuropathic pain conditions in the general population. Pain 31: 137: 681–8

Dogra S, Beydoun S, Mazzola J et al. (2005) Oxcarbazepine in painful diabetic neuropathy: A randomized, placebo-controlled study. European Journal of Pain 9: 543–54

Donofrio P, Walker F, Hunt V et al. (1991) Treatment of painful diabetic neuropathy with topical capsaicin: A multicenter, double-blind, vehicle-controlled study. Archives of Internal Medicine 151: 2225–2229

Drummond MF, Sculpher MJ, Torrance GW et al. (2005) Methods for the economic evaluation of health care programmes. Oxford: Oxford University Press

Dworkin RH, Corbin AE, Young JP Jr. et al. (2003) Pregabalin for the treatment of postherpetic neuralgia: a randomized, placebo-controlled trial. Neurology 60: 1274–83

Dworkin RH, Turk DC, Farrar JT et al. (2005) Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. Pain 113: 9–19

Dworkin RH, O'Connor AB, Backonja M et al. (2007) Pharmacologic management of neuropathic pain: evidence-based recommendations. Pain 132: 237–51

Dworkin RH, Turk DC, Wyrwich KW et al. (2008) Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. Journal of Pain 9:105–21.

Eisenberg E, Lurie Y, Braker C et al. (2001) Lamotrigine reduces painful diabetic neuropathy: a randomized, controlled study. Neurology 57: 505–9

Estanislao L, Carter K, McArthur J et al. (2004) A randomized controlled trial of 5% lidocaine gel for HIV-associated distal symmetric polyneuropathy. Journal of Acquired Immune Deficiency Syndromes 37: 1584–6

Finnerup NB, Sindrup SH, Bach FW et al. (2002) Lamotrigine in spinal cord injury pain: a randomized controlled trial. Pain 96: 375–83.

Fox-Rushby JA, GL Griffith, JR Ross et al. (2010) The clinical and cost-effectiveness of different treatment pathways for neuropathic pain [NP]. NIHR Health Technology Assessment (HTA) programme, ref. 05/30/03. In press. Available from www.hta.ac.uk/1527

Freynhagen R, Strojek K, Griesing T et al. (2005) Efficacy of pregabalin in neuropathic pain evaluated in a 12-week, randomised, double-blind, multicentre, placebo-controlled trial of flexible- and fixed-dose regimens. Pain 115: 254–63

Galer BS, Jensen MP, Ma T et al. (2002) The lidocaine patch 5% effectively treats all neuropathic pain qualities: results of a randomized, double-blind, vehicle-controlled, 3-week efficacy study with use of the neuropathic pain scale. Clinical Journal of Pain 18: 297–301

Gatti A, Sabato AF, Occhioni R et al. (2009) Controlled-release oxycodone and pregabalin in the treatment of neuropathic pain: Results of a multicenter Italian study. European Neurology 61: 129–37

Gilron I, Bailey JM, Tu D et al. (2009) Nortriptyline and gabapentin, alone and in combination for neuropathic pain: a double-blind, randomised controlled crossover trial. Lancet 374: 1252–61

Gimbel JS, Richards P, Portenoy RK (2003) Controlled-release oxycodone for pain in diabetic neuropathy: a randomized controlled trial. Neurology 60: 927–34

Goldstein DJ, Lu Y, Detke MJ et al. (2005) Duloxetine vs. placebo in patients with painful diabetic neuropathy. Pain 116: 109–18

Gordh TE, Stubhaug A, Jensen TS et al. (2008) Gabapentin in traumatic nerve injury pain: a randomized, double-blind, placebo-controlled, cross-over, multi-center study. Pain 138: 255–66

Graff-Radford SB, Shaw LR, Naliboff BN (2000) Amitriptyline and fluphenazine in the treatment of postherpetic neuralgia. Clinical Journal of Pain 16: 188–92

Grosskopf J, Mazzola J, Wan Y et al. (2006) A randomized, placebo-controlled study of oxcarbazepine in painful diabetic neuropathy. Acta Neurologica Scandinavica 114: 177–80

Hahn K, Arendt G, Braun JS et al. (2004) A placebo-controlled trial of gabapentin for painful HIV-associated sensory neuropathies. Journal of Neurology 251: 1260–6

Hanna M, O'Brien C, Wilson MC (2008) Prolonged-release oxycodone enhances the effects of existing gabapentin therapy in painful diabetic neuropathy patients. European Journal of Pain 12: 804–13

Harati Y, Gooch C, Swenson M et al. (1998) Double-blind randomized trial of tramadol for the treatment of the pain of diabetic neuropathy. Neurology 50: 1842–6

Ho KY, Huh BK, White WD et al. (2008) Topical amitriptyline versus lidocaine in the treatment of neuropathic pain. The Clinical Journal of Pain 24: 51–5

Hoch JS, Briggs AH, Willan AR (2002) Something old, something new, something borrowed, something blue: a framework for the marriage of health econometrics and cost-effectiveness analysis. Health Economics 11: 415–30

Huse E, Larbig W, Flor H et al. (2001) The effect of opioids on phantom limb pain and cortical reorganization. Pain 90: 47–55

International Association for the Study of Pain (2007) IASP Pain terminology [online]. Available from www.iasp-pain.org/AM/Template.cfm?Section=Home&Template=/CM/HTMLDisplay.cfm&ContentID=3058#Neuropathic [accessed 26 August 2009]

Jensen TS, Backonja MM, Hernandez Jimenez S et al. (2006) New perspectives on the management of diabetic peripheral neuropathic pain. Diabetes & Vascular Disease Research 3: 108–19

Jung BF, Johnson RW, Griffin DR et al. (2004) Risk factors for postherpetic neuralgia in patients with herpes zoster. Neurology 62: 1545–51

Kalso E, Tasmuth T, Neuvonen PJ (1996) Amitriptyline effectively relieves neuropathic pain following treatment of breast cancer. Pain 64: 293–302

Kautio AL, Haanpaa M, Saarto T et al. (2008) Amitriptyline in the treatment of chemotherapy-induced neuropathic symptoms. Journal of Pain and Symptom Management 35: 31–9

Kehlet H, Jensen TS, Woolf CJ (2006) Persistent postsurgical pain: risk factors and prevention. Lancet 367: 1618–25

Khoromi S, Patsalides A, Parada S et al. (2005) Topiramate in chronic lumbar radicular pain. The Journal of Pain: Official Journal of the American Pain Society 6: 829–36

Khoromi S, Cui L, Nackers L et al. (2007) Morphine, nortriptyline and their combination vs. placebo in patients with chronic lumbar root pain. Pain 130: 66–75

Kieburtz K, Simpson D, Yiannoutsos C et al. (1998) A randomized trial of amitriptyline and mexiletine for painful neuropathy in HIV infection. Neurology 51: 1682–8

Kishore-Kumar R, Max MB, Schafer SC et al. (1990) Desipramine relieves postherpetic neuralgia. Clinical Pharmacology & Therapeutics 47: 305–12

Kochar DK, Jain N, Agarwal RP et al. (2002) Sodium valproate in the management of painful neuropathy in type 2 diabetes - a randomized placebo controlled study. Acta Neurologica Scandinavica 106: 248–52

Kochar DK, Rawat N, Agrawal RP et al. (2004) Sodium valproate for painful diabetic neuropathy: A randomized double-blind placebo-controlled study. QJM: An International Journal of Medicine 97: 33–8

Leijon G, Boivie J (1989) Central post-stroke pain--a controlled trial of amitriptyline and carbamazepine. Pain 36: 27–36

Lesser H, Sharma U, Lamoreaux L et al. (2004) Pregabalin relieves symptoms of painful diabetic neuropathy: a randomized controlled trial. Neurology 63: 2104–10

Levendoglu F, Ogun CO, Ozerbil O et al. (2004) Gabapentin is a first line drug for the treatment of neuropathic pain in spinal cord injury. Spine 29: 743–51

Low PA, Opfer-Gehrking TL, Dyck PJ et al. (1995) Double-blind, placebo-controlled study of the application of capsaicin cream in chronic distal painful polyneuropathy. Pain 62: 163–8

Luria Y, Brecker C, Daoud D et al. (2000) Lamotrigine in the treatment of painful diabetic neuropathy: A randomized, placebo-controlled study. Progress in Pain Research and Management 16: 857–62

Max MB, Schafer SC, Culnane M et al. (1988) Amitriptyline, but not lorazepam, relieves postherpetic neuralgia. Neurology 38: 1427–32

Max MB, Kishore-Kumar R, Schafer SC et al. (1991) Efficacy of desipramine in painful diabetic neuropathy: a placebo-controlled trial. Pain 45: 3–9

McCarberg B (2006) Pharmacotherapy for neuropathic pain: The old and the new. Advanced Studies in Medicine 6: 399–408

McCleane G (1999) 200 mg daily of lamotrigine has no analgesic effect in neuropathic pain: a randomised, double-blind, placebo controlled trial. Pain 83: 105–7

McCleane G (2000) The analgesic efficacy of topical capsaicin is enhanced by glyceryl trinitrate in painful osteoarthritis: a randomized, double blind, placebo controlled study. European Journal of Pain 4: 355–60

Meier T, Wasner G, Faust M et al. (2003) Efficacy of lidocaine patch 5% in the treatment of focal peripheral neuropathic pain syndromes: a randomized, double-blind, placebo-controlled study. Pain 106: 151–8

Mikkelsen T, Werner MU, Lassen B et al. (2004) Pain and sensory dysfunction 6 to 12 months after inguinal herniotomy. Anesthesia Analgesia 99: 146–51

Morello CM, Leckband SG, Stoner CP et al. (1999) Randomized double-blind study comparing the efficacy of gabapentin with amitriptyline on diabetic peripheral neuropathy pain. Archives of Internal Medicine 159: 1931–7

National Institute for Health and Clinical Excellence (2009) The guidelines manual. London: National Institute for Health and Clinical Excellence. Available from: www.nice.org.uk/GuidelinesManual

Nicol CF (1969) A four year double-blind study of tegretol in facial pain. Headache 9: 54–7

Nikolajsen L, Finnerup NB, Kramp S et al. (2006) A randomized study of the effects of gabapentin on postamputation pain. Anesthesiology 105: 1008–15

Paice JA, Ferrans CE, Lashley FR et al. (2000) Topical capsaicin in the management of HIV-associated peripheral neuropathy. Journal of Pain and Symptom Management 19: 45–52

Rao RD, Michalak JC, Sloan JA et al. (2007) Efficacy of gabapentin in the management of chemotherapy-induced peripheral neuropathy: a phase 3 randomized, double-blind, placebo-controlled, crossover trial (N00C3). Cancer 110: 2110–8

Rao RD, Flynn PJ, Sloan JA et al. (2008) Efficacy of lamotrigine in the management of chemotherapy-induced peripheral neuropathy: a phase 3 randomized, double-blind, placebo-controlled trial, N01C3. Cancer 112: 2802–8

Raskin P, Donofrio PD, Rosenthal NR et al. (2004) Topiramate vs placebo in painful diabetic neuropathy: analgesic and metabolic effects. Neurology 63: 865–73

Raskin J, Pritchett Y, Chappell AS et al. (2005) Duloxetine in the treatment of diabetic peripheral neuropathic pain - results from three clinical trials. Poster presented at the 9th Congress of the European Federation of Neurological Societies; 17–20 September 2005, Athens, Greece

Rice AS, Maton S (2001) Gabapentin in postherpetic neuralgia: A randomised, double blind, placebo controlled study. Pain 94: 215–24

Richter RW, Portenoy R, Sharma U et al. (2005) Relief of painful diabetic peripheral neuropathy with pregabalin: a randomized, placebo-controlled trial. The Journal of Pain: Official Journal of the American Pain Society 6: 253–60

Rintala DH, Holmes SA, Courtade D et al. (2007) Comparison of the effectiveness of amitriptyline and gabapentin on chronic neuropathic pain in persons with spinal cord injury. Archives of Physical Medicine and Rehabilitation 88: 1547–60 (erratum in Archives of Physical Medicine and Rehabilitation 89: 1206)

Robinson LR, Czerniecki JM, Ehde DM et al. (2004) Trial of amitriptyline for relief of pain in amputees: results of a randomized controlled study. Archives of Physical Medicine and Rehabilitation 85: 1–6

Rosenstock J, Tuchman M, Lamoreaux L et al. (2004) Pregabalin for the treatment of painful diabetic peripheral neuropathy: a double-blind, placebo-controlled trial. Pain 110: 628–38

Rowbotham M, Harden N, Stacey B et al. (1998) Gabapentin for the treatment of postherpetic neuralgia: a randomized controlled trial. JAMA: the Journal of the American Medical Association 280: 1837–42

Rowbotham MC, Goli V, Kunz NR et al. (2004) Venlafaxine extended release in the treatment of painful diabetic neuropathy: a double-blind, placebo-controlled study. Pain 110: 697–706 (erratum in Pain 113: 248)

Sabatowski R, Galvez R, Cherry DA et al. (2004) Pregabalin reduces pain and improves sleep and mood disturbances in patients with post-herpetic neuralgia: results of a randomised, placebo-controlled clinical trial. Pain 109: 26–35

Schmader KE (2002) Epidemiology and impact on quality of life of postherpetic neuralgia and painful diabetic neuropathy. The Clinical Journal of Pain 18: 350–4

Scheffler NM, Sheitel PL, Lipton MN (1991) Treatment of painful diabetic neuropathy with capsaicin 0.075%. Journal of the American Podiatric Medical Association 81: 288–93

Serpell MG Neuropathic pain study group (2002) Gabapentin in neuropathic pain syndromes: a randomised, double-blind, placebo-controlled trial. Pain 99: 557–66

Shipton E (2008) Post-surgical neuropathic pain. ANZ Journal of Surgery 78: 548–55

Siddall PJ, Cousins MJ, Otte A et al. (2006) Pregabalin in central neuropathic pain associated with spinal cord injury: a placebo-controlled trial. Neurology 67: 1792–800

Simpson DA (2001) Gabapentin and venlafaxine for the treatment of painful diabetic neuropathy. Journal of Clinical Neuromuscular Disease 3: 53–62

Simpson DM, Olney R, McArthur JC et al. (2000) A placebo-controlled trial of lamotrigine for painful HIV-associated neuropathy. Neurology 54: 2115–9

Simpson DM, McArthur JC, Olney R et al. (2003) Lamotrigine for HIV-associated painful sensory neuropathies: a placebo-controlled trial. Neurology 60: 1508–14

Sindrup SH, Bach FW, Madsen C et al. (2003) Venlafaxine versus imipramine in painful polyneuropathy: a randomized, controlled trial. Neurology 60: 1284–9

Smith DG, Ehde DM, Hanley MA et al. (2005) Efficacy of gabapentin in treating chronic phantom limb and residual limb pain. Journal of Rehabilitation Research & Development 42: 645–54

Smith BH, Torrance N (2010) Neuropathic pain. In: Croft PR, editor. Chronic pain epidemiology: from aetiology to public health. Oxford: Oxford University Press, in press (ISBN 9780199235766)

Stacey BR, Barrett JA, Whalen E et al. (2008) Pregabalin for postherpetic neuralgia: placebo-controlled trial of fixed and flexible dosing regimens on allodynia and time to onset of pain relief. Journal of Pain 9: 1006–17

Tandan R, Lewis GA, Krusinski PB et al. (1992) Topical capsaicin in painful diabetic neuropathy. Controlled study with long-term follow-up. Diabetes Care 15: 8–14

Tasmuth T, Hartel B, Kalso E (2002) Venlafaxine in neuropathic pain following treatment of breast cancer. European Journal of Pain 6: 17–24

Thienel U, Neto W, Schwabe SK et al. (2004) Topiramate in painful diabetic polyneuropathy: findings from three double-blind placebo-controlled trials. Acta Neurologica Scandinavica 110: 221–31

Tölle T, Freynhagen R, Versavel M et al. (2008) Pregabalin for relief of neuropathic pain associated with diabetic neuropathy: A randomized, double-blind study. European Journal of Pain 12: 203–13

van Seventer R, Sadosky A, Lucero M et al. (2006) A cross-sectional survey of health state impairment and treatment patterns in patients with postherpetic neuralgia. Age and Ageing 35: 132–7

Vestergaard K, Andersen G, Gottrup H et al. (2001) Lamotrigine for central poststroke pain: a randomized controlled trial. Neurology 56: 184–90

Vinik AI, Tuchman M, Safirstein B et al. (2007) Lamotrigine for treatment of pain associated with diabetic neuropathy: results of two randomized, double-blind, placebo-controlled studies. Pain 128: 169–79

Vranken JH, Dijkgraaf MG, Kruis MR et al. (2008) Pregabalin in patients with central neuropathic pain: a randomized, double-blind, placebo-controlled trial of a flexible-dose regimen. Pain 136: 150–7

Vrethem M, Boivie J, Arnqvist H et al. (1997) A comparison a amitriptyline and maprotiline in the treatment of painful polyneuropathy in diabetics and nondiabetics. Clinical Journal of Pain 13: 313–23

Wailoo AJ, Sutton AJ, Cooper NJ et al. (2008) Cost-effectiveness and value of information analyses of neuraminidase inhibitors for the treatment of influenza. Value Health. 11: 160–71

Watson CP, Evans RJ (1992) The postmastectomy pain syndrome and topical capsaicin: a randomized trial. Pain 51: 375–9

Watson CP, Tyler KL, Bickers DR et al. (1993) A randomized vehicle-controlled trial of topical capsaicin in the treatment of postherpetic neuralgia. Clinical Therapeutics 15: 510–26

Watson CP, Vernich L, Chipman M et al. (1998) Nortriptyline versus amitriptyline in postherpetic neuralgia: a randomized trial. Neurology 51: 1166–71

Wernicke JF, Pritchett YL, D'Souza DN et al. (2006) A randomized controlled trial of duloxetine in diabetic peripheral neuropathic pain. Neurology 67: 1411–20

World Health Organization (2007) International Statistical Classification of Diseases and Related Health Problems (ICD), 10th revision. Available at: http://apps.who.int/classifications/apps/icd/icd10online/

Wu CL, Agarwal S, Tella PK et al. (2008) Morphine versus mexiletine for treatment of postamputation pain: a randomized, placebo-controlled, crossover trial. Anesthesiology 109: 289–96

Yucel A, Ozyalcin S, Koknel TG et al. (2005) The effect of venlafaxine on ongoing and experimentally induced pain in neuropathic pain patients: a double blind, placebo controlled study. European Journal of Pain 9: 407–16

Ziegler D (2008) Painful diabetic neuropathy: treatment and future aspects. Diabetes/Metabolism Research and Reviews 24 (Suppl. 1): S52–7

7.2 Glossary

Absolute risk Measures the probability of an event or outcome occurring (e.g. an adverse reaction to the drug being tested) in the group of people under study. Studies that compare two or more groups of patients may report results in terms of the Absolute risk reduction.
Absolute risk reduction (ARR) (risk difference) The ARR is the difference in the risk of an event occurring between two groups of patients in a study – for example if 6% of patients die after receiving a new experimental drug and 10% of patients die after having the old drug treatment then the ARR is 10% - 6% = 4%. Thus by using the new drug instead of the old drug 4% of patients can be prevented from dying. Here the ARR measures the risk reduction associated with a new treatment. See also Absolute risk.
Absolute risk increase (risk difference) Same as ARR but with different direction of effect.
Bias Influences on a study that can lead to invalid conclusions about a treatment or intervention. Bias in research can make a treatment look better or worse than it really is. Bias can even make it look as if the treatment works when it actually doesn't. Bias can occur by chance or as a result of systematic errors in the design and execution of a study. Bias can occur at different stages in the research process, e.g. in the collection, analysis, interpretation, publication or review of research data. For examples see Selection bias, Performance bias, Information bias, Confounding, Publication bias.
Clinical effectiveness The extent to which a specific treatment or intervention, when used under usual or everyday conditions, has a beneficial effect on the course or outcome of disease compared with no treatment or other routine care. (Clinical trials that assess effectiveness are sometimes called management trials.) Clinical 'effectiveness' is not the same as efficacy.
Comorbidity Co-existence of a disease or diseases in the people being studied in addition to the health problem that is the subject of the study.
Confidence interval A way of expressing certainty about the findings from a study or group of studies, using statistical techniques. A confidence interval describes a range of possible effects (of a treatment or intervention) that are consistent with the results of a study or group of studies. A wide confidence interval indicates a lack of certainty or precision about the true size of the clinical effect and is seen in studies with too few patients. Where confidence intervals are narrow they indicate more precise estimates of effects and a larger sample of patients studied. It is usual to interpret a '95%' confidence interval as the range of effects within which we are 95% confident that the true effect lies.
Consensus methods A variety of techniques that aim to reach an agreement on a particular issue. Formal consensus methods include Delphi and nominal group techniques, and consensus development conferences. In the development of clinical guidelines, consensus methods may be used where there is a lack of strong research evidence on a particular topic.
Cost-effectiveness analysis An economic evaluation that compares alternative options for a specific patient group looking at a single effectiveness dimension measured in a non-monetary (natural) unit. It expresses the result in the form of an incremental (or average or marginal) cost-

effectiveness ratio.

Economic evaluation

A comparison of alternative courses of action in terms of both their costs and consequences. In health economic evaluations the consequences should include health outcomes.

Guideline Development Group

A group of healthcare professionals, patients, carers and technical staff who develop the recommendations for a clinical guideline. The short clinical guidelines team or national collaborating centre responsible for developing the guideline recruits a guideline development group to work on the guideline. Staff from the short guidelines team or the national collaborating centre review the evidence and support the guideline development group. The group writes draft guidance, and then revises it after a consultation with organisations registered as stakeholders.

Generalisability

The extent to which the results of a study hold true for a population of patients beyond those who participated in the research. See also External validity.

Heterogeneity

Or lack of homogeneity. The term is used in meta-analyses and systematic reviews when the results or estimates of effects of treatment from separate studies seem to be very different - in terms of the size of treatment effects or even to the extent that some indicate beneficial and others suggest adverse treatment effects. Such results may occur as a result of differences between studies in terms of the patient populations, outcome measures, definition of variables or duration of follow-up.

Number needed to treat to benefit (NNTB)

This measures the impact of a treatment or intervention. It states how many patients need to be treated with the treatment in question in order to prevent an event which would otherwise occur. e.g. if the NNTB=4, then 4 patients would have to be treated to prevent one bad outcome. The closer the NNTB is to 1, the better the treatment is. Analogous to the NNTB is the Number needed to treat to harm (NNTH), which is the number of patients that would need to receive a treatment to cause one additional adverse event. e.g. if the NNTH=4, then 4 patients would have to be treated for one bad outcome to occur.

Number needed to treat to harm (NNTH)

See NNTB.

Quality-adjusted life year (QALY)

A measure of health outcome which looks at both length of life and quality of life. QALYS are calculated by estimating the years of life remaining for a patient following a particular care pathway and weighting each year with a quality of life score (on a zero to one scale). One QALY is equal to one year of life in perfect health, or two years at 50% health, and so on.

Randomised controlled trial

A study to test a specific drug or other treatment in which people are randomly assigned to two (or more) groups: one (the experimental group) receiving the treatment that is being tested, and the other (the comparison or control group) receiving an alternative treatment, a placebo (dummy treatment) or no treatment. The two groups are followed up to compare differences in outcomes to see how effective the experimental treatment was. (Through randomisation, the groups should be similar in all aspects apart from the treatment they receive during the study.)

Relative risk

A summary measure which represents the ratio of the risk of a given event or outcome

(e.g. an adverse reaction to the drug being tested) in one group of subjects compared with another group. When the 'risk' of the event is the same in the two groups the relative risk is 1. In a study comparing two treatments, a relative risk of 2 would indicate that patients receiving one of the treatments had twice the risk of an undesirable outcome than those receiving the other treatment. Relative risk is sometimes used as a synonym for risk ratio.
Systematic review A review in which evidence from scientific studies has been identified, appraised and synthesised in a methodical way according to predetermined criteria. May or may not include a meta-analysis.

7.3 Abbreviations

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

8 Contributors

8.1 The Guideline Development Group

Peter Barry (Chair)

Consultant in Paediatric Intensive Care, University Hospitals of Leicester NHS Trust and Honorary Senior Lecturer, Department of Child Health, University of Leicester

Tracey Cole

Patient and carer representative

Paula Crawford

Lead Clinical Pharmacist, Musgrave Park Hospital, Belfast

Peter Crome

Professor of Geriatric Medicine, Keele University and Consultant Geriatrician, North Staffordshire Combined Healthcare NHS Trust

Niru Goenka

Consultant Physician, Countess of Chester NHS Foundation Trust

Clair Haslam (resigned from GDG after meeting 3)

Nurse Consultant, Pain Management and Neuromodulation, The Walton Centre, Liverpool

John Lee

Consultant in Pain Medicine, University College London (UCL) Hospitals and Honorary Senior Lecturer, UCL

Vera Neumann

Consultant and Honorary Senior Lecturer in Rehabilitation Medicine, Leeds Teaching Hospitals NHS Trust and University of Leeds

David Rowbotham

Professor of Anaesthesia and Pain Management, Department of Health Sciences, Leicester Medical School, University of Leicester

Blair H. Smith
Professor of Primary Care Medicine, University of Aberdeen, and GP, Peterhead Medical Practice

Heather Wallace
Patient and carer representative

8.1.1 Co-opted member

The following person was not a full member of the Guideline Development Group but was co-opted onto the group as an expert adviser:

Soloman Tesfaye
Consultant Physician/Endocrinologist, Royal Hallamshire Hospital, Sheffield and Honorary Professor of Diabetic Medicine, University of Sheffield

8.2 The short clinical guidelines technical team

A short clinical guidelines technical team was responsible for this guideline throughout its development. It prepared information for the Guideline Development Group, drafted the guideline and responded to consultation comments. The following NICE employees made up the technical team for this guideline.

Emma Banks
Guidelines Coordinator

Nicole Elliott
Guidelines Commissioning Manager (until September 2009)

Sarah Glover
Information Specialist

Michael Heath
Programme Manager

Victoria Kelly
Project Manager

Fergus Macbeth
Director, Centre for Clinical Practice

Stefanie Reken (née Kuntze)
Technical Analyst (Health Economics)

Beth Shaw
Technical Adviser

Toni Tan
Technical Analyst

Judith Thornton
Technical Analyst

Claire Turner
Guidelines Commissioning Manager (from September 2009)

8.3 The Guideline Review Panel

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

Robert Walker (Chair)
General Practitioner, Workington

John Harley
Clinical Governance and Prescribing Lead and General Practitioner, North Tees PCT

Ailsa Donnelly
Lay member

Sarah Fishburn
Lay member

8.4 Declarations of interest

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

8.5 Authorship and citation

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

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