Neuropathic pain

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

NICE clinical guideline

Draft for consultation, September 2011

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

Contents

Appendices 10.1 to 10.11 are in separate files.

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

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 2011) defines: neuropathic pain as 'pain caused by a lesion or disease of the somatosensory nervous system'. This is further delineated as central neuropathic pain 'pain caused by a lesion or disease of the central somatosensory nervous system', and peripheral neuropathic pain 'pain caused by a lesion or disease of the peripheral somatosensory nervous system'.

Neuropathic pain is very challenging to manage because of the heterogeneity of its aetiologies, symptoms and underlying mechanisms (Beniczky et al. 2005). Examples of common conditions that have peripheral neuropathic pain as a symptom are painful diabetic neuropathy, post-herpetic neuralgia, trigeminal neuralgia, radicular pain, pain after surgery and neuropathic cancer pain (that is, chemotherapy-induced neuropathy and neuropathy secondary to tumour 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.

Drug recommendations

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

The guideline will assume that prescribers will use a drug's summary of product characteristics (SPC) and the British National Formulary (BNF) to inform decisions made with individual patients (this includes obtaining information on special warnings, precautions for use, contraindications and adverse effects of pharmacological treatments). 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. Where recommendations have been made for the use of drugs outside their licensed indications ('off-label use'), these drugs are marked with a footnote in the recommendations. Licensed indications are listed in table 1.

Table 1 Licensed indications for recommended pharmacological treatments for neuropathic pain (August 2011)

Amitriptyline	Not licensed for neuropathic pain
Duloxetine	Licensed for painful diabetic neuropathy
Gabapentin	Licensed for peripheral neuropathic pain
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

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.

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/en/DH_103643) and the code of practice that accompanies the Mental Capacity Act (available from www.dh.gov.uk/en/SocialCare/Deliveringsocialcare/MentalCapacity). In Wales, healthcare professionals should follow advice on consent from the Welsh 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 Recommendations

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.

List of all recommendations

Key principles of care

1.1.1 Consider referring the person to a specialist pain service and/or a condition-specific service[1] at any stage, including at initial presentation and at the regular clinical reviews (see recommendation 1.1.9), if:

- they have severe pain **or**
- their pain significantly limits their daily activities and participation[2] **or**

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

[2] The World Health Organization ICF (International Classification of Functioning, Disability and Health) (2001) defines participation as 'A person's involvement in a life situation.' It includes

- their underlying health condition has deteriorated.

1.1.2 Continue existing treatments for people whose neuropathic pain is already effectively managed[3].

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).

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[4])
- any other medication the person is taking.

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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] 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).

[4] Refer if necessary to 'Anxiety' (NICE clinical guideline 113), '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).

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[5] (such as ability to work and drive)
- mood (in particular, whether the person may have depression and/or anxiety[6])
- quality of sleep
- overall improvement as reported by the person.

[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] Refer if necessary to 'Anxiety' (NICE clinical guideline 113), '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).

First-line treatment

1.1.10 Offer oral amitriptyline* or gabapentin as first-line treatment (see recommendation 1.1.11 for people with painful diabetic neuropathy). (For dosages please see box 1 Drug dosages).

1.1.11 For people with painful diabetic neuropathy, offer oral duloxetine as first-line treatment. If duloxetine is contraindicated, offer oral amitriptyline*. (For dosages please see box 1 Drug dosages).

1.1.12 Based on both the early and regular clinical reviews:

- If improvement is satisfactory, continue the treatment; consider gradually reducing the dose over time if improvement is sustained.
- If amitriptyline* results in satisfactory pain reduction as first-line treatment but the person cannot tolerate the adverse effects, consider oral imipramine* or nortriptyline* as an alternative.
- If gabapentin results in satisfactory pain reduction as first-line treatment but the person has difficulty adhering to the dosage schedule or cannot tolerate the adverse effects, consider oral pregabalin as an alternative. (For dosages please see box 1 Drug dosages).

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 (see recommendation 1.1.16 for people with painful diabetic neuropathy):

- If first-line treatment was with amitriptyline* (or imipramine* or nortriptyline*), switch to or combine with oral gabapentin (or

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* 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 (September 2011). Informed consent should be obtained and documented.

pregabalin as an alternative if gabapentin is effective but the person has difficulty adhering to the dosage schedule or cannot tolerate the adverse effects).

- If first-line treatment was with gabapentin (or 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).

1.1.14 For people with painful diabetic neuropathy, 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 duloxetine, switch to oral amitriptyline* (or imipramine* or nortriptyline* as an alternative if amitriptyline is effective but the person cannot tolerate the adverse effects) or switch to or combine with oral gabapentin (or pregabalin as an alternative if gabapentin is effective but the person has difficulty adhering to the dosage schedule or cannot tolerate the adverse effects).
- If first-line treatment was with amitriptyline* (or imipramine* or nortriptyline*), switch to or combine with gabapentin (or pregabalin as an alternative if gabapentin is effective but the person has difficulty adhering to the dosage schedule or cannot tolerate the adverse effects).

Third-line treatment

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

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* 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 (September 2011). Informed consent should be obtained and documented.

- refer the person to a specialist pain service and/or a condition-specific service[7] **and**
- while waiting for referral:
  - consider oral tramadol as third-line treatment instead of or in combination[8] with the second-line treatment (For dosages please see box 1 Drug dosages).
  - consider a topical lidocaine patch for treatment of localised pain for people who are unable to take oral medication because of medical conditions and/or disability.

Other treatments

1.1.16 Do not start treatment with a topical capsaicin 8% patch or with opioids (such as morphine or oxycodone) other than tramadol without an assessment by a specialist pain service or a condition-specific service[7].

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[7] 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 1 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)**
- **Higher doses should be considered in consultation with a specialist pain service.**

Drug	Starting dose	Maximum dose
Amitriptyline*	10 mg/day	75 mg/day

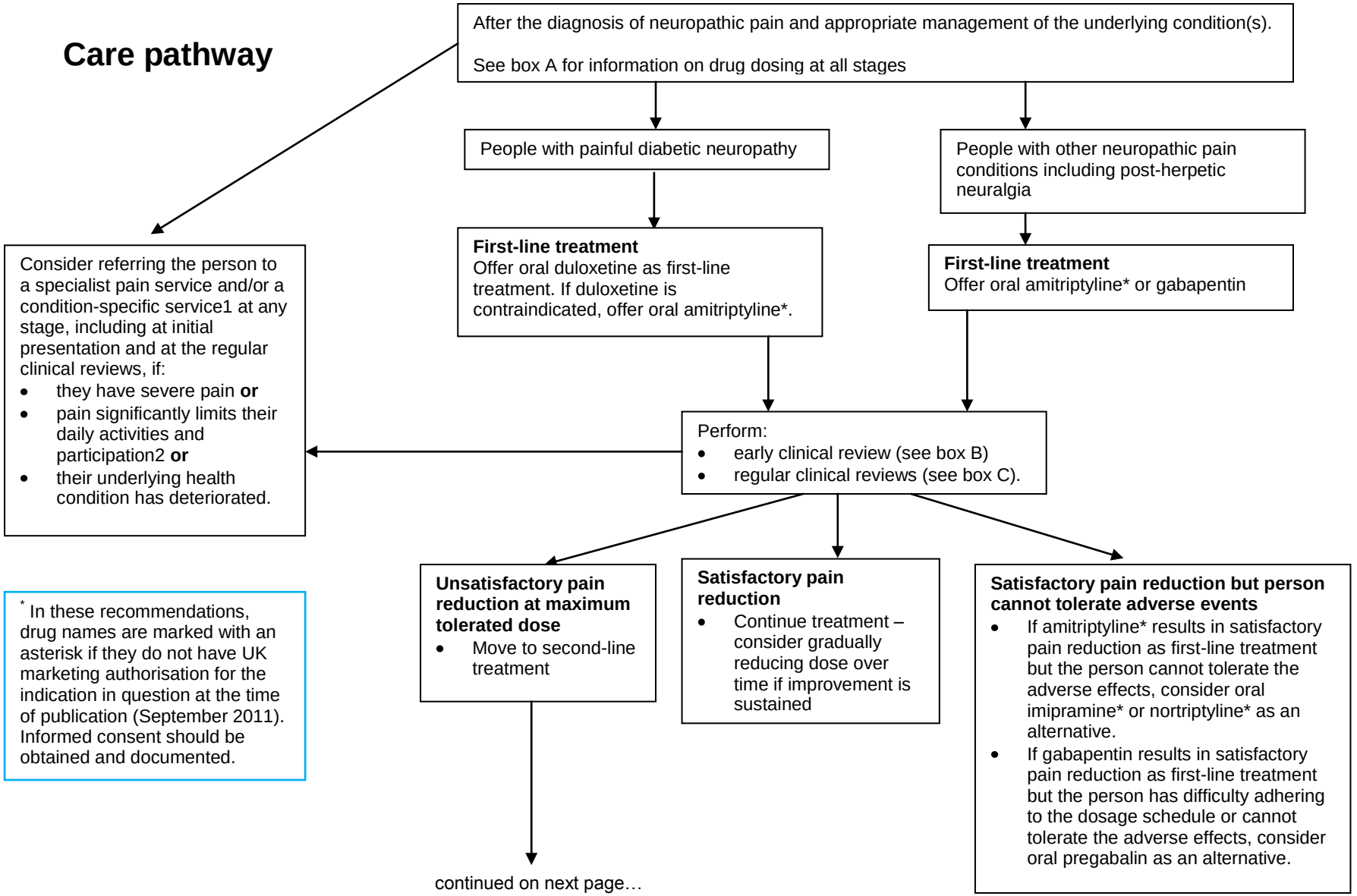
[7] A condition-specific service is a specialist service that provides treatment for the underlying health condition that is causing neuropathic pain. Examples include neurology, diabetology and oncology services.

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

Gabapentin	300 mg once daily on day 1, then 300 mg twice daily on day 2, then 300 mg 3 times daily on day 3 *or* initially 300 mg 3 times daily on day 1[c]	3600 mg/day
Pregabalin	150 mg/day [a] (divided into 2 doses)	600 mg/day (divided into 2 doses)
Duloxetine	60 mg/day [a]	120 mg/day
Tramadol [b]	50-100mg not more often than every 4 hours	400 mg/day

* Not licensed for this indication at time of publication (December 2011). Informed consent should be obtained and documented.
[a] A lower starting dose may be appropriate for some people.
[b] As monotherapy. More conservative titration may be required if used as combination therapy.
[c] A less rapid escalation schedule may be more appropriate.

2 Care pathway



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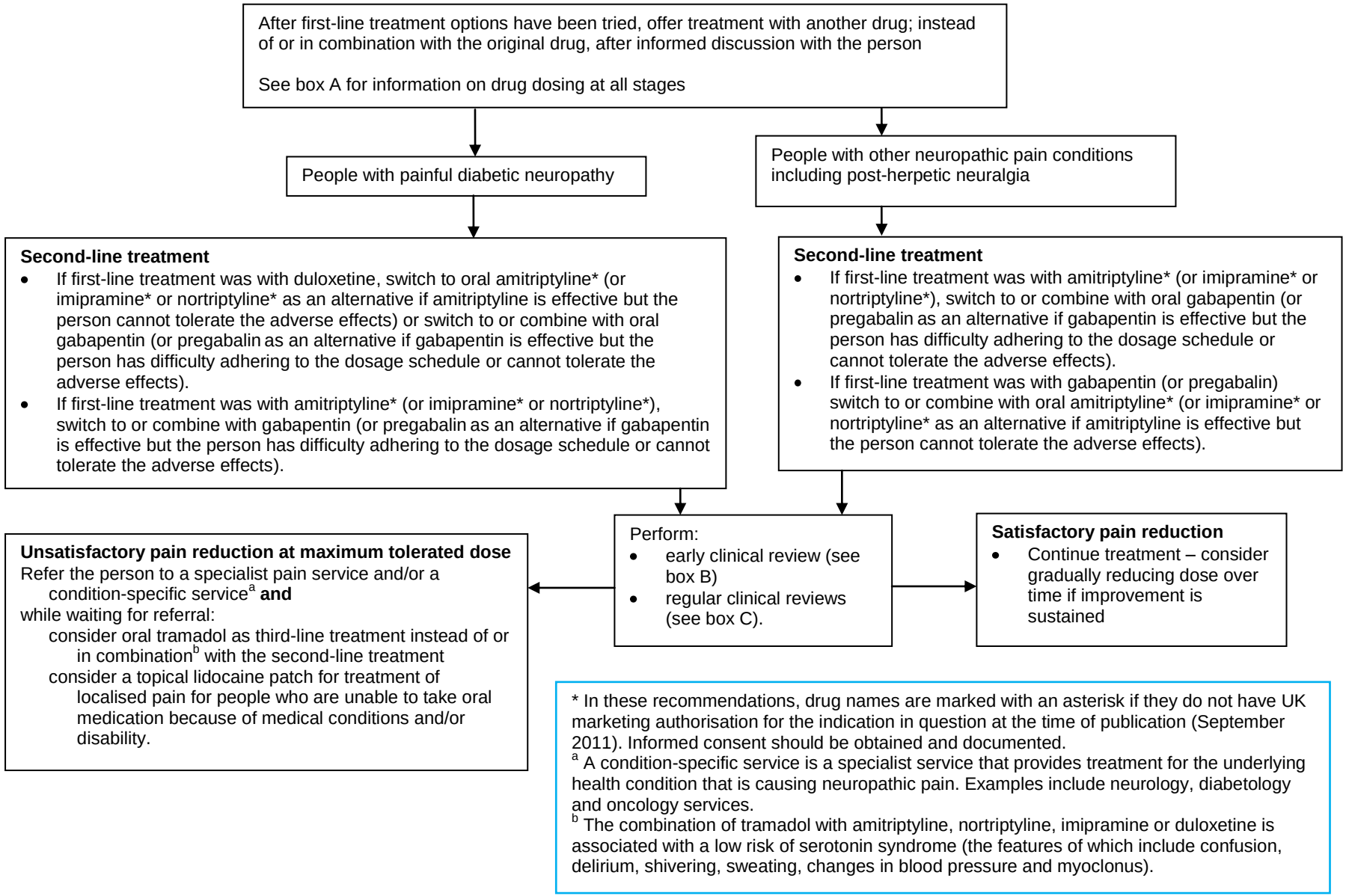
After first-line treatment options have been tried, offer treatment with another drug; instead of or in combination with the original drug, after informed discussion with the person
See box A for information on drug dosing at all stages
People with painful diabetic neuropathy
People with other neuropathic pain conditions including post-herpetic neuralgia
Second-line treatment
If first-line treatment was with duloxetine, switch to oral amitriptyline* (or imipramine* or nortriptyline* as an alternative if amitriptyline is effective but the person cannot tolerate the adverse effects) or switch to or combine with oral gabapentin (or pregabalin as an alternative if gabapentin is effective but the person has difficulty adhering to the dosage schedule or cannot tolerate the adverse effects).
If first-line treatment was with amitriptyline* (or imipramine* or nortriptyline*), switch to or combine with gabapentin (or pregabalin as an alternative if gabapentin is effective but the person has difficulty adhering to the dosage schedule or cannot tolerate the adverse effects).
Second-line treatment
If first-line treatment was with amitriptyline* (or imipramine* or nortriptyline*), switch to or combine with oral gabapentin (or pregabalin as an alternative if gabapentin is effective but the person has difficulty adhering to the dosage schedule or cannot tolerate the adverse effects).
If first-line treatment was with gabapentin (or 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).
Perform:
early clinical review (see box B)
regular clinical reviews (see box C).
Unsatisfactory pain reduction at maximum tolerated dose
Refer the person to a specialist pain service and/or a condition-specific service[a] and
while waiting for referral:
consider oral tramadol as third-line treatment instead of or in combination[b] with the second-line treatment
consider a topical lidocaine patch for treatment of localised pain for people who are unable to take oral medication because of medical conditions and/or disability.
Satisfactory pain reduction
Continue treatment – consider gradually reducing dose over time if improvement is sustained
* 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 (September 2011). Informed consent should be obtained and documented.
[a] 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.
[b] The combination of tramadol with amitriptyline, nortriptyline, imipramine or duloxetine is associated with a low risk of serotonin syndrome (the features of which include confusion, delirium, shivering, sweating, changes in blood pressure and myoclonus).

Other treatments

- Do not start treatment with a topical capsaicin 8% patch or with opioids (such as morphine or oxycodone) other than tramadol without an assessment by a specialist pain service or a condition-specific service11.
- Pharmacological treatments other than those recommended in this guideline that are started by a specialist pain service or a condition-specific service may continue to be prescribed in non-specialist settings, with a multidisciplinary care plan, local shared care agreements and careful management of adverse effects. 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.

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
Gabapentin	300 mg once daily on day 1, then 300 mg twice daily on day 2, then 300 mg three times daily on day 3 **or** initially 300 mg three times daily on day 1[a]	3600 mg/day
Pregabalin	150 mg/day[b] (divided into two doses)	600 mg/day (divided into two doses)
Duloxetine	60 mg/day[b]	120 mg/day
Tramadol	50–100mg not more often than every 4 hours[c]	400 mg/day

* Not licensed for this indication at time of publication (September 2011). Informed consent should be obtained and documented.
[a] A less rapid escalation schedule may be more appropriate for some people.
[b] A lower starting dose may be appropriate for some people.
[c] As monotherapy. More conservative titration may be needed 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 (such as ability to work and drive)
- mood (in particular, possible depression and/or anxiety)
- quality of sleep
- overall improvement as reported by the person.

3 Evidence review and recommendations

For details of how this guideline was developed see appendix 10.1 – 10.11.

3.1 Methodology

Based on the guideline scope, neuropathic pain is treated as a 'blanket condition' in this guideline regardless of its aetiologies, unless there is sufficient, 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. Hence, the structure of this guideline, the categorisation of neuropathic pain conditions with relevant pharmacological treatments, and analyses were based on this prior rationale.

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

Population and conditions

Adults (aged 18 years old or older with neuropathic pain conditions. The different neuropathic pain conditions that were included in this guideline are listed in Table 3. Because the scope of this guideline is to provide recommendations for neuropathic pain as a chronic condition, adults with pain arising directly from trauma and surgical procedures for less than 3 months were excluded.

Settings

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

Treatments and comparators

Table 4 lists the 34 different pharmacological treatments were considered for neuropathic pain in the four main drug classes (antidepressants, anti-

epileptics, opioid analgesics and topical treatments). The guideline sought to investigate:

- the clinical efficacy of the individual listed 34 pharmacological treatments as monotherapy (placebo-controlled trials)
- the clinical efficacy of individual pharmacological treatments against each other (head-to-head monotherapy comparative trials)
- the clinical efficacy of combination therapy against monotherapy or other combination therapy (head-to-head combination therapy comparative trials).

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

Critical outcomes

The critical outcomes for meta-analysis, based on the globally accepted 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/impression of pain; and adverse effects. Specific adverse effects for each drug class were selected and agreed by the GDG through survey questionnaires (see appendix 10.3A), based on their expert knowledge and experience (including that of patient and carer members).

Literature search

Systematic literature searches were carried out to identify all randomised controlled trials on the 34 different pharmacological treatments (listed in Table 4) for neuropathic pain conditions (listed in Table 3). For full search strategies please see appendix XXX.(Please note full search strategies will be available on publication of the guideline).

Analysis and synthesis

For this guideline, meta-analysis was adopted as the analytical method for analysing the evidence and the GRADE methodology was adopted to synthesize and presented the results. Overall, a fixed-effects model meta-

analysis was carried out on the critical outcomes by individual pharmacological treatments across all neuropathic pain conditions. However, as previously stated, if evidence was sufficient, valid and robust, the meta-analysis would be carried out by individual pharmacological treatments of specific neuropathic conditions (for example, painful diabetic neuropathy, post-herpetic neuralgia). If there was significant heterogeneity from the meta-analysis, a random-effects model was adopted for the meta-analysis with potential sources for the heterogeneity noted in the full GRADE profiles. The outcome would be downgraded by one level due to 'inconsistency' as described in the GRADE methodology. All results from the meta-analyses (relative risk or risk ratio [RR] and absolute risk [AR], with 95% confidence intervals [CI]) are presented in the summary profiles in the guideline with subsequent evidence statements, and in the full GRADE profiles in the appendices (for full GRADE profiles, see appendix 9). No studies were excluded on the basis of outcomes reported.

For the completeness of the evidence base, included studies that did not report the critical 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 10.10). These pain outcomes (other than the critical outcomes) are referred to as 'other reported pain outcomes' in this guideline. The other reported pain outcomes in the included studies are also presented in the summary profiles in the guideline, subsequent evidence statements, and in the full GRADE profiles in the appendices, with the outcome downgraded by one level due to 'indirectness' as described in the GRADE methodology. These 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 critical 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, if evidence on the critical 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 critical outcomes or other pain outcomes, study characteristics were summarised in the evidence tables only for information (see the evidence tables in appendix 10.10 for full information on each included study).

For more details on the review protocols and specific inclusion and exclusion criteria, please see appendix 10.2.

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

Table 4 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

3.1.1 Evidence Review

Review questions

Based on the scope and methodology set out in section 3.1 above, three review questions were formulated. As stated in section 3.1 above, if sufficient,

valid and robust evidence showed the clinical efficacy of a particular treatment for a specific neuropathic pain condition, evidence would be analysed based on that particular neuropathic pain condition (for example, painful diabetic neuropathy, post-herpetic neuralgia, and other neuropathic pain conditions) in each review question below.

Review question 1

What is the clinical efficacy of antidepressants, anti-epileptics, opioid analgesics, topical lidocaine and topical capsaicin as monotherapy (against placebo) for the management of neuropathic pain conditions in adults in non-specialist settings?

Review question 2

What is the clinical efficacy of antidepressants, anti-epileptics, opioid analgesics, topical lidocaine and topical capsaicin as combination therapy (against monotherapy or other combination therapy) for the management of neuropathic pain in adults in non-specialist settings?

Review question 3

What is the clinical efficacy of antidepressants, compared with anti-epileptics, opioid analgesics, topical lidocaine and topical capsaicin (and vice-versa) as monotherapy for the management of neuropathic pain in adults in non-specialist settings?

Overall summary of evidence

A total of 29,237 studies were retrieved by the systematic searches for the guideline (antidepressants = 3641, anti-epileptics = 6167, opioid analgesics = 12,075, topical capsaicin and topical lidocaine = 7196, neurogenic pain = 158). From the 29,237 studies, 101 randomised placebo-controlled trials of monotherapy, 14 head-to-head comparative trials of monotherapy and combination therapy were included, based on the inclusion and exclusion criteria suggested by the GDG through two short survey questionnaires[9]. The

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

searches did not identify any placebo-controlled studies that met the inclusion and exclusion criteria for 15 of the pharmacological treatments (see table 5). The 115 included studies are summarised in table 6.

Table 5 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 6 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)	5	Duloxetine	30%, 50%, AEs
Antidepressants (SNRIs)	4	Venlafaxine	50%, Global, mean pain intensity score, AEs

Subtotal	**24**		
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	16	Pregabalin	30%, 50%, Global, mean pain intensity score, AEs
Subtotal	**50**		
Opioid analgesics	5	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	**9**		
Topical treatments	13	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	**18**		
Antidepressants vs anti-epileptics	3	Amitriptyline vs gabapentin	30%, Global, AEs, mean change in pain intensity score, mean change in pain relief score
Antidepressants vs anti-epileptics	1	Amitriptyline vs pregabalin	50%, Global, AEs
Antidepressants vs anti-epileptics	1	Nortriptyline vs gabapentin	50%, mean change in pain relief score, AEs
Antidepressants vs anti-epileptics	1	Amitriptyline vs carbamazepine	Global, AEs
Antidepressants 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
Antidepressants vs antidepressants	1	Amitriptyline vs nortriptyline	AEs
Antidepressants vs antidepressants	1	Imipramine vs venlafaxine	Global, AEs

Anti-epileptics + opioids vs anti-epileptics	1	Gabapentin + oxycodone vs gabapentin	Mean pain relief score, AEs
Anti-epileptics + opioids vs anti-epileptics vs opioids	1	Pregabalin + oxycodone vs pregabalin 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
Antidepressants + anti-epileptics vs antidepressants vs anti-epileptics	1	Amitriptyline + pregabalin vs amitriptyline vs pregabalin	50%
Subtotal	**14**		
TOTAL	**115**		

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.

Structure of the guideline and analyses

From the 115 included studies, nearly 50% were on two specific neuropathic pain conditions, namely painful diabetic neuropathy (PDN; 34 studies) and post-herpetic neuralgia (PHN; 21 studies). Consequently, these two specific neuropathic conditions were perceived as having sufficient and robust evidence and hence meta-analyses were carried out for individual pharmacological treatments for PDN and PHN.

The other 60 included studies are on various other neuropathic pain conditions (for example, spinal cord injury, neuropathic cancer pain, HIV-related neuropathy, post-stroke neuropathic pain, phantom limb pain, central pain, radiculopathy, polyneuropathy, post-traumatic neuropathic pain including post-surgical neuropathic pain, or mixed neuropathic pain). Because none of these neuropathic pain conditions had significant numbers of studies available (unlike like PDN and PHN), a meta-analysis was done of the 60 included studies as ‘other neuropathic pain conditions’ for each drug.

Issues on key principles of care were also discussed after decisions were made on which pharmacological treatments should be recommended.

Therefore, the guideline is structured under three sections as follow: PDN, PHN, and other neuropathic pain conditions, with discussion on key principles of care for all neuropathic pain conditions combined.

The structure of the guideline is based on the chronological order of how the GDG assessed and discussed the evidence to allow readers to understand the rationales and decisions made at each stage. However, the structure of the guideline does not match the order of the recommendations because the GDG felt that recommendations need to be ordered to aid implementation, rather than by the order the evidence was analysed.

3.1.2 Health economics

A search was conducted for published health economic analysis and no appropriate publications were identified. Full details are presented in appendix 10.11 including reasons for exclusion. However, the GDG had access to a relevant in development health technology assessment (HTA) report that is due for publication after guideline development had ended. This draft HTA report by Fox-Rushby et al (Project abstract available from www.hta.ac.uk/1527) reviewed the clinical and cost effectiveness of different treatment pathways for neuropathic pain. A overview is presented in appendix 10.11. Below is a discussion on the applicability of this study to the clinical guideline.

Applicability of the HTA model to the guideline

It is recognised that the methodology adopted for the draft HTA report, in relation to both the efficacy review and the health economic evaluation, was systematic and of high quality. Therefore, this discussion will contrast the approaches used for the draft HTA report and the current clinical guideline and consider their potential impact on interpretation and generalisability for this guideline. Then the remaining limitations of the model will be discussed.

Decision problem

The draft HTA report reviewed the evidence on only two conditions, namely PHN and PDN. Other sub-populations were considered difficult to model

because of lack of data, as shown by the effectiveness and economic reviews of the literature conducted for this guideline.

The drugs covered by the draft HTA report differed to those included in this guideline. In particular, amitriptyline was excluded from the economic analysis because the available evidence was poor. In addition, the analysis included a number of treatments that the GDG considered were unsuitable for primary care such as venlafaxine and epidural methylprednisolone. The doses used in the model may not be representative of clinical practice and therefore may reduce the generalisability of the results. In addition, the model could not consider combination treatment and therefore, could not be used to inform a clinical pathway. However, the GDG were able to combine the results of the economic analysis with their clinical opinion within the framework of the guideline to produce recommendations.

Clinical data

The clinical data included in the HTA model were based on a systematic search for randomised controlled trial (RCT) data completed in 2009. The search strategy and included studies differed from those in the clinical evidence review in this guideline, which included a number of new head-to-head studies and data for the recently licensed capsaicin 8% patch.

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. In particular, the drug doses were modelled as prescribed in the clinical trials. However, drug doses in trials do not necessarily reflect doses prescribed in practice, which may be substantially higher. This is an important issue and affects the evidence of both clinical and cost effectiveness.

In addition, the data on minor adverse events are possibly unrepresentative. In a drug trial, a patient experiencing minor adverse events may be asked to continue to take the drug for the short trial duration. By 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.

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.

Quality of life

For the health economic modelling in the draft 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 commonly used 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.

If a drug does not provide a 50% pain reduction or more, then it does not incur any health benefits in the HTA model. However, introducing a lower cut-off point such as 30% pain reduction, could 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 lower cut-off added, but this is unlikely to change the ordering of the treatments in the analysis.

Resource use and costs

For both the PHN and PDN models, expert opinion supplemented the data if insufficient published data were available to populate the model. 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 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; second, 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.

Conclusion

The draft HTA report broadly overlaps with the guideline's clinical questions; however, there are a number of significant differences from the guideline. This limits the generalisability of the HTA model's results. The GDG concluded that the HTA analysis was partially applicable and had minor limitations. Therefore, the outputs of the HTA report will be considered alongside the clinical evidence, information on acquisition costs and GDG experience when assessing the cost effectiveness of treatments.

3.2 Painful diabetic neuropathy (PDN)

3.2.1 Review questions

Review question 1

What is the clinical efficacy of antidepressants, anti-epileptics, opioid analgesics, topical lidocaine and topical capsaicin as monotherapy (against placebo) for the management of neuropathic pain condition (painful diabetic neuropathy) in adults in non-specialist settings?

Review question 2

What is the clinical efficacy of antidepressants, anti-epileptics, opioid analgesics, topical lidocaine and topical capsaicin as combination therapy (against monotherapy or other combination therapy) for the management of neuropathic pain (painful diabetic neuropathy) in adults in non-specialist settings?

Review question 3

What is the clinical efficacy of antidepressants, compared with anti-epileptics, opioid analgesics, topical lidocaine and topical capsaicin (and vice-versa) as monotherapy for the management of neuropathic pain (painful diabetic neuropathy) in adults in non-specialist settings?

3.2.2 Evidence review

A total of 34 randomised controlled trials were included for painful diabetic neuropathy (PDN). Of the 34 listed included pharmacological treatments in (Table 4), no study was identified or met the inclusion and exclusion criteria for the following pharmacological treatments (see table 7).

For the characteristics of included studies please see Tables 8–12.

Table 7 Pharmacological treatments for which no study was identified or met the inclusion and exclusion criteria for PDN

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

Table 8 Characteristics of included studies for PDN: antidepressants as monotherapy (placebo-controlled trials)

Author	Study period	Condition	Treatment (oral)	Titration or fixed dosage (mg/day)	Mean dose (mg/day)	Outcomes
Max et al. (1991)	6 weeks	PDN	Desipramine	12.5–250	201	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
Gao et al. (2010)	12 weeks	PDN	Duloxetine	30-120	N/A	30%, 50%, AEs
Rowbotham et al. (2004)	6 weeks	PDN	Venlafaxine	75, 150–225	N/A	50%, AEs
PDN = painful diabetic neuropathy; Global = patient-reported global improvement; 30% = at least 30% pain reduction; 50% = at least 50% pain reduction; AEs = adverse effects; N/A = not applicable.						

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340 **Table 9 Characteristics of included studies for PDN: anti-epileptics as**
341 **monotherapy (placebo-controlled trials)**

Author	Study period	Condition	Treatment (oral)	Titration or fixed dosage (mg/day)	Outcomes
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
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
Backonja et al. (1998)	8 weeks	PDN	Gabapentin	to 3600	Global, AEs
Simpson (2001)	8 weeks	PDN	Gabapentin	to 3600	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
Satoh et al. (2011)	14 weeks	PDN	Pregabalin	300, 600	50%, AEs
PDN = painful diabetic neuropathy; Global = patient-reported global improvement; 30% = at least 30% pain reduction; 50% = at least 50% pain reduction; AEs = adverse effects.					

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Table 10 Characteristics of included studies for PDN: opioid analgesics as monotherapy (placebo-controlled trials)

Author	Study period	Condition	Treatment (oral)	Titration or fixed dosage (mg/day)	Outcomes
Harati et al. (1998)	4 weeks	PDN	Tramadol	200–400	Mean pain intensity score, AEs
Gimbel et al. (2003)	6 weeks	PDN	Oxycodone	10–120	Mean change in pain intensity score, AEs
PDN = painful diabetic neuropathy; Global = patient-reported global improvement; 30% = at least 30% pain reduction; 50% = at least 50% pain reduction; AEs = adverse effects.					

Table 11 Characteristics of included studies for PDN: topical capsaicin and topical lidocaine as monotherapy (placebo-controlled trials)

Author	Study period	Condition	Treatment (topical)	Titration or fixed dosage (times/day)	Outcomes
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
PDN = painful diabetic neuropathy; Global = patient-reported global improvement; AEs = adverse effects.					

Table 12 Characteristics of included studies for PDN: comparative trials and combination therapy (randomised controlled trials)

Author	Study period	Condition	T1	T2	Titration or fixed dosage (mg/day)	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
Dallocchio et al. (2000)	12 weeks	PDN	Amitriptyline	Gabapentin	Ami: 10–90 Gaba: 400–2400	Mean change in pain relief score, AEs
Bansal et al. (2009)	5 weeks	PDN	Amitriptyline	Pregabalin	Ami: 10-50 Pre: 150-600	Global, 50%, 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
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

Author	Study period	Condition	T1	T2	Titration or fixed dosage (mg/day)	Outcomes
T1 = treatment 1; T2 = treatment 2; PDN = painful diabetic neuropathy; Global = patient-reported global improvement; 50% = at least 50% pain reduction; AEs = adverse effects.						

Summary profiles

Meta-analyses were conducted based on the methodology stated in section 3.1 and presented in the following summary profiles based on individual pharmacological treatments (for full GRADE profiles, see appendix 10.9).

Antidepressants

Table 13 Summary profile – desipramine as monotherapy (placebo-controlled trials)

No of studies	Desipramine	Placebo	Relative risk (95% CI)	Absolute risk	Quality
Primary outcome: patient-reported global improvement/impression of change (follow-up 6 weeks)					
1[1]	11/20 (55%)	2/20 (10%)	RR 5.50 (1.39 to 21.71)	45 more per 100 (from 4 more to 100 more)	MODERATE
Primary outcome: number of withdrawals due to adverse effects (follow-up 6 weeks)					
1[1]	2/20 (10%)	0/20 (0%)	RR 5.00 (0.26 to 98.00)	–	VERY LOW
Primary outcome: dry mouth (adverse effects) (follow-up 6 weeks)					
1[1]	8/20 (40%)	9/20 (45%)	RR 0.89 (0.43 to 1.83)	5 fewer per 100 (from 26 fewer to 37 more)	VERY LOW
Primary outcome: sedation (adverse effects) (follow-up 6 weeks)					
1[1]	8/20 (40%)	8/20 (40%)	RR 1.00 (0.47 to 2.14)	0 fewer per 100 (from 21 fewer to 46 more)	VERY LOW
Primary outcome: any adverse effects: unspecified (follow-up 6 weeks)					
1[1]	18/20 (90%)	17/20 (85%)	RR 1.06 (0.84 to 1.34)	5 more per 100 (from 14 fewer to 29 more)	VERY LOW
[1] Max et al. (1991).					

Table 14 Summary profile – duloxetine as monotherapy (placebo-controlled trials)

No of studies	Duloxetine	Placebo	Relative risk (95% CI)	Absolute risk	Quality
Primary outcome: patient-reported 30% pain reduction (follow-up 12 weeks)					
2[1]	220/327 (67.3%)	111/215 (51.6%)	RR 1.33 (0.95 to 1.88)	17 more per 100 (from 3 fewer to 45 more)	MODERATE
Primary outcome: patient-reported 50% pain reduction (follow-up 12 weeks)					
4[2]	485/896 (54.1%)	164/443 (37%)	RR 1.51 (1.17 to 1.94)	19 more per 100 (from 6 more to 35 more)	MODERATE
Primary outcome: number of withdrawals due to adverse effects (follow-up 12 weeks)					
4[2]	113/906	21/448	RR 2.63 (1.68 to 4.12)	8 more per 100 (from 3	

	(12.5%)	(4.7%)		more to 15 more)	MODERATE
Primary outcome: dizziness (adverse effects) (follow-up 12 weeks)					
3[3]	90/674 (13.4%)	26/332 (7.8%)	RR 1.81 (1.17 to 2.79)	6 more per 100 (from 1 more to 14 more)	MODERATE
Primary outcome: dry mouth (adverse effects) (follow-up 12 weeks)					
2[4]	37/448 (8.3%)	10/224 (4.5%)	RR 1.61 (0.82 to 3.20)	3 more per 100 (from 1 fewer to 10 more)	LOW
Primary outcome: gastrointestinal disturbances (adverse effects) (follow-up 12 weeks)					
2[5]	28/332 (8.4%)	8/217 (3.7%)	RR 2.53 (1.13 to 5.67)	6 more per 100 (from 0 more to 17 more)	LOW
Primary outcome: vomiting (adverse effects) (follow-up 12 weeks)					
1[6]	6/106 (5.7%)	5/109 (4.6%)	RR 1.23 (0.39 to 3.92)	1 more per 100 (from 3 fewer to 13 more)	VERY LOW
Primary outcome: any adverse effects: unspecified (follow-up 12 weeks)					
1[6]	86/106 (81.1%)	78/109 (71.6%)	RR 1.13 (0.98 to 1.32)	9 more per 100 (from 1 fewer to 23 more)	MODERATE
[1] Gao et al. (2010); Wernicke et al. (2006). [2] Gao et al. (2010); Goldstein et al. (2005); Raskin et al. (2005); Wernicke et al. (2006). [3] Gao et al. (2010); Goldstein et al. (2005); Wernicke et al. (2006). [4] Gao et al. (2010); Goldstein et al. (2005). [5] Gao et al. (2010); Wernicke et al. (2006). [6] Gao et al. (2010).					

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364 **Table 15 Summary profile – venlafaxine as monotherapy (placebo-**
365 **controlled trials)**

No of studies	Venlafaxine	Placebo	Relative risk (95% CI)	Absolute risk	Quality
Primary outcome: patient-reported 50% pain reduction (follow-up 6 weeks)					
1[1]	77/163 (47.2%)	27/80 (33.8%)	RR 1.40 (0.99 to 1.98)	13 more per 100 (from 0 fewer to 33 more)	MODERATE
Primary outcome: vomiting (adverse effects) (follow-up 6 weeks)					
1[1]	9/164 (5.5%)	0/81 (0%)	RR 9.44 (0.56 to 160.24)	–	VERY LOW
[1] Rowbotham et al. (2004).					

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367 *Anti-epileptics*

368 **Table 16 Summary profile – gabapentin as monotherapy (placebo-**
369 **controlled trials)**

No of studies	Gabapentin	Placebo	Relative risk (95% CI)	Absolute risk	Quality
Primary outcome: patient-reported global improvement/impression of change (follow-up 8 weeks)					
2[1]	62/106 (58.5%)	32/103 (31.1%)	RR 1.88 (1.35 to 2.61)	27 more per 100 (from 11 more to 50 more)	MODERATE
Primary outcome: number of withdrawals due to adverse effects (follow-up 8 weeks)					
2[1]	8/114 (7%)	6/111 (5.4%)	RR 1.29 (0.46 to 3.60)	2 more per 100 (from 3 fewer to 14 more)	LOW
Primary outcome: dizziness (adverse effects) (follow-up 8 weeks)					
2[1]	26/111 (23.4%)	5/108 (4.6%)	RR 5.05 (2.02 to 12.67)	19 more per 100 (from 5 more to 54 more)	LOW
Primary outcome: somnolence (adverse effects) (follow-up 8 weeks)					
2[1]	25/111 (22.5%)	6/108 (5.6%)	RR 4.05 (1.73 to 9.47)	17 more per 100 (from 4 more to 47 more)	LOW

[1] Backonja et al (1998); Simpson et al. (2001).

370

371 **Table 17 Summary profile – pregabalin as monotherapy (placebo-**
372 **controlled trials)**

No of studies	Pregabalin	Placebo	Relative risk (95% CI)	Absolute risk	Quality
Primary outcome: patient-reported 30% pain reduction (follow-up 5 weeks)					
1[1]	103/162 (63.6%)	32/97 (33%)	RR 1.93 (1.42 to 2.62)	31 more per 100 (from 14 more to 53 more)	MODERATE
Primary outcome: patient-reported 50% pain reduction (follow-up 5 to 14 weeks)					
5[2]	298/808 (36.9%)	91/459 (19.8%)	RR 1.87 (1.33 to 2.63)	17 more per 100 (from 7 more to 32 more)	MODERATE
Primary outcome: patient-reported global improvement/impression of change (follow-up 5 to 12 weeks)					
2[3]	208/396 (52.5%)	49/174 (28.2%)	RR 1.89 (1.04 to 3.45)	25 more per 100 (from 1 more to 69 more)	LOW
Primary outcome: number of withdrawals due to adverse effects (follow-up 5 to 14 weeks)					
6[4]	97/1039 (9.3%)	28/569 (4.9%)	RR 2.13 (1.40 to 3.23)	6 more per 100 (from 2 more to 11 more)	MODERATE
Primary outcome: dizziness (adverse effects) (follow-up 5 to 14 weeks)					
6[4]	222/1039 (21.4%)	31/569 (5.4%)	RR 4.53 (3.14 to 6.54)	19 more per 100 (from 12 more to 30 more)	MODERATE
Primary outcome: somnolence (adverse effects) (follow-up 5 to 14 weeks)					
6[4]	155/1039 (14.9%)	26/569 (4.6%)	RR 3.71 (2.46 to 5.58)	12 more per 100 (from 7 more to 21 more)	MODERATE
Primary outcome: weight gain (adverse effects) (follow-up 6 to 14 weeks)					
4[5]	60/723 (8.3%)	4/402 (1%)	RR 7.82 (3.12 to 19.60)	7 more per 100 (from 2 more to 19 more)	LOW
Primary outcome: any adverse effects: unspecified (follow-up 8 to 14 weeks)					
2[6]	159/257 (61.9%)	68/206 (33%)	RR 1.87 (1.50 to 2.32)	29 more per 100 (from 17 more to 44 more)	MODERATE

[1] Lesser et al. (2004). [2] Lesser et al. (2004); Richter et al. (2005); Rosenstock et al. (2004); Tölle et al. (2008); Satoh et al. (2011). [3] Lesser et al. (2004); Tölle et al. (2008). [4] Arezzo et al. (2008); Lesser et al. (2004); Richter et al. (2005); Rosenstock et al. (2004); Tölle et al. (2008); Satoh et al. (2011). [5] Arezzo et al. (2008); Richter et al. (2005); Tölle et al. (2008); Satoh et al. (2011). [6] Rosenstock et al. (2004); Sath et al. (2011).

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374 **Table 18 Summary profile – lamotrigine as monotherapy (placebo-**
375 **controlled trials)**

No of studies	Lamotrigine	Placebo	Relative risk (95% CI)	Absolute risk	Quality
Primary outcome: patient-reported 30% pain reduction (follow-up 19 weeks)					
2[1]	110/324 (34%)	41/120 (34.2%)	RR 1.00 (0.74 to 1.33)	0 fewer per 100 (from 9 fewer to 11 more)	MODERATE
Primary outcome: patient-reported 50% pain reduction (follow-up 8 to 19 weeks)					
3[2]	92/351 (26.2%)	35/146 (24%)	RR 1.13 (0.81 to 1.57)	3 more per 100 (from 5 fewer to 14 more)	MODERATE
Primary outcome: patient-reported global improvement/impression of change (follow-up 8 weeks)					
1[3]	7/22 (31.8%)	2/21 (9.5%)	RR 3.34 (0.78 to 14.29)	22 more per 100 (from 2 fewer to 100 more)	MODERATE

Primary outcome: number of withdrawals due to adverse effects (follow-up 8 to 19 weeks)					
4[4]	72/579 (12.4%)	16/220 (7.3%)	RR 1.58 (0.94 to 2.66)	4 more per 100 (from 0 fewer to 12 more)	LOW
Primary outcome: dizziness (adverse effects) (follow-up 8 to 19 weeks)					
3[2]	43/559 (7.7%)	12/200 (6%)	RR 1.40 (0.73 to 2.68)	2 more per 100 (from 2 fewer to 10 more)	LOW
Primary outcome: any adverse effects: unspecified (follow-up 8 to 19 weeks)					
3[2]	415/559 (74.2%)	137/200 (68.5%)	RR 1.05 (0.89 to 1.25)	3 more per 100 (from 8 fewer to 17 more)	HIGH
[1] Vinik et al. (2007a); Vinik et al. (2007b). [2] Eisenberg et al. (2001); Vinik et al. (2007a); Vinik et al. (2007b). [3] Eisenberg et al. (2001) .[4] Eisenberg et al. (2001); Luria et al. (2000); Vinik et al. (2007a); Vinik et al. (2007b).					

376

377 **Table 19 Summary profile – topiramate as monotherapy (placebo-**
378 **controlled trials)**

No of studies	Topiramate	Placebo	Relative risk (95% CI)	Absolute risk	Quality
Primary outcome: patient-reported 30% pain reduction (follow-up 12 weeks)					
1[1]	103/208 (49.5%)	37/109 (33.9%)	RR 1.46 (1.09 to 1.96)	16 more per 100 (from 3 more to 33 more)	MODERATE
Primary outcome: patient-reported 50% pain reduction (follow-up 12 weeks)					
1[1]	74/208 (35.6%)	23/109 (21.1%)	RR 1.69 (1.12 to 2.53)	15 more per 100 (from 3 more to 32 more)	MODERATE
Primary outcome: patient-reported global improvement/impression of change (follow-up 12 weeks)					
1[1]	112/208 (53.8%)	37/109 (33.9%)	RR 1.59 (1.19 to 2.12)	20 more per 100 (from 6 more to 38 more)	MODERATE
Primary outcome: no. of withdrawals due to adverse effects (follow-up 12 to 22 weeks)					
2[2]	265/1099 (24.1%)	41/493 (8.3%)	RR 2.90 (2.12 to 3.96)	16 more per 100 (from 9 more to 25 more)	HIGH
Primary outcome: dizziness (adverse effects) (follow-up 12 weeks)					
1[1]	15/211 (7.1%)	6/109 (5.5%)	RR 1.29 (0.52 to 3.23)	2 more per 100 (from 3 fewer to 12 more)	VERY LOW
Primary outcome: somnolence (adverse effects) (follow-up 12 to 22 weeks)					
2[2]	108/1096 (9.9%)	19/493 (3.9%)	RR 2.56 (1.59 to 4.11)	6 more per 100 (from 2 more to 12 more)	MODERATE
Primary outcome: fatigue (adverse effects) (follow-up 12 to 22 weeks)					
2[2]	158/1096 (14.4%)	44/493 (8.9%)	RR 1.58 (1.15 to 2.16)	5 more per 100 (from 1 more to 10 more)	MODERATE
Primary outcome: any adverse effects: unspecified (follow-up 12 weeks)					
1[1]	170/214 (79.4%)	77/109 (70.6%)	RR 1.12 (0.98 to 1.29)	8 more per 100 (from 1 fewer to 20 more)	MODERATE
[1] Raskin et al. (2004). [2]Raskin et al. (2004); [3] Thienel et al. (2004).					

379

Table 20 Summary profile – oxcarbazepine as monotherapy (placebo-controlled trials)

No of studies	Oxcarbazepine	Placebo	Relative risk (95% CI)	Absolute risk	Quality
Primary outcome: patient-reported 30% pain reduction (follow-up 16 weeks)					
1[1]	31/69 (44.9%)	22/77 (28.6%)	RR 1.57 (1.01 to 2.44)	16 more per 100 (from 0 more to 41 more)	MODERATE
Primary outcome: patient-reported 50% pain reduction (follow-up 16 weeks)					
1[1]	24/69 (34.8%)	14/77 (18.2%)	RR 1.91 (1.08 to 3.39)	17 more per 100 (from 1 more to 43 more)	MODERATE
Primary outcome: patient-reported global improvement/impression of change (follow-up 16 weeks)					
2[2]	97/229 (42.4%)	52/149 (34.9%)	RR 1.16 (0.90 to 1.49)	6 more per 100 (from 3 fewer to 17 more)	MODERATE
Primary outcome: number of withdrawals due to adverse effects (follow-up 16 weeks)					
3[3]	102/398 (25.6%)	16/236 (6.8%)	RR 3.83 (2.29 to 6.40)	19 more per 100 (from 9 more to 37 more)	MODERATE
Primary outcome: dizziness (adverse effects) (follow-up 16 weeks)					
2[2]	58/310 (18.7%)	3/159 (1.9%)	RR 8.90 (2.81 to 28.24)	15 more per 100 (from 3 more to 51 more)	LOW
Primary outcome: somnolence (adverse effects) (follow-up 16 weeks)					
2[2]	21/310 (6.8%)	3/159 (1.9%)	RR 2.95 (1.04 to 8.35)	4 more per 100 (from 0 more to 14 more)	LOW
Primary outcome: fatigue (adverse effects) (follow-up 16 weeks)					
2[2]	31/310 (10%)	7/159 (4.4%)	RR 1.83 (0.83 to 4.00)	4 more per 100 (from 1 fewer to 13 more)	LOW
[1] Dogra et al. (2005). [2] Dogra et al. (2005); Beydoun et al. (2006). [3] Dogra et al. (2005); Beydoun et al. (2006); Grosskopf et al. (2006).					

Table 21 Summary profile – sodium valproate as monotherapy (placebo-controlled trials)

No of studies	Sodium valproate	Placebo	Relative risk (95% CI)	Absolute risk	Quality
Primary outcome: number of withdrawals owing to adverse effects (follow-up 4 to 12 weeks)					
2[1]	2/52 (3.8%)	0/51 (0%)	RR 2.93 (0.32 to 27.29)	–	LOW
Primary outcome: any adverse effects: unspecified (follow-up 12 weeks)					
1[2]	4/20 (20%)	1/20 (5%)	RR 4.00 (0.49 to 32.72)	15 more per 100 (from 3 fewer to 100 more)	VERY LOW
Other reported pain outcome: pain intensity (scale: VASpi-10 cm) (follow-up 12 weeks)					
1[2]	20	20	Treatment = 6.2 (1.4); Placebo = 6.9 (1.0) p > 0.05		LOW
Other reported pain outcome: pain relief (scale: VASpr-100 mm) (follow-up 12 weeks)					
1[3]	22	21	Treatment = 30.0 (99.4); Placebo = 60.0 (84.2) p < 0.001		LOW
1 Kochar et al. (2002); Kochar et al. (2004). [2] Agrawal et al. (2009). [3] Kochar et al. (2004).					

Note: no study on sodium valproate that reported the critical outcomes on pain was identified or met the inclusion and exclusion criteria.

Table 22 Summary profile – tramadol as monotherapy (placebo-controlled trials)

No of studies	Tramadol	Placebo	Relative risk (95% CI)	Absolute risk	Quality
Primary outcome: withdrawals due to adverse effects (follow-up 4 weeks)					
1[1]	9/65 (13.8%)	1/66 (1.5%)	RR 9.14 (1.19 to 70.10)	12 more per 100 (from 0 more to 100 more)	VERY LOW
Primary outcome: constipation (adverse effects) (follow-up 4 weeks)					
1[1]	14/65 (21.5%)	2/66 (3%)	RR 7.11 (1.68 to 30.04)	19 more per 100 (from 2 more to 88 more)	VERY LOW
Primary outcome: somnolence/drowsiness (adverse effects) (follow-up 4 weeks)					
1[1]	8/65 (12.3%)	4/66 (6.1%)	RR 2.03 (0.64 to 6.42)	6 more per 100 (from 2 fewer to 33 more)	VERY LOW
Primary outcome: nausea (adverse effects) (follow-up 4 weeks)					
1[1]	15/65 (23.1%)	2/66 (3%)	RR 7.62 (1.81 to 31.99)	20 more per 100 (from 2 more to 94 more)	VERY LOW
Primary outcome: dizziness (adverse effects) (follow-up 4 weeks)					
1[1]	3/65 (4.6%)	0/66 (0%)	RR 7.11 (0.37 to 134.91)	–	VERY LOW
Other reported pain outcome: pain intensity (Scale: VASpi-10 cm) (follow-up 4 weeks)					
1[1]	65	66	Treatment = 1.4 (0.1); Placebo = 2.2 (0.1) p < 0.001		LOW
[1] Harati et al. (1998).					

Note: no study on tramadol that reported the critical outcomes on pain was identified or met the inclusion and exclusion criteria.

Table 23 Summary profile– oxycodone as monotherapy (placebo-controlled trials)

No of studies	Oxycodone	Placebo	Relative risk (95% CI)	Absolute risk	Quality
Primary outcome: withdrawals owing to adverse effects (follow-up 6 weeks)					
1[1]	7/82 (8.5%)	4/77 (5.2%)	RR 1.64 (0.50 to 5.39)	3 more per 100 (from 3 fewer to 23 more)	VERY LOW
Primary outcome: somnolence/drowsiness (adverse effects) (follow-up 6 weeks)					
1[1]	33/82 (40.2%)	1/77 (1.3%)	RR 30.99 (4.34 to 221.09)	39 more per 100 (from 4 more to 100 more)	VERY LOW
Primary outcome: nausea (adverse effects) (follow-up 6 weeks)					
1[1]	30/82 (36.6%)	6/77 (7.8%)	RR 4.70 (2.07 to 10.65)	29 more per 100 (from 8 more to 75 more)	VERY LOW
Primary outcome: dizziness (adverse effects) (follow-up 6 weeks)					
1[1]	26/82 (31.7%)	8/77 (10.4%)	RR 3.05 (1.47 to 6.33)	21 more per 100 (from 5 more to 55 more)	VERY LOW
Primary outcome: vomiting (adverse effects) (follow-up 6 weeks)					
1[1]	17/82 (20.7%)	2/77 (2.6%)	RR 7.98 (1.91 to 33.41)	18 more per 100 (from 2 more to 84 more)	VERY LOW

Other reported pain outcome: pain intensity (Scale: NRSpi 11-point) (follow-up 6 weeks)				
1[1]	82	77	Treatment = −2.6 (2.54); Placebo = −1.5 (2.19) p < 0.001	LOW
[1] Gimbel et al. (2003).				

396

397 Note: no study on oxycodone that reported the critical outcomes on pain was
398 identified or met the inclusion and exclusion criteria.

399 *Topical treatments*

400 **Table 24 Summary profile – topical capsaicin (0.075% cream) as**
401 **monotherapy (placebo-controlled trials)**

No of studies	Topical capsaicin (0.075% cream)	Placebo cream	Relative risk (95% CI)	Absolute risk	Quality
Primary outcome: patient-reported global improvement/impression of change (follow-up 8 weeks)					
1[1]	23/40 (57.5%)	26/40 (65%)	RR 0.88 (0.62 to 1.26)	8 fewer per 100 (from 25 fewer to 17 more)	MODERATE
Primary outcome: withdrawals owing to adverse effects (follow-up 8 weeks)					
2[2]	3/39 (7.7%)	0/37 (0%)	RR 3.84 (0.45 to 32.92)	-	LOW
Primary outcome: burning (adverse effects) (follow-up 8 weeks)					
2[2]	23/39 (59%)	7/37 (18.9%)	RR 3.11 (1.52 to 6.37)	40 more per 100 (from 10 more to 100 more)	LOW
[1] Tandan et al. (1992). [2] Schefflet et al. (1991); Tandan et al. (1992).					

402

403 *Head-to-head comparative trials (monotherapy)*

404 **Table 25 Summary profile – pregabalin vs amitriptyline as monotherapy**
405 **(comparative trials)**

No of studies	Pregabalin	Amitriptyline	Relative risk (95% CI)	Absolute risk	Quality
Primary outcome: patient-reported 50% pain reduction (follow-up 5 weeks)					
1[1]	21/51 (41.2%)	15/51 (29.4%)	RR 1.40 (0.82 to 2.39)	12 more per 100 (from 5 fewer to 41 more)	MODERATE
Primary outcome: patient-reported global improvement/impression of change (follow-up 5 weeks)					
1[1]	34/51 (66.7%)	32/51 (62.7%)	RR 1.08 (0.82 to 1.44)	5 more per 100 (from 11 fewer to 28 more)	MODERATE
Primary outcome: number of withdrawals due to adverse effects (follow-up 5 weeks)					
1[1]	6/51 (11.8%)	17/51 (33.3%)	RR 0.35 (0.15 to 0.82)	22 fewer per 100 (from 6 fewer to 28 fewer)	VERY LOW
Primary outcome: dizziness (adverse effects) (follow-up 5 weeks)					
1[1]	3/51 (5.9%)	2/51 (3.9%)	RR 1.5 (0.26 to 8.60)	2 more per 100 (from 3 fewer to 30 more)	VERY LOW
Primary outcome: somnolence (adverse effects) (follow-up 5 weeks)					
1[1]	3/51 (5.9%)	7/51 (13.7%)	RR 0.43 (0.12 to 1.56)	8 fewer per 100 (from 12 fewer to 8 more)	VERY LOW
[1] Bansal et al. (2009).					

406

407 **Table 26 Summary profile – amitriptyline vs gabapentin as monotherapy**
408 **(comparative trials)**

No of studies	Amitriptyline	Gabapentin	Relative risk (95% CI)	Absolute risk	Quality
Primary outcome: patient-reported global improvement/impression of change (follow-up 6 weeks)					
1[1]	14/21 (66.7%)	11/21 (52.4%)	RR 1.27 (0.77 to 2.11)	14 more per 100 (from 12 fewer to 58 more)	MODERATE
Primary outcome: number of withdrawals owing to adverse effects (follow-up 6 weeks)					
1[1]	2/25 (8%)	1/25 (4%)	RR 2.00 (0.19 to 20.67)	4 more per 100 (from 3 fewer to 79 more)	VERY LOW
Primary outcome: any adverse effects: unspecified (follow-up 6 to 12 weeks)					
2[2]	28/37 (75.7%)	22/38 (57.9%)	RR 1.58 (0.49 to 5.15)	34 more per 100 (from 30 fewer to 100 more)	LOW
Primary outcome: dizziness (adverse effects) (follow-up 12 weeks)					
1[1]	2/25 (8%)	7/25 (28%)	RR 0.29 (0.07 to 1.24)	20 fewer per 100 (from 26 fewer to 7 more)	VERY LOW
Primary outcome: sedation (adverse effects) (follow-up 12 weeks)					
1[1]	8/25 (32%)	12/25 (48%)	RR 0.67 (0.33 to 1.35)	16 fewer per 100 (from 32 fewer to 17 more)	VERY LOW

[1] Morello et al. (1999). [2] Morello et al. (1999); Dallocchio et al. (2000).

409

410 **Table 27 Summary profile – amitriptyline vs topical capsaicin (0.075%**
411 **cream) as monotherapy (comparative trials)**

No of studies	Amitriptyline	Capsaicin cream (0.075%)	Relative risk (95% CI)	Absolute risk	Quality
Primary outcome: sedation (adverse effects) (follow-up 8 weeks)					
1[1]	69/117 (59%)	0/118 (0%)	∞ (∞)	–	VERY LOW
Primary outcome: burning (adverse effects) (follow-up 8 weeks)					
1[1]	0/117 (0%)	68/118 (57.6%)	0.00 (0.00, ∞)	–	VERY LOW
Other reported pain outcome: pain relief (Scale: VASpr-100 mm) (follow-up 8 weeks)					
1[1]	108	104	Amitriptyline = 57.0 (3.6); Capsaicin cream = 55.1 (3.5), p > 0.05		LOW
Other reported pain outcome: pain intensity (Scale: VASpi-100 mm) (follow-up 8 weeks)					
1[1]	108	104	Amitriptyline = −29.1 (2.9); Capsaicin cream = −26.1 (2.9), p > 0.05		LOW

[1] Biesbroeck et al. (1995).

412

413 Note: no study on amitriptyline vs topical capsaicin (0.075% cream) that
414 reported the critical outcomes on pain was identified or met the inclusion and
415 exclusion criteria.

Head-to-head comparative trials (combination therapy)

Table 28 Summary profile – gabapentin + oxycodone as combination therapy vs gabapentin alone (comparative trials)

No of studies	Gabapentin + oxycodone	Gabapentin alone	Relative risk (95% CI)	Absolute risk	Quality
Primary outcome: number of withdrawals owing to adverse effects (follow-up 12 weeks)					
1[1]	27/168 (16%)	9/167 (5.3%)	RR 3.00 (1.45 to 6.19)	11 more per 100 (from 2 more to 28 more)	VERY LOW
Primary outcome: constipation (adverse effects) (follow-up 12 weeks)					
1[1]	45/168 (26.8%)	10/167 (6%)	RR 4.47 (2.33 to 8.58)	21 more per 100 (from 8 more to 45 more)	VERY LOW
Primary outcome: nausea (adverse effects) (follow-up 12 weeks)					
1[1]	43/168 (25.6%)	18/167 (10.8%)	RR 2.37 (1.43 to 3.94)	15 more per 100 (from 5 more to 32 more)	VERY LOW
Primary outcome: dizziness (adverse effects) (follow-up 12 weeks)					
1[1]	25/168 (14.9%)	6/167 (3.6%)	RR 4.14 (1.74 to 9.84)	11 more per 100 (from 3 more to 32 more)	VERY LOW
Primary outcome: somnolence (adverse effects) (follow-up 12 weeks)					
1[1]	37/168 (22%)	9/167 (5.4%)	RR 4.09 (2.04 to 8.20)	17 more per 100 (from 6 more to 39 more)	VERY LOW
Primary outcome: any adverse effects: unspecified (follow-up 12 weeks)					
1[1]	147/168 (87.5%)	119/167 (71.3%)	RR 1.23 (1.10 to 1.37)	16 more per 100 (from 7 more to 26 more)	MODERATE
Other non-primary outcome: pain relief (scale: box scale-11) (follow-up 12 weeks)					
1[1]	169	169	Gabapentin + Oxycodone = 2.1 (2.61); Gabapentin = 1.5 (2.38), p = 0.007		LOW

[1] Hanna et al. (2008).

Note: no study on gabapentin plus oxycodone as combination therapy vs gabapentin alone that reported the critical outcomes on pain was identified or met the inclusion and exclusion criteria.

3.2.3 Evidence statements

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

3.2.3.1 No study on clomipramine, dosulepin (dothiepin), doxepin, imipramine, lofepramine, nortriptyline, trimipramine, citalopram, fluoxetine, paroxetine, sertraline, carbamazepine, phenytoin, buprenorphine, co-codamol, codeine phosphate, co-dydramol, dihydrocodeine, fentanyl, morphine and topical lidocaine was identified or met the inclusion and exclusion criteria for PDN.

Antidepressants as monotherapy against placebo

Desipramine (linked to table 13)

Critical outcomes (pain)

3.2.3.2 Moderate quality evidence from one study with 40 patients with PDN, showed that desipramine is more effective than placebo in achieving patient-reported global improvement/impression of change from baseline up to 6 weeks' follow-up.

Critical outcomes (adverse effects)

3.2.3.3 Very low quality evidence from one study with 40 patients with PDN, showed that there is no significant difference between desipramine and placebo in patients withdrawing from studies due to adverse effects, dry mouth, sedation or any adverse effects (unspecified) from baseline up to 6 weeks' follow-up.

Duloxetine (linked to table 14)

Critical outcomes (pain)

3.2.3.4 Moderate quality evidence from two studies with 542 patients with PDN, showed that there is no significant difference between duloxetine and placebo in achieving at least 30% pain reduction from baseline up to 12 weeks' follow-up.

3.2.3.5 Moderate quality evidence from four studies with 1339 patients with PDN, showed that duloxetine is more effective than placebo in achieving at least 50% pain reduction.

Critical outcomes (adverse effects)

3.2.3.6 Moderate quality evidence from four studies with 1354 patients with PDN and three studies with 1006 patients with PDN, showed that patients on duloxetine are more likely to withdraw from studies due to adverse effects and to experience dizziness compared with placebo from baseline up to 12 weeks' follow-up.

3.2.3.7 Low quality evidence from two studies with 672 patients with PDN, showed that there is no significant difference between patients on

duloxetine and placebo in experiencing dry mouth from baseline up to 12 weeks' follow-up.

3.2.3.8 *Low quality evidence from two studies with 549 patients with PDN, showed that patients on duloxetine are more likely to experience gastrointestinal disturbances compared with placebo from baseline up to 12 weeks' follow-up.*

3.2.3.9 *Very low quality evidence from one study with 215 patients with PDN, showed that there is no significant difference between patients on duloxetine and placebo in experiencing vomiting from baseline up to 12 weeks' follow-up.*

3.2.3.10 *Moderate quality evidence from one study with 215 patients with PDN, showed that there is no significant difference between patients on duloxetine and placebo in experiencing any adverse effects (unspecified) from baseline up to 12 weeks' follow-up.*

Venlafaxine (linked to table 15)

Critical outcomes (pain)

3.2.3.11 *Moderate quality evidence from one study with 243 patients with PDN, showed that there is no significant difference between venlafaxine and placebo in achieving at least 50% pain reduction from baseline up to 6 weeks' follow-up.*

Critical outcomes (adverse effects)

3.2.3.12 *Very low quality evidence from one study with 217 patients with PDN, showed that there is no significant difference between patients on venlafaxine and placebo in experiencing vomiting from baseline up to 6 weeks' follow-up.*

Anti-epileptics as monotherapy against placebo

Gabapentin (linked to table 16)

Critical outcomes (pain)

3.2.3.13 *Moderate quality evidence from two studies with 209 patients with PDN, showed that gabapentin is more effective than placebo in*

achieving patient-reported global improvement/impression of change from baseline up to 8 weeks' follow-up.

Critical outcomes (adverse effects)

3.2.3.14 Low quality evidence from two studies with 225 patients with PDN, showed that there is no significant difference between patients on gabapentin and placebo withdrawing from studies due to adverse effects from baseline up to 8 weeks' follow-up.

3.2.3.15 Low quality evidence from two studies with 219 patients with PDN and also another two studies with 219 patients with PDN, showed that patients on gabapentin are more likely to experience dizziness and somnolence compared with placebo from baseline up to 8 weeks' follow-up.

Pregabalin (linked to table 17)

Critical outcomes (pain)

3.2.3.16 Moderate quality evidence from one study with 259 patients, and another five studies with 1267 patients with PDN, showed that pregabalin is more effective than placebo in achieving at least 30% and at least 50% pain reduction from baseline up to 14 weeks' follow-up.

3.2.3.17 Low quality evidence from two studies with 570 patients with PDN, showed that pregabalin is more effective than placebo in achieving patient-reported global improvement/impression of change from baseline up to 12 weeks' follow-up.

Critical outcomes (adverse effects)

3.2.3.18 Moderate quality evidence from six studies with 1608 patients with PDN, showed that more patients on pregabalin withdraw from studies due to adverse effects, or experience dizziness and somnolence compared with placebo from baseline up to 14 weeks' follow-up.

3.2.3.19 Low quality evidence from four studies with 1125 patients with PDN, showed that patients on pregabalin are more likely to experience weight gain compared with placebo from baseline up to 14 weeks' follow-up.

3.2.3.20 Moderate quality evidence from two studies with 463 patients with PDN, showed that patients on pregabalin are more likely to experience any adverse effects (unspecified) compared with placebo from baseline up to 14 weeks' follow-up.

Lamotrigine (linked to table 18)

Critical outcomes (pain)

3.2.3.21 Moderate quality evidence from two studies with 444 patients, three studies with 497 patients, and one study with 43 patients with PDN, showed that there is no significant difference between lamotrigine and placebo in achieving at least 30% or at least 50% pain reduction and global improvement/impression of change respectively from baseline up to 19 weeks' follow-up.

Critical outcomes (adverse effects)

3.2.3.22 Low quality evidence from four studies with 799 patients, and three studies with 759 patients with PDN, showed that there is no significant difference between patients on lamotrigine and placebo in withdrawal due to adverse effects and dizziness from baseline up to 19 weeks' follow-up.

3.2.3.23 High quality evidence from three studies with 759 patients with PDN, showed that there is no significant difference between patients on lamotrigine and placebo in experiencing any adverse effects (unspecified) from baseline up to 19 weeks' follow-up.

Topiramate (linked to table 19)

Critical outcomes (pain)

3.2.3.24 Moderate quality evidence from one study with 317 patients with PDN, showed that topiramate is more effective than placebo in achieving at least 30% or at least 50% pain reduction and global

improvement/impression of change from baseline up to 12 weeks' follow-up.

Critical outcomes (adverse effects)

3.2.3.25 High quality evidence from two studies with 1592 patients with PDN, showed that patients on topiramate are more likely to withdraw from studies due to adverse effects compared with placebo from baseline up to 22 weeks' follow-up.

3.2.3.26 Moderate quality evidence from two studies with 1589 patients with PDN, showed that patients on topiramate are more likely to experience somnolence and fatigue compared with placebo from baseline up to 22 weeks' follow-up.

3.2.3.27 Very low quality evidence from one study with 320 patients with PDN, showed that there is no significant difference between patients on topiramate and placebo in experiencing dizziness from baseline up to 22 weeks' follow-up.

3.2.3.28 Moderate quality evidence from one study with 323 patients with PDN, showed that there is no significant difference between patients on topiramate and placebo in experiencing any adverse effects (unspecified) from baseline up to 22 weeks' follow-up.

Oxcarbazepine (linked to table 20)

Critical outcomes (pain)

3.2.3.29 Moderate quality evidence from one study with 146 patients with PDN, showed that oxcarbazepine is more effective than placebo in achieving at least 30% and at least 50% pain reduction from baseline up to 16 weeks' follow-up.

3.2.3.30 Moderate quality evidence from two studies with 378 patients with PDN, showed that there is no significant difference between oxcarbazepine and placebo in achieving global improvement/impression of change from baseline up to 16 weeks.

Critical outcomes (adverse effects)

3.2.3.31 Moderate quality evidence from three studies with 634 patients with PDN, showed that patients on oxcarbazepine are more likely to withdraw from studies due to adverse effects compared with placebo from baseline up to 16 weeks' follow-up.

3.2.3.32 Low quality evidence from two studies with 469 patients with PDN, showed that patients on oxcarbazepine are more likely to experience dizziness and somnolence compared with placebo from baseline up to 16 weeks' follow-up.

3.2.3.33 Low quality evidence from two studies with 469 patients with PDN, showed that there is no significant difference between patients on oxcarbazepine and placebo in experiencing fatigue from baseline up to 16 weeks' follow-up.

Sodium valproate (linked to table 21)

Critical outcomes (pain)

3.2.3.34 No study on sodium valproate that reported the critical outcomes on pain was identified or met the inclusion and exclusion criteria.

Critical outcomes (adverse effects)

3.2.3.35 Low quality evidence from two studies with 103 patients with PDN, showed that there is no significant difference between patients on sodium valproate and placebo withdrawing from studies due to adverse effects from baseline up to 12 weeks' follow-up.

3.2.3.36 Very low quality evidence from one study with 40 patients with PDN, showed that there is no significant difference between patients on sodium valproate and placebo in experiencing any adverse effects (unspecified) from baseline up to 12 weeks' follow-up.

Other reported pain outcomes

3.2.3.37 Low quality evidence from one study with 40 patients with PDN, showed that there is no significant difference on pain intensity

scores between patients on sodium valproate and placebo from baseline up to 12 weeks' follow-up.

3.2.3.38 *Low quality evidence from one study with 43 patients with PDN, showed that patients on sodium valproate are more likely to have better scores in pain relief scale than placebo from baseline up to 12 weeks' follow-up.*

Opioid analgesics as monotherapy against placebo

Tramadol (linked to table 22)

Critical outcomes (pain)

3.2.3.39 *No study on tramadol that reported the critical outcomes on pain was identified or met the inclusion and exclusion criteria.*

Critical outcomes (adverse effects)

3.2.3.40 *Very low quality evidence from one study with 131 patients with PDN, showed that patients on tramadol are more likely to withdraw from studies due to adverse effects, constipation and nausea compared with placebo from baseline up to 4 weeks' follow-up.*

3.2.3.41 *Very low quality evidence from one study with 131 patients with PDN, showed that there is no significant difference between patients on tramadol and placebo in experiencing somnolence and dizziness from baseline up to 4 weeks' follow-up.*

Other reported pain outcomes

3.2.3.42 *Low quality evidence from one study with 131 patients with PDN, showed that patients on tramadol are more likely to have better scores in pain intensity scale than placebo from baseline up to 4 weeks' follow-up.*

Oxycodone (linked to table 23)

Critical outcomes (pain)

3.2.3.43 *No study on oxycodone that reported the critical outcomes on pain was identified or met the inclusion and exclusion criteria.*

Critical outcomes (adverse effects)

3.2.3.44 Very low quality evidence from one study with 159 patients with PDN, showed that patients on oxycodone are more likely to experience somnolence, nausea, dizziness and vomiting compared with placebo from baseline up to 6 weeks' follow-up.

3.2.3.45 Very low quality evidence from one study with 159 patients with PDN, showed that there is no significant difference between patients on oxycodone and placebo withdrawing from studies due to adverse effects from baseline up to 6 weeks' follow-up.

Other reported pain outcomes

3.2.3.46 Low quality evidence from one study with 159 patients with PDN, showed that patients on oxycodone are more likely to have better scores in pain intensity scale than placebo from baseline up to 6 weeks' follow-up.

Topical treatments as monotherapy against placebo

Topical capsaicin (0.075% cream) (linked to table 24)

Critical outcomes (pain)

3.2.3.47 Moderate quality evidence from one study with 80 patients with PDN, showed that there is no significant difference between patients on topical capsaicin (0.075% cream) and placebo in achieving global improvement/impression of change from baseline up to 8 weeks' follow-up.

Critical outcomes (adverse effects)

3.2.3.48 Low quality evidence from two studies with 76 patients with PDN, showed that patients on topical capsaicin (0.075% cream) are more likely to experience burning compared with placebo from baseline up to 8 weeks' follow-up.

3.2.3.49 Low quality evidence from two studies with 76 patients with PDN, showed that there is no significant difference between patients on topical capsaicin (0.075% cream) and placebo withdrawing from

studies due to adverse effects from baseline up to 8 weeks' follow-up.

Head-to-head comparative trials (monotherapy)

Pregabalin vs amitriptyline (linked to table 25)

Critical outcomes (pain)

3.2.3.50 Moderate quality evidence from one study with 102 patients with PDN, showed that there is no significant difference between patients on pregabalin and patients on amitriptyline in achieving at least 50% pain reduction and global improvement/impression of change from baseline up to 5 weeks' follow-up.

Critical outcomes (adverse effects)

3.2.3.51 Very low quality evidence from one study with 102 patients with PDN, showed that there is no significant difference between patients on pregabalin and patients on amitriptyline withdrawing from studies due to adverse effects, or experiencing dizziness and somnolence from baseline up to 5 weeks' follow-up.

Amitriptyline vs gabapentin (linked to table 26)

Critical outcomes (pain)

3.2.3.52 Moderate quality evidence from one study with 42 patients with PDN, showed that there is no significant difference between patients on amitriptyline and patients on gabapentin in achieving global improvement/impression of change from baseline up to 6 weeks' follow-up.

Critical outcomes (adverse effects)

3.2.3.53 Very low quality evidence from one study with 50 patients with PDN, showed that there is no significant difference between patients on amitriptyline and patients on gabapentin withdrawing from studies due to adverse effects, or experiencing dizziness and sedation from baseline up to 12 weeks' follow-up.

3.2.3.54 Low quality evidence from two studies with 75 patients with PDN, showed that there is no significant difference between patients on

amitriptyline and patients on gabapentin in experiencing any adverse effects (unspecified) from baseline up to 12 weeks' follow-up.

Amitriptyline vs topical capsaicin (0.075% cream) (linked to table 27)

Critical outcomes (pain)

3.2.3.55 No study on amitriptyline vs topical capsaicin (0.075% cream) that reported the critical outcomes on pain was identified or met the inclusion and exclusion criteria.

Critical outcomes (adverse effects)

3.2.3.56 Very low quality evidence from one study with 235 patients with PDN, showed that there is no significant difference between patients on amitriptyline and patients on topical capsaicin (0.075% cream) in experiencing sedation and burning from baseline up to 8 weeks' follow-up.

Other reported pain outcomes

3.2.3.57 Low quality evidence from one study with 212 patients with PDN, showed that there is no significant difference on pain intensity scores and pain relief scores between patients on amitriptyline and patients on topical capsaicin (0.075% cream) from baseline up to 8 weeks' follow-up.

Head-to-head comparative trial (combination therapy)

Gabapentin + oxycodone as combination therapy vs gabapentin alone (linked to table 28)

Critical outcomes (pain)

3.2.3.58 No study on gabapentin + oxycodone as combination therapy vs gabapentin alone that reported the critical outcomes on pain was identified or met the inclusion and exclusion criteria.

Critical outcomes (adverse effects)

3.2.3.59 Very low quality evidence from one study with 335 patients with PDN, showed that there patients on gabapentin + oxycodone are more likely to withdraw from studies due to adverse effects, or

experience constipation, nausea, dizziness and somnolence compared with gabapentin alone from baseline up to 12 weeks' follow-up.

3.2.3.60 Moderate quality evidence from one study with 335 patients with PDN, showed that patients on gabapentin + oxycodone are more likely to experience any adverse effects (unspecified) compared with gabapentin alone from baseline up to 12 weeks' follow-up.

Other reported pain outcomes

3.2.3.61 Low quality evidence from one study with 338 patients with PDN, showed that patients on gabapentin + oxycodone are more likely to have better scores in pain relief scale than gabapentin alone from baseline up to 12 weeks' follow-up.

3.2.4 Health economic modelling

This is a summary of the modelling carried out for this review question. See appendix 10.11 for full details of the modelling carried out for the guideline.

The analysis presented results in terms of decreasing mean net monetary benefit (NMB) associated with each drug at a threshold of £20,000 and £30,000 per QALY gained. All comparisons were made with placebo.

The cost effectiveness results for PDN are presented in table 1HE and table 2Table HE. It was not possible to calculate an incremental based on the results presented in the draft report due to rounding. The mean net benefits indicated that the two most cost effective treatments are duloxetine 60mg and 20mg. All the other treatments were associated with higher costs and lower effectiveness. At £20,000 threshold only duloxetine 60mg, 20mg, gabapentin 3600mg and venlafaxine were cost effective treatment options. At £30,000 duloxetine 120mg and pregabalin (300-600mg) became cost effective as well. At both thresholds, treatments associated with the highest probability of being cost effective were duloxetine 60mg, 20mg and gabapentin 3600mg. It was noted from standard deviations around the point estimates of total QALYs and costs that there was considerable overlap in terms of QALY gains, but that

there was significant difference in terms of cost. This suggested that the acquisition cost of the treatments was the main driver of differences between the treatment options.

Table 29 PDN incremental cost effectiveness results

Drug	Mean incremental net benefit (£) per person at a threshold per QALY of:	
	£30,000	£20,000
Single dose comparators		
Duloxetine 60 mg	4375	2311
Duloxetine 20 mg	4088	2376
Gabapentin 3600 mg	3632	2057
Venlafaxine 225 mg	2798	1730
Duloxetine 120 mg	1192	−577
Pregabalin 600 mg	665	−1180
Pregabalin 300 mg	386	−1351
Venlafaxine 75 mg	−141	−159
Oxcarbazepine 1200 mg	−2783	−2800
Oxcarbazepine 600 mg	−3133	−2568
Pregabalin 150 mg	−3530	−3729
Topiramate 400 mg	−3903	−5190
Oxcarbazepine 1800 mg	−6119	−5368
Single and flexible dose comparators		
Duloxetine 60 mg	4375	2311
Duloxetine 20 mg	4088	2376
Gabapentin (3600 mg)	3632	2057
Venlafaxine 225 mg	2798	1730
Duloxetine 120 mg	1192	−577
Pregabalin flexible dose (150–600 mg)	−126	−1665
Venlafaxine 75 mg	-141	−159
Topiramate 400 mg	−3903	−5190
Oxcarbazepine flexible dose (600–1800 mg)	−4941	−4281

Table 30 PDN probabilistic results

Single dose analysis			Flexible dose analysis		
Drug	**Probability of being the most cost-effective drug at a threshold per QALY of:**		**Drug**	**Probability of being the most cost-effective drug at a threshold per QALY of:**	
	£30,000	**£20,000**		**£30,000**	**£20,000**
Duloxetine 60 mg	0.321	0.301	Duloxetine 60 mg	0.348	0.307
Duloxetine 20 mg	0.293	0.328	Duloxetine 20 mg	0.312	0.333
Gabapentin	0.191	0.218	Gabapentin	0.210	0.222

3600 mg			(3600 mg)		
Pregabalin 300 mg	0.073	0.017	Venlafaxine 225 mg	0.081	0.124
Venlafaxine 225 mg	0.070	0.121	Duloxetine 120 mg	0.047	0.009
Duloxetine 120 mg	0.042	0.009	Venlafaxine 75 mg	0.001	0.005
Pregabalin 600 mg	0.009	0.001	Pregabalin flexible dose (150–600 mg)	0.001	0.000
Venlafaxine 75 mg	0.001	0.005	Topiramate 400 mg	0.000	0.000
Oxcarbazepine 1200 mg	0.000	0.000	Oxcarbazepine flexible dose (600–1800 mg)	0.000	0.000
Oxcarbazepine 600 mg	0.000	0.000	Placebo	0.000	0.000
Oxcarbazepine 1800 mg	0.000	0.000			
Pregabalin 150 mg	0.000	0.000			
Topiramate 400 mg	0.000	0.000			
Placebo	0.000	0.000			

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769 **Sensitivity analysis and uncertainty**

770 Numerous sensitivity analyses were conducted to explore how the model's
771 inputs affected its results and, in particular, the extent to which single
772 parameters would need to be altered before different options became cost
773 effective ('threshold analysis').. At a £30,000 threshold duloxetine 60 mg was
774 the most cost-effective option across the analyses apart from:

775 • When key clinical parameters were equalised across the treatments,
776 duloxetine 20 mg became the most cost-effective option.
777 • If gabapentin 3600 mg was free; it became the most cost-effective option.
778 Although the differences in NMB between gabapentin 3600 mg and
779 duloxetine 60 mg was still very small.
780 • When duloxetine 60 mg, duloxetine 20 mg and gabapentin 3600 mg all had
781 very high and similar NMB and all have high and occasionally similar
782 probabilities of being cost effective.

783 All the duloxetine doses, gabapentin 3600 mg and pregabalin 300 mg were all
784 associated with positive NMB across all scenarios. The highest dose for
785 oxcarbazepine is never cost effective and topiramate is only cost effective if its
786 price is reduced to zero. Venlafaxine 75 mg became the most cost-effective

option when all clinical parameters were equalised across treatments because it was the least costly.

At a £20,000 threshold, the results of the sensitivity analysis changed slightly. Under most scenarios duloxetine 20 mg was the most cost-effective option. There was greater variation in the results with alternatives having higher NMBs. However, for the majority of the analyses the results mirrored those obtained at a £30,000 threshold, including the results of the probabilistic analysis.

Under the flexible dose analysis the results are very similar to the single-dose analysis. The price of pregabalin has to fall to 80% and 20% of its current value for it to be considered cost effective at £30,000 and £20,000 thresholds respectively.

Health economics evidence statements – PDN

3.2.4.1 Partially applicable evidence from one study with minor limitations, showed that duloxetine was the most cost-effective treatment for PDN compared with gabapentin, oxcarbazepine, pregabalin, topiramate and venlafaxine

3.2.4.2 Partially applicable evidence from one study with minor limitations, showed that gabapentin was the second most cost-effective treatment for PDN compared with oxcarbazepine, pregabalin, topiramate and venlafaxine

3.2.5 Evidence to recommendations

Relative value of different outcomes	The GDG agreed and endorsed the international IMMPACT recommendations that the critical outcomes on pain should be both subjective measures of pain reduction (patient-reported at least 30% pain reduction and at least 50% pain reduction on a numerical rating scale or visual analogue scale), and the overall feeling of well-being reported by the patients (patient-reported global improvement/impression of change). The GDG agreed that comparing mean scores from a 10-point pain scale between groups was of less importance because it is more prone to bias and does not illustrate the proportion of patients achieving a certain

	magnitude of effects. The GDG also agreed that, apart from the efficacy of pharmacological treatments on pain outcomes, the adverse effects of individual treatments should also be considered to balance the benefit and harm to patients. Because numerous specific adverse effects are related to each pharmacological treatment, the GDG decided to define between five and seven critical adverse effects for each class of drug that they would consider when making recommendations. A questionnaire was completed by GDG members to select the critical adverse effects outcomes (see appendix 10.3A for the questionnaire and selected outcomes).
Quality of evidence	The GDG agreed that when discussing the quality of evidence, consideration of the number of studies, the size of the study population and the magnitude of effects are important. Overall, the GDG agreed that the core evidence-base is from placebo-controlled trials, and evidence on head-to-head comparative trials and trials on combination therapy is very limited. Hence, the GDG felt that they could not confidently draw conclusions solely based on this evidence. The focus of the discussion was based on the placebo-controlled trials and evidence from health economics evaluation. **Placebo-controlled trials** For antidepressants, only studies on duloxetine (an SNRI), venlafaxine (an SNRI) and desipramine (a TCA) were identified or met the inclusion and exclusion criteria for the PDN analysis. The GDG agreed that all three drugs have moderate-quality evidence on the critical pain outcomes but most evidence was for duloxetine. Hence, the GDG agreed that duloxetine seems to have better evidence of efficacy compared with venlafaxine and desipramine. For anti-epileptics, the GDG agreed that evidence on the efficacy of lamotrigine and sodium valproate was insufficient. The GDG also agreed that evidence for the efficacy of topiramate and oxcarbazepine was limited and most evidence seems to be for pregabalin and gabapentin (with moderate-quality). Therefore, the GDG felt that pregabalin and gabapentin should be the focus for discussion. For opioid analgesics and topical treatment, the GDG agreed that evidence on the efficacy of topical capsaicin (0.075% cream) was insufficient, and the

	low-quality evidence on tramadol and oxycodone was for non-critical outcomes.
Trade-off between clinical benefits and harms	*Desipramine* Although there was some evidence for the efficacy of desipramine, it is no longer listed in the BNF, and so should not be used in clinical practice. *Venlafaxine* Based on information from the MHRA, the GDG agreed that the use of venlafaxine would need specialist care and regular monitoring, and so it should not be initiated in non-specialist settings. *Topiramate and oxcarbazepine* The evidence showed that patients on either of these drugs were more likely to withdraw because of adverse effects than patients on gabapentin or pregabalin. **Duloxetine, gabapentin and pregabalin** *Duloxetine* Cost-effectiveness evidence (see section below on economic considerations) demonstrated that duloxetine was the most cost-effective treatment for painful diabetic neuropathy (PDN). Therefore, the GDG decided that duloxetine should be recommended as first-line treatment for people with PDN. 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. If duloxetine is contraindicated, the GDG agreed that amitriptyline should be the alternative antidepressant based on evidence from head-to-head comparative trials (see evidence statements 3.2.3.50 and 3.2.3.52), which indicated that amitriptyline is equally as effective as gabapentin and pregabalin for PDN. Furthermore, because amitriptyline (a TCA) has different pharmacological profiles compared with duloxetine (an SNRI), the GDG agreed that amitriptyline also has a role as second-line treatment if patients did not have satisfactory pain reduction on duloxetine, based on the extrapolation of evidence from PHN and other neuropathic pain conditions. Although the GDG agreed with the role of amitriptyline, they were also

	concerned that many people who have 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 extrapolated evidence (see section 3.4.7) on efficacy in relation to global improvement for these drugs. Both are relatively low-cost drugs, and for this patient population they are potentially cost effective, provided that they do not cause other adverse effects that would reduce the potential gain in quality of life obtained by switching from amitriptyline. *Gabapentin and pregabalin* 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 would achieve pain reduction with the other), and the cost-effectiveness evidence (see section below on economic considerations) demonstrated that gabapentin was more cost-effective than pregabalin for PDN, the GDG agreed that gabapentin should be the second-line treatment for PDN as monotherapy or as combination therapy with duloxetine (or amitriptyline). Because gabapentin and pregabalin have similar efficacy, the GDG also agreed that pregabalin should be an alternative if gabapentin is effective but the person cannot tolerate the adverse effects or has difficulty adhering to the dosage schedule.
Economic considerations	The evidence from the cost effectiveness analysis indicated that duloxetine was the most cost-effective treatment for most of the doses explored in the analysis and therefore the GDG recommended it as first-line treatment. The GDG noted that no cost effectiveness evidence was presented on the role of amitriptyline, as the draft HTA report searches only extended to 2009 and only included placebo controlled trials, therefore, did not include head-to-head trials of amitriptyline and gabapentin.. However, the GDG noted that there was evidence from the clinical review (see clinical review) and their own clinical experience that indicated amitriptyline was as effective as pregabalin and gabapentin. The GDG considered that any differences in the rates of adverse events that did not lead to discontinuation would have an insignificant impact on the cost effectiveness results. The GDG was mindful

	that the results from the cost effectiveness analysis were driven by the acquisition price of the treatments. The GDG noted that amitriptyline's acquisition price (approximately £4 per 6 week treatment at 75mg at 2011 prices from the NHS drug tariff) was significantly lower than gabapentin's (£13.91 per 6 week treatment at 1800mg at 2011 prices from teh NHS drug tariff) and pregablin's (£96.60 per 6 weeks of treatment at 2011 prices from teh NHS drug tariff). Therefore, the GDG concluded that that amitriptyline represented a cost effective alternative to duloxetine. The GDG considered that it was not appropriate to use the results of the draft HTA report to examine sequencing of treatments as the model did not consider class effects, titration practices and treatment switching. These factors resulted in sequences based solely on the outcome of the economic model being clinically inappropriate. The GDG considered the relative cost effectiveness of gabapentin and pregabalin. It acknowledged that gabapentin was most likely to be cost effective because of its lower acquisition cost. However, if gabapentin was effective but the person could not tolerate the adverse events then pregabalin represented a cost-effective alternative.
Other considerations	The GDG agreed that if first-line treatment did not result in satisfactory pain reduction, a drug from another therapeutic class should be recommended as second-line treatment, either as monotherapy or as combination therapy with first-line treatment, instead of trying another drug from the same therapeutic class. The GDG also agreed that if first-line and second-line treatment did not result in satisfactory pain reduction, the person should be referred to a specialist pain service and/or a condition-specific service. Although evidence on tramadol and oxycodone was of low-quality and investigated non-critical outcomes, the GDG felt that opioid analgesics could be recommended as third-line treatment as rescue analgesics to ensure the continuity of treatment while a person is waiting for referral to a specialist pain service and/or a condition-specific service. Because the GDG was concerned about the risk of long-term dependence, the severe adverse effects and the potential fatality of overdose with oxycodone, the GDG felt oxycodone should not be initiated without an assessment by a specialist pain service or a condition-specific service. However, the GDG also came to the consensus that recommending

	tramadol was valid and appropriate as third-line treatment for neuropathic pain in non-specialist settings, either as monotherapy or as combination therapy with second-line treatment, because this drug is already commonly used in non-specialist settings. 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. 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 lack of evidence for PDN, the GDG felt that it could not recommend the use of topical lidocaine as first-line or second-line treatment. However, topical lidocaine may have 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. Because amitriptyline is not licensed for neuropathic pain, the GDG came to the consensus that its initial dosage and titration should be lower than as recommended for this indication in the BNF.

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3.2.6 Recommendations and research recommendations for PDN

Recommendations

First-line treatment

1.1.10 Offer oral amitriptyline* or gabapentin as first-line treatment (see recommendation 1.1.13 for people with painful diabetic neuropathy).

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

1.1.12 Based on both the early and regular clinical reviews:

- If improvement is satisfactory, continue the treatment; consider gradually reducing the dose over time if improvement is sustained.
- If amitriptyline* results in satisfactory pain reduction as first-line treatment but the person cannot tolerate the adverse effects, consider oral imipramine* or nortriptyline* as an alternative.
- If gabapentin results in satisfactory pain reduction as first-line treatment but the person has difficulty adhering to the dosage schedule or cannot tolerate the adverse effects, consider oral pregabalin 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 (see recommendation 1.1.16 for people

* 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 (September 2011). Informed consent should be obtained and documented.

with painful diabetic neuropathy):

- If first-line treatment was with amitriptyline* (or imipramine* or nortriptyline*), switch to or combine with oral gabapentin (or pregabalin as an alternative if gabapentin is effective but the person has difficulty adhering to the dosage schedule or cannot tolerate the adverse effects).
- If first-line treatment was with gabapentin (or 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).

1.1.14 For people with painful diabetic neuropathy, 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 duloxetine, switch to oral amitriptyline* (or imipramine* or nortriptyline* as an alternative if amitriptyline is effective but the person cannot tolerate the adverse effects) or switch to or combine with oral gabapentin (or pregabalin as an alternative if gabapentin is effective but the person has difficulty adhering to the dosage schedule or cannot tolerate the adverse effects).
- If first-line treatment was with amitriptyline* (or imipramine* or nortriptyline*), switch to or combine with gabapentin (or pregabalin as an alternative if gabapentin is effective but the person has difficulty adhering to the dosage schedule or cannot tolerate the adverse effects).

* 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 (September 2011). Informed consent should be obtained and documented.

Third-line treatment

1.1.15 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 a topical lidocaine patch for treatment of localised pain for people who are unable to take oral medication because of medical conditions and/or disability.

Other treatments

1.1.16 Do not start treatment with a topical capsaicin 8% patch or 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.

Research recommendations

See appendix B for full details of research recommendations.

[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 a low risk of serotonin syndrome (the features of which include confusion, delirium, shivering, sweating, changes in blood pressure and myoclonus).

3.3 Post-herpetic neuralgia (PHN)

3.3.1 Review questions

Review question 1

What is the clinical efficacy of antidepressants, anti-epileptics, opioid analgesics, topical lidocaine and topical capsaicin as monotherapy (against placebo) for the management of neuropathic pain condition (post-herpetic neuralgia) in adults in non-specialist settings?

Review question 2

What is the clinical efficacy of antidepressants, anti-epileptics, opioid analgesics, topical lidocaine and topical capsaicin as combination therapy (against monotherapy or other combination therapy) for the management of neuropathic pain (post-herpetic neuralgia) in adults in non-specialist settings?

Review question 3

What is the clinical efficacy of antidepressants, compared with anti-epileptics, opioid analgesics, topical lidocaine and topical capsaicin (and vice-versa) as monotherapy for the management of neuropathic pain (post-herpetic neuralgia) in adults in non-specialist settings?

3.3.2 Evidence review

A total of 21 randomised controlled trials were included for post-herpetic neuralgia (PHN). Of the 34 included pharmacological treatments in (see table 4), no study was identified or met the inclusion and exclusion criteria for the following pharmacological treatments (see table 31).

For the characteristics of included studies please see tables 32–36.

Table 31 Pharmacological treatments for which no study was identified or met the inclusion and exclusion criteria for PHN

Drug class: subclass	Drug
Antidepressants: tricyclic antidepressants (TCAs)	Clomipramine Dosulepin (dothiepin) Doxepin Imipramine Lofepramine

	Trimipramine
Antidepressants: selective serotonin reuptake inhibitors (SSRIs)	Citalopram Fluoxetine Paroxetine Sertraline
Antidepressants: serotonin–norepinephrine reuptake inhibitors (SNRIs)	Duloxetine Venlafaxine
Anti-epileptics (anticonvulsants)	Carbamazepine Lamotrigine Oxcarbazepine Phenytoin Sodium valproate Topiramate
Opioid analgesics	Buprenorphine Co-codamol Codeine phosphate Co-dydramol Dihydrocodeine Fentanyl Morphine Oxycodone

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842 **Table 32 Characteristics of included studies: antidepressants (placebo-**
843 **controlled trials)**

Author	Study period	Condition	Treatment (oral)	Titration or fixed dosage (mg/day)	Mean dose (mg/day)	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
Kishore-Kumar et al. (1990)	6 weeks	PHN	Desipramine	12.5–250	167	Global, AEs
PHN = post-herpetic neuralgia; Global = patient-reported global improvement; AEs = adverse effects.						

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845 **Table 33 Characteristics of included studies: anti-epileptics (placebo-**
846 **controlled trials)**

Author	Study period	Condition	Treatment (oral)	Titration or fixed dosage (mg/day)	Outcomes
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
Dworkin et	8 weeks	PHN	Pregabalin	150–600	30%, 50%, AEs

al.(2003)					
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
PHN = post-herpetic neuralgia; Global = patient-reported global improvement; 30% = at least 30% pain reduction; 50% = at least 50% pain reduction; AEs = adverse effects.					

847

848 **Table 34 Characteristics of included studies: opioid analgesics (placebo-**
849 **controlled trials)**

Author	Study period	Condition	Treatment (oral)	Titration or fixed dosage (mg/day)	Outcomes
Boureau et al. (2003)	6 weeks	PHN	Tramadol	100–400	50%
PHN = post-herpetic neuralgia; 50% = at least 50% pain reduction					

850

851 **Table 35 Characteristics of included studies: topical capsaicin and**
852 **topical lidocaine (placebo-controlled trials)**

Author	Study period	Condition	Treatment (topical)	Titration or fixed dosage (times/day)	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
Backonja et al. (2008)	12 weeks	PHN	Capsaicin	8% patch, applied 1-hour with 3-months effects	30%, Global, AEs
Irving et al. (2011)	12 weeks	PHN	Capsaicin	8% patch, applied 1-hour with 3-months effects	30%, 50%, Global, AEs
Webster et al. (2010a)	12 weeks	PHN	Capsaicin	8% patch, applied 1-hour with 3-months effects	30%, 50%, Global, AEs
Webster et al. (2010b)	8 weeks	PHN	Capsaicin	8% patch, applied 1-hour with 3-months effects	30%, 50%, Global, AEs
Galer et al. (2002)	3 weeks	PHN	Lidocaine	5% patch, 1	Mean change in pain relief score
PHN = post-herpetic neuralgia; PDN = painful diabetic neuropathy; Global = patient-reported global improvement; 40% = at least 40% pain reduction; 50% = at least 50% pain reduction; AEs = adverse effects.					

853

854 **Table 36 Characteristics of included studies: comparative trials and**
855 **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						
Chandra et al. (2006)	9 weeks	PHN	Nortriptyline	Gabapentin	Nort: 50–100 Gaba: 900–2700	50%, Mean change in pain

						relief score, AEs
Achar et al. (2010)	8 weeks	PHN	Amitriptyline	Pregabalin	Ami: 25 Pre: 150	50%
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
Combination therapy						
Anti-epileptics + antidepressants vs anti-epileptics vs antidepressants						
Achar et al. (2010)	8 weeks	PHN	Pregabalin + Amitriptyline	Pregabalin	Combination: Pre 150 + Ami 25 Pre: 150	50%
Achar et al. (2010)	8 weeks	PHN	Pregabalin + Amitriptyline	Amitriptyline	Combination: Pre 150 + Ami 25 Ami: 25	50%
T1 = treatment 1; T2 = treatment 2; PHN = post-herpetic neuralgia; 50% = at least 50% pain reduction; AEs = adverse effects.						

856

857 **Summary profiles**

858 Meta-analyses were conducted based on the methodology stated in section
859 3.1 and presented in the following summary profiles based on individual
860 pharmacological treatments (for full GRADE profiles, see appendix XXX).

861 *Antidepressants*

862 **Table 37 Summary profile – amitriptyline as monotherapy (placebo-**
863 **controlled trials)**

No of studies	Amitriptyline	Placebo	Relative risk (95% CI)	Absolute risk	Quality
Primary outcome: patient-reported global improvement/impression of change (follow-up 6 weeks)					
1[1]	16/34 (47.1%)	4/25 (16%)	RR 2.94 (1.12 to 7.73)	31 more per 100 (from 2 more to 100 more)	MODERATE
Primary outcome: number of withdrawals due to adverse effects (follow-up 6 to 8 weeks)					
2[2]	6/74 (8.1%)	3/75 (4%)	RR 1.88 (0.54 to 6.62)	4 more per 100 (from 2 fewer to 22 more)	LOW
Primary outcome: dizziness (adverse effects) (follow-up 6 weeks)					
1[1]	11/62 (17.7%)	15/62 (24.2%)	RR 0.73 (0.37 to 1.47)	7 fewer per 100 (from 15 fewer to 11 more)	VERY LOW
Primary outcome: dry mouth (adverse effects) (follow-up 6 weeks)					
1[1]	38/62 (61.3%)	24/62 (38.7%)	RR 1.58 (1.09 to 2.29)	22 more per 100 (from 3 more to 50 more)	VERY LOW
Primary outcome: sedation (adverse effects) (follow-up 6 weeks)					
1[1]	38/62 (61.3%)	24/62 (38.7%)	RR 1.58 (1.09 to 2.29)	22 more per 100 (from 3 more to 50 more)	VERY LOW
Primary outcome: any adverse effects: unspecified (follow-up 6 weeks)					
1[1]	55/62 (88.7%)	45/62 (72.6%)	RR 1.22 (1.02 to 1.46)	16 more per 100 (from 1 more to 33 more)	LOW
[1] Max et al. (1988). [2] Graff-Radford et al. (2000); Max et al. (1988).					

864

865 **Table 38 Summary profile – desipramine as monotherapy (placebo-**
866 **controlled trials)**

No of studies	Desipramine	Placebo	Relative risk (95% CI)	Absolute risk	Quality
Primary outcome: patient-reported global improvement/impression of change (follow-up 6 weeks)					
1[1]	12/19 (63.2%)	2/19 (10.5%)	RR 6.00 (1.55 to 23.26)	53 more per 100 (from 6 more to 100 more)	MODERATE
Primary outcome: no. of withdrawals due to adverse effects (follow-up 6 weeks)					
1[1]	5/19 (26.3%)	3/19 (15.8%)	RR 1.67 (0.46 to 6.01)	11 more per 100 (from 9 fewer to 79 more)	VERY LOW
Primary outcome: dizziness (adverse effects) (follow-up 6 weeks)					
1[1]	3/19 (15.8%)	2/19 (10.5%)	RR 1.50 (0.28 to 7.99)	5 more per 100 (from 8 fewer to 74 more)	VERY LOW
Primary outcome: dry mouth (adverse effects) (follow-up 6 weeks)					
1[1]	11/19 (57.9%)	5/19 (26.3%)	RR 2.20 (0.95 to 5.12)	32 more per 100 (from 1 fewer to 100 more)	VERY LOW
Primary outcome: sedation (adverse effects) (follow-up 6 weeks)					
1[1]	3/19 (15.8%)	0/19 (0%)	RR 7.00 (0.39 to 126.92)	–	VERY LOW
Primary outcome: any adverse effects: unspecified (follow-up 6 weeks)					
1[1]	19/19 (100%)	15/19 (78.9%)	RR 1.26 (0.98 to 1.61)	21 more per 100 (from 2 fewer to 48 more)	VERY LOW

[1] Kishore-Kumar et al. (1990).

867

868 *Anti-epileptics*

869 **Table 39 Summary profile – gabapentin as monotherapy (placebo-**
870 **controlled trials)**

No of studies	Gabapentin	Placebo	Relative risk (95% CI)	Absolute risk	Quality
Primary outcome: patient-reported 50% pain reduction (follow-up 7 weeks)					
1[1]	59/178 (33.1%)	13/94 (13.8%)	RR 2.40 (1.39 to 4.14)	19 more per 100 (from 5 more to 43 more)	MODERATE
Primary outcome: patient-reported global improvement/impression of change (follow-up 7 to 8 weeks)					
2[2]	133/299 (44.5%)	38/207 (18.4%)	RR 2.52 (1.29 to 4.94)	28 more per 100 (from 5 more to 72 more)	LOW
Primary outcome: number of withdrawals due to adverse effects (follow-up 7 to 8 weeks)					
2[2]	49/336 (14.6%)	18/227 (7.9%)	RR 1.87 (1.1 to 3.19)	7 more per 100 (from 1 more to 17 more)	LOW
Primary outcome: dizziness (adverse effects) (follow-up 7 weeks)					
1[1]	72/223 (32.3%)	11/111 (9.9%)	RR 3.26 (1.8 to 5.89)	22 more per 100 (from 8 more to 48 more)	VERY LOW
Primary outcome: somnolence (adverse effects) (follow-up 7 weeks)					
1[1]	42/223 (18.8%)	7/111 (6.3%)	RR 2.99 (1.39 to 6.43)	13 more per 100 (from 2 more to 34 more)	VERY LOW
Primary outcome: any adverse effects: unspecified (follow-up 7 to 8 weeks)					
2[2]	192/336 (57.1%)	63/227 (27.8%)	RR 2.04 (1.62 to 2.58)	29 more per 100 (from 17 more to 44 more)	MODERATE

[1] Rice et al. (2001). [2] Rice et al. (2001); Rowbotham et al. (1998)

871

872 **Table 40 Summary profile – pregabalin as monotherapy (placebo-**
873 **controlled trials)**

No of studies	Pregabalin	Placebo	Relative risk (95% CI)	Absolute risk	Quality
Primary outcome: patient-reported 30% pain reduction (follow-up 4 to 13 weeks)					
3[1]	251/451 (55.7%)	59/233 (25.3%)	RR 2.30 (1.82 to 2.91)	33 more per 100 (from 21 more to 48 more)	HIGH
Primary outcome: patient-reported 50% pain reduction (follow-up 4 to 13 weeks)					
4[2]	217/608 (35.7%)	46/314 (14.6%)	RR 2.63 (1.97 to 3.52)	24 more per 100 (from 14 more to 37 more)	MODERATE
Primary outcome: patient-reported global improvement/impression of change (follow-up 8 to 13 weeks)					
2[3]	107/340 (31.5%)	21/140 (15%)	RR 2.11 (1.38 to 3.22)	17 more per 100 (from 6 more to 33 more)	MODERATE
Primary outcome: number of withdrawals due to adverse effects (follow-up 4 to 13 weeks)					
4[2]	110/700 (15.7%)	21/348 (6%)	RR 2.68 (1.38 to 5.21)	10 more per 100 (from 2 more to 25 more)	LOW
Primary outcome: dizziness (adverse effects) (follow-up 4 to 13 weeks)					
4[2]	184/700 (26.3%)	37/348 (10.6%)	RR 2.40 (1.49 to 3.84)	15 more per 100 (from 5 more to 30 more)	LOW
Primary outcome: somnolence (adverse effects) (follow-up 4 to 13 weeks)					
4[2]	121/700 (17.3%)	18/348 (5.2%)	RR 3.57 (2.2 to 5.79)	13 more per 100 (from 6 more to 25 more)	MODERATE
Primary outcome: gait disturbances (adverse effects) (follow-up 4 to 13 weeks)					
3[4]	17/543 (3.1%)	1/267 (0.37%)	RR 5.31 (1.24 to 22.74)	2 more per 100 (from 0 more to 8 more)	LOW
Primary outcome: any adverse effects: unspecified (follow-up 4 to 8 weeks)					
2[5]	198/268 (73.9%)	92/174 (52.9%)	RR 1.46 (1.25 to 1.71)	24 more per 100 (from 13 more to 38 more)	MODERATE

[1] Dworkin et al. (2003); Stacey et al. (2008); van Seventer et al. (2006). [2] Dworkin et al. (2003); Sabatowski et al. (2004); Stacey et al. (2008); van Seventer et al. (2006). [3] Sabatowski et al. (2004); van Seventer et al. (2006). [4] Dworkin et al. (2003); Stacey et al. (2008); van Seventer et al. (2006) . [5] Dworkin et al. (2003); Stacey et al. (2008).

874
875 *Opioid analgesics*

876 **Table 41 Summary profile – tramadol as monotherapy (placebo-**
877 **controlled trials)**

No of studies	Tramadol	Placebo	Relative risk (95% CI)	Absolute risk	Quality
Primary outcome: patient-reported 50% pain reduction					
1[1]	41/53 (77.4%)	31/55 (56.4%)	RR 1.37 (1.04 to 1.81)	21 more per 100 (from 2 more to 46 more)	MODERATE

[1] Boureau et al. (2003)

878
879 Note: no study on tramadol as monotherapy that reported the critical
880 outcomes on adverse effects was identified or met the inclusion and exclusion
881 criteria.

882

883 *Topical treatments*

884 **Table 42 Summary profile – topical capsaicin (8% patch) as**
885 **monotherapy (placebo-controlled trials)**

No of studies	Capsaicin 8% patch	Control	Relative risk (95% CI)	Absolute risk	Quality
Primary outcome: patient-reported 30% pain reduction (follow-up 8 to 12 weeks)					
4[1]	324/741 (43.7%)	188/531 (35.4%)	RR 1.26 (1.09 to 1.45)	9 more per 100 (from 3 more to 16 more)	HIGH
Primary outcome: patient-reported 50% pain reduction (follow-up 8 to 12 weeks)					
3[2]	158/536 (29.5%)	70/334 (21%)	RR 1.43 (1 to 2.04)	9 more per 100 (from 0 more to 22 more)	LOW
Primary outcome: patient-reported global improvement/impression of change (follow-up 8 to 12 weeks)					
4[1]	360/741 (48.6%)	182/531 (34.3%)	RR 1.39 (1.21 to 1.59)	13 more per 100 (from 7 more to 20 more)	HIGH
Primary outcome: number of withdrawals due to adverse effects (follow-up 8 to 12 weeks)					
4[1]	6/742 (0.81%)	3/531 (0.56%)	RR 1.32 (0.38 to 4.68)	0 more per 100 (from 0 fewer to 2 more)	LOW
Primary outcome: burning sensation (adverse effects) (follow-up 12 weeks)					
1[3]	3/103 (2.9%)	0/53 (0%)	RR 3.63 (0.19 to 60.09)	-	LOW
Primary outcome: site pain (adverse effects) (follow-up 8 to 12 weeks)					
4[1]	253/742 (34.1%)	104/531 (19.6%)	RR 2.18 (1.53 to 3.11)	23 more per 100 (from 10 more to 41 more)	MODERATE
Primary outcome: site pruritus (adverse effects) (follow-up 8 to 12 weeks)					
4[1]	50/742 (6.7%)	24/531 (4.5%)	RR 1.18 (0.75 to 1.87)	1 more per 100 (from 1 fewer to 4 more)	LOW
Primary outcome: site papules (adverse effects) (follow-up 8 to 12 weeks)					
3[4]	38/639 (5.9%)	13/478 (2.7%)	RR 2.53 (1.39 to 4.61)	4 more per 100 (from 1 more to 10 more)	LOW
Primary outcome: any adverse effects: unspecified (follow-up 8 to 12 weeks)					
4[1]	618/742 (83.3%)	422/531 (79.5%)	RR 1.14 (1.08 to 1.2)	11 more per 100 (from 6 more to 16 more)	HIGH

[1] Backonja et al. (2008); Irving et al. (2011); Webster et al. (2010a); Webster et al. (2010b). [2] Irving et al. (2011); Webster et al. (2010a); Webster et al. (2010b). [3] Webster et al. (2010a). [4] Backonja et al. (2008); Irving et al. (2011); Webster et al. (2010b).

886

887 **Table 43 Summary profile – topical capsaicin (0.075% cream) as**
888 **monotherapy (placebo-controlled trials)**

No of studies	Capsaicin 0.075% cream	Control	Relative risk (95% CI)	Absolute risk	Quality
Primary outcome: patient-reported 40% pain reduction (follow-up 6 weeks)					
1[1]	7/16 (43.8%)	1/16 (6.3%)	RR 7.00 (0.97 to 50.57)	38 more per 100 (from 0 fewer to 100 more)	MODERATE
Primary outcome: burning (adverse effects) (follow-up mean 6 weeks)					
2[2]	50/90 (55.6%)	25/85 (29.4%)	RR 1.88 (1.30 to 2.72)	26 more per 100 (from 9 more to 51 more)	LOW
Primary outcome: number of withdrawals due to adverse effects (follow-up 6 weeks)					
1[3]	13/74 (17.6%)	1/69 (1.4%)	RR 12.12 (1.63 to 90.23)	16 more per 100 (from 1 more to 100 more)	VERY LOW

[1] Bernstein et al. (1989). [2] Bernstein et al. (1989); Watson et al. (1993). [3] Watson et al. (1993).

Table 44 Summary profile – topical lidocaine (5% patch) as monotherapy (placebo-controlled trials)

No of studies	Topical lidocaine 5% patch	Control	Relative risk (95% CI)	Absolute risk	Quality
Other reported pain outcome: pain relief (scale: Neuropathic Pain Scale) (follow-up 3 weeks)					
1[1]	67	29	Treatment = −15.3 (17.9) Control = −7.7 (14.2) p = 0.043		LOW

[1] Galer et al. (2002).

Note: no study on topical lidocaine (5% patch) as monotherapy that reported the critical outcomes on pain and adverse effects was identified or met the inclusion and exclusion criteria.

Head-to-head comparative trials (monotherapy)

Table 45 Summary profile – amitriptyline vs pregabalin as monotherapy (comparative trials)

No of studies	Amitriptyline	Pregabalin	Relative risk (95% CI)	Absolute risk	Quality
Primary outcome: patient-reported 75% pain reduction (follow-up 8 weeks)					
1[1]	2/15 (13.3%)	8/15 (53.3%)	RR 0.25 (0.06 to 0.99)	40 fewer per 100 (from 1 fewer to 50 fewer)	LOW

[1] Achar et al. (2010).

Note: no study on amitriptyline vs pregabalin as monotherapy that reported the critical outcomes on adverse effects was identified or met the inclusion and exclusion criteria.

Table 46 Summary profile – amitriptyline vs nortriptyline as monotherapy (comparative trials)

No of studies	Amitriptyline	Nortriptyline	Relative risk (95% CI)	Absolute risk	Quality
Primary outcome: dry mouth (adverse effects) (follow-up 5 weeks)					
1[1]	28/33 (84.8%)	26/33 (78.8%)	RR 1.08 (0.86 to 1.35)	6 more per 100 (from 11 fewer to 28 more)	VERY LOW
Primary outcome: dizziness (adverse effects) (follow-up 5 weeks)					
1[1]	3/33 (9.1%)	1/33 (3%)	RR 3.00 (0.33 to 27.4)	6 more per 100 (from 2 fewer to 80 more)	VERY LOW
Primary outcome: drowsiness (adverse effects) (follow-up 5 weeks)					
1[1]	4/33 (12.1%)	6/33 (19.4%)	RR 0.67 (0.21 to 2.13)	6 fewer per 100 (from 15 fewer to 22 more)	VERY LOW

Primary outcome: any adverse effects: unspecified (follow-up 5 weeks)					
1[1]	31/33 (93.9%)	31/33 (93.9%)	RR 1.00 (0.88 to 1.13)	0 fewer per 100 (from 11 fewer to 12 more)	VERY LOW
[1] Watson et al. (1998).					

905

906 Note: no study on amitriptyline vs nortriptyline as monotherapy that reported
907 the critical outcomes on pain was identified or met the inclusion and exclusion
908 criteria

909 **Table 47 Summary profile – nortriptyline vs gabapentin as monotherapy**
910 **(comparative trials)**

No of studies	Nortriptyline	Gabapentin	Relative risk (95% CI)	Absolute risk	Quality
Primary outcome: patient-reported 50% pain reduction (follow-up 9 weeks)					
1[1]	9/36 (25%)	7/34 (20.6%)	RR 1.21 (0.51 to 2.90)	4 more per 100 (from 10 fewer to 39 more)	MODERATE
Primary outcome: somnolence (adverse effects) (follow-up 9 weeks)					
1[1]	6/36 (16.7%)	4/34 (11.8%)	RR 1.42 (0.44 to 4.59)	5 more per 100 (from 7 fewer to 42 more)	VERY LOW
Primary outcome: dry mouth (adverse effects) (follow-up 9 weeks)					
1[1]	18/36 (50%)	0/34 (0%)	RR ∞ (∞)	–	VERY LOW
[1] Chandra et al. (2006).					

911

912 *Head-to-head comparative trials (combination therapy)*

913 **Table 48 Summary profile – pregabalin + amitriptyline as combination**
914 **therapy vs amitriptyline alone (comparative trials)**

No of studies	Pregabalin + amitriptyline	Amitriptyline	Relative risk (95% CI)	Absolute risk	Quality
Primary outcome: patient-reported 75% pain reduction (follow-up 8 weeks)					
1[1]	11/15 (73.3%)	2/15 (13.3%)	RR 5.5 (1.46 to 20.71)	60 more per 100 (from 6 more to 100 more)	MODERATE
[1] Achar et al. (2010).					

915

916 Note: no study on pregabalin + amitriptyline as combination therapy vs
917 amitriptyline alone that reported the critical outcomes on adverse effects was
918 identified or met the inclusion and exclusion criteria.

Table 49 Summary profile – pregabalin + amitriptyline as combination therapy vs pregabalin alone (comparative trials)

No of studies	Pregabalin + amitriptyline	Pregabalin	Relative (95% CI)	Absolute	Quality
Primary outcome: patient-reported 75% pain reduction (follow-up 8 weeks)					
1[1]	11/15 (73.3%)	8/15 (53.3%)	RR 1.38 (0.78 to 2.41)	20 more per 100 (from 12 fewer to 75 more)	MODERATE
[1] Achar et al. (2010).					

Note: No study on pregabalin + amitriptyline as combination therapy vs pregabalin alone that reported the critical outcomes on adverse effects was identified or met the inclusion and exclusion criteria.

3.3.3 Evidence statements

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

3.3.3.1 No study on clomipramine, dosulepin (dothiepin), doxepin, imipramine, lofepramine, trimipramine, citalopram, fluoxetine, paroxetine, sertraline, duloxetine, venlafaxine, carbamazepine, lamotrigine, oxcarbazepine, phenytoin, sodium valproate, topiramate, buprenorphine, co-codamol, codeine phosphate, co-dydramol, dihydrocodeine, fentanyl, morphine and oxycodone was identified or met the inclusion and exclusion criteria for PHN.

Antidepressants as monotherapy against placebo

Amitriptyline (linked to table 37)

Critical outcomes (pain)

3.3.3.2 Moderate quality evidence from one study with 59 patients with PHN, showed that amitriptyline is more effective than placebo in achieving global improvement/impression of change from baseline up to 6 weeks' follow-up.

Critical outcomes (adverse effects)

3.3.3.3 Low quality evidence from two studies with 149 patients with PHN, showed that there is no significant difference between patients on amitriptyline and placebo withdrawing from studies due to adverse effects from baseline up to 8 weeks' follow-up.

3.3.3.4 *Very low quality evidence from one study with 124 patients with PHN, showed that there is no significant difference between patients on amitriptyline and placebo in experiencing dizziness from baseline up to 8 weeks' follow-up.*

3.3.3.5 *Very low quality evidence from one study with 124 patients with PHN, showed that patients on amitriptyline are more likely to experience dry mouth and sedation compared with placebo from baseline up to 6 weeks' follow-up.*

3.3.3.6 *Low quality evidence from one study with 124 patients with PHN, showed that patients on amitriptyline are more likely to experience any adverse effects (unspecified) compared with placebo from baseline up to 6 weeks' follow-up.*

Desipramine (linked to table 38)

Critical outcomes (pain)

3.3.3.7 *Moderate quality evidence from one study with 38 patients with PHN, showed that desipramine is more effective than placebo in achieving global improvement/impression of change from baseline up to 6 weeks' follow-up.*

Critical outcomes (adverse effects)

3.3.3.8 *Very low quality evidence from one study with 38 patients with PHN, showed that there is no significant difference between patients on desipramine and placebo withdrawing from studies due to adverse effects, or experiencing dizziness, dry mouth, sedation and any adverse effects (unspecified) from baseline up to 6 weeks' follow-up.*

Anti-epileptics as monotherapy against placebo

Gabapentin (linked to table 39)

Critical outcomes (pain)

3.3.3.9 *Moderate quality evidence from one study with 272 patients with PHN, showed that gabapentin is more effective than placebo in*

achieving at least 50% pain reduction from baseline up to 7 weeks' follow-up.

3.3.3.10 *Low quality evidence from two studies with 506 patients with PHN, showed that gabapentin is more effective than placebo in achieving global improvement/impression of change from baseline up to 8 weeks' follow-up.*

Critical outcomes (adverse effects)

3.3.3.11 *Low quality evidence from two studies with 563 patients with PHN, showed that patients on gabapentin are more likely to withdraw from studies due to adverse effects compared with placebo from baseline up to 8 weeks' follow-up.*

3.3.3.12 *Moderate quality evidence from two studies with 563 patients with PHN, showed that patients on gabapentin are more likely to experience any adverse effects (unspecified) compared with placebo from baseline up to 8 weeks' follow-up.*

3.3.3.13 *Very low quality evidence from one study with 334 patients with PHN, showed that patients on gabapentin are more likely to experience dizziness and somnolence compared with placebo from baseline up to 7 weeks' follow-up.*

Pregabalin (linked to table 40)

Critical outcomes (pain)

3.3.3.14 *High quality evidence from three studies with 684 patients with PHN, showed that pregabalin is more effective than placebo in achieving at least 30% pain reduction from baseline up to 13 weeks' follow-up.*

3.3.3.15 *Moderate quality evidence from four studies with 922 patients with PHN, showed that pregabalin is more effective than placebo in achieving at least 50% pain reduction from baseline up to 13 weeks' follow-up.*

3.3.3.16 Moderate quality evidence from two studies with 480 patients with PHN, showed that pregabalin is more effective than placebo in achieving at global improvement/impression of change from baseline up to 13 weeks' follow-up.

Critical outcomes (adverse effects)

3.3.3.17 Low quality evidence from four studies with 1048 patients with PHN, showed that patients on pregabalin are more likely to withdraw from studies due to adverse effects, and experience dizziness compared with placebo from baseline up to 13 weeks' follow-up.

3.3.3.18 Moderate quality evidence from four studies with 1048 patients with PHN, showed that patients on pregabalin are more likely to experience somnolence compared with placebo from baseline up to 13 weeks' follow-up.

3.3.3.19 Low quality evidence from three studies with 810 patients with PHN, showed that patients on pregabalin are more likely to experience gait disturbances compared with placebo from baseline up to 13 weeks' follow-up.

3.3.3.20 Moderate quality evidence from two studies with 442 patients with PHN, showed that patients on pregabalin are more likely to experience any adverse effects (unspecified) compared with placebo from baseline up to 8 weeks' follow-up.

Opioid analgesics as monotherapy against placebo

Tramadol (linked to table 41)

Critical outcomes (pain)

3.3.3.21 Moderate quality evidence from one study with 108 patients with PHN, showed that tramadol is more effective than placebo in achieving at least 50% pain reduction from baseline up to 13 weeks' follow-up.

Critical outcomes (adverse effects)

3.3.3.22 No study on tramadol as monotherapy that reported the critical outcomes on adverse effects was identified or met the inclusion and exclusion criteria.

Topical treatments as monotherapy against placebo

Topical capsaicin (8% patch) (linked to table 42)

Critical outcomes (pain)

3.3.3.23 High quality evidence from four studies with 1272 patients with PHN, showed that topical capsaicin (8% patch) is more effective than placebo in achieving at least 30% pain reduction and global improvement/impression of change from baseline up to 12 weeks' follow-up.

3.3.3.24 Low quality evidence from three studies with 870 patients with PHN, showed that topical capsaicin (8% patch) is more effective than placebo in achieving at least 50% pain reduction from baseline up to 12 weeks' follow-up.

Critical outcomes (adverse effects)

3.3.3.25 Low quality evidence from four studies with 1273 patients with PHN, showed that there is no significant difference between patients on topical capsaicin (8% patch) and placebo withdrawing from studies due to adverse effects and experiencing site pruritus from baseline up to 12 weeks' follow-up.

3.3.3.26 Low quality evidence from one study with 156 patients with PHN, showed that there is no significant difference between patients on topical capsaicin (8% patch) and placebo in experiencing burning sensation from baseline up to 12 weeks' follow-up.

3.3.3.27 Moderate quality evidence from four studies with 1273 patients with PHN, showed that patients on topical capsaicin (8% patch) are more likely to experience site pain compared with placebo from baseline up to 12 weeks' follow-up.

3.3.3.28 High quality evidence from four studies with 1273 patients with PHN, showed that patients on topical capsaicin (8% patch) are more likely to experience any adverse effects (unspecified) compared with placebo from baseline up to 12 weeks' follow-up.

3.3.3.29 Low quality evidence from three studies with 1117 patients with PHN, showed that patients on topical capsaicin (8% patch) are more likely to experience site papules compared with placebo from baseline up to 12 weeks' follow-up.

Topical capsaicin (0.075% cream) (linked to table 43)

Critical outcomes (pain)

3.3.3.30 Moderate quality evidence from one study with 32 patients with PHN, showed that there is no significant difference between patients on topical capsaicin (0.075% cream) and placebo in achieving 40% pain reduction from baseline up to 6 weeks' follow-up.

Critical outcomes (adverse effects)

3.3.3.31 Low quality evidence from two studies with 175 patients with PHN, showed that patients on topical capsaicin (0.075% cream) are more likely to experience burning compared with placebo from baseline up to 6 weeks' follow-up.

3.3.3.32 Very low quality evidence from one study with 143 patients with PHN, showed that patients on topical capsaicin (0.075% cream) are more likely to withdraw from studies due to adverse effects compared with placebo from baseline up to 6 weeks' follow-up.

Topical lidocaine (5% patch) (linked to table 44)

Critical outcomes (pain)

3.3.3.33 No study on topical lidocaine (5% patch) as monotherapy that reported the critical outcomes on pain was identified or met the inclusion and exclusion criteria.

Critical outcomes (adverse effects)

3.3.3.34 No study on topical lidocaine (5% patch) as monotherapy that reported the critical outcomes on adverse effects was identified or met the inclusion and exclusion criteria.

Other reported pain outcomes

3.3.3.35 Low quality evidence from one study with 96 patients with PHN, showed that patients on topical lidocaine (5% patch) are more likely to have better scores in pain relief scale compared with placebo from baseline up to 3 weeks' follow-up.

Head-to-head comparative trials (monotherapy)

Amitriptyline vs pregabalin (linked to table 45)

Critical outcomes (pain)

3.3.3.36 Low quality evidence from one study with 30 patients with PHN, showed that there is no significant difference between patients on amitriptyline and patients on pregabalin in achieving 75% pain reduction from baseline up to 8 weeks' follow-up.

Critical outcomes (adverse effects)

3.3.3.37 No study on amitriptyline vs pregabalin as monotherapy that reported the critical outcomes on adverse effects was identified or met the inclusion and exclusion criteria.

Amitriptyline vs nortriptyline (linked to table 46)

Critical outcomes (pain)

3.3.3.38 No study on amitriptyline vs nortriptyline as monotherapy that reported the critical outcomes on pain was identified or met the inclusion and exclusion criteria.

Critical outcomes (adverse effects)

3.3.3.39 Very low quality evidence from one study with 66 patients with PHN, showed that there is no significant difference between patients on amitriptyline and patients on nortriptyline in experiencing dry mouth, dizziness, drowsiness and any adverse effects (unspecified) from baseline up to 5 weeks' follow-up.

Nortriptyline vs gabapentin (linked to table 47)

Critical outcomes (pain)

3.3.3.40 Moderate quality evidence from one study with 70 patients with PHN, showed that there is no significant difference between patients on nortriptyline and patients on gabapentin in achieving at least 50% pain reduction from baseline up to 9 weeks' follow-up.

Critical outcomes (adverse effects)

3.3.3.41 Very low quality evidence from one study with 70 patients with PHN, showed that there is no significant difference between patients on nortriptyline and patients on gabapentin in experiencing somnolence and dry mouth from baseline up to 9 weeks' follow-up.

Head-to-head comparative trials (combination therapy)

Pregabalin + amitriptyline as combination therapy vs amitriptyline alone (linked to table 48)

Critical outcomes (pain)

3.3.3.42 Moderate quality evidence from one study with 30 patients with PHN, showed that pregabalin + amitriptyline is more effective than amitriptyline alone in achieving 75% pain reduction from baseline up to 8 weeks' follow-up.

Critical outcomes (adverse effects)

3.3.3.43 No study on pregabalin + amitriptyline as combination therapy vs amitriptyline alone that reported the critical outcomes on adverse effects was identified or met the inclusion and exclusion criteria.

Pregabalin + amitriptyline as combination therapy vs pregabalin alone (linked to table 49)

Critical outcomes (pain)

3.3.3.44 Moderate quality evidence from one study with 30 patients with PHN, showed that there is no significant difference between pregabalin + amitriptyline and pregabalin alone in achieving 75% pain reduction from baseline up to 8 weeks follow-up.

Critical outcomes (adverse effects)

3.3.3.45 No study on pregabalin + amitriptyline as combination therapy vs pregabalin alone that reported the critical outcomes on adverse effects was identified or met the inclusion and exclusion criteria.

3.3.4 Health economic modelling

The analysis presented results in terms of decreasing mean net monetary benefit associated with each drug at a threshold of £20,000 and £30,000 per QALY gained with all comparisons to placebo.

The cost effectiveness results for the PHN model are presented in tables 50 and 51. These results indicate that, of the single doses considered, gabapentin 3600 mg is the most cost-effective option at both thresholds; pregabalin 150 mg is the second most cost effective option, followed by pregabalin 300 mg. The flexible dosing analysis indicates that gabapentin is the most cost effective. Pregabalin and oxycodone are associated with very low probabilities of being cost effective.

Table 50 PHN incremental cost effectiveness results

Drug	Mean incremental net benefit (£) per person at a threshold per QALY of:	
	£20,000	£30,000
Single dose comparators		
Gabapentin 3600 mg	2010	2974
Pregabalin 150 mg	1268	2260
Pregabalin 300 mg	846	1616
Gabapentin 1800 mg	976	1430
Gabapentin 2400 mg	964	1430
Oxycodone 60 mg	400	914
Pregabalin 600 mg	194	616
Lidocaine 5% patch	−1248	−1015
Single and flexible-dose comparators		
Gabapentin flexible-dose (1800–3600 mg)	1303	1921
Pregabalin flexible dose (150–600 mg)	707	1403
Oxycodone 60 mg	400	914
Lidocaine 5% patch	−1248	−1015

Table 51 PHN probabilistic results

Single dose analysis			Flexible dose analysis		
Drug	**Probability of being the most cost-effective drug at a threshold per QALY of:**		**Drug**	**Probability of being the most cost-effective drug at a threshold per QALY of:**	
	£20,000	**£30,000**		**£20,000**	**£30,000**
Gabapentin 3600 mg	0.656	0.573	Gabapentin flexible dose (1800–3600 mg)	0.8885	0.719
Pregabalin 150 mg	0.172	0.252	Pregabalin flexible dose (150–600 mg)	0.0605	0.1815
Pregabalin 300 mg	0.060	0.092	Oxycodone 60 mg	0.051	0.0995
Gabapentin 1800 mg	0.059	0.041	Lidocaine 5% patch	0	0
Gabapentin 2400 mg	0.046	0.031	Placebo	0	0
Oxycodone 60 mg	0.005	0.008			
Pregabalin 600 mg	0.003	0.005			
Lidocaine 5% patch	0	0			
Placebo	0	0			

Sensitivity and scenario analyses

Numerous sensitivity analyses were conducted to explore how the model's inputs affected its results and, in particular, the extent to which single parameters would need to be altered before different options became cost effective ('threshold analysis'). The key variables that affected the decision are summarised below.

Price changes – pregabalin

When the price of pregabalin was reduced to 20% of its current price (or a reduction in 80%) for the single-dose analysis pregabalin became the intervention with the highest mean incremental net benefit at £20,000 and £30,000 thresholds. In the flexible-dose analysis, at a £20,000 threshold, pregabalin again had the highest mean incremental net benefit. However, at a £30,000 threshold the price only had to fall to 40% of its current price for it to become the most cost-effective option.

Reduced pill burden – gabapentin

If the number of pills for gabapentin were reduced, so that the overall dose remained the same, but pills of larger dose sizes were used, and all other

drugs were kept the same, this resulted in the highest drug costs to gabapentin. The outcome of this change was that pregabalin 150 mg had the, marginally (£50), highest net benefit at £30,000 threshold and a very similar probability of being cost effective (0.03 difference in probabilities). These results were repeated at £20,000 threshold but the differences were reduced. These results were not replicated for the flexible-dose analysis. Gabapentin remained the most cost-effective option, and at the £20,000 threshold the probabilities were very different, although at the £30,000 threshold the differences were much smaller.

Lidocaine patches

Even if the price of lidocaine patches and the number of patches reduced to 1.03 patches, it remained the least cost-effective option.

Oxycodone

The price of oxycodone needs to be reduced by 40% (60%) of current prices at £30,000 (£20,000) thresholds for oxycodone to become as cost effective as pregabalin.

Time horizon

If the time horizon was reduced to 1 year, then the net benefits were reduced across all the treatments, but the difference between gabapentin and pregabalin increased.

Utilities

Changing the assumptions around utilities resulted in the differences between gabapentin and pregabalin being reduced, particularly for the single-dose analysis.

Health economics evidence statements – PHN

3.3.4.1 Partially applicable evidence from one study with minor limitations, showed that gabapentin was the most cost effective treatment for PHN compared with oxycodone, pregabalin and lidocaine 5% patch.

3.3.5 Evidence to recommendations

Because the evidence-base for post-herpetic neuralgia (PHN) is similar to that for other neuropathic pain conditions (that all other neuropathic pain conditions apart from PDN and PHN), the GDG felt that it may be more appropriate to discuss the evidence for PHN alongside the evidence for other neuropathic pain conditions. Hence, for evidence to recommendations for PHN, please see section 3.4.5.

3.3.6 Recommendations and research recommendations

Recommendations

Please see section 3.4.6.

Research recommendations

See appendix B for full details of research recommendations.

3.4 Other neuropathic pain conditions

3.4.1 Review questions

Review question 1

What is the clinical efficacy of antidepressants, anti-epileptics, opioid analgesics, topical lidocaine and topical capsaicin as monotherapy (against placebo) for the management of neuropathic pain condition (other than PDN and PHN) in adults in non-specialist settings?

Review question 2

What is the clinical efficacy of antidepressants, anti-epileptics, opioid analgesics, topical lidocaine and topical capsaicin as combination therapy (against monotherapy or other combination therapy) for the management of neuropathic pain (other than PDN and PHN) in adults in non-specialist settings?

Review question 3

What is the clinical efficacy of antidepressants, compared with anti-epileptics, opioid analgesics, topical lidocaine and topical capsaicin (and vice-versa) as monotherapy for the management of neuropathic pain (other than PDN and PHN) in adults in non-specialist settings?

3.4.2 Evidence review

A total of 60 randomised controlled trials were included for other neuropathic pain conditions (other than PDN and PHN). Of the 34 listed included pharmacological treatments in (Table 4), no study was identified or met the inclusion and exclusion criteria for the following pharmacological treatments (see table 52).

For the characteristics of included studies please see Table 53 to 57.

Table 52 Pharmacological treatments for which no studies met the inclusion and exclusion criteria for other neuropathic pain conditions

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

1261 **Table 53 Characteristics of included studies: antidepressants (placebo-**
1262 **controlled trials)**

Author	Study period	Condition	Treatment (oral)	Titration or fixed dosage (mg/day)	Mean dose (mg/day)	Outcomes
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
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
Vranken et al. (2011)	8 weeks	Central pain	Duloxetine	60-120	99.1	Global, 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; 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.

1263

1264 **Table 54 Characteristics of included studies: anti-epileptics (placebo-**
1265 **controlled trials)**

Author	Study period	Condition	Treatment (oral)	Titration or fixed dosage (mg/day)	Outcomes
Leijon and Boivie (1989)	4 weeks	PSP	Carbamazepine	200–800	Global
Nicol (1969)	46 months	TN	Carbamazepine	100–2400	Global
Khoromi et al. (2005)	6 weeks	Radi	Topiramate	50–400	Global, 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
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
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
Simpson et al. (2010)	14 weeks	HIV-RN	Pregabalin	150-600	30%, 50%, Global, AEs
van Seventer et al. (2010)	8 weeks	Post-Trauma	Pregabalin	150-600	30%, Global, AEs
Moon et al. (2010)	8 weeks	Mixed NP	Pregabalin	150-600	30%, 50%, Global, AEs
MS-NP = multiple sclerosis neuropathic pain (central pain); NP-NI = nerve injury neuropathic pain; CenP = central pain; 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; Post-Trauma = post-traumatic pain (including post-surgical pain); Global = patient-reported global improvement; 30% = at least 30% pain reduction; 50% = at least 50% pain reduction; AEs = adverse effects. TN = Trigeminal neuralgia					

Table 55 Characteristics of included studies: opioid analgesics (placebo-controlled trials)

Author	Study period	Condition	Treatment (oral)	Titration or fixed dosage (mg/day)	Outcomes
Arbaiza and Vidal (2007)	6 weeks	NP cancer	Tramadol	**68.75	Mean pain intensity score, AEs
Sindrup et al. (1999)	4 weeks	Poly	Tramadol	100–400	Mean pain intensity score, AEs
Norrbrink et al. (2009)	4 weeks	SCI	Tramadol	150-400	Global, AEs
Huse et al. (2001)	4 weeks	PhanLP	Morphine	70–300	50%
Khoromi et al. (2007a)	6 weeks	Radi	Morphine	15–180	Global, AEs
Wu et al.	7 weeks	PhanLP	Morphine	15–90	30%, 50%, AEs

(2008)					

**mean mg/6 hours; NP cancer = neuropathic cancer pain; PhanLP = phantom limb pain; Poly = polyneuropathy; Radi = radiculopathy; SCI = spinal cord injury ; Global = patient-reported global improvement; 30% = at least 30% pain reduction; 50% = at least 50% pain reduction; AEs = adverse effects.

Table 56 Characteristics of included studies: topical capsaicin and topical lidocaine (placebo-controlled trials)

Author	Study period	Condition	Treatment (topical)	Titration or fixed dosage (times/day)	Outcomes
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
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
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

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; 50% = at least 50% pain reduction; AEs = adverse effects.

Table 57 Characteristics of included studies: comparative trials and combination therapy (randomised controlled trials)

Author	Study period	Condition	T1	T2	Titration or fixed dosage (mg/day)	Outcomes
Cross-class head-to-head comparison						
TCAs vs anti-epileptics						
Rintala et al. (2007)	8 weeks	SCI	Amitriptyline	Gabapentin	Ami: max 150 Gaba: max 3600	30%, 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
Anti-epileptics vs topical lidocaine						
Baron et	4	PDN	Pregabalin	Topical lidocaine	Pre: 150-600	30%, 50%,

al. (2009)	weeks	PHN			5% Lido: 3–4 patches up to 12 hours/day	Global, AEs
Within-class head-to-head comparison						
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						
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						
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; 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.						

Summary profiles

Meta-analyses were conducted based on the methodology stated in section 3.1 and presented in the following summary profiles based on individual pharmacological treatments (for full GRADE profiles, see appendix XXX).

Antidepressants

Table 58 Summary profile – amitriptyline as monotherapy (placebo-controlled trials)

No of studies	Amitriptyline	Placebo	Relative risk (95% CI)	Absolute risk	Quality
Primary outcome: patient-reported 30% pain reduction (follow-up 4 to 8 weeks)					
2[1]	33/55 (60%)	13/55 (23.6%)	RR 2.54 (1.51 to 4.28)	36 more per 100 (from 12 more to 78 more)	MODERATE
Primary outcome: patient-reported global improvement/impression of change (follow-up 4 to 9 weeks)					
4[2]	58/111 (52.3%)	37/115 (32.2%)	RR 1.78 (0.76 to 4.21)	25 more per 100 (from 8 fewer to 100 more)	LOW
Primary outcome: number of withdrawals due to adverse effects (follow-up 4 to 9 weeks)					
6[3]	18/201 (9%)	8/201 (4%)	RR 2.03 (0.95 to 4.32)	4 more per 100 (from 0 fewer to 13 more)	LOW

Primary outcome: dizziness (adverse effects) (follow-up 4 to 6 weeks)					
2[4]	2/31 (6.5%)	3/32 (9.4%)	RR 0.70 (0.13 to 3.73)	3 fewer per 100 (from 8 fewer to 26 more)	LOW
Primary outcome: dry mouth (adverse effects) (follow-up 4 to 6 weeks)					
4[5]	44/110 (40%)	33/105 (31.4%)	RR 1.30 (0.95 to 1.79)	9 more per 100 (from 2 fewer to 25 more)	LOW
Blurred vision (adverse effects) (follow-up 6 weeks)					
2[6]	4/62 (6.5%)	5/59 (8.5%)	RR 0.81 (0.24 to 2.79)	2 fewer per 100 (from 6 fewer to 15 more)	LOW
Primary outcome: gastrointestinal disturbances (adverse effects) (follow-up 6 weeks)					
1[7]	1/18 (5.6%)	1/19 (5.3%)	RR 1.06 (0.07 to 15.64)	0 more per 100 (from 5 fewer to 77 more)	VERY LOW
Primary outcome: sedation (adverse effects) (follow-up 4 weeks)					
1[8]	2/35 (5.7%)	1/33 (3%)	RR 1.89 (0.18 to 19.83)	3 more per 100 (from 2 fewer to 57 more)	VERY LOW
Primary outcome: Vomiting (adverse effects) (follow-up 6 weeks)					
2[9]	2/62 (3.2%)	3/59 (5.1%)	RR 0.82 (0.02 to 30.99)	1 fewer per 100 (from 5 fewer to 100 more)	LOW
Primary outcome: any adverse effects: unspecified (follow-up 4 to 6 weeks)					
3[10]	78/92 (84.8%)	49/88 (55.7%)	RR 1.91 (0.6 to 6.09)	51 more per 100 (from 22 fewer to 100 more)	LOW

[1] Rintala et al. (2007); Vrethem et al. (1997). [2] Kautio et al. (2008); Kieburtz et al. (1998); Leijon et al. (1989); Vretham et al. (1997). [3] Cardenas et al. (2002); Kautio et al. (2008); Kieburtz et al. (1998); Rintala et al. (2007); Robinson et al. (2004); Vretham et al. (1997). [4] Kalso et al. (1996); Robinson et al. (2004). [5] Cardenas et al. (2002); Kalso et al. (1996); Robinson et al. (2004); Vretham et al. (1997). [6] Cardenas et al. (2002); Robinson et al. (2004). [7] Robinson et al. (2004). [8] Vretham et al. (1997). [9] Cardena et al. (2002); Robinson et al. (2004). [10] Cardenas et al. (2002); Leijon et al. (1989); Vretham et al. (1997).

Table 59 Summary profile – nortriptyline as monotherapy (placebo-controlled trials)

No of studies	Nortriptyline	Placebo	Relative risk (95% CI)	Absolute risk	Quality
Primary outcome: patient-reported global improvement/impression of change (follow-up 7 weeks)					
1[1]	12/31 (38.7%)	11/33 (33.3%)	RR 1.16 (0.6 to 2.24)	5 more per 100 (from 13 fewer to 41 more)	MODERATE
Primary outcome: dry mouth (adverse effects) (follow-up 7 weeks)					
1[1]	10/28 (35.7%)	6/28 (21.4%)	RR 1.67 (0.7 to 3.96)	14 more per 100 (from 6 fewer to 63 more)	VERY LOW
Blurred vision (adverse effects) (follow-up 7 weeks)					
1[1]	0/28 (0%)	3/28 (10.7%)	RR 0.14 (0.01 to 2.64)	9 fewer per 100 (from 11 fewer to 18 more)	VERY LOW
Primary outcome: gastrointestinal disturbances (adverse effects) (follow-up 7 weeks)					
1[1]	1/28 (3.6%)	0/28 (0%)	RR 3.00 (0.13 to 70.64)	–	VERY LOW
Primary outcome: any adverse effects: unspecified (follow-up 7 weeks)					
1[1]	19/28 (67.9%)	14/28 (50%)	RR 1.36 (0.87 to 2.13)	18 more per 100 (from 6 fewer to 57 more)	VERY LOW

[1] Khoromi et al. (2007).

Table 60 Summary profile – imipramine as monotherapy (placebo-controlled trials)

No of studies	Imipramine	Placebo	Relative risk (95% CI)	Absolute risk	Quality
Primary outcome: patient-reported global improvement/impression of change (follow-up 4 weeks)					
1[1]	14/33 (42.4%)	2/33 (6.1%)	RR 7.00 (1.72 to 28.41)	36 more per 100 (from 4 more to 100 more)	MODERATE
Primary outcome: number of withdrawals due to adverse effects (follow-up 4 weeks)					
1[1]	13/33 (39.4%)	6/33 (18.2%)	RR 2.17 (0.94 to 5.01)	21 more per 100 (from 1 fewer to 73 more)	VERY LOW
Primary outcome: dry mouth (adverse effects) (follow-up 4 weeks)					
1[1]	12/33 (36.4%)	3/33 (9.1%)	RR 4.00 (1.24 to 12.88)	27 more per 100 (from 2 more to 100 more)	VERY LOW
[1] Sindrup et al. (2003a)					

Table 61 Summary profile – duloxetine as monotherapy (placebo-controlled trials)

No of studies	Duloxetine	Control	Relative risk (95% CI)	Absolute risk	Quality
Primary outcome: patient-reported global improvement/impression of change (follow-up 8 weeks)					
1[1]	11/24 (45.8%)	4/24 (16.7%)	RR 2.75 (1.02 to 7.44)	29 more per 100 (from 0 more to 100 more)	MODERATE
Primary outcome: dizziness (adverse effects) (follow-up 8 weeks)					
1[1]	4/24 (16.7%)	2/24 (8.3%)	RR 2.00 (0.4 to 9.91)	8 more per 100 (from 5 fewer to 74 more)	VERY LOW
Primary outcome: dry mouth (adverse effects) (follow-up 8 weeks)					
1[1]	1/24 (4.2%)	0/24 (0%)	RR 3.00 (0.13 to 70.16)	–	VERY LOW
[1] Vranken et al. (2011).					

Table 63 Summary profile – venlafaxine as monotherapy (placebo-controlled trials)

No of studies	Venlafaxine	Placebo	Relative risk (95% CI)	Absolute risk	Quality
Primary outcome: patient-reported global improvement/impression of change (follow-up 4 to 8 weeks)					
2[1]	28/69 (40.6%)	10/52 (19.2%)	RR 1.89 (0.65 to 5.52)	17 more per 100 (from 7 fewer to 87 more)	LOW
Primary outcome: number of withdrawals due to adverse effects (follow-up 4 to 8 weeks)					
3[2]	16/86 (18.6%)	7/86 (8.1%)	RR 2.07 (0.96 to 4.49)	9 more per 100 (from 0 fewer to 28 more)	LOW
Primary outcome: dry mouth (adverse effects) (follow-up 4 weeks)					
2[3]	12/46 (26.1%)	9/46 (19.6%)	RR 1.33 (0.68 to 2.62)	6 more per 100 (from 6 fewer to 32 more)	LOW
Primary outcome: any adverse effects: unspecified (follow-up 8 weeks)					
1[4]	23/40 (57.5%)	11/20 (55%)	RR 1.05 (0.65 to 1.69)	3 more per 100 (from 19 fewer to 38 more)	VERY LOW
[1] Sindrup et al. (2003b); Yucel et al. (2004). [2] Sindrup et al. (2003b); Tasmuth et al. (2002); Yucel et al. (2004). [3] Sindrup et al. (2003b); Tasmuth et al. (2002). [4] Yucel et al. (2004).					

Anti-epileptics

Table 63 Summary profile – gabapentin as monotherapy (placebo-controlled trials)

No of studies	Gabapentin	Placebo	Relative risk (95% CI)	Absolute risk	Quality
Primary outcome: patient-reported 30% pain reduction (follow-up 8 weeks)					
1[1]	5/22 (22.7%)	6/22 (27.3%)	RR 0.83 (0.3 to 2.33)	5 fewer per 100 (from 19 fewer to 36 more)	MODERATE
Primary outcome: patient-reported 50% pain reduction (follow-up 8 weeks)					
1[2]	32/153 (20.9%)	21/152 (13.8%)	RR 1.51 (0.92 to 2.5)	7 more per 100 (from 1 fewer to 21 more)	MODERATE
Primary outcome: patient-reported global improvement/impression of change (follow-up 5 to 8 weeks)					
3[3]	92/263 (35%)	41/259 (15.8%)	RR 2.21 (1.6 to 3.06)	19 more per 100 (from 9 more to 33 more)	MODERATE
Primary outcome: number of withdrawals due to adverse effects (follow-up 4 to 8 weeks)					
5[4]	32/349 (9.2%)	25/344 (7.3%)	RR 1.26 (0.77 to 2.06)	2 more per 100 (from 2 fewer to 8 more)	LOW
Primary outcome: dizziness (adverse effects) (follow-up 4 to 8 weeks)					
5[5]	89/398 (22.4%)	28/391 (7.2%)	RR 2.62 (1.58 to 4.36)	12 more per 100 (from 4 more to 24 more)	MODERATE
Primary outcome: somnolence (adverse effects) (follow-up 4 to 8 weeks)					
3[6]	41/187 (21.9%)	12/182 (6.6%)	RR 3.17 (1.74 to 5.8)	14 more per 100 (from 5 more to 32 more)	LOW
Primary outcome: sedation (adverse effects) (follow-up 8 weeks)					
1[7]	0/20 (0%)	1/20 (5%)	RR 0.33 (0.01 to 7.72)	3 fewer per 100 (from 5 fewer to 34 more)	VERY LOW
Primary outcome: fatigue (adverse effects) (follow-up 5 to 6 weeks)					
2[8]	32/211 (15.2%)	19/209 (9.1%)	RR 1.68 (1 to 2.82)	6 more per 100 (from 0 more to 17 more)	LOW
Primary outcome: any adverse effects: unspecified (follow-up 4 to 8 weeks)					
3[9]	110/196 (56.1%)	69/195 (35.4%)	RR 1.58 (1.21 to 2.07)	21 more per 100 (from 7 more to 38 more)	MODERATE

[1] Rintala et al. (2007). [2] Serpell et al. (2002). [3] Gordh et al. (2008); Serpell et al. (2002); Smith et al. (2005). [4] Gordh et al. (20087; Hahn et al. (2004); Nikolajsen et al. (2006); Rintala et al. (2007); Serpell et al. (2002). [5] Bone et al. (2002); Gordh et al. (2008); Hahn et al. (2004); Rao et al. (2007); Serpell et al. (2002). [6] Bone et al. (2002); Hahn et al. (2004); Serpell et al. (2002). [7] Levendoglu et al. (2004). [8] Gordh et al. (2008); Rao et al. (2007). [9] Levendoglu et al. (2004); Nikolajsen et al. (2006); Serpell et al. (2002).

Table 64 Summary profile – pregabalin as monotherapy (placebo-controlled trials)

No of studies	Pregabalin	Placebo	Relative risk (95% CI)	Absolute risk	Quality
Primary outcome: patient-reported 30% pain reduction (follow-up 12 to 14 weeks)					
5[1]	403/782 (51.5%)	178/488 (36.5%)	RR 1.44 (1.07 to 1.94)	16 more per 100 (from 3 more to 34 more)	MODERATE
Primary outcome: patient-reported 50% pain reduction (follow-up 8 to 14 weeks)					
4[2]	253/655	96/361	RR 1.65 (0.94 to 2.89)	17 more per 100 (from	

	(38.6%)	(26.6%)		2 fewer to 50 more)	MODERATE
Primary outcome: patient-reported global improvement/impression of change (follow-up 8 to 14 weeks)					
4[3]	448/713 (62.8%)	255/421 (60.6%)	RR 1.11 (0.85 to 1.45)	7 more per 100 (from 9 fewer to 27 more)	MODERATE
Primary outcome: number of withdrawals due to adverse effects (follow-up 4 to 14 weeks)					
6[4]	114/803 (14.2%)	32/508 (6.3%)	RR 2.07 (1.41 to 3.05)	7 more per 100 (from 3 more to 13 more)	MODERATE
Primary outcome: dizziness (adverse effects) (follow-up 4 to 14 weeks)					
5[5]	165/606 (27.2%)	43/430 (10%)	RR 2.63 (1.52 to 4.54)	16 more per 100 (from 5 more to 35 more)	LOW
Primary outcome: somnolence (adverse effects) (follow-up 4 to 14 weeks)					
5[5]	123/606 (20.3%)	36/430 (8.4%)	RR 2.56 (1.32 to 4.96)	13 more per 100 (from 3 more to 33 more)	LOW
Primary outcome: fatigue (adverse effects) (follow-up 8 weeks)					
1[6]	15/127 (11.8%)	10/127 (7.9%)	RR 1.50 (0.7 to 3.21)	4 more per 100 (from 2 fewer to 17 more)	VERY LOW
Primary outcome: any adverse effects: unspecified (follow-up 8 weeks)					
2[7]	180/289 (62.3%)	97/205 (47.3%)	RR 1.47 (1.27 to 1.71)	22 more per 100 (from 13 more to 34 more)	MODERATE

[1] Freynhagen et al. (2005); Moon et al. (2010); Siddall et al. (2006); Simpson et al. (2010); van Seventer et al. (2010). [2] Freynhagen et al. (2005); Moon et al. (2010); Siddall et al. (2006); Simpson et al. (2010). [3] Freynhagen et al. (2005); Moon et al. (2010); Simpson et al. (2010); van Seventer et al. (2010). [4] Freynhagen et al. (2005); Moon et al. (2010); Siddall et al. (2006); Simpson et al. (2010); van Seventer et al. (2010); Vranken et al. (2008). [5] Freynhagen et al. (2005); Siddall et al. (2006); Simpson et al. (2010); van Seventer et al. (2010); Vranken et al. (2008). [6] van Seventer et al. (2010). [7] Moon et al. (2010); van Seventer et al. (2010).

Table 65 Summary profile – lamotrigine as monotherapy (placebo-controlled trials)

No of studies	Lamotrigine	Placebo	Relative risk (95% CI)	Absolute risk	Quality
Primary outcome: patient-reported 30% pain reduction (follow-up 11 weeks)					
1[1]	5/11 (45.5%)	2/11 (18.2%)	RR 2.50 (0.61 to 10.25)	27 more per 100 (from 7 fewer to 100 more)	MODERATE
Primary outcome: number of withdrawals due to adverse effects (follow-up 8 to 14 weeks)					
7[2]	26/358 (7.3%)	12/284 (4.2%)	RR 1.81 (0.97 to 3.38)	3 more per 100 (from 0 fewer to 10 more)	LOW
Primary outcome: dizziness (adverse effects) (follow-up 10 to 11 weeks)					
2[3]	2/78 (2.6%)	2/77 (2.6%)	RR 1.03 (0.16 to 6.81)	0 more per 100 (from 2 fewer to 15 more)	LOW
Primary outcome: fatigue (adverse effects) (follow-up 10 to 11 weeks)					
2[3]	4/78 (5.1%)	4/77 (5.2%)	RR 0.99 (0.27 to 3.68)	0 fewer per 100 (from 4 fewer to 14 more)	LOW
Primary outcome: any adverse effects: unspecified (follow-up 8 to 9 weeks)					
2[4]	31/58 (53.4%)	21/58 (36.2%)	RR 1.95 (0.35 to 10.9)	34 more per 100 (from 24 fewer to 100 more)	VERY LOW

[1] Breuer et al. (2007). [2] Breuer et al. (2007); Finnerup et al. (2002); McCleane et al. (1999); Rao et al. (2008); Simpson et al. (2000); Simpson et al. (2003); Vestergaard et al. (2001). [3] Breuer et al. (2007); Rao et al. (2008). [4] Finnerup et al. (2002); Vestergaard et al. (2001).

1306 **Table 66 Summary profile – topiramate as monotherapy (placebo-**
1307 **controlled trials)**

No of studies	Topiramate	Placebo	Relative risk (95% CI)	Absolute risk	Quality
Primary outcome: patient-reported global improvement/impression of change (follow-up 6 weeks)					
1[1]	15/29 (51.7%)	7/29 (24.1%)	RR 2.14 (1.03 to 4.47)	28 more per 100 (from 1 more to 84 more)	MODERATE
Primary outcome: number of withdrawals due to adverse effects (follow-up 6 weeks)					
1[1]	10/41 (24.4%)	0/41 (0%)	RR 21.00 (1.27 to 364.93)	-	VERY LOW
Primary outcome: fatigue (adverse effects) (follow-up 6 weeks)					
1[1]	10/29 (34.5%)	9/29 (31%)	RR 1.11 (0.53 to 2.33)	3 more per 100 (from 15 fewer to 41 more)	VERY LOW
Primary outcome: any adverse effects: unspecified (follow-up 6 weeks)					
1[1]	25/29 (86.2%)	21/29 (72.4%)	RR 1.19 (0.91 to 1.56)	14 more per 100 (from 7 fewer to 41 more)	VERY LOW
[1] Khoromi et al. (2005).					

1308

1309 **Table 67 Summary profile – carbamazepine as monotherapy (placebo-**
1310 **controlled trials)**

No of studies	Carbamazepine	Placebo	Relative risk (95% CI)	Absolute risk	Quality
Primary outcome: patient-reported global improvement/impression of change (follow-up 1 to 46 months)					
2[1]	20/34 (58.8%)	7/22 (31.8%)	RR 1.88 (0.16 to 22.41)	28 more per 100 (from 27 fewer to 100 more)	LOW
Primary outcome: any adverse effects: unspecified (follow-up 4 weeks)					
1[2]	13/15 (86.7%)	7/15 (46.7%)	RR 1.86 (1.04 to 3.30)	40 more per 100 (from 2 more to 100 more)	VERY LOW
[1] Leijon et al. (1989); Nicol et al. (1969). [2] Leijon et al. (1989).					

1311
1312 *Opioid analgesics*

1313 **Table 68 Summary profile – tramadol as monotherapy (placebo-**
1314 **controlled trials)**

No of studies	Tramadol	Placebo	Relative risk (95% CI)	Absolute risk	Quality
Primary outcome: patient-reported global improvement/impression of change (follow-up 4 weeks)					
1[1]	4/12 (33.3%)	0/12 (0%)	RR 4.88 (0.28 to 83.67)	-	MODERATE
Primary outcome: number of withdrawals due to adverse effects (follow-up 4 to 6 weeks)					
3[2]	21/86 (24.4%)	4/75 (5.3%)	RR 3.52 (1.37 to 9.03)	13 more per 100 (from 2 more to 43 more)	LOW
Primary outcome: constipation (adverse effects) (follow-up 4 to 6 weeks)					
2[3]	18/68 (26.5%)	6/57 (10.5%)	RR 2.09 (0.42 to 10.37)	11 more per 100 (from 6 fewer to 99 more)	VERY LOW
Primary outcome: nausea (adverse effects) (follow-up 4 to 6 weeks)					
2[3]	20/68 (29.4%)	6/57 (10.5%)	RR 2.47 (1.1 to 5.55)	15 more per 100 (from 1 more to 48 more)	LOW
Primary outcome: dizziness (adverse effects) (follow-up 4 to 6 weeks)					
2[3]	27/68	5/57	RR 3.64 (1 to 13.21)	23 more per 100 (from	

	(39.7%)	(8.8%)		0 more to 100 more)	VERY LOW
Primary outcome: any adverse effects (unspecified) (follow-up 4 to 6 weeks)					
3[2]	56/81 (69.1%)	19/69 (27.5%)	RR 2.07 (1.14 to 3.77)	29 more per 100 (from 4 more to 76 more)	VERY LOW
[1] Norrbrink et al. (2009). [2] Arbaiza et al. (2007); Norrbrink et al. (2009); Sindrup et al. (2003). [3] Norrbrink et al. (2009); Sindrup et al. (2003).					

1315

1316 **Table 69 Summary profile – morphine as monotherapy (placebo-**
1317 **controlled trials)**

No of studies	Morphine	Placebo	Relative risk (95% CI)	Absolute risk	Quality
Primary outcome: patient-reported 30% pain reduction (follow-up 7 weeks)					
1[1]	33/50 (66%)	19/43 (44.2%)	RR 1.49 (1.01 to 2.21)	22 more per 100 (from 0 more to 53 more)	MODERATE
Primary outcome: patient-reported 50% pain reduction (follow-up 4 to 7 weeks)					
2[2]	28/62 (45.2%)	14/55 (25.5%)	RR 1.75 (1.04 to 2.96)	19 more per 100 (from 1 more to 50 more)	MODERATE
Primary outcome: patient-reported global improvement/impression of change (follow-up 6 weeks)					
1[3]	13/32 (40.6%)	11/33 (33.3%)	RR 1.22 (0.64 to 2.31)	7 more per 100 (from 12 fewer to 44 more)	MODERATE
Primary outcome: number of withdrawals due to adverse effects (follow-up 6 weeks)					
1[3]	9/55 (16.4%)	1/55 (1.8%)	RR 9.00 (1.18 to 68.66)	15 more per 100 (from 0 more to 100 more)	VERY LOW
Primary outcome: constipation (adverse effects) (follow-up 6 weeks)					
2[4]	35/78 (44.9%)	4/71 (5.6%)	RR 8.12 (3.05 to 21.61)	40 more per 100 (from 12 more to 100 more)	VERY LOW
Primary outcome: somnolence/drowsiness (adverse effects) (follow-up 6 to 7 weeks)					
2[4]	16/78 (20.5%)	4/71 (5.6%)	RR 3.39 (1.17 to 9.76)	13 more per 100 (from 1 more to 49 more)	LOW
Primary outcome: nausea (adverse effects) (follow-up 6 to 7 weeks)					
2[4]	6/78 (7.7%)	1/71 (1.4%)	RR 3.94 (0.69 to 22.46)	4 more per 100 (from 0 fewer to 30 more)	LOW
Primary outcome: dizziness (adverse effects) (follow-up 6 to 7 weeks)					
2[4]	6/78 (7.7%)	3/71 (4.2%)	RR 1.86 (0.49 to 7.04)	4 more per 100 (from 2 fewer to 26 more)	LOW
Primary outcome: any adverse effects (unspecified) (follow-up 6 to 7 weeks)					
2[4]	53/78 (67.9%)	21/71 (29.6%)	RR 2.32 (1.26 to 4.28)	39 more per 100 (from 8 more to 97 more)	VERY LOW
[1] Wu et al. (2008). [2] Huse et al. (2001); Wu et al. (2008). [3] Khoromi et al. (2007). [4] Khoromi et al. (2007); Wu et al. (2008).					

1318

1319 *Topical treatments*

1320 **Table 70 Summary profile – topical capsaicin (0.075% cream) as**
1321 **monotherapy (placebo-controlled trials)**

No of studies	Capsaicin 0.075% cream	Control	Relative risk (95% CI)	Absolute risk	Quality
Primary outcome: patient-reported 50% pain reduction (follow-up 6 weeks)					
1[1]	8/13 (61.5%)	3/9 (33.3%)	RR 2.05 (0.73 to 5.80)	35 more per 100 (from 9 fewer to 100 more)	MODERATE

Primary outcome: number of withdrawals due to adverse effects (follow-up 4 to 8 weeks)					
3[2]	24/167 (14.4%)	5/161 (3.1%)	RR 3.95 (1.65 to 9.42)	9 more per 100 (from 2 more to 26 more)	LOW
Primary outcome: burning (adverse effects) (follow-up 4 to 8 weeks)					
4[3]	155/225 (68.9%)	62/231 (26.8%)	RR 2.46 (1.33 to 4.58)	39 more per 100 (from 9 more to 96 more)	LOW
[1] Watson and Evans (1992). [2] Donofrio et al. (1991); Paice et al. (2000); Watson & Evans (1992). [3] Donofrio et al. (1991); Low et al. (1995); Paice et al. (2000); Watson & Evans (1992).					

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1323 **Table 71 Summary profile – topical lidocaine (5% patch/cream) as**
1324 **monotherapy (placebo-controlled trials)**

No of studies	Lidocaine 5% patch/cream	Control	Relative risk (95% CI)	Absolute risk	Quality
Primary outcome: withdrawals due to adverse effects (follow-up 1 week)					
1[1]	1/58 (1.7%)	0/58 (0%)	RR 3.00 (0.12 to 72.15)	–	VERY LOW
Primary outcome: rash (adverse effects) (follow-up 1 week)					
1[1]	10/58 (17.2%)	11/58 (19.3%)	RR 0.91 (0.42 to 1.97)	2 fewer per 100 (from 11 fewer to 19 more)	VERY LOW
Primary outcome: skin irritation (adverse effects) (follow-up 1 week)					
1[3]	5/35 (14.3%)	3/35 (8.6%)	RR 1.67 (0.43 to 6.45)	6 more per 100 (from 5 fewer to 47 more)	VERY LOW
[1] Meier et al. (2003). [3] Ho et al. (2008).					

1325

1326 Note: No study on topical lidocaine (5% patch/cream) as monotherapy that
1327 reported the critical outcomes on pain was identified or met the inclusion and
1328 exclusion criteria.

1329

No of studies	Lidocaine 5% patch/cream	Control	Relative risk (95% CI)	Absolute risk	Quality
Other reported pain outcome: pain intensity (scale: NRSpi 11-point) (follow-up 4 weeks)					
1[1]	8	13	Treatment = 4.4 (2.12) Placebo = 4.8 (1.71); p = 0.92		LOW
Other reported pain outcome: pain relief (scale: Global Pain Relief Scale) (follow-up 2 weeks)					
1[2]	61	59	Treatment = 2.25 (5.94) Placebo = 2.23 (5.45); p = 0.715		LOW
Other reported pain outcome: pain intensity (scale: VASpi-100mm) (follow-up 1 week)					
1[3]	30	31	Treatment = −5.7 (17.5) Placebo = −7.6 (23.9); p = 0.88		LOW
Other reported pain outcome: pain intensity (Scale: VASpi-100mm) (follow-up 1 week)					
1[4]	40	40	Treatment = NR Placebo = NR; p = 0.002		LOW
[1] Cheville et al. (2009). [2] Estanislao et al. (2004). [3] Ho et al. (2008). [4] Meier et al. (2003).					

1330

1331 *Head-to-head comparative trials (monotherapy)*

1332 **Table 72 Summary profile – amitriptyline vs gabapentin as monotherapy**

(comparative trials)

No of studies	Amitriptyline	Gabapentin	Relative risk (95% CI)	Absolute risk	Quality
Primary outcome: patient-reported 30% pain reduction (follow-up 8 weeks)					
1[1]	13/22 (59.1%)	5/22 (22.7%)	RR 2.60 (1.12 to 6.05)	36 more per 100 (from 3 more to 100 more)	MODERATE
Primary outcome: number of withdrawals owing to adverse effects (follow-up 8 weeks)					
1[1]	2/38 (5.3%)	2/38 (5.3%)	RR 1.00 (0.15 to 6.74)	–	VERY LOW
[1] Rintala et al. (2007).					

Table 73 Summary profile – amitriptyline vs carbamazepine as monotherapy (comparative trials)

No of studies	Amitriptyline	Carbamazepine	Relative risk (95% CI)	Absolute risk	Quality
Primary outcome: patient-reported global improvement/impression of change (follow-up 4 weeks)					
1[1]	10/15 (66.7%)	5/14 (35.7%)	RR 1.87 (0.85 to 4.11)	31 more per 100 (from 5 fewer to 100 more)	MODERATE
Primary outcome: any adverse effects: unspecified (follow-up 4 weeks)					
1[1]	14/15 (93.3%)	13/14 (92.9%)	RR 1.01 (0.82 to 1.23)	1 more per 100 (from 17 fewer to 21 more)	VERY LOW
[1] Leijon and Boivie (1989).					

Table 74 Summary profile – pregabalin vs oxycodone as monotherapy (comparative trials)

No of studies	Pregabalin	Oxycodone	Relative risk (95% CI)	Absolute risk	Quality
Primary outcome: number of withdrawals owing to adverse effects (follow-up 3 months)					
1[1]	9/134 (6.7%)	11/106 (10.4%)	RR 0.65 (0.28 to 1.50)	4 fewer per 100 (from 7 fewer to 5 more)	VERY LOW
Other pain outcome: mean pain intensity (NRS-11 point) (follow-up 3 months)					
1[1]	134	106	Pregabalin = decreased 46%; Oxycodone = decreased 76%; p <0.05		VERY LOW
[1] Gatti et al. (2009).					

Note: no study on pregabalin vs oxycodone as monotherapy that reported the critical outcomes on pain was identified or met the inclusion and exclusion criteria.

Table 75 Summary profile – pregabalin vs topical lidocaine (5% patch) as monotherapy (comparative trials)

No of studies	Pregabalin	Lidocaine 5% patch	Relative risk (95% CI)	Absolute risk	Quality
Primary outcome: patient-reported 30% pain reduction (follow-up 4 weeks)					
1[1]	74/137 (54%)	85/144 (59%)	RR 0.92 (0.74 to 1.12)	5 fewer per 100 (from 15 fewer to 7 more)	LOW
Primary outcome: patient-reported 50% pain reduction (follow-up 4 weeks)					
1[1]	44/137 (32.1%)	56/144 (38.9%)	RR 0.83 (0.60 to 1.14)	7 fewer per 100 (from 16 fewer to 5 more)	LOW
Primary outcome: patient-reported global improvement/impression of change (follow-up 4 weeks)					
1[1]	65/137 (47.4%)	72/144 (50%)	RR 0.95 (0.75 to 1.21)	3 fewer per 100 (from 12 fewer to 11 more)	LOW
Primary outcome: number of withdrawals owing to adverse effects (follow-up 4 weeks)					
1[1]	36/153 (23.5%)	4/155 (2.6%)	RR 9.12 (3.33 to 25.0)	21 more per 100 (from 6 more to 62 more)	VERY LOW
Primary outcome: any adverse effects: unspecified (follow-up 4 weeks)					
1[1]	63/153 (41.2%)	9/155 (5.8%)	RR 7.09 (3.66 to 13.7)	35 more per 100 (from 15 more to 74 more)	VERY LOW
[1] Baron et al. (2009).					

Table 76 Summary profile – imipramine vs venlafaxine as monotherapy (comparative trials)

No of studies	Imipramine	Venlafaxine	Relative risk (95% CI)	Absolute risk	Quality
Primary outcome: patient-reported global improvement/impression of change (follow-up 4 weeks)					
1[1]	14/33 (42.4%)	8/33 (24.2%)	RR 1.75 (0.85 to 3.60)	18 more per 100 (from 4 fewer to 63 more)	MODERATE
Primary outcome: dizziness (adverse effects) (follow-up 4 weeks)					
1[1]	3/33 (9.1%)	2/33 (6.1%)	RR 1.50 (0.27 to 8.40)	3 more per 100 (from 4 fewer to 45 more)	VERY LOW
Primary outcome: dry mouth (adverse effects) (follow-up 4 weeks)					
1[1]	12/33 (36.4%)	4/33 (12.1%)	RR 3.00 (1.08 to 8.35)	24 more per 100 (from 1 more to 89 more)	VERY LOW
Primary outcome: any adverse effects: unspecified (follow-up 4 weeks)					
1[1]	13/33 (39.4%)	11/33 (33.3%)	RR 1.18 (0.62 to 2.25)	6 more per 100 (from 13 fewer to 42 more)	VERY LOW
[1] Sindrup et al. (2003).					

Head-to-head comparative trials (combination therapy)

Table 77 Summary profile – pregabalin + oxycodone as combination therapy vs pregabalin alone (comparative trials)

No of studies	Pregabalin + oxycodone	Pregabalin	Relative risk (95% CI)	Absolute risk	Quality
Primary outcome: number of withdrawals owing to adverse effects (follow-up 3 months)					
1[1]	10/169 (5.9%)	9/134 (6.7%)	RR 0.88 (0.37 to 2.11)	1 fewer per 100 (from 4 fewer to 7 more)	VERY LOW
Other pain outcome: mean pain intensity (NRS-11 point) (follow-up 3 months)					
1[1]	169	134	Pregabalin + oxycodone = decreased 80% Pregabalin = decreased 46%; p <0.05		VERY LOW

[1] Gatti et al. (2009).

Note: no study on pregabalin + oxycodone as combination therapy vs pregabalin alone that reported the critical outcomes on pain was identified or met the inclusion and exclusion criteria.

Table 78 Summary profile – pregabalin + oxycodone as combination therapy vs oxycodone alone (comparative trials)

No of studies	Pregabalin + oxycodone	Oxycodone	Relative risk (95% CI)	Absolute risk	Quality
Primary outcome: number of withdrawals owing to adverse effects (follow-up 3 months)					
1[1]	10/169 (5.9%)	11/106 (10.4%)	RR 0.51 (0.22 to 1.19)	5 fewer per 100 (from 8 fewer to 2 more)	VERY LOW
Other pain outcome: mean pain intensity (NRS-11 point) (follow-up 3 months)					
1[1]	169	106	Pregabalin + oxycodone = decreased 80% Oxycodone = decreased 76%; p >0.05		VERY LOW
[1] Gatti et al. (2009).					

Note: No study on pregabalin + oxycodone as combination therapy vs oxycodone alone that reported the critical outcomes on pain was identified or met the inclusion and exclusion criteria.

Table 79 Summary profile – gabapentin + nortriptyline as combination therapy vs gabapentin alone (comparative trials)

No of studies	Gabapentin + nortriptyline	Gabapentin	Relative (95% CI)	Absolute	Quality
Other pain outcome: daily pain scores (numerical rating scale) (follow-up 6 weeks)					
1[1]	45	45	Combination lower than gabapentin = −0.9 (−1.4 to −0.3)		LOW
[1] Gilron et al. (2009).					

Note: no study on gabapentin + nortriptyline as combination therapy vs gabapentin alone e that reported the critical outcomes on pain and adverse effects was identified or met the inclusion and exclusion criteria.

3.4.3 Evidence statements

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

3.4.3.1 No study on clomipramine, desipramine, dosulepin (dothiepin), doxepin, lofepramine, trimipramine, citalopram, fluoxetine,

paroxetine, sertraline, oxcarbazepine, phenytoin, sodium valproate, buprenorphine, co-codamol, codeine phosphate, co-dydramol, dihydrocodeine, fentanyl was identified or met the inclusion and exclusion criteria for other neuropathic pain conditions (apart from PDN and PHN).

Antidepressants as monotherapy against placebo

Amitriptyline (linked to table 58)

Critical outcomes (pain)

3.4.3.2 Moderate quality evidence from two studies with 110 patients with other neuropathic pain (apart from PDN and PHN), showed that amitriptyline is more effective than placebo in achieving at least 30% pain reduction from baseline up to 8 weeks' follow-up.

3.4.3.3 Low quality evidence from three studies with 226 patients with other neuropathic pain (apart from PDN and PHN), showed that there is no significant difference between patients on amitriptyline and placebo in achieving global improvement/impression of change from baseline up to 9 weeks' follow-up.

Critical outcomes (adverse effects)

3.4.3.4 Low quality evidence from six studies with 402 patients with other neuropathic pain (apart from PDN and PHN), showed that there is no significant difference between patients on amitriptyline and placebo withdrawing from studies due to adverse effects from baseline up to 9 weeks' follow-up.

3.4.3.5 Low quality evidence from two studies with 63 patients with other neuropathic pain (apart from PDN and PHN), showed that there is no significant difference between patients on amitriptyline and placebo in experiencing dizziness from baseline up to 6 weeks' follow-up.

3.4.3.6 Low quality evidence from four studies with 215 patients with other neuropathic pain (apart from PDN and PHN), showed that there is no significant difference between patients on amitriptyline and

placebo in experiencing dry mouth from baseline up to 6 weeks' follow-up.

3.4.3.7 *Low quality evidence from two studies with 121 patients with other neuropathic pain (apart from PDN and PHN), showed that there is no significant difference between patients on amitriptyline and placebo in experiencing blurred vision and vomiting from baseline up to 6 weeks' follow-up.*

3.4.3.8 *Very low quality evidence from one study with 37 patients with other neuropathic pain (apart from PDN and PHN), showed that there is no significant difference between patients on amitriptyline and placebo in experiencing gastrointestinal disturbances from baseline up to 6 weeks' follow-up.*

3.4.3.9 *Very low quality evidence from one study with 68 patients with other neuropathic pain (apart from PDN and PHN), showed that there is no significant difference between patients on amitriptyline and placebo in experiencing sedation from baseline up to 4 weeks' follow-up.*

3.4.3.10 *Low quality evidence from three studies with 180 patients with other neuropathic pain (apart from PDN and PHN), showed that there is no significant difference between patients on amitriptyline and placebo in experiencing any adverse effects (unspecified) from baseline up to 6 weeks' follow-up.*

Nortriptyline (linked to table 59)

Critical outcomes (pain)

3.4.3.11 *Moderate quality evidence from one study with 64 patients with other neuropathic pain (apart from PDN and PHN), showed that there is no significant difference between nortriptyline and placebo in achieving global improvement/impression of change from baseline up to 7 weeks follow-up.*

Critical outcomes (adverse effects)

3.4.3.12 Very low quality evidence from one study with 56 patients with other neuropathic pain (apart from PDN and PHN), showed that there is no significant difference between patients on nortriptyline and placebo in experiencing dry mouth, blurred vision, gastrointestinal disturbances and any adverse effects (unspecified) from baseline up to 7 weeks' follow-up.

Imipramine (linked to table 60)

Critical outcomes (pain)

3.4.3.13 Moderate quality evidence from one study with 66 patients with other neuropathic pain (apart from PDN and PHN), showed that imipramine is more effective than placebo in achieving global improvement/impression of change from baseline up to 4 weeks' follow-up.

Critical outcomes (adverse effects)

3.4.3.14 Very low quality evidence from one study with 66 patients with other neuropathic pain (apart from PDN and PHN), showed that there is no significant difference between patients on imipramine and placebo withdrawing from studies due to adverse effects from baseline up to 4 weeks' follow-up.

3.4.3.15 Very low quality evidence from one study with 66 patients with other neuropathic pain (apart from PDN and PHN), showed that patients on imipramine are more likely to experience dry mouth from baseline up to 4 weeks' follow-up.

Duloxetine (linked to table 61)

Critical outcomes (pain)

3.4.3.16 Moderate quality evidence from one study with 48 patients with other neuropathic pain (apart from PDN and PHN), showed that duloxetine is more effective than placebo in achieving global improvement/impression of change from baseline up to 8 weeks' follow-up.

Critical outcomes (adverse effects)

3.4.3.17 Very low quality evidence from one study with 48 patients with other neuropathic pain (apart from PDN and PHN), showed that there is no significant difference between patients on duloxetine and placebo in experiencing dizziness and dry mouth from baseline up to 8 weeks' follow-up.

Venlafaxine (linked to table 62)

Critical outcomes (pain)

3.4.3.18 Low quality evidence from two studies with 121 patients with other neuropathic pain (apart from PDN and PHN), showed that there is no significant difference between venlafaxine and placebo in achieving global improvement/impression of change from baseline up to 8 weeks follow-up.

Critical outcomes (adverse effects)

3.4.3.19 Low quality evidence from three studies with 172 patients with other neuropathic pain (apart from PDN and PHN), showed that there is no significant difference between patients on venlafaxine and placebo withdrawing from studies due to adverse effects from baseline up to 8 weeks' follow-up.

3.4.3.20 Low quality evidence from two studies with 92 patients with other neuropathic pain (apart from PDN and PHN), showed that there is no significant difference between patients on venlafaxine and placebo in experiencing dry mouth from baseline up to 4 weeks' follow-up.

3.4.3.21 Very low quality evidence from one study with 60 patients with other neuropathic pain (apart from PDN and PHN), showed that there is no significant difference between patients on venlafaxine and placebo in experiencing any adverse effects (unspecified) from baseline up to 8 weeks' follow-up.

Anti-epileptics as monotherapy against placebo

Gabapentin (linked to table 63)

Critical outcomes (pain)

3.4.3.22 Moderate quality evidence from one study with 44 patients, and one study with 305 patients with other neuropathic pain (apart from PDN and PHN), showed that there is no significant difference between gabapentin and placebo in achieving at least 30% and 50% pain reduction respectively from baseline up to 8 weeks' follow-up.

3.4.3.23 Moderate quality evidence from three studies with 522 patients with other neuropathic pain (apart from PDN and PHN), showed that gabapentin is more effective than placebo in achieving global improvement/impression of change from baseline up to 8 weeks' follow-up.

Critical outcomes (adverse effects)

3.4.3.24 Low quality evidence from five studies with 693 patients with other neuropathic pain (apart from PDN and PHN), showed that there is no significant difference between patients on gabapentin and placebo withdrawing from studies due to adverse effects from baseline up to 8 weeks' follow-up.

3.4.3.25 Moderate quality evidence from five studies with 789 patients with other neuropathic pain (apart from PDN and PHN), showed that patients on gabapentin are more likely to experience dizziness compared with placebo from baseline up to 8 weeks' follow-up.

3.4.3.26 Low quality evidence from three studies with 369 patients with other neuropathic pain (apart from PDN and PHN), showed that patients on gabapentin are more likely to experience somnolence compared with placebo from baseline up to 8 weeks' follow-up.

3.4.3.27 Low quality evidence from two studies with 420 patients with other neuropathic pain (apart from PDN and PHN), showed that patients

on gabapentin are more likely to experience fatigue compared with placebo from baseline up to 6 weeks' follow-up.

3.4.3.28 Very low quality evidence from one study with 40 patients with other neuropathic pain (apart from PDN and PHN), showed that there is no significant difference between patients on gabapentin and placebo in experiencing sedation from baseline up to 8 weeks' follow-up.

3.4.3.29 Moderate quality evidence from three studies with 391 patients with other neuropathic pain (apart from PDN and PHN), showed that patients on gabapentin are more likely to experience any adverse effects (unspecified) compared with placebo from baseline up to 8 weeks' follow-up.

Pregabalin (linked to table 64)

Critical outcomes (pain)

3.4.3.30 Moderate quality evidence from five studies with 1270 patients with other neuropathic pain (apart from PDN and PHN), showed that pregabalin is more effective than placebo in achieving at least 30% pain reduction from baseline up to 14 weeks' follow-up.

3.4.3.31 Moderate quality evidence from four studies with 1016 patients, and four studies with 1134 patients with other neuropathic pain (apart from PDN and PHN), showed that there is no significant difference between pregabalin and placebo in achieving at least 50% pain reduction and global improvement/impression of change respectively from baseline up to 14 weeks' follow-up.

Critical outcomes (adverse effects)

3.4.3.32 Moderate quality evidence from six studies with 1311 patients with other neuropathic pain (apart from PDN and PHN), showed that patients on pregabalin are more likely withdraw from studies due to adverse effects compared with placebo from baseline up to 14 weeks' follow-up.

3.4.3.33 Low quality evidence from five studies with 1036 patients with other neuropathic pain (apart from PDN and PHN), showed that patients on pregabalin are more likely to experience dizziness and somnolence compared with placebo from baseline up to 14 weeks' follow-up.

3.4.3.34 Very low quality evidence from one study with 154 patients with other neuropathic pain (apart from PDN and PHN), showed that there is no significant difference between patients on pregabalin and placebo in experiencing fatigue from baseline up to 8 weeks' follow-up.

3.4.3.35 Moderate quality evidence from two studies with 494 patients with other neuropathic pain (apart from PDN and PHN), showed that patients on pregabalin are more likely to experience any adverse effects (unspecified) compared with placebo from baseline up to 8 weeks' follow-up.

Lamotrigine (linked to table 65)

Critical outcomes (pain)

3.4.3.36 Moderate quality evidence from one study with 22 patients with other neuropathic pain (apart from PDN and PHN), showed that there is no significant difference between lamotrigine and placebo in achieving at least 30% pain reduction from baseline up to 11 weeks' follow-up.

Critical outcomes (adverse effects)

3.4.3.37 Low quality evidence from seven studies with 642 patients with other neuropathic pain (apart from PDN and PHN), showed that there is no significant difference between patients on lamotrigine and placebo withdrawing from studies due to adverse effects from baseline up to 14 weeks' follow-up.

3.4.3.38 Low quality evidence from two studies with 155 patients with other neuropathic pain (apart from PDN and PHN), showed that there is no significant difference between patients on lamotrigine and

placebo in experiencing dizziness and fatigue from baseline up to 11 weeks' follow-up.

3.4.3.39 *Very low quality evidence from two studies with 116 patients with other neuropathic pain (apart from PDN and PHN), showed that there is no significant difference between patients on lamotrigine and placebo in experiencing any adverse effects (unspecified) from baseline up to 9 weeks' follow-up.*

Topiramate (linked to table 66)

Critical outcomes (pain)

3.4.3.40 *Moderate quality evidence from one study with 58 patients with other neuropathic pain (apart from PDN and PHN), showed that topiramate is more effective than placebo in achieving global improvement/impression of change from baseline up to 6 weeks' follow-up.*

Critical outcomes (adverse effects)

3.4.3.41 *Very low quality evidence from one study with 82 patients with other neuropathic pain (apart from PDN and PHN), showed that patients on topiramate are more likely to withdraw from studies due to adverse effects compared with placebo from baseline up to 6 weeks' follow-up.*

3.4.3.42 *Very low quality evidence from one study with 58 patients with other neuropathic pain (apart from PDN and PHN), showed that there is no significant difference between patients on topiramate and placebo in experiencing fatigue and any adverse effects (unspecified) from baseline up to 6 weeks' follow-up.*

Carbamazepine (linked to table 67)

Critical outcomes (pain)

3.4.3.43 *Low quality evidence from two studies with 56 patients with other neuropathic pain (apart from PDN and PHN), showed that there is no significant difference between carbamazepine and placebo in*

achieving global improvement/impression of change from baseline up to 46 months' follow-up.

Critical outcomes (adverse effects)

3.4.3.44 Very low quality evidence from one study with 30 patients with other neuropathic pain (apart from PDN and PHN), showed that patients on carbamazepine are more likely to experience any adverse effects (unspecified) compared with placebo from baseline up to 4 weeks' follow-up.

Opioid analgesics as monotherapy against placebo

Tramadol (linked to table 68)

Critical outcomes (pain)

3.4.3.45 Moderate quality evidence from one study with 24 patients with other neuropathic pain (apart from PDN and PHN), showed that there is no significant difference between tramadol and placebo in achieving global improvement/impression of change from baseline up to 4 weeks' follow-up.

Critical outcomes (adverse effects)

3.4.3.46 Low quality evidence from three studies with 161 patients with other neuropathic pain (apart from PDN and PHN), showed that patients on tramadol are more likely to withdraw from studies due to adverse effects compared with placebo from baseline up to 6 weeks' follow-up.

3.4.3.47 Low quality evidence from two studies with 125 patients with other neuropathic pain (apart from PDN and PHN), showed that patients on tramadol are more likely to experience nausea compared with placebo from baseline up to 6 weeks' follow-up.

3.4.3.48 Very low quality evidence from two studies with 125 patients with other neuropathic pain (apart from PDN and PHN), showed that patients on tramadol are more likely to experience dizziness compared with placebo from baseline up to 6 weeks' follow-up.

3.4.3.49 *Very low quality evidence from two studies with 125 patients with other neuropathic pain (apart from PDN and PHN), showed that there is no significant difference between patients on tramadol and placebo in experiencing constipation from baseline up to 6 weeks' follow-up.*

3.4.3.50 *Very low quality evidence from three studies with 150 patients with other neuropathic pain (apart from PDN and PHN), showed that patients on tramadol are more likely to experience any adverse effects (unspecified) compared with placebo from baseline up to 6 weeks' follow-up.*

Morphine (linked to table 69)

Critical outcomes (pain)

3.4.3.51 *Moderate quality evidence from one study with 93 patients, two studies with 117 patients and one study with 65 patients with other neuropathic pain (apart from PDN and PHN), showed that morphine is more effective than placebo in achieving at least 30% or 50% pain reduction and global improvement/impression of change respectively from baseline up to 7 weeks' follow-up.*

Critical outcomes (adverse effects)

3.4.3.52 *Very low quality evidence from one study with 110 patients with other neuropathic pain (apart from PDN and PHN), showed that patients on morphine are more likely to withdraw from studies due to adverse effects compared with placebo from baseline up to 6 weeks' follow-up.*

3.4.3.53 *Very low quality evidence from two studies with 149 patients with other neuropathic pain (apart from PDN and PHN), showed that patients on morphine are more likely to experience constipation and any adverse effects (unspecified) compared with placebo from baseline up to 7 weeks' follow-up.*

3.4.3.54 *Low quality evidence from two studies with 149 patients with other neuropathic pain (apart from PDN and PHN), showed that patients*

on morphine are more likely to experience somnolence compared with placebo from baseline up to 7 weeks' follow-up.

3.4.3.55 Low quality evidence from two studies with 149 patients with other neuropathic pain (apart from PDN and PHN), showed that there is no significant difference between patients on morphine and placebo in experiencing nausea and dizziness from baseline up to 7 weeks' follow-up.

Topical treatments as monotherapy against placebo

Topical capsaicin (0.075% cream) (linked to table 70)

Critical outcomes (pain)

3.4.3.56 Moderate quality evidence from one study with 22 patients with other neuropathic pain (apart from PDN and PHN), showed that there is no significant difference between topical capsaicin (0.075% cream) and placebo in achieving at least 50% pain reduction from baseline up to 6 weeks' follow-up.

Critical outcomes (adverse effects)

3.4.3.57 Low quality evidence from three studies with 328 patients and four studies with 456 patients with other neuropathic pain (apart from PDN and PHN), showed that patients on between topical capsaicin (0.075% cream) are more likely to withdraw from studies due to adverse effects and burning compared with placebo from baseline up to 8 weeks' follow-up.

Topical lidocaine (5% patch/cream) (linked to table 71)

Critical outcomes (pain)

3.4.3.58 No study on topical lidocaine (5% patch/cream) as monotherapy that reported the critical outcomes on pain was identified or met the inclusion and exclusion criteria.

Critical outcomes (adverse effects)

3.4.3.59 Very low quality evidence from one study with 116 patients with other neuropathic pain (apart from PDN and PHN), showed that there is no significant difference between patients on topical

lidocaine (5% patch/cream) and placebo withdrawing from studies due to adverse effects, or experiencing skin rash from baseline up to 1 week follow-up.

3.4.3.60 Very low quality evidence from one study with 70 patients with other neuropathic pain (apart from PDN and PHN), showed that there is no significant difference between patients on topical lidocaine (5% patch/cream) and placebo in experiencing skin irritation from baseline up to 1 week follow-up.

Other reported pain outcomes

3.4.3.61 Low quality evidence from one study with 21 patients and one study with 71 patients with other neuropathic pain (apart from PDN and PHN), showed that there is no significant difference between patients on topical lidocaine (5% patch/cream) and placebo in pain intensity scores from baseline up to 4 weeks' follow-up.

3.4.3.62 Low quality evidence from one study with 120 patients with other neuropathic pain (apart from PDN and PHN), showed that there is no significant difference between patients on topical lidocaine (5% patch/cream) and placebo in pain relief scores from baseline up to 4 weeks' follow-up.

3.4.3.63 Low quality evidence from one study with 80 patients with other neuropathic pain (apart from PDN and PHN), showed that patients on topical lidocaine (5% patch/cream) have better pain relief scores compared with placebo from baseline up to 1 week follow-up.

Head-to-head comparative trials (monotherapy)

Amitriptyline vs gabapentin (linked to table 72)

Critical outcomes (pain)

3.4.3.64 Moderate quality evidence from one study with 44 patients with other neuropathic pain (apart from PDN and PHN), showed that amitriptyline is more effective than gabapentin in achieving at least 30% pain reduction from baseline up to 8 weeks' follow-up.

Critical outcomes (adverse effects)

3.4.3.65 Very low quality evidence from one study with 76 patients with other neuropathic pain (apart from PDN and PHN), showed that there is no significant difference between patients on amitriptyline and patients on gabapentin withdrawing from studies due to adverse effects from baseline up to 8 weeks' follow-up.

Amitriptyline vs carbamazepine (linked to table 73)

Critical outcomes (pain)

3.4.3.66 Moderate quality evidence from one study with 29 patients with other neuropathic pain (apart from PDN and PHN), showed that there is no significant difference between amitriptyline and carbamazepine in achieving global improvement/impression of change from baseline up to 4 weeks' follow-up.

Critical outcomes (adverse effects)

3.4.3.67 Very low quality evidence from one study with 29 patients with other neuropathic pain (apart from PDN and PHN), showed that there is no significant difference between patients on amitriptyline and patients on carbamazepine in experiencing any adverse effects (unspecified) from baseline up to 4 weeks' follow-up.

Pregabalin vs oxycodone (linked to table 74)

Critical outcomes (pain)

3.4.3.68 No study on pregabalin vs oxycodone as monotherapy that reported the critical outcomes on pain was identified or met the inclusion and exclusion criteria.

Critical outcomes (adverse effects)

3.4.3.69 Very low quality evidence from one study with 240 patients with other neuropathic pain (apart from PDN and PHN), showed that there is no significant difference between patients on pregabalin and patients on oxycodone withdrawing from studies due to adverse effects from baseline up to 12 weeks' follow-up.

Other reported pain outcomes

3.4.3.70 Very low quality evidence from one study with 140 patients with other neuropathic pain (apart from PDN and PHN), showed that patients on oxycodone have better pain relief scores compared with patients on pregabalin from baseline up to 12 weeks' follow-up.

Pregabalin vs topical lidocaine (5% patch) (linked to table 75)

Critical outcomes (pain)

3.4.3.71 Low quality evidence from one study with 281 patients with other neuropathic pain (apart from PDN and PHN), showed that there is no significant difference between pregabalin and topical lidocaine (5% patch) in achieving at least 30% or 50% pain reduction and global improvement/impression of change from baseline up to 4 weeks' follow-up.

Critical outcomes (adverse effects)

3.4.3.72 Very low quality evidence from one study with 308 patients with other neuropathic pain (apart from PDN and PHN), showed that patients on pregabalin are more likely to withdraw from studies due to adverse effects, and experience any adverse effects (unspecified) compared with topical lidocaine (5% patch) from baseline up to 4 weeks' follow-up.

Imipramine vs venlafaxine (linked to table 76)

Critical outcomes (pain)

3.4.3.73 Moderate quality evidence from one study with 66 patients with other neuropathic pain (apart from PDN and PHN), showed that there is no significant difference between imipramine and venlafaxine in achieving global improvement/impression of change from baseline up to 4 weeks' follow-up.

Critical outcomes (adverse effects)

3.4.3.74 Very low quality evidence from one study with 66 patients with other neuropathic pain (apart from PDN and PHN), showed that there is no significant difference between patients on imipramine

and venlafaxine in experiencing dizziness and any adverse effects (unspecified) from baseline up to 4 weeks' follow-up.

3.4.3.75 Very low quality evidence from one study with 66 patients with other neuropathic pain (apart from PDN and PHN), showed that patients on imipramine are more likely to experience dry mouth compared with venlafaxine from baseline up to 4 weeks' follow-up.

Head-to-head comparative trials (combination therapy)

Pregabalin + oxycodone as combination therapy vs pregabalin alone (linked to table 77)

Critical outcomes (pain)

3.4.3.76 No study on pregabalin + oxycodone as combination therapy vs pregabalin alone that reported the critical outcomes on pain was identified or met the inclusion and exclusion criteria.

Critical outcomes (adverse effects)

3.4.3.77 Very low quality evidence from one study with 303 patients with other neuropathic pain (apart from PDN and PHN), showed that there is no significant difference between patients on pregabalin + oxycodone and patients on pregabalin alone withdrawing from studies due to adverse effects from baseline up to 12 weeks' follow-up.

Other reported pain outcomes

3.4.3.78 Very low quality evidence from one study with 303 patients with other neuropathic pain (apart from PDN and PHN), showed that patients on pregabalin + oxycodone have better pain intensity scores compared with pregabalin alone from baseline up to 12 weeks' follow-up.

Pregabalin + oxycodone as combination therapy vs oxycodone alone (linked to table 78)

Critical outcomes (pain)

3.4.3.79 No study on pregabalin + oxycodone as combination therapy vs oxycodone alone that reported the critical outcomes on pain was identified or met the inclusion and exclusion criteria.

Critical outcomes (adverse effects)

3.4.3.80 Very low quality evidence from one study with 275 patients with other neuropathic pain (apart from PDN and PHN), showed that there is no significant difference between patients on pregabalin + oxycodone and patients on oxycodone alone withdrawing from studies due to adverse effects from baseline up to 12 weeks' follow-up.

Other reported pain outcomes

3.4.3.81 Very low quality evidence from one study with 275 patients with other neuropathic pain (apart from PDN and PHN), showed that there is no significant difference in pain intensity scores between patients on pregabalin + oxycodone and patients on oxycodone alone from baseline up to 12 weeks' follow-up.

Gabapentin + nortriptyline as combination therapy vs gabapentin alone (linked to table 79)

Critical outcomes (pain)

3.4.3.82 No studies on gabapentin + nortriptyline as combination therapy vs gabapentin alone that reported the critical outcomes on pain were identified or met the inclusion and exclusion criteria.

Critical outcomes (adverse effects)

3.4.3.83 No studies on gabapentin + nortriptyline as combination therapy vs gabapentin alone that reported the critical outcomes on adverse effects were identified or met the inclusion and exclusion criteria.

Other reported pain outcomes

3.4.3.84 Low quality evidence from one study with 90 patients with other neuropathic pain (apart from PDN and PHN), showed that there is no significant difference in daily pain scores between patients on gabapentin + nortriptyline and patients on gabapentin alone from baseline up to 6 weeks' follow-up.

3.4.4 Health economic modelling

No appropriate economic analyses were identified in the literature to inform recommendations for other neuropathic conditions other than PDN and PHN. The GDG considered that it would be appropriate to extrapolate results from the draft HTA reports analysis of PHN and PDN with consideration given to the findings of the clinical review. However, the GDG noted that for both models the QALY differences were negligible and that costs were the main contributor to difference in cost effectiveness. Therefore, given this information the GDG felt confident that it could extrapolate the results.

Health economics evidence statements – neuropathic pain excluding PDN and PHN

3.4.4.1 No cost effectiveness or economic study comparing treatments for neuropathic pain excluding PHN and PDN was identified or met the inclusion and exclusion criteria.

3.4.5 Evidence to recommendations

As stated in section 3.3.5, this section will consider both the evidence-base for post-herpetic neuralgia (PHN) and for other neuropathic pain conditions (that is all other neuropathic pain conditions apart from PDN and PHN).

Relative value of different outcomes	The relative value of different outcomes considered by the GDG for PHN and other neuropathic pain conditions are the same as in PDN (please see section 3.2.5).
Quality of evidence	The GDG agreed that when discussing the quality of evidence, considerations of the number of studies, the size of the study population and the magnitude of effects are important.

	Overall, the GDG agreed that the core evidence-base is from placebo-controlled trials, and evidence on head-to-head comparative trials and trials on combination therapy is very limited. Hence, the GDG felt that it could not confidently draw conclusions solely based on this evidence. The focus of the discussion is based on the placebo-controlled trials and evidence from health economics evaluation. **Antidepressants** *For post-herpetic neuralgia (PHN)* The GDG agreed that there is moderate-quality evidence on the statistically significant efficacy of amitriptyline for 30% pain reduction, and desipramine for global improvement/impression of change. *For other neuropathic pain conditions (that is all other neuropathic pain conditions apart from PDN and PHN)* The GDG agreed that there is also moderate-quality evidence on the statistically significant efficacy of amitriptyline in 30% pain reduction, and of imipramine and duloxetine in global improvement/impression of change. The GDG agreed that there was insufficient evidence on the efficacy of nortriptyline and venlafaxine. *Overall* Amitriptyline seems to have moderate-quality evidence on its efficacy for both PHN and other neuropathic pain conditions (apart from PDN) in 30% pain reduction. **Anti-epileptics** *For post-herpetic neuralgia (PHN)* The GDG agreed that there is moderate-quality evidence on the statistically significant efficacy of gabapentin in 30% pain reduction, and high/moderate-quality evidence on the significant efficacy of pregabalin in 30%, 50% pain reduction and global improvement/impression of change. *For other neuropathic pain conditions (that is all other neuropthic pain conditions apart from PDN and PHN)* The GDG agreed that there is also moderate-quality evidence on the statistically significant efficacy of gabapentin in global improvement/impression of change, pregabalin in 30% pain reduction, and topiramate in global improvement/impression of change. However, the moderate-quality evidence on topiramate is based on a single study with small sample size (less than 100) by comparison with gabapentin (nine

	studies) and pregabalin (six studies). Hence, the GDG was concerned that the effect size for topiramate in this single study may be an overestimate. The GDG agreed that there was insufficient evidence on the efficacy of lamotrigine and carbamazepine. *Overall* Gabapentin and pregabalin seem to have high to moderate quality evidence on efficacy for both PHN and other neuropathic pain conditions (that is all other neuropthic pain conditions apart from PDN and PHN) in all critical outcomes on pain. **Opioid analgesics** *For post-herpetic neuralgia (PHN)* The GDG agreed that there is moderate-quality evidence on the significant efficacy of tramadol in 50% pain reduction for PHN. *For other neuropathic pain conditions (other than PDN and PHN)* The GDG agreed that there is moderate-quality evidence on the statistically significant efficacy of morphine in 30% and 50% pain reduction. There is a lack of evidence on the efficacy of tramadol for other neuropathic pain conditions (that is all other neuropthic pain conditions apart from PDN and PHN). *Overall* Both tramadol and morphine seem to have some evidence on efficacy in different neuropathic pain conditions. **Topical treatments** *For post-herpetic neuralgia (PHN)* The GDG agreed that there is high-quality evidence on the significant efficacy of topical capsaicin (8% patch) in 30% pain reduction and global improvement/impression of change, and low-quality evidence on 50% pain reduction for PHN. Moreover, this treatment is licensed for peripheral neuropathic pain (excluding PDN). The GDG agreed that there was insufficient evidence on the efficacy of topical capsaicin (0.075% cream) and the low-quality evidence on topical lidocaine (5% patch) was on non-critical pain outcomes. *For other neuropathic pain conditions (other than PDN and PHN)* The GDG agreed that there was insufficient evidence on the efficacy of

	topical capsaicin (0.075% cream) and the low-quality evidence on topical lidocaine (5% patch) was on non-critical pain outcomes. *Overall* The GDG agreed that there is high-quality evidence on the significant efficacy of topical capsaicin (8% patch), and limited low-quality evidence on non-critical outcome on pain for topical lidocaine (5% patch).
Trade-off between clinical benefits and harms	*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. *Amitriptyline* The GDG agreed that based on the evidence, amitriptyline should be recommended as one of the first-line and second-line treatments (as monotherapy or in combination with other first-line treatment) for PHN and for other neuropathic pain conditions (apart from PDN and PHN). Although the GDG agreed with the role of amitriptyline, they were also 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 imipramine in global improvement/impression of change, and nortriptyline was shown to be equally as effective as gabapentin in a head-to-head comparison study (see evidence statements 3.3.3.40 and 3.3.3.41). Both are relatively low-cost drugs, and for this patient population they are potentially cost effective, provided that they do not cause other adverse effects that would reduce the potential gain in quality of life obtained by switching from amitriptyline. *Gabapentin and pregabalin* The GDG agreed that, based on the evidence, gabapentin and pregabalin should be recommended as one of the first-line and second-line treatments (as monotherapy or in combination with other first-line treatments) for PHN and other neuropathic pain conditions (apart from PDN and PHN). Both pregabalin and gabapentin have high affinity for the alpha-2-delta subunit of the voltage-dependent calcium channel in the central nervous system. Therefore if a person has unsatisfactory pain reduction with one drug, they are highly unlikely to have satisfactory pain

	reduction with the other. Additionally, the cost-effectiveness evidence (see section below on economic considerations) demonstrated that gabapentin was more cost-effective than pregabalin for PHN. The GDG agreed that gabapentin should be a first-line treatment and a second-line treatment (as monotherapy or combination therapy with amitriptyline [or nortriptyline or imipramine]) for PHN and other neuropathic pain conditions (apart from PDN and PHN). Because gabapentin and pregabalin have similar efficacy, the GDG also agreed that pregabalin should be an alternative if gabapentin is effective but the person cannot tolerate the adverse effects or has difficulty adhering to the dosage schedule. *Tramadol and morphine:* The GDG agreed that the evidence on morphine and tramadol was limited. Because the GDG was concerned about the risk of long-term dependence, the severe adverse effects and the potential fatality of overdose with morphine, the GDG felt that morphine should not be initiated without an assessment by a specialist pain service or a condition-specific service. However, the GDG also agreed that if patients did not have satisfactory pain reduction after first- and second-line treatment, they should be referred to a specialist pain service and/or a condition-specific service. Although evidence on tramadol was limited, the GDG came to the consensus that recommending tramadol is valid and appropriate as third-line treatment (as rescue analgesics) for PHN, PDN and other neuropathic pain conditions in non-specialist settings, either as monotherapy or as combination therapy with second-line treatment, because this drug is already commonly used in non-specialist settings. This will ensure continuity of treatment while a person is waiting for referral to a specialist pain service and/or a condition-specific service. *Topical capsaicin (8% patch) and topical lidocaine (5% patch):* Although there is high-quality evidence on topical capsaicin (8% patch) for PHN and it is licensed for peripheral neuropathic pain (except for PDN), the GDG agreed that the application of topical capsaicin (8% patch) would need specialised training and would need the presence of a trained healthcare professional for 2 hours with the patient. Hence, currently topical capsaicin (8% patch) is not commonly used in non-specialist

	settings. The GDG agreed that topical capsaicin (8% patch) should not be initiated without an assessment by a specialist pain service or a condition-specific service. However, the GDG acknowledged that in the near future, there may be more healthcare professionals trained in using this treatment in non-specialist settings, and therefore the recommendation on topical capsaicin (8% patch) should be re-assessed during the routine 3-year review of this guideline. The GDG agreed that there is only low-quality evidence on topical lidocaine (5% patch), and it was for non-critical pain outcomes. 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 lack of moderate or high-quality evidence, the GDG felt that they could not recommend the use of topical lidocaine as first-line or second-line treatment. 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.
Economic considerations	The GDG considered the results of the PHN and PDN analyses together and noted that in both cases gabapentin was a cost-effective option. For PHN, gabapentin was the most cost effective option with the highest net monetary benefit and also the highest probability of being cost effective. Therefore, the GDG felt confident in recommending gabapentin as first-line treatment. It noted that, in the PHN analysis, pregabalin was the second most cost-effective option and that if gabapentin is effective, but the person cannot tolerate the adverse events, then pregabalin is likely to be the most cost-effective option for them. For similar reasons as for PDN, given the low acquisition cost of amitriptyline and similar efficacy to gabapentin and pregabalin, from the clinical review and GDG opinion amitriptyline would be a cost-effective alternative to gabapentin.
Other considerations	The GDG agreed that if first-line treatment did not result in satisfactory pain reduction, a drug from another therapeutic class should be recommended as second-line treatment, either as monotherapy or as combination therapy with first-line treatment, instead of trying another drug

	from the same therapeutic class. 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). *Other treatments* The GDG also came to the consensus that, to ensure continuity of care, pharmacological treatments other than those recommended in this guideline that are started in a specialist pain service or a condition-specific service may continue to be prescribed in non-specialist settings, with a multidisciplinary care plan, local shared care agreements and careful management of adverse effects. *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. Only one study on carbamazepine for treating trigeminal neuralgia met the inclusion and exclusion criteria of this guideline. However, the GDG acknowledged that carbamazepine (within its licensed indication) has been the routine treatment for trigeminal neuralgia in clinical practice since the 1960s. Anecdotal evidence from clinical experience also showed that carbamazepine may be effective for treating this condition. Because trigeminal neuralgia is an extremely painful condition, and 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 practice will continue. Consequently, the GDG came to the consensus that a research recommendation should be made to further investigate the efficacy of carbamazepine for treating trigeminal neuralgia (see section 3.4.6).

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3.4.6 Recommendations and research recommendations

Recommendations

First-line treatment

1.1.10 Offer oral amitriptyline* or gabapentin as first-line treatment (see recommendation 1.1.13 for people with painful diabetic neuropathy).

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

1.1.12 Based on both the early and regular clinical reviews:

- If improvement is satisfactory, continue the treatment; consider gradually reducing the dose over time if improvement is sustained.
- If amitriptyline* results in satisfactory pain reduction as first-line treatment but the person cannot tolerate the adverse effects, consider oral imipramine* or nortriptyline* as an alternative.
- If gabapentin results in satisfactory pain reduction as first-line treatment but the person has difficulty adhering to the dosage schedule or cannot tolerate the adverse effects, consider oral pregabalin 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 (see recommendation 1.1.16 for people with painful diabetic neuropathy):

* 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 (September 2011). Informed consent should be obtained and documented.

- If first-line treatment was with amitriptyline* (or imipramine* or nortriptyline*), switch to or combine with oral gabapentin (or pregabalin as an alternative if gabapentin is effective but the person has difficulty adhering to the dosage schedule or cannot tolerate the adverse effects).
- If first-line treatment was with gabapentin (or 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).

1.1.14 For people with painful diabetic neuropathy, 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 duloxetine, switch to oral amitriptyline* (or imipramine* or nortriptyline* as an alternative if amitriptyline is effective but the person cannot tolerate the adverse effects) or switch to or combine with oral gabapentin (or pregabalin as an alternative if gabapentin is effective but the person has difficulty adhering to the dosage schedule or cannot tolerate the adverse effects).
- If first-line treatment was with amitriptyline* (or imipramine* or nortriptyline*), switch to or combine with gabapentin (or pregabalin as an alternative if gabapentin is effective but the person has difficulty adhering to the dosage schedule or cannot tolerate the adverse effects).

Third-line treatment

1.1.15 If satisfactory pain reduction is not achieved with second-line

* 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 (September 2011). Informed consent should be obtained and documented.

treatment:

- refer the person to a specialist pain service and/or a condition-specific service[12] **and**
- while waiting for referral:
  - consider oral tramadol as third-line treatment instead of or in combination[13] with the second-line treatment
  - consider a topical lidocaine patch for treatment of localised pain for people who are unable to take oral medication because of medical conditions and/or disability.

Other treatments

1.1.16 Do not start treatment with a topical capsaicin 8% patch or with opioids (such as morphine or oxycodone) other than tramadol without an assessment by a specialist pain service or a condition-specific service[12].

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[12] may continue to be prescribed in non-specialist settings, with a multidisciplinary care plan, local shared care agreements and careful management of adverse effects.

Research recommendations

See appendix B for full details of research recommendations.

[12] 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.

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

3.4.7 Evidence to recommendations (key principles of care)

After the assessment and discussion of the evidence of the efficacy of different pharmacological treatments for neuropathic pain conditions (including PDN and PHN) and recommendations for treatment were derived, the GDG felt that patient's care (other than the prescription of drugs) is also very important and that this should be further discussed in order to derive recommendations for good principles of care based on informal consensus. No evidence was considered within this section and therefore there were no evidence statements. The recommendations were based on the expertise and experience of the GDG.

Relative value of different outcomes	The GDG agreed that apart from the critical outcomes on pain and adverse effects of pharmacological treatments (as stated in section 3.2.5 and 3.4.5), other elements of care such as patient's experience, patient's information needs, patient's preference and different lifestyle factors are also important to be considered in a patient's care pathway.
Quality of evidence	Not applicable
Trade-off between clinical benefits and harms	The GDG acknowledged that the low-quality evidence on adverse effects for both antidepressants and anti-epileptics was restricted by which particular adverse effects were collected in the trials and how data on events were collected. 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, 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 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 the recommended treatments, 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.
Economic considerations	Not applicable
Other considerations	The GDG stressed that both early and regular clinical reviews are important 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. Because referral to specialist pain services is not an exit from non-specialist care, but the start of a collaborative, ongoing approach to management, the GDG felt that the gateway for referrals to specialist pain services, as well as other condition-specific services, should not be at the end of the care pathway. Clinicians or healthcare professionals in non-specialist settings should consider making referrals at any stage of the care pathway, including at initial presentation and at the regular clinical reviews, if the person has severe pain or there are changes in, or deterioration of, the person's pain, health condition, and/or daily activities and participation. 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.

3.4.8 Recommendations and research recommendations

Recommendations

1.1.1	Consider referring the person to a specialist pain service and/or a condition-specific service[14] at any stage, including at initial

[14] 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.

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[15] **or**
- their underlying health condition has deteriorated.

1.1.2 Continue existing treatments for people whose neuropathic pain is already effectively managed[16].

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).

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

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

[16] 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).

- patient preference
- lifestyle factors (such as occupation)
- any mental health problems (such as depression and/or anxiety[17])
- 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[18] (such as ability to work and drive)
- mood (in particular, whether the person may have depression

[17] Refer if necessary to 'Anxiety' (NICE clinical guideline 113), '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).

[18] 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.

and/or anxiety[19])

- quality of sleep
- overall improvement as reported by the person.

4 Notes on the scope of the guideline

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

5 Implementation

NICE has developed tools to help organisations implement this guidance (see www.nice.org.uk/guidance/CG[xxx])'. Note: these details will apply when the guideline is published.

6 Other versions of this guideline

6.1 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 N[xxxx]). Note: these details will apply when the guideline is published.

6.2 NICE pathway

The recommendations from this guideline have been incorporated into a NICE pathway, which is available from http://pathways.nice.org.uk/pathways/[xxx]

[19] Refer if necessary to 'Anxiety' (NICE clinical guideline 113), '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).

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

6.3 'Understanding NICE guidance'

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

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

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

7 Related NICE guidance

Published

- Anxiety. NICE clinical guideline 113 (2011). Available from www.nice.org.uk/guidance/CG113
- 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
- Type 1 diabetes. NICE clinical guideline 15 (2004; amended 2009). Available from www.nice.org.uk/guidance/CG15

8 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. Please see our website for information about updating the guideline.

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10 Glossary and abbreviations

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, for example 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. If 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.

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. For example, if the NNTB = 4, then four 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. For example if the NNTH = 4, then four 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 2 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 (for example, 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.

Please see the NICE glossary (www.nice.org.uk/website/glossary/glossary.jsp) for an explanation of terms not described above.

Abbreviations

Abbreviation	Term
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
PDN	Painful diabetic neuropaty
PHN	Post herpetic neuralgia
QALY	Quality-adjusted life year
RCT	Randomised controlled trial
RR	Relative risk
SD	Standard deviation
SE	Standard error

Appendix A Contributors and declarations of interests

The Guideline Development Group

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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.

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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.

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Declarations of interests

[Add declarations here]