Appendix C Guideline scope

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

SCOPE

1 Guideline title

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

1.1 Short title

Neuropathic pain – pharmacological management

2 The remit

The Department of Health has asked NICE: 'To prepare a short clinical guideline on the pharmacological management of neuropathic pain in adults, in non-specialist settings.' [Update]

3 Clinical need for the guideline

3.1 Epidemiology

a) Neuropathic pain refers to pain caused by a lesion or disease of the somatosensory nervous system. This can result from a heterogeneous group of disorders affecting the peripheral and central nervous systems. Common examples of peripheral neuropathic pain include painful diabetic neuropathy, post-herpetic neuralgia, radiculopathy, and trigeminal neuralgia. Common examples of central neuropathic pain include multiple sclerosis, pain after stroke and after spinal cord injury.

b) The main clinical features of neuropathic pain are continuous or intermittent spontaneous pain, typically described as burning, aching or shooting in quality. It is an unpleasant sensory and

emotional experience and can have a significant impact on the quality of life, general health, psychological health, and social and economic wellbeing of people with neuropathic pain.

c) Neuropathic pain is an important cause of chronic pain and commonly occurs in people with diabetes and following herpes zoster infection. Neuropathic pain is diagnosed and managed in primary care and secondary care as well as by specialist pain management services (services that provide comprehensive assessment and multi-modal management of all types of pain, including neuropathic pain). However, there is limited evidence on the incidence and prevalence of neuropathic pain outside of specialist pain management services. A descriptive epidemiological study of neuropathic pain in a UK general practice population shows that post-herpetic neuralgia has the highest incidence (40 per 100,000 person years observation) followed by trigeminal neuralgia (27 per 100,000 person years observation) and painful diabetic neuropathy (15 per 100,000 person years observation). This is likely to be an underestimate because not all cases will have been correctly identified.

d) There is also evidence that the incidence of post-herpetic neuralgia and painful diabetic neuropathy increases with age and, in the case of the latter, the duration of diabetes.

3.2 Current practice

a) Several pharmacological treatments are commonly used to manage neuropathic pain outside of specialist pain management services. These include antidepressants (tricyclic antidepressants [TCAs] and selective serotonin reuptake inhibitors [SSRIs]) and anti-epileptic drugs (such as gabapentin, pregabalin and carbamazepine). Topical agents (capsaicin and lidocaine) can also be used. Opioids can also be used to treat neuropathic pain, but not all neuropathic pain is opioid-responsive. The use of strong opioids for treating non-malignant chronic pain conditions is

controversial because of concerns about the long-term side effect profile of the drugs. Some commonly used treatments (such as amitriptyline) are unlicensed for use in neuropathic pain, which may limit prescription by practitioners. There is uncertainty about which drugs should be used for neuropathic pain, and in what order (sequence).

b) There is evidence that neuropathic pain is commonly managed in primary care and other settings outside of specialist pain management services. However, there is considerable variation in practice in terms of how therapy is initiated, whether therapeutic doses are achieved, the concomitant use of different drugs, and whether the different types of drugs are used in the correct sequence. This may lead to inadequate pain control and considerable morbidity. Better management of neuropathic pain in non-specialist settings could not only reduce such variation but also ensure that only those people who need specialist assessment and interventions are referred on.

4 The guideline

The guideline development process is described in detail on the NICE website (see section 6, ‘Further information’).

This scope defines what the guideline will (and will not) examine, and what the guideline developers will consider. The scope is based on the referral from the Department of Health.

The areas that will be addressed by the guideline are described in the following sections.

4.1 Population

4.1.1 Groups that will be covered

a) Adults with neuropathic pain.

4.1.2 Groups that will not be covered

a) Children and young people with neuropathic pain.

4.2 Settings

4.2.1 Healthcare settings that will be covered

a) All settings where care is delivered for NHS patients, except specialist pain management services.

4.2.2 Healthcare settings that will not be covered

a) Specialist pain management services.

4.3 Clinical management

4.3.1 Key clinical issues that will be covered

a) Use of the drug therapeutic classes detailed below, and their positioning within the care pathway for the management of neuropathic pain outside of specialist pain management services. This will include use of individual drugs as monotherapy and/or in combination, if clearly supported by evidence.

b) Note that guideline recommendations will normally fall within licensed indications; recommendations outside of a licensed indication may be made but only if clearly supported by the evidence. The guideline will assume that prescribers will use a drug's summary of product characteristics to inform decisions made with individual patients. It is noted that a number of drugs are used for neuropathic pain that do not have a UK marketing authorisation (licence) for this use and so are considered to be used 'off-label'. This is indicated in the text.

c) The following antidepressants will be considered:

- Tricyclic antidepressants (TCAs):
  - amitriptyline (off-label use)
  - clomipramine (off-label use)

  - dosulepin (off-label use)
  - doxepin (off-label use)
  - imipramine (off-label use)
  - lofepramine (off-label use)
  - nortriptyline (off-label use)
  - trimipramine (off-label use).
- Selective serotonin reuptake inhibitors (SSRIs):
  - citalopram (off-label use)
  - escitalopram (off-label use)
  - fluoxetine (off-label use)
  - paroxetine (off-label use)
  - sertraline (off-label use).
- Other antidepressants:
- duloxetine (licensed for diabetic peripheral neuropathic pain only)
  - mirtazapine (off-label use)
  - reboxetine (off-label use)
  - trazodone (off-label use)
  - venlafaxine (off-label use).

d) The following anti-epileptics (anticonvulsants) will be considered:

- carbamazepine (licensed for use in paroxysmal pain of trigeminal neuralgia only)
- oxcarbazepine (off-label use)
- gabapentin (licensed for use in peripheral neuropathic pain such as painful diabetic neuropathy and post-herpetic neuralgia only)
- pregabalin (licensed for use in central and peripheral neuropathic pain)
- phenytoin (licensed for use in trigeminal neuralgia only as second-line therapy if carbamazepine is ineffective or patients cannot tolerate carbamazepine)
- lacosamide (off-label use)
- lamotrigine (off-label use)

- levetiracetam (off-label use)
- sodium valproate (off-label use)
- topiramate (off-label use).

e) The following opioid analgesics will be considered:

(Please note that for this section, the summary product characteristics (SPC) varies according to the individual manufacturer end drug, please refer to the SPC for full details)

- paracetamol and opioid combinations:
  - co-codamol (licensed for mild, moderate, and severe pain)
  - co-dydramol (licensed for mild to moderate pain)
- morphine (licensed for chronic pain)
- dihydrocodeine (licensed for moderate to severe pain)
- oxycodone (licensed for severe pain, post-operative pain, and also moderate pain in patients with cancer)
- oxycodone with naloxone (licensed for severe pain which can be adequately managed only with opioid analgesics)
- tapentadol (licensed for moderate to severe acute pain or severe chronic pain in adults, which can be adequately managed only with opioid analgesics)
- tramadol (licensed for moderate to severe pain)
- buprenorphine (licensed for moderate to severe pain)
- fentanyl (licensed for severe pain or breakthrough cancer pain).

f) The following additional drugs will be considered:

- cannabis sativa extract (Sativex; off-label use, although it is licensed as an adjunct in moderate to severe spasticity in multiple sclerosis)
- flecainide (off-label use)
- 5-HT_1-receptor agonists (such as sumatriptan; off-label use for each of these)

- topical lidocaine (lidocaine medicated plaster, Versatis, is licensed for neuropathic pain associated with previous herpes zoster infection [post-herpetic neuralgia only])
- topical capsaicin (Axsain cream is licensed for the treatment of neuralgia associated with and following Herpes Zoster infections [post-herpetic neuralgia] and diabetic peripheral polyneuropathy only; Qutenza patch is licensed for peripheral neuropathic pain in non-diabetic adults only).

g) The above listed interventions will be compared with:

- placebo
- each other, if relevant evidence is available.

4.3.2 Clinical issues that will not be covered

a) Diagnosis and assessment of neuropathic pain.

b) Treatments other than those listed in 4.3.1 a–e.

c) Treatment of the underlying causes of neuropathic pain and any associated disease-specific management.

d) Acute post-surgical pain.

e) Treatment of pain other than neuropathic pain.

4.4 Main outcomes

a) Patient-reported global improvement, patient-reported pain relief, or both, measured on any standard subjective scales for pain intensity or pain relief (global improvement or pain relief of 30% or 50% or greater, or 50% or more reduction of the score on a validated pain scale).

b) Patient-reported improvement in daily physical and emotional functioning, including sleep.

c) Major adverse effects (defined as leading to withdrawal from treatment), and minor adverse effects (all adverse effects noted in patients' reports).

d) Overall improvement in quality of life.

e) Resource use and costs.

4.5 Review questions

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

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

4.6 Economic aspects

Developers will take into account both clinical and cost effectiveness when making recommendations involving a choice between alternative interventions. A review of the economic evidence will be conducted and analyses will be carried out as appropriate. The preferred unit of effectiveness is the quality-adjusted life year (QALY), and the costs considered will usually be only from an NHS and personal social services (PSS) perspective. Further detail on the methods can be found in 'The guidelines manual' (see 'Further information').

4.7 Status

4.7.1 Scope

This is the final version of the scope.

4.7.2 Timing

The development of the guideline recommendations will begin in July 2012.

5 Related NICE guidance

5.1 Published guidance

5.1.1 NICE guidance to be updated

This guideline will update and replace the following NICE guidance:

- Neuropathic pain – pharmacological management. NICE clinical guideline 96 (2010).

5.1.2 Other related NICE guidance

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

5.2 Guidance under development

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

- Type 1 diabetes (update). NICE clinical guideline. Publication expected 2014.
- Type 2 diabetes (update). NICE clinical guideline. Publication expected 2014.

6 Further information

Information on the guideline development process is provided in the following documents, available from the NICE website:

- How NICE clinical guidelines are developed: an overview for stakeholders the public and the NHS
- The guidelines manual.

Information on the progress of the guideline will also be available from the NICE website.

Appendix D How this guideline was developed

This guideline was developed in accordance with the process for short clinical guidelines set out in The guidelines manual (2012). There is more information about how NICE clinical guidelines are developed on the NICE website. A booklet, 'How NICE clinical guidelines are developed: an overview for stakeholders, the public and the NHS' is available.

Additional methods used

Please see appendix L for a full summary of the additional methods used.

Search strategies

The evidence reviews used to develop the guideline recommendations were underpinned by systematic literature searches, following the methods described in The guidelines manual (2012). The aim of the systematic searches was to comprehensively identify the published evidence to answer the review questions developed by the Guideline Development Group and Internal Clinical Guidelines Technical Team.

The search strategies for the review questions were developed by the Information Services Team with advice from the Internal Clinical Guidelines Technical Team. Structured questions were developed using the PICO (population, intervention, comparison, outcome) model and translated into search strategies using subject heading and free text terms. The strategies were run across a number of databases with no date restrictions imposed on the searches.

The NHS Economic Evaluation Database (NHS EED) and the Health Economic Evaluations Database (HEED) were searched for economic evaluations. Search filters for economic evaluations and quality of life studies were used on bibliographic databases. There were no date restrictions imposed on the searches.

Guideline Development Group members were also asked to alert the Internal Clinical Guidelines Technical Team to any additional evidence, published, unpublished or in press, that met the inclusion criteria.

Scoping searches

When the guideline was initially referred to NICE, scoping searches were undertaken on the following websites and databases between October 28th and November 3rd 2008 to provide information for scope development and project planning. Browsing or simple search strategies were employed.

The search results were used to provide information for scope development and project planning.

Guidance/guidelines	**Systematic reviews/economic evaluations**
Canadian Medical Association Infobase	Cochrane Database of Systematic Reviews (CDSR)
Clinical Evidence	Database of Abstracts of Reviews of Effects (DARE)
Clinical Knowledge Summaries (Prodigy)	Health Economic Evaluations Database (HEED)
Department of Health	Health Technology Assessment (HTA) Database
Guidelines International Network (GIN)	National Institute for Health Research (NIHR) Health Technology Assessment Programme
National Health and Medical	NHS Economic Evaluation Database (NHS EED)
National Institute for Health and Clinical Excellence (NICE) - published & in development	NHS R&D Service Delivery and Organisation Programme
New Zealand Guidelines Group	The NIHR Health Services and Delivery Research (HS&DR)
NLH Guidelines Finder	Trip Database
NLH Specialist Libraries	
Professional bodies/associations/societies (British	

Pain Society, International Association for the Study of Pain, Chronic Pain Policy Society, Diabetes UK, Multiple Sclerosis Society)	
Protocols and Care Pathways Database	
Research Council (Australia)	
Royal Colleges	
Scottish Intercollegiate Guidelines Network (SIGN)	
US National Guideline Clearinghouse	

Ahead of the development searches in 2012 for the full update of the guideline, additional scoping searches were conducted to identify any new drugs that had been licensed since the initial scoping in 2008. The BNF, New Drugs Online and the electronic Medicines Compendium websites were searched between 26th and 27th April 2012.

Main searches

The following sources were searched for the topics presented in the sections below.

- CINAHL (EBSCO)
- Cochrane Central Register of Controlled Trials – CENTRAL (Wiley)
- Cochrane Database of Systematic Reviews – CDSR (Wiley)
- Database of Abstracts of Reviews of Effects – DARE (CRD up to May 2009 and Wiley after May 2009)
- EMBASE (Ovid)
- Health Economic Evaluations Database – HEED (Wiley)
- Health Technology Assessment Database – HTA (CRD up to May 2009 and Wiley after May 2009)
- MEDLINE (Ovid)
- MEDLINE In-Process (Ovid)
- NHS Economic Evaluations Database – NHS EED (CRD up to May 2009 and Wiley after May 2009)

Systematic review searches

The searches were conducted between 17th and 31st July 2012 and one strategy was designed to identify evidence on the following clinical questions:

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

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

The MEDLINE search strategy is presented below and was translated for use in all of the databases listed above.

1. (neuropathic* adj3 pain*).tw.
2. Diabetic Neuropathies/
3. (diabet* adj3 neurop*).tw.
4. Neuralgia, Postherpetic/
5. (postherp* adj3 neuralg*).tw.
6. Trigeminal Neuralgia/
7. (trigemin* adj3 neuralg*).tw.
8. (central* adj3 pain).tw.
9. Facial Pain/
10. Facial Neuralgia/
11. ((facial* or face) adj3 (pain* or neuralg*)).tw.
12. Burning Mouth Syndrome/
13. (burning adj3 mouth*).tw.
14. (HIV adj3 neuropath*).tw.
15. (neuropath* adj3 cancer* adj3 pain*).tw.
16. Pain, Postoperative/
17. (pain* adj3 (post-treatment* or post treatment* or posttreatment* or surg* or post-op* or postop* or post op*)).tw.
18. Phantom Limb/
19. (phantom adj3 limb*).tw.
20. Polyneuropathies/
21. (pain* adj3 polyneuropath*).tw.
22. (mixed adj3 neuropath* adj3 pain*).tw.
23. exp Nerve Compression Syndromes/
24. exp Peripheral Nervous System Diseases/
25. ((compress* or peripher*) adj3 (neurop* or nerv*)).tw.
26. Spinal Cord Injuries/
27. (spinal cord adj3 (injury or injuries or injured)).tw.
28. ((post amputation or post-amputation or postamputation) adj3 pain*).tw.
29. (stroke* adj3 pain*).tw.
30. (idiopathic* adj3 (pain* or neuropath*)).tw.
31. exp Multiple Sclerosis/
32. (MS or multiple sclerosis).tw.

33. Stroke/
34. Radiculopathy/
35. (radiculopath* or radicular pain*).tw.
36. exp Complex regional pain syndromes/
37. (complex adj3 region* adj3 pain*).tw.
38. CRPS.tw.
39. (sympathetic* adj3 dystroph*).tw.
40. (hand* adj3 shoulder* adj3 syndrom*).tw.
41. (sudek* adj3 atroph*).tw.
42. causalgi*.tw.
43. (neurogen* adj3 pain*).tw.
44. or/1-43
45. anticonvulsants/
46. (Anti convulsant* or anticonvulsant* or anti-convulsant* or anti epileptic* or antiepileptic* or anti-epileptic*).ti,ab.
47. Carbamazepine/
48. (Carbamazepine or Amizepin or Amizepine or Atretol or Biston or Calepsin or Carbamazepin or Carbategral or Carbatrol or Convuline or Epimax or Epitol or Equetro or Finlepsin or Lexin or Mazepine or Neurotol or Neurotop or Servimazepin or Sirtal or Tegral or Tegretal or Tegretol or Tegrital or Telesmin or Teril or Timonil).ti,ab.
49. (Oxcarbazepine or Apydan or Oxocarbamazepine or Oxocarbazepine or Timox or Trileptal).ti,ab.
50. (Gabapentin or Neurontin or Neurotonin).ti,ab.
51. (Pregabalin or Lyrica).ti,ab.
52. Phenytoin/
53. (Phenytoin or Alepsin or Aleviatin or Antilepsin or Antisacer or Cansoin or Citrullamon or Comital or Danten or Dantoin or Denyl or Difetoin or Differenin or Difhydan or Di Hydan or Dihydan or Dilantin or Dintoin or Dintoina or Diphantoin or Diphantoine or Diphantoin or Diphedal or Diphedan or Diphenin or Diphenine or Diphentoin or Diphenylan or Diphenytoin or Ekko or Epanutin or Epelin or Epilantin or Eptal or Eptoin or Fenantoin or Fenitoin or Fenytoin or Fenytoine or Hidantal or Hydantin or Hydantinal or Hydantoinal or Idantoin or Lepitoin or Minetoin or Neosidantoina or Phenhydan or Phenhydane or Phenybin or Phenydan or Phenydantin or Phenytoine or Phenytoin or Phenytoinum or Phenytonium or Sanepil or Sodantoin or Sodanton or Solantoin or Solantyl or Tacosal or Zentropil).ti,ab.
54. (Lamotrigine or Labileno or Lamictal).ti,ab.
55. Valproic acid/
56. (Sodium valproate or Alpha Propylvalerate or Alpha Propylvaleric Acid or Apilepsin or Convulex or Depacon or Depakene or Depakin or Depakine or Deprakine or Dipropylacetate or Dipropylacetatic Acid or Dipropyl Acetic Acid or Dipropylacetic Acid or Diprosin or Epilim or Ergenyl or Everiden or Goilim or Labazene or Leptilan or Leptilanil or Mylproin or Myproic Acid or Orfiril or Orlept or Propymal or Valerin or Valparin or Valpro or Valproate or Valproate Sodium or Vupral).ti,ab.
57. (Topiramate or Epitomax or Topamax or Topimax).ti,ab.
58. (lacosamide* or vimpat* or erlosamide* or harkoseride*).tw.
59. (levetiracetam* or keppra* or etiracetam*).tw.

60. or/45-59
61. exp Antidepressive Agents, Tricyclic/
62. tricyclic*.ti.
63. tetracyclic*.ti,ab.
64. (tricyclic* adj2 (antidepress* or drug*)).ti,ab.
65. (tricyclic* adj2 (antidepress* or agent*)).ti,ab.
66. (tricyclic* adj2 (antidepress* or med*)).ti,ab.
67. (tetracyclic* adj2 (antidepress* or drug*)).ti,ab.
68. (tetracyclic* adj2 (antidepress* or agent*)).ti,ab.
69. (tetracyclic* adj2 (antidepress* or med*)).ti,ab.
70. Amitriptyline/
71. (adepress or adepril or ambivalon or amitid or amitril or amitriptylene or amitriptylin* or amitryptiline or amitryptilline or amitryptine or amitryptyline or amytriptiline or amytriptyline or amytryptiline or antitriptyline or damilene or damylene or elatrol or elavil or endep or enovil or etafon or etafron or euplit or lantron or laroxal or laroxyl or lentizol or propheptadien redomex or sarboten or saroten* or sarotex or stelminal or sylvemid or teperin or terepin or triptanol or triptizol or triptyl* or triptyline or tryptanol or tryptizol).tw.
72. (triptafen or triptafen-M).tw.
73. Clomipramine/
74. (clomipramin* or anafranil or anafranilin or anafranyl or chlomipramine or chloroimipramine or domipramine or hydiphen or monochlor imipramine or monochlorimipramine or monochloroimipramine).tw.
75. Dothiepin/
76. (dothiepin or dosulepin* or altapin or depresym or idom or prothiaden* or prothiadiene or prothiadine or protiaden).tw.
77. Doxepin/
78. (doxepin* or adapin* or aponal or co dox or curatin or deptran or desidax or quitaxon or silenor or sinequan or sinquan* or zonalon or sinepin).tw.
79. Imipramine/
80. (imipramin* or antideprin or berkomin or chrytemin or deprinol or Ia pram or imavate or imidol or imipramide or imiprimin or imizin or janimine or melopramin* or norpramine or presamine or pryleugan or psychoforin* or servipromine or sk pramine or tofranil or trofranil).tw.
81. Lofepramine/
82. (lofepramine or gamanil or gamonil or amplit or lopramine or tymelyt or feprapax or lomont).tw.
83. Nortriptyline/
84. (nortriptylin* or acetexa or allegron or atilev or altilev or avantyl or aventyl or desitriptyline or desmethylamitriptyline or martimil or noramitriptyline or noritren or nortrilen* or nortryptilin* or nortryptyline or pamelor or paxtibi or psychostyl or sensaval).tw.
85. Trimipramine/
86. (trimipramine or herphonal or stangyl or trimepramine or trimiprimin* or trimepropimine or trimoprimine or surmontil).tw.
87. Citalopram/
88. (citalopram or celexa or cipramil or cytalopram or elopram or nitalapram or sepram or seropram).tw.

89. Fluoxetine/
90. (fluoxetine or fluctin* or flunirin or fluoxifar or lovan or prosac or prozac or prozamin or sarafem).tw.
91. Paroxetine/
92. (paroxetine or aropax or deroxat or dexorat or motivan or paxil or pexeva or tagonis or seroxat).tw.
93. Sertraline/
94. (sertraline or gladen or lustral or serad or serlain or tresleen or zoloft).tw.
95. (duloxetin* or cymbalta or ariclaim or xeristar or yentreve).tw.
96. (venlafaxine or effexor or efexor or trevilor).tw.
97. Desipramine/
98. (demethylimipramine or desipramine or desimipramine or desipramin or desmethyl imipramin or desmethylimipramin or desmethyl imipramine or desmethylimipramine or despiramine or dmi or norimipramine or norpramin or norpramine or nortimil or pentrofane or pertofran or pertofrane or pertofrin or pertrofran or petrofran or petrofrane or petylyl or sertofran).tw.
99. (Escitalopram* or Cipralex*or Lexapro*).tw.
100. Trazodone/
101. (Trazodone* or molipaxin* or Desyrel* or Oleptro* or Trialodine*).tw.
102. (Mirtazapine* or zispin* or soltab* or Remeron*).tw.
103. (reboxetine* or edronax*).tw.
104. or/61-103
105. Analgesics, Opioid/
106. (opioid adj3 analgesic*).tw.
107. opioids.tw.
108. Acetaminophen/
109. (acetaminophen or paracetamol or percogesic).tw.
110. 108 or 109
111. Codeine/
112. codeine.tw.
113. 111 or 112
114. 110 and 113
115. (co codamol or cocodamol or co-codamol or codipar or empracet or hypertussin K or hypertussin S or kapake or lindilane or medocodene or nedolon or panadeine or paracodal or solpadol or talvosilen or treuphadol or tylex).tw.
116. dihydrocodeine.tw.
117. 110 and 116
118. (codydramol or co-dydramol or co dydramol or codidramol or paramol).tw.
119. 105 or 106 or 107 or 114 or 115 or 117 or 118
120. Morphine/
121. (anpec or cis morphine or cyclimorph or duromorph or epimorph or microcrystalline morphine suspension or minijet or miro or morfin or morfine or morphgesic or morphin or morphine or morphia or morphinium or morphium or mst continus or mxl or opso or oramorph or sevredol or skenan or trans morphine or zomorph).tw.

122. dihydrocodeine.tw.
123. Oxycodone/
124. (bionine or bionone or bolodorm or broncodal or bucodal or cafacodal or cardanon or codenon or dihydrone or dihydrohydroxycodeinone or dihydrohydroxydodeinone or dinarkon or endone or eubine or eucodal or eucodale or eudin or eukdin or eukodal or eumorphal or eurodamine or eutagen or hydrocodal or hydroxycodeinoma or ludonal or medicodal or narcobasina or narcobasine or narcosin or nargenol or narodal or nucodan or opton or ossicodone or oxanest or oxicone or oxiconum or oxikon or oxycodeinonhydrochloride or oxycodone hydrochloride or oxycodonhydrochlorid or oxycodone or oxycodyl or oxycone or oxycontin or oxygesic or oxykon or oxynorm or pancodine or pavinal or pronarcin or remoxy or roxicodone or roxycodone or sinthiodal or stupenal or tebodal or tekodin or thecodin).tw.
125. Tramadol/
126. (contramal or dolzam or dromadol or kontram XL or larapam or mabron or melanate or nobligan or topalgic or tradorec XL or tramadol hydrochloride or tramadolium chloride or tramagit or tramake or tramal or tramundin or tramundin retard or trodon or trondon or ultram or zamadol or zydol).tw.
127. Buprenorphine/
128. (buprenorphine or buprenex or buprex or butrans or finibron or lepetan or subutex or temgesic or transtec).tw.
129. Fentanyl/
130. (actiq or duragesic or durogesic or fentamyl or fentanil or fentanyl or leptanal or matrifen or phentanyl or tilofyl or transfenta).tw.
131. (tapentadol* or palexia* or nucynta*).tw.
132. (targinact* or suboxone*)
133. or/119-132
134. phosphate.tw.
135. Phosphates/
136. 134 or 135
137. 114 and 136
138. (codein phosphate or codicompren retard or colrex compound or galcodine or kodein or tricodein or tussipect).tw.
139. 133 or 137 or 138
140. Lidocaine/
141. (Anestacon or Anestacone or Aritmal or Astracaine or Betacaine or Cidancaina or Corus or Dalcaine or Dolicaine or Duncaine or Esracain or Gravocain or Isicaine or Leostesin or Lida Mantle or Lidocain or Lidocaine or Lidocaton or Lidocor or Lidocorit or Lidoderm or Lidopain or Lidothesin or Lignocaine or Lignostab or Lincaine or Liquocaine or Maricaine or Neolidocaton or Novutox or Penles or Rucaina or Ruciana or Solcaine or Vasocaine or Versatis or Xidocaine or Xiline or Xilyne or Xylcaine or Xylestesin or Xylocain or Xylocaine or Xylocard or Xylocitin or Xyloneural or Xylonor or Xyloproct or Xyloton or Xylotox or Xylyne).ti,ab.
142. Capsaicin/
143. (Algrx or Axsain or Biozone or Capsaicine or Capsaicin or Capsicaine or Capsidol or Capsig or Captrix or Dolenon or Dolorac or Styptysat or Zostrix).ti,ab.

144. or/140-143
145. Flecainide/
146. (flecainide* or tambocor*).tw.
147. Serotonin 5-HT1 Receptor Agonists/
148. ((5ht1 or 5-ht1) adj3 (agonist* or block* or receptor*)).tw.
149. (almotriptan* or almogran* or axert*).tw.
150. (eletriptan* or relpax*).tw.
151. (frovatriptan* or migard* or frova*).tw.
152. (naratriptan* or naramig* or amerge*).tw.
153. (rizatriptan* or maxalt*).tw.
154. Sumatriptan/
155. (sumatriptan* or imigran* or imitrex or sumavel*).tw.
156. (zolmitriptan* or zomig*).tw.
157. (nabiximols* or sativex*).tw.
158. (cannab* adj3 extract*).tw.
159. or/145-158
160. 60 or 104 or 139 or 144 or 159
161. 44 and 160
162. Animals/ not Humans/
163. 160 not 162
164. Limit 162 to English language

Search filters to retrieve reports of randomised controlled trials and systematic reviews were appended to identify relevant evidence.

In addition search filters were also applied to separately identify economic evaluations and quality of life evidence. These searches were conducted between 23rd and 29th August 2012.

RCT and SR filters

1. Randomized Controlled Trial.pt.
2. Controlled Clinical Trial.pt.
3. Clinical Trial.pt.
4. exp Clinical Trials as Topic/
5. Placebos/
6. Random Allocation/
7. Double-Blind Method/
8. Single-Blind Method/
9. Cross-Over Studies/
10. ((random* or control* or clinical*) adj2 (trial* or stud*)).tw.
11. (random* adj2 allocat*).tw.
12. placebo*.tw.
13. ((singl* or doubl* or trebl* or tripl*) adj (blind* or mask*)).tw.
14. (crossover* or (cross adj over*)).tw.
15. or/1-15
16. Meta-Analysis.pt.
17. Meta-Analysis as Topic/

18. Review.pt.
19. exp Review Literature as Topic/
20. (metaanaly* or metanaly* or (meta adj2 analy*)).tw.
21. (review* or overview*).ti.
22. (systematic* adj4 (review* or overview*)).tw.
23. ((quantitative* or qualitative*) adj4 (review* or overview*)).tw.
24. ((studies or trial*) adj1 (review* or overview*)).tw.
25. (integrat* adj2 (research or review* or literature)).tw.
26. (pool* adj1 (analy* or data)).tw.
27. (handsearch* or (hand adj2 search*)).tw.
28. (manual* adj2 search*).tw.
29. or/16-28
30. 15 or 29

Economic filters

1. Economics/
2. exp "Costs and Cost Analysis"/
3. Economics, Dental/
4. exp Economics, Hospital/
5. exp Economics, Medical/
6. Economics, Nursing/
7. Economics, Pharmaceutical/
8. Budgets/
9. exp Models, Economic/
10. Markov Chains/
11. Monte Carlo Method/
12. Decision Trees/
13. econom*.tw.
14. cba.tw.
15. cea.tw.
16. cua.tw.
17. markov*.tw.
18. (monte adj carlo).tw.
19. (decision adj2 (tree* or analys*)).tw.
20. (cost or costs or costing* or costly or costed).tw.
21. (price* or pricing*).tw.
22. budget*.tw.
23. expenditure*.tw.
24. (value adj2 (money or monetary)).tw.
25. (pharmacoeconomic* or (pharmaco adj economic*)).tw.
26. or/1-25
27. "Quality of Life"/
28. quality of life.tw.
29. "Value of Life"/
30. Quality-Adjusted Life Years/
31. quality adjusted life.tw.
32. (qaly* or qald* or qale* or qtime*).tw.
33. disability adjusted life.tw.
34. daly*.tw.

35. Health Status Indicators/
36. (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or sortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw.
37. (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw.
38. (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw.
39. (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw.
40. (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw.
41. (euroqol or euro qol or eq5d or eq 5d).tw.
42. (qol or hql or hqol or hrqol).tw.
43. (hye or hyes).tw.
44. health* year* equivalent*.tw.
45. utilit*.tw.
46. (hui or hui1 or hui2 or hui3).tw.
47. disutili*.tw.
48. rosser.tw.
49. quality of wellbeing.tw.
50. quality of well-being.tw.
51. qwb.tw.
52. willingness to pay.tw.
53. standard gamble*.tw.
54. time trade off.tw.
55. time tradeoff.tw.
56. tto.tw.
57. or/26-56
58. 25 or 57

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Review questions and review protocols

List of key clinical issues and review questions

Key Clinical Issues	Review Questions
The following to manage neuropathic pain outside specialist pain management services: • The use of antidepressants, antiepileptics (anticonvulsants), opioid analgesics, flecainide, $5HT_1$-receptor agonists, topical lidocaine, and topical capsaisin as monotherapy. • The use of antidepressants, antiepileptics (anticonvulsants), opioid analgesics, cannabis sativa, flecainide, $5HT_1$-receptor agonists, topical lidocaine, and topical capsaisin as combination (or adjunct) therapy. • The positioning of the above pharmacological treatments as monotherapy and/or combination therapy within the care pathway.	c) What is the clinical effectiveness of different pharmacological treatments <u>as monotherapy</u> compared with each other or placebo for the management of neuropathic pain in adults, outside of specialist pain management services? d) What is the clinical effectiveness of different pharmacological treatments <u>as combination therapy</u> compared with other combination therapies, monotherapy or placebo for the management of neuropathic pain in adults, outside of specialist pain management services?

	Details	Additional comments	Status
Review question 1	What is the clinical effectiveness of different pharmacological treatments as monotherapy compared with each other or placebo for the management of neuropathic pain in adults, outside of specialist pain management services?		
Objectives	To review the clinical effectiveness of different pharmacological treatments as monotherapy compared with each other or placebo for the management of neuropathic pain conditions in adults, outside of specialist pain management services.		
Language	English only		
Study design	RCTs, systematic reviews **Exclusion:** RCTs with enriched enrolment or single-blind placebo run-in period	While enriched enrollment studies may help determine the true biological effect of a drug, they can reduce the generalisability of clinical trial results. This is because the patients being compared in the studies do not necessarily represent those who present in practice. Including these studies could potentially introduce bias into the review and the analysis.	After the review protocol was agreed, the GDG agreed to exclude studies with a single-blind placebo run-in period (where only patients with symptoms after this period were randomised); there are similar concerns about the generalisability of these studies to enriched enrolment studies.
Status	Full, published papers only		

Population	**Inclusion:** • Adults (aged ≥ 18 years old) with neuropathic pain managed in settings other than specialist pain management services. **Exclusion:** • Children and adolescents (aged < 18 years old) with neuropathic pain.	Neuropathic pain conditions or search terms to include in the search strategy: • Neuropathic pain • Neurogenic pain • Mixed neuropathic pain • Painful/Diabetic neuropathies • Postherpetic neuralgia • Trigeminal Neuralgia • Central pain • Facial Neuralgia • HIV-related neuropathy • Cancer pain • Postoperative pain • Phantom limb pain • Polyneuropathies • Nerve Compression Syndromes • Peripheral Nervous System Diseases • Spinal Cord Injuries • Post amputation pain • Post stroke pain • Multiple Sclerosis • Radiculopathy or radicular pain • Complex regional pain syndrome	After the review protocol was agreed, the GDG agreed to exclude atypical facial pain, burning mouth syndrome, and idiopathic pain as there is controversy about whether or not the pain is neuropathic. Studies on fibromyalgia were also excluded; studies on carpal tunnel syndrome were excluded if it was not clear if the pain was neuropathic.
Intervention	**Inclusion:** Drugs listed below as monotherapy: 1) Tricyclic antidepressants (TCAs): amitriptyline | doxepin | nortriptyline		

clomipramine	imipramine	trimipramine
dosulepin	lofepramine	

2) Selective serotonin reuptake inhibitors (SSRIs):

citalopram	fluoxetine	sertraline
escitalopram	paroxetine	

3) Other antidepressant drugs:

duloxetine	trazodone
mirtazapine	venlafaxine
reboxetine	

4) Antiepileptics (anticonvulsants):

carbamazepine	phenytoin	sodium valproate
oxcarbazepine	lacosamide	topiramate
gabapentin	lamotrigine	
pregabalin	levetiracetam	

5) Opioid analgesics:

co-codamol	oxycodone	buprenorphine
co-dydramol	oxycodone with naloxone	fentanyl
morphine	tapentadol	
dihydrocodeine	tramadol	

6) Additional drugs:

flecainide	topical lidocaine
5HT1-receptor agonists (almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, and zolmitriptan)	topical capsaicin

Exclusion:

- Treatments other than those listed above.

Comparator	Head-to-head comparisons of the individuals drugs listed above or compared with placebo/active placebo	For the possibility of providing indirect comparisons between the treatments of interest (for the network metaanalysis), we may consider including studies with additional comparators outside this decision dataset (ie. in the synthesis dataset).	
Outcomes	• Patient-reported pain relief/intensity reduction measured on any standard subjective scale such as: – Visual analogue scales (VAS), verbal rating scales (VRS), and numerical rating scales (NRS) (against baseline) – Proportion of patients who attained a particular level of global improvement or pain relief/intensity reduction (ie. 30% or 50% or greater from baseline) • Patient-reported global improvement. • Patient-reported improvement in daily physical and emotional functioning, including sleep. • Major adverse effects (defined as leading to withdrawal from treatment), and minor adverse effects (all adverse effects noted in patients' reports). *[based on the IMMPACT Recommendations, Dworkin et al. (2005)]* • Overall improvement in quality of life. • Treatment withdrawal • Use of rescue medication **Note:** a separate review of health economics and cost-effectiveness will include the following outcomes: • Resource use and costs.	Where appropriate or if sufficient data available, outcomes will be pooled by meta-analysis: • For 7-point scale of patient-reported global impression of change (PGIC), the top 2 categories (very much or much improved) were considered clinically significant. • Pain relief/reduction scales will be presented as continuous outcomes (mean difference) and dichotomized as 30% or 50% or greater as cut-off points (odds ratios). • For VASpi, VASpr, VRSpi, VRSpi, and NRS, the results will be reported in GRADE profiles. • Improvement of sleep (dichotomized as 'yes' or 'no') will be pooled as odds ratios if there is	PGIC – only data from studies reporting 7-point scales were extracted (as other scales could not be meaningfully synthesised with the 7-point scores). After the review protocol was agreed, the GDG agreed that it was okay to combine results from tools to a common scale for 10-point or 100-point scales. The GDG also agreed it was okay to combine 30% and 50% response rates from different studies, regardless of the tool used to measure this (ie.

		sufficient data. Adverse effects (leading to withdrawals and/or incidence rates) will be pooled as hazard ratios, if possible.(please also see 'review strategies' for synthesising different types of outcomes)	VAS, NRS, VRS). The GDG felt that the various tools for measuring physical and emotional functioning are quite different and it is inappropriate to combine results from any of these tools together into a standardised mean difference.
Other criteria for inclusion/exclusion of studies	**Inclusion:** • Only RCTs comply with the criteria stated in the above sections will be included. • Only studies with at least 4 weeks study period will be included. • For crossover studies, only studies with at least 1 week washout period, or with analysis of carry-over effects will be included. **Exclusion:** • Diagnosis and assessment of neuropathic pain. • Service delivery issues. • Studies on non-pharmacological treatment. • Treatment of the underlying causes of neuropathic pain and any associated disease-specific management. • Treatment of pain other than neuropathic pain. • Treatment of acute post-surgical pain • Studies on terminal pain, psychogenic pain, somatoform pain, musculoskeletal pain, but not neuropathic pain. • Studies on experimentally induced pain. • Pre-emptive/prevention analgesia studies (eg: pre-emptive analgesia studies on medical/surgical operations with 24-hour or 1 week post-operation as end-point).		Lidocaine and capsaicin spray were considered to act differently than other topic medications applied to the skin (ie. through the blood stream) so were excluded. Pre-emptive analgesia studies were later excluded all together, regardless of follow-up period as studies with the intention of prevention rather than treatment are quite different in

	• Single-dose rescue analgesic studies with follow-up less than 72 hours. • Studies on the treatment of spasticity or spasm (but not neuropathic pain) and that measure spasticity or spasm (but not neuropathic pain). • Concentration-response pharmacokinetic studies. • For antidepressants and anticonvulsants, administration of drugs through IV or epidural or topical application (but no restriction on the route of administration for opioid analgesics). • Lidocaine and capsaicin spray. • Open-label trials or not RCT • Studies with study sample < 10		nature and it would be inappropriate to synthesise these studies together.
Search strategies	RCTs, systematic reviews	No date restriction for drugs newly added to the scope. However, for drugs that were in the previous guidance, searches will be performed since the last search only. For the possibility of providing indirect comparisons between treatments of interest (for the network metaanalysis), we may consider performing another search later for additional comparators outside this decision dataset.	
Review strategies	• The NICE Methodology Checklist for Randomised Controlled Trials will be used as a guide to appraise the quality of individual studies. • Data on all included studies will be summarised in evidence tables. • All key outcomes from evidence will be presented in GRADE profiles and further summarized in evidence statements. • Where statistically possible, a meta-analytical approach will be used to give an overall summary effect (it is likely that network meta-analysis/meta-analyses will be performed).	The GDG agreed that the most appropriate presentation of the data is in three categories: central pain, peripheral pain and trigeminal neuralgia.	In order to minimize the time involved with extracting multiple time points, while maintaining the ability to compare studies at different time

	• To maximise the amount of study data that can be synthesised into an overall treatment effect, conversion of dichotomous measures into continuous measures will be explored (ie. converting odds ratios into standardised mean differences). • Outcomes will be extracted for multiple time points, starting from 4 weeks and for as many points afterwards to enable common time points of comparison between studies. • If possible, subgroup analysis will be undertaken on underlying causes of neuropathic pain.		points, an analysis of the available data was performed. Data was extracted at: • 4 weeks +/- 7 days • 8 weeks +/- 7 days • 12 weeks +/- 14 days • study endpoint (if not one of the above)
Identified key studies	Please see earlier version of this guideline. None known for 5Ht1-receptor agonists or other drugs newly added.		

1

2

	Details	**Additional comments**	**Status**
Review question 2	What is the clinical effectiveness of different pharmacological treatments as combination therapy compared with other combination therapies, monotherapy or placebo for the management of neuropathic pain in adults, outside of specialist pain management services?		
Objectives	To review the clinical effectiveness of different pharmacological treatments as combination therapy compared with other combination therapies, monotherapy or placebo for the management of neuropathic pain conditions		

	in adults, outside of specialist pain management services.		
Language	English only		
Study design	RCTs, systematic reviews **Exclusion:** RCTs with enriched enrolment or single-blind placebo run-in period	While enriched enrollment studies may help determine the true biological effect of a drug, they can reduce the generalisability of clinical trial results as the patients being compared in the studies do not necessarily represent those who present in practice. Including these studies could potentially introduce bias into the review and the analysis.	After the review protocol was agreed, the GDG agreed to exclude studies with a single-blind placebo run-in period (where only patients with symptoms after this period were randomised); there are similar concerns about the generalisability of these studies to enriched enrolment studies.
Status	Full, published papers only		
Population	**Inclusion:** • Adults (aged ≥ 18 years old) with neuropathic pain managed in settings other than specialist pain management services. **Exclusion:** • Children and adolescents (aged < 18 years old) with neuropathic pain.	Neuropathic pain conditions or search terms to include in the search strategy: • Neuropathic pain • Neurogenic pain • Mixed neuropathic pain • Painful/Diabetic neuropathies • Postherpetic neuralgia • Trigeminal Neuralgia	After the review protocol was agreed, the GDG agreed to exclude atypical facial pain, burning mouth syndrome, and idiopathic pain as there is controversy about whether or

<table>
<tr>
<td></td>
<td></td>
<td>• Central pain
• Facial Neuralgia
• HIV-related neuropathy
• Cancer pain
• Postoperative pain
• Phantom limb pain
• Polyneuropathies
• Nerve Compression Syndromes
• Peripheral Nervous System Diseases
• Spinal Cord Injuries
• Post amputation pain
• Post stroke pain
• Multiple Sclerosis
• Radiculopathy or radicular pain
• Complex regional pain syndrome</td>
<td>not the pain is neuropathic.

Studies on fibromyalgia were also excluded; studies on carpal tunnel syndrome were excluded if it was not clear if the pain was neuropathic.</td>
</tr>
<tr>
<td>Intervention</td>
<td><u>Inclusion:</u>
Drugs listed below as combination therapy:

1) Tricyclic antidepressants (TCAs):
<table>
<tr><td>amitriptyline</td><td>doxepin</td><td>nortriptyline</td></tr>
<tr><td>clomipramine</td><td>imipramine</td><td>trimipramine</td></tr>
<tr><td>dosulepin</td><td>lofepramine</td><td></td></tr>
</table>
2) Selective serotonin reuptake inhibitors (SSRIs):
<table>
<tr><td>citalopram</td><td>fluoxetine</td><td>sertraline</td></tr>
<tr><td>escitalopram</td><td>paroxetine</td><td></td></tr>
</table>
3) Other antidepressant drugs:
<table>
<tr><td>duloxetine</td><td>trazodone</td></tr>
<tr><td>mirtazapine</td><td>venlafaxine</td></tr>
</table></td>
<td></td>
<td>Sativex/ nabiximol was the primary cannabis extract considered. Dronabinol (a pure isomer of THC that is generated synthetically) and nabilone (a synthetic molecule) were not considered.</td>
</tr>
</table>

<table>
<tr>
<td></td>
<td>
<table>
<tr><td>reboxetine</td><td></td></tr>
</table>

4) Antiepileptics (anticonvulsants):
<table>
<tr><td>carbamazepine</td><td>phenytoin</td><td>sodium valproate</td></tr>
<tr><td>oxcarbazepine</td><td>lacosamide</td><td>topiramate</td></tr>
<tr><td>gabapentin</td><td>lamotrigine</td><td></td></tr>
<tr><td>pregabalin</td><td>levetriracetam</td><td></td></tr>
</table>

5) Opioid analgesics:
<table>
<tr><td>co-codamol</td><td>oxycodone</td><td>buprenorphine</td></tr>
<tr><td>co-dydramol</td><td>oxycodone with naloxone</td><td>fentanyl</td></tr>
<tr><td>morphine</td><td>tapentadol</td><td></td></tr>
<tr><td>dihydrocodeine</td><td>tramadol</td><td></td></tr>
</table>

6) Additional drugs:
<table>
<tr><td>Cannabis sativa extract</td><td>topical lidocaine</td></tr>
<tr><td>flecainide</td><td>topical capsaicin</td></tr>
<tr><td>5HT1-receptor agonists (almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, and zolmitriptan)</td><td></td></tr>
</table>

<u>Exclusion:</u>
Treatments other than those listed above.
</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Comparator</td>
<td>Other combination therapies, monotherapy or placebo/active placebo</td>
<td>For the possibility of providing indirect comparisons outside of the decision dataset (for the network metaanalysis), we may consider including studies with additional comparators outside the decision dataset (ie. in the synthesis dataset).</td>
<td></td>
</tr>
</table>

Outcomes	• Patient-reported pain relief/intensity reduction measured on any standard subjective scale such as:
	  – Visual analogue scales (VAS), verbal rating scales (VRS), and numerical rating scales (NRS) (against baseline)
	  – Proportion of patients who attained a particular level of global improvement or pain relief/intensity reduction (ie. 30% or 50% or greater from baseline)
	• Patient-reported global improvement.
	• Patient-reported improvement in daily physical and emotional functioning, including sleep.
	• Major adverse effects (defined as leading to withdrawal from treatment), and minor adverse effects (all adverse effects noted in patients' reports).
	[based on the IMMPACT Recommendations, Dworkin et al. (2005)]
	
	• Overall improvement in quality of life.
	• Treatment withdrawal
	• Use of rescue medication
	
	Note: a separate review of health economics and cost-effectiveness will include the following outcomes:
	• Resource use and costs.
		Where appropriate or if sufficient data available, outcomes will be pooled by meta-analysis:
		• For 7-point scale of patient-reported global impression of change (PGIC), the top 2 categories (very much or much improved) were considered clinically significant.
		• Pain relief/reduction scales will be presented as continuous outcomes (mean difference) and dichotomized as 30% or 50% or greater as cut-off points (odds ratios).
		• For VASpi, VASpr, VRSpi, VRSpi, and NRS, the results will be reported in GRADE profiles.
		• Improvement of sleep (dichotomized as 'yes' or 'no') will be pooled as odds ratios if there is sufficient data.
		Adverse effects (leading to withdrawals and/or incidence rates) will be pooled as hazard ratios, if possible. (please also see 'review strategies' for synthesising different types of outcomes)
			PGIC – only data from studies reporting 7-point scales were extracted (as other scales could not be meaningfully synthesised with the 7-point scores).
			
			After the review protocol was agreed, the GDG agreed that it was okay to combine results from tools to a common scale for 10-point or 100-point scales.
			
			The GDG also agreed it was okay to combine 30% and 50% response rates from different studies, regardless of the tool used to measure this (ie. VAS, NRS, VRS).
			
			The GDG felt that the various tools for measuring physical and emotional functioning are quite different and it is inappropriate to

			combine results from any of these tools together into a standardised mean difference.
Other criteria for inclusion/exclusion of studies	**Inclusion:** • Only RCTs comply with the criteria stated in the above sections will be included. • Only studies with at least 4 weeks study period will be included. • For crossover studies, only studies with at least 1 week washout period, or with analysis of carry-over effects will be included. **Exclusion:** • Diagnosis and assessment of neuropathic pain. • Service delivery issues. • Studies on non-pharmacological treatment. • Treatment of the underlying causes of neuropathic pain and any associated disease-specific management. • Treatment of pain other than neuropathic pain. • Treatment of acute post-surgical neuropathic pain • Studies on terminal pain, psychogenic pain, somatoform pain, musculoskeletal pain, but not neuropathic pain. • Studies on experimentally induced pain. • Pre-emptive/preventive analgesia studies with follow-up less than 4 weeks (eg: pre-emptive analgesia studies on medical/surgical operations with 24-hour or 1 week post-operation as end-point). • Single-dose rescue analgesic studies with follow-up less than 72 hours. • Studies on the treatment of spasticity or spasm (but not neuropathic pain) and that measure spasticity or spasm (but not neuropathic pain). • Concentration-response pharmacokinetic studies. • For antidepressants and anticonvulsants, administration of drugs through IV or epidural or topical application (but no restriction on the route of administration for opioid analgesics).		For cannabis extract, smoked cannabis was excluded. Lidocaine and capsaicin spray were considered to act differently than other topic medications applied to the skin (ie. through the blood stream) so were excluded. Pre-emptive analgesia studies were later excluded all together, regardless of follow-up period as studies with the intention of prevention rather than treatment are quite different in nature and it would be inappropriate to synthesise these

	• Smoked cannabis • Lidocaine and capsaicin spray. • Open-label trials or not RCT • Studies with study sample < 10		studies.
Search strategies	RCTs, systematic reviews	No date restriction for drugs newly added to the scope. However, for drugs that were in the previous guidance, searches will be performed since the last search only. For the possibility of providing indirect comparisons between the treatments of interest (for the network metaanalysis), we may consider performing another search later for additional comparators outside this decision dataset.	
Review strategies	• The NICE Methodology Checklist for Randomised Controlled Trials will be used as a guide to appraise the quality of individual studies. • Data on all included studies will be summarised in evidence tables. • All key outcomes from evidence will be presented in GRADE profiles and further summarized in evidence statements. • Where statistically possible, a meta-analytical approach will be used to give an overall summary effect (it is likely that network meta-analysis/meta-analyses will be performed). • To maximise the amount of study data that can be synthesised into an overall treatment effect, conversion of dichotomous measures into continuous measures will be explored (ie. converting odds ratios into standardised mean differences). • Outcomes will be extracted for multiple time points, starting from 4 weeks and for as many points afterwards to enable common time points of comparison between studies.	The GDG agreed that the most appropriate presentation of the data is in three categories: central pain, peripheral pain and trigeminal neuralgia.	In order to minimize the time involved with extracting multiple time points, while maintaining the ability to compare studies at different time points, an analysis of the available data was performed. Data was extracted at: • 4 weeks +/- 7 days

	• If possible, subgroup analysis will be undertaken on underlying causes of neuropathic pain.		• 8 weeks +/- 7 days • 12 weeks +/- 14 days study endpoint (if not one of the above)
Identified key studies	Please see earlier version of this guideline. For *cannabis sativa*: Nurmikko TJ, Serpell MG, Hoggart B, Toomey PJ, Morlion BJ, Haines D. Sativex successfully treats neuropathic pain characterised by allodynia: a randomised, double-blind, placebo-controlled clinical trial. Pain. 2007 Dec 15;133(1-3):210-20. Epub 2007 Nov 7. Rog DJ, Nurmikko TJ, Young CA. Randomized controlled study of cannabis-based medicine in central pain in multiple sclerosis. Neurology. 2005; 65:812-819. Berman JS, Symonds C, Birch R. Efficacy of two cannabis-based medicinal extracts for relief of central neuropathic pain from brachial plexus avulsion: results of a randomised controlled trial. Pain 2004;112: 299-306 Rog DJ. Nurmikko TJ, Young CA. Oromucosal delta-9-tetrahydrocannabinol and cannabidiol for neuropathic pain associated with multiple sclerosis;an uncontrolled, open-label 2 year extension trial. Clin Ther 2007;29:2068-2079. Johnson JR, Burnell-Nugent M, Lossignol D et al. Multi-center, double-blind, randomised, placebo-controlled, parallel group study of the efficacy, safety and tolerability of THC:CBD extract and THC extract in patients with intractable cancer pain. J Pain Sympt Management 2010; 39: 167-179 Portenoy RK, Ganae-Motan E, Allende S et al. Nabiximols for opioid treated canbcer patient with poorly controlled chronic pain: a randomised parallel group, graded-dose study. J Pain 2012; 13: 438-449. None known for 5Ht1-receptor agonists or other drugs newly added.		

Excluded studies (2013)

(please see last few pages for studies in existing guideline which are now excluded)

Excluded studies from updated and new searches

Abrams D.I., Jay C.A., Shade S.B., Vizoso H., Reda H., Press S., et al. Cannabis in painful HIV-associated sensory neuropathy: a randomized placebo-controlled trial. Neurology 2007;68(7):515-21. Exclude on intervention: administration other than oral for anti-depressants and anti-convulsants, other than topical lidocaine/capsaicin, or other than cannabis extract (ie. not smoked cannabis)

Achar A., Chakraborty P.P., Bisai S., Biswas A., Guharay T. Comparative study of clinical efficacy of amitriptyline and pregabalin in postherpetic neuralgia. Acta Dermatovenerologica Croatica 2012;20(2):89-94. Exclude on study design: 'enriched' or open-label RCT

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Deer T.R., Smith H.S., Burton W., Pope E., Doleys M., Levy R.M., et al. Comprehensive consensus based guidelines on intrathecal drug delivery systems in the treatment of pain caused by cancer pain. Pain Physician.14 (3) (pp E283-E312), 2011.Date of Publication: May/June 2011. 2011;(3):E283-3112. Exclude on study design: systematic review or meta-analysis that does not include all comparators or indications of interest, or includes comparators or indications that are not of interest

DeFrates Sean & Cook Aaron. Pharmacologic treatment of neuropathic pain following spinal cord injury. Orthopedics 2011;34(3):203-07. Exclude on study characteristics: narrative review, commentary, or editorial

"Del Pozo E., Pereira-Perez E., Gonzalez-Contreras L.G. The effectiveness of levetiracetam in the treatment of neuropathic pain OT - Eficacia del levetiracetam en el tratamiento del dolor neuropatico. Revista de Neurologia.53 (2) (pp 65-72), 2011.Date of Publication: July 2011. 2011;(2):65-72." Exclude on study characteristics: not English

Dellemijn PL, Vanneste JA (1997) Randomised double-blind active-placebo-controlled crossover trial of intravenous fentanyl in neuropathic pain. Lancet 349: 753-8. Exclude on intervention: Pre-emptive/prevention analgesia study with follow-up < 4 weeks.

Derry S., Moore R.A. Topical capsaicin (low-concentration) for chronic neuropathic pain in adults. Cochrane Database of Systematic Reviews 2012; (9):CD010111. Exclude on study design: systematic review or meta-analysis that does not include all comparators or indications of interest

Devers A, Galer BS (2000) Topical lidocaine patch relieves a variety of neuropathic pain conditions: an open-label study. Clinical Journal of Pain 16: 205-8. Exclude on study design: not RCT or SR of RCTs

Dharmshaktu P., Tayal V., Kalra B.S. Efficacy of antidepressants as analgesics: a review. [Review]. Journal of Clinical Pharmacology 2012;52(1):6-17. Exclude on study design: systematic review or meta-analysis that does not include all comparators or indications of interest, or includes comparators or indications that are not of interest

Dinat N, Hatta N (2010) A double blind randomised controlled crossover trial comparing amitriptyline and placebo for the treatment of moderate to severe hiv neuropathy. European Journal of Pain Supplements Conference: 3rd International Congress on Neuropathic Pain Athens Greece. Conference Start: 20100527 Conference End: 20100530. Conference: 3rd International Congress on Neuropathic Pain Athens Greece. Conference Start: 20100527

Conference End: 20100530. Conference Publication: 137-8. Exclude on study characteristics: not full-text publication (ie. conference abstract)

Dirks J, Fredensborg BB, Christensen D et al. (2002) A randomized study of the effects of single-dose gabapentin versus placebo on postoperative pain and morphine consumption after mastectomy.[see comment]. Anesthesiology 97: 560-4. Exclude on population: not NP (or something other than chronic postoperative surgical NP) or for underlying cause of NP

Dorfman D, Dalton A, Khan A et al. (1999) Treatment of painful distal sensory polyneuropathy in HIV-infected patients with a topical agent: results of an open-label trial of 5% lidocaine gel. AIDS 13: 1589-90. Exclude on study design: not RCT or SR of RCTs

Drake HF, Harries AJ, Gamester RE et al. (1990) Randomized double-blind study of topical capsaicin for treatment of post-herpetic neuralgia. Pain : S58. Exclude on study characteristics: not full-text publication (ie. conference abstract)

Drewes AM, Andreasen A, Poulsen LH (1994) Valproate for treatment of chronic central pain after spinal cord injury. A double-blind cross-over study. Paraplegia 32: 565-9. Exclude on study design: Study period less than 4 weeks.

Durand J.P., Deplanque G., Montheil V., Gornet J.M., Scotte F., Mir O., et al. Efficacy of venlafaxine for the prevention and relief of oxaliplatin-induced acute neurotoxicity: results of EFFOX, a randomized, double-blind, placebo-controlled phase III trial. Annals of Oncology 2012;23(1):200-05. Exclude on study characteristics: study length < 4 weeks

Dworkin R.H., O'Connor A.B., Audette J., Baron R., Gourlay G.K., Haanpaa M.L., et al. Recommendations for the pharmacological management of neuropathic pain: an overview and literature update. Mayo Clinic Proceedings 2010;85(3:Suppl):Suppl-14. Exclude on study characteristics: narrative review, commentary, or editorial

Dworkin RH, Turk DC, Peirce-Sandner S et al. (2010) Research design considerations for confirmatory chronic pain clinical trials: IMMPACT recommendations. Pain 149: 177-93. Exclude on study characteristics: narrative review, commentary, or editorial

Dworkin RH, Turk DC, Katz NP et al. (2011) Evidence-based clinical trial design for chronic pain pharmacotherapy: A blueprint for ACTION. Pain 152: S107-S115. Exclude on study characteristics: narrative review, commentary, or editorial

Dworkin RH, Barbano RL, Tyring SK et al. (2009) A randomized, placebo-controlled trial of oxycodone and of gabapentin for acute pain in herpes zoster. Pain 142: 209-17. Exclude on population: not NP (or something other than chronic postoperative surgical NP) or for underlying cause of NP

Eckmann M.S., Ramamurthy S., Griffin J.G. Intravenous regional ketorolac and lidocaine in the treatment of complex regional pain syndrome of the lower extremity: a randomized, double-blinded, crossover study. Clinical Journal of Pain 2011;27(3):203-06. Exclude on intervention: administration other than oral for anti-depressants and anti-convulsants &anti-convuls or other than topical lidocaine/capsaicin

Edelsberg J., Lord C., Oster G. Systematic review of data from randomized controlled trials on the efficacy, safety and tolerability of drugs used to treat painful diabetic neuropathy. Journal of Pain Management.4 (4) (pp 339-351), 2011.Date of Publication: 2011. 2011;(4):339-51. Administration exclusion: unable to obtain from British Library

Edelsberg J.S., Lord C., Oster G. Systematic review and meta-analysis of efficacy, safety, and tolerability data from randomized controlled trials of drugs used to treat postherpetic neuralgia. [Review]. Annals of Pharmacotherapy 2011;45(12):1483-90. Exclude on study design: systematic review or meta-analysis that does not include all comparators or indications of interest, or includes comparators or indications that are not of interest

Edelsberg J, Oster G (2009) Summary measures of number needed to treat: How much clinical guidance do they provide in neuropathic pain? European Journal of Pain 13: 11-6. Exclude on study characteristics: narrative review, commentary, or editorial

Edwards KR, Hes MS, LaMoreaux LK et al. (1998) Gabapentin (Neurontin) for pain associated with diabetic peripheral neuropathy: a double-blind, placebo-controlled study (945-210) [abstract]. Neurology 50: A378-A379. Exclude on study characteristics: not full-text publication (ie. conference abstract)

Eide PK, Jorum E, Stubhaug A et al. (1994) Relief of post-herpetic neuralgia with the N-methyl-D-aspartic acid receptor antagonist ketamine: a double-blind, cross-over comparison with morphine and placebo. Pain 58: 347-54. Exclude on intervention: Pre-emptive/prevention analgesia study with follow-up < 4 weeks

Elkaradawy S., Nasr M., Elkerm Y., Deeb M.E., Yassine O. The effect of multimodal balanced anaesthesia and long term gabapentin on neuropathic pain, nitric oxide and interleukin-1beta following breast surgery. Egyptian Journal of Anaesthesia.28 (1) (pp 67-78), 2012.Date of Publication: January 2012. 2012;(1):67-78. Exclude on study design: not all patients in the treatment group had the drug of interest

Ellemann K, Sjögren P, Banning AM et al. (1989) Trial of intravenous lidocaine on painful neuropathy in cancer patients. The Clinical journal of pain 5: 291-4. Exclude on intervention: administration other than oral for anti-depressants & anti-convulsants or other than topical lidocaine/capsaicin

Ellison N, Loprinzi CL, Kugler J et al. (1997) Phase III placebo-controlled trial of capsaicin cream in the management of surgical neuropathic pain in cancer patients. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 15: 2974-80. Exclude on study design: Crossover study with no washout and analysis of carry over effects showed significant results.

Enggaard TP, Poulsen L, Arendt-Nielsen L et al. (2001) The analgesic effect of codeine as compared to imipramine in different human experimental pain

models. Pain 92: 277-82. Exclude on population: not NP (or something other than chronic postoperative surgical NP) or for underlying cause of NP

Enggaard TP, Klitgaard NA, Gram LF et al. (2001) Specific effect of venlafaxine on single and repetitive experimental painful stimuli in humans. Clinical Pharmacology & Therapeutics 69: 245-51. Exclude on population: not NP (or something other than chronic postoperative surgical NP) or for underlying cause of NP

Erdogan C., cel M., Akg++n H., Kask+õ T., Semai Bek V., õil Z. Effects of topiramate on peripheral nerve excitability. Journal of Clinical Neurophysiology 2012;29(3):268-70. Exclude on study design: not RCT or SR of RCTs

Eriksen J.R. Pain and convalescence following laparoscopic ventral hernia repair. Danish Medical Bulletin 2011;58(12):B4369. Exclude on population: not NP (or something other than chronic postoperative surgical NP) or for underlying cause of NP

Evers S., Afra J., Frese A., Goadsby P.J., Linde M., May A., Sandor P.S. EFNS guideline on the drug treatment of migraine - Revised report of an EFNS task force. European Journal of Neurology.16 (9) (pp 968-981), 2009.Date of Publication: September 2009. 2009;(9):968-81. Exclude on study characteristics: narrative review, commentary, or editorial

Falah M., Madsen C., Holbech J.V., Sindrup S.H. A randomized, placebo-controlled trial of levetiracetam in central pain in multiple sclerosis. European Journal of Pain 2012;16(6):860-69. Administration exclusion: unable to obtain from British Library

Farlow M.R. & Somogyi M. Transdermal patches for the treatment of neurologic conditions in elderly patients: A review. Primary Care Companion to the Journal of Clinical Psychiatry.13 (6) , 2011.Date of Publication: 2011. 2011;(6):n. pag. Exclude on study design: systematic review or meta-analysis that does not include all comparators or indications of interest, or includes comparators or indications that are not of interest

Farrar J.T., Messina J., Xie F., Portenoy R.K. A Novel 12-Week Study, with Three Randomized, Double-Blind Placebo-Controlled Periods to Evaluate Fentanyl Buccal Tablets for the Relief of Breakthrough Pain in Opioid-Tolerant Patients with Noncancer-Related Chronic Pain. Pain Medicine.11 (9) (pp 1313-1327), 2010.Date of Publication: September 2010. 2010;(9):1313-27. Exclude on study population: mixed neuropathic and non-neuropathic pain (or likely to include a mix of both)

Fassoulaki A, Patris K, Sarantopoulos C et al. (2002) The analgesic effect of gabapentin and mexiletine after breast surgery for cancer. Anesthesia and Analgesia 95: 985-91. Exclude on population: not NP (or something other than chronic postoperative surgical NP) or for underlying cause of NP

Fassoulaki A., Sarantopoulos C., Melemeni A., Hogan Q. EMLA reduces acute and chronic pain after breast surgery for cancer. Regional Anesthesia and Pain Medicine.25 (4) (pp 350-355), 2000.Date of Publication: July 2000. 2000;(4):350-55. Exclude on intervention: not drug of interest / non-pharmacological treatment

Ferrell B, Wisdom C, Wenzl C et al. (1989) Effects of controlled-released morphine on quality of life for cancer pain. Oncology Nursing Forum 16: 521-6. Exclude on intervention: Compared controlled-release morphine with short-acting morphine.

Fidman B. & Nogid A. Role of tapentadol immediate release (nucynta) in the management of moderate-to-severe pain. P and T.35 (6) (pp 330-333+357), 2010.Date of Publication: June 2010. 2010;(6):330-3+35757. Exclude on study characteristics: narrative review, commentary, or editorial

Finnerup N.B. Is duloxetine useful for central neuropathic pain? Pain.152 (2) (pp 243-244), 2011.Date of Publication: February 2011. 2011;(2):243-44. Exclude on study characteristics: narrative review, commentary, or editorial

Finnerup N.B., Sindrup S.H., Jensen T.S. The evidence for pharmacological treatment of neuropathic pain. Pain.150 (3) (pp 573-581), 2010.Date of Publication: September 2010. 2010;(3):573-81. Exclude on study design:

systematic review or meta-analysis that does not include all comparators or indications of interest, or includes comparators or indications that are not of interest

Finnerup NB, Biering-S+©rensen F, Johannesen IL et al. (2005) Intravenous lidocaine relieves spinal cord injury pain: a randomized controlled trial. Anesthesiology 102: 1023-30. Exclude on intervention: administration other than oral for anti-depressants & anti-convulsants or other than topical lidocaine/capsaicin

Fishbain DA, Lewis JE, Cole B et al. (2006) Lidocaine 5% patch: an open-label naturalistic chronic pain treatment trial and prediction of response. Pain Medicine 7: 135-42. Exclude on study design: not RCT or SR of RCTs

Fishbain D., Berman K., Kajdasz D.K. Erratum: Duloxetine for neuropathic pain based on recent clinical trials (Current Pain and Headache Reports (2006) 10:3 (199-204) DOI: 10.1007/s11916-006-0046-7). Current Pain and Headache Reports.15 (5) (pp 333), 2011.Date of Publication: October 2011. 2011;(5):333. Exclude on study characteristics: narrative review, commentary, or editorial

Forssell H, Tasmuth T, Tenovuo O et al. (2004) Venlafaxine in the treatment of atypical facial pain: a randomized controlled trial. Journal of Orofacial Pain 18: 131–7. Exclude on population: not NP (or something other than chronic postoperative surgical NP) or for underlying cause of NP

Frampton J.E. Tapentadol immediate release: a review of its use in the treatment of moderate to severe acute pain. [Review]. Drugs 2010;70(13):1719-43. Exclude on population: not NP (or something other than chronic postoperative surgical pain) or treating the underlying cause of NP

Freeman R, Raskin P, Hewitt DJ et al. (2007) Randomized study of tramadol/acetaminophen versus placebo in painful diabetic peripheral neuropathy. Current Medical Research & Opinion 23: 147-61. Exclude on intervention: combination treatment includes drugs not in scope

Friedman B.W., Solorzano C., Esses D., Xia S., Hochberg M., Dua N., et al. Treating headache recurrence after emergency department discharge: a randomized controlled trial of naproxen versus sumatriptan. Annals of Emergency Medicine 2010;56(1):7-18. Exclude on study characteristics: study length < 4 weeks

Furlan A.D., Sandoval J.A., Mailis-Gagnon A., Tunks E. Opioids for chronic noncancer pain: A meta-analysis of effectiveness and side effects. CMAJ.174 (11) (pp 1589-1594), 2006.Date of Publication: 23 May 2006. 2006;(11):1589-94. Exclude on study design: systematic review or meta-analysis that does not include all comparators or indications of interest, or includes comparators or indications that are not of interest

Fusco B.M., Marabini S., Maggi C.A., Fiore G., Geppetti P. Preventative effect of repeated nasal applications of capsaicin in cluster headache. Pain.59 (3) (pp 321-325), 1994.Date of Publication: 1994. 1994;(3):321-25. Exclude on study design: not RCT or SR of RCTs

Galer BS, Rowbotham MC, Perander J et al. (1999) Topical lidocaine patch relieves postherpetic neuralgia more effectively than a vehicle topical patch: results of an enriched enrollment study. Pain 80: 533-8. Exclude on study design: 'enriched' or open-label RCT

Garrett W.E., Kaeding C.C., ElAttrache N.S., Xerogeanes J.W., Hewitt M.S., Skrepnik N.V., et al. Novel drug OMS103HP reduces pain and improves joint motion and function for 90 days after arthroscopic meniscectomy. Arthroscopy 2011;27(8):1060-70. Exclude on intervention: not drug of interest / non-pharmacological treatment

Gatoulis S.C., Voelker M., Fisher M. Assessment of the efficacy and safety profiles of aspirin and acetaminophen with codeine: results from 2 randomized, controlled trials in individuals with tension-type headache and postoperative dental pain. Clinical Therapeutics 2012;34(1):138-48. Exclude on population: not NP (or something other than chronic postoperative surgical NP) or for underlying cause of NP

"Gaul C., Diener H.-C., Muller O.M. Cluster headache: Clinical features and therapeutic options. [German, English] OT - Clusterkopfschmerz: Klinisches bild und therapeutische optionen. Deutsches Arzteblatt.108 (33) (pp 543-549), 2011.Date of Publication: 19 Aug 2011. 2011;(33):543-49." Exclude on population: not NP (or something other than chronic postoperative surgical NP) or for underlying cause of NP

Gaynor P., McCarberg B., Zheng W., Shoemaker S., Duenas H. Weight change with long-term duloxetine use in chronic painful conditions: an analysis of 16 clinical studies. [Review]. International Journal of Clinical Practice 2011;65(3):341-49. Exclude on study design: not RCT or SR of RCTs

Geraud G., Compagnon A., Rossi A. Zolmitriptan versus a combination of acetylsalicylic acid and metoclopramide in the acute oral treatment of migraine: a double-blind, randomised, three-attack study. Headache: The Journal of Head & Face Pain 2003;43(3):299-301. Exclude on study characteristics: not full-text publication (ie. conference abstract)

Gerson GR, Jones RB, Luscombe DK (1977) Studies on the concomitant use of carbamazepine and clomipramine for the relief of post-herpetic neuralgia. Postgraduate Medical Journal 53: Suppl-9. Exclude as inappropriate/unclear comparator: Control group included the use of trancutaneous electrical nerve stimulation (TEN).

Gill D., Derry S., Wiffen P.J., Moore R.A. Valproic acid and sodium valproate for neuropathic pain and fibromyalgia in adults. [Review]. Cochrane Database of Systematic Reviews 2011;(10):CD009183. Exclude on population: includes patients without neuropathic pain

Gilron I, Bailey JM, Tu D et al. (2005) Morphine, gabapentin, or their combination for neuropathic pain.[see comment]. New England Journal of Medicine 352: 1324-34. Exclude on study design: Crossover study, author reported significant carry over effects.

Gilron I, Booher SL, Rowan JS et al. (2001) Topiramate in trigeminal neuralgia: a randomized, placebo-controlled multiple crossover pilot study.

Clinical Neuropharmacology 24: 109-12. Exclude on study characteristics: study size < 10

Gilron I, Bailey JM, Tu D et al. (2005) Morphine, gabapentin, or their combination for neuropathic pain. New England Journal of Medicine 352: 1324-34. Exclude on study design: Crossover study, author reported analysis of significant carry over effect.

Gilron I, Orr E, Tu D et al. (2005) A placebo-controlled randomized clinical trial of perioperative administration of gabapentin, rofecoxib and their combination for spontaneous and movement-evoked pain after abdominal hysterectomy. [see comment]. Pain 113: 191-200. Exclude on population: not NP (or something other than chronic postoperative surgical NP) or for underlying cause of NP

Gilron I, Wajsbrot D, Therrien F et al. (2011) Pregabalin for peripheral neuropathic pain: a multicenter, enriched enrollment randomized withdrawal placebo-controlled trial. Clinical Journal of Pain 27: 185-93. Exclude on study design: 'enriched' or open-label RCT

Gobel H, Stadler T (1995) Treatment of pain due to postherpetic neuralgia with tramadol - Results of an open, parallel pilot study vs clomipramine with or without levomepromazine. Clinical Drug Investigation 10: 208-14. Exclude on study characteristics: not English

Gobel H, Stadler T (1997) [Treatment of post-herpes zoster pain with tramadol. Results of an open pilot study versus clomipramine with or without levomepromazine]. [French]. Drugs 53: Suppl-9. Exclude on study characteristics: not English

Goebel A, Lawson A, Allen S et al. (2008) Buprenorphine injection to the stellate ganglion in the treatment of upper body chronic pain syndromes. European Journal of Pain: Ejp 12: 266-74. Exclude on study population: mixed neuropathic and non-neuropathic pain (or likely to include a mix of both)

Goebel A. Morphine and Memantine Treatment of Long-Standing Complex Regional Pain Syndrome. Pain Medicine.13 (3) (pp 357-358), 2012.Date of Publication: March 2012. 2012;(3):357-58. Exclude on study characteristics: narrative review, commentary, or editorial

Gomez-Perez FJ, Rull JA, Dies H et al. (1985) Nortriptyline and fluphenazine in the symptomatic treatment of diabetic neuropathy. A double-blind cross-over study. Pain 23: 395-400. Exclude on intervention: combination treatment includes drugs not in scope (fluphenazine was added to nortriptyline).

Gordon NC, Heller PH, Gear RW et al. (1994) Interactions between fluoxetine and opiate analgesia for postoperative dental pain. Pain 58: 85-8. Exclude on intervention: Pre-emptive/prevention analgesia study with follow-up < 4 weeks

Gorson KC, Schott C, Herman R et al. (1999) Gabapentin in the treatment of painful diabetic neuropathy: a placebo controlled, double blind, crossover trial. Journal of neurology, neurosurgery, and psychiatry 66: 251-2. Exclude on study quality: Author reported washout as inadequate.

Gray P., Kirby J., Smith M.T., Cabot P.J., Williams B., Doecke J., Cramond T. Pregabalin in severe burn injury pain: a double-blind, randomised placebo-controlled trial. Pain 2011;152(6):1279-88. Exclude on population: not NP (or something other than chronic postoperative surgical NP) or for underlying cause of NP

Gribble L, Gouni R, Eriksson M et al. (2010) A double-blind randomised study comparing the effects of pregabalin, duloxetine and amitryptiline on aspects of neuropathic pain, mood and sleep in diabetic subjects with painful neuropathy. Diabetologia Conference: 46th Annual Meeting of the European Association for the Study of Diabetes, EASD 2010 Stockholm Sweden. Conference Start: 20100920 Conference End: 20100924. Conference: 46th Annual Meeting of the European Association for the Study of Diabetes, EASD 2010 Stockholm Sweden. Conference Start: 20100920 Conference End: 20100924.

Conference Publication: S16-S17. Exclude on study characteristics: not full-text publication (ie. conference abstract)

Grotenhermen F. Cannabinoids do not reduce objective measurements in muscle spasticity, but people with multiple sclerosis perceive some benefit. Evidence-Based Healthcare.8 (3) (pp 159-161), 2004.Date of Publication: June 2004. 2004;(3):159-61. Exclude on study characteristics: narrative review, commentary, or editorial

Guay D.R. Oxcarbazepine, topiramate, zonisamide, and levetiracetam: potential use in neuropathic pain. American Journal of Geriatric Pharmacotherapy 2003;1(1):18-37. Exclude on study design: systematic review or meta-analysis that does not include all comparators or indications of interest, or includes comparators or indications that are not of interest

Gutierrez T. & Hohmann A.G. Cannabinoids for the treatment of neuropathic pain: Are they safe and effective? Future Neurology.6 (2) (pp 129-133), 2011.Date of Publication: March 2011. 2011;(2):129-33. Exclude on study characteristics: narrative review, commentary, or editorial

Hagen N.A., Thirlwell M., Eisenhoffer J., Quigley P., Harsanyi Z., Darke A. Efficacy, safety, and steady-state pharmacokinetics of once-a-day controlled-release morphine (MS Contin XL) in cancer pain. Journal of Pain and Symptom Management.29 (1) (pp 80-90), 2005.Date of Publication: January 2005. 2005;(1):80-90. Exclude on study characteristics: study length < 4 weeks

Hall S. Adjuvant analgesics in pain management. Nurse Prescribing 2010;8(3):122-29. Exclude on study characteristics: narrative review, commentary, or editorial

Hansen M.S., Mathiesen O., Trautner S., Dahl J.B. Intranasal fentanyl in the treatment of acute pain - a systematic review. Acta Anaesthesiologica Scandinavica 2012;56(4):407-19. Exclude on population: not NP (or something other than chronic postoperative surgical NP) or for underlying cause of NP

Hanu-Cernat Dalvina, Phipps Alex, Raphael Jon. Pregabalin Assay in a Patient with Widespread Neuropathic Pain and Late Onset Gluten Intolerance. Pain Medicine 2011;12(8):1262-66. Exclude on study design: not RCT or SR of RCTs

Harati Y, Gooch C, Swenson M et al. (2000) Maintenance of the long-term effectiveness of tramadol in treatment of the pain of diabetic neuropathy. Journal of Diabetes & its Complications 14: 65-70. Exclude on study design: not RCT or SR of RCTs

Harke H, Gretenkort P, Ladleif HU et al. (2001) The response of neuropathic pain and pain in complex regional pain syndrome I to carbamazepine and sustained-release morphine in patients pretreated with spinal cord stimulation: a double-blinded randomized study. Anesthesia & Analgesia 92: 488-95. Exclude on intervention: Some participants from the study sample also received spinal cord stimulation treatment.

Harris J.A. & Murphy J.A. Lacosamide: an adjunctive agent for partial-onset seizures and potential therapy for neuropathic pain. Annals of Pharmacotherapy 2009;43(11):1809-17. Exclude on study design: systematic review or meta-analysis that does not include all comparators or indications of interest, or includes comparators or indications that are not of interest

Harrison S.D., Balawi S.A., Feinmann C., Harris M. Atypical facial pain: a double-blind placebo-controlled crossover pilot study of subcutaneous sumatriptan. European Neuropsychopharmacology 1997;7(2):83-88. Exclude on study characteristics: study length < 4 weeks

Hayton T., Furby J., Smith K.J., Altmann D.R., Brenner R., Chataway J., et al. Longitudinal changes in magnetisation transfer ratio in secondary progressive multiple sclerosis: data from a randomised placebo controlled trial of lamotrigine. Journal of Neurology 2012;259(3):505-14. Exclude on population: not NP (or something other than chronic postoperative surgical NP) or for underlying cause of NP

Hearn L., Derry S., Moore R.A. Lacosamide for neuropathic pain and fibromyalgia in adults. [Review]. Cochrane Database of Systematic Reviews 2012;2:CD009318. Exclude on population: includes patients without neuropathic pain

Heiskanen TE, Ruismaki PM, Seppala TA et al. (2000) Morphine or oxycodone in cancer pain? Acta Oncologica 39: 941-7. Exclude on study characteristics: study size < 10 (Only 4 participants had neuropathic pain).

Hempenstall K., Nurmikko T.J., Johnson R.W., A'Hern R.P., Rice A.S. Analgesic therapy in postherpetic neuralgia: a quantitative systematic review. PLoS Medicine / Public Library of Science 2005;2(7):e164. Exclude on study design: systematic review or meta-analysis that does not include all comparators or indications of interest, or includes comparators or indications that are not of interest

Herrmann DN, Barbano RL, Hart-Gouleau S et al. (2005) An open-label study of the lidocaine patch 5% in painful idiopathic sensory polyneuropathy. Pain Medicine 6: 379-84. Exclude on study design: not RCT or SR of RCTs

Hewitt DJ, Ho TW, Galer B et al. (2011) Impact of responder definition on the enriched enrollment randomized withdrawal trial design for establishing proof of concept in neuropathic pain. Pain 152: 514-21.Hill CM, Balkenohl M, Thomas DW et al. (2001) Pregabalin in patients with postoperative dental pain. European Journal of Pain 5: 119-24. Exclude on study characteristics: narrative review, commentary, or editorial

Hota D (2009) Randomized double-blind study comparing the efficacy and safety of amitriptyline vs. pregabalin in painful diabetic neuropathy in indian patients: Preliminary report. Basic and Clinical Pharmacology and Toxicology Conference: 9th Congress of the European Association for Clinical Pharmacology and Therapeutics Edinburgh United Kingdom. Conference Start: 20090712 Conference End: 20090715. Conference: 9th Congress of the European Association for Clinical Pharmacology and Therapeutics Edinburgh United Kingdom. Conference Start: 20090712 Conference End: 20090715.

Conference Publication: 63. Exclude on study characteristics: not full-text publication (ie. conference abstract)

Hota D, Jose V, Bhannsali A et al. (2009) Randomized double-blind clinical trial comparing efficacy and safety of lamotrigine vs. amitriptyline in painful diabetic neuropathy. Pain Practice Conference: 5th World Congress - World Institute of Pain. Conference: 5th World Congress - World Institute of Pain. Conference Publication: 39.Huot M-P, Chouinard P, Girard F et al. (2008) Gabapentin does not reduce post-thoracotomy shoulder pain: A randomized, double-blind placebo-controlled study. Canadian Journal of Anesthesia 55: 337-43. Exclude on study characteristics: not full-text publication (ie. conference abstract)

Hota D, Jose V, Bhannsali A et al. (2009) Randomized double-blind clinical trial comparing efficacy and safety of lamotrigine vs. amitriptyline in painful diabetic neuropathy. Pain Practice Conference: 5th World Congress - World Institute of Pain. Conference: 5th World Congress - World Institute of Pain. Conference Publication: 39. Exclude on study characteristics: not full-text publication (ie. conference abstract)

Hota D, Kaur H, Bansal D et al. (2010) Randomised double-blind clinical trial comparing efficacy and safety of duloxetine vs. amitriptyline in painful diabetic neuropathy. European Journal of Pain Supplements Conference: 3rd International Congress on Neuropathic Pain Athens Greece. Conference Start: 20100527 Conference End: 20100530. Conference: 3rd International Congress on Neuropathic Pain Athens Greece. Conference Start: 20100527 Conference End: 20100530. Conference Publication: 82. Exclude on study characteristics: not full-text publication (ie. conference abstract)

Hoy S.M. Tapentadol extended release: in adults with chronic pain. [Review]. Drugs 2012;72(3):375-93. Exclude on study design: systematic review or meta-analysis that does not include all comparators or indications of interest, or includes comparators or indications that are not of interest

Hui A.C., Wong S.M., Leung H.W., Man B.L., Yu E., Wong L.K. Gabapentin for the treatment of carpal tunnel syndrome: a randomized controlled trial.

European Journal of Neurology 2011;18(5):726-30. Exclude on population: not NP (or something other than chronic postoperative surgical NP) or for underlying cause of NP

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Mariconti P, Collini R (2008) Tramadol SR in arthrosic and neuropathic pain.[see comment]. Minerva Anestesiologica 74: 63-8. Exclude on study design: not RCT or SR of RCTs

Martin C, Martin A, Rud C et al. (1988) [Comparative study of sodium valproate and ketoprofen in the treatment of postoperative pain]. Annales françaises d'anesthèsie et de rèanimation 7: 387-92. Exclude on intervention: administration other than oral for anti-depressants & anti-convulsants or other than topical lidocaine/capsaicin

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Metry A, Ishak S, Khattab A (2008) Does gabapentin have preemptive effects in women undergoing mastectomy?. [Italian, English]. Acta Anaesthesiologica Italica / Anaesthesia and Intensive Care in Italy 59: 62-76. Exclude on population: not NP (or something other than chronic postoperative surgical NP) or for underlying cause of NP

Mick G. & Correa-Illanes G. Topical pain management with the 5% lidocaine medicated plaster - a review. Current Medical Research & Opinion 2012;28(6):937-51. Exclude on study design: systematic review or meta-analysis that does not include all comparators or indications of interest, or includes comparators or indications that are not of interest

Mikami K., Jorge R.E., Adams H.P. Jr., Davis P.H., Leira E.C., Jang M., Robinson R.G. Effect of antidepressants on the course of disability following

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Morlion B. Pharmacotherapy of low back pain: targeting nociceptive and neuropathic pain components. [Review]. Current Medical Research & Opinion 2011;27(1):11-33. Exclude on study design: systematic review or meta-analysis that does not include all comparators or indications of interest, or includes comparators or indications that are not of interest

Mucci-LoRusso P, Berman BS, Silberstein PT et al. (1998) Controlled-release oxycodone compared with controlled-release morphine in the treatment of cancer pain: A randomized, double-blind, parallel-group study. European Journal of Pain 2: 239-49. Exclude on study population: mixed neuropathic and non-neuropathic pain (or likely to include a mix of both)

Mueller ME, Gruenthal M, Olson WL et al. (1997) Gabapentin for relief of upper motor neuron symptoms in multiple sclerosis. Archives of Physical

Medicine & Rehabilitation 78: 521-4. Exclude on study design: Study period less than 4 weeks.

Murphy T.P., Byrne D.P., Curtin P., Baker J.F., Mulhall K.J. Can a periarticular levobupivacaine injection reduce postoperative opiate consumption during primary hip arthroplasty? Clinical Orthopaedics & Related Research 2012;470(4):1151-57. Exclude on population: not NP (or something other than chronic postoperative surgical NP) or for underlying cause of NP

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Mystakidou K, Parpa E, Tsilika E et al. (2003) Long-term management of noncancer pain with transdermal therapeutic system-fentanyl. Journal of Pain 4: 298-306. Exclude on study design: not RCT or SR of RCTs

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Nalamachu S., Crockett R.S., Gammaitoni A.R., Gould E.M. A comparison of the lidocaine patch 5% vs naproxen 500 mg twice daily for the relief of pain associated with carpal tunnel syndrome: A 6-week, randomized, parallel-group study. MedGenMed Medscape General Medicine.8 (3) , 2006.Date of Publication: 2006. 2006;(3):n. pag. Exclude on intervention: not drug of interest / non-pharmacological treatment

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mixed neuropathic and non-neuropathic pain (or likely to include a mix of both)

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Otto M, Bach FW, Jensen TS et al. (2004) Valproic acid has no effect on pain in polyneuropathy: a randomized, controlled trial. Neurology 62: 285-8. Exclude on study design: Crossover study with no washout, and no analysis of carry over effect.

Palangio M., Damask M.J., Morris E., Doyle Jr, Jiang J.G., Landau C.J., De Padova A. Combination hydrocodone and ibuprofen versus combination codeine and acetaminophen for the treatment of chronic pain. Clinical Therapeutics.22 (7) (pp 879-892), 2000.Date of Publication: 2000. 2000;(7):879-92. Exclude on intervention: combination treatment includes drugs not in scope

Pandey CK, Bose N, Garg G et al. (2002) Gabapentin for the treatment of pain in Guillain-Barre syndrome: A double-blinded, placebo-controlled, crossover study. Anesthesia and Analgesia 95: 1719-23. Exclude on population: not NP (or something other than chronic postoperative surgical NP) or for underlying cause of NP

Panerai AE, Monza G, Movilia P et al. (1990) A randomized, within-patient, cross-over, placebo-controlled trial on the efficacy and tolerability of the tricyclic antidepressants chlorimipramine and nortriptyline in central pain.[see

comment]. Acta Neurologica Scandinavica 82: 34-8. Exclude on study design: Study period less than 4 weeks.

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Turkington RW (1980) Depression masquerading as diabetic neuropathy. JAMA 243: 1147-50. Exclude on outcome: No measurement of pain, primary outcome is treatment for depression.

Uceyler N., Offenbacher M., Petzke F., Hauser W., Sommer C. New treatment options for fibromyalgia: critical appraisal of duloxetine. Neuropsychiatric Disease & Treatment 2008;4(3):525-29. Exclude on population: not NP (or something other than chronic postoperative surgical NP) or for underlying cause of NP

Vadalouca A., Raptis E., Moka E., Zis P., Sykioti P., Siafaka I. Pharmacological treatment of neuropathic cancer pain: a comprehensive review of the current literature. [Review]. Pain Practice 2012;12(3):219-51. Exclude on study design: systematic review or meta-analysis that does not

include all comparators or indications of interest, or includes comparators or indications that are not of interest

van de Vusse A.C., Stomp-van den Berg SG, Kessels A.H., Weber W.E. Randomised controlled trial of gabapentin in Complex Regional Pain Syndrome type 1 [ISRCTN84121379]. BMC Neurology 2004;4:13. Exclude on study characteristics: study length < 4 weeks

van,Seventer R., Serpell,M., Bach,F.W., Morlion,B., Zlateva,G., Bushmakin,A.G., et al. Relationships between changes in pain severity and other patient-reported outcomes: an analysis in patients with posttraumatic peripheral neuropathic pain. Health & Quality of Life Outcomes 2011;9:17.

Exclude on study design: duplicate publication/further analysis of study excluded because of use of placebo run-in period

van SR, Murphy K, Temple J et al. (2009) Pregabalin is effective in the treatment of posttraumatic peripheral neuropathic pain. Journal of Pain Conference: 28th Annual Scientific Meeting of the American Pain Society, APS San Diego, CA United States. Conference Start: 20090507 Conference End: 20090509. Conference: 28th Annual Scientific Meeting of the American Pain Society, APS San Diego, CA United States. Conference Start: 20090507 Conference End: 20090509. Conference Publication: S35. Exclude on study characteristics: not full-text publication (ie. conference abstract)

Ventafridda V., Bonezzi C., Caraceni A., De Conno F., Guarise G., Ramella G., et al. Antidepressants for cancer pain and other painful syndromes with deafferentation component: comparison of amitriptyline and trazodone. Italian Journal of Neurological Sciences 1987;8(6):579-87. Exclude on study characteristics: study length < 4 weeks

Ventafridda V., Caraceni A., Saita L., Bonezzi C., De Conno F., Guarise G., et al. Trazodone for deafferentation pain. Comparison with amitriptyline. Psychopharmacology 1988;95:Suppl-9. Exclude on study characteristics: study length < 4 weeks

Vidal O (2010) Pregabaline monotherapy in cancer patients. European Journal of Pain Supplements Conference: 3rd International Congress on Neuropathic Pain Athens Greece. Conference Start: 20100527 Conference End: 20100530. Conference: 3rd International Congress on Neuropathic Pain Athens Greece. Conference Start: 20100527 Conference End: 20100530. Conference Publication: 126. Exclude on study characteristics: not full-text publication (ie. conference abstract)

Viola V, Newnham HH, Simpson RW (2006) Treatment of intractable painful diabetic neuropathy with intravenous lignocaine. Journal of Diabetes & its Complications 20: 34-9. Exclude on intervention: administration other than oral for anti-depres&anti-convuls or other than topical lidocaine/capsaicin

Vlassakov K.V., Narang S., Kissin I. Local anesthetic blockade of peripheral nerves for treatment of neuralgias: Systematic analysis. Anesthesia and Analgesia.112 (6) (pp 1487-1493), 2011.Date of Publication: June 2011. 2011;(6):1487-93. Exclude on intervention: not drug of interest / non-pharmacological treatment

Vorobeychik Y., Gordin V., Mao J., Chen L. Combination therapy for neuropathic pain: A review of current evidence. CNS Drugs.25 (12) (pp 1023-1034), 2011.Date of Publication: 2011. 2011;(12):1023-34. Exclude on study design: systematic review or meta-analysis that does not include all comparators or indications of interest, or includes comparators or indications that are not of interest

Vorobeychik Y., Gordin V., Mao J., Chen L. Combination therapy for neuropathic pain: a review of current evidence. [Review]. CNS Drugs 2011;25(12):1023-34. Exclude on study design: systematic review or meta-analysis that does not include all comparators or indications of interest, or includes comparators or indications that are not of interest

Vranken J, Van D, V, Kruis R et al. (2009) Duloxetine in patients with central neuropathic pain: A randomized, double-blind, placebo-controlled trial of a flexible-dose regimen. European Journal of Pain Conference: 6th Congress of the European Federation of IASP Chapters: Pain in Europe 6th, EFIC Lisbon

Portugal. Conference Start: 20090909 Conference End: 20090912. Conference: 6th Congress of the European Federation of IASP Chapters: Pain in Europe 6th, EFIC Lisbon Portugal. Conference Start: 20090909 Conference End: 20090912. Conference Publication: S195. Exclude on study characteristics: not full-text publication (ie. conference abstract)

Wade D.T., Collin C., Stott C., Duncombe P. Meta-analysis of the efficacy and safety of Sativex (nabiximols), on spasticity in people with multiple sclerosis. Multiple Sclerosis 2010;16(6):707-14. Exclude on population: not NP (or something other than chronic postoperative surgical pain) or treating the underlying cause of NP

Wade D.T., Makela P., Robson P., House H., Bateman C. Do cannabis-based medicinal extracts have general or specific effects on symptoms in multiple sclerosis? A double-blind, randomized, placebo-controlled study on 160 patients. Multiple Sclerosis 2004;10(4):434-41. Exclude on study design: not all patients in the treatment group had neuropathic pain

Wade D.T., Robson P., House H., Makela P., Aram J. A preliminary controlled study to determine whether whole-plant cannabis extracts can improve intractable neurogenic symptoms. Clinical Rehabilitation 2003;17(1):21-29. Exclude on study design: 'enriched' or open-label RCT

Wade W.E. & Spruill W.J. Tapentadol hydrochloride: a centrally acting oral analgesic. Clinical Therapeutics 2009;31(12):2804-18. Exclude on study design: systematic review or meta-analysis that does not include all comparators or indications of interest, or includes comparators or indications that are not of interest

Wagner T., Roth-Daniek A., Sell A., England J., Kern K.-U. Capsaicin 8% patch for peripheral neuropathic pain: Review of treatment best practice from 'real-world clinical experience. Pain Management.2 (3) (pp 239-250), 2012.Date of Publication: May 2012. 2012;(3):239-50. Exclude on study characteristics: narrative review, commentary, or editorial

Wallace M. & Pappagallo M. Qutenza[REGISTERED]: a capsaicin 8% patch for the management of postherpetic neuralgia. [Review]. Expert Review of Neurotherapeutics 2011;11(1):15-27. Exclude on study characteristics: narrative review, commentary, or editorial

Wallace MS, Barger D, Schulteis G (2008) The effect of chronic oral desipramine on capsaicin-induced allodynia and hyperalgesia: a double-blinded, placebo-controlled, crossover study. Anesthesia & Analgesia 95: 973-8. Exclude on population: not NP (or something other than chronic postoperative surgical NP) or for underlying cause of NP

Wallace MS, Dyck JB, Rossi SS et al. (1996) Computer-controlled lidocaine infusion for the evaluation of neuropathic pain after peripheral nerve injury. Pain 66: 69-77. Exclude on intervention: administration other than oral for anti-depres&anti-convuls or other than topical lidocaine/capsaicin

Wallace MS, Schulteis G (2008) Effect of chronic oral gabapentin on capsaicin-induced pain and hyperalgesia: a double-blind, placebo-controlled, crossover study. The Clinical journal of pain 24: 544-9. Exclude on population: not NP (or something other than chronic postoperative surgical NP) or for underlying cause of NP

Wallace MS, Irving G, Cowles VE (2010) Gabapentin extended-release tablets for the treatment of patients with postherpetic neuralgia: a randomized, double-blind, placebo-controlled, multicentre study. Clinical Drug Investigation 30: 765-76. Exclude on intervention: not drug of interest / non-pharmacological treatment

Wang Q.P. & Bai M. Topiramate versus carbamazepine for the treatment of classical trigeminal neuralgia: a meta-analysis. [Review]. CNS Drugs 2011;25(10):847-57. Exclude on study design: systematic review or meta-analysis that does not include all comparators or indications of interest, or includes comparators or indications that are not of interest

Watson C.P.N., Gilron I., Sawynok J., Lynch M.E. Nontricyclic antidepressant analgesics and pain: Are serotonin norepinephrine reuptake inhibitors (SNRIs)

any better? Pain.152 (10) (pp 2206-2210), 2011.Date of Publication: October 2011. 2011;(10):2206-10. Exclude on study design: systematic review or meta-analysis that does not include all comparators or indications of interest, or includes comparators or indications that are not of interest

Watson CP, Moulin D, Watt-Watson J et al. (2003) Controlled-release oxycodone relieves neuropathic pain: a randomized controlled trial in painful diabetic neuropathy. Pain 105: 71-8. Exclude on study design: Crossover study with no washout and no analysis of carry over effects. 4 weeks study.

Webb J, Kamali F (1998) Analgesic effects of lamotrigine and phenytoin on cold-induced pain: a crossover placebo-controlled study in healthy volunteers. Pain 76: 357-63. Exclude on population: not NP (or something other than chronic postoperative surgical NP) or for underlying cause of NP

Webster L.R., Nunez M., Tark M.D., Dunteman E.D., Lu B., Tobias J.K., Vanhove G.F. Tolerability of NGX-4010, a capsaicin 8% dermal patch, following pretreatment with lidocaine 2.5%/prilocaine 2.5% cream in patients with post-herpetic neuralgia. BMC Anesthesiology 2011;11:25. Exclude on study design: 'enriched' or open-label RCT

Wernicke JF, Raskin J, Rosen A et al. (2006) Duloxetine in the long-term management of diabetic peripheral neuropathic pain: An open-label, 52-week extension of a randomized controlled clinical trial. Current Therapeutic Research - Clinical and Experimental 67: 283-304. Exclude as inappropriate/unclear comparator

Wernicke JF, Wang F, Pritchett YL et al. (2007) An open-label 52-week clinical extension comparing duloxetine with routine care in patients with diabetic peripheral neuropathic pain. Pain Medicine 8: 503-13. Exclude as inappropriate/unclear comparator

Wiffen P.J., Derry S., Moore R.A. Lamotrigine for acute and chronic pain. [Review][Update of Cochrane Database Syst Rev. 2007;(2):CD006044; PMID: 17443611]. Cochrane Database of Systematic Reviews 2011;(2):CD006044. Exclude on population and study design: includes patients without neuropathic

pain and systematic review or meta-analysis that does not include all comparators or indications of interest, or includes comparators or indications that are not of interest

Wiffen Philip J., McQuay Henry J., Edwards Jayne, Moore R.Andrew. Gabapentin for acute and chronic pain. Cochrane Database of Systematic Reviews 2011;(3):n. pag. Exclude on population: includes patients without neuropathic pain

Wilder-Smith CH, Hill LT, Laurent S (2005) Postamputation pain and sensory changes in treatment-naive patients: characteristics and responses to treatment with tramadol, amitriptyline, and placebo. Anesthesiology 103: 619-28. Exclude on study design: Crossover study with no washout and no analysis of carry over effects. Early crossover.

Wissel J., Haydn T., Müller J., Brenneis C., Berger T., Poewe W., Schelosky L.D. Low dose treatment with the synthetic cannabinoid Nabilone significantly reduces spasticity-related pain : a double-blind placebo-controlled cross-over trial. Journal of Neurology 253 (10): 1337-41. Exclude on patient population and intervention: study for spasticity, not neuropathic pain and nabilone is a synthetic molecule so not considered cannabis extract.

Wolff R.F., Bala M.M., Westwood M., Kessels A.G., Kleijnen J. 5% lidocaine-medicated plaster vs other relevant interventions and placebo for post-herpetic neuralgia (PHN): a systematic review. [Review]. Acta Neurologica Scandinavica 2011;123(5):295-309. Exclude on study design: systematic review or meta-analysis that does not include all comparators or indications of interest, or includes comparators or indications that are not of interest

Wu H., Sultana R., Taylor K.B., Szabo A. A prospective randomized double-blinded pilot study to examine the effect of botulinum toxin type A injection versus Lidocaine/Depomedrol injection on residual and phantom limb pain: initial report. Clinical Journal of Pain 2012;28(2):108-12. Exclude on intervention: administration other than oral for anti-depressants and anti-convulsants or other than topical lidocaine/capsaicin

Wu CL, Tella P, Staats PS et al. (2002) Analgesic effects of intravenous lidocaine and morphine on postamputation pain: a randomized double-blind, active placebo-controlled, crossover trial. Anesthesiology 96: 841-8. Exclude on study design: Study period less than 4 weeks.

Wymer J., Garrison C., Simpson J., Koch B., Study Group. A multicenter, randomized, double-blind, placebo-controlled trial to assess the efficacy and safety of lacosamide in subjects with painful distal diabetic neuropathy. Neurology 2006;66(Suppl 2):A202. Exclude on study characteristics: not full-text publication (ie. conference abstract)

Wymer J.M., Garrison C., Simpson J., Koch B. A multicenter, randomized double-blind, placebo-controlled trial assessing the efficacy and safety of lacosamide in painful distal diabetic neuropathy. Ann Neurol 2006;60(Suppl 3 (Suppl 10 on cover)):S68. Exclude on study characteristics: not full-text publication (ie. conference abstract)

Wymer J.P., Simpson J., Sen D., Bongardt S., Lacosamide S.P. Efficacy and safety of lacosamide in diabetic neuropathic pain: an 18-week double-blind placebo-controlled trial of fixed-dose regimens. Clinical Journal of Pain 2009;25(5):376-85. Exclude on study design: 'enriched' or open-label RCT

Yang Mi, Zhou Muke, He Li, Chen Ning, Zakrzewska Joanna M. Non-antiepileptic drugs for trigeminal neuralgia. Cochrane Database of Systematic Reviews 2011;(1):n. pag. Exclude on study design: systematic review or meta-analysis that does not include all comparators or indications of interest, or includes comparators or indications that are not of interest

Yang Y, Yan J-Q, Guo Q-L et al. (2009) Safety and efficacy of oral oxycodone-acetaminophen versus tramadol in treatment of postherpetic neuralgia. [Chinese]. Chinese Journal of New Drugs 18 (6) (pp 527-529) Administrative exclusion: Not available from the British Library

Yildirim K, Sisecioglu M, Karatay S et al. (2003) The effectiveness of gabapentin in patients with chronic radiculopathy. Pain Clinic 15: 213-8. Exclude on study characteristics: randomisation not described

Young A. & Buvanendran A. Multimodal systemic and intra-articular analgesics. [Review]. International Anesthesiology Clinics 2011;49(4):117-33. Exclude on study characteristics: narrative review, commentary, or editorial

Zaccara G., Gangemi P., Perucca P., Specchio L. The adverse event profile of pregabalin: a systematic review and meta-analysis of randomized controlled trials. [Review]. Epilepsia 2011;52(4):826-36. Exclude on study design: systematic review or meta-analysis that does not include all comparators or indications of interest, or includes comparators or indications that are not of interest

Zaccara G., Perucca P., Gangemi P.F. The adverse event profile of pregabalin across different disorders: a meta-analysis. European Journal of Clinical Pharmacology 2012;68(6):903-12. Exclude on study design: systematic review or meta-analysis that does not include all comparators or indications of interest, or includes comparators or indications that are not of interest

Zajicek J., Fox P., Sanders H., Wright D., Vickery J., Nunn A., et al. Cannabinoids for treatment of spasticity and other symptoms related to multiple sclerosis (CAMS study): multicentre randomised placebo-controlled trial. Lancet 2003;362(9395):1517-26. Exclude on patient population: study for spasticity, not neuropathic pain

Zajicek J.P., Sanders H.P., Wright D.E., Vickery P.J., Ingram W.M., Reilly S.M., et al. Cannabinoids in multiple sclerosis (CAMS) study: safety and efficacy data for 12 months follow up. Journal of Neurology, Neurosurgery & Psychiatry 2005;76(12):1664-69. Exclude on patient population: study for spasticity, not neuropathic pain

Zakrzewska J.M. Insufficient evidence to recommend topical lidocaine as first-line treatment for postherpetic neuralgia. Evidence-Based Dentistry 2007;8(3):85-86. Exclude on study design: systematic review or meta-analysis that does not include all comparators or indications of interest, or includes comparators or indications that are not of interest

Zakrzewska J.M. Robust randomised control trials needed for drug treatments for trigeminal neuralgia. Evidence-Based Dentistry 2006;7(4):107. Exclude on study design: systematic review or meta-analysis that does not include all comparators or indications of interest, or includes comparators or indications that are not of interest

Zakrzewska Joanna M. & Akram Harith. Neurosurgical interventions for the treatment of classical trigeminal neuralgia. Cochrane Database of Systematic Reviews 2011;(9):n. pag. Exclude on intervention: not drug of interest / non-pharmacological treatment

Zakrzewska JM, Chaudhry Z, Nurmikko TJ et al. (1997) Lamotrigine (lamictal) in refractory trigeminal neuralgia: results from a double-blind placebo controlled crossover trial.[see comment]. Pain 73: 223-30. Exclude on study design: Study period less than 4 weeks.

Zhang J., Ho K.Y., Wang Y. Efficacy of pregabalin in acute postoperative pain: a meta-analysis. [Review]. British Journal of Anaesthesia 2011;106(4):454-62. Exclude on population: not NP (or something other than chronic postoperative surgical NP) or for underlying cause of NP

Zhou Y. & Warycha B. Are opioids effective and necessary for chronic non-malignant pain. British Journal of Medical Practitioners.5 (1) , 2012.Date of Publication: March 2012. 2012;(1):n. pag. Exclude on study characteristics: narrative review, commentary, or editorial

Zilliox L. & Russell J.W. Maintaining efficacy in the treatment of diabetic peripheral neuropathic pain: role of duloxetine. Diabetes, Metabolic Syndrome and Obesity Targets and Therapy 2010;3:7-17. Exclude on study design: systematic review or meta-analysis that does not include all comparators or indications of interest, or includes comparators or indications that are not of interest

Studies included in the previous guideline but now excluded

Achar A, Chatterjee G, Ray TG, Naskar B. Comparative study of clinical efficacy with amitriptyline, pregabalin, and amitriptyline plus pregabalin

combination in postherpetic neuralgia. Indian Journal of Dermatology, Venereology & Leprology 2010;76(1):63-65. Exclude on study characteristics: letter to editor

Baron R, Mayoral V, Leijon G, Binder A, Steigerwald I, Serpell M. Efficacy and safety of 5% lidocaine (lignocaine) medicated plaster in comparison with pregabalin in patients with postherpetic neuralgia and diabetic polyneuropathy: interim analysis from an open-label, two-stage adaptive, randomized, controlled trial. Clinical Drug Investigation 2009;29(4):231-41. Exclude on study design: open-label RCT

Dallocchio C, Buffa C, Mazzarello P, Chiroli S. Gabapentin vs. amitriptyline in painful diabetic neuropathy: An open- label pilot study. Journal of Pain and Symptom Management 2000;20(4):280-85. Exclude on study design: open-label RCT

Estanislao L, Carter K, McArthur J, Olney R, Simpson D, Lidoderm-HIV Neuropathy Group. A randomized controlled trial of 5% lidocaine gel for HIV-associated distal symmetric polyneuropathy. Journal of acquired immune deficiency syndromes (1999) 2004;37(5):1584-86. Exclude on study characteristics: study length < 4 weeks

Galer BS, Jensen MP, Ma T, Davies PS, Rowbotham MC. The lidocaine patch 5% effectively treats all neuropathic pain qualities: results of a randomized, double-blind, vehicle-controlled, 3-week efficacy study with use of the neuropathic pain scale. The Clinical journal of pain 2002;18(5):297-301. Exclude on study characteristics: study length < 4 weeks

Gatti A, Sabato AF, Occhioni R, Colini BG, Reale C. Controlled-release oxycodone and pregabalin in the treatment of neuropathic pain: Results of a multicenter Italian study. European Neurology 2009;61(3):129-37. Exclude on study design: open-label RCT

Ho K, Kuh BK, White WD, Yeh C, Miller EJ. Topical amitriptyline versus lidocaine in the treatment of neuropathic pain. Clinical Journal of Pain 2008;24(1):51-55. Exclude on study characteristics: study length < 4 weeks

Kishore-Kumar R, Max MB, Schafer SC, Gaughan AM, Smoller B, Gracely RH, Dubner R. Desipramine relieves postherpetic neuralgia. Clinical Pharmacology & Therapeutics 1990;47(3):305-12. Exclude on intervention: desipramine no longer in scope

Max MB, Kishore-Kumar R, Schafer SC, Meister B, Gracely RH, Smoller B, Dubner R. Efficacy of desipramine in painful diabetic neuropathy: a placebo-controlled trial. Pain 1991;45(1):3-9. Exclude on intervention: desipramine no longer in scope

Meier T, Wasner G, Faust M, Kuntzer T, Ochsner F, Hueppe M, et al. Efficacy of lidocaine patch 5% in the treatment of focal peripheral neuropathic pain syndromes: a randomized, double-blind, placebo-controlled study. Pain 2003;106(01/02/2012):151-58. Exclude on study characteristics: study length < 4 weeks

Nicol CF. A four year double-blind study of tegretol in facial pain. Headache 1969;9(1):54-57. Exclude on intervention/comparator: randomised groups no longer comparable as 17 of 24 patients allocated to placebo crossed over to carbamazepine during the study

Serpell MG & Neuropathic pain study group. Gabapentin in neuropathic pain syndromes: a randomised, double-blind, placebo-controlled trial. Pain 2002;99(3):557-66. Exclude on study design: 'enriched' RCT

van Seventer R, Bach FW, Toth CC, Serpell M, Temple J, Murphy TK, Nimour M. Pregabalin in the treatment of post-traumatic peripheral neuropathic pain: a randomized double-blind trial. European Journal of Neurology 2010;17:1082-1089. Exclude on study design: use of placebo run-in period

Excluded studies: Literature search on health economic evidence

Abernethy AP, Samsa GP (2003) A clinical decision and economic analysis model of cancer pain management. American Journal of Managed Care 9(10): 651-64. Reason for exclusion: Exclude on intervention - not pharmacological management

de Salas-Cansado M, Perez C, Saldana MT et al. (2012) A cost-effectiveness analysis of the effect of pregabalin versus usual care in the treatment of refractory neuropathic pain in routine medical practice in Spain. Pain Medicine 13: 699-710. Reason for exclusion: Exclude on design - doesn't meet NICE ref case (productivity costs)

Hens MJ, Alonso-Ferreira V, Villaverde-Hueso A et al. (2012) Cost-effectiveness analysis of burning mouth syndrome therapy. Community Dentistry & Oral Epidemiology 40: 185-92. Reason for exclusion: Exclude on design - not a CUA

Ikenberg R (2012) Cost-effectiveness of tapentadol prolonged release compared with oxycodone controlled release in the UK in patients with severe non-malignant chronic pain who failed 1st line treatment with morphine. Journal of Medical Economics 15(4):724-736 Reason for exclusion: Exclude on design - not a CUA

Johnston A (2007) Cost-effectiveness of pregabalin: a UK perspective. Expert Review of Pharmacoeconomics & Outcomes Research 7: 327-33. Reason for exclusion: Exclude on design - not a CUA

Kwong WJ, Ozer-Stillman I, Miller JD et al. (2010) Cost-effectiveness analysis of tapentadol immediate release for the treatment of acute pain. Clinical Therapeutics 32: 1768-81. Reason for exclusion: Exclude on design - not a CUA

Liedgens H, Hertel N, Gabriel A et al. (2008) Cost-effectiveness analysis of a lidocaine 5% medicated plaster compared with gabapentin and pregabalin for

treating postherpetic neuralgia: a german perspective. Clinical Drug Investigation 28: 583-601. Reason for exclusion: Exclude as duplicate - study already included with correct perspective

Neighbors DM, Bell TJ, Wilson J (2001) Economic evaluation of the fentanyl transdermal system for the treatment of chronic moderate to severe pain. Journal of Pain and Symptom Management 21: 129-43. Reason for exclusion: Exclude on population - not neuropathic pain

O'Connor AB (2009) Neuropathic pain: Quality-of-life impact, costs and cost effectiveness of therapy. PharmacoEconomics.27 (2) (pp 95-112), 2009.Date of Publication: 2009. 95-112. Reason for exclusion: Exclude on design - not a CUA

Obradovic M (2012) Cost-effectiveness of tapentadol in severe chronic pain in Spain: a cost analysis of data from RCTs. Clinical Therapeutics 34(4):926-943 Reason for exclusion: Exclude on design - not a CUA

Owen M, Lorgelly P (2010) Chronic pain following donor nephrectomy - A study of the incidence, nature and impact of chronic post-nephrectomy pain. European Journal of Pain 14: 732-4. Reason for exclusion: Exclude on design - not a CUA

Reinoso F, Duran P, Garcia FJ et al. (2003) Cost-effectiveness analysis of three epidural analgesia techniques for the management of paediatric postoperative pain. Revista de la Sociedad Espanola del Dolor 10(8): 469-74. Reason for exclusion: Exclude on population - children

Sanansilp V, Lertakyamanee J (1995) Cost-effectiveness analysis of patient-controlled analgesia, intramuscular q.i.d. injection and p.r.n. injection for postoperative pain relief. Journal of the Medical Association of Thailand 78: 600-4. Reason for exclusion: Exclude on population - not neuropathic pain

Simpson EL, Duenas A, Holmes MW et al. (2009) Spinal cord stimulation for chronic pain of neuropathic or ischaemic origin: Systematic review and

economic evaluation. Health Technology Assessment 13: iii-72. Reason for exclusion: Exclude on design - not a CUA

Singh D (2003) The use of gabapentin for the treatment of postherpetic neuralgia. Clinical Therapeutics.25 (3) (pp 852-889), 2003.Date of Publication: 01 Mar 2003. 852-89. Reason for exclusion: Exclude on design - not a CUA

Smith KJ (2007) Sequential medication strategies for postherpetic neuralgia: a cost-effectiveness analysis.[see comment]. Journal of Pain 8: 396-404. Reason for exclusion: Excluded - conference abstracts

Vissers DC (2011) An economic evaluation of short-acting opioids for treatment of breakthrough pain in patients with cancer. Value in Health 14(2):274-281. Reason for exclusion: Exclude on design - not a CUA

Ward A, Bozkaya D, Fleischmann J et al. (2007) Modeling the economic and health consequences of managing chronic osteoarthritis pain with opioids in Germany: comparison of extended-release oxycodone and OROS hydromorphone. Current Medical Research and Opinion 23(10): 2333-45. Reason for exclusion: Exclude on design - not a CUA

Wu EQ, Birnbaum HG, Mareva MN et al. (2006) Cost-effectiveness of duloxetine versus routine treatment for U.S. patients with diabetic peripheral neuropathic pain.[see comment]. Journal of Pain 7: 399-407. Reason for exclusion: Exclude on design - not a CUA