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.

This appendix explains methods of searching, data extraction, clinical effectiveness analyses, syntheses, and quality assessment in more detail and highlights any deviations from the Guidelines Manual (2012).

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were also asked to alert the Internal Clinical Guidelines Technical Team to any additional evidence, published, unpublished or in press, that met the inclusion criteria.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

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

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

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

2 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, 5HT1-receptor agonists, topical lidocaine, and topical capsaicin as monotherapy. The use of antidepressants, antiepileptics (anticonvulsants), opioid analgesics, cannabis sativa, flecainide, 5HT1-receptor agonists, topical lidocaine, and topical capsaicin as combination (or adjunct) therapy. The positioning of the above pharmacological treatments as monotherapy and/or combination therapy within the care pathway.	What is the clinical effectiveness of different pharmacological treatments as monotherapy compared with each other or placebo for the management of neuropathic pain in adults, outside of specialist pain management services? What is the clinical effectiveness of different pharmacological treatments as combination therapy compared with other combination therapies, monotherapy or placebo for the management of neuropathic pain in adults, outside of specialist pain management services?

	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 of RCTs **Exclusion:** RCTs with enriched enrolment or single-blind placebo run-in period	While enriched enrolment 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		

<table>
<tr>
<td>Population</td>
<td><u>Inclusion:</u>
• Adults (aged ≥ 18 years old) with neuropathic pain managed in settings other than specialist pain management services.

<u>Exclusion:</u>
• Children and adolescents (aged < 18 years old) with neuropathic pain.</td>
<td>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</td>
<td>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.</td>
</tr>
<tr>
<td>Intervention</td>
<td><u>Inclusion:</u>
Drugs listed below as monotherapy:

1) Tricyclic antidepressants (TCAs):
<table><tr><td>amitriptyline</td><td>doxepin</td><td>nortriptyline</td></tr></table></td>
<td></td>
<td></td>
</tr>
</table>

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	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 meta-analysis), 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 patient-reported global impression of change (PGIC) (the 7-point tool measuring patient-reported global improvement), the top 2 categories (very much or much improved – this was considered 'moderate improvement') 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.	Patient-reported global improvement – only data from studies reporting the 7-point PGIC tool 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 example, 10-point or 100-point scales). For pain outcomes, they considered a reduction of 2 points to be clinical significant.

		• 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)	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). Please note that overall improvement in quality of life and treatment withdrawal were listed in the review protocol and these data were extracted into the evidence tables, but because they were not prioritised as the top critical and important outcomes, results were not pooled or presented in GRADE profiles 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. It was also not possible to perform meta-analysis for 'use of rescue medication'. Despite having acknowledged that these outcomes should be critical or important to decision-making, the GDG felt it was inappropriate to use such inconsistent data to inform their decisions and, so, did not consider these outcomes when writing recommendations.
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.		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.

	• 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). • 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		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 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 meta-analysis), 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 prioritised outcomes from evidence where it was possible to pool results will be presented in GRADE profiles and further summarised 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. • If possible, subgroup analysis will be undertaken on underlying causes of neuropathic pain.	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 • 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.		

	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 of RCTs **Exclusion:** RCTs with enriched enrolment or single-blind placebo run-in period	While enriched enrolment 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		

<table>
<tr><td>Population</td><td><u>Inclusion:</u>
• Adults (aged ≥ 18 years old) with neuropathic pain managed in settings other than specialist pain management services.

<u>Exclusion:</u>
• Children and adolescents (aged < 18 years old) with neuropathic pain.</td><td>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</td><td>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.</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></table></td><td></td><td>Sativex/ nabiximol was the primary cannabis extract considered. Dronabinol (a pure</td></tr>
</table>

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	valproate
oxcarbazepine	lacosamide	topiramate
gabapentin	lamotrigine	
pregabalin	levetriracetam	

5) Opioid analgesics:

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

6) Additional drugs:

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

Exclusion:

isomer of THC that is generated synthetically) and nabilone (a synthetic molecule) were not considered.

	• Treatments other than those listed above.		
Comparator	Other combination therapies, monotherapy or placebo/active placebo	For the possibility of providing indirect comparisons outside of the decision dataset (for the network meta-analysis), we may consider including studies with additional comparators outside the 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 patient-reported global impression of change (PGIC) (the 7-point scale measuring patient-reported global improvement), the top 2 categories (very much or much improved – this was considered 'moderate improvement') 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	Patient-reported global improvement-only data from studies reporting the 7-point PGIC tool 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 example, 10-point or 100-point scales). For pain outcomes, they considered a reduction of 2 points to be clinical

		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)	significant. 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). Please note that overall improvement in quality of life and treatment withdrawal were listed in the review protocol and these data were extracted into the evidence tables, but because they were not prioritised as the top critical and important outcomes, results were not pooled or presented in GRADE profiles 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. It was also not possible to perform meta-analysis for 'use of rescue medication'. Despite having acknowledged that these outcomes should be critical or important to decision-making, the GDG felt it was inappropriate to use such inconsistent patchy data to inform their decisions and, so, did not consider these outcomes when writing recommendations.
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:**		For cannabis extract, smoked cannabis was excluded. Lidocaine and capsaicin spray were considered to

	• 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). • Smoked cannabis • Lidocaine and capsaicin spray. • Open-label trials or not RCT • Studies with study sample < 10		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 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 meta-analysis), we may consider performing another search later for additional comparators outside this decision dataset.	
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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 cancer 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.		

3 Data extraction

3.1 Time-points

The included evidence reported a variety of follow-up periods. In order to enable the comparison of studies with different follow-up periods, the GDG felt it important to extract outcomes at common time-points. Given the number and heterogeneity of the time-points reported in the literature, it was important to prioritise which time-points were extracted, while maintaining the ability to compare studies. Before data extraction commenced, the time-points where outcomes data were reported across the available literature were mapped and common time-points across the studies were chosen. The resulting time-points where outcomes were then extracted from the literature (when available) were as follows:

- 28 days +/- 7 days (4 weeks +/- 1 week)
- 56 days +/- 7 days (8 weeks +/- 1 week)
- 84 days +/- 14 days (12 weeks +/- 2 weeks)
- study end-point (if not one of the above).

If a study had more than one data-point available in this time period, the later time period was chosen. Rationale for including within 14 days for the 12-week time point, rather than within 7 days was to be able to include more data from more studies and possibly, more interventions (which was of particular interest due to the differential reporting of different studies). This meant that in some instances it was possible to include an outcome at 10 weeks and at 14 weeks in the same synthesis. Exploratory sensitivity analysis suggested that this did not have a significant impact on the overall results from the analyses.

Extracting data for some time-points required the extraction of data from graphs, where numerical data were not available. This was typically performed only where dispersion was also available from the graph (for example, where error-bars were provided), and was performed by digitising the images in question and 'measuring' them with an electronic ruler.

A small number of studies reported some outcomes as averages of repeated measures over a period of follow-up, such as a mean change from baseline value to an average of measurements over weeks 2–12. In such cases, the data were recorded as reporting at the end of that period of follow-up (that is, at week 12 in this example).

3.2 Measurement tools extracted

A large number of different measurement tools were used in the literature for a number of critical and important outcomes (particularly global improvement, physical and emotional functioning and pain). The tools for which data were extracted were those prioritised by the GDG, based on clinical relevance, the reliability and validity of the tools for measuring particular outcomes, and the frequency to which they appeared in the literature.

Tools extracted	**Tools not extracted**
Patient-reported global pain: Patient-reported global impression of change (PGIC, 7-point)[1] Patient global impression of improvement (PGI-I)	Patient-reported global pain: Global assessment of therapeutic effect (GATE) Global pain relief (GPR) Global symptom score (GSS)
Physical and emotional functioning (including sleep)[2]: Brief pain inventory (BPI) - interference with function Beck's depression index (BDI) Centre for epidemiological studies-depression scale (CES-D) Hamilton rating scale for depression (HAMD) - 17 point Hamilton Depression Scale (HDS) (21-item version) Medical outcomes study sleep questionnaire (MOS) Profile of mood states (POMS) Hospital Anxiety & Depression Scale (Zigmund & Snaith) Euroqol - 5 dimensions (EQ-5D) Short form - 36 questions (SF-36)	Physical and emotional functioning (including sleep): Athens insomnia scale (AIS) Beck's anxiety index (BAI) Brief stress scale (BSS) Craig handicap assessment and reporting techniques (CHART) Expanded Disability status scale (EDSS) Functional independence measure (FIM) General Health Questionnaire (GHQ-12) Linear analog self-assessment scale (LASA) (NCCTG QoL) Minnesota Multiphasic Personality Inventory (MMPI) Zung pain and distress index (PAD) Pain catastrophising scale (PCS) Pain disability index (PDI) Sleep affective score (SAS) Self-assessment of treatment (SAT) Self-rating depression scale (Zung) (SDS)

	Spielberger State/Trait Anxiety Inventory (SSTAI/STAI) Sickness impact profile (SIP) Satisfaction with life scale (SWLS) West Haven-Yale multidimensional pain inventory (WHYMPI) pain intensity, life control, affective distress, interference with pain, social support, activity)
Pain: Numerical pain rating scale (NRS / NPRS) Neuropathic pain scale (NPS) Visual analogue scale for pain relief (VAS/VAS-PR) Visual analogue scale for pain intensity (VAS/VAS-PI) Visual rating scale (VRS) Brief pain inventory (BPI) McGill Pain Questionnaire (MPQ) / Short form McGill pain Questionnaire (SFMPQ) Sternback Pain intensity (SPI)	Pain: Oswestry Back Pain disability index (ODI) Pain-related self-statement scale (PRSS) Quality of life index (QLI)
	Others: Clinical global impression of change (CGIC) Clinical global impression of severity (CGI-S)
[1] PGIC was the primary tool for measuring patient-reported global improvement. This is the tool recommended by IMMPACT group (Dworkin et al. 2005) and is the tool most frequently used in the literature. [2] while outcomes related to physical and emotional functioning were extracted, the GDG felt it was inappropriate to synthesise results from different tools due to the variation in what different tools measured.	

4 Adverse effects: prioritising important events and approach to synthesis

The GDG was sent a questionnaire seeking the members' views on the 5 most important adverse effects to be considered for each drug class. The 6 top-rated outcomes for each drug type were extracted from each of the studies. Some GDG members listed additional adverse effects in the free-text section of the questionnaire. Since it was not possible to determine if other GDG members would prioritise these events if they had seen them listed in the questionnaire, these were also extracted.

To aid decision making, GDG advice was sought on those adverse effects judged to be clinically similar and therefore appropriate to be combined for analysis. In some cases it was not possible to combine adverse effects because they had been reported separately in a study, so to combine them would risk double counting. This is explained in table 1.

Table 1 Groupings of adverse effects for syntheses

Category	Comments
Blurred vision	None.
Burning pain	Includes studies that report 'burning sensation'
Cognitive impairment	Includes impaired attention and dissociation. The GDG felt these were similar enough to include under one larger subheading of ‘cognitive impairment’ (2 studies reporting 'mental change' were excluded as it was unclear what this meant).
Confusion	Not able to combine with cognitive impairment (because of duplicate reporting in some studies) so presented on its own.
Constipation	None.
Dizziness or vertigo	The GDG felt that combining dizziness and vertigo may be more useful to clinicians, because a diagnosis of vertigo requires determining certain physical features (which they thought were not likely to have been consistently applied in the studies) and that vertigo may be incorrectly categorised as dizziness. Six studies that reported ‘vertigo’ were excluded because they also reported dizziness separately. 'Balance disorder' was included in this synthesis but 3 studies reporting this were excluded because they reported both vertigo and dizziness separately.
Dry mouth	None
Fatigue or tiredness	Tiredness was considered similar enough to fatigue to combine both in one synthesis. Unable to be combined with lethargy (see below).
Gait disturbance	None.
Lethargy	While some GDG members felt this was similar enough to combine with fatigue and tiredness, it was not possible because some studies reported lethargy separately from fatigue (2 of the 4 studies that reported lethargy). It was necessary to exclude 1 study that reported ‘lethargy and fatigue’ as a combined outcome.
Mood disturbance	The GDG felt it was appropriate to include both depression and euphoria under a larger subheading of ‘mood disturbance’.
Nausea	Nausea was reported in 58 studies and vomiting was reported in19; separate syntheses were done for nausea and for vomiting (3 studies reported ‘nausea and vomiting’ as one outcome but we felt it was inappropriate to include the results of these studies into either the nausea or vomiting syntheses).
Oedema	None.
Peripheral oedema	None.
Pruritus	None.

Rash / urticaria / overall erythema (not restricted to site)	The GDG felt it was acceptable to combine these general symptoms (differentiated from site-related).
Somnolence (including drowsiness and sedation)	Drowsiness, sedation and somnolence were considered similar enough to combine in one synthesis. One study reported 'daytime somnolence' and 'night-time somnolence': the rate reported for 'daytime somnolence' was included in this synthesis.
Urine retention	None.
Vomiting	As above under 'nausea'.
Weight gain	None.

There were 6 outcomes which were prioritised by the GDG as important but no evidence on these was identified in studies that met the inclusion/exclusion criteria:

- Addiction/dependence
- Anaphylaxis
- Disorientation
- Dyspnoea
- Hallucinations/paranoia/delusions
- Heaviness, pressure or tightness of any part of the body

The following were identified in free text by GDG members but no evidence was found in studies that met the inclusion/exclusion criteria:

- General neuroendocrine adverse effects
- Hormonal dysfunction
- Hyperalgesia
- Hyponatraemia
- Immunosupression
- Pituitary axis suppression
- Risk of transferring cream to eye or other sensitive parts of the body
- Sudden death (likely from cardiac arrhythmias)
- Tolerance
- Transient pain flare

Three adverse effects were extracted from the literature, but were not suitable for analysis. They are listed below with the reason why analysis was not undertaken:

- Postural hypotension was seen as important for antidepressants (reported in 2 studies: 1 comparing nortriptyline with gabapentin and another comparing amitriptyline with pregabalin; this network is not connected).
- Pro-arrhythmic effects for antidepressants (such as, arrhythmias, dysrhythmias, palpitation, and tachycardia) (reported in 5 studies: 2 showing there was no significant difference between amitriptyline and placebo, venlafaxine and placebo, and venlafaxine, imipramine and placebo, 2 showing insignificant differences between tramadol and placebo and amitriptyline and placebo) .
- Sexual dysfunction (2 studies showed no significant difference between treatments).

5 Placebo / active placebo

While most of the studies used a sham placebo, some used an active placebo, often used for topical treatments or with amitriptyline to mimic some of the minor side effects associated with these treatments. While a potential analgesic effect of active placebo cannot be absolutely dismissed, the GDG considered that any analgesic effect was likely to be minimal so, for the purposes of the analysis, agreed to combining the placebo and active placebo as 'placebo'.

6 Crossover studies

Twenty-seven of the 116 included trials were crossover studies. The incorporation of data from RCTs of parallel and crossover design in single quantitative syntheses is a subject of methodological debate (see Elbourne et al. 2002). The following approaches were considered:

- The optimal method is to include data from crossover studies in a way that exploits the increased precision the crossover design provides. This is straightforward where within-patient differences from a paired analysis are

reported by authors; alternatively, methods are available that can impute these data if the correlation between treatment periods is known (or can be calculated) (see Elbourne et al. 2002). Unfortunately, very few of the included studies provided sufficient data to enable this approach to be adopted.

- Another method sometimes used is to restrict attention to the first period of randomised treatment in each crossover trial only. In this way, a parallel trial of half the size is derived. This approach is suboptimal, as it discards data from the remainder of the trial, and relies on data being reported in a way that facilitates the extraction of data from the initial period only. In the assembled evidence for this guideline, only 3 of 27 crossover studies reported the first treatment period separately. This approach was therefore rejected.
- An extreme option is to exclude all crossover studies from consideration. The GDG felt uncomfortable about this idea, particularly because the 27 studies constituted a large proportion of the head-to-head data available, and tended to be across a number of drugs and populations that were not covered elsewhere in the evidence base.
- Finally, it is possible simply to ignore the crossover design of the trials, and analyse them as if they had a parallel design. This method is not generally recommended, as it is ignores within-patient correlations and therefore discards the design advantages of crossover trials. However, this means that the approach is conservative, as it results in the trials having less weight in syntheses than they would have if paired data were used (or imputed). Therefore, when compared with the only practicable alternative of excluding crossover studies entirely (that is, giving them no weight at all), this was clearly a superior option.

For these reasons, a decision was taken to treat data from all crossover RCTs as if they had been derived from parallel trials. However, in recognition of the imperfect nature of this approach, the inclusion of crossover trials in a synthesis was a criterion of downgrading for risk of bias to reflect increased uncertainty in the assembled evidence (see section 11).

7 Dosage

Studies that appeared to employ different dosages for those with abnormal creatinine clearance levels (defined by each study) have been categorised as 'flexible' dosing, even if those with normal levels had a fixed dosage. This is to capture that not all patients have received the same dosage.

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

8 Approach to missing data

The evidence tables record whether or not studies stated that they performed intention-to-treat (ITT) analysis. The included studies were inconsistent in the use of ITT analysis. Many of those that did use ITT analyses used the last observation carried forward (LOCF) imputation, which is thought to overestimate treatment effects, Unfortunately, it is difficult to adequately deal with this data for continuous outcomes without individual patient data reported for each individual study. It has been suggested that responder analysis, which defines withdrawal as nonresponse, be used in systematic reviews to reduce this bias which is an issue particularly when adverse event withdrawals are high (Moore, 2011).

For dichotomous outcomes, the reviewers were able to perform ITT analyses and all patients randomised were included in the denominators. This assumes that all missing or discontinued patients (including those that have withdrawal) were non-events. The health economic model approached this similarly.

For favourable outcomes (ie. for patients who achieved a particular level of pain relief), this assumes that patients missing from the analysis did not achieve this level of pain relief. If this assumption was incorrect, this type of analysis could underestimate the true result. However, it is more likely that missing patients did not achieve the specified level of pain relief so it was felt appropriate to make this assumption.

For unfavourable outcomes such as adverse events, this assumes that patients missing from the analysis did not have the specified adverse event. If this assumption was incorrect, this type of analysis could underestimate the rate of adverse events. However, it is unlikely that those who drop out of the trial will continue on the treatment they have been allocated to and then be unlikely they will have adverse events due to this treatment.

Occasionally, the proportion of number of patients which achieved a particular outcome was only reported as a percentage and the total number of patients included in this outcome was not reported; for these studies, the total number of patients achieving the outcome was estimated based on the denominator reported for other dichotomous outcomes or on those randomised. It was not possible to perform an intention-to-treat analysis for continuous outcomes without access to individual patient data.

9 Approach to extracting continuous outcomes

9.1 Creating a normalised outcome from different measuring tools

In order to include as many studies as possible in each individual synthesis, and as the studies reported various tools for measuring pain, the GDG agreed that it was appropriate to convert these different measures onto a common 10-point scale. The GDG felt it was inappropriate to normalise 4-point or smaller scales because of concern about the precision of these scales, and 'converting' them to a normalised 10-point scale may inappropriately inflate the effect estimates of the treatments.

For studies reporting more than 1 tool measuring pain or sleep, the hierarchy of measures preferred when producing single normalised measures was:

- Numerical rating scale
- Visual analogue scale
- Brief Pain Inventory average score or Short-Form McGill for normalised pain measures; Brief Pain Inventory of sleep for normalised sleep interference
- Anything else (for pain, this included Present Pain Intensity for McGill Pain Questionnaire and the Steinbach Pain Inventory)

The above order was based partially from IMMPACT recommendations about tools (Dworkin et al. 2005) and also on data availability (that is, numerical ratings scales were most frequently reported).

9.1.1 Different types of pain scores

Pain was measured in different ways in the included studies. Some studies reported measures such as worst pain, least pain, or pain at the present time, in addition to average pain. Only average mean pain scores were extracted as other measures of pain such as 'worst pain' are difficult to interpret.

Some studies also reported different characteristics of pain, such as allodynia and dysesthetic pain as continuous measures in addition to overall pain. While it was considered important to measure different characteristics of pain to distinguish neuropathic pain from other types of pain that patients may also experience (many patients often have both neuropathic and non-neuropathic pain), this was not consistently reported in the literature. As a result, the ability to meaningfully synthesise these types of pain scores was limited.

9.1.2 Baseline continuous scores

Mean difference from baseline to follow-up was the point of synthesis for all continuous measures. However, mean difference was not always reported in the included studies and it was sometimes necessary to calculate the mean difference from the baseline and follow-up scores.

The mean difference is simply the follow-up measurement minus the baseline value. However, the standard deviation (SD) of mean differences is also required for syntheses. To estimate this, it is necessary to specify the correlation between measurements at the 2 junctures. These were estimated from studies in the effectiveness evidence base. Where a study reports SD at baseline (σ_b), SD at follow-up (σ_f) and the SD of changes between baseline and follow-up (σ_c), the correlation (C) between baseline and follow-up for that study may be estimated by:

$$C = \frac{\sigma_b^2 + \sigma_f^2 - \sigma_c^2}{2 \times \sigma_b \times \sigma_f} . \quad (1)$$

C was calculated for each arm (regardless of treatment assignment) in each study reporting the necessary information. These values were combined by a weighted average according to the number of people in the arm, and the resulting average C used to impute SDs of mean differences in studies not reporting them, using the formula:

$$\sigma_c = \sqrt{\sigma_b^2 + \sigma_f^2 - \left(2 \times C \times \sigma_b \times \sigma_f\right)} . \quad (2)$$

For all calculations, where a baseline pain score was only reported for all patients combined (not for each arm individually), the overall baseline data for all patients in the studies was used for each arm. However, using the same baseline pain score for each arm assumes that randomisation has been adequate and that patients in each group at baseline were similar. Where this is not the case, using this approach could bias results. However, as using the overall baseline pain score allowed mean differences to be calculated and include more studies in the synthesis, the advantages were considered to outweigh the limitations.

10 Synthesis methods

Where possible, meta-analyses were conducted to combine the results of studies for each outcome.

Pairwise meta-analyses were performed using a frequentist approach in Excel.

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

A hierarchical Bayesian NMA was performed using the software WinBUGS version 1.4.3. The models were based on the approach and code provided in the NICE Decision Support Unit's Technical Support Documents on evidence synthesis, particularly Technical Support Document 2 ('A generalised linear modelling framework for pairwise and network meta-analysis of randomised controlled trials'; see http://www.nicedsu.org.uk/).

10.1 Choice of model (random- versus fixed-effects)

A random-effects model was chosen for all meta-analyses because of the relatively heterogeneous populations across the trials. An assumption was made that the different effects are estimating a common distribution. Although a fixed-effects model may have represented a minority of datasets adequately, the value of using a consistent model to estimate all outcomes was felt to outweigh the disadvantage of presenting some models with a superfluous random effects term.

An exception to this principle was in instances where there was only one study for each link in the network. In this case, no data are available to

estimate the random-effects term; therefore, the assumption was deemed inappropriate and a fixed-effects model was used.

10.2 Dichotomous outcomes

In datasets containing studies with 'zero cells' (that is, trials in which no events occurred in 1 or more arm), substantial instability was encountered when performing syntheses. To address this problem, a constant of 0.5 was added to all cell counts (effectively adding 0.5 to the numerator and 1 to the denominator of the proportion). Studies in which all numerators were 0 – that is, studies in which the event of interest was not observed in any relevant arm – were excluded from syntheses, as they do not provide any evidence of effect.

Two alternative models were explored for synthesising dichotomous outcomes: the first relied on a logit link function and produced results in the form of log odds ratios; the second had a complementary log–log ('cloglog') link function, which takes into consideration time to the event, and produces effect estimates in the form of hazard ratios.

There were negligible differences between results from the two types of model. However, it was observed that the cloglog model can be unstable when there are no or few events in either arm (even when a constant was added to studies with zero cells); this problem was particularly common for individual adverse effects. For this reason, logit models were used in the final syntheses (it was also noted that producing results as odds ratios may be more helpful for model validation, as they provide a straightforward point of comparison with frequentist syntheses of direct evidence).

The WinBUGS code used for the logit-link model is provided in Appendix K.

There were 2 exceptions to this principle, where cloglog models were used in preference: withdrawal due to adverse effects (where it might be particularly important to account for differences in follow-up), and the individual adverse effect data that were used in the health economic model (dizziness/vertigo

and nausea). In the latter case, a cloglog model was preferred because it provided results in a form that was more convenient for the model.

10.3 Continuous outcomes

Identity-link models, which rely on a normal likelihood, were used for continuous outcomes. It should be emphasised that these models do not assume that the measures being synthesised are, themselves, normally distributed (which is unlikely to be the case with pain scores); rather, they assume that the sample means are normally distributed (which, according to Central Limit Theorem, will invariably be the case regardless of skewness in the underlying data).

For the synthesis, we were unable to include the outcomes from studies where continuous data were reported in the form of median differences or as percentage change from baseline in syntheses as it is not possible to combine outcomes with these measures with mean differences (the point of synthesis chosen) without access to individual patient data.

The WinBUGS code used for this model is provided in Appendix K.

10.4 Categorical outcomes

One further analysis was performed in which dichotomous data reporting 30% pain relief and 50% pain relief were treated as categorical. That is, people are categorised into those with less than 30% pain relief, those with more than 30% but less than 50% pain relief and those with 50% pain relief or greater. The probability of achieving each of these outcomes with each of the drugs is derived from a single synthesis model that incorporates reported 30% and 50% response rates from all trials reporting 1 or both (network meta-analysis for ordered categorical data using a generalised linear model with probit link function; see Dias et al., NICE DSU Technical Support Document 2 for technical details).

Relative effects are estimated as *z*-scores – standard deviations on a standard normal distribution – which can then be converted into probabilities. Please note that the use of a standard normal distribution for this

transformation does not imply any assumption about the distribution of the underlying variable (in this case, pain relief): the model is not configured to recognise relief as fundamentally associated with the quantities 30% and 50%; rather, it treats these thresholds as arbitrary and estimates response probabilities from the response data alone.

More formally, the probability (p) of patients in arm k of trial i achieving category j is modelled as

$$p_{ikj} = \Phi\left(\mu_i + z_j + \delta_{i,t_{ik},t_{i1}} I_{\{k\neq 1\}}\right), \quad (3)$$

where Φ represents the cumulative distribution function of the standard normal distribution, μ_i is the trial-specific baseline probability of achieving the first response category with the 'control' treatment, z_j represents the differences on the standard normal scale between the response to category j and the response to category $j-1$, $\delta_{i,t_{ik},t_{i1}}$ is the trial-specific treatment effect of the treatment in arm k relative to the treatment in arm 1 (the 'control' treatment), and $I\{k\neq 1\}$ is an indicator function taking the value 0 where treatment k is the 'control' treatment, and 1 otherwise. The choice of which treatment is designated as 'control' is arbitrary. In the syntheses reported here, placebo arms, where available, were assumed to be the 'control'; in the case of head-to-head trials, the distinction was made alphabetically.

The z_j are modelled as fixed effects – that is, a single estimate of the difference between categories is shared across all trials. The $\delta_{i,t_{ik},t_{i1}}$ are modelled as random effects – that is, they are assumed exchangeable and drawn from a shared distribution. In this implementation, normal distributions of treatment effects are assumed, the mean ($d_{t_{ik},t_{i1}}$) is specific to each pairwise comparison of interest and the variance (σ^2) is assumed to be common to all comparisons. That is,

$$\delta_{i,t_{ik},t_{i1}} \sim N(d_{t_{ik},t_{i1}}, \sigma^2). \quad (4)$$

Data from all follow-up times are included in the synthesis of relative effects, to provide a single estimate of relative probability of response for each treatment compared with a common baseline (placebo). In the few instances where a trial provided estimates of response at more than 1 timepoint, only the latest-reported was used, to avoid double-counting of trial participants.

These probabilities are then applied to a series of absolute probabilities of response, estimated in a separate baseline model comprising data from the placebo arms of all included trials (see Dias et al., NICE DSU Technical Support Document 5 for technical details). These juncture-specific absolute (baseline) results and the time-independent estimates of relative effect are combined to estimate probability of response over time (at 4, 8, 12, 16 and 20 weeks' follow-up).

For instance, if the probability of achieving 50% pain relief with placebo after 8 weeks' treatment is 0.185 and the *z*-score associated with gabapentin compared with placebo is −0.367, the probability of 50% response with gabapentin can be estimated as

$$1-\Phi\left(\Phi^{-1}\left[1-0.185\right]-0.367\right) = 0.299 ,$$

where Φ again represents the cumulative distribution function of the standard normal distribution, and Φ-1 is the inverse function of the same.

The WinBUGS code used for this model is provided in Appendix K.

10.5 Prior distributions

Non-informative prior distributions were used in all models. Trial baselines and treatment effects were assigned $N(0, 100^2)$ priors, and the between-trial standard deviations used in random-effects models were given $U(0, 5)$ priors. It was felt that this standard deviation was appropriate for both dichotomous and continuous measures. This is recommended in NICE Decision Support Unit's Technical Support Documents (see NICE DSU Technical Support Document 2: A Generalised Linear Modelling Framework for Pairwise and Network Meta-Analysis of Randomised Controlled Trials) for dichotomous

outcomes. It was felt appropriate to also use the same value for continuous outcomes since it is not plausible that the SD would be greater than 5 where continuous outcomes are on an 11-point scale.

In the categorical model, the mean treatment effect estimates were given vague prior distributions ($d_{t_{ik},t_{i1}} \sim N[0,100^2]$), as were the trial-specific baseline parameters ($\mu_i \sim N[0,100^2]$). For the variance parameter, a vague prior was applied to the standard deviation of the distribution and transformed in the model code: $\sigma \sim U(0,2)$.

10.6 Running the model

In the first instance, models were run with 10,000 burn-ins and 50,000 iterations. Three separate chains with different initial values were used. If models did not appear to converge well, they were re-run with more burn-ins.

Syntheses were assessed for any points that significantly deviated from the other data-points and the reasons for any deviate points were investigated.

10.7 Outputs of network meta-analyses

As network meta-analyses do not result in a single point estimate, the results of the meta-analyses were presented in a number of ways.

- Relative effectiveness matrix, showing an estimate of effect for each treatment compared with each of its comparators; an estimate of effect based on direct evidence only (pairwise random-effects meta-analysis or the results from an individual study where only one study was available for a datapoint) is also presented for comparisons where data are available
- Caterpillar plot of the relative effectiveness of each drug compared with placebo (this includes any direct estimate and also the results of the NMA)
- Probability of each treatment being best
- Median rank with 95% credible interval
- Histograms demonstrating the probability of each treatment at each possible rank ('rankograms').

10.8 Assessing how well the model fit the data

The residual deviance was used and compared to the number of data-points to assess how well the model fit the data. This was recorded in the results section for each model run.

Estimates of residual deviance from the NMA models were also compared with analogous estimates from an 'inconsistency' model, to highlight any inconsistency between direct and indirect evidence (see NICE DSU Technical Support Document 4: Inconsistency in Networks of Evidence Based on Randomised Controlled Trials). There was negligible evidence of inconsistency of this type in any of the syntheses (this is to be expected, as the evidence base is dominated by placebo-controlled trials, with very little head-to-head data). Accordingly, these additional results have not been presented.

11 Dose-adjusted syntheses

In recognition of heterogeneity of dosages investigated in the included trials, a more complicated synthesis model was also explored. This model included an additional term for each comparator that sought to estimate the relationship between dose and effect in reported response rates. These terms were incorporated as additional coefficients in the linear model.

Because this type of approach makes substantial additional demands on the available data, it was only explored for the largest datasets available – in particular, those that were likely to contribute to the health economic model.

Other potential covariates of outcome – including fixed versus flexible dose regimens, baseline pain status, age, sex and diagnosis – were explored both in combination with and instead of dose–response adjustment. These did not provide informative results or improve model fit.

Models were run for 50,000 burn-ins and 10,000 captured iterations. Where there was judged to be evidence of conspicuous autocorrelation on inspection of diagnostic graphics, results were instead based on 10,000 iterations

thinned from 100,000. In either event, the 10,000 lines of raw output ('CODA file') were stored and used in the health economic model.

11.1 Dose-adjusted categorical model

Incorporating a dose–response term into the model discussed in section 10.4 above, the estimated probability of response becomes a combination of baseline (placebo) expectation + relative effect for the drug in question + amount effect is observed to vary with dose (the covariate is centred around the mean dose for the comparator in the dataset).

Expressed algebraically, the model in equation (3) is extended such that

$$p_{ikj} = \Phi\left(\mu_i + z_j + \left[\delta_{i,t_{ik},t_{t1}} + \beta_{t_{ik}}\left(x_{ik} - \bar{x}_{t_{ik}}\right) - \beta_{t_{i1}}\left(x_{i1} - \bar{x}_{t_{i1}}\right)\right] I_{\{k\neq 1\}}\right), \quad (5)$$

where $\beta_{t_{ik}}$ and $\beta_{t_{i1}}$ are dose–response coefficients for the 'treatment' and 'control' arms of each comparison, x_{ik} and x_{i1} represent the doses at which the treatments in these arms were delivered, and $\bar{x}_{t_{ik}}$ and $\bar{x}_{t_{i1}}$ are the mean doses observed for those treatments in the dataset under synthesis. The dose–response coefficients are given moderately vague prior distributions ($\beta_t \sim N[0,2^2]$).

The WinBUGS code used for this model is provided in Appendix K.

Using this model, estimates of response probability can be computed for any specified dose level. The GDG was asked to estimate typical maintenance dosages for each drug in the decision-set, and these values were used as the expected dosage with which effects were calculated. In all cases, the dosages specified by the GDG were within the range of dosages observed in the trial evidence on which the model was based; therefore, the model was not asked to extrapolate beyond its data. For some less commonly used drugs, the GDG was unable to provide estimates of typical practice; for these, the mean value of dosages used in the trials was used instead.

11.2 Dose-adjusted dichotomous model

An identical approach was used to adjust the linear predictor in cloglog models for withdrawal due to adverse effects. Similar models were attempted for individual adverse effects (dizziness/vertigo and nausea); however, due to sparse data and a large number of zero-counts, these models proved intractable.

12 Quality assessment

GRADE was used to assess the quality of evidence for the chosen outcomes as specified in the Guidelines Manual.

12.1 GRADE for pairwise meta-analyses

Risk of bias was assessed for:

- Appropriateness of randomisation method
- Adequacy of concealment methods
- Study design – outcomes were downgraded if 50% or more studies in the synthesis were crossover studies
- Comparability of groups at baseline including use of concomitant pain medications, which could have a significant effect on the outcome reported, and which may be incorrectly attributed to the study drug. As a result, individual studies where concomitant drug use between groups (where permitted) was not reported, were treated with caution. Outcomes were downgraded if 50% or more studies that had differing or unclear concomitant drug use at baseline[1][2].
- If the same care was received by each group during the study (this included whether patient in the trial were allowed to vary any concomitant pain medications during the trial)
- Blinding

[1] It should be noted that a large number of studies excluded many concomitant pain medications but still allowed the use of SSRIs. As SSRIs were in the scope of the guideline as a treatment option for neuropathic pain, we recorded that these studies had concomitant pain medication usage and explained this detail in the evidence table.

[2] Throughout the guideline, 'concomitant pain medication' is referred to as 'concomitant drug' usage (not to be confused with concomitant medication for the underlying cause of neuropathic pain or other comorbidities).

- Adequacy of length of follow-up (the GDG felt that a minimum of 8 weeks was required for most drugs but that a minimum of 4 weeks was required for topical capsaicin)
- Comparability of those who completed treatment in each group.

Imprecision was assessed as follows:

- Dichotomous outcomes – use optimal information size (OIS) as calculated from http://www.stat.ubc.ca/~rollin/stats/ssize/b2.html.
- Continuous outcomes – in the absence of guidance on how to determine OIS for continuous outcomes, an OIS of 400 was used as recommended by GRADE.

- Inconsistency was assessed using I^2. If there was considerable heterogeneity (as defined in the Cochrane Handbook for Systematic Reviews of Interventions) between studies in the meta-analysis, the outcome was downgraded 1 level.

12.2 Modified GRADE for network meta-analyses

The use of GRADE to assess the quality of studies addressing a particular review question for pairwise comparisons of interventions is relatively established. However, the use of GRADE to assess the quality of evidence across a network meta-analysis is still a developing methodology. While most criteria for pairwise meta-analyses still apply, it is important to adapt some of the criteria to take into consideration additional factors, such as how each 'link' or pairwise comparison within the network applies to the others. As a result, the following was used when applying modified GRADE to a network meta-analysis.

Risk of bias

In addition to the usual criteria to assess the risk of bias or 'limitations' of studies for each pairwise analysis within a network, the risk of bias was assessed for each direct comparison and then an assessment was made about how the risk of bias from the direct comparisons would affect the

indirect comparisons. Additionally, there was an assessment of treatment effect modifiers and if they differed between links in the network.

For studies with a large proportion of studies in a network, some decision rules were applied with respect to downgrading.

- If 50% or more studies in the network were inadequate or unclear for a particular parameter of quality, the outcome was downgraded by 1 level.
- As with pairwise meta-analyses, studies with differences in concomitant drug use between groups, or if concomitant drug use between groups (where permitted) was not reported, were treated with caution. Additionally, if there were differences in concomitant drug usage among the studies included in different links across the network, the overall outcome was downgraded.

Inconsistency

Inconsistency was assessed for the heterogeneity of individual pairwise comparisons in the network and also for between direct and indirect comparisons, where both were available (that is, where there were 'loops' in the network).

Heterogeneity across studies for each direct pairwise meta-analysis was assessed using I^2. This allowed for the assessment of heterogeneity within the included studies using the following decision rules:

- If there was considerable heterogeneity for 1 link or more in a network, the outcome was downgraded 1 level.
- If there were more than 1 link in the network with considerable, substantial or moderate heterogeneity, consider downgrading 2 levels.

To assess for consistency for each pairwise comparison where both direct and indirect evidence are available, the values of the direct and indirect estimates were compared to see if they were similar. (see also section 10.8 above about assessing consistency)

The overall value of tau was also assessed to compare heterogeneity across the network.

Indirectness

As with pairwise meta-analyses, studies included in a network were assessed for how well they fit the PICO (population, intervention, comparator, outcome) specified in the review protocol.

Imprecision

This was assessed for a number of variables:

- Sufficient head-to-head trials in the network.
- Sufficient number of studies to form the network (if there is a high proportion of 'links' formed with only 1 trial, the outcome was downgraded).
- Overall certainty/uncertainty of the effect estimates (size of credible intervals, including for each drug compared to placebo and also size of credible intervals for the overall rankings within the network)[3].
- For networks, imprecision was considered around both the direct and indirect effect estimates.

When assessing imprecision for pairwise comparisons, or for networks with only 1 trial for all 'links' in the network, the confidence interval around the direct estimate was used (since the results were largely led by a non-informative prior).

13 References

Dias, S., Welton, N.J., Sutton, A.J. & Ades, A.E. NICE DSU Technical Support Document 2: A Generalised Linear Modelling Framework for Pairwise and Network Meta-Analysis of Randomised Controlled Trials. 2011; last updated March 2013; available from http://www.nicedsu.org.uk.

Dias, S., Welton, N.J., Sutton, A.J., Caldwell, D.M., Lu, G. & Ades, A.E. NICE DSU Technical Support Document 4: Inconsistency in Networks of Evidence

[3] As ORs are quite difficult to interpret, a confidence interval was considered 'wide' if it was 4 or greater; an outcome was downgraded for imprecision if 50% or more interventions had wide confidence intervals for the OR when they were compared to placebo.

Based on Randomised Controlled Trials. 2011; last updated April 2012; available from http://www.nicedsu.org.uk.

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

Elbourne DR, Altman DG, Higgins JPT et al. (2002) Meta-analyses involving cross-over trials: methodological issues. International Journal of Epidemiology 31: 140–49.

Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

14 Excluded studies

(please see last few pages for studies in the previous version of this guideline [CG96] 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

Affaitati G, Fabrizio A, Savini A et al. (2009) A randomized, controlled study comparing a lidocaine patch, a placebo patch, and anesthetic injection for treatment of trigger points in patients with myofascial pain syndrome: evaluation of pain and somatic pain thresholds. Clinical Therapeutics 31: 705-

20. Exclude on population: not NP (or something other than chronic postoperative surgical NP) or for underlying cause of NP

Agarwal S, Polydefkis M, Block B et al. (2007) Transdermal fentanyl reduces pain and improves functional activity in neuropathic pain states. Pain Medicine 8: 554-62. Exclude on study design: not RCT or SR of RCTs

Ahuja R.B., Gupta R., Gupta G., Shrivastava P. A comparative analysis of cetirizine, gabapentin and their combination in the relief of post-burn pruritus. Burns 2011;37(2):203-07. Exclude on population: not NP (or something other than chronic postoperative surgical NP) or for underlying cause of NP

al Balawi S., Tariq M., Feinmann C. A double-blind, placebo-controlled, crossover, study to evaluate the efficacy of subcutaneous sumatriptan in the treatment of atypical facial pain. International Journal of Neuroscience 1996;86(3-4):301-09. Exclude on study characteristics: study length < 4 weeks

Alper B.S. Evidence-based medicine. Lidocaine and sumatriptan each reduce pain in trigeminal neuralgia. Clinical Advisor for Nurse Practitioners 2007;10(3):174-76. Exclude on study characteristics: narrative review, commentary, or editorial

Alviar M.J., Hale T., Dungca M. Pharmacologic interventions for treating phantom limb pain. [Review]. Cochrane Database of Systematic Reviews 2011;12:CD006380.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

Ammendolia C., Stuber K., de Bruin L.K., Furlan A.D., Kennedy C.A., Rampersaud Y.R., et al. Nonoperative treatment of lumbar spinal stenosis with neurogenic claudication: a systematic review. Spine 2012;37(10):E609-16. Administration exclusion: unable to obtain from British Library

Ananth K., Richeimer S., Durham M.J. Managing chronic pain: Consider psychotropics and other non-opioids. Current Psychiatry.11 (2) (pp 38-43),

2012.Date of Publication: February 2012. 2012;(2):38-43. Exclude on study characteristics: narrative review, commentary, or editorial

Anon. BET 3: Can pregabalin effectively diminish acute herpetic pain and reduce the incidence of post-herpetic neuralgia? Emergency Medicine Journal 2012;29(2):166-67. Exclude on study design: not RCT or SR of RCTs

Anon. Duloxetine (Cymbalta) for diabetic neuropathic pain. Medical Letter on Drugs and Therapeutics.47 (1215-1216) (pp 67-68), 2005.Date of Publication: 2005. 2005;(1215-1216):67-68. Exclude on study characteristics: narrative review, commentary, or editorial

Anon. Flecainide in cancer nerve pain. Lancet 1991;337(8753):1347. Exclude on study characteristics: narrative review, commentary, or editorial

Al-Mujadi H, Refai AR, Katzarov MG et al. (2006) Preemptive gabapentin reduces postoperative pain and opioid demand following thyroid surgery. Canadian Journal of Anesthesia 53: 268-73. Exclude on population: not NP (or something other than chronic postoperative surgical NP) or for underlying cause of NP

Anon. Fluoxetine enhances motor recovery if given soon after an ischaemic stroke. Australian Journal of Pharmacy.92 (1094) (pp 91), 2011.Date of Publication: July 2011. 2011;(1094):91. Exclude on study characteristics: narrative review, commentary, or editorial

Anon. Gabapentin for neuropathic pain. Drug and Therapeutics Bulletin.49 (5) (pp 50), 2011.Date of Publication: May 2011. 2011;(5):50. Exclude on study characteristics: narrative review, commentary, or editorial

Anon. Review: Pregabalin and other drugs reduce pain in patients with painful diabetic neuropathy. Annals of Internal Medicine 2011;155(10):JC508. 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

Aragona M., Onesti E., Tomassini V., Conte A., Gupta S., Gilio F., et al. Psychopathological and cognitive effects of therapeutic cannabinoids in multiple sclerosis: a double-blind, placebo controlled, crossover study. Clinical Neuropharmacology 2009;32(1):41-47. Exclude on population: not NP (or something other than chronic postoperative surgical pain) or treating the underlying cause of NP

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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

Eisenberg E, McNicol ED, Carr DB. Opioids for neuropathic pain. Cochrane Database of Systematic Reviews 2006; (3): CD006146. Exclude on study design: systematic review or meta-analysis that does not include all comparators or indications of interest

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 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

Ifuku Masataka, Iseki Masako, Hidaka Ikuhiro, Morita Yoshihito, Komatus Syuji, Inada Eiichi. Replacement of Gabapentin with Pregabalin in

Postherpetic Neuralgia Therapy. Pain Medicine 2011;12(7):1112-16. Exclude on study design: not RCT or SR of RCTs

Iohom G., Abdalla H., O'Brien J., Szarvas S., Larney V., Buckley E., et al. The associations between severity of early postoperative pain, chronic postsurgical pain and plasma concentration of stable nitric oxide products after breast surgery. Anesthesia and Analgesia.103 (4) (pp 995-1000), 2006.Date of Publication: October 2006. 2006;(4):995-1000. Exclude on population: not NP (or something other than chronic postoperative surgical NP) or for underlying cause of NP

Irving G, Backonja M, Rauck R et al. (2012) NGX-4010, a capsaicin 8% dermal patch, administered alone or in combination with systemic neuropathic pain medications, reduces pain in patients with postherpetic neuralgia. Clinical Journal of Pain 28: 101-7. Exclude on population: further analysis of studies already included

Iskedjian M., Bereza B., Gordon A., Piwko C., Einarson T.R. Meta-analysis of cannabis based treatments for neuropathic and multiple sclerosis-related pain. Current Medical Research & Opinion 2007;23(1):17-24. 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

Jadad AR, Carroll D, Glynn CJ et al. (1992) Morphine responsiveness of chronic pain: double-blind randomised crossover study with patient-controlled analgesia.[see comment]. Lancet 339: 1367-71. Exclude on study design: Study period less than 4 weeks

Jenkins T, Smart T, Hackman F et al. (2010) Pregabalin in post-traumatic peripheral neuropathic pain: Efficient assessment of efficacy in a randomised, double-blind, placebo-controlled crossover study. 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: 89. Exclude on study characteristics: not full-text publication (ie. conference abstract)

Jensen MP, Chiang YK, Wu J (2009) Assessment of pain quality in a clinical trial of gabapentin extended release for postherpetic neuralgia. Clinical Journal of Pain 25: 286-92. Exclude on intervention: not drug of interest / non-pharmacological treatment

Jenson MG, Royal MA, Mowa V et al. (2001) Gabapentin and levetiracetam for the treatment of neuropathic pain: a prospective open-label trial. American Journal of Pain Management 11: 125-8. Exclude on study characteristics: open-label

Jensen TS, Backonja M-M, Hernandez JS et al. (2006) New perspectives on the management of diabetic peripheral neuropathic pain. Diabetes and Vascular Disease Research 3: 108-19. Administrative exclusion: Duplication of publication - Gimbel 2003 study.

Jia H-Y, Li Q-F, Song D-P et al. (2006) Effects of venlafaxine and carbamazepine for painful peripheral diabetic neuropathy: A randomized, double-blind and double-dummy, controlled multi-center trial. Chinese Journal of Evidence-Based Medicine 6: 321-8. Exclude on study design: Study period less than 4 weeks.

Jones V.M., Moore K.A., Peterson D.M. Capsaicin 8% topical patch (Qutenza)--a review of the evidence. Journal of Pain & Palliative Care Pharmacotherapy 2011;25(1):32-41. 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

Jose VM, Bhansali A, Hota D et al. (2007) Randomized double-blind study comparing the efficacy and safety of lamotrigine and amitriptyline in painful diabetic neuropathy. Diabetic medicine: a journal of the British Diabetic Association 24: 377-83. Exclude on study characteristics: narrative review, commentary, or editorial

Jose VM, Bhansali A, Hota D et al. (2007) Randomized double-blind study comparing the efficacy and safety of lamotrigine and amitriptyline in painful diabetic neuropathy. Diabetic Medicine 24: 377-83. Exclude on study characteristics: narrative review, commentary, or editorial

Joshi G.P., Rawal N., Kehlet H., PROSPECT collaboration, Bonnet F., Camu F., et al. Evidence-based management of postoperative pain in adults undergoing open inguinal hernia surgery. [Review]. British Journal of Surgery 2012;99(2):168-85. Exclude on population: not NP (or something other than chronic postoperative surgical NP) or for underlying cause of NP

Kadiroglu AK, Sit D, Kayabasi H et al. (2008) The effect of venlafaxine HCl on painful peripheral diabetic neuropathy in patients with type 2 diabetes mellitus. Journal of Diabetes & its Complications 22: 241-5. Exclude on quality: Low quality, inappropriate randomisation method, blinding not clear, no report on withdrawals or dropouts.

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Kanai A., Suzuki A., Kobayashi M., Hoka S. Intranasal lidocaine 8% spray for second-division trigeminal neuralgia. British Journal of Anaesthesia.97 (4) (pp 559-563), 2006.Date of Publication: 15 Oct 2006. 2006;(4):559-63. Exclude on intervention: administration other than oral for anti-depressants and anti-convulsants or other than topical lidocaine/capsaicin

Kastrup J, Petersen P, Dejgard A et al. (1987) Intravenous lidocaine infusion--a new treatment of chronic painful diabetic neuropathy? Pain 28: 69-75. Exclude on intervention: administration other than oral for anti-depres&anti-convuls or other than topical lidocaine/capsaicin

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Killian JM, Fromm GH (1968) Carbamazepine in the treatment of neuralgia. Use of side effects. Archives of Neurology 19: 129-36. Exclude on study design: Study period less than 4 weeks.

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Lemos L, Fontes R, Flores S et al. (2010) Effectiveness of the association between carbamazepine and peripheral analgesic block with ropivacaine for the treatment of trigeminal neuralgia. Journal of pain research 3: 201-12. Exclude on intervention: not drug of interest / non-pharmacological treatment. Exclude on population: children/young people

Leppert W (2001) Analgesic efficacy and side effects of oral tramadol and morphine administered orally in the treatment of cancer pain. Nowotwory 51: 257-66. Exclude on study population: mixed neuropathic and non-neuropathic pain (or likely to include a mix of both)

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Lunn-Michael P.T., Hughes-Richard A.C., Wiffen Philip J. Duloxetine for treating painful neuropathy or chronic pain. Cochrane Database of Systematic Reviews 2009;(4):n. pag. Exclude on population: includes patients without neuropathic pain

Lynch M.E. & Campbell F. Cannabinoids for treatment of chronic non-cancer pain; a systematic review of randomized trials. [Review]. British Journal of Clinical Pharmacology 2011;72(5):735-44. Exclude on study population: mixed neuropathic and non-neuropathic pain (or likely to include a mix of both)

Lynch ME, Clark AJ, Sawynok J (2003) A pilot study examining topical amitriptyline, ketamine, and a combination of both in the treatment of neuropathic pain. Clinical Journal of Pain 19: 323-8. Exclude on intervention: administration other than oral for anti-depressants & anti-convulsants or other than topical lidocaine/capsaicin

Lynch ME, Clark AJ, Sawynok J et al. (2005) Topical amitriptyline and ketamine in neuropathic pain syndromes: an open-label study. Journal of Pain 6: 644-9. Exclude on intervention: administration other than oral for anti-depressants & anti-convulsants or other than topical lidocaine/capsaicin

Majeed F. & Kamal A.K. Can selective serotonin reuptake inhibitors (SSRI) improve motor recovery after stroke? What is the role of neuroplasticity? JPMA - Journal of the Pakistan Medical Association 2011;61(11):1147-48. Exclude on study characteristics: narrative review, commentary, or editorial

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Manfredi PL (2003) Opioids versus antidepressants in postherpetic neuralgia: a randomized, placebo-controlled trial.[comment]. Neurology 60: 1052-3. Exclude on study characteristics: narrative review, commentary, or editorial

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Manchikanti L., Vallejo R., Manchikanti IV K.N., Benyamin R.M., Datta S., Christo P.J. Effectiveness of long-term opioid therapy for chronic non-cancer pain. Pain Physician.14 (2) (pp E133-E156), 2011.Date of Publication: March/April 2011. 2011;(2):E133-56. 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

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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

Martin W.J. & Forouzanfar T. The efficacy of anticonvulsants on orofacial pain: a systematic review. [Review]. Oral Surgery Oral Medicine Oral Pathology Oral Radiology & Endodontics 2011;111(5):627-33. 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

Max MB, Culnane M, Schafer SC et al. (1987) Amitriptyline relieves diabetic neuropathy pain in patients with normal or depressed mood. Neurology 37: 589-96. Exclude on study characteristics: randomisation not described

Max MB, Lynch SA, Muir J et al. (1992) Effects of desipramine, amitriptyline, and fluoxetine on pain in diabetic neuropathy.[see comment]. New England Journal of Medicine 326: 1250-6. Exclude on study characteristics: randomisation not described

McCleane GJ (1999) Intravenous infusion of phenytoin relieves neuropathic pain: a randomized, double-blinded, placebo-controlled, crossover study.[see comment]. Anesthesia & Analgesia 89: 985-8. Exclude on intervention: administration other than oral for anti-depressants & anti-convulsants or other than topical lidocaine/capsaicin

McCleane GJ (2000) Topical doxepin hydrochloride reduces neuropathic pain: A randomized, double-blind, placebo controlled study. Pain Clinic 12: 47-50. Exclude on intervention: administration other than oral for anti-depressants & anti-convulsants or other than topical lidocaine/capsaicin

McCleane G. Lacosamide for pain. [Review]. Expert Opinion on Investigational Drugs 2010;19(9):1129-34. 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

McDonald A.A. & Portenoy R.K. How to use antidepressants and anticonvulsants as adjuvant analgesics in the treatment of neuropathic cancer pain. Journal of Supportive Oncology.4 (1) (pp 43-52), 2006.Date of Publication: January 2006. 2006;(1):43-52. Exclude on study design: not RCT or SR of RCTs

McMillan Roddy. Trigeminal neuralgia -- a review of a disabling facial condition. Dental Nursing 2011;7(11):618-23. Exclude on study characteristics: narrative review, commentary, or editorial

McNicol Ewan D., Strassels Scott, Goudas Leonidas, Lau Joseph, Carr Daniel B. NSAIDS or paracetamol, alone or combined with opioids, for cancer pain. Cochrane Database of Systematic Reviews 2005;(2):n. pag. Exclude on intervention: not drug of interest / non-pharmacological treatment

Medrik-Goldberg T, Lifschitz D, Pud D et al. (1999) Intravenous lidocaine, amantadine, and placebo in the treatment of sciatica: A double-blind, randomized, controlled study. Regional Anesthesia and Pain Medicine 24: 534-40. Exclude on intervention: administration other than oral for anti-depres&anti-convuls or other than topical lidocaine/capsaicin

Medel RJ, Marquez ME, Ribera CM (2008) Evidence in duloxetine treatment of diabetic neuropathy. [Spanish]. DOLOR 23: 122-9. Exclude: Non English

Mendis Victor. Role of tapentadol in pain management. British Journal of Hospital Medicine (17508460) 2012;73(3):143-48. Exclude on study characteristics: narrative review, commentary, or editorial

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 stroke. American Journal of Geriatric Psychiatry 2011;19(12):1007-15. Exclude on population: not NP (or something other than chronic postoperative surgical NP) or for underlying cause of NP

Milligan T.A., Hurwitz S., Bromfield E.B. Efficacy and tolerability of levetiracetam versus phenytoin after supratentorial neurosurgery. Neurology 2008;71(9):665-70. Exclude on study design: not RCT or SR of RCTs

Moore R.A., Derry S., Aldington D., Cole P.,Wiffen P.J. Amitriptyline for neuropathic pain and fibromyalgia in adults. Cochrane Database of Systematic Reviews 2012;(12):CD008242. Exclude on population and study design: includes patients without neuropathic pain and a 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

Moore R.A., Wiffen P.J., Derry S., McQuay H.J. Gabapentin for chronic neuropathic pain and fibromyalgia in adults. [Review]. Cochrane Database of Systematic Reviews 2011;(3):CD007938. Exclude on population and study design: includes patients without neuropathic pain and a 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

Moore RA, Straube S, Wiffen PJ, Derry S, McQuay HJ. Pregabalin for acute and chronic pain in adults. Cochrane Database of Systematic Reviews 2009; (3): CD007076. Exclude on study design: systematic review or meta-analysis that does not include all comparators or indications of interest

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

Mustafa A, El-Sonbaty M, Saad A et al. (2010) Morphine sulphate tablets for chronic pain management: A prospective comparative study versus anti-depressant. Stem Cell 1: 5-11. Exclude on study population: mixed neuropathic and non-neuropathic pain (or likely to include a mix of both)

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

Mystakidou K, Tsilika E, Parpa E et al. (2003) Long-term cancer pain management in morphine pre-treated and opioid naive patients with transdermal fentanyl. International Journal of Cancer 107: 486-92. Exclude on study design: not RCT or SR of RCTs

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

Naliboff B.D., Wu S.M., Schieffer B., Bolus R., Pham Q., Baria A., et al. A randomized trial of 2 prescription strategies for opioid treatment of chronic nonmalignant pain. Journal of Pain.12 (2) (pp 288-296), 2011.Date of Publication: February 2011. 2011;(2):288-96. Exclude on study population: mixed neuropathic and non-neuropathic pain (or likely to include a mix of both)

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Olesen S.S., Graversen C., Olesen A.E., Frokjaer J.B., Wilder-Smith O., van Goor H., et al. Randomised clinical trial: pregabalin attenuates experimental visceral pain through sub-cortical mechanisms in patients with painful chronic pancreatitis. Alimentary Pharmacology & Therapeutics 2011;34(8):878-87.

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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.

Pappagallo M, Campbell JN (1994) Chronic opioid therapy as alternative treatment for post-herpetic neuralgia. Annals of Neurology 35: Suppl-6. Exclude on study design: not RCT or SR of RCTs

Park J.H., Kim J.H., Yun S.C., Roh S.W., Rhim S.C., Kim C.J., Jeon S.R. Evaluation of efficacy and safety of fentanyl transdermal patch (Durogesic D-TRANS) in chronic pain. Acta Neurochirurgica 2011;153(1):181-90. Exclude on study design: not RCT or SR of RCTs

Pascual J. Subcutaneous sumatriptan for trigeminal neuralgia? Headache: The Journal of Head & Face Pain 2006;46(4):583-85. Exclude on study characteristics: narrative review, commentary, or editorial

Pascual ML, Fleming RR, Gana TJ et al. (2007) Open-label study of the safety and effectiveness of long-term therapy with extended-release tramadol in the management of chronic nonmalignant pain. Current Medical Research and Opinion 23: 2531-42. Exclude on study design: not RCT or SR of RCTs

Pasero Chris. Tapentadol for Multimodal Pain Management. Journal of PeriAnesthesia Nursing 2011;26(5):343-47. Exclude on study characteristics: narrative review, commentary, or editorial

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Peloso-Paul Michael J., Gross Anita, Haines Ted, Trinh Kien, Goldsmith Charles H., Burnie Stephen J., -Cervical-Overview-Group. Medicinal and injection therapies for mechanical neck disorders. Cochrane Database of Systematic Reviews 2007;(3):n. pag. Exclude on population: not NP (or something other than chronic postoperative surgical NP) or for underlying cause of NP

Penza P, Campanella A, Martini A et al. (2008) Short- and intermediate-term efficacy of buprenorphine TDS in chronic painful neuropathies: Research report. Journal of the Peripheral Nervous System 13: 283-8. Exclude on study design: not RCT or SR of RCTs

Perez R.S., Zollinger P.E., Dijkstra P.U., Thomassen-Hilgersom I.L., Zuurmond W.W., Rosenbrand K.C.J., Geertzen J.H. Evidence based guidelines for complex regional pain syndrome type 1. BMC Neurology.10 , 2010.Article Number: 20.Date of Publication: 31 Mar 2010. 2010;:n. pag. Exclude on study design: systematic review or meta-analysis that does not include all comparators or studies of interest

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Taylor F.R. Efficacy and safety of lacosamide in diabetic neuropathic pain: An 18-week double-blind placebo-controlled trial of fixed-dose regimens. Clin J Pain. 2009;25:376-385: Comments. Headache.50 (2) (pp 337), 2010.Date of

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Tepper S.J. Dental and facial pain. Headache: The Journal of Head & Face Pain 2005;45(2):186-88. Exclude on study characteristics: not full-text publication (ie. conference abstract)

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Tran de Q.H., Duong S., Bertini P., Finlayson R.J. Treatment of complex regional pain syndrome: a review of the evidence. Canadian Journal of Anaesthesia 2010;57(2):149-66. Exclude on study design: systematic review or meta-analysis that does not include all comparators or studies of interest

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relief of ongoing neuropathic pain. The Clinical journal of pain 22: 266-71. Exclude on intervention: administration other than oral for anti-depressants & anti-convulsants or other than topical lidocaine/capsaicin

Tuncer S, Bariskaner H, Reisli R et al. (2005) Effect of gabapentin on postoperative pain: A randomized, placebo-controlled clinical study. Pain Clinic 17: 95-9. Exclude on population: not NP (or something other than chronic postoperative surgical NP) or for underlying cause of NP

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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

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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, Babul N (1998) Efficacy of oxycodone in neuropathic pain: a randomized trial in postherpetic neuralgia. Neurology 50: 1837-41. Exclude on study design: Crossover study with no washout and no analysis of carry over effects. 4 weeks study.

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 PJ, Derry S, Moore RA, McQuay HJ. Carbamazepine for acute and chronic pain in adults. Cochrane Database of Systematic Reviews 2011; (1): CD005451. Exclude on study design: systematic review or meta-analysis that does not include all comparators or indications of interest

Wiffen P.J., Derry S., Moore R.A. Lamotrigine for acute and chronic pain.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

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 M, Chen N, He L, Yang M, Zhu C, Wu F. Oxcarbazepine for neuropathic pain. Cochrane Database of Systematic Reviews 2013; (3): CD007963. Exclude on study design: systematic review or meta-analysis that does not include all comparators or indications of interest

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

Nikolajsen L, Finnerup NB, Kramp S et al. (2006) A randomized study of the effects of gabapentin on postamputation pain. Anesthesiology 105: 1008-15. Exclude on intervention: Pre-emptive/prevention analgesia 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