National Institute for Health and Care Excellence

Final

Low back pain and sciatica in over 16s: assessment and management

[A] Evidence review for pharmacological management of sciatica

NICE guideline NG59

Evidence review underpinning recommendations 1.2.16 to 1.2.21 and research recommendations in the NICE guideline

September 2020

This evidence review was developed by the National Guideline Centre

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1 Pharmacological management of sciatica

1.1 Review question

What is the clinical and cost effectiveness of pharmacological treatment in the management of sciatica?

1.1 Introduction

Sciatica is a general term for pain in the leg as a result of nerve compression or irritation in the lumbar spine. This is sometimes referred to as radicular pain. Many people with low back pain have referred pain in the leg, without nerve compression. The commonest cause is impingement or inflammation of the lumbosacral nerve roots and is frequently associated with herniation of a lumbar intervertebral disc. In older people, additional anatomical changes may be important. Anatomical structures and abnormal movement in the back can also cause pain to be felt or 'referred' to the leg. It can be difficult to differentiate referred pain from sciatica, and the two may co-exist. The pharmacological management of back pain, including referred pain, was included in 'Low back pain and sciatica in over 16s: assessment and management' (NG59).

People with sciatica typically have severe pain at onset and a slower and less complete recovery than people with back pain without sciatica. A review of pharmacological interventions for sciatica is important because people with sciatica commonly present in primary care. Drugs for neuropathic pain are frequently prescribed for sciatica in addition to opioids and other analgesics. There is high variability of prescribing volumes between CCGs and different population groups. A significant proportion of people continue taking medication for sciatica in the longer term.

When NG59 was first published in 2016, the guideline cross-referenced 'Neuropathic pain in adults: pharmacological management in non-specialist settings' (CG173) for the pharmacological management of sciatica. A MHRA drug safety update in April 2019 advised that gabapentin and pregabalin were reclassified as controlled drugs. This triggered an exceptional surveillance review for NG59. The frequent presentation for relief of leg pain associated with back pain and sciatica in primary care, the unknown efficacy of drugs for neuropathic pain in sciatica, and the reclassification of some drugs used to treat sciatica coupled with the variation in prescribing patterns warrants a fresh review of the pharmacological management of sciatica.

1.1.2 Summary of the protocol

Table 1: PICO characteristics of review question

Population	Inclusion: • People aged 16 or above with sciatica. Exclusion: • Mixed chronic pain (not just sciatica). Mixed populations of children and people aged 16 and over will be included if ≥80% are 16 and over.
Interventions	• Pharmacological treatment (oral/sublingual, rectal, intra-muscular and transdermal but not intravenous) ○ Paracetamol ○ Non-steroidal anti-inflammatory drugs

	○ Opioid analgesics ○ Muscle relaxants - Benzodiazepines - Other muscle relaxants ○ Antidepressants - SSRIs - SNRIs - Tri-cyclic antidepressants - Other ○ Antiepileptics - Gabapentinoids - Other antiepileptics ○ Steroids ○ Nefopam
Comparisons	• All compared to each other • Placebo • Usual care/waiting-list
Outcomes	**Critical:** • Quality of life (for example SF-12, SF-36 or EQ-5D) at ≤ 4 months (continuous) • Quality of life (for example SF-12, SF-36 or EQ-5D) at > 4 months (continuous) • Pain severity (for example VAS or NRS) at ≤ 4 months (continuous) • Pain severity (for example VAS or NRS) at >4 months (continuous) • Function (for example, RMDQ or ODI) at ≤ 4 months (continuous) • Function (disability scores) at ≤ 4 months (continuous) • Psychological distress (HADS, GHQ, BDI and STAI) at ≤ 4 months (continuous) • Psychological distress (HADS, GHQ, BDI and STAI) at >4 months (continuous) **Important:** • Healthcare utilisation (prescribing, investigations, hospitalisation or health professional visit) at ≤ 4 months (dichotomous) • Healthcare utilisation (prescribing, investigations, hospitalisation or health professional visit) at > 4 months (dichotomous) • Adverse events (morbidity) at ≤ 4 months (dichotomous) • Adverse events (morbidity) at > 4 months (dichotomous) • Adverse events (mortality) at ≤ 4 months (dichotomous) • Adverse events (mortality) at > 4 months (dichotomous) • Responder criteria (≥ 30% improvement in pain or function) at ≤ 4 months (dichotomous) • Responder criteria (≥ 30% improvement in pain or function) at ≤ 4 months (dichotomous). For separation of time points: • ≤4 months: defined as anything that is less than or including 4 months. If a study reports data for 2 time-points between these boundaries (e.g. 2 months and 3 months), then the data closest to 4 months will be used (i.e. in this example it would be 3 months). • >4: Defined as 4 to 12 months or end of trial. If a study reports data for 2 time-points between these boundaries (e.g. 6 months and 12 months), then the data closest to 1 year will be used (i.e. in this example it would be 12 months). NB: if a time point greater than 12 months is also reported, e.g. 6 months and 18 months, then the later time point will be extracted as the last time point is most relevant.

	Any validated scale will be used. Measures will be pooled where appropriate.
Study design	RCTs and systematic reviews of RCTs at the first instance, if insufficient RCT evidence is found then comparative non-randomised studies will be included for that respective class

This review focuses on the management of sciatica only. Pharmacological management of low back pain, and mixed populations of low back pain and sciatica are considered in a separate chapter in the full guideline: Low back pain and sciatica in over 16s: assessment and management. For full details see the review protocol in Appendix A.

1.1.3 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in appendix A and the methods document.

Declarations of interest were recorded according to NICE's conflicts of interest policy.

1.1.4 Effectiveness evidence

1.1.4.1 Included studies

Eight randomised-controlled trial studies were included in the review[17, 26, 33, 47, 57, 71, 85, 144]; these are summarised in Table 2 below. Evidence from these studies is summarised in the clinical evidence summary below (Table 3, Table 4, Table 5,

Table 6, Table 7).

Clinical studies comparing the following interventions was identified:

- Non-steroidal anti-inflammatory drugs compared to placebo
- Benzodiazepines compared to placebo
- Gabapentinoids compared to placebo
- Corticosteroids compared to gabapentinoids
- Corticosteroids compared to placebo.

No relevant clinical studies comparing any other interventions were identified. No Cochrane reviews were included. Due to insufficient evidence, comparative non-randomised studies were checked for eligibility, of which none satisfied the inclusion criteria.

See also the study selection flow chart in Appendix C, study evidence tables in Appendix D, forest plots in Appendix E and GRADE tables in Appendix F.

1.1.4.2 Excluded studies

Three Cochrane reviews were identified but were not included in the review as they included the wrong populations for this review protocol (either mixed neuropathic pain[32] or studies where the focus was low back pain rather than sciatica[112, 113]).

See the excluded studies list in Appendix J.

1.1.5 Summary of studies included in the effectiveness evidence

Table 2: Summary of studies included in the evidence review

Study	Intervention and comparison	Population	Outcomes	Comments
Baron 2010[17]	**Antiepileptics – Gabapentinoids** (n=111) Pregabalin 150-600mg/day for 5 weeks. **Placebo** (n=107) Concomitant medication/care: People were permitted to continue established medication not excluded in the protocol (antiepileptics, nerve blocks, high-potency opioids, and opioid combinations). Recue medications included paracetamol no more than 4 grams/day or	**Chronic lumbosacral radiculopathy due to spinal stenosis or disc herniation** N = 218 Chronicity of pain: Chronic pain (at least 3 months duration)	Pain severity at up to 4 months Psychological distress at up to 4 months Adverse events (morbidity) at up to 4 months Adverse events (mortality) at up to 4 months	Enrichment study. Includes a run in single arm trial of pregabalin to identify responders to pregabalin and only includes these participants in the study.

Study	Intervention and comparison	Population	Outcomes	Comments
	paracetamol/codeine no more than 4 grams/60mg/day.			
Brotz 2010[26]	**Muscle relaxants – Benzodiazepines** (n=30) Diazepam 2x5mg daily for 5 days. **Placebo** (n=30) Concomitant medication/care: Mechanical physiotherapy and the use of a basic analgesic and anti-inflammatory agent were permitted.	**Sciatica without or with neurological deficit attributable to lumbar disc prolapse** N = 60 Chronicity of pain: Not stated / Unclear	Responder criteria (pain) at up to 4 months	
Dreiser 2001[33]	**Non-steroidal anti-inflammatory drugs** (n=352) Meloxicam 7.5mg or 15mg once a day for 7 days. **Placebo** (n=180) Concomitant medication/care: No additional information.	**Common sciatica** N = 532 Chronicity of pain: Not stated / Unclear	Pain severity at up to 4 months Adverse events (morbidity) at up to 4 months	A pooled analysis of two studies which are reported separately. One of the included studies was an inter-class comparison and so was not included in the review.
Goldberg 2015[47]	**Corticosteroids** (n=181) Prednisone 20mg daily for 5 days, then 40mg daily for 5 days, then 20mg daily for 5 days (15 days in total). **Placebo** (n=88) Concomitant medication/care: Both groups received usual care for their symptoms (apart from NSAIDs, which were not allowed for 3 weeks after randomisation).	**Leg pain extending below the knee in a nerve root distribution with a herniated disc confirmed by MRI** N = 269 Chronicity of pain: Not stated / Unclear	Quality of life at up to 4 months and >4 months Pain severity at up to 4 months and >4 months Function at up to 4 months and >4 months Adverse events (morbidity) at up to 4 months Responder criteria (pain) at up to 4 months and >4 months	

Study	Intervention and comparison	Population	Outcomes	Comments
Herrmann 2009[57]	**Non-steroidal anti-inflammatory drugs** (n=57) Diclofenac 50mg twice a day for days 1 and 5, 50mg three times a day for days 2-3. **Placebo** (n=57) A third group was included in the study (Lornoxicam). This was not included in the final analysis as Lornoxicam is not licensed for use in the United Kingdom. Concomitant medication/care: No additional information.	**Sciatica or lumbosciatica** N = 114 Chronicity of pain: Acute pain (<3 months duration)	Adverse events (morbidity) at up to 4 months	The paper reports pain (as measured on a 100mm VAS). Due to no variance data being reported for the comparison of diclofenac compared to placebo, this could not be included in the analysis.
Ko 2016[71]	**Corticosteroids** (n=20) Triamcinolone 4mg twice daily for 2 weeks then tapered or doubled depending on efficacy and continued for 12 weeks. **Antiepileptics – Gabapentinoids** (n=20) Pregabalin 7.5mg* twice daily or gabapentin 100mg three times daily for 2 weeks then tapered or doubled depending on efficacy and continued for 12 weeks. Concomitant medication/care: No additional information.	**Lumbar radiating pain** N = 40 Chronicity of pain: Not stated / Unclear	Quality of life at up to 4 months Pain severity at up to 4 months Function at up to 4 months	*Stakeholder correspondence confirmed that the dose reported in the paper is a typographical error and should read 75mg.

Study	Intervention and comparison	Population	Outcomes	Comments
Mathieson 2017[85] Subsidiary papers: Mathieson 2016[83] Mathieson 2013[86]	**Antiepileptics – Gabapentinoids** (n=108) Pregabalin, starting at 75mg twice daily increased to a maximum of 300mg twice daily **Placebo** (n=101) Concomitant medication/care: People could receive additional care as agreed by the study clinicians	**Moderate-to-severe sciatica** N = 209 Chronicity of pain: Mixed (for a minimum of 1 week and a maximum of 1 year)	Quality of life at up to 4 months and >4 months Pain severity at up to 4 months and >4 months Function at up to 4 months and >4 months Adverse events (morbidity) at >4 months	
Yildirim 2013[144]	**Antiepileptics – Gabapentinoids** (n=25) Gabapentin **Placebo** (n=25) Concomitant medication/care: No other treatments for lumbosciatalgia were permitted	**L5 or S1 radiculopathy** N = 50 Chronicity of pain: Chronic (mean duration [SD]): 68.5 (59.8) months	Pain severity at up to 4 months Adverse events (morbidity) at up to 4 months	

See Appendix D for full evidence tables.

1.1.6 Summary of the effectiveness evidence

Table 3: Clinical evidence summary: non-steroidal anti-inflammatory drugs compared to placebo

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		MID for imprecision
				Risk with Placebo	Risk difference with Non-steroidal anti-inflammatory drugs (95% CI)	
Pain severity (VAS, 0-100, high is poor, change score) at up to 4 months	532 (1 study) 7 days	⊕⊕⊕⊕ HIGH		The mean pain severity in the control groups was -24	The mean pain severity in the intervention groups was **4.5 lower** (9.3 lower to 0.3 higher)	MID = 10
Adverse events (morbidity) at up to 4 months	646 (2 studies) 6 days	⊕⊕⊕⊖ MODERATE[1] due to imprecision	RR 1.41 (0.94 to 2.11)	102 per 1000	**42 more per 1000** (from 6 fewer to 113 more)	MID = 0.8-1.25

[1] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 4: Clinical evidence summary: benzodiazepines compared to placebo

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		MID for imprecision
				Risk with Placebo	Risk difference with Benzodiazepines (95% CI)	
Responder criteria (pain reduction of VAS of 50% of more) at up to 4 months	58 (1 study) 1 weeks	⊕⊕⊕⊖ MODERATE[1] due to imprecision	RR 0.52 (0.33 to 0.84)	793 per 1000	**381 fewer per 1000** (from 127 fewer to 531 fewer)	MID = 0.8 1.25

[1] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 5: Clinical evidence summary: gabapentinoids compared to placebo

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		MID for imprecision
				Risk with Placebo	Risk difference with Gabapentinoids (95% CI)	
Quality of life (SF-12 physical component, 0-100, high is good, final value) at up to 4 months	174 (1 study) 12 weeks	⊕⊕⊕⊖ MODERATE[1] due to imprecision		The mean quality of life in the control groups was 42.4	The mean quality of life in the intervention groups was **1.6 lower** (4.47 lower to 1.27 higher)	MID = 2
Quality of life (SF-12 mental component, 0-100, high is good, final value) at up to 4 months	174 (1 study) 12 weeks	⊕⊕⊕⊖ MODERATE[1] due to imprecision		The mean quality of life in the control groups was 50.6	The mean quality of life in the intervention groups was **0.8 lower** (3.95 lower to 2.35 higher)	MID = 3
Quality of life (SF-12 physical component, 0-100, high is good, final value) at >4 months	162 (1 study) 52 weeks	⊕⊕⊕⊖ MODERATE[1] due to imprecision		The mean quality of life in the control groups was 44.0	The mean quality of life in the intervention groups was **1.8 lower** (4.99 lower to 1.39 higher)	MID = 2
Quality of life (SF-12 mental component, 0-100, high is good, final value) at >4 months	162 (1 study) 52 weeks	⊕⊕⊖⊖ LOW[1] due to imprecision		The mean quality of life in the control groups was 51.0	The mean quality of life in the intervention groups was **0.2 higher** (3.27 lower to 3.67 higher)	MID = 3
Pain severity (VAS, NRS, 0-10, high is poor, final value and change score) at up to 4 months	408 (2 studies) 9 weeks	⊕⊕⊕⊕ HIGH		The mean pain severity in the control groups was 1.6	The mean pain severity in the intervention groups was **0.16 lower** (0.53 lower to 0.21 higher)	MID = 1
Pain severity (pain at rest, 0-3, high is poor, final value) at up to 4 months	43 (1 study) 8 weeks	⊕⊕⊕⊖ MODERATE[2] due to risk of bias		The mean pain severity in the control groups was 1.36	The mean pain severity in the intervention groups was **0.80 lower**	MID = 0.3 (10% of the scale)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		MID for imprecision
				Risk with Placebo	Risk difference with Gabapentinoids (95% CI)	
					(1.15 to 0.45 lower)	
Pain severity (NRS, 0-10, high is poor, final value) at >4 months	178 (1 study) 52 weeks	⊕⊕⊕⊖ MODERATE[1] due to imprecision		The mean pain severity in the control groups was 3.0	The mean pain severity in the intervention groups was **0.4 higher** (0.45 lower to 1.25 higher)	MID = 1
Function (Roland Disability Questionnaire, 0-23, high is poor, final value) at up to 4 months	181 (1 study) 12 weeks	⊕⊕⊖⊖ LOW[1] due to imprecision		The mean function in the control groups was 8.7	The mean function in the intervention groups was **0.1 lower** (2.21 lower to 2.01 higher)	MID = 2
Function (Roland Disability Questionnaire, 0-23, high is poor, final value) at >4 months	162 (1 study) 52 weeks	⊕⊕⊕⊖ MODERATE[1] due to imprecision		The mean function in the control groups was 7.4	The mean function in the intervention groups was **0.8 higher** (1.48 lower to 3.08 higher)	MID = 2
Psychological distress (HADS anxiety subscale, 0-21, high is poor, change score) at up to 4 months	201 (1 study) 5 weeks	⊕⊕⊖⊖ LOW[1,2] due to risk of bias, imprecision		The mean psychological distress in the control groups was 0.82	The mean psychological distress in the intervention groups was **1.01 lower** (1.78 to 0.24 lower)	MID = 2.1 (10% of the scale)
Psychological distress (HADS depression subscale, 0-21, high is poor, change score) at up to 4 months	201 (1 study) 5 weeks	⊕⊕⊖⊖ LOW[1,2] due to risk of bias, imprecision		The mean psychological distress in the control groups was 0.56	The mean psychological distress in the intervention groups was **1.13 lower** (1.77 to 0.49 lower)	MID = 2.1 (10% of the scale)
Adverse event (morbidity) at up to 4 months	267 (2 studies) 7 weeks	⊖⊖⊖⊖ VERY LOW[1,2,3] due to risk of bias, inconsistency, imprecision	RR 1.02 (0.74 to 1.39)			
				341 per 1000	**7 more per 1000** (from 89 fewer to 133 more)	MID = 0.8-1.25

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		MID for imprecision
				Risk with Placebo	Risk difference with Gabapentinoids (95% CI)	
Adverse event (morbidity) at >4 months	217 (1 study) 52 weeks	⨁⨁⨁⊖ MODERATE[1] due to imprecision	RR 1.54 (1.17 to 2.02)	402 per 1000	**217 more per 1000** (from 68 more to 410 more)	MID = 0.8-1.25
Adverse event (mortality) at up to 4 months	217 (1 study) 5 weeks	⨁⊖⊖⊖ VERY LOW[2,5] due to risk of bias, imprecision	RD 0.00 (-0.20 to 0.20)	0 per 1000	**0 fewer per 1000** (from 20 fewer to 20 more)[4]	See footnote[5]

[1] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[2] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[3] Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)
[4] Absolute effect calculated by risk difference due to zero events in at least one arm of one study
[5] Downgraded by for imprecision for mortality due to the confidence interval crossing the line of no effect, sample size also considered due to there being zero events.

Table 6: Clinical evidence summary: Corticosteroids compared to placebo

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		MID for imprecision
				Risk with Placebo	Risk difference with Steroids (95% CI)	
Quality of life (SF-36 physical component summary, 0-100, high is good, change score) at up to 4 months	267 (1 study) 3 weeks	⊕⊕⊕⊖ MODERATE[1] due to imprecision		The mean quality of life in the control groups was 2.8	The mean quality of life in the intervention groups was **3 higher** (1.15 to 4.85 higher)	MID = 2
Quality of life (SF-36 mental component summary, 0-100, high is good, change score) at up to 4 months	267 (1 study) 3 weeks	⊕⊕⊕⊖ MODERATE[1] due to imprecision		The mean quality of life in the control groups was -0.7	The mean quality of life in the intervention groups was **1.9 higher** (0.79 lower to 4.59 higher)	MID = 3
Quality of life (SF-36 physical component summary, 0-100, high is good, change score) at >4 months	234 (1 study) 52 weeks	⊕⊕⊕⊖ MODERATE[1] due to imprecision		The mean quality of life in the control groups was 15.7	The mean quality of life in the intervention groups was **2.3 higher** (0.62 lower to 5.22 higher)	MID = 2
Quality of life (SF-36 mental component summary, 0-100, high is good, change score) at >4 months	234 (1 study) 52 weeks	⊕⊕⊕⊖ MODERATE[1] due to imprecision		The mean quality of life in the control groups was 3.1	The mean quality of life in the intervention groups was **3.8 higher** (0.84 to 6.76 higher)	MID = 3
Pain severity (NRS, 0-10, high is poor, change score) at up to 4 months	267 (1 study) 3 weeks	⊕⊕⊕⊕ HIGH		The mean pain severity in the control groups was -2.8	The mean pain severity in the intervention groups was **0.2 lower** (0.85 lower to 0.45 higher)	MID = 1

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		MID for imprecision
				Risk with Placebo	Risk difference with Steroids (95% CI)	
Pain severity (NRS, 0-10, high is poor, change score) at >4 months	234 (1 study) 52 weeks	⊕⊕⊕⊖ MODERATE[1] due to imprecision		The mean pain severity in the control groups was -4.6	The mean pain severity in the intervention groups was **0.6 lower** (1.35 lower to 0.15 higher)	MID = 1
Function (Oswestry Disability Index, 0-100, high is poor, change score) at up to 4 months	267 (1 study) 3 weeks	⊕⊕⊕⊕ HIGH		The mean function in the control groups was -13.3	The mean function in the intervention groups was **5.7 lower** (9.97 to 1.43 lower)	MID = 10
Function (Oswestry Disability Index, 0-100, high is poor, change score) at >4 months	234 (1 study) 52 weeks	⊕⊕⊕⊖ MODERATE[1] due to imprecision		The mean function in the control groups was -30.4	The mean function in the intervention groups was **7.4 lower** (12.68 to 2.12 lower)	MID = 10
Adverse events (morbidity) at up to 4 months	267 (1 study) 3 weeks	⊕⊕⊕⊕ HIGH	RR 2.06 (1.38 to 3.08)			
				239 per 1000	**253 more per 1000** (from 91 more to 497 more)	MID = 0.8-1.25
Responder criteria (improvement of pain NRS of no less than 3 points) at up to 4 months	267 (1 study) 3 weeks	⊕⊕⊕⊖ MODERATE[1] due to imprecision	RR 1.01 (0.78 to 1.29)			
				511 per 1000	**5 more per 1000** (from 112 fewer to 148 more)	MID = 0.8-1.25
Responder criteria (improvement of pain NRS of no less than 3 points) at >4 months	234 (1 study) 52 weeks	⊕⊕⊕⊕ HIGH	RR 1.07 (0.93 to 1.23)			
				779 per 1000	**55 more per 1000** (from 55 fewer to 179 more)	MID = 0.8-1.25

[1] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 7: Clinical evidence summary: Corticosteroids compared to gabapentinoids

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		MID for imprecision
				Risk with Gabapentinoids	Risk difference with Corticosteroids (95% CI)	
Quality of life (SF-36 physical component score, 0-100, high is good, final value) at up to 4 months	40 (1 study) 12 weeks	⊕⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision		The mean quality of life in the control groups was 58.7	The mean quality of life in the intervention groups was **5 lower** (17.99 lower to 7.99 higher)	MID = 2
Quality of life (SF-36 mental component score, 0-100, high is good, final value) at up to 4 months	40 (1 study) 12 weeks	⊕⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision		The mean quality of life in the control groups was 57.5	The mean quality of life in the intervention groups was **1.1 higher** (10.8 lower to 13 higher)	MID = 2
Pain severity (NRS, 0-10, high is poor, final value) at up to 4 months	40 (1 study) 12 weeks	⊕⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision		The mean pain severity in the control groups was 3.2	The mean pain severity in the intervention groups was **1.2 lower** (2.69 lower to 0.29 higher)	MID = 1
Function (Oswestry disability index, 0-100, high is poor, final value) at up to 4 months	40 (1 study) 12 weeks	⊕⊕⊖⊖ LOW[1] due to risk of bias		The mean function in the control groups was 8.5	The mean function in the intervention groups was **1.8 higher** (3.38 lower to 6.98 higher)	MID = 10

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

See Appendix F for full GRADE tables.

1.1.7 Economic evidence

1.1.7.1 Included studies

No health economic studies were included.

1.1.7.2 Excluded studies

One economic study relating to this review question was identified but was excluded due to a combination of limited applicability and methodological limitations.[38, 75] This is listed in Appendix J, with reasons for exclusion given.

See also the health economic study selection flow chart in Appendix G.

1.1.8 Summary of included economic evidence

No study was included.

1.1.9 Economic model

This area was not prioritised for new cost-effectiveness analysis.

1.1.10 Evidence statements

Effectiveness

See the summary of evidence in Table 3, Table 4, Table 5,

Table 6, Table 7.

Economic

- No relevant economic evaluations were identified.

1.1.11 The committee's discussion and interpretation of the evidence

1.1.11.1. The outcomes that matter most

The outcomes for this review were: quality of life, pain severity, function, psychological distress, healthcare utilisation, adverse events (morbidity and mortality), and responder criteria for pain and function. The committee agreed that quality of life, pain severity, function and psychological distress were critical to decision making. Each of these outcomes are important to people with sciatica and are important tools for monitoring the condition. The remaining outcomes were considered as important for decision making.

There was limited evidence for all outcomes relevant to this review protocol. No studies reported healthcare utilisation as an outcome. As healthcare use was not a critical outcome, the committee agreed they could formulate recommendations without this information.

1.1.11.2 The quality of the evidence

The quality of the evidence according to GRADE criteria varied from high to very low, with the majority being of moderate quality. Where evidence was downgraded this was mostly due to imprecision in the point estimate. For gabapentinoids compared to placebo and steroids compared to gabapentinoids, some outcomes were also downgraded due to risk of bias due to baseline differences, incomplete outcome reporting and trial design (discussed below).

The quality was considered by the committee when making recommendations. The recommendation against the use of gabapentinoids was made with careful consideration by the committee as there were 2 outcomes for pain severity at less than 4 months that showed conflicting clinical efficacy. High quality evidence showed no clinically important difference, and evidence of moderate quality showed a clinically important benefit. The difference in evidence quality and other limitations (discussed in 1.1.12.3 benefits and harms section) resulted in the committee placing more weight on the higher quality evidence when making the recommendation.

It was noted that one of the studies informing the evidence for gabapentinoids was an enriched enrolment trial. The committee discussed the drawbacks of this study for informing true response in an untested population. However it was agreed this was accounted for in the risk of bias rating and consequently the quality of evidence. Due to the limited amount of evidence it was agreed more informative to retain this study within the review, noting its limitations.

There was an absence of evidence for paracetamol, opioids, antidepressants, nefopam, antiepileptic drugs other than gabapentinoids and muscle relaxants other than benzodiazepines. All other interventions were at least compared to placebo, with the only head-to-head comparison being corticosteroids compared to gabapentinoids. In some cases, the committee agreed it was appropriate to make recommendations based on expert consensus opinion. Consensus recommendations were made where there was existing knowledge of harms considered alongside the absence of evidence of benefit. For others, the committee recommended further research. These were considered appropriate where

there was some uncertainty as to whether the medicines may be of benefit, and the known risk of harms was considered to be lower. There were some medicines for which the committee agreed not to make any recommendation, nor recommend further research. These included medicines rarely prescribed for sciatica in current clinical practice and so the committee agreed the absence of a recommendation would not change clinical practice and a research recommendation would not be of value. Further detail of how these considerations were made for each intervention is covered in the section below on benefits and harms.

Non-randomised studies were included in the search for this review. However, none were identified that fulfilled the criteria for inclusion.

1.1.11.3 Benefits and harms

Non-steroidal anti-inflammatory drugs (NSAIDs) compared to placebo

Two studies reported outcomes comparing NSAIDs to placebo. The evidence was for pain severity and adverse events (morbidity) at up to 4 months. The evidence relating to these outcomes was rated as high to moderate quality and showed no clinically important difference between the two interventions. While the evidence was only in two different types of NSAIDs (meloxicam and diclofenac), the committee agreed that the evidence may be applicable to other types of NSAID. The committee agreed that there was insufficient evidence of benefit to support a recommendation for the use of NSAIDs in people with sciatica. The committee discussed that most clinicians were aware of the BNF drug monographs highlighting the risks of harms from NSAIDs. The committee also noted that NSAIDs were unlikely to be continued if they were not helpful. Therefore, they agreed that a recommendation should not be made for or against their use without sufficient evidence demonstrating benefit or harm from NSAIDs, but that it was important to highlight the risks and lack of evidence for benefit in a recommendation as well as including a research recommendation on the topic.

Benzodiazepines compared to placebo

One study reported an outcome comparing benzodiazepines to placebo. The evidence was for responder criteria for pain at up to 4 months. This suggested that more people receiving placebo had a 50% reduction in pain compared to those receiving benzodiazepines. The difference between placebo and benzodiazepines was considered clinically important although there was some uncertainty in the estimate. The evidence relating to this outcome was of moderate quality as a result of the imprecision. There was no evidence from any of the critical outcomes specified in the protocol. Given the lack of evidence for benefit and the evidence of worse outcome for pain, alongside the potential harms of misuse of benzodiazepines, the committee agreed to recommend against their use for sciatica.

Antiepileptics (gabapentinoids) compared to placebo

Three studies reported outcomes comparing gabapentinoids to placebo. These outcomes included quality of life, pain severity, physical function, psychological distress and adverse events (morbidity) at short and longer term follow up. Adverse events (mortality) was also reported, but at up to 4 months only. These outcomes varied from high to very low quality.

There were 2 separate outcomes for pain at less than 4 months. One showed no clinically important difference (based on 2 studies and 408 people rated as high quality evidence), whereas the other showed a clinically important benefit (this evidence was from 1 study and 43 people rated as moderate quality evidence). Given the difference in quality of evidence and the small number of participants informing the latter outcome, the committee agreed that they would attach more weight to the better quality evidence showing no clinically important difference while making recommendations. Furthermore, there was no clinically important difference in quality of life, function and psychological distress, with a clinically important

harm from gabapentinoids for adverse events (morbidity) at longer term follow up. Although there was some imprecision associated with all of these outcomes, the effects consistently suggested no difference between interventions (with the exception of adverse events as noted above).

The committee questioned the dose of pregabalin used in one study (Ko 2016[71]) where the dose appeared to be particularly low (7.5mg twice daily). Stakeholder feedback revealed that this was a typographical error in the study and that the dose was actually 75mg twice daily, which better reflects the dose used in current practice.

The committee discussed their understanding of the potential harms of misuse of gabapentinoids, as well as their reclassification as controlled drugs in 2019. They therefore agreed to recommend against their use for sciatica.

The committee agreed that whilst all the evidence was for gabapentinoids, there was no reason to suggest other antiepileptics would be more effective for people with sciatica, nor have fewer associated harms, and therefore agreed the recommendation should cover all antiepileptics.

Corticosteroids compared to placebo

One study compared corticosteroids to placebo. The evidence included quality of life, pain severity, function and responder criteria at up to 4 months and longer term. Adverse events (morbidity) was also reported, but at less than 4 months only. These outcomes varied from high to moderate quality.

There was evidence of a clinically important benefit for one of the two outcomes for quality of life at up to 4 months (the physical component summary of SF-36) and for both quality of life measures at the longer term follow up. There was some imprecision associated with all of the quality of life results. No clinically important difference was observed for pain severity or function, with imprecision only associated with the longer term follow up results. Given the lack of effect on pain severity and function, the committee agreed that the suggested benefits for quality of life from a single study were not convincing enough to convey a benefit of corticosteroids. There was also evidence of a clinically important harm in adverse events (morbidity) at up to 4 months.

Corticosteroids compared to antiepileptics (gabapentinoids)

One study reported outcomes comparing corticosteroids to gabapentinoids. These outcomes included quality of life, pain severity and function at up to 4 months. The evidence relating to these outcomes ranged from low to very low quality. The sample size was small (n=40) leading to very wide confidence intervals and downgrading for imprecision in all of the results with the exception of function. There was evidence of a worse outcome with corticosteroids for one of the 2 quality of life outcomes (the physical component score of SF-36) while the other showed no clinically important difference. However, the difference between the 2 groups of participants was minimal after taking into account baseline differences in the 2 randomised groups. There was evidence of clinically important benefit for corticosteroids in terms of pain severity, but no clinically important difference for function at up to 4 months. The committee also noted that the dose of oral corticosteroids was low and the dose of gabapentinoids used in this study were particularly low (pregabalin 7.5mg twice daily or gabapentin 100mg three times daily), and so this may have had an effect on the outcomes. Given the size of the study (40 people), low quality of the evidence, and concerns about the doses used, the committee agreed that little weight could be placed on this evidence.

The committee agreed that with lack of evidence of benefit compared to placebo, associated evidence of harms, and unconvincing results when compared to gabapentinoids, a recommendation should be made against the use of corticosteroids for sciatica. The committee noted that the evidence was only for oral corticosteroids (rather than other routes of administration) and therefore the recommendation is specific to oral use.

Other drug classes

The committee was surprised at the lack of evidence comparing opioids to placebo or other medicines. They agreed that opioids pose a significant risk of harm to people when used incorrectly. Through clinical experience, they agreed that long-term use of opioids was unlikely to be beneficial and given that the harms from opioids are more likely for people when they have been on them for a longer period of time, they agreed to recommend against their use for chronic sciatica. Due to the lack of evidence about their effectiveness in acute sciatica, and committee consensus that opioids may be of benefit when used short term for pain relief, the committee agreed that further research was warranted to inform updates of this guideline. A research recommendation was therefore drafted for this population.

There was no evidence comparing antidepressants to placebo or other medicines. The committee's clinical experience was that antidepressants are commonly used for sciatica and it was noted that they are recommended for other causes of neuropathic pain. The committee agreed there was a lower risk of harm compared to some of the other medicines (for example, long term use of opioids), however their widespread use despite the lack of evidence for their use for sciatica led the committee to recommend further research to inform future updates of this guidance.

There was no evidence for the use of paracetamol, nefopam or muscle relaxants other than benzodiazepines in sciatica. The committee did not make a recommendation regarding these. The committee noted that these are not widely prescribed for management of sciatica alone in current practice and therefore neither a recommendation nor further research were required. A recommendation for the use of paracetamol for people with low back pain is already included within this guideline.

Given the lack of clinical benefit for any of the pharmacological treatments for sciatica included in this review, the committee made no recommendations to offer a specific pharmacological agent. They recommended against use of other treatments where the known potential risks are very likely to outweigh any as yet unknown clinical benefit (gabapentinoids and other antiepileptics, opioids, benzodiazepines). They considered that the recommendations included in the guideline for non-pharmacological or invasive treatment options should be considered as the basis for managing sciatica, as appropriate.

1.1.11.4 Cost effectiveness and resource use

No health economic evidence was found for this question.

The committee agreed that there was no consistent evidence of effectiveness for the management of sciatica for any of the drugs included in the review protocol.

As antiepileptics, oral corticosteroids and benzodiazepines were also found to be harmful, they are unlikely to be cost effective in treating sciatica. Therefore, the recommendation not to use these drugs should reduce drug-related harms. It might lead to an increased use of other recommended treatments but overall should improve the efficiency of the NHS.

The cost effectiveness of antidepressants and opioid analgesics in the treatment of sciatica is uncertain and therefore research has been prioritised.

1.1.11.5 Other factors the committee took into account

The potential harms associated with abrupt discontinuation of certain medicines when used long term prompted the committee to include recommendations on discussing the harms of continuing these medicines with people who are already receiving them. They agreed to include a consensus recommendation that healthcare professionals consider how to withdraw them appropriately if agreed that they should no longer be used. The committee was aware that NICE has a guideline in development for safe prescribing and withdrawal

management of medicines associated with dependence or withdrawal symptoms. The committee were also aware of a review from Public Health England (Dependence and withdrawal associated with some prescribed medicines, 2019[82, 134]) that described the association of abrupt cessation of such drugs with the emergence of withdrawal symptoms. These symptoms might be reduced by using a tapering regime. This helped inform the recommendations in this review. They also discussed the importance of discussion with individual patients about the options for sciatica management, taking into account clinical features, comorbidities and the patient's preferences and expectations. It was agreed that the decision to stop medication should follow an informed discussion with the patient and be a shared decision. The committee noted that this echoed one of the themes in the NICE guideline on Patient experience in adult NHS services and wished to draw attention to section 1.3 "Tailoring healthcare services for each patient" which covers an individualised approach, taking account of patient view and preferences, and section 1.5 including "shared decision-making".

The committee noted the importance of diagnosing sciatica correctly. Sciatica may be misdiagnosed in people with chronic muscular low back pain referring to the leg or leg pain for another reason. Response to medicines is likely to vary depending on the cause of leg pain. The committee considered this while looking at the evidence, as some studies confirmed the clinical presentation of sciatica symptoms with the use of imaging while others did not.

The committee discussed the fact that the symptoms of sciatica can be affected by a range of biological, social and psychological factors. The committee thought that this might explain the heterogeneity in response to treatment for sciatica. They wished to draw attention to the non-pharmacological treatments recommended in this guideline which should be considered alongside pharmacological interventions.

For the recommendations on opioids where separate decisions have been made for acute and chronic sciatica it was considered important to note that chronic pain is pain which lasts for more than three months. Pain may be continuous or intermittent and may fluctuate in intensity. When pain becomes chronic a number of unhelpful neuroadaptations occur which make pain refractory to usual interventions. All pain is influenced by psychological and social factors but these become much more prominent when pain becomes chronic. This means that treatments designed to interrupt pain signals which are successfully used to treat acute pain have little benefit when treating chronic pain. Also, for this reason, exacerbations of chronic pain are less likely to respond to treatment.

1.1.12 Recommendations supported by this evidence review

This evidence review supports recommendations 1.2.16 to 1.2.21 and the research recommendations on opioids for the management of acute sciatica and antidepressants and NSAIDs for the management of sciatica.

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Appendices

Appendix A – Review protocol

Review protocol for pharmacological treatment in the management of sciatica

ID	Field	Content
0.	PROSPERO registration number	CRD42020170282
1.	Review title	What is the clinical and cost effectiveness of pharmacological treatment in the management of sciatica?
2.	Review question	What is the clinical and cost effectiveness of pharmacological treatment in the management of sciatica?
3.	Objective	To determine the most clinically and cost effective pharmacological treatment for people aged 16 or over with sciatica
4.	Searches	The following databases (from inception) will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE • Epistemonikos Searches will be restricted by: • English language studies • Human studies • Letters and comments are excluded

		Other searches: Inclusion lists of relevant systematic reviews will be checked by the reviewer. The searches may be re-run 6 weeks before the final committee meeting and further studies retrieved for inclusion if relevant. The full search strategies will be published in the final review.
5.	Condition or domain being studied	'Sciatica' is a term that describes neuropathic pain radiating into the lower limbs usually caused by compression or irritation of the lumbosacral nerve roots. Also commonly referred to as radicular pain.
6.	Population	Inclusion: • People aged 16 or above with sciatica. Exclusion: • Mixed chronic pain (not just sciatica) Mixed populations of children and people aged 16 and over will be included if ≥80% are 16 and over.
7.	Intervention/Exposure/Test	• Pharmacological treatment (oral/sublingual, rectal, intra-muscular and transdermal but not intravenous) o Paracetamol o Non-steroidal anti-inflammatory drugs o Opioid analgesics o Muscle relaxants - Benzodiazepines - Other muscle relaxants o Antidepressants - SSRIs - SNRIs - Tri-cyclic antidepressants

		- Other ○ Anticonvulsants - Gabapentinoids - Other anticonvulsants • Steroids • Nefopam
8.	Comparator/Reference standard/Confounding factors	• All compared to each other • Placebo • Usual care/waiting-list
9.	Types of study to be included	RCTs and systematic reviews will be included in the first instance. If insufficient RCT evidence to form a recommendation is found for a drug class (or sub-class as stated in the intervention list), comparative non-randomised studies will be included for that class. Published NMAs and IPDs will be considered for inclusion. Crossover trials and conference abstracts will be excluded.
10.	Other exclusion criteria	• Non-English language • Within-class comparison • Intervention or comparison group containing an invasive intervention (e.g. surgery, epidurals, facet-joint blocks/injections).
11.	Context	All settings will be included as this covers both acute and chronic sciatica people may present to primary care or have been referred for specialist management.
12.	Primary outcomes (critical outcomes)	**Critical:** • Quality of life (for example SF-12, SF-36 or EQ-5D) at ≤ 4 months (continuous) • Quality of life (for example SF-12, SF-36 or EQ-5D) at > 4 months (continuous) • Pain severity (for example VAS or NRS) at ≤ 4 months (continuous)

		• Pain severity (for example VAS or NRS) at >4 months (continuous) • Function (for example, RMDQ or ODI) at ≤ 4 months (continuous) • Function (disability scores) at ≤ 4 months (continuous) • Psychological distress (HADS, GHQ, BDI and STAI) at ≤ 4 months (continuous) • Psychological distress (HADS, GHQ, BDI and STAI) at >4 months (continuous) For separation of time points: • ≤4 months: defined as anything that is less than or including 4 months. If a study reports data for 2 time-points between these boundaries (e.g. 2 months and 3 months), then the data closest to 4 months will be used (i.e. in this example it would be 3 months). • >4: Defined as 4 to 12 months or end of trial. If a study reports data for 2 time-points between these boundaries (e.g. 6 months and 12 months), then the data closest to 1 year will be used (i.e. in this example it would be 12 months). NB: if a time point greater than 12 months is also reported, e.g. 6 months and 18 months, then the later time point will be extracted as the last time point is most relevant. Any validated scale will be used. Measures will be pooled where appropriate.
13.	Secondary outcomes (important outcomes)	**Important:** • Healthcare utilisation (prescribing, investigations, hospitalisation or health professional visit) at ≤ 4 months (dichotomous) • Healthcare utilisation (prescribing, investigations, hospitalisation or health professional visit) at > 4 months (dichotomous) • Adverse events (morbidity) at ≤ 4 months (dichotomous) • Adverse events (morbidity) at > 4 months (dichotomous) • Adverse events (mortality) at ≤ 4 months (dichotomous) • Adverse events (mortality) at > 4 months (dichotomous) • Responder criteria (≥ 30% improvement in pain or function) at ≤ 4 months (dichotomous) • Responder criteria (≥ 30% improvement in pain or function) at ≤ 4 months (dichotomous). Same criteria apply for time points as per critical outcomes.
14.	Data extraction (selection and coding)	EndNote will be used for reference management, sifting, citations and bibliographies. All references identified by the searches and from other sources will be screened for inclusion. 10% of the abstracts will be reviewed

		by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. EviBASE will be used for data extraction.
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual. • Systematic reviews: Risk of Bias in Systematic Reviews (ROBIS) • Randomised Controlled Trial: Cochrane RoB (2.0) • Non randomised study, including cohort studies: Cochrane ROBINS-I 10% of all evidence reviews are quality assured by a senior research fellow. This includes checking: • papers were included /excluded appropriately • a sample of the data extractions • correct methods are used to synthesise data • a sample of the risk of bias assessments Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary.
16.	Strategy for data synthesis	• Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). • GRADEpro will be used to assess the quality of evidence for each outcome, taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) will be appraised for each outcome. Publication bias is tested for when there are more than 5 studies for an outcome. The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/ • Where meta-analysis is not possible, data will be presented and quality assessed individually per outcome. • WinBUGS will be used for network meta-analysis, if possible given the data identified.

		Heterogeneity between the studies in effect measures will be assessed using the I^2 statistic and visually inspected. An I^2 value greater than 50% will be considered indicative of substantial heterogeneity. Sensitivity analyses will be conducted based on pre-specified subgroups using stratified meta-analysis to explore the heterogeneity in effect estimates. If this does not explain the heterogeneity, the results will be presented pooled using random-effects.		
17.	Analysis of sub-groups	Subgroups that will be investigated if heterogeneity is present based on: • Chronicity of sciatica; Acute or chronic, defined as <3 months or ≥3 months. • Individual drugs within a class (or subclass as stated in the protocol).		
18.	Type and method of review	☒	Intervention	
		☐	Diagnostic	
		☐	Prognostic	
		☐	Qualitative	
		☐	Epidemiologic	
		☐	Service Delivery	
		☐	Other (please specify)	
19.	Language	English		
20.	Country	England		
21.	Anticipated or actual start date	12/02/20		
22.	Anticipated completion date	August 2020		
23.	Stage of review at time of this submission	Review stage	Started	Completed
		Preliminary searches	☐	☐

		Piloting of the study selection process	☐	☐
		Formal screening of search results against eligibility criteria	☐	☐
		Data extraction	☐	☐
		Risk of bias (quality) assessment	☐	☐
		Data analysis	☐	☐
24.	Named contact	5a. Named contact National Guideline Centre 5b Named contact e-mail Lowbackpain@nice.org.uk 5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE) and the National Guideline Centre		
25.	Review team members	From the National Guideline Centre: Serena Carville George Wood Margaret Constanti Lina Gulhane		

		Katie Broomfield
26.	Funding sources/sponsor	This systematic review is being completed by the National Guideline Centre which receives funding from NICE.
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10169
29.	Other registration details	N/A
30.	Reference/URL for published protocol	N/A
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.
32.	Keywords	Sciatica, Radicular pain, Radiculopathy, Pharmacological management
33.	Details of existing review of same topic by same authors	N/A

34.	Current review status	☒	Ongoing
		☐	Completed but not published
		☐	Completed and published
		☐	Completed, published and being updated
		☐	Discontinued
35.	Additional information	N/A	
36.	Details of final publication	www.nice.org.uk	

Table 8: Health economic review protocol

Review question	Health economic evidence
Objectives	To identify health economic studies relevant to the review question.
Search criteria	• Populations, interventions and comparators must be as specified in the clinical review protocol above. • Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) • Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	A health economic study search will be undertaken using population-specific terms and a health economic study filter – see appendix B below.
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2005, abstract-only studies and studies from non-OECD countries or the USA will also be excluded. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual (2014).[93]

Inclusion and exclusion criteria

- If a study is rated as both 'Directly applicable' and with 'Minor limitations' then it will be included in the guideline. A health economic evidence table will be completed and it will be included in the health economic evidence profile.
- If a study is rated as either 'Not applicable' or with 'Very serious limitations' then it will usually be excluded from the guideline. If it is excluded then a health economic evidence table will not be completed and it will not be included in the health economic evidence profile.
- If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included.

Where there is discretion

The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below.

The health economist will be guided by the following hierarchies.

Setting:

- UK NHS (most applicable).
- OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden).
- OECD countries with predominantly private health insurance systems (for example, Switzerland).
- Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations.

Health economic study type:

- Cost–utility analysis (most applicable).
- Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis).
- Comparative cost analysis.
- Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations.

Year of analysis:

	• The more recent the study, the more applicable it will be. • Studies published in 2005 or later but that depend on unit costs and resource data entirely or predominantly from before 2005 will be rated as 'Not applicable'. • Studies published before 2005 will be excluded before being assessed for applicability and methodological limitations. *Quality and relevance of effectiveness data used in the health economic analysis:* • The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

Appendix B – Literature search strategies

Pharmacological management of sciatica search strategy A

This literature search strategy was used for the following review question:

- What is the clinical and cost effectiveness of pharmacological treatment in the management of sciatica?

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual.[93]

For more information, please see the Methodology review published as part of the accompanying documents for this guideline.

B.1 Clinical search literature search strategy

Searches were constructed using a PICO framework where population (P) terms were combined with Intervention (I) and in some cases Comparison (C) terms. Outcomes (O) are rarely used in search strategies for interventions as these concepts may not be well described in title, abstract or indexes and therefore difficult to retrieve. Search filters were applied to the search where appropriate.

Table 9: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 20 February 2020	Exclusions Randomised controlled trials Systematic review studies Observational studies
Embase (OVID)	1974 – 20 February 2020	Exclusions Randomised controlled trials Systematic review studies Observational studies
The Cochrane Library (Wiley)	Cochrane Reviews to 2020 Issue 2 of 12 CENTRAL to 2020 Issue 2 of 12	None
Epistemonikos (The Epistemonikos Foundation)	Inception to 20 February 2020	

Medline (Ovid) search terms

1.	exp Sciatic Neuropathy/
2.	Radiculopathy/
3.	(lumbago or sciatic*).ti,ab.
4.	(radiculopathy or radiculitis or radicular pain* or radicular syndrome*).ti,ab.
5.	(nerve root* adj5 (pain* or avulsion or compress* or disorder* or pinch* or inflam* or imping* or irritat* or entrap* or trap*)).ti,ab.
6.	(sacral nerve* adj5 (pain* or avulsion or compress* or disorder* or pinch* or inflam* or imping* or irritat* or entrap* or trap*)).ti,ab.
7.	or/1-6
8.	letter/
9.	editorial/

10.	news/
11.	exp historical article/
12.	Anecdotes as Topic/
13.	comment/
14.	case report/
15.	(letter or comment*).ti.
16.	or/8-15
17.	randomized controlled trial/ or random*.ti,ab.
18.	16 not 17
19.	animals/ not humans/
20.	exp Animals, Laboratory/
21.	exp Animal Experimentation/
22.	exp Models, Animal/
23.	exp Rodentia/
24.	(rat or rats or mouse or mice).ti.
25.	or/18-24
26.	7 not 25
27.	limit 26 to English language
28.	analgesics/
29.	analgesic*.ti,ab.
30.	exp cyclooxygenase 2 inhibitors/
31.	((cox2 or cox-2 or coxii or cox-ii) adj2 inhibitor*).ti,ab.
32.	((cyclo-oxygenase2 or cyclo-oxygenase-2 or cyclooxygenase-2 or cyclooxygenase2) adj2 inhibitor*).ti,ab.
33.	((cyclo-oxygenase-ii or cyclo-oxygenaseii or cyclooxygenase-ii or cyclooxygenaseii) adj2 inhibitor*).ti,ab.
34.	exp anti-inflammatory agents, non-steroidal/
35.	(nsaid* or non-steroid* or non-narcotic* or pharmacolog*).ti,ab.
36.	(ibuprofen or aspirin or naproxen or fenoprofen or flurbiprofen or ketoprofen or dexketoprofen or dexibuprofen or tiaprofenic acid or diclofenac or aceclofenac or indometacin or mefenamic acid or meloxicam or nabumetone or phenylbutazone or piroxicam or sulindac or tenoxicam or tolfenamic acid or ketorolac or celecoxib or etoricoxib or aceclofenac or acemetacin or diclofenac or etodolac).ti,ab.
37.	acetaminophen/
38.	(acetaminophen or paracetamol).ti,ab.
39.	exp analgesics, opioid/
40.	(fentanyl or hydrocodone or hydromorphone or levorphanol or meperidine or morphine or oxycodone or oxymorphone or pentazocine or propoxyphene or sufentanil or tramadol or codeine or tapentadol or acetylsalicyl* or carbasalate calcium or diflunisal or aceclofenac or alclofenac or diclofenac or indomethacin or sulindac or meloxicam or piroxicam or dexibuprofen or dexketoprofen or fenoprofen or flurbiprofen or ibuprofen or ketoprofen or naproxen or tiapro* or metamizol or phenylbutazone or phenazone or propyphenazone or celecoxib or etoricoxib or nabumeton or parecoxib).ti,ab.
41.	exp muscle relaxants, central/
42.	exp benzodiazepines/
43.	(muscle relaxant* or benzodiazepine*).ti,ab.

44.	(diazepam or tetrazepam or cyclobenzaprine or carisoprodol or chlorzoxazone or meprobramate or methocarbamol or metaxalone or orphenadrine or tizanidine or flupirtine or baclofen or dantrolene).ti,ab.
45.	exp antidepressive agents/
46.	(antidepress* or anti-depress*).ti,ab.
47.	serotonin norepinephrine reuptake inhibitor*.ti,ab.
48.	selective serotonin reuptake inhibitor*.ti,ab.
49.	(SSRI* or SNRI*).ti,ab.
50.	(amoxapine or bupropion or citalopram or fluoxetine or fluvoxamine or maprotiline or mianserin or paroxetine or quipazine or ritanserin or sulpiride or trazodone or tryptophan or viloxazine or amitriptyline).ti,ab.
51.	(clomipramine or desipramine or dothiepin or doxepin or imipramine or iprindole or lofepramine or nortriptyline or opipramol or protriptyline or trimipramine or nortriptyline or duloxetine or mirtazapine or venlafaxine or amitriptyline).ti,ab.
52.	exp anticonvulsants/
53.	(anticonvulsant* or anti convulsant* or gabapentin or pregabalin or carbamazepine or phenytoin or topiramate or lamotrigine or valproic acid or sodium valproate).ti,ab.
54.	exp steroids/
55.	(glucocorticosteroid* or corticosteroid* or glucocorticoid* or steroid*).ti,ab.
56.	(prednisone or prednisolone or methylprednisolone or dexamethasone or betamethasone or hydrocortisone).ti,ab.
57.	Nefopam/
58.	(nefopam or acupan).ti,ab.
59.	or/28-58
60.	27 and 59
61.	randomized controlled trial.pt.
62.	controlled clinical trial.pt.
63.	randomi#ed.ab.
64.	placebo.ab.
65.	randomly.ab.
66.	clinical trials as topic.sh.
67.	trial.ti.
68.	or/61-67
69.	Meta-Analysis/
70.	Meta-Analysis as Topic/
71.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
72.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
73.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
74.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
75.	(search* adj4 literature).ab.
76.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
77.	cochrane.jw.
78.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
79.	or/69-78

80.	Epidemiologic studies/
81.	Observational study/
82.	exp Cohort studies/
83.	(cohort adj (study or studies or analys* or data)).ti,ab.
84.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
85.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort* or data)).ti,ab.
86.	Controlled Before-After Studies/
87.	Historically Controlled Study/
88.	Interrupted Time Series Analysis/
89.	(before adj2 after adj2 (study or studies or data)).ti,ab.
90.	exp case control study/
91.	case control*.ti,ab.
92.	Cross-sectional studies/
93.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
94.	or/80-93
95.	60 and (68 or 79 or 94)

Embase (Ovid) search terms

1.	exp Sciatic Neuropathy/
2.	Radiculopathy/
3.	(lumbago or sciatic*).ti,ab.
4.	(radiculopathy or radiculitis or radicular pain* or radicular syndrome*).ti,ab.
5.	(nerve root* adj5 (pain* or avulsion or compress* or disorder* or pinch* or inflam* or imping* or irritat* or entrap* or trap*)).ti,ab.
6.	(sacral nerve* adj5 (pain* or avulsion or compress* or disorder* or pinch* or inflam* or imping* or irritat* or entrap* or trap*)).ti,ab.
7.	or/1-6
8.	letter.pt. or letter/
9.	note.pt.
10.	editorial.pt.
11.	case report/ or case study/
12.	(letter or comment*).ti.
13.	or/8-12
14.	randomized controlled trial/ or random*.ti,ab.
15.	13 not 14
16.	animal/ not human/
17.	nonhuman/
18.	exp Animal Experiment/
19.	exp Experimental Animal/
20.	animal model/
21.	exp Rodent/
22.	(rat or rats or mouse or mice).ti.
23.	or/15-22
24.	7 not 23

25.	limit 24 to English language
26.	analgesics/
27.	analgesic*.ti,ab.
28.	exp cyclooxygenase 2 inhibitor/
29.	((cox2 or cox-2 or coxii or cox-ii) adj2 inhibitor*).ti,ab.
30.	((cyclo-oxygenase2 or cyclo-oxygenase-2 or cyclooxygenase-2 or cyclooxygenase2) adj2 inhibitor*).ti,ab.
31.	((cyclo-oxygenase-ii or cyclo-oxygenaseii or cyclooxygenase-ii or cyclooxygenaseii) adj2 inhibitor*).ti,ab.
32.	exp nonsteroid antiinflammatory agent/
33.	(nsaid* or non-steroid* or non-narcotic* or pharmacolog*).ti,ab.
34.	(ibuprofen or aspirin or naproxen or fenoprofen or flurbiprofen or ketoprofen or dexketoprofen or dexibuprofen or tiaprofenic acid or diclofenac or aceclofenac or indometacin or mefenamic acid or meloxicam or nabumetone or phenylbutazone or piroxicam or sulindac or tenoxicam or tolfenamic acid or ketorolac or celecoxib or etoricoxib or aceclofenac or acemetacin or diclofenac or etodolac).ti,ab.
35.	paracetamol/
36.	(acetaminophen or paracetamol).ti,ab.
37.	exp narcotic analgesic agent/
38.	(fentanyl or hydrocodone or hydromorphone or levorphanol or meperidine or morphine or oxycodone or oxymorphone or pentazocine or propoxyphene or sufentanil or tramadol or codeine or tapentadol or acetylsalicyl* or carbasalate calcium or diflunisal or aceclofenac or alclofenac or diclofenac or indomethacin or sulindac or meloxicam or piroxicam or dexibuprofen or dexketoprofen or fenoprofen or flurbiprofen or ibuprofen or ketoprofen or naproxen or tiapro* or metamizol or phenylbutazone or phenazone or propyphenazone or celecoxib or etoricoxib or nabumeton or parecoxib).ti,ab.
39.	exp central muscle relaxant/
40.	exp benzodiazepine derivative/
41.	(muscle relaxant* or benzodiazepine*).ti,ab.
42.	(diazepam or tetrazepam or cyclobenzaprine or carisoprodol or chlorzoxazone or meprobramate or methocarbamol or metaxalone or orphenadrine or tizanidine or flupirtine or baclofen or dantrolene).ti,ab.
43.	exp antidepressant agent/
44.	(antidepress* or anti-depress*).ti,ab.
45.	serotonin norepinephrine reuptake inhibitor*.ti,ab.
46.	selective serotonin reuptake inhibitor*.ti,ab.
47.	(SSRI* or SNRI*).ti,ab.
48.	(amoxapine or bupropion or citalopram or fluoxetine or fluvoxamine or maprotiline or mianserin or paroxetine or quipazine or ritanserin or sulpiride or trazodone or tryptophan or viloxazine or amitriptyline).ti,ab.
49.	(clomipramine or desipramine or dothiepin or doxepin or imipramine or iprindole or lofepramine or nortriptyline or opipramol or protriptyline or trimipramine or nortriptyline or duloxetine or mirtazapine or venlafaxine or amitriptyline).ti,ab.
50.	exp anticonvulsive agent/
51.	(anticonvulsant* or anti convulsant* or gabapentin or pregabalin or carbamazepine or phenytoin or topiramate or lamotrigine or valproic acid or sodium valproate).ti,ab.
52.	exp steroid/
53.	(glucocorticosteroid* or corticosteroid* or glucocorticoid* or steroid*).ti,ab.
54.	(prednisone or prednisolone or methylprednisolone or dexamethasone or betamethasone or hydrocortisone).ti,ab.

55.	Nefopam/
56.	(nefopam or acupan).ti,ab.
57.	or/26-56
58.	25 and 57
59.	random*.ti,ab.
60.	factorial*.ti,ab.
61.	(crossover* or cross over*).ti,ab.
62.	((doubl* or singl*) adj blind*).ti,ab.
63.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
64.	crossover procedure/
65.	single blind procedure/
66.	randomized controlled trial/
67.	double blind procedure/
68.	or/59-67
69.	systematic review/
70.	Meta-Analysis/
71.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
72.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
73.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
74.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
75.	(search* adj4 literature).ab.
76.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
77.	cochrane.jw.
78.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
79.	or/69-78
80.	Clinical study/
81.	Observational study/
82.	family study/
83.	longitudinal study/
84.	retrospective study/
85.	prospective study/
86.	cohort analysis/
87.	follow-up/
88.	cohort*.ti,ab.
89.	87 and 88
90.	(cohort adj (study or studies or analys* or data)).ti,ab.
91.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
92.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort* or data)).ti,ab.
93.	(before adj2 after adj2 (study or studies or data)).ti,ab.
94.	exp case control study/

95.	case control*.ti,ab.
96.	cross-sectional study/
97.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
98.	or/80-86,89-97
99.	58 and (68 or 79 or 98)

Cochrane Library (Wiley) search terms

#1.	MeSH descriptor: [Sciatic Neuropathy] explode all trees
#2.	MeSH descriptor: [Radiculopathy] explode all trees
#3.	(lumbago or sciatic*):ti,ab
#4.	(radiculopathy or radiculitis or radicular pain* or radicular syndrome*):ti,ab
#5.	(nerve root* near/5 (pain* or avulsion or compress* or disorder* or pinch* or inflam* or imping* or irritat* or entrap* or trap*)):ti,ab
#6.	(sacral nerve* near/5 (pain* or avulsion or compress* or disorder* or pinch* or inflam* or imping* or irritat* or entrap* or trap*)):ti,ab
#7.	[or #1-#6]
#8.	MeSH descriptor: [Analgesics] explode all trees
#9.	analgesic*:ti,ab
#10.	MeSH descriptor: [Cyclooxygenase 2 Inhibitors] explode all trees
#11.	((cox2 or cox-2 or coxii or cox-ii) near/2 inhibitor*):ti,ab
#12.	((cyclo-oxygenase2 or cyclo-oxygenase-2 or cyclooxygenase-2 or cyclooxygenase2) near/2 inhibitor*):ti,ab
#13.	((cyclo-oxygenase-ii or cyclo-oxygenaseii or cyclooxygenase-ii or cyclooxygenaseii) near/2 inhibitor*):ti,ab
#14.	MeSH descriptor: [Anti-Inflammatory Agents, Non-Steroidal] explode all trees
#15.	(nsaid* or non-steroid* or non-narcotic* or pharmacolog*):ti,ab
#16.	(ibuprofen or aspirin or naproxen or fenoprofen or flurbiprofen or ketoprofen or dexketoprofen or dexibuprofen or tiaprofenic acid or diclofenac or aceclofenac or indometacin or mefenamic acid or meloxicam or nabumetone or phenylbutazone or piroxicam or sulindac or tenoxicam or tolfenamic acid or ketorolac or celecoxib or etoricoxib or aceclofenac or acemetacin or diclofenac or etodolac):ti,ab
#17.	MeSH descriptor: [Acetaminophen] explode all trees
#18.	(acetaminophen or paracetamol):ti,ab
#19.	MeSH descriptor: [Analgesics, Opioid] explode all trees
#20.	(fentanyl or hydrocodone or hydromorphone or levorphanol or meperidine or morphine or oxycodone or oxymorphone or pentazocine or propoxyphene or sufentanil or tramadol or codeine or tapentadol or acetylsalicyl* or carbasalate calcium or diflunisal or aceclofenac or alclofenac or diclofenac or indomethacin or sulindac or meloxicam or piroxicam or dexibuprofen or dexketoprofen or fenoprofen or flurbiprofen or ibuprofen or ketoprofen or naproxen or tiapro* or metamizol or phenylbutazone or phenazone or propyphenazone or celecoxib or etoricoxib or nabumeton or parecoxib):ti,ab
#21.	MeSH descriptor: [Muscle Relaxants, Central] explode all trees
#22.	MeSH descriptor: [Benzodiazepines] explode all trees
#23.	(muscle relaxant* or benzodiazepine*):ti,ab
#24.	(diazepam or tetrazepam or cyclobenzaprine or carisoprodol or chlorzoxazone or meprobramate or methocarbamol or metaxalone or orphenadrine or tizanidine or flupirtine or baclofen or dantrolene):ti,ab
#25.	MeSH descriptor: [Antidepressive Agents] explode all trees
#26.	(antidepress* or anti-depress*):ti,ab

#27.	serotonin norepinephrine reuptake inhibitor*:ti,ab
#28.	selective serotonin reuptake inhibitor*:ti,ab
#29.	(SSRI* or SNRI*):ti,ab
#30.	(amoxapine or bupropion or citalopram or fluoxetine or fluvoxamine or maprotiline or mianserin or paroxetine or quipazine or ritanserin or sulpiride or trazodone or tryptophan or viloxazine or amitriptyline):ti,ab
#31.	(clomipramine or desipramine or dothiepin or doxepin or imipramine or iprindole or lofepramine or nortriptyline or opipramol or protriptyline or trimipramine or nortriptyline or duloxetine or mirtazapine or venlafaxine or amitriptyline):ti,ab
#32.	MeSH descriptor: [Anticonvulsants] explode all trees
#33.	(anticonvulsant* or anti convulsant* or gabapentin or pregabalin or carbamazepine or phenytoin or topiramate or lamotrigine or valproic acid or sodium valproate):ti,ab
#34.	MeSH descriptor: [Steroids] explode all trees
#35.	(glucocorticosteroid* or corticosteroid* or glucocorticoid* or steroid*):ti,ab
#36.	(prednisone or prednisolone or methylprednisolone or dexamethasone or betamethasone or hydrocortisone):ti,ab
#37.	MeSH descriptor: [Nefopam] explode all trees
#38.	(Nefopam or acupan):ti,ab
#39.	[or #8-#38]
#40.	#7 and #39

Epistemonikos search terms

1.	sciatic* or radiculopathy or radiculitis or radicular pain* or lumbago

B.2 Health Economics literature search strategy

Health economic evidence was identified by conducting a broad search relating to low back pain and sciatica population in NHS Economic Evaluation Database (NHS EED – this ceased to be updated after March 2015) and the Health Technology Assessment database (HTA) with no date restrictions. NHS EED and HTA databases are hosted by the Centre for Research and Dissemination (CRD). Additional searches were run on Medline and Embase.

Table 10: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline	2014 – 20 February 2020	Exclusions Health economics studies
Embase	2014 – 20 February 2020	Exclusions Health economics studies
Centre for Research and Dissemination (CRD)	HTA - Inception – 20 February 2020 NHSEED - Inception to March 2015	None

Medline (Ovid) search terms

1.	exp Sciatic Neuropathy/
2.	Radiculopathy/
3.	(lumbago or sciatic*).ti,ab.
4.	(radiculopathy or radiculitis or radicular pain* or radicular syndrome*).ti,ab.

5.	(nerve root* adj5 (pain* or avulsion or compress* or disorder* or pinch* or inflam* or imping* or irritat* or entrap* or trap*)).ti,ab.
6.	(sacral nerve* adj5 (pain* or avulsion or compress* or disorder* or pinch* or inflam* or imping* or irritat* or entrap* or trap*)).ti,ab.
7.	or/1-6
8.	letter/
9.	editorial/
10.	news/
11.	exp historical article/
12.	Anecdotes as Topic/
13.	comment/
14.	case report/
15.	(letter or comment*).ti.
16.	or/8-15
17.	randomized controlled trial/ or random*.ti,ab.
18.	16 not 17
19.	animals/ not humans/
20.	exp Animals, Laboratory/
21.	exp Animal Experimentation/
22.	exp Models, Animal/
23.	exp Rodentia/
24.	(rat or rats or mouse or mice).ti.
25.	or/18-24
26.	7 not 25
27.	limit 26 to English language
28.	analgesics/
29.	analgesic*.ti,ab.
30.	exp cyclooxygenase 2 inhibitors/
31.	((cox2 or cox-2 or coxii or cox-ii) adj2 inhibitor*).ti,ab.
32.	((cyclo-oxygenase2 or cyclo-oxygenase-2 or cyclooxygenase-2 or cyclooxygenase2) adj2 inhibitor*).ti,ab.
33.	((cyclo-oxygenase-ii or cyclo-oxygenaseii or cyclooxygenase-ii or cyclooxygenaseii) adj2 inhibitor*).ti,ab.
34.	exp anti-inflammatory agents, non-steroidal/
35.	(nsaid* or non-steroid* or non-narcotic* or pharmacolog*).ti,ab.
36.	(ibuprofen or aspirin or naproxen or fenoprofen or flurbiprofen or ketoprofen or dexketoprofen or dexibuprofen or tiaprofenic acid or diclofenac or aceclofenac or indometacin or mefenamic acid or meloxicam or nabumetone or phenylbutazone or piroxicam or sulindac or tenoxicam or tolfenamic acid or ketorolac or celecoxib or etoricoxib or aceclofenac or acemetacin or diclofenac or etodolac).ti,ab.
37.	acetaminophen/
38.	(acetaminophen or paracetamol).ti,ab.
39.	exp analgesics, opioid/
40.	(fentanyl or hydrocodone or hydromorphone or levorphanol or meperidine or morphine or oxycodone or oxymorphone or pentazocine or propoxyphene or sufentanil or tramadol or codeine or tapentadol or acetylsalicyl* or carbasalate calcium or diflunisal or aceclofenac or alclofenac or diclofenac or indomethacin or sulindac or meloxicam or

	piroxicam or dexibuprofen or dexketoprofen or fenoprofen or flurbiprofen or ibuprofen or ketoprofen or naproxen or tiapro* or metamizol or phenylbutazone or phenazone or propyphenazone or celecoxib or etoricoxib or nabumeton or parecoxib).ti,ab.
41.	exp muscle relaxants, central/
42.	exp benzodiazepines/
43.	(muscle relaxant* or benzodiazepine*).ti,ab.
44.	(diazepam or tetrazepam or cyclobenzaprine or carisoprodol or chlorzoxazone or meprobramate or methocarbamol or metaxalone or orphenadrine or tizanidine or flupirtine or baclofen or dantrolene).ti,ab.
45.	exp antidepressive agents/
46.	(antidepress* or anti-depress*).ti,ab.
47.	serotonin norepinephrine reuptake inhibitor*.ti,ab.
48.	selective serotonin reuptake inhibitor*.ti,ab.
49.	(SSRI* or SNRI*).ti,ab.
50.	(amoxapine or bupropion or citalopram or fluoxetine or fluvoxamine or maprotiline or mianserin or paroxetine or quipazine or ritanserin or sulpiride or trazodone or tryptophan or viloxazine or amitriptyline).ti,ab.
51.	(clomipramine or desipramine or dothiepin or doxepin or imipramine or iprindole or lofepramine or nortriptyline or opipramol or protriptyline or trimipramine or nortriptyline or duloxetine or mirtazapine or venlafaxine or amitriptyline).ti,ab.
52.	exp anticonvulsants/
53.	(anticonvulsant* or anti convulsant* or gabapentin or pregabalin or carbamazepine or phenytoin or topiramate or lamotrigine or valproic acid or sodium valproate).ti,ab.
54.	exp steroids/
55.	(glucocorticosteroid* or corticosteroid* or glucocorticoid* or steroid*).ti,ab.
56.	(prednisone or prednisolone or methylprednisolone or dexamethasone or betamethasone or hydrocortisone).ti,ab.
57.	Nefopam/
58.	(nefopam or acupan).ti,ab.
59.	or/28-58
60.	27 and 59
61.	economics/
62.	value of life/
63.	exp "costs and cost analysis"/
64.	exp Economics, Hospital/
65.	exp Economics, medical/
66.	Economics, nursing/
67.	economics, pharmaceutical/
68.	exp "Fees and Charges"/
69.	exp budgets/
70.	budget*.ti,ab.
71.	cost*.ti.
72.	(economic* or pharmaco?economic*).ti.
73.	(price* or pricing*).ti,ab.
74.	(cost* adj2 (effectiv* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
75.	(financ* or fee or fees).ti,ab.
76.	(value adj2 (money or monetary)).ti,ab.

77.	or/61-76
78.	60 and 77

Embase (Ovid) search terms

1.	exp Sciatic Neuropathy/
2.	Radiculopathy/
3.	(lumbago or sciatic*).ti,ab.
4.	(radiculopathy or radiculitis or radicular pain* or radicular syndrome*).ti,ab.
5.	(nerve root* adj5 (pain* or avulsion or compress* or disorder* or pinch* or inflam* or imping* or irritat* or entrap* or trap*)).ti,ab.
6.	(sacral nerve* adj5 (pain* or avulsion or compress* or disorder* or pinch* or inflam* or imping* or irritat* or entrap* or trap*)).ti,ab.
7.	or/1-6
8.	letter.pt. or letter/
9.	note.pt.
10.	editorial.pt.
11.	case report/ or case study/
12.	(letter or comment*).ti.
13.	or/8-12
14.	randomized controlled trial/ or random*.ti,ab.
15.	13 not 14
16.	animal/ not human/
17.	nonhuman/
18.	exp Animal Experiment/
19.	exp Experimental Animal/
20.	animal model/
21.	exp Rodent/
22.	(rat or rats or mouse or mice).ti.
23.	or/15-22
24.	7 not 23
25.	limit 24 to English language
26.	analgesics/
27.	analgesic*.ti,ab.
28.	exp cyclooxygenase 2 inhibitor/
29.	((cox2 or cox-2 or coxii or cox-ii) adj2 inhibitor*).ti,ab.
30.	((cyclo-oxygenase2 or cyclo-oxygenase-2 or cyclooxygenase-2 or cyclooxygenase2) adj2 inhibitor*).ti,ab.
31.	((cyclo-oxygenase-ii or cyclo-oxygenaseii or cyclooxygenase-ii or cyclooxygenaseii) adj2 inhibitor*).ti,ab.
32.	exp nonsteroid antiinflammatory agent/
33.	(nsaid* or non-steroid* or non-narcotic* or pharmacolog*).ti,ab.
34.	(ibuprofen or aspirin or naproxen or fenoprofen or flurbiprofen or ketoprofen or dexketoprofen or dexibuprofen or tiaprofenic acid or diclofenac or aceclofenac or indometacin or mefenamic acid or meloxicam or nabumetone or phenylbutazone or piroxicam or sulindac or tenoxicam or tolfenamic acid or ketorolac or celecoxib or etoricoxib or aceclofenac or acemetacin or diclofenac or etodolac).ti,ab.

35.	paracetamol/
36.	(acetaminophen or paracetamol).ti,ab.
37.	exp narcotic analgesic agent/
38.	(fentanyl or hydrocodone or hydromorphone or levorphanol or meperidine or morphine or oxycodone or oxymorphone or pentazocine or propoxyphene or sufentanil or tramadol or codeine or tapentadol or acetylsalicyl* or carbasalate calcium or diflunisal or aceclofenac or alclofenac or diclofenac or indomethacin or sulindac or meloxicam or piroxicam or dexibuprofen or dexketoprofen or fenoprofen or flurbiprofen or ibuprofen or ketoprofen or naproxen or tiapro* or metamizol or phenylbutazone or phenazone or propyphenazone or celecoxib or etoricoxib or nabumeton or parecoxib).ti,ab.
39.	exp central muscle relaxant/
40.	exp benzodiazepine derivative/
41.	(muscle relaxant* or benzodiazepine*).ti,ab.
42.	(diazepam or tetrazepam or cyclobenzaprine or carisoprodol or chlorzoxazone or meprobramate or methocarbamol or metaxalone or orphenadrine or tizanidine or flupirtine or baclofen or dantrolene).ti,ab.
43.	exp antidepressant agent/
44.	(antidepress* or anti-depress*).ti,ab.
45.	serotonin norepinephrine reuptake inhibitor*.ti,ab.
46.	selective serotonin reuptake inhibitor*.ti,ab.
47.	(SSRI* or SNRI*).ti,ab.
48.	(amoxapine or bupropion or citalopram or fluoxetine or fluvoxamine or maprotiline or mianserin or paroxetine or quipazine or ritanserin or sulpiride or trazodone or tryptophan or viloxazine or amitriptyline).ti,ab.
49.	(clomipramine or desipramine or dothiepin or doxepin or imipramine or iprindole or lofepramine or nortriptyline or opipramol or protriptyline or trimipramine or nortriptyline or duloxetine or mirtazapine or venlafaxine or amitriptyline).ti,ab.
50.	exp anticonvulsive agent/
51.	(anticonvulsant* or anti convulsant* or gabapentin or pregabalin or carbamazepine or phenytoin or topiramate or lamotrigine or valproic acid or sodium valproate).ti,ab.
52.	exp steroid/
53.	(glucocorticosteroid* or corticosteroid* or glucocorticoid* or steroid*).ti,ab.
54.	(prednisone or prednisolone or methylprednisolone or dexamethasone or betamethasone or hydrocortisone).ti,ab.
55.	Nefopam/
56.	(nefopam or acupan).ti,ab.
57.	or/26-56
58.	25 and 57
59.	health economics/
60.	exp economic evaluation/
61.	exp health care cost/
62.	exp fee/
63.	budget/
64.	funding/
65.	budget*.ti,ab.
66.	cost*.ti.
67.	(economic* or pharmaco?economic*).ti.
68.	(price* or pricing*).ti,ab.

69.	(cost* adj2 (effectiv* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
70.	(financ* or fee or fees).ti,ab.
71.	(value adj2 (money or monetary)).ti,ab.
72.	or/59-71
73.	58 and 72

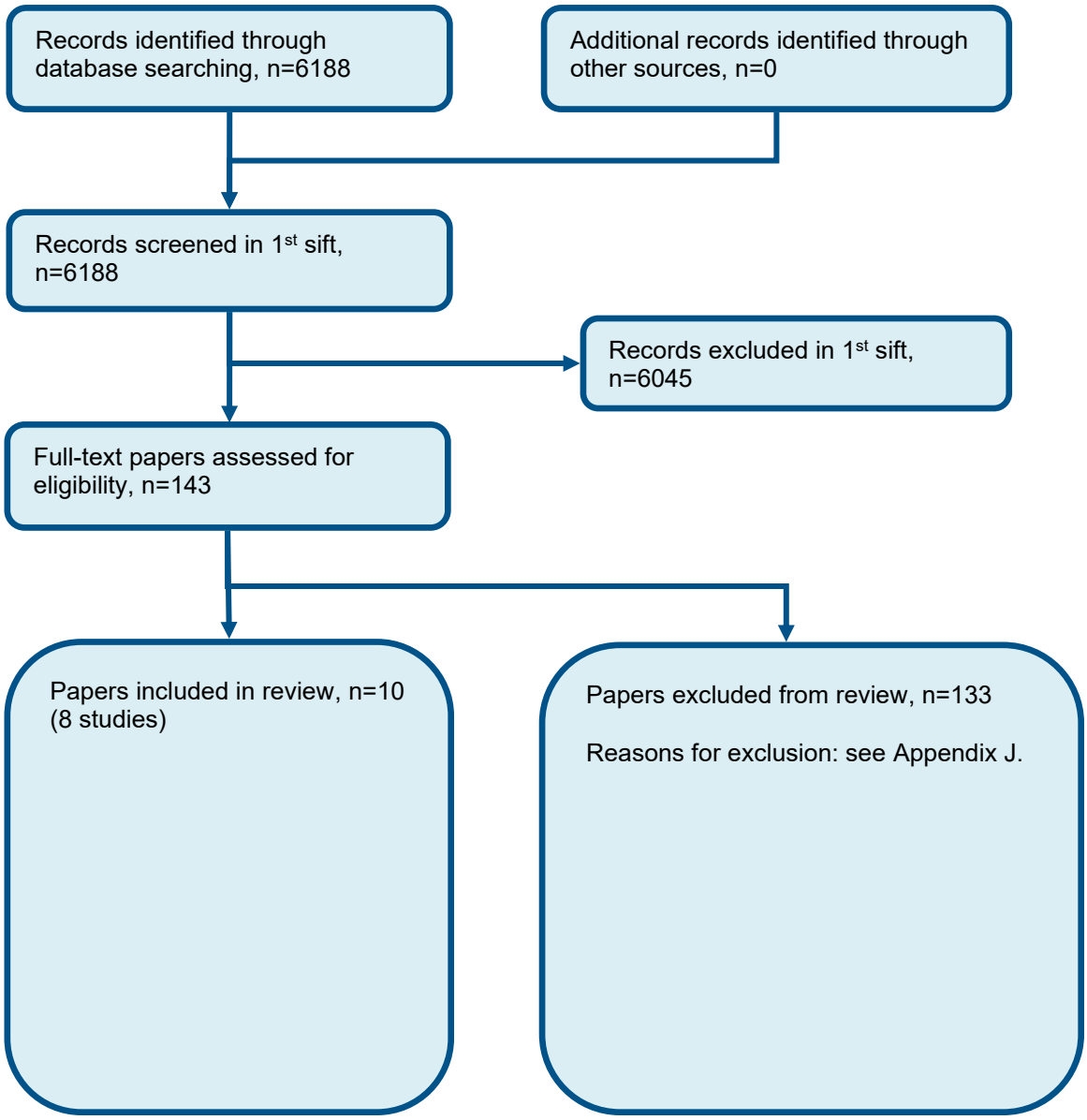
NHS EED and HTA (CRD) search terms

#1.	MeSH DESCRIPTOR Sciatic Neuropathy EXPLODE ALL TREES
#2.	MeSH DESCRIPTOR Radiculopathy EXPLODE ALL TREES
#3.	(lumbago or sciatic*)
#4.	((radiculopathy or radiculitis or radicular pain* or radicular syndrome*))
#5.	(nerve root* adj5 (pain* or avulsion or compress* or disorder* or pinch* or inflam* or imping* or irritat* or entrap* or trap*))
#6.	(sacral nerve* adj5 (pain* or avulsion or compress* or disorder* or pinch* or inflam* or imping* or irritat* or entrap* or trap*))
#7.	#1 OR #2 OR #3 OR #4 OR #5 OR #6
#8.	MeSH DESCRIPTOR Analgesics EXPLODE ALL TREES
#9.	(analgesic*)
#10.	MeSH DESCRIPTOR Cyclooxygenase 2 Inhibitors EXPLODE ALL TREES
#11.	((cox2 or cox-2 or coxii or cox-ii) adj2 inhibitor*)
#12.	((cyclo-oxygenase2 or cyclo-oxygenase-2 or cyclooxygenase-2 or cyclooxygenase2) adj2 inhibitor*)
#13.	MeSH DESCRIPTOR Anti-Inflammatory Agents, Non-Steroidal EXPLODE ALL TREES
#14.	((nsaid* or non-steroid* or non-narcotic* or pharmacolog*))
#15.	((ibuprofen or aspirin or naproxen or fenoprofen or flurbiprofen or ketoprofen or dexketoprofen or dexibuprofen or tiaprofenic acid or diclofenac or aceclofenac or indometacin or mefenamic acid or meloxicam or nabumetone or phenylbutazone or piroxicam or sulindac or tenoxicam or tolfenamic acid or ketorolac or celecoxib or etoricoxib or aceclofenac or acemetacin or diclofenac or etodolac))
#16.	MeSH DESCRIPTOR Acetaminophen EXPLODE ALL TREES
#17.	((acetaminophen or paracetamol))
#18.	MeSH DESCRIPTOR Analgesics, Opioid EXPLODE ALL TREES
#19.	((fentanyl or hydrocodone or hydromorphone or levorphanol or meperidine or morphine or oxycodone or oxymorphone or pentazocine or propoxyphene or sufentanil or tramadol or codeine or tapentadol or acetylsalicyl* or carbasalate calcium or diflunisal or aceclofenac or alclofenac or diclofenac or indomethacin or sulindac or meloxicam or piroxicam or dexibuprofen or dexketoprofen or fenoprofen or flurbiprofen or ibuprofen or ketoprofen or naproxen or tiapro* or metamizol or phenylbutazone or phenazone or propyphenazone or celecoxib or etoricoxib or nabumeton or parecoxib))
#20.	MeSH DESCRIPTOR Muscle Relaxants, Central EXPLODE ALL TREES
#21.	MeSH DESCRIPTOR Benzodiazepines EXPLODE ALL TREES
#22.	((muscle relaxant* or benzodiazepine*))
#23.	((diazepam or tetrazepam or cyclobenzaprine or carisoprodol or chlorzoxazone or meprobramate or methocarbamol or metaxalone or orphenadrine or tizanidine or flupirtine or baclofen or dantrolene))
#24.	MeSH DESCRIPTOR Antidepressive Agents EXPLODE ALL TREES
#25.	((antidepress* or anti-depress*))
#26.	(serotonin norepinephrine reuptake inhibitor*)
#27.	(selective serotonin reuptake inhibitor*)

#28.	((SSRI* or SNRI*))
#29.	((amoxapine or bupropion or citalopram or fluoxetine or fluvoxamine or maprotiline or mianserin or paroxetine or quipazine or ritanserin or sulpiride or trazodone or tryptophan or viloxazine or amitriptyline))
#30.	((clomipramine or desipramine or dothiepin or doxepin or imipramine or iprindole or lofepramine or nortriptyline or opipramol or protriptyline or trimipramine or nortriptyline or duloxetine or mirtazapine or venlafaxine or amitriptyline))
#31.	MeSH DESCRIPTOR Anticonvulsants EXPLODE ALL TREES
#32.	((anticonvulsant* or anti convulsant* or gabapentin or pregabalin or carbamazepine or phenytoin or topiramate or lamotrigine or valproic acid or sodium valproate))
#33.	MeSH DESCRIPTOR Steroids EXPLODE ALL TREES
#34.	((glucocorticosteroid* or corticosteroid* or glucocorticoid* or steroid*))
#35.	((prednisone or prednisolone or methylprednisolone or dexamethasone or betamethasone or hydrocortisone))
#36.	MeSH DESCRIPTOR Nefopam EXPLODE ALL TREES
#37.	((nefopam or acupan))
#38.	#8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37
#39.	#7 AND #38

Appendix C – Effectiveness evidence study selection

Figure 1: Flow chart of clinical study selection for the review of the pharmacological management of sciatica



Appendix D – Effectiveness evidence

Study	Baron 2010[17]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=217)
Countries and setting	Conducted in Belgium, Canada, Germany, Italy, Spain, Sweden, Turkey, USA; Setting: Outpatient follow up
Line of therapy	Unclear
Duration of study	Intervention + follow up: 5 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: A diagnosis of chronic lumbosacral radiculopathy due to spinal stenosis or disk herniation. The pain had to radiate to the calf or foot in a distribution consistent with the L5 or S1 nerve root, involvement had to be localised to areas of sensory changes or muscle weakness.
Stratum	Overall (acute, chronic) with sciatica
Subgroup analysis within study	Not applicable
Inclusion criteria	Men and women aged 18 years or older with pain consistent with a diagnosis of chronic lumbosacral radiculopathy due to spinal stenosis or disk herniation. The pain had to radiate to the calf or foot in a distribution consistent with L5 or S1 nerve root involvement and had to be localised with areas of sensory changes or muscle weakness. If the person was experiencing pain in both the lower back and the calf or foot, the pain intensity in the calf or foot had to be greater than the pain in the lower back, as measured by a visual analogue scale. Pain had to be present for at least 3 months prior to the study, stable for at least 4 weeks, and mean weekly pain score of >4 at the end of screening.
Exclusion criteria	Lumbosacral radiculopathy neuropathic pain for >4 years; surgery for lumbosacral radiculopathy in the previous 6 months; more than one previous spinal surgery for L5-S1 pain/radiculopathy; epidural injection for lumbosacral radiculopathy in the previous 6 weeks
Recruitment/selection of patients	The study consisted of five phases: screening; 1-week single blind placebo run-in phase to identify and exclude placebo responders (no less than 50% pain reduction); 4-week single blind pregabalin treatment phase using flexible-dose pregabalin 150-600mg/day to identify responders (no less than 30^ pain reduction with pregabalin) who continued to the double-blind phase; 5-week double blind treatment phase where

	people were randomised to pregabalin or placebo; and a 1 week phase where people tapered off their study medication. This is an enrichment trial.
Age, gender and ethnicity	Age - Mean (SD): 52.6 (12.0). Gender (M:F): 104:113. Ethnicity: White = 210, Black = 5, Other = 2
Further population details	1. Chronicity of pain: Chronic pain (at least 3 months duration)
Indirectness of population	No indirectness
Interventions	(n=111) Intervention 1: Antiepileptics - Gabapentinoids. Pregabalin at the optimal dose established during the single blind phase (150-600mg/day). Duration 5 weeks. Concurrent medication/care: People were permitted to continue concomitant medication (including analgesics) as long as the medication was not prohibited by the protocol and the dose had been stable for at least 30 days prior to the start of the study. Prohibited medications included antiepileptics, nerve blocks, high-potency opioids, and opioid combinations. Rescue medications (paracetamol no more than 4g/day or paracetamol/codeine no more than 4g/60mg/day. Indirectness: No indirectness (n=107) Intervention 2: Placebo/Sham. Matching placebo per day (pregabalin dose during the single blind phase tapered off during the first 7 days, then placebo for 4 weeks). Duration 5 weeks. Concurrent medication/care: People were permitted to continue concomitant medication (including analgesics) as long as the medication was not prohibited by the protocol and the dose had been stable for at least 30 days prior to the start of the study. Prohibited medications included antiepileptics, nerve blocks, high-potency opioids, and opioid combinations. Rescue medications (paracetamol no more than 4g/day or paracetamol/codeine no more than 4g/60mg/day. Indirectness: No indirectness
Funding	Study funded by industry (This study was funded by Pfizer Inc., Editorial support was provided by Papia Das and Alison Gagnon of UBC Scientific Solutions and funded by Pfizer Inc.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GABAPENTINOIDS versus PLACEBO/SHAM

Protocol outcome 1: Pain severity (VAS/NRS) at Up to 4 months
- Actual outcome for Overall (acute, chronic) with sciatica: Mean change in pain score at 5 weeks; Group 1: mean -0.16 (SD 1.59); n=111, Group 2: mean 0.05 (SD 1.59); n=107; Visual analogue scale 0-10 Top=High is poor outcome; Comments: Reports mean scores and a p-value. SD calculated from this. Reported pregabalin: -0.16. Reported placebo: 0.05. P-value = 0.332.

Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports gender, age, race, BMI, primary cause of lumbosacral radiculopathy, baseline pain score; Group 1 Number missing: 13, Reason: 1 randomised to pregabalin but did not receive treatment. 3 adverse events, 2 lack of efficacy, 2 lost to follow up, 2 patient wish, 3 other; Group 2 Number missing: 18, Reason: 6 adverse events, 6 lack of efficacy, 1 patient wish, 5 other

Protocol outcome 2: Psychological distress (HADS/GHQ/BDI/STAI) at Up to 4 months
- Actual outcome for Overall (acute, chronic) with sciatica: HADS Anxiety at 5 weeks; Group 1: mean -0.19 (SD 2.77); n=100, Group 2: mean 0.82 (SD 2.77); n=101; HADS anxiety subscale 0-21 Top=High is poor outcome; Comments: Reports mean scores and a p-value. SD calculated from this. Reported pregabalin: -0.19 (n=100). Reported placebo: 0.82 (101). P-value = 0.0105.
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports gender, age, race, BMI, primary cause of lumbosacral radiculopathy, baseline pain score; Group 1 Number missing: 11; Group 2 Number missing: 6
- Actual outcome for Overall (acute, chronic) with sciatica: HADS Depression at 5 weeks; Group 1: mean -0.57 (SD 2.3); n=100, Group 2: mean 0.56 (SD 2.3); n=101; HADS depression 0-21 Top=High is poor outcome; Comments: Reports mean scores and a p-value. SD calculated from this. Reported pregabalin: -0.57 (n=100). Reported placebo: 0.56 (101). P-value = 0.0006.
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports gender, age, race, BMI, primary cause of lumbosacral radiculopathy, baseline pain score; Group 1 Number missing: 11; Group 2 Number missing: 6

Protocol outcome 3: Adverse events (morbidity) at Up to 4 months
- Actual outcome for Overall (acute, chronic) with sciatica: Any adverse events at 5 weeks; Group 1: 45/110, Group 2: 45/107; Comments: Includes Gabapentin: Dizziness = 4, Somnolence = 1, Fatigue = 0, Dry mouth = 1, Vertigo = 0, Constipation = 1, Headache = 1, Weight increased = 3, Peripheral oedema = 5. Placebo: Dizziness = 2, somnolence = 1, fatigue = 2, dry mouth = 1, vertigo = 0, constipation = 0, headache = 4, weight increased = 2, peripheral oedema = 2.
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports gender, age, race, BMI, primary cause of lumbosacral radiculopathy, baseline pain score; Group 1 Number missing: 1, Reason: 1 randomised to pregabalin but did not receive treatment; Group 2 Number missing: 0

Protocol outcome 4: Adverse event (mortality) at Up to 4 months
- Actual outcome for Overall (acute, chronic) with sciatica: Patient deaths at 5 weeks; Group 1: 0/110, Group 2: 0/107; Comments: "There were no patient deaths during the study"
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports gender, age, race, BMI, primary cause of lumbosacral radiculopathy, baseline pain score; Group 1 Number missing: 1, Reason: 1 randomised to pregabalin but did not receive treatment; Group 2 Number missing: 0

Protocol outcomes not reported by the study	Quality of life at Up to 4 months; Quality of life at > 4 months; Pain severity (VAS/NRS) at >4 months; Function (disability scores) at Up to 4 months; Function (disability scores) at >4 months; Psychological distress (HADS/GHQ/BDI/STAI) at >4 months; Healthcare utilisation (prescribing, investigations, hospitalisation or health professional visit) at Up to 4 months; Healthcare utilisation (prescribing, investigations, hospitalisation or health professional visit) at >4 months; Adverse events (morbidity) at >4 months; Adverse event (mortality) at >4 months; Responder criteria (pain) at Up to 4 months; Responder criteria (pain) at >4 months

Study	Brotz 2010[26]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=60)
Countries and setting	Conducted in Germany; Setting: Outpatient follow up
Line of therapy	Unclear
Duration of study	Follow up (post intervention): 1 year
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Sciatica without or with neurological deficit attributable to lumbar disc prolapse
Stratum	Overall (acute, chronic) with sciatica
Subgroup analysis within study	Not applicable
Inclusion criteria	Age between 18 and 75 years; sciatica without or with neurological deficit attributable to lumbar disc prolapse, CT or MRI confirmation of lumbar disc prolapse, pain centralization within the first physical therapy session and informed consent. The length of pain history was not specified in the inclusion criteria.
Exclusion criteria	Bladder or bowel disturbance or acute (<24 hour) development of paresis grade 1 or plegia (because these patients were considered candidates for surgery); people who had taken benzodiazepines for more than 2 weeks; any history of benzodiazepine intolerance; prior surgery for disc prolapse; prior trauma to the vertebral column
Recruitment/selection of patients	No additional information
Age, gender and ethnicity	Age - Median (range): Diazepam: 43 (30-68). Placebo: 42.5 (22-61). Gender (M:F): 34:26. Ethnicity: Not stated
Further population details	1. Chronicity of pain: Not stated / Unclear (States that length of symptoms was not a required inclusion criteria).
Extra comments	.
Indirectness of population	No indirectness
Interventions	(n=30) Intervention 1: Muscle relaxants - Benzodiazepines. Diazepam 2x5mg daily for 5 days and then tapered down. Duration 5 days. Concurrent medication/care: Mechanical physiotherapy and the use of a basic analgesic and anti-inflammatory agent (diclofenac) was permitted. Indirectness: No indirectness (n=30) Intervention 2: Placebo/Sham. Two placebo tablets once a day. Duration 5 days. Concurrent medication/care: Mechanical physiotherapy and the use of a basic analgesic and anti-inflammatory agent (diclofenac) was permitted. Indirectness: No

	indirectness
Funding	Academic or government funding (The study was supported by a grant from the Medical Faculty of the University of Tübingen (AKF 57-0-0).)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: BENZODIAZEPINES versus PLACEBO/SHAM Protocol outcome 1: Responder criteria (pain) at Up to 4 months - Actual outcome for Overall (acute, chronic) with sciatica: Pain reduction of VAS of 50% or more at 1 week; Group 1: 12/29, Group 2: 23/29; Comments: Risk ratio: 0.5 (0.3-0.8). Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age, gender, employment status, referred pain, disability score, pain on VAS, straight leg raise, hours with pain, sensory loss and paresis; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life at Up to 4 months; Quality of life at > 4 months; Pain severity (VAS/NRS) at Up to 4 months; Pain severity (VAS/NRS) at >4 months; Function (disability scores) at Up to 4 months; Function (disability scores) at >4 months; Psychological distress (HADS/GHQ/BDI/STAI) at Up to 4 months; Psychological distress (HADS/GHQ/BDI/STAI) at >4 months; Healthcare utilisation (prescribing, investigations, hospitalisation or health professional visit) at Up to 4 months; Healthcare utilisation (prescribing, investigations, hospitalisation or health professional visit) at >4 months; Adverse events (morbidity) at Up to 4 months; Adverse events (morbidity) at >4 months; Adverse event (mortality) at Up to 4 months; Adverse event (mortality) at >4 months; Responder criteria (pain) at >4 months

Study	Dreiser 2001[33]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	2 (only 1 has been included as only 1 has a valid comparison) (n=532)
Countries and setting	Conducted in Argentina, France, Germany, Spain, United Kingdom; Setting: Outpatient follow up
Line of therapy	Unclear
Duration of study	Intervention + follow up: 7 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Radiculalgia preceded or accompanied by low back pain
Stratum	Overall (acute, chronic) with sciatica:
Subgroup analysis within study	Not applicable:
Inclusion criteria	People of either sex, aged 18 years or above, with common sciatica defined by at least five of the eight following criteria: radiculalgia preceded or accompanied by low back pain; sudden onset during exertion or wrong movement; pain evolution with a mechanical rhythm; absence of progressive aggravation; history of low back pain; antalgic spine deviation or localised spinal stiffness; sciatica pain exacerbated by finger pressure in a localised paravertebral point at the L4-L5 or L5-S1 height; sciatica pain exacerbated by coughing or defecation. Onset of pain within 3 days; pain intensity no less than 50mm on a 100mm horizontal visual analogue scale on day 1; monoradiculalgia (L5 or S1); positive straight-leg-raising test no more than 60 degrees; and a requirement for NSAIDs
Exclusion criteria	Treatment with any NSAID within 3 days of commencement of the trial; adverse events due to NSAIDs; hypersensitivity to analgesics, antipyretics, or NSAIDs; concomitant treatment with anti-coagulants, lithium, other NSAIDs, or analgesic agents (except aspirin up to 325mg/day); previous or active peptic ulcer; former lumbar surgery; or symptomatic sciatica during the previous 6 months; cauda equina syndrome; paralysing sciatica; sciatica requiring surgery; hyperalgic sciatica; bilateral, swing sciatica; troncular sciatica; sciatica due to tumour; spondylodiscitis; known lumbar canal narrowing
Recruitment/selection of patients	No additional information
Age, gender and ethnicity	Age - Mean (SD): 47 (14). Gender (M:F): 234:298. Ethnicity: Not stated
Further population details	1. Chronicity of pain: Not stated / Unclear (Not superacute, but no other specification).

Extra comments	. Paper reports two studies, one comparing meloxicam to placebo, one comparing diclofenac to meloxicam. Only the placebo controlled study has been included in this analysis.
Indirectness of population	No indirectness
Interventions	(n=352) Intervention 1: Non-steroidal anti-inflammatory drugs - Meloxicam. Meloxicam 7.5mg or 15mg once a day. Duration 7 days. Concurrent medication/care: No additional information. Indirectness: No indirectness (n=180) Intervention 2: Placebo/Sham. Placebo once a day. Duration 7 days. Concurrent medication/care: No additional information. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MELOXICAM versus PLACEBO/SHAM

Protocol outcome 1: Pain severity (VAS/NRS) at Up to 4 months
- Actual outcome for Overall (acute, chronic) with sciatica: Pain (mm VAS, least square means) at 1 week; Group 1: mean -28.5 (SD 26.6); n=352, Group 2: mean -24 (SD 26.8); n=180; VAS 0-100 Top=High is poor outcome; Comments: Reports least square means and standard error. Calculated standard deviation from this. Reported meloxicam 7.5mg: -27 (2). Reported meloxicam 15mg: -30 (2). Reported placebo: -24 (2). Calculated SD meloxicam 7.5mg: 26.2. Calculated SD meloxicam 15mg: 26.9. Calculated SD placebo: 26.8.
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Repots age, gender, body mass index, history of sciatica, disease duration, L5 type sciatica, S1 type sciatica, and baseline values of outcomes; Group 1 Number missing: 20, Reason: Meloxicam 7.5mg: 2 adverse events, 3 lack of efficacy, 1 administrative. Meloxicam 15mg: 2 adverse events, 9 lack of efficacy, 1 administrative, 2 total pain relief; Group 2 Number missing: 12, Reason: 3 adverse events, 8 lack of efficacy, 1 administrative

Protocol outcome 2: Adverse events (morbidity) at Up to 4 months
- Actual outcome for Overall (acute, chronic) with sciatica: At least one adverse event at 1 week; Group 1: 64/352, Group 2: 24/180
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Repots age, gender, body mass index, history of sciatica, disease duration, L5 type sciatica, S1 type sciatica, and baseline values of outcomes; Group 1 Number missing: 16, Reason: Meloxicam 7.5mg: 3 lack of efficacy, 1 administrative. Meloxicam 15mg: 9 lack of efficacy, 1 administrative, 2 total pain relief; Group 2 Number missing: 9, Reason: 8 lack of efficacy, 1 administrative

Protocol outcomes not reported by the study	Quality of life at Up to 4 months; Quality of life at > 4 months; Pain severity (VAS/NRS) at >4 months; Function (disability scores) at Up to 4 months; Function (disability scores) at >4 months; Psychological distress (HADS/GHQ/BDI/STAI) at Up

	to 4 months; Psychological distress (HADS/GHQ/BDI/STAI) at >4 months; Healthcare utilisation (prescribing, investigations, hospitalisation or health professional visit) at Up to 4 months; Healthcare utilisation (prescribing, investigations, hospitalisation or health professional visit) at >4 months; Adverse events (morbidity) at >4 months; Adverse event (mortality) at Up to 4 months; Adverse event (mortality) at >4 months; Responder criteria (pain) at Up to 4 months; Responder criteria (pain) at >4 months

Study	Goldberg 2015[47]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=269)
Countries and setting	Conducted in USA; Setting: Outpatient follow up
Line of therapy	Unclear
Duration of study	Follow up (post intervention): 52 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Leg pain extending below the knee in a nerve root distribution, with a herniated disc confirmed by MRI, and a score of 30 points or higher on the Oswestry Disability Index
Stratum	Overall (acute, chronic) with sciatica
Subgroup analysis within study	Not applicable
Inclusion criteria	People aged 18 to 70 years, reported leg pain extending below the knee in a nerve root distribution, had a herniated disk confirmed by MRI, and scored 30 points or higher on the Oswestry Disability Index. A positive straight-leg raise test result was initially an inclusion criterion that was eliminated after 14 months to improve recruitment and allow interaction analyses with this characteristic.
Exclusion criteria	Onset of radicular pain more than 3 months prior; previous lumbar surgery; oral or epidural steroid treatment in the prior 3 months; diabetes; substantial or progressive motor loss; and/or ongoing litigation or workers compensation claim.
Recruitment/selection of patients	Participants were recruited from primary care practices at 3 Kaiser Permanente Northern California facilities and from a daily extract of the electronic medical record.
Age, gender and ethnicity	Age - Mean (SD): 46.0 (12.1). Gender (M:F): 149:120. Ethnicity: Native American: 5, Asian: 32, African American: 6, Pacific Islander: 2, White: 179, >1 race: 19, declined to state race: 26. Ethnicity Hispanic: 62.
Further population details	1. Chronicity of pain: Not stated / Unclear
Indirectness of population	No indirectness
Interventions	(n=181) Intervention 1: Steroids. Prednisolone 20mg daily for 5 days, then 40mg daily for 5 days, then 20mg daily for 5 days. Duration 15 days. Concurrent medication/care: Nonsteroidal anti-inflammatory drugs were not allowed for 3 weeks after randomization, but otherwise all people in both treatment groups received usual care for their symptoms. Indirectness: No indirectness (n=88) Intervention 2: Placebo/Sham. Matching placebo. Duration 15 days.

	Concurrent medication/care: Nonsteroidal anti-inflammatory drugs were not allowed for 3 weeks after randomization, but otherwise all people in both treatment groups received usual care for their symptoms. Indirectness: No indirectness
Funding	Academic or government funding (The study was supported by grant RO1 AR053960 from the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) of the US National Institutes of Health to Drs Goldberg and Avins)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: STEROIDS versus PLACEBO/SHAM

Protocol outcome 1: Quality of life at Up to 4 months
- Actual outcome for Overall (acute, chronic) with sciatica: SF-36 physical component summary at 3 weeks; Group 1: mean 5.8 (SD 7.9); n=179, Group 2: mean 2.8 (SD 6.9); n=88; SF-36 physical component summary 0-100 Top=High is good outcome; Comments: Reports mean change scores and 95% confidence intervals. SDs calculated from this. Reported prednisone: 5.8 (4.7 to 7.0). Reported placebo: 2.8 (1.3 to 4.2). Baseline prednisone: 30.4 (6.8). Baseline placebo: 30.9 (6.2).
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age, gender, race, ethnicity, education and baseline values of outcomes; Group 1 Number missing: 4, Reason: 2 lost to follow up, 1 started prohibited concomitant medication, 1 gastrointestinal symptoms; Group 2 Number missing: 2, Reason: 1 early epidural steroid injection, 1 upper gastrointestinal tract bleeding
- Actual outcome for Overall (acute, chronic) with sciatica: SF-36 mental component summary at 3 weeks; Group 1: mean 1.2 (SD 9.6); n=179, Group 2: mean -0.7 (SD 11); n=88; SF-36 mental component summary 0-100 Top=High is good outcome; Comments: Reports mean change scores and 95% confidence intervals. SDs calculated from this. Reported prednisone: 1.2 (-0.2 to 2.6). Reported placebo: -0.7 (-3.0 to 1.6). Baseline prednisone: 48.5 (11.6). Baseline placebo: 49.3 (12.3).
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age, gender, race, ethnicity, education and baseline values of outcomes; Group 1 Number missing: 4, Reason: 2 lost to follow up, 1 started prohibited concomitant medication, 1 gastrointestinal symptoms; Group 2 Number missing: 2, Reason: 1 early epidural steroid injection, 1 upper gastrointestinal tract bleeding

Protocol outcome 2: Quality of life at > 4 months
- Actual outcome for Overall (acute, chronic) with sciatica: SF-36 physical component summary at 52 weeks; Group 1: mean 18 (SD 9.6); n=157, Group 2: mean 15.7 (SD 11.2); n=77; SF-36 physical component summary 0-100 Top=High is good outcome; Comments: Reports mean change scores and 95% confidence intervals. SDs calculated from this. Reported prednisone: 18.0 (16.5 to 19.5). Reported placebo: 15.7 (13.2 to 18.2). Baseline prednisone: 30.4 (6.8). Baseline placebo: 30.9 (6.2).
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age, gender, race, ethnicity, education and baseline values of outcomes; Group 1 Number missing: 28, Reason: 2 lost to follow up, 1 started prohibited concomitant medication, 1 gastrointestinal symptoms, 23 unable to be contacted, 1 withdrew; Group 2 Number missing: 13, Reason: 1 early epidural steroid injection, 1 upper gastrointestinal tract bleeding, 10 unable to be contacted, 1 withdrew from the study

- Actual outcome for Overall (acute, chronic) with sciatica: SF-36 mental component summary at 52 weeks; Group 1: mean 6.9 (SD 11.5); n=157, Group 2: mean 3.1 (SD 10.5); n=77; SF-36 mental component summary 0-100 Top=High is good outcome; Comments: Reports mean change scores and 95% confidence intervals. SDs calculated from this. Reported prednisone: 6.9 (5.1 to 8.7). Reported placebo: 3.1 (0.7 to 5.4). Baseline prednisone: 48.5 (11.6). Baseline placebo: 49.3 (12.3).
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age, gender, race, ethnicity, education and baseline values of outcomes; Group 1 Number missing: 28, Reason: 2 lost to follow up, 1 started prohibited concomitant medication, 1 gastrointestinal symptoms, 23 unable to be contacted, 1 withdrew; Group 2 Number missing: 13, Reason: 1 early epidural steroid injection, 1 upper gastrointestinal tract bleeding, 10 unable to be contacted, 1 withdrew from the study

Protocol outcome 3: Pain severity (VAS/NRS) at Up to 4 months
- Actual outcome for Overall (acute, chronic) with sciatica: Pain numerical rating scale score - below waist, average at 3 weeks; Group 1: mean -3 (SD 2.4); n=179, Group 2: mean -2.8 (SD 2.6); n=88; NRS 0-10 Top=High is poor outcome; Comments: Reports mean change scores and 95% confidence intervals. SDs calculated from this. Reported prednisone: -3.0 (-3.3 to -2.6). Reported placebo: -2.8 (-3.3 to -2.2). Baseline prednisone: 6.76 (2.0). Baseline placebo: 6.9 (1.8).
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age, gender, race, ethnicity, education and baseline values of outcomes; Group 1 Number missing: 4, Reason: 2 lost to follow up, 1 started prohibited concomitant medication, 1 gastrointestinal symptoms; Group 2 Number missing: 2, Reason: 1 early epidural steroid injection, 1 upper gastrointestinal tract bleeding

Protocol outcome 4: Pain severity (VAS/NRS) at >4 months
- Actual outcome for Overall (acute, chronic) with sciatica: Pain numerical rating scale score - below waist, average at 52 weeks; Group 1: mean -5.2 (SD 2.9); n=157, Group 2: mean -4.6 (SD 2.7); n=77; NRS 0-10 Top=High is poor outcome; Comments: Reports mean change scores and 95% confidence intervals. SDs calculated from this. Reported prednisone: -5.2 (-5.6 to -4.7). Reported placebo: -4.6 (-5.2 to -4.0). Baseline prednisone: 6.76 (2.0). Baseline placebo: 6.9 (1.8).
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age, gender, race, ethnicity, education and baseline values of outcomes; Group 1 Number missing: 28, Reason: 2 lost to follow up, 1 started prohibited concomitant medication, 1 gastrointestinal symptoms, 23 unable to be contacted, 1 withdrew; Group 2 Number missing: 13, Reason: 1 early epidural steroid injection, 1 upper gastrointestinal tract bleeding, 10 unable to be contacted, 1 withdrew from the study

Protocol outcome 5: Function (disability scores) at Up to 4 months
- Actual outcome for Overall (acute, chronic) with sciatica: Oswestry Disability Index score at 3 weeks; Group 1: mean -19 (SD 18.1); n=179, Group 2: mean -13.3 (SD 16); n=88; Oswestry Disability Index 0-100 Top=High is poor outcome; Comments: Reports mean change scores and 95% confidence intervals. SDs calculated from this. Reported prednisone: -19.0 (-21.6 to -16.3). Reported placebo: -13.3 (-16.7 to -10.0). Baseline prednisone: 51.2 (14.5). Baseline placebo: 51.1 (11.5).
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age, gender, race, ethnicity, education and baseline

values of outcomes; Group 1 Number missing: 4, Reason: 2 lost to follow up, 1 started prohibited concomitant medication, 1 gastrointestinal symptoms; Group 2 Number missing: 2, Reason: 1 early epidural steroid injection, 1 upper gastrointestinal tract bleeding

Protocol outcome 6: Function (disability scores) at >4 months
- Actual outcome for Overall (acute, chronic) with sciatica: Oswestry Disability Index score at 52 weeks; Group 1: mean -37.8 (SD 18.2); n=157, Group 2: mean -30.4 (SD 19.9); n=77; Oswestry Disability Index 0-100 Top=High is poor outcome; Comments: Reports mean change scores and 95% confidence intervals. SDs calculated from this. Reported prednisone: -37.8 (-40.7 to -35.0). Reported placebo: -30.4 (-34.8 to -25.9). Baseline prednisone: 51.2 (14.5). Baseline placebo: 51.1 (11.5).
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age, gender, race, ethnicity, education and baseline values of outcomes; Group 1 Number missing: 28, Reason: 2 lost to follow up, 1 started prohibited concomitant medication, 1 gastrointestinal symptoms, 23 unable to be contacted, 1 withdrew; Group 2 Number missing: 13, Reason: 1 early epidural steroid injection, 1 upper gastrointestinal tract bleeding, 10 unable to be contacted, 1 withdrew from the study

Protocol outcome 7: Adverse events (morbidity) at Up to 4 months
- Actual outcome for Overall (acute, chronic) with sciatica: Total reporting at least 1 adverse event at 3 weeks; Group 1: 88/179, Group 2: 21/88; Comments: Includes: Prednisone: Insomnia = 46, nervousness = 33, increased appetite = 40, indigestion = 20, headache = 32, joint pain = 10, sweating = 35, other = 46. Placebo: Insomnia = 9, nervousness = 7, increased appetite = 9, indigestion = 6, headache = 13, joint pain = 10, sweating = 15, other = 16
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age, gender, race, ethnicity, education and baseline values of outcomes; Group 1 Number missing: 4, Reason: 2 lost to follow up, 1 started prohibited concomitant medication, 1 gastrointestinal symptoms; Group 2 Number missing: 2, Reason: 1 early epidural steroid injection, 1 upper gastrointestinal tract bleeding

Protocol outcome 8: Responder criteria (pain) at Up to 4 months
- Actual outcome for Overall (acute, chronic) with sciatica: Improvement in pain numerical rating scale score of no less than 3 points at 3 weeks; Group 1: 92/179, Group 2: 45/88
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age, gender, race, ethnicity, education and baseline values of outcomes; Group 1 Number missing: 4, Reason: 2 lost to follow up, 1 started prohibited concomitant medication, 1 gastrointestinal symptoms; Group 2 Number missing: 2, Reason: 1 early epidural steroid injection, 1 upper gastrointestinal tract bleeding

Protocol outcome 9: Responder criteria (pain) at >4 months
- Actual outcome for Overall (acute, chronic) with sciatica: Improvement in pain numerical rating scale score of no less than 3 points at 52 weeks; Group 1: 131/157, Group 2: 60/77
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age, gender, race, ethnicity, education and baseline values of outcomes; Group 1 Number missing: 28, Reason: 2 lost to follow up, 1 started prohibited concomitant medication, 1 gastrointestinal symptoms, 23 unable to be contacted, 1 withdrew; Group 2 Number missing: 13, Reason: 1 early epidural steroid injection, 1 upper gastrointestinal tract bleeding, 10 unable

to be contacted, 1 withdrew from the study	
Protocol outcomes not reported by the study	Psychological distress (HADS/GHQ/BDI/STAI) at Up to 4 months; Psychological distress (HADS/GHQ/BDI/STAI) at >4 months; Healthcare utilisation (prescribing, investigations, hospitalisation or health professional visit) at Up to 4 months; Healthcare utilisation (prescribing, investigations, hospitalisation or health professional visit) at >4 months; Adverse events (morbidity) at >4 months; Adverse event (mortality) at Up to 4 months; Adverse event (mortality) at >4 months

Study	Herrmann 2009[57]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=171)
Countries and setting	Conducted in Germany; Setting: Outpatient follow up
Line of therapy	Unclear
Duration of study	Intervention + follow up: 5 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Pain radiating along the sciatic nerve (including radiative pain below the knee) that worsened with the straight leg-raising test (<60 degrees). Lumbosciatica was defined as sciatica associated with paravertebral pain limited by the superior spina iliaca and the gluteal folds. The intensity of unprovoked pain had to be at least 70mm on an 100mm VAS.
Stratum	Overall (acute, chronic) with sciatica
Subgroup analysis within study	Not applicable
Inclusion criteria	People enrolled were male or female outpatients aged 18-70 years recruited from general practice. Inclusion criteria were: written informed consent, a diagnosis of acute sciatica or lumbo-sciatica with onset within the last 72 hours, any previous attacks had to be resolved at least 3 months earlier.
Exclusion criteria	Neurological symptoms of a herniated intervertebral disc (paraesthesia and muscular weakness or paralysis); cauda equina syndrome; ankylosing spondylitis; rheumatoid arthritis; past or present significant disease; past or present drug or alcohol abuse; history of hospitalisation or bed rest; physiotherapy or hypersensitivity to NSAIDs or other analgesics; use of other NSAIDs within 1 week; corticosteroids within 4 weeks; non-narcotic analgesics within 12 hours of intake of study treatment; anxiolytics, antidepressants and/or muscle relaxants; topical treatment of the lumbar spine with NSAIDs or other antirheumatic agents; anticoagulants, immunosuppressants, or drugs interacting with oxicams.
Recruitment/selection of patients	No additional information
Age, gender and ethnicity	Age - Mean (SD): 49.7 (13.5). Gender (M:F): 76:95. Ethnicity: Caucasian: 282, Asian: 18
Further population details	1. Chronicity of pain: Acute pain (<3 months duration)
Extra comments	This paper reports pain on a visual analogue scale as the primary outcome. This data is reported incompletely without variance data for the comparison of diclofenac compared to placebo and so could not be included in the analysis

Indirectness of population	No indirectness
Interventions	(n=57) Intervention 1: Non-steroidal anti-inflammatory drugs - Diclofenac. Diclofenac 50mg twice a day for days 1 and 5, 50mg three times a day for days 2-3. Duration 5 days. Concurrent medication/care: No additional information. Indirectness: No indirectness (n=57) Intervention 2: Non-steroidal anti-inflammatory drugs - Lornoxicam. Lornoxicam 8mg once a day on days 1 and 5. Lornoxicam 8mg twice a day on days 2-4. Duration 5 days. Concurrent medication/care: No additional information. Indirectness: No indirectness Comments: Lornoxicam is not licensed for use in the United Kingdom and so was not included in the analysis (n=57) Intervention 3: Placebo/Sham. Matching placebo for diclofenac and tenoxicam. Duration 5 days. Concurrent medication/care: No additional information. Indirectness: No indirectness
Funding	Study funded by industry (Nycomed Pharma Austria supplied study treatment and co-sponsored the study with Merckle GmbH, Ulm, Germany. The authors would like to thank ScopeMedical Ltd for their editorial assistance with the manuscript.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DICLOFENAC versus PLACEBO/SHAM

Protocol outcome 1: Adverse events (morbidity) at Up to 4 months
- Actual outcome for Overall (acute, chronic) with sciatica: Number of people with adverse events at 5 days; Group 1: 7/57, Group 2: 4/57; Comments: Includes 9 events in the diclofenac group, 7 events in the placebo group. This included: Diclofenac: Dyspepsia = 2, diarrhoea = 1, nausea = 1, abdominal pain = 1, sputum = 1, hyperuricaemia = 1, bilirubinaemia = 1, cramp legs = 1. Placebo: diarrhoea = 2, nausea = 1, abdominal pain = 1, flatulence = 1, hyperuricaemia = 1, myalgia = 1. Of these the severity was noted: Diclofenac: mild = 3, moderate = 4, severe = 2. Placebo: mild = 6, moderate = 1.
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports gender, ethnicity, age, weight, height, pain intensity, people with a history of low back pain, duration of low back pain, number of previous attacks, percentage of people with abnormal musculoskeletal findings and percentage of people using analgesics during prior 12 months; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcomes not reported by the study	Quality of life at Up to 4 months; Quality of life at > 4 months; Pain severity (VAS/NRS) at Up to 4 months; Pain severity (VAS/NRS) at >4 months; Function (disability scores) at Up to 4 months; Function (disability scores) at >4 months; Psychological distress (HADS/GHQ/BDI/STAI) at Up to 4 months; Psychological distress (HADS/GHQ/BDI/STAI) at >4 months; Healthcare utilisation (prescribing,

	investigations, hospitalisation or health professional visit) at Up to 4 months; Healthcare utilisation (prescribing, investigations, hospitalisation or health professional visit) at >4 months; Adverse events (morbidity) at >4 months; Adverse event (mortality) at Up to 4 months; Adverse event (mortality) at >4 months; Responder criteria (pain) at Up to 4 months; Responder criteria (pain)Define at >4 months

Study	Ko 2016[71]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=40)
Countries and setting	Conducted in South Korea; Setting: Outpatient follow up
Line of therapy	Unclear
Duration of study	Intervention + follow up: 12 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Lumbar radiating pain indicated by at least two of the following symptoms: dermatomal pain distribution (LANSS no less than 12); increased leg pain on coughing, sneezing, straining; decreased muscle strength; sensory loss or reflex loss; positive straight leg raising test with positive relief test
Stratum	Overall (acute, chronic) with sciatica
Subgroup analysis within study	Not applicable
Inclusion criteria	Lumbar radiating pain (indicated by at least two of the following symptoms): dermatomal pain distribution (LANSS no more than 12); increased leg pain on coughing, sneezing, straining; decreased muscle strength; sensory loss or reflex loss; positive straight leg raising test with positive relief test. Pain intensity needing medication (visual analogue scale >3).
Exclusion criteria	Indication for surgical intervention; previously underwent spinal surgery; pregnant; pending worker's compensation or other secondary gain; unable to follow (planned to move); contraindication of the intended medication; severe coexisting illness (renal failure, upper gastrointestinal bleeding or major psychiatric diseases)
Recruitment/selection of patients	No additional information
Age, gender and ethnicity	Age - Mean (SD): 62.6 (13.0). Gender (M:F): 13:27. Ethnicity: Not stated
Further population details	1. Chronicity of pain: Not stated / Unclear
Indirectness of population	No indirectness
Interventions	(n=20) Intervention 1: Steroids. Triamcinolone 4mg twice daily for 2 weeks. Then tapered or doubled depending on side effects or the therapeutic effect, and the patients were monitored for 12 weeks. Duration 14 weeks. Concurrent medication/care: No additional information. Indirectness: No indirectness (n=20) Intervention 2: Antiepileptics - Gabapentinoids. Pregabalin 7.5mg* twice daily for 2 weeks or gabapentin 100mg three times daily for 2 weeks. Then tapered or

	doubled depending on side effects or the therapeutic effect, and the patients were monitored for 12 weeks. Duration 14 weeks. Concurrent medication/care: No additional information. Indirectness: No indirectness
Funding	Academic or government funding (This work was supported by a grant from the Research Institute of Medical Science, Catholic University of Daegu in 2014)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: STEROIDS versus GABAPENTINOIDS

Protocol outcome 1: Quality of life at Up to 4 months
- Actual outcome for Overall (acute, chronic) with sciatica: SF-36 physical component score at 12 weeks; Group 1: mean 53.7 (SD 21.7); n=20, Group 2: mean 58.7 (SD 20.2); n=20; SF-36 physical component score 0-100 Top=High is good outcome; Comments: Baseline steroids: 43.8 (24.4). Baseline gabapentinoids: 49.5 (13.3).
Risk of bias: All domain - Very high, Selection – Very High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports sex, age, and baseline values of outcomes. Baseline values for SF-36 subscales were significantly different at baseline.; Group 1 Number missing: 7, Reason: 7 missing, no reason given; Group 2 Number missing: 7, Reason: 7 missing, no reason given
- Actual outcome for Overall (acute, chronic) with sciatica: SF-36 mental component score at 12 weeks; Group 1: mean 58.6 (SD 19.7); n=20, Group 2: mean 57.5 (SD 18.7); n=20; SF-36 mental component score 0-100 Top=High is good outcome; Comments: Baseline steroids: 54.7 (24.0). Baseline gabapentinoids: 60.7 (16.1).
Risk of bias: All domain - Very high, Selection – Very High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports sex, age, and baseline values of outcomes. Baseline values for SF-36 subscales were significantly different at baseline.; Group 1 Number missing: 7, Reason: 7 missing, no reason given; Group 2 Number missing: 7, Reason: 7 missing, no reason given

Protocol outcome 2: Pain severity (VAS/NRS) at Up to 4 months
- Actual outcome for Overall (acute, chronic) with sciatica: Radiative pain - NRS at 12 weeks; Group 1: mean 2 (SD 2.6); n=20, Group 2: mean 3.2 (SD 2.2); n=20; NRS 0-10 Top=High is poor outcome; Comments: Baseline steroids: 4.9 (2.9). Baseline gabapentinoids: 4.8 (2.0).
Risk of bias: All domain – Very High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports sex, age, and baseline values of outcomes. Baseline values for SF-36 subscales were significantly different at baseline.; Group 1 Number missing: 7, Reason: 7 missing, no reason given; Group 2 Number missing: 7, Reason: 7 missing, no reason given

Protocol outcome 3: Function (disability scores) at Up to 4 months
- Actual outcome for Overall (acute, chronic) with sciatica: Oswestry disability index at 12 weeks; Group 1: mean 10.3 (SD 9.6); n=20, Group 2: mean 8.5 (SD 6.9); n=20; Oswestry disability index 0-100 Top=High is poor outcome; Comments: Baseline steroids: 11.5 (5.9), baseline gabapentinoids: 10.6 (6.8)
Risk of bias: All domain – Very High, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports sex, age, and baseline values of

outcomes. Baseline values for SF-36 subscales were significantly different at baseline.; Group 1 Number missing: 7, Reason: 7 missing, no reason given; Group 2 Number missing: 7, Reason: 7 missing, no reason given	
Protocol outcomes not reported by the study	Quality of life at > 4 months; Pain severity (VAS/NRS) at >4 months; Function (disability scores) at >4 months; Psychological distress (HADS/GHQ/BDI/STAI) at Up to 4 months; Psychological distress (HADS/GHQ/BDI/STAI) at >4 months; Healthcare utilisation (prescribing, investigations, hospitalisation or health professional visit) at Up to 4 months; Healthcare utilisation (prescribing, investigations, hospitalisation or health professional visit) at >4 months; Adverse events (morbidity) at Up to 4 months; Adverse events (morbidity) at >4 months; Adverse event (mortality) at Up to 4 months; Adverse event (mortality) at >4 months; Responder criteria (pain) at Up to 4 months; Responder criteria (pain) at >4 months

**Stakeholder correspondence confirmed that the dose reported in the paper is a typographical error and should read 75mg.*

Study (subsidiary papers)	Mathieson 2017[85] (Mathieson 2016[83], Mathieson 2013[86])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=209)
Countries and setting	Conducted in Australia; Setting: Outpatient follow up
Line of therapy	Unclear
Duration of study	Follow up (post intervention): 52 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Radiating pain into one leg below the knee, accompanied by nerve-root or spinal-nerve involvement as indicated by the presence of at least one of the following clinical features: dermatomal leg pain, myotomal weakness, sensory deficits, or diminished reflex, as determined by the trial clinician
Stratum	Overall (acute, chronic) with sciatica
Subgroup analysis within study	Not applicable
Inclusion criteria	People with moderate-to-severe sciatica. Current episode of sciatica that had been present for a minimum of 1 week and a maximum of 1 year, leg pain that had been at least moderate in intensity or had resulted in at least moderate interference with daily activities during the previous week (as measured by modifications of items 7 and 8 in the Medical Outcomes Study 36-Item Short-Form Health Survey), an age of at least 18 years, and either an adequate understanding of English or the availability of interpretation services for the participant to complete the trial.
Exclusion criteria	People were excluded from participation in the trial if they had a known or suspected serious pathologic condition of the spine (e.g., the cauda equina syndrome); if they were pregnant, were breast-feeding, or were planning conception (men [with their partners] and women) during the first 8 weeks of the trial; if they were considering or planning to undergo spinal surgery or other interventional procedures (e.g. a glucocorticoid injection) for sciatica during the first 8 weeks of the trial; if they had contraindications to pregabalin; if they were taking medication for neuropathic pain, antiepileptic medication, antidepressant medication, or sedative medication and were unable to cease taking such medications; or if they had severe depression or suicidal thoughts (a score of at least 20 on the Patient Health Questionnaire [scores range from 1 to 27, with scores of at least 20 indicating severe depression] or a score of 2 or 3 on question 9 [regarding suicidal thoughts] of the questionnaire).

Recruitment/selection of patients	People who visited a trial clinician as an outpatient in New South Wales, Australia or those screened by clinicians who were not involved in the trial and would then be referred to a trial clinician
Age, gender and ethnicity	Age - Mean (SD): 53.8 (16.7). Gender (M:F): 92:115. Ethnicity: Not stated
Further population details	1. Chronicity of pain: Mixed (For a minimum of 1 week and a maximum of 1 year).
Extra comments	.
Indirectness of population	No indirectness
Interventions	(n=108) Intervention 1: Antiepileptics - Gabapentinoids. Pregabalin, starting at 150mg per day (75mg twice daily). This dose was adjusted to a maximum of 600mg per day (300mg twice daily) depending on the patient's progress and the side effects at each dose level. In the trial, the starting dose was increased each week for 3 weeks, from the starting dose of 150mg per day to 300mg per day, then to 450mg per day, and then to a maintenance phase that was initiated at a dose of 600mg per day for 4 weeks, subsequently over the course of 1 week, the dose was gradually decreased and the regimen discontinued. If an adequate decrease in leg pain was reported before the 8 week period was completed, the decrease in dose to subsequent cessation of the trial regimen could take place earlier. Duration 12 weeks. Concurrent medication/care: People could receive additional medical care if it was considered to be suitable by the trial clinician. Such care could include physical therapies and could also include other analgesic medications (except for adjuvant analgesic agents), which would ideally be prescribed in accordance with the World Health Organisation pain ladder. Trial clinicians were asked not prescribe certain medicines (antiepileptic medications, selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, tricyclic antidepressants, topical lidocaine, and benzodiazepines) or to schedule interventional procedures. If the use of such medications or procedures was unavoidable, people were permitted to stop taking pregabalin or placebo but could remain in the trial. Indirectness: No indirectness (n=101) Intervention 2: Placebo/Sham. Matching placebo. Duration 12 weeks. Concurrent medication/care: People could receive additional medical care if it was considered to be suitable by the trial clinician. Such care could include physical therapies and could also include other analgesic medications (except for adjuvant analgesic agents), which would ideally be prescribed in accordance with the World Health Organisation pain ladder. Trial clinicians were asked not prescribe certain medicines (antiepileptic medications, selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, tricyclic antidepressants, topical lidocaine, and benzodiazepines) or to schedule interventional procedures. If the use of

	such medications or procedures was unavoidable, people were permitted to stop taking pregabalin or placebo but could remain in the trial. Indirectness: No indirectness
Funding	Study funded by industry (Supported by a grant (ID APP1042073) from the National Health and Medical Research Council of Australia)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GABAPENTINOIDS versus PLACEBO/SHAM

Protocol outcome 1: Quality of life at Up to 4 months
- Actual outcome for Overall (acute, chronic) with sciatica: SF-12 physical component at 12 weeks; Group 1: mean 40.8 (SD 10.1); n=90, Group 2: mean 42.4 (SD 9.2); n=84; SF-12 physical component 0-100 Top=High is good outcome; Comments: Baseline pregabalin: 36.2 (9.4). Baseline placebo: 36.5 (9.6). Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports sex, age, dermatomal pain, motor deficit, neurologic deficit, sensory deficit, pain in both legs, pain on straight-leg raising manoeuvre, clinical suspected level of spine associated with leg pain, duration of symptoms and baseline values of outcomes; Group 1 Number missing: 9, Reason: Overall: 2 excluded after randomisation due to taking an excluded medicine, 9 withdrew consent, 6 were lost to follow up; Group 2 Number missing: 8, Reason: Overall: 7 withdrew consent, 7 were lost to follow-up
- Actual outcome for Overall (acute, chronic) with sciatica: SF-12 mental component at 12 weeks; Group 1: mean 49.8 (SD 10.7); n=90, Group 2: mean 50.6 (SD 10.5); n=84; SF-12 mental component 0-100 Top=High is poor outcome; Comments: Baseline pregabalin: 47.4 (11.7). Baseline placebo: 46.3 (12.4). Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports sex, age, dermatomal pain, motor deficit, neurologic deficit, sensory deficit, pain in both legs, pain on straight-leg raising manoeuvre, clinical suspected level of spine associated with leg pain, duration of symptoms and baseline values of outcomes; Group 1 Number missing: 9, Reason: Overall: 2 excluded after randomisation due to taking an excluded medicine, 9 withdrew consent, 6 were lost to follow up; Group 2 Number missing: 8, Reason: Overall: 7 withdrew consent, 7 were lost to follow-up

Protocol outcome 2: Quality of life at > 4 months
- Actual outcome for Overall (acute, chronic) with sciatica: SF-12 physical component at 52 weeks; Group 1: mean 42.2 (SD 11.2); n=83, Group 2: mean 44 (SD 9.5); n=79; SF-12 physical component 0-100 Top=High is good outcome; Comments: Baseline pregabalin: 36.2 (9.4). Baseline placebo: 36.5 (9.6). Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports sex, age, dermatomal pain, motor deficit, neurologic deficit, sensory deficit, pain in both legs, pain on straight-leg raising manoeuvre, clinical suspected level of spine associated with leg pain, duration of symptoms and baseline values of outcomes; Group 1 Number missing: 15, Reason: Overall: 2 excluded after randomisation due to taking an excluded medicine, 9 withdrew consent, 6 were lost to follow up; Group 2 Number missing: 14, Reason: Overall: 7 withdrew consent, 7 were lost to follow-up
- Actual outcome for Overall (acute, chronic) with sciatica: SF-12 mental component at 52 weeks; Group 1: mean 51.2 (SD 11); n=83, Group 2: mean 51 (SD 11.5); n=79; SF-12 mental component 0-100 Top=High is good outcome; Comments: Baseline pregabalin: 47.4 (11.7). Baseline placebo: 46.3 (12.4). Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports sex, age, dermatomal pain, motor deficit, neurologic deficit, sensory deficit, pain in both legs, pain on straight-leg raising manoeuvre, clinical suspected level of spine associated with leg pain, duration of symptoms and baseline values of outcomes; Group 1 Number missing: 15, Reason: Overall: 2 excluded after randomisation due to taking an excluded

medicine, 9 withdrew consent, 6 were lost to follow up; Group 2 Number missing: 14, Reason: Overall: 7 withdrew consent, 7 were lost to follow-up

Protocol outcome 3: Pain severity (VAS/NRS) at Up to 4 months
- Actual outcome for Overall (acute, chronic) with sciatica: Leg pain intensity (NRS) at 12 weeks; Group 1: mean 3.2 (SD 2.7); n=97, Group 2: mean 3.2 (SD 2.7); n=93; NRS 0-10 Top=High is poor outcome; Comments: Baseline pregabalin: 6.3 (1.8). Baseline placebo: 6.1 (1.9).
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports sex, age, dermatomal pain, motor deficit, neurologic deficit, sensory deficit, pain in both legs, pain on straight-leg raising manoeuvre, clinical suspected level of spine associated with leg pain, duration of symptoms and baseline values of outcomes; Group 1 Number missing: 9, Reason: Overall: 2 excluded after randomisation due to taking an excluded medicine, 9 withdrew consent, 6 were lost to follow up; Group 2 Number missing: 8, Reason: Overall: 7 withdrew consent, 7 were lost to follow-up

Protocol outcome 4: Pain severity (VAS/NRS) at >4 months
- Actual outcome for Overall (acute, chronic) with sciatica: Leg pain intensity (NRS) at 52 weeks; Group 1: mean 3.4 (SD 3.2); n=91, Group 2: mean 3 (SD 2.6); n=87; NRS 0-10 Top=High is poor outcome; Comments: Baseline pregabalin: 6.3 (1.8). Baseline placebo: 6.1 (1.9).
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports sex, age, dermatomal pain, motor deficit, neurologic deficit, sensory deficit, pain in both legs, pain on straight-leg raising manoeuvre, clinical suspected level of spine associated with leg pain, duration of symptoms and baseline values of outcomes; Group 1 Number missing: 15, Reason: Overall: 2 excluded after randomisation due to taking an excluded medicine, 9 withdrew consent, 6 were lost to follow up; Group 2 Number missing: 14, Reason: Overall: 7 withdrew consent, 7 were lost to follow-up

Protocol outcome 5: Function (disability scores) at Up to 4 months
- Actual outcome for Overall (acute, chronic) with sciatica: Roland Disability Questionnaire for Sciatica score at 12 weeks; Group 1: mean 8.6 (SD 7.2); n=92, Group 2: mean 8.7 (SD 7.3); n=89; Roland Disability Questionnaire for Sciatica 0-23 Top=High is poor outcome; Comments: Baseline pregabalin: 14.8 (5.0). Baseline placebo: 15.3 (4.5).
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports sex, age, dermatomal pain, motor deficit, neurologic deficit, sensory deficit, pain in both legs, pain on straight-leg raising manoeuvre, clinical suspected level of spine associated with leg pain, duration of symptoms and baseline values of outcomes; Group 1 Number missing: 9, Reason: Overall: 2 excluded after randomisation due to taking an excluded medicine, 9 withdrew consent, 6 were lost to follow up; Group 2 Number missing: 8, Reason: Overall: 7 withdrew consent, 7 were lost to follow-up

Protocol outcome 6: Function (disability scores) at >4 months
- Actual outcome for Overall (acute, chronic) with sciatica: Roland Disability Questionnaire for Sciatica score at 52 weeks; Group 1: mean 8.2 (SD 7.6); n=83, Group 2: mean 7.4 (SD 7.2); n=79; Roland Disability Questionnaire for Sciatica 0-23 Top=High is poor outcome; Comments: Baseline pregabalin: 14.8 (5.0). Baseline placebo: 15.3 (4.5).
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports sex, age, dermatomal pain, motor deficit, neurologic deficit, sensory deficit, pain in both legs, pain on straight-leg raising manoeuvre, clinical suspected level of spine associated with leg pain, duration of symptoms and baseline values of outcomes; Group 1 Number missing: 15, Reason: Overall: 2 excluded after randomisation due to taking an excluded

medicine, 9 withdrew consent, 6 were lost to follow up; Group 2 Number missing: 14, Reason: Overall: 7 withdrew consent, 7 were lost to follow-up Protocol outcome 7: Adverse events (morbidity) at >4 months - Actual outcome for Overall (acute, chronic) with sciatica: Number of people with adverse events at 52 weeks; Group 1: 68/106, Group 2: 43/101; Comments: Includes Pregabalin: dizziness = 42, dorsalgia = 19, sweating = 9, malaise = 9. Placebo: dizziness = 13, dorsalgia = 10, sweating = 8, malaise = 3. Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports sex, age, dermatomal pain, motor deficit, neurologic deficit, sensory deficit, pain in both legs, pain on straight-leg raising manoeuvre, clinical suspected level of spine associated with leg pain, duration of symptoms and baseline values of outcomes; Group 1 Number missing: 15, Reason: Overall: 2 excluded after randomisation due to taking an excluded medicine, 9 withdrew consent, 6 were lost to follow up; Group 2 Number missing: 14, Reason: Overall: 7 withdrew consent, 7 were lost to follow-up	
Protocol outcomes not reported by the study	Psychological distress (HADS/GHQ/BDI/STAI) at Up to 4 months; Psychological distress (HADS/GHQ/BDI/STAI) at >4 months; Healthcare utilisation (prescribing, investigations, hospitalisation or health professional visit) at Up to 4 months; Healthcare utilisation (prescribing, investigations, hospitalisation or health professional visit) at >4 months; Adverse events (morbidity) at Up to 4 months; Adverse event (mortality) at Up to 4 months; Adverse event (mortality) at >4 months; Responder criteria (pain) at Up to 4 months; Responder criteria (pain) at >4 months

Study (subsidiary papers)	Yildirim 2003[144]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=50)
Countries and setting	Conducted in Turkey; Setting: Outpatient follow up
Line of therapy	Unclear
Duration of study	Intervention + follow up: 8 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Lumbosciatalgia secondary to L5 or S1 radiculopathy. The majority (84%) had unilateral radiculopathy, while the remainder had bilateral. Spinal MRI showed that all people had 4-5 and/or L5-S1 bulging and/or protrusion without significant spinal stenosis. Chronic pain and nerve impairment were the main symptoms of the people under study.
Stratum	Overall (acute, chronic) with sciatica
Subgroup analysis within study	Not applicable
Inclusion criteria	People with lumbosciatalgia secondary to L5 or S1 radiculopathy. All people had previously been treated with non-steroidal anti-inflammatory drugs, combined or not with vitamin B complex. People did not receive drugs (skeletal muscle relaxants, steroids, NSAIDs) or were treated with only minimal doses of analgesics during the last three weeks before the study.
Exclusion criteria	Contraindications to gabapentin treatment; severe depression; severe nephropathy; chronic alcoholism; pregnancy; spinal surgery; coexistence of another type of pain.
Recruitment/selection of patients	No additional information
Age, gender and ethnicity	Age - Mean (SD): 39.3 (9.2). Gender (M:F): 18:32. Ethnicity: Not stated
Further population details	1. Chronicity of pain: Chronic pain (at least 3 months duration) (Mean duration = 68.5 (59.8) months).
Extra comments	Mean duration of radiculopathy (mean [SD]): 68.5 (59.8) months
Indirectness of population	No indirectness
Interventions	(n=25) Intervention 1: Antiepileptics - Gabapentinoids. Oral gabapentin from 900mg per day to 3600mg per day divided in 3 doses. Gabapentin was initiated gradually, starting from 900mg for the first days, then the dosage was usually increased every 3 days up to 3600mg per day, but when side effects were observed the dosage was reduced to tolerable levels. Duration 8 weeks. Concurrent medication/care: During the study, people took no other medication for their radiculopathy. Indirectness: No indirectness

	(n=25) Intervention 2: Placebo/Sham. Matching placebo three times a day. Duration 8 weeks. Concurrent medication/care: During the study, people took no other medication for their radiculopathy. Indirectness: No indirectness
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GABAPENTINOIDS versus PLACEBO/SHAM Protocol outcome 1: Pain severity (VAS/NRS) at Up to 4 months - Actual outcome for Overall (acute, chronic) with sciatica: Pain at rest at 8 weeks; Group 1: mean 0.56 (SD 0.58); n=23, Group 2: mean 1.36 (SD 0.59); n=20; Pain at rest 0-3 Top=High is poor outcome; Comments: Baseline gabapentin: 1.60 (0.94). Baseline placebo: 1.68 (0.67). Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age, gender, duration of radiculopathy and baseline outcome values (including pain score); Group 1 Number missing: 2, Reason: 2 people dropped out due to adverse events; Group 2 Number missing: 5, Reason: 5 people dropped out due to lack of clinical efficacy Protocol outcome 2: Adverse events (morbidity) at Up to 4 months - Actual outcome for Overall (acute, chronic) with sciatica: Adverse side effect (dizziness and somnolence) at 8 weeks; Group 1: 2/23, Group 2: 0/20; Comments: Gabapentinoids: 1 = dizziness, 1 = somnolence Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age, gender, duration of radiculopathy and baseline outcome values (including pain score); Group 1 Number missing: 2, Reason: 2 people dropped out due to adverse events; Group 2 Number missing: 5, Reason: 5 people dropped out due to lack of clinical efficacy	
Protocol outcomes not reported by the study	Quality of life at Up to 4 months; Quality of life at > 4 months; Pain severity (VAS/NRS) at >4 months; Function (disability scores) at Up to 4 months; Function (disability scores) at >4 months; Psychological distress (HADS/GHQ/BDI/STAI) at Up to 4 months; Psychological distress (HADS/GHQ/BDI/STAI) at >4 months; Healthcare utilisation (prescribing, investigations, hospitalisation or health professional visit) at Up to 4 months; Healthcare utilisation (prescribing, investigations, hospitalisation or health professional visit) at >4 months; Adverse events (morbidity) at >4 months; Adverse event (mortality) at Up to 4 months; Adverse event (mortality) at >4 months; Responder criteria (pain) at Up to 4 months; Responder criteria (pain) at >4 months

Appendix E – Forest plots

E.1 Non-steroidal anti-inflammatory drugs compared to placebo

Figure 2: Pain severity (VAS, 0-100, high is poor, change score) at up to 4 months

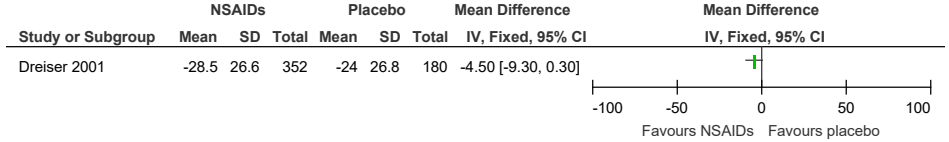
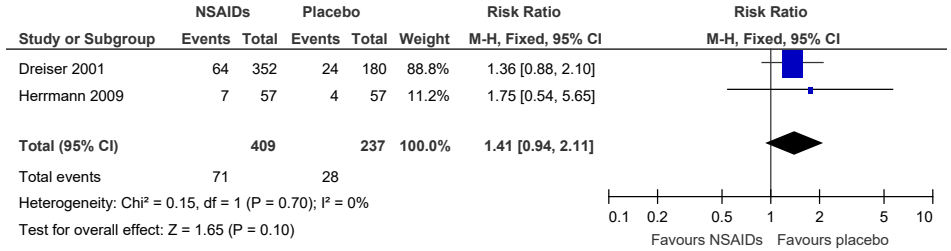
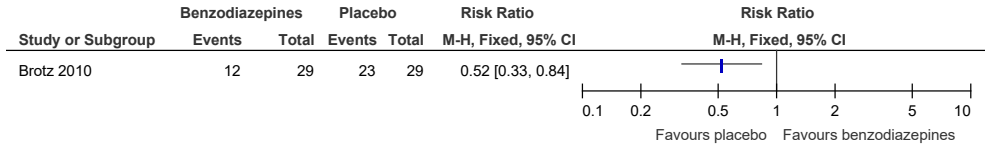


Figure 3: Adverse events (morbidity) at up to 4 months



E.2 Benzodiazepines compared to placebo

Figure 4: Responder criteria (pain reduction of VAS of 50% of more) at up to 4 months



E.3 Gabapentinoids compared to placebo

Figure 5: Quality of life (SF-12 physical component, 0-100, high is good, final value) at up to 4 months

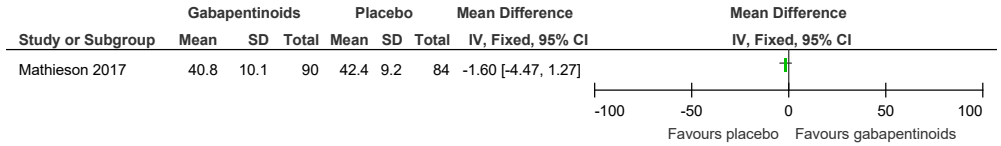


Figure 6: Quality of life (SF-12 mental component, 0-100, high is good, final value) at up to 4 months

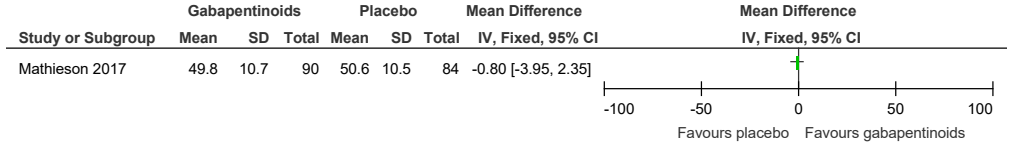


Figure 7: Quality of life (SF-12 physical component, 0-100, high is good, final value) at >4 months

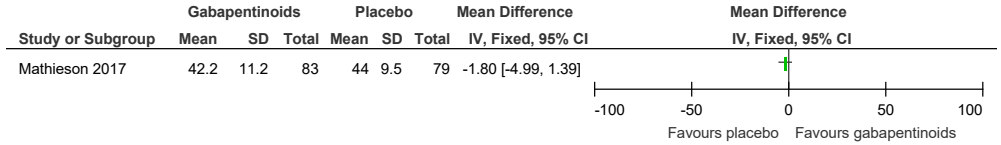


Figure 8: Quality of life (SF-12 mental component, 0-100, high is good, final value) at >4 months

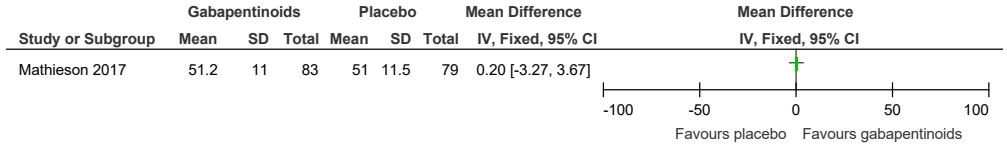


Figure 9: Pain severity (VAS, NRS, 0-10, high is poor, final value and change score) at up to 4 months

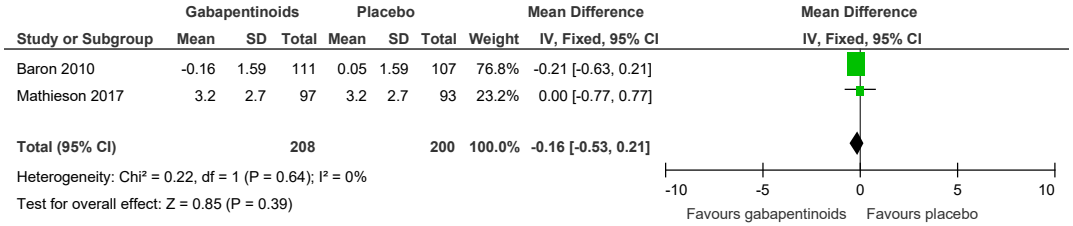


Figure 10: Pain severity (pain at rest, 0-3, high is poor, final value) at up to 4 months

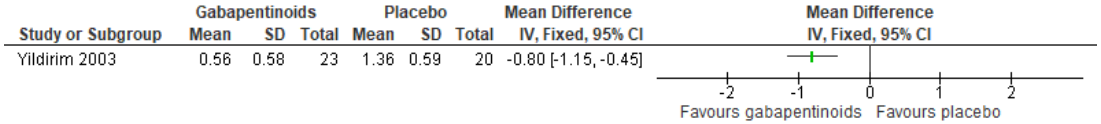


Figure 11: Pain severity (NRS, 0-10, high is poor, final value) at >4 months

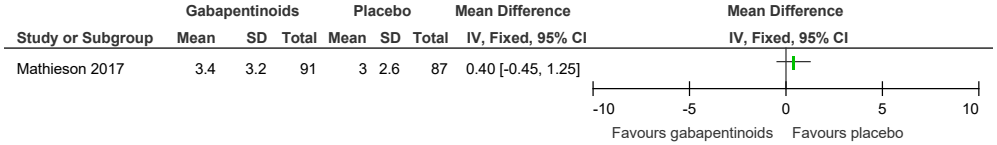


Figure 12: Function (Roland Disability Questionnaire, 0-23, high is poor, final value) at up to 4 months

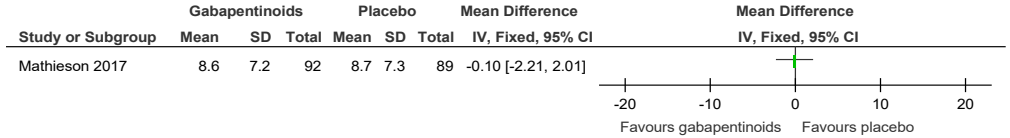


Figure 13: Function (Roland Disability Questionnaire, 0-23, high is poor, final value) at >4 months

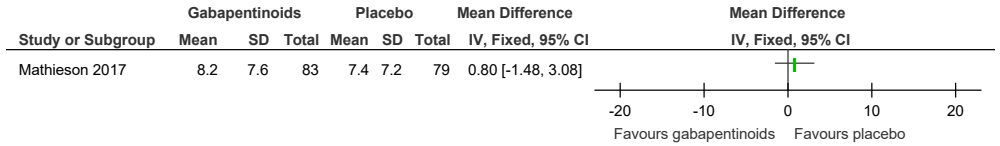


Figure 14: Psychological distress (HADS anxiety subscale, 0-21, high is poor, change score) at up to 4 months

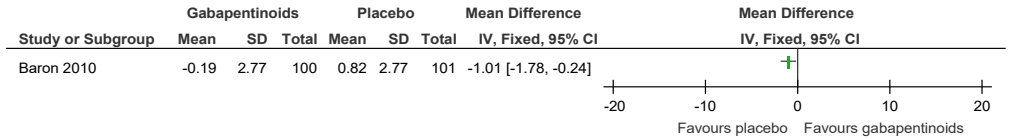


Figure 15: Psychological distress (HADS depression subscale, 0-21, high is poor, change score) at > 4 months

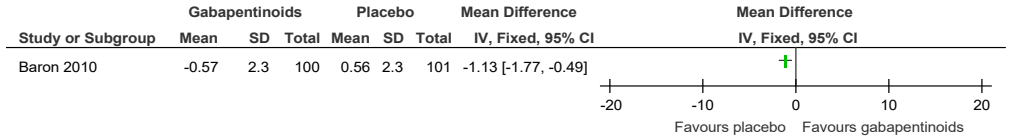


Figure 16: Adverse event (morbidity) at up to 4 months

Study or Subgroup	Gabapentinoids Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Baron 2010	45	110	45	107	98.9%	0.97 [0.71, 1.33]
Yildirim 2003	2	25	0	25	1.1%	5.00 [0.25, 99.16]
Total (95% CI)		**135**		**132**	**100.0%**	**1.02 [0.74, 1.39]**
Total events	47		45			

Heterogeneity: Chi² = 1.17, df = 1 (P = 0.28); I² = 14%
Test for overall effect: Z = 0.10 (P = 0.92)

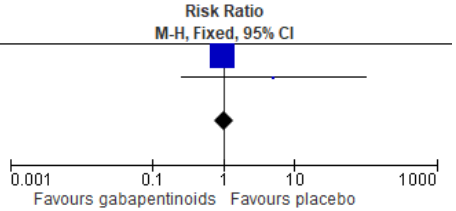


Figure 17: Adverse event (morbidity) at >4 months

Study or Subgroup	Gabapentinoids Events	Total	Placebo Events	Total	Risk Ratio M-H, Fixed, 95% CI
Baron 2010	68	110	43	107	1.54 [1.17, 2.02]

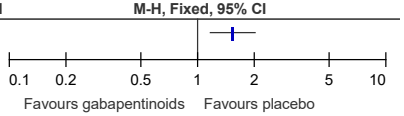
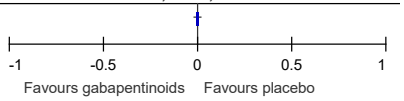


Figure 18: Adverse event (mortality) at up to 4 months

Study or Subgroup	Gabapentinoids Events	Total	Placebo Events	Total	Risk Difference M-H, Fixed, 95% CI
Baron 2010	0	110	0	107	0.00 [-0.02, 0.02]



E.4 Corticosteroids compared to placebo

Figure 19: Quality of life (SF-36 physical component summary, 0-100, high is good, change score) at up to 4 months

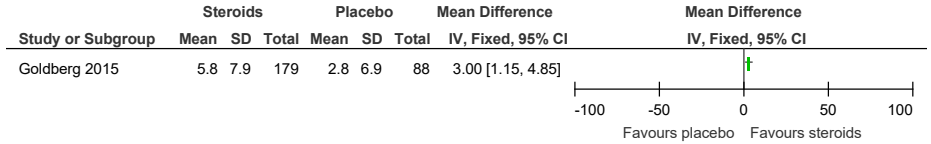


Figure 20: Quality of life (SF-36 mental component summary, 0-100, high is good, change score) at up to 4 months

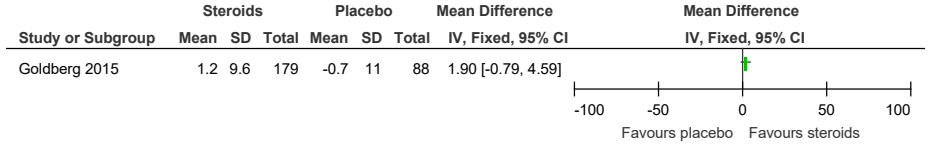


Figure 21: Quality of life (SF-36 physical component summary, 0-100, high is good, change score) at >4 months

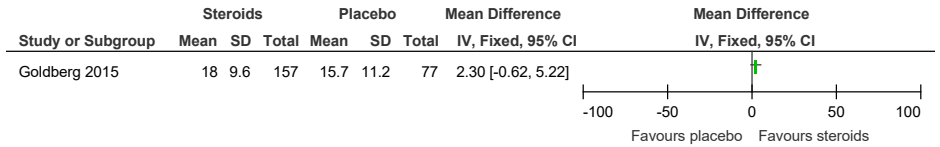


Figure 22: Quality of life (SF-36 mental component summary, 0-100, high is good, change score) at >4 months

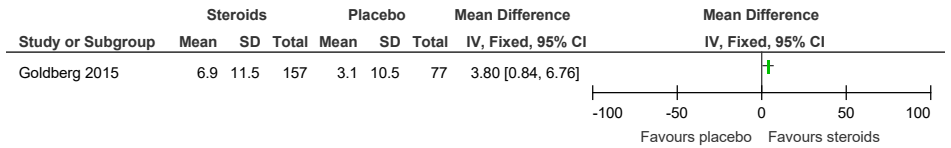


Figure 23: Pain severity (NRS, 0-10, high is poor, change score) at up to 4 months

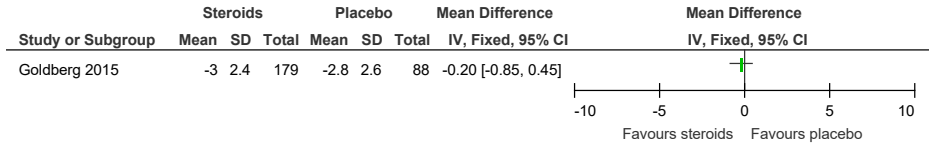


Figure 24: Pain severity (NRS, 0-10, high is poor, change score) at >4 months

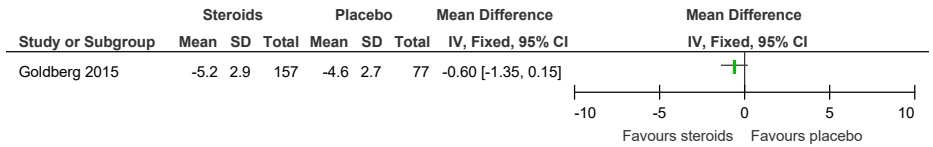


Figure 25: Function (Oswestry Disability Index, 0-100, high is poor, change score) at up to 4 months

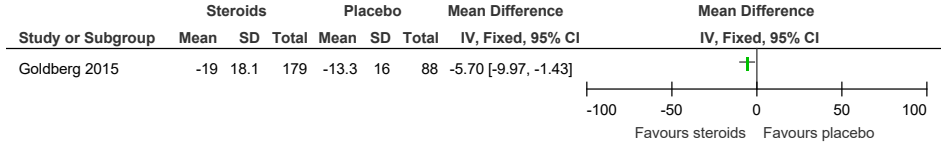


Figure 26: Function (Oswestry Disability Index, 0-100, high is poor, change score) at >4 months

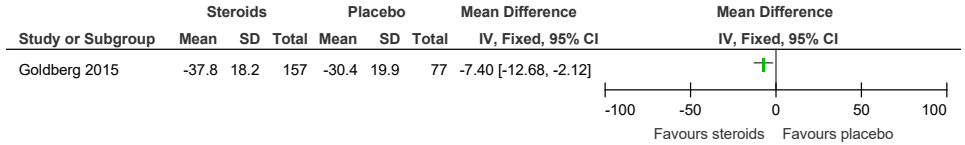


Figure 27: Adverse events (morbidity) at up to 4 months

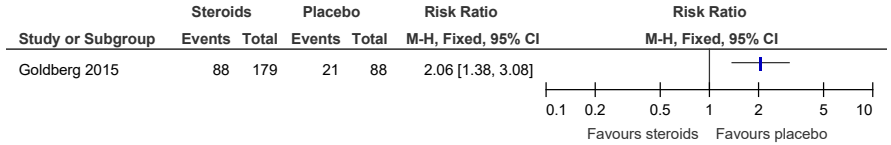


Figure 28: Responder criteria (improvement of pain NRS of no less than 3 points) at up to 4 months

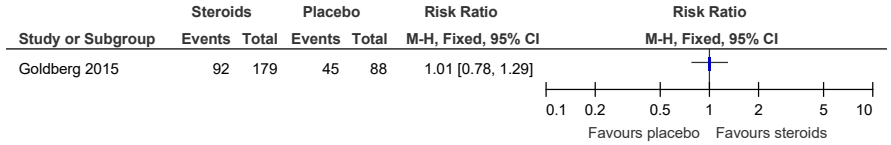
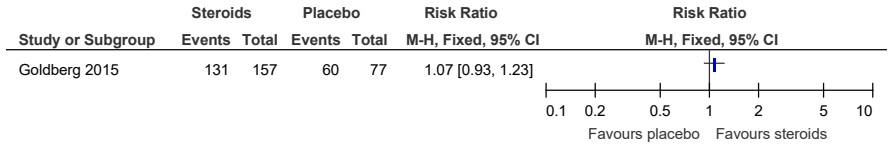


Figure 29: Responder criteria (improvement of pain NRS of no less than 3 points) at >4 months



E.5 Corticosteroids compared to gabapentinoids

Figure 30: Quality of life (SF-36 physical component score, 0-100, high is good, final value) at up to 4 months

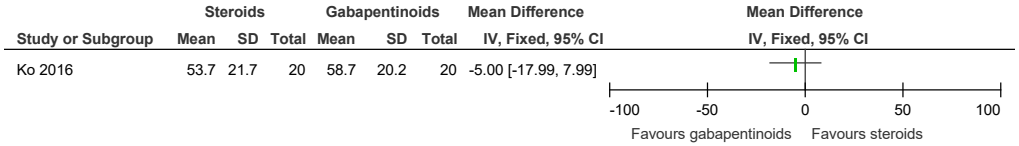


Figure 31: Quality of life (SF-36 mental component score, 0-100, high is good, final value) at up to 4 months

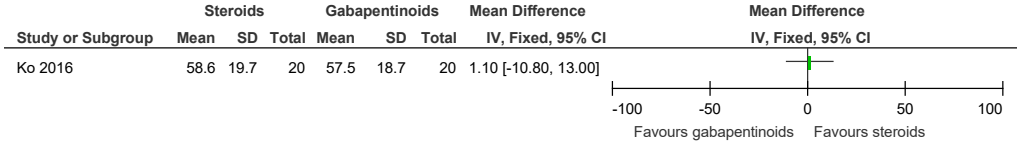


Figure 32: Pain severity (NRS, 0-10, high is poor, final value) at up to 4 months

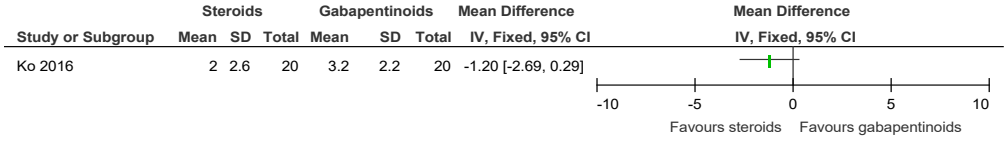
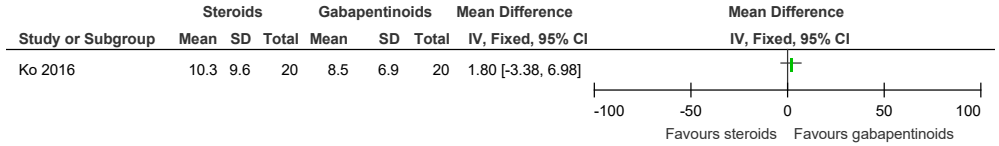


Figure 33: Function (Oswestry disability index, 0-100, high is poor, final value) at up to 4 months



Appendix F – GRADE tables

Table 11: Clinical evidence profile: non-steroidal anti-inflammatory drugs compared to placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Non-steroidal anti-inflammatory drugs	Placebo	Relative (95% CI)	Absolute		
Pain severity (VAS, 0-100, high is poor, change score) at up to 4 months (follow-up 7 days; measured with: VAS; range of scores: 0-100; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	352	180	-	MD 4.5 lower (9.3 lower to 0.3 higher)	⊕⊕⊕⊕ HIGH	CRITICAL
Adverse events (morbidity) at up to 4 months (follow-up mean 6 days)												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	71/409 (17.4%)	10.2%	RR 1.41 (0.94 to 2.11)	42 more per 1000 (from 6 fewer to 113 more)	⊕⊕⊕O MODERATE	IMPORTANT

[1] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 12: Clinical evidence profile: benzodiazepines compared to placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Benzodiazepines	Placebo	Relative (95% CI)	Absolute		
Responder criteria (pain reduction of VAS of 50% of more) at up to 4 months (follow-up 1 weeks)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	12/29 (41.4%)	79.3%	RR 0.52 (0.33 to 0.84)	381 fewer per 1000 (from 127 fewer to 531 fewer)	⊕⊕⊕O MODERATE	IMPORTANT

[1] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 13: Clinical evidence profile: gabapentinoids compared to placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Gabapentinoids	Placebo	Relative (95% CI)	Absolute		

Quality of life (SF-12 physical component, 0-100, high is good, final value) at up to 4 months (follow-up 12 weeks; measured with: SF-12 physical component; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	90	84	-	MD 1.6 lower (4.47 lower to 1.27 higher)	⊕⊕⊕O MODERATE	CRITICAL
Quality of life (SF-12 mental component, 0-100, high is good, final value) at up to 4 months (follow-up 12 weeks; measured with: SF-12 mental component; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	90	84	-	MD 0.8 lower (3.95 lower to 2.35 higher)	⊕⊕⊕O MODERATE	CRITICAL
Quality of life (SF-12 physical component, 0-100, high is good, final value) at >4 months (follow-up 52 weeks; measured with: SF-12 physical component; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	83	79	-	MD 1.8 lower (4.99 lower to 1.39 higher)	⊕⊕⊕O MODERATE	CRITICAL
Quality of life (SF-12 mental component, 0-100, high is good, final value) at >4 months (follow-up 52 weeks; measured with: SF-12 mental component; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	83	79	-	MD 0.2 higher (3.27 lower to 3.67 higher)	⊕⊕OO LOW	CRITICAL
Pain severity (VAS, NRS, 0-10, high is poor, final value and change score) at up to 4 months (follow-up mean 9 weeks; measured with: VAS, NRS; Better indicated by lower values)												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	208	200	-	MD 0.16 lower (0.53 lower to 0.21 higher)	⊕⊕⊕⊕ HIGH	CRITICAL
Pain severity (pain at rest, 0-3, high is poor, final value) at up to 4 months (follow-up 8 weeks; range of scores: 0-3; Better indicated by lower values)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	23	20	-	MD 0.80 lower (1.15 to 0.45 lower)	⊕⊕⊕O MODERATE	CRITICAL
Pain severity (NRS, 0-10, high is poor, final value) at >4 months (follow-up 52 weeks; measured with: NRS; range of scores: 0-10; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	91	87	-	MD 0.4 higher (0.45 lower to 1.25 higher)	⊕⊕⊕O MODERATE	CRITICAL
Function (Roland Disability Questionnaire, 0-23, high is poor, final value) at up to 4 months (follow-up 12 weeks; measured with: Roland Disability Questionnaire; range of scores: 0-23; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	92	89	-	MD 0.1 lower (2.21 lower to 2.01 higher)	⊕⊕OO LOW	CRITICAL
Function (Roland Disability Questionnaire, 0-23, high is poor, final value) at >4 months (follow-up 52 weeks; measured with: Roland Disability Questionnaire; range of scores: 0-23; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	83	79	-	MD 0.8 higher (1.48 lower to 3.08 higher)	⊕⊕⊕O MODERATE	CRITICAL
Psychological distress (HADS anxiety subscale, 0-21, high is poor, change score) at up to 4 months (follow-up 5 weeks; measured with: HADS anxiety subscale; range of scores: 0-21; Better indicated by lower values)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[1]	none	100	101	-	MD 1.01 lower (1.78 to 0.24 lower)	⊕⊕OO LOW	CRITICAL
Psychological distress (HADS depression subscale, 0-21, high is poor, change score) at up to 4 months (follow-up 5 weeks; measured with: HADS depression subscale; range of scores: 0-21; Better indicated by lower values)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[1]	none	100	101	-	MD 1.13 lower (1.77 to 0.49 lower)	⊕⊕OO LOW	CRITICAL
Adverse event (morbidity) at up to 4 months (follow-up 5 weeks)												

2	randomised trials	serious[2]	serious[3]	no serious indirectness	very serious[1]	none	47/135 (34.8%)	45/132 (34.1%)	RR 1.02 (0.74 to 1.39)	7 more per 1000 (from 89 fewer to 133 more)	⊕OOO VERY LOW	IMPORTANT
Adverse event (morbidity) at >4 months (follow-up 52 weeks)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	68/110 (61.8%)	40.2%	RR 1.54 (1.17 to 2.02)	217 more per 1000 (from 68 more to 410 more)	⊕⊕⊕O MODERATE	IMPORTANT
Adverse event (mortality) at up to 4 months (follow-up 5 weeks)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[4]	none	0/110 (0%)	0%	RD 0.00 (-0.02 to 0.02)	0 fewer per 1000 (from 20 fewer to 20 more)[5]	⊕⊕OO LOW	IMPORTANT

[1] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[2] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[3] Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)
[4] Downgraded for imprecision due to crossing line of no effect (for mortality). Sample size also considered due to there being zero events
[5] Absolute effect calculated by risk difference due to zero events in at least one arm of one study

Table 14: Clinical evidence profile: Corticosteroids compared to placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Steroids**	**Placebo**	**Relative (95% CI)**	**Absolute**		
Quality of life (SF-36 physical component summary, 0-100, high is good, change score) at up to 4 months (follow-up 3 weeks; measured with: SF-36 physical component summary; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	179	88	-	MD 3 higher (1.15 to 4.85 higher)	⊕⊕⊕O MODERATE	CRITICAL
Quality of life (SF-36 mental component summary, 0-100, high is good, change score) at up to 4 months (follow-up 3 weeks; measured with: SF-36 mental component summary; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	179	88	-	MD 1.9 higher (0.79 lower to 4.59 higher)	⊕⊕⊕O MODERATE	CRITICAL
Quality of life (SF-36 physical component summary, 0-100, high is good, change score) at >4 months (follow-up 52 weeks; measured with: SF-36 physical component summary; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	157	77	-	MD 2.3 higher (0.62 lower to 5.22 higher)	⊕⊕⊕O MODERATE	CRITICAL
Quality of life (SF-36 mental component summary, 0-100, high is good, change score) at >4 months (follow-up 52 weeks; measured with: SF-36 mental component summary; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	157	77	-	MD 3.8 higher (0.84 to 6.76 higher)	⊕⊕⊕O MODERATE	CRITICAL
Pain severity (NRS, 0-10, high is poor, change score) at up to 4 months (follow-up 3 weeks; measured with: NRS; range of scores: 0-10; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	179	88	-	MD 0.2 lower (0.85 lower to 0.45 higher)	⊕⊕⊕⊕ HIGH	CRITICAL

Pain severity (NRS, 0-10, high is poor, change score) at >4 months (follow-up 52 weeks; measured with: NRS; range of scores: 0-10; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	157	77	-	MD 0.6 lower (1.35 lower to 0.15 higher)	⊕⊕⊕O MODERATE	CRITICAL
Function (Oswestry Disability Index, 0-100, high is poor, change score) at up to 4 months (follow-up 3 weeks; measured with: Oswestry Disability Index; range of scores: 0-100; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	179	88	-	MD 5.7 lower (9.97 to 1.43 lower)	⊕⊕⊕⊕ HIGH	CRITICAL
Function (Oswestry Disability Index, 0-100, high is poor, change score) at >4 months (follow-up 52 weeks; measured with: Oswestry Disability Index; range of scores: 0-100; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	157	77	-	MD 7.4 lower (12.68 to 2.12 lower)	⊕⊕⊕O MODERATE	CRITICAL
Adverse events (morbidity) at up to 4 months (follow-up 3 weeks)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	88/179 (49.2%)	23.9%	RR 2.06 (1.38 to 3.08)	253 more per 1000 (from 91 more to 497 more)	⊕⊕⊕⊕ HIGH	IMPORTANT
Responder criteria (improvement of pain NRS of no less than 3 points) at up to 4 months (follow-up 3 weeks)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	92/179 (51.4%)	51.1%	RR 1.01 (0.78 to 1.29)	5 more per 1000 (from 112 fewer to 148 more)	⊕⊕⊕O MODERATE	IMPORTANT
Responder criteria (improvement of pain NRS of no less than 3 points) at >4 months (follow-up 52 weeks)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	131/157 (83.4%)	77.9%	RR 1.07 (0.93 to 1.23)	55 more per 1000 (from 55 fewer to 179 more)	⊕⊕⊕⊕ HIGH	IMPORTANT

[1] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

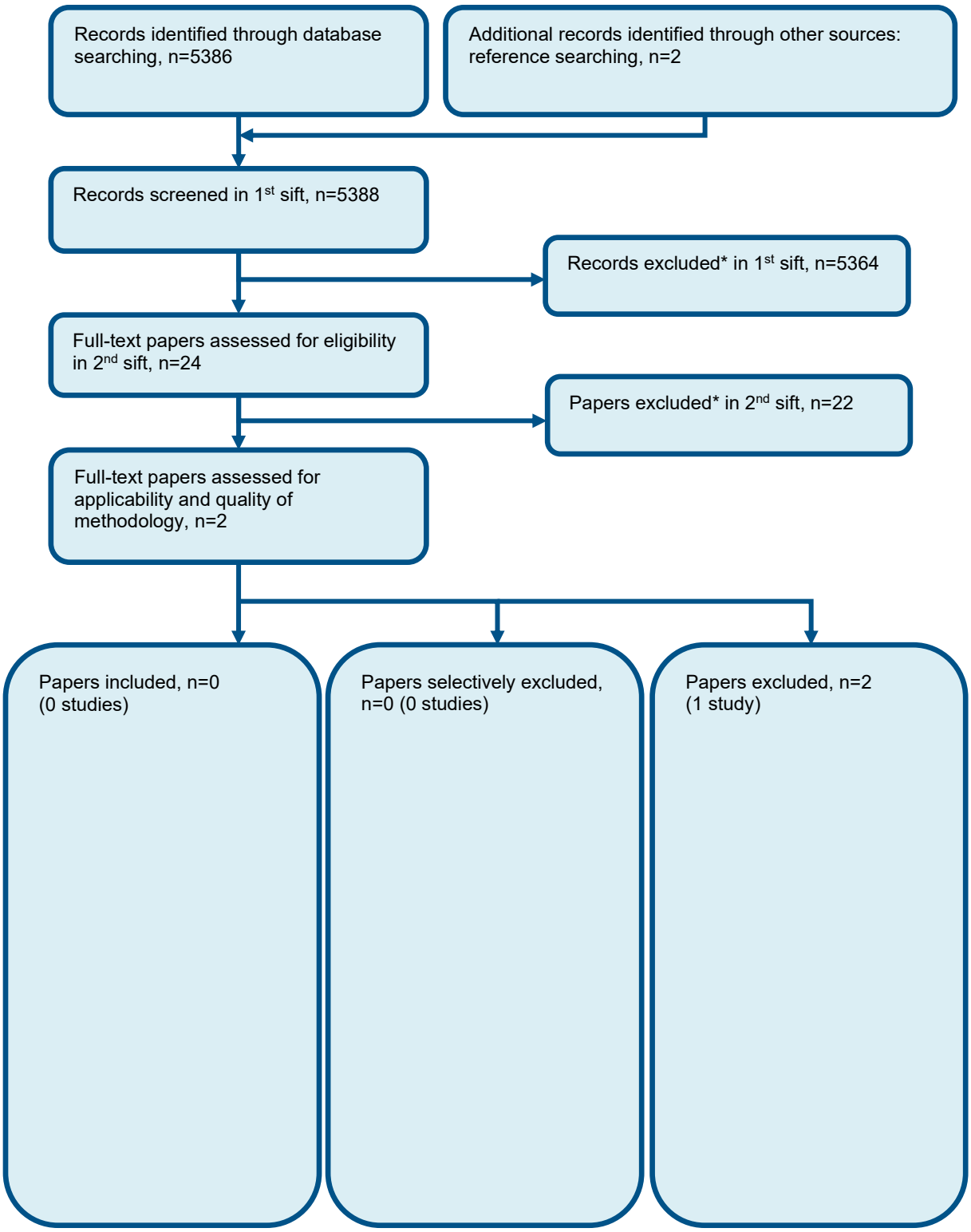
Table 15: Clinical evidence profile: Corticosteroids compared to gabapentinoids

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Steroids**	**Gabapentinoids**	**Relative (95% CI)**	**Absolute**		
Quality of life (SF-36 physical component score, 0-100, high is good, final value) at up to 4 months (follow-up 12 weeks; measured with: SF-36 physical component score; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	20	20	-	MD 5 lower (17.99 lower to 7.99 higher)	⊕OOO VERY LOW	CRITICAL
Quality of life (SF-36 mental component score, 0-100, high is good, final value) at up to 4 months (follow-up 12 weeks; measured with: SF-36 mental component score; range of scores: 0-100; Better indicated by higher values)												

1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	20	20	-	MD 1.1 higher (10.8 lower to 13 higher)	⊕OOO VERY LOW	CRITICAL
Pain severity (NRS, 0-10, high is poor, final value) at up to 4 months (follow-up 12 weeks; measured with: NRS; range of scores: 0-10; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	20	20	-	MD 1.2 lower (2.69 lower to 0.29 higher)	⊕OOO VERY LOW	CRITICAL
Function (Oswestry disability index, 0-100, high is poor, final value) at up to 4 months (follow-up 12 weeks; measured with: Oswestry disability index; range of scores: 0-100; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	20	20	-	MD 1.8 higher (3.38 lower to 6.98 higher)	⊕⊕OO LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Appendix G – Economic evidence study selection



* Non-relevant population, intervention, comparison, design or setting; non-English language

Appendix H – Economic evidence tables

No studies were included.

Appendix I – Health economic model

No original economic modelling was undertaken.

Appendix J – Excluded studies

Clinical studies

Table 16: Studies excluded from the clinical review

Study	Exclusion reason
Abdel Shaheed 2020[1]	Systematic review; references checked
ACTRN 2008[2]	Trial citation only
ACTRN 2013[3]	Trial citation only
ACTRN 2015[4]	Trial citation only
Al-Hihi 2017[5]	Commentary only
Ansari 2018[6]	Mixed chronic pain (not just low back pain)
Aoki 1984[7]	Not available in English language
Aoki 1989[12]	Not available in English language
Aoki 1989[11]	Not available in English language
Aoki 1990[8]	Not available in English language
Aoki 1991[13]	Not available in English language
Aoki 1995[9]	Not available in English language
Aoki 1995[10]	Not available in English language
Arriagada 1992[14]	Not available in English language
Auvinet 1995[15]	Inappropriate comparison
Babej-Dolle 1994[16]	Paper not available through any library and not available to purchase digitally
Beliveau 1971[18]	Incorrect interventions
Benditz 2017[19]	Incorrect study design
Blonna 2004[20]	Incorrect stratum. Not available in English language
Borms 1988[21]	Incorrect comparison
Bosch 1995[23]	Not in English language
Bosch 1996[22]	Not available in English language
Brasser 2009[24]	Abstract only
Braun 1982[25]	Not available in English language
Cevei 2011[27]	Abstract only
Checchia 2017[28]	Incorrect study design
Corts 1989[29]	Not available in English language
CTRI 2018[30]	Trial citation only
Cyteval 2006[31]	Incorrect study design. Incorrect interventions
Derry 2019[32]	Systematic review: study designs inappropriate. Incorrect stratum. Cochrane review; references checked
Ebell 2017[34]	Abstract only
Enke 2018[35]	Systematic review; references checked
Evansa 2011[36]	Abstract only
Finckh 2006[37]	Incorrect interventions
Friedman 2008[39]	Not guideline condition. Not review population
Gallagher 2015[40]	Systematic review is not relevant to review question or unclear PICO
Gastaldi 2019[41]	Incorrect interventions

Study	Exclusion reason
Gelijkens 2014[42]	Abstract only
Geurts 2002[43]	Not guideline condition. Not review population
Ghahreman 2011[44]	Conference abstract only
Ghozlan 1996[45]	Paper not available through any library and not available to purchase digitally
Ginies 2005[46]	Not available in English language
Goldie 1968[48]	Not guideline condition. Not review population
Grevsten 1975[49]	Not available in English language
Guo 2017[50]	Systematic review; references checked
Hadzic 2013[51]	Incorrect interventions
Haimovic 1985[52]	Abstract only
Haimovic 1986[53]	No usable outcomes
Hamza 2009[54]	Incorrect study design
Hasue 1997[55]	Paper not available through any library and not available to purchase digitally
Helliwell 1985[56]	Paper not available through any library and not available to purchase digitally
Holve 2008[58]	Not guideline condition. Not review population
Hwang 2019[59]	Mixed chronic pain (not just low back pain)
IRCT 2010[60]	Trial citation only
IRCT 2014[61]	Trial citation only
ISRCTN 2006[62]	Trial citation only
Jung Yong 1999[63]	Not available in English language
Kageyama 1982[64]	Not available in English language
Kasimcan 2010[65]	Incorrect study design. Inappropriate comparison
Kaye 2014[66]	Incorrect study design
Khoromi 2005[68]	Incorrect interventions
Khoromi 2007[67]	Crossover study
Klessinger 2013[69]	Not available in English language
Klessinger 2014[70]	Incorrect study design
Koleva 2011[72]	Abstract only
Kuroki 1995[73]	Not available to order - unlikely to be relevant
Kwasucki 2002[74]	Not available in English language
Lewis 2011[75]	Health technology assessment; references checked. Included populations mixed with low back pain and studies with the wrong design
Lo 2010[76]	Abstract only
Lobb 2010[77]	Papers not available through any library and not available to purchase digitally
Machado 2017[78]	Systematic review; references checked
Mahersi 2012[79]	Abstract only
Malik 2015[80]	Not guideline condition. Not review population
Marks 2014[81]	Not available in English language
Mathieson 2019[84]	Systematic review; references checked
Mazieres 1983[87]	Papers not available through any library and not available to purchase digitally

Study	Exclusion reason
Mele 1993[88]	Not available in English language
Metscher 2001[89]	Not available in English language
Misirlioglu 2013[90]	Unable to access - unlikely to be related (wrong population)
Muller-Fassbender 1985[91]	Not available in English language
Nakashima 2019[92]	Inappropriate comparison
NCT 2001[94]	Trial citation only
NCT 2005[95]	Trial citation only
NCT 2005[97]	Trial citation only
NCT 2006[98]	Trial citation only
NCT 2008[99]	Trial citation only
NCT 2009[100]	Trial citation only
NCT 2010[101]	Trial citation only
NCT 2012[102]	Not available in English language
NCT 2013[103]	Not available in English language
NCT 2017[104]	Trial citation only
NCT 2005[96]	Trial citation only
Oka 2018[105]	Inappropriate comparison
Ono 1987[106]	Papers not available through any library and not available to purchase digitally
Persson 2012[107]	Incorrect study design
Pinto 2012[108]	Systematic review; references checked
Pinto 2017[109]	Systematic review; references checked
Plested 2010[110]	Systematic review is not relevant to review question or unclear PICO
Radcliff 2011[111]	Abstract only
Rasmussen-Barr 2016[112]	Cochrane review; references checked. Systematic review is not relevant to review question or unclear PICO
Rasmussen-Barr 2017[113]	Cochrane review; references checked. Systematic review is not relevant to review question or unclear PICO
Rastogi 1994[114]	Papers not available through any library and not available to purchase digitally
Robertson 2016[115]	Systematic review; references checked
Robertson 2016[116]	Incorrect interventions
Roncoroni 2011[117]	Not guideline condition. Not review population. Systematic review is not relevant to review question or unclear PICO
Rubens-Duval 1967[118]	Not available in English language
Sabaté López 1992[119]	Not available in English language
Sakakida 1984[120]	Not available in English language
Sampath 1999[121]	Incorrect stratum
Schuermans 1988[122]	Incorrect comparison.
Schukro 2016[123]	Not guideline condition. Not review population
Shirokov 2008[124]	Not available in English language
Song 1995[125]	Papers not available through any library and not available to purchase digitally
Stratz 1990[126]	Not available in English Language
Sucu 2016[127]	Incorrect study design. Incorrect interventions

Study	Exclusion reason
Sugioka 1994[128]	Not available in English language
Suzan 2013[129]	Incorrect study design
Swezey 1999[130]	Not guideline condition. Not review population. Incorrect study design. Incorrect interventions
Tsuyama 1984[136]	Not available in English language
Tafazal 2006[131]	Abstract only
Takahashi 2014[132]	Incorrect study design. Incorrect interventions
Tarulli 2007[133]	Narrative review only
Tervo 1976[135]	Papers not available through any library and not available to purchase digitally
Visconti 2019[137]	Incorrect study design
Vroomen 2000[138]	Systematic review is not relevant to review question or unclear PICO. Systematic review; references checked
Weber 1980[139]	Papers not available through any library and not available to purchase digitally
Weber 1993[140]	Papers not available through any library and not available to purchase digitally
Weiner 1997[141]	Incorrect study design. Incorrect interventions
Williams 2017[142]	Discontinued study
Yamamoto 1989[143]	Not available in English language
Younus 2017[145]	Abstract only
Zaoui 2009[146]	Abstract only
Zhou 2017[147]	Protocol only

Health Economic studies

Table 17: Studies excluded from the health economic review

Reference	Reason for exclusion
Fitzsimmons 2014[38, 75]	Excluded due to a combination of applicability and methodological limitations. Different classes of non-opioid drugs were all lumped together. The effectiveness data for opioid drugs are based on 3 studies, all of which were excluded in the clinical review. Baseline EQ-5D data were taken from a more severe population. Adverse events for drugs were not included.

Appendix K – Research recommendations – full details

K.1.1 Research recommendation

What is the clinical and cost effectiveness of opioids for the management of acute sciatica?

K.1.2 Why this is important

Opioids are commonly used for management of pain, however in recent years concern has arisen about the risks of dependence associated with opioids and other related harms. There was a lack of evidence for the use of opioids for sciatica identified in the review. Whilst their use for chronic sciatica is not recommended, there may be some benefit from using them short term for acute sciatica. Research is required to determine whether this is true.

K.1.3 Rationale for research recommendation

Importance to 'patients' or the population	There are a limited number of effective treatments for sciatica and no oral pharmacological treatments are currently recommended for use. Effective treatment of acute sciatica could prevent this from becoming chronic in those where it would not have resolved spontaneously and would be of benefit to patients.
Relevance to NICE guidance	No evidence was identified for the use of opioids in the management of sciatica. Concerns about the harms of using opioids long term informed a recommendation against their use for chronic sciatica, but no recommendation was made for acute sciatica. Research on this topic would enable a recommendation to be made in future updates of this guideline.
Relevance to the NHS	The outcome of this research may offer a pharmacological treatment option for people with acute sciatica and may also prevent people from progressing to chronic sciatica.
National priorities	Medium
Current evidence base	No evidence for opioids was identified in the review of pharmacological treatment for sciatica described in this evidence review. Although there are known harms of long term use of opioids, evidence for short term use for acute sciatica is required.
Equality considerations	None known

K.1.4 Modified PICO table

Population	People aged 16 and over with acute sciatica.
Intervention	Opioids
Comparator	Placebo
Outcome	**Critical:** Quality of life (for example EQ5D or SF36); pain severity (for example VAS or NRS), function (RMDQ or ODI), Psychological distress (HADS, GHQ, BDI or STAI)

	Important: Healthcare utilisation, Adverse events (morbidity and mortality), Responder criteria (≥ 30% improvement in pain or function)
Study design	Randomised controlled trial
Timeframe	Short term follow up is required to determine the use for acute sciatica (less than 3 months duration) however long term follow up would also be of benefit to determine if benefits are maintained or if there are any longer term adverse effects after treatment stops.
Additional information	None

K.1.5 Research recommendation

What is the clinical and cost effectiveness of antidepressants for the management of sciatica?

K.1.6 Why this is important

Antidepressants are very widely prescribed for sciatica and other neuropathic pain conditions. NICE's guideline for pharmacological management of neuropathic pain (CG173) recommends amitriptyline and duloxetine as 2 of the possible initial treatment options for neuropathic pain, however it was noted that whilst sciatica was previously considered within that guideline, there was very little evidence in populations with sciatica. In this updated review, no evidence relevant to this review protocol was identified for antidepressants in people with sciatica. Given how commonly they are used, evidence is required to inform recommendations specific to people with sciatica.

K.1.7 Rationale for research recommendation

Importance to 'patients' or the population	There are a limited number of effective treatments for sciatica and no oral pharmacological treatments are currently recommended for use. Antidepressants are commonly prescribed and therefore evidence of their effectiveness in this condition is important for people with sciatica to determine whether these should be recommended.
Relevance to NICE guidance	No evidence was identified for the use of antidepressants in the management of sciatica. Research on this topic would enable a recommendation to be made in future updates of this guideline.
Relevance to the NHS	The outcome of this research may offer a pharmacological treatment option for people with sciatica.
National priorities	Medium
Current evidence base	No evidence for antidepressants relevant to the review protocol was identified in the review of pharmacological treatment for sciatica described in this evidence review.
Equality considerations	None known

K.1.8 Modified PICO table

Population	People aged 16 and over with sciatica.
Intervention	Antidepressants: SSRIs SNRIs TCAs Other antidepressants
Comparator	Placebo
Outcome	**Critical:** Quality of life (for example EQ5D or SF36); pain severity (for example VAS or NRS), function (RMDQ or ODI), Psychological distress (HADS, GHQ, BDI or STAI) **Important:** Healthcare utilisation, Adverse events (morbidity and mortality), Responder criteria (≥ 30% improvement in pain or function)
Study design	Randomised controlled trial
Timeframe	Short term and long term follow up (minimum 1 year) is required to determine the use for acute and chronic sciatica and also to determine whether benefits are maintained or if there are long term adverse effects.
Additional information	None

K.1.9 Research recommendation

What is the clinical and cost effectiveness of NSAIDs for the management of sciatica?

K.1.10 Why this is important

NSAIDs are widely used for the management of pain, including sciatica. In this updated evidence review, there was very limited evidence for their use in people with sciatica. Given the side effect profile and their common use, evidence is required to inform recommendations specific to people with sciatica.

K.1.11 Rationale for research recommendation

Importance to 'patients' or the population	There are a limited number of effective treatments for sciatica and no oral pharmacological treatments are currently recommended for use. NSAIDs are commonly used and therefore evidence of their effectiveness in this condition is important for people with sciatica to determine whether these should be recommended.
Relevance to NICE guidance	Limited evidence was identified for the use of NSAIDs in the management of sciatica. Research on this topic would enable a recommendation to be made in future updates of this guideline.
Relevance to the NHS	The outcome of this research may offer a pharmacological treatment option for people with sciatica.

National priorities	Low
Current evidence base	Very limited evidence for NSAIDs relevant to the review protocol was identified in the review of pharmacological treatment for sciatica. The committee considered this insufficient to make a recommendation for or against their use.
Equality considerations	None known

K.1.12 Modified PICO table

Population	People aged 16 and over with sciatica.
Intervention	NSAIDs
Comparator	Placebo
Outcome	**Critical:** Quality of life (for example EQ5D or SF36); pain severity (for example VAS or NRS), function (RMDQ or ODI), Psychological distress (HADS, GHQ, BDI or STAI) **Important:** Healthcare utilisation, Adverse events (morbidity and mortality), Responder criteria (≥ 30% improvement in pain or function)
Study design	Randomised controlled trial
Timeframe	Short term and long term follow up (minimum 1 year) is required to determine the use for acute and chronic sciatica and also to determine whether benefits are maintained or if there are long term adverse effects.
Additional information	None