

PRACTICE

UNCERTAINTIES

Which pain medications are effective for sciatica (radicular leg pain)?

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Sciatica is commonly seen in primary care. Its prevalence in the general population varies between 3% and 14%, depending on the definition used.¹ The prognosis of acute sciatica is generally favourable: data from a prospective study of 183 patients with a median disease duration of 16 days show that in approximately one third of patients, symptoms improve greatly (ie, measured on a 4 point scale, 1=worsened, 2=remained unchanged, 3=improved, and 4=improved greatly) within two weeks, and about three quarters of patients reported any improvement within 12 weeks.² Nevertheless, in another study of 172 patients, 30% continued to report persistent and disabling symptoms after one year.³

Sciatica is a symptom rather than a specific diagnosis⁴ and is used broadly to refer to pain that radiates along the path of the sciatic nerve.⁵

The commonest cause of sciatica is impingement of lumbosacral nerve roots, as they emerge from the spinal canal, by a herniated intervertebral disc (fig 1). Other causes of impingement include spondylolisthesis and spinal tumours or cysts.⁴ For this reason, symptoms of sciatica often co-exist with low back pain, but disturbances along the course of the sciatic nerve can also arise from locations other than the lower back (ie, due to piriformis syndrome, diabetic radiculopathy, and hip fracture or dislocation).⁵

Patients with sciatica are more disabled and consume more health resources, including medication, than those with non-specific low back pain.⁶

There is no reference standard to classify radicular leg pain, however it seems reasonable to diagnose a patient with radicular leg pain if they report pain from the low back radiating down below the knee in one leg. Patients will often have a positive result on one or more neurological tests, indicating nerve root tension or neurological deficit.⁴ Box 1 shows key signs and symptoms commonly associated with radicular leg pain which

can be used by clinicians to distinguish it from non-specific low back pain. This is based on expert opinion.⁷

One of the first steps in managing a patient who presents with radicular leg pain is prescription of analgesia.⁸ There is uncertainty, however, about which pain medications are the most effective.

What is the evidence of the uncertainty?

Although most pain medications used for radicular leg pain in clinical practice have been investigated in randomised controlled trials, considerable uncertainty exists because of the low to moderate quality of most trials and the difficulty in comparing trials that differ in terms of population, intervention, comparator, outcomes, and study design.

Table 1⇓ summarises evidence on the efficacy of each class of drugs. The emphasis in this table is on evidence generated from randomised placebo controlled trials, including only patients with radicular leg pain and focusing on clinical endpoints. Where available, we report results from systematic reviews with meta-analysis, otherwise single trials are used to summarise the evidence (table 1⇓).

Acetaminophen versus placebo

No randomised placebo controlled trials investigating the efficacy of acetaminophen for sciatica were identified.

Non-steroidal anti-inflammatory drugs (NSAIDs) versus placebo

A 2016 systematic review⁹ pooling data from three trials found that NSAIDs are no more effective than placebo in reducing pain or disability, but did find a statistically significant improvement in global improvement associated with NSAIDs compared with placebo at short term follow-up (up to three weeks; n=753, risk ratio=1.14; 95% confidence interval 1.03 to 1.27). It should be noted, however, that the overall quality of

What you need to know

- The most effective pain medication to treat patients with sciatica or radicular leg pain is unclear
- In approximately one third of patients, symptoms improve within two weeks; in three quarters of patients, symptoms improve within 12 weeks, but about a third of patients have persistent and disabling symptoms after one year³
- Medications used for the treatment of sciatica can have considerable side effects

Box 1: Key signs and symptoms that distinguish radicular leg pain from lower back pain

- Unilateral leg pain, which is worse than any associated back pain
- Pain radiating below the knee (and can radiate into the foot and toes)
- Numbness or pins and needles in a dermatomal distribution
- Positive result on a straight leg raise test (ie, radiating pain between 30 and 70 degrees of hip flexion)
- Weakness or reflex changes, or both, in a myotomal distribution

evidence using the GRADE approach for these outcomes varies from low to very low. Evidence from four trials suggests an increased risk of adverse events (n=967, risk ratio=1.40; 95% confidence interval 1.02 to 1.93) when using NSAIDs compared with placebo. Most adverse events identified in the 2016 systematic review⁹ were reported to be mild and consisted of headache, dizziness and gastrointestinal problems, such as nausea, dyspepsia, epigastric burning, and abdominal pain.

Systemic corticosteroids versus placebo

In a 2012 systematic review¹⁰ from our group, a meta-analysis of two trials shows moderate quality evidence favouring corticosteroids over placebo in reducing pain (n=138, weighted mean difference on 0 to 100 scale=-12.2; 95% confidence interval -20.9 to -3.4) at short term follow-up (ie, more than two weeks and up to three months). In two subsequent trials^{11 12} the results were less favourable. One of these trials¹¹ with moderate risk of bias (n=58; 8 mg of intravenous dexamethasone) reported pain relief at 24 hours (mean difference on a 0 to 10 scale=-1.86; 95% confidence interval -0.31 to -3.42) but not at six weeks. Another large trial¹² with low risk of bias (n=269; 15 days of a reducing dose of oral prednisone), however, showed a small reduction in disability (without concomitant improvement in pain) in favour of corticosteroids at three weeks (mean difference on a 0 to 100 scale=-6.4; 95% confidence interval -10.9 to -1.9) and at one year (mean difference=-7.4; 95% confidence interval -12.5 to -2.2). Evidence from the 2012 systematic review¹⁰ and the largest subsequent trial¹² shows that adverse events, such as insomnia and nervousness, were more common in the corticosteroid group compared with the placebo group (table 1⇓).

Benzodiazepines versus placebo

One small trial¹³ with low risk of bias (n=60) investigating the efficacy of benzodiazepines compared with placebo was identified and found no difference between groups for disability at one week and one year follow-up (table 1⇓). The drug treatment was even associated with the lower likelihood of experiencing ≥50% improvement in pain at one week (risk ratio=0.5; 95% confidence interval 0.3 to 0.8) and a longer hospital stay (benzodiazepine group, median=10 days versus placebo, median=8 days; P=0.008) compared with placebo. Adverse events were not assessed in this trial.

Anticonvulsants versus placebo

We identified four trials with moderate^{14 15} to low^{16 17} risk of bias testing anticonvulsants (gabapentin, pregabalin, and topiramate) against placebo in patients with chronic¹⁴⁻¹⁶ or mixed¹⁷ duration

of symptoms. In the earliest trial¹⁴ (n=50) use of gabapentin was associated with a statistically significant reduction in pain (mean difference on a 0 to 100 scale=-26.6; 95% confidence interval -38.3 to -14.9) at two month follow-up, but subsequent trials, including a crossover trial¹⁵ (n=29), a trial¹⁶ using an enrichment trial design (n=217), and a 2017 randomised controlled trial,¹⁷ (n=209) found that topiramate¹⁵ and pregabalin^{16 17} were no more effective than placebo to reduce pain and improve function at short and long term follow-up (table 1⇓). All trials reported a similar proportion of adverse events in the anticonvulsant and placebo groups (table 1⇓).

Antidepressants versus placebo

A small crossover trial¹⁸ (n=28) with a four arm design found no statistically significant differences in pain and disability between the antidepressant (nortriptyline) and placebo group at 10 day follow-up. However, another small crossover trial²⁰ (n=25) found a statistically significant effect for reducing pain of antidepressants (duloxetine) over placebo (mean difference on a 0 to 10 scale=-1.8; 95% confidence interval -0.8 to -2.8) after a four week treatment period. In another trial with a three arm design¹⁹ (n=60), antidepressants (amitriptyline) were also more effective than placebo to reduce pain (mean difference on a 0 to 10 scale=-1.4; 95% confidence interval -0.1 to -2.8) after a two week treatment period. All trials reported a similar proportion of adverse events in the antidepressant and placebo groups (table 1⇓).

Opioids versus placebo

One small crossover trial¹⁸ with a four arm design (n=28) including a comparison between morphine and placebo, was identified. This trial did not show a benefit from morphine over placebo to reduce pain (mean difference on a 0-100 scale=-3.0; 95% confidence interval -17.4 to 11.4) and disability (mean difference on a 0-100 scale=-4.8; 95% confidence interval -13.2 to 3.7) at 10 day follow-up. Adverse events, such as constipation, drowsiness, and dizziness, were more common in the opioid group compared with the placebo group (table 1⇓).

Biological agents versus placebo

We identified a systematic review²¹ investigating the efficacy of biological agents (adalimumab, etanercept, and infliximab) targeting tumour necrosis factor α , compared with placebo. Pooled data from only randomised placebo controlled trials show that compared with placebo biological agents did not reduce pain (6 trials, n=211, mean difference on a 0-100 scale=-10.29; 95% confidence interval -24.03 to 3.45), and disability (6 trials, n=211, mean difference on a 0-100

scale=-2.8; 95% confidence interval -11.3 to 5.7), or increase the proportion of patients who expressed an improvement or recovery (3 trials, n=141, odds ratio=1.3, 95% confidence interval 0.5 to 3.7) at short term follow-up (ie, more than four weeks and up to six weeks). Similar effects were found for medium term (ie, six months) and long term (ie, 12 months) follow-ups. The proportion of adverse events did not differ between the biological agents and the placebo group (table 1¹¹).

Is ongoing research likely to provide relevant evidence?

We searched for ongoing trials (box 2, table 2¹²). Three (ie, one two-arm and two three-arm) ongoing randomised placebo controlled trials were identified. The largest trials identified are likely to provide evidence on the effectiveness of acetaminophen, opioids, and biological agents.

What should we do in the light of the uncertainty?

Explain to patients that there is a lack of evidence to support the prescription of any particular pain medication, and that these drugs can have side effects. Medication should be seen as one possible option within a range of conservative treatments for radicular leg pain. At the same time, clinicians should explain the natural history of radicular leg pain (as described earlier).

If drug treatment is desired, a reasonable approach is to make a personalised treatment plan depending on the duration and severity of pain, the patient's age, history of medication use, and preference for medication, comorbidities and the safety profiles, and side effects of pain medications. If offering a NSAID as first line, discuss factors for adverse events (eg, being older, having kidney disease). Paracetamol is a simple and cheap alternative first-line analgesic, but its efficacy for treating radicular pain is unknown.

If NSAIDs are contraindicated, not tolerated, or have been ineffective, and the disc herniation is confirmed on imaging, systemic corticosteroids can be offered for patients with acute symptoms. The results of a 2015 large trial¹² with low risk of bias shows that corticosteroids might benefit those patients with acute radicular leg pain with confirmed disc herniation and moderate disability (ie, at least 30 points on Oswestry Disability Index). Monitoring of side effects is also indicated during the course of treatment.

Patients with clinical features of chronic neuropathic pain (eg, allodynia or hyperalgesia), who had an inadequate response to NSAIDs might benefit from a trial of antidepressant medication. In this case, given the evidence from the latest trials^{19 20} on antidepressants, clinicians can consider the evidence based recommendation on the prescription of antidepressants from the UK's National Institute for Health and Care Excellence guideline on neuropathic pain.²⁵

Follow up patients regularly when prescribing any type of pain medication. In many cases patients do not find sufficient pain relief using pain medication, therefore encourage patients to try guideline endorsed non-drug treatments²⁶ such as a (group) exercise or psychological programme, especially if there are psychosocial obstacles to recovery present.

After a course of conservative management including drug and non-drug treatments, refer patients with persistent and disabling sciatica (eg, after a 6-8 week period) to specialised care.

We have read and understood BMJ policy on declaration of interests and declare that we have no competing interests.

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Box 2: Search strategy for published trials, unpublished or ongoing trials, and study selection

We have updated the evidence on this topic by searching the Cochrane Library and Medline for trials, systematic reviews, and evidence based clinical practice guidelines after the final search date (15 March 2010) of a previous systematic review¹⁰ published in 2012 covering all types of drugs administered in primary care settings for radicular leg pain. We used the search strategy described in this systematic review to search for new trials investigating the efficacy of drugs commonly administered in primary care combined with terms related to biological agents.

We also searched for unpublished or ongoing trials by searching ClinicalTrials.gov, the International Standard Randomized Controlled Trial Number register, and the Australian New Zealand Clinical Trials Registry. This search was aided by the World Health Organization International Clinical Trials Registry Platform search portal.

Education into Practice

- When you next meet a patient taking medication for sciatica, what options would you consider?
- How would you discuss the relative benefits and harms of these options?
- Based on reading this article is there anything that you would do differently in your practice?

How patients were involved in this article

One patient who suffered from sciatica in the past commented on the manuscript. This patient was treated with weak opioids (ie, tramadol) and emphasised the importance of communicating to patients about the lack of robust evidence for pain medications and the associated potential side effects.

Tables**Table 1 | Summary of evidence for pharmacological interventions generated from randomised placebo controlled trials**

PPharmacological interventions* author, year (study type)	Outcomes	Follow-up	Sample size; magnitude of effect**	Comments
Acetaminophen (paracetamol) versus placebo	-	-	-	No trials identified.
Non-steroidal anti-inflammatory drugs (NSAIDs) versus placebo				
Rasmussen-Barr et al, 2016 (SR) ⁹	Pain (0-100 scale)	Short term (up to 3 weeks)	n=918 (3 trials); MD=-4.6, 95% CI: -11.1 to 2.0	SR found significant effect for global improvement (ie, greater likelihood of experiencing an improvement) but not for pain and disability. Long term effects remain unknown. Overall quality of evidence using the GRADE approach for these outcomes vary from "very low" to "low" quality evidence. Side effects (at short term follow-up) occurred in 1 out of 20 patients
	Disability (0-100 scale)		n=214 (1 trial); No pooled estimate, no difference between the groups	
	% of patients who expressed an improvement		n=753 (3 trials); RR=1.1, 95% CI: 1.0 to 1.3	
	Adverse events		n=967 (4 trials); RR=1.4, 95% CI: 1.0 to 1.9	
Systemic corticosteroids versus placebo				
Pinto et al, 2012 (SR) ¹⁰	Pain (0-100 scale)	Immediate term (≤2weeks)	n=84 (2 trials); MD -1.8, 95% CI: -11.1 to 7.5	SR found "moderate" quality evidence (ie, using GRADE) favouring corticosteroids over placebo in reducing pain at short term follow-up. In two subsequent RCTs results were less
	Disability (0-100 scale)		n=24 (1 trial); MD=-10.5, 95% CI: -29.9 to 8.9	
	Adverse events		corticosteroid group (n=42): 3 (7%) versus placebo (n=42): 0 (0%)	
	Pain (0-100 scale)	Short term (>2 and ≤12 weeks)	n=138 (2 trials); MD=-12.2, 95% CI -20.9 to -3.4	

Table 1 (continued)

PParmacological interventions* author, year (study type)	Outcomes	Follow-up	Sample size; magnitude of effect**	Comments
	Adverse events		corticosteroid group (n=70): 14 events (20%) versus placebo (n=72): 8 events (11%)	favourable. The largest trial with low risk of bias showed a small reduction in disability (without concomitant improvement in pain) in favour of corticosteroids at 3 weeks. Another finding from this trial was a higher proportion of patients experiencing at least 1 adverse event in the steroid group
Balakrishnamoorthy et al, 2015 (RCT) ¹¹	Pain (0-100 scale)	24 hours	n=46; MD=-1.9, 95% CI: -3.4 to -0.3	
		6 weeks	n=35; MD=-1.45, 95% CI: -3.7 to 0.8	
	Disability (0-100 scale)	24 hours	n=48; MD=3.0, 95% CI: -9.1 to 15.1	
		6 weeks	n=36; MD=-2.9, 95% CI: -19.3 to 13.4	
	Adverse events	up to 6 weeks	Incidence of adverse events between groups was similar (18% versus 15%)†	
Goldberg et al, 2015 (RCT) ¹²	Pain (0-10 scale)	3 weeks	n=267; MD=-0.3, 95% CI: -1.0 to 0.4	
		1 year	n=234; MD=-0.6, 95% CI: -1.3 to 0.2	
	Disability (0-100 scale)	3 weeks	n=267; MD=-6.4, 95% CI: -10.9 to -1.9	
		1 year	n=234; MD=-7.4, 95% CI: -12.5 to -2.2	
	% of patients who expressed an improvement	3 weeks	n=267; RR=1.2, 95% CI: 1.0 to 1.4	
		1 year	n=234; RR=1.1, 95% CI: 1.0 to 1.2	
	Adverse events	3 weeks	corticosteroid group (n=179): 88 (49%) versus placebo (n=88): 21 (24%), P<0.001	
Benzodiazepines versus placebo				
Brötz et al, 2010 ¹³	% of patients experiencing a reduction of ≥50% in pain	1 week	n=58; RR=0.5, 95%CI: 0.3 to 0.8	Only one RCT identified which found that the drug treatment was associated with the lower likelihood of experiencing a reduction of ≥50% in pain at 1 week and longer hospital stay
	Disability (0-24)		benzodiazepine group, median reduction=3.0 versus placebo, median reduction=5.0 (P=0.67)	
	Hospital stay	-	n=60; benzodiazepine group, median=10 days versus placebo group, median=8 days (P=0.0008)	
Anticonvulsants versus Placebo				
Yildirim et al, 2003 (RCT) ¹⁴	Pain (0-100 scale)	2 months	n=43; MD=-26.6, 95% CI: -38.3 to -14.9***	While in the earliest RCT anticonvulsants were associated with a substantial reduction in pain, three subsequent trials did not find any benefit from anticonvulsants over placebo
	Adverse events		anticonvulsant group (n=25): 2 (8%), no data reported for the placebo group	
Khoromi et al, 2005 (crossover trial) ¹⁵	Pain (0-100 scale)	8 weeks	n=29; MD=-7.4, 95% CI: -21.2 to 6.4***	
	Disability (0-100 scale)		n=29; MD=-2.0, 95% CI: -10.0 to 6.0***	
	Adverse events		anticonvulsant group (n=29): 25 (86%) versus placebo group (n=29): 21 (72%)	
Baron et al, 2010 (enrichment trial) ¹⁶	Pain (0-10 scale)	35 days	n=217; anticonvulsant group, mean change score=-0.16 versus placebo group, mean change score=0.05 (P=0.332)	
	Disability (0-23 scale)		no statistically significant difference (data not shown)†	
	Global impression of change (1-7 scale)		no statistically significant difference (data not shown)†	
	Adverse events		anticonvulsant group (n=110): 45 (41%) versus placebo group (n=107): 45 (42%)	
Mathieson et al, 2017 (RCT) ¹⁷	Pain (0-10 scale)	8 weeks	n=207; MD=0.5, 95% CI: -0.2 to 1.2	
		1 year	n=207; MD=0.3, 95% CI: -0.5 to 1.0	
	Disability (0-23 scale)	8 weeks	n=207; MD=0.1, 95% CI: -1.8 to 2.0	
		1 year	n=207; MD=0.2, 95% CI: -1.8 to 2.2	

Table 1 (continued)

PPharmacological interventions* author, year (study type)	Outcomes	Follow-up	Sample size; magnitude of effect**	Comments
	Global perceived effect (−5 to+5 scale)	8 weeks	n=207; MD=−0.6, 95% CI: −1.3 to 0.2	
		1 year	n=207; MD=−0.2, 95% CI: −1.0 to 0.6	
	Serious adverse events		anticonvulsant group (n=106): 2 (2%) versus placebo group (n=107): 6 (6%)	
Antidepressants versus placebo				
Khoromi et al, 2007 (crossover trial) ¹⁸	Pain (0-100 scale)	10 days	n=28, MD=−7.0, 95% CI: −21.1 to 7.1***	In the earliest trial no substantial differences in pain and disability between the antidepressant and placebo were reported. However, two subsequent trials were more positive with regards to the effects of antidepressants
	Disability (0-100 scale)		n=28, MD=−3.0, 95% CI: −11.5 to 5.5***	
	Adverse events		antidepressant group (n=28): 19 (68%) versus placebo group (n=28): 14 (50%)	
Vanelderen et al, 2015 (RCT) ¹⁹	Pain (0-10 scale)	2 weeks	n=40; MD=−1.4, 95% CI: −0.1 to −2.8	
	Adverse events		antidepressant group (n=20): 2 (10%) versus placebo group (n=20): 0 (0%)	
Schukro et al, 2016 (crossover trial) ²⁰	Pain (0-10 scale)	4 weeks	n=25; MD=−1.8, 95% CI: −0.8 to −2.8	
	Adverse events		antidepressant group (n=31): 20 (65%) versus placebo group (n=29): 18 (62%)	
Opioid analgesics versus placebo				
Khoromi et al, 2007 (crossover trial) ¹⁸	Pain (0-100 scale)	10 days	n=28, MD=−3.0, 95% CI: −17.4 to 11.4***	One small trial identified which failed to show a benefit from opioids over placebo to reduce pain
	Disability (0-100 scale)		n=28, MD=−4.8, 95% CI: −13.2 to 3.7***	
	Adverse events		opioid group (n=28): 26 (93%) versus placebo group (n=28): 14 (50%)	
Biological agents versus placebo				
Williams et al, 2013 (SR) ²¹	Pain (0-100 scale)	Short term (>4 to ≤6 weeks)	n=211 (6 trials); MD=−10.3, 95% CI: −24.0 to 3.5	The pooling data from only RCTs shows that the biological agents are no more effective than placebo. Similar non-significant effects were found for medium and long term follow-ups (data not reported)
	Disability (0-100 scale)		n=211 (6 trials); MD=−2.8, 95% CI: −11.3 to 5.7	
	% of patients who expressed an improvement		n=141 (3 trials); OR=1.3, 95% CI: 0.5 to 3.7	
	Adverse events		n=283 (7 trials); OR=1.1, 95% CI: 0.4 to 3.1	

CI: confidence interval; MD: mean difference; OR: odds ratio; RCT: randomised controlled trial; RR: risk ratio; SR: systematic review * If systematic reviews of high quality are available only trials published after their search period are summarised ** For risk ratio, values greater than 1 indicate an increase likelihood of the outcome occurring in the drug treatment group. For mean difference, negative values for pain and disability and positive values for global perceived effect favour pharmacological interventions. Bold text highlights statistically significant effects. Sample size for single trials refers to the number of patients analysed. *** Magnitude of effect or adverse events extracted from Pinto et al (2012)¹⁰ †As reported in the publication

Table 2| Ongoing trials of pain medication for radicular leg pain

Name of trial (country, year of registration, registration number)	Population (target sample size)	Intervention and comparison	Primary outcomes
Safety and efficacy of nonsteroidal anti-inflammatory drug (NSAID) and glucocorticoids in acute sciatica – TéAGS ²² (France, 2013, NCT01816334)	Patient with clinical diagnosis of sciatica and concordant imaging evidence (n=50)	1. Corticosteroids 2. NSAIDs 3. Placebo	Leg pain (0-100 visual analogue scale)
IV Paracetamol vs IV Morphine vs Placebo in Sciatalgia ²³ (Turkey, 2015, NCT02504996)	Patient with sciatica diagnosed by clinical assessment alone (n=300)	1. Acetaminophen 2. Morphine 3. Placebo	Leg pain (0-100 visual analogue scale)
A randomised controlled trial of adalimumab injection plus physiotherapy compared with placebo plus physiotherapy for patients with sciatica ²⁴ (United Kingdom, 2014, ISRCTN14569274)	Patient with clinical diagnosis of sciatica and concordant imaging evidence (n=332)	1. Adalimumab 2. Placebo	Disability (Oswestry Disability Index)

Figure

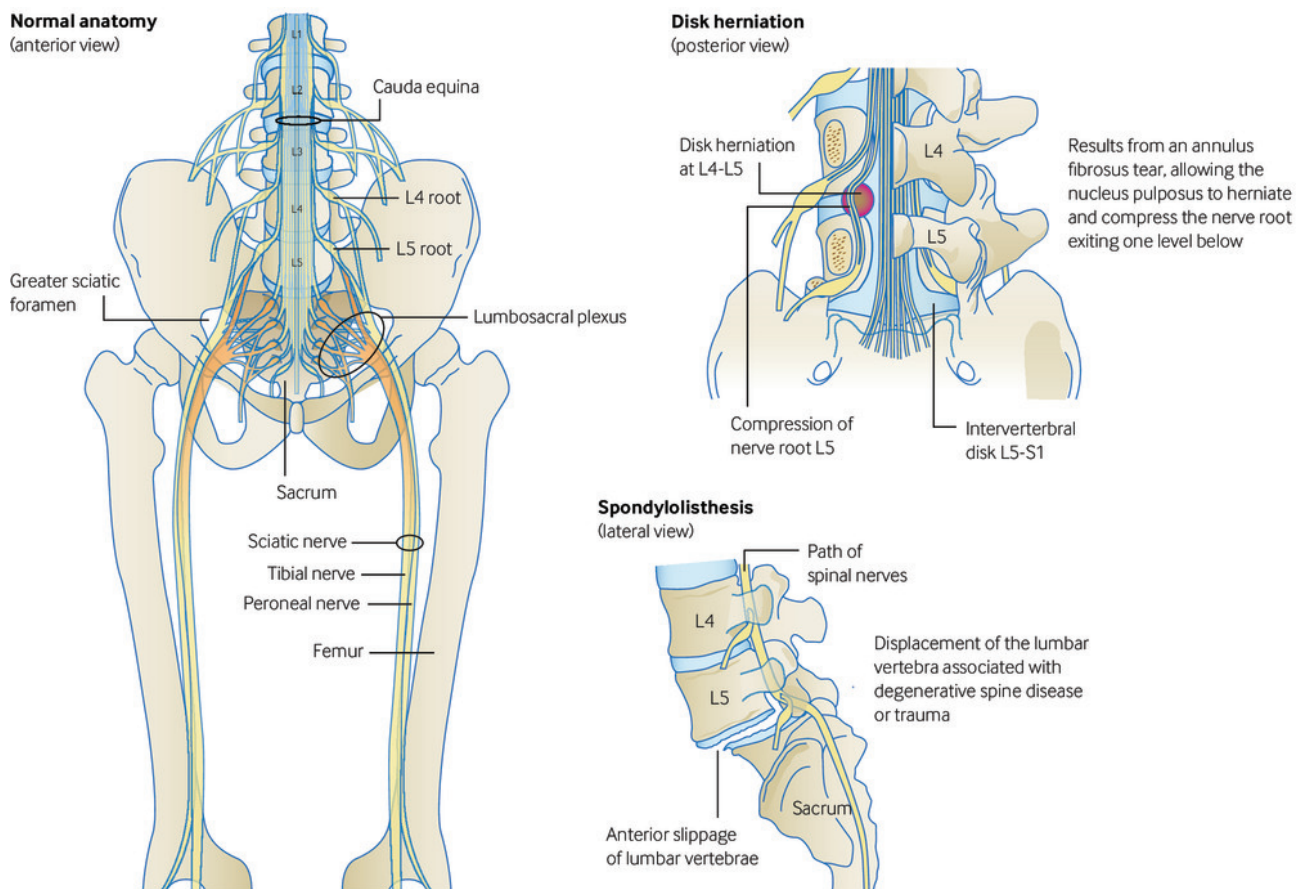


Fig 1 Common causes of sciatica. Disc herniation is the commonest cause. Spondylolisthesis can cause impingement