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Dr Navjoyt Ladher
Research Editor
MANUSCRIPT COMMITTEE
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Surgical versus non-surgical treatment for sciatica: a systematic review and meta-analysis of randomised controlled trials

Dear Dr Ladher,

Thank you for considering our manuscript and for the opportunity to revise our work. We also thank the BMJ Committee and reviewers for their constructive comments. Below is a point-by-point response to the issues raised by the committee and reviewers. Changes to the manuscript are included below (highlighted in yellow). Quoted sentences from the manuscript and supplementals are *italicised*.

Yours sincerely,
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No.	Committee comments	Response
	Statistical editor	
1	All languages, all alternative interventions, focused patient groups, recent search – looks well done.	We thank the editors for this feedback on our review.
2	One of 24 included papers a conference abstract [52] - surprising that this would include sufficient information for a meta-analysis. Can the authors clarify please?	We followed the recommendation of Cochrane Handbook (https://training.cochrane.org/handbook/current/chapter-04) to include conference abstracts and unpublished data where appropriate. The Greenfield 2001[1] study met our inclusion criteria, provided a description of both interventions, reported Means and N per group, p-values of between-group differences for outcomes relevant to our review, which allowed us to include it in the meta-analysis. **Reference:** 1. Greenfield K, Nelson RJ, Findlay GD, Egger M, Sanford E. Microdiscectomy and conservative treatment for lumbar disc herniation with back pain and sciatica: a randomised clinical trial. Proceedings of the International Society for the Study of the Lumbar Spine 2003:245.
3	Last sentence of conclusion states: "Discectomy may be an option for people who require rapid leg pain relief and disability improvement." - how helpful is this as surely all patients want rapid leg pain relief?	We agree that all patients would like rapid pain relief, but in this case, this desire must be balanced against the disadvantages of surgery (eg, risks, costs etc). We have reworded this as follows:

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		"Discectomy may be an option for people with sciatica who feel that the rapid relief offered by discectomy outweighs the risks and costs associated with surgery."
	Research editor	
4	*The 2007 Cochrane review on "Surgical interventions for lumbar disc prolapse" included 40 trials and 2 non-randomised studies - many more than were included in this systematic review. The conclusions were similar. There are another 16 Cochrane reviews in the library evaluating treatments for sciatica. How much does this new review add?	Our review provides a timely update on the 2007 Cochrane review.[1] Key studies in the field have been published in the past 15 years,[2-13] which have been captured by our review, making it the most rigorous and comprehensive review on this topic to date. The 2007 Cochrane review included only 9 trials comparing surgical vs non-surgical treatments (discectomy=4, chemonucleolysis=5). Other included trials compared one technique of discectomy vs another (n=9), discectomy vs another surgical treatment (n=7), and different types of barrier membrane following discectomy (n=8). In contrast, we included 24 trials in the surgery versus non-surgical treatment comparisons. Further, in our primary comparison of discectomy vs non-surgical treatment, we identified 12 trials (vs only 3 trials in the Cochrane review). In the comparison of discectomy vs non-surgical treatment, the Cochrane review only descriptively reviewed a few trials and concluded that discectomy could provide fast relief in selected patients with sciatica. Our review was able to pool results for this comparison, and is the first review to present a meta-analysis of this comparison across all time points until 5 years. The additional data in our review provides estimates of

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		effect based on existing trial evidence, to guide better informed patient and clinician decision making and important directions for future research in this field. The other 16 Cochrane reviews of treatment for sciatica consist of non-surgical treatment: pharmacological treatment, spinal manipulation, traction, and epidural steroids injection etc. Although the 2007 review addresses a related topic to ours, it needed to be updated, and other reviews were more limited in scope to ours eg, comparing minimally invasive microdiscectomy vs open/micro discectomy. **References (bolded authors are authors in our review):** 1. Gibson JNA, Waddell G. Surgical interventions for lumbar disc prolapse. Cochrane Database Syst Rev 2007(2) doi: 10.1002/14651858.CD001350.pub4 2. **Peul WC,** van Houwelingen HC, van den Hout WB, Brand R, Eekhof JAH, Tans JTJ, Thomeer RTWM, **Koes BW**. Surgery versus Prolonged Conservative Treatment for Sciatica. The New England journal of medicine 2007;356(22):2245-56. doi: 10.1056/NEJMoa064039 3. **Peul WC**, van den Hout WB, Brand R, Thomeer RT, **Koes BW**. Prolonged conservative care versus early surgery in patients with sciatica caused by lumbar disc herniation: two year results of a randomised controlled trial. BMJ 2008;336(7657):1355-8. doi: 10.1136/bmj.a143 [published Online First: 2008/05/27] 4. Weinstein JN, Lurie JD, Tosteson TD, Tosteson ANA, Blood EA, Abdu WA, Herkowitz H, Hilibrand A, Albert T, Fischgrund J, Weinstein JN, Lurie JD, Tosteson TD, Tosteson ANA, Blood EA, Abdu WA, Herkowitz H, Hilibrand A, Albert T, Fischgrund J. Surgical versus nonoperative treatment for lumbar disc herniation: four-year results for the Spine Patient

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		11. Matsuyama Y, Chiba K, Toyama Y, Iwata H, Seo T. A multicenter, randomized, double-blind, dose-finding study of condoliase in patients with lumbar disc herniation. J Neurosurg Spine 2018;28(5):499-511. doi: http://dx.doi.org/10.3171/2017.7.SPINE161327 12. **Bailey CS**, Bailey SI, Rasoulinejad P, Taylor D, Sequeira K, Miller T, Watson J, Rosedale R, Gurr KR, Siddiqi F, Glennie A, Urquhart JC. Surgery versus Conservative Care for Persistent Sciatica Lasting 4 to 12 Months. The New England journal of medicine 2020;382(12):1093-102. doi: 10.1056/NEJMoa1912658 13. Wilby MJ, Best A, Wood E, Burnside G, Bedson E, Short H, Wheatley D, Hill-McManus D, Sharma M, Clark S, Baranidharan G, Price C, Mannion R, Hutchinson PJ, Hughes DA, Marson A, Williamson PR. Surgical microdiscectomy versus transforaminal epidural steroid injection in patients with sciatica secondary to herniated lumbar disc (NERVES): a phase 3, multicentre, open-label, randomised
5	*Looks to be a well done meta-analysis on this research question, but there are many published meta-analyses, including network meta-analyses, with very similar conclusions. Can the authors clarify what this study adds to earlier work, and should the major earlier reviews be referenced?	Previous reviews have substantial methodological shortcomings which were addressed by our review.[1-3] Below is a description of the issues with the earlier reviews. We mentioned the shortcomings of these reviews in the introduction and discussion, and how our review has overcome these important limitations to enable a meaningful and timely contribution to discussions around the use of surgery in this population. INTRODUCTION Recent systematic reviews on this topic have several shortcomings. They have combined data from heterogeneous populations (eg, people with lumbar disc herniation, stenosis, and spondylolisthesis), which have distinct clinical courses and require different surgical procedures.[1] Others have excluded studies published in languages

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		other than English, newly published trials, and trials comparing surgery to other commonly used interventional treatments such as epidural injections.[2] Another network meta-analysis lumped data from different time points. It did not provide a nuanced interpretation of the outcomes for pain and disability.[3] Hence, the current evidence supporting surgery for sciatica is undetermined, warranting a comprehensive update. DISCUSSION **Strengths of this review** This review provides the most comprehensive synthesis of the evidence on surgical procedures for sciatica to date. Different from recent reviews,[1,2,3] we included trials conducted in a homogeneous population/surgical procedure/comparator, studies published in English and other languages, and new robust trials published recently, making this review the most comprehensive update on the evidence for the surgical management of sciatica that can provide more informative and nuanced results than the recent network meta-analysis which lumped results across all timepoint into one value. **Evidence update and meaning of the study** Compared to the most recent review which only pooled data on disability at short term and 24 months,[2] our review provides results on leg pain, disability, back pain, and adverse events from the immediate-term to 5 years post-randomisation. Thus, unlike the

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		equivocal benefits previously reported by another review, we found discectomy was initially beneficial but the effect declined over time, compared to either non-surgical care or epidural steroid injections. We discussed the 2007 Cochrane review of surgical interventions for lumbar disc prolapse in comment #4. Please refer to that comment for more details. Chen and colleagues[1] conducted a systematic review of surgical versus non-operative treatment for lumbar disc herniation. That review pooled data from trials testing heterogeneous interventions (discectomy, laminectomy, plasma decompression, nucleoplasty etc), comparisons (non-surgical treatment, epidural steroids injection), and populations (people with lumbar disc herniation, stenosis, and spondylolisthesis) together (please refer to the figures 2, 4-10 in that paper). This approach made the results difficult to interpret from a clinical perspective. Clark and colleagues[2] only identified 7 trials, major trials in the field were missed or not published by the time they did the searches (April 2019). They were not able to pool data for pain outcomes (a core outcome in back pain clinical research)[4] because they included a limited number of studies. Due to the limited data, they only pooled data for disability outcomes at short−term (6−26 weeks) and long−term (2 years). In contrast,

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		we were able to pool data for both leg pain and back pain from 7 and 5 trials, respectively. The recent network meta-analysis conducted by Rickers and colleagues[3] investigated the effect of a wide range of surgical procedures (open/micro/tubular/endoscopic discectomy) and conservative treatments. However data on pain and disability outcomes from different time points for each comparison were lumped into one overall effect estimate and authors concluded that all surgical treatments were superior to conservative treatment. Our methods provide a different and more nuanced interpretation of the findings; that the outcome of some surgical treatments (eg, discectomy) compared to non-surgical treatment changes over time. For example, we have demonstrated that discectomy was superior in the short-term, but no better than non-surgical treatment from 1 year after surgery. We believe this to be a substantial difference for general medical readers. **References:** 1. Chen BL, Guo JB, Zhang HW, Zhang YJ, Zhu Y, Zhang J, Hu HY, Zheng YL, Wang XQ. Surgical versus non-operative treatment for lumbar disc herniation: a systematic review and meta-analysis. Clin Rehabil 2018;32(2):146-60. doi: 10.1177/0269215517719952 [published Online First: 2017/07/19] 2. Clark R, Weber RP, Kahwati L. Surgical Management of Lumbar Radiculopathy: a Systematic Review. Journal of general internal medicine : JGIM 2020;35(3):855-64. doi: 10.1007/s11606-019-05476-8

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		3. Rickers KW, Pedersen PH, Tvedebrink T, Eiskjær SP. Comparison of interventions for lumbar disc herniation: a systematic review with network meta-analysis. The spine journal 2021 doi: 10.1016/j.spinee.2021.02.022 4. Chiarotto A, Deyo RA, Terwee CB, Boers M, Buchbinder R, Corbin TP, Costa LO, Foster NE, Grotle M, Koes BW, Kovacs FM, Lin CW, Maher CG, Pearson AM, Peul WC, Schoene ML, Turk DC, van Tulder MW, Ostelo RW. Core outcome domains for clinical trials in non-specific low back pain. *Eur Spine J* 2015;24(6):1127-42. doi: 10.1007/s00586-015-3892-3 [published Online First: 20150405]
6	* This is an important and still contentious issue. However, I thought it's currently well acknowledged that nonsurgical care remains the mainstay of initial treatment for most patients with lumbar disc herniation, while those with persistent symptoms despite adequate conservative therapy are considered for surgery[Int J Spine Surg. 2020 Feb; 14(1): 1–17]. Thus I would be more interested in a slightly modified RQ: how well does surgery work for patients who have failed the initial non-surgical treatment (rather than "any patient").	We agree it is an important but contentious issue. A consideration in regards to this comment is that most trials were not designed to answer the question proposed by the reviewer. For example, Only 4 out of 12 (33%) trials of discectomy versus non-surgical treatment included failing non-surgical treatment as an inclusion criteria. To address this comment, we have conducted an exploratory post-hoc subgroup analysis where we explored the moderating effect of 'failing non-surgical treatment' as an inclusion criteria (supplemental file 10). We found some evidence that people who have not previously failed non-surgical treatment prior may have better outcomes of leg pain in the immediate-term and disability in the short term, but not at any other time point. We describe the findings of this new analysis in the results and discussion, making sure to remind readers that this was a post-hoc analysis.

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7	* The publication of included studies spans 1983~2021- could any evolvement of either non-surgical or surgical therapies modify the results?	The technique of discectomy has evolved over the past 20 years, and less invasive approaches (eg, microdiscectomy) are now used in many countries. From the trials included, we conducted a subgroup analysis of open (old) vs micro (new) discectomy. No significant differences were found for leg pain at any time point, and for disability at most time points (except for short term) (supplemental file 10), suggesting that the evolvement of surgical techniques did not have a noticeable effect on treatment benefits. To address this comment, we also conducted a post-hoc regression analysis where we investigated year of publication as a predictor of effect size on leg pain and disability. The rationale for this analysis is that we used year of publication as a proxy for surgical and non-surgical technological evolvement over the years. We found that year of publication was not a predictor of effect size for either outcome. These analyses are reported in supplemental files 20 a, b and summarised below: Leg pain, coefficient = -0.19, 95% CI -0.57 to 0.20; p-value=0.35 Disability, coefficient = -0.15, 95% CI -0.48 to 0.17; p-value=0.35
8	* The title: “surgical versus non-surgical treatment for sciatica”, is it more accurate to use "lumbar disc herniation with Radiculopathy"?	We acknowledge various terms have been used to describe this condition such as sciatica, lumbar radicular pain, or lumbar radiculopathy. We have used the term of ‘sciatica’ with reference to some key publications.[1-6] However, we also note the IASP discourage the use of the term ‘sciatica’.[7]

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We would be happy to be guided by the editors on BMJ's preferred term and modify the title from sciatica to radiculopathy (or "lumbar disc herniation with radiculopathy") if required.

References (bolded authors are authors in our review):

1. **Peul WC**, van Houwelingen HC, van den Hout WB, Brand R, Eekhof JAH, Tans JTJ, Thomeer RTWM, **Koes BW**. Surgery versus Prolonged Conservative Treatment for Sciatica. The New England journal of medicine 2007;356(22):2245-56. doi: 10.1056/NEJMoa064039
2. Mathieson S, Maher CG, McLachlan AJ, Latimer J, **Koes BW**, Hancock MJ, **Harris I**, Day RO, Billot L, Pik J, Jan S, **Lin CWC**. Trial of Pregabalin for Acute and Chronic Sciatica. N Engl J Med 2017;376(12):1111-20. doi: 10.1056/NEJMoa1614292
3. **Koes BW**, van Tulder MW, **Peul WC**. Diagnosis and treatment of sciatica. BMJ (Clinical research ed) 2007;334(7607):1313-17. doi: 10.1136/bmj.39223.428495.BE
4. Ropper AH, Zafonte RD. Sciatica. N Engl J Med 2015;372(13):1240-48. doi: 10.1056/NEJMra1410151
5. Jensen RK, Kongsted A, Kjaer P, **Koes B**. Diagnosis and treatment of sciatica. BMJ 2019;367:l6273. doi: 10.1136/bmj.l6273
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		Schug S, Simpson DM, Smith BH, Svensson P, Vlaeyen JWS, Wang S-J, Barke A, Rief W, Treede R-D, Classification Committee of the Neuropathic Pain Special Interest G. The IASP classification of chronic pain for ICD-11: chronic neuropathic pain. Pain 2019;160(1):53-59. doi: 10.1097/j.pain.0000000000001365
9	* The "non-surgical (non-pharmacological or pharmacological) treatment" seems to cover a wide range of different therapies and varied greatly across studies (table 1). Should this be further categorized to more homogeneous subgroups to see how the findings might change?	We agree that non-surgical treatments varied greatly across included trials. We made an effort to describe the treatments as comprehensively as possible, however their description was typically poor. We attempted to explore the issue of heterogeneity of non-surgical interventions by conducting a post-hoc subgroup analysis. We were only able to group trials that described whether analgesics were used (or not) as part of the non-surgical treatment strategy provided in the control group. We only found an interaction between using an analgesic and the effect of surgical treatment on leg pain at the medium-term. The effect of surgical treatment was significantly higher in those who did not use analgesics versus those who did (*MD -3.1 95% CI -5.7 to -0.4 vs MD -21.4 95% CI -30.3 to -12.4; p-value for interaction <0.01; supplemental file 10*). We could not group analgesics by type (eg, opioids). No further subgroup analysis was possible due to the poor reporting of non-surgical comparators, with most trials failing to adequately describe what types of treatments participants received, who provided these treatments, how they were provided and how much treatment they received.

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10	* Nonsurgical treatment approaches vary widely. I agree with the reviewer who wonders why the authors are so careful to distinguish various interventional/surgical techniques but lump all nonsurgical treatments together. Looking at Table 1, some nonsurgical groups got bedrest, others got various unusual types of massage, educational booklets, or various medications. I would like to know what the "analgesics" used might have been. I wonder if, as doctors use fewer opioids, patients who are suffering from severe pain are more likely to choose surgery. If nonsurgical treatment were standardized, intensive, and timely, perhaps fewer people would need surgery.	This is certainly an important and clinically relevant question. Unfortunately the lack of details provided in the trials with regards to elements such as dose, and frequency limit interpretation around these issues. The Weinstein (2006) trial[1] is the only one that reported the percentages of participants taking specific non-surgical treatment (eg, 46% took 'narcotics' (as defined by the study), 60% took NSAIDs, etc.). The Bailey (2020) trial[2] provided the classes of analgesics, but again the strength and dose were not reported. We discussed the issues with heterogeneous non-surgical groups in the manuscript. In the discussion, we stated: '*Reporting of non-surgical comparators was generally poor, with most trials failing at describing what types of treatments participants received, who provided these treatments, how they were provided and how much treatment they received. It is therefore unknown whether discectomy is truly superior to non-surgical treatment, or if non-surgical treatment provided in the control arms of many trials represent a sub-optimal non-surgical approach to treating sciatica.*' **References:** 1. Weinstein JN, Lurie JD, Tosteson TD, Tosteson ANA, Blood EA, Abdu WA, Herkowitz H, Hilibrand A, Albert T, Fischgrund J, Weinstein JN, Lurie JD, Tosteson TD, Tosteson ANA, Blood EA, Abdu WA, Herkowitz H, Hilibrand A, Albert T, Fischgrund J. Surgical versus nonoperative treatment for lumbar disc herniation: four-year results for the Spine Patient

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		Outcomes Research Trial (SPORT). Spine (03622436) 2008;33(25):2789-800. doi: 10.1097/BRS.0b013e31818ed8f4 2. Bailey CS, Bailey SI, Rasoulinejad P, Taylor D, Sequeira K, Miller T, Watson J, Rosedale R, Gurr KR, Siddiqi F, Glennie A, Urquhart JC. Surgery versus Conservative Care for Persistent Sciatica Lasting 4 to 12 Months. The New England journal of medicine 2020;382(12):1093-102. doi: 10.1056/NEJMoa1912658
11	* It's surprising to see so many RCTs did not report loss-to-follow-up and cross-over (table 1), which is very important. Is this information obtainable?	Previously we only presented data on loss to follow-up at 12 months and crossover. Following the editor's comment, we have added more data on the proportion of participants lost to follow-up at other time points to Table 1.
12	* The crossover rates are tremendously high. Perhaps this is unsurprising since as one of the reviewers notes, these are patients with imaging findings suggesting a need for surgery. On the other hand, who would agree to be randomized to surgery vs nonsurgical approaches? They must be people who would like to avoid surgery if possible, or perhaps have less severe pain. This makes the crossover numbers even more concerning. I agree with the authors that this may end up underestimating the benefits of surgery.	We agree that cross-over rates in some trials are high and may have underestimated the benefits of surgery. We would however disagree that certain imaging findings would suggest a need for surgery. Imaging findings at baseline do not distinguish between patients who did and those who did not undergo delayed surgery[1,2]. We addressed the issue of trials recruiting participants who had failed non-surgical treatment in comment #6. Please refer to that comment for further details. **References (bolded authors are authors in our review):** 1. el Barzouhi A, Vleggeert-Lankamp CL, Lycklama à Nijeholt GJ, Van der Kallen BF, van den Hout WB, **Koes BW, Peul WC**; Leiden-Hague Spine Intervention Prognostic Study Group. Predictive value of MRI in decision making for disc surgery for sciatica. J Neurosurg Spine. 2013 Dec;19(6):678-87.

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		2. el Barzouhi A, Vleggeert-Lankamp CL, Lycklama à Nijeholt GJ, Van der Kallen BF, van den Hout WB, Jacobs WC, **Koes BW, Peul WC**; Leiden-The Hague Spine Intervention Prognostic Study Group. Magnetic resonance imaging in follow-up assessment of sciatica. N Engl J Med. 2013 Mar 14;368(11):999-1007.
13	* Adverse events - there were quite a few dural tears in the discectomy groups. **I wonder how carefully participants were followed up for long term problems from these and other AEs**. The interpretation could do a better job of incorporating information about adverse events with information about benefits.	Adverse events reporting is inconsistent in surgical trials,[1] and often there is limited information in the included trials about whether or how specific adverse events (eg, dural tear), were followed-up for a determination of long term complications. Details of reported adverse events are presented in *supplemental file 9.* Dural tear and wound complications were the most frequent surgery-related adverse events reported in the discectomy group. But the included RCTs are likely underpowered to detect harms owing to the small sample sizes. Thus, we incorporate results from a systematic review of 42 (observational) studies investigating the complication rates after discectomy in the discussion.[2] Following texts were added to the discussion: ‘We did not find an increased risk of adverse events when discectomy was compared to non-surgical treatment. But the included trials had a high crossover rate between groups and were likely underpowered to detect adverse events. In a review of observational studies (n=42 studies; >4000 participants), 12.5 to 13.3% people had an adverse event. Reoperation, recurrent disc complications, dural tear, nerve root injury, wound

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		complications were the most common adverse events in open/microdiscectomy. These data provide further context and insights on the safety profile of discectomy for sciatica. **Reference:** 1. Zhou X, Li L, Lin L, Ju K, Kwong JSW, Xu C. Methodological quality for systematic reviews of adverse events with surgical interventions: a cross-sectional survey. BMC Med Res Methodol 2021;21(1):223-23. doi: 10.1186/s12874-021-01423-6 2. Shriver MF, Xie JJ, Tye EY, et al. Lumbar microdiscectomy complication rates: a systematic review and meta-analysis. Neurosurgical Focus FOC 2015;39(4):E6. doi: 10.3171/2015.7.FOCUS15281
14	* given that nearly all of these studies did not blind patients or the assessors, it's difficult to conclude the superiority of discetomy. Is more caution required around the conclusion?	We used the GRADE framework to assess the certainty of evidence for each outcome.[1] Risk of bias due to performance and detection bias are assessed as part of the framework. For all outcomes, we downgraded the certainty of evidence due to limitations in study design – one of the reasons being lack of blinding of patients and assessors. **Reference:** 1. Santesso N, Glenton C, Dahm P, Garner P, Akl EA, Alper B, Brignardello-Petersen R, Carrasco-Labra A, De Beer H, Hultcrantz M, Kuijpers T, Meerpohl J, Morgan R, Mustafa R, Skoetz N, Sultan S, Wiysonge C, Guyatt G, Schünemann HJ. GRADE guidelines 26: informative statements to communicate the findings of systematic reviews of interventions. J Clin Epidemiol 2020;119:126-35. doi: https://doi.org/10.1016/j.jclinepi.2019.10.014
15	* It is difficult to get a feel for the magnitude or clinical importance of the pain relief or disability reductions achieved with	The approach we used is consistent with the recommendations in the ACP guideline, which provides category descriptors (small, moderate or large) for the effect size of an intervention in relation to a control.[1] It does not judge whether that effect is or isn't

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<table>
<tr><td></td><td>discectomy. Is it possible to make these outcomes more understandable for patients or lay readers?</td><td>clinically worthwhile based on an arbitrary numerical threshold, thereby removing the patient from the decision making.

We also discussed why we did not use MCID in the response to comment #32.

Reference:
1. Chou R, Deyo R, Friedly J, et al. Nonpharmacologic Therapies for Low Back Pain: A Systematic Review for an American College of Physicians Clinical Practice Guideline. Ann Intern Med 2017;166(7):493-505. doi: 10.7326/M16-2459</td></tr>
<tr><td>16</td><td>*Ref. 14 is not a systematic review, as stated on p.5 and 13.</td><td>We have double-checked the reference. Ref.14 is a systematic review.

Since we added a reference in the revised manuscript, the previous ref. 14 is now ref.15.

Reference:
Clark R, Weber RP, Kahwati L. Surgical Management of Lumbar Radiculopathy: a Systematic Review. J Gen Intern Med. 2020 Mar;35(3):855-864.</td></tr>
<tr><td></td><td>Reviewer 1</td><td></td></tr>
<tr><td>17</td><td>The authors divide the surgeries into types of surgeries, but they do not do the same for comparators. For example, there are different types of epidural steroid injections, but the authors do not specify the type unless it's listed in the title. This is important because</td><td>Thank you for your comment.

We do agree with the reviewer that the evidence for pharmacological management of sciatica is limited; some of this work has been carried out by our team.[1,2] Unfortunately, all of the included trials either used a combination of pharmacological interventions, or</td></tr>
</table>

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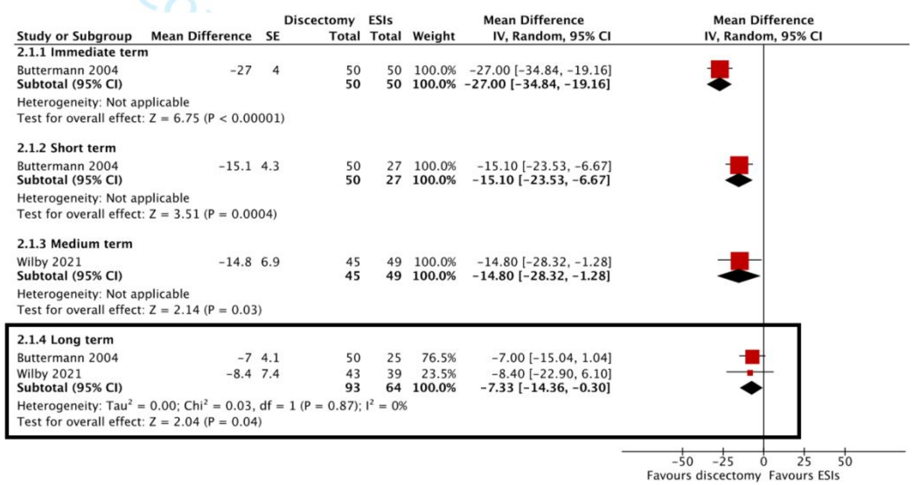
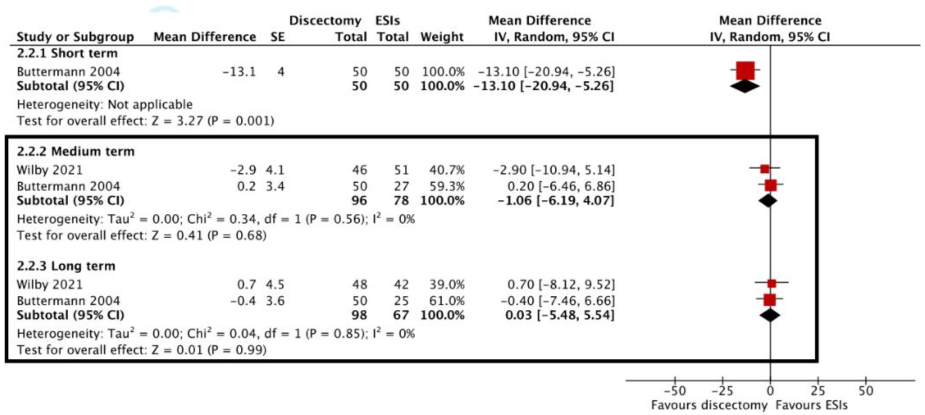
	particularly for a herniated disc which is more likely to cause unilateral pain, transforaminal ESI are generally acknowledged to be more efficacious. The same hold true for pharmacological treatments, with antidepressants have the strongest evidence for efficacy (but not strong), gabapentinoids having conflicting evidence, and very little evidence for NSAIDs and muscle relaxants, which are often used (not even mentioned on guidelines for neuropathic pain).	provided limited description on the use of analgesics, therefore it was not feasible to stratify analysis based on different drug classes. A 2020 Cochrane review of epidural injections for lumbar radicular pain found no difference in its subgroup analysis of different approaches: caudal, interlaminar, and transforaminal approaches.[3] We included two trials investigating discectomy vs epidural steroids injection (Buttermann 2004, Wilby 2021).[4,5] Buttermann used an interlaminar approach while Wilby used a transforaminal approach. We note that the effect on pain was fairly similar between trials – see forest plots for leg pain and disability below (*supplementary file 13*). We also note that statistical heterogeneity between two trials were 0% in the comparisons where they were pooled together.

a. Leg pain, discectomy vs epidural steroid injections



b. Disability, discectomy vs epidural steroid injections



References (bolded authors are authors in our review):

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		1. **Ferreira GE**, McLachlan AJ, **Lin C-WC**, Zadro JR, **Abdel-Shaheed C**, O'Keeffe M, Maher CG. Efficacy and safety of antidepressants for the treatment of back pain and osteoarthritis: systematic review and meta-analysis. BMJ 2021;372:m4825. doi: 10.1136/bmj.m4825 2. Enke O, New HA, New CH, Mathieson S, McLachlan AJ, Latimer J, Maher CG, **Lin CC**. Anticonvulsants in the treatment of low back pain and lumbar radicular pain: a systematic review and meta-analysis. CMAJ 2018;190(26):E786-e93. doi: 10.1503/cmaj.171333 3. Oliveira CB, Maher CG, Ferreira ML, Hancock MJ, Oliveira VC, McLachlan AJ, **Koes BW**, Ferreira PH, Cohen SP, Pinto RZ. Epidural corticosteroid injections for lumbosacral radicular pain. Cochrane Database Syst Rev 2020;4:Cd013577. doi: 10.1002/14651858.Cd013577 [published Online First: 2020/04/10] 4. Buttermann GR. Treatment of Lumbar Disc Herniation: Epidural Steroid Injection Compared with Discectomy: A Prospective, Randomized Study. *Journal of bone and joint surgery American volume* 2004;86(4):670-79. [published Online First: American volume] 5. Wilby MJ, Best A, Wood E, et al. Surgical microdiscectomy versus transforaminal epidural steroid injection in patients with sciatica secondary to herniated lumbar disc (NERVES): a phase 3, multicentre, open-label, randomised controlled trial and economic evaluation. *The Lancet Rheumatology* 2021;3(5):e347-e56. doi: 10.1016/S2665-9913(21)00036-9
18	The authors consider treatments such as plasma disc decompression, ozone ablation and chemonucleolysis to be "surgical", but many people would disagree. In fact, the websites Wikipedia and Spine-Health specifically refer to chemonucleolysis as non-	We adopted a similar approach to the 2007 Cochrane review with regards to surgical classifications,[1] where chemonucleolysis was regarded a surgical procedure. We note that there is debate about the classification of this procedure, however we have stratified the findings based on procedure type and did not pool results across procedures. This approach enables readers to make an assessment regarding each intervention individually.

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	surgical. They are percutaneous like ESI and involve injections into disc that radiologists and pain doctors do (like platelet-rich plasma injected into discs, older intradiscal ablative treatments that were modified to treat herniated disc and treatments such as nucleoplasty or disc DeKompressor). These percutaneous treatments are also only indicated for small herniations (and often "contained").	**References:** 1. Gibson JNA, Waddell G. Surgical interventions for lumbar disc prolapse. Cochrane Database Syst Rev 2007(2) doi: 10.1002/14651858.CD001350.pub4
19	Page 5, introduction: Minor point, but it is contestable (and probably not true) that HNP accounts for 90% of cases of sciatica. It certainly depends on the population, but as IASP recommends, "sciatica" is non-specific (really a lay term) and usually refers to radicular pain, which can be caused by HNP, stenosis or even degenerative disc degeneration with complete annular tears (chemical irritation). Moreover, HNP and spinal stenosis often co-occur, with one recent	We agree with the reviewer that the pathologies of sciatica vary among different population. A sciatica review published in the NEJM reported 85% of cases with sciatica associated with lumber disc herniation.[1] In the introduction of our review, we updated ‘90%’ to ’85-90%’. The editor has also suggest using alternative terminology such as “disc herniation associated with radiculopathy” or “radiculopathy” rather than “sciatica”. We are happy to be guided by the editors on this point. **References:**

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	study finding this happens almost 25% of the time (Mutubuki et al. Eur J Pain 2020).	1. Ropper AH, Zafonte RD. Sciatica. N Engl J Med 2015;372(13):1240-48. doi: 10.1056/NEJMra1410151
20	Page 6, line 30: You probably mean "radiologic" rather than radiographic, as x-rays cannot identify disc herniation.	Thanks for pointing out the typo. We have amended it to 'radiologic'.
21	Page 7, lines 12-14: I would defer to a statistician but I'm not sure that "borrowing" SDs from similar studies is valid (since they may vary significantly and they are very important for statistical analysis).	This approach is recommended by the Cochrane Handbook when there is no information on variability measures (chapter 6.5.2.7, https://training.cochrane.org/handbook/current/chapter-06).
22	Bottom of page 8: Please note whether (or which) of the surgeries included fusions or instrumentation (often used for multi-level procedures or those accompanied by instability). It is also likely that single vs. multi-level procedures have different outcomes.	None of the surgical procedures reported included fusion or instrumentation. The data was not sufficient for us to conduct subgroup analysis on single vs multi-level procedures. Based on the descriptions of the trials, the majority of participants received a single-level procedure.
23	Dividing symptoms duration into < or > 3 months doesn't seem to be a good cutoff besides that that is the cutoff that IASP uses to separate acute from chronic pain. Some payers	We have attempted to conduct a regression analysis of using duration of symptoms as a continuous variable.

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	(and guidelines) don't authorize or recommend injections or surgeries for acute pain because the natural course is for improvement. In a validated instrument evaluating ESI (Bicket et al. Reg Anesth Pain Med 2016, AQUARIUS), the international panel concluded that studies should ideally not be done in those with < 3 months of pain, while similar problems arise in people with long-standing (> 2 years) of pain (i.e. central sensitization).	Some trials did not report the mean duration of symptoms. For example, McMorland only reported it as a categorical variable (eg, 3 participants with 3-6 months duration); Weinstein reported 81%/76% of participants had <6 months duration since recent episode; Greenfield and Huo did not report symptom duration.[1-4] Using data from the trials that did report mean duration of symptoms, we conducted a post-hoc regression analysis using duration of symptoms as a continuous variable. Trials with various durations of symptoms reported similar outcomes for leg pain. But trials with longer duration of symptoms reported higher effect in improving disability. These analyses are reported in supplemental files 20 c, d and summarised below: Leg pain, coefficient=-1.03, 95% CI -2.34 to 0.27; p-value=0.12 Disability, coefficient=-1.87, 95% CI -2.63 to -1.11; p-value<0.01 **References:** 1. Weinstein JN, Lurie JD, Tosteson TD, Tosteson ANA, Blood EA, Abdu WA, Herkowitz H, Hilibrand A, Albert T, Fischgrund J, Weinstein JN, Lurie JD, Tosteson TD, Tosteson ANA, Blood EA, Abdu WA, Herkowitz H, Hilibrand A, Albert T, Fischgrund J. Surgical versus nonoperative treatment for lumbar disc herniation: four-year results for the Spine Patient Outcomes Research Trial (SPORT). Spine (03622436) 2008;33(25):2789-800. doi: 10.1097/BRS.0b013e31818ed8f4

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		2. McMorland GDC, Suter EP, Casha SMDPF, du Plessis SJMD, Hurlbert RJMDPFF. Manipulation or Microdiskectomy for Sciatica? A Prospective Randomized Clinical Study. J Manipulative Physiol Ther 2010;33(8):576-84. doi: 10.1016/j.jmpt.2010.08.013 3. Huo F. A comparative analysis of conservative versus surgical treatment for lumbar disc prolapse. China Journal of Modern Drug Apply 2016(4):55-57. 4. Greenfield K, Nelson RJ, Findlay GD, et al. Microdiscectomy and conservative treatment for lumbar disc herniation with back pain and sciatica: a randomised clinical trial. Proceedings of the International Society for the Study of the Lumbar Spine 2003:245.
24	In the text, I would note mortality or serious complication rates between groups. It will of course not be statistically significant because of the low numbers, but the deaths of a few people is incredibly important & clinically relevant- and few people ever view supplemental files.	On page 13 of the manuscript, we have added 'All trials stated that there were no surgery-related deaths.'
	Reviewer 2	
25	1. Currently the emphasis is strongly on discectomy with only limited information in the main paper about other surgical options. This does not fit with the title or the objective of the manuscript which includes any type of surgery. I would advise the authors to put less emphasis on discectomy, and potentially	Discectomy is the most common surgical procedure in treating sciatica and for that reason we chose to present it as the review's primary comparison. We were also concerned with the length of the manuscript and that presenting too many comparisons would dilute the focus on the key results and impact the interpretability of the study. We would however be happy to follow the advice form the editorial board on this issue.

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	include an overall meta-analysis, independent of type of surgery (see my comment below).	We would disagree with the reviewer's suggestion to provide an overall meta-analysis estimate of all surgical procedures. This would introduce substantial clinical heterogeneity and issues with indirectness. It is also our opinion that an overall pooled effect does not help inform clinicians and patients better on the benefits and harms of surgical versus non-surgical treatments for sciatica.
26	The authors point out the very high cross-over rates in many studies, which may well influence the interpretation of this review. These are included in table format, but I suggest mentioning them in text in the results section as well, as this is a major problem in this literature that limits (or prevents?) interpretation. Would it be possible to do a sensitivity analysis, excluding those papers with high cross over? Or had all papers such high cross over?	We have added 'High crossover rates from the non-surgical arm to surgery (ranged from 30% to 54%) occurred in many trials which means the effects of surgery on clinical outcomes could have been underestimated, particularly in the later time points. As mentioned above, the included trials are underpowered and inappropriately designed to effectively evaluate adverse event occurrence.' to the manuscript (page 15). In the primary comparison, all included trials had similar high crossover rates from non-surgical treatment to surgery (34.4 to 44.6%). Thus a sensitivity analysis would not be informative.
27	3. My third and most important concern is a clinical one: as the authors correctly mention in the introduction and discussion, current care for patients with sciatica is a stepwise model of care starting with conservative	Thank you for this comment and for giving us the opportunity to clarify some key aspects of the review. We agree that many people who are clinically diagnosed with sciatica in primary care (without an MRI for instance) will not have clinical features that would justify referral for surgery (eg, absence of disc herniation with concordant symptoms). ***Our review***

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	treatment which is then escalated to injections or surgery. This means that if a patient is considered for surgery, in most instances they will have had a course of 'failed' non-surgical care (unless there is significant motor deficit). Second, patients who can ethically be put forward for surgery have to have a clear indication for surgery (e.g, clear disc herniation). However many patients with sciatica do not have a clear MRI finding which indicates surgery. Therefore, studies using surgery already involve a highly select group of patients. So my question is: how valid is the comparison of surgery and non-surgical care in a population that has a) a clear indication for surgery and b) is likely to already have failed conservative care? Is that really a fair (and useful) comparison? In order to address this important issue, I suggest the authors carefully evaluate the inclusion criteria of the included studies. How	***does not cover that patient group***. We only included trials where adults were diagnosed with sciatica (any duration of symptoms) ***due to a herniated disc diagnosed through imaging*** (please refer to page 6 of the manuscript and our PROSPERO protocol). There is large variability in how the term 'sciatica' is defined in the literature and interpreted by clinicians, which may be contributing to the confusion. We would be happy to revise our title to better reflect the population (see commnent #8), and would be happy to be guided by the editors on this matter. Most trials (8 out of 12, 66%) included in our review ***did not*** list failing non-surgical treatment as an eligibility criteria. A similar question was raised by the research editor (please refer to comment #6 for more details). We performed a post-hoc subgroup analysis where we divided trials in subgroups that had vs did not have failure of non-surgical treatment as an eligibility criteria. We found interaction effects at the immediate term (leg pain) and short term (disability) favouring surgery over non-surgical treatment, with participants in trials who had not failed non-surgical treatment before displaying better outcomes with surgery. We do point out that this subgroup analysis is post-hoc and limited by the small number of trials included, particularly those in the subgroup that enrolled participants who had previously failed non-surgical care. We have included this post hoc analysis in supplementary file 10.

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	were these populations defined? Did they have standard care (e.g., had to fail non-surgical care to be considered for surgery), or did studies indeed include patients who did not have previous non-surgical treatment (I suspect this is highly unlikely as potentially unethical). Did they have a clear indication for surgery? Importantly, I suggest that this point is added in the discussion to put the results (and the potentially biased question) in perspective. E.g, the authors' recommendation to encourage clinicians to discuss potential rapid relief of leg pain with surgery and the potential need for delayed surgery seems supported by their review findings, however this is most likely based on a population that has already failed conservative care and has a clear indication for surgery and is therefore unlikely to be generalised to the broader population of 'sciatica'. Pending the findings of the analysis of the inclusion criteria, but I	

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	would predict that this statement is likely overstating the actual clinical implications of this review.	
28	Page 7, line 12: when it was not possible to estimate SD, the authors borrowed them from a similar study included in the review. Why were authors not contacted for data? How was 'similar study' defined? Also, in how many instances was this the case?	Only one trial (Feldman 1986) did not report enough information for us to get the SDs. No email address for the corresponding author was provided in the manuscript, which was published 36 years ago. Following to the recommendation of the Cochrane Handbook, we borrowed the SDs from the Burton 2000 trial as they had a similar sample size, participant, and intervention procedure. **References:** 1. Feldman J, Menkes CJ, Pallardy G. Double-blind study of the treatment of discal lumbosciatica by chemonucleolysis. *Rev Rhum Mal Osteoartic* 1986;53(3):147-52. 2. Burton AK, Tillotson KM, Cleary J. Single-blind randomised controlled trial of chemonucleolysis and manipulation in the treatment of symptomatic lumbar disc herniation. *European spine journal : official publication of the European Spine Society, the European Spinal Deformity Society, and the European Section of the Cervical Spine Research Society* 2000;9(3):202-7.
29	I commend the authors for including industry funding without declaration of autonomy as part of their risk of bias assessment.	We are glad to see the reviewer's endorsement of this approach.

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30	Why were continuous pain and disability outcomes transformed to a 0-100 scale? The use of standardized mean differences would have corrected for the differences in scales. For interpretability particularly of the well-established disability scales I think the actual numbers would be more useful rather than a transformed number (particularly for clinicians who I think will be the main audience for this review). What was the reasoning of using transformation rather than standardised mean differences and reporting raw data?	We wanted to ensure that results were easily understandable to a clinical audience. Converting pain and disability outcomes to a common scale (eg, 0-10, 0-100) provides accessible information on the magnitude of effect and is common practice in meta-analysis of treatment effects reporting data for these outcomes.[1-3] We have a different view to the reviewer that using standardised mean differences would have been better for interpretability. There is evidence that clinicians have a poor understanding of what standardised mean differences mean and find them to be the least useful statistic compared to a range of other presentations (eg, relative risks, mean differences presented in natural units, etc.).[4] **References (bolded authors are authors in our review):** 1. **Ferreira GE**, McLachlan AJ, **Lin C-WC**, Zadro JR, **Abdel-Shaheed C**, O'Keeffe M, Maher CG. Efficacy and safety of antidepressants for the treatment of back pain and osteoarthritis: systematic review and meta-analysis. BMJ 2021;372:m4825. doi: 10.1136/bmj.m4825 2. **Abdel Shaheed C**, Maher CG, Williams KA, Day R, McLachlan AJ. Efficacy, Tolerability, and Dose-Dependent Effects of Opioid Analgesics for Low Back Pain: A Systematic Review and Meta-analysis. JAMA Internal Medicine 2016;176(7):958-68. doi: 10.1001/jamainternmed.2016.1251 3. Cashin AG, Folly T, Bagg MK, Wewege MA, Jones MD, Ferraro MC, Leake HB, Rizzo RRN, Schabrun SM, Gustin SM, Day R, Williams CM, McAuley JH. Efficacy, acceptability, and safety of muscle relaxants for adults with non-specific low back pain: systematic review and meta-analysis. BMJ 2021;374:n1446. doi: 10.1136/bmj.n1446

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		4. Johnston BC, Alonso-Coello P, Friedrich JO, Mustafa RA, Tikkinen KAO, Neumann I, Vandvik PO, Akl EA, da Costa BR, Adhikari NK, Dalmau GM, Kosunen E, Mustonen J, Crawford MW, Thabane L, Guyatt GH. Do clinicians understand the size of treatment effects? A randomized survey across 8 countries. Can Med Assoc J 2016;188(1):25. doi: 10.1503/cmaj.150430
31	Subgroup analyses: The original protocol only included one subgroup analysis for duration of symptoms. Therefore, the additional subgroup analyses reported in the paper should be declared as post-hoc analyses.	We thank the reviewer for pointing out this error. We have added annotations where appropriate.
32	The authors decided to use the ACP guidelines for low back pain to classify the size of effects as they did not was to adopt an approach on arbitrary minimum clinically important thresholds. Can you explain why you consider these effect sizes to be less arbitrary?	The approach used in the ACP guideline provides three category descriptors for the effect size of an intervention in relation to a control.[1] It does not judge whether that effect is or isn't worthwhile based on an arbitrary numerical threshold, thereby removing the patient from the decision making. It is our view that these decisions about clinical importance should be jointly made by the patient and treating clinician, and will vary depending on a host of factors such as cost, convenience of the treatment, potential harms etc. Methodologies to determine the smallest worthwhile effect of an intervention have been proposed.[2] The smallest worthwhile effect needs to be specific to a population and to a comparison of interest (eg, treatment A vs treatment B). Because we are unaware of any study describing the smallest worthwhile effect of surgery in comparison to non-

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		surgical treatments for people with sciatica, choosing a number as the minimum clinically important threshold would present an arbitrary choice. **Reference:** 1. Chou R, Deyo R, Friedly J, et al. Nonpharmacologic Therapies for Low Back Pain: A Systematic Review for an American College of Physicians Clinical Practice Guideline. Ann Intern Med 2017;166(7):493-505. doi: 10.7326/M16-2459 2. Johnston BC, Alonso-Coello P, Friedrich JO, Mustafa RA, Tikkinen KAO, Neumann I, Vandvik PO, Akl EA, da Costa BR, Adhikari NK, Dalmau GM, Kosunen E, Mustonen J, Crawford MW, Thabane L, Guyatt GH. Do clinicians understand the size of treatment effects? A randomized survey across 8 countries. Can Med Assoc J 2016;188(1):25. doi: 10.1503/cmaj.150430
33	There are inconsistencies in the flow diagram, the numbers do not add up. For instance, the total records identified from all databases add up to 3765. Duplicates add up to 1169. 3765-1169=2596. However, the flow chart says 2569 studies were screened. Then again, 64 studies were assessed for eligibility, and 38 excluded. This would amount to a total of 26 studies included in the review, however only 24 were included. Can you please check these discrepancies?	We have double checked the numbers in Figure 1 and our numbers were correct. Duplicates add up to 1196, not 1169. We indeed included 26 publications after screening. As some trials published multiple papers with different follow-up time points, the total number of included trials was 24. The numbers in the study flow chart (Figure 1) were updated after rerunning the searches in response to comment #38.

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34	Apparently 18 trials did not blind participants and personnel. Can you clarify whether that was indeed 'AND'? Blinding of participants is not possible in e.g., a surgery vs pharmacology trial and only potentially achievable in sham surgery trials. But blinding of personnel is essential. Is it too strict to downgrade a study if patients were not blinded in such study designs but personnel was?	We can confirm that it is 'AND'. Blinding of personnel (ie, healthcare providers) is also difficult to achieve in surgical trials (https://handbook-5-1.cochrane.org/chapter_8/8_4_introduction_to_sources_of_bias_in_clinical_trials.htm).
35	The review title is "surgical versus non-surgical treatment for sciatica". However, the study focusses strongly on discectomy as a type of surgery with most other analyses moved to supplemental data and given little room in discussion and abstract. To address the study title, I would have expected an overall meta-analysis independent of type of surgery and non-surgical treatment. This could have been followed by the currently presented subgroup analyses, as I agree that in	Please refer to the comment #25. We removed 'sensitivity analysis' from method and results sections, as we only ran subgroup analyses. Some post-hoc meta-regression analyses were added (supplemental file 20).

	particular the conservative treatments are heterogenous and worthwhile to explore separately. In the results section, results are divided into subgroup and sensitivity analysis. I suggest that this is also separated in the methods section: which analyses were sensitivity analyses and which subgroup analyses.	
36	Discussion: I suggest pointing out that the non-surgical comparison group is highly heterogenous (e.g, including pharmacology, physiotherapy, advice, combination therapy). I agree it is not worthwhile splitting them up, but this should at least be pointed out in the discussion to recognise the complexity/heterogeneity.	We have stated in the manuscript *'Reporting of non-surgical comparators was generally poor, with most trials failing at describing what types of treatments participants received, who provided these treatments, how they were provided and how much treatment they received.'*
37	Table 1: please correct Table title: comparing	Thank you. We have modified the title accordingly.
38	Supplemental file 1: The search terms contain several spelling mistakes, which could have led to missing studies. E.g., discectomy which	'Diskectomy' is the American English spelling of 'discectomy'. 'Dickectomy' was a mistake, we have rerun the relevant searches. No new studies were identified, the flow chart has been updated.

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	is the main surgical procedure of interest in this review is misspelt with a k in several searches. Further, dickectomy is included in the search terms (thank you for the giggle, I wonder what the searches revealed on this term □). I would recommend to rerun the searches where these spelling mistakes were made to assure no studies were missed.	
39	Supplemental file 10: Meta-regression Why was the mean duration of symptoms analysed as a dichotomised variable in the meta-regression and not a continuous variable? Also for study size: why dichotomising rather than leaving the measure continuous to avoid losing information?	Please refer to comment#23 for details about how we handled duration of symptoms in the meta-regression. Post-hoc regression analyses using sample size as a continuous were also conducted. These analyses are reported in supplemental files 20 e, f and summarised below: Leg pain, coefficient = 0.018, 95% CI 0.006 to 0.030; p-value<0.01 Disability, coefficient = 0.007, 95% CI -0.002 to 0.016; p-value=0.13
40	Overall: in several places discectomy is misspelt as diskectomy, e.g., Supplemental file 2.	Diskectomy was not a spelling mistake. It is the American English spelling of 'discectomy'.
41	Not all abbreviations added to legends of tables, e.g., NR	We have double-checked and added all abbreviation.

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