BMJ Open

Radiofrequency denervation for chronic back pain: a systematic review and meta-analysis

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-035540
Article Type:	Original research
Date Submitted by the Author:	05-Nov-2019
Complete List of Authors:	Chappell, Mary; Cambridgeshire County Council, Public Health Directorate Lakshman, Raj; Cambridgeshire County Council, Public Health Directorate; University of Cambridge, Medical Research Council Epidemiology Unit Trotter, Patrick; Cambridge University Hospitals NHS Foundation Trust Abrahams, Mark; Cambridge University Hospitals NHS Foundation Trust Lee, Michael; University of Cambridge, Division of Anaesthesia
Keywords:	Back pain < ORTHOPAEDIC & TRAUMA SURGERY, Rheumatology < INTERNAL MEDICINE, Neurology < INTERNAL MEDICINE, PAIN MANAGEMENT

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Radiofrequency denervation for chronic back pain: a systematic review and meta-analysis

Mary E Chappell[1], Raj Lakshman[1,2], Patrick Trotter[3], Mark J Abrahams[3], Michael C Lee[4]

[1]Public Health Directorate, Cambridgeshire County Council, Cambridge, UK

[2]Medical Research Council Epidemiology Unit, University of Cambridge, Cambridge UK

[3]Cambridge University Hospitals NHS Foundation trust, Cambridge, UK

[4]Division of Anaesthesia, University of Cambridge, Cambridge, UK

Correspondence to: Mary E Chappell, Public Health Directorate, Cambridgeshire County Council, Cambridge CB3 0AP, UK. Tel. 01223 729037

Email mary.chappell@cambridgeshire.gov.uk

Word count:

Abstract 205

Main text 4,080

Abstract

Objectives: To assess the effectiveness of radiofrequency denervation of lumbosacral anatomical targets for the management of chronic back pain.

Design: Systematic review and meta-analysis of randomised controlled trials.

Methods: A database search (Medline, Medline in Process, Embase, CINHAL and the Cochrane library) was conducted to April 2019 for placebo or no-treatment controlled trials of radiofrequency denervation for the management of chronic back pain. Included trials were quality assessed using the Cochrane risk of bias tool and the quality of outcomes assessed using the GRADE approach. Meta-analysis was conducted to calculate mean difference in post-treatment pain score.

Results: Nineteen randomised controlled trials were included in the review. There appears to be short-term effectiveness (3-6 months) of radiofrequency denervation for a number of indications (facet joint, sacroiliac joint and inter-vertebral discs) but the placebo effect is large, additional intervention effect size is small (<1 on a 11 point (0-10) pain scale). Longer-term effectiveness is uncertain.

Conclusions: Radiofrequency denervation of lumbosacral targets is likely to have a small positive effect for the management of patients with chronic back pain. The quality of evidence for the majority of outcomes is low or very low quality and there is still a degree of uncertainty, particularly around the duration of effect.

Strengths and limitations of this study:

- This review brings together a number of recent trials with earlier trials so that there is a sizable sum of evidence on which to assess the effectiveness of radiofrequency denervation for back pain.
- Due to the invasive nature of the procedure, it is difficult to perform truly patient or provider blinded trials and this brings some uncertainty around findings.
- There is limited reporting of long-term outcomes for the effectiveness of radiofrequency denervation.

Introduction

Back pain is an extremely common symptom experienced by people of all ages, and can be attributed to a wide variety of disease processes.[1,2] Low back pain is now the leading cause of disability worldwide and back pain is associated with a substantial economic burden, with high medical and societal costs.[3] Studies have shown that a large proportion of medical costs come from hospital admissions and physical therapy for the management of back pain.[4] However, there are also indirect costs associated with chronic or recurrent back pain that are difficult to quantify relating to work absenteeism and related productivity.[1,3,4] In many cases, back pain is non-specific, or structural pathology amendable to surgical correction cannot be identified.[5–7] Hence, patients and practitioners continue to seek non-surgical alternatives for the management of back pain.

Radiofrequency denervation (RD) involves the application of an alternating electric current (250 to 500kHz) via a needle probe to induce a highly localised rise in tissue temperature at the needle tip.[8] The needle tip is usually placed under fluoroscopic guidance to enable selective ablation of sensory nerve branches that supply facet joints, sacroiliac joint or other structures that comprise the lumbosacral spine. RD would therefore offer relief of pain by attenuating sensory signals from the lumbosacral spine.[9]

Despite its use for over 20 years,[10] the effectiveness of RD targeted at the anatomy of lumbosacral spine is not yet established, with randomised controlled trials (RCTs) continuing to be performed. A number of trials have been published since the publication of the last high quality review in 2015[11] and our systematic review aimed to bring together this evidence in an attempt to evaluate whether RD is an effective intervention for the management of chronic non-specific back pain.

Materials and Methods

Search strategy

A search was conducted in Medline, Medline in Process, Embase, CINHAL and the Cochrane library from January 2014 to April 2019 (Appendix 1). Previous systematic reviews were used to obtain additional relevant studies published pre 2014.

Inclusion criteria

RCTs comparing RD of the spine with a control in patients with back pain with or without sciatica were included. Only trials of radiofrequency procedures for the purpose of ablating or denaturing sensory nerve branches or nociceptors that supply the lumbosacral spine were considered for inclusion. Trials of pulsed RF,[12] or other forms of 'neuromodulatory' procedures that do not aim to ablate or denature these targets, were excluded from the review. Control groups where there was no active treatment were considered for inclusion but trials with potentially effective comparators e.g. corticosteroid injections, were excluded. Only trials of patients with back pain without a definite or surgically remediable cause (chronic non-specific back pain) were included in the review. The outcome for the review was patient-reported pain score e.g. Visual Analogue Scale or Numeric Rating Scale.

Data collection and quality assessment

Trial characteristics were recorded from included studies. Study results were extracted independently by two authors (MC, PT), with any disagreements resolved by consensus. The overall strength of evidence was assessed using the GRADE approach.[13] Risk of bias was assed using the Cochrane Risk of Bias tool.[14] Any outcome where more than half of trials were considered to have a high or unclear risk of bias was downgraded. Outcomes were also downgraded where heterogeneity

in the meta-analysis was greater than 50%. Optimal sample size was taken to be 85 participants per study arm (as calculated in the Juch 2017 trial[15]) and studies with less than 170 participants, and/or where the 95% confidence intervals included the line of no effect, were downgraded for imprecision. Publication bias was assessed using funnel plots and outcomes downgraded where there was a high certainty of publication bias.

Data analysis

Meta-analyses were conducted in RevMan with fixed effects models. Pain score data were reported on a 0-10 point scale (Visual Analogue Scale or Numeric Rating Scale) in all studies and the mean difference was therefore calculated without standardisation as done in the previous Cochrane review.[11] Studies with different spinal targets e.g. facet joints, sacroiliac joints or inter-vertebrae disc, were separated in the analysis. For facet joint pain, a plot of treatment versus no treatment/sham was produced by fixed effects meta-analysis of scores for each arm. A sensitivity analysis was conducted to check the validity of findings by removing studies considered to have a particularly high risk of bias. Subgroup analysis to explore study heterogeneity was not conducted because of the small number of studies and high likelihood of reaching spurious conclusions.

Results

Study characteristics

The search identified 922 citations of which 229 were duplicates. Studies were excluded as shown in figure 1. Of the 693 citations reviewed 8 new trials were identified as well as 11 from a previous Cochrane review.[11] Exclusions were made as shown in figure 1. Nineteen trials were included in the review and their

characteristics are shown in appendix 2. Trials investigated the effectiveness of RD of the facet joint (supplied by medial branch of the dorsal spinal ramus),[15–23] the sacroiliac joints,[15,24–27] the intervertebral discs[28–32], or vertebrae end-plate (supplied by the basivertebral nerve).[33] The majority of trials used a sham control group but one large trial compared RD with no treatment (both groups received an exercise program) and one small trial compared RD plus conventional medical with conventional medical management alone (including self-care, medications and physical and cognitive therapy).

Study quality

Sham-controlled trials generally appear to have conducted adequate randomisation but allocation concealment was often unclear. Processes were in place to blind patients and providers and outcome assessors. In some trials maintenance of blinding was unclear as it was evident that patients undergoing sham procedures were offered RD in case of sham treatment failure. In these cases, blinding would have been broken. Most trials did not report dropouts and there was unclear risk of attrition bias. The outcome for this review was pain score and this was reported in all trials and reporting bias was not considered to be an issue in the review. Four trials were identified as having high risk of bias and were removed in the sensitivity analysis.[16,18,23,24]

Overall quality of the evidence

The majority of outcomes were graded down for imprecision and all outcomes were downgraded for potential risk of bias. Consequently almost all outcomes were graded as low quality. However, in some cases, high heterogeneity was also present and these outcomes were graded as very low quality. Publication bias was

suggested by asymmetry in a number of the funnel plots. However, there was uncertainty due to the small numbers of studies and outcomes were not graded down for publication bias.

Study findings

Results of the meta-analyses are shown in table 1.

RD of the facet joints

Meta-analysis of pain scores at 1-3 months post procedure (longest time point used for studies with multiple time points) (marked on a 0-10 scale) is shown in figure 2 and table 1. The effect size was significant and similar when all trials were included (7 trials, MD -0.48, CI -0.81, -0.15) or where just the sham-controlled trials were included (6 trials, MD -0.51, CI -0.90, -0.11). At six and twelve months after the procedure, there was still a significant effect but the effect size was lower for all trials compared with sham-controlled trials only (table 1). A plot of change in meta-analysed pain score over time after the procedure for facet joint RD and control groups is shown in figure 3. When this was plotted with sham-controlled trials alone, a similar pattern was observed (available on request).

RD of the sacroiliac joints

Figure 4 shows the meta-analysis of trials for pain score at 1-3 months (longest time point used for studies with multiple time points). There was a significant effect of RD for the analysis including all trials (5 trials, MD -0.97, CI -1.38, -0.57) or just sham-controlled trials (4 trials, MD -1.13, CI -1.63, -0.63). Only one trial[15] assessed outcome at later time points and this showed no significant difference compared to a no treatment control (table 1).

RD of the intervertebral discs

Pain score at 1-3 months post-treatment was significantly lower for RD compared with control in all trials (4 trials, MD -0.98, CI -1.62, -0.33) or just sham-controlled trials (3 trials, MD -0.63, CI -1.36, 0.10) (figure 5). The effect was still significant at 6 months (table 1).

RD of the vertebrae body and end plate

One recent trial of RD for vertebrae body and end plate (basivertebral nerve ablation)[33] did not show significant benefits of RD compared with sham at 3, 6 or 12 months (table 1).

Sensitivity analysis

Four studies were removed in the sensitivity analysis due to a high risk of methodological bias[16,18,23,24] and the two non-sham controlled trials were also removed.[15,31] The removal of these trials did not largely affect outcome at 1-3 months for facet joint sham trials (4 trials, MD -0.59, CI -1.10, -0.08) or sacroiliac sham trials (3 trials, MD -0.84, CI -1.37, -0.32) but the facet joint sham trial outcome at 6 months became non-significant (1 trial, MD 0.18, CI -2.80, 3.16).

Discussion

Main findings

This systematic review presents evidence suggesting that RD of the lumbosacral spine is likely to have a small positive effect in patients with chronic back pain. The quality of evidence for the majority of findings is low or very low quality and there is still a degree of uncertainty around this assertion, particularly around the duration of effect. The size of benefit appears to be small (<1 point on a 0-10 pain scale) and there is limited evidence investigating effectiveness at more than 6 months. These

assertions apply to RD for facet and sacroiliac joints, whereas evidence for benefit to other targets is more limited. There is a suggestion that there may be a benefit of RD for intervertebral discs but there is some inconsistency, with short-term outcomes showing insignificant effect.

What is also clear from the review is that both treatment and sham/no treatment groups improved during the trials e.g. in the facet joint trials shown in figure 2. In the sham controlled studies, this may, in part, be due to placebo effect. However, the large trial by Juch et al[15] used a “no additional treatment” control (both groups received an exercise program) but all study arms improved over time. This may be because a high proportion of control study participants actually received RD (~30%) due to cross-over during the trial. However, this may also be explained by self-selection of participants who volunteer for research trials,[34] and hence are likely to make more of an active effort to manage their back pain. Such participants may be more likely to engage with, and be diligent in, exercise programs and seek medical assistance where needed.

In the trial by Juch et al., control group improvements may also be explained by the conservative management that they received. The exercise program employed was multi-disciplinary and comprised individual sessions over 8-12 hours focused on quality of movement and behaviour, with access to psychological care. There is evidence suggesting that patients with chronic back pain can benefit from pain management programs that are of sufficient quality and duration.[35] Where patients have not received an adequate trial of conservative therapy, they may benefit from further exercise programs and other conservative management. It remains unclear whether patients who are either unable or unwilling to engage with conservative approaches to pain management would benefit from RD based interventions as a

first-line or isolated modality of treatment. Hence, there should be some reservation when considering the use of RD treatment as a first-line, or isolated modality of pain management.

Regression to the mean may also have played a role in control group improvements since patients in the trial were recruited with elevated pain, responsive to an anaesthetic block. Back pain has been shown to have a varied aetiology, with some patients experiencing fluctuating levels of pain over time, whilst other experience constant high levels of pain.[36,37] For the majority of trials that reported it, duration of back pain in participants prior to enrolment was 2-5 years and a proportion of these were likely to have had high levels of constant pain. Some, however, may have been experiencing fluctuating or recurrent pain within this period since the actual inclusion criteria for most trials was pain for >3 or 6 months based on patient recall. If they were recruited at a point where their pain had flared acutely, there would be a natural tendency for that painful episode to resolve over time.

Strengths and limitations

A major strength of this review is that it collates a larger body of evidence than previous systematic reviews, with the addition of a number of recent trials and thorough assessment of the quality of the evidence. The review is able to tentatively answer the question about the effectiveness of RD for back pain; an assertion that, to date, has proved to be very difficult due a paucity of evidence in this field.

This review utilises evidence from a previous Cochrane review[11] but the inclusion criteria for our review had a narrower scope (included only sham- or conservative management-controlled trials of conventional neuro-ablative RD). Since the previous

review appears to be of high quality, and we updated it with a thorough search of the literature to date, there is assurance that all relevant trials were included.

A limitation of this review is that it was difficult to truly assess risk of bias in trials included in the review. Trial integrity rested heavily on the blinding of participants and the outcome was likely to be highly subject to patients' preconceptions of the different interventions given. Most trials did not report information that providers gave patients about the different possible treatment arms e.g. did providers suggest to patients that RD was the effective treatment and that sham or no treatment would be ineffective? Where blinding was broken, these viewpoints may have influenced patients' response. In some of the sham-controlled studies this was clearly evident. For example, in some studies, before randomisation, patients were told that, if randomised to sham, they could receive RD if they gained no benefit. Where blinding was broken, these opinions were likely to influence patients' perception of their pain. In other studies information from providers was not reported and it is difficult to assess whether this type of bias occurred.

The review may also be limited in its ability to ascertain the technical quality of individual research trials. Even when examining the reported trial methodology, it is difficult to conclusively identify trials that employed procedures that may be more or less successful in denervating the specific lumbosacral anatomy. Some aspects of RD procedures in earlier trials are considered outdated[38,39] but the advantages of more recent procedures for RD remain unproven, and there is no clear evidence of their superiority. Sensitivity analysis based on technical quality was therefore considered unhelpful and not performed.

The review is also limited by the lack of long term data from trials. Most studies do not attempt to blind patients for more than 3 months and the longer follow up

outcomes are considered to be at higher risk of bias. It is still therefore unclear whether RD of lumbosacral anatomy has long-term benefits for back pain.

Finally, the review is limited in its ability to identify any aspects of patient or intervention characteristics that may make RD treatment more likely to be beneficial. There is to date no reliable predictor of benefit on back pain for RD procedures based on clinical or imaging findings or diagnostic injections.[40] The relative advantages of different RD technologies used in included trials (e.g. 'cooled'[24,25,31] and 'bipolar'[29,31] RD) remains to be established. Due to the small number of studies at each time point, sub-group analysis was not considered appropriate. However, the publication of more sham-controlled trials and trials comparing different RD technologies may make this type of investigation possible. Technical advances and advances in knowledge and experience may allow RD to become a more effective treatment and it is important that these developments are formally assessed and published.

In conclusion, despite the limitations in this review and the published literature, it is possible to conclude that there is likely to be a beneficial effect of RD of selected lumbosacral anatomical targets for chronic back pain. However, the mean size of effect appears to be small and, overall, clinical significance may be marginal. Hence, chronic back pain remains a highly challenging condition to treat.

Acknowledgements Thanks to Julie Aikens and Kerry Herbert at Hinchingbrooke Healthcare Library for their assistance in designing and running the search strategies for the review.

Contributors: MC contributed to the planning of this work, selected articles for inclusion, extracted data, quality assessed studies and drafted and re-drafted the manuscript. RL contributed to the planning of this work, reviewed the manuscript and approved the final version. PT extracted data from the trials, reviewed the manuscript and approved the final version. MA contributed to the planning of this work, reviewed the manuscript and approved the final version. ML contributed to the planning of this work, reviewed the manuscript and approved the final version.

Funding This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors. RL is supported by the Medical Research Council (MC_UU_12015/2). MCL is supported by AABGI Foundation project grant (RCZB/071).

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information.

Patient and Public Involvement This research was done without patient involvement.

References

1 Hartvigsen J, Hancock MJ, Kongsted A, *et al.* What low back pain is and why we need to pay attention. *Lancet* 2018;391:2356–67. doi:10.1016/S0140-6736(18)30480-X

2 Hoy D, Bain C, Williams G, *et al.* A systematic review of the global prevalence of low back pain. *Arthritis Rheum* 2012;64:2028–37. doi:10.1002/art.34347

3 Maniadakis N, Gray A. The economic burden of back pain in the UK. *Pain* 2000;84:95–103. doi:10.1016/S0304-3959(99)00187-6

4 Dagenais S, Caro J, Haldeman S. A systematic review of low back pain cost of illness studies in the United States and internationally. *Spine J* 2008;8:8–20. doi:10.1016/j.spinee.2007.10.005

5 National Institute of Health and Care Excellence. Low back pain and sciatica in over 16s: assessment and management. 2016.

6 Chou R, Baisden J, Carragee EJ, *et al.* Surgery for Low Back Pain: A Review of the Evidence for an American Pain Society Clinical Practice Guideline. *Spine (Phila Pa 1976)* 2009;34:1094–109.

7 Chou R, Loeser JD, Owens DK, *et al.* Interventional Therapies, Surgery, and Interdisciplinary Rehabilitation for Low Back Pain: An Evidence-Based Clinical Practice Guideline From the American Pain Society. *Spine (Phila Pa 1976)* 2009;34:1066–77. doi:10.1097/BRS.0b013e3181a1390d

8 Kline M. Radiofrequency techniques in clinical practice. In: *Waldman SD, Winnie AP, eds. Interventional Pain Management. Philadelphia, PA: Saunders*. 1996.

9 Wray JK, Dixon B, Przkora R. *Radiofrequency Ablation*. 2019.

10 Manchikanti L, Hirsch J, Pampati V, *et al.* Utilization of Facet Joint and Sacroiliac Joint Interventions in Medicare Population from 2000 to 2014: Explosive Growth Continues! *Curr Pain Headache Rep* 2016;20:58.

11 Maas E, Ostelo R, Niemisto L, *et al.* Radiofrequency denervation for chronic low back pain. *Cochrane Database Syst Rev* 2015;:Art. No.: CD008572. doi:10.1001/jama.2017.16386

12 Brandon R, Cohen D, Edward T, *et al.* Pulsed Radiofrequency Neuromodulation in Interventional Pain Management—A Growing Technology. *J Radiol Nurs* 2018;37:181–7.

13 Schünemann H, Brożek J, Guyatt G, *et al.*, editors. *GRADE Handbook: Handbook for grading the quality of evidence and the strength of recommendations using the GRADE approach*.

14 Higgins JP, Savovic J, Page MJ, *et al.*, editors. *Revised Cochrane risk-of-bias tool for randomized trials (RoB 2)*. 2019.

15 Juch JNS, Maas ET, Ostelo RWJG, *et al.* Effect of Radiofrequency Denervation on Pain Intensity Among Patients With Chronic Low Back Pain. *JAMA* 2017;318:68–81.

16 Gallagher J, Petriccione di Vadi P, Wedley J, *et al.* Radiofrequency facet joint denervation in the treatment of low back pain: a prospective controlled double-blind study to assess its efficacy. *Pain Clin* 1994;7:193–8.

17 Leclaire R, Fortin L, Lambert R, *et al.* Radiofrequency Facet Joint Denervation in the Treatment of Low Back Pain: A Placebo-Controlled Clinical Trial to Assess Efficacy. *Spine (Phila Pa 1976)* 2001;26:1411–6.

doi:10.1097/00007632-200107010-00003

18 Moussa WMM, Khedr W. Percutaneous radiofrequency facet capsule denervation as an alternative target in lumbar facet syndrome. *Clin Neurol Neurosurg* 2016;150:96–104. doi:10.1016/j.clineuro.2016.09.004

19 van Kleef M, Barendse GAM, Kessels A, *et al.* Randomised trial of radiofrequency lumbar facet denervation for chronic low back pain. *Spine (Phila Pa 1976)* 1999;24:1937–42.

20 Van Tilburg CWJ, Schuurmans FA, Stronks DL, *et al.* Randomized sham-controlled double-blind multicenter clinical trial to ascertain the effect of percutaneous radiofrequency treatment for sacroiliac joint pain: Three-month results. *Clin J Pain* 2016;32:921–6. doi:10.1097/AJP.0000000000000351

21 Van Wijk RMAW, Geurts JWM, Wynne HJ, *et al.* Radiofrequency denervation of lumbar facet joints in the treatment of chronic low back pain: A randomized, double-blind, sham lesion-controlled trial. *Clin J Pain* 2005;21:335–44.

22 Nath S, Nath CA, Pettersson K. Percutaneous Lumbar Zygapophysial (Facet) Joint Neurotomy Using Radiofrequency Current, in the Management of Chronic Low Back Pain. *Spine (Phila Pa 1976)* 2008;33:1291–1297. doi:10.1109/ICCGI.2010.42

23 Tekin I, Mirzai H, Ok G, *et al.* A comparison of conventional and pulsed radiofrequency denervation in the treatment of chronic facet joint pain. *Clin J Pain* 2007;23:524–9. doi:10.1097/AJP.0b013e318074c99c

24 Cohen SP, Hurley RW, Buckenmaier CC, *et al.* Randomized Placebo-Controlled Study Evaluating Lateral Branch Radiofrequency Denervation for Sacroiliac Joint Pain. *Anesthesiology* 2008;109:279–88.

doi:10.1038/mp.2011.182.doi

25 Patel N, Gross A, Brown L, *et al.* A Randomized, Placebo-Controlled Study to Assess the Efficacy of Lateral Branch Neurotomy for Chronic Sacroiliac Joint Pain. *Pain Med* 2012;13:383–98. doi:10.1111/j.1526-4637.2012.01328.x

26 Van Tilburg C, Stronks D, Groeneweg J, *et al.* Randomised sham-controlled double-blind multicentre clinical trial to ascertain the effect of percutaneous radiofrequency treatment for lumbar facet joint pain. *Spine (Phila Pa 1976)* 2016;98-B:1526–33.

27 Mehta V, Poply K, Husband M, *et al.* The Effects of Radiofrequency Neurotomy Using a Strip-Lesioning Device on Patients with Sacroiliac Joint Pain: Results from a Single-Center, Randomized, Sham-Controlled Trial. *Pain Physician* 2018;21:607–18.

28 Barendse GAM, van den Berg SGM, Kessels AHF, *et al.* Randomized Controlled Trial of Percutaneous Intradiscal Radiofrequency Thermocoagulation for Chronic Discogenic Back Pain. Lack of Effect From a 90-Second 70 C Lesion. *Spine (Phila Pa 1976)* 2001;26:287–92. doi:10.1097/00007632-200102010-00014

29 Kapural L, Vrooman B, Sarwar S, *et al.* A Randomized, Placebo-Controlled Trial of Transdiscal Radiofrequency, Biacuplasty for Treatment of Discogenic Lower Back Pain. *Pain Med* 2013;14:362–73. doi:10.1111/pme.12023

30 van Tilburg CWJ, Stronks DL, Groeneweg JG, *et al.* Randomized sham-controlled, double-blind, multicenter clinical trial on the effect of percutaneous radiofrequency at the ramus communicans for lumbar disc pain. *Eur J Pain* 2017;21:520–9. doi:10.1002/ejp.945

31 Desai MJ, Kapural L, Petersohn JD, *et al.* A prospective, randomized, multicenter, open-label clinical trial comparing intradiscal biacuplasty to conventional medical management for discogenic lumbar back pain. *Spine (Phila Pa 1976)* 2016;41:1065–74. doi:10.1097/BRS.0000000000001412

32 Kvarstein G, Måwe L, Indahl A, *et al.* A randomized double-blind controlled trial of intra-annular radiofrequency thermal disc therapy - A 12-month follow-up. *Pain* 2009;145:279–86. doi:10.1016/j.pain.2009.05.001

33 Fischgrund JS, Rhyne A, Franke J, *et al.* Intraosseous basivertebral nerve ablation for the treatment of chronic low back pain: a prospective randomized double-blind sham-controlled multi-center study. *Eur Spine J* 2018;27:1146–56. doi:10.1007/s00586-018-5496-1

34 The Cochrane Collaboration. Introduction to sources of bias in clinical trials. In: *Cochrane Handbook for Systematic Reviews of Interventions*. 2011.

35 Morley S, Williams A, Hussain S. Estimating the clinical effectiveness of cognitive behavioural therapy in the clinic: Evaluation of a CBT informed pain management programme. *Pain* 2008;137:670–80.

36 Dunn K, Croft P. Epidemiology and natural history of low back pain. *Eura Medicophys* 2004;40:9–13.

37 Dunn K, Jordan K, Croft P. Characterizing the course of low back pain: a latent class analysis. *Am J Epidemiol* 2006;63:754–61.

38 Dreyfuss P, Baker R. Comment on: Radiofrequency facet joint denervation in the treatment of low back pain: a placebo-controlled clinical trial to assess efficacy. *Spine (Phila Pa 1976)* 2002;27:556–7.

39 Kapural L, Provenzano D, Narouze S. RE: Juch JNS, et al. Effect of

Radiofrequency Denervation on Pain Intensity Among Patients With Chronic Low Back Pain: The Mint Randomized Clinical Trials. JAMA 2017;318(1):68–81. *Neuromodulation* 2017;20:844. doi:10.1111/ner.12729

40 Cohen SP, Julie JH, Brummett C. Facet joint pain-advances in patient selection and treatment. *Nat Rev Rheumatol* 2013;9:101–16. doi:10.1038/nrrheum.2012.198

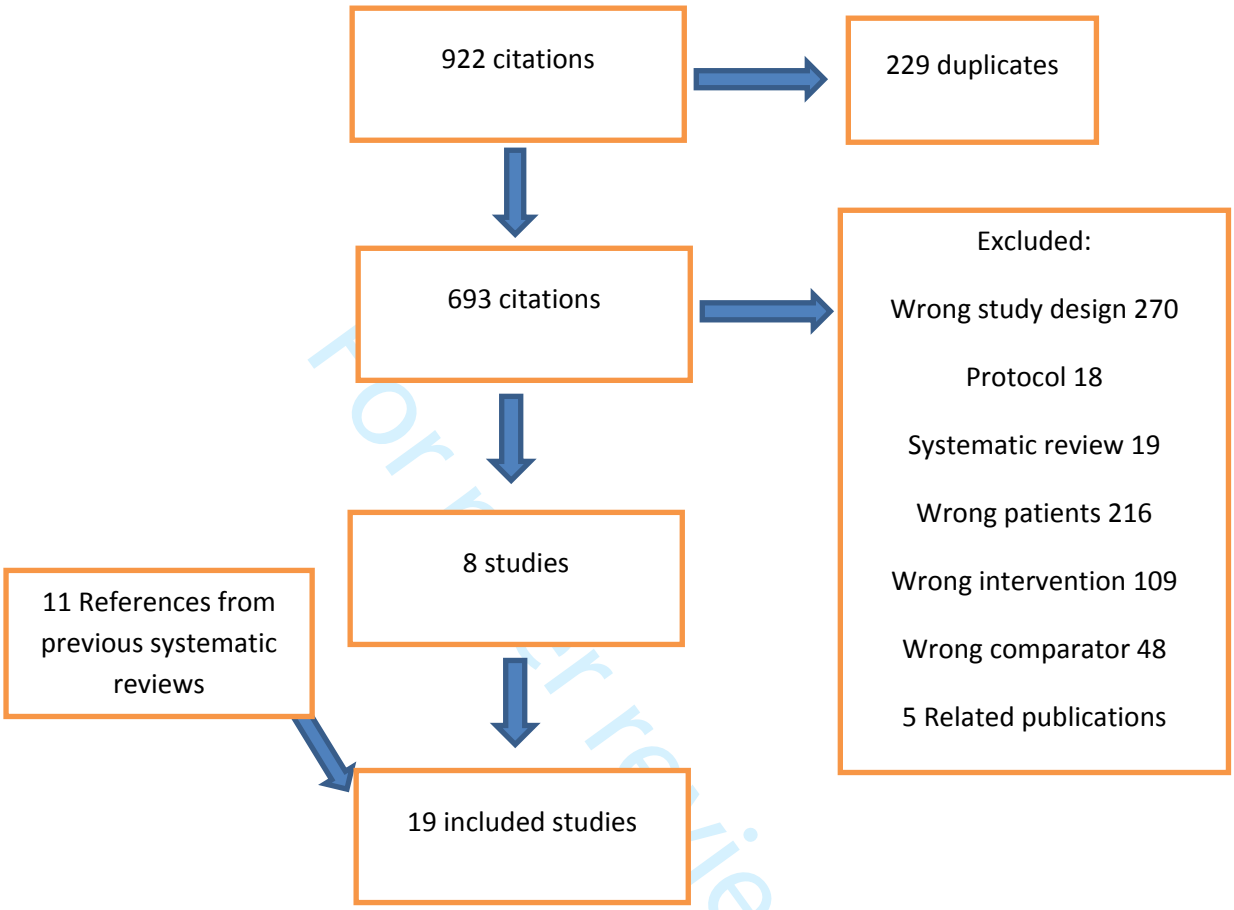
Table 1 Results of the meta-analyses of randomised controlled trials

	All trials					Sham controlled trials				
	k	N	MD (95% CI)	I^2	GRADE*	k	N	MD (95% CI)	I^2	GRADE*
RD of the facet joints										
1-3 months	7	599	-0.48 (-0.81, -0.15)	59%	Low	6	348	-0.51 (-0.90, -0.11)	66%	Low
1 month	4	411	-0.64 (-1.08, -0.21)	22%	Moderate	3	160	-0.48 (-1.17, 0.21)	43%	Low
2 months	2	282	-0.83 (-1.36, -0.30)	44%	Low	1	31	-1.94 (-3.65, -0.23)	NA	Very low
3 months	4	478	-0.41 (-0.76, -0.03)	64%	Low	3	127	-0.37 (-0.83, 0.08)	76%	Very low (R, H, I)
6 months	4	361	-0.57 (-1.01, -0.13)	42%	Low	3	110	-0.90 (-1.53, -0.28)	32%	Low (R, I)
1 year	2	291	-0.71 (-1.20, -0.21)	89%	Very low	1	40	-1.50 (-2.21, -0.79)	NA	Very low
RD of the sacroiliac joints										
1-3 months	5	384	-0.97 (-1.38, -0.57)	83%	Low	4	156	-1.13 (-1.63, -0.63)	87%	Very low
1 month	4	367	-0.91 (-1.32, -0.51)	82%	Low	3	139	-0.81 (-1.36, -0.26)	88%	Very low
2 months	1	228	-0.47 (-1.04, 0.10)	NA	Low					
3 months	4	356	-0.78 (-1.20, -0.37)	73%	Low	3	128	-0.84 (-1.37, -0.32)	81%	Very low
6 months	1	228	-0.28 (-1.00, 0.44)	NA	Low					
12 months	1	228	-0.19 (-0.92, 0.54)	NA	Low					
RD of the intervertebral discs										
1-3 months	4	200	-0.98 (-1.62, -0.33)	40%	Low	3	144	-0.63 (-1.36, 0.10)	0%	Low
1 month	3	176	-0.61 (-1.31, 0.09)	61%	Low	2	116	-0.16 (-0.97, 0.65)	0%	Low (R,I)
2 months	1	28	0.28 (-1.95, 2.51)	NA	Very low	1	28	0.28 (-1.95, 2.51)	NA	Very low
3 months	3	172	-1.09 (-1.76, -0.42)	45%	Low	2	116	-0.74 (-1.51, 0.03)	0%	Low
6 months	3	127	-1.74 (-2.58, -0.91)	0%	Low	2	75	-1.63 (-2.58, -0.68)	0%	Low
12 months	1	20	-1.70 (-3.63, 0.23)	NA	Very low	1	20	-1.70 (-3.63, 0.23)	NA	Very low
RD of the vertebrae body and endplate										
3 months	1	205	-0.34 (-1.09, 0.41)	NA	Moderate	1	205	-0.34 (-1.09, 0.41)	NA	Moderate
6 months	1	205	-0.67 (-1.44, 0.10)	NA	Moderate	1	205	-0.67 (-1.44, 0.10)	NA	Moderate
12 months	1	205	-0.50 (-1.29, 0.29)	NA	Moderate	1	205	-0.50 (-1.29, 0.29)	NA	Moderate

k, number of trials; N, number of participants; MD, Mean difference.

*GRADE assessment of the quality of the evidence

Figure 1 PRISMA flow diagram



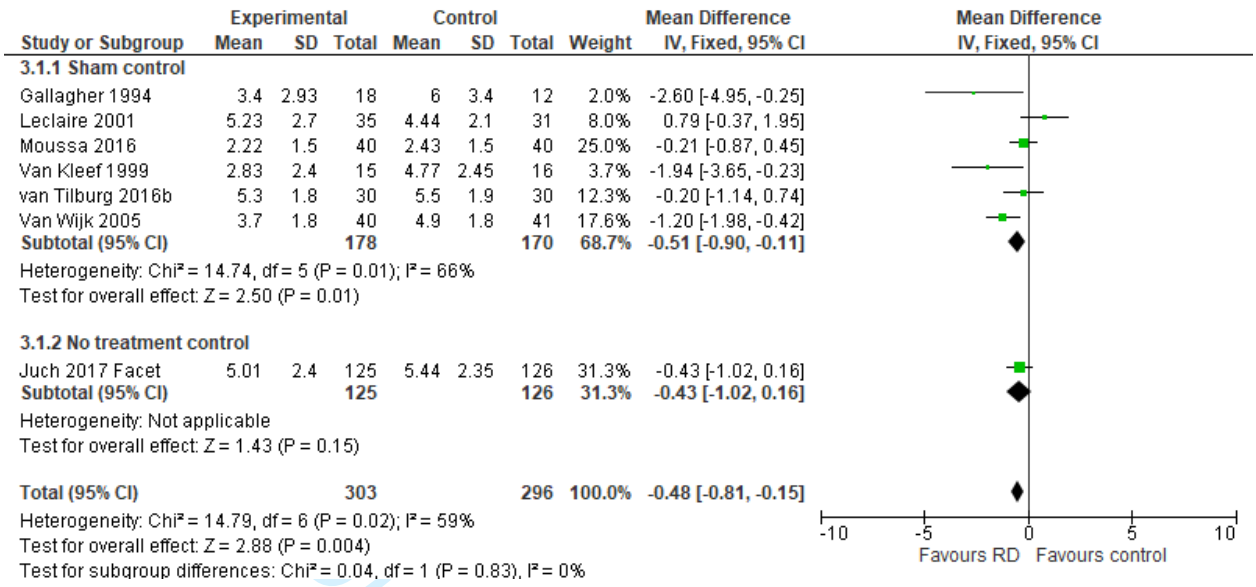


Figure 2 Post treatment pain score for radiofrequency denervation of the facet joints versus control at 1-3 month follow-up (longest time point used for studies with multiple time points)

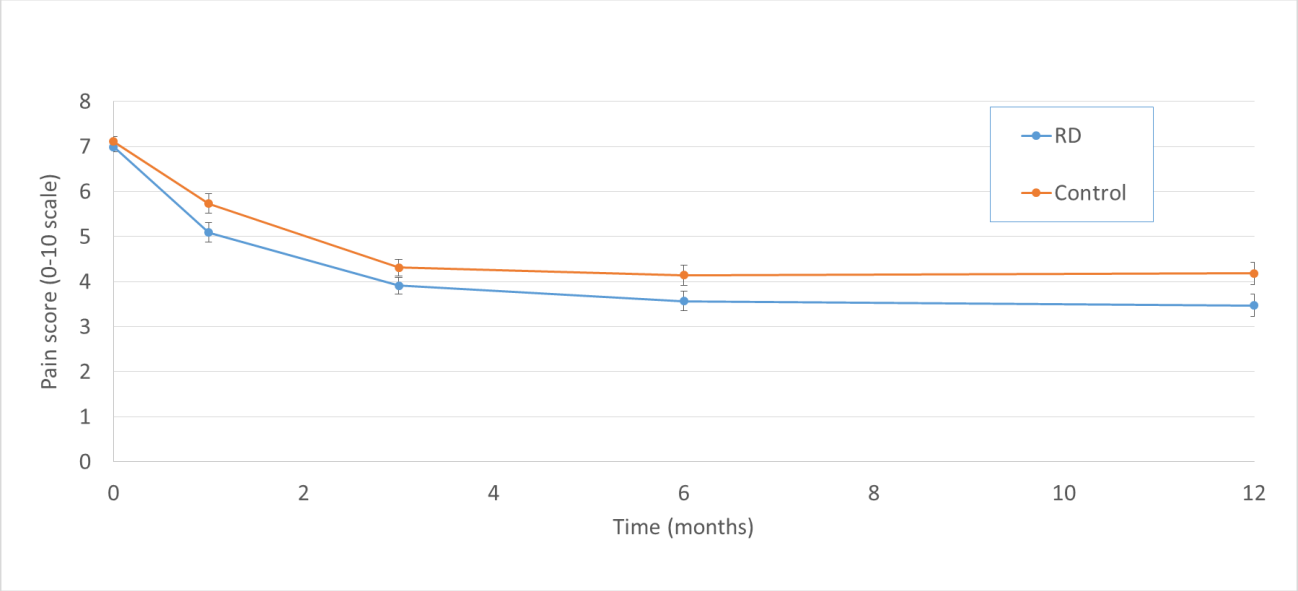


Figure 3 Change in back pain score (closed bound 0-10 scale) for patients with facet joint pain following radiofrequency denervation or control treatment

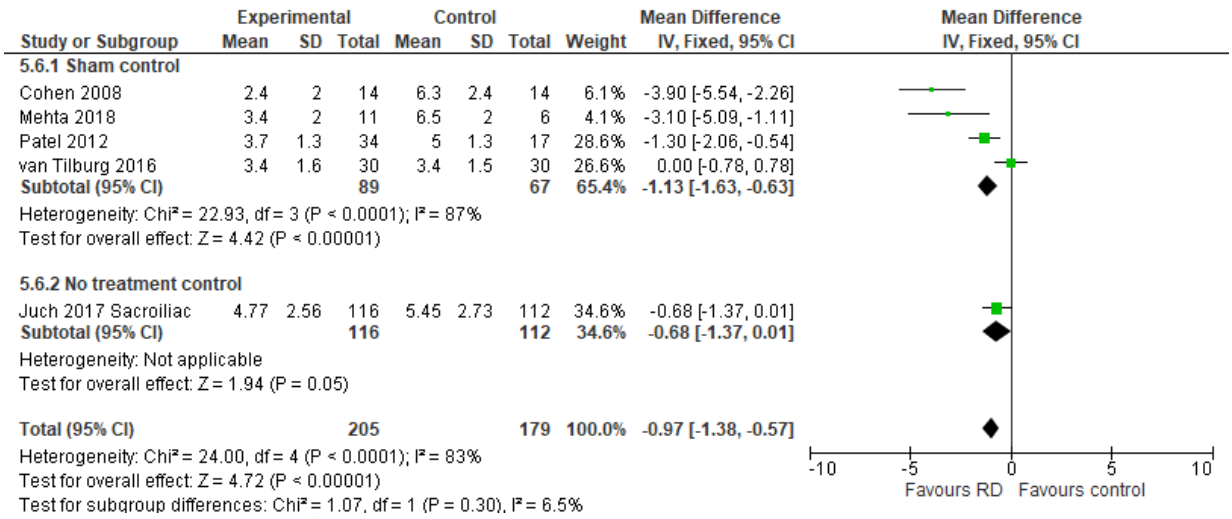


Figure 4 Post treatment pain score for radiofrequency denervation of the sacroiliac joints versus control at 1-3 month follow-up (longest time point used for studies with multiple time points)

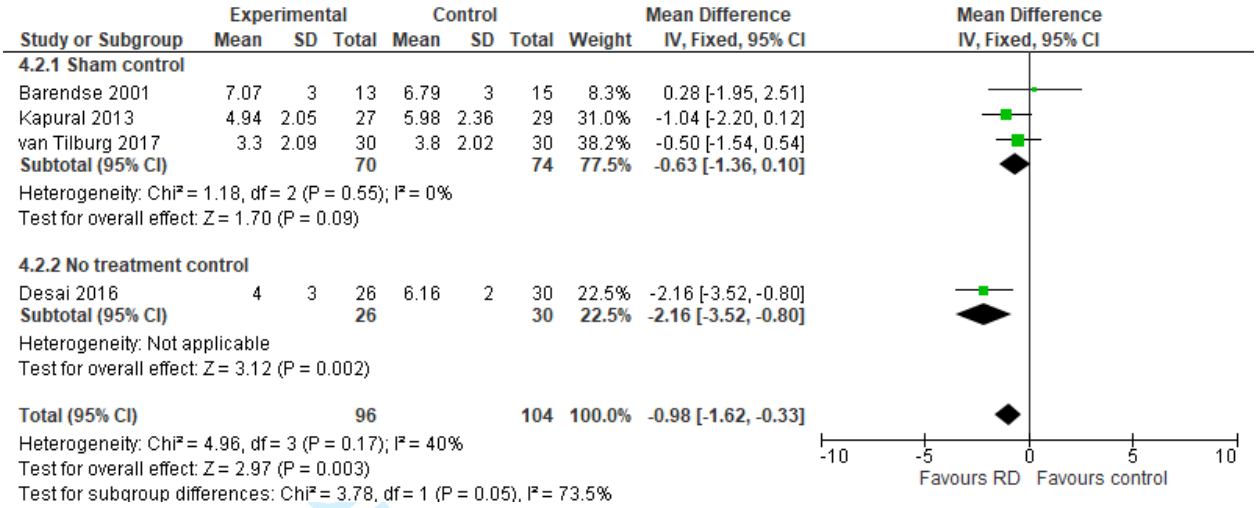


Figure 5 Post treatment pain score for radiofrequency denervation of the intervertebral discs versus control at 1-3 month follow-up (longest time point used for studies with multiple time points)

Appendix 1 Search strategies

Medline and Embase

#	Database	Search term
1	Medline	(randomized controlled trial).pt
2	Medline	(controlled clinical trial).pt
3	Medline	(randomi*ed).ab
4	Medline	(placebo).ti,ab
5	Medline	(drug therapy).fs
6	Medline	(randomly).ti,ab
7	Medline	(trial).ti,ab
8	Medline	(groups).ti,ab
9	Medline	(1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8)
10	Medline	(animals NOT (humans AND animals)).su
11	Medline	9 not 10
12	Medline	(dorsalgia).ti,ab
13	Medline	exp "BACK PAIN"/
14	Medline	(backache).ti,ab
15	Medline	(lumbar ADJ pain).ti,ab
16	Medline	(coccyx).ti,ab
17	Medline	(coccydynia).ti,ab
18	Medline	(sciatica).ti,ab
19	Medline	"SCIATIC NEUROPATHY"/

20	Medline	(spondylosis).ti,ab
21	Medline	(lumbago).ti,ab
22	Medline	(12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21)
23	Medline	exp SPINE/
24	Medline	(discitis).ti,ab
25	Medline	exp "SPINAL DISEASES"/
26	Medline	(disc ADJ degeneration).ti,ab
27	Medline	(disc ADJ prolapse).ti,ab
28	Medline	(disc ADJ herniation).ti,ab
29	Medline	(spinal fusion).su
30	Medline	(facet ADJ joints).ti,ab
31	Medline	(intervertebral disc).su
32	Medline	(postlaminectomy).ti,ab
33	Medline	(arachnoiditis).ti,ab
34	Medline	(failed ADJ back).ti,ab
35	Medline	(23 OR 24 OR 25 OR 26 OR 27 OR 28 OR 29 OR 30 OR 31 OR 32 OR 33 OR 34)
36	Medline	(22 OR 35)
37	Medline	exp "RADIO WAVES"/
38	Medline	exp "PULSED RADIOFREQUENCY TREATMENT"/
39	Medline	(radiofrequency).af
40	Medline	(radio frequency).af

41	Medline	exp ELECTROCOAGULATION/
42	Medline	(electrocoag*).af
43	Medline	(thermocoag*).af
44	Medline	neurotom* OR (neuroly*).af
45	Medline	(37 OR 38 OR 39 OR 40 OR 41 OR 42 OR 43 OR 44)
46	Medline	(11 AND 36 AND 45)
47	EMBASE	"CLINICAL TRIAL"/
48	EMBASE	"CONTROLLED CLINICAL TRIAL"/
49	EMBASE	"CONTROLLED STUDY"/
50	EMBASE	"RANDOMIZED CONTROLLED TRIAL"/
51	EMBASE	"DOUBLE BLIND PROCEDURE"/
52	EMBASE	"SINGLE BLIND PROCEDURE"/
53	EMBASE	"CROSSOVER PROCEDURE"/
54	EMBASE	PLACEBO/
55	EMBASE	(allocat*).ti,ab
56	EMBASE	(assign*).ti,ab
57	EMBASE	(blind*).ti,ab
58	EMBASE	(clinic* ADJ25 (study OR trial)).ti,ab
59	EMBASE	(crossover OR cross-over).ti,ab
60	EMBASE	(factorial*).ti,ab
61	EMBASE	(followup OR follow-up).ti,ab
62	EMBASE	(prospectiv*).ti,ab

63	EMBASE	(placebo*).ti,ab
64	EMBASE	(random*).ti,ab
65	EMBASE	((singl* OR doubl* OR trebl* OR trip*) ADJ25 (blind* OR mask*)).ti,ab
66	EMBASE	(volunteer*).ti,ab
67	EMBASE	(47 OR 48 OR 49 OR 50 OR 51 OR 52 OR 53 OR 54 OR 55 OR 56 OR 57 OR 58 OR 59 OR 60 OR 61 OR 62 OR 63 OR 64 OR 65 OR 66)
68	EMBASE	exp animals/ or exp invertebrate/ or animal experiment/ or animal model/ or animal tissue/ or animal cell/ or nonhuman/
69	EMBASE	exp ANIMALS/
70	EMBASE	exp INVERTEBRATE/
71	EMBASE	ANIMAL EXPERIMENT/
72	EMBASE	ANIMAL MODEL/
73	EMBASE	ANIMAL TISSUE/
74	EMBASE	ANIMAL CELL/
75	EMBASE	NONHUMAN/
76	EMBASE	71 or 72 or 73 or 74 or 75
77	EMBASE	exp ANIMALS/
78	EMBASE	exp INVERTEBRATE/
79	EMBASE	(76 OR 77 OR 78)
80	EMBASE	77 or 78
81	EMBASE	HUMAN/ OR NORMAL HUMAN/ OR HUMAN CELL/
82	EMBASE	(76 AND 77 AND 78 AND 81)

83	EMBASE	(dorsalgia).ti,ab
84	EMBASE	(back pain).ti,ab
85	EMBASE	exp BACKACHE/
86	EMBASE	(lumbar ADJ pain).ti,ab
87	EMBASE	(coccyx).ti,ab
88	EMBASE	(coccydynia).ti,ab
89	EMBASE	(sciatica).ti,ab
90	EMBASE	ISCHIALGIA/
91	EMBASE	(spondylosis).ti,ab
92	EMBASE	(lumbago).ti,ab
93	EMBASE	(back disorder*).ti,ab
94	EMBASE	(83 OR 84 OR 85 OR 86 OR 87 OR 88 OR 89 OR 90 OR 91 OR 92 OR 93)
95	EMBASE	exp SPINE/
96	EMBASE	(discitis OR diskitis).ti,ab
97	EMBASE	exp "SPINE DISEASE"/
98	EMBASE	(disc ADJ degeneration).ti,ab
99	EMBASE	(disc ADJ prolapse).ti,ab
100	EMBASE	(disc ADJ herniation).ti,ab
101	EMBASE	(spinal fusion).ti,ab
102	EMBASE	(facet ADJ joints).ti,ab
103	EMBASE	(intervertebral disk OR Intervertebral disc).ti,ab
104	EMBASE	(postlaminectomy).ti,ab

105	EMBASE	(arachnoiditis).ti,ab
106	EMBASE	(failed ADJ back).ti,ab
107	EMBASE	(95 OR 96 OR 97 OR 98 OR 99 OR 100 OR 101 OR 102 OR 103 OR 104 OR 105 OR 106)
108	EMBASE	94 or 107
109	EMBASE	exp PULSED RADIOFREQUENCY TREATMENT/
110	EMBASE	exp RADIOFREQUENCY/
111	EMBASE	exp RADIOFREQUENCY RADIATION/
112	EMBASE	(radiofrequency OR radio-frequency).ti,ab
113	EMBASE	exp THERMOCOAGULATION/ OR thermocoag*
114	EMBASE	exp ELECTROCOAGULATION/ OR electrocoag*
115	EMBASE	(neurotom* OR neuroly*).ti,ab
116	EMBASE	(109 OR 110 OR 111 OR 112 OR 113 OR 114 OR 115)
117	EMBASE	(108 AND 116)
118	Medline	46 [DT 2014-2019]

Medline in process

#	Database	Search term
1	Medline	("randomi*ed controlled trial").ti,ab
2	Medline	("controlled clinical trial").ti,ab
3	Medline	("randomi*ed").ab
4	Medline	(placebo).ti,ab
5	Medline	("drug therapy").fs

6	Medline	(randomly).ti,ab
7	Medline	(trial).ti,ab
8	Medline	(groups).ti,ab
9	Medline	(1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8)
10	Medline	(dorsalgia).ti,ab
11	Medline	("back pain").ti,ab
12	Medline	(backache).ti,ab
13	Medline	("lumber pain").ti,ab
14	Medline	(coccyx).ti,ab
15	Medline	(coccydynia).ti,ab
16	Medline	(sciatica*).ti,ab
17	Medline	(spondylosis).ti,ab
18	Medline	(lumbago).ti,ab
19	Medline	(10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18)
20	Medline	(spine OR sacrum OR "lumber vertebrae" OR "intervertebral disc*").ti,ab
21	Medline	(discitis).ti,ab
22	Medline	("disc degeneration").ti,ab
23	Medline	("disc prolapse").ti,ab
24	Medline	("disc herniation").ti,ab
25	Medline	("spinal fusion").ti,ab
26	Medline	("facet joints").ti,ab

27	Medline	(postlaminectomy).ti,ab
28	Medline	(arachnoiditis).ti,ab
29	Medline	("failed back").ti,ab
30	Medline	(20 OR 21 OR 22 OR 23 OR 24 OR 25 OR 26 OR 27 OR 28 OR 29)
31	Medline	(19 OR 30)
32	Medline	(radiowave* OR "radio wave*").ti,ab
33	Medline	(radiofrequency OR "radio frequency").ti,ab
34	Medline	(electrocoag*).ti,ab
35	Medline	(thermocoag*).ti,ab
36	Medline	(neurotom* OR neuroloy*).ti,ab
37	Medline	(32 OR 33 OR 34 OR 35 OR 36)
38	Medline	(9 AND 31 AND 37)
39	Medline	38 [Document status In Data Review OR In Process OR PubMed not MEDLINE OR Publisher]

Cinahl

#	Database	Search term
1	CINAHL	exp "CLINICAL TRIALS"/
2	CINAHL	("randomi*ed controlled trial*").ti,ab
3	CINAHL	(clinical ADJ3 trial).ti,ab
4	CINAHL	(double-blind).ti,ab
5	CINAHL	(single-blind).ti,ab
6	CINAHL	(triple-blind).ti,ab

7	CINAHL	(1 OR 2 OR 3 OR 4 OR 5 OR 6)
8	CINAHL	"PLACEBO EFFECT"/
9	CINAHL	PLACEBOS/
10	CINAHL	(placebo*).ti,ab
11	CINAHL	(random*).ti,ab
12	CINAHL	(8 OR 9 OR 10 OR 11)
13	CINAHL	"RANDOM SAMPLE"/
14	CINAHL	exp "STUDY DESIGN"/
15	CINAHL	(latin square).ti,ab
16	CINAHL	exp "COMPARATIVE STUDIES"/
17	CINAHL	exp "EVALUATION RESEARCH"/
18	CINAHL	exp "PROSPECTIVE STUDIES"/
19	CINAHL	(13 OR 14 OR 15 OR 16 OR 17 OR 18)
20	CINAHL	(follow-up stud*).ti,ab
21	CINAHL	(followup stud*).ti,ab
22	CINAHL	(control*).ti,ab
23	CINAHL	(prospectiv*).ti,ab
24	CINAHL	(volunteer*).ti,ab
25	CINAHL	(20 OR 21 OR 22 OR 23 OR 24)
26	CINAHL	(7 OR 12 OR 19 OR 25)
27	CINAHL	ANIMALS/
28	CINAHL	26 not 27

29	CINAHL	("dorsalgia").ti,ab
30	CINAHL	exp "BACK PAIN"/
31	CINAHL	"LOW BACK PAIN"/
32	CINAHL	("backache").ti,ab
33	CINAHL	(lumbar ADJ1 pain).ti,ab
34	CINAHL	(lumbar ADJ5 pain).ti,ab
35	CINAHL	(29 OR 30 OR 31 OR 32 OR 33 OR 34)
36	CINAHL	COCCYX/
37	CINAHL	SCIATICA/
38	CINAHL	(sciatica).ti,ab
39	CINAHL	(coccyx).ti,ab
40	CINAHL	(coccydynia).ti,ab
41	CINAHL	"LUMBAR VERTEBRAE"/
42	CINAHL	(lumbar ADJ2 vertebra).ti,ab
43	CINAHL	(36 OR 37 OR 38 OR 39 OR 40 OR 41 OR 42)
44	CINAHL	"THORACIC VERTEBRAE"/
45	CINAHL	exp SPONDYLOLYSIS/
46	CINAHL	(lumbago).ti,ab
47	CINAHL	(44 OR 45 OR 46)
48	CINAHL	(35 OR 43 OR 47)
49	CINAHL	(28 AND 48)
50	CINAHL	(radiofrequency OR radio-frequency).ti,ab

51	CINAHL	(thermocoag*).ti,ab
52	CINAHL	exp ELECTROCOAGULATION/ OR electrocoag*
53	CINAHL	(neurotom* OR neuroly*).ti,ab
54	CINAHL	"RADIO WAVES"/
55	CINAHL	(50 OR 51 OR 52 OR 53 OR 54)
56	CINAHL	(49 AND 55)
57	CINAHL	56 [DT 2014-2019]

Cochrane

#	Database	Search term
1	Cochrane	MeSH descriptor: [Back Pain] explode all trees
2	Cochrane	dorsalgia
3	Cochrane	backache
4	Cochrane	MeSH descriptor: [Low Back Pain] explode all trees
5	Cochrane	lumbar next pain or coccyx or coccydynia or spondylosis
6	Cochrane	MeSH descriptor: [Spine] explode all trees
7	Cochrane	MeSH descriptor: [Spinal Diseases] explode all trees
8	Cochrane	lumbago OR discitis OR disc near degeneration OR disc near prolapse OR disc near herniation
9	Cochrane	spinal fusion
10	Cochrane	facet near joints
11	Cochrane	MeSH descriptor: [Intervertebral Disk] explode all trees
12	Cochrane	postlaminectomy

13	Cochrane	arachnoiditis
14	Cochrane	failed near back
15	Cochrane	MeSH descriptor: [Cauda Equina] explode all trees
16	Cochrane	lumbar near vertebra*
17	Cochrane	spinal near stenosis
18	Cochrane	slipped near (disc* or disk*)
19	Cochrane	degenerat* near (disc* or disk*)
20	Cochrane	stenosis near (spine or root or spinal)
21	Cochrane	displace* near (disc* or disk*)
22	Cochrane	prolap* near (disc* or disk*)
23	Cochrane	MeSH descriptor: [Sciatic Neuropathy] explode all trees
24	Cochrane	sciatic*
25	Cochrane	back disorder*
26	Cochrane	back near pain
27	Cochrane	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #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
28	Cochrane	MeSH descriptor: [Radio Waves] explode all trees
29	Cochrane	MeSH descriptor: [Pulsed Radiofrequency Treatment] explode all trees
30	Cochrane	radiofrequency
31	Cochrane	radio frequency or radio-frequency
32	Cochrane	MeSH descriptor: [Electrocoagulation] explode all trees
33	Cochrane	electrocoag*

34	Cochrane	thermocoag*
35	Cochrane	neurotom* or neuroly*
36	Cochrane	#28 or #29 or #30 or #31 or #32 or #33 or #34 or #35
37	Cochrane	#27 and #36 in Trials

Appendix 2 Study characteristics

Study	N	Inclusion criteria		Mean age (SD)	Mean pain score (SD)	Intervention	Control	Funding
RD of the facet joints								
Gallagher 1994	41	Low back pain >3 months duration with symptoms typical of facet joint pain	Improvement (n=30) or equivocal (n=11) response to anaesthetic block	NR	VAS RD 5.8 (1.78); Sham 7.2 (1.94)	Nerves above and below painful joint denervated at 80° for 90 seconds.	Nerves also identified with stimulation but no heat lesion made	NR
Juch 2017	251	Low back pain without response to conservative management and considered to be related to the facet joint	Positive response to anaesthetic block (reported 50% pain relief 30-90 minutes after block)	RD 53.0 (11.5); Control 52.6 (10.8)	NRS RD 7.14 (1.38) Control 7. 19 (1.29)	Denervation at 90° for 90s of L3-4, L4-5 or L5-S1 with exercise program	Exercise program	The Netherlands Organization for Health Research and Development, by the Dutch Society for Anesthesiology, and the Dutch health insurance companies
Leclaire 2001	70	Low back pain for >3 months	“Significant” relief of back pain for >24h following facet injections	RD 46.7 (9.3); Sham 46.4 (9.8)	VAS RD 5.19 (2.67); Sham 5.15 (2.08)	RD with fluoroscopic guidance at 80°C for 90s of at least 2 levels	Nerves also identified with stimulation but electrode only heated to 37°C	Institut de recherche en sante´ and se´curite´ du travail du Que´bec
Moussa 2016	80	Low back pain for >1 year without response to conservative management	Complete or near complete reduction of CLBP on VAS 30 min after 2	RD capsule 58.1 (NR); RD conventional 56.5 (NR);	VAS RD 8.22 (NR); Sham 7.83 (NR)	RD of facet capsule on medial and lateral aspect or	Same procedure without elect current turned on	No funding received

			injections separated by >2 weeks	Sham 55.9 (NR)		conventional RD at 85°C for 90s		
Nath 2008	40	Low back pain for >2 years, not responded to previous treatment, pain attributable to lumbar facet joints	80% pain relief on 3 medial branch blocks	56 (range, 36–79)	VAS RD 5.98 (NR); Sham 4.38 (NR)	RD at 85°C for 60s with additional lesions just lateral and medial to the target nerve	Same procedure as RD but electrode tip remained at body temperature	No funding received
Tekin 2007	40	Back pain for >6 months with focal pain over the facet joints and unresponsive to conservative treatments	>50% reduction in VAS pain 30 minutes after diagnostic medial branch block	RD 60.5 (8.5); Sham 57.9 (9.3)	VAS RD 6.5 (1.5); Sham 6.8 (1.6)	RD at same levels as diagnostic blocks at 80°C for 90s.	Same procedure as RD but with current switched off	Not reported
Van Kleef 1999	32	Low back pain of >12 months duration, failure of conservative management	>50% reduction in pain following diagnostic nerve block of L3-L5 Baseline VAS score of >4	RD 46.6 (7.4); Sham 41.4 (7.5)	VAS RD 5.2 (1.7); Sham 5.2 (1.6)	RD at 80°C for 60s	Same procedure as RD but with current switched off	The Nederlandse organisatie voor wetenschappelijk
Van Tilburg 2016	60	Low back pain for >3 months and failure of conservative management	Decrease of >2 on medial branch block	RD 65 (12); Sham 58 (12)	NRS RD 7.2 (1.4); Sham 7.4 (0.8)	RD at 80°C for 60s per level for three steps with physiotherapy	Same procedure as RD but with current switched off with physiotherapy	No funding from a commercial party
Van Wijk 2005	81	Low back pain for >6 months	≥50% reduction on	RD 46.9 (11.5);	VAS RD 5.8 (1.8);	RD 80°C for 60 seconds	Same procedure as	Grant from the Dutch Health

			diagnostic block	Sham 48.1 (12.6)	Sham 6.5 (1.8)	at the levels concerned	RD but with current switched off	Insurance Council
RD of the sacroiliac joints								
Cohen 2008	28	Axial low back or buttock pain ≥ 6 months, tenderness overlying the sacroiliac joint(s), failure to respond to conservative therapy	≥ 75% pain relief for ≥3h following diagnostic sacroiliac joint injection, but back near baseline within 2 months	RD 51.9 (13.6); Sham 51.8 (13.1)	VAS RD 6.1 (1.8); Sham 6.5 (1.9)	RD 80°C for 90 seconds using cooling probe technology (Cooled RD)	Same procedure as RD but no current applied	John P. Murtha Neuroscience and Pain Institute, the Army Regional Anesthesia & Pain Medicine Initiative, and National Institutes of Health grant # MH075884
Juch 2017	228	Low back pain without response to conservative management, considered to be related to the sacroiliac joint.	Positive response to anaesthetic block (reported 50% pain relief 30-90 minutes after block)	RD 51.6 (10.9); Control 51.1 (12.2)	NRS RD 7.17 (1.65); Control 7.06 (1.43)	RD - 60° for 2.5 min per lesion of S1, S2 and S3 with exercise program	Exercise program	The Netherlands Organization for Health Research and Development, by the Dutch Society for Anesthesiology, and the Dutch health insurance companies
Mehta 2018	17	CLBP for >6 months. >5 on NRS	>80% pain reduction on 2 diagnostic blocks	RD 56.6 (NR); Sham 62.6 (NR)	VAS RD 8.1 (0.8); Sham 7.3 (0.8)	RD of the L5 medial branch of the primary dorsal root nerve and strip lesioning of the lateral branches	Identical to active RD treatment except that no RF energy was applied	None

						of the S1, 2, and 3 nerve roots		
Patel 2012	51	Pain for ≥6 months, 3-day average NRS between 4 and 8, failure of conservative management	≥75% pain reduction for 4h-7 days on two sets of anaesthetic blocks and back to baseline by start of the study	RD 56 (15); Sham 64 (14)	NRS RD 6.1 (1.3); Sham 5.8 (1.3)	RD at 60°C for 150s of L5 dorsal ramus and then acral lateral branches of S1, S2 and S3 (cooled RD)	Same procedure as RD but RF energy was not delivered.	Baylis Medical
Van Tilburg 2016	60	Sacroiliac joint pain for >3 months, failure of conservative management	Decrease of ≥2 on NRS following diagnostic block	RD 59.5 (27); Sham 62 (18)	NRS RD 7.2 (1.4); Sham 7.5 (1.2)	85°C each step for 90s, total of 5 steps	Same procedure as RD but no heat lesions made	Not reported
RD of the intervertebral discs								
Barendse 2001	28	Non-specific LBP for >1y, failure of conservative management	>50% pain relief 30 minutes after an analgesic discography at L4–L5 and L5–S1. Patients with multilevel pain excluded	RD 40.8 (7.5); Sham 45.2 (8.4)	VAS RD 6.5 (1.3); Sham 5.5 (1.1)	70°C for 90s without anaesthetic	Same procedure as RD but no current applied	Not reported
Desai 2016	63	Lumbar discogenic pain for ≥6 months, unresponsive to conservative management	Diagnosed via provocation discography - definite single-level concordant	Mean age 41 (11); Control 43 (11)	VAS RD 6.7 (NR); Sham 7 (NR)	RD at 50°C for 15 minutes and then 60°C for 2.5 min (bopolar cooled RD) with conventional	Conventional medical management	Halyard Health, Inc. (formerly Kimberly-Clark Health Care)

			pain on manometry			medical management		
Kapural 2013	55	CLBP unresponsive to conservative management for ≥6 months; no surgical interventions within previous 3 months	Single-level degenerative disc disease or two-level disease without evidence of additional degenerative changes in other disc spaces on MRI	RD 40.4 (10.3); Sham 38.4 (10.4)	VAS RD 7.13 (1.61); Sham 7.18 (1.98)	RD at 45°C bipolar for 15 minutes or 50°C bipolar for 15 minutes and monopolar at 60°C for 2.5 minutes	Mimicked active treatment, except that introducers and electrodes positioned just outside of the disc, and no RF energy delivered	Baylis Medical
Kvarstein 2009	20	Unremitting low back pain for more than 6 months; Pain intensity ≥5 /10 and low back pain greater than leg pain; Failure on conservative treatment	Positive one-level pain provocation discography	RD 44.7 (10.1); Sham 39.6 (8.9)	NRS RD 4.6 (1.8); Sham 5.5 (2.0)	RD increased by 5°C every second minute to 4-min interval at 65°C (from 50°C)	Exposed to a similar intervention, but the annulus was not exposed to RF heating	Radionics, TYCO Healthcare Group provided the discTRODE probes
Van Tilburg 2017	60	Low back pain >3 months and symptoms suggestive of lumbar disc problem	Reduction of ≥2 on a numerical rating scale (0–10) after a diagnostic ramus communicans test block	RD 50.5 (13.9); Sham 50.1 (12.3)	NRS 7.8 (1.05); Sham 7.8 (1.05)	RD treatment at 80 °C for 60s per level	Same procedure but without RF treatment	No support received that influenced submitted work
RD of the vertebrae body and endplate								

Fischgrund 2018	225	CLBP ≥6 months, not responded to conservative treatment, Type 1 or Type 2 Modic changes required at the proposed treatment levels	No diagnostic block for inclusion	RD 46.9 (range 26–69); Sham 47.1 (range 25–69)	VAS RD 6.73 (1.38); Sham 6.64 (1.34)	Thermal ablation at the terminus of the basivertebral nerve 85°C for 15 min	Same procedure as RD but only docking introducer cannula 1–2 mm into the pedicle and simulating RD	Not reported

CLBP, chronic low back pain; N, number of trials; NRS, numeric rating scale; RD, radiofrequency denervation; SD, standard deviation; VAS, visual analogue scale.

BMJ Open

Radiofrequency denervation for chronic back pain: a systematic review and meta-analysis

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-035540.R1
Article Type:	Original research
Date Submitted by the Author:	02-May-2020
Complete List of Authors:	Chappell, Mary; Cambridgeshire County Council, Public Health Directorate Lakshman, Raj; Cambridgeshire County Council, Public Health Directorate; University of Cambridge, Medical Research Council Epidemiology Unit Trotter, Patrick; Cambridge University Hospitals NHS Foundation Trust Abrahams, Mark; Cambridge University Hospitals NHS Foundation Trust Lee, Michael; University of Cambridge, Division of Anaesthesia
Primary Subject Heading:	Rheumatology
Secondary Subject Heading:	Neurology
Keywords:	Back pain < ORTHOPAEDIC & TRAUMA SURGERY, Rheumatology < INTERNAL MEDICINE, Neurology < INTERNAL MEDICINE, PAIN MANAGEMENT

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Radiofrequency denervation for chronic back pain: a systematic review and meta-analysis

Mary E Chappell[1], Raj Lakshman[1,2], Patrick Trotter[3], Mark J Abrahams[3], Michael C Lee[4]

[1]Public Health Directorate, Cambridgeshire County Council, Cambridge, UK

[2]Medical Research Council Epidemiology Unit, University of Cambridge, Cambridge UK

[3]Cambridge University Hospitals NHS Foundation trust, Cambridge, UK

[4]Division of Anaesthesia, University of Cambridge, Cambridge, UK

Correspondence to: Mary E Chappell, Public Health Directorate, Cambridgeshire County Council, Cambridge CB3 0AP, UK. Tel. 01223 729037

Email mary.chappell@cambridgeshire.gov.uk

Word count:

Abstract 204

Main text 4,080

Abstract

Objectives: To assess the effectiveness of radiofrequency denervation of lumbosacral anatomical targets for the management of chronic back pain.

Design: Systematic review and meta-analysis of randomised controlled trials.

Methods: A database search (Medline, Medline in Process, Embase, CINHAL and the Cochrane library) was conducted to April 2019 for placebo or no-treatment controlled trials of radiofrequency denervation for the management of chronic back pain. Included trials were quality assessed using the Cochrane risk of bias tool and the quality of outcomes assessed using the GRADE approach. Meta-analysis was conducted to calculate mean difference in post-treatment pain score.

Results: Nineteen randomised controlled trials were included in the review. There appears to be short-term pain relief (1-3 months) provided by radiofrequency denervation of sacroiliac joint and inter-vertebral discs but the placebo effect is large and additional intervention effect size is small (<1 on a 11 point (0-10) pain scale). Longer-term effectiveness is uncertain.

Conclusions: Radiofrequency denervation of selected lumbosacral targets appears to have a small, short-term, positive effect for the management of patients with chronic back pain. However, the quality of evidence for the majority of outcomes is low or very low quality and there is still a degree of uncertainty, particularly around the duration of effect.

Strengths and limitations of this study:

- This review brings together a number of recent trials with earlier trials so that there is a sizable sum of evidence on which to assess the effectiveness of radiofrequency denervation for back pain.
- Due to the invasive nature of the procedure, it is difficult to perform truly patient or provider blinded trials and this brings some uncertainty around findings.
- There is limited reporting of long-term outcomes for the effectiveness of radiofrequency denervation.

Introduction

Back pain is an extremely common symptom experienced by people of all ages, and can be attributed to a wide variety of disease processes.[1,2] Low back pain is now the leading cause of disability worldwide and back pain is associated with a substantial economic burden, with high medical and societal costs.[3] Studies have shown that a large proportion of medical costs come from hospital admissions and physical therapy for the management of back pain.[4] However, there are also indirect costs associated with chronic or recurrent back pain that are difficult to quantify relating to work absenteeism and related productivity.[1,3,4] In many cases, back pain is non-specific, or structural pathology amendable to surgical correction cannot be identified.[5–7] Hence, patients and practitioners continue to seek non-surgical alternatives for the management of back pain.

Radiofrequency denervation (RD) involves the application of an alternating electric current (250 to 500kHz) via a needle probe to induce a highly localised rise in tissue temperature at the needle tip.[8] The needle tip is usually placed under fluoroscopic guidance to enable selective ablation of sensory nerve branches that supply facet joints, sacroiliac joint or other structures that comprise the lumbosacral spine. RD would therefore offer relief of pain by attenuating sensory signals from the lumbosacral spine.[9]

Despite its use for over 20 years,[10] the effectiveness of RD targeted at the anatomy of lumbosacral spine is not yet established, with randomised controlled trials (RCTs) continuing to be performed. A number of trials have been published since the publication of the last high quality review in 2015[11] and our systematic review aimed to bring together this evidence in an attempt to evaluate whether RD is an effective intervention for the management of chronic non-specific back pain.

Materials and Methods

Search strategy

A search was conducted in Medline, Medline in Process, Embase, CINHAL and the Cochrane library from January 2014 to April 2019 (Appendix 1). Previous systematic reviews were used to obtain additional relevant studies published pre 2014.

Inclusion criteria

RCTs comparing RD of the spine with a control in patients with back pain with or without sciatica were included. Only trials of radiofrequency procedures for the purpose of ablating or denaturing sensory nerve branches or nociceptors that supply the lumbosacral spine were considered for inclusion. Trials of pulsed RF,[12] or other forms of 'neuromodulatory' procedures that do not aim to ablate or denature these targets, were excluded from the review. Control groups where there was no active treatment were considered for inclusion but trials with potentially effective comparators e.g. corticosteroid injections, were excluded. Only trials of patients with back pain without a definite or surgically remediable cause (chronic non-specific back pain) were included in the review. The outcome for the review was patient-reported pain score e.g. Visual Analogue Scale or Numeric Rating Scale.

Data collection and quality assessment

Trial characteristics were recorded from included studies. Study results were extracted independently by two authors (MC, PT), with any disagreements resolved by consensus. The overall strength of evidence was assessed using the GRADE approach.[13] Risk of bias was assed using the Cochrane Risk of Bias tool.[14] Any outcome where more than half of trials were considered to have a high or unclear risk of bias was downgraded. Outcomes were also downgraded where heterogeneity

in the meta-analysis was greater than 50%. Optimal sample size was taken to be 85 participants per study arm (as calculated in the Juch 2017 trial[15]) and studies with less than 170 participants, and/or where the 95% confidence intervals included the line of no effect, were downgraded for imprecision. Publication bias was assessed using funnel plots and outcomes downgraded where there was a high certainty of publication bias.

Data analysis

Meta-analyses were conducted in RevMan[16] with random effects models since the included studies investigated effectiveness in different population groups with varying intervention and control group treatments. Pain score at 1-3 months was taken as the primary outcome (longest time point used for studies reporting multiple time points), allowing outcome from a larger number of studies to be combined. Pain score data were reported on a 0-10 point scale (Visual Analogue Scale or Numeric Rating Scale) in all studies and the mean difference was therefore calculated without standardisation as done in the previous Cochrane review.[11] Studies with different spinal targets e.g. facet joints, sacroiliac joints or inter-vertebrae disc, were separated in the analysis. For facet joint pain, a plot of treatment versus no treatment/sham was produced by fixed effects meta-analysis of scores for each arm. A sensitivity analysis was conducted to check the validity of findings by removing studies considered to have a particularly high risk of bias. Subgroup analysis to explore study heterogeneity was not conducted because of the small number of studies and high likelihood of reaching spurious conclusions.

Results

Study characteristics

The search identified 922 citations of which 229 were duplicates. Studies were excluded as shown in figure 1. Of the 693 citations reviewed 8 new trials were identified as well as 11 from a previous Cochrane review.[11] Exclusions were made as shown in figure 1. Nineteen trials were included in the review and their characteristics are shown in appendix 2. Trials investigated the effectiveness of RD of the facet joint (supplied by medial branch of the dorsal spinal ramus),[15,17–24] the sacroiliac joints,[15,25–28] the intervertebral discs[29–33], or vertebrae end-plate (supplied by the basivertebral nerve).[34] The majority of trials used a sham control group but one large trial compared RD with no treatment (both groups received an exercise program) and one small trial compared RD plus conventional medical with conventional medical management alone (including self-care, medications and physical and cognitive therapy).

Study quality

Sham-controlled trials generally appear to have conducted adequate randomisation but allocation concealment was often unclear. Processes were in place to blind patients and providers and outcome assessors. In some trials maintenance of blinding was unclear as it was evident that patients undergoing sham procedures were offered RD in case of sham treatment failure. In these cases, blinding would have been broken. Most trials did not report dropouts and there was unclear risk of attrition bias. The outcome for this review was pain score and this was reported in all trials and reporting bias was not considered to be an issue in the review. Four trials were identified as having high risk of bias and were removed in the sensitivity analysis.[17,19,24,25]

Overall quality of the evidence

The majority of outcomes were graded down for imprecision and all outcomes were downgraded for potential risk of bias. Consequently almost all outcomes were graded as low quality. However, in some cases, high heterogeneity was also present and these outcomes were graded as very low quality. Publication bias was suggested by asymmetry in a number of the funnel plots. However, there was uncertainty due to the small numbers of studies and outcomes were not graded down for publication bias.

Study findings

Results of the meta-analyses are shown in table 1.

RD of the facet joints

Meta-analysis of pain scores at 1-3 months post procedure (longest time point used for studies with multiple time points) (marked on a 0-10 scale) was performed to allow combination of data from the maximum number of studies, and results are shown in figure 2 and table 1. The effect size was similar when all trials were included (7 trials, MD -0.56, CI -1.13, 0.01) or where just the sham-controlled trials were included (6 trials, MD -0.63, CI -1.39, 0.12) but the effect was not significant for either. We also considered outcomes at 6 and 12 months, where data were available to explore longer term outcomes, but did not find any significant effect (table 1).

RD of the sacroiliac joints

Figure 3 shows the meta-analysis of trials for pain score at 1-3 months (longest time point used for studies with multiple time points). There was a significant effect of RD for the analysis including all trials (5 trials, MD -1.53, CI -2.62, -0.45) or just sham-controlled trials (4 trials, MD -1.89, CI -3.45, -0.34). Only one trial[15] assessed

outcome at later time points and this showed no significant difference compared to a no treatment control (table 1).

RD of the intervertebral discs

Pain score at 1-3 months post-treatment was significantly lower for RD compared with control in all trials (4 trials, MD -0.98, CI -1.84, -0.12) but not for sham-controlled trials alone (3 trials, MD -0.63, CI -1.36, 0.10) (figure 4). Pain score was significantly lower for RD when all trials and sham-controlled trials were considered at 6 months but, for one trial assessing outcome at one year, it was not (table 1).

RD of the vertebrae body and end plate

One recent trial of RD for vertebrae body and end plate (basivertebral nerve ablation)[34] did not show significant benefits of RD compared with sham at 3, 6 or 12 months (table 1).

Sensitivity analysis

Four studies were removed in the sensitivity analysis due to a high risk of methodological bias[17,19,24,25] and the two non-sham controlled trials were also removed.[15,32] After the removal of these trials, outcome at 1-3 months for facet joint sham trials was still not significant (4 trials, MD -0.57, CI -1.60, 0.46) and 1-3 month outcome for sacroiliac sham trials became non-significant (3 trials, MD -1.21, CI -2.59, 0.16). The facet joint sham trial outcome at 6 months also became non-significant (1 trial, MD 0.18, CI -2.80, 3.16).

Discussion

Main findings

This systematic review presents evidence suggesting that RD of the lumbosacral spine may have a small positive but short-lived effect in patients with chronic back pain, depending on the precise part of the anatomy that is being targeted by the procedure. The quality of evidence for the majority of findings is low or very low quality and there is still a degree of uncertainty around this assertion, particularly around the duration of effect. The size of benefit appears to be small (<1 point on a 0-10 pain scale) and there is limited data for outcomes beyond 6 months. These assertions apply to RD for sacroiliac joints, whereas evidence for benefit to other targets is more limited. RD for facet joints did not show a significant benefit on 1-3 month outcome. There is a suggestion that there may be a benefit of RD for intervertebral discs but there is some inconsistency, with insignificant effect even for short-term outcomes.

What is also clear from the review is that both treatment and sham/no treatment groups improved during the trials. In the sham controlled studies, this may, in part, be due to placebo effect. However, the large trial by Juch et al[15] used a “no additional treatment” control (both groups received an exercise program) but all study arms improved over time. This may be because a high proportion of control study participants actually received RD (~30%) due to cross-over during the trial. However, this may also be explained by self-selection of participants who volunteer for research trials,[35] and hence are likely to make more of an active effort to manage their back pain. Such participants may be more likely to engage with, and be diligent in, exercise programs and seek medical assistance where needed.

In the trial by Juch et al., control group improvements may also be explained by the conservative management that they received. The exercise program employed was multi-disciplinary and comprised individual sessions over 8-12 hours focused on

quality of movement and behaviour, with access to psychological care. There is evidence suggesting that patients with chronic back pain can benefit from pain management programs that are of sufficient quality and duration.[36] Where patients have not received an adequate trial of conservative therapy, they may benefit from further exercise programs and other conservative management. It remains unclear whether patients who are either unable or unwilling to engage with conservative approaches to pain management would benefit from RD based interventions as a first-line or isolated modality of treatment. Hence, there should be some reservation when considering the use of RD treatment as a first-line, or isolated modality of pain management.

Regression to the mean may also have played a role in control group improvements since patients in the trial were recruited with elevated pain, responsive to an anaesthetic block. Back pain has been shown to have a varied aetiology, with some patients experiencing fluctuating levels of pain over time, whilst other experience constant high levels of pain.[37,38] For the majority of trials that reported it, duration of back pain in participants prior to enrolment was 2-5 years and a proportion of these were likely to have had high levels of constant pain. Some, however, may have been experiencing fluctuating or recurrent pain within this period since the actual inclusion criteria for most trials was pain for >3 or 6 months based on patient recall. If they were recruited at a point where their pain had flared acutely, there would be a natural tendency for that painful episode to resolve over time.

Strengths and limitations

A major strength of this review is that it collates a larger body of evidence than previous systematic reviews, with the addition of a number of recent trials and thorough assessment of the quality of the evidence. The review is able to tentatively

answer the question about the effectiveness of RD for back pain; an assertion that, to date, has proved to be very difficult due a paucity of evidence in this field.

This review utilises evidence from a previous Cochrane review[11] but the inclusion criteria for our review had a narrower scope (included only sham- or conservative management-controlled trials of conventional neuro-ablative RD). Since the previous review appears to be of high quality, and we updated it with a thorough search of the literature to date, there is assurance that all relevant trials were included.

A limitation of this review is that it was difficult to truly assess risk of bias in trials included in the review. Trial integrity rested heavily on the blinding of participants and the outcome was likely to be highly subject to patients' preconceptions of the different interventions given. Most trials did not report information that providers gave patients about the different possible treatment arms e.g. did providers suggest to patients that RD was the effective treatment and that sham or no treatment would be ineffective? Where blinding was broken, these viewpoints may have influenced patients' response. In some of the sham-controlled studies this was clearly evident. For example, in some studies, before randomisation, patients were told that, if randomised to sham, they could receive RD if they gained no benefit. Where blinding was broken, these opinions were likely to influence patients' perception of their pain. In other studies information from providers was not reported and it is difficult to assess whether this type of bias occurred.

The review may also be limited in its ability to ascertain the technical quality of individual research trials. Even when examining the reported trial methodology, it is difficult to conclusively identify trials that employed procedures that may be more or less successful in denervating the specific lumbosacral anatomy. Some aspects of RD procedures in earlier trials are considered outdated[39,40] but the advantages of

more recent procedures for RD remain unproven, and there is no clear evidence of their superiority. Sensitivity analysis based on technical quality was therefore considered unhelpful and not performed.

The review is also limited by the lack of long term data from trials. Most studies do not attempt to blind patients for more than 3 months and the longer follow up outcomes are considered to be at higher risk of bias. It is still therefore unclear whether RD of lumbosacral anatomy has long-term benefits for back pain.

Finally, the review is limited in its ability to identify any aspects of patient or intervention characteristics that may make RD treatment more likely to be beneficial. There is to date no reliable predictor of benefit on back pain for RD procedures based on clinical or imaging findings or diagnostic injections.[41] The relative advantages of different RD technologies used in included trials (e.g. 'cooled'[25,26,32] and 'bipolar'[30,32] RD) remains to be established. Due to the small number of studies at each time point, sub-group analysis was not considered appropriate. However, the publication of more sham-controlled trials and trials comparing different RD technologies may make this type of investigation possible. Technical advances and advances in knowledge and experience may allow for better selection of anatomical targets and patients for RD and hence improve clinical outcomes: it is important that these developments are formally assessed and published.

In conclusion, within the limitations in this review and the published literature, there appears to be at least short-term benefit from RD of selected lumbosacral anatomical targets for chronic back pain. However, the mean size of effect appears to be small and, overall, clinical significance may be marginal. Hence, chronic back pain remains a highly challenging condition to treat.

Acknowledgements Thanks to Julie Aikens and Kerry Herbert at Hinchingbrooke Healthcare Library for their assistance in designing and running the search strategies for the review.

Contributors: MC contributed to the planning of this work, selected articles for inclusion, extracted data, quality assessed studies and drafted and re-drafted the manuscript. RL contributed to the planning of this work, reviewed the manuscript and approved the final version. PT extracted data from the trials, reviewed the manuscript and approved the final version. MA contributed to the planning of this work, reviewed the manuscript and approved the final version. ML contributed to the planning of this work, reviewed the manuscript and approved the final version.

Funding This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors. RL is supported by the Medical Research Council (MC_UU_12015/2). MCL is supported by AABGI Foundation project grant (RCZB/071).

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information.

Patient and Public Involvement This research was done without patient involvement.

References

1 Hartvigsen J, Hancock MJ, Kongsted A, *et al.* What low back pain is and why we need to pay attention. *Lancet* 2018;**391**:2356–67. doi:10.1016/S0140-6736(18)30480-X

2 Hoy D, Bain C, Williams G, *et al.* A systematic review of the global prevalence of low back pain. *Arthritis Rheum* 2012;**64**:2028–37. doi:10.1002/art.34347

3 Maniadakis N, Gray A. The economic burden of back pain in the UK. *Pain* 2000;**84**:95–103. doi:10.1016/S0304-3959(99)00187-6

4 Dagenais S, Caro J, Haldeman S. A systematic review of low back pain cost of illness studies in the United States and internationally. *Spine J* 2008;**8**:8–20. doi:10.1016/j.spinee.2007.10.005

5 National Institute of Health and Care Excellence. Low back pain and sciatica in over 16s: assessment and management. 2016.

6 Chou R, Baisden J, Carragee EJ, *et al.* Surgery for Low Back Pain: A Review of the Evidence for an American Pain Society Clinical Practice Guideline. *Spine (Phila Pa 1976)* 2009;**34**:1094–109.

7 Chou R, Loeser JD, Owens DK, *et al.* Interventional Therapies, Surgery, and Interdisciplinary Rehabilitation for Low Back Pain: An Evidence-Based Clinical

Practice Guideline From the American Pain Society. *Spine (Phila Pa 1976)* 2009;**34**:1066–77. doi:10.1097/BRS.0b013e3181a1390d

8 Kline M. Radiofrequency techniques in clinical practice. In: *Waldman SD, Winnie AP, eds. Interventional Pain Management. Philadelphia, PA: Saunders*. 1996.

9 Wray JK, Dixon B, Przkora R. *Radiofrequency Ablation*. 2019.

10 Manchikanti L, Hirsch J, Pampati V, *et al.* Utilization of Facet Joint and Sacroiliac Joint Interventions in Medicare Population from 2000 to 2014: Explosive Growth Continues! *Curr Pain Headache Rep* 2016;**20**:58.

11 Maas E, Ostelo R, Niemisto L, *et al.* Radiofrequency denervation for chronic low back pain. *Cochrane Database Syst Rev* 2015;:Art. No.: CD008572. doi:10.1001/jama.2017.16386

12 Brandon R, Cohen D, Edward T, *et al.* Pulsed Radiofrequency Neuromodulation in Interventional Pain Management—A Growing Technology. *J Radiol Nurs* 2018;**37**:181–7.

13 Schünemann H, Brożek J, Guyatt G, *et al.*, editors. *GRADE Handbook: Handbook for grading the quality of evidence and the strength of recommendations using the GRADE approach*.

14 Higgins JP, Savovic J, Page MJ, *et al.*, editors. *Revised Cochrane risk-of-bias tool for randomized trials (RoB 2)*. 2019.

15 Juch JNS, Maas ET, Ostelo RWJG, *et al.* Effect of Radiofrequency Denervation on Pain Intensity Among Patients With Chronic Low Back Pain. *JAMA* 2017;**318**:68–81.

16 Review Manager (RevMan) [Computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

17 Gallagher J, Petriccione di Vadi P, Wedley J, *et al.* Radiofrequency facet joint denervation in the treatment of low back pain: a prospective controlled double-blind study to assess its efficacy. *Pain Clin* 1994;**7**:193–8.

18 Leclaire R, Fortin L, Lambert R, *et al.* Radiofrequency Facet Joint Denervation in the Treatment of Low Back Pain: A Placebo-Controlled Clinical Trial to Assess Efficacy. *Spine (Phila Pa 1976)* 2001;**26**:1411–6. doi:10.1097/00007632-200107010-00003

19 Moussa WMM, Khedr W. Percutaneous radiofrequency facet capsule denervation as an alternative target in lumbar facet syndrome. *Clin Neurol Neurosurg* 2016;**150**:96–104. doi:10.1016/j.clineuro.2016.09.004

20 van Kleef M, Barendse GAM, Kessels A, *et al.* Randomised trial of radiofrequency lumbar facet denervation for chronic low back pain. *Spine (Phila Pa 1976)* 1999;**24**:1937–42.

21 Van Tilburg CWJ, Schuurmans FA, Stronks DL, *et al.* Randomized sham-controlled double-blind multicenter clinical trial to ascertain the effect of percutaneous radiofrequency treatment for sacroiliac joint pain: Three-month results. *Clin J Pain* 2016;**32**:921–6. doi:10.1097/AJP.0000000000000351

22 Van Wijk RMAW, Geurts JWM, Wynne HJ, *et al.* Radiofrequency denervation of lumbar facet joints in the treatment of chronic low back pain: A randomized, double-blind, sham lesion-controlled trial. *Clin J Pain* 2005;**21**:335–44.

23 Nath S, Nath CA, Pettersson K. Percutaneous Lumbar Zygapophysial (Facet) Joint Neurotomy Using Radiofrequency Current, in the Management of

Chronic Low Back Pain. *Spine (Phila Pa 1976)* 2008;**33**:1291–1297. doi:10.1109/ICCGI.2010.42

24 Tekin I, Mirzai H, Ok G, *et al.* A comparison of conventional and pulsed radiofrequency denervation in the treatment of chronic facet joint pain. *Clin J Pain* 2007;**23**:524–9. doi:10.1097/AJP.0b013e318074c99c

25 Cohen SP, Hurley RW, Buckenmaier CC, *et al.* Randomized Placebo-Controlled Study Evaluating Lateral Branch Radiofrequency Denervation for Sacroiliac Joint Pain. *Anesthesiology* 2008;**109**:279–88. doi:10.1038/mp.2011.182.doi

26 Patel N, Gross A, Brown L, *et al.* A Randomized, Placebo-Controlled Study to Assess the Efficacy of Lateral Branch Neurotomy for Chronic Sacroiliac Joint Pain. *Pain Med* 2012;**13**:383–98. doi:10.1111/j.1526-4637.2012.01328.x

27 Van Tilburg C, Stronks D, Groeneweg J, *et al.* Randomised sham-controlled double-blind multicentre clinical trial to ascertain the effect of percutaneous radiofrequency treatment for lumbar facet joint pain. *Spine (Phila Pa 1976)* 2016;**98**-**B**:1526–33.

28 Mehta V, Poply K, Husband M, *et al.* The Effects of Radiofrequency Neurotomy Using a Strip-Lesioning Device on Patients with Sacroiliac Joint Pain: Results from a Single-Center, Randomized, Sham-Controlled Trial. *Pain Physician* 2018;**21**:607–18.

29 Barendse GAM, van den Berg SGM, Kessels AHF, *et al.* Randomized Controlled Trial of Percutaneous Intradiscal Radiofrequency Thermocoagulation for Chronic Discogenic Back Pain. Lack of Effect From a 90-Second 70 C Lesion. *Spine (Phila Pa 1976)* 2001;**26**:287–92.

doi:10.1097/00007632-200102010-00014

30 Kapural L, Vrooman B, Sarwar S, *et al.* A Randomized, Placebo-Controlled Trial of Transdiscal Radiofrequency, Biacuplasty for Treatment of Discogenic Lower Back Pain. *Pain Med* 2013;**14**:362–73. doi:10.1111/pme.12023

31 van Tilburg CWJ, Stronks DL, Groeneweg JG, *et al.* Randomized sham-controlled, double-blind, multicenter clinical trial on the effect of percutaneous radiofrequency at the ramus communicans for lumbar disc pain. *Eur J Pain* 2017;**21**:520–9. doi:10.1002/ejp.945

32 Desai MJ, Kapural L, Petersohn JD, *et al.* A prospective, randomized, multicenter, open-label clinical trial comparing intradiscal biacuplasty to conventional medical management for discogenic lumbar back pain. *Spine (Phila Pa 1976)* 2016;**41**:1065–74. doi:10.1097/BRS.0000000000001412

33 Kvarstein G, Måwe L, Indahl A, *et al.* A randomized double-blind controlled trial of intra-annular radiofrequency thermal disc therapy - A 12-month follow-up. *Pain* 2009;**145**:279–86. doi:10.1016/j.pain.2009.05.001

34 Fischgrund JS, Rhyne A, Franke J, *et al.* Intraosseous basivertebral nerve ablation for the treatment of chronic low back pain: a prospective randomized double-blind sham-controlled multi-center study. *Eur Spine J* 2018;**27**:1146–56. doi:10.1007/s00586-018-5496-1

35 The Cochrane Collaboration. Introduction to sources of bias in clinical trials. In: *Cochrane Handbook for Systematic Reviews of Interventions*. 2011.

36 Morley S, Williams A, Hussain S. Estimating the clinical effectiveness of cognitive behavioural therapy in the clinic: Evaluation of a CBT informed pain management programme. *Pain* 2008;**137**:670–80.

37 Dunn K, Croft P. Epidemiology and natural history of low back pain. *Eura Medicophys* 2004;**40**:9–13.

38 Dunn K, Jordan K, Croft P. Characterizing the course of low back pain: a latent class analysis. *Am J Epidemiol* 2006;**63**:754–61.

39 Dreyfuss P, Baker R. Comment on: Radiofrequency facet joint denervation in the treatment of low back pain: a placebo-controlled clinical trial to assess efficacy. *Spine (Phila Pa 1976)* 2002;**27**:556–7.

40 Kapural L, Provenzano D, Narouze S. RE: Juch JNS, et al. Effect of Radiofrequency Denervation on Pain Intensity Among Patients With Chronic Low Back Pain: The Mint Randomized Clinical Trials. JAMA 2017;318(1):68–81. *Neuromodulation* 2017;**20**:844. doi:10.1111/ner.12729

41 Cohen SP, Julie JH, Brummett C. Facet joint pain-advances in patient selection and treatment. *Nat Rev Rheumatol* 2013;**9**:101–16. doi:10.1038/nrrheum.2012.198

Table 1 Results of the meta-analyses of randomised controlled trials

	All trials					Sham controlled trials				
	k	N	MD (95% CI)	I^2	GRADE*	k	N	MD (95% CI)	I^2	GRADE*
RD of the facet joints										
1-3 months	7	599	-0.56 (-1.13, 0.01)	59%	Low	6	348	-0.63 (-1.39, 0.12)	66%	Low
6 months	4	361	-0.66 (-1.37, 0.05)	42%	Low	3	110	-1.05 (-2.21, 0.10)	32%	Low
1 year	2	291	-0.72 (-2.24, 0.80)	89%	Very low	1	40	-1.50 (-2.21, -0.79)	NA	Very low
RD of the sacroiliac joints										
1-3 months	5	384	-1.53 (-2.62, -0.45)	83%	Low	4	156	-1.89 (-3.45, -0.34)	87%	Very low
6 months	1	228	-0.28 (-1.00, 0.44)	NA	Low					
12 months	1	228	-0.19 (-0.92, 0.54)	NA	Low					
RD of the intervertebrae discs										
1-3 months	4	200	-0.98 (-1.84, -0.12)	40%	Low	3	144	-0.63 (-1.36, 0.10)	0%	Low
6 months	3	127	-1.74 (-2.58, -0.91)	0%	Low	2	75	-1.63 (-2.58, -0.68)	0%	Low
12 months	1	20	-1.70 (-3.63, 0.23)	NA	Very low	1	20	-1.70 (-3.63, 0.23)	NA	Very low
RD of the vertebrae body and endplate										
3 months	1	205	-0.34 (-1.09, 0.41)	NA	Moderate	1	205	-0.34 (-1.09, 0.41)	NA	Moderate
6 months	1	205	-0.67 (-1.44, 0.10)	NA	Moderate	1	205	-0.67 (-1.44, 0.10)	NA	Moderate
12 months	1	205	-0.50 (-1.29, 0.29)	NA	Moderate	1	205	-0.50 (-1.29, 0.29)	NA	Moderate

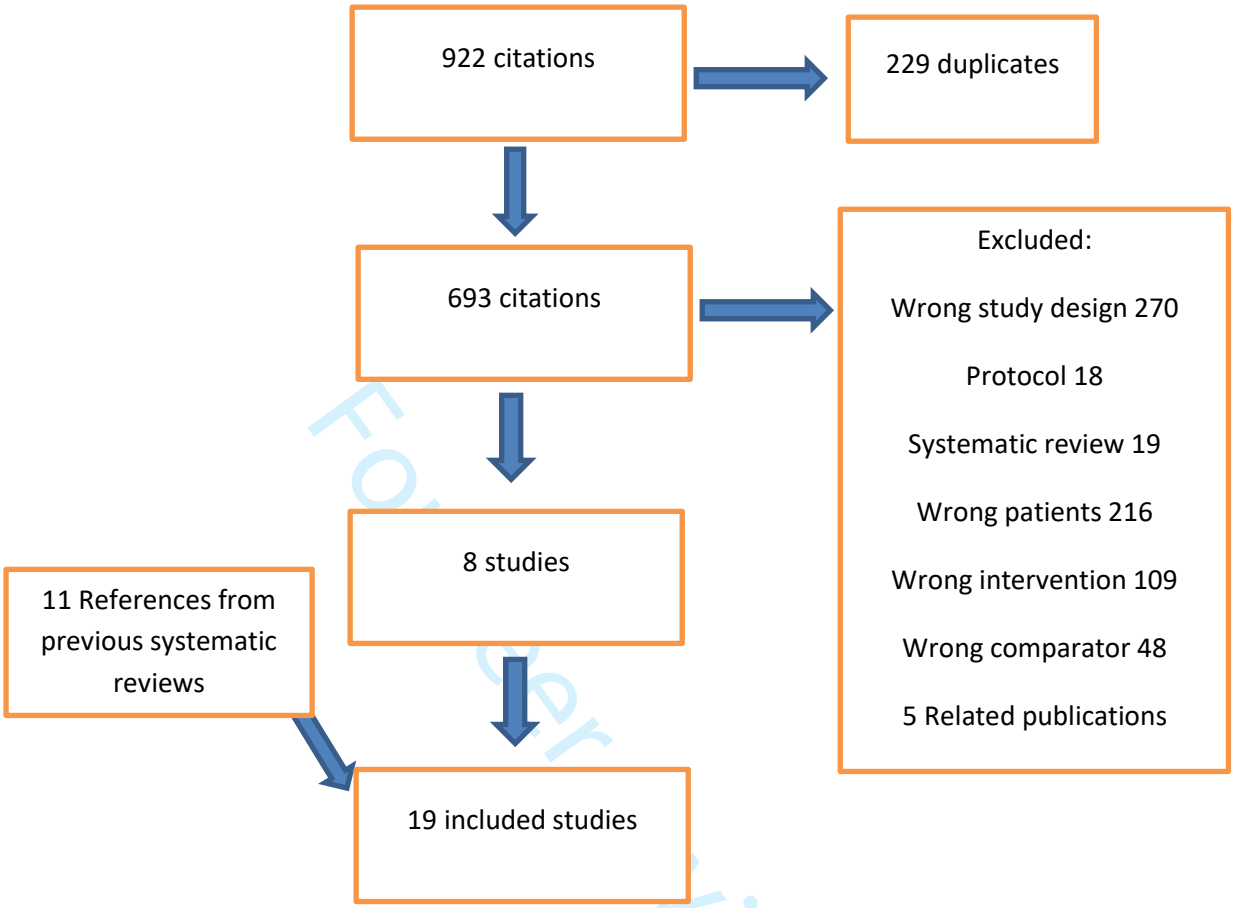
k, number of trials; N, number of participants; MD, Mean difference.
*GRADE assessment of the quality of the evidence

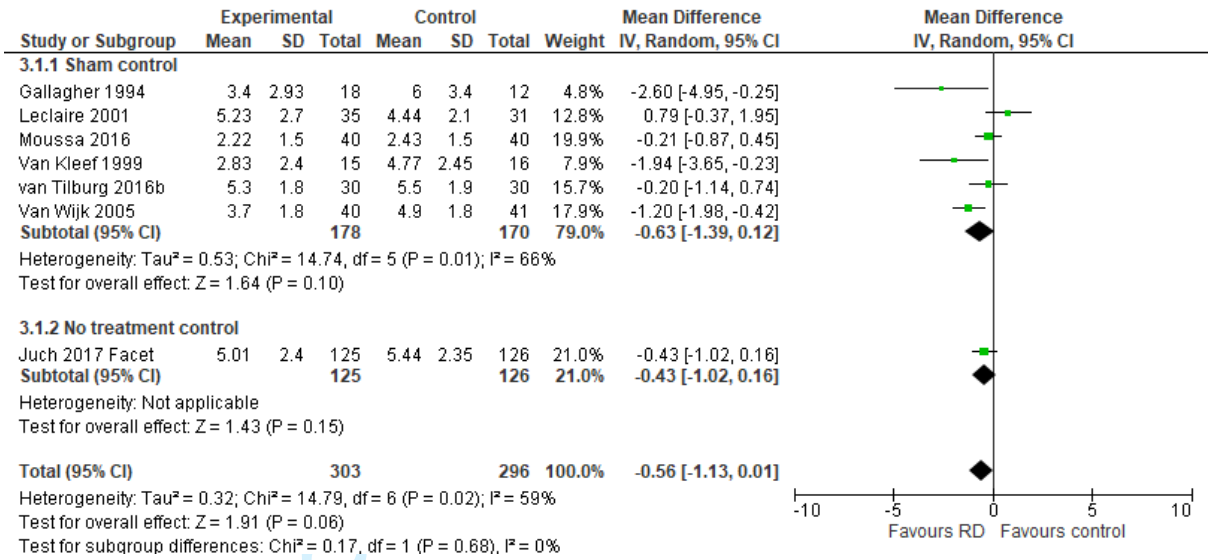
Figure 1 PRISMA flow diagram

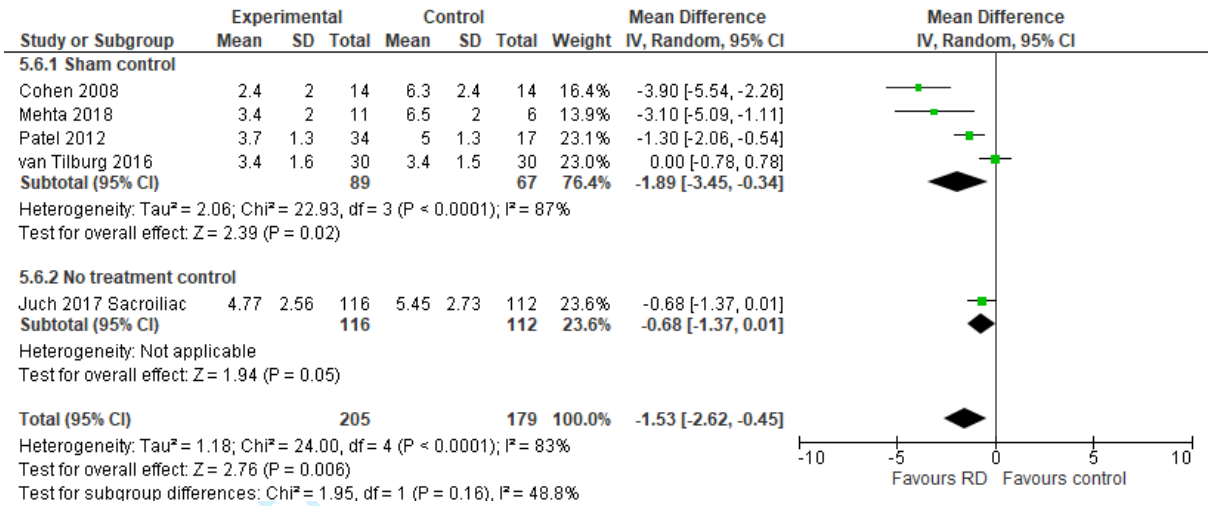
Figure 2 Post treatment pain score for radiofrequency denervation of the facet joints versus control at 1-3 month follow-up (longest time point used for studies with multiple time points)

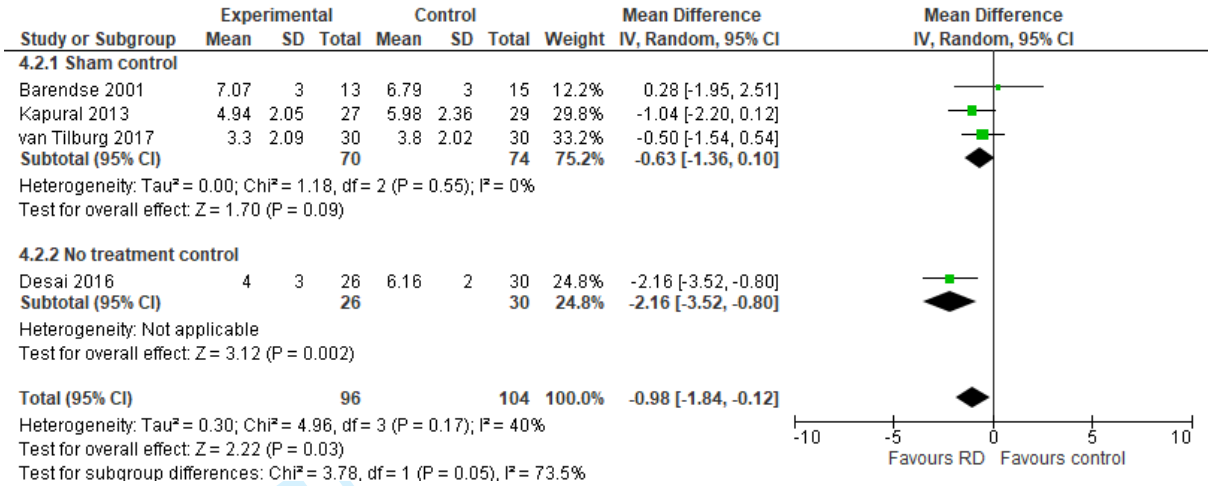
Figure 3 Post treatment pain score for radiofrequency denervation of the sacroiliac joints versus control at 1-3 month follow-up (longest time point used for studies with multiple time points)

Figure 4 Post treatment pain score for radiofrequency denervation of the intervertebral discs versus control at 1-3 month follow-up (longest time point used for studies with multiple time points)









Appendix 1 Search strategies

Medline and Embase

#	Database	Search term
1	Medline	(randomized controlled trial).pt
2	Medline	(controlled clinical trial).pt
3	Medline	(randomi*ed).ab
4	Medline	(placebo).ti,ab
5	Medline	(drug therapy).fs
6	Medline	(randomly).ti,ab
7	Medline	(trial).ti,ab
8	Medline	(groups).ti,ab
9	Medline	(1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8)
10	Medline	(animals NOT (humans AND animals)).su
11	Medline	9 not 10
12	Medline	(dorsalgia).ti,ab
13	Medline	exp "BACK PAIN"/
14	Medline	(backache).ti,ab
15	Medline	(lumbar ADJ pain).ti,ab
16	Medline	(coccyx).ti,ab
17	Medline	(coccydynia).ti,ab
18	Medline	(sciatica).ti,ab
19	Medline	"SCIATIC NEUROPATHY"/

20	Medline	(spondylosis).ti,ab
21	Medline	(lumbago).ti,ab
22	Medline	(12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21)
23	Medline	exp SPINE/
24	Medline	(discitis).ti,ab
25	Medline	exp "SPINAL DISEASES"/
26	Medline	(disc ADJ degeneration).ti,ab
27	Medline	(disc ADJ prolapse).ti,ab
28	Medline	(disc ADJ herniation).ti,ab
29	Medline	(spinal fusion).su
30	Medline	(facet ADJ joints).ti,ab
31	Medline	(intervertebral disc).su
32	Medline	(postlaminectomy).ti,ab
33	Medline	(arachnoiditis).ti,ab
34	Medline	(failed ADJ back).ti,ab
35	Medline	(23 OR 24 OR 25 OR 26 OR 27 OR 28 OR 29 OR 30 OR 31 OR 32 OR 33 OR 34)
36	Medline	(22 OR 35)
37	Medline	exp "RADIO WAVES"/
38	Medline	exp "PULSED RADIOFREQUENCY TREATMENT"/
39	Medline	(radiofrequency).af
40	Medline	(radio frequency).af

41	Medline	exp ELECTROCOAGULATION/
42	Medline	(electrocoag*).af
43	Medline	(thermocoag*).af
44	Medline	neurotom* OR (neuroly*).af
45	Medline	(37 OR 38 OR 39 OR 40 OR 41 OR 42 OR 43 OR 44)
46	Medline	(11 AND 36 AND 45)
47	EMBASE	"CLINICAL TRIAL"/
48	EMBASE	"CONTROLLED CLINICAL TRIAL"/
49	EMBASE	"CONTROLLED STUDY"/
50	EMBASE	"RANDOMIZED CONTROLLED TRIAL"/
51	EMBASE	"DOUBLE BLIND PROCEDURE"/
52	EMBASE	"SINGLE BLIND PROCEDURE"/
53	EMBASE	"CROSSOVER PROCEDURE"/
54	EMBASE	PLACEBO/
55	EMBASE	(allocat*).ti,ab
56	EMBASE	(assign*).ti,ab
57	EMBASE	(blind*).ti,ab
58	EMBASE	(clinic* ADJ25 (study OR trial)).ti,ab
59	EMBASE	(crossover OR cross-over).ti,ab
60	EMBASE	(factorial*).ti,ab
61	EMBASE	(followup OR follow-up).ti,ab
62	EMBASE	(prospectiv*).ti,ab

63	EMBASE	(placebo*).ti,ab
64	EMBASE	(random*).ti,ab
65	EMBASE	((singl* OR doubl* OR trebl* OR trip*) ADJ25 (blind* OR mask*)).ti,ab
66	EMBASE	(volunteer*).ti,ab
67	EMBASE	(47 OR 48 OR 49 OR 50 OR 51 OR 52 OR 53 OR 54 OR 55 OR 56 OR 57 OR 58 OR 59 OR 60 OR 61 OR 62 OR 63 OR 64 OR 65 OR 66)
68	EMBASE	exp animals/ or exp invertebrate/ or animal experiment/ or animal model/ or animal tissue/ or animal cell/ or nonhuman/
69	EMBASE	exp ANIMALS/
70	EMBASE	exp INVERTEBRATE/
71	EMBASE	ANIMAL EXPERIMENT/
72	EMBASE	ANIMAL MODEL/
73	EMBASE	ANIMAL TISSUE/
74	EMBASE	ANIMAL CELL/
75	EMBASE	NONHUMAN/
76	EMBASE	71 or 72 or 73 or 74 or 75
77	EMBASE	exp ANIMALS/
78	EMBASE	exp INVERTEBRATE/
79	EMBASE	(76 OR 77 OR 78)
80	EMBASE	77 or 78
81	EMBASE	HUMAN/ OR NORMAL HUMAN/ OR HUMAN CELL/
82	EMBASE	(76 AND 77 AND 78 AND 81)

83	EMBASE	(dorsalgia).ti,ab
84	EMBASE	(back pain).ti,ab
85	EMBASE	exp BACKACHE/
86	EMBASE	(lumbar ADJ pain).ti,ab
87	EMBASE	(coccyx).ti,ab
88	EMBASE	(coccydynia).ti,ab
89	EMBASE	(sciatica).ti,ab
90	EMBASE	ISCHIALGIA/
91	EMBASE	(spondylosis).ti,ab
92	EMBASE	(lumbago).ti,ab
93	EMBASE	(back disorder*).ti,ab
94	EMBASE	(83 OR 84 OR 85 OR 86 OR 87 OR 88 OR 89 OR 90 OR 91 OR 92 OR 93)
95	EMBASE	exp SPINE/
96	EMBASE	(discitis OR diskitis).ti,ab
97	EMBASE	exp "SPINE DISEASE"/
98	EMBASE	(disc ADJ degeneration).ti,ab
99	EMBASE	(disc ADJ prolapse).ti,ab
100	EMBASE	(disc ADJ herniation).ti,ab
101	EMBASE	(spinal fusion).ti,ab
102	EMBASE	(facet ADJ joints).ti,ab
103	EMBASE	(intervertebral disk OR Intervertebral disc).ti,ab
104	EMBASE	(postlaminectomy).ti,ab

105	EMBASE	(arachnoiditis).ti,ab
106	EMBASE	(failed ADJ back).ti,ab
107	EMBASE	(95 OR 96 OR 97 OR 98 OR 99 OR 100 OR 101 OR 102 OR 103 OR 104 OR 105 OR 106)
108	EMBASE	94 or 107
109	EMBASE	exp PULSED RADIOFREQUENCY TREATMENT/
110	EMBASE	exp RADIOFREQUENCY/
111	EMBASE	exp RADIOFREQUENCY RADIATION/
112	EMBASE	(radiofrequency OR radio-frequency).ti,ab
113	EMBASE	exp THERMOCOAGULATION/ OR thermocoag*
114	EMBASE	exp ELECTROCOAGULATION/ OR electrocoag*
115	EMBASE	(neurotom* OR neuroly*).ti,ab
116	EMBASE	(109 OR 110 OR 111 OR 112 OR 113 OR 114 OR 115)
117	EMBASE	(108 AND 116)
118	Medline	46 [DT 2014-2019]

Medline in process

#	Database	Search term
1	Medline	("randomi*ed controlled trial").ti,ab
2	Medline	("controlled clinical trial").ti,ab
3	Medline	("randomi*ed").ab
4	Medline	(placebo).ti,ab
5	Medline	("drug therapy").fs

6	Medline	(randomly).ti,ab
7	Medline	(trial).ti,ab
8	Medline	(groups).ti,ab
9	Medline	(1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8)
10	Medline	(dorsalgia).ti,ab
11	Medline	("back pain").ti,ab
12	Medline	(backache).ti,ab
13	Medline	("lumber pain").ti,ab
14	Medline	(coccyx).ti,ab
15	Medline	(coccydynia).ti,ab
16	Medline	(sciatica*).ti,ab
17	Medline	(spondylosis).ti,ab
18	Medline	(lumbago).ti,ab
19	Medline	(10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18)
20	Medline	(spine OR sacrum OR "lumber vertebrae" OR "intervertebral disc*").ti,ab
21	Medline	(discitis).ti,ab
22	Medline	("disc degeneration").ti,ab
23	Medline	("disc prolapse").ti,ab
24	Medline	("disc herniation").ti,ab
25	Medline	("spinal fusion").ti,ab
26	Medline	("facet joints").ti,ab

27	Medline	(postlaminectomy).ti,ab
28	Medline	(arachnoiditis).ti,ab
29	Medline	("failed back").ti,ab
30	Medline	(20 OR 21 OR 22 OR 23 OR 24 OR 25 OR 26 OR 27 OR 28 OR 29)
31	Medline	(19 OR 30)
32	Medline	(radiowave* OR "radio wave*").ti,ab
33	Medline	(radiofrequency OR "radio frequency").ti,ab
34	Medline	(electrocoag*).ti,ab
35	Medline	(thermocoag*).ti,ab
36	Medline	(neurotom* OR neuroloy*).ti,ab
37	Medline	(32 OR 33 OR 34 OR 35 OR 36)
38	Medline	(9 AND 31 AND 37)
39	Medline	38 [Document status In Data Review OR In Process OR PubMed not MEDLINE OR Publisher]

Cinahl

#	Database	Search term
1	CINAHL	exp "CLINICAL TRIALS"/
2	CINAHL	("randomi*ed controlled trial*").ti,ab
3	CINAHL	(clinical ADJ3 trial).ti,ab
4	CINAHL	(double-blind).ti,ab
5	CINAHL	(single-blind).ti,ab
6	CINAHL	(triple-blind).ti,ab

7	CINAHL	(1 OR 2 OR 3 OR 4 OR 5 OR 6)
8	CINAHL	"PLACEBO EFFECT"/
9	CINAHL	PLACEBOS/
10	CINAHL	(placebo*).ti,ab
11	CINAHL	(random*).ti,ab
12	CINAHL	(8 OR 9 OR 10 OR 11)
13	CINAHL	"RANDOM SAMPLE"/
14	CINAHL	exp "STUDY DESIGN"/
15	CINAHL	(latin square).ti,ab
16	CINAHL	exp "COMPARATIVE STUDIES"/
17	CINAHL	exp "EVALUATION RESEARCH"/
18	CINAHL	exp "PROSPECTIVE STUDIES"/
19	CINAHL	(13 OR 14 OR 15 OR 16 OR 17 OR 18)
20	CINAHL	(follow-up stud*).ti,ab
21	CINAHL	(followup stud*).ti,ab
22	CINAHL	(control*).ti,ab
23	CINAHL	(prospectiv*).ti,ab
24	CINAHL	(volunteer*).ti,ab
25	CINAHL	(20 OR 21 OR 22 OR 23 OR 24)
26	CINAHL	(7 OR 12 OR 19 OR 25)
27	CINAHL	ANIMALS/
28	CINAHL	26 not 27

29	CINAHL	("dorsalgia").ti,ab
30	CINAHL	exp "BACK PAIN"/
31	CINAHL	"LOW BACK PAIN"/
32	CINAHL	("backache").ti,ab
33	CINAHL	(lumbar ADJ1 pain).ti,ab
34	CINAHL	(lumbar ADJ5 pain).ti,ab
35	CINAHL	(29 OR 30 OR 31 OR 32 OR 33 OR 34)
36	CINAHL	COCCYX/
37	CINAHL	SCIATICA/
38	CINAHL	(sciatica).ti,ab
39	CINAHL	(coccyx).ti,ab
40	CINAHL	(coccydynia).ti,ab
41	CINAHL	"LUMBAR VERTEBRAE"/
42	CINAHL	(lumbar ADJ2 vertebra).ti,ab
43	CINAHL	(36 OR 37 OR 38 OR 39 OR 40 OR 41 OR 42)
44	CINAHL	"THORACIC VERTEBRAE"/
45	CINAHL	exp SPONDYLOLYSIS/
46	CINAHL	(lumbago).ti,ab
47	CINAHL	(44 OR 45 OR 46)
48	CINAHL	(35 OR 43 OR 47)
49	CINAHL	(28 AND 48)
50	CINAHL	(radiofrequency OR radio-frequency).ti,ab

51	CINAHL	(thermocoag*).ti,ab
52	CINAHL	exp ELECTROCOAGULATION/ OR electrocoag*
53	CINAHL	(neurotom* OR neuroly*).ti,ab
54	CINAHL	"RADIO WAVES"/
55	CINAHL	(50 OR 51 OR 52 OR 53 OR 54)
56	CINAHL	(49 AND 55)
57	CINAHL	56 [DT 2014-2019]

Cochrane

#	Database	Search term
1	Cochrane	MeSH descriptor: [Back Pain] explode all trees
2	Cochrane	dorsalgia
3	Cochrane	backache
4	Cochrane	MeSH descriptor: [Low Back Pain] explode all trees
5	Cochrane	lumbar next pain or coccyx or coccydynia or spondylosis
6	Cochrane	MeSH descriptor: [Spine] explode all trees
7	Cochrane	MeSH descriptor: [Spinal Diseases] explode all trees
8	Cochrane	lumbago OR discitis OR disc near degeneration OR disc near prolapse OR disc near herniation
9	Cochrane	spinal fusion
10	Cochrane	facet near joints
11	Cochrane	MeSH descriptor: [Intervertebral Disk] explode all trees
12	Cochrane	postlaminectomy

13	Cochrane	arachnoiditis
14	Cochrane	failed near back
15	Cochrane	MeSH descriptor: [Cauda Equina] explode all trees
16	Cochrane	lumbar near vertebra*
17	Cochrane	spinal near stenosis
18	Cochrane	slipped near (disc* or disk*)
19	Cochrane	degenerat* near (disc* or disk*)
20	Cochrane	stenosis near (spine or root or spinal)
21	Cochrane	displace* near (disc* or disk*)
22	Cochrane	prolap* near (disc* or disk*)
23	Cochrane	MeSH descriptor: [Sciatic Neuropathy] explode all trees
24	Cochrane	sciatic*
25	Cochrane	back disorder*
26	Cochrane	back near pain
27	Cochrane	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #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
28	Cochrane	MeSH descriptor: [Radio Waves] explode all trees
29	Cochrane	MeSH descriptor: [Pulsed Radiofrequency Treatment] explode all trees
30	Cochrane	radiofrequency
31	Cochrane	radio frequency or radio-frequency
32	Cochrane	MeSH descriptor: [Electrocoagulation] explode all trees
33	Cochrane	electrocoag*

34	Cochrane	thermocoag*
35	Cochrane	neurotom* or neuroly*
36	Cochrane	#28 or #29 or #30 or #31 or #32 or #33 or #34 or #35
37	Cochrane	#27 and #36 in Trials

Appendix 2 Study characteristics

Study	N	Inclusion criteria		Mean age (SD)	Mean pain score (SD)	Intervention	Control	Funding
RD of the facet joints								
Gallagher 1994	41	Low back pain >3 months duration with symptoms typical of facet joint pain	Improvement (n=30) or equivocal (n=11) response to anaesthetic block	NR	VAS RD 5.8 (1.78); Sham 7.2 (1.94)	Nerves above and below painful joint denervated at 80° for 90 seconds.	Nerves also identified with stimulation but no heat lesion made	NR
Juch 2017	251	Low back pain without response to conservative management and considered to be related to the facet joint	Positive response to anaesthetic block (reported 50% pain relief 30-90 minutes after block)	RD 53.0 (11.5); Control 52.6 (10.8)	NRS RD 7.14 (1.38) Control 7. 19 (1.29)	Denervation at 90° for 90s of L3-4, L4-5 or L5-S1 with exercise program	Exercise program	The Netherlands Organization for Health Research and Development, by the Dutch Society for Anesthesiology, and the Dutch health insurance companies
Leclaire 2001	70	Low back pain for >3 months	“Significant” relief of back pain for >24h following facet injections	RD 46.7 (9.3); Sham 46.4 (9.8)	VAS RD 5.19 (2.67); Sham 5.15 (2.08)	RD with fluoroscopic guidance at 80°C for 90s of at least 2 levels	Nerves also identified with stimulation but electrode only heated to 37°C	Institut de recherche en sante´ and se´curite´ du travail du Que´bec
Moussa 2016	80	Low back pain for >1 year without response to conservative management	Complete or near complete reduction of CLBP on VAS 30 min after 2	RD capsule 58.1 (NR); RD conventional 56.5 (NR);	VAS RD 8.22 (NR); Sham 7.83 (NR)	RD of facet capsule on medial and lateral aspect or	Same procedure without elect current turned on	No funding received

			injections separated by >2 weeks	Sham 55.9 (NR)		conventional RD at 85°C for 90s		
Nath 2008	40	Low back pain for >2 years, not responded to previous treatment, pain attributable to lumbar facet joints	80% pain relief on 3 medial branch blocks	56 (range, 36–79)	VAS RD 5.98 (NR); Sham 4.38 (NR)	RD at 85°C for 60s with additional lesions just lateral and medial to the target nerve	Same procedure as RD but electrode tip remained at body temperature	No funding received
Tekin 2007	40	Back pain for >6 months with focal pain over the facet joints and unresponsive to conservative treatments	>50% reduction in VAS pain 30 minutes after diagnostic medial branch block	RD 60.5 (8.5); Sham 57.9 (9.3)	VAS RD 6.5 (1.5); Sham 6.8 (1.6)	RD at same levels as diagnostic blocks at 80°C for 90s.	Same procedure as RD but with current switched off	Not reported
Van Kleef 1999	32	Low back pain of >12 months duration, failure of conservative management	>50% reduction in pain following diagnostic nerve block of L3-L5 Baseline VAS score of >4	RD 46.6 (7.4); Sham 41.4 (7.5)	VAS RD 5.2 (1.7); Sham 5.2 (1.6)	RD at 80°C for 60s	Same procedure as RD but with current switched off	The Nederlandse organisatie voor wetenschappelijk
Van Tilburg 2016	60	Low back pain for >3 months and failure of conservative management	Decrease of >2 on medial branch block	RD 65 (12); Sham 58 (12)	NRS RD 7.2 (1.4); Sham 7.4 (0.8)	RD at 80°C for 60s per level for three steps with physiotherapy	Same procedure as RD but with current switched off with physiotherapy	No funding from a commercial party
Van Wijk 2005	81	Low back pain for >6 months	≥50% reduction on	RD 46.9 (11.5);	VAS RD 5.8 (1.8);	RD 80°C for 60 seconds	Same procedure as	Grant from the Dutch Health

			diagnostic block	Sham 48.1 (12.6)	Sham 6.5 (1.8)	at the levels concerned	RD but with current switched off	Insurance Council
RD of the sacroiliac joints								
Cohen 2008	28	Axial low back or buttock pain ≥ 6 months, tenderness overlying the sacroiliac joint(s), failure to respond to conservative therapy	≥ 75% pain relief for ≥3h following diagnostic sacroiliac joint injection, but back near baseline within 2 months	RD 51.9 (13.6); Sham 51.8 (13.1)	VAS RD 6.1 (1.8); Sham 6.5 (1.9)	RD 80°C for 90 seconds using cooling probe technology (Cooled RD)	Same procedure as RD but no current applied	John P. Murtha Neuroscience and Pain Institute, the Army Regional Anesthesia & Pain Medicine Initiative, and National Institutes of Health grant # MH075884
Juch 2017	228	Low back pain without response to conservative management, considered to be related to the sacroiliac joint.	Positive response to anaesthetic block (reported 50% pain relief 30-90 minutes after block)	RD 51.6 (10.9); Control 51.1 (12.2)	NRS RD 7.17 (1.65); Control 7.06 (1.43)	RD - 60° for 2.5 min per lesion of S1, S2 and S3 with exercise program	Exercise program	The Netherlands Organization for Health Research and Development, by the Dutch Society for Anesthesiology, and the Dutch health insurance companies
Mehta 2018	17	CLBP for >6 months. >5 on NRS	>80% pain reduction on 2 diagnostic blocks	RD 56.6 (NR); Sham 62.6 (NR)	VAS RD 8.1 (0.8); Sham 7.3 (0.8)	RD of the L5 medial branch of the primary dorsal root nerve and strip lesioning of the lateral branches	Identical to active RD treatment except that no RF energy was applied	None

						of the S1, 2, and 3 nerve roots		
Patel 2012	51	Pain for ≥6 months, 3-day average NRS between 4 and 8, failure of conservative management	≥75% pain reduction for 4h-7 days on two sets of anaesthetic blocks and back to baseline by start of the study	RD 56 (15); Sham 64 (14)	NRS RD 6.1 (1.3); Sham 5.8 (1.3)	RD at 60°C for 150s of L5 dorsal ramus and then acral lateral branches of S1, S2 and S3 (cooled RD)	Same procedure as RD but RF energy was not delivered.	Baylis Medical
Van Tilburg 2016	60	Sacroiliac joint pain for >3 months, failure of conservative management	Decrease of ≥2 on NRS following diagnostic block	RD 59.5 (27); Sham 62 (18)	NRS RD 7.2 (1.4); Sham 7.5 (1.2)	85°C each step for 90s, total of 5 steps	Same procedure as RD but no heat lesions made	Not reported
RD of the intervertebral discs								
Barendse 2001	28	Non-specific LBP for >1y, failure of conservative management	>50% pain relief 30 minutes after an analgesic discography at L4–L5 and L5–S1. Patients with multilevel pain excluded	RD 40.8 (7.5); Sham 45.2 (8.4)	VAS RD 6.5 (1.3); Sham 5.5 (1.1)	70°C for 90s without anaesthetic	Same procedure as RD but no current applied	Not reported
Desai 2016	63	Lumbar discogenic pain for ≥6 months, unresponsive to conservative management	Diagnosed via provocation discography - definite single-level concordant	Mean age 41 (11); Control 43 (11)	VAS RD 6.7 (NR); Sham 7 (NR)	RD at 50°C for 15 minutes and then 60°C for 2.5 min (bopolar cooled RD) with conventional	Conventional medical management	Halyard Health, Inc. (formerly Kimberly-Clark Health Care)

			pain on manometry			medical management		
Kapural 2013	55	CLBP unresponsive to conservative management for ≥6 months; no surgical interventions within previous 3 months	Single-level degenerative disc disease or two-level disease without evidence of additional degenerative changes in other disc spaces on MRI	RD 40.4 (10.3); Sham 38.4 (10.4)	VAS RD 7.13 (1.61); Sham 7.18 (1.98)	RD at 45°C bipolar for 15 minutes or 50°C bipolar for 15 minutes and monopolar at 60°C for 2.5 minutes	Mimicked active treatment, except that introducers and electrodes positioned just outside of the disc, and no RF energy delivered	Baylis Medical
Kvarstein 2009	20	Unremitting low back pain for more than 6 months; Pain intensity ≥5 /10 and low back pain greater than leg pain; Failure on conservative treatment	Positive one-level pain provocation discography	RD 44.7 (10.1); Sham 39.6 (8.9)	NRS RD 4.6 (1.8); Sham 5.5 (2.0)	RD increased by 5°C every second minute to 4-min interval at 65°C (from 50°C)	Exposed to a similar intervention, but the annulus was not exposed to RF heating	Radionics, TYCO Healthcare Group provided the discTRODE probes
Van Tilburg 2017	60	Low back pain >3 months and symptoms suggestive of lumbar disc problem	Reduction of ≥2 on a numerical rating scale (0–10) after a diagnostic ramus communicans test block	RD 50.5 (13.9); Sham 50.1 (12.3)	NRS 7.8 (1.05); Sham 7.8 (1.05)	RD treatment at 80 °C for 60s per level	Same procedure but without RF treatment	No support received that influenced submitted work
RD of the vertebrae body and endplate								

Fischgrund 2018	225	CLBP ≥6 months, not responded to conservative treatment, Type 1 or Type 2 Modic changes required at the proposed treatment levels	No diagnostic block for inclusion	RD 46.9 (range 26–69); Sham 47.1 (range 25–69)	VAS RD 6.73 (1.38); Sham 6.64 (1.34)	Thermal ablation at the terminus of the basivertebral nerve 85°C for 15 min	Same procedure as RD but only docking introducer cannula 1–2 mm into the pedicle and simulating RD	Not reported

CLBP, chronic low back pain; N, number of trials; NRS, numeric rating scale; RD, radiofrequency denervation; SD, standard deviation; VAS, visual analogue scale.

BMJ Open

Radiofrequency denervation for chronic back pain: a systematic review and meta-analysis

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-035540.R2
Article Type:	Original research
Date Submitted by the Author:	15-May-2020
Complete List of Authors:	Chappell, Mary; Cambridgeshire County Council, Public Health Directorate Lakshman, Raj; Cambridgeshire County Council, Public Health Directorate; University of Cambridge, Medical Research Council Epidemiology Unit Trotter, Patrick; Cambridge University Hospitals NHS Foundation Trust Abrahams, Mark; Cambridge University Hospitals NHS Foundation Trust Lee, Michael; University of Cambridge, Division of Anaesthesia
Primary Subject Heading:	Rheumatology
Secondary Subject Heading:	Neurology
Keywords:	Back pain < ORTHOPAEDIC & TRAUMA SURGERY, Rheumatology < INTERNAL MEDICINE, Neurology < INTERNAL MEDICINE, PAIN MANAGEMENT

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Radiofrequency denervation for chronic back pain: a systematic review and meta-analysis

Mary E Chappell[1], Raj Lakshman[1,2], Patrick Trotter[3], Mark J Abrahams[3], Michael C Lee[4]

[1]Public Health Directorate, Cambridgeshire County Council, Cambridge, UK

[2]Medical Research Council Epidemiology Unit, University of Cambridge, Cambridge UK

[3]Cambridge University Hospitals NHS Foundation trust, Cambridge, UK

[4]Division of Anaesthesia, University of Cambridge, Cambridge, UK

Correspondence to: Mary E Chappell, Public Health Directorate, Cambridgeshire County Council, Cambridge CB3 0AP, UK. Tel. 01223 729037

Email mary.chappell@cambridgeshire.gov.uk

Word count:

Abstract 221

Main text 4,188

Abstract

Objectives: To assess the effectiveness of radiofrequency denervation of lumbosacral anatomical targets for the management of chronic back pain.

Design: Systematic review and meta-analysis of randomised controlled trials.

Methods: A database search (Medline, Medline in Process, Embase, CINHAL and the Cochrane library) was conducted to April 2019 for placebo or no-treatment controlled trials of radiofrequency denervation for the management of chronic back pain. Included trials were quality assessed using the Cochrane risk of bias tool and the quality of outcomes assessed using the GRADE approach. Meta-analysis was conducted to calculate mean difference in post-treatment pain score.

Results: Nineteen randomised controlled trials were included in the review. There appears to be short-term pain relief (1-3 months) provided by radiofrequency denervation of the sacroiliac joint (5 trials, MD -1.53, CI -2.62, -0.45) and inter-vertebral discs (4 trials, MD -0.98, CI -1.84, -0.12) but the placebo effect is large and additional intervention effect size is small (<1 on a 11 point (0-10) pain scale). Longer-term effectiveness (>6 months) is uncertain.

Conclusions: Radiofrequency denervation of selected lumbosacral targets appears to have a small, short-term, positive effect for the management of patients with chronic back pain. However, the quality of evidence for the majority of outcomes is low or very low quality and there is still a degree of uncertainty, particularly around the duration of effect.

Strengths and limitations of this study:

- This review brings together a number of recent trials with earlier trials so that there is a sizable sum of evidence on which to assess the effectiveness of radiofrequency denervation for back pain.
- Due to the invasive nature of the procedure, it is difficult to perform truly patient or provider blinded trials and this brings some uncertainty around findings.
- There is limited reporting of long-term outcomes (>6 months) for the effectiveness of radiofrequency denervation.

Introduction

Back pain is an extremely common symptom experienced by people of all ages, and can be attributed to a wide variety of disease processes.[1,2] Low back pain is now the leading cause of disability worldwide and back pain is associated with a substantial economic burden, with high medical and societal costs.[3] Studies have shown that a large proportion of medical costs come from hospital admissions and physical therapy for the management of back pain.[4] However, there are also indirect costs associated with chronic or recurrent back pain that are difficult to quantify relating to work absenteeism and related productivity.[1,3,4] In many cases, back pain is non-specific, or structural pathology amenable to surgical correction cannot be identified.[5–7] Hence, patients and practitioners continue to seek non-surgical alternatives for the management of back pain.

Radiofrequency denervation (RD) involves the application of an alternating electric current (250 to 500kHz) via a needle probe to induce a highly localised rise in tissue temperature at the needle tip.[8] The needle tip is usually placed under fluoroscopic guidance to enable selective ablation of sensory nerve branches that supply facet joints, sacroiliac joint or other structures that comprise the lumbosacral spine. RD would therefore offer relief of pain by attenuating sensory signals from the lumbosacral spine.[9]

Despite its use for over 20 years,[10] the effectiveness of RD targeted at the anatomy of the lumbosacral spine is not yet established, with randomised controlled trials (RCTs) continuing to be performed. A number of trials have been published since the publication of the last high quality review in 2015[11] and our systematic review aimed to bring together this evidence in an attempt to evaluate whether RD is an effective intervention for the management of chronic non-specific back pain.

Materials and Methods

Search strategy

A search was conducted in Medline, Medline in Process, Embase, CINHAL and the Cochrane library from January 2014 to April 2019 (Appendix 1). Previous systematic reviews were used to obtain additional relevant studies published pre 2014.

Inclusion criteria

RCTs comparing RD of the spine with a control in patients with back pain with or without sciatica were included. Only trials of radiofrequency procedures for the purpose of ablating or denaturing sensory nerve branches or nociceptors that supply the lumbosacral spine were considered for inclusion. Trials of pulsed RF,[12] or other forms of 'neuromodulatory' procedures that do not aim to ablate or denature these targets, were excluded from the review. Control groups where there was no active treatment were considered for inclusion but trials with potentially effective comparators e.g. corticosteroid injections, were excluded. Only trials of patients with back pain without a definite or surgically remediable cause (chronic non-specific back pain) were included in the review. The outcome for the review was patient-reported pain score e.g. Visual Analogue Scale or Numeric Rating Scale.

Data collection and quality assessment

Trial characteristics were recorded from included studies. Study results were extracted independently by two authors (MC, PT), with any disagreements resolved by consensus. The overall strength of evidence was assessed using the GRADE approach.[13] Risk of bias was assed using the Cochrane Risk of Bias tool.[14] Any outcome where more than half of trials were considered to have a high or unclear risk of bias was downgraded. Outcomes were also downgraded where heterogeneity

in the meta-analysis was greater than 50%. Optimal sample size was taken to be 85 participants per study arm (as calculated in the Juch 2017 trial[15]) and studies with less than 170 participants, and/or where the 95% confidence intervals included the line of no effect, were downgraded for imprecision. Publication bias was assessed using funnel plots and outcomes downgraded where there was a high certainty of publication bias.

Data analysis

Meta-analyses were conducted in RevMan[16] with random effects models since the included studies investigated effectiveness in different population groups with varying intervention and control group treatments. Pain score at 1-3 months was taken as the primary outcome (longest time point used for studies reporting multiple time points), allowing outcome from a larger number of studies to be combined. Pain score data were reported on a 0-10 point scale (Visual Analogue Scale or Numeric Rating Scale) in all studies and the mean difference was therefore calculated without standardisation as done in the previous Cochrane review.[11] Studies with different spinal targets e.g. facet joints, sacroiliac joints or inter-vertebrae disc, were separated in the analysis. A sensitivity analysis was conducted to check the validity of findings by removing studies considered to have a particularly high risk of bias. Subgroup analysis to explore study heterogeneity was not conducted because of the small number of studies and high likelihood of reaching spurious conclusions.

Results

Study characteristics

The search identified 922 citations of which 229 were duplicates. Studies were excluded as shown in figure 1. Of the 693 citations reviewed, 8 new trials were

identified as well as 11 from a previous Cochrane review.[11] Exclusions were made as shown in figure 1. Nineteen trials were included in the review and their characteristics are shown in appendix 2. Trials investigated the effectiveness of RD of the facet joint (supplied by medial branch of the dorsal spinal ramus),[15,17–24] the sacroiliac joints,[15,25–28] the intervertebral discs,[29–33] or vertebrae end-plate (supplied by the basivertebral nerve).[34] The majority of trials used a sham control group but one large trial compared RD with no treatment (both groups received an exercise program) and one small trial compared RD plus conventional medical with conventional medical management alone (including self-care, medications and physical and cognitive therapy).

Study quality

Sham-controlled trials generally appear to have conducted adequate randomisation but allocation concealment was often unclear. Processes were in place to blind patients and providers and outcome assessors. In some trials, maintenance of blinding was unclear as it was evident that patients undergoing sham procedures were offered RD in case of sham treatment failure. In these cases, blinding would have been broken. Most trials did not report dropouts and there was unclear risk of attrition bias. The outcome for this review was pain score and this was reported in all trials and reporting bias was not considered to be an issue in the review. Four trials were identified as having high risk of bias and were removed in the sensitivity analysis.[17,19,24,25]

Overall quality of the evidence

The majority of outcomes were graded down for imprecision and all outcomes were downgraded for potential risk of bias. Consequently, almost all outcomes were

graded as low quality. However, in some cases, high heterogeneity was also present and these outcomes were graded as very low quality. Publication bias was suggested by asymmetry in a number of the funnel plots. However, there was uncertainty due to the small numbers of studies and outcomes were not graded down for publication bias.

Study findings

Results of the meta-analyses are shown in table 1.

RD of the facet joints

Meta-analysis of pain scores at 1-3 months post procedure (longest time point used for studies with multiple time points) (marked on a 0-10 scale) is shown in figure 2 and table 1. The effect size was similar when all trials were included (7 trials, MD -0.56, CI -1.13, 0.01) or where just the sham-controlled trials were included (6 trials, MD -0.63, CI -1.39, 0.12) but the effect was not significant for either. We also considered outcomes at 6 and 12 months, where data were available to explore longer term outcomes, but did not find any significant effect (table 1).

RD of the sacroiliac joints

Figure 3 shows the meta-analysis of trials for pain score at 1-3 months (longest time point used for studies with multiple time points). There was a significant effect of RD for the analysis including all trials (5 trials, MD -1.53, CI -2.62, -0.45) or just sham-controlled trials (4 trials, MD -1.89, CI -3.45, -0.34). Only one trial[15] assessed outcome at later time points and this showed no significant difference compared to a no treatment control (table 1).

RD of the intervertebral discs

Pain score at 1-3 months post-treatment was significantly lower for RD compared with control in all trials (4 trials, MD -0.98, CI -1.84, -0.12) but not for sham-controlled trials alone (3 trials, MD -0.63, CI -1.36, 0.10) (figure 4). Pain score was significantly lower for RD when all trials and sham-controlled trials were considered at 6 months but, for one trial assessing outcome at one year, it was not (table 1).

RD of the vertebrae body and end plate

One trial of RD for vertebrae body and end plate (basivertebral nerve ablation)[34] did not show significant benefits of RD compared with sham at 3, 6 or 12 months (table 1).

Sensitivity analysis

Four studies were removed in the sensitivity analysis due to a high risk of methodological bias[17,19,24,25] and the two non-sham controlled trials were also removed.[15,32] After the removal of these trials, outcome at 1-3 months for facet joint sham trials was still not significant (4 trials, MD -0.57, CI -1.60, 0.46) and 1-3 month outcome for sacroiliac sham trials became non-significant (3 trials, MD -1.21, CI -2.59, 0.16). The facet joint sham trial outcome at 6 months also became non-significant (1 trial, MD 0.18, CI -2.80, 3.16).

Discussion

Main findings

This systematic review presents evidence suggesting that RD of the lumbosacral spine may have a small positive but short-lived effect in patients with chronic back pain, depending on the precise part of the anatomy that is being targeted by the procedure. The quality of evidence for the majority of findings is low or very low quality and there is still a degree of uncertainty around this assertion, particularly

around the duration of effect. The size of benefit appears to be small (<1 point on a 0-10 pain scale) and there is limited data for outcomes beyond 6 months. These assertions apply to RD for sacroiliac joints, whereas evidence for benefit to other targets is more limited. RD for facet joints did not show a significant benefit on 1-3 month outcome. There is a suggestion that there may be a benefit of RD for intervertebral discs but there is some inconsistency, with insignificant effect for short-term outcomes.

What is also clear from the review is that both treatment and sham/no treatment groups improved during the trials. In the sham controlled trials, this may, in part, be due to placebo effect. However, the large trial by Juch et al[15] used a "no additional treatment" control (both groups received an exercise program) but all study arms improved over time. This may be because a high proportion of control study participants actually received RD (~30%) due to cross-over during the trial. However, this may also be explained by self-selection of participants who volunteer for research trials,[35] and hence are likely to make more of an active effort to manage their back pain. Such participants may be more likely to engage with, and be diligent in, exercise programs and seek medical assistance where needed.

In the trial by Juch et al., control group improvements may also be explained by the conservative management that they received. The exercise program employed was multi-disciplinary and comprised individual sessions over 8-12 hours focused on quality of movement and behaviour, with access to psychological care. There is evidence suggesting that patients with chronic back pain can benefit from pain management programs that are of sufficient quality and duration.[36] Where patients have not received an adequate trial of conservative therapy, they may benefit from further exercise programs and other conservative management. It remains unclear

whether patients who are either unable or unwilling to engage with conservative approaches to pain management would benefit from RD based interventions as a first-line or isolated modality of treatment. Hence, there should be some reservation when considering the use of RD treatment as a first-line, or isolated modality of pain management.

Regression to the mean may also have played a role in control group improvements since patients in the trial were recruited with elevated pain, responsive to an anaesthetic block. Back pain has been shown to have a varied aetiology, with some patients experiencing fluctuating levels of pain over time, whilst other experience constant high levels of pain.[37,38] For the majority of trials that reported it, duration of back pain in participants prior to enrolment was 2-5 years and a proportion of these were likely to have had high levels of constant pain. Some, however, may have been experiencing fluctuating or recurrent pain within this period since the actual inclusion criteria for most trials was pain for >3 or 6 months based on patient recall. If they were recruited at a point where their pain had flared acutely, there would be a natural tendency for that painful episode to resolve over time.

Strengths and limitations

A major strength of this review is that it collates a larger body of evidence than previous systematic reviews, with the addition of a number of recent trials and thorough assessment of the quality of the evidence. The review is able to tentatively answer the question about the effectiveness of RD for back pain; an assertion that, to date, has proved to be very difficult due a paucity of evidence in this field.

This review utilises evidence from a previous Cochrane review[11] but the inclusion criteria for our review had a narrower scope (included only sham- or conservative

management-controlled trials of conventional neuro-ablative RD). Since the previous review appears to be of high quality, and we updated it with a thorough search of the literature to date, there is assurance that all relevant trials were included.

A limitation of this review is that it was difficult to truly assess risk of bias in trials included in the review. Trial integrity rested heavily on the blinding of participants and the outcome was likely to be highly subject to patients' preconceptions of the different interventions given. Most trials did not report information that providers gave patients about the different possible treatment arms e.g. did providers suggest to patients that RD was the effective treatment and that sham or no treatment would be ineffective? Where blinding was broken, these viewpoints may have influenced patients' response. In some of the sham-controlled studies this was clearly evident. For example, in some studies, before randomisation, patients were told that, if randomised to sham, they could receive RD if they gained no benefit. Where blinding was broken, these opinions were likely to influence patients' perception of their pain. In other studies information from providers was not reported and it is difficult to assess whether this type of bias occurred.

The review may also be limited in its ability to ascertain the technical quality of individual research trials. Even when examining the reported trial methodology, it is difficult to conclusively identify trials that employed procedures that may be more or less successful in denervating the specific lumbosacral anatomy. Some aspects of RD procedures in earlier trials are considered outdated[39,40] but the advantages of more recent procedures for RD remain unproven, and there is no clear evidence of their superiority. Sensitivity analysis based on technical quality was therefore considered unhelpful and not performed.

The review is also limited by the lack of long term data from trials. Most studies do not attempt to blind patients for more than 3 months and the longer follow up outcomes are considered to be at higher risk of bias. It is still therefore unclear whether RD of lumbosacral anatomy has long-term benefits for back pain.

Finally, the review is limited in its ability to identify any aspects of patient or intervention characteristics that may make RD treatment more likely to be beneficial. There is to date no reliable predictor of benefit on back pain for RD procedures based on clinical or imaging findings or diagnostic injections.[41] The relative advantages of different RD technologies used in included trials (e.g. 'cooled'[25,26,32] and 'bipolar'[30,32] RD) remains to be established. Due to the small number of studies at each time point, sub-group analysis was not considered appropriate. However, the publication of more sham-controlled trials and trials comparing different RD technologies may make this type of investigation possible. Technical advances and advances in knowledge and experience may allow for better selection of anatomical targets and patients for RD and hence improve clinical outcomes. It is important that these developments are formally assessed and published.

In conclusion, within the limitations in this review and the published literature, there appears to be at least short-term benefit from RD of selected lumbosacral anatomical targets for chronic back pain. However, the mean size of effect appears to be small and, overall, clinical significance may be marginal. Hence, chronic back pain remains a highly challenging condition to treat.

Acknowledgements Thanks to Julie Aikens and Kerry Herbert at Hinchingbrooke Healthcare Library for their assistance in designing and running the search strategies for the review.

Contributors: MC contributed to the planning of this work, selected articles for inclusion, extracted data, quality assessed studies and drafted and re-drafted the manuscript. RL contributed to the planning of this work, reviewed the manuscript and approved the final version. PT extracted data from the trials, reviewed the manuscript and approved the final version. MA contributed to the planning of this work, reviewed the manuscript and approved the final version. ML contributed to the planning of this work, reviewed the manuscript and approved the final version.

Funding This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors. RL is supported by the Medical Research Council (MC_UU_12015/2). MCL is supported by AABGI Foundation project grant (RCZB/071).

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information.

Patient and Public Involvement This research was done without patient involvement.

References

1 Hartvigsen J, Hancock MJ, Kongsted A, *et al.* What low back pain is and why we need to pay attention. *Lancet* 2018;**391**:2356–67. doi:10.1016/S0140-6736(18)30480-X

2 Hoy D, Bain C, Williams G, *et al.* A systematic review of the global prevalence of low back pain. *Arthritis Rheum* 2012;**64**:2028–37. doi:10.1002/art.34347

3 Maniadakis N, Gray A. The economic burden of back pain in the UK. *Pain* 2000;**84**:95–103. doi:10.1016/S0304-3959(99)00187-6

4 Dagenais S, Caro J, Haldeman S. A systematic review of low back pain cost of illness studies in the United States and internationally. *Spine J* 2008;**8**:8–20. doi:10.1016/j.spinee.2007.10.005

5 National Institute of Health and Care Excellence. Low back pain and sciatica in over 16s: assessment and management. 2016.

6 Chou R, Baisden J, Carragee EJ, *et al.* Surgery for Low Back Pain: A Review of the Evidence for an American Pain Society Clinical Practice Guideline. *Spine (Phila Pa 1976)* 2009;**34**:1094–109.

7 Chou R, Loeser JD, Owens DK, *et al.* Interventional Therapies, Surgery, and Interdisciplinary Rehabilitation for Low Back Pain: An Evidence-Based Clinical Practice Guideline From the American Pain Society. *Spine (Phila Pa 1976)* 2009;**34**:1066–77. doi:10.1097/BRS.0b013e3181a1390d

8 Kline M. Radiofrequency techniques in clinical practice. In: *Waldman SD, Winnie AP, eds. Interventional Pain Management. Philadelphia, PA: Saunders*. 1996.

9 Wray JK, Dixon B, Przkora R. *Radiofrequency Ablation*. 2019.

10 Manchikanti L, Hirsch J, Pampati V, *et al.* Utilization of Facet Joint and Sacroiliac Joint Interventions in Medicare Population from 2000 to 2014: Explosive Growth Continues! *Curr Pain Headache Rep* 2016;**20**:58.

11 Maas E, Ostelo R, Niemisto L, *et al.* Radiofrequency denervation for chronic low back pain. *Cochrane Database Syst Rev* 2015;:Art. No.: CD008572. doi:10.1001/jama.2017.16386

12 Brandon R, Cohen D, Edward T, *et al.* Pulsed Radiofrequency Neuromodulation in Interventional Pain Management—A Growing Technology. *J Radiol Nurs* 2018;**37**:181–7.

13 Schünemann H, Brożek J, Guyatt G, *et al.*, editors. *GRADE Handbook: Handbook for grading the quality of evidence and the strength of recommendations using the GRADE approach*.

14 Higgins JP, Savovic J, Page MJ, *et al.*, editors. *Revised Cochrane risk-of-bias tool for randomized trials (RoB 2)*. 2019.

15 Juch JNS, Maas ET, Ostelo RWJG, *et al.* Effect of Radiofrequency Denervation on Pain Intensity Among Patients With Chronic Low Back Pain. *JAMA* 2017;**318**:68–81.

16 Review Manager (RevMan) [Computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

17 Gallagher J, Petriccione di Vadi P, Wedley J, *et al.* Radiofrequency facet joint denervation in the treatment of low back pain: a prospective controlled double-blind study to assess its efficacy. *Pain Clin* 1994;**7**:193–8.

18 Leclaire R, Fortin L, Lambert R, *et al.* Radiofrequency Facet Joint Denervation in the Treatment of Low Back Pain: A Placebo-Controlled Clinical Trial to Assess Efficacy. *Spine (Phila Pa 1976)* 2001;**26**:1411–6. doi:10.1097/00007632-200107010-00003

19 Moussa WMM, Khedr W. Percutaneous radiofrequency facet capsule denervation as an alternative target in lumbar facet syndrome. *Clin Neurol Neurosurg* 2016;**150**:96–104. doi:10.1016/j.clineuro.2016.09.004

20 van Kleef M, Barendse GAM, Kessels A, *et al.* Randomised trial of radiofrequency lumbar facet denervation for chronic low back pain. *Spine (Phila Pa 1976)* 1999;**24**:1937–42.

21 Van Tilburg CWJ, Schuurmans FA, Stronks DL, *et al.* Randomized sham-controlled double-blind multicenter clinical trial to ascertain the effect of percutaneous radiofrequency treatment for sacroiliac joint pain: Three-month results. *Clin J Pain* 2016;**32**:921–6. doi:10.1097/AJP.0000000000000351

22 Van Wijk RMAW, Geurts JWM, Wynne HJ, *et al.* Radiofrequency denervation of lumbar facet joints in the treatment of chronic low back pain: A randomized, double-blind, sham lesion-controlled trial. *Clin J Pain* 2005;**21**:335–44.

23 Nath S, Nath CA, Pettersson K. Percutaneous Lumbar Zygapophysial (Facet) Joint Neurotomy Using Radiofrequency Current, in the Management of Chronic Low Back Pain. *Spine (Phila Pa 1976)* 2008;**33**:1291–1297. doi:10.1109/ICCGI.2010.42

24 Tekin I, Mirzai H, Ok G, *et al.* A comparison of conventional and pulsed radiofrequency denervation in the treatment of chronic facet joint pain. *Clin J Pain* 2007;**23**:524–9. doi:10.1097/AJP.0b013e318074c99c

25 Cohen SP, Hurley RW, Buckenmaier CC, *et al.* Randomized Placebo-Controlled Study Evaluating Lateral Branch Radiofrequency Denervation for Sacroiliac Joint Pain. *Anesthesiology* 2008;**109**:279–88. doi:10.1038/mp.2011.182.doi

26 Patel N, Gross A, Brown L, *et al.* A Randomized, Placebo-Controlled Study to Assess the Efficacy of Lateral Branch Neurotomy for Chronic Sacroiliac Joint Pain. *Pain Med* 2012;**13**:383–98. doi:10.1111/j.1526-4637.2012.01328.x

27 Van Tilburg C, Stronks D, Groeneweg J, *et al.* Randomised sham-controlled double-blind multicentre clinical trial to ascertain the effect of percutaneous radiofrequency treatment for lumbar facet joint pain. *Spine (Phila Pa 1976)* 2016;**98**-**B**:1526–33.

28 Mehta V, Poply K, Husband M, *et al.* The Effects of Radiofrequency Neurotomy Using a Strip-Lesioning Device on Patients with Sacroiliac Joint Pain: Results from a Single-Center, Randomized, Sham-Controlled Trial. *Pain Physician* 2018;**21**:607–18.

29 Barendse GAM, van den Berg SGM, Kessels AHF, *et al.* Randomized Controlled Trial of Percutaneous Intradiscal Radiofrequency Thermocoagulation for Chronic Discogenic Back Pain. Lack of Effect From a 90-Second 70 C Lesion. *Spine (Phila Pa 1976)* 2001;**26**:287–92. doi:10.1097/00007632-200102010-00014

30 Kapural L, Vrooman B, Sarwar S, *et al.* A Randomized, Placebo-Controlled

Trial of Transdiscal Radiofrequency, Biacuplasty for Treatment of Discogenic Lower Back Pain. *Pain Med* 2013;**14**:362–73. doi:10.1111/pme.12023

31 van Tilburg CWJ, Stronks DL, Groeneweg JG, *et al.* Randomized sham-controlled, double-blind, multicenter clinical trial on the effect of percutaneous radiofrequency at the ramus communicans for lumbar disc pain. *Eur J Pain* 2017;**21**:520–9. doi:10.1002/ejp.945

32 Desai MJ, Kapural L, Petersohn JD, *et al.* A prospective, randomized, multicenter, open-label clinical trial comparing intradiscal biacuplasty to conventional medical management for discogenic lumbar back pain. *Spine (Phila Pa 1976)* 2016;**41**:1065–74. doi:10.1097/BRS.0000000000001412

33 Kvarstein G, Måwe L, Indahl A, *et al.* A randomized double-blind controlled trial of intra-annular radiofrequency thermal disc therapy - A 12-month follow-up. *Pain* 2009;**145**:279–86. doi:10.1016/j.pain.2009.05.001

34 Fischgrund JS, Rhyne A, Franke J, *et al.* Intraosseous basivertebral nerve ablation for the treatment of chronic low back pain: a prospective randomized double-blind sham-controlled multi-center study. *Eur Spine J* 2018;**27**:1146–56. doi:10.1007/s00586-018-5496-1

35 The Cochrane Collaboration. Introduction to sources of bias in clinical trials. In: *Cochrane Handbook for Systematic Reviews of Interventions*. 2011.

36 Morley S, Williams A, Hussain S. Estimating the clinical effectiveness of cognitive behavioural therapy in the clinic: Evaluation of a CBT informed pain management programme. *Pain* 2008;**137**:670–80.

37 Dunn K, Croft P. Epidemiology and natural history of low back pain. *Eura Medicophys* 2004;**40**:9–13.

38 Dunn K, Jordan K, Croft P. Characterizing the course of low back pain: a latent class analysis. *Am J Epidemiol* 2006;**63**:754–61.

39 Dreyfuss P, Baker R. Comment on: Radiofrequency facet joint denervation in the treatment of low back pain: a placebo-controlled clinical trial to assess efficacy. *Spine (Phila Pa 1976)* 2002;**27**:556–7.

40 Kapural L, Provenzano D, Narouze S. RE: Juch JNS, et al. Effect of Radiofrequency Denervation on Pain Intensity Among Patients With Chronic Low Back Pain: The Mint Randomized Clinical Trials. JAMA 2017;318(1):68–81. *Neuromodulation* 2017;**20**:844. doi:10.1111/ner.12729

41 Cohen SP, Julie JH, Brummett C. Facet joint pain-advances in patient selection and treatment. *Nat Rev Rheumatol* 2013;**9**:101–16. doi:10.1038/nrrheum.2012.198

Table 1 Results of the meta-analyses of randomised controlled trials

	All trials					Sham controlled trials				
	k	N	MD (95% CI)	I^2	GRADE*	k	N	MD (95% CI)	I^2	GRADE*
RD of the facet joints										
1-3 months	7	599	-0.56 (-1.13, 0.01)	59%	Low	6	348	-0.63 (-1.39, 0.12)	66%	Low
6 months	4	361	-0.66 (-1.37, 0.05)	42%	Low	3	110	-1.05 (-2.21, 0.10)	32%	Low
1 year	2	291	-0.72 (-2.24, 0.80)	89%	Very low	1	40	-1.50 (-2.21, -0.79)	NA	Very low
RD of the sacroiliac joints										
1-3 months	5	384	-1.53 (-2.62, -0.45)	83%	Low	4	156	-1.89 (-3.45, -0.34)	87%	Very low
6 months	1	228	-0.28 (-1.00, 0.44)	NA	Low					
12 months	1	228	-0.19 (-0.92, 0.54)	NA	Low					
RD of the intervertebrae discs										
1-3 months	4	200	-0.98 (-1.84, -0.12)	40%	Low	3	144	-0.63 (-1.36, 0.10)	0%	Low
6 months	3	127	-1.74 (-2.58, -0.91)	0%	Low	2	75	-1.63 (-2.58, -0.68)	0%	Low
12 months	1	20	-1.70 (-3.63, 0.23)	NA	Very low	1	20	-1.70 (-3.63, 0.23)	NA	Very low
RD of the vertebrae body and endplate										
3 months	1	205	-0.34 (-1.09, 0.41)	NA	Moderate	1	205	-0.34 (-1.09, 0.41)	NA	Moderate
6 months	1	205	-0.67 (-1.44, 0.10)	NA	Moderate	1	205	-0.67 (-1.44, 0.10)	NA	Moderate
12 months	1	205	-0.50 (-1.29, 0.29)	NA	Moderate	1	205	-0.50 (-1.29, 0.29)	NA	Moderate

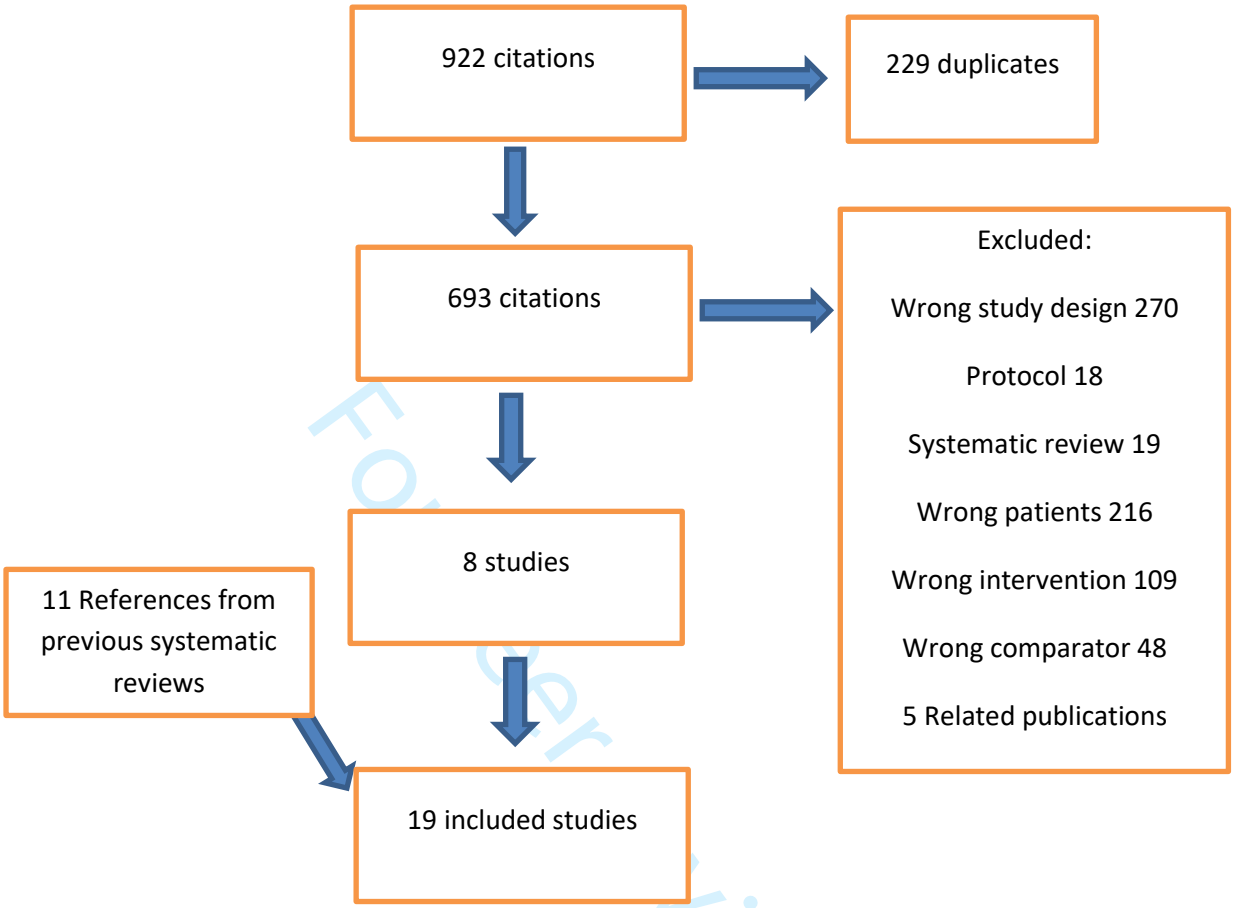
k, number of trials; N, number of participants; MD, Mean difference.
*GRADE assessment of the quality of the evidence

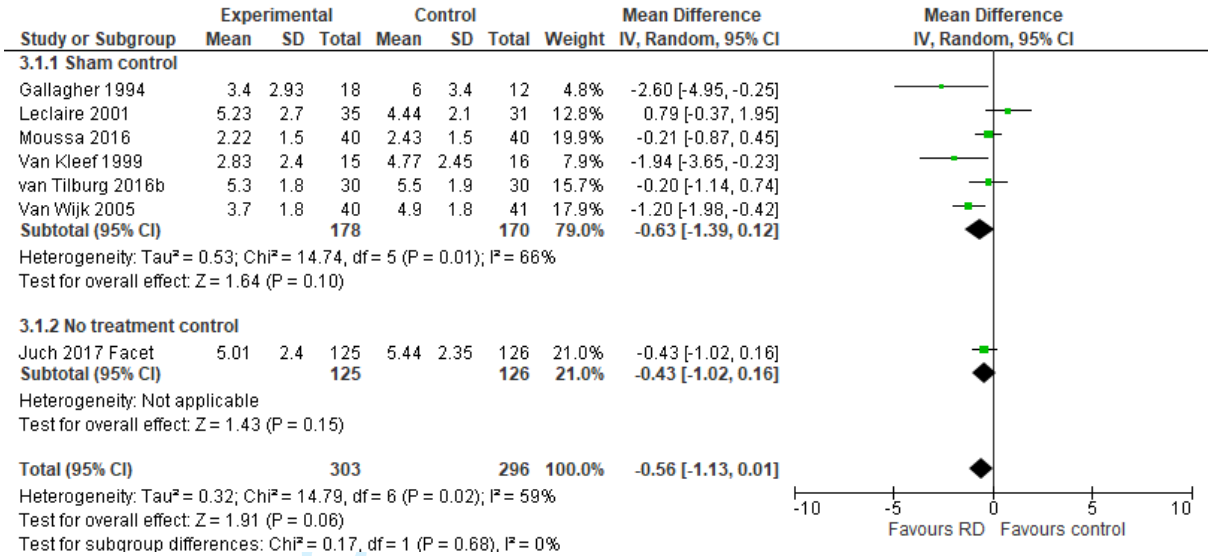
Figure 1 PRISMA flow diagram

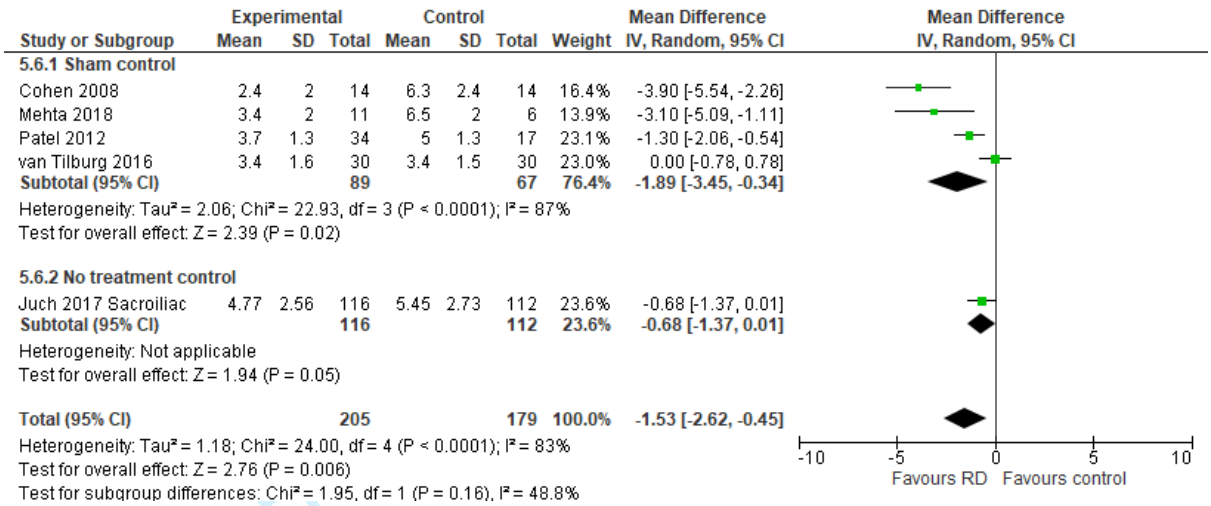
Figure 2 Post treatment pain score for radiofrequency denervation of the facet joints versus control at 1-3 month follow-up (longest time point used for studies with multiple time points)

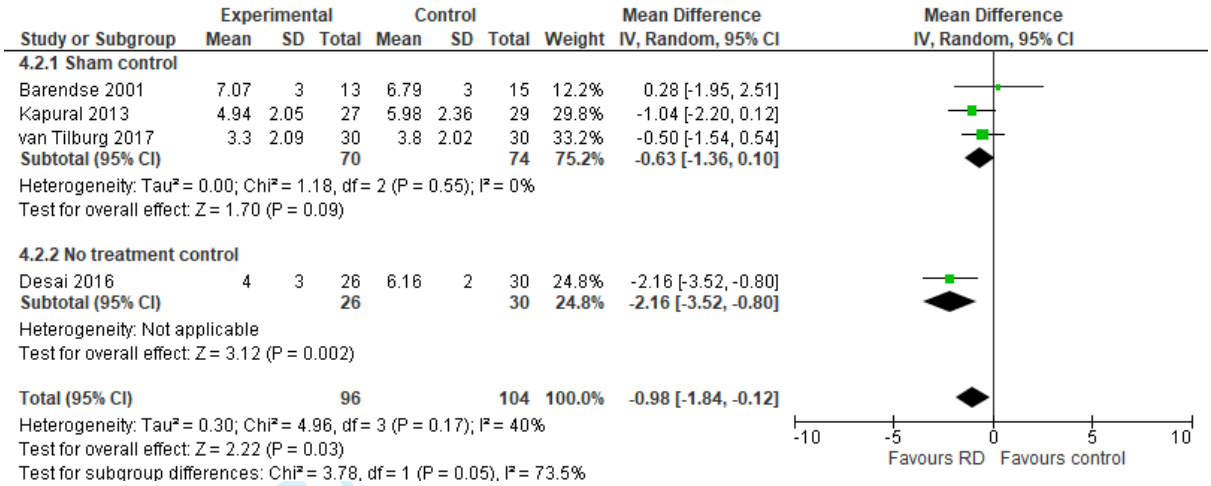
Figure 3 Post treatment pain score for radiofrequency denervation of the sacroiliac joints versus control at 1-3 month follow-up (longest time point used for studies with multiple time points)

Figure 4 Post treatment pain score for radiofrequency denervation of the intervertebral discs versus control at 1-3 month follow-up (longest time point used for studies with multiple time points)









Appendix 1 Search strategies

Medline and Embase

#	Database	Search term
1	Medline	(randomized controlled trial).pt
2	Medline	(controlled clinical trial).pt
3	Medline	(randomi*ed).ab
4	Medline	(placebo).ti,ab
5	Medline	(drug therapy).fs
6	Medline	(randomly).ti,ab
7	Medline	(trial).ti,ab
8	Medline	(groups).ti,ab
9	Medline	(1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8)
10	Medline	(animals NOT (humans AND animals)).su
11	Medline	9 not 10
12	Medline	(dorsalgia).ti,ab
13	Medline	exp "BACK PAIN"/
14	Medline	(backache).ti,ab
15	Medline	(lumbar ADJ pain).ti,ab
16	Medline	(coccyx).ti,ab
17	Medline	(coccydynia).ti,ab
18	Medline	(sciatica).ti,ab
19	Medline	"SCIATIC NEUROPATHY"/

20	Medline	(spondylosis).ti,ab
21	Medline	(lumbago).ti,ab
22	Medline	(12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21)
23	Medline	exp SPINE/
24	Medline	(discitis).ti,ab
25	Medline	exp "SPINAL DISEASES"/
26	Medline	(disc ADJ degeneration).ti,ab
27	Medline	(disc ADJ prolapse).ti,ab
28	Medline	(disc ADJ herniation).ti,ab
29	Medline	(spinal fusion).su
30	Medline	(facet ADJ joints).ti,ab
31	Medline	(intervertebral disc).su
32	Medline	(postlaminectomy).ti,ab
33	Medline	(arachnoiditis).ti,ab
34	Medline	(failed ADJ back).ti,ab
35	Medline	(23 OR 24 OR 25 OR 26 OR 27 OR 28 OR 29 OR 30 OR 31 OR 32 OR 33 OR 34)
36	Medline	(22 OR 35)
37	Medline	exp "RADIO WAVES"/
38	Medline	exp "PULSED RADIOFREQUENCY TREATMENT"/
39	Medline	(radiofrequency).af
40	Medline	(radio frequency).af

41	Medline	exp ELECTROCOAGULATION/
42	Medline	(electrocoag*).af
43	Medline	(thermocoag*).af
44	Medline	neurotom* OR (neuroly*).af
45	Medline	(37 OR 38 OR 39 OR 40 OR 41 OR 42 OR 43 OR 44)
46	Medline	(11 AND 36 AND 45)
47	EMBASE	"CLINICAL TRIAL"/
48	EMBASE	"CONTROLLED CLINICAL TRIAL"/
49	EMBASE	"CONTROLLED STUDY"/
50	EMBASE	"RANDOMIZED CONTROLLED TRIAL"/
51	EMBASE	"DOUBLE BLIND PROCEDURE"/
52	EMBASE	"SINGLE BLIND PROCEDURE"/
53	EMBASE	"CROSSOVER PROCEDURE"/
54	EMBASE	PLACEBO/
55	EMBASE	(allocat*).ti,ab
56	EMBASE	(assign*).ti,ab
57	EMBASE	(blind*).ti,ab
58	EMBASE	(clinic* ADJ25 (study OR trial)).ti,ab
59	EMBASE	(crossover OR cross-over).ti,ab
60	EMBASE	(factorial*).ti,ab
61	EMBASE	(followup OR follow-up).ti,ab
62	EMBASE	(prospectiv*).ti,ab

63	EMBASE	(placebo*).ti,ab
64	EMBASE	(random*).ti,ab
65	EMBASE	((singl* OR doubl* OR trebl* OR trip*) ADJ25 (blind* OR mask*)).ti,ab
66	EMBASE	(volunteer*).ti,ab
67	EMBASE	(47 OR 48 OR 49 OR 50 OR 51 OR 52 OR 53 OR 54 OR 55 OR 56 OR 57 OR 58 OR 59 OR 60 OR 61 OR 62 OR 63 OR 64 OR 65 OR 66)
68	EMBASE	exp animals/ or exp invertebrate/ or animal experiment/ or animal model/ or animal tissue/ or animal cell/ or nonhuman/
69	EMBASE	exp ANIMALS/
70	EMBASE	exp INVERTEBRATE/
71	EMBASE	ANIMAL EXPERIMENT/
72	EMBASE	ANIMAL MODEL/
73	EMBASE	ANIMAL TISSUE/
74	EMBASE	ANIMAL CELL/
75	EMBASE	NONHUMAN/
76	EMBASE	71 or 72 or 73 or 74 or 75
77	EMBASE	exp ANIMALS/
78	EMBASE	exp INVERTEBRATE/
79	EMBASE	(76 OR 77 OR 78)
80	EMBASE	77 or 78
81	EMBASE	HUMAN/ OR NORMAL HUMAN/ OR HUMAN CELL/
82	EMBASE	(76 AND 77 AND 78 AND 81)

83	EMBASE	(dorsalgia).ti,ab
84	EMBASE	(back pain).ti,ab
85	EMBASE	exp BACKACHE/
86	EMBASE	(lumbar ADJ pain).ti,ab
87	EMBASE	(coccyx).ti,ab
88	EMBASE	(coccydynia).ti,ab
89	EMBASE	(sciatica).ti,ab
90	EMBASE	ISCHIALGIA/
91	EMBASE	(spondylosis).ti,ab
92	EMBASE	(lumbago).ti,ab
93	EMBASE	(back disorder*).ti,ab
94	EMBASE	(83 OR 84 OR 85 OR 86 OR 87 OR 88 OR 89 OR 90 OR 91 OR 92 OR 93)
95	EMBASE	exp SPINE/
96	EMBASE	(discitis OR diskitis).ti,ab
97	EMBASE	exp "SPINE DISEASE"/
98	EMBASE	(disc ADJ degeneration).ti,ab
99	EMBASE	(disc ADJ prolapse).ti,ab
100	EMBASE	(disc ADJ herniation).ti,ab
101	EMBASE	(spinal fusion).ti,ab
102	EMBASE	(facet ADJ joints).ti,ab
103	EMBASE	(intervertebral disk OR Intervertebral disc).ti,ab
104	EMBASE	(postlaminectomy).ti,ab

105	EMBASE	(arachnoiditis).ti,ab
106	EMBASE	(failed ADJ back).ti,ab
107	EMBASE	(95 OR 96 OR 97 OR 98 OR 99 OR 100 OR 101 OR 102 OR 103 OR 104 OR 105 OR 106)
108	EMBASE	94 or 107
109	EMBASE	exp PULSED RADIOFREQUENCY TREATMENT/
110	EMBASE	exp RADIOFREQUENCY/
111	EMBASE	exp RADIOFREQUENCY RADIATION/
112	EMBASE	(radiofrequency OR radio-frequency).ti,ab
113	EMBASE	exp THERMOCOAGULATION/ OR thermocoag*
114	EMBASE	exp ELECTROCOAGULATION/ OR electrocoag*
115	EMBASE	(neurotom* OR neuroly*).ti,ab
116	EMBASE	(109 OR 110 OR 111 OR 112 OR 113 OR 114 OR 115)
117	EMBASE	(108 AND 116)
118	Medline	46 [DT 2014-2019]

Medline in process

#	Database	Search term
1	Medline	("randomi*ed controlled trial").ti,ab
2	Medline	("controlled clinical trial").ti,ab
3	Medline	("randomi*ed").ab
4	Medline	(placebo).ti,ab
5	Medline	("drug therapy").fs

6	Medline	(randomly).ti,ab
7	Medline	(trial).ti,ab
8	Medline	(groups).ti,ab
9	Medline	(1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8)
10	Medline	(dorsalgia).ti,ab
11	Medline	("back pain").ti,ab
12	Medline	(backache).ti,ab
13	Medline	("lumber pain").ti,ab
14	Medline	(coccyx).ti,ab
15	Medline	(coccydynia).ti,ab
16	Medline	(sciatica*).ti,ab
17	Medline	(spondylosis).ti,ab
18	Medline	(lumbago).ti,ab
19	Medline	(10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18)
20	Medline	(spine OR sacrum OR "lumber vertebrae" OR "intervertebral disc*").ti,ab
21	Medline	(discitis).ti,ab
22	Medline	("disc degeneration").ti,ab
23	Medline	("disc prolapse").ti,ab
24	Medline	("disc herniation").ti,ab
25	Medline	("spinal fusion").ti,ab
26	Medline	("facet joints").ti,ab

27	Medline	(postlaminectomy).ti,ab
28	Medline	(arachnoiditis).ti,ab
29	Medline	("failed back").ti,ab
30	Medline	(20 OR 21 OR 22 OR 23 OR 24 OR 25 OR 26 OR 27 OR 28 OR 29)
31	Medline	(19 OR 30)
32	Medline	(radiowave* OR "radio wave*").ti,ab
33	Medline	(radiofrequency OR "radio frequency").ti,ab
34	Medline	(electrocoag*).ti,ab
35	Medline	(thermocoag*).ti,ab
36	Medline	(neurotom* OR neuroloy*).ti,ab
37	Medline	(32 OR 33 OR 34 OR 35 OR 36)
38	Medline	(9 AND 31 AND 37)
39	Medline	38 [Document status In Data Review OR In Process OR PubMed not MEDLINE OR Publisher]

Cinahl

#	Database	Search term
1	CINAHL	exp "CLINICAL TRIALS"/
2	CINAHL	("randomi*ed controlled trial*").ti,ab
3	CINAHL	(clinical ADJ3 trial).ti,ab
4	CINAHL	(double-blind).ti,ab
5	CINAHL	(single-blind).ti,ab
6	CINAHL	(triple-blind).ti,ab

7	CINAHL	(1 OR 2 OR 3 OR 4 OR 5 OR 6)
8	CINAHL	"PLACEBO EFFECT"/
9	CINAHL	PLACEBOS/
10	CINAHL	(placebo*).ti,ab
11	CINAHL	(random*).ti,ab
12	CINAHL	(8 OR 9 OR 10 OR 11)
13	CINAHL	"RANDOM SAMPLE"/
14	CINAHL	exp "STUDY DESIGN"/
15	CINAHL	(latin square).ti,ab
16	CINAHL	exp "COMPARATIVE STUDIES"/
17	CINAHL	exp "EVALUATION RESEARCH"/
18	CINAHL	exp "PROSPECTIVE STUDIES"/
19	CINAHL	(13 OR 14 OR 15 OR 16 OR 17 OR 18)
20	CINAHL	(follow-up stud*).ti,ab
21	CINAHL	(followup stud*).ti,ab
22	CINAHL	(control*).ti,ab
23	CINAHL	(prospectiv*).ti,ab
24	CINAHL	(volunteer*).ti,ab
25	CINAHL	(20 OR 21 OR 22 OR 23 OR 24)
26	CINAHL	(7 OR 12 OR 19 OR 25)
27	CINAHL	ANIMALS/
28	CINAHL	26 not 27

29	CINAHL	("dorsalgia").ti,ab
30	CINAHL	exp "BACK PAIN"/
31	CINAHL	"LOW BACK PAIN"/
32	CINAHL	("backache").ti,ab
33	CINAHL	(lumbar ADJ1 pain).ti,ab
34	CINAHL	(lumbar ADJ5 pain).ti,ab
35	CINAHL	(29 OR 30 OR 31 OR 32 OR 33 OR 34)
36	CINAHL	COCCYX/
37	CINAHL	SCIATICA/
38	CINAHL	(sciatica).ti,ab
39	CINAHL	(coccyx).ti,ab
40	CINAHL	(coccydynia).ti,ab
41	CINAHL	"LUMBAR VERTEBRAE"/
42	CINAHL	(lumbar ADJ2 vertebra).ti,ab
43	CINAHL	(36 OR 37 OR 38 OR 39 OR 40 OR 41 OR 42)
44	CINAHL	"THORACIC VERTEBRAE"/
45	CINAHL	exp SPONDYLOLYSIS/
46	CINAHL	(lumbago).ti,ab
47	CINAHL	(44 OR 45 OR 46)
48	CINAHL	(35 OR 43 OR 47)
49	CINAHL	(28 AND 48)
50	CINAHL	(radiofrequency OR radio-frequency).ti,ab

51	CINAHL	(thermocoag*).ti,ab
52	CINAHL	exp ELECTROCOAGULATION/ OR electrocoag*
53	CINAHL	(neurotom* OR neuroly*).ti,ab
54	CINAHL	"RADIO WAVES"/
55	CINAHL	(50 OR 51 OR 52 OR 53 OR 54)
56	CINAHL	(49 AND 55)
57	CINAHL	56 [DT 2014-2019]

Cochrane

#	Database	Search term
1	Cochrane	MeSH descriptor: [Back Pain] explode all trees
2	Cochrane	dorsalgia
3	Cochrane	backache
4	Cochrane	MeSH descriptor: [Low Back Pain] explode all trees
5	Cochrane	lumbar next pain or coccyx or coccydynia or spondylosis
6	Cochrane	MeSH descriptor: [Spine] explode all trees
7	Cochrane	MeSH descriptor: [Spinal Diseases] explode all trees
8	Cochrane	lumbago OR discitis OR disc near degeneration OR disc near prolapse OR disc near herniation
9	Cochrane	spinal fusion
10	Cochrane	facet near joints
11	Cochrane	MeSH descriptor: [Intervertebral Disk] explode all trees
12	Cochrane	postlaminectomy

13	Cochrane	arachnoiditis
14	Cochrane	failed near back
15	Cochrane	MeSH descriptor: [Cauda Equina] explode all trees
16	Cochrane	lumbar near vertebra*
17	Cochrane	spinal near stenosis
18	Cochrane	slipped near (disc* or disk*)
19	Cochrane	degenerat* near (disc* or disk*)
20	Cochrane	stenosis near (spine or root or spinal)
21	Cochrane	displace* near (disc* or disk*)
22	Cochrane	prolap* near (disc* or disk*)
23	Cochrane	MeSH descriptor: [Sciatic Neuropathy] explode all trees
24	Cochrane	sciatic*
25	Cochrane	back disorder*
26	Cochrane	back near pain
27	Cochrane	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #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
28	Cochrane	MeSH descriptor: [Radio Waves] explode all trees
29	Cochrane	MeSH descriptor: [Pulsed Radiofrequency Treatment] explode all trees
30	Cochrane	radiofrequency
31	Cochrane	radio frequency or radio-frequency
32	Cochrane	MeSH descriptor: [Electrocoagulation] explode all trees
33	Cochrane	electrocoag*

34	Cochrane	thermocoag*
35	Cochrane	neurotom* or neuroly*
36	Cochrane	#28 or #29 or #30 or #31 or #32 or #33 or #34 or #35
37	Cochrane	#27 and #36 in Trials

Appendix 2 Study characteristics

Study	N	Inclusion criteria		Mean age (SD)	Mean pain score (SD)	Intervention	Control	Funding
RD of the facet joints								
Gallagher 1994	41	Low back pain >3 months duration with symptoms typical of facet joint pain	Improvement (n=30) or equivocal (n=11) response to anaesthetic block	NR	VAS RD 5.8 (1.78); Sham 7.2 (1.94)	Nerves above and below painful joint denervated at 80° for 90 seconds.	Nerves also identified with stimulation but no heat lesion made	NR
Juch 2017	251	Low back pain without response to conservative management and considered to be related to the facet joint	Positive response to anaesthetic block (reported 50% pain relief 30-90 minutes after block)	RD 53.0 (11.5); Control 52.6 (10.8)	NRS RD 7.14 (1.38) Control 7. 19 (1.29)	Denervation at 90° for 90s of L3-4, L4-5 or L5-S1 with exercise program	Exercise program	The Netherlands Organization for Health Research and Development, by the Dutch Society for Anesthesiology, and the Dutch health insurance companies
Leclaire 2001	70	Low back pain for >3 months	“Significant” relief of back pain for >24h following facet injections	RD 46.7 (9.3); Sham 46.4 (9.8)	VAS RD 5.19 (2.67); Sham 5.15 (2.08)	RD with fluoroscopic guidance at 80°C for 90s of at least 2 levels	Nerves also identified with stimulation but electrode only heated to 37°C	Institut de recherche en sante´ and se´curite´ du travail du Que´bec
Moussa 2016	80	Low back pain for >1 year without response to conservative management	Complete or near complete reduction of CLBP on VAS 30 min after 2	RD capsule 58.1 (NR); RD conventional 56.5 (NR);	VAS RD 8.22 (NR); Sham 7.83 (NR)	RD of facet capsule on medial and lateral aspect or	Same procedure without elect current turned on	No funding received

			injections separated by >2 weeks	Sham 55.9 (NR)		conventional RD at 85°C for 90s		
Nath 2008	40	Low back pain for >2 years, not responded to previous treatment, pain attributable to lumbar facet joints	80% pain relief on 3 medial branch blocks	56 (range, 36–79)	VAS RD 5.98 (NR); Sham 4.38 (NR)	RD at 85°C for 60s with additional lesions just lateral and medial to the target nerve	Same procedure as RD but electrode tip remained at body temperature	No funding received
Tekin 2007	40	Back pain for >6 months with focal pain over the facet joints and unresponsive to conservative treatments	>50% reduction in VAS pain 30 minutes after diagnostic medial branch block	RD 60.5 (8.5); Sham 57.9 (9.3)	VAS RD 6.5 (1.5); Sham 6.8 (1.6)	RD at same levels as diagnostic blocks at 80°C for 90s.	Same procedure as RD but with current switched off	Not reported
Van Kleef 1999	32	Low back pain of >12 months duration, failure of conservative management	>50% reduction in pain following diagnostic nerve block of L3-L5 Baseline VAS score of >4	RD 46.6 (7.4); Sham 41.4 (7.5)	VAS RD 5.2 (1.7); Sham 5.2 (1.6)	RD at 80°C for 60s	Same procedure as RD but with current switched off	The Nederlandse organisatie voor wetenschappelijk
Van Tilburg 2016	60	Low back pain for >3 months and failure of conservative management	Decrease of >2 on medial branch block	RD 65 (12); Sham 58 (12)	NRS RD 7.2 (1.4); Sham 7.4 (0.8)	RD at 80°C for 60s per level for three steps with physiotherapy	Same procedure as RD but with current switched off with physiotherapy	No funding from a commercial party
Van Wijk 2005	81	Low back pain for >6 months	≥50% reduction on	RD 46.9 (11.5);	VAS RD 5.8 (1.8);	RD 80°C for 60 seconds	Same procedure as	Grant from the Dutch Health

			diagnostic block	Sham 48.1 (12.6)	Sham 6.5 (1.8)	at the levels concerned	RD but with current switched off	Insurance Council
RD of the sacroiliac joints								
Cohen 2008	28	Axial low back or buttock pain ≥ 6 months, tenderness overlying the sacroiliac joint(s), failure to respond to conservative therapy	≥ 75% pain relief for ≥3h following diagnostic sacroiliac joint injection, but back near baseline within 2 months	RD 51.9 (13.6); Sham 51.8 (13.1)	VAS RD 6.1 (1.8); Sham 6.5 (1.9)	RD 80°C for 90 seconds using cooling probe technology (Cooled RD)	Same procedure as RD but no current applied	John P. Murtha Neuroscience and Pain Institute, the Army Regional Anesthesia & Pain Medicine Initiative, and National Institutes of Health grant # MH075884
Juch 2017	228	Low back pain without response to conservative management, considered to be related to the sacroiliac joint.	Positive response to anaesthetic block (reported 50% pain relief 30-90 minutes after block)	RD 51.6 (10.9); Control 51.1 (12.2)	NRS RD 7.17 (1.65); Control 7.06 (1.43)	RD - 60° for 2.5 min per lesion of S1, S2 and S3 with exercise program	Exercise program	The Netherlands Organization for Health Research and Development, by the Dutch Society for Anesthesiology, and the Dutch health insurance companies
Mehta 2018	17	CLBP for >6 months. >5 on NRS	>80% pain reduction on 2 diagnostic blocks	RD 56.6 (NR); Sham 62.6 (NR)	VAS RD 8.1 (0.8); Sham 7.3 (0.8)	RD of the L5 medial branch of the primary dorsal root nerve and strip lesioning of the lateral branches	Identical to active RD treatment except that no RF energy was applied	None

						of the S1, 2, and 3 nerve roots		
Patel 2012	51	Pain for ≥6 months, 3-day average NRS between 4 and 8, failure of conservative management	≥75% pain reduction for 4h-7 days on two sets of anaesthetic blocks and back to baseline by start of the study	RD 56 (15); Sham 64 (14)	NRS RD 6.1 (1.3); Sham 5.8 (1.3)	RD at 60°C for 150s of L5 dorsal ramus and then acral lateral branches of S1, S2 and S3 (cooled RD)	Same procedure as RD but RF energy was not delivered.	Baylis Medical
Van Tilburg 2016	60	Sacroiliac joint pain for >3 months, failure of conservative management	Decrease of ≥2 on NRS following diagnostic block	RD 59.5 (27); Sham 62 (18)	NRS RD 7.2 (1.4); Sham 7.5 (1.2)	85°C each step for 90s, total of 5 steps	Same procedure as RD but no heat lesions made	Not reported
RD of the intervertebral discs								
Barendse 2001	28	Non-specific LBP for >1y, failure of conservative management	>50% pain relief 30 minutes after an analgesic discography at L4–L5 and L5–S1. Patients with multilevel pain excluded	RD 40.8 (7.5); Sham 45.2 (8.4)	VAS RD 6.5 (1.3); Sham 5.5 (1.1)	70°C for 90s without anaesthetic	Same procedure as RD but no current applied	Not reported
Desai 2016	63	Lumbar discogenic pain for ≥6 months, unresponsive to conservative management	Diagnosed via provocation discography - definite single-level concordant	Mean age 41 (11); Control 43 (11)	VAS RD 6.7 (NR); Sham 7 (NR)	RD at 50°C for 15 minutes and then 60°C for 2.5 min (bopolar cooled RD) with conventional	Conventional medical management	Halyard Health, Inc. (formerly Kimberly-Clark Health Care)

			pain on manometry			medical management		
Kapural 2013	55	CLBP unresponsive to conservative management for ≥6 months; no surgical interventions within previous 3 months	Single-level degenerative disc disease or two-level disease without evidence of additional degenerative changes in other disc spaces on MRI	RD 40.4 (10.3); Sham 38.4 (10.4)	VAS RD 7.13 (1.61); Sham 7.18 (1.98)	RD at 45°C bipolar for 15 minutes or 50°C bipolar for 15 minutes and monopolar at 60°C for 2.5 minutes	Mimicked active treatment, except that introducers and electrodes positioned just outside of the disc, and no RF energy delivered	Baylis Medical
Kvarstein 2009	20	Unremitting low back pain for more than 6 months; Pain intensity ≥5 /10 and low back pain greater than leg pain; Failure on conservative treatment	Positive one-level pain provocation discography	RD 44.7 (10.1); Sham 39.6 (8.9)	NRS RD 4.6 (1.8); Sham 5.5 (2.0)	RD increased by 5°C every second minute to 4-min interval at 65°C (from 50°C)	Exposed to a similar intervention, but the annulus was not exposed to RF heating	Radionics, TYCO Healthcare Group provided the discTRODE probes
Van Tilburg 2017	60	Low back pain >3 months and symptoms suggestive of lumbar disc problem	Reduction of ≥2 on a numerical rating scale (0–10) after a diagnostic ramus communicans test block	RD 50.5 (13.9); Sham 50.1 (12.3)	NRS 7.8 (1.05); Sham 7.8 (1.05)	RD treatment at 80 °C for 60s per level	Same procedure but without RF treatment	No support received that influenced submitted work
RD of the vertebrae body and endplate								

Fischgrund 2018	225	CLBP ≥6 months, not responded to conservative treatment, Type 1 or Type 2 Modic changes required at the proposed treatment levels	No diagnostic block for inclusion	RD 46.9 (range 26–69); Sham 47.1 (range 25–69)	VAS RD 6.73 (1.38); Sham 6.64 (1.34)	Thermal ablation at the terminus of the basivertebral nerve 85°C for 15 min	Same procedure as RD but only docking introducer cannula 1–2 mm into the pedicle and simulating RD	Not reported

CLBP, chronic low back pain; N, number of trials; NRS, numeric rating scale; RD, radiofrequency denervation; SD, standard deviation; VAS, visual analogue scale.