

COMPARATIVE CLINICAL EFFECTIVENESS OF MANAGEMENT STRATEGIES FOR SCIATICA: SYSTEMATIC REVIEW AND NETWORK META-ANALYSES

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ABSTRACT

Background

There are numerous treatment approaches for sciatica. Previous systematic reviews have not compared all these strategies together.

Purpose

To compare the clinical effectiveness of different treatment strategies for sciatica simultaneously.

Study design

Systematic review and network meta-analysis.

Methods:

We searched 28 electronic databases and online trial registries, along with bibliographies of previous reviews, for comparative studies evaluating any intervention to treat sciatica in adults, with outcome data on global effect or pain intensity. Network meta-analysis methods were used to simultaneously compare all treatment strategies and allow indirect comparisons of treatments between studies. The study was funded by the UK National Institute for Health Research (NIHR) HTA programme; there are no potential conflict of interests.

Results

Of 122 relevant studies, 90 were randomised controlled trials (RCTs) or quasi-RCTs. Interventions were grouped into 21 treatment strategies. Internal and external validity of included studies was very low. For overall recovery as the outcome, compared with inactive control or conventional care, there was a statistically significant improvement following disc surgery, epidural injections, non-opioid analgesia, manipulation, and acupuncture. Traction, percutaneous discectomy and exercise therapy were significantly inferior to epidural injections or surgery. For pain reduction

as the outcome, epidural injections and biological agents were significantly better than inactive control, but similar findings for disc surgery were not statistically significant. Biological agents were significantly better for pain reduction than bed rest, non-opioids, and opioids, ~~or radiofrequency treatment~~. Opioids, education/advice alone, bed rest, and percutaneous discectomy ~~and radiofrequency treatment~~ were inferior to most other treatment strategies; although these findings represented large effects, they were statistically equivocal.

Conclusions

For the first time many different treatment strategies for sciatica have been compared in the same systematic review and meta-analysis. This approach has provided new data to assist shared decision-making. The findings support the effectiveness of non-opioid medication, epidural injections and disc surgery. They also suggest that spinal manipulation, acupuncture, and experimental treatments such as anti-inflammatory biological agents, may be considered. The findings do not support the effectiveness of opioid analgesia, bed rest, exercise therapy, education/advice (when used alone), percutaneous discectomy or traction. The issue of how best to estimate the effectiveness of treatment approaches according to their order within a sequential treatment pathway remains an important challenge.

KEY WORDS

Systematic Review; Sciatica; Intervertebral disc herniation; network meta-analyses; indirect treatment comparisons; Clinical Effectiveness; treatment strategies

INTRODUCTION

Sciatica is the term used for the syndrome characterised by radicular leg pain, with or without sensory deficits, radiating along the distribution of the sciatic nerve.¹⁻³ In about 90% of cases, it is caused by an intervertebral disc herniation resulting in nerve root irritation.⁴⁻⁶ It is a common reason for seeking medical advice,^{7,8} and has considerable economic consequence in terms of healthcare resources and lost productivity.⁷ The diagnosis and management of sciatica varies considerably within and between countries,⁴ which may reflect treatment availability, clinician preference and socio-economic variables rather than evidence-based practice.

Previous systematic reviews (including meta-analyses) have evaluated the effectiveness of various individual treatment approaches for sciatica, including conservative treatments,⁹⁻¹² epidural steroid injections,^{9,11,13,14} and surgical procedures.¹⁵ However, numerous treatments have not been directly compared. Furthermore, in order to choose the optimal treatment(s), it would be more helpful if all candidate treatments could be compared in the same analysis, as opposed to using a series of simple but inefficient standard pairwise meta-analyses comparing only two treatments at a time. It has been acknowledged that there is difficulty in interpreting the findings of multiple comparisons with low power, due to the small number of participants or events, which are inclined to result in statistically insignificant findings.^{16,17}

A network meta-analysis,¹⁸ by contrast, enables the simultaneous comparison of more than two treatment approaches, whilst combining data derived from both direct within-study comparisons between two treatment strategies (e.g A vs B) and comparisons constructed from two studies that have one treatment in common (e.g. A vs B, B vs C).¹⁷ This type of analysis can only be applied to connected networks of randomised controlled trials (RCTs),¹⁹ but preserves the within-trial randomised comparison of each study¹⁹ and allows information on treatment strategies to be “borrowed” from other studies within the network, thereby increasing the total sample size.^{20,21} Network meta-analysis conducted using Bayesian methods²²⁻²⁴ also allows the treatment strategies to be ranked in terms of clinical effectiveness with an estimate of the probability that each strategy is ‘best’.²⁵

Our primary aims were to simultaneously compare the clinical effectiveness of different treatment strategies for sciatica using network meta-analyses, in order to identify the best treatment and to provide estimates for all possible pairwise comparisons, based on both direct and indirect evidence. Our secondary aims were

to demonstrate the feasibility of using network meta-analyses as a rational basis for clinical decision making when a number of treatment options are available and where a series of conventional systematic reviews have failed to help with real-world treatment decisions. The analyses presented in this paper represent a refinement of initial network meta-analyses conducted as part of a broader Health Technology Assessment (HTA) evaluating the clinical and cost effectiveness of treatments for sciatica. A full account of the study methods and literature search are presented in the HTA monograph (which also includes the protocol).¹⁶

METHODS

Search strategy

Included studies were identified via an extensive literature search described in full, including the search strategy, in the HTA monograph.¹⁶ The search incorporated 28 electronic databases and trial registries including MEDLINE, EMBASE, and AMED. Databases were searched from inception until December 2009 without language restriction. The reference lists of previous systematic reviews and included studies were also scanned for further references.

Study selection and data extraction

This review included any comparative study (experimental or observational) with adults who had sciatica diagnosed clinically, or where clinical imaging confirmed lumbar disc prolapse consistent with the clinical findings. The essential clinical criterion was radicular leg pain worse than back pain.¹⁶ Studies of sciatica caused by conditions other than a prolapsed intervertebral disc were included if it was documented that radicular leg pain was worse than back pain. If imaging was used, it had to demonstrate evidence of nerve root compromise. Studies that included participants with non-specific low back pain were only included if the findings for patients with sciatica were reported separately. Any type of intervention to treat

sciatica was considered. These were categorised, for the purpose of the present analyses, into one of 21 categories (See Table 1). Interventions that included a combination of more than one treatment strategy (or mixed treatments) were excluded from the network meta-analyses due to uncertainty regarding the extent of interaction between the combined interventions. The same applied to post-surgical interventions due to surgery being included as a separate treatment category. Studies comparing interventions that were grouped under the same treatment strategy were also excluded. Three further studies evaluating experimental interventions for sciatica (common peroneal nerve block,²⁶ proteolytic enzyme,²⁷ and colchicine²⁸) were excluded from the analyses as these interventions did not fit the treatment categorisation. For the present network meta-analyses we concentrated on overall response and pain intensity rather than back specific function, **so three studies which only reported outcome data for back specific function were excluded.**²⁹⁻

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[Table 1: Treatment categorisation]

Two reviewers screened studies for inclusion independently. Data were extracted by one reviewer and checked by a second using the original paper, whilst quality assessment was done by two reviewers independently. Any disagreements were resolved by discussion. The quality of both trials and observational studies was assessed using the same checklist, which was based on one used by the Back Review Group of the Cochrane Collaboration for RCTs³² and another recommended by the Guidelines for Systematic Reviews in Health Promotion and Public Health Taskforce³³ (developed by the Effective Public Health Practice Project, Canada³⁴). The criteria covered external validity, selection bias and confounding, detection bias, performance bias, and attrition bias. Studies were coded as strong, moderate or weak for each domain, estimating the risk of bias.

Outcome measures

Overall response or global effect was analysed as a binary outcome (treatment success vs failure) and synthesised using odds ratios (ORs). Where studies reported overall response in terms of both overall improvement and improvement in leg pain, the data on overall improvement were used. For studies that reported both physician and patient perceived global effect, the data for patients' perceived effect were used.

Pain intensity (on a scale of 0-100) was analysed as a continuous outcome measure using weighted mean difference (WMD). We only included pain assessment from one location from each study using the preference hierarchy of leg pain then overall pain. Where feasible, missing data were estimated from the published data, using standard methods, such as standard deviations (SDs) derived from standard errors (SEs).³⁵ Where mean values were unavailable but the medians were reported, these were used instead. If SDs for baseline values were available these were substituted for missing SDs. For studies that did not report sufficient data to derive the SDs, they were imputed using the weighted mean,³⁶ which was calculated separately for each intervention category.

Statistical analysis

The network meta-analyses were based on a single time point, using the findings from individual studies closest to six months follow-up. Sensitivity analyses were conducted to assess the impact of excluding non-randomised studies (observational studies and non-RCTs).

The network meta-analyses were conducted using a hierarchical random-effects model¹⁸ within the Bayesian framework. Bayesian methods are based on the idea that unknown quantities, such as population means or proportions, have probability

distributions.²³ You start with a distribution that is based on prior knowledge or subjective belief about the population and then update this using data from your included studies. However, using non-informative priors (such as, a normal distribution with a large variance) means that the results are based predominantly on the data from the included studies, and as such will mirror those obtained using frequentist or classical meta-analysis methods. Bayesian methods are implemented using model-based simulations, which means that they can be used to perform complex analyses that incorporate multiple data sources and allow for various parameter uncertainties within a single coherent model, which is why we chose to use these methods.

Our network meta-analyses were conducted using WinBUGS1.4.3 software,³⁷ which uses Markov chain Monte Carlo (MCMC) simulation methods to run thousands of simulated iterations based on the data and description of the proposed distributions for relevant parameters. The iterative simulations are generally started at multiple points in order to ensure the samples are drawn from the whole sampling frame. The first 50,000 iterations (or burn-in) were discarded, and the results are based on a further sample of at least 50,000 simulations, ensuring that the multiple simulation strings have converged and distributions were informed by later simulations.

Numerical methods such as the Brooks-Gelman-Rubin statistic³⁷ and the inspection of the auto-correlation and history plots, which are routine assessments made when using MCMC methods, were used to check that convergence had occurred. The model fit was checked by the global goodness of fit statistic, residual deviance. If the model is an adequate fit, it is expected that the residual deviance should be roughly equal to the number of data points.¹⁹ Non-informative priors were used for normal distributions for means, and uniform distributions for standard deviations. The treatment strategy 'inactive control' was used as the reference treatment. This included interventions that represent the non (active) treatment of sciatica, such as

no treatment, sham treatment, or placebo (two studies used active placebo). The WinBUGS codes (or models) that we used are presented in Supplementary Material (Web Appendix A). The robustness of the network meta-analyses were also evaluated by comparing the findings (where head to head studies were available) with those of standard 'direct' pairwise meta-analyses¹⁶ conducted using a random-effects model³⁸ based on frequentist methods²²⁻²⁴ in Stata 10.

The assumptions of a random-effects network meta-analysis are that (1) the treatment effects are additive (i.e. the relative effect of treatment A vs C can be estimated from the effect of A vs B and B vs C);^{19,39,40} (2) study-specific treatment effects are drawn from a common distribution (exchangeable);^{19,41} and (3) this common distribution or heterogeneity is constant between the different comparisons.^{19,41} We evaluated heterogeneity between studies, defined as the variability of the results across studies within each treatment comparison over and above chance,⁴² by examining the findings of standard pairwise meta-analyses using visual inspection of the forest plots, as well as Chi² statistic to test for the I² statistic to quantify statistical heterogeneity.^{43,44}

RESULTS

Included studies

As seen in Figure 1, 122 studies were included in the revised network meta-analyses⁴⁵⁻¹⁶⁵ (one publication included two studies¹¹⁹), 86 were RCTs^{48,49,51,52,54,56-62,64,66,67,69-71,73-76,78-83,85,87-90,93,95-97,99-101,103,105-107,110,111,114-124,126-128,130,132-141,143-145,149-155,158,159,161,164} and four Q-RCTs.^{46,91,104,109} The network meta-analysis of global effect included 95 studies (68 RCTs/Q-RCTs) and pain intensity 53 studies (46 RCTs/Q-RCTs). A description of the interventions, populations, study design, and outcome

data for the pairwise studies are presented in Supplementary Material (Web Appendix B).

[Figure 1: flow diagram showing the number of references identified, publications retrieved for assessment, and studies included in the review]

Eleven (9%) studies had a strong overall quality rating^{58,79,97,99,116,128,132,140,152,155,161} and eight (7%) had a strong overall external validity rating;^{97,100,116,121,128,140,153,155} five (4%) of which had a strong rating for both.^{97,116,128,140,155} Only 26 (21%) studies used both adequate randomisation and adequate or partially adequate (using sealed envelopes, n=16) allocation concealment.

The proportion of studies that limited inclusion to patients with acute sciatica (duration of symptoms <3 months) was much higher in conservative treatments, such as traction (71%), bed rest (80%), and non-opioid medication (53%), than more invasive treatments (such as disc surgery 8%, chemonucleolysis 3%, and epidural 5%). However, most studies did not report the duration of sciatica, or included patients with acute and chronic sciatica. The presence of disc herniation was also confirmed by imaging in a high proportion of studies evaluating invasive treatments such as percutaneous discectomy (100%), disc surgery (86%) and chemonucleolysis (84%). Previous treatment was poorly reported in many studies, but the proportion of studies that reported patients who had received previous treatment was higher for invasive treatments such as disc surgery (70%), percutaneous discectomy (100%), and chemonucleolysis (88%), than for conservative treatments such as non-opioids (20%), traction (29%), and acupuncture (33%). The mean pain score (where reported), at baseline for each treatment strategy were fairly similar (ranging from 59 to 69) with the exception of biological agents (78).

Figure 2 shows the network of treatment comparisons for the network meta-analysis of global effect and Figure 3 shows the same for the analysis of pain intensity.

[Figure 2: Network of treatment strategies for sciatica for comparative studies reporting global effect]

[Figure 3: Network of treatment strategies for sciatica for comparative studies reporting pain intensity]

Summary effect estimates for the comparison of each intervention strategy with inactive control are presented in Figures 4-5. The corresponding confidence intervals (CIs) provide an indication of the uncertainty surrounding the effect sizes, which needs to be taken into account when interpreting the data (especially the probability of being best). The probabilities for each treatment strategy being best (or most effective) are presented in Supplementary Material (Web Appendix C). The network meta-analyses also provide a full set of comparisons for all treatment strategies, the findings of which are presented in Tables 2-3. The summary effect sizes derived from the network meta-analyses can be directly compared with the summaries of pairwise meta-analyses (derived using Stata 10), which are presented in the same matrices (top right hand corner); statistically significant findings are indicated by shading. The results of sensitivity analyses restricted to RCTs and Q-RCTs are presented in Supplementary Material (Web Appendix C-D).

[Figure 4: Plot of the odds ratios (ORs) of global effect for different treatment strategies compared with inactive control from the network meta-analysis]

[Figure 5: Plot of the weighted mean difference for pain intensity for different treatment strategies compared with inactive control from the network meta-analysis]

[Table 2: Results (odds ratios, with 95% confidence intervals/credible intervals) of the network meta-analysis for global effect]

[Table 3: Results (weighted mean difference, with 95% confidence intervals/credible intervals) of the network meta-analysis for pain intensity]

Overall response

In terms of overall response or global effect, the following treatment comparisons with inactive control (A) or conventional care (B) were statistically significant at the 5% level: disc surgery (C), epidural injections (D), non-opioids (F), intra-operative interventions (G), which includes interventions such as barrier membranes and steroids used during the surgical procedure, spinal manipulation (I), acupuncture (J), and chemonucleolysis (E). Intradiscal injections (S) were found to be statistically significantly worse than disc surgery (C), epidural injections (D), non-opioids (F), intra-operative interventions (G), manipulation (I), and acupuncture (J). Percutaneous discectomy (Q) was found to be inferior to disc surgery (C), epidural injections (D), and intra-operative interventions (G). Traction (H) and exercise therapy (K) were also found to be inferior to epidural injections and intra-operative interventions. Radio frequency treatment (U) was statistically significantly inferior to disc surgery (C), epidural injections (D), intra-operative interventions (G), and acupuncture (J). Finally, chemonucleolysis (E) was statistically significantly less effective than epidural injections, disc surgery, and intra-operative interventions. The largest treatment effects for the comparison with inactive control were for biological agents and acupuncture, which also had the highest probability of being best (0.57 and 0.26

respectively). The comparison of biological agents with the following treatments also showed large effect estimates (OR >10), but these were not statistically significant: chemonucleolysis (E), traction (H), exercise therapy (K), passive physical therapy (such as ultrasound and transcutaneous electrical nerve stimulation) (L), bed rest (N), opioid medication (O), percutaneous discectomy (Q), intradiscal injections (S), and radio frequency treatment (U), all of which were associated with very wide confidence intervals. This reflects the limited evidence available for biological agents, which included a small placebo controlled RCT (n=24) that reported a large effect estimate in favour of biological agents (OR 10.0; 95% CI: 0.65, 166.67. see Supplementary Material Table C1).

The results of the sensitivity analyses excluding observational studies and non-RCTs showed broad agreement with the main analyses. For global effect, the most notable discrepancies occurred with biological agents compared with chemonucleolysis, conventional, and care exercise therapy. A more detailed narrative of the differences between the analyses with and without the non-randomised studies is presented in the Supplementary Material (Web Appendix D)

Pain intensity

In terms of pain intensity, the only treatment comparisons with inactive control that were statistically significant were epidural injections (D) and biological agents (M). Biological agents, which had the highest probability of being best (0.33), were also found to be statistically significantly better at reducing pain than non-opioids (F), bed rest (N), opioids (O) and radio frequency treatment (U); these findings were all associated with wide credible intervals. When considering the magnitude of effect, bed rest (N), education/advice alone (P), percutaneous discectomy (Q), and radiofrequency treatment (U) tended to fare worse when compared with most treatment strategies, with findings showing a non-statistically significant difference of

more than 25 points. Acupuncture (J), had the second highest probability of being best (0.19) and resulted in reductions of pain intensity of more than 25 points compared with bed rest, opioids, education/advice alone, percutaneous discectomy and radio frequency treatment, none of which were statistically significant and all had wide credible intervals.

For pain intensity the most notable discrepancies between the network meta-analysis with and without observational studies and non-RCTs only occurred with biological agents (vs inactive control, conventional care, disc surgery, non-opioids, intra-operative interventions, acupuncture, exercise therapy, opioids, and neuropathic painmodulators). Biological agents no longer had the highest probability of being best (0.03; see Supplementary material Table C4). These discrepancies are likely to be due to the small number of included studies with a limited number of participants evaluating biological agents (2 RCTs n=131; 1 non-randomised RCT n=72; and 1 historical cohort study n=10).

Between study heterogeneity, model fit and comparison with standard pairwise meta-analyses

Based on the Gelman-Rubin statistic, convergence occurred at around 6-8000 iterations for both outcome measures (global effect, pain intensity). The auto-correlation and history plots also showed good convergence. The goodness of fit of the models to the data, measured by the residual deviance, was found to be good for all three outcomes (Supplementary Material, Web Appendix E).

The results of the evaluation of between-study heterogeneity showed a moderate to high level¹⁶ of statistical heterogeneity for many of the pairwise comparisons, as well as across all studies as a whole. The heterogeneity was greater for the analysis of

pain intensity than global effect, with an I^2 statistic of less than 75% (i.e. moderate or less) for all but one pairwise comparison (epidural injections vs conventional care). The observed values for I^2 are presented in Figure 1. Heterogeneity did not improve when non-randomised studies were removed.

The comparison of the results from the network meta-analyses with that of the conventional pairwise meta-analyses showed broad agreement with slightly more discrepancies for the analyses of pain intensity. These discrepancies were greatest for comparisons that had very little direct evidence, **such as biological agents**.

DISCUSSION

This is the first systematic review that has included all treatment strategies for sciatica in the same analysis using a network meta-analysis method that includes indirect comparisons. The advantages of such analyses are that they can simultaneously compare more than two treatments in the same coherent analysis; provide relative effect estimates for all treatment comparisons, even those that have not been directly compared in head to head trials; enable the estimation of the probability that each treatment is best; and reduce the uncertainty in the treatment effect estimates.

Summary of results

In terms of overall response or global effect, there was a statistically significant improvement following disc surgery, epidural injections, non-opioid medication, intra-operative interventions, manipulation, and acupuncture when compared with inactive control or conventional care. **Epidural injections, disc surgery, and intra-operative interventions were also statistically significantly better than percutaneous**

discectomy, chemonucleolysis, intradiscal injections, and radiofrequency treatment., with epidural injections, and intra-operative interventions also statistically significantly better than both traction, and exercise therapy. While biological agents and acupuncture had the highest probability of being best and had the largest effect estimates when compared with inactive control, these findings were associated with very wide credible intervals, reflecting the lack of information on these effect estimates.

In terms of pain intensity, there was a statistically significant reduction in pain following epidural injections and biological agents compared with inactive control, but there was no significant difference between disc surgery and inactive control. Biological agents had the highest probability of being best, and were also statistically significantly better than non-opioid medication, opioid medication, bed rest, and radio frequency treatment. However, when the analysis was restricted to RCTs, biological agents no longer had the highest probability of being best and were not found to be statistically better than any other treatments. When considering the magnitude of effect, bed rest, education/advice alone, percutaneous discectomy, and radiofrequency treatment were considerably inferior when compared with most treatment strategies, but these findings were not statistically significant and were associated with wide credible intervals.

Overall, the results of the sensitivity analyses excluding non-randomised studies showed broad agreement with the main analyses, with the findings generally becoming non-statistically significant due to broader credible intervals for the analyses restricted to RCTs and Q-RCTs. The most notable discrepancies occurred with treatment strategies that were associated with a small number of included studies such as those reporting treatment with biological agents.

Findings of previous reviews

Previous reviews of non-surgical treatments have either found no evidence of effectiveness,^{9,10} conflicting evidence,^{11,12} or have reached different conclusions concerning the effectiveness of epidural steroid injections.^{9,11,13,14,166,167} A Cochrane systematic review of surgical interventions did not combine the results of four RCTs comparing discectomy with non-surgical treatment due to heterogeneity, and concluded that the results showed a temporary benefit of disc surgery at one year follow-up.¹⁵ In that review the effectiveness of discectomy was justified by using informal indirect comparison of chemonucleolysis with placebo, and chemonucleolysis with disc surgery; chemonucleolysis was more effective than placebo and discectomy more effective than chemonucleolysis, therefore disc surgery was superior to placebo. Using our network meta-analyses, it was possible to make a more robust statement on disc surgery compared with placebo: disc surgery was statistically significantly better than placebo in terms of global effect but not for pain intensity.

Strengths and weaknesses

One of the main strengths of our network meta-analyses is the wide range of treatment strategies used to treat sciatica that were not only considered in the same review, but compared simultaneously in the same analysis. Another strength is that they were based on a systematic and comprehensive search of the literature up (until December 2009) that covered any therapeutic intervention for sciatica. Although we acknowledge that these searches are not current, and as such, more recent relevant data is likely to have been excluded.

The RCT is widely regarded as the design of choice when assessing the effectiveness of health care interventions¹⁶⁸ and we acknowledge the controversy

over the inclusion of non-randomised evidence. Non-randomised studies were included in the search because some treatment approaches may not have been evaluated by RCTs, and also to increase the precision of the findings for interventions evaluated by a limited number of studies. Observational studies can have better external validity than RCTs^{169,170} and provide more generalisable findings. However, observational studies are likely to be affected by selection bias and confounding, and may therefore yield estimates of association that deviate from the true underlying relationship beyond the play of chance.¹⁷¹ As it happens, most of the RCTs did not report the method of generating the randomisation sequence or allocation concealment, which means that selection bias or confounding might still be present. Excluding the non-randomised studies in a sensitivity analysis did not affect the structure of the network and the overall findings of both series of network meta-analyses were similar, although less precise for the analyses of RCTs.

Network meta-analysis methods enabled us to go beyond the pairwise comparisons reported in previous systematic reviews. They allowed us to simultaneously compare all the available treatment strategies for sciatica and provided estimates of relative treatment effects for all conceivable comparisons, even those where there was no direct evidence available. However, the small number of relevant studies for some comparisons, statistical heterogeneity (within pairwise comparisons), and potential inconsistency (between pairwise comparisons) within the networks means that the encouraging results for interventions such as biological agents should be interpreted with caution.

In order to answer the question of which is the optimum treatment for sciatica and provide generalisable findings, we were interested in the average treatment effect of each treatment approach (to represent the diversity used in clinical practice). We therefore pooled clinically heterogeneous studies. We used a random-effects model

to pool the data, which is based on the assumption that different studies assessed different, yet related, treatment effects. However, included studies also varied in study design and risk of bias (methodological diversity). There was considerable ($I^2 \geq 75\%$)⁴³ statistically significant between-study heterogeneity present for a number of comparisons within the pairwise meta-analyses, especially in the analyses of pain intensity, and it was not possible to ascertain how much was due to clinical or methodological diversity. This needs to be taken into consideration in future work.

The network meta-analyses relied on the key assumption that the relative treatment effect of one treatment versus another is the same across the entire set of studies.^{18,41} The use of random-effects models meant that it was assumed that the common distribution of effects was the same across all sets of studies. A further assumption made in the analyses was that the relative efficacy of different treatments is the same at different stages in the care pathway. Pragmatically, sciatica is often treated with a stepped care approach starting with conservative treatments, such as non-opioid medication, progressing if necessary to more invasive treatments such as epidural injections or surgery. This means that the population of patients treated with conservative treatments was likely to differ from those treated with invasive treatments, resulting in confounding and inconsistency within the network. Although descriptive characteristics were generally poorly reported by included studies, there was a trend for studies evaluating invasive treatments to report a history of previous treatments and include patients with a diagnosis confirmed by imaging, and for studies of conservative treatments to limit inclusion to patients with acute sciatica. Due to the breadth of the review and the novel and speculative use of network meta-analysis methods, we have not yet incorporated stepped care approaches in the network meta-analyses. The optimum sequence of treatment modalities and what sequence is best for which patients is therefore not yet known and awaits further analysis.

The network meta-analyses were based on a single time point, outcome data closest to six months, which may be considered as a limitation of the analyses. The HTA monograph¹⁶ included an assessment of each treatment strategy at short (≤ 6 weeks), medium (> 6 weeks to ≤ 6 months) and long (> 6 months) term follow-up, but this evaluation was based on multiple pairwise analyses, with each analysis needing to be interpreted independently. Further research is needed to incorporate multiple time points within the network meta-analyses in order to incorporate data at different follow-up periods.

For the pain intensity outcome, where the SDs were missing (and could not be estimated from the published data) these were imputed using the weighted mean SD^{36,172} for each treatment strategy (11 studies). This is based on the assumption that the variance is similar between studies and the data are not skewed.¹⁷³ We also used medians to represent the mean for two studies. We considered that it was better to use these methods in order to incorporate more of the evidence base, as ignoring the findings of these studies may induce bias in the summary effect estimate.¹⁷² Furukawa, et al.³⁶ have previously shown that it is safe to borrow SDs from other studies.

There were insufficient studies to explore the presence of publication or reporting bias for most treatment comparisons. However, a funnel plot of studies comparing surgery and chemonucleolysis showed no evidence of publication bias.¹⁶ The benefit (or effectiveness) of different treatment strategies for sciatica should be considered along with potential harms. Although the present paper does not report adverse effects, they are reported elsewhere.¹⁶

CONCLUSIONS

The use of network meta-analyses has enabled us to provide new information on the relative effectiveness of treatments for sciatica. This can help clinicians and patients in shared decision making, as well as providing data for healthcare policy development. The findings provide support for the effectiveness of some common therapies for sciatica such as non-opioid medication, epidural injections and disc surgery. They also suggest that less frequently used treatments such as manipulation and acupuncture, and experimental treatments such as cytokine modulating biological agents, may be considered. The findings of this review do not support the effectiveness of opioid medication, either for pain intensity or global effect. Furthermore, there is no support for the effectiveness of numerous other interventions such as bed rest, exercise therapy, percutaneous discectomy or traction. The lack of support for education/advice should not be taken to imply that patients should not be given information or advice; rather it is not an effective treatment if delivered alone.

Further research is needed to confirm or refute these findings where we found limited evidence, and to explore the impact of heterogeneity and the range of clinical questions most suited for the use of network meta-analyses. There is also scope to develop more sophisticated methods, such as building on the confidence profile method,¹⁷⁰ bias-adjusted results,¹⁷⁴ or Bayesian statistics,¹⁶⁹ to incorporate information relating to differences in study design or internal and external validity in the network meta-analyses, as well as data on multiple follow-up periods. The issue of how best to estimate the effectiveness of treatment approaches according to their order within a sequential treatment pathway remains an important challenge.

REFERENCES

1. Deyo RA, Rainville J, Kent DL. What can the history and physical examination tell us about low back pain? . *Journal of the American Medical Association*. 1992;268(6):760-765.
2. Bush K, Cowan N, Katz DE, et al. The natural history of sciatica associated with disc pathology; a prospective study with clinical and independent radiological follow-up. *Spine* 1992;18:1433-1438.
3. Tubach F, Beaute J, Leclerc A. Natural history and prognostic indicators of sciatica. *Journal of Clinical Epidemiology* 2004;57:174-179.
4. Koes BW, van Tulder MW, Peul WC. Clinical Review: Diagnosis and treatment of sciatica *BMJ*. 2007;334:1313-1317.
5. Weber H, Holme I, Amlie E. The natural course of acute sciatica with nerve root symptoms in a double-blind placebo-controlled trial evaluating the effect of piroxicam. *Spine* 1993;18:1433-1438.
6. Mixer WJ, Barr JS. Rupture of the intervertebral disc with involvement of the spinal canal. . *N Engl J Med* 1934;211:210-215.
7. Samanta A, Beardsley J. Evidence based case report: Sciatica: which intervention? . *BMJ* 1999;319:302-303.
8. Konstantinou K, Dunn KM. Sciatica: Review of epidemiological studies and prevalence estimates. *Spine* 2008;33:2464-2472.
9. Vroomen PC, de Krom MC, Slofstra PD, Knottnerus JA. Conservative treatment of sciatica: a systematic review. *J Spinal Disord*. Dec 2000;13(6):463-469.
10. Hagen KB, Hilde G, Jamtvedt G, Winnem M. Best rest for acute low back pain and sciatica. *The Cochrane Database of Systematic Reviews* 2004.
11. Luijsterburg PAJ, Verhagen AP, Ostelo RWJG, van Os TAG, Peul WC, Koes BW. Effectiveness of conservative treatments for the lumbosacral radicular syndrome: a systematic review. *European Spine Journal*. Jul 2007;16(7):881-899.
12. Clarke JA, van Tulder MW, Blomberg SEI, et al. Traction for low-back pain with or without sciatica. *Cochrane Database of Systematic Reviews*. 2007(2).
13. Boswell MV, Hansen HC, Trescot AM, Hirsch JA. Epidural steroids in the management of chronic spinal pain and radiculopathy. *Pain Physician*. Jul 2003;6(3):319-334.
14. Abdi S, Datta S, Trescot AM, et al. Epidural steroids in the management of chronic spinal pain: a systematic review. *Pain Physician*. Jan 2007;10(1):185-212.
15. Gibson JNA, Waddell G. Surgical interventions for lumbar disc prolapse. *Cochrane Database of Systematic Reviews*. 2007(2).
16. Lewis R, Williams N, Matar HE, et al. The effectiveness and cost effectiveness of management strategies for sciatica: systematic review and economic model. *Health Technology Assessment*. 2011;15(39).
17. Psaty BM, Lumley T, Furberg CD, et al. Health Outcomes Associated With Various Antihypertensive Therapies Used as First-Line Agents: A Network Meta-analysis *Jama*. 2003;289(19):2534-2544
18. Lu G, Ades AE. Combination of direct and indirect evidence in mixed treatment comparisons. *Statistics in Medicine*. 2004;23(15449338):3105-3124.

19. Cooper NJ, Sutton AJ, Lu G, Khunti K. Mixed Comparison of Stroke Prevention Treatments in Individuals With Nonrheumatic Atrial Fibrillation *Archives of Internal Medicine*. 2006;166:1269-1275.
20. Anothaisintawee T, Attia J, Nickel JC, et al. Management of Chronic Prostatitis/ Chronic Pelvic Pain Syndrome: A Systematic Review and Network Meta-analysis *Jama*. 2011;305 (1):78-86.
21. Higgins JPT, Whitehead A. Borrowing strength from external trials in a meta-analysis. *Statistics in Medicine* 1996;15:2733-2749.
22. Sutton AJ, Abrams KR. Bayesian methods in meta-analysis and evidence synthesis. *Statistical Methods in Medical Research*. 2001;10:277-303.
23. Bland MJ, Altman DG. Statistics notes: Bayesians and frequentists. *BMJ*. October 24 1998;317(166):1151–1160.
24. Ashby D, Smith AFM. Evidence-based medicine as Bayesian decision-making. *Statistics in Medicine*. 2000;19:3291-3305.
25. Salanti G, Ades AE, Ioannidis JPA. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. *Journal of Clinical Epidemiology*. 2011;64:163-171.
26. Tajiri K, Takahashi K, Ikeda K, Tomita K. Common peroneal nerve block for sciatica. *Clinical Orthopaedics and Related Research*. 1998(347):203-207. <http://www.mrw.interscience.wiley.com/cochrane/clcentral/articles/952/CN-00148952/frame.html>
27. Gibson T, Dilke TF, Grahame R. Chymoral in the treatment of lumbar disc prolapse. *Rheumatology & Rehabilitation*. Aug 1975;14(3):186-190.
28. El-Zahaar MS. The Egyptian experience in the use of colchicine in lumbar disc disease. *Journal of Neurological and Orthopaedic Medicine and Surgery*. 1995;16(3):147-152.
29. Thomas KC, Fisher CG, Boyd M, Bishop P, Wing P, Dvorak MF. Outcome evaluation of surgical and nonsurgical management of lumbar disc protrusion causing radiculopathy. *Spine*. Jun 1 2007;32(13):1414-1422.
30. Lavayne MH, Bilsky MH. Epidural steroids, postoperative morbidity, and recovery in patients undergoing microsurgical lumbar discectomy. *Journal of Neurosurgery*. Jul 1992;77(1):90-95.
31. Ejeskar A, Nachemson A, Herberts P, et al. Surgery versus chemonucleolysis for herniated lumbar discs. A prospective study with random assignment. *Clin Orthop*. Apr 1983(174):236-242.
32. van Tulder MW, Furlan A, Bombardier C, Bouter LM, Editorial Board of the Cochrane Collaboration Back Review Group. Updated method guidelines for systematic reviews in the Cochrane collaboration back review group. *Spine*. 2003;28(12):1290-1299.
33. Jackson N, Waters E, For the Guidelines for Systematic Reviews in Health Promotion and Public Health Taskforce. Criteria for the systematic review of health promotion and public health interventions. *Health Promotion International*. 2005;20(4):367-374.
34. Effective Public Health Practice Project. Quality Assessment tool for Quantitative Studies. 2009;2007(31 July, 2007).
35. Higgins JPT, Deeks JJ. Chapter 7: Selecting studies and collecting data. In: Higgins JPT, Green S, eds. *Cochrane handbook for systematic reviews of interventions*. Chichester (UK): John Wiley & Sons Ltd; 2008.

36. Furukawa TA, Barbui C, Cipriani A, Brambilla P, Watanabe N. Imputing missing standard deviations in meta-analyses can provide accurate results. *J Clin Epidemiol.* Jan 2006;59(1):7-10.
37. Spiegelhalter DJ, Thomas A, Best NG, Lunn DJ, eds. *WinBUGS Version v1.4. User manual.* Cambridge: MRC Biostatistics Unit; 2003.
38. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Controlled clinical trials* 1986;7:177-188.
39. Song F, Altman DG, Glenny A-M, Deeks JJ. Validity of indirect comparison for estimating efficacy of competing interventions: empirical evidence from published meta-analyses. *BMJ.* 2003;326:472-476.
40. Bucher HC, Guyatt GH, Griffith LE, Walter SD. The Results of Direct and Indirect Treatment Comparisons in Meta-Analysis of Randomized Controlled Trials. *J Clin Epidemiol.* 1997;50(6):683-691.
41. Caldwell DM, Ades AE, Higgins JPT. Simultaneous comparison of multiple treatments: combining direct and indirect evidence. *BMJ.* 2005;331(16223826):897-900.
42. Stettler C, Allemann S, Wandel S, et al. Drug eluting and bare metal stents in people with and without diabetes: collaborative network meta-analysis *BMJ.* 2008;337:a1331.
43. Deeks JJ, Higgins JPT, Altman DG. Chapter 9: Analysing data and undertaking meta-analyses. In: Higgins JPT, Green S, eds. *Cochrane Handbook for Systematic Reviews of Interventions.* Chichester (UK): John Wiley & Sons; 208.
44. Higgins JPT, Thompson SG, Deeks JJ, G. AD. Measuring inconsistency in meta-analyses. *BMJ.* 2003;327(7414):557-560
45. Alexander AH, Burkus JK, Mitchell JB, Ayers WV. Chymopapain chemonucleolysis versus surgical discectomy in a military population. *Clin Orthop Relat Res.* 1989(244):158-165.
46. Aminmansour B, Khalili HA, Ahmadi J, Nourian M. Effect of high-dose intravenous dexamethasone on postlumbar discectomy pain. *Spine.* Oct 1 2006;31(21):2415-2417.
47. Atlas SJ, Deyo RA, Keller RB, et al. The Maine Lumbar Spine Study .2. 1-year outcomes of surgical and nonsurgical management of sciatica. *Spine.* Aug 1996;21(15):1777-1786.
48. Becker C, Heidersdorf S, Drewlo S, de Rodriguez SZ, Kramer J, Willburger RE. Efficacy of epidural perineural injections with autologous conditioned serum for lumbar radicular compression: an investigator-initiated, prospective, double-blind, reference-controlled study. *Spine.* Aug 1 2007;32(17):1803-1808.
49. Bernsmann K, Kramer J, Ziozios I, Wehmeier J, Wiese M. Lumbar micro disc surgery with and without autologous fat graft - A prospective randomized trial evaluated with reference to clinical and social factors. *Arch. Orthop. Trauma Surg.* Sep 2001;121(8):476-480.
50. Bonafe A, Tremoulet M, Sabatier J, et al. Foraminal and Lateroforaminal Herniated Disks - Midterm Results of Percutaneous Treatment with Chemonucleolysis or Nucleotomy. *Neurochirurgie.* 1993;39(2):110-115.
51. Bontoux D, Alcalay M, Debiais F, et al. Treatment of Lumbar-Disk Herniation with Intradiscal Injection of Chymopapain or Triamcinolone Hexacetonid - a Comparative-Study of 80 Cases. *Rev Rhum Engl Ed.* Apr 1990;57(4):327-331.

52. Bourgeois P, Benoist M, Palazzo E, et al. Multicenter, randomized and double-blind study of triamcinolone hexacetonide versus chymopapain in the treatment of lumbar sciatica. Preliminary results at six months. *Rev Rhum Mal Osteo Articulaires*. 1988(10):767-769.
53. Brown MD, Tompkins JS. Pain response post-chemonucleolysis or disc excision. *Spine*. Mar 1989;14(3):321-326.
54. Buchner M, Zeifang F, Brocai DR, Schiltenswolf M. Epidural corticosteroid injection in the conservative management of sciatica. *Clin Orthop*. Jun 2000(375):149-156.
55. Buric J. Ozone chemyonucleolysis vs microdiscectomy. Prospective controlled study with 18 months follow-up. *Rivista Italiana di Ossigeno-Ozonoterapia*. Apr 2005;4(1):49-54.
56. Burton AK, Tillotson KM, Cleary J. Single-blind randomised controlled trial of chemonucleolysis and manipulation in the treatment of symptomatic lumbar disc herniation. *European Spine Journal*. Jun 2000;9(3):202-207.
57. Bush K, Hillier S. A controlled study of caudal epidural injections of triamcinolone plus procaine for the management of intractable sciatica. *Spine*. May 1991;16(5):572-575.
58. Carette S, Leclaire R, Marcoux S, et al. Epidural corticosteroid injections for sciatica due to herniated nucleus pulposus. *New England Journal of Medicine*. Jun 1997;336(23):1634-1640.
59. Cengiz SL, Baysefer A. Efficacy of Adcon-L gel or Healon-GV in epidural fibrosis after lumbar microdiscectomy. *Neurosciences*. Apr 2007;12(2):109-113.
60. Chatterjee S, Foy PM, Findlay GF. Report of a controlled clinical trial comparing automated percutaneous lumbar discectomy and microdiscectomy in the treatment of contained lumbar disc herniation. *Spine*. Mar 15 1995;20(6):734-738.
61. Chen M-r, Wang P, Cheng G, Guo X, Wei G-w, Cheng X-h. The warming acupuncture for treatment of sciatica in 30 cases. *J Tradit Chin Med*. 2009;29(1):50-53.
62. Cohen S, Bogduk N, Dragovich A, et al. Randomized, double-blind, placebo-controlled, dose-response, and preclinical safety study of transforaminal epidural etanercept for the treatment of sciatica. *Anesthesiology*. 2009;110(5):1116-1126.
63. Coomes EN. Comparison between Epidural Anaesthesia and Bed Rest in Sciatica. *British Medical Journal*. 1961;1(5218):20-24.
64. Crawshaw C, Frazer AM, Merriam WF, Mulholland RC, Webb JK. A comparison of surgery and chemonucleolysis in the treatment of sciatica. A prospective randomized trial. *Spine*. Mar 1984;9(2):195-198.
65. Dabezies EJ, Brunet M. Chemonucleolysis vs laminectomy. *Orthopedics*. Jan-Feb 1978;1(1):26-29.
66. Dabezies EJ, Langford K, Morris J, Shields CB, Wilkinson HA. Safety and efficacy of chymopapain (Discase) in the treatment of sciatica due to a herniated nucleus pulposus. Results of a randomized, double-blind study. *Spine*. May 1988;13(5):561-565.
67. Debi R, Halperin N, Mirovsky Y. Local application of steroids following lumbar discectomy. *J Spinal Disord Tech*. Aug 2002;15(4):273-276.
68. Dei-Anang K, Weigand H, Mader U. Is the Percutaneous Discectomy an Alternative to Chemonucleolysis. *Radiologe*. 1990;30(2):70-74.

69. Dilke TF, Burry HC, Grahame R. Extradural corticosteroid injection in management of lumbar nerve root compression. *British Medical Journal*. Jun 16 1973;2(5867):635-637.
70. Dincer U, Kiralp MZ, Cakar E, Yasar E, Dursan H. Caudal epidural injection versus non-steroidal anti-inflammatory drugs in the treatment of low back pain accompanied with radicular pain. *Joint Bone Spine*. Oct 2007;74(5):467-471.
71. Dreiser RL, Le Parc JM, Velicitat P, Lleu PL. Oral meloxicam is effective in acute sciatica: two randomised, double-blind trials versus placebo or diclofenac. *Inflammation Research*. Mar 2001;50 Suppl 1:S17-23.
72. Dubourg G, Rozenberg S, Fautrel B, et al. A pilot study on the recovery from paresis after lumbar disc herniation. *Spine*. Jul 1 2002;27(13):1426-1431; discussion 1431.
73. Duplan B, Cabanel G, Piton JL, Grauer JL, Phelip X. Acupuncture and sciatica in the acute phase. Double-blind study of 30 cases. *Semaine des Hopitaux*. Dec 8 1983;59(45):3109-3114.
74. Feldman J, Menkes CJ, Pallardy G, et al. Double-blind study of the treatment of disc lumbosciatica by chemonucleolysis. *Rev Rhum Mal Osteoartic*. Mar 1986;53(3):147-152.
75. Finckh A, Zufferey P, Schurch M-A, Balague F, Waldburger M, So AKL. Short-term efficacy of intravenous pulse glucocorticoids in acute discogenic sciatica. A randomized controlled trial. *Spine*. Feb 15 2006;31(4):377-381.
76. Gallucci M, Limbucci N, Zugaro L, et al. Sciatica: treatment with intradiscal and intraforaminal injections of steroid and oxygen-ozone versus steroid only. *Radiology*. Mar 2007;242(3):907-913.
77. Genevay S, Stingelin S, Gabay C. Efficacy of etanercept in the treatment of acute, severe sciatica: a pilot study. *Ann Rheum Dis*. Sep 2004;63(9):1120-1123.
78. Gerszten PC, Moossy JJ, Flickinger JC, Welch WC. Low-dose radiotherapy for the inhibition of peridural fibrosis after reexploratory nerve root decompression for postlaminectomy syndrome. *Journal of Neurosurgery*. Oct 2003;99(3 Suppl):271-277.
79. Geurts JWM, van Wijk R, Wynne HJ, et al. Radiofrequency lesioning of dorsal root ganglia for chronic lumbosacral radicular pain: a randomised, double-blind, controlled trial. *Lancet*. Jan 2003;361(9351):21-26.
80. Ghoname EA, White PF, Ahmed HE, Hamza MA, Craig WF, Noe CE. Percutaneous electrical nerve stimulation: an alternative to TENS in the management of sciatica. *Pain*. Nov 1999;83(2):193-199.
81. Glasser RS, Knego RS, Delashaw JB, Fessler RG. The perioperative use of corticosteroids and bupivacaine in the management of lumbar disc disease. *Journal of Neurosurgery*. Mar 1993;78(3):383-387.
82. Gogan WJ, Fraser RD. Chymopapain - a 10-Year, Double-Blind-Study. *Spine*. Apr 1992;17(4):388-394.
83. Goldie I. A clinical trial with indomethacin (indomee(R)) in low back pain and sciatica. *Acta Orthop Scand Suppl*. 1968;39(1):117-128.
84. Graham CE. Chemonucleolysis: a double blind study comparing chemonucleolysis with intra discal hydrocortisone: in the treatment of backache and sciatica. *Clin Orthop*. Jun 1976(117):179-192.
85. Grevsten S, Johansson H. Phenylbutazone in treatment of acute lumbago-sciatica. *Zeitschrift fur Rheumatologie*. Nov-Dec 1975;34(11-12):444-447.

86. Hansson E, Hansson T. The cost-utility of lumbar disc herniation surgery. *European Spine Journal*. Mar 2007;16(3):329-337.
87. Hedeboe J, Buhl M, Ramsing P. Effects of using dexamethasone and placebo in the treatment of prolapsed lumbar disc. *Acta Neurologica Scandinavica*. Jan 1982;65(1):6-10.
88. Helliwell M, Robertson JC, Ellis RM. Outpatient treatment of low back pain and sciatica by a single extradural corticosteroid injection. *Br J Clin Pract*. 1985;39(6):228-231.
89. Herrmann WA, Geertsens MS. Efficacy and safety of lornoxicam compared with placebo and diclofenac in acute sciatica/lumbo-sciatica: an analysis from a randomised, double-blind, multicentre, parallel-group study. *Int J Clin Pract*. 2009;63(11):1613-1621.
90. Hofstee DJ, Gijtenbeek JMM, Hoogland PH, et al. Westeinde sciatica trial: randomized controlled study of bed rest and physiotherapy for acute sciatica. *Journal of Neurosurgery*. Jan 2002;96(1 Suppl):45-49.
91. Holve RL, Barkan H. Oral steroids in initial treatment of acute sciatica. *J Am Board Fam Med*. 2008;21(5):469-474.
92. Hoogmartens M, Van Loon L, Demedts D, Desmet L. Comparative study of the results obtained with discectomy and chemonucleolysis. *Acta Orthop Belg*. Mar-Apr 1976;42(2):134-138.
93. Javid MJ, Nordby EJ, Ford LT, et al. Safety and efficacy of chymopapain (Chymodiactin) in herniated nucleus pulposus with sciatica. Results of a randomized, double-blind study. *Journal of the American Medical Association*. May 13 1983;249(18):2489-2494.
94. Javid MJ. Chemonucleolysis Versus Laminectomy - a Cohort Comparison of Effectiveness and Charges. *Spine*. Sep 1995;20(18):2016-2022.
95. Jensen TT, Asmussen K, Berg-Hansen EM, et al. First-time operation for lumbar disc herniation with or without free fat transplantation. Prospective triple-blind randomized study with reference to clinical factors and enhanced computed tomographic scan 1 year after operation. *Spine*. May 1 1996;21(9):1072-1076.
96. Jirattanaphochai K, Jung S, Thienthong S, Krisanaprakornkit W, Sumananont C. Peridural methylprednisolone and wound infiltration with bupivacaine for postoperative pain control after posterior lumbar spine surgery - A randomized double-blinded placebo-controlled trial. *Spine*. 2007;32(6):609-616.
97. Karppinen J, Malmivaara A, Kurunlahti M, et al. Periradicular infiltration for sciatica - A randomized controlled trial. *Spine*. May 2001;26(9):1059-1067.
98. Karppinen J, Korhonen T, Malmivaara A, et al. Tumor necrosis factor-alpha monoclonal antibody, infliximab, used to manage severe sciatica. *Spine*. Apr 15 2003;28(8):750-753; discussion 753-754.
99. Khoromi S, Patsalides A, Parada S, Salehi V, Meegan JM, Max MB. Topiramate in chronic lumbar radicular pain. *The Journal of Pain*. 2005;6(12):829-836.
100. Khoromi S, Cui L, Nackers L, Max MB. Morphine, nortriptyline and their combination vs. placebo in patients with chronic lumbar root pain. *Pain*. Jul 2007;130(1-2):66-75.
101. Kim KD, Wang JC, Robertson DP, et al. Reduction of radiculopathy and pain with Oxiplex/SP gel after laminectomy, laminotomy, and discectomy: a pilot clinical study. *Spine*. May 15 2003;28(10):1080-1087; discussion 1087-1088.

102. Kim M-J, Lee S-H, Jung E-S, et al. Targeted percutaneous transforaminal endoscopic discectomy in 295 patients: comparison with results of microscopic discectomy. *Surg Neurol.* Dec 2007;68(6):623-631.
103. Klenerman L, Greenwood R, Davenport HT, White DC, Peskett S. Lumbar epidural injections in the treatment of sciatica. *Br. J. Rheumatol.* Feb 1984;23(1):35-38.
104. Koranda I, Sefrna F. Effectiveness of conservative and surgical treatment of lumboschiadic syndrome. *Cas Lek Cesk.* Aug 2 1995;134(15):474-477.
105. Korhonen T, Karppinen J, Paimela L, et al. The treatment of disc herniation-induced sciatica with infliximab - Results of a randomized, controlled, 3-month follow-up study. *Spine.* Dec 2005;30(24):2724-2728.
106. Kwasucki J, Olbrych K, ska B, Stepie A, Dec S, Maksymiuk G. Assessment of dexamethasone effectiveness in the treatment of ischalgia. *Neurol Neurochir Pol.* 1993;27(4):515-522.
107. Kwasucki J, Stepien A, Maksymiuk G, Olbrych-Karpinska B. Evaluation of analgesic action of fluvoxamine compared with efficacy of imipramine and tramadol for treatment of sciatica--open trial. *Wiad Lek.* 2002;55(1-2):42-50.
108. Lagarrigue J, Lazorthes Y, Verdier JC, Richaud J. Comparative Results of Surgery and Nucleolysis in 1085 Cases of Herniated Lumbar Disc. *Neurochirurgie.* 1991;37(2):96-105.
109. Laiq N, Khan MN, Iqbal MJ, Khan S. Comparison of Epidural Steroid Injections with conservative management in patients with lumbar radiculopathy. *J Coll Physicians Surg Pak.* 2009;19(9):539-543.
110. Larsson U, Choler U, Lidstrom A, et al. Auto Traction for Treatment of Lumbago Sciatica a Multicenter Controlled Investigation. *Acta Orthop Scand Suppl.* 1980;51(5):791-798.
111. Lavignolle B, Vital JM, Baulny D, Grenier F, Castagnera L. Comparative study of surgery and chemonucleolysis in the treatment of sciatica caused by a herniated disk. *Acta Orthop Belg.* 1987;53(2):244-249.
112. Lee SH, Lee SJ, Park KH, et al. Comparison of percutaneous manual and endoscopic laser discectomy with chemonucleolysis and automated nucleotomy. *Orthopade.* 1996;25(1):49-55.
113. Lee SH, Chung SE, Ahn Y, Kim TH, Park JY, Shin SW. Comparative radiologic evaluation of percutaneous endoscopic lumbar discectomy and open microdiscectomy: A matched cohort analysis. *Mount Sinai Journal of Medicine.* Sep 2006;73(5):795-801.
114. Lidstrom A, Zachrisson M. Physical therapy on low back pain and sciatica. An attempt at evaluation. *Scand J Rehabil Med.* 1970;2(1):37-42.
115. Ljunggren AE, Walker L, Weber H, Amundsen T. Manual traction versus isometric exercises in patients with herniated intervertebral lumbar discs. *Physiotherapy Theory and Practice.* Dec 1992;8(4):207-213.
116. Luijsterburg PAJ, Verhagen AP, Ostelo RWJG, et al. Physical therapy plus general practitioners' care versus general practitioners' care alone for sciatica: a randomised clinical trial with a 12-month follow-up. *European Spine Journal.* Apr 2008;17(4):509-517.
117. Lundin A, Magnuson A, Axelsson K, Kogler H, Samuelsson L. The effect of perioperative corticosteroids on the outcome of microscopic lumbar disc surgery. *European Spine Journal.* Dec 2003;12(6):625-630.

118. Mackay MA, Fischgrund JS, Herkowitz HN, Kurz LT, Hecht B, Schwartz M. The Effect of Interposition Membrane on the Outcome of Lumbar Laminectomy and Discectomy. *Spine*. Aug 1995;20(16):1793-1796.
119. Mathews JA, Mills SB, Jenkins VM, et al. Back pain and sciatica: controlled trials of manipulation, traction, sclerosant and epidural injections. *Br J Rheumatol*. 1987;26(6):416-423.
120. Mayer HM, Brock M. Percutaneous Endoscopic Discectomy - Surgical Technique and Preliminary-Results Compared to Microsurgical Discectomy. *Journal of Neurosurgery*. Feb 1993;78(2):216-225.
121. Moret NC, van der Stap M, Hagmeijer R, Molenaar A, Koes BW. Design and feasibility of a randomized clinical trial to evaluate the effect of vertical traction in patients with a lumbar radicular syndrome. *Manual Therapy*. 1998;3(4):203-211.
122. Muralikuttan KP, Hamilton A, Kernohan WG, Mollan RA, Adair IV. A prospective randomized trial of chemonucleolysis and conventional disc surgery in single level lumbar disc herniation. *Spine*. Apr 1992;17(4):381-387.
123. Murata Y, Kato Y, Miyamoto K, Takahashi K. Clinical study of low back pain and radicular pain pathways by using l2 spinal nerve root infiltration: a randomized, controlled, clinical trial. *Spine*. 2009;34(19):2008-2013.
124. North RB, Kidd DH, Farrokhi F, Piantadosi SA. Spinal cord stimulation versus repeated lumbosacral spine surgery for chronic pain: a randomized, controlled trial. *Neurosurgery*. 2005;56(1):98-106; discussion 106-107.
125. Norton WL. Chemonucleolysis versus surgical discectomy. Comparison of costs and results in workers' compensation claimants. *Spine*. Jun 1986;11(5):440-443.
126. Osterman H, Seitsalo S, Karppinen J, Malmivaara A. Effectiveness of microdiscectomy for lumbar disc herniation: a randomized controlled trial with 2 years of follow-up. *Spine*. Oct 1 2006;31(21):2409-2414.
127. Ozturk B, Gunduz OH, Ozoran K, Bostanoglu S. Effect of continuous lumbar traction on the size of herniated disc material in lumbar disc herniation. *Rheumatology International*. May 2006;26(7):622-626.
128. Peul WC, Van Houwelingen HC, Van Den Hout WB, et al. Surgery versus prolonged conservative treatment for sciatica. *New England Journal of Medicine*. 31 2007;356(22):2245-2256.
129. Popiolek A, Domanik A, Mazurkiewicz G. Epidural injections of steroids in the treatment of patients with chronic sciatica in discopathy. *Neurol Neurochir Pol*. Sep-Oct 1991;25(5):640-646.
130. Porsman O, Friis H. Prolapsed lumbar disc treated with intramuscularly administered dexamethasonephosphate. A prospectively planned, double-blind, controlled clinical trial in 52 patients. *Scandinavian Journal of Rheumatology*. 1979;8(3):142-144.
131. Postacchini F, Lami R, Massobrio M. Chemonucleolysis versus surgery in lumbar disc herniations: correlation of the results to preoperative clinical pattern and size of the herniation. *Spine*. Mar 1987;12(2):87-96.
132. Price C, Arden N, Coglán L, Rogers P. Cost-effectiveness and safety of epidural steroids in the management of sciatica. *Health Technology Assessment*. Aug 2005;9(33):1-58.
133. Rasmussen S, Krum-Moller DS, Lauridsen LR, et al. Epidural steroid following discectomy for herniated lumbar disc reduces neurological

- impairment and enhances recovery: a randomized study with two-year follow-up. *Spine*. 2008;33(19):2028-2033.
134. Rattanatharn R, Sanjaroensuttikul N, Anadirekkul P, Chaivisate R, Wannasetta W. Effectiveness of lumbar traction with routine conservative treatment in acute herniated disc syndrome. *Journal of the Medical Association of Thailand*. Sep 2004;87 Suppl 2:S272-277.
 135. Reust P, Chantraine A, Vischer TL. Treatment of lumbar sciatica with or without neurological deficit using mechanical traction. A double-blind study. *Schweizerische Medizinische Wochenschrift*. Feb 27 1988;Journal Suisse de Medecine. 118(8):271-274.
 136. Revel M, Payan C, Vallee C, et al. Automated Percutaneous Lumbar Discectomy Versus Chemonucleolysis in the Treatment of Sciatica - a Randomized Multicenter Trial. *Spine*. Jan 1993;18(1):1-7.
 137. Richter HP, Kast E, Tomczak R, Besenfelder W, Gaus W. Results of applying ADCON-L gel after lumbar discectomy: the German ADCON-L study. *Journal of Neurosurgery*. Oct 2001;95(2 Suppl):179-189.
 138. Ridley MG, Kingsley GH, Gibson T, Grahame R. Outpatient lumbar epidural corticosteroid injection in the management of sciatica. *Br. J. Rheumatol*. Aug 1988;27(4):295-299.
 139. Ronnberg K, Lind B, Zoega B, et al. Peridural scar and its relation to clinical outcome: a randomised study on surgically treated lumbar disc herniation patients. *European Spine Journal*. 2008;17(12):1714-1720.
 140. Santilli V, Beghi E, Finucci S. Chiropractic manipulation in the treatment of acute back pain and sciatica with disc protrusion: a randomized double-blind clinical trial of active and simulated spinal manipulations. *Spine J*. Mar-Apr 2006;6(2):131-137.
 141. Schwetschenau PR, Ramirez A, Johnston J. Double blind evaluation of intradiscal chymopapain for herniated lumbar discs; early results. *J Neurosurg*. 1976;45(6):622-627.
 142. Shvartzman L, Weingarten E, Sherry H, Levin S, Persaud A. Cost-effectiveness analysis of extended conservative therapy versus surgical intervention in the management of herniated lumbar intervertebral disc. *Spine*. Feb 1992;17(2):176-182.
 143. Snoek W, Weber H, Jorgensen B. Double-Blind Evaluation of Extradural Methyl Prednisolone for Herniated Lumbar Discs. *Acta Orthop Scand Suppl*. 1977;48(6):635-641.
 144. Steffen R. Laser discotomy/Chemonucleolysis in the therapy of displaced lumbar intervertebral disc - prospective randomised comparison. *Hefte zur der Unfallchirurg*. 1999:215-221.
 145. Stula D. Chemonucleolysis with Chymopapain in Intervertebral-Disk Hernia - a Randomized Comparative-Study of Patients Following Surgery. *Neurochirurgia (Stuttg)*. Sep 1990;33(5):169-172.
 146. Styczynski T, Zarski S, Drozdowska Z, et al. Clinical Evaluation of the Effectiveness of Traction Treatment of Patients with Herniation of Lumbar Intervertebral Discs. *Reumatologia (Warsaw)*. 1991;29(3-4):275-281.
 147. Tassi GP. Comparison of results of 500 microdiscectomies and 500 percutaneous laser disc decompression procedures for lumbar disc herniation. *Photomed Laser Surg*. Dec 2006;24(6):694-697.

148. Tregonning GD, Transfeldt EE, McCulloch JA, Macnab I, Nachemson A. Chymopapain versus conventional surgery for lumbar disc herniation. 10-year results of treatment. *J Bone Joint Surg Br.* May 1991;73(3):481-486.
149. de Tribolet N, Porchet F, Lutz TW, et al. Clinical assessment of a novel antiadhesion barrier gel: prospective, randomized, multicenter, clinical trial of ADCON-L to inhibit postoperative peridural fibrosis and related symptoms after lumbar discectomy. *Am J Orthop.* 1998;27(2):111-120.
150. Unlu Z, Tasci S, Tarhan S, Pabuscu Y, Islak S. Comparison of 3 physical therapy modalities for acute pain in lumbar disc herniation measured by clinical evaluation and magnetic resonance imaging. *J Manipulative Physiol Ther.* Mar 2008;31(3):191-198.
151. Vad VB, Bhat AL, Lutz GE, Cammisa F. Transforaminal epidural steroid injections in lumbosacral radiculopathy: a prospective randomized study. *Spine.* Jan 1 2002;27(1):11-16.
152. Valat JP, Giraudeau B, Rozenberg S, et al. Epidural corticosteroid injections for sciatica: a randomised, double blind, controlled clinical trial. *Ann Rheum Dis.* Jul 2003;62(7):639-643.
153. van Alphen HA, Braakman R, Bezemer PD, Broere G, Berfelo MW. Chemonucleolysis versus discectomy: a randomized multicenter trial. *Journal of Neurosurgery.* Jun 1989;70(6):869-875.
154. Veihelmann A, Devens C, Trouillier H, Birkenmaier C, Gerdesmeyer L, Refior HJ. Epidural neuroplasty versus physiotherapy to relieve pain in patients with sciatica: a prospective randomized blinded clinical trial. *J Orthop Sci.* Jul 2006;11(4):365-369.
155. Vroomen PC, de Krom MC, Wilmink JT, Kester AD, Knottnerus JA. Lack of effectiveness of bed rest for sciatica. *New England Journal of Medicine.* Feb 11 1999;340(6):418-423.
156. Watters WC, Mirkovic S, Boss J. Treatment of the isolated lumbar intervertebral disc herniation: microdiscectomy versus chemonucleolysis. *Spine (Phila Pa 1976).* 1988;13(3):360-362.
157. Watts C, Hutchison G, Stern J, Clark K. Comparison of intervertebral disc disease treatment by chymopapain injection and open surgery. *Journal of Neurosurgery.* Apr 1975;42(4):397-400.
158. Weber H. Lumbar disc herniation. A controlled, prospective study with ten years of observation. *Spine.* Mar 1983;8(2):131-140.
159. Weber H, Holme I, Amlie E. The natural course of acute sciatica with nerve root symptoms in a double-blind placebo-controlled trial evaluating the effect of piroxicam. *Spine.* Sep 1 1993;18(11):1433-1438.
160. Wehling P, Reinecke J. Acupuncture together with cytokine depressing herbs in comparison to injection therapy with steroids in sciatic pain. *Schmerz.* Jun 13 1997;11(3):180-184.
161. Weinstein JN, Tosteson TD, Lurie JD, et al. Surgical vs nonoperative treatment for lumbar disk herniation: the Spine Patient Outcomes Research Trial (SPORT): a randomized trial. *Journal of the American Medical Association.* Nov 22 2006;296(20):2441-2450.
162. Weinstein JN, Lurie JD, Tosteson TD, et al. Surgical vs nonoperative treatment for lumbar disk herniation: The Spine Patient Outcomes Research Trial (SPORT) observational cohort. *Journal of the American Medical Association.* 22 2006;296(20):2451-2459.

163. Weinstein J, Spratt KF, Lehmann T, McNeill T, Hejna W. Lumbar disc herniation. A comparison of the results of chemonucleolysis and open discectomy after ten years. *J Bone Joint Surg Am.* Jan 1986;68(1):43-54.
164. Yildirim K, Sisecioglu M, Karatay S, et al. The effectiveness of gabapentin in patients with chronic radiculopathy. *The Pain Clinic.* 2003;15(3):213-218.
165. Zeiger HE, Jr. Comparison of chemonucleolysis and microsurgical discectomy for the treatment of herniated lumbar disc. *Spine.* Oct 1987;12(8):796-799.
166. Armon C, Argoff CE, Samuels J, Backonja MM. Assessment: Use of epidural steroid injections to treat radicular lumbosacral pain: Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology.* Mar 2007;68(10):723-729.
167. Chou R, Atlas SJ, Stanos SP, Rosenquist RW. Nonsurgical interventional therapies for low back pain: a review of the evidence for an American Pain Society clinical practice guideline. *Spine* 2009;34(10):1078-1093.
168. Deeks JJ, Dinnes J, D'Amico R, et al. Evaluating non-randomised intervention studies. *Health Technol Assess.* 2003;7(27).
169. Turner RM, Spiegelhalter DJ, Smith GCS, Thompson SG. Bias modelling in evidence synthesis. *J R Stat Soc Ser A Stat Soc.* 2009;172(19381328):21-47.
170. Eddy DM, Hasselblad V, Shachter R. An introduction to Bayesian methods for Meta-analysis: The Confidence Profile Method. *Medical Decision Making.* 1990;10:15-23.
171. Egger M, Smith GD, Altman D, Schneider M. Chapter 12: Systematic reviews of observational studies. In: Egger M, Smith GD, Altman D, eds. *Systematic Reviews in Health Care: Meta-analysis in Context.* London: BMJ Books; 2001.
172. Wiebe N, Vandermeer B, Platt RW, Klassen TP, Moher D, Barrowman NJ. A systematic review identifies a lack of standardization in methods for handling missing variance data. *J Clin Epidemiol.* Apr 2006;59(4):342-353.
173. Higgins JPT, Green S. *Cochrane Handbook for Systematic Reviews of Interventions.* Vol Version 5.0.2. 2 ed. Chichester (UK): John Wiley & Sons Ltd; 2009.
174. Thompson S, Ekelund U, Jebb S, et al. A proposed method of bias adjustment for meta-analyses of published observational studies. *International Journal of Epidemiology* 2011;40:765-777