Pain Physician 2015; 18:E939-E1004 • ISSN 2150-1149

Systematic Review

Efficacy of Epidural Injections in Managing Chronic Spinal Pain: A Best Evidence Synthesis

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Background: Epidural injections have been used since 1901 in managing low back pain and sciatica. Spinal pain, disability, health, and economic impact continue to increase, despite numerous modalities of interventions available in managing chronic spinal pain. Thus far, systematic reviews performed to assess the efficacy of epidural injections in managing chronic spinal pain have yielded conflicting results.

Objective: To evaluate and update the clinical utility of the efficacy of epidural injections in managing chronic spinal pain.

Study Design: A systematic review of randomized controlled trials of epidural injections in managing chronic spinal pain.

Methods: In this systematic review, randomized trials with a placebo control or an active-control design were included. The outcome measures were pain relief and functional status improvement.

The quality of each individual article was assessed by Cochrane review criteria, as well as the Interventional Pain Management Techniques - Quality Appraisal of Reliability and Risk of Bias Assessment (IPM-QRB). Best evidence synthesis was conducted based on the qualitative level of evidence (Level I to V).

Data sources included relevant literature identified through searches of PubMed for a period starting in 1966 through August 2015; Cochrane reviews; and manual searches of the bibliographies of known primary and review articles.

Results: A total of 52 trials met inclusion criteria. Meta-analysis was not feasible.
The evidence in managing lumbar disc herniation or radiculitis is Level II for long-term improvement either with caudal, interlaminar, or transforaminal epidural injections with no significant difference among the approaches.

The evidence is Level II for long-term management of cervical disc herniation with interlaminar epidural injections.

The evidence is Level II to III in managing thoracic disc herniation with an interlaminar approach.

The evidence is Level II for caudal and lumbar interlaminar epidural injections with Level III evidence for lumbar transforaminal epidural injections for lumbar spinal stenosis.

The evidence is Level III for cervical spinal stenosis management with an interlaminar approach.

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Disclaimer: There was no external funding in the preparation of this manuscript.
Conflict of interest: See Page E954

Manuscript received: 08-30-2015
Revised manuscript received: 10-10-2015
Accepted for publication: 10-15-2015

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The evidence is Level II for axial or discogenic pain without facet arthropathy or disc herniation treated with caudal or lumbar interlaminar injections in the lumbar region; whereas it is Level III in the cervical region treated with cervical interlaminar epidural injections.

The evidence for post lumbar surgery syndrome is Level II with caudal epidural injections and for post cervical surgery syndrome it is Level III with cervical interlaminar epidural injections.

Limitations: Even though this is a large systematic review with inclusion of a large number of randomized controlled trials, the paucity of high quality randomized trials literature continues to confound the evidence.

Conclusion: This systematic review, with an assessment of the quality of manuscripts and outcome parameters, shows the efficacy of epidural injections in managing a multitude of chronic spinal conditions.

Key words: Chronic pain, spinal pain, epidural injections, local anesthetic, steroids, interlaminar epidural injections, caudal epidural injections, transforaminal epidural injections

Pain Physician 2015; 18:E939-E1004

Reports describing the state of health and burden of pain in the United States from 1990 through 2010 stated that low back pain is the number one condition and neck pain the number 4 condition leading to disability (1-3). The Institute of Medicine (IOM) report on relieving pain in America (4) described pain among US citizens as astonishing, and that its estimated financial costs range from $560 billion to $630 billion per year (5). However, Martin et al (6), in assessing the effect of chronic spinal pain on the US economy, found that costs were close to $86 billion. From 1997 through 2005 costs increased 65%; patients seeking spine-related care increased 49%. A further analysis of components of chronic pain from the IOM study and Gaskin and Richard's analysis (5) shows that approximately $100 billion are being spent on chronic noncancer pain in the United States, with approximately 40 million Americans suffering with chronic noncancer pain, and others suffering with multiple other conditions such as arthritis, joint pain, and functional disability. The expenditure of $100 billion is similar to the estimates of Martin et al (6). Freburger et al (7), in a survey conducted in 1992 and repeated in 2006 in North Carolina, showed a rapid overall increase for low back pain of 162%, from 3.9% in 1992 to 10.2% in 2005. These findings were echoed by multiple authors reporting variable prevalences of spinal pain with a significant recurrence of 24% to 80% (2,3,8,9). Studies assessing the prevalence and impact in the general population of low back and neck pain have shown that a significant proportion of patients report having chronic low back pain with lower extremity pain, or neck pain with upper extremity pain and disability (1-3).

Along with increasing prevalence and disability are increasing modalities of treatments and uncontrollable health care expenditures (10-19). Among various modalities applied in managing painful conditions of the spine, epidural injections are one of the most commonly utilized nonsurgical interventions (16-19). Epidural injections are administered utilizing caudal, interlaminar, and transforaminal approaches (9). The caudal approach is limited to the lumbosacral spine. Interlaminar and transforaminal approaches have been utilized in the cervical, thoracic, and lumbar spine. Even though all 3 modalities deliver medication into the epidural space, there are important differences among these approaches (9,20-23). An interlaminar approach is deemed to be the best for delivering the medication close to the pathology's assumed site, but the transforaminal approach is considered a target-specific modality, requiring very small volumes to reach the primary site of pathology—namely the ventrolateral epidural space (9,20-23). In contrast to interlaminar and transforaminal epidural injections, caudal epidural injections are considered to be the least specific modality and require relatively high volumes to reach the pathologic location (9,20-23). However, caudal epidurals are considered to be the safest and technically easiest to perform with minimal risks for inadvertent dural puncture and other complications. They remain the major and preferred modality of pain relief intervention in post lumbar spine surgery syndrome.

Epidural injections have been studied in managing disc herniation, spinal stenosis, post surgery syndrome, and axial or discogenic pain without facet joint pain or radiculitis in the cervical, thoracic, and lumbar regions (9,20-32). The debate continues regarding the efficacy of epidural steroid injections via the various approaches in the 3 regions because of the varying opinions rendered in multiple systematic reviews and guidelines (9,20-32). Some authors have concluded that due to a lack of effectiveness or efficacy, epidural injections are not medically necessary in managing pain and function, not only in spinal stenosis, post surgery syndrome, and axial spinal pain, but also in disc herniation and radiculitis (25,26,30,31,33). These systematic reviews, and some clinical trials that served as the basis for these conclusions, have been challenged (9,25,34,35) as flawed in their assessment and their combining of trials with variable designs and designations of active-controlled trials as placebo-controlled trials. In fact, a systematic review by Pinto et al (25) concluded that there was high quality evidence showing that epidural steroid injections was superior to placebo in patients with sciatica even though no long-term effect was seen. However, on leg pain and disability, they did find that the injections have small, short-term effects. This systematic review by Pinto et al also had multiple deficiencies, with inclusion of multiple heterogeneous studies as homogeneous and considering local anesthetic injections as placebo (34). Manchikanti et al (20-23) in recent systematic reviews challenged the methodological perspective utilized by Pinto et al (25) and focused the review on clinical aspects with an appropriate methodologic quality assessment. In contrast to Pinto et al (25), Manchikanti et al (22), utilizing Cochrane review quality assessment criteria and grading of the strength of evidence based on best evidence synthesis, found strong evidence for short-term efficacy from multiple high-quality trials and moderate evidence for long-term efficacy from at least one high-quality trial for fluoroscopically guided caudal, lumbar interlaminar, and lumbar transforaminal epidural injections in managing lumbar disc herniation in terms of pain relief and functional improvement.

Multiple other systematic reviews also have shown variable effectiveness for all 3 approaches in managing pain due to spinal stenosis, post surgery syndrome, and axial spinal pain. Recently, an Agency for Healthcare Research and Quality (AHRQ) Technology Assessment Report by Chou et al (30) also conducted a highly inappropriate analysis and conclusion with a lack of evidence similar to previously published reports, with criticism of inappropriate publication by AHRQ which failed to meet established criteria by IOM including intellectual bias and numerous conflicts of interest (36). In addition to the debate on effectiveness, indications, medical necessity, and significant increases in utilization patterns along with various complications have been the focus of epidural injections (16-19,37-45). Manchikanti et al (16) in an updated assessment of utilization of interventional pain management techniques in the fee-for-service Medicare population from 2000 through 2013 showed an overall increase in epidural injections of 102% with an annual increase of 5.6%, with an increase in epidural injections per 100,000 fee-for-service Medicare population of 31% from 2000 through 2013 and an annual increase of 2.1%. However, a majority of the increases were seen for lumbar transforaminal epidural injections with an increase of 577% per 100,000 fee-for-service Medicare population compared to 11.3% for lumbar interlaminar epidural injections from 2000 through 2013.

Consequently, the objective of this systematic review is to assess the efficacy of epidural injections in managing chronic spinal pain due to disc herniation, radiculitis, discogenic pain without facet joint pain or sacroiliac joint pain, spinal stenosis, and post surgery syndrome utilizing caudal, interlaminar, and transforaminal approaches with or without steroids.

1.0 Methods

The methodology utilized in this systematic review followed the review process derived from evidence-based systematic reviews and meta-analyses of randomized trials (46-51).

1.1 Criteria for Considering Studies for This Review

1.1.1 Types of Trials

Randomized controlled trials

1.1.2 Types of Participants

Patients in chosen trials had been suffering with chronic spinal pain secondary to disc herniation, discogenic pathology without disc herniation or radiculitis or facet joint arthropathy, spinal stenosis, and post surgery syndrome.

1.1.3 Types of Interventions

Caudal, interlaminar, and transforaminal epidural injections with or without steroids.

1.1.4 Types of Outcome Measures

- The primary outcome parameter was pain relief.
- The secondary outcome measure was functional status improvement.

1.2 Literature Search

All available trials, in all languages, from all countries, providing appropriate management with outcome evaluations were considered for inclusion. Searches were performed from the following sources without language restrictions:

1. PubMed from 1966
   www.ncbi.nlm.nih.gov/pubmed
2. Cochrane Library
   www.thecochranelibrary.com
3. US National Guideline Clearinghouse (NGC)
   www.guideline.gov/
4. Previous systematic reviews and cross references
5. Clinical Trials
   www.clinicaltrials.gov/
6. All other sources including non-indexed journals and abstracts

The search period was from 1966 through August 2015.

1.3 Search Strategy

The search strategy emphasized chronic spinal pain treated with epidural injections.

The search terminology was as follows:

((((((((((((((((chronic low back pain) OR chronic mild back OR upper back pain) OR chronic neck pain) OR disc herniation) OR discogenic pain) OR herniated lumbar discs) OR nerve root compression) OR lumbosciatic pain) OR postlaminectomy) OR lumbar surgery syndrome) OR radicular pain) OR radiculitis) OR sciatica) OR spinal fibrosis) OR spinal stenosis) AND ((((((((((epidural injection) OR epidural steroid) OR epidural perineural injection) OR interlaminar epidural) OR intraarticular corticosteroid) OR nerve root blocks) OR periradicular infiltration) OR transforaminal injection) OR corticosteroid) OR methylprednisolone))) AND ((meta-analysis [pt] OR randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized controlled trials [mh] OR random allocation [mh] OR double-blind method [mh] OR single-blind method [mh] OR clinical trial [pt] OR clinical trials [mh] OR ("clinical trial" [tw]) OR ((singl* [tw] OR doubl* [tw] OR trebl* [tw] OR tripl* [tw]) AND (mask* [tw] OR blind* [tw])) OR (placebos [mh] OR placebo* [tw] OR random* [tw] OR research design [mh:noexp]) NOT (animals [mh] NOT human [mh]))).

1.4 Data Collection and Analysis

The review focused on randomized trials for efficacy, and observational studies for reports of complications. The population of interest was patients suffering with chronic spinal pain for at least 3 months. Only epidural injections with or without steroids were evaluated. All of the studies providing appropriate management and with outcome evaluations of 3 months or longer and statistical evaluations were reviewed. Reports without appropriate diagnosis, non-systematic reviews, book chapters, and case reports were excluded.

1.4.1 Data Extraction and Management

Two review authors independently, in an unblinded, standardized manner, developed search criteria, searched for relevant literature, selected the manuscripts, and extracted the data from the included studies. Disagreements were resolved by discussion between the 2 reviewers; if no consensus could be reached, a third author was called in to break the impasse.

If there was a conflict of interest with a reviewed manuscript (concerning authorship), or if the reviewer was also one of the authors or had any type of conflict, the involved reviewer did not review the manuscript for methodologic quality assessment.

1.4.2 Inclusion and Exclusion Criteria

This review focused only on randomized trials for assessment of efficacy. The population of interest was patients suffering with chronic spinal pain of at least 3 months. Patients with acute trauma, fractures, malignancies, and inflammatory diseases were excluded.

Only studies with at least 3 months of follow-up and randomized trials with at least 25 patients in each group or with an appropriate sample size determination for the specific pathology were included.

1.4.3 Methodological Quality or Validity Assessment

The quality of each individual article used in this analysis was assessed by Cochrane review criteria (Appendix 1) (48) and Interventional Pain Management techniques -- Quality Appraisal of Reliability and Risk of Bias Assessment (IPM – QRB) for randomized trials (Appendix 2) (49).

Utilizing Cochrane review criteria, studies meeting the inclusion criteria with at least 8 of 12 criteria were considered high quality; 4 to 7 were considered moderate quality. Those meeting criteria of less than 4 were considered as low quality and were excluded.

Based on IPM-QRB criteria for randomized trials, the studies meeting the inclusion criteria but scoring less than 16 were considered as low quality and were excluded; studies scoring from 16 to 31 were considered as moderate quality; and studies scoring from 32 to 48 were considered as high quality.

All epidural injections were also evaluated separately for disc herniation, discogenic pain, spinal stenosis, and post surgery syndrome in the lumbar, cervical, and thoracic spines.

Methodologic quality assessment was performed by multiple review authors with groups of 2 authors reviewing 4 to 6 manuscripts. The assessment was carried out independently in an unblinded, standardized manner to assess the methodologic quality and internal validity of all the studies considered for inclusion. Reviewers performed their methodological quality assessment so as to prevent any discrepancies. If discrepancies occurred, a third reviewer performed an assessment and a consensus was reached. Issues beyond that were discussed by all reviewers and then resolved.

1.4.4 Meta-Analysis

A meta-analysis was performed if there was at least 3 clinically homogenous randomized trials that met the inclusion criteria for each modality and condition evaluated.

1.5 Outcome of the Studies

It is generally accepted that a minimum of 20% change in pain scores is clinically meaningful, based upon previous trials and US Food and Drug Administration (FDA) requirements (49,50). In recent years, significant literature has been published describing the minimal clinically important difference using item response theory models (52), for health-related quality of life outcomes (53), and multiple approaches for estimating minimal clinically important differences (54). Thus, it has become important to look at the outcomes based on patient perspective (55,56). This literature also emphasizes multiple facts of comparison between 2 groups in active control trials or occasionally in placebo-controlled trials from baseline to follow-up periods rather than assessing the differences between 2 groups. In addition, in interventional pain management trials, multiple publications have adopted robust outcome measures defined as significant improvement with at least 50% improvement in pain and functional status rather than 10% or 20% improvement described thus far (57-77). For the present analysis either 50% relief from the baseline pain score or a change of at least 3 points on an 11-point pain scale of 0 to 10 was considered to be clinically significant. For functional status improvement the change was 30% or more of disability scores or 50% improvement from baseline.

A randomized trial was judged to be positive if the epidural injection therapy was clinically relevant and effective, either with a placebo control or outcome results from baseline to the follow-up period for active control trials. This indicates that the difference in the effect for the primary outcome measure is statistically significant on the conventional 5% level. A negative study was one where no difference was seen between the treatments or that no improvement from baseline could be measured. Reference point measurements were considered at 3 months, 6 months, and one year.

1.6 Summary Measures

Summary measures included a 50% or more reduction of pain and/or function in at least 50% of the patients, or at least a 3-point decrease in pain scores or 30% 30% or more reduction in disability scores or 50% improvement in disability from baseline for functional status improvement. The improvement of anything less than 6 months is considered as short-term; whereas, longer than 6 months is considered as long-term.

1.7 Analysis of Evidence

The analysis of the evidence was performed based on the best evidence synthesis, modified and collated from multiple available criteria, including Cochrane review criteria and United States Preventive Task Force (USPSTF) criteria as illustrated in Table 1 (51). The analysis was conducted using 5 levels of evidence ranging from strong to opinion- or consensus-based. The results of best evidence as per grading was utilized.

At least 2 of the review authors independently, in an unblinded, standardized manner, analyzed the evidence. Any disagreements between reviewers were resolved by a third author and consensus. If there were any conflicts of interest (e.g., authorship), those reviewers were recused from assessment and analysis.

2.0 Results

Figure 1 shows a flow diagram of the study selection as recommended by Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) (47).

Table 1. *Qualitative modified approach to grading of evidence.*

Level I	Evidence obtained from multiple relevant high quality randomized controlled trials
Level II	Evidence obtained from at least one relevant high quality randomized controlled trial or multiple relevant moderate or low quality randomized controlled trials
Level III	Evidence obtained from at least one relevant moderate or low quality randomized controlled trial with multiple relevant observational studies or Evidence obtained from at least one relevant high quality nonrandomized trial or observational study with multiple moderate or low quality observational studies
Level IV	Evidence obtained from multiple moderate or low quality relevant observational studies
Level V	Opinion or consensus of large group of clinicians and/or scientists

Adapted from Manchikanti L, Falco FJE, Benyamin RM, Kaye AD, Boswell MV, Hirsch JA. A modified approach to grading of evidence. P*ain Physician* 2014; 17:E319-E325 (51).

Based on extensive search criteria, numerous manuscripts were identified and considered for inclusion (58-183). Of all the 126 manuscripts of epidural trials identified, multiple trials were excluded for not meeting inclusion criteria with select trials shown in Appendix 3 (78-89,91,92,94-102,112,115,124,131,137-159,165,174-183). Subsequently, 52 trials were included (33,60-71,74,75,90,93,103-111,113,114,116-123,125,127,129,130,132-135,147,160,161,168-173).

2.1 Methodological Quality Assessment

A methodological quality assessment of the randomized controlled trials meeting inclusion criteria was carried out utilizing Cochrane review (48) criteria and IPM – QRB (49) criteria as shown in Appendices 4 and 5.

2.2 Study Characteristics

A description of the various studies included is shown below in a tabular format as well as a descriptive format.

2.2.1 Tabular Description of Study Characteristics

Appendices 6 through 9 show the study characteristics of included trials based on each approach: caudal epidural injections, lumbar interlaminar epidural injections, lumbar transforaminal epidural injections, and cervical/thoracic interlaminar epidural injections.

2.2.2 Descriptive Characteristics

Of the 52 trials examining the efficacy of epidural injections, 14 examined the role of caudal epidural injections (65,66,70,74,90,105,107-111,168,170,171); 17 examined lumbar interlaminar epidural injections (33,62,63,71,75,93,107,113,114,116-122,169); 18 examined lumbar transforaminal epidural injections (33,67,93,103,104,106,107,113,114,123,125,127,129,130,132,161,172,173); 8 examined cervical interlaminar epidural injections (60,61,68,69,133-135,160); and one trial examined thoracic interlaminar epidural injections (64).

There were 36 high quality trials (33,60-71,74,75,90,93,103,105,106,108,114,116-121, 123,125,127,129,130,132,169,172) and 16 moderate quality trials (104,107,109-111,113,122,133-135,160,161,168,170,171,173) utilizing Cochrane review criteria and 28 high quality trials (60-71, 74,75,93,103, 105,106,108,116,118,123,125,129,130,132,169,172) and 23 moderate quality trials (33,90,104,107,109-111,113,114,117, 119-122,127,133-135,160,161,168,169,171,173), and one low quality trial (170) utilizing IPM-QRB criteria. There were 28 trials (60-71,74,75,93,103,105,106,108,116,118,123,125,129,130,132,169,172) which were high quality using both Cochrane review criteria and IPM-QRB criteria.

Of the 14 trials that examined the efficacy of caudal epidural injections, 8 examined disc herniation/radiculitis (74,90,107-110,168,170), 3 examined spinal stenosis (65,105,171), one examined axial or discogenic pain (66), and 2 examined post surgery syndrome (70,111).

There were 17 trials that examined the efficacy of lumbar interlaminar epidural injections, 13 examined disc herniation/radiculitis (71,75,93,107,113,114,116-121,169), 5 examined spinal stenosis (33,62,113,121,122), and one examined axial or discogenic pain (63).

There were 18 trials that examined the efficacy of lumbar transforaminal epidural injections, 15 examined disc herniation/radiculitis (67,93,104,107, 113,114,123,125,127,129,130,132,161,172,173), and 4 examined spinal stenosis (33,103,106,113).

There were 8 trials that examined the efficacy of cervical interlaminar epidural injections, 5 examined disc herniation/radiculitis (69,133-135,160), one examined spinal stenosis (60), one examined axial or discogenic

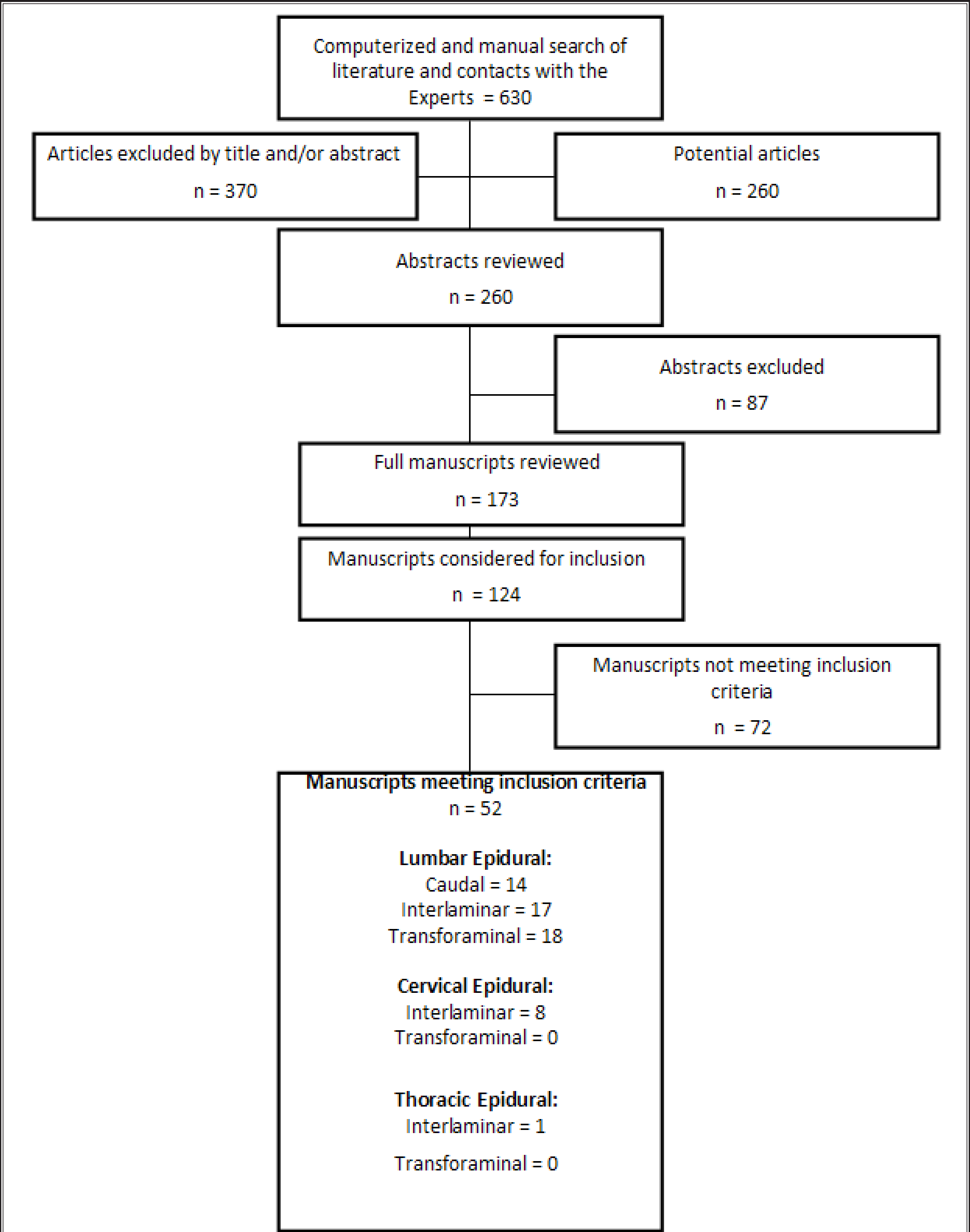

Fig. 1. *Flow diagram illustrating published literature evaluating epidural injections in managing spinal pain.*

pain (68), and one examined post surgery syndrome (61).

There was one trial that examined the efficacy of thoracic interlaminar epidural injections in mid back and upper back pain (64).

2.2.2.1 Caudal Epidural Injections

Fourteen studies examined caudal epidural injections for efficacy (65,66,70,74,90,105,107-111,168,170,171). Using Cochrane and IPM-QRB criteria, 6 of the 14 studies were determined to be high quality (65,66,70,74,105,108) and 6 of 14 were determined to be moderate quality (107,109,110,111,168,171). There was a difference between the 2 assessment criteria regarding 2 studies (90,170), with Cochrane being high quality and IPM-QRB criteria being moderate quality in one study (90), and in another study Cochrane being moderate quality and IPM-QRB being low quality (170).

Manchikanti et al conducted 4 studies (65,66,70,74). They used an identical protocol in each study: an active control design with a 2-year follow-up. These studies evaluated the efficacy of epidural injections in 2 groups: one group received a local anesthetic only and the other group received a local anesthetic with a steroid. In these 4 studies, a total of 480 patients were evaluated for one of the following conditions: lumbar disc herniation; lumbar discogenic pain without facet joint or sacroiliac joint pain; lumbar central spinal stenosis; and lumbar postsurgery syndrome.

Each of these trials reported that caudal epidural injections, whether with local anesthetic only or local anesthetic with steroid, were efficacious in 50% to 80% of those treated. These patients were divided into those who responded to the treatment and those who did not. A responsive patient was one who had at least a 50% improvement in both pain and function for 3 weeks with the initial 2 injections. Those who responded and those who did not were not significantly different for any of the pathologies studied, no matter which injection was received.

Responsive group patients in all 4 studies had superior outcomes; it should be noted that none of the studies had a placebo control. But each study only enrolled patients with chronic pain and homogeneity was maintained because the patients in each study had a similar diagnosis. Each study established the efficacy of local anesthetic with steroid for the pathology treated; in addition, the patients in the disc herniation study had a higher quality of pain relief at 6 and 12 months. The mechanisms of action of local anesthetics and steroids have an abundance of experimental and clinical evidence (20-24,57-77,184-192). Further, there have been previous descriptions concerning the effectiveness of sodium chloride injected into the epidural space and joint spaces (20,120,193-197).

Sayegh et al's study (90) had a mixed rating with the 2 criteria used. Cochrane criteria rated it high quality while IPM-QRB criteria rated it as moderate quality. Patients in this study had either acute or subacute sciatica. This randomized controlled study reported significant improvement for those receiving local anesthetic alone or with steroids. However, they reported that adding steroids provided a superior outcome because the onset of relief was faster, longer lasting, and of a higher quality.

Epidural saline was used by Iverson et al (109) in their study. One group received epidural injections of saline while the other group received saline with steroids—neither group had any significant improvement. This study was heavily criticized (9,198-200). Among the reasons for criticism were the large number of patients who had acute pain, no local anesthetic was used, and many of them had improved and were still randomized into the study.

Ackerman and Ahmad (107) compared the efficacy of caudal epidural injections with lumbar interlaminar and transforaminal epidural injections. This was a relatively small study showing the superiority of both lumbar interlaminar epidural injections and transforaminal epidural injections over caudal epidural injections. The authors utilized both local anesthetic and steroids.

Dashfield et al (108) assessed and compared caudal epidural steroid injections with targeted steroid placement during spinal endoscopy for chronic sciatica. Their study showed that epidural injections without passage of endoscopy equipment was superior.

Murakibhavi and Khemka (110) compared caudal epidural steroid injections in a randomized controlled trial of disc herniation either with conservative treatment measures which included medication as well as physiotherapy, whereas the intervention group received caudal epidural steroid injections with 20 mL of normal saline, 2 mL of 2% preservative-free lidocaine, and 2 mL or 80 mg of triamcinolone acetate. The authors showed complete long-term relief in 86% of the patients in the caudal epidural group compared to 24% in the conservative management group. This was a moderate quality trial without blinding comparing conservative modalities to epidural injections.

Park et al (105) studied the role of caudal epidural steroid injection for the treatment of unilateral lower lumbar radicular pain utilizing a single-blinded randomized design comparing ultrasound-guided versus fluoroscopy-guided procedures. They included a total of 110 patients with 55 patients in each group. In a short-term follow-up of 12 weeks they showed improvement with pain and function in both groups.

Revel et al (111) studied forceful epidural injections for the treatment of lumbosciatic pain with postoperative lumbar spine fibrosis. They included 60 patients with persistent or recurrent lumbosciatic pain after surgery and with epidural fibrosis. This was a moderate quality study with positive results.

Béliveau et al (170) compared caudal procaine with procaine with Depo-medron in 24 patients in each group with 16 of 24 patients in procaine group and 18 of 24 patients with procaine + Depo-medron group improving 7 of 24 in procaine group and 10 of 24 in procaine + Depo-medron group also showed complete pain relief at 3 month follow-up.

Datta and Upadeaway (168) compared 3 different steroid agents for treatment of low back pain through caudal approach with allocation of patients into 4 groups with one group receiving local anesthetic alone (bupivacaine), whereas 3 groups received 3 types of steroids with bupivacaine with total dose equivalent to 210 mg of methylprednisolone or 3 injections with methylprednisolone acetate, triamcinolone acetonide, and betamethasone acetate. All injections were administered with 10 to 15 mL volume with 0.125% bupivacaine alone or bupivacaine mixed with 80 mg of methylprednisolone, 80 mg of triamcinolone, or 15 mg of dexamethasone. The procedures were performed blindly without fluoroscopy and a significant proportion of patients had disc herniations at L3/4, either individually or in combination, in the majority of the patients, the level at which caudal epidural has poor spread pattern, specifically when performed without fluoroscopy. Visual Analog Scales (VAS) improved the most in methylprednisolone and triamcinolone group from baseline scores of 7.4 to 4.9 in methylprednisolone group and 4.8 in triamcinolone group. In contrast, dexamethasone group improved from 7.3 to 5.2 and local anesthetic alone group improved from 7.2 to 6.18. These results in a short-term follow-up show that methylprednisolone and triamcinolone with local anesthetic in rather high doses were more effective than high dose dexamethasone and bupivacaine alone. Thus, the results show that there is significant improvement with steroids when local anesthetics are added.

Huda et al (171), utilizing a blind approach, assessed 70 patients. They compared methylprednisolone or triamcinolone mixed with bupivacaine and normal saline with a total of 20 mL volume. In the methylprednisolone group, at the end of 6 months, 68.5% of the patients reported improvement, whereas improvement was seen in 40% of the patients in the triamcinolone group. The results are impressive considering that patients received only one injection of steroid with bupivacaine.

2.2.2.2 Lumbar Interlaminar Epidural Injections

Lumbar interlaminar epidural injections were studied for efficacy in 17 randomized controlled trials (33,62,63,71,75,93,107,113,114,116-122,169). Using both Cochrane and IPM-QRB criteria, 8 studies were rated high quality (62,63,71,75,93,116,118,169), while 3 were rated moderate quality (107,113,122). The 2 review criteria differed in their assessment of 6 trials (33,114,117,119-121); Cochrane rated them as high quality and IPM-QRB as moderate quality.

Manchikanti et al conducted 3 of these studies (62,63,71). They used an identical protocol in each study: an active control design with a 2-year follow-up. These studies evaluated the efficacy of epidural injections in 2 groups: one group received a local anesthetic only and the other group received a local anesthetic with a steroid. In these 3 studies, a total of 360 patients were evaluated for one of the following conditions: lumbar disc herniation; lumbar discogenic pain without facet joint or sacroiliac joint pain; and lumbar central spinal stenosis. Similar outcomes were seen in 60% to 84% of the patients in these studies. Both Cochrane and IPM-QRB rated these studies as high quality (10 of 12 and either 43 or 44 of 48, respectively).

These studies divided patients into responsive and nonresponsive groups. A patient was considered responsive if a 50% improvement in pain and function was achieved in the first 3 weeks with the initial 2 injections. Nonresponsive patients in each pathology studied were: interlaminar injections of local anesthetic only - 10 with disc herniation, 5 with discogenic pain, and 9 with central stenosis; local anesthetic with steroids—1 with disc herniation, 6 with discogenic pain, and 7 with central stenosis. These results show that there were many in the nonresponsive local anesthetic disc herniation group, but no differences were noted between the subgroups in the other pathologies studied. Also, the addition of steroids to the local anesthetic appears to result in superior outcomes for pain at 6 months and functional status at 12 months for those with disc herniation (71). Patients who do not respond to local anesthetic alone for disc herniation may achieve a better outcome with the addition of steroids. Of interest is the fact that none of these studies had a placebo group.

Fukusaki et al (122) injected patients in their study without the benefit of image guidance. The 53 patients in their study were placed into 3 groups: 16 received epidural saline injections, 18 received bupivacaine, and 19 received bupivacaine and methylprednisolone. At 3 months, none of the injectates were effective.

In a study that received widespread attention, Carette et al (120) reported that at 3 months neither normal saline nor saline with depo-methylprednisolone injected in the lumbar epidural spine was effective, despite some initial improvement reported with the saline and steroid injection. Their methodology and conclusions have been criticized (201-204).

Ackerman and Ahmad (107) compared caudal, interlaminar, and transforaminal epidural injections. They reported similar efficacy for caudal and transforaminal injections, but superiority for transforaminal in mid-term results in a small, moderate-quality trial.

Two studies were conducted by Ghai et al (75,93). In the first study (93) they compared parasagittal interlaminar and transforaminal epidural steroid injections without local anesthetic in 62 patients. The results showed significant improvement at 3 months, 6 months, and 12 months in 78%, 75%, 69% of patients in the parasagittal interlaminar group compared to 77%, 77%, 77% in the transforaminal epidural group. This was a relatively small active control trial with a long-term follow-up assessing the role of parasagittal interlaminar epidural injections and transforaminal epidural injections, showing equal improvement with steroids without local anesthetic. In the second study, Ghai et al (75) compared local anesthetic alone with local anesthetic with steroids in disc herniation or radiculitis. In an active-control trial of 34 patients in the local anesthetic group and 35 in the local anesthetic with steroid group, they administered 8 mL of local anesthetic of 0.5% lidocaine, or 6 mL of local anesthetic with steroid of 80 mg of methylprednisolone. The results showed effectiveness in both groups at the end of 12 months. There was a superiority of steroids at the 3-month assessment; however, this dissipated over time.

Friedly et al (33) conducted a study of epidural injections, promoted as the definitive and ideal trial, with 400 patients and 26 pain physicians in multiple settings utilizing interlaminar and transforaminal approaches with local anesthetic alone or with steroids. This study's design was not conducive for determining the efficacy of epidural injections for spinal stenosis with a single modality. A major problem with their study was their failure to consider high-quality randomized studies and their focus on low-quality studies. Other problems with their study was the short, 6-week follow-up; mixed approaches, interlaminar and transforaminal; differential values of significance (*P* value of 0.05 for the combined group and 0.025 for individual groups) and no consistency in the injectate volumes (35). Adverse events were much higher than would have been expected, the results were inaccurately interpreted, and the conclusions reached were inappropriate (35).

Candido et al (169) assessed correlation of pain relief with concordant pressure paraesthesia during parasagittal interlaminar lumbar epidural injections with local anesthetic alone or with local anesthetic and steroids with 53 patients randomized to each group. Patients were administered with 120 mg of methylprednisolone acetate, combined with preservative free lidocaine, and normal saline with a total volume of 4 mL. They showed effectiveness of steroid mixed with local anesthetic with lateral parasagittal interlaminar approaches in 55% of patients at one year follow-up with pain and function. The results were superior in parasagittal group with pain relief, disability, and opioid intake.

The characteristics of multiple other studies are shown in Appendix 7. Of importance is Dilke et al (117) who showed efficacy in 1973; whereas, Arden et al (119) in 2005 showed a lack of efficacy utilizing the same design with a true placebo with placebo injection being administered to the interspinous ligament.

2.2.2.3 Lumbar Transforaminal Epidural Injections

Lumbar transforaminal epidural injections' efficacy were evaluated in 18 randomized controlled trials (33, 67,93,103,104,106,107,113,114,123,125,127,129,130, 132,161,172,173). Evaluated with both Cochrane and IPM-QRB criteria, 10 were high-quality (67,93,103,106, 123,125,129,130,132,172) and 5 were moderate-quality (104,107,113,161,173). Cochrane criteria graded 3 studies as high-quality, but IPM-QRB criteria graded them as moderate-quality (33,114,127).

Cohen et al (161), in a seemingly flawless study, assessed epidural steroid injections compared to gabapentin for lumbosacral radicular pain. However, the study had numerous flaws including using a safe triangle approach when injecting particulate steroids, a flawed design and analysis of the data, and an inordinately high proportion of patients who withdrew from the study even at the 3-month follow-up. The inclusion criteria were also extremely weak with some patients who had less than 3 months of pain and some who had 3 to 6 months (39-41,205). The gabapentin dosage was higher than usually administered in clinical settings at 1800 to 3600 mg per day without proven efficacy (206). Overall this trial showed no significant improvement in either group.

Ghahreman et al's (123) follow-up period was even shorter—only one month. Their study was also small, but included multiple arms. They reported that local anesthetic with steroids was vastly superior to local anesthetic alone: 54% improvement versus only a 7% improvement. This study also had an arm that received a true placebo—sodium chloride solution injected away from the nerve root. They reported a lack of efficacy for this placebo, but when one study arm was injected with sodium chloride into the source of pain, there was a significant effect, though not as great as local anesthetic with steroids.

Karppinen et al (125) conducted a high-quality study as graded by both Cochrane and IPM-QRB criteria. Their study looked at the efficacy of a single injection of either sodium chloride solution or local anesthetic with steroid. They followed patients for up to one year. Patients who received sodium chloride fared better at 3 months and 6 months, but there was no significant difference at one year. However, in a subgroup analysis, they reported that in patients who had disc protrusions, local anesthetic with steroid had a better efficacy than just sodium chloride. There has been significant related criticism (207,208).

Manchikanti et al (67) conducted an active control trial that followed 120 patients for 2 years. They used an infraneural approach, injecting either local anesthetic alone or local anesthetic with steroid. At the end of the 2-year study period, 65% of those who received local anesthetic alone and 57% who received local anesthetic with steroid had significant improvement in all measured categories: pain intensity, function, and medication reduction. A subcategory analysis of patients who responded to the treatment—determined as those who had at least a 50% improvement in pain and function for 3 weeks with the first 2 injections—reported that 80% of those who received local anesthetic alone saw improvement and 73% of those who received local anesthetic with steroid saw improvement.

In a small study by Riew et al (128,129), patients with disc herniation were injected either with local anesthetic alone or local anesthetic with steroid. Their outcome measure was avoidance of surgery; 33% of those in the local anesthetic alone group and 71% in the local anesthetic with steroid group avoided surgery. While both treatments were deemed effective, local anesthetic with steroid was deemed superior.

Ng et al (130) conducted a study of 86 patients evenly split into groups that received either local anesthetic alone or local anesthetic with steroid. At 3 months, the treatment was considered to be effective in 47.5% of the patients who received local anesthetic alone and 41.5% of the patients who received local anesthetic with steroid.

Tafazal et al (132) conducted a study on spinal stenosis and disc herniation treated either with local anesthetic alone or local anesthetic with steroid. Only disc herniation inclusion criteria were met. Superior results were reported for sciatica with similar efficacy for local anesthetic alone and local anesthetic with steroid.

The remaining trials were of an active control nature with Vad et al (104) comparing transforaminal epidural injections with local anesthetic with steroid with trigger point injections, demonstrating an overwhelming superiority for transforaminal epidural injections; however, this was a moderate quality trial, barely meeting inclusion criteria. Ackerman and Ahmad (107) compared caudal, interlaminar, and transforaminal approaches which showed transforaminal to be superior to interlaminar and caudal; however, this was a small trial with only a 6-month follow-up; it was also of moderate quality. Jeong et al (127) compared a ganglionic and pre-ganglionic approach in a large population; however, with only a 6-month follow-up, no significant difference was shown between pre-ganglionic and ganglionic approaches. Rados et al (114), Lee et al (113), and Ghai et al (93) compared interlaminar epidural injections with transforaminal, while Rados and Lee utilized a standard epidural injection technique; Ghai et al (93) utilized a parasagittal interlaminar approach. Lee et al (113) showed no significant difference between both approaches, whereas Rados et al (114) showed the superiority of transforaminal in a small study and Ghai et al (93) showed no significant difference with a parasagittal approach compared to a transforaminal approach.

As described in the section on interlaminar epidural injections, Friedly et al (33) conducted an inappropriate and flawed assessment combining lumbar interlaminar epidural injections with lumbar transforaminal epidural injections. There were multiple flaws in the design as well as the analysis leading to an inappropriate interpretation and conclusions (35).

Park et al (103) assessed the role of transforaminal epidural injections using either a supraneural approach, otherwise known as a safe triangle approach, comparing it to the Kambin triangle approach. This was a relatively small study showing no significant difference between both approaches. Koh et al (106) compared 2 solutions: local anesthetic with hyaluronidase steroid to either normal saline or hypertonic saline. This was a small study with short-term follow-up. Overall it showed hypertonic saline may prolong improvement. Lee et al (113) compared transforaminal epidural injections with interlaminar injections and showed the superiority of transforaminal epidural injections over interlaminar epidural injections utilizing local anesthetic with steroids.

In one trial, transforaminal epidural injections were compared with autologous condition serum with corticosteroids (173) and in another trial (172), particulate versus nonparticulate corticosteroids were compared. Comparative effectiveness of transforaminal with particulate versus nonparticulate corticosteroid showed effectiveness of triamcinolone and dexamethasone with pain relief and improvement in functional status up to 6 months, without clear differences between groups. Becker et al (173 compared local anesthetic with 10 mg of triamcinolone or 5 mg of triamcinolone and compared to conditioned autologous serum with a modified or alternate technique with improvement seen in all groups. However, autologous condition serum showed a consistent pattern of superiority over both triamcinolone groups.

2.2.2.4 Cervical Interlaminar Epidural Injections

Eight studies (60,61,64,68,69,133-135,160) met the inclusion criteria. Cochrane and IPM-QRB criteria graded 4 of them to be high quality (60,61,68,69) and 4 of them to be moderate quality (133-135,160).

Manchikanti et al conducted 4 active control studies (60,61,68,69). These studies enrolled 356 patients and examined the use of local anesthetic alone or local anesthetic with steroid for the following etiologies: disc herniation, discogenic pain without facet joint pain, central spinal stenosis, and postsurgery syndrome. Two studies had a minimum one-year follow-up and the other 2 had a 2-year follow-up. Both Cochrane and IPM-QRB criteria graded all of them as high-quality.

All 4 of these studies found there to be similar results for the efficacy of the 2 injectates in each etiology. These studies analyzed outcomes based on subgroups that were either responsive or nonresponsive to the treatment that was received. A responsive patient was one who received at least 3 weeks of 50% improvement with the first 2 treatments. Responsive group patients in all etiologies, as seen in Appendix 6, had superior outcomes.

Cohen et al (160) performed a double-blind randomized controlled trial assessing a conservative management group that received medication and physical therapy with an epidural injection group that received steroid alone and with a combination group that received epidural steroids as well as conservative management. The study may be criticized for various flaws in the design as well as its analysis with a large number of noncompliant patients; it appears that patients may have done better around 3 months (209). Thus, the results of this trial are considered undetermined. Further, the authors did not provide information on the number of injections.

Castagnera et al (133), Stav et al (134), and Pasqualucci et al (135) were utilized due to lack of multiple randomized trials, meeting appropriate inclusion criteria of 50 patients. The patients included were 24 by Castagnera et al (133), 42 by Stav et al (134), and 40 by Pasqualucci et al (135). Overall, all 3 trials showed positive results either comparing local anesthetic with steroids or steroid plus morphine (133) with steroid plus morphine showing positive results. Stav et al (134) compared local anesthetic with steroids to intramuscular steroid with the epidural local anesthetic with steroids injection group showing positive results. Pasqualucci et al (135) assessed bupivacaine with methylprednisolone acetate, comparing single versus continuous infusion groups with significant improvement in both groups, with the continuous improvement group showing better results.

2.2.2.5 Thoracic Interlaminar Epidural Injections

A single study, conducted by Manchikanti et al (64), assessed thoracic interlaminar epidural injections. It was graded as high quality using both Cochrane and IPM-QRB criteria. This active-control study had a follow-up of 2 years and reported on the efficacy of epidural injections of local anesthetic alone or local anesthetic with steroid. The 110 patients in the study had various pain etiologies including: disc herniation, discogenic pain, central spinal stenosis, and postsurgery syndrome. Similar to other studies conducted by Manchikanti and colleagues, patients were put into subgroups of responsive and nonresponsive patients. Responsive patients were those who had at least a 50% improvement in pain and function for at least 3 weeks with the first 2 injections. Only 4 patients were nonresponsive who received local anesthetic alone, while only 6 were nonresponsive who received local anesthetic with steroid.

2.3 Meta-analysis

There was limited homogeneity among the 52 trials that met the inclusion criteria for methodological quality assessment because different spinal regions were studied, techniques differed as did injectates, and fluoroscopy was not always utilized. Homogeneity was observed between 2 trials by Manchikanti et al (71) and Ghai et al (75) with both approaches utilizing a local anesthetic, 0.5% preservative-free lidocaine with or without steroids under fluoroscopy with an interlaminar approach. Of the 52 trials, 13 trials by Manchikanti et al assessing the role of epidural injections were similar in many aspects (60-71,74). But they differed based on the pathology studied, such as the spinal region, disc herniation, spinal stenosis, postsurgery syndrome, or discogenic pain. Furthermore, the trials by Manchikanti et al were all performed by one group of authors in the same setting with similar protocols.

Of all the caudal epidural injections, there were only 2 studies which met the criteria of longer than 6 months of follow-up in disc herniation (74,90); there were no other studies meeting the inclusion criteria for meta-analysis in the lumbar interlaminar group.

Among the various studies of lumbar interlaminar epidural injections, there were no similarities among more than 2 trials studying local anesthetic and local anesthetic with steroids. There were no homogenous studies either in the lumbar transforaminal group or cervical interlaminar groups. Consequently, a meta-analysis was not feasible for individual conditions. Further, meta-analysis was also not feasible for individual approaches as the majority of the studies in each group were performed by the same group of authors with a lack of other trials to be included.

2.4 Analysis of Evidence

2.4.1 Disc Herniation

The evidence is Level II in managing lumbar disc herniation with caudal epidural injections with 2 trials showing long-term effectiveness (74,90); lumbar interlaminar epidural injections with 5 trials showing long-term effectiveness (71,75,93,116,118,) and 2 trials showing a lack of effectiveness (119,120), and, finally, transforaminal epidural injections with 4 trials showing long-term effectiveness (67,93,104,129) and one trial showing unclear results of effectiveness (125).

In the cervical spine, the evidence is Level II for disc herniation based on 3 long-term trials showing effectiveness (69,133,134) with no trials showing a lack of effectiveness.

In the thoracic spine, the evidence is Level III based on only one RCT with long-term follow-up showing effectiveness (64); however, with a heterogenous population which included disc herniation.

2.4.2 Spinal Stenosis

For lumbar central stenosis, the evidence is Level II with caudal epidural injections based on one trial showing long-term effectiveness (105), Level II for lumbar interlaminar epidural injections based on one high quality randomized trial with long-term effectiveness, the evidence with lumbar interlaminar epidural injections is Level II based on one high quality RCT (62), the evidence with lumbar transforaminal epidural injections is Level III based on 3 trials showing short-term effectiveness (103,106,113) and one showing a lack of effectiveness (33).

The evidence is Level III for cervical central spinal stenosis (60) showing positive results with a one-year follow-up.

2.4.3 Discogenic Pain

The evidence for lumbar axial discogenic pain without facet joint pain or sacroiliac joint pain is Level II for caudal epidural injections based on one trial (66) showing long-term effectiveness, and with lumbar interlaminar epidural injections based on one long-term trial (63) with no evidence available for transforaminal epidural injections.

In the thoracic spine, the evidence is Level III based on only one RCT with long-term follow-up showing effectiveness (64); however, with a heterogenous population which included discogenic pain.

2.4.4 Postsurgery Syndrome

The evidence for lumbar postsurgery syndrome is Level II for caudal epidural injections based on one long-term trial showing effectiveness (70).

The evidence is Level III for cervical postsurgery syndrome (61) based on one trial showing positive results with a one-year follow-up.

3.0 Discussion

This systematic review assessed the efficacy of epidural injections performed for chronic spinal pain utilizing caudal, interlaminar (lumbar, thoracic, cervical) or lumbar transforaminal approaches. There is Level I-II evidence based on multiple highly relevant, quality, randomized trials with a best evidence synthesis for epidural injections in managing spinal pain for cervical and lumbar interlaminar, caudal, and lumbar transforaminal injections. There is Level II-III evidence for thoracic interlaminar epidural injections. However, the evidence is Level II based on at least one relevant high quality randomized controlled trial in managing central spinal stenosis, axial/discogenic pain without facet joint pain, disc herniation, or sacroiliac joint pain, and spinal postsurgery syndrome in the cervical and lumbar spines.

These results are similar to several other systematic reviews performed recently (20-23,32), whereas they have some similarities to others (25,26) and are in contradiction to other systematic reviews (25,30). Significant variations in methodology have been discussed with all systematic reviews, specifically with epidural injections. As discussed earlier, multiple systematic reviews are inappropriately utilizing active controlled trials with local anesthetic as placebo-controlled trials, thereby arriving at erroneous conclusions. Further, some authors (33) also utilized different assessment values, with a significant *P* value of 0.05; whereas, with a subgroup analysis of interlaminar and transforaminal approaches they decreased the P value to be 0.025, thus creating imbalance. The study could have been designed appropriately utilizing either only transforaminal epidural injections or interlaminar epidural injections (35). Further, they also compared the differences between local anesthetic and steroids and did not utilize the improvement from baseline to the follow-up period. A recent AHRQ assessment went even further: not only that they did not follow IOM rules (4,36), but in methodologic quality assessment they interjected another factor that if a study is published more than once it loses its value. In contrast, a rigorous evaluation of trials with best evidence synthesis showed appropriate results (20-23).

Recently there has been significant debate in reference to epidural injections with catastrophic neurological complications related to cervical transforaminal epidural injections (41,39-44). Some complications also have been reported with lumbar and thoracic transforaminal epidural injections; however, the complications have been minimal with interlaminar or caudal epidural injections. The FDA issued a warning about the risks of serious, though rare, complications and the lack of effectiveness in epidurally administered steroids (37).

Epidurally administered steroids have been the subject of debate regarding their potential for catastrophic complications, especially when administered via the cervical transforaminal route (37-45,210-243). An FDA warning claimed that epidural steroid injections were not effective and could cause serious complications, albeit rare (37,38). In addition, multiple inappropriate standards were published without any scientific basis. These standards also lacked an ethical basis since the same group developed safety standards for epidural injections. Standards for safe administration of epidural injections also continue to promote blind epidural injections in pregnant women, contradictory to their own standards (39-44,242).

The FDA's warning was not about all epidural injections—it only covered cervical transforaminal epidurals that use particulate steroids. Cervical and thoracic epidural injections barely make up a fraction of the total of all epidural injections (16). This manuscript shows that epidural injections, whether of local anesthetic alone or local anesthetic with steroid, are efficacious when administered by a caudal, interlaminar, or lumbar transforaminal approach. The steroids in these examined studies were all particulate steroids. Only particulate steroids have been associated with catastrophic complications (37-45,211-219,242,243). Experimental evidence also shows neurological toxic effects occur predominantly with particulate steroids (37-45,242,244,245). In addition, the majority of evidence provided in safety of neurological complication was shown to be flawed, including limiting cervical interlaminar entry below C6-C7 (246,247), and routine use of digital substraction angiography (248,249).

This systematic review of high-quality randomized controlled studies that graded highly for methodological quality and that included a follow-up of at least one year concludes that epidural administration of local anesthetic alone or local anesthetic with steroid are equally efficacious. When it comes to managing disc herniation and radiculitis, there is Level II evidence that local anesthetic with steroid is superior to local anesthetic alone.

A review of the current literature on interventional techniques in general and epidural injections in particular shows significant misunderstandings with underpinnings of intellectual bias, in reference to placebo and nocebo effects, comparative effectiveness studies, active control trials with interpretation of local anesthetic as placebo with conclusions reaching that neither treatment is effective when actually both treatments are effective (25,30,33). Among multiple design flaws to reach preformed conclusions, use of outcome parameters with comparison between 2 active control groups rather than baseline to follow-up periods is a major issue (9,20-24,35,162,163). In reference to active control trials, the literature has repeatedly shown both experimentally as well as clinically similar effectiveness of local anesthetics alone with or without steroids (9,20-25,35,162,163). This fact has been ignored and authors continue to consider local anesthetics as placebo. The magnitude of placebo effects (250) and nocebo effects (251,252), patient-clinician communication, and therapeutic outcomes (252), avoidance of nocebo effects to optimize treatment outcome (253), lack of differences between treatment and placebo effects (254), placebos without deception (255), and placebo use in clinical settings (256,257) have been extensively described. Kaptchuk and Miller (250) described that placebo effects are improvements in a patient's symptoms that are attributable to their participation in the therapeutic encounter, with its "rituals, symbols, and interactions," rather than a simplistic view of effect of an inert substance. In addition, placebo effects rely on complex neurobiologic mechanisms involving neurotransmitters and activation of specific, quantifiable, and relevant areas of the brain (250). However, many medications utilized in pain also act through these pathways. According to Kaptchuk and Miller (250): "Research reviews have estimated that 4% to 26% of patients who are randomly assigned to placebos in trials discontinue their use because of perceived adverse effects" or nocebo effects. In fact, in a systematic review, a majority of the adverse events were attributed to nocebo effects (258). Another meta-analysis of the magnitude of nocebo effects (251) concluded that the magnitudes and range of effect sizes of nocebo effects were similar to those of placebo effects. Further, in studies where nocebo effects were induced by a combination of verbal suggestions and condition, the effect sizes were larger and higher than in studies where nocebo effects were induced by verbal suggestions alone. Overall the findings were similar to those in the placebo literature. Further, similar to placebo, nocebo responses demonstrate the powerful interaction between the therapeutic context and the patient's mind-brain interaction (252). Just as placebo effects are seen with supportive and attentive health care, legitimately creating a therapeutic bias, negative information, behavior, and expectations induce nocebo effects.

Thus, placebo effects are often considered by researchers as unworthy and illegitimate without scientific basis, injecting bias and prejudice. However, this attitude obscures a core truth of medicine which is to heal along with convergence of nocebo effects which must be avoided to optimize treatment outcome (250,253). Even though distinct neurobiologic mechanisms are activated in placebo and nocebo effects, placebos may provide relief and nocebos may adversely affect therapeutic outcomes. The therapeutic benefits associated with placebo effects and adverse consequences associated with nocebo effects primarily address subjective and self appraised symptoms, but they do not alter the pathophysiology of disease beyond their symptomatic manifestations. In a systematic review and meta-analysis (254) assessing 115 trials with continuous outcomes, there was no difference between treatment and placebo effects; however, in the trials with binary outcomes (N=37) treatments were significantly more effective than placebos. Further treatment and placebo effects were not different in 22 out of 28 predefined subgroup analyses. In this meta-analysis after all the criteria for reducing bias were ruled out, placebos were more effective than treatments. The authors concluded that placebos with comparatively powerful effects can benefit patients either alone or as a part of a therapeutic regimen. Consequently, placebo and nocebo interactions are crucial when assessing the literature.

Multiple studies also have been conducted in reference to a cost utility analysis of epidural injections. Cost utility is important considering that policy decisions are made based on quality of life improvement in some sectors. The studies have shown the cost utility of epidural injections and percutaneous adhesiolysis (259-262).

The outcome assessments also have been associated with significant bias and misunderstandings. In fact, authors with preconceived ideas have designed trials with differential assessment of outcomes and also designed the trials so that their preconceived goals can be realized (33,35). Further, the comparison of outcomes between 2 control groups when both involve active interventions has no value. Recent literature (53-57) has clearly demonstrated the value of outcomes from baseline to follow-up periods rather than between 2 groups. The cost utility of epidural injections is superior to numerous other modalities of treatments including spinal cord stimulation and surgical interventions

(261,263). There also have been studies assessing outcome predictors based on magnetic resonance imaging (264), epidurographic contrast medium flow patterns (167,265), and multiple other factors (266,267); however, there has not been any significant evidence of any factors to pinpoint the efficacy of epidural injections.

Another conclusion from this analysis is that injecting local anesthetic alone for most etiologies might be preferable to injecting local anesthetic with steroid. Omitting steroid could lessen the risk of rare, but possibly fatal complications, such as meningitis (20-24,37-46,242). Also rare are serious complications from cervical injections that might or might not be diminished by using a transforaminal approach. Such complications are uncommon in lumbar injections.

Patients who have had surgery should be considered to be high risk. Patients with postsurgery syndrome do not, according to the literature, have better outcomes when a steroid is added to a local anesthetic injection. Additional research is needed for this patient group, especially in the areas of lumbar interlaminar injections and any type of transforaminal injection.

In addition to the aforementioned patients with postsurgery syndrome, other high-risk patients are those with diabetes and a risk of hyperglycemia; those at a high risk of osteopenia and osteoporosis; those at risk for avascular necrosis; those with a risk for adverse effects with suppression of the hypothalamic-pituitary-adrenocortical axis scheduled for major surgery; and those with poor wound healing and immunosuppression.

The current manuscript does have some limitations. There was no meta-analysis performed. Manchikanti et al contributed a disproportionate number of the studies that were assessed. Therefore, further trials are warranted. Physicians should carefully select patients for the interventional techniques examined in the current manuscript and discuss with their patients all aspects of shared decision-making regarding these techniques and the use of local anesthetic alone or local anesthetic with steroid.

4.0 Conclusion

This systematic review with appropriate assessment of the quality of the manuscripts with inclusion of 52 trials showed Level I to Level III evidence in managing various painful conditions of the spine including disc herniation, axial or discogenic pain, central spinal stenosis, and postsurgery syndrome, utilizing caudal and interlaminar approaches in the lumbar spine, an interlaminar approach in the thoracic and cervical spines, and a transforaminal approach in the lumbar spine.

Acknowledgments

The authors wish to thank Vidyasagar Pampati, MSc, for statistical assistance, and Tom Prigge, MA, and Laurie Swick, BS for manuscript review, and Tonie M. Hatton and Diane E. Neihoff, transcriptionists, for their assistance in preparation of this manuscript. We would like to thank the editorial board of *Pain Physician* for review and criticism in improving the manuscript.

Conflicts Of Interest

Dr. Benyamin is a consultant and lecturer for Boston Scientific and Kimberly Clark. Dr. Datta receives research support from Sucampo Pharmaceuticals and an honorarium from Smith and Nephew Dr. Gupta has been paid honorarium for presenting at meetings and teaching on the interventional pain medicine cadaver courses and by pharmaceutical companies for presenting to health care professionals. Pharmaceutical companies and companies that manufacture equipment used in pain medicine have supported meetings organized by Dr S Gupta. Dr. Alan Kaye is a speaker for Depomed, Inc. Dr. Manchikanti has provided limited consulting services to Semnur Pharmaceuticals, Incorporated, which is developing nonparticulate steroids. Dr. Racz is a Consultant for and has family ownership of Epimed International, is a Consultant to Cosman RF company, and has Medtronic patent issues. Dr Staats Is a Consultant for Medtronic, Boston Scientific, St Jude, Electrocore Medical, Currently is involved in research funded by Boston Scientific, St Jude, Spinal Modulation, Vertos.

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Appendix 1. *Sources of risk of bias and Cochrane Review rating system.*

A	1. Was the method of randomization adequate?	A random (unpredictable) assignment sequence. Examples of adequate methods are coin toss (for studies with 2 groups), rolling a dice (for studies with 2 or more groups), drawing of balls of different colors, drawing of ballots with the study group labels from a dark bag, computer-generated random sequence, pre-ordered sealed envelopes, sequentially-ordered vials, telephone call to a central office, and pre-ordered list of treatment assignments. Examples of inadequate methods are alternation, birth date, social insurance/ security number, date in which they are invited to participate in the study, and hospital registration number.	Yes/No/ Unsure
B	2. Was the treatment allocation concealed?	Assignment generated by an independent person not responsible for determining the eligibility of the patients. This person has no information about the persons included in the trial and has no influence on the assignment sequence or on the decision about eligibility of the patient.	Yes/No/ Unsure
C	Was knowledge of the allocated interventions adequately prevented during the study?		
	3. Was the patient blinded to the intervention?	This item should be scored "yes" if the index and control groups are indistinguishable for the patients or if the success of blinding was tested among the patients and it was successful.	Yes/No/ Unsure
	4. Was the care provider blinded to the intervention?	This item should be scored "yes" if the index and control groups are indistinguishable for the care providers or if the success of blinding was tested among the care providers and it was successful.	Yes/No/ Unsure
	5. Was the outcome assessor blinded to the intervention?	Adequacy of blinding should be assessed for the primary outcomes. This item should be scored "yes" if the success of blinding was tested among the outcome assessors and it was successful or: –for patient-reported outcomes in which the patient is the outcome assessor (e.g., pain, disability): the blinding procedure is adequate for outcome assessors if participant blinding is scored "yes" –for outcome criteria assessed during scheduled visit and that supposes a contact between participants and outcome assessors (e.g., clinical examination): the blinding procedure is adequate if patients are blinded, and the treatment or adverse effects of the treatment cannot be noticed during clinical examination –for outcome criteria that do not suppose a contact with participants (e.g., radiography, magnetic resonance imaging): the blinding procedure is adequate if the treatment or adverse effects of the treatment cannot be noticed when assessing the main outcome –for outcome criteria that are clinical or therapeutic events that will be determined by the interaction between patients and care providers (e.g., co-interventions, hospitalization length, treatment failure), in which the care provider is the outcome assessor: the blinding procedure is adequate for outcome assessors if item "4" (caregivers) is scored "yes" –for outcome criteria that are assessed from data of the medical forms: the blinding procedure is adequate if the treatment or adverse effects of the treatment cannot be noticed on the extracted data.	Yes/No/ Unsure
D	Were incomplete outcome data adequately addressed?		
	6. Was the drop-out rate described and acceptable?	The number of participants who were included in the study but did not complete the observation period or were not included in the analysis must be described and reasons given. If the percentage of withdrawals and drop-outs does not exceed 20% for short-term follow-up and 30% for long-term follow-up and does not lead to substantial bias a "yes" is scored.	Yes/No/ Unsure
	7. Were all randomized participants analyzed in the group to which they were allocated?	All randomized patients are reported/analyzed in the group they were allocated to by randomization for the most important moments of effect measurement (minus missing values) irrespective of non-compliance and co-interventions.	Yes/No/ Unsure
E	8. Are reports of the study free of suggestion of selective outcome reporting?	In order to receive a "yes," the review author determines if all the results from all pre-specified outcomes have been adequately reported in the published report of the trial. This information is either obtained by comparing the protocol and the report, or in the absence of the protocol, assessing that the published report includes enough information to make this judgment.	Yes/No/ Unsure
F	Other sources of potential bias:		
	9. Were the groups similar at baseline regarding the most important prognostic indicators?	In order to receive a "yes," groups have to be similar at baseline regarding demographic factors, duration and severity of complaints, percentage of patients with neurological symptoms, and value of main outcome measure(s).	Yes/No/ Unsure
	10. Were co-interventions avoided or similar?	This item should be scored "yes" if there were no co-interventions or they were similar between the index and control groups.	Yes/No/ Unsure
	11. Was the compliance acceptable in all groups?	The reviewer determines if the compliance with the interventions is acceptable, based on the reported intensity, duration, number, and frequency of sessions for both the index intervention and control intervention(s). For example, physiotherapy treatment is usually administered over several sessions; therefore, it is necessary to assess how many sessions each patient attended. For single-session interventions (e.g., surgery), this item is irrelevant.	Yes/No/ Unsure
	12. Was the timing of the outcome assessment similar in all groups?	Timing of outcome assessment should be identical for all intervention groups and for all important outcome assessments.	Yes/No/ Unsure

Source: Furlan AD, Pennick V, Bombardier C, van Tulder M; Editorial Board, Cochrane Back Review Group. 2009 updated method guidelines for systematic reviews in the Cochrane Back Review Group. *Spine (Phila Pa 1976)* 2009; 34:1929-1941 (48).

Appendix 2. Item checklist for assessment of randomized controlled trials of IPM techniques utilizing IPM – QRB.

		Scoring
I.	**TRIAL DESIGN AND GUIDANCE REPORTING**	
1.	**CONSORT or SPIRIT**	
	Trial designed and reported without any guidance	0
	Trial designed and reported utilizing minimum criteria other than CONSORT or SPIRIT criteria or trial was conducted prior to 2005	1
	Trial implies it was based on CONSORT or SPIRIT without clear description with moderately significant criteria for randomized trials or the trial was conducted before 2005	2
	Explicit use of CONSORT or SPIRIT with identification of criteria or trial conducted with high level reporting and criteria or conducted before 2005	3
2.	**Type and Design of Trial**	
	Poorly designed control group (quasi selection, convenient sampling)	0
	Proper active-control or sham procedure with injection of active agent	2
	Proper placebo control (no active solutions into active structures)	3
3.	**Setting/Physician**	
	General setting with no specialty affiliation and general physician	0
	Specialty of anesthesia/PMR/neurology/radiology/ortho, etc.	1
	Interventional pain management with interventional pain management physician	2
4.	**Imaging**	
	Blind procedures	0
	Ultrasound	1
	CT	2
	Fluoro	3
5.	**Sample Size**	
	Less than 50 participants in the study without appropriate sample size determination	0
	Sample size calculation with less than 25 patients in each group	1
	Appropriate sample size calculation with at least 25 patients in each group	2
	Appropriate sample size calculation with 50 patients in each group	3
6.	**Statistical Methodology**	
	None or inappropriate	0
	Appropriate	1
7.	**Inclusiveness of Population**	
7a.	For epidural procedures:	
	Poorly identified mixed population	0
	Clearly identified mixed population	1
	Disorders specific trials (i.e. well defined spinal stenosis and disc herniation, disorder specific, disc herniation or spinal stenosis or post surgery syndrome)	2
7b.	For facet or sacroiliac joint interventions:	
	No diagnostic blocks	0
	Selection with single diagnostic blocks	1
	Selection with placebo or dual diagnostic blocks	2
8.	**Duration of Pain**	
	Less than 3 months	0
	3 to 6 months	1
	> 6 months	2

Appendix 2 (cont.). Item checklist for assessment of randomized controlled trials of IPM techniques utilizing IPM – QRB.

		Scoring
9.	**Previous Treatments**	
	Conservative management including drug therapy, exercise therapy, physical therapy, etc.	
	Were not utilized	0
	Were utilized sporadically in some patients	1
	Were utilized in all patients	2
10.	**Duration of Follow-up with Appropriate Interventions**	
	Less than 3 months or 12 weeks for epidural or facet joint procedures, etc. and 6 months for intradiscal procedures and implantables	0
	3 to 6 months for epidural or facet joint procedures, etc., or 1 year for intradiscal procedures or implantables	1
	6 months to 17 months for epidurals or facet joint procedures, etc., and 2 years or longer for discal procedures and implantables	2
	18 months or longer for epidurals and facet joint procedures, etc., or 5 years or longer for discal procedures and implantables	3
IV.	**OUTCOMES**	
11.	**Outcomes Assessment Criteria for Significant Improvement**	
12.	**Analysis of all Randomized Participants in the Groups**	
	Not performed	0
	Performed without intent-to-treat analysis without inclusion of all randomized participants	1
	All participants included with or without intent-to-treat analysis	2
13.	Description of Drop Out Rate	
	No description of dropouts, despite reporting of incomplete data or ≥ 20% withdrawal	0
	Less than 20% withdrawal in one year in any group	1
	Less than 30% withdrawal at 2 years in any group	2
14.	**Similarity of Groups at Baseline for Important Prognostic Indicators**	
	Groups dissimilar with significant influence on outcomes with or without appropriate randomization and allocation	0
	Groups dissimilar without influence on outcomes despite appropriate randomization and allocation	1
	Groups similar with appropriate randomization and allocation	2
15.	**Role of Co-Interventions**	
	Co-interventions were provided but were not similar in the majority of participants	0
	No co-interventions or similar co-interventions were provided in the majority of the participants	1
V.	**RANDOMIZATION**	
16.	**Method of Randomization**	
	Quasi randomized or poorly randomized or not described	0
	Adequate randomization (coin toss, drawing of balls of different colors, drawing of ballots)	1
	High quality randomization (Computer generated random sequence, pre-ordered sealed envelopes, sequentially ordered vials, telephone call, pre-ordered list of treatment assignments, etc.)	2
VI.	**ALLOCATION CONCEALMENT**	
17.	Concealed Treatment Allocation	
	Poor concealment of allocation (open enrollment) or inadequate description of concealment	0
	Concealment of allocation with borderline or good description of the process with probability of failure of concealment	1
	High quality concealment with strict controls (independent assignment without influence on the assignment sequence)	2
VII.	**BLINDING**	
18.	**Patient Blinding**	
	Patients not blinded	0
	Patients blinded adequately	1

Appendix 2 (cont.). Item checklist for assessment of randomized controlled trials of IPM techniques utilizing IPM – QRB.

19.	**Care Provider Blinding**	
	Care provider not blinded	0
	Care provider blinded adequately	1
20.	**Outcome Assessor Blinding**	
	Outcome assessor not blinded or was able to identify the groups	0
	Performed by a blinded independent assessor with inability to identify the assignment-based provider intervention (i.e., subcutaneous injection, intramuscular distant injection, difference in preparation or equipment use, numbness and weakness, etc.)	1
VIII.	**CONFLICTS OF INTEREST**	
21.	**Funding and Sponsorship**	
	Trial included industry employees	-3
	Industry employees involved; high levels of funding with remunerations by industry or an organization funded with conflicts	-3
	Industry or organizational funding with reimbursement of expenses with some involvement	0
	Industry or organization funding of expenses without involvement	1
	Funding by internal resources only with supporting entity unrelated to industry	2
	Governmental funding without conflict such as NIH, NHS, AHRQ	3
22.	**Conflicts of Interest**	
	None disclosed with potential implied conflict	0
	Marginally disclosed with potential conflict	1
	Well disclosed with minor conflicts	2
	Well disclosed with no conflicts	3
	Hidden conflicts with poor disclosure	–1
	Misleading disclosure with conflicts	–2
	Major impact related to conflicts	–3
	TOTAL	48

Source: Manchikanti L, et al. Assessment of methodologic quality of randomized trials of interventional techniques: Development of an interventional pain management specific instrument. *Pain Physician* 2014; 17:E263-E290 (49).

Appendix 3. Partial list of excluded or unsuitable randomized trials with brief explanation.

Study	Condition studied	Number of patients	Reason for exclusion	
			Followup period	Other reason(s)
Caudal				
McCahon et al, 2011 (79)	Lumbar radiculitis	33	12 weeks	This was a pilot study assessing the dose response of caudal methylprednisolone with levobupivacaine in patients with chronic low-back pain. They included all types of patients with low-back and lower-extremity pain in a small sample.
Makki et al, 2010 (80)	Lumbar disc herniation	57	6 weeks	A study evaluating the outcome of caudal epidural injections affected by patient positioning.
McGregor et al, 2001 (81)	Lumbar radiculitis	44	6 weeks	A small pilot study with short-term followup comparing interlaminar vs caudal epidural injections.
Zahaar, 1991 (82)	Lumbar neural compression syndromes	63	1 year	A study evaluating high-volume injections of local anesthetic and sodium chloride solution with or without steroids blindly; all patients had acute herniated nucleus pulposus or spinal stenosis.
Czarski, 1965 (83)	Sciatica	Not available	Not available	Inability to obtain the full manuscript; published in 1965.
Laiq et al, 2009 (84)	Acute lumbar radiculopathy	50	6 months	A quasi-randomized study including only patients with acute and subacute pain without fluoroscopy.
Mathews et al, 1987 (85)	Radiculitis	57	1 year	A study including only patients with acute and subacute pain.
Breivik et al, 1976 (86)	Disc herniation, arachnoiditis, and normal MRI findings	35	6 months	A small number of patients with disc herniation with excessive volumes of injectate (> 120 mL).
Bush and Hillier, 1991 (87)	Unilateral sciatica	23	4 weeks	A small number of patients with acute pain, with 33% (4 of 12) in the active group and 27% (3 of 11) in the placebo group.
Hesla and Breivik, 1979 (88)	Disc herniation and post surgery syndrome	69	1 year	A small number of patients with disc herniation that utilized excessive volumes of injectate (> 120 mL).
Cervera-Irimia et al, 2013 (94)	Disc herniation and degenerative disc disease	46	24 weeks	Small trial with nonsteroidal anti-inflammatory drugs or caudal epidural in acute disc herniation.
Yousef et al, 2010 (112)	Post lumbar surgery syndrome	38	1 year	This trial was randomized and prospective, however sample size was small with a total of 38 patients with 20 patients in fluoroscopically guided caudal epidural injections with hypertonic saline along with a steroid and local anesthetic; whereas, the second group consisted of 18 patients with fluoroscopically guided caudal epidural steroid, hypertonic saline, local anesthetic, and hyaluronidase. Even though this trial showed positive results, because of the small size and combination of too many variables assessing hypertonic sodium chloride solution and hyaluronidase, it was excluded.
Lumbar Interlaminar				
Koc et al, 2009 (78)	Lumbar spinal stenosis	29	6 months	In this assessment a total of 29 patients were randomized into 3 groups with 10 in an inpatient physical therapy program for 2 weeks, with 10 receiving interlaminar epidural steroid injections, and 9 patients serving as the controls.
McGregor et al, 2001 (81)	Lumbar radiculitis	44	6 weeks	A small study with short-term follow-up comparing interlaminar vs caudal epidural injection.
Rahimzadeh et al, 2014 (89)	Post surgery syndrome	24	4 weeks	This trial evaluated 24 patients with the addition of hyaluronidase with interlaminar and transforaminal epidural injections.
Evansa et al, 2014 (91)	Degenerative spinal disorders	112	3 months	The primary outcome measure was the feasibility of ultrasound-guided injections with multiple disorders combined.
Candido et al, 2008 (92)	Disc herniation	60	Primary outcome immediate, secondary outcomes 6 months	Primary outcome measures assessed ventral epidural flow.
Buchner et al, 2000 (95)	Sciatica	36	6 months	A small number of patients, with 17 and 19 in each group.
Rogers et al, 1992 (96)	Sciatica	30	1 month	A small study with short-term followup.

Appendix 3 (cont.). Partial list of excluded or unsuitable randomized trials with brief explanation.

Study	Condition studied	Number of patients	Reason for exclusion	
			Followup period	Other reason(s)
Cuckler et al, 1985 (97)	Radicular pain	36	20 months with one or 2 injections	A small study in acute disc herniation.
Ridley et al, 1988 (98)	Sciatica	35	6 months	A small study with inclusion of acute disc herniation.
Klenerman et al, 1984 (99)	Sciatica	74 patients in 4 groups	2 months	The inclusion criteria were unilateral sciatica for less than 6 months, thus including a majority of acute and subacute patients.
Valat et al, 2003 (100)	Lumbar radiculitis	85	35 days	The inclusion criteria were of sciatica of more than 15 days and less than 180 days, thus including many subacute and acute patients with sciatica, with a short-term followup
Bronfort et al, 2004 (101)	Lumbar radiculitis	32	52 weeks	A study including acute and subacute pain in patients in a small sample.
Snoek et al, 1977 (138)	Lumbar disc herniation	51	14 months	The authors evaluated a single epidural injection in acute and subacute radiculitis. The inclusion criteria were patients with lumbar root compression syndrome of 12 days' to 36 weeks' duration, thus including a large number of acute and subacute pain patients, in a fairly small sample.
Gelalis et al, 2009 (139)	Lumbar disc herniation	40	2 months	A study evaluating lumbar radiculitis secondary to acute and subacute pain in a small sample with short-term follow-up.
Ghai et al, 2013 (140)	Lumbosacral radiculitis	37	6 months	A study including a small number of patients and providing no new information with only a 6-month follow-up.
Serrao et al, 1992 (143)	Chronic low back pain	28	2 months	Intrathecal midazolam compared with epidural steroid in a pilot study.
Rocco et al, 1989 (144)	Postlaminectomy syndrome	24	30 days	The effect of epidural steroids was compared with morphine in the treatment of postlaminectomy syndrome in only 24 patients.
Price et al, 2000 (145)	Chronic low back pain	200	Immediate	Comparison of needle placement accuracy.
Mobaleghi et al, 2011 (146)	Disc herniation and stenosis	40 Disc herniation = 32. Stenosis = 28	6 months	Blind prospective evaluation. Small number of patients.
Buttermann, 2004 (159)	Lumbar disc herniation	100	3 years	The authors compared epidural steroid injection with surgery in an open study. Obviously, surgery was more effective than a single epidural injection.
Lumbar Transforaminal				
Rahimzadeh et al, 2014 (89)	Post surgery syndrome	24	4 weeks	This trial evaluated 24 patients with the addition of hyaluronidase with interlaminar and transforaminal epidural injections.
Candido et al, 2008 (92)	Disc herniation	60	Primary outcome immediate, secondary outcomes 6 months	Primary outcome measures assessed ventral epidural flow.
Park, 2013 (102)	Lumbar disc herniation	59	3 months	The authors compared transforaminal tramadol with morphine in a short-term, small trial in a heterogenous population.
Park et al, 2010 (131)	Lumbar disc herniation	106	1 month	This trial comparing the effectiveness of lumbar transforaminal epidural injection with particulate and nonparticulate corticosteroids in lumbar radiculitis showed the superiority of triamcinolone; however, it was of short-term follow-up.
Nam & Park, 2011 (137)	Lumbar scoliosis and stenosis	Lidocaine group = 19 Lidocaine with steroids = 17	12 weeks	Small randomized trial with complex assessment of scoliosis and stenosis showed positive results in both groups with somewhat superior results with steroids.

Appendix 3 (cont.). Partial list of excluded or unsuitable randomized trials with brief explanation.

Study	Condition studied	Number of patients	Reason for exclusion	
			Followup period	Other reason(s)
Borghi et al, 2013 (141)	Chronic low back and sciatica	72	90 days	This study involved 72 patients and was a nonrandomized, prospective observational study. It assessed the periradicular injection of meloxicam for treating chronic low back pain and sciatica and concluded that meloxicam 10 mg appears to be a useful alternative to opioid and nonopioid analgesics for patients with intractable low back pain due to nerve root inflammation. The study was excluded due to a lack of randomization, lack of use of local anesthetic or steroid.
Kraiwattanapong et al, 2014 (142)	Spondylolisthesis	33	12 months	The study was excluded since it was a prospective cohort rather than a randomized trial. Further, it included only 33 patients for a procedure which is not commonly employed for such a condition. Transforaminal epidural injection, a risky procedure, was applied for spondylolisthesis, which is not commonly treated with transforaminal epidural injections.
Ghahreman and Bogduk, 2011 (124)	Lumbar radiculitis with disc herniation	71	3 months	A subgroup analysis of another study published by the same authors.
Gerszten et al, 2010 (148)	Disc herniation	90	1 year	The authors utilized 2 dissimilar modalities of treatment with inapplicable results.
Burgher et al, 2011 (149)	Acute radiculopathy secondary to disc herniation	26	1 month	A small study in acute radiculitis with short-term followup.
Park et al, 2011 (150)	Lumbar disc herniations	40 patients	8 weeks	A study including a total of only 40 patients with 20 in each group with short-term follow-up, comparing 2 different approaches.
Thomas et al, 2003 (151)	Disc herniation	31	6 days and 30 days	The inclusion criteria were duration of lumbar radiculitis of less than 3 months in a small number of patients with short-term follow-up.
Kraemer et al, 1997 (152)	Lumbar radiculitis	49 patients with 24 and 25 in each group	Unclear	The authors performed epidural perineural injections blindly and injected either sodium chloride solution or triamcinolone.
Kang et al, 2011 (153)	Lumbar disc herniation	160	2 weeks	A study evaluating corticosteroid dosage with short-term followup
Cohen et al, 2009 (154)	Disc herniation	24	1 month	A study including patients with subacute lumbosacral radiculopathy of 2 months to 1 year with short-term follow-up.
Gallucci et al, 2007 (155)	Disc herniation	159	6 months	The majority of the subacute pain patients were assessed with intradiscal and intraforaminal injection of steroid and oxygen-ozone vs steroid only with all the procedures performed under computed tomography scanning. It is not a common practice to utilize high volumes of solutions with a combination of intradiscal and intraforaminal injections, along with oxygen-ozone. The study was excluded even though results were positive in both groups.
Gharibo et al, 2011 (156)	Disc herniation	42	10-16 days	A study evaluating a small number of patients in acute pain with subacute radiculitis with short-term follow-up.
Ahadian et al, 2011 (157)	Disc herniation and spinal stenosis	98	12 weeks	The inclusion criteria were a previously favorable response to transforaminal epidural steroid injections to evaluate the response of epidural dexamethasone.
Ohtori et al, 2012 (158)	Spinal stenosis	80	one month	The study evaluated the effectiveness of the tumor necrosis factor– alpha inhibitor etanercept, compared with dexamethasone for treatment of sciatica. Inclusion criteria were an average 2.5 months of pain duration with inclusion of acute or subacute radiculitis.
Cohen et al, 2012 (147)	Subacute sciatica	84	one month	
Cervical Transforaminal				
Anderberg et al, 2007 (165)	Cervical radiculopathy	40	3 weeks	This study evaluated the role of epidural steroid injections with a cervical transforaminal approach in 40 patients; however, with a short-term follow-up of 3 weeks. The results were the same with or without steroids with local anesthetic.

Appendix 4. *Methodological quality assessment of randomized trials utilizing Cochrane review criteria.*

	Manchikanti et al (74)	Ackerman & Ahmad (107)	Dashfield et al (108)	Iversen et al (109)	Murakibhavi & Khemka (110)	Revel et al (111)	Manchikanti et al (65)	Manchikanti et al (66)	Manchikanti et al (70)	Sayegh et al (90)	Park et al (105)
Randomization adequate	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y
Concealed treatment allocation	Y	N	Y	Y	N	N	Y	Y	Y	Y	Y
Patient blinded	Y	N	Y	Y	Y	N	Y	Y	Y	Y	Y
Care provider blinded	N	N	N	N	N	N	Y	N	Y	Y	N
Outcome assessor blinded	N	N	N	U	N	U	N	N	N	Y	N
Drop-out rate described	Y	Y	Y	Y	Y	N	Y	Y	Y	N	Y
All randomized participants analyzed in the group	Y	Y	Y	N	Y	N	Y	Y	Y	N	Y
Reports of the study free of suggestion of selective outcome reporting	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Groups similar at baseline regarding most important prognostic indicators	Y	Y	Y	N	N	Y	Y	Y	Y	Y	Y
Co-interventions avoided or similar	Y	Y	N	Y	N	Y	Y	Y	Y	Y	Y
Compliance acceptable in all group	Y	Y	Y	N	Y	N	Y	Y	Y	Y	Y
Time of outcome assessment in all groups similar	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Score	10/12	7/12	9/12	7/12	7/12	5/12	11/12	10/12	11/12	10/12	10/12

Y = Yes; N = No; U = Unclear

Source: Furlan AD, Pennick V, Bombardier C, van Tulder Ml; Editorial Board, Cochrane Back Review Group. 2009 updated method guidelines for systematic reviews in the Cochrane Back Review Group. Spine (Phila Pa 1976) 2009; 34:1929-1941 (48).

Appendix 4 (Continued). *Methodological quality assessment of randomized trials utilizing Cochrane review criteria.*

	Lee et al (113)	Rados et al (114)	Amr (116)	Dilke et al (117)	Pirbudak et al (118)	Arden et al (119)	Carette et al (120)	Wilson-MacDonald et al (121)	Fukasaki et al (122)	Manchikanti et al (62)
Randomization adequate	N	Y	Y	N	Y	Y	Y	Y	N	Y
Concealed treatment allocation	N	N	Y	N	Y	Y	Y	Y	N	Y
Patient blinded	N	N	Y	Y	Y	Y	Y	Y	N	Y
Care provider blinded	N	N	Y	N	Y	N	N	N	N	Y
Outcome assessor blinded	N	N	Y	Y	Y	Y	Y	Y	U	N
Drop-out rate described	Y	Y	Y	Y	Y	Y	Y	Y	N	Y
All randomized participants analyzed in the group	N	Y	N	Y	Y	N	Y	Y	Y	Y
Reports of the study free of suggestion of selective outcome reporting	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Groups similar at baseline regarding most important prognostic indicators	Y	Y	Y	N	Y	Y	Y	N	Y	N
Co-interventions avoided or similar	Y	Y	Y	Y	Y	Y	Y	Y	N	Y
Compliance acceptable in all group	Y	Y	Y	Y	Y	N	Y	Y	Y	Y
Time of outcome assessment in all groups similar	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Score	6/12	8/12	11/12	8/12	11/12	9/12	11/12	10/12	5/12	10/12

	Manchikanti et al (63)	Manchikanti et al (71)	Ghahreman et al (123)	Karppinen et al (125)	Jeong et al (127)	Riew et al (129)	Ng et al (130)	Tafazal et al (132)	Vad et al (104)	Manchikanti et al (67)
Randomization adequate	Y	Y	Y	Y	U	U	Y	Y	U	Y
Concealed treatment allocation	Y	Y	Y	Y	U	U	Y	Y	N	Y
Patient blinded	Y	Y	Y	Y	Y	Y	Y	Y	N	Y
Care provider blinded	Y	Y	Y	Y	N	N	N	Y	N	Y
Outcome assessor blinded	N	N	Y	Y	Y	Y	Y	N	U	N
Drop-out rate described	Y	Y	Y	Y	Y	Y	Y	Y	N	Y
All randomized participants analyzed in the group	Y	Y	Y	Y	Y	Y	Y	N	N	Y
Reports of the study free of suggestion of selective outcome reporting	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Groups similar at baseline regarding most important prognostic indicators	N	N	N	Y	Y	U	Y	Y	Y	N
Co-interventions avoided or similar	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Compliance acceptable in all group	Y	Y	Y	Y	Y	Y	Y	Y	U	Y
Time of outcome assessment in all groups similar	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Score	10/12	10/12	11/12	12/12	9/12	8/12	11/12	10/12	4/12	10/12

Y = Yes; N = No; U = Unclear

Source: Furlan AD, Pennick V, Bombardier C, van Tulder Ml; Editorial Board, Cochrane Back Review Group. 2009 updated method guidelines for systematic reviews in the Cochrane Back Review Group. Spine (Phila Pa 1976) 2009; 34:1929-1941 (48).

Appendix 4 (Continued). ***Methodological quality assessment of randomized trials utilizing Cochrane review criteria.***

	Park et al (103)	Castagnera et al (133)	Stav et al (134)	Pasqualucci et al (135)	Manchikanti et al (60)	Manchikanti et al (61)	Manchikanti et al (64)	Manchikanti et al (68)	Manchikanti et al (69)	Koh et al (106)	Friedly et al (33)
Randomization adequate	Y	U	N	N	Y	Y	Y	Y	Y	Y	Y
Concealed treatment allocation	Y	U	N	N	Y	Y	Y	Y	Y	Y	Y
Patient blinded	Y	U	N	N	Y	Y	Y	Y	Y	Y	Y
Care provider blinded	N	U	N	N	Y	Y	Y	Y	Y	N	N
Outcome assessor blinded	N	U	N	N	N	N	N	N	N	N	N
Drop-out rate described	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
All randomized participants analyzed in the group	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y
Reports of the study free of suggestion of selective outcome reporting	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N
Groups similar at baseline regarding most important prognostic indicators	Y	Y	Y	Y	N	N	Y	N	Y	Y	Y
Co-interventions avoided or similar	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Compliance acceptable in all group	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Time of outcome assessment in all groups similar	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Score	10/12	7/12	7/12	7/12	10/12	10/12	11/12	10/12	11/12	9/12	9/12

	Cohen et al (160)	Ghai et al (93)	Ghai et al (75)	Cohen et al (161)	Datta & Upadhyay (168)	Candido et al (169)	Béliveau (170)	Huda et al (171)	Kennedy et al (172)	Becker et al (173)
Randomization adequate	Y	Y	Y	Y	Y	Y	N	Y	Y	N
Concealed treatment allocation	N	Y	Y	Y	Y	Y	N	N	Y	N
Patient blinded	N	N	Y	N	N	N	N	N	N	N
Care provider blinded	N	N	N	N	N	N	N	N	N	N
Outcome assessor blinded	N	N	N	N	N	N	N	N	N	N
Drop-out rate described	Y	Y	N	N	N	Y	Y	Y	Y	Y
All randomized participants analyzed in the group	N	Y	Y		Y	Y	Y	Y	Y	Y
Reports of the study free of suggestion of selective outcome reporting	Y	Y	Y	N	Y	Y	Y	Y	Y	Y
Groups similar at baseline regarding most important prognostic indicators	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Co-interventions avoided or similar	Y	Y	Y	Y	Y	Y	U	Y	Y	U
Compliance acceptable in all group	N	Y	Y	N	N	Y	Y	Y	Y	Y
Time of outcome assessment in all groups similar	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Score	6/12	9/12	9/12	5/12	7/12	9/12	6/12	8/12	9/12	6/12

Y = Yes; N = No; U = Unclear

Source: Furlan AD, Pennick V, Bombardier C, van Tulder Ml; Editorial Board, Cochrane Back Review Group. 2009 updated method guidelines for systematic reviews in the Cochrane Back Review Group. Spine (Phila Pa 1976) 2009; 34:1929-1941 (48).

Appendix 5. *Methodologic quality assessment of randomized trials utilizing IPM – QRB.*

		Manchikanti et al (74)	Ackerman & Ahmad (107)	Dashfield et al (108)	Iversen et al (109)	Murakibhavi & Khemka (110)	Revel et al (111)	Manchikanti et al (65)	Manchikanti et al (66)	Manchikanti et al (70)	Sayegh et al (90)
I.	TRIAL DESIGN AND GUIDANCE REPORTING										
1.	CONSORT or SPIRIT	3	0	1	2	2	1	3	3	3	2
II.	DESIGN FACTORS										
2.	Type and Design of Trial	2	2	2	2	2	2	2	2	2	2
3.	Setting/Physician	2	2	2	1	1	1	2	2	2	1
4.	Imaging	3	3	3	1	3	0	3	3	3	0
5.	Sample Size	3	1	1	2	2	1	3	3	3	3
6.	Statistical Methodology	1	1	1	1	1	1	1	1	1	1
III.	PATIENT FACTORS										
7.	Inclusiveness of Population	2	2	1	2	2	2	2	2	2	1
8.	Duration of Pain	2	1	2	1	1	1	2	2	2	0
9.	Previous Treatments	2	0	0	0	0	1	2	2	2	0
10.	Duration of Follow-up with Appropriate Interventions	3	2	2	1	1	2	3	3	3	1
IV.	OUTCOMES										
11.	Outcomes Assessment Criteria for Significant Improvement	4	1	2	0	4	2	4	4	4	2
12.	Analysis of all Randomized Participants in the Groups	2	2	2	2	2	0	2	2	2	0
13.	Description of Drop Out Rate	2	2	2	1	2	2	2	2	2	0
14.	Similarity of Groups at Baseline for Important Prognostic Indicators	1	1	1	0	0	1	1	1	1	2
15.	Role of Co-Interventions	1	1	1	1	0	1	1	1	1	1
V.	RANDOMIZATION										
16.	Method of Randomization	2	0	2	2	0	2	2	2	2	2
VI.	ALLOCATION CONCEALMENT										
17.	Concealed Treatment Allocation	2	0	2	2	2	0	2	2	2	2
VII.	BLINDING										
18.	Patient Blinding	1	0	1	1	1	1	1	1	1	1
19.	Care Provider Blinding	1	0	0	0	0	0	1	1	1	1
20.	Outcome Assessor Blinding	0	0	0	0	0	0	0	0	0	1
VIII.	CONFLICTS OF INTEREST										
21.	Funding and Sponsorship	2	1	2	3	0	2	2	2	2	2
22.	Conflicts of Interest	3	3	3	3	1	2	3	3	3	3
TOTAL		44	25	33	28	27	25	44	44	44	28

Source: Manchikanti L, et al. Assessment of methodologic quality of randomized trials of interventional techniques: Development of an interventional pain management specific instrument. Pain Physician 2014; 17:E263-E290 (49).

Appendix 5 (Continued). ***Methodologic quality assessment of randomized trials utilizing IPM – QRB.***

		Park et al (105)	Lee et al (113)	Rados et al (114)	Amr (116)	Dilke et al (117)	Pirbudak et al (118)	Arden et al (119)	Carette et al (120)	Wilson-MacDonald et al (121)
I.	TRIAL DESIGN AND GUIDANCE REPORTING									
1.	CONSORT or SPIRIT	2	2	2	2	0	2	3	1	3
II.	DESIGN FACTORS									
2.	Type and Design of Trial	2	2	2	2	3	2	3	2	2
3.	Setting/Physician	1	1	3	3	2	2	1	2	1
4.	Imaging	3	3	3	3	0	0	0	0	0
5.	Sample Size	3	1	1	3	3	2	3	3	0
6.	Statistical Methodology	1	1	1	1	1	1	1	1	1
III.	PATIENT FACTORS									
7.	Inclusiveness of Population	1	1	1	2	2	2	2	2	1
8.	Duration of Pain	0	1	2	2	0	2	1	0	2
9.	Previous Treatments	0	2	0	2	0	2	0	0	2
10.	Duration of Follow-up with Appropriate Interventions	1	1	2	3	1	2	0	0	1
IV.	OUTCOMES									
11.	Outcomes Assessment Criteria for Significant Improvement	2	2	2	2	2	2	2	0	2
12.	Analysis of all Randomized Participants in the Groups	2	2	2	1	2	2	1	2	2
13.	Description of Drop Out Rate	2	1	2	2	2	2	2	1	1
14.	Similarity of Groups at Baseline for Important Prognostic Indicators	2	1	2	2	2	2	2	1	1
15.	Role of Co-Interventions	0	1	1	1	1	1	0	0	1
V.	RANDOMIZATION									
16.	Method of Randomization	2	0	2	2	1	2	2	2	2
VI.	ALLOCATION CONCEALMENT									
17.	Concealed Treatment Allocation	2	0	0	2	1	2	2	2	2
VII.	BLINDING									
18.	Patient Blinding	1	0	0	1	1	1	1	1	1
19.	Care Provider Blinding	0	0	0	1	0	1	0	0	0
20.	Outcome Assessor Blinding	0	0	0	1	1	1	1	1	1
VIII.	CONFLICTS OF INTEREST									
21.	Funding and Sponsorship	3	3	0	0	0	0	3	3	2
22.	Conflicts of Interest	3	3	2	0	3	2	1	3	3
	TOTAL	33	28	30	38	28	35	31	27	31

Source: Manchikanti L, et al. Assessment of methodologic quality of randomized trials of interventional techniques: Development of an interventional pain management specific instrument. Pain Physician 2014; 17:E263-E290 (49).

Appendix 5 (Continued). *Methodologic quality assessment of randomized trials utilizing IPM – QRB.*

		Fukasaki et al (122)	Manchikanti et al (62)	Manchikanti et al (63)	Manchikanti et al (71)	Ghahreman et al (123)	Karppinen et al (125)	Jeong et al (127)	Riew et al (129)	Ng et al (130)
I.	TRIAL DESIGN AND GUIDANCE REPORTING									
1.	CONSORT or SPIRIT	0	3	3	3	3	2	2	1	2
II.	DESIGN FACTORS									
2.	Type and Design of Trial	2	2	2	2	2	2	2	2	2
3.	Setting/Physician	1	2	2	2	2	1	1	1	1
4.	Imaging	0	3	3	3	3	3	3	3	3
5.	Sample Size	0	3	3	3	2	3	3	2	2
6.	Statistical Methodology	1	1	1	1	1	1	1	1	1
III.	PATIENT FACTORS									
7.	Inclusiveness of Population	2	2	2	2	2	2	1	2	2
8.	Duration of Pain	1	2	2	2	1	0	0	1	2
9.	Previous Treatments	0	2	2	2	0	0	0	2	2
10.	Duration of Follow-up with Appropriate Interventions	1	3	3	3	0	1	2	2	1
IV.	OUTCOMES									
11.	Outcomes Assessment Criteria for Significant Improvement	1	4	4	4	4	2	2	1	1
12.	Analysis of all Randomized Participants in the Groups	1	2	2	2	2	2	2	2	2
13.	Description of Drop Out Rate	1	2	2	2	2	1	2	2	2
14.	Similarity of Groups at Baseline for Important Prognostic Indicators	1	0	1	1	1	2	2	2	2
15.	Role of Co-Interventions	0	1	1	1	0	0	1	0	1
V.	RANDOMIZATION									
16.	Method of Randomization	1	2	2	2	2	2	1	1	2
VI.	ALLOCATION CONCEALMENT									
17.	Concealed Treatment Allocation	0	2	2	2	2	2	0	0	2
VII.	BLINDING									
18.	Patient Blinding	0	1	1	1	1	1	1	1	1
19.	Care Provider Blinding	0	1	1	1	1	1	0	1	1
20.	Outcome Assessor Blinding	0	0	0	0	1	1	1	0	0
VIII.	CONFLICTS OF INTEREST									
21.	Funding and Sponsorship	2	2	2	2	2	2	2	2	2
22.	Conflicts of Interest	3	3	3	3	3	3	2	3	3
TOTAL		18	43	44	44	37	34	31	32	37

Source: Manchikanti L, et al. Assessment of methodologic quality of randomized trials of interventional techniques: Development of an interventional pain management specific instrument. Pain Physician 2014; 17:E263-E290 (49).

Appendix 5 (Continued). *Methodologic quality assessment of randomized trials utilizing IPM – QRB.*

		Tafazal et al (132)	Vad et al (104)	Manchikanti et al (67)	Park et al (103)	Castagnera et al (133)	Stav et al (134)	Pasqualucci et al (135)	Manchikanti et al (60)	Manchikanti et al (61)	Manchikanti et al (64)
I.	TRIAL DESIGN AND GUIDANCE REPORTING										
1.	CONSORT or SPIRIT	2	1	3	2	1	1	1	3	3	3
II.	DESIGN FACTORS										
2.	Type and Design of Trial	2	2	2	2	2	2	2	2	2	2
3.	Setting/Physician	1	1	2	1	1	1	1	2	2	2
4.	Imaging	3	2	3	3	0	0	0	3	3	3
5.	Sample Size	1	1	3	3	0	0	0	2	2	3
6.	Statistical Methodology	1	1	1	1	1	1	1	1	1	1
III.	PATIENT FACTORS										
7.	Inclusiveness of Population	1	2	2	1	2	2	1	2	2	1
8.	Duration of Pain	1	0	2	0	2	2	2	2	2	2
9.	Previous Treatments	2	0	2	0	2	2	2	2	2	2
10.	Duration of Follow-up with Appropriate Interventions	1	1	3	1	1	1	1	2	2	3
IV.	OUTCOMES										
11.	Outcomes Assessment Criteria for Significant Improvement	2	2	4	2	2	2	2	4	4	4
12.	Analysis of all Randomized Participants in the Groups	1	0	2	2	2	2	2	2	2	2
13.	Description of Drop Out Rate	1	0	2	2	2	2	2	2	2	2
14.	Similarity of Groups at Baseline for Important Prognostic Indicators	1	0	1	2	1	1	1	1	1	1
15.	Role of Co-Interventions	1	1	1	0	1	1	1	1	1	1
V.	RANDOMIZATION										
16.	Method of Randomization	2	0	2	2	0	0	0	2	2	2
VI.	ALLOCATION CONCEALMENT										
17.	Concealed Treatment Allocation	2	0	2	2	0	0	0	2	2	2
VII.	BLINDING										
18.	Patient Blinding	1	0	1	2	0	0	0	1	1	1
19.	Care Provider Blinding	1	0	1	0	0	0	0	1	1	1
20.	Outcome Assessor Blinding	0	0	0	0	0	0	0	0	0	0
VIII.	CONFLICTS OF INTEREST										
21.	Funding and Sponsorship	2	0	2	3	2	2	2	2	2	2
22.	Conflicts of Interest	3	2	3	3	3	3	3	3	3	3
TOTAL		32	16	44	34	25	25	24	42	42	43

Source: Manchikanti L, et al. Assessment of methodologic quality of randomized trials of interventional techniques: Development of an interventional pain management specific instrument. Pain Physician 2014; 17:E263-E290 (49).

Appendix 5 (Continued). *Methodologic quality assessment of randomized trials utilizing IPM – QRB.*

		Manchikanti et al (68)	Manchikanti et al (69)	Koh et al (106)	Friedly et al (33)	Cohen et al (160)	Ghai et al (93)	Ghai et al (75)	Cohen et al (161)	Datta & Upadhyay (168)	Candido et al (169)
I.	TRIAL DESIGN AND GUIDANCE REPORTING										
1.	CONSORT or SPIRIT	3	3	2	3	3	3	3	3	1	2
II.	DESIGN FACTORS										
2.	Type and Design of Trial	2	2	2	2	2	2	2	3	2	2
3.	Setting/Physician	2	2	2	2	2	2	2	2	2	2
4.	Imaging	3	3	3	3	3	3	3	3	0	3
5.	Sample Size	3	3	1	3	3	2	2	1	2	2
6.	Statistical Methodology	1	1	1	0	1	1	1	1	1	1
III.	PATIENT FACTORS										
7.	Inclusiveness of Population	2	2	1	1	2	2	2	1	2	2
8.	Duration of Pain	2	2	1	1	0	2	1	1	1	1
9.	Previous Treatments	2	2	0	1	0	2	1	0	0	2
10.	Duration of Follow-up with Appropriate Interventions	3	3	2	0	1	3	3	0	1	2
IV.	OUTCOMES										
11.	Outcomes Assessment Criteria for Significant Improvement	4	4	2	0	0	4	4	0	2	2
12.	Analysis of all Randomized Participants in the Groups	2	2	0	2	0	2	2	0	1	2
13.	Description of Drop Out Rate	2	2	2	2	2	2	0	0	0	2
14.	Similarity of Groups at Baseline for Important Prognostic Indicators	1	0	2	2	1	2	2	2	1	2
15.	Role of Co-Interventions	1	1	1	0	0	1	1	0	0	1
V.	RANDOMIZATION										
16.	Method of Randomization	2	2	2	2	2	2	2	2	2	2
VI.	ALLOCATION CONCEALMENT										
17.	Concealed Treatment Allocation	2	2	2	2	0	2	2	2	2	2
VII.	BLINDING										
18.	Patient Blinding	1	1	1	0	0	0	1	0	0	0
19.	Care Provider Blinding	1	1	1	0	0	0	0	0	0	0
20.	Outcome Assessor Blinding	0	0	0	0	0	0	0	0	0	0
VIII.	CONFLICTS OF INTEREST										
21.	Funding and Sponsorship	2	2	2	3	1	2	2	2	0	2
22.	Conflicts of Interest	3	3	2	1	1	3	3	3	0	3
TOTAL		44	43	32	30	25	42	39	26	20	37

Source: Manchikanti L, et al. Assessment of methodologic quality of randomized trials of interventional techniques: Development of an interventional pain management specific instrument. Pain Physician 2014; 17:E263-E290 (49).

Appendix 5 (Continued). *Methodologic quality assessment of randomized trials utilizing IPM – QRB.*

		Béliveau (170)	**Huda et al (171)**	**Kennedy et al (172)**	**Becker et al (173)**
I.	TRIAL DESIGN AND GUIDANCE REPORTING				
1.	CONSORT or SPIRIT	0	1	3	1
II.	DESIGN FACTORS				
2.	Type and Design of Trial	2	2	2	2
3.	Setting/Physician	1	2	2	1
4.	Imaging	0	0	3	3
5.	Sample Size	1	2	2	2
6.	Statistical Methodology	1	1	1	1
III.	PATIENT FACTORS				
7.	Inclusiveness of Population	1	2	2	2
8.	Duration of Pain	0	1	0	1
9.	Previous Treatments	0	2	2	2
10.	Duration of Follow-up with Appropriate Interventions	1	1	1	1
IV.	OUTCOMES				
11.	Outcomes Assessment Criteria for Significant Improvement	2	2	2	2
12.	Analysis of all Randomized Participants in the Groups	2	2	2	2
13.	Description of Drop Out Rate	2	1	1	1
14.	Similarity of Groups at Baseline for Important Prognostic Indicators	2	2	2	2
15.	Role of Co-Interventions	0	1	1	1
V.	RANDOMIZATION				
16.	Method of Randomization	0	1	2	0
VI.	ALLOCATION CONCEALMENT				
17.	Concealed Treatment Allocation	0	0	2	0
VII.	BLINDING				
18.	Patient Blinding	0	0	0	0
19.	Care Provider Blinding	0	0	0	0
20.	Outcome Assessor Blinding	0	0	0	0
VIII.	CONFLICTS OF INTEREST				
21.	Funding and Sponsorship	0	0	0	2
22.	Conflicts of Interest	0	0	0	0
TOTAL		15	23	30	26

Source: Manchikanti L, et al. Assessment of methodologic quality of randomized trials of interventional techniques: Development of an interventional pain management specific instrument. Pain Physician 2014; 17:E263-E290 (49).

Appendix 6. *Characteristics of caudal epidural injections.*

Study Study Characteristics Methodological Quality Scoring	Participants and Interventions	Outcome Measures	Pain Relief and Function				Results				Comment(s)
								Long-Term			
			3 mos.	6 mos.	12 mos.	24 mos.	Short-term ≤ 6 mos.	> 6 mos.	≥ 12 mos.	24 mos.	
Manchikanti et al, 2012 (74) RA, AC, F Disc herniation or radiculopathy Quality Scores: Cochrane = 10/12 IPM-QRB = 44/48	Total = 120 Lidocaine = 60 Lidocaine with steroids = 60 Lidocaine vs. lidocaine mixed with steroid Number of injections = 1 to 5	NRS, ODI, employment status, opioid intake Responsive category was defined as at least 3 weeks of significant improvement with the first 2 procedures. Significant improvement: 50% improvement in pain and function.	Overall: LA 62% vs. LA with steroid 72% Responsive: LA 77% vs LA with steroid 80%	Overall: LA 72% vs LA with steroid 73% Responsive: LA 87% vs LA with steroid 86%	Overall: LA 67% vs LA with steroid 72% Responsive: LA 85% vs LA with steroid 84%	Overall: LA 60% vs LA with steroid 65% Responsive: LA 77% vs LA with steroid 76%	Lidocaine & lidocaine with steroid effective	Lidocaine & lidocaine with steroid effective	Lidocaine & lidocaine with steroid effective	Lidocaine & lidocaine with steroid effective	• Positive double-blind randomized trial with superiority of steroids with average pain relief for steroids. Overall improvement with local anesthetic alone or with steroids was similar. • Nonresponsive patients were also similar with 13 and 10 in local anesthetic only and with steroids group. • Over a period of 2 years, on average, a total of 5-6 injections were provided.
Sayegh et al, 2009 (90) RA, AC, B Disc herniation or radiculopathy Quality Scores: Cochrane = 10/12 IPM-QRB = 28/48	Total = 183 Local anesthetic = 90 Local anesthetic with steroid = 93 Caudal administered blindly Number of injections = 1 to 3 over a period of one year	ODI, straight leg raising	Mean ODI: LA = 23.5 LA with steroid = 8.7 Negative straight leg raising: LA 51% versus LA with steroid 73%	Mean ODI: LA = 13.6 LA with steroid = 5.8 Negative straight leg raising: LA 68% versus LA with steroid 84%	Mean ODI: LA = 13.0 LA with steroid = 4.91 Negative straight leg raising: LA 71% versus LA with steroid 85%	NA	LA (lidocaine) & LA (lidocaine) with steroid effective – steroid superior	LA (lidocaine) & LA (lidocaine) with steroid effective – steroid superior	LA (lidocaine) & LA (lidocaine) with steroid effective – steroid superior	NA	• Caudal epidural injections containing local anesthetic and steroids were more effective with faster action and greater relief from symptoms while local anesthetic actions were more progressive and likely less notable improvement. • Both local anesthetic and local anesthetic and steroid group showed significant improvement from baseline with mean ODI and straight leg raising, even though steroid group results were superior with significant difference when comparing both groups.

Appendix 6 (Cont.). *Characteristics of caudal epidural injections.*

Study Study Characteristics Methodological Quality Scoring	Participants and Interventions	Outcome Measures	Pain Relief and Function				Results				Comment(s)
			3 mos.	6 mos.	12 mos.	24 mos.	Short-term ≤ 6 mos.	Long-Term > 6 mos.	≥ 12 mos.	24 mos.	
Manchikanti et al, 2012 (65) RA, AC, F Central spinal stenosis Quality Scores: Cochrane = 11/12 IPM-QRB = 44/48	Total = 100 Lidocaine = 50 Lidocaine + steroid = 50 Lidocaine 0.5% vs. lidocaine mixed with steroid. Average number of injections = 5 to 6 for 2 years	NRS, ODI, employment status, opioid intake Responsive category was defined as at least 3 weeks of significant improvement with the first 2 procedures. Significant improvement: 50% improvement in pain and function.	Overall: LA 58% vs LA with steroid 48% Responsive: LA 78% vs. LA with steroid 65%	Overall: LA 54% vs LA with steroid 50% Responsive: LA 73% vs. LA with steroid 68%	Overall: LA 44% vs LA with steroid 46% Responsive: LA 54% vs. LA with steroid 62%	Overall: LA 38% vs LA with steroid 44% Responsive: LA 51% vs LA with steroid 57%	Both treatments effective	Both treatments effective	Both treatments effective	Both treatments effective	• Double-blind design in a practical setting. • Similar results with local anesthetic or with local anesthetic and steroids. • Nonresponsive patients: local anesthetic = 13, steroids = 13. • A total of 5-6 injections on average were provided over a period of 2 years; compared to all patients with significant improvement of 38% in local anesthetic group, 44% in steroid group.
Béliveau, 1971 (170) RA, AC, B Disc herniation or radiculopathy Quality Scores: Cochrane = 6/12 IPM-QRB = 15/48	Total = 48 Local anesthetic with procaine = 24 Procaine plus Depo-Medrone = 24 Caudal administration blindly Number of injections: 1 to 3	Completely relieved, improved, unchanged, worse, 3 months	Local anesthetic group = 67% Improved or completely relieved With local anesthetic, 75% of the patients improved or completely relieved with procaine plus Depo-Medrone. Positive results in both groups	NA	NA	NA	Positive results in both groups	NA	NA	NA	• Béliveau conducted one of the earlier studies and published the results in 1971. The results were similar with local anesthetic alone, procaine, or local anesthetic with steroid. • The follow-up was from one to 3 months.

Appendix 6 (Cont.). *Characteristics of caudal epidural injections.*

Study Study Characteristics Methodological Quality Scoring	Participants and Interventions	Outcome Measures	Pain Relief and Function				Results				Comment(s)
			3 mos.	6 mos.	12 mos.	24 mos.	Short-term ≤ 6 mos.	Long-Term > 6 mos.	≥ 12 mos.	24 mos.	
Manchikanti et al, 2012 (66) RA, AC, F Axial or discogenic Quality Scores: Cochrane = 10/12 IPM-QRB = 44/48	Total = 120 Lidocaine = 60 Lidocaine with steroids = 60 Lidocaine vs. lidocaine mixed with steroid Average number of injections = 5 to 6 for 2 years	NRS pain scale, ODI, employment status, opioid intake Responsive category was defined as at least 3 weeks of significant improvement with the first 2 procedures. Significant improvement: 50% improvement in pain and function.	Overall: LA 60% vs LA with steroid 72% Responsive: LA 87% vs LA with steroid 88%	Overall: LA 62% vs LA with steroid 72% Responsive: LA 89% vs. LA with steroid 93%	Overall: LA 56% vs LA with steroid 68% Responsive: LA 84% vs. LA with steroid 85%	Overall: LA 54% vs LA with steroid 60% Responsive: LA 84% vs LA with steroid 73%	P	P	P	P	• Positive randomized double-blind trial with similar results with local anesthetic or with local anesthetic and steroids. • There was an inordinately high proportion of patients failing to respond initially in both groups, 23 in local anesthetic group, and 19 in steroid group. • On average, a total of 5-6 injections were provided over a period of 2 years.
Manchikanti et al, 2012 (70) RA, AC, F Post surgery syndrome Quality Scores: Cochrane = 11/12 IPM-QRB = 44/48	Total = 140 Lidocaine = 70 Lidocaine + steroid = 70 Lidocaine vs. lidocaine mixed with non-particulate betamethasone Average number of injections = 5 to 6 for 2 years	NRS, ODI, employment status, opioid intake Responsive category was defined as at least 3 weeks of significant improvement with the first 2 procedures. Significant improvement: 50% improvement in pain and function.	Overall: LA 56% vs LA with steroid 54% Responsive: LA 76% vs. LA with steroid 67%	Overall: LA 56% vs LA with steroid 61% Responsive: LA 74% vs. LA with steroid 78%	Overall: LA 53% vs LA with steroid 59% Responsive: LA 70% vs. LA with steroid 75%	Overall: LA 47% vs LA with steroid 58% Responsive: LA 62% vs LA with steroid 69%	P	P	P	P	• Positive results with local anesthetics with or without steroids. • Similar results with local anesthetic or with local anesthetic and steroids. • Nonresponsive patients: local anesthetic = 17, steroids = 15. • On average, 5-6 injections were provided over a period of 2 years; compared to all patients with significant improvement of 47% in local anesthetic group, 58% in steroid group.

Appendix 6 (Cont.). *Characteristics of caudal epidural injections.*

Study Study Characteristics Methodological Quality Scoring	Participants and Interventions	Outcome Measures	Pain Relief and Function				Results				Comment(s)
							Short-term ≤ 6 mos.	Long-Term			
			3 mos.	6 mos.	12 mos.	24 mos.		> 6 mos.	≥ 12 mos.	24 mos.	
Revel et al, 1996 (111) RA, AC, B Post surgery syndrome Quality Scores: Cochrane = 5/12 IPM-QRB = 25/48	Total = 60 Prednisolone acetate and saline or prednisolone alone Number of injections = 6	Pain relief, Waddell's, and Main's Functional Score, Schober's test, finger to floor distance, straight leg raising, use of analgesics, satisfaction index, five-level satisfaction index	NA	19% vs 45%	NA	NA	P	NA	NA	NA	Moderate quality study with positive results.
Ackerman & Ahmad, 2007 (107) RA, AC, F Disc herniation or radiculopathy Quality Scores: Cochrane = 7/12 IPM-QRB = 25/48	Total = 90 Caudal = 30 Interlaminar = 30 Transforaminal = 30 Methylprednisolone + saline Number of injections = 1 to 3	Numeric pain score (0 - 10), rating of pain relief, ODI, BDI, contrast dispersion pattern Follow-up: 24 weeks	Caudal = 57% Interlaminar = 60% Transforaminal = 83%	Caudal = 57% Interlaminar = 60% Transforaminal = 83%	NA	NA	Effective in all arms	Effective in all arms	NA	NA	Positive mid-term results in a relatively small trial.
Dashfield et al, 2005 (108) RA, AC, F Disc herniation or radiculopathy Quality Scores: Cochrane = 9/12 IPM-QRB = 33/48	Total = 60 Caudal = 30 Endoscopy =30 Lidocaine with triamcinolone Number of injections = 1	Pain relief, SF-MPQ, HADS scores	SI	SI	NA	NA	Lidocaine with triamcinolone effective	Lidocaine with triamcinolone effective	NA	NA	Positive mid-term results in a relatively small trial.
Park et al, 2013 (105) RA, AC, F Spinal stenosis Quality Scores: Cochrane = 10/12 IPM-QRB = 33/48	Total = 68 Fluoroscopy = 36 Ultrasound = 32 Caudal = 20 mL of drug with 5 mL of Omnipaque, 15 mL of 0.5% lidocaine, 10 mg or 2 mL of dexamethasone	Verbal numeric rating scale = 50%, ODI = 40%, Satisfaction scale Follow-up: 12 weeks	Ultrasound 76.4% Fluoroscopy 74.5%	NA	NA	NA	Effectiveness shown both with ultrasound and fluoroscopy with lidocaine and dexamethasone	NA	NA	NA	Positive short-term results with ultrasound and fluoroscopy.

Appendix 6 (Cont.). *Characteristics of caudal epidural injections.*

Study Study Characteristics Methodological Quality Scoring	Participants and Interventions	Outcome Measures	Pain Relief and Function				Results				Comment(s)
			3 mos.	6 mos.	12 mos.	24 mos.	Short-term ≤ 6 mos.	Long-Term > 6 mos.	Long-Term ≥ 12 mos.	Long-Term 24 mos.	
Datta & Upadhyay, 2010 (168) RA, AC, B Disc herniation or radiculopathy Quality Scores: Cochrane = 7/12 IPM-QRB = 20/48	Total =163 patients Group A = 10 to 15 mL of 0.125% bupivacaine Group B = 10 to 15 mL of 0.125% bupivacaine and 80 mg of methylprednisolone Group C = 10 to 15 mL of 0.125% bupivacaine and 80 mg of triamcinolone Group D = 10 to 15 mL of 0.125% bupivacaine and 15 mg of dexamethasone	Complete pain relief and satisfactory pain relief, presence of muscle spasm, disability status, Roland-Morris questionnaire, adjuvant therapy	Follow-up was only 3 months Group A = 59% Group B = 82% Group C = 81% Group D = 73%	NA	NA	NA	Effective in all arms with superiority of steroids over bupivacaine alone.	NA	NA	NA	Even though published in 2010, this trial was performed without fluoroscopy. Authors utilized various types of epidural steroids with bupivacaine and comparing bupivacaine alone.
Huda et al, 2010 (171) RA, AC, B Spinal stenosis Quality Scores: Cochrane = 8/12 IPM-QRB =23/48	Total = 70 Triamcinolone group = 35 Methylprednisolone group =35 Either triamcinolone 80 mg or methylprednisolone 80 mg were mixed with 0.125% bupivacaine diluted in normal saline to a total volume of 20 mL in each group.	VAS at 1, 3, and 6 months, increase in the claudication distance Follow-up: 1, 3, and 6 months	Triamcinolone group = 70% Methylprednisolone group = 86%	Triamcinolone = 40 Methylprednisolone = 68.5%	NA	NA	Both drugs mixed with bupivacaine were effective	Methylprednisolone superior	NA	NA	• Relatively small study with superiority of methylprednisolone in bupivacaine compared to triamcinolone. • Blind trial despite publication in 2010

Appendix 6 (Cont.). *Characteristics of caudal epidural injections.*

Study Study Characteristics Methodological Quality Scoring	Participants and Interventions	Outcome Measures	Pain Relief and Function				Results				Comment(s)
								Long-Term			
			3 mos.	6 mos.	12 mos.	24 mos.	Short-term ≤ 6 mos.	> 6 mos.	≥ 12 mos.	24 mos.	
Murakibhavi & Khemka, 2011 (110) RA, NTC, F Disc herniation or radiculopathy Quality Scores: Cochrane = 7/12 IPM-QRB = 27/48	Group A = 50 control conservative management Group B = 52 caudal epidural with lidocaine and methylprednisolone Total = 102 patients Conservative management or caudal epidural steroid injections	VAS, ODI, BDI, NPI	Group A = 32% Group B = 92%	Group A = 24% Group B = 86%	NA	NA	Steroids effective	Steroids effective	NA	NA	Positive short-term results, with methylprednisolone and lidocaine.
Iversen et al, 2011 (109) RA, PC, UL Disc herniation or radiculopathy Quality Scores: Cochrane = 7/12 IPM-QRB = 28/48	Total = 116 Sham = 40 Epidural saline = 39 Epidural saline with steroids = 37 Number of injections = 2 for one year	ODI, EQLS, VAS Follow-up: 12 months with only initial procedures	No significant difference	No significant difference	No significant difference	NA	Lack of efficacy	Lack of efficacy	Lack of efficacy	NA	• Negative results for both epidural saline and epidural steroids in a study with numerous deficiencies with a flawed design with and without local anesthetic. • There were no significant differences between epidural saline and epidural saline with steroids.

Source: Manchikanti L, et al. Assessment of methodologic quality of randomized trials of interventional techniques: Development of an interventional pain management specific instrument. Pain Physician 2014; 17:E263-E290 (49).

RA = Randomized; AC = Active Control; F = Fluoroscopy; DB = Double-Blind; B = Blind; PC = Placebo Control; NTC = No treatment control; UL = Ultrasound; P = Positive; N = Negative; NA = Not Applicable; U = Unclear; SI = Significant Improvement; LA = local anesthetic; NRS = Numeric Rating Scale; ODI = Oswestry Disability Index; BDI = Beck Depression Inventory; SF-MPQ = Short-Form McGill Pain Questionnaire; HADS = Hospital Anxiety and Depression Scale; EQLS = European Quality of Life Scale; VAS = Visual Analog Scale; NPI = Numerical Pain Intensity; IPM – QRB = Interventional Pain Management techniques -- Quality Appraisal of Reliability and Risk of Bias Assessment

Appendix 7. *Characteristics of lumbar interlaminar epidural injections.*

Study Study Characteristics Methodological Quality Scoring	Participants and Interventions	Outcome Measures	Pain Relief and Function				Results				Comment(s)
			3 mos.	6 mos.	12 mos.	24 mos.	Short-term ≤ 6 mos.	Long-Term > 6 mos.	Long-Term ≥ 12 mos.	Long-Term 24 mos.	
Manchikanti et al, 2014 (71) RA, AC, F Disc herniation or radiculopathy Quality Scores: Cochrane = 10/12 IPM-QRB = 44/48	Total = 120 Local anesthetic = 60 Local anesthetic and steroids = 60 Xylocaine or Xylocaine with non-particulate Celestone Average number of injections = 5 to 6 for 2 years	NRS, ODI, employment status, opioid intake, significant improvement 50% or greater of NRS scores and ODI scores Responsive category was defined as at least 3 weeks of significant improvement with the first 2 procedures. Significant improvement: 50% improvement in pain and function.	Overall: Lidocaine 72% vs. lidocaine with steroid 82% Responsive: Lidocaine 86% vs. lidocaine with steroid 83%	Overall: Lidocaine 63% vs. lidocaine with steroid 85% Responsive: Lidocaine 76% vs. lidocaine with steroid 86%	Overall: Lidocaine 67% vs. lidocaine with steroid 85% Responsive: Lidocaine 80% vs. lidocaine with steroid 86%	Overall: Lidocaine 60% vs lidocaine with steroid 70% Responsive: Lidocaine 72% vs. lidocaine with steroid 71%	Both treatments are effective	Both treatments are effective	Both treatments are effective	Both treatments are effective	• Positive randomized trial with long-term follow-up. • Overall, similar results with local anesthetic or with local anesthetic and steroids with significant improvement. • Steroids were superior at 6 months with pain relief and 12 months with functional status • A significantly higher proportion of patients non-responsive to the first 2 injections in the local anesthetic group 10 vs one. • On average, a total of 5-6 injections were provided over a period of 2 years.
Ghai et al, 2015 (75) RA, DB, AC, F Disc herniation or radiculopathy Quality Scores: Cochrane = 9/12 IPM-QRB = 39/48	Total = 69 Lidocaine = 34 Lidocaine + methylprednisolone = 35 Local anesthetic group: 8 mL of 0.5% lidocaine Lidocaine + methylprednisolone: 6 ml of 0.5% lidocaine mixed with 80 mg (2 mL) of methylprednisolone acetate Average procedures: 2	Numeric rating scale and functional disability using Modified Oswestry Disability Questionnaire Follow-up: 1 year	Lidocaine: 50% Lidocaine with methylprednisolone: 86%,	Lidocaine: 56% Lidocaine with methylprednisolone: 86%	Lidocaine: 59% Lidocaine with methylprednisolone: 89%	NA	Both arms effective. Steroids superior	Both arms effective. Steroids superior	Both arms effective. Steroids superior	NA	This active control trial with a long-term follow-up comparing lidocaine alone with lidocaine with methylprednisolone showed similar results after 3 months, even though quality of relief was superior in the local anesthetic with steroid group.

Appendix 7 (cont). *Characteristics of lumbar interlaminar epidural injections.*

Study Study Characteristics Methodological Quality Scoring	Participants and Interventions	Outcome Measures	Pain Relief and Function				Results				Comment(s)
			3 mos.	6 mos.	12 mos.	24 mos.	Short-term ≤ 6 mos.	Long-Term			
								> 6 mos.	≥ 12 mos.	24 mos.	
Manchikanti et al 2015 (62) RA, AC, F Central spinal stenosis Quality Scores: Cochrane = 10/12 IPM-QRB = 43/48	Total = 120 Local anesthetics = 60 Local anesthetics and steroids = 60 Lidocaine alone or with Celestone Average number of injections = 5 to 6 for 2 years	NRS, ODI, employment status, opioid intake Responsive was defined as those patients responding with at least 3 weeks of improvement with the first 2 procedures. Significant improvement: 50% improvement in pain and function.	Overall: LA 83% vs LA with steroid 77% Responsive: LA 90% vs LA with steroid 86%	Overall: LA 72% vs LA with steroid 75% Responsive: LA 78% vs LA with steroid 83%	Overall: LA 77% vs LA with steroid 67% Responsive: LA 84% vs LA with steroid 71%	Overall: LA 72% vs LA with steroid 73% Responsive: LA 84% vs LA with steroid 85%	Both treatments effective	Both treatments effective	Both treatments effective	Both treatments effective	• Positive results in a large active control trial. • Both local anesthetic alone or with steroids were effective with no significant difference between the groups. • On average, a total of 5-6 injections were administered over a period of 2 years.
Friedly et al, 2014 (33) RA, AC, F Central and foraminal spinal stenosis Quality Scores: Cochrane = 9/12 IPM-QRB = 30/48	Total = 400 Lidocaine Group: Interlaminar = 139 Transforaminal = 61 Glucocorticoids plus Lidocaine Group: Interlaminar = 143 Transforaminal = 57 Lidocaine alone or glucocorticoid plus lidocaine Variable doses	NRS, RMDQ	Significant improvement. At 3 weeks and 6 weeks RMDQ scores were significantly less in glucocorticoid-lidocaine group compared to lidocaine group. Leg pain was also significantly less in the steroid group compared to lidocaine alone group.	NA	NA	NA	Both treatments effective with superiority of steroid with lidocaine	NA	NA	NA	Large trial with flawed design and assessment with positive results at 3 months. Even though based on flawed analysis it shows negative results. Multiple flaws include not only the design and analysis of the data, but patient selection, technical considerations, and inherent bias.
Manchikanti et al, 2013 (63) RA, AC, F Axial or discogenic Quality Scores: Cochrane = 10/12 IPM-QRB = 44/48	Total = 120 Local anesthetics = 60 Local anesthetics and steroids = 60 Lidocaine alone or with Celestone Average number of injections = 5 to 6 for 2 years	NRS, ODI, employment status, opioid intake Responsive was defined as those patients responding with at least 3 weeks of improvement with the first 2 procedures. Significant improvement: 50% improvement in pain and function.	Overall: LA 83% vs LA with steroid 77% Responsive: LA 90% vs LA with steroid 86%	Overall: LA 72% vs LA with steroid 75% Responsive: LA 78% vs LA with steroid 83%	Overall: LA 77% vs LA with steroid 67% Responsive: LA 84% vs LA with steroid 71%	Overall: LA 72% vs LA with steroid 67% Responsive: LA 78% vs LA with steroid 70%	P	P	P	P	• Positive results in a large active control trial. • Both local anesthetic alone or with steroids were effective with no significant difference between the groups. • On average, a total of 5-6 injections were administered over a period of 2 years.

Appendix 7 (cont). *Characteristics of lumbar interlaminar epidural injections.*

Study Study Characteristics Methodological Quality Scoring	Participants and Interventions	Outcome Measures	Pain Relief and Function				Results				Comment(s)
			3 mos.	6 mos.	12 mos.	24 mos.	Short-term ≤ 6 mos.	Long-Term			
								> 6 mos.	≥ 12 mos.	24 mos.	
Ackerman & Ahmad, 2007 (107) RA, AC, F Disc herniation or radiculopathy Quality Scores: Cochrane = 7/12 IPM-QRB = 25/48	Total = 90 Caudal = 30 Interlaminar = 30 Transforaminal = 30 Methylprednisolone + saline Number of injections = 1 to 3	Numeric pain score (0 - 10), rating of pain relief, ODI, BDI, contrast dispersion pattern Follow-up: 24 weeks	Caudal = 57% Interlaminar = 60% Transforaminal = 83%	Caudal = 57% Interlaminar = 60% Transforaminal = 83%	NA	NA	Effective in all arms	Effective in all arms	NA	NA	• Positive mid-term results in a relatively small trial. • Shows effectiveness of steroids with all approaches with superiority of transforaminal
Lee et al, 2009 (113) RA, AC, F Disc herniation and spinal stenosis Quality Scores: Cochrane = 6/12 IPM-QRB = 28/48	Total: 99 Interlaminar Group = 42 Bilateral Transforaminal Group = 57 Interlaminar Group: 8 mL of lidocaine 0.5% and 40 mg of triamcinolone Transforaminal Group: 4 mL of lidocaine 0.5% and 0.5 mL or 20 mg of triamcinolone acetonide on each side Number of injections: 1 to 3	NRS, PSI, Roland 5 point pain score with at least 2 point improvement Follow-up: 4 months	Roland Score: Transforaminal with lidocaine and triamcinolone= 3.39 to 1.79 Interlaminar with lidocaine and triamcinolone = 3.31 to 2.19 SI in both groups	NA	NA	NA	Both arms effective. Transforaminal somewhat superior	NA	NA	NA	• Short-term follow-up with positive results, with inability to draw conclusions. • Lack of placebo controlled group.
Rados et al, 2011 (114) RA, AC, F Disc herniation or radiculopathy Quality Scores: Cochrane = 8/12 IPM-QRB = 30/48	Total = 64 IL = 32 TF = 32 Lidocaine with methylprednisolone Number of injections = 1 to 3	VAS, ODI, 50% pain relief Follow-up: 6 months	NA	Interlaminar lidocaine with methylprednisolone = 53% Transforaminal lidocaine with methylprednisolone = 63%	NA	NA	Effective with both approaches	NA	NA	NA	• Positive results with short follow-up period in comparison of 2 approaches with lidocaine with methylprednisolone

Appendix 7 (cont). *Characteristics of lumbar interlaminar epidural injections.*

Study Study Characteristics Methodological Quality Scoring	Participants and Interventions	Outcome Measures	Pain Relief and Function				Results				Comment(s)
								Long-Term			
			3 mos.	6 mos.	12 mos.	24 mos.	Short-term ≤ 6 mos.	> 6 mos.	≥ 12 mos.	24 mos.	
Ghai et al, 2014 (93) RA, AC, F Disc herniation or radiculopathy Quality Scores: Cochrane = 9/12 IPM-QRB = 42/48	Total = 62 Parasagittal interlaminar = 32 Transforaminal = 30 2 mL of methylprednisolone (80 mg) mixed with 2 mL of normal saline for both PIL and transforaminal groups Number of epidural steroid injections: Transforaminal group: 60 PIL group: 58 Average procedures: 2	Visual analog scale, Oswestry Disability questionnaire, significant improvement, greater than 50% pain relief from baseline, Patient Global Impression	PIL group: 78% Transforaminal group: 77%	PIL group: 75% Transforaminal group: 77%	PIL group: 69% Transforaminal group: 77%	NA	Effectiveness in both arms	Effectiveness in both arms	Effectiveness in both arms	NA	This is relatively small active control trial with a long-term follow-up assessing the role of parasagittal interlaminar epidural injections and transforaminal epidural injections showing equal improvement with steroids without local anesthetic.
Candido et al, 2013 (169) RA, AC, F Disc herniation or radiculopathy Quality Scores: Cochrane = 9/12 IPM-QRB = 37/48	106 patients Midline interlaminar = 53 Parasagittal interlaminar = 53 120 mg methylprednisolone with 2 mL of 0.5% lidocaine Number of Injections: Not available	Pain relief, disability, NRS, ODI, use of opioid medication Follow-up: 12 months	ODI: Midline = 36% Parasagittal = 51% Pain: Midline = 29% Parasagittal = 50%	ODI: Midline = 21% Parasagittal = 55% Pain: Midline = 29% Parasagittal = 53%	ODI: Midline = 15% Parasagittal = 56% Pain: Midline = 28% Parasagittal = 55%	NA	Parasagittal superior	Parasagittal superior	Parasagittal superior	NA	• The authors showed significant evidence that parasagittal approach with injection of local anesthetic and steroids was superior to midline approach of interlaminar epidural injections. • This study shows combination of methylprednisolone with lidocaine was superior administered with a parasagittal approach compared to midline approach.

Appendix 7 (cont). *Characteristics of lumbar interlaminar epidural injections.*

Study Study Characteristics Methodological Quality Scoring	Participants and Interventions	Outcome Measures	Pain Relief and Function				Results				Comment(s)
							Short-term	Long-Term			
			3 mos.	6 mos.	12 mos.	24 mos.	≤ 6 mos.	> 6 mos.	≥ 12 mos.	24 mos.	
Amr, 2011 (116) RA, AC, F Disc herniation or radiculopathy Quality Scores: Cochrane = 11/12 IPM-QRB = 38/48	Total = 200 Local anesthetic + steroid = 100 Local anesthetic + steroid + ketamine = 100 Triamcinolone plus preservative free ketamine and 0.9% saline Number of injections = 1	Pain scores, Oswestry low back pain disability questionnaire	SI in ketamine group	SI in ketamine group	SI in ketamine group	NA	Effective with addition of ketamine to bupivacaine and triamcinolone	Effective with addition of ketamine to bupivacaine and triamcinolone	Effective with addition of ketamine to bupivacaine and triamcinolone	NA	• Positive randomized trial for ketamine with long-term follow-up with ketamine with local anesthetic and steroid.
Pirbudak et al, 2003 (118) RA, B, AC Disc herniation or radiculopathy Quality Scores: Cochrane = 11/12 IPM-QRB = 35/48	Total = 92 Epidural = 46 Epidural + amitriptyline = 46 Betamethasone and bupivacaine or with addition of amitriptyline Number of injections = 1 to 3	VAS, ODI Follow-up: 9 months	SI in both groups	SI in both groups	SI in both groups	NA	Epidural steroids effective in both arms with superiority with amitriptyline	Epidural steroids effective in both arms with superiority with amitriptyline	P	NA	• Active control trial with positive results with betamethasone and bupivacaine with addition of amitriptyline.

Appendix 7 (cont). *Characteristics of lumbar interlaminar epidural injections.*

Study Study Characteristics Methodological Quality Scoring	Participants and Interventions	Outcome Measures	Pain Relief and Function				Results				Comment(s)
								Long-Term			
			3 mos.	6 mos.	12 mos.	24 mos.	Short-term ≤ 6 mos.	> 6 mos.	≥ 12 mos.	24 mos.	
Wilson-MacDonald et al, 2005 (121) RA, B, AC Disc herniation or radiculopathy and spinal stenosis Quality Scores: Cochrane = 10/12 IPM-QRB = 31/48	Total = 60 Epidural group = 26 Control group = 34 Treatment: Epidural injection of 8 mL of 0.5% bupivacaine with 40 mg of methylprednisolone. Control Group: 8 mL of bupivacaine 0.5% and 80 mg of methylprednisolone placed outside the epidural space described as intramuscular. Number of injections: 1 to 2	Oxford Pain Chart and ODI 6 weeks in all patients	SI in the treatment group	U	U	U	Showed effectiveness of epidural steroid with local anesthetic	NA	NA	NA	• This is a small study performed without fluoroscopy. The authors also used control group as intramuscular injection with local anesthetic and steroid outside the epidural space which may become epidural. Consequently, this trial is considered as active control. • Improvement seen at 6 weeks. May be appropriate for 1 procedure
Dilke et al, 1973 (117) RA, B, PC Disc herniation or radiculopathy Quality Scores: Cochrane = 8/12 IPM-QRB = 28/48	Total = 100 Epidural = 50 Interspinous = 50 Methylprednisolone in normal saline or interspinous ligament Number of injections = 1-2	Pain relief, analgesic consumption, changes in straight leg raising, or neurological signs Follow-up: 3 months	Placebo 8% Steroids 32%	NA	NA	NA	No significant effect of steroid	NA	NA	NA	Placebo control trial with lack of response.
Arden et al, 2005 (119) RA, B, PC Disc herniation or radiculopathy Quality Scores: Cochrane = 9/12 IPM-QRB = 31/48	Total = 228 Steroid group = 120 Placebo group = 108 Triamcinolone and bupivacaine or normal saline into interspinous ligament Number of injections = 3	ODQ, pain relief, VAS, SF-36, 75% improvement Follow-up: 12 months with only one procedure	75% improvement 12.5% bupivacaine with triamcinolone vs. Placebo 3.7% at 3 weeks	NSI	NSI	NA	Lack of effectiveness with both solutions	Lack of effectiveness of bupivacaine with triamcinolone	Lack of effectiveness of bupivacaine with triamcinolone	NA	• Lack of efficacy after 6 weeks • Meaningful follow-up only 3 months

Appendix 7 (cont). *Characteristics of lumbar interlaminar epidural injections.*

Study Study Characteristics Methodological Quality Scoring	Participants and Interventions	Outcome Measures	Pain Relief and Function				Results				Comment(s)
			3 mos.	6 mos.	12 mos.	24 mos.	Short-term ≤ 6 mos.	Long-Term > 6 mos.	Long-Term ≥ 12 mos.	Long-Term 24 mos.	
Carette et al, 1997 (120) RA, B, PC Disc herniation or radiculopathy Quality Scores: Cochrane = 11/12 IPM-QRB = 27/48	Total = 158 Methylprednisolone = 78 Placebo = 80 Normal saline vs depo methylprednisolone and procaine Number of injections = 1 to 3	VAS and ODI Follow-up: 3 months	NSI	NA	NA	NA	Lack of effectiveness of epidural steroid with saline	N	N	NA	• Methylprednisolone with epidural saline was superior in the short-term. • Overall, there was no significant difference between sodium chloride solution alone or sodium chloride solution with steroids. • Methylprednisolone with saline or saline alone were equally ineffective except in short-term.
Fukasaki et al, 1998 (122) RA, B, AC, PC Spinal stenosis Quality Scores: Cochrane = 5/12 IPM-QRB = 18/48	Total = 53 Epidural saline = 16 Mepivacaine = 18 Mepivacaine and methylprednisolone = 19 Saline or mepivacaine ora combination of mepivacaine and methylprednisolone Number of injections = 1-3	Walking distance Excellent > 100 m Good 20 - 100 m Outcomes: 3 months	Saline 6.3% LA = 5.6% LA with steroid 5.3%	NA	NA	NA	Lack of effectiveness all groups	NA	NA	NA	• In this assessment steroid patients showed better improvement after one week; however, this dissipated at the end of 3 months. All 3 groups provided lack of significant improvement. • There was no difference between saline and local anesthetic and steroids with lack of effectiveness with all 3 solutions.

RA = Randomized; AC = Active Control; F = Fluoroscopy; B = Blind; PC = Placebo Control; DB = Double-Blind; P = Positive; N = Negative; NA = Not Applicable; U = Unclear; SI = Significant Improvement; LA = local anesthetic; NRS = Numeric Rating Scale; ODI = Oswestry Disability Index; PSI = Patient Satisfaction Index; VAS = Visual Analog Scale; ODQ = Oswestry Disability Questionnaire; SF-36 = Short-Form 36; PIL = Parasagittal Interlaminar; RMDQ = = Roland Morris Disability Questionnaire; IPM – QRB = Interventional Pain Management techniques -- Quality Appraisal of Reliability and Risk of Bias Assessment

Appendix 8. *Characteristics of lumbar transforaminal epidural injections.*

Study Study Characteristics Methodological Quality Scoring	Participants and Interventions	Outcome Measures	Pain Relief and Function				Results				Comment(s)
								Long-Term			
			3 mos.	6 mos.	12 mos.	24 mos.	Short-term ≤ 6 mos.	> 6 mos.	≥ 12 mos.	24 mos.	
Manchikanti et al 2014 (67) RA, AC, F Disc herniation or radiculopathy Quality Scores: Cochrane = 10/12 IPM-QRB = 44/48	Total = 120 Lidocaine = 60 Lidocaine with steroids = 60 Lidocaine vs lidocaine mixed with steroid with infraneural approach Average number of injections = 5 to 6 for 2 years	NRS pain scale, ODI, employment status, opioid intake Responsive category was defined as at least 3 weeks of significant improvement with the first 2 procedures. Significant improvement: 50% improvement in pain and function.	Overall: LA 75% vs LA with steroid 67% Responsive: LA 90% vs LA with steroid 82%	Overall: LA 73% vs LA with steroid 67% Responsive LA 88% vs LA with steroid 87%	Overall: LA 75% vs LA with steroid 57% Responsive LA 92% vs LA with steroid 73%	Overall: LA 65% vs LA with steroid 57% Responsive LA 80% vs LA with steroid 73%	Effectiveness in both groups. Lidocaine alone or with steroids effective.	Effectiveness in both groups. Lidocaine alone or with steroids effective.	Effectiveness in both groups. Lidocaine alone or with steroids effective.	Effectiveness in both groups. Lidocaine alone or with steroids effective.	• Similar results with local anesthetic or with local anesthetic and steroids. • Nonresponsive patients: local anesthetic = 11, steroids = 15. • Local anesthetics were somewhat superior, though not statistically significant. • On average, a total of 5-6 injections were administered over a period of 2 years.
Riew et al, 2000 (129) RA, AC, F Disc herniation or radiculopathy Quality Scores: Cochrane = 8/12 IPM-QRB = 32/48	Total = 55 Bupivacaine = 27 Bupivacaine + steroid = 28 Bupivacaine 0.25% or bupivacaine with 6 mg of betamethasone Number of injections = 1 to 4	North American Spine Society Outcome Instrument and operative treatment considered as failure of injection treatment Success was defined as avoidance of surgical intervention. Full data available for 1 year.	NA	NA	33% in bupivacaine group vs. 71% in bupivacaine with betamethasone avoided surgery	NA	NA	NA	33% in bupivacaine group vs. 71% in bupivacaine with betamethasone avoided surgery	NA	• Positive results in avoiding surgery in 33% of bupivacaine group and 71% in the steroid group. • The assessment was based on avoidance of surgery. Steroids with local anesthetic were superior to local anesthetic alone. •

Appendix 8 (Cont.). *Characteristics of lumbar transforaminal epidural injections.*

Study Study Characteristics Methodological Quality Scoring	Participants and Interventions	Outcome Measures	Pain Relief and Function: 3 mos.	Pain Relief and Function: 6 mos.	Pain Relief and Function: 12 mos.	Pain Relief and Function: 24 mos.	Results: Short-term ≤ 6 mos.	Results: Long-Term > 6 mos.	Results: Long-Term ≥ 12 mos.	Results: Long-Term 24 mos.	Comment(s)
Tafazal et al, 2009 (132) RA, AC, F Disc herniation or radiculopathy and spinal stenosis Quality Scores: Cochrane = 10/12 IPM-QRB = 32/48	Total: 150 patients Lumbar disc herniation: 76 Local anesthetic = 34 Local anesthetic with steroid = 42 Local anesthetic group: Injection of 2 mL of 0.25% bupivacaine Local anesthetic with steroid group: Injection of 2 mL of 0.25% bupivacaine and 40 mg of methylprednisolone. Bupivacaine only: Lumbar disc herniation: 34 Foraminal stenosis: 25 Bupivacaine with steroids Lumbar disc herniation: 42 Foraminal stenosis: 23 Number of injections = 1 to 3	VAS, ODI, LBOS Avoidance of surgery Outcomes: 12 weeks 1 year for surgery Excellent outcome	ODI: LA 13.8 ± 3.7 versus LA with steroid 13.6 ± 3.1 VAS leg pain: LA 24.3 ± 5.5 versus LA with steroid 27.4.6 ± 4.7	NA	Disc herniation group showed greater reduction in the ODI with a mean change of 15 points from baseline of 46.6 in the bupivacaine only group and 43.4 in bupivacaine and steroid group. There was a mean change in the VAS of 26 mm in the disc prolapse group.	NA	Excellent to good outcomes in 54% Bupivacaine alone and bupivacaine with steroid are both effective	NA	The requirements for treatments were the same in local anesthetic alone group or local anesthetic with steroids. Overall surgery rates was 18%, the surgery rate was 22% in the bupivacaine only group and 14% in the bupivacaine and steroid group.	NA	• There was no significant difference between both groups. Surgery was avoided in both groups. • Corticosteroid addition to local anesthetic failed to provide any additional benefit when compared to local anesthetic injection alone.
Ng et al, 2005 (130) RA, AC, F Disc herniation or radiculopathy Quality Scores: Cochrane = 11/12 IPM-QRB = 37/48	Total = 86 Disc herniation = 48 Stenosis = 32 Bupivacaine only: Disc herniation = 26 Foraminal stenosis = 15 Bupivacaine + steroid with methylprednisolone Disc herniation = 23 Stenosis = 17 Number of injections = 1	VAS, ODI, change in walking distance, claudication, satisfaction of the outcome Follow-up: 3 months	Bupivacaine = 47.5% Bupivacaine + steroid = 41.5%	NA	NA	NA	Bupivacaine alone and bupivacaine plus steroid were equally effective	NA	NA	NA	• Positive results in a small study with short-term follow-up. • Both groups showed similar improvement when administered with bupivacaine alone or bupivacaine with steroids. • Local anesthetic alone or local anesthetic with steroids were equally effective.

Appendix 8 (Cont.). *Characteristics of lumbar transforaminal epidural injections.*

Study Study Characteristics Methodological Quality Scoring	Participants and Interventions	Outcome Measures	Pain Relief and Function				Results				Comment(s)
			3 mos.	6 mos.	12 mos.	24 mos.	Short-term ≤ 6 mos.	Long-Term > 6 mos.	Long-Term ≥ 12 mos.	Long-Term 24 mos.	
Park et al 2012 (103) RA, AC, F Spinal stenosis Quality Scores: Cochrane = 10/12 IPM-QRB = 34/48	Total = 62 Supraneural approach = 32 Kambin triangle approach = 30 2 mL solution 0.5% lidocaine with 20 mg triamcinolone	>50% pain relief, VNS, ODI	VNS Supraneural: 6.28 ± 0.88 to 2.65 ± 0.46 Kambin Triangle: 6.45 ± 0.94 to 2.63 ± 0.52 ODI Supraneural: 51.64 ± 10.31 to 28.67 ± 4.23 Kambin Triangle: 52.18 ± 8.94 to 27.84 ± 4.49	NA	NA	NA	Both approaches effective	NA	NA	NA	Relatively small trial with similar and positive results with both techniques
Vad et al, 2002 (104) RA, AC, F Disc herniation or radiculopathy Quality Scores: Cochrane = 4/12 IPM-QRB = 16/48	Total: 50 patients Transforaminal: 25 Trigger point injections: 25 Transforaminal injections were performed by safe triangle approach or sacral foramen injection utilizing contrast followed by 1.5 mL of betamethasone acetate 9 mg and 1.5 mL of 2% preservative free Xylocaine. Trigger point injections were performed with 3 mL of normal saline	Outcome measures included visual numeric score, Roland-Morris score, finger to floor distance, and patient satisfaction score. Outcomes were measured at 3 weeks, 6 weeks, 3 months, 6 months, and 12 months.	In transforaminal group 84% showed improvement. In trigger point injection group 48% showed improvement	In transforaminal group 84% showed improvement. In trigger point injection group 48% showed improvement	In transforaminal group 84% showed improvement. In trigger point injection group 48% showed improvement.	NA	Transforaminal steroids with lidocaine effective	Transforaminal steroids with lidocaine effective	Transforaminal steroids with lidocaine effective	NA	This is a randomized trial, but randomization was by patient choice with patients receiving either a high dose transforaminal epidural steroid injection or saline trigger point injection. Study yielded positive results for transforaminal epidural injections at one-year follow-up.

Appendix 8 (Cont.). *Characteristics of lumbar transforaminal epidural injections.*

Study Study Characteristics Methodological Quality Scoring	Participants and Interventions	Outcome Measures	Pain Relief and Function				Results				Comment(s)
								Long-Term			
			3 mos.	6 mos.	12 mos.	24 mos.	Short-term ≤ 6 mos.	> 6 mos.	≥ 12 mos.	24 mos.	
Ackerman & Ahmad, 2007 (107) RA, AC, F Disc herniation or radiculopathy Quality Scores: Cochrane = 7/12 IPM-QRB = 25/48	Total=90 Caudal = 30 Interlaminar = 30 Transforaminal = 30 Steroid and saline with local anesthetic Number of injections = 1 to 3	Numeric pain score (0 - 10), rating of pain relief, ODI, BDI, contrast dispersion pattern Follow-up: 24 weeks	Caudal = 57% Interlaminar = 60% Transforaminal = 83%	Caudal = 57% Interlaminar = 60% Transforaminal = 83%	NA	NA	Effective in all arms	Effective in all arms	NA	NA	• Positive mid-term results in a relatively small trial. • Shows effectiveness of steroids with all approaches with superiority of transforaminal
Rados et al, 2011 (114) RA, AC, F Disc herniation or radiculopathy Quality Scores: Cochrane = 8/12 IPM-QRB = 30/48	Total=64 Interlaminar = 32 Transforaminal = 32 Lidocaine with methylprednisolone Number of injections = 1 to 3	VAS, ODI, 50% pain relief Follow-up: 6 months	NA	Interlaminar lidocaine with methylprednisolone =53% Transforaminal lidocaine with methylprednisolone = 63%	NA	NA	NA	Effective with both approaches	NA	NA	• Positive results with short follow-up period in comparison of 2 approaches with lidocaine with methylprednisolone
Jeong et al, 2007 (127) RA, AC, F Disc herniation or radiculopathy Quality Scores: Cochrane = 9/12 IPM-QRB = 31/48	Total=193 Ganglionic = 104 Preganglionic = 89 0.5 mL of bupivacaine hydrochloride and 40 mg of 1 mL of triamcinolone Number of injections = 1	VAS Follow-up: 7-30 days 6 months	Preganglionic = 88.4% Ganglionic = 70.9%	Preganglionic = 60.4% Ganglionic = 67.2%	NA	NA	Both approaches effective	Both approaches effective	NA	NA	Moderate quality study with mid-term positive results.

Appendix 8 (Cont.). *Characteristics of lumbar transforaminal epidural injections.*

Study Study Characteristics Methodological Quality Scoring	Participants and Interventions	Outcome Measures	Pain Relief and Function				Results				Comment(s)
			3 mos.	6 mos.	12 mos.	24 mos.	Short-term ≤ 6 mos.	Long-Term > 6 mos.	Long-Term ≥ 12 mos.	Long-Term 24 mos.	
Ghai et al, 2014 (93) RA, DB, AC, F Disc herniation or radiculopathy Quality Scores: Cochrane = 9/12 IPM-QRB = 42/48	Total = 62 Parasagittal interlaminar = 32 Transforaminal = 30 2 mL of methylprednisolone (80 mg) mixed with 2 mL of normal saline for both PIL and transforaminal groups Number of epidural steroid injections: Transforaminal group: 60 PIL group: 58 Average procedures: 2	Visual analog scale, Oswestry Disability questionnaire, significant improvement, greater than 50% pain relief from baseline, Patient Global Impression	PIL group: 78% Transforaminal group: 77%	PIL group: 75% Transforaminal group: 77%	PIL group: 69% Transforaminal group: 77%	NA	Effectiveness in both arms	Effectiveness in both arms	Effectiveness in both arms	NA	This relatively small active control trial with a long-term follow-up assessed the role of parasagittal interlaminar epidural injections and transforaminal epidural injections showing equal improvement with steroids without local anesthetic.
Lee et al, 2009 (113) RA, AC, F Spinal stenosis Quality Scores: Cochrane = 9/12 IPM-QRB = 28/48	Total=93 Interlaminar = 34 Transforaminal = 59 Interlaminar vs transforaminal epidural injections. Transforaminal – 4 mL of Lidocaine 0.5% and 0.5 mL of triamcinolone acetonide 20 mg Interlaminar – 8 mL of Lidocaine 0.5% and 1 mL of triamcinolone acetonide 40 mg Number of injections = 1 to 3	NRS, PSI, Roland 5-point pain score with at least 2 point improvement	Roland Score: Transforaminal with lidocaine and triamcinolone= 3.39 to 1.79 Interlaminar with lidocaine and triamcinolone = 3.31 to 2.19	NA	NA	NA	SI in both groups Both arms effective. Transforaminal somewhat superior	NA	NA	NA	• Short-term follow-up with positive results, with inability to draw conclusions. • Lack of placebo controlled group.

Appendix 8 (Cont.). ***Characteristics of lumbar transforaminal epidural injections.***

Study Study Characteristics Methodological Quality Scoring	Participants and Interventions	Outcome Measures	Pain Relief and Function				Results				Comment(s)
			3 mos.	6 mos.	12 mos.	24 mos.	Short-term ≤ 6 mos.	Long-Term > 6 mos.	Long-Term ≥ 12 mos.	Long-Term 24 mos.	
Koh et al, 2013 (106) RA, AC, F Spinal stenosis Quality Scores: Cochrane = 9/12 IPM-QRB = 32/48	Total = 53 Control = 26 Intervention = 27 Both groups 2 mL of 1% lidocaine with 1,500 unites of hyaluronidase Control: Normal saline plus triamcinolone Intervention: Hypertonic saline plus triamcinolone	NRS, ODI, substantial response ≥ or 4 point reduction in INR Follow-up: 3 months	> 50% improvement 19.2% vs 59.3%	NA	NA	NA	Local anesthetic with triamcinolone, hypertonic saline, and hyaluronidase more effective than local anesthetic with triamcinolone	NA	NA	NA	Small trial with short-term positive results. Hypertonic saline may prolong improvement.
Friedly et al, 2014 (33) RA, AC, F Spinal stenosis Quality Scores: Cochrane = 9/12 IPM-QRB = 30/48	Total = 400 Lidocaine Group: Interlaminar = 139 Transforaminal = 61 Glucocorticoids plus lidocaine Group: Interlaminar = 143 Transforaminal = 57 Lidocaine alone or glucocorticoid plus lidocaine Variable doses	NRS, RMDQ Follow-up: 6 weeks	No significant difference was reported between local anesthetic and steroid with RMDQ scores or NRS for leg pain.	NA	NA	NA	Both treatments effective	NA	NA	NA	Large trial with flawed design and assessment with positive results at 3 months. Even though based on flawed analysis it shows negative results. Multiple flaws include not only the design and analysis of the data, but patient selection, technical considerations, and inherent bias.
Kennedy et al, 2014 (172) RA, AC, F Disc herniation or radiculopathy Quality Scores: Cochrane = 9/12 IPM-QRB = 30/48	Total patients = 78 Dexamethasone 15 mg or 1.5 mL = 41 patients Triamcinolone 60 mg or 1.5 mL = 37 patients Number of Injections: 1 to 3	NRS, ODI, at least 50% reduction in pain and disability scores	Dexamethasone group 73% reduction in pain scores, 68% reduction in ODI scores Triamcinolone group 73% reduction in pain scores, 68% reduction in ODI scores	Dexamethasone group 73% reduction in pain scores, 71% reduction in ODI scores Triamcinolone group 76% reduction in pain scores, 65% reduction in ODI scores	NA	NA	Both drugs effective	Both drugs effective	NA	NA	• This is one of the studies showing effectiveness of steroids without local anesthetic. • Relatively small study with short-term follow-up only

Appendix 8 (Cont.). *Characteristics of lumbar transforaminal epidural injections.*

Study Study Characteristics Methodological Quality Scoring	Participants and Interventions	Outcome Measures	Pain Relief and Function				Results				Comment(s)
								Long-Term			
			3 mos.	6 mos.	12 mos.	24 mos.	Short-term ≤ 6 mos.	> 6 mos.	≥ 12 mos.	24 mos.	
Becker et al, 2007 (173) RA, AC, F Quality Scores: Cochrane = 6/12 IPM-QRB = 26/48	Total number of patients = 84 Modified perineural injection technique Group I = 27 patients, 5 mg triamcinolone with 1 mL unspecified local anesthetic Group II = 25 patients, 10 mg triamcinolone with 1 mL unspecified local anesthetic Group III = 32 patients, autologous condition serum Number of Injections: 3	VAS, ODI Follow-up: 26 weeks	Significant improvement in all groups with autologous condition serum superior to steroids at 26 week follow-up.	Significant improvement in all groups with autologous condition serum superior to steroids at 26 week follow-up.	NA	NA	Steroids with local anesthetic and autologous serum were effective	Steroids with local anesthetic and autologous serum were effective	NA	NA	• Small study with short-term follow-up.
Ghahreman et al, 2010 (123) RA, PC, F Disc herniation or radiculopathy Quality Scores: Cochrane = 11/12 IPM-QRB = 37/48	Total=150 5 groups with 28, 37, 27, 28, 30 Transforaminal injection of 2 mL of 0.5% bupivacaine in the local anesthetic group Transforaminal local anesthetic with steroid, 40 mg per mL or 70 mg of triamcinolone Number of injections = 1 to 3 for 12 months	At least 50% pain relief at least 1 month after treatment, SF-36, Roland-Morris Follow-up: 1-3 months	At one month follow-up: Transforaminal local anesthetic = 7% Transforaminal epidural with steroids = 54%	NA	NA	NA	Effectiveness only in steroids with local anesthetic.	NA	NA	NA	• In this short-term assessment in a small number of patients, high-dose steroids (70 mg of triamcinolone) were superior to local anesthetic and saline. • They described worst outcomes with transforaminal bupivacaine, even worse than intramuscular saline. • Only successful patients were followed to 12 months, very small numbers to draw conclusions (15 of 150 patients).

Appendix 8 (Cont.). *Characteristics of lumbar transforaminal epidural injections.*

Study Study Characteristics Methodological Quality Scoring	Participants and Interventions	Outcome Measures	Pain Relief and Function				Results				Comment(s)
								Long-Term			
			3 mos.	6 mos.	12 mos.	24 mos.	Short-term ≤ 6 mos.	> 6 mos.	≥ 12 mos.	24 mos.	
Karppinen et al, 2001 (125) RA, PC, F Disc herniation or radiculopathy Quality Scores: Cochrane = 12/12 IPM-QRB = 34/48	Total=160 Methylprednisolone-bupivacaine = 80 Saline = 80 Sodium chloride solution, or methylprednisolone (40 mg) and bupivacaine (5 mg) Number of injections = 1	VAS, ODI, Nottingham Health Profile, cost, physical examination Follow-up: 12 months with only initial procedures	A significant treatment effect in favor of saline treatment for back pain.	The treatment effects in both leg pain and back pain favored the saline treatment.	There were no treatment effects in favor of either treatment.	NA	Lack of effectiveness of steroid with bupivacaine	Lack of effectiveness of steroid with bupivacaine	Lack of effectiveness of steroid with bupivacaine	NA	• An ineffective or inappropriate placebo design, without applicable results. • Overall saline appears to have been superior at 3 months and 6 months, but no significant difference at one year between both groups. • Leg pain decreased on average by 65% in both groups. • Surgery was avoided in the majority of the patients with 18 patients in the steroid group and 15 in the saline group undergoing surgery.

Appendix 8 (Cont.). *Characteristics of lumbar transforaminal epidural injections.*

Study Study Characteristics Methodological Quality Scoring	Participants and Interventions	Outcome Measures	Pain Relief and Function				Results				Comment(s)
			3 mos.	6 mos.	12 mos.	24 mos.	Short-term ≤ 6 mos.	Long-Term > 6 mos.	Long-Term ≥ 12 mos.	Long-Term 24 mos.	
Cohen et al, 2015 (161) RA, PC, F Disc herniation or radiculopathy Quality Scores: Cochrane = 5/12 IPM-QRB = 26/48	Total = 122 Transforaminal with steroids = 62 Transforaminal placebo injection = 60 Intervention group with injection of 60 mg of depomethylprednisolone plus 1 mL of 0.25% bupivacaine with a total volume of 3 mL. For sham injections a small volume of saline followed by an additional 3 mL was injected. Sham: Gabapentin ranging from 1800 mg to 3600 mg per day. Number of injections = 1	NRS with average leg pain Oswestry Disability Index A positive outcome was defined as a one point decrease in leg pain coupled with a positive global perceived effect. . Follow-up: 3 months	No significant difference from the primary outcome measures either between the groups or from baseline.	NA	NA	NA	Lack of effectiveness of steroids with bupivacaine.	NA	NA	NA	Even though this trial appears to be appropriate it has numerous flaws in the concept, design, and analysis of the data. In this study the authors utilized a risky technique with supraneural approach in performing the procedure, with injection of particulate steroids with bupivacaine which has not been tested frequently in the epidural group and administered high doses of gabapentin in the sham group. The number of patients withdrawn from the study was inordinately high due to negative outcomes in 23 of 73 patients in the epidural group and 39 of 72 patients in the placebo group. The authors also combined interlaminar and transforaminal epidural patients with the data analysis.

RA = Randomized; AC = Active Control; F = Fluoroscopy; PC = Placebo Control; DB = Double-Blind; P = Positive; N = Negative; NA = Not Applicable; U = Unclear; SI = Significant Improvement; LA = local anesthetic; VNS = Visual Numeric Scale; IPM – QRB = Interventional Pain Management techniques -- Quality Appraisal of Reliability and Risk of Bias Assessment; NRS = Numeric Rating Scale; PSI = Patient Satisfaction Index; ODI = Oswestry Disability Index; VAS = Visual Analog Scale; LBOS = Low Back Outcome Score; PIL = Parasagittal Interlaminar; RMDQ = Roland Morris Disability Questionnaire

Appendix 9. *Characteristics of cervical/thoracic interlaminar epidural injections.*

Study Study Characteristics Methodological Quality Scoring	Participants and Interventions	Outcome Measures	Pain Relief and Function				Results				Comment(s)
								Long-Term			
			3 mos.	6 mos.	12 mos.	24 mos.	Short-term ≤ 6 mos.	> 6 mos.	≥ 12 mos.	24 mos.	
Cohen et al, 2014 (160) RA, AC, F Cervical disc herniation or radiculopathy Quality Scores: Cochrane = 6/12 IPM-QRB = 25/48	Total = 169 Conservative treatment group = 59 (medical therapy and physical modalities) Epidural steroid injection group = 58 (3 mL of solution containing 60 mg of depo-methylprednisolone and normal saline) Combination therapy group = 55 (epidural steroid injection and pharmacotherapy with gabapentin and physical modalities)	Within group changes and between group changes, pain, NRS, Neck Disability Index	Positive outcome: Conservative group: 26.8% Epidural group: 36.7% Combination therapy group: 56.9%	Positive outcome: Conservative group: 23.6% Epidural group: 25.5% Combination therapy group: 44%	NA	NA	U	NA	NA	NA	Undetermined results at 3 months for epidural steroid injection without local anesthetic combined with conservative management, with borderline response in 36.7% at 3 months and 25.5% at 6 months with epidural injections. This trial included acute and chronic pain patients. Number of injections provided is not shown. Local anesthetic was not utilized. There was a large number of patients who were not compliant in conservative and combination groups.
Manchikanti et al 2013 (69) RA, AC, DB, F Cervical disc herniation or radiculopathy Quality Scores: Cochrane = 11/12 IPM-QRB = 43/48	Total = 120 Local anesthetic = 60 Local anesthetic with steroids = 60 Local anesthetic or with Celestone Average number of injections = 5 to 6 for 2 years	NRS, NDI, employment status, opioid intake Significant improvement > 50% pain relief and > 50% functional status improvement	Overall: LA 83% vs LA with steroid 70% Responsive: LA 91% vs LA with steroid 84%	Overall: LA 82% vs LA with steroid 73% Responsive: LA 91% vs LA with steroid 86%	Overall: LA 72% vs LA with steroid 68% Responsive: LA 77% vs LA with steroid 82%	Overall: LA 72% vs LA with steroid 68% Responsive: LA 77% vs LA with steroid 80%	P	P	P	P	• Positive results in a randomized large trial performed under fluoroscopy with long-term follow-up. • Similar results with local anesthetic or with local anesthetic and steroids. • Overall, a total of 5-6 injections were administered over a period of 2 years.
Castagnera et al, 1994 (133) RA, AC, B Cervical disc herniation or radiculopathy Quality Scores: Cochrane = 7/12 IPM-QRB = 25/48	Total = 24 Steroid = 14 Steroid + morphine = 10 Local anesthetic with steroid or local anesthetic with steroid plus morphine Number of injections=1	Pain relief, visual analog scale, work status	78.5% vs 80%	78.5% vs 80%	78.5% vs 80%	NA	P	P = steroids N = local anesthetics	P	NA	A small study with positive results

Appendix 9 (cont.). *Characteristics of cervical/thoracic interlaminar epidural injections.*

Study Study Characteristics Methodological Quality Scoring	Participants and Interventions	Outcome Measures	Pain Relief and Function				Results				Comment(s)
			3 mos.	6 mos.	12 mos.	24 mos.	Short-term ≤ 6 mos.	Long-Term > 6 mos.	Long-Term ≥ 12 mos.	Long-Term 24 mos.	
Stav et al, 1993 (134) RA, AC, B Cervical disc herniation or radiculopathy Quality Scores: Cochrane = 7/12 IPM-QRB = 25/48	Total = 42 Cervical epidural steroid/lidocaine injection = 25 Steroid/lidocaine injection into posterior neck muscles = 17 Local anesthetic with steroid or intramuscular steroid Number of injections=1 to 3	Pain relief, change in range of motion, reduction of daily dose of analgesics, return to work	NA	NA	68% vs11.8%	NA	NA	NA	P	NA	A small study showing satisfactory improvement
Pasqualucci et al, 2007 (135) RA, AC, B Cervical disc herniation or radiculopathy Quality Scores: Cochrane = 7/12 IPM-QRB = 24/48	Total = 160 Pain onset 15-30 days = 40 Pain onset 31-60 days = 40 Pain onset 61 to 180 days = 40 Pain > 180 days = 40 Bupivacaine with methylprednisolone acetate	Pain control of greater than 80%, pain-free hours of sleep	NA	Single vs continuous 58.5%, 73.7% improvement	NA	NA	NA	NA	NA	NA	Small study with positive results with a complicated design with mixture of acute and chronic patients.
Manchikanti et al, 2012 (60) RA, AC, F Cervical spinal stenosis Quality Scores: Cochrane = 10/12 IPM-QRB = 42/48	Total = 60 Local anesthetic only = 30 Local anesthetic with steroids = 30 Local anesthetic or with Celestone Average number of injections = 3 to 4 for 1 year	NRS, NDI, employment status, opioid intake Significant improvement > 50% pain relief and > 50% functional status improvement Responsive was defined as those patients responding with at least 3 weeks of improvement with the first 2 procedures.	Overall: LA 77% vs LA with steroid 87% Responsive: LA 79% vs LA with steroid 82%	Overall: LA 87% vs LA with steroid 80% Responsive: LA 79% vs LA with steroid 92%	Overall: LA 73% vs LA with steroid 70% Responsive: LA 90% vs LA with steroid 89%	NA	P	P	P	NA	• Preliminary results of a large randomized trial performed under fluoroscopy with positive results. • Similar results with local anesthetic or with local anesthetic and steroids. • Overall, 3-4 injections were provided over a period of 1 year.

Appendix 9 (cont.). *Characteristics of cervical/thoracic interlaminar epidural injections.*

Study Study Characteristics Methodological Quality Scoring	Participants and Interventions	Outcome Measures	Pain Relief and Function				Results				Comment(s)
			3 mos.	6 mos.	12 mos.	24 mos.	Short-term ≤ 6 mos.	Long-Term > 6 mos.	Long-Term ≥ 12 mos.	Long-Term 24 mos.	
Manchikanti et al 2014 (68) RA, DB, AC, F Cervical axial or discogenic Quality Scores: Cochrane = 10/12 IPM-QRB = 44/48	Total = 120 Local anesthetic only = 60 Local anesthetic with steroids = 60 Local anesthetic or with Celestone Average number of injections = 5 to 6 for 2 years	NRS, NDI, opioid intake, employment, changes in weight Significant improvement > 50% pain relief and > 50% functional status improvement	Overall: LA 68% vs LA with steroid 77% Responsive: LA 75% vs LA with steroid 82%	Overall: LA 67% vs LA with steroid 73% Responsive: LA 73% vs LA with steroid 79%	Overall: LA 72% vs LA with steroid 68% Responsive: LA 78% vs LA with steroid 83%	Overall: LA 73% vs LA with steroid 70% Responsive: LA 78% vs LA with steroid 75%	P	P	P	p	• Positive results of a large randomized controlled trial performed under fluoroscopy. • Similar results with local anesthetic or with local anesthetic and steroids. • A total of 5-6 injections on average were provided over a period of 2 years.
Manchikanti et al, 2012 (61) RA, AC, F Cervical post surgery syndrome Quality Scores: Cochrane = 10/12 IPM-QRB = 42/48	Total = 56 Local anesthetic only = 28 Local anesthetic with steroids = 28 Local anesthetic or with Celestone Average number of injections = 3 to 4 for one year	NRS, NDI, employment status, opioid intake Significant improvement > 50% pain relief and > 50% functional status improvement Responsive was defined as those patients responding with at least 3 weeks of improvement with the first 2 procedures.	Overall: LA 68% vs LA with steroid 68% Responsive: LA 83% vs LA with steroid 72%	Overall: LA 64% vs LA with steroid 71% Responsive: LA 78% vs LA with steroid 80%	Overall: LA 71% vs LA with steroid 64% Responsive: LA 87% vs LA with steroid 72%	NA	P	P	P	NA	• An active-control trial conducted with fluoroscopy with positive results. • Similar results with local anesthetic or with local anesthetic and steroids. • On average, 3-4 injections were provided.
Manchikanti et al, 2014 (64) RA, AC, DB, F Thoracic pain Quality Scores: Cochrane = 11/12 IPM-QRB = 43/48	Total = 110 Local anesthetic only = 55 Local anesthetic with steroids = 55 6 mL of local anesthetic only or 6 mL of local anesthetic with 6 mg of nonparticulate betamethasone Average number of injections = 5 - 6 for 2 years	NRS, ODI, employment status, opioid intake Significant improvement > 50% pain relief and > 50% functional status improvement	Overall: LA 78% vs LA with steroid 82% Responsive: LA 88% vs LA with steroid 86%	Overall: LA 74% vs LA with steroid 84% Responsive: LA 84% vs LA with steroid 90%	Overall: LA 71% vs LA with steroid 84% Responsive: LA 80% vs LA with steroid 90%	Overall: LA 71% vs LA with steroid 80% Responsive: LA 80% vs LA with steroid 86%	P	P	P	P	• First large randomized trial with active control design and long-term follow-up. • Similar results with local anesthetic or with local anesthetic and steroids. • On average, 5-6 total procedures were performed over a period of 2 years.

RA = Randomized; AC = Active Control; F = Fluoroscopy; B = Blind; DB = Double-Blind; P = Positive; N = Negative; NA = Not Applicable; U = Unclear; SI = Significant Improvement; LA = local anesthetic; IPM – QRB = Interventional Pain Management techniques -- Quality Appraisal of Reliability and Risk of Bias Assessment; NRS = Numeric Rating Scale; NDI = Neck Disability Index