Systematic Review

Epidural Injections for Lumbar Radiculopathy and Spinal Stenosis: A Comparative Systematic Review and Meta-Analysis

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Background: The prevalence of chronic low back pain and related disability is rapidly increasing as are the myriad treatments, including epidural injections. Even though epidural injections are one of the most commonly performed procedures in managing low back and lower extremity pain, starting in 1901 with local anesthetic alone, conflicting recommendations have been provided, despite the extensive literature. Recently Chou et al performed a technology assessment review for Agency for Healthcare Research and Quality (AHRQ) part of which was published in Annals of Internal Medicine showing lack of effectiveness of epidural steroid injections in managing lumbar radiculopathy and spinal stenosis. In contrast, multiple other publications have supported the efficacy and use of epidural injections.

Purpose: To assess the efficacy of 3 categories of epidural injections for lumbar and spinal stenosis: performed with saline with steroids, local anesthetic alone, or steroids with local anesthetic and separate facts from opinions.

Data Sources: PubMed, Cochrane Library, US National Guideline Clearinghouse, prior systematic reviews, and reference lists. The literature search was performed through August 2015.
Study Selection: Randomized trials, either placebo or active control, of epidural injections for lumbar radiculopathy and spinal stenosis.

Data Extraction: Data extraction and methodological quality assessment were performed utilizing Cochrane review methodologic quality assessment and Interventional Pain Management Techniques - Quality Appraisal of Reliability and Risk of Bias Assessment (IPM-QRB). Evidence was summarized utilizing principles of best evidence synthesis.

Data Synthesis: Thirty-nine randomized controlled trials met inclusion criteria. There were 9 placebo-controlled trials evaluating epidural corticosteroid injections, either with sodium chloride solution or bupivacaine, compared to placebo injections. There were 12 studies comparing local anesthetic alone to local anesthetic with steroid.

Results A meta-analysis of 5 studies utilizing sodium chloride or bupivacaine with steroid showed a lack of efficacy.

A comparison of lidocaine to lidocaine with steroids in 7 studies showed significant effectiveness from baseline to long-term follow-up periods. Meta-analysis showed a similar effectiveness for pain and function without non-inferiority of lidocaine compared to lidocaine with steroid at 3 months and 12 months.

Limitations: The review was restricted to the data available with at least 3 months of follow-up, which excluded some studies. The inclusion criteria were restricted to English language studies.

Conclusion: Epidural corticosteroid injections for radiculopathy or spinal stenosis with sodium chloride solution or bupivacaine were shown to be ineffective. Lidocaine alone or lidocaine in conjunction with steroids were significantly effective.

Key Words: Epidural injections, epidural steroids, lumbar radiculopathy, spinal stenosis, lidocaine, steroids, bupivacaine

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A U.S. Burden of Disease Collaborators report for the period 1990 through 2010 has shown the impact of low back pain on the state of the nation's health. Low back pain is the number one condition leading to disability (1). The escalating prevalence of low back pain, with an increase of 162% from 1992 to 2006 in the United States (2) and increases globally (1,3) with estimated expenditures of $100 billion in the United States alone, remains a major concern (4). Despite the many treatment modalities (5) that are available, disability related to low back pain continues to increase.

Epidural injections are one of the most commonly performed procedures in managing low back and lower extremity pain, specifically for managing radiculopathy secondary to a herniated disc and for spinal stenosis (6). Epidural injections for lumbago have been performed with local anesthetic alone since 1901, as described by Sicard (7-9), Cathelin (8,10), and Pasquier and Leri (11). In fact, Sicard (7,9) acquired the reputation as the "pain doctor" for treating patients from all over France. Steroids were added in the early 1950s following the descriptions of Robecchi and Capra (12) and Lievre et al (13). Epidural injections during the first 50 years were limited to local anesthetic alone (14,15). Since then, conflicting recommendations have been provided, despite multiple randomized controlled trials (RCTs), systematic reviews, and clinical guidelines, with some supporting the efficacy and use of epidural injections (16-20), and some high profile publications concluding they lack efficacy (21-25). Lewis et al (26,27) in 2 manuscripts funded by National Health Services (NHS) and Health Technology Assessment Program have presented positive results for epidural injections. In the Health Technology Assessment (26), in a systematic review and economic model of the clinical effectiveness and cost effectiveness of management strategies for sciatica, supported the effectiveness of epidural corticosteroid injections and disc surgery. In the second manuscript, Lewis et al (27) in a systematic review and network meta-analyses of comparative clinical effectiveness of management strategies for sciatica with review of 122 relevant studies and 21 treatment strategies showed statistically significant improvement with epidural injections. Further, this network meta-analyses also showed epidural injections were superior to traction, percutaneous discectomy, and exercise therapy. This is in contrast to the U.S. publications of Agency for Healthcare Research and Quality (AHRQ) (22,23). Further, despite the conflicting data, growth of epidural injections continues to escalate (6). The beginning of this escalation of the use of epidural injections may be traced back to a 1991 publication showing lack of efficacy of intraarticular injections (28) and another 1997 high profile trial (29) showing a lack of efficacy of epidural steroid injections (30).

Discordant conclusions brought on multiple challenges related to the conduct of the RCTs based on approach (transforaminal, interlaminar, or caudal), control design (active-control versus placebo-control), technical performance (with or without fluoroscopy), alternate techniques, and outcomes assessments (absolute difference between 2 groups or minimum clinically important difference [MCID] with assessment of proportion of patients). Institute of Medicine (IOM) (31) described multiple issues related to the design of the systematic reviews related to inclusion criteria (placebo versus active-control or all active controls converted to placebo), methodological quality assessment of the trials, outcomes assessment, and perceived intellectual bias with conflicts of interest. IOM also extensively described the role of bias and conflicts of interest and need to minimize the bias and conflicts of interest. IOM defined conflict of interest as, "a set of circumstances that creates a risk that professional judgement or actions regarding the primary interest will be unduly influenced by a secondary interest." While primary interests are well known with financial conflicts of interest, IOM has described secondary interests, such as the pursuit of professional advancement, future funding opportunities and recognition, and the desire to do favors for friends and colleagues, as potential conflicts. In fact, such descriptions have been provided in the past illustrating hidden conflicts of interest not only by academicians, but by agencies which advise the policy makers and those preparing reviews for these organizations (32,33). In addition, on the same lines (34) the Institute for Transitional Medicine and Therapeutics has described confluence (not conflict of interest) in which they describe conflicts of interest represents a complex ecosystem that requires development of a uniform approach to minimize bias in clinical research across the academic sector. They showed that the term conflict of interest is pejorative, disclosure policies have focused on financial gains only, whereas in academia the prospect of fame may be even more seductive than fortune. We believe that the reviews by Chou et al (22,23) are with significant intellectual bias and undisclosed confluence of interest, tainting the value of the publications.

Further, Chou et al seemed to confuse facts (veri-

fiable) with their own opinions (judgements based on facts) and beliefs (conviction based on personal values), ultimately leading to prejudicial statements – opinions based on insufficient or unexamined evidence.

The purpose of this systematic review, therefore, is to assess the efficacy or lack thereof of injections of epidural steroids with saline, local anesthetics alone, or local anesthetic with steroids. We will critically evaluate and compare our results with those of the AHRQ technology assessment (22,23).

Methods

The methodology utilized in this systematic review and critical assessment of the AHRQ technology assessment report (22) and subsequent publication (23) includes utilization of IOM standards for systematic reviews of comparative effectiveness research (31) and multiple other publications relevant to systematic reviews (35-39). There was no external funding in preparation of this or previously published manuscripts (19).

This manuscript focuses on the effectiveness of epidural injections for radiculopathy or spinal stenosis when provided with a mixture of sodium chloride solution or with local anesthetic in placebo-controlled trials. In addition, the effectiveness of local anesthetic alone is compared to local anesthetic with steroids and with testing for non-inferiority of local anesthetics alone compared to local anesthetics with steroids.

We variably defined placebo interventions as administration of an inert substance into the epidural space, over the nerve root, or in remote tissues. An active substance such as corticosteroid into soft tissues was also considered as a placebo. All local anesthetic injections into the epidural space or over the nerve root were considered to be active-controls.

All randomized trials utilized in Chou et al's systematic review (23) were considered for inclusion. In addition, all other RCTs meeting pre-specified criteria were included.

Data Sources and Searches

The literature search was performed through August 2015, in addition to the inclusion of all studies that were utilized in Kaye et al's (19) and Chou et al's (23) systematic reviews. Searches were performed from various sources including PubMed from 1966, Embase, Cochrane Library, US National Guideline Clearinghouse, previous systematic reviews and cross references, and all other sources including unindexed journals and abstracts through August 2015.

Search Criteria

((((((((((((((((chronic low back pain) OR chronic mild back OR upper back 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])))

Study Selection

Study selection was based on predefined inclusion criteria with reports of at least 3 months of outcomes assessments and RCTs with placebo- or active-control design. We included epidural injections with sodium chloride solution, local anesthetic, or steroids administered through caudal, interlaminar, or transforaminal approaches. Predefined outcomes were measurement of pain and function with description of composite outcomes.

Data Extraction and Methodological Quality Assessment

Data extraction and quality assessment were updated from a recent systematic review performed by multiple authors (19).

At least 2 of the review authors independently, in an unblinded standardized manner, acquired the literature, selected the studies, performed the methodological quality assessment, and analyzed the evidence. Any disagreements between reviewers were resolved by a third author and consensus. If there were any conflicts of interest with a manuscript, e.g., authorship, the review authors were recused from assessment and analysis.

The quality assessment of each individual article used in this analysis was performed by comparing the

analysis performed by Chou et al (22,23) with an independent assessment using Cochrane review criteria (Appendix Table 1) (37) and Interventional Pain Management Techniques - Quality Appraisal of Reliability and Risk of Bias Assessment (IPM-QRB) criteria (Appendix Table 2) (38).

Utilizing Cochrane review criteria (37) or IPM-QRB (38), studies meeting the inclusion criteria with a score of at least 8 of 12 or 32 to 48, respectively, were considered high quality and 4 to 7 or 16 to 31 were considered moderate quality; these were included in the review. Those with a score of less than 4 or 16 were considered low quality.

Chou et al (22,23) utilized Cochrane review criteria (37) and rated individual studies as poor, fair, or good.

Chou et al (23) misinterpreted the publication of a consecutive number of patients completing follow-up as compromising randomization or blinding and considering these results as a subgroup of patients, thus downgrading the methodological quality rating for these trials. This was inappropriate, and was not done in this assessment.

Data Synthesis and Analysis

Data were synthesized utilizing qualitative and quantitative measurements. Evidence was assessed based on best evidence synthesis for qualitative analysis as shown in Table 1 (39). A meta-analysis was performed when there were at least 3 homogenous studies.

The meta-analysis was performed using RevMan 5.1 (Review Manager (RevMan) [Computer program]. Version 5.1. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2008). For pain and functional status improvement data, the studies were reported as the standardized mean differences (SMD) with 95% confidence intervals (CI). Data were plotted with forest plots to evaluate treatment effects. Heterogeneity was interpreted through I2 statistics.

For this analysis, treatment with lidocaine was considered as non-inferior to treatment with lidocaine with steroid. Utilization of non-inferiority analysis captures clinically relevant information between 2 arms: local anesthetic and local anesthetic with steroids.

To test for non-inferiority, the 95% CI for the differences in mean pain and functional improvement between 2 groups were calculated. If the lower limit of CI fell to about 10% of the maximal range of each scale ≥ 10 or < 10, the non-inferiority was accepted.

All analyses were based on each modality of treatment and the solution injected. Short-term improvement was defined as any improvement of 3 months and long-term evidence was described as greater than 6 months.

Qualitative and quantitative measurements were assessed which indicated the direction of a treatment's effect and the magnitude of a treatment's effect. For placebo-controlled trials, the net effect between 2 treatments was utilized; however, for active-controlled trials, the differences between baseline and at the follow-up period were utilized. This is in contrast to Chou et al who utilized differences between 2 active-controlled trials and also considered a larger number of studies as placebo even though these studies were active-control (22,23). We believe that in both of the above situations, Chou et al made an error in methodology.

Even though minimum change of 20% in pain scales is widely accepted, the evolving concepts of MCID have shown to be patient centered and practical. Multiple publications have alluded to the fact, adapting to the clinically relevant outcome measures defined as significant improvement with at least 50% improvement in pain and functional status (16-19,40-46). There is also ample literature documenting the necessity to use, when comparing two groups in an active control trial, changes from baseline to follow up, instead of absolute changes between groups (16-19, 41-46).

Table 1. *Modified grading of qualitative 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

Developed and modified from: Manchikanti L, et al. A modified approach to grading of evidence. *Pain Physician* 2014; 17:E319-E325 (39).

Consequently, in this report, we have utilized either 50% relief from the baseline pain score or a change of at least 3 points on an 11 point pain scale. A ≥ 30% decrease of disability scores was considered as clinically significant.

Results

Figure 1 shows the literature search and selection of the manuscripts for inclusion. After full text review and exclusion of duplicates, we identified 39 trials (29,47-84) meeting inclusion criteria. Of these, a total of 11 studies assessed caudal epidural injections (47-57), 16 studies assessed interlaminar epidural injections (29,50,58-63,65-72), and 18 studies assessed transforaminal epidural injections (50,61,63,64,67,72-84). Of these, 3 caudal epidural trials (53-55), 4 interlaminar trials (61,70-72), and 6 transforaminal trials assessed the role of epidural injections in spinal stenosis (61,64,72,75,80,81).

Of the 59 trials included by Chou et al (23), multiple trials did not meet present predefined inclusion criteria (85-118) with 4 duplicate studies (88,89,99,106). Of the 39 included trials in this review, 10 trials (51,52,61,62,64-66,73,75,82) were not included in Chou et al's review

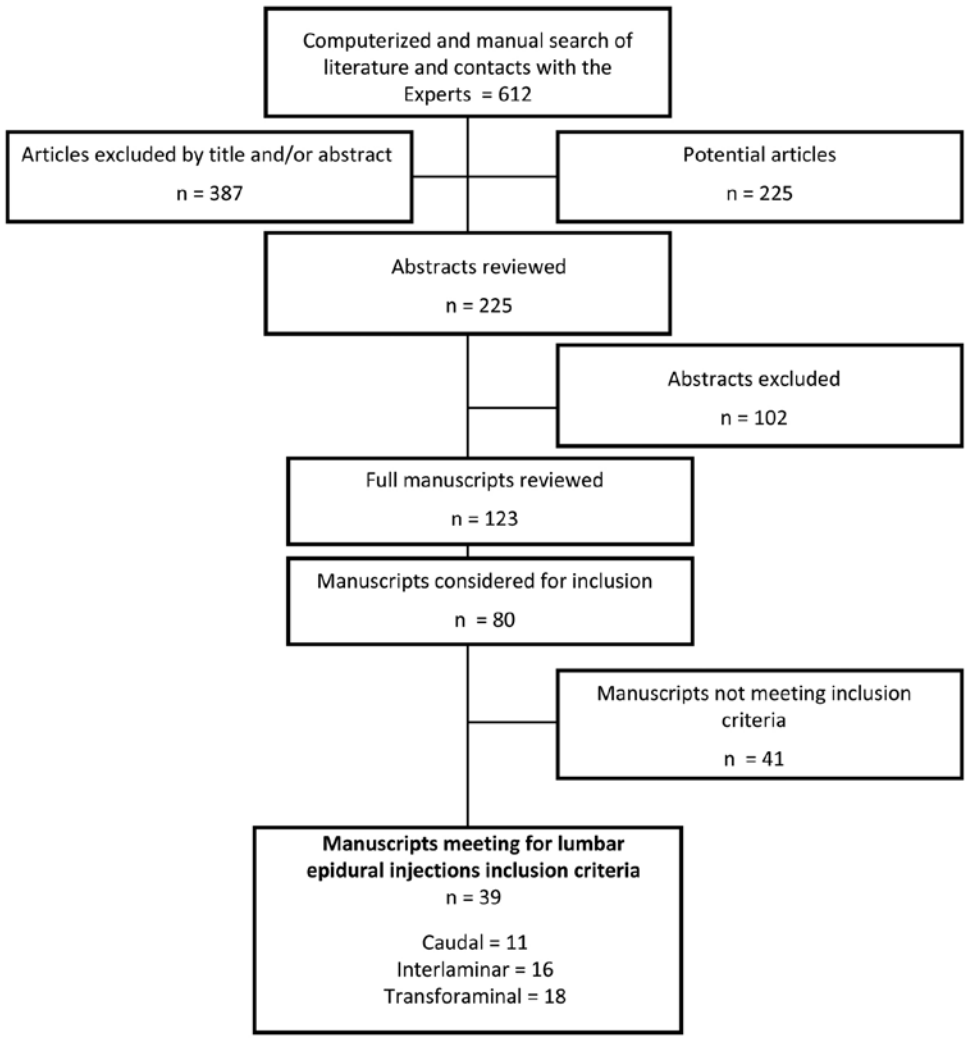


Fig. 1. *Flow diagram illustrating published literature evaluating epidural injection therapy in managing disc herniation or radiculopathy and spinal stenosis.*

(23), consequently, only 29 trials were included in both reviews.

Of these, fluoroscopy was not utilized in any of the caudal- or interlaminar placebo-controlled trials.

Methodological Quality Assessment

Appendix Tables 3 and 4 show the scoring for methodological quality assessment of all RCTs utilizing Cochrane review criteria (37) and IPM-QRB criteria (38).

Table 2 shows the scoring for methodological quality assessment of RCTs of lumbar epidural injections, with a comparison between Cochrane review criteria (37), IPM-QRB criteria (38), and Chou et al's assessment (22,23).

There were significant differences in the quality rating scorings with only 5 of 29, or 17% agreement, between Chou et al's (23) and our scoring. Chou et al (23) showed substantial discrimination for 2 studies reducing their rating from high to poor (60,74), whereas for other studies, they reduced them from high to fair. Chou et al (23) also provided poor inclusion criteria, along with a lack of appropriate review of the manuscripts, reaching the conclusion that certain data were not provided. In fact, it was clearly provided. The resultant impact was to facilitate their reduction of methodological quality scores. This assessment also shows the importance of interventional pain management-specific scoring utilizing IPM-QRB criteria, which has shown assessment results that are different from Cochrane review derived data. There was agreement between Cochrane review scoring and IPM-QRB scoring in 29 of 39 trials. Generally, IPM-QRB scoring was shown at a lower grading than Cochrane review criteria, which was illustrated in 10 trials.

Effectiveness of Epidural Injections

Descriptive characteristics of included studies are shown in Appendix Tables 5-7.

There was one placebo-controlled trial with a caudal approach (47), 5 placebo-controlled trials with a lumbar interlaminar approach (29,58,59,68,71), and 3 placebo-controlled trials utilizing a transforaminal approach (76,78,82). There was one caudal trial without placebo; however, no treatment was utilized as the control (50). Only one study (71) assessed effectiveness in spinal stenosis with a placebo.

Of the remaining studies included in this assessment, 12 studies compared local anesthetic alone with local anesthetic and steroids. The remaining studies either compared technical aspects or dose responses.

Analysis of Evidence

Based on the qualitative synthesis of evidence of 9 placebo-controlled trials (29,47,58,59,68,71,76,78,82), epidural steroid injections with saline showed a lack of effectiveness in 3 trials with 131 patients (29,47,71) and short-term (3 months) effectiveness in one trial with 50 patients (58). Adding bupivacaine to steroids showed very short-term (3-6 weeks) effectiveness in 3 trials with 173 patients (59,68,76), whereas 2 trials with 142 patients (78,82) reported a lack of effectiveness. There were no placebo-controlled trials available with lidocaine, and one trial (71), with the addition of mepivacaine, showed a lack of effectiveness. Appendix Table 5 shows the data.

A meta-analysis (Tables 3 and 4) shows results of pain relief and functional status improvement of placebo-controlled trials of epidural steroids with saline or bupivacaine with follow-up data of 3 months and 6 months. Among the 9 placebo-controlled trials, 3 trials (58,68,76) were excluded from the meta-analysis as Dilke et al (58) presented pain relief on an ordinal scale, Wilson-McDonald et al (68) lacked data which could be used in meta-analysis, and Ghahreman et al (76) showed baseline and one month follow-up data, with later follow-up data not amenable for meta-analysis.

Among 5 studies with a total of 763 patients, steroid was mixed with saline in 2 studies with 232 patients (29,47) and with bupivacaine in 3 studies with 531 patients (59,78,82). There was no difference between placebo- and steroid-treated groups with either steroid mixed with saline or steroid mixed with bupivacaine as shown in Table 3A.

As shown in Table 3B, only 3 studies with 462 patients utilizing a mixture of bupivacaine with steroids (47,59,78) met inclusion criteria and provided data for meta-analysis with 6 month follow-up. They showed no difference between placebo and steroid with bupivacaine treated groups of patients.

Functional improvement is shown in Table 4. Short-term follow-up is shown in Table 4A and long-term follow-up of 6 months in Table 4B, with no difference between placebo and steroid solutions mixed with saline or bupivacaine.

Multiple active-controlled trials assessed the role of local anesthetic alone compared to local anesthetic with steroids. Among these, Friedly et al (72) was excluded as the outcomes were provided only for a 6 week time point. In addition, Riew et al (79), which also was excluded from the meta-analysis, did not provide data on pain relief and functional status.

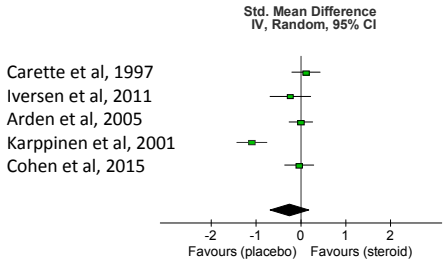
Table 2. *Methodological quality assessment of epidural injections with caudal, interlaminar, and transforaminal approaches in managing pain of disc herniation/radiculitis and spinal stenosis.*

Trial	Present Analysis			Concordance and Discordance of Results.	
	Cochrane Criteria	IPM-QRB Criteria	Quality Grading (high, moderate, low) Cochrane/IPM-QRB	Based on Cochrane Review Criteria by Chou et al	Present Analysis Compared with Chou et al's Analysis
Carette et al (29)	11/12	27/48	High/Moderate	Fair	3
Iversen et al (47)	7/12	28/48	Moderate	Good	2
Manchikanti et al (48)	10/12	44/48	High	Fair	3
Sayegh et al (49)	10/12	28/48	High/Moderate	Fair	3
Ackerman & Ahmad (50)	7/12	25/48	Moderate	Fair	1
Dashfield et al (51)	9/12	33/48	High	NA	NA
Murakibhavi & Khemka (52)	7/12	27/48	Moderate	NA	NA
Manchikanti et al (53)	11/12	44/48	High	Fair	3
Park et al (54)	10/12	33/48	High	Fair	3
Huda et al (55)	8/12	23/48	High/Moderate	Fair	3
Béliveau (56)	6/12	15/48	Moderate/Low	Poor	3
Datta & Upadhyay (57)	7/12	20/48	Moderate	Poor	3
Dilke et al (58)	8/12	28/48	High/Moderate	Fair	3
Arden et al (59)	9/12	31/48	High/Moderate	Fair	3
Manchikanti et al (60)	10/12	44/48	High	Poor	4
Lee et al (61)	6/12	28/48	Moderate	NA	NA
Ghai et al (62)	9/12	39/48	High	NA	NA
Rados et al (63)	8/12	30/48	High/Moderate	Fair	3
Park et al (64)	10/12	34/48	High	NA	NA
Amr (65)	11/12	38/48	High	NA	NA
Pirbudak et al (66)	12/12	35/48	High	NA	NA
Ghai et al (67)	9/12	42/48	High	Good	1
Wilson-MacDonald et al (68)	10/12	31/48	High/Moderate	Fair	3
Candido et al (69)	9/12	37/48	High	Fair	3
Manchikanti et al (70)	10/12	43/48	High	NA	NA
Fukusaki et al (71)	5/12	18/48	Moderate	Poor	3
Friedly et al (72)	9/12	30/48	High/Moderate	Good	1
Vad et al (73)	4/12	16/48	Moderate	NA	NA
Manchikanti et al (74)	10/12	44/48	High	Poor	4
Koh et al (75)	9/12	32/48	High	NA	NA
Ghahreman et al (76)	11/12	37/48	High	Good	1
Jeong et al (77)	9/12	31/48	High/Moderate	Fair	3
Karppinen et al (78)	12/12	34/48	High	Good	1
Riew et al (79)	8/12	32/48	High	Fair	3
Tafazal et al (80)	10/12	32/48	High	Fair	3
Ng et al (81)	11/12	37/48	High	Fair	3
Cohen et al (82)	5/12	26/48	Moderate	NA	NA
Becker et al (83)	6/12	26/48	Moderate	Fair	3
Kennedy et al (84)	9/12	30/48	High	Fair	3

Key for 1 - 4: 1 = Correlation of present criteria with Chou et al's analysis; 2 = Discordance with Chou et al's criteria being higher; 3 = Discordance with Chou et al's criteria being lower; 4 = Discordance with Chou et al's criteria being poor from high.

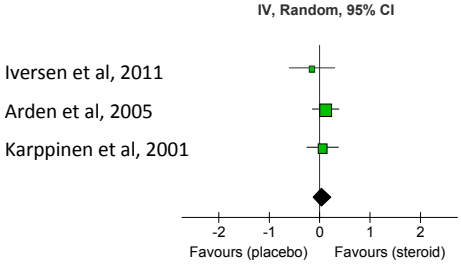
Table 3. *Results of pain relief of placebo-controlled trials of epidural steroids with saline or bupivacaine.*

Study	Steroid with Sodium Chloride Solution or Bupivacaine			Placebo			Weight	Std. Mean Difference
	Mean	SD	Total	Mean	SD	Total		IV, Fixed, 95% CI
Carette et al, 1997 (29) Saline with steroid	2.6	3.6	77	2.3	3.4	79	20.40%	0.11(-0.20,0.43)
Iversen et al, 2011 (47) Saline with steroid	6.6	5	37	7.8	5	39	18.30%	-0.24 (-0.69, 0.21)
Arden et al, 2005 (59) Steroid with bupivacaine	4.7	5	120	4.7	5	108	21.10%	0.00 (-0.26, 0.26)
Karppinen et al, 2001 (78) Steroid with bupivacaine	2.6	1	79	3.7	1	79	20.10%	-1.09 (-1.43, -0.76)
Cohen et al, 2015 (82) Steroid with bupivacaine	1	2.5	72	1.1	2.7	73	20.20%	-0.04 (-0.36, 0.29)
Total (95% CI)			385			378	100.00%	-0.25 (-0.68,0.18)
Heterogeneity: Chi² = 34.45, df = 4 (P < 0.00001); I² = 88%								
Test for overall effect: Z = 1.13 (P = 0.26)								



A. Short term follow-up with minimum 3 months of pain relief.

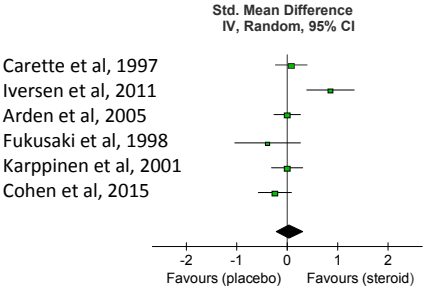
Study	Steroid with Sodium Chloride Solution or Bupivacaine			Placebo			Weight	Std. Mean Difference
	Mean	SD	Total	Mean	SD	Total		IV, Fixed, 95% CI
Iversen et al, 2011 (47)	0	12	37	2	14	39	16.40%	-0.15 (-0.60, 0.30)
Arden et al, 2005 (59)	4.9	5	120	4.3	5	108	49.30%	0.12 (-0.14, 0.38)
Karppinen et al, 2001 (78)	2.3	5	78	2	5	80	34.30%	0.06 (-0.25, 0.37)
Total (95% CI)			235			227	100.00%	0.05 (-0.13, 0.24)
Heterogeneity: Chi² = 0.75, df = 2 (P = 0.69); I² = 0%								
Test for overall effect: Z = 0.58 (P = 0.56)								



B. Long-term follow-up of 6 months of pain relief.

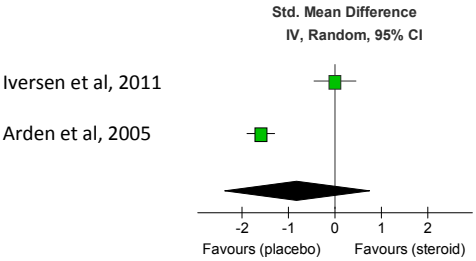
Table 4. *Results of functional status improvement of placebo control trials of epidural steroids with saline or bupivacaine.*

Study	Steroid with Sodium Chloride Solution or Bupivacaine			Placebo			Weight	Std. Mean Difference
	Mean	SD	Total	Mean	SD	Total		IV, Fixed, 95% CI
Carette et al, 1997 (29)	17.3	20.6	77	15.4	25.5	79	18.60%	0.08(-0.23, 0.40)
Iversen et al, 2011 (47)	4	3	37	1.4	3	39	14.00%	0.86 (0.39, 1.33)
Arden et al, 2005 (59)	32	5	120	32	5	108	20.30%	0.00 (-0.26, 0.26)
Fukusaki et al, 1998 (71)	10	8	19	13	7	18	10.00%	-0.39 (-0.04, 0.26)
Karppinen et al, 2001 (78)	20	5	80	20	5	80	18.80%	0.00 (-0.31, 0.31)
Cohen et al, 2015 (82)	6.2	15.8	73	10.2	16.7	72	18.20%	-0.24 (-0.57, 0.08)
Total (95% CI)			406			396	100.00%	0.05 (-0.21, 0.32)
Heterogeneity: Chi² = 14.89, df = 5 (P = 0.007); I² = 68%								
Test for overall effect: Z = 0.39 (P = 0.70)								



A. Long term follow-up of 3 months of functional status.

Study	Steroid with Sodium Chloride Solution or Bupivacaine			Placebo			Weight	Std. Mean Difference
	Mean	SD	Total	Mean	SD	Total		IV, Fixed, 95% CI
Iversen et al, 2011 (47)	1.9	8.2	39	1.9	4.2	37	49.40%	0.00 (-0.45, 0.45)
Arden et al, 2005 (59)	31	5	108	39	5	120	50.60%	-1.59 (-1.89, 1.30)
Total (95% CI)			147			157	100.00%	-0.81 (-2.37, 0.76)
Heterogeneity: Chi² = 24.24, df = 1 (P < 0.00001); I² = 96%								
Test for overall effect: Z = 1.01 (P < 0.31)								



B. Long-term follow-up of 6 months of functional status.

There were 7 trials assessing lidocaine as a sole agent or lidocaine with steroids (48,49,53,60,62,70,74) and 3 trials (79-81) assessing bupivacaine alone in comparison to bupivacaine with steroid. All 3 of the bupivacaine trials showed positive results with similar results shown in 2 trials by Tafazal et al (80) and Ng et al (81); however, Riew et al (79) showed positive results only with bupivacaine combined with steroid to avoid surgical interventions. Since there were only 2 trials of bupivacaine eligible for inclusion, meta-analysis included only 7 active-controlled trials comparing lidocaine alone to lidocaine with steroids.

Based on a qualitative synthesis of evidence of 7 active-controlled trials comparing lidocaine to lidocaine with steroid, effectiveness was equal in both groups except in disc herniation where potential superiority was demonstrated.

Tables 5 and 6 show the data on active-controlled trials with assessment of the non-inferiority of lidocaine to lidocaine with steroid.

As shown in Table 5A, 6 studies with 649 patients were utilized for pain improvement ratings (48,53,60,62,70,74), comparing lidocaine to lidocaine with steroid. They showed no difference in pain improvement between both groups at 3 or 12 months.

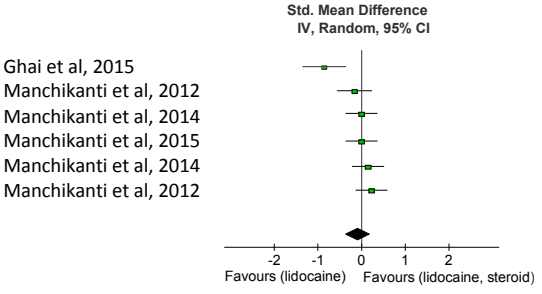
Functional status was also assessed with inclusion of 6 studies at 3 months and 7 studies at 12 months (Table 6) (48,49,53,60,62,70,74) showing no difference in functional improvement between lidocaine alone or lidocaine with steroid at 3 or 12 months. This analysis showed the effectiveness of lidocaine and lidocaine with steroid for pain relief and functional status at 3 months and also 12 months with results slightly favoring local anesthetic alone.

Discussion

This systematic review, with qualitative and quantitative analysis, shows a lack of effectiveness for epidural steroid injections administered in combination with sodium chloride solution or bupivacaine, which contradicts the results of Chou et al (22,23) and also fails to support the assumption that therapeutic effects in epidural steroids are primarily related to the corticosteroid (22,23). Utilizing a qualitative analysis, there is good evidence, based on 3 randomized controlled trials (29,47,71) with inclusion of 131 patients, that there is no significant effect for epidural corticosteroids administered with a mixture of sodium chloride solution

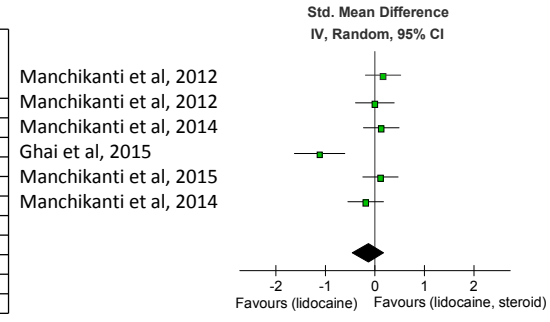
Table 5. *Results of pain relief improvement of active-control trials of epidural lidocaine compared with epidural lidocaine with steroids.*

Study	Lidocaine, steroid with Sodium Chloride Solution or Bupivacaine			Lidocaine only			Weight	Std. Mean Difference
	Mean	SD	Total	Mean	SD	Total		IV, Fixed, 95% CI
Manchikanti et al, 2012 (48)	4.4	1.7	60	4	1.8	60	17.50%	0.23 (-0.13, 0.59)
Manchikanti et al, 2012 (53)	3.5	1.9	50	3.8	1.8	50	16.40%	-0.16 (-0.55, 0.23)
Manchikanti et al, 2014 (60)	4.5	1	60	4.3	1.6	60	17.50%	0.15 (-0.21, 0.51)
Ghai et al, 2015 (62)	3.5	1.6	35	4.8	1.4	34	13.50%	-0.86 (-1.35, -0.36)
Manchikanti et al, 2015 (70)	4.3	1.5	60	4.3	1.3	60	17.50%	0.00 (-0.36, 0.36)
Manchikanti et al, 2014 (74)	4.2	1.5	60	4.2	1.8	60	17.50%	0.00 (-0.36, 0.36)
Total (95% CI)			325			324	100.00%	-0.08 (-0.34, 0.19)
Heterogeneity: Chi² = 14.12, df = 5 (P = 0.01); I² = 65%								
Test for overall effect: Z = 0.57 (P = 0.57)								



A. Short term follow-up with minimum 3 months of pain relief.

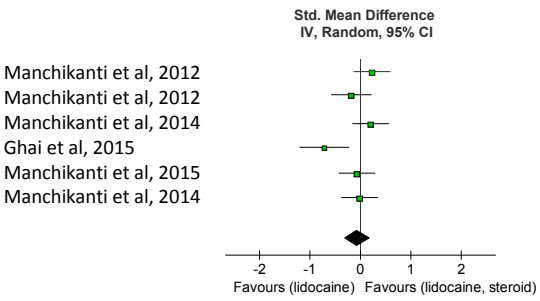
Study	Lidocaine, steroid with Sodium Chloride Solution or Bupivacaine			Lidocaine only			Weight	Std. Mean Difference
	Mean	SD	Total	Mean	SD	Total		IV, Fixed, 95% CI
Manchikanti et al, 2012 (48)	4.2	1.8	60	3.9	1.8	60	17.30%	0.17 (-0.19, 0.52)
Manchikanti et al, 2012 (53)	3.4	2	50	3.4	1.8	50	16.60%	0.00 (-0.39, 0.39)
Manchikanti et al, 2014 (60)	4.3	1.4	60	4.1	1.7	60	17.30%	0.13 (-0.23, 0.41)
Ghai et al, 2015 (62)	3.6	1.6	35	5.3	1.4	34	14.10%	-1.12 (-1.63, -0.61)
Manchikanti et al, 2015 (70)	4.4	1.7	60	4.2	1.8	60	17.30%	0.11 (-0.24, 0.47)
Manchikanti et al, 2014 (74)	4	1.6	60	4.3	1.6	60	17.30%	-0.19 (-0.54, 0.17)
Total (95% CI)			325			324	100.00%	-0.12 (-0.44, 0.20)
Heterogeneity: Chi² = 23.37, df = 5 (P = 0.0003); I² = 79%								
Test for overall effect: Z = 0.74 (P = 0.46)								



B. Long-term follow-up of 6 months of pain relief.

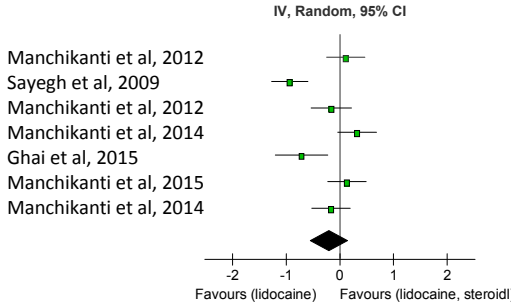
Table 6. *Results of functional status improvement of active control trials of epidural lidocaine compared with epidural lidocaine with steroids.*

Study	Lidocaine, steroid with Sodium Chloride Solution or Bupivacaine			Lidocaine only			Weight	Std. Mean Difference
	Mean	SD	Total	Mean	SD	Total		IV, Fixed, 95% CI
Manchikanti et al, 2012 (48)	14.3	6.5	60	12.7	7.2	60	17.60%	0.23 (-0.13, 0.59)
Manchikanti et al, 2012 (53)	11.3	7.4	50	12.6	6.8	50	16.30%	-0.18 (-0.57, 0.21)
Manchikanti et al, 2014 (60)	15.6	4.2	60	14.5	6.3	60	17.60%	0.20(-0.15, 0.56)
Ghai et al, 2015 (62)	18.8	14.3	35	28.6	12.8	34	13.20%	-0.71(-1.20, 0..23)
Manchikanti et al, 2015 (70)	15.3	6.2	60	15.7	5.3	60	17.60%	-0.07 (-0.43, 0.29)
Manchikanti et al, 2014 (74)	13.3	6.4	60	13.4	7.2	60	17.60%	-0.01 (-0.37, 0.34)
Total (95% CI)			325			324	100.00%	0.06 (-0.30, 0.18)
Heterogeneity: Chi² = 12.89, df = 5 (P = 0.02); I² = 61%								
Test for overall effect: Z = 0.51 (P = 0.61)								



A. Short term follow-up with minimum 3 months of functional status improvement

Study	Lidocaine, steroid with Sodium Chloride Solution or Bupivacaine			Lidocaine only			Weight	Std. Mean Difference
	Mean	SD	Total	Mean	SD	Total		IV, Fixed, 95% CI
Manchikanti et al, 2012 (48)	14.4	7.2	60	13.6	7.3	60	14.50%	0.11 (-0.25, 0.47)
Sayegh et al, 2009 (49)	4.9	7.1	81	13	10.1	70	14.80%	-0.93 (-1.27, -0.60)
Manchikanti et al, 2012 (53)	11.1	7.6	50	12.3	7.3	60	14.30%	-0.16 (-0.54, 0.22)
Manchikanti et al, 2014 (60)	16.1	4.8	60	14.2	6.8	60	14.50%	0.33 (-0.04, 0.68)
Ghai et al, 2015 (62)	19.8	14.3	35	29.6	12.8	34	12.80%	-0.71 (-1.20, -0.23)
Manchikanti et al, 2015 (70)	16.8	6.4	60	15.9	7.2	60	14.50%	0.13 (-0.23, 0.49)
Manchikanti et al, 2014 (74)	13.9	6.5	60	15	6.9	60	14.50%	-0.16 (-0.52, 0.20)
Total (95% CI)			406			404	100.00%	-0.19 (-0.54, 0.15)
Heterogeneity: Chi² = 42.96, df = 6 (P < 0.00001); I² = 86%								
Test for overall effect: Z = 1.10 (P = 0.27)								



B. Long-term follow-up of 12 months of functional status improvement.

– meaning an epidural steroid administered alone without local anesthetic. There is very low level evidence, based on one trial with short-term effect at 3 months with the inclusion of 50 patients (58), that a mixture of steroid with sodium chloride solution may be effective. The combination of steroids with bupivacaine demonstrated no effect based on 2 trials with 142 patients (78,82) who received steroid with bupivacaine, whereas 3 trials showed a very short-term effect of 3 to 6 weeks with the inclusion of 173 patients (59,68,76). However, a quantitative analysis with inclusion of 5 trials showed a lack of effectiveness for steroid mixed with sodium chloride solution or bupivacaine (29,47,59,78,82). Thus, there is significant evidence to show a lack of effectiveness of epidural steroid injections mixed with sodium chloride solution and moderate evidence to show that bupivacaine mixed with steroid is ineffective. In contrast, comparing active-controlled trials with lidocaine alone to lidocaine with steroid showed significant efficacy for lidocaine alone and lidocaine with steroids for pain and function with a minimum 12-month follow-up (48,49,53,60,62,70,74). Further, a quantitative analysis with a non-inferiority assessment of lidocaine also showed similar efficacy with lidocaine alone compared to lidocaine with steroids. Based on the qualitative analysis, there is evidence for the efficacy of bupivacaine and bupivacaine with steroids (79-81); however, with limited trials and a lack of data amenable for meta-analysis, a quantitative analysis was not feasible.

These results contrast with those recently published by Chou et al (23). Chou et al (23) utilized a novel theory converting active-controlled trials into placebo-controlled trials to prove their hypothesis that epidural steroids do not work. The reported rationale for epidural steroids is that they reduce inflammation around nerve roots; however, has not been proven and is considered as a post hoc argument (119). Proponents of corticosteroids described efficacy, based on hypothesis of inflammation, derived from postmortem studies and operative experience showing the inflammation of lumbar nerve roots. However, thus far there is no definitive evidence to show a response from steroids

based on inflammatory or noninflammatory lumbar radiculopathy. Thus, other factors may play an active role. In fact, it has been reported that steroids have a reversible local anesthetic effect, producing the perceived benefit with epidural injections in addition to or rather than anti-inflammatory effect (120-125). In addition, other postulated mechanisms of action of local anesthetics and steroids with their effect on multiple pathophysiologic mechanisms of chronic pain include noxious peripheral stimulation, excess nociception, resulting in the sensitization of the pain pathways at several neuronal levels, phenotype changes as part of neural plasticity, and excess release of neurotransmitters causing complex central responses including hyperalgesia or wind up (16-20,126-129). In fact, local anesthetics alone were utilized without steroids from 1901 to 1953 (7,9,14,15), until the role of steroids was described (12,13) and thereafter (16-20,130). Further, experimental evidence also shows the prolonged effect of epidural ropivacaine in a rat model of neuropathic pain (131) and lack of additional benefit in nerve root infiltration for lumbar disc herniation with the addition of corticosteroids (132).

Active-controlled trials with use of local anesthetics alone or local anesthetic with steroid represent practical aspects. Conversion of these active-controlled trials to placebo-controlled trials, reaching conclusions of the lack of effectiveness based on the lack of difference between 2 groups, due to non-inferiority, despite substantial improvement in these patients with baseline assessments, is in contradiction to the principles of comparative effectiveness research. In fact, comparative effectiveness research has been defined as research designed to discover which interventions were best, under what circumstances, for whom, and at what cost (133,134). Further, comparative effectiveness research methods include not only RCTs, but also active-controlled trials, nonrandomized comparison studies, prospective and retrospective observational studies, along with multiple other data including meta-analysis (135). In the age of a lack of evidence of effectiveness for a majority of the interventions used in spinal pain, active-controlled trials are crucial; however, misinterpretation of these trials as placebo-controlled trials does not advance scientific methodology. Meta-analysis is a valuable form of comparative effectiveness research (135); however, it is crucial to understand that comparative effectiveness research as in active-controlled trials are non-inferiority or equivalence trials, aiming to determine the extent to which interventions are effective, not whether they are better than control conditions. The emphasis must be on the effect size of the intervention rather than the differences in the effect sizes of the interventions. Inappropriate methodology as utilized by Chou et al (23) leads to not only inappropriate conclusions, but may significantly affect access to often effective modalities and also the advancement of science. Further, the cost utility analysis of caudal epidural injections showed favorable results at a quality-adjusted life year (QALY) of $2,200 (136).

In reference to the placebo effect, there is overwhelming literature describing placebo and nocebo effects and their influence not only in experimental evidence generation, but specifically in pain (137-146). There is widespread information specifically from the National Institute of Health (NIH) indicating various favorable and unfavorable consequences of placebo and nocebo aspects. Instead of calling all responses placebo, clinicians must recognize the importance of placebos and their therapeutic effect (137-140,146-148). In addition, there is extensive literature discussing various perceptions, acceptability, efficacy, and utilization of placebos in clinical treatments (146-152). It is essential that clinicians understand the role of placebos and nocebos in treating pain.

Managing bias and conflict of interest in conducting a systematic review is crucial. While the major focus appears to surround the financial conflicts of interest based on industry sponsorship, very little attention has been focused towards professional or intellectual bias. The IOM (31) has defined "gold standard" practices for creating guidelines and systematic reviews (153). However, despite many of the reviews of the systematic reviews and participants of AHRQ from the authorship of the IOM manuals, routinely attempt to design rules to fit their needs and also alter them based on settings to favor their conclusions. IOM has specifically described to eliminate perceived potential or actual professional or intellectual bias. Certainly, there are multiple circumstances that create a risk that professional judgement or action regarding a primary interest will be unduly influenced by a secondary interest not only by private physicians and practitioners, but also academicians, policy makers, and agencies and the authors influencing these agencies. It is a well known fact that many authors fail to fully disclose their conflicts of interest despite the disclosure policies. Further, while it has been a standard practice to disclose financial conflicts and it is not a requirement for researchers, policy makers, and policy advisors to disclose intellectual and pro-

fessional biases that may be similarly influential (154). Consequently, the NIH and others have revised their policies for managing financial conflicts of interest in biomedical research to improve compliance, strengthen oversight, and expand transparency in this area (155). This has resulted in statements to disclose any other relationships or activities that readers could perceive to influence, or that give the appearance of potentially influencing the research such as personal, professional, political, institutional, religious, other associations (156,157). The Cochrane Collaboration also requires members of the review team to disclose competing interests "when they judge relevant." Similarly, the Patient-Centered Outcomes Research Institute (PCORI), requires individuals serving on the board of governors, the methodology committee, and expert advisory panels to disclose both financial and personal associations (157-160). Secondary interest has been described as the pursuit of professional advancement, future funding opportunities, and recognition, and desire to do favors for friends and colleagues (161). Despite all these requirements, there has been lack of transparency in publications, specifically in major journal, academics, manuscripts published by governmental agencies including IOM, AHRQ, and authors of the manuscripts related to authoritative publications from AHRQ, IOM, and others (23,24,32,33). This was clearly shown in recent publication (34) entitled Confluence, Not Conflict of Interest, describing the necessity for the name change. Cappola and FitzGerald (34) have defined confluence of interest versus conflict of interest and have shown the potential bias extending far beyond the investigator and the sponsor, but which included the departments, research institutes, universities, multiple nonprofit funders such as NIH and foundations, as well as the journals that might, for example, generate advertising revenue from sponsors. Despite the clear descriptions, Cappola and FitzGerald have missed multiple other influences exerted with intellectual bias and confluence of interest by authors providing the same opinions benefiting them and some of the hidden sponsors over and over again without real analysis of the literature. The reviews by Chou et al, are perfect examples embodying the confluence of interest, as well as many publications in major journals considered as high impact which generally only publish negative manuscripts from those playing dual roles of policy making along with hidden advocacy (22,23,32,33,51,72,82,86,162-166). Our systematic review/meta-analysis makes extensive efforts to minimize such conflicts, intellectual bias, and confluence of interest with inclusion of clinicians, academicians, and methodologists. In addition, it is also important to identify the differences between facts, opinions, beliefs, and prejudice. While facts are verifiable and evidence can be researched, an opinion is a judgement based on facts, even though it is an honest attempt to draw a reasonable conclusion from factual evidence. Unlike an opinion, a belief is a conviction based on cultural or personal faith or values, but prejudice is an opinion based on insufficient or unexamined evidence beyond opinion or conviction.

Conclusion

In conclusion, this systematic review with appropriate design and methodological quality assessment, and utilization of clinically meaningful measures, shows that epidural steroids with sodium chloride solution or bupivacaine may not be effective, whereas, either lidocaine alone or lidocaine with steroid have shown significant evidence of efficacy both in radiculopathy and spinal stenosis.

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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 (38).

Appendix 3. *Methodological quality assessment of randomized trials utilizing Cochrane review criteria.*

	Manchikanti et al (48)	Ackerman & Ahmad (50)	Dashfield et al (51)	Iversen et al (47)	Murakibhavi & Khemka (52)	Manchikanti et al (53)	Sayegh et al (49)	Park et al (54)	Lee et al (61)	Rados et al (63)
Randomization adequate	Y	N	Y	Y	Y	Y	Y	Y	N	Y
Concealed treatment allocation	Y	N	Y	Y	N	Y	Y	Y	N	N
Patient blinded	Y	N	Y	Y	Y	Y	Y	Y	N	N
Care provider blinded	N	N	N	N	N	Y	Y	N	N	N
Outcome assessor blinded	N	N	N	U	N	N	Y	N	N	N
Drop-out rate described	Y	Y	Y	Y	Y	Y	N	Y	Y	Y
All randomized participants analyzed in the group	Y	Y	Y	N	Y	Y	N	Y	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	Y	Y	Y	N	N	Y	Y	Y	Y	Y
Co-interventions avoided or similar	Y	Y	N	Y	N	Y	Y	Y	Y	Y
Compliance acceptable in all group	Y	Y	Y	N	Y	Y	Y	Y	Y	Y
Time of outcome assessment in all groups similar	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Score	10/12	7/12	9/12	7/12	7/12	11/12	10/12	10/12	6/12	8/12

Y = Yes; N = No; U = Unclear

Source: Furlan AD, et al; 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 (37).

Appendix 3 (Continued). *Methodological quality assessment of randomized trials utilizing Cochrane review criteria.*

	Amr (65)	Dilke et al (58)	Pirbudak et al (66)	Arden et al (59)	Carette et al (29)	Wilson-MacDonald et al (68)	Fukasaki et al (71)	Manchikanti et al (70)	Manchikanti et al (60)	Ghahreman et al (76)
Randomization adequate	Y	N	Y	Y	Y	Y	N	Y	Y	Y
Concealed treatment allocation	Y	N	Y	Y	Y	Y	N	Y	Y	Y
Patient blinded	Y	Y	Y	Y	Y	Y	N	Y	Y	Y
Care provider blinded	Y	N	Y	N	N	N	N	Y	Y	Y
Outcome assessor blinded	Y	Y	Y	Y	Y	Y	U	N	N	Y
Drop-out rate described	Y	Y	Y	Y	Y	Y	N	Y	Y	Y
All randomized participants analyzed in the group	N	Y	Y	N	Y	Y	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	N	Y	Y	Y	N	Y	N	N	N
Co-interventions avoided or similar	Y	Y	Y	Y	Y	Y	N	Y	Y	Y
Compliance acceptable in all group	Y	Y	Y	N	Y	Y	Y	Y	Y	Y
Time of outcome assessment in all groups similar	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Score	11/12	8/12	12/12	9/12	11/12	10/12	5/12	10/12	10/12	11/12

	Karppinen et al (81)	**Jeong et al (77)**	**Riew et al (79)**	**Ng et al (81)**	**Tafazal et al (80)**	**Vad et al (73)**	**Manchikanti et al (74)**	**Park et al (64)**	**Koh et al (75)**	**Friedly et al (72)**
Randomization adequate	Y	U	U	Y	Y	U	Y	Y	Y	Y
Concealed treatment allocation	Y	U	U	Y	Y	N	Y	Y	Y	Y
Patient blinded	Y	Y	Y	Y	Y	N	Y	Y	Y	Y
Care provider blinded	Y	N	N	N	Y	N	Y	N	N	N
Outcome assessor blinded	Y	Y	Y	Y	N	U	N	N	N	N
Drop-out rate described	Y	Y	Y	Y	Y	N	Y	Y	Y	Y
All randomized participants analyzed in the group	Y	Y	Y	Y	N	N	Y	Y	N	Y
Reports of the study free of suggestion of selective outcome reporting	Y	Y	Y	Y	Y	Y	Y	Y	Y	N
Groups similar at baseline regarding most important prognostic indicators	Y	Y	U	Y	Y	Y	N	Y	Y	Y
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	U	Y	Y	Y	Y
Time of outcome assessment in all groups similar	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Score	12/12	9/12	8/12	11/12	10/12	4/12	10/12	10/12	9/12	9/12

Y = Yes; N = No; U = Unclear

Source: Furlan AD, et al; 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 (37).

Appendix 3 (Continued). *Methodological quality assessment of randomized trials utilizing Cochrane review criteria.*

	Ghai et al (67)	**Ghai et al (62)**	**Cohen et al (82)**	**Datta & Upadhyay (57)**	**Candido et al (69)**	**Béliveau (56)**	**Huda et al (55)**	**Kennedy et al (84)**	**Becker et al (83)**
Randomization adequate	Y	Y	Y	Y	Y	N	Y	Y	N
Concealed treatment allocation	Y	Y	Y	Y	Y	N	N	Y	N
Patient blinded	N	Y	N	N	N	N	N	N	N
Care provider blinded	N	N	N	N	N	N	N	N	N
Outcome assessor blinded	N	N	N	N	N	N	N	N	N
Drop-out rate described	Y	N	N	N	Y	Y	Y	Y	Y
All randomized participants analyzed in the group	Y	Y	N	Y	Y	Y	Y	Y	Y
Reports of the study free of suggestion of selective outcome reporting	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
Co-interventions avoided or similar	Y	Y	Y	Y	Y	U	Y	Y	U
Compliance acceptable in all group	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
Score	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, et al; 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 (37).

Appendix 4. *Methodological quality assessment of randomized trials utilizing IPM – QRB.*

		Manchikanti et al (48)	Ackerman & Ahmad (50)	Dashfield et al (51)	Iversen et al (47)	Murakibhavi & Khemka (52)	Manchikanti et al (53)	Sayegh et al (49)	Park et al (54)	Lee et al (61)	Rados et al (63)
I.	TRIAL DESIGN AND GUIDANCE REPORTING										
1.	CONSORT or SPIRIT	3	0	1	2	2	3	2	2	2	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	2	1	1	1	3
4.	Imaging	3	3	3	1	3	3	0	3	3	3
5.	Sample Size	3	1	1	2	2	3	3	3	1	1
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	1	1	1	1
8.	Duration of Pain	2	1	2	1	1	2	0	0	1	2
9.	Previous Treatments	2	0	0	0	0	2	0	0	2	0
10.	Duration of Follow-up with Appropriate Interventions	3	2	2	1	1	3	1	1	1	2
IV.	OUTCOMES										
11.	Outcomes Assessment Criteria for Significant Improvement	4	1	2	0	4	4	2	2	2	2
12.	Analysis of all Randomized Participants in the Groups	2	2	2	2	2	2	0	2	2	2
13.	Description of Drop Out Rate	2	2	2	1	2	2	0	2	1	2
14.	Similarity of Groups at Baseline for Important Prognostic Indicators	1	1	1	0	0	1	2	2	1	2
15.	Role of Co-Interventions	1	1	1	1	0	1	1	0	1	1
V.	RANDOMIZATION										
16.	Method of Randomization	2	0	2	2	0	2	2	2	0	2
VI.	ALLOCATION CONCEALMENT										
17.	Concealed Treatment Allocation	2	0	2	2	2	2	2	2	0	0
VII.	BLINDING										
18.	Patient Blinding	1	0	1	1	1	1	1	1	0	0
19.	Care Provider Blinding	1	0	0	0	0	1	1	0	0	0
20.	Outcome Assessor Blinding	0	0	0	0	0	0	1	0	0	0
VIII.	CONFLICTS OF INTEREST										
21.	Funding and Sponsorship	2	1	2	3	0	2	2	3	3	0
22.	Conflicts of Interest	3	3	3	3	1	3	3	3	3	2
TOTAL		44	25	33	28	27	44	28	33	28	30

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 (38).

Appendix 4 (Continued). *Methodological quality assessment of randomized trials utilizing IPM – QRB.*

		Amr (65)	Dilke et al (58)	Pirbudak et al (66)	Arden et al (59)	Carette et al (29)	Wilson-MacDonald et al (68)	Fukasaki et al (71)	Manchikanti et al (70)	Manchikanti et al (60)	Ghahreman et al (76)
I.	TRIAL DESIGN AND GUIDANCE REPORTING										
1.	CONSORT or SPIRIT	2	0	2	3	1	3	0	3	3	3
II.	DESIGN FACTORS										
2.	Type and Design of Trial	2	3	2	3	2	2	2	2	2	2
3.	Setting/Physician	3	2	2	1	2	1	1	2	2	2
4.	Imaging	3	0	0	0	0	0	0	3	3	3
5.	Sample Size	3	3	2	3	3	0	0	3	3	2
6.	Statistical Methodology	1	1	1	1	1	1	1	1	1	1
III.	PATIENT FACTORS										
7.	Inclusiveness of Population	2	2	2	2	2	1	2	2	2	2
8.	Duration of Pain	2	0	2	1	0	2	1	2	2	1
9.	Previous Treatments	2	0	2	0	0	2	0	2	2	0
10.	Duration of Follow-up with Appropriate Interventions	3	1	2	0	0	1	1	3	3	0
IV.	OUTCOMES										
11.	Outcomes Assessment Criteria for Significant Improvement	2	2	2	2	0	2	1	4	4	4
12.	Analysis of all Randomized Participants in the Groups	1	2	2	1	2	2	1	2	2	2
13.	Description of Drop Out Rate	2	2	2	2	1	1	1	2	2	2
14.	Similarity of Groups at Baseline for Important Prognostic Indicators	2	2	2	2	1	1	1	0	1	1
15.	Role of Co-Interventions	1	1	1	0	0	1	0	1	1	0
V.	RANDOMIZATION										
16.	Method of Randomization	2	1	2	2	2	2	1	2	2	2
VI.	ALLOCATION CONCEALMENT										
17.	Concealed Treatment Allocation	2	1	2	2	2	2	0	2	2	2
VII.	BLINDING										
18.	Patient Blinding	1	1	1	1	1	1	0	1	1	1
19.	Care Provider Blinding	1	0	1	0	0	0	0	1	1	1
20.	Outcome Assessor Blinding	1	1	1	1	1	1	0	0	0	1
VIII.	CONFLICTS OF INTEREST										
21.	Funding and Sponsorship	0	0	0	3	3	2	2	2	2	2
22.	Conflicts of Interest	0	3	2	1	3	3	3	3	3	3
TOTAL		38	28	35	31	27	31	18	43	44	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 (38).

Appendix 4 (Continued). *Methodological quality assessment of randomized trials utilizing IPM – QRB.*

		Karppinen et al (78)	Jeong et al (77)	Riew et al (79)	Ng et al (81)	Tafazal et al (80)	Vad et al (73)	Manchikanti et al (74)	Park et al (64)	Koh et al (75)
I.	TRIAL DESIGN AND GUIDANCE REPORTING									
1.	CONSORT or SPIRIT	2	2	1	2	2	1	3	2	2
II.	DESIGN FACTORS									
2.	Type and Design of Trial	2	2	2	2	2	2	2	2	2
3.	Setting/Physician	1	1	1	1	1	1	2	1	2
4.	Imaging	3	3	3	3	3	2	3	3	3
5.	Sample Size	3	3	2	2	1	1	3	3	1
6.	Statistical Methodology	1	1	1	1	1	1	1	1	1
III.	PATIENT FACTORS									
7.	Inclusiveness of Population	2	1	2	2	1	2	2	1	1
8.	Duration of Pain	0	0	1	2	1	0	2	0	1
9.	Previous Treatments	0	0	2	2	2	0	2	0	0
10.	Duration of Follow-up with Appropriate Interventions	1	2	2	1	1	1	3	1	2
IV.	OUTCOMES									
11.	Outcomes Assessment Criteria for Significant Improvement	2	2	1	1	2	2	4	2	2
12.	Analysis of all Randomized Participants in the Groups	2	2	2	2	1	0	2	2	0
13.	Description of Drop Out Rate	1	2	2	2	1	0	2	2	2
14.	Similarity of Groups at Baseline for Important Prognostic Indicators	2	2	2	2	1	0	1	2	2
15.	Role of Co-Interventions	0	1	0	1	1	1	1	0	1
V.	RANDOMIZATION									
16.	Method of Randomization	2	1	1	2	2	0	2	2	2
VI.	ALLOCATION CONCEALMENT									
17.	Concealed Treatment Allocation	2	0	0	2	2	0	2	2	2
VII.	BLINDING									
18.	Patient Blinding	1	1	1	1	1	0	1	2	1
19.	Care Provider Blinding	1	0	1	1	1	0	1	0	1
20.	Outcome Assessor Blinding	1	1	0	0	0	0	0	0	0
VIII.	CONFLICTS OF INTEREST									
21.	Funding and Sponsorship	2	2	2	2	2	0	2	3	2
22.	Conflicts of Interest	3	2	3	3	3	2	3	3	2
TOTAL		34	31	32	37	32	16	44	34	32

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 (38).

Appendix 4 (Continued). *Methodological quality assessment of randomized trials utilizing IPM – QRB.*

		Friedly et al (72)	Ghai et al (67)	Ghai et al (62)	Cohen et al (82)	Datta & Upadhyay (57)	Candido et al (69)	Béliveau (56)	Huda et al (55)	Kennedy et al (84)	Becker et al (83)
I.	TRIAL DESIGN AND GUIDANCE REPORTING										
1.	CONSORT or SPIRIT	3	3	3	3	1	2	0	1	3	1
II.	DESIGN FACTORS										
2.	Type and Design of Trial	2	2	2	3	2	2	2	2	2	2
3.	Setting/Physician	2	2	2	2	2	2	1	2	2	1
4.	Imaging	3	3	3	3	0	3	0	0	3	3
5.	Sample Size	3	2	2	1	2	2	1	2	2	2
6.	Statistical Methodology	0	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	2
8.	Duration of Pain	1	2	1	1	1	1	0	1	0	1
9.	Previous Treatments	1	2	1	0	0	2	0	2	2	2
10.	Duration of Follow-up with Appropriate Interventions	0	3	3	0	1	2	1	1	1	1
IV.	OUTCOMES										
11.	Outcomes Assessment Criteria for Significant Improvement	0	4	4	0	2	2	2	2	2	2
12.	Analysis of all Randomized Participants in the Groups	2	2	2	0	1	2	2	2	2	2
13.	Description of Drop Out Rate	2	2	0	0	0	2	2	1	1	1
14.	Similarity of Groups at Baseline for Important Prognostic Indicators	2	2	2	2	1	2	2	2	2	2
15.	Role of Co-Interventions	0	1	1	0	0	1	0	1	1	1
V.	RANDOMIZATION										
16.	Method of Randomization	2	2	2	2	2	2	0	1	2	0
VI.	ALLOCATION CONCEALMENT										
17.	Concealed Treatment Allocation	2	2	2	2	2	2	0	0	2	0
VII.	BLINDING										
18.	Patient Blinding	0	0	1	0	0	0	0	0	0	0
19.	Care Provider Blinding	0	0	0	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	3	2	2	2	0	2	0	0	0	2
22.	Conflicts of Interest	1	3	3	3	0	3	0	0	0	0
TOTAL		30	42	39	26	20	37	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 (38).

Appendix 5. *Assessment of placebo-control epidural injections in managing lumbosacral disc herniation or radiculopathy and spinal stenosis.*

Study Study Characteristics Methodological Quality Scoring	Participants and Interventions	Outcome Measures	Pain Relief and Function and Results				Comparative Comment(s) with Chou et al (22,23)
			3 mos.	6 mos.	12 mos.	24 mos.	
CAUDAL							
Iversen et al, 2011 (47) RA, PC, UL Disc herniation or radiculopathy Quality Scores: Cochrane = 7/12 IPM-QRB = 28/48 Chou et al (23) = Good	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 Lack of efficacy	No significant difference Lack of efficacy	No significant difference Lack of efficacy	NA NA	• Negative results for sham injections and both epidural saline and epidural steroids in a study with numerous deficiencies with a flawed design with and without local anesthetic. • Injections were administered initially. • Chou et al (23) rated as "good" compared to moderate in this assessment.
INTERLAMINAR							
Carette et al, 1997 (29) RA, B, PC Disc herniation or radiculopathy Quality Scores: Cochrane = 11/12 IPM-QRB = 27/48 Chou et al (23) = Fair	Total = 158 Methylprednisolone = 78 Placebo = 80 Isotonic saline vs depo methylprednisolone and isotonic saline Number of injections: 1 to 3	VAS and ODI Follow-up: 3 months	NSI Lack of effectiveness of epidural steroid with saline	NA NA	NA NA	NA 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.
Dilke et al, 1973 (58) RA, B, PC Disc herniation or radiculopathy Quality Scores: Cochrane = 8/12 IPM-QRB = 28/48 Chou et al (23) = Fair	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% No significant effect of steroid	NA NA	NA NA	NA NA	• Placebo control trial with lack of response. •
Arden et al, 2005 (59) RA, B, PC Disc herniation or radiculopathy Quality Scores: Cochrane = 9/12 IPM-QRB = 31/48 Chou et al (23) = Fair	Total = 228 Steroid group = 120 Placebo group = 108 Triamcinolone and bupivacaine or normal saline into interspinous ligament Number of injections: 1	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 Lack of effect with both solutions	NSI Lack of effectiveness of bupivacaine with triamcinolone	NSI Lack of effectiveness of bupivacaine with triamcinolone	NA NA	• Lack of efficacy after 6 weeks • Meaningful follow-up only 3 months • 50% improvement not considered • Limited procedures with probably appropriate response for one injection Chou et al (23) considered 12 month follow-up.

Appendix 5 (continued). ***Assessment of placebo-control epidural injections in managing lumbosacral disc herniation or radiculopathy and spinal stenosis.***

Study Study Characteristics Methodological Quality Scoring	Participants and Interventions	Outcome Measures	Pain Relief and Function and Results				Comparative Comment(s) with Chou et al (22,23)
			3 mos.	6 mos.	12 mos.	24 mos.	
Wilson-MacDonald et al, 2005 (68) RA, B, PC Disc herniation or radiculopathy Quality Scores: Cochrane = 10/12 IPM-QRB = 31/48 Chou et al (23) = Fair	Total = 92 Epidural group = 44 Control group = 48 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 Follow-up: 6 weeks in all patients	SI in the treatment group Showed effectiveness of epidural steroid with local anesthetic	U NA	U NA	U 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 • Chou et al (23) have not separated disc herniation from spinal stenosis group of patients.
Fukusaki et al, 1998 (71) RA, B, AC, PC Spinal stenosis Quality Scores: Cochrane = 5/12 IPM-QRB = 18/48 Chou et al (23) = Poor	Total = 53 Epidural saline = 16 Mepivacaine = 18 Mepivacaine and methylprednisolone = 19 Saline or mepivacaine or a 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% Lack of effectiveness all groups	NA NA	NA 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.
TRANSFORAMINAL							
Ghahreman et al, 2010 (76) RA, PC, F Disc herniation or radiculopathy Quality Scores: Cochrane = 11/12 IPM-QRB = 37/48 Chou et al (23) = Good	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% Effectiveness only in steroids with local anesthetic.	NA NA	NA 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). • Even then, Chou et al (23) considered follow-up as 12 months.

Appendix 5 (continued). ***Assessment of placebo-control epidural injections in managing lumbosacral disc herniation or radiculopathy and spinal stenosis.***

Study Study Characteristics Methodological Quality Scoring	Participants and Interventions	Outcome Measures	Pain Relief and Function and Results				Comparative Comment(s) with Chou et al (22,23)
			3 mos.	6 mos.	12 mos.	24 mos.	
Karppinen et al, 2001 (78) RA, PC, F Disc herniation or radiculopathy Quality Scores: Cochrane = 12/12 IPM-QRB = 34/48 Chou et al (23) = Good	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. Lack of effectiveness of steroid with bupivacaine	The treatment effects in both leg pain and back pain favored the saline treatment. Lack of effectiveness of steroid with bupivacaine	There were no treatment effects in favor of either treatment. Lack of effectiveness of steroid with bupivacaine	NA 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.
Cohen et al, 2015 (82) RA, PC, F Disc herniation or radiculopathy Quality Scores: Cochrane = 5/12 IPM-QRB = 26/48 Chou et al (23) = NA	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 Lack of effectiveness of steroids with bupivacaine.	NA NA	NA 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. • This trial was not included by Chou et al (23)

RA = Randomized; PC = Placebo control; UL = Ultrasound; B = Blind; AC = Active-control; F = Fluoroscopy; IPM-QRB = Interventional Pain Management Techniques - Quality Appraisal of Reliability and Risk of Bias Assessment; ODI = Oswestry Disability Index; EQLS = European quality of life measure; VAS = Visual Analogue Scale; SF-36 = Short Form (36) Health Survey; NRS = Numeric Rating Scale; ODQ = Oswestry low back pain disability questionnaire; NSI = No significant improvement; LA = local anesthetic; NA = Not applicable; P = Positive

Appendix 6. *Assessment of active control epidural injections with local anesthetic in managing disc herniation or radiculopathy and spinal stenosis.*

Study Study Characteristics Methodological Quality Scoring	Participants and Interventions	Outcome Measures	Pain Relief and Function and Results				Comparative Comment(s) with Chou et al (22,23)
			3 mos.	6 mos.	12 mos.	24 mos.	
CAUDAL							
Manchikanti et al, 2012 (48) RA, AC, F Disc herniation or radiculopathy Quality Scores: Cochrane = 10/12 IPM-QRB = 44/48 Chou et al (23) = Fair	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: Lidocaine 62% vs. lidocaine with steroid 72% Responsive: Lidocaine 77% vs lidocaine with steroid 80% Lidocaine & lidocaine with steroid effective	Overall: Lidocaine 72% vs. lidocaine with steroid 73% Responsive: Lidocaine 87% vs. lidocaine with steroid 86% Lidocaine & lidocaine with steroid effective	Overall: Lidocaine 67% vs. lidocaine with steroid 72% Responsive: Lidocaine 85% vs. lidocaine with steroid 84% Lidocaine & lidocaine with steroid effective	Overall: Lidocaine 60% vs. lidocaine with steroid 65% Responsive: Lidocaine 77% vs. lidocaine with steroid 76% Lidocaine & lidocaine with steroid effective	• Positive double-blind randomized trial with some 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. • Chou et al (23) inappropriately converted Lidocaine arm to placebo. • The trial clearly presented imaging findings and indications, yet Chou et al (23) misinformed the readers and misinterpreted available findings. • Chou et al (23) downgraded the methodological quality scoring with inappropriate reasoning.

Appendix 6 (continued). ***Assessment of active control epidural injections with local anesthetic in managing disc herniation or radiculopathy and spinal stenosis.***

Study Study Characteristics Methodological Quality Scoring	Participants and Interventions	Outcome Measures	Pain Relief and Function and Results				Comparative Comment(s) with Chou et al (22,23)
			3 mos.	6 mos.	12 mos.	24 mos.	
Sayegh et al, 2009 (49) RA, AC, B Disc herniation or radiculopathy Quality Scores: Cochrane = 10/12 IPM-QRB = 28/48 Chou et al (23) = Fair	Total = 183 Local anesthetic (lidocaine) = 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 (lidocaine) = 23.5 LA (lidocaine)with steroid = 8.7 Negative straight leg raising: LA (lidocaine) 51% versus LA (lidocaine) with steroid 73% LA (lidocaine) & LA (lidocaine) with steroid effective – steroid superior	Mean ODI: LA (lidocaine) = 13.6 LA (lidocaine) with steroid = 5.8 Negative straight leg raising: LA (lidocaine) 68% versus LA (lidocaine) with steroid 84% LA (lidocaine) & LA (lidocaine) with steroid effective – steroid superior	Mean ODI: LA (lidocaine) = 13.0 LA (lidocaine) with steroid = 4.91 Negative straight leg raising: LA (lidocaine) 71% versus LA (lidocaine) with steroid 85% 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.
Manchikanti et al, 2012 (53) RA, AC, F Central spinal stenosis Quality Scores: Cochrane = 11/12 IPM-QRB = 44/48 Chou et al (23) = Fair	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% Both treatments effective	Overall: LA 54% vs LA with steroid 50% Responsive: LA 73% vs. LA with steroid 68% Both treatments effective	Overall: LA 44% vs LA with steroid 46% Responsive: LA 54% vs. LA with steroid 62% Both treatments effective	Overall: LA 38% vs LA with steroid 44% Responsive: LA 51% vs LA with steroid 57% 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. • The trial clearly presented imaging findings and indications, yet Chou et al (23) misinformed the readers and misinterpreted available findings. • Chou et al (23) downgraded the methodological quality scoring with inappropriate reasoning.

Appendix 6 (continued). ***Assessment of active control epidural injections with local anesthetic in managing disc herniation or radiculopathy and spinal stenosis.***

Study Study Characteristics Methodological Quality Scoring	Participants and Interventions	Outcome Measures	Pain Relief and Function and Results				Comparative Comment(s) with Chou et al (22,23)
			3 mos.	6 mos.	12 mos.	24 mos.	
Béliveau, 1971 (56) RA, AC, B Disc herniation or radiculopathy Quality Scores: Cochrane = 6/12 IPM-QRB = 15/48 Chou et al (23) = Poor	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	• 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. Chou et al showed follow-up as one week. The procedure was performed pre-fluoroscopy era.
INTERLAMINAR							
Manchikanti et al, 2014 (60) RA, AC, F Disc herniation or radiculopathy Quality Scores: Cochrane = 10/12 IPM-QRB = 44/48 Chou et al (23) = Poor	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% Both treatments are effective	Overall: Lidocaine 63% vs. lidocaine with steroid 85% Responsive: Lidocaine 76% vs. lidocaine with steroid 86% Both treatments are effective	Overall: Lidocaine 67% vs. lidocaine with steroid 85% Responsive: Lidocaine 80% vs. lidocaine with steroid 86% Both treatments are effective	Overall: Lidocaine 60% vs lidocaine with steroid 70% Responsive: Lidocaine 72% vs. lidocaine with steroid 71% 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. • Despite including 3 manuscripts, Chou et al (23) considered this as a one-year study instead of 2 years. • Inappropriately downgraded the evidence from good to poor. • The trial clearly presented imaging findings and indications, yet Chou et al (23) misinformed the readers and misinterpreted available findings.

Appendix 6 (continued). ***Assessment of active control epidural injections with local anesthetic in managing disc herniation or radiculopathy and spinal stenosis.***

Study Study Characteristics Methodological Quality Scoring	Participants and Interventions	Outcome Measures	Pain Relief and Function and Results				Comparative Comment(s) with Chou et al (22,23)
			3 mos.	6 mos.	12 mos.	24 mos.	
Ghai et al, 2015 (62) RA, AC, F Disc herniation or radiculopathy Quality Scores: Cochrane = 9/12 IPM-QRB = 39/48 Chou et al (23) = NA	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% Both arms effective. Steroids superior	Lidocaine: 56% Lidocaine with methylprednisolone: 86% Both arms effective. Steroids superior	Lidocaine: 59% Lidocaine with methylprednisolone: 89% Both arms effective. Steroids superior	NA 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. • Chou et al's (23) search missed this manuscript.
Manchikanti et al, 2015 (70) RA, AC, F Central spinal stenosis Quality Scores: Cochrane = 10/12 IPM-QRB = 43/48 Chou et al (23) = Fair	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% Both treatments effective	Overall: LA 72% vs LA with steroid 75% Responsive: LA 78% vs LA with steroid 83% Both treatments effective	Overall: LA 77% vs LA with steroid 67% Responsive: LA 84% vs LA with steroid 71% Both treatments effective	Overall: LA 72% vs LA with steroid 73% Responsive: LA 84% vs LA with steroid 85% 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. • Chou et al (23) failed to identify 24 month follow-up even though it was published. • Chou et al (23) converted local anesthetic group into placebo and also inappropriately downgraded the quality scores. • The trial clearly presented imaging findings and indications, yet Chou et al (23) misinformed the readers and misinterpreted available findings.

Appendix 6 (continued). ***Assessment of active control epidural injections with local anesthetic in managing disc herniation or radiculopathy and spinal stenosis.***

Study Study Characteristics Methodological Quality Scoring	Participants and Interventions	Outcome Measures	Pain Relief and Function and Results				Comparative Comment(s) with Chou et al (22,23)
			3 mos.	6 mos.	12 mos.	24 mos.	
INTERLAMINAR AND TRANSFORAMINAL							
Friedly et al, 2014 (72) RA, AC, F Central and foraminal spinal stenosis Quality Scores: Cochrane = 9/12 IPM-QRB = 30/48 Chou et al (23) = Good	Total = 400 Lidocaine: Transforaminal = 61 Interlaminar = 139 Lidocaine with steroid: Transforaminal = 57 Interlaminar = 143 Lidocaine alone or glucocorticoid plus lidocaine Variable doses	NRS, RMDQ Follow-up: 6 weeks	Interlaminar: Both treatments effective with superiority of steroid with lidocaine Transforaminal: Neither lidocaine nor lidocaine with steroids was effective at 3 and 6 weeks.	NA NA	NA NA	NA NA	• Large trial with inappropriate design and assessment. • Based on inappropriate analysis, the results were negative. • Multiple issues include not only the design and analysis of the data, but patient selection, technical considerations, inherent bias, and complications. • The inclusion criteria was inappropriate with combination of central stenosis and foraminal stenosis.
TRANSFORAMINAL							
Manchikanti et al, 2014 (74) RA, AC, F Disc herniation or radiculopathy Quality Scores: Cochrane = 10/12 IPM-QRB = 44/48 Chou et al (23) = Poor	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% Effectiveness in both groups. Lidocaine alone or with steroids effective.	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%	• 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. • Inappropriate conversion of active-control to placebo control by Chou et al (23). • Improper methodological quality with significant downgrading from good to poor by Chou et al (23). • The trial clearly presented imaging findings and indications, yet Chou et al (23) misinformed the readers and misinterpreted available findings.

Appendix 6 (continued). *Assessment of active control epidural injections with local anesthetic in managing disc herniation or radiculopathy and spinal stenosis.*

Study Study Characteristics Methodological Quality Scoring	Participants and Interventions	Outcome Measures	Pain Relief and Function and Results				Comparative Comment(s) with Chou et al (22,23)
			3 mos.	6 mos.	12 mos.	24 mos.	
Riew et al, 2000 (79) RA, AC, F Disc herniation or radiculopathy Quality Scores: Cochrane = 8/12 IPM-QRB = 32/48 Chou et al (23) = Fair	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	NA NA	33% in bupivacaine group vs. 71% in bupivacaine with betamethasone avoided surgery.	NA 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. • Local anesthetic with steroids were superior to local anesthetic alone. • Chou et al (23) tried to use data over longer period. • Lack of correlation of methodological quality with downgrading by Chou et al (23).
Tafazal et al, 2009 (80) RA, AC, F Disc herniation or radiculopathy and spinal stenosis (foraminal) Quality Scores: Cochrane = 10/12 IPM-QRB = 32/48 Chou et al (23) = Fair	Total: 150 patients Lumbar disc herniation = 76 Stenosis = 48 Local anesthetic = 34/25 Local anesthetic with steroid = 42/23 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 Outcomes: Excellent to poor	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 Excellent to good outcomes in 54% Bupivacaine alone and bupivacaine with steroid are both effective	NA 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 NA	• Relatively small study with effectiveness illustrated in disc herniation and stenosis. • Patients with lumbar spinal stenosis responded less markedly compared to those of disc herniation. • 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. • Chou et al (23) inappropriately converted this trial into placebo control. • Chou et al (23) also has not utilized the results for spinal stenosis. • Chou et al (23) also combined this trial with the trial by Ng et al (81) which is a different trial from the same institution.

Appendix 6 (continued). ***Assessment of active control epidural injections with local anesthetic in managing disc herniation or radiculopathy and spinal stenosis.***

Study Study Characteristics Methodological Quality Scoring	Participants and Interventions	Outcome Measures	Pain Relief and Function and Results				Comparative Comment(s) with Chou et al (22,23)
			3 mos.	6 mos.	12 mos.	24 mos.	
Ng et al, 2005 (81) RA, AC, F Disc herniation or radiculopathy and spinal stenosis (foraminal) Quality Scores: Cochrane = 11/12 IPM-QRB = 37/48 Chou et al (23) = Fair	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% Bupivacaine alone and bupivacaine plus steroid were equally effective	NA NA	NA NA	NA NA	• Positive results in a small study with short-term follow-up. • Chou et al (23) described this study along with Tafazal et al (73) even though both are 2 separate independent studies. • 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. • Chou et al converted this into a placebo control trial. • The response in disc herniation and stenosis was similar.

RA = Randomized; AC = Active-control; DB = Double-blind; B = Blind; F = Fluoroscopy; IPM-QRB = Interventional Pain Management Techniques - Quality Appraisal of Reliability and Risk of Bias Assessment; NRS = Numeric Rating Scale; ODI = Oswestry Disability Index; RMDQ = Roland-Morris Disability questionnaire; LBOS = Low back outcome score; LA = local anesthetic; NA = Not applicable

Appendix 7. *Assessment of active control trials comparing technique and dose response of injected drugs of epidural injections in managing disc herniation or radiculopathy and spinal stenosis.*

Study **Study Characteristics** **Methodological Quality Scoring**	**Participants and Interventions**	**Outcome Measures**	**Pain Relief and Function and Results**				**Comparative Comment(s) with Chou et al (22,23)**
			3 mos.	**6 mos.**	**12 mos.**	**24 mos.**	
Ackerman & Ahmad, 2007 (50) RA, AC, F Disc herniation or radiculopathy Quality Scores: Cochrane = 7/12 IPM-QRB = 25/48 Chou et al (23) = Fair	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% Effective in all arms	Caudal = 57% Interlaminar = 60% Transforaminal = 83% Effective in all arms	NA NA	NA NA	• Positive mid-term results in a relatively small trial. • Shows effectiveness of steroids with all approaches with superiority of transforaminal compared to caudal and interlaminar.
Dashfield et al, 2005 (51) RA, AC, F Disc herniation or radiculopathy Quality Scores: Cochrane = 9/12 IPM-QRB = 33/48 Chou et al (22) = Fair	Total = 60 Caudal = 30 Endoscopy =30 Lidocaine with triamcinolone Number of injections: 1	Pain relief, SF-MPQ, HADS scores	SI Lidocaine with triamcinolone effective	SI Lidocaine with triamcinolone effective	NA NA	NA NA	• Positive mid-term results in a relatively small trial. • Chou et al (22) utilized this study in assessment of the evidence in Technology Assessment. However, they (23) excluded this study from the systematic review.
Park et al, 2013 (54) RA, AC, F Spinal stenosis Quality Scores: Cochrane = 10/12 IPM-QRB = 33/48 Chou et al (23) = Fair	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% Effectiveness shown both with ultrasound and fluoroscopy with lidocaine and dexamethasone	NA NA	NA NA	NA NA	• Positive short-term results with ultrasound and fluoroscopy.
Huda et al, 2010 (55) RA, AC, B Spinal stenosis Quality Scores: Cochrane = 8/12 IPM-QRB =23/48 Chou et al (23) = Fair	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% Both drugs mixed with bupivacaine were effective	Triamcinolone = 40 Methylprednisolone = 68.5% Methylprednisolone superior	NA	NA	• Relatively small study without fluoroscopy published in 2010 with a caudal approach utilizing high volumes of injectate showing positive results with triamcinolone or methylprednisolone mixed with bupivacaine.

Appendix 7 (continued). *Assessment of active control trials comparing technique and dose response of injected drugs of epidural injections in managing disc herniation or radiculopathy and spinal stenosis.*

Study **Study Characteristics** **Methodological Quality Scoring**	**Participants and Interventions**	**Outcome Measures**	**Pain Relief and Function and Results**				**Comparative Comment(s) with Chou et al (22,23)**
			3 mos.	**6 mos.**	**12 mos.**	**24 mos.**	
Datta & Upadhyay, 2011 (57) RA, AC, B Disc herniation or radiculopathy Quality Scores: Cochrane = 7/12 IPM-QRB = 20/48 Chou et al (23) = Poor	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% 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.
Lee et al, 2009 (61) RA, AC, F Spinal stenosis Quality Scores: Cochrane = 6/12 IPM-QRB = 28/48 Chou et al (23) = NA	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 Both arms effective. Transforaminal somewhat superior	NA NA	NA NA	NA NA	• Short-term follow-up with positive results, with inability to draw conclusions. • Lack of placebo controlled group. • Chou et al (23) have not included this trial.
Rados et al, 2011 (63) RA, AC, F Disc herniation or radiculopathy Quality Scores: Cochrane = 8/12 IPM-QRB = 30/48 Chou et al (23) = Fair	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 = 53% Transforaminal = 63% Effective with both approaches	NA NA	NA NA	• Positive results with short follow-up period in comparison of 2 approaches with lidocaine with methylprednisolone

Appendix 7 (continued). *Assessment of active control trials comparing technique and dose response of injected drugs of epidural injections in managing disc herniation or radiculopathy and spinal stenosis.*

Study **Study Characteristics** **Methodological Quality Scoring**	**Participants and Interventions**	**Outcome Measures**	**Pain Relief and Function and Results**				**Comparative Comment(s) with Chou et al (22,23)**
			3 mos.	**6 mos.**	**12 mos.**	**24 mos.**	
Park et al, 2012 (64) RA, AC, F Spinal stenosis Quality Scores: Cochrane = 10/12 IPM-QRB = 34/48 Chou et al (23) = NA	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 Both approaches effective	NA NA	NA NA	NA NA	• Relatively small trial with similar and positive results with both techniques. • Chou et al (23) excluded this manuscript from inclusion in their analysis.
Ghai et al, 2014 (67) RA, AC, F Disc herniation or radiculopathy Quality Scores: Cochrane = 9/12 IPM-QRB = 42/48 Chou et al (23) = Good	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% Effectiveness in both arms	PIL group: 75% Transforaminal group: 77% Effectiveness in both arms	PIL group: 69% Transforaminal group: 77% Effectiveness in both arms	NA 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 (69) RA, AC, F Disc herniation or radiculopathy Quality Scores: Cochrane = 9/12 IPM-QRB = 37/48 Chou et al (23) = Fair	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	• 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 (continued). *Assessment of active control trials comparing technique and dose response of injected drugs of epidural injections in managing disc herniation or radiculopathy and spinal stenosis.*

Study **Study Characteristics** **Methodological Quality Scoring**	**Participants and Interventions**	**Outcome Measures**	**Pain Relief and Function and Results**				**Comparative Comment(s) with Chou et al (22,23)**
			3 mos.	**6 mos.**	**12 mos.**	**24 mos.**	
Friedly et al, 2014 (72) RA, AC, F Central and foraminal spinal stenosis Quality Scores: Cochrane = 9/12 IPM-QRB = 30/48 Chou et al (23) = Good	Total = 400 Lidocaine: Transforaminal = 62 Interlaminar = 139 Lidocaine with steroid: Transforaminal = 57 Interlaminar = 143 Lidocaine alone or glucocorticoid plus lidocaine Variable doses	NRS, RMDQ Follow-up: 6 weeks	Transforaminal: No significant difference was reported between local anesthetic and steroid with RMDQ scores or NRS for leg pain. Both treatments effective Interlaminar: 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. Both treatments effective with superiority of steroid with lidocaine	NA NA	NA NA	NA NA	• Large trial with inappropriate design and assessment with positive results at 3 months. • Based on inappropriate analysis, the results were negative. • Multiple issues include not only the design and analysis of the data, but patient selection, technical considerations, inherent bias, and complications. • The inclusion criteria was inappropriate with combination of central stenosis and foraminal stenosis.
Vad et al, 2002 (73) RA, AC, F Disc herniation or radiculopathy Quality Scores: Cochrane = 4/12 IPM-QRB = 16/48 Chou et al (23) = NA	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 lidocaine. 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 Transforaminal steroids with lidocaine effective	In transforaminal group 84% showed improvement. In trigger point injection group 48% showed improvement Transforaminal steroids with lidocaine effective	In transforaminal group 84% showed improvement. In trigger point injection group 48% showed improvement. Transforaminal steroids with lidocaine effective	NA 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 7 (continued). *Assessment of active control trials comparing technique and dose response of injected drugs of epidural injections in managing disc herniation or radiculopathy and spinal stenosis.*

Study **Study Characteristics** **Methodological Quality Scoring**	**Participants and Interventions**	**Outcome Measures**	**Pain Relief and Function and Results**				**Comparative Comment(s) with Chou et al (22,23)**
			3 mos.	**6 mos.**	**12 mos.**	**24 mos.**	
Koh et al, 2013 (75) RA, AC, F Spinal stenosis Quality Scores: Cochrane = 9/12 IPM-QRB = 32/48 Chou et al (23) = NA	Total = 53 Control = 26 Intervention = 27 Both groups 2 mL of 1% lidocaine with 1,500 units 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% Local anesthetic with triamcinolone, hypertonic saline, and hyaluronidase more effective than local anesthetic with triamcinolone	NA NA	NA NA	NA NA	Small trial with short-term positive results. Hypertonic saline may prolong improvement.
Jeong et al, 2007 (77) RA, AC, F Disc herniation or radiculopathy Quality Scores: Cochrane = 9/12 IPM-QRB = 31/48 Chou et al (23) = Fair	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: ≥ 6 months	NA NA	Preganglionic = 60.4% Ganglionic = 67.2% Both approaches effective	NA NA	NA NA	• Moderate quality study with mid-term positive results. • Similar results with both approaches
Becker et al, 2007 (83) RA, AC, F Disc herniation or radiculopathy Quality Scores: Cochrane = 6/12 IPM-QRB = 26/48 Chou et al (23) = Fair	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.	Significant improvement in all groups with autologous condition serum superior to steroids.	NA	NA	• Small study with short-term follow-up. • At 26 week follow-up, steroids with local anesthetic and autologous serum were effective
Kennedy et al, 2014 (84) RA, AC, F Disc herniation or radiculopathy Quality Scores: Cochrane = 9/12 IPM-QRB = 30/48 Chou et al (23) = Fair	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 Both drugs effective	Dexamethasone group 73% reduction in pain scores, 71% reduction in ODI scores Triamcinolone group 76% reduction in pain scores, 65% reduction in ODI scores Both drugs effective	NA NA	NA NA	• This is one of the studies showing effectiveness of steroids without local anesthetic. • Relatively small study with short-term follow-up only. • Particulate and nonparticulate steroids were equally effective.

Appendix 7 (continued). *Assessment of active control trials comparing technique and dose response of injected drugs of epidural injections in managing disc herniation or radiculopathy and spinal stenosis.*

Study **Study Characteristics** **Methodological Quality Scoring**	**Participants and Interventions**	**Outcome Measures**	**Pain Relief and Function and Results**				**Comparative Comment(s) with Chou et al (22,23)**
			3 mos.	**6 mos.**	**12 mos.**	**24 mos.**	
Amr, 2011 (65) RA, AC, F Disc herniation or radiculopathy Quality Scores: Cochrane = 11/12 IPM-QRB = 38/48 Chou et al (23) = NA	Total = 200 Local anesthetic + steroid = 100 Local anesthetic + steroid + ketamine = 100 Bupivacaine with 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 Effective with addition of ketamine to bupivacaine and triamcinolone	SI in ketamine group Effective with addition of ketamine to bupivacaine and triamcinolone	SI in ketamine group Effective with addition of ketamine to bupivacaine and triamcinolone	NA NA	• Positive randomized trial for ketamine with long-term follow-up • Chou et al (23) excluded despite 1 year follow-up
Pirbudak et al, 2003 (66) RA, B, AC Disc herniation or radiculopathy Quality Scores: Cochrane = 12/12 IPM-QRB = 35/48 Chou et al (23) = NA	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 Epidural steroids effective in both arms with superiority with amitriptyline	SI in both groups Epidural steroids effective in both arms with superiority with amitriptyline	NA NA	NA NA	• Active control trial with positive results with betamethasone and bupivacaine with addition of amitriptyline. • Chou et al (23) excluded this trial.
Murakibhavi & Khemka, 2011 (52) Disc herniation or radiculopathy RA, NTC, F Quality Scores: Cochrane = 7/12 IPM-QRB = 27/48 Chou et al (23) = NA	Group A = 50 control conservative management Group B = 52 caudal epidural with lidocaine and methylprednisolone injection Total = 102 patients Conservative management or caudal epidural steroid injections	VAS, ODI, BDI, NPI	Group A = 32% Group B = 92% Steroids effective	Group A = 24% Group B = 86% Steroids effective	NA NA	NA NA	• Positive short-term results. • Not included by Chou et al (23)

RA = Randomized; AC = Active-control; F = Fluoroscopy; B = Blind; NTC = No treatment control; IPM-QRB = Interventional Pain Management Techniques - Quality Appraisal of Reliability and Risk of Bias Assessment; PIL = parasagittal interlaminar; ODI = Oswestry Disability Index; BDI = Beck Depression Inventory; SF-MPQ = Short form McGill Pain questionnaire; HADS = Hospital anxiety depression score; VAS = Visual Analogue Scale; NPI = Numerical pain intensity; NRS = Numeric Rating Scale; RMDQ = Roland-Morris Disability questionnaire; PSI = Patient Satisfaction Index; VNS = Visual numeric pain scale; INR = international normalized ratio; NA = Not applicable; SI = significant improvement

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