International Centre for Allied Health Evidence

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Systematic Review of the Literature

The Effectiveness of Lumbar Epidural Injection of Steroid via a Transforaminal approach

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Abbreviations

The following abbreviations are used in this report and are collated here for readers convenience

Abbreviation		Abbreviation	
AHCPR	Agency for Health Care Policy and Research	**PICO**	Population, Intervention, Comparator, Outcome
CI	Confidence Interval	**PLA2**	Phospholipase A2
CT	Computer Tomography	**RCT**	Randomised Controlled trial
FL	Fluoroscopy	**RF**	Radiofrequency
IL	Interlaminar	**RMQ**	Roland Morris Questionnaire
ILESI	Interlaminar Lumbar Epidural Steroid Injection	**SIGN**	Scottish Intercollegiate Guidelines Network
L1-5	Lumbar levels 1 - 5	**SPECT**	Single Photon Emission Computed Tomography
LBP	Low Back Pain	**SR**	Systematic Review
LEI	Lumbar Epidural Injection	**TF**	Transforaminal
LESI	Lumbar Epidural Steroid Injection	**TFLESI**	Transforaminal Lumbar Epidural Steroid Injection
MRI	Magnetic Resonance Imaging	**UK RCGP**	United Kingdom Royal College of General Practitioner
NRS	Numerical Rating Scale	**US**	Ultrasound
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs	**VA/DoD**	Veterans Affairs/Department of Defence
ODI	Oswestry Disability Index	**VAS**	Visual Analogue Scale
	Quality Ratings		
AQ	Acceptable Quality	**LQ**	Low Quality
CS	Can't say	**NA**	Not Applicable
HQ	High Quality	**R**	Reject (Unacceptable Quality)
QS	Quality of Study		

EXECUTIVE SUMMARY

Objective of the Review	The objective of this systematic review is to synthesise the evidence related to the effectiveness of injection of steroid with or without local anaesthetic to the lumbar epidural space via the transforaminal approach as a form of interventional pain management. In order to review the evidence this review aims to answer the following research questions a) What is the evidence for the effectiveness of steroid injections into the lumbar epidural space via the transforaminal approach with or without local anaesthetic in relieving pain and/or in improving functional outcomes in patients with pain? b) What is the evidence for the safety of steroid injections into the lumbar epidural space via the transforaminal approach with or without local anaesthetic?
Evidence sourced	The search yielded 1,752 articles. After scrutiny, 1693 articles were excluded as duplicates or failing to meet the inclusion criteria (shown in Figure 1), leaving 59 studies for inclusion in this review including 16 Systematic Reviews, 14 randomised controlled trials, 19 cohort studies and 10 case studies.
What is the evidence for the effectiveness of steroid injections into the lumbar epidural space via transforaminal approach in relieving pain and/or in improving functional outcomes in patients with pain?	1. The evidence does not support the use of lumbar epidural steroids injections, via the transforaminal approach, for the first line relief of pain or improving disability in patients with radicular symptoms or low back pain. (Level B) 2. The evidence suggests that the transforaminal approach is effective in reducing pain in patients with radiculopathy, particularly secondary to herniation of nucleus pulposus and particularly in the short term. (Level A) 3. The evidence suggests that the transforaminal approach is not as effective in reducing disability and improving functional outcomes in patients with radiculopathy, particularly secondary to herniation of nucleus pulposus. (Level B) 4. The evidence suggests that the transforaminal approach is more effective in reducing pain due to radiculopathy compared to other approaches. (Level A) 5. For radiculopathy of non-specific causes, the evidence suggests that the optimal approaches for reducing pain and improving functional outcomes are the transforaminal or interlaminar approaches in the short or long term. (Level B) 6. For radiculopathy secondary to herniated disc the evidence suggests that the optimal approach for reducing pain and improving functional outcomes is the transforaminal approach in the short or long term. (Level B) 7. For pain due to a herniated disc, the evidence suggests that all approaches are equally effective in the short-term approach for reducing pain and improving functional outcomes with possibly slightly better long term effects with the transforaminal approach. (Level B)

What is the evidence for the safety of steroid injections into the lumbar epidural space via transforaminal approach?	1. Minor complications associated with lumbar epidural steroids injections, via the transforaminal approach, are not uncommon but rarely require significant medical attention. (Level B) 2. Major complications associated with lumbar epidural steroids injections, via the transforaminal approach, are rare. (Level B) 3. Transforaminal LESIs are associated with a higher incidence of major complications compared to other approaches. (Level B)
What is the evidence for the economic benefit of steroid injections into the lumbar epidural space via transforaminal approach?	The evidence suggests that lumbar epidural steroids injections, via the transforaminal approach, may present a cost-effective intervention in the short term through reducing other health expenditure, reducing the need for expensive surgery and reducing sick days. Any significant cost effectiveness associated with lumbar epidural steroids injections, via the transforaminal approach, is dependent on repeat injections on an as needed basis. (Level C)

1. Background

1.1 Objective of this Review

The objective of this systematic review is to synthesise the evidence related to the effectiveness of injection of steroid with or without local anaesthetic to the lumbar epidural space via a transforaminal approach as a form of interventional pain management.

In order to review the evidence this review aims to answer the following research questions

a) What is the evidence for the effectiveness of steroid injections into the lumbar epidural space via a transforaminal approach with or without local anaesthetic in relieving pain and/or in improving functional outcomes in patients with pain?
b) What is the evidence for the safety of steroid injections into the lumbar epidural space via a transforaminal approach with or without local anaesthetic?

1.2 Description of the Intervention

Epidural injections are one of the most commonly performed procedures in interventional pain medicine (Cohen et al. 2013). Epidural injections for pain management have most commonly included local anaesthetics or steroids. Recently there has been a trend towards the use of other injectates to attempt to augment the effect of the epidural injections, including O_2, N_2O (Turan et al. 2015) and hyaluronidase (Rahimzadeh et al. 2014).

The first therapeutic epidural injection was performed in 1885 by neurologist James Leonard Corning, who injected a local anaesthetic between the lower lumbar spinous in a healthy man to treat ''seminal incontinence''. Since then the use of caudal and lumbar epidural injections for the treatment of low back pain has continued to evolve. The initial injectates used up to the 1950s to treat low back pain involved a mixture of local anaesthetic and saline. The use of corticosteroids to manage low back pain was first recorded in 1953 by Lievre et al., with the first modern controlled trial evaluating epidural steroid injections performed in 1970 by Swerdlow and Sayle-Creer.

Steroids - Rationale

Pure mechanical compression of nerves has been shown to induce painless neurologic deficits such as altered sensation (paresthesia) and motor weakness (Macnab 1971). The generation of pain in the low back, particularly related to radiculopathy is multifactorial, and local inflammation is considered to be a potential factor to be considered. In 1951 Lindahl and Rexed (1951) found histologic evidence of inflammation in nerve root biopsies obtained at surgery from patients suffering from sciatica due to proven disc herniation. Nachemson (1988) noted a fibrinous reaction in the epidural and perineural tissues of some patients undergoing surgery for radicular pain suggesting local inflammation (Nachemson 1988).

Experimental evidence suggests a biochemical source of neural injury in lumbar disc disease. Annular damage (fissures, tears, and herniations) leads to the escape of

nuclear material, which causes an inflammatory reaction, local nociceptor stimulation, potential nerve injury, and subsequently pain. When this occurs by fissures reaching the outer disc annulus, which is innervated, it may serve to explain back pain, and somatic referred pain into the lower limb. When the fissure extends through the annulus, the inflammatory process leads to radicular limb pain. This process may explain those instances of severe radicular pain occurring in the absence of gross neural compression (Cannon and Aprill 2000).

Locally, corticosteroids act to inhibit the inflammatory response induced by mechanical, chemical, or immunologic agents. This inhibition occurs in specific leukocyte functions, including leukocyte aggregation at inflammatory sites, prevention of degranulation of granulocytes, mast cells, and macrophages, and stabilisation of lysosomal and other membranes (Di Rosa et al. 1986). Corticosteroids also inhibit PLA2 activity, therefore interrupting the arachidonic acid cascade. It has also been shown that local application of cortisone blocks transmission in normal nociceptive C-fibres, potentially blocking nociceptive nerves in the manner of local anaesthetics.

Several different steroid preparations may be used, with or without local anaesthetic or normal saline to increase the volume of the injectate. Typical steroids used include methylprednisolone acetate, betamethasone acetate/propionate, and triamcinolone acetate. The benefits of adding a local anaesthetic include potential immediate pain relief for the patient which provides feedback to the practitioner that the steroid solution is near the presumed site of pathology.

Techniques

Lumbar epidural steroid injections (LESI) aim to deliver a steroid preparation into the epidural and perineural spaces of the lumbar spine and can be achieved through three separate routes, the caudal-sacral approach, the interlaminar and the transforaminal approach.

The transforaminal approach delivers injectate into the epidural space to a specific nerve root and the ventral epidural space, using fluoroscopic guidance for precise needle placement. If fluoroscopy is available, and the patient has unilateral signs and symptoms, then the transforaminal route is usually employed. For central and posterolateral disc herniations, the injection is usually performed one level below. For foraminal and extraforaminal disc herniations or foraminal stenosis, the injection is placed at that level.

Cannon and Aprill (2000) suggest that if fluoroscopy was not available, the caudal route was preferable for disc pathology at the L5/S 1 level. For disc levels above L5/S 1, the interlaminar route is usually preferred because it is closer to the pathologic level and given the tendency of solutions injected via the caudal route to not flow above the L4/5 level.

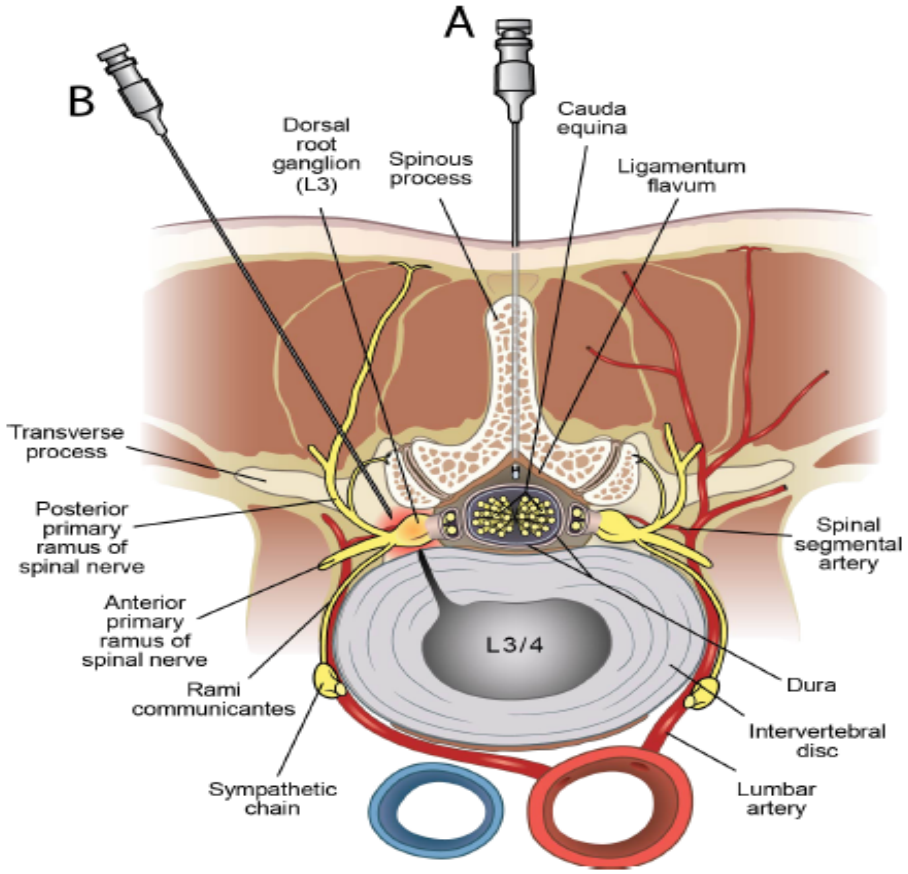

Figure 1: A: Transforaminal Approach
(Adapted from Cohen et al. 2013)

Optimal volume

Even with the use of fluoroscopy and contrast along with traditional injection routes, there is no guarantee that the medication will reach the pathologic site. Bryan et al. (2000) performed a series of 100 caudal LESI using fluoroscopy and contrast and showed that 31% of the injections spread to the dorsal epidural space only (i.e., no ventral flow). Similar problems can occur with the interlaminar approach, which places the medication dorsally without any guarantee that it will flow ventrally or even bilaterally in the epidural space.

For the transforaminal approach, there is less variation in the volume of medication needed to reach the pathologic site. If the needle is placed in the ventral aspect of the root canal, the contrast (and therefore medication) usually flows in the ventral epidural space (Cannon and Aprill 2000).

Indications

Conditions

LESI are done for the relief of pain thought to be arising as a result of inflammation that

affects the neural elements in the epidural and perineural spaces of the spine. Cannon and Aprill (2000) suggested that LESI were most commonly used in patients with radicular pain rather than in those with low back or somatic referred pain.

Radicular pain is characteristic in its quality. It is shooting or lancinating pain that travels down the affected limb in characteristic patterns reminiscent of dermatomes. It is often associated with altered sensation, typically paraesthesia, in a similar distribution and is commonly associated with low back pain or a history of recurring low back pain. The clinical diagnosis is supported by physical findings suggesting nerve root tension.

Somatic referred pain is deep and aching in character and less clearly defined in its distribution. It usually arises from a primary spinal pain generator such as injury or pathology affecting the disc, facet joint, or spinal ligaments. The coexistence of radicular and somatic referred limb pain can confound the diagnostic process and make it harder to predict which patient will have a successful response.

A few studies have looked at which patient characteristics predict a less favourable response to an epidural steroid injection. LESI are usually prescribed in patients with radiculopathy caused by discopathy or degenerative stenosis of the spinal canal (D'Orazio et al. 2015). They have also been used in patients with back pain secondary to spondylosis with or without significant associated radiculopathy. Patients referring an axial pain not irradiating to a specific territory, myofascial pain, or neurogenic claudication and severe or worsening neurological deficit respond less to treatment (D'Orazio et al. 2015).

Acuteness

The optimal time frame for the use of LESI is also a concern. Most patients have had some type of conservative treatment prior to injection. This may have consisted of analgesics, oral steroids, physical therapy, manual medicine, or other modalities. Usually, failure to improve with conservative treatment or severity of symptoms dictates when to intervene.

Response to treatment may depend on the acuteness of the presentation, for example, an injection performed early in the treatment process in a patient with an acute radiculopathy that impairs functional activities and sleep may reduce local inflammation and help prevent epidural and perineural fibrosis, which can occur early and may lead to permanent damage and symptoms.

1.3 Safety/Risk

Although complications are possible with any invasive procedure, LESI are considered relatively safe, with complications uncommon, usually temporary and rarely serious. Potential complications can be related to both the technique and the injected medications. Cannon and Aprill (2000) presented a summary of the common complications involved with epidural steroid injections.

Potential Complications

Technical

1. Temporary exacerbation of pain during injection and after anaesthetic wears off; usually lasts 1 or 2 days before steroids begin to work
2. Dural puncture; should be recognised if done fluoroscopically, thus avoiding injection of medication and spinal block
3. Headache from inadvertent dural puncture or pushing a large volume of solution quickly into the epidural space
4. Vasovagal reactions if injected with a needle
5. Intravascular injection of medication; prevented by using fluoroscopy
6. Potential nerve root injury with improper transforaminal technique
7. Infection*
8. Epidural hematoma

Medication-induced

1. Steroid; anxiety, agitation, insomnia, facial flushing, a feeling of warmth or low-grade fever (usually less than 100 degrees F), headaches, elevated blood sugar for a few days in diabetics, suppression of hypothalamic-pituitary axis for up to 3 months (no adverse effects have been documented), one case report of pseudoallergic reaction.
2. Allergy to anaesthetic or contrast if used

2. Methodology

2.1 Review question

What is the effectiveness of injection of steroid into the lumbar epidural space via the transforaminal approach with or without local anaesthetic as a form of interventional pain management?

2.2 Methods

A systematic review of the published research literature was undertaken to provide a synthesis of the available research evidence related to the effectiveness of lumbar epidural steroid injection via the transforaminal approach with or without local anaesthetic as a form of interventional pain management. All published and accessible research evidence was sought through a systematic and rigorous search strategy. The evidence base for this review included research evidence from existing systematic reviews, meta-analyses, and high-level primary research (randomised controlled trials, prospective cohort studies). Where no systematic reviews, randomised controlled trials or prospective cohort studies were located then other primary study designs (excluding commentary /expert opinion) were considered.

2.3 Search strategy

The search was developed using a standard PICO structure (see Table 1). Only English articles published, using human participants, which were accessible in full text were included.

Table 1 Criteria for considering studies in the review

Population	Humans
Intervention	Injection of steroid with or without local anaesthetic to the lumbar epidural space via the transforaminal approach
Comparator	Any active treatment or placebo.
Outcomes	• Pain-related primary outcome; • Functional outcomes (range of motion, reduction of disability, return to work, quality of life) • Safety and risk • Relationship to imaging • Best practice recommendations • Cost effectiveness

A combination of search terms (Table 2) were used to identify and retrieve articles in the following databases:

- OVID
  - EMBASE,
  - MEDLINE,
  - AMED,
- ICONDA,
- CINAHL,
- PubMed,
- Pre-Medline,
- The Cochrane Library,
- Scopus,
- TRIP database

Table 2 Search terms for the review

Search term 1	Search terms 2	Search terms 3	Search terms 4
• Pain • Risk • Complication* • Adverse events	• Injections, • Epidural • Spinal .	• Lumbar • Low back Sciatica Lumbar Radiculopathy	• Steroid • Betamethasone • Dexamethasone • Fluocortolone • Methylprednisolone • Paramethasone • Prednisolone • Prednisone • Triamcinolone • Hydrocortisone • Cortisone • Methandrostenolone • Stanozolol • Methenolone • Oxymetholone • Oxandrolone • Nandrolone • Diflucortolone • Fluprednisolone

The titles and abstracts identified from the above search strategy were assessed for eligibility by the *i*CAHE researchers. Full-text copies of eligible articles were retrieved for full examination. Reference lists of included full-text articles were searched for relevant literature not located through database searching.

2.4 Study Selection

Inclusion Criteria

- Study types: Systematic reviews, all primary research designs (randomised controlled trials, cohort studies (prospective or retrospective), case studies or case series)
- Participants: Patients with lumbar (low back) pain with or without lumbar radiculopathy
- Intervention: Steroid injections with or without local anaesthetic to the lumbar epidural space via the transforaminal approach
- Controls: any active treatment or placebo, or no-intervention control
- Outcomes: Pain relief (primary) functional outcomes, safety and risk (secondary)
- Publication criteria – English language, full text available, in peer reviewed journal

	Exclusion criteria • Studies only available in abstract form e.g. conference presentations • Other epidural approaches (caudal-sacral, interlaminar) • Grey literature and no-English language material • Studies involving healthy volunteers or experimentally induced pain • Studies on interventions involving other spinal levels (thoracic or cervical), where the data for lumbar cannot be extracted.
2.5 Critical Appraisal	The SIGN (Scottish Intercollegiate Guidelines Network) checklist specific to the study design of the included studies was used to assess the methodological quality of the included studies. The SIGN checklist asks a number of questions with 'yes' (Y), 'no' (N), 'can't say' (CS) or 'not applicable' (NA) as responses with the appraiser giving an overall rating of quality, based on the responses to questions of either high quality (HQ ++), acceptable (A+), low quality (LQ-) or unacceptable R(0). Copies of the SIGN checklist are provided in Appendix 1

2.6 Data Extraction	Data was extracted from the identified publications using a data extraction tool which was specifically developed for this review. The following information was extracted from individual studies:
	• Evidence source (Author, date, country)
	• Study design
	• Level of evidence
	• Characteristics of participants
	• Interventions
	  ○ Epidural approach
	  ○ Steroid used
	  ○ Use of imaging
	• Outcome measures
	  ○ Pain
	  ○ Functional outcomes
	  ○ Safety and Risk
	• Results

2.7 Data Synthesis	As described, for this review each study was graded for overall methodological quality using the SIGN checklist specific to the study design of the included studies. Recommendations from the literature were made and scored according to a modification of the SIGN Evidence Grading matrix (see Table 3). The modification was to add levels 1 and 2 to differentiate between the 1+ and 1-, 2+ and 2- levels of evidence.

Table 3: Modified SIGN Evidence Grading Matrix

Levels of scientific evidence	
1++	High-quality meta-analyses, high-quality systematic reviews of clinical trials with very little risk of bias
1+	Well-conducted meta-analyses, systematic review of clinical trials or well-conducted clinical trials with low risk of bias
1	Meta-analyses, systematic reviews of clinical trials or clinical trials with a moderate (acceptable) level risk of bias.
1-	Meta-analyses, systematic reviews of clinical trials or clinical trials with high risk of bias.
2++	High-quality systematic reviews of cohort or case and control studies; cohort or case and control studies with very low risk of bias and high probability of establishing a causal relationship
2+	Well-conducted cohort or case and control studies with low risk of bias and moderate probability of establishing a causal relationship
2	Cohort or case and control studies with moderate risk of bias and potential risk that the relationship is not causal.
2-	Cohort or case and control studies with high risk of bias and significant risk that the relationship is not causal.
3	Non-analytical studies, such as case reports and case series.
4	Expert opinion.

To standardise the strengths of recommendations from the extensive literature used for this review, a structured system was developed to incorporate a number of quality measures. Four measures were selected as important variables for the assessment of strength of recommendations from the primary and secondary research sources. These were:

a) Combination of data via meta-analysis
b) Quality of systematic review/trials
c) Number of randomised controlled trials
d) Consistency of the evidence

A scoring system was developed, based on a 0 and 1 score for each of these variables.

1. Combination of data via meta-analysis : Yes = 1, No = 0
2. Quality of systematic review: HQ/Acc (+) =1, LQ(0)/R = 0
3. Number of randomised controlled trials: ≥ 5 randomised controlled trials = 1, < 5=0
4. Consistency: ≥ 75% agreement = 1, < 75% agreement = 0

This allowed for a maximum potentials score of 4 and a minimum score of 0, which reflected a measure of the evidence strength across a range of studies. The resultant score was transferred to the SIGN Evidence Grading matrix.

Total Score	SIGN Evidence Grading matrix score
4	1++
3	1+
2	1
1/0	1-

Final recommendations were graded according to the Scottish Intercollegiate Guidelines Network (SIGN) Grades of Recommendations (Table 4)

Table 4: Scottish Intercollegiate Guidelines Network (SIGN) Grades of Recommendations

Grades of Recommendations	
A	At least one meta-analysis, systematic review or clinical trial classified as 1++ and directly applicable to the target population of the guideline, or a volume of scientific evidence comprising studies classified as 1+ and which are highly consistent with each other.
B	A body of scientific evidence comprising studies classified as 2++, directly applicable to the target population of the guideline and highly consistent with each other, or scientific evidence extrapolated from studies classified as 1++ or 1+.
C	A body of scientific evidence comprising studies classified as 2+, directly applicable to the target population of the guideline and highly consistent with each other, or scientific evidence extrapolated from studies classified as 2++.
D	Level 3 or 4 scientific evidence, or scientific evidence extrapolated from studies classified as 2+

3. Results

3.1 Evidence Sources

The search yielded 1,752 articles. After scrutiny, 1,693 articles were excluded as duplicates or failing to meet the inclusion criteria (shown in Figure 1), leaving 59 studies for inclusion in this review. Figure 1 illustrates the process involved in study selection.

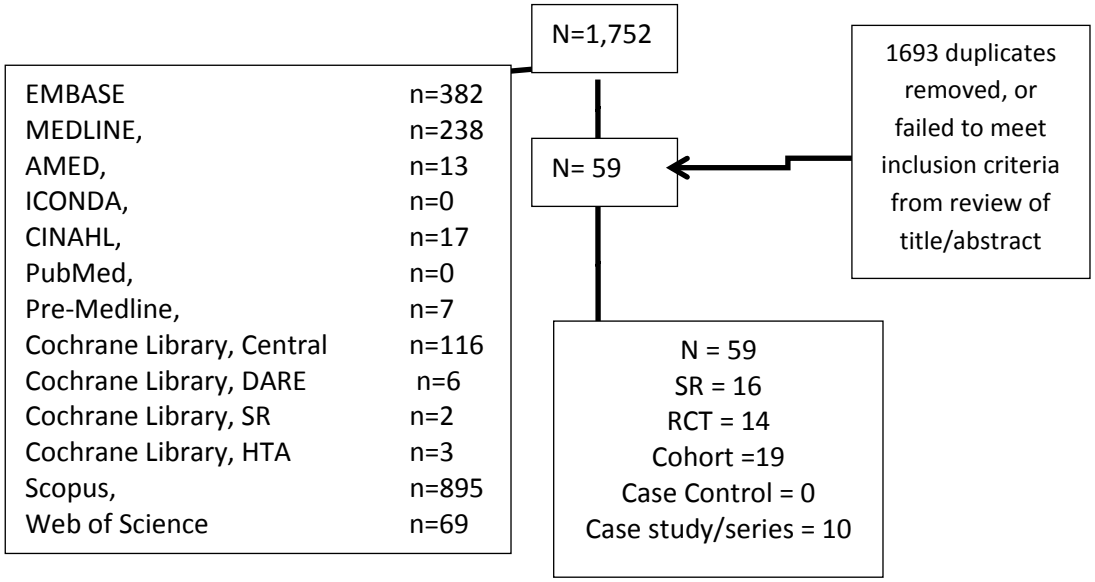

Figure 1: Flow chart of search results

3.2 Appraisal of the Evidence

The literature found for this report varied significantly in quality according to the SIGN critical appraisal checklists.

	N=	HQ(++)	AQ(+)	LQ(-)	R(0)
Systematic reviews	16	4	8	3	1
Randomised controlled trials	14	7	4	3	0
Cohort studies	19	0	3	16	0

The critical appraisal scores for each study in this review are presented in Appendix 2.

The main issues affecting the methodological quality of the studies include:

Systematic reviews

A) Studies did not address the potential for publication bias in reporting their reviews
B) Very few studies addressed the potential for publication status to affect the studies included.
C) Conflicts of interest were not identified or reported
D) Excluded studies were not listed
E) Review findings were often reported as LESI rather than by the individual approach used. It was difficult to isolate the potential effectiveness of individual approaches. For this review, only those studies which focussed on the

transforaminal approach or from which the data for the transforaminal approach could be extracted were included.

F) Reviews often failed to differentiate between primary and secondary outcomes when synthesising their findings. Most systematic reviews used pain as a primary outcome and functional disability/surgery sparing, etc., as secondary outcomes but failed to differentiate between the two when synthesising the study findings in their reviews.

Randomised controlled trials

A) The studies often failed to ensure that the only difference between the two groups (intervention vs. control) was the treatment under investigation. With the small numbers reported in the randomised controlled trials, it was difficult to ensure that the effect of confounders was dealt with. This was particularly important when considering the effect of secondary outcomes.

B) A number of studies failed to report the use of intention to treat analysis when reporting the study's findings.

C) Subjects and investigators were rarely blinded to the intervention involved.

D) Most studies poorly defined the patient presentations in their inclusion criteria. Radiculopathy is a poor diagnostic category when considering a mechanical type intervention, however most studies into the effectiveness of LESI reported patient inclusion criteria of low back pain with radiculopathy. Some were more specific requiring MRI evidence of herniated nucleus pulposus as the cause of the radiculopathy. Likewise, with spinal stenosis, many studies failed to report if this represented central spinal stenosis or lateral stenosis.

Cohort studies

A) The baseline characteristics of the subjects were poorly described making it difficult to be confident that the groups were as similar as possible in all characteristics except for their exposure status, or the presence of specific prognostic factors or prognostic markers relevant to the study in question.

B) The sampling was rarely reported as consecutive, even with the retrospective cohort studies, making it difficult to be confident that all cases were reported on.

C) Outcomes were often poorly defined with most studies reporting on self-reported complications or only reporting severe adverse events.

3.3 Findings

Lumbar epidural steroid injections have presented a fertile ground for primary research and secondary evidence synthesis with an extensive number of systematic reviews published on this topic. This review will focus on studies which have reported results for the transforaminal approach.

The last significant secondary evidence review was presented by Shamliyan et al. (2014). This review involved a review of evidence published up to January 10th, 2014 and included 18 systematic reviews, which reported on a total of 76 randomised controlled clinical trials. Only data from Shamliyan et al. (2014) review related to steroid injections via the transforaminal approach will be presented in this report. Due to the nature of Shamliyan et al.'s (2014) review, only randomised controlled trials that were published after this date and hence were not included in Shamliyan et al.'s (2014) review were included in this review on the effectiveness of LESI.

The extensive search strategy used in this review identified a further 15 systematic reviews that were not included in Shamliyan et al.'s (2014) review. Eleven (11) of these reviews were published within the search period of Shamliyan et al.'s (2014) review and four (4) were published subsequently.

An extra 14 randomised controlled trials were identified that had been published since Shamliyan et al.'s review and, hence were not included in that review. This current review sought to take a comprehensive review of the efficacy of LESI so included primary clinical trials where both the intervention and control group received LESIs if the data presented allowed a comparison within both groups to the baseline data.

3.4 Outcome Measures – Pain and Function

3.4.1 Systematic Reviews

Shamliyan et al. (2014)

Shamliyan et al. (2014) (QS:AQ(+)) presented a SR investigating the short-term and the long-term efficacy and safety of epidural steroid injections in the treatment of chronic lumbosacral pain in community-dwelling adults and what patient characteristics may modify treatment benefits and harms. This review included guidelines, systematic reviews, and randomised controlled clinical trials in English, and large observational cohorts to assess treatment safety. Eighteen (18) systematic reviews were identified that synthesised data from 65 randomised controlled trials, with a further 11 randomised controlled trials that were not included in these reviews also identified. The search strategy included all relevant articles published in the English language up to January 10, 2014.

This comprehensive review presented an overview of the systematic reviews following the framework of the Cochrane collaboration. Although they did not undertake a meta-analysis, the authors calculated absolute risk difference, the number needed to treat, and the number of attributable events per 1000 treated based on data from the published randomised trials, using Meta-Analyst© software and STATA© software. They

also attempted to examine the role of patient characteristics, by undertaking subgroup analyses by patient demographics, pain type, prior treatment response, and comorbidities in systematic reviews and randomised trials, including significant interaction effects.

To assess the quality of evidence, the authors looked for a dose-response association, the strength of association, and evidence of any reporting bias. The strength of the association was graded as large (when the relative risk (RR) was greater than 2), very large (when the RR was greater than 5.38), and small (when the RR was significant but less than 2). For continuous standardised measures of pain and function, the magnitude of the effect was defined based on standardised mean differences in standard deviation units, with small, corresponding to standardised mean differences in standard deviation units of 0 to 0.5, moderate, 0.5 to 0.8, and large, greater than 0.8.

High quality of evidence was assigned to well-designed randomised controlled trials with consistent findings. The quality of evidence was downgraded to moderate if at least 1 of 4 strength of evidence criteria was not met, and to low if 2 or more criteria were not met.

A low quality of evidence was assigned to nonrandomized studies, and upgraded for the rating if there was a strong or dose-response association. Evidence was defined as insufficient when no studies provided valid information about treatment effects. This approach was applied regardless of whether the results were statistically significant.

The authors identified that the SRs provided conflicting conclusions. A high-quality systematic review, which did not distinguish between interlaminar, caudal, or transforaminal epidural injection techniques for lumbosacral radicular syndrome, found no clinically important benefits with use of epidural steroids. A number of other systematic reviews, which included results from both randomised controlled trials and observational studies stratified by injection techniques and type of spinal disorders, reported good evidence of short-term and long-term pain reduction and improvement in function with epidural steroids (Boswell et al. 2007, Machikanti et al. 2012, Parr et al. 2012, Benyamin et al. 2012).

Shamliyan et al (2014) concluded that while the reviews have focused on statistically significant changes in outcomes most reviews failed to address the rates of clinically significant improvements in pain and disability, number needed to treat, or attributable events for clinical decision making.

In terms of the evidence related to transforaminal approach Shamliyan et al. (2014) reported:

- Transforaminal epidural approach had a non-significant effect on leg pain in the short term compared to placebo (3 randomised controlled trials (n=270), moderate evidence quality, OR 0.6 (0.4; 1.1))

- Transforaminal epidural approach had a significant effect on leg pain in the long term compared to placebo (1 RCT (n=48), very low evidence quality, OR 0.2 (0.1; 0.6))
- A statistically significant short-term reduction in leg pain was reported with caudal injection
- Transforaminal epidural approach had a non-significant effect on disability in the short term compared to placebo (2 RCTs (n=205), low evidence quality, OR 0.8 (0.5; 1.3))
- A statistically significant reduction in short-term disability was reported with caudal injection
- Transforaminal epidural approach had a non-significant effect on the need for surgery compared to control within 12 months (7 RCTs (n=456), moderate evidence quality, RR 1.06 (0.74; 1.52))

Shamliyan et al (2014) concluded that:

- When considering injection technique, no single specific injection technique improved lumbar pain.
- No evidence to suggest that a series of epidural injections was any more effective than a single injection,
- No evidence of improvement in benefits with increasing dose.
- No consistent evidence of superior efficacy of one steroid over the others. In fact injection of anaesthetic alone resulted in reduction in pain and disability similar to that derived from a combination of steroids with anaesthetic
- Conclusions about the cost-effectiveness of epidural steroid injections were inconsistent.

Appendix 2 presents the details extracted from the 18 SRs included in Shamliyan et al's (2014) study and the extra 15 SRs which explored the efficacy of LESI, with or without anaesthetics, specifically via a transforaminal approach.

Abdi et al. (2005)

Abdi et al. (2005) (QS:AQ(+)) undertook a systematic review into the role of lumbar epidural steroid injections (LESI) in the management of chronic spinal pain (axial and radicular) in terms of both effectiveness and safety. This review included both cervical and lumbar and looked at each of the three approaches individually. The outcome measures included pain relief, functional improvement, psychological status and return to work. Short-term improvement was defined as less than 6 weeks, and long-term improvement was defined as 6 weeks or longer. They included both randomised controlled trials, and prospective cohort studies in their review. They identified 4 prospective cohorts into transforaminal LESI. They concluded that the evidence for lumbar transforaminal LESI for lumbar nerve root pain was strong for short-term and moderate for long-term improvement. The evidence was limited for lumbar radicular pain in post lumbar laminectomy syndrome.

Study	QS	Conclusions	Level of Evidence
Abdi et al. (2005)	AQ(+)	For lumbar transforaminal LESI, the evidence for use in radicular pain was strong for short-term and moderate for long-term improvement in pain and functional outcomes.	1+

Bhargava et al (2005)

Bhargava et al (2005) (QS:LQ(-)) undertook a limited systematic review of injection therapy for lumbar radiculopathy, limiting research evidence from 2003 to 2005. This review included both full text and abstracts of all research designs (both RCT and cohort studies). They concluded that all approaches to the interlaminar, caudal, and transforaminal epidural space provide long-term relief in 27—56% patients and that while conclusive evidence was lacking, epidural space steroid instillation via the transforaminal approach for the treatment of lumbar radicular pain seemed effective. Whilst three common techniques are used to deliver medication into the epidural space. Of these, a transforaminal approach seemed to be the best route for delivering medication to the ventral epidural space and/or the dorsal root ganglia.

Study	QS	Conclusions	Level of Evidence
Bhargava et al. (2005)	LQ(-)	• All approaches to the interlaminar, caudal, and transforaminal epidural space provide long-term relief in 27—56% patients with radiculopathy.	1-
		• Epidural space steroid instillation via the transforaminal approach for the treatment of lumbar radicular pain seemed effective.	1-
		• The transforaminal approach seemed to be the best route for delivering medication to the ventral epidural space and/or the dorsal root ganglia.	1-

Buenaventura et al (2009)

Buenaventura et al (2009) (QS:AQ(+)) undertook a systematic review of the effectiveness of transforaminal LESI for managing lumbar (low-back) and sciatica (leg) pain. Whilst they included both randomised controlled trials and prospective cohort studies in their search strategy they identified only 4 RCTs that met their inclusion criteria for consideration of the effectiveness of transforaminal LESI with 4 prospective cohorts included in their review of complications.

The outcome measures of interest included pain relief, functional assessment, psychological improvement, return to work, and change in opioid intake. They concluded that overall the evidence for transforaminal LESI was strong with Level II-1 for short-term relief and Level II-2 for long-term improvement in the management of lumbar nerve root and low back pain.

Study	QS	Conclusions	Level of Evidence
Buenaventura et al 2009	AQ(+)	• Transforaminal LESI have significant effect in relieving chronic pain of lumbar disc herniation and radiculitis with indicated evidence levels of Level II-1 for short-term relief and Level II-2 for long-term relief	1

Colimon and Villalobos (2010)

Colimon and Villalobos (2010) presented a review of the literature related to the three approaches to LESI. They classified the quality of the evidence according to the US Preventive Services Task Force (USPSTF) grading. Unfortunately, they failed to provide any details on the search strategy they undertook to find the evidence, nor much evidence on the number and characteristics of the studies that underpinned their findings.

Study	QS	Conclusions	Level of Evidence
Colimon and Villalobos 2010	R(0)	An ESI via transforaminal approach is indicated for chronic LBP and/or pain in the lower limbs because of HIVD and radiculopathy, spinal stenosis, or failed back surgery syndrome. The level of evidence for the procedure for lumbar pain and lower limb pain is: ● Level II-1 for short-term pain relief. ● Level II-2 for long-term pain relief. The degree of recommendation is: ● 1C for lumbar pain and pain in the lower limb.	1-

Benny and Azari (2011)

Benny and Azari (2011) (QS:AQ(+)) completed a systematic review that focused on the efficacy of lumbosacral transforaminal LESI. They did not limit their study to randomised controlled trials only but included observational cohort studies (retrospective and prospective). They reported on 8 randomised trials, 4 retrospective studies and 8

prospective studies. The majority of the studies they reviewed included radicular pain as a result of discogenic etiologies, most commonly a herniated nucleus pulpous. There were a few studies which reported the effectiveness of transforaminal LESI in patients with spinal stenosis, however, these were lower level studies (i.e. prospective cohort studies, not randomised controlled trials). They reported that all 8 of the randomised controlled trials that were included showed a positive outcome in both the short term and long term in reducing pain.

All studies used either CT guidance or fluoroscopic guided transforaminal LESI, and in both cases the studies showed that transforaminal LESI were effective. There was no study which directly compared the two of these approaches.

Benny and Azari (2011) also reported that the composition of the mixture used as an injectate varied from study to study. While some studies used a mixture of steroid and lidocaine others used only steroid depending on the preference of the physician performing the study, with no difference in effectiveness reported.

They concluded that the evidence was strong (ie. obtained from well-designed controlled trials without randomization) for use of transforaminal lumbar epidural injections of steroid for short term effect and moderate (ie. obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group) for long term relief in managing radicular pain caused by nerve root irritation as a result of impingement, with an overall grading recommendation of Strong, based on moderate quality evidence.

Study	QS	Conclusions	Level of Evidence
Benny and Azari 2011	AQ(+)	Transforaminal LESI effective in both short-term and long-term management of radiculopathy due to spinal stenosis or lumbar herniation.	1+

Fritzler and Sarafini (2011)

Fritzler and Sarafini (2011) (QS:(LQ-)) undertook a review that focused on the effectiveness of interventional pain management techniques (including epidural steroid injections (LESI)) in placebo-controlled trials. This review used broad inclusion criteria but failed to report on the methodological quality of the included studies. They identified 4 placebo-controlled randomised controlled trials that studied the efficacy of LESI for lower extremity sciatica/radiculopathy and concluded that LESIs appear superior to placebo in providing transient benefit with respect to patient disability scores up to 3 weeks and VAS pain scores up to 6 weeks. There appeared to be no evidence of benefit over placebo in terms of improved physical function, rates of return to work, or the need for future surgery. Transforaminal LESIs appeared superior to placebo in improving patient satisfaction and pain levels for a minimum of 2 weeks and potentially up to 16 months on average.

Study	QS	Conclusions	Level of Evidence
Fritzler and Sarafini 2011	LQ(-)	Transforaminal ESIs appear superior to placebo in improving patient satisfaction and pain levels for a minimum of 2 weeks and potentially up to 16 months on average.	1-

Bresnahan et al (2013)

Bresnahan et al (2013) (QS:AQ(+)) undertook a systematic review into the effectiveness of LESI for spinal stenosis and expanded the study to investigate the Reimbursement amounts. They identified and reviewed 6 randomised controlled trials and 2 large observational studies. They concluded that both LESIs and anaesthetic injections alone resulted in better short-term improvement (<6 months) in walking distance compared with control injections, however, there was little evidence of a long-term effect. Across the studies, the authors could find no differences between LESIs and anaesthetic injections in self-reported improvement in pain. One study indicated that transforaminal approaches had better improvement in pain scores (<4 months) compared with interlaminar injections.

Study	QS	Conclusions	Level of Evidence
Bresnahan et al. 2013	AQ (+)	• Transforaminal approaches had better improvement in pain scores (4 months) compared with interlaminar injections.	1

Cohen et al (2013)

Cohen et al (2013) (QS:AQ(+)) undertook a comprehensive systematic review of the evidence for epidural steroids (including both lumbar and cervical). This review divided the evidence according to the three approaches to LESI and used levels of evidence based on US Preventive Services Task Force (USPSTF) criteria with comparative effectiveness described using USPSTF levels of certainty.

<u>Lumbar transforaminal (TF) approach</u>

The authors concluded that systematic reviews in this area were hampered by significant heterogeneity but generally found good evidence supporting short-term relief and mixed evidence in favour of long-term benefit for transforaminal ESIs in treating back pain with radicular symptoms due to disc herniation. One review found good evidence for the treatment of radicular pain secondary to disc herniation, but only fair or limited evidence for the treatment of spinal stenosis, postsurgical pain, or axial pain in the absence of disc herniation. Reviews dedicated specifically to either spinal stenosis or postsurgical pain were lacking. Subgroup analyses in several clinical

studies showed either comparable benefit in patients with herniated disc and spinal stenosis or only a small benefit in favour of herniated disc.

Cohen et al. (2013) also explored the characteristics of the injectate which they reported differed among studies and may have impacted on patient outcome. Both the dose and volume of steroid varied depending on the route of injection, with amounts of each typically increasing as transforaminal, interlaminar, and caudal ESI are performed, respectively. Owlia et al. (2007) identified that an interlaminar ESI dose of 40 mg of methylprednisolone provided a similar reduction in pain with fewer adverse effects compared with 80 mg. Kang et al. (2011) evaluating the effect of steroid dose during transforaminal ESI found no differences in efficacy between triamcinolone doses of 10, 20, and 40 mg, although 5 mg failed to provide a similar level of benefit. Rabinovitch et al. (2009) concluded there was an independent, beneficial effect for volume, as the use of higher volumes may result in pain relief in and of itself. Revel et al. (1996) found that steroid injected in a volume of 40 mL of saline provided superior pain relief than when the same dose of steroid was injected by itself at 18 months' follow-up.

Cohen et al. (2013) also attempted to review the literature related to different types of steroid injections but reported that the evidence was mostly limited to underpowered randomised or retrospective studies comparing particulate to nonparticulate steroids. Among 3 RCTs comparing different steroid preparations, 2 reported a nonsignificant benefit in favor of the depo-steroid group, with the study reporting a statistically significant difference for depo-steroids using the largest study cohort, suggesting a stronger powered finding they concluded in summary that there was conflicting evidence with a low degree of certainty that depo-steroids provided superior relief compared with non-depot steroids.

When considering the different pathologies, the efficacy of LESI varied. Lumbar herniated nucleus pulposus (HNP) represented the most commonly studied condition, with the most comprehensive SRs demonstrating level I evidence supporting the role of ESI, particularly for short-term relief of pain. For intermediate- and long-term benefit (>3 months), the benefit was significantly smaller and may well represent the effect of disease evolution. They reported more limited evidence for the effectiveness of ESI for other pathologies, with the evidence for LESI in spinal stenosis less robust than for herniated disc, but greater than that for failed back surgery syndrome and axial back pain.

Study	QS	Conclusions	Level of Evidence
Cohen et al. 2013	AQ(+)	Transforaminal injections are more likely to yield positive results than interlaminar or caudal injections	1+

MacVicar et al. (2013)

MacVicar et al. 2013 (QS:LQ(-)) completed a SR into the effectiveness of transforaminal LESI and included all study designs. They identified 39 primary research studies that reviewed the effect of transforaminal LESI on pain and concluded that for miscellaneous conditions, the available evidence was limited and was neither compelling nor conclusive. For disc herniation, the evidence was sufficiently abundant to show that transforaminal LESI whilst not universally effective, nevertheless, benefited a substantial proportion of patients, and was not a placebo. They identified that success rates were higher in patients with contained herniations that cause only low-grade compression of the nerve.

Study	QS	Conclusions	Level of Evidence
MacVicar et al. 2013	LQ(-)	• Transforaminal LESI effective in reducing pain, restoring function, reducing the need for other health care, and avoiding surgery in patients with lumbar radicular pain caused by contained disc herniations.	1

May and Comer (2013)

May and Comer (2013) (QS:AQ(+)) presented a SR comparing the effectiveness of surgery to non-surgical treatment (which included LESI) for spinal stenosis. They reported on 9 studies which looked at different methods of LESI with or without an anaesthetic. In 6 high-quality trials, LESI produced no statistically significant differences compared to physical therapy, saline, saline and anaesthetic or anaesthetic injection at long-term follow-up, with significant differences in short-term pain reported in one trial only. Bilateral transforaminal injections appeared to be more effective than an interlaminar steroid injection for spinal stenosis. Percutaneous adhesiolysis and decompression surgery were more effective than LESI. The authors concluded that there was strong evidence (6 randomised controlled trials; n = 239) that LESI were no more effective than active controls, and LESIs were no more effective than saline or anaesthetic in 5 out of 6 studies.

Study	QS	Conclusions	Level of Evidence
May and Comer 2013	AQ (+)	Bilateral transforaminal injection was more effective than an interlaminar steroid injection in patients with spinal stenosis	1

Chien et al. (2014)

Chien et al. (2014) presented a SR comparing the transforaminal to the interlaminar approaches to epidural steroid injections. They included all primary studies comparing the two approaches in patients suffering from unilateral lumbosacral radicular pain secondary to intervertebral disc herniations/degeneration. They identified 12 studies

that specifically compared transforaminal to interlaminar approaches of epidural steroid injection for the treatment of unilateral lumbosacral radicular pain secondary to intervertebral disc herniations, and limited this to 5 (prospective) and 3 (retrospective) studies (n=506). They concluded that both transforaminal ESI and interlaminar LESI were effective in reducing pain and improving functional scores in unilateral LSRP. In the treatment of pain, transforaminal ESI demonstrated non-clinically significant superiority to interlaminar LESI only at the 2-week follow-up. Based on 2 studies, interlaminar LESI demonstrated non-clinically significant superiority to transforaminal ESI in functional improvement.

Study	QS	Conclusions	Level of Evidence
Chien et al. 2014	HQ (++)	• Transforaminal fluoroscopy guided LESI more effective compared to fluoroscopy guided interlaminar LESI in reducing pain in radiculopathy secondary to IV disc herniation/degeneration in the short term	1-
		• Transforaminal fluoroscopy guided LESI no more effective compared to interlaminar fluoroscopy guided LESI in reducing pain in radiculopathy secondary to IV disc herniation/degeneration in the long term	1-
		• Transforaminal fluoroscopy guided LESI no more effective compared to interlaminar fluoroscopy guided LESI in functional improvement in patients with radiculopathy secondary to IV disc herniation/degeneration in the long or short term	1

Bicket et al. (2015)

Bicket et al. (2015) (QS:HQ(++)) undertook a systematic review/meta-analysis of the effectiveness of lumbar epidural steroid injections (LESI) in reducing the need for spinal surgery in patients with spinal pain. Surgical outcomes were divided by time intervals into short-term (<1 year) and long-term (>1 year) results. They identified 26 RCT studies representing 1707 LESI patients and 1616 control subjects. Bicket et al. reported on 22 studies that compared LESI with non-LESI controls, with 5 studies comparing the outcomes of the short-term (<1 year) need for surgery, and 17 reporting on the outcomes of long term (<1 year) need for surgery. These studies were included in subsequent meta-analyses. They reported that LESI demonstrated a trend to reduction in the need for surgery for short-term (<1 year) outcomes (risk ratio, 0.68; 95% confidence interval, 0.41–1.13; p=.14) but not long-term (>1 year) outcomes (RR: 0.95, 0.77–1.19, p5.68).

The authors also undertook a secondary analysis, which sought to analyse the cross-over data presented in studies comparing surgical care with non-surgical care in which patients had LESI (n=4). Whilst the authors admitted this secondary analysis was not at the same level of evidence as the meta-analysis they felt it provided useful information

regarding the ability of LESI to prevent surgery in a clinical, rather than controlled, setting. This secondary analysis provided low-level evidence suggesting that between one-third and half of the patients considering surgery who undergo LESI could avoid surgery.

Study	QS	Conclusions	Level of Evidence
Bicket et al. 2015	HQ (++)	Surgical rates did not differ when ESI were stratified by transforaminal (20.7% [52 out of 251] vs. 22.6% [72 out of 318]; RR, 1.01, 95% CI, 0.68–1.51; I2527%; p=0.96) (4 randomised controlled trials)	1++

Manchikanti et al (2015)

Manchikanti et al (2015) (QS:AQ(+)) also divided the LESI into the three approaches in their systematic review into the efficacy of epidural injections in the treatment of lumbar central spinal stenosis. They identified 7 randomised controlled trials that matched their inclusion criteria, which included both anaesthetics and steroid injectates. One randomised controlled trial investigated caudal LEI, 5 investigated interlaminar LEI and 2 investigated transforaminal LESI. Due to lack of homogeneity and the limited number of trials in each category no meta-analysis was performed. This systematic review, based on a high-quality methodological quality assessment concluded that caudal epidural injections and lumbar interlaminar epidural injections of local anaesthetic with or without steroid provide effective and significant improvement in pain and function in central spinal stenosis.

There was level II evidence for long-term results for caudal and interlaminar approaches. However, the evidence is Level III for short-term efficacy based on two moderate quality randomised controlled trials of transforaminal LEI. An interlaminar approach was reported to be superior to a caudal approach and a caudal approach superior to a transforaminal one.

The authors acknowledged that the findings of their systematic review did not correlate with other systematic reviews (Kovacs et al. 2011, Ammendolia et al. 2012, and Bresnahan et al. 2013), however they felt this may have reflected the poor methodological quality of these three reviews, with issues such as lack of standardisation of intervention, inclusion of low-quality studies, poor search strategies and evidence selection processes.

Study	QS	Conclusions	Level of Evidence
Manchikanti et al. 2015	AQ(+)	• Transforaminal LEI effective for reducing pain in patients with spinal stenosis in short-term	1

		• LEI with anaesthetic no more effective than LEI with anaesthetic and steroid in long or short term	1

Bhatia et al. (2016)

Bhatia et al. (2016) (QS:HQ(++)) undertook a SR/MA into the effectiveness of transforaminal LESI for the treatment of lumbosacral radicular pain from herniated intervertebral discs. They explored a wide range of outcomes including pain (up to 12 months) disability, psychological function and quality of life, as well as potential complications. They identified 8 randomised controlled trials which they incorporated into their meta-analysis. They concluded that on the basis of the quality of evidence and the strength of effect, it was recommended that, in outpatients with lumbosacral radicular pain secondary to herniated intervertebral discs, transforaminal LESI should be used to reduce pain up to 3 months after the intervention (strong recommendation; moderate-quality evidence). The modest analgesic benefit should be discussed with patients, and their preferences and values considered before proceeding with this intervention. This intervention should not be used to reduce physical disability at 1 to 3 months after the intervention (strong recommendation; high-quality evidence) or incidence of surgery at 12 months after the intervention (strong recommendation; moderate-quality evidence). They also noted that there was a lack of information about appropriate dosages and number of procedures. Whilst they concluded that dosage was unclear when the mean difference in pain scores was compared in the 4 randomised controlled trials (n=516) that used low doses of steroids (<40mg) (Mean Diff=-0.54 (-0.67 to -0.42)) was lower than those with higher doses (Mean Diff=-2.04 (-2.42 to –1.65))

Study	QS	Conclusions	Level of Evidence
Bhatia et al. 2016	HQ (++)	• Transforaminal LESI should be used to reduce pain up to 3 months in patients with radiculopathy from herniated lumbar disc	1++
		• Transforaminal LESI should not be used to reduce physical disability up to 3 months after the intervention or incidence of surgery at 12 months after the intervention in patients with radiculopathy from herniated lumbar disc	1++

Wei et al. (2016)

Wei et al. (2016) (QS:AQ(+)) presented a SR comparing the effectiveness of transforaminal and interlaminar approaches for pain and functional outcomes in patients with Low back pain with lumbosacral radicular pain. They included both observational studies (n=4) and randomised controlled trials (n=9) in their review representing 931 patients. They concluded that transforaminal LESI produced better

pain relief compared with interlaminar LESI in randomised controlled trials (p<0.01), but not in the observational studies (p=0.62), however, there was no difference in functional improvements and Oswestry disability index (ODI) scores. There were also no differences between transforaminal and interlaminar LESI in regard to procedure frequency, surgery rate, and ventral epidural spread.

Study	QS	Conclusions	Level of Evidence
Wei et al. 2016	AQ (+)	• Transforaminal LESI produced better pain relief compared with interlaminar LESI in randomised controlled trials, but not in observational studies.	1 / 2-
		• Transforaminal LESI produced no better functional improvement and Oswestry disability index (ODI) score than interlaminar LESI	1
		• There were no differences between transforaminal and interlaminar LESI in regard to procedure frequency, surgery rate, and ventral epidural spread.	1

3.4.2 Randomised Controlled Trials

The last date of searching of the systematic reviews identified was July 2014, (Manchikanti et al. 2015), however, this review only focussed on the use of LESI for patients with spinal stenosis. The last relevant search dates for RCTs was to February 2013 (Cohen 2013, Bicket et al. 2015). Therefore a search of the relevant literature was undertaken from February 2013 to July 2016. A total of 14 relevant randomised controlled trials were identified in this review. Appendix 6 presents the randomised controlled trials that were included in the SRs reported above. Appendix 7 presents the data of these RCTs extracted from the systematic reviews.

Koh et al. (2013)

Koh et al. (2013) (QS:AQ(+)) undertook a double-blind, randomised, active-control trial comparing the effect of adding hypertonic saline to conventional transforaminal epidural steroid injections (TFEI) to provide pain relief for chronic radiculopathy patients secondary to lateral canal spinal stenosis. They randomised 53 patients to receive FG-TFLESI, involving either 2 mL of sodium chloride solution + triamcinolone acetonide or 2ml of triamcinolone acetonide. Outcome measures were taken at baseline, one, 2, 3, 4, and 6 months post procedure and included numerical rating scale (NRS) of pain, the Oswestry disability index (ODI), the proportion of substantial and moderate responders, and patient satisfaction. The results of this study suggested that the transforaminal LEI was a useful modality in treating pain secondary to lateral canal spinal stenosis, and the short-term functional outcomes were also improved significantly, but that transforaminal LEI showed limited long-term effects in treating patients with spinal stenosis. The addition of hypertonic saline demonstrated superior short-term pain relieving efficacy compared with conventional lumbar TFEI, but the

overall mid- and long-term results showed no advantage.

Study	QS	Conclusions
Koh et al. (2013)	AQ (+)	• Transforaminal LESI was a useful modality in treating pain secondary to lateral canal spinal stenosis, and the short-term functional outcomes were also improved significantly, • Transforaminal LESI showed limited long-term effects in treating patients with spinal stenosis. • The addition of hypertonic saline demonstrated superior short-term pain relieving efficacy compared with conventional transforaminal LESI, but the overall mid- and long-term results showed no advantage.

Rados et al. (2013)

Rados et al. (2013) (QS:LQ(-)) undertook a randomised, prospective study to compare the efficacy of interlaminar (IL) and transforaminal (TF) steroid injections over 6 months in patients with unilateral chronic lumbar radicular pain. 64 subjects with unilateral radicular pain were randomised into two groups, one received interlaminar LESI (involving 80 mg Depo-Medrol (methylprednisolone), mixed with 8 ml of 0.5% lidocaine), the other receiving transforaminal LESI (involving 40 mg Depo-Medrol in 3 ml of 0.5% lidocaine). The patients received a series of three interlaminar or transforaminal ESIs, at 2-week intervals. The outcome measure was the painDETECT questionnaire (PD-Q), which is designed to detect neuropathic pain components in back pain. The authors concluded that steroids were efficient in decreasing chronic radicular pain, both by way of interlaminar and transforaminal approach. Steroids were efficient not only in alleviating the overall pain, they also reduce the neuropathic component. There was no statistically significant difference in the efficiency of the two dosages and the two volumes of steroids with the interlaminar and transforaminal distribution of steroids (i.e. 40 mg steroids in 3 ml of 0.5% lidocaine with the transforaminal approach is as efficient as a dose of 80 mg steroids in 8 ml of 0.5% lidocaine via laminar approach).

Study	QS	Conclusions
Rados et al. (2013)	LQ (-)	Steroids are efficient in reducing the overall pain, and the neuropathic component in chronic lumbar radicular pain, whether it is distributed by the interlaminar or transforaminal approach, and at either 3ml or 8ml dose.

Zhang et al. (2013)

Zhang et al. (2013) (QS:AQ(+)) undertook a randomised controlled trial of the clinical effectiveness of oxygen-ozone therapy combined with steroid compared with injection of ozone alone in 172 adult patients with low back pain and radicular pain due to disc herniation. Injections were performed in both the intradiscal and intraforaminal space with one group including 1ml of betamethasone. Visual analogue scale (VAS) and the Japanese Orthopedic Association's evaluation system for lower back pain syndrome (JOA score) were administered before treatment and at 3 weeks, 6 and 12-month

follow-up period. Satisfactory clinical outcomes were obtained in both groups, with better effects in the epidural group at 3 weeks follow-up. However, there were no significant differences between two groups at 6 and 12 months with 79%-.80% improvement in the JOA and a 72% decrease in VAS score in both groups at the 12 months reassessment point.

Study	QS	Conclusions
Zhang et al. (2013)	AQ(+)	• There was no significant statistical difference between the treatment of epidural injection of oxygen ozone combined with steroid and ozone only in the 6 and 12 months follow-up. • LESI effective in reducing pain in patients with low back pain and radicular pain due to disc herniation over 12 months

Friedly et al. (2014)

Friedly et al. (2014) (QS:AQ(+)) conducted a multicentre, double-blind RCT into the effectiveness of LESI (both transforaminal ESI and interlaminar LESI) of glucocorticoids plus lidocaine or lidocaine alone in 400 patients with lumbar central spinal stenosis and moderate-to-severe leg pain and disability over a 6 week period. The injectates involved 1 to3 ml of lidocaine followed by 1 to 3 ml of triamcinolone, betamethasone, dexamethasone or methylprednisolone. At 6 weeks, there were no significant between-group differences in the RMDQ score (adjusted difference −1.0 points; 95% CI, −2.1 to 0.1; P = 0.07) or the intensity of leg pain (adjusted difference, −0.2 points; 95% CI, −0.8 to 0.4; P = 0.48). A pre-specified secondary subgroup analysis with stratification according to type of injection (interlaminar vs. transforaminal) likewise showed no significant differences at 6 weeks. On reviewing the study data there were significant differences in the interlaminar LESI group at the 3 week mark between the two treatment groups with the interlaminar LESI demonstrating statistically significant improvements in RMDQ and leg pain score with the combined LES+AI group compared to the LEAI group, whilst transforaminal LESI failed to reach statistical significance at the 3 week mark between groups.

Study	QS	Conclusions
Friedly et al. (2014)	AQ (+)	• Interlaminar LESI demonstrates statistically significant improvements in RMDQ and leg pain score with the combined LES+AI group compared to the LEAI group • Transforaminal LESI failed to reach statistical significance at the 3 week mark between groups.

Ghai et al. (2014)

Ghai et al. (2014) (QS:(HQ++)) undertook a randomised, double-blind, active-control study, comparing the effectiveness of parasagittal interlaminar LESI with transforaminal LESI for managing low back pain with lumbosacral radicular pain in the same type of patients as Hashemi et al. (2015). 62 patients were randomly allocated into either the parasagittal interlaminar LESI or the transforaminal LESI group. Both groups received fluoroscopically guided epidural injections of methylprednisolone (80 mg) (via 2 mL of methylprednisolone acetate (I mL = 40mg) with 2 mL sterile normal

saline). Outcome measures included Pain levels (via VAS scores), disability (via ODI Scores) and patient satisfaction via a 7-point Patient Global Impression of Change (PGIC) at 2 weeks, 1, 2, 3, 6, 9, and 12 months post-intervention. Effective pain relief (≥ 50% pain relief from baseline on VAS) was observed in 76% (90% CI 60.6 – 88.5%) of patients in the transforaminal group and 78% (90% CI 62.8 – 89.3%) of patients in the parasagittal interlaminar (P = 1.00) group at 3 months. The pain relief survival period was comparable in both groups (P = 0.98). Significant reduction in VAS and improvement in MODQ were observed at all time points post-intervention compared to baseline (P < 0.001) in both groups. On average, patients in the parasagittal interlaminar group received 1.84 and patients in the transforaminal group received 1.92 procedures annually. The authors concluded that epidural injection delivered through the parasagittal interlaminar approach is equivalent in achieving effective pain relief and functional improvement to the transforaminal approach for the management of low back pain with lumbosacral radicular pain. The parasagittal interlaminar approach can be considered a suitable alternative to the transforaminal approach for its equivalent effectiveness, probable better safety profile, and technical ease.

Study	QS	Conclusions
Ghai et al. (2014)	HQ (++)	• Parasagittal fluoroscopy guided interlaminar LESI effective in reducing pain in patients with low back pain with lumbosacral radicular pain at 12 months. • Parasagittal fluoroscopy guided interlaminar LESI effective in improving disability (via ODI Scores) in patients with low back pain with lumbosacral radicular pain at 12 months.

Manchikanti et al. (2014b)

Manchikanti et al. (2014b) (QS:AQ(+)) presented a randomised, double-blind, active-controlled trial with a 2-year follow-up of the effectiveness of lumbar transforaminal epidural injections of local anaesthetic with or without steroids in managing chronic low back and lower extremity pain in patients with disc herniation and radiculitis. They randomly allocated 120 patients to one group treated with transforaminal E**A**I (lidocaine 1%, 1.5 mL + 0.5ml sodium chloride) and the second group treated with transforaminal LEA-SI (lidocaine 1%, 1.5 mL + 0.5ml betamethasone). Outcome measures included numeric rating scale (NRS) of pain, functional status with Oswestry Disability Index (ODI), employment status and opioid intake over 2 years. At 2 years there was significant improvement in all participants in 65% who received local anaesthetic alone and 57% who received local anaesthetic and steroid. This study suggested a lack of superiority of steroids compared with local anaesthetic at 2-year follow-up.

Study	QS	Conclusions
Manchikanti et al. (2014b)	AQ (+)	• At 2 years there was significant improvement in 65% of participants who received local anaesthetic alone and 57% who received local anaesthetic and steroid, via lumbar transforaminal approach.

		• This study suggested a lack of superiority of steroids compared with local anaesthetic at 2-year follow-up.

Rahimzadeh et al (2014)

Rahimzadeh et al (2014) (QS:AQ(+)) undertook a prospective randomized trial of 25 subjects with low back pain due to failed back syndrome, who were randomly assigned to receive a transforaminal epidural injection of either bupivacaine 5 mg (1 mL) + triamcinolone 40 mg (1 mL) + saline solution 10% (2 mL) + hyaluronidase 1,500 IU reconstituted in 1 mL distilled water (HYL) or bupivacaine 5 mg (1 mL) + triamcinolone 40 mg (1mL) + saline solution 10% (2 mL) + 1 mL distilled water (NSL) in a double-blind fashion. Pain scores and total analgesic requirement were significantly lower in the HYL group at 2 and 4 weeks after blockade ($P < 0.01$). Patient satisfaction was higher in the HYL group. This study was hampered by its small subject size, but the results were interesting over the short term.

Study	QS	Conclusions
Rahimzadeh et al. (2014)	AQ(+)	• Adding hyaluronidase to the epidural injectate during transforaminal LESI was more effective in the management of chronic low back pain in patients with failed back surgery syndrome over a period of 4 weeks

Sinofsky et al. (2014)

Sinofsky et al. (2014) (QS:LQ(-) reported a secondary analysis of a prospective randomised double-blind study of the short-term benefit of interlaminar and transforaminal epidural steroid injections. They specifically looked at the relationship between concordant versus discordant provocation during interlaminar epidural steroid injection and its effects on pain reduction at follow-up. 48 patients with radicular lumbosacral pain had interlaminar epidural steroid injections (80 mg methylprednisolone and 2 mL of normal saline) under fluoroscopic guidance. Patients were asked to report if pain was provoked, and whether the pain was concordant or discordant with their baseline pain. Outcome measures included self-rated percentage of pain improvement, activity levels and analgesic consumption at 2-week follow-up. Provocation was observed in 37 out of 48 patients (77%), which was classified as concordant (22/37, 60%) or discordant (15/37, 40%) pain. The concordant group achieved a significant decrease in self-reported pain as compared to the discordant group at 2-week follow-up (61%, $t = 2.45$, $P < 0.01$), however, there was no significant differences between groups in regard to improvements in activity level and analgesic use. Concordant provocation during interlaminar epidural injection may, therefore, be a predictor of outcome.

Study	QS	Conclusions
Sinofsky et al. (2014)	LQ(-)	With LESI, via interlaminar or transforaminal approach concordant provocation is related to decrease in self-reported pain as compared to the discordant group at 2-week follow-up, however, there was no significant differences between groups in regard to improvements in activity level and analgesic use.

Chun and Park (2015)

Chun and Park (2015) (QS:HQ(++)) investigated the effect of different injectate volumes, using a combination of lidocaine and dexamethasone via a transforaminal approach, comparing 3mg (low injectate volume) with an 8mg (high injectate volume) dose in 66 patients with radiculopathy secondary to either spinal stenosis or HNP. Unfortunately, they did not subclassify their patient group, so it is impossible to identify if the effect was different between different patient groups. They classified benefit as meaningful pain relief i.e. ≥ 50% reduction from baseline VAS score at the 4 week mark. They also took secondary outcomes including the Roland-Morris Disability Questionnaire (RMDQ, range 0 – 24) score and adverse effects. Both groups demonstrated clinically and statistically significant improvement in radicular pain, and it was revealed the high volume group demonstrated significant pain relief compared to the low volume group (33.3 ± 25 vs. 46.3 ± 25, P < 0.05). Both groups demonstrated clinically and statistically significant improvement in functional status according to the RMDQ (P < 0.05)., however, there was no significant difference in functional status between the 2 groups (10.4 ± 4 vs. 11.5 ± 4, P > 0.05)

Study	QS	Conclusions
Chun and Park (2015)	HQ (++)	• Both groups (high and low volume) demonstrated clinically and statistically significant improvement in radicular pain • The high volume group demonstrated significant pain relief compared to the low volume group. • Both groups demonstrated clinically and statistically significant improvement in functional status according to the RMDQ (P < 0.05), however, there was no significant difference in functional status between the 2 groups

Cohen et al (2015)

Cohen et al (2015) (QS:(HQ++)) investigated the use of LESI (both interlaminar (4ml) and transforaminal (3ml)) compared with gabapentin (orally) in 145 patients with radiculopathy secondary to either spinal stenosis or HNP. Unfortunately, they did not sub classify their patient group so it is impossible to identify if the effect was different between different patient groups. This was a unique study as they blinded patients and researchers by using sham epidurals and placebo pills. They reviewed outcomes over a three month period. They reported no significant differences in pain scores at one month (adjusted difference 0.4, 95% confidence interval −0.3 to 1.2; P=0.25) and three months (adjusted difference 0.3, −0.5 to 1.2; P=0.43). One month after treatment LESI patients had greater reductions in worst leg pain (−3.0, SD 2.8) than those treated with gabapentin (−2.0, SD 2.9; P=0.04) and were more likely to experience a positive successful outcome (66% v 46%; number needed to treat=5.0, 95% confidence interval 2.8 to 27.0; P=0.02). At three months, there were no significant differences between the two treatments.

Study	QS	Conclusions
Cohen et al (2015)	HQ (++)	• LESI (interlaminar and transforaminal) no better than oral gabapentin in pain scores at one month and three months. • One month after treatment LESI patients had greater reductions in worst leg pain than those treated with gabapentin and were more likely to experience a positive, successful outcome. • At three months, there were no significant differences between the two treatments.

Denis et al (2015)

Denis et al (2015) (QS:HQ(++)) undertook a randomised double-blind controlled trial comparing equivalent doses of a nonparticulate (dexamethasone) with a particulate (betamethasone) corticosteroid in lumbar transforaminal epidural steroid injections (TFESIs) in 56 patients with MRI evidence of either a herniated disc or foraminal stenosis. Outcome measures included pain (VAS), functional improvement (Oswestry Disability Index (ODI) at 3 months. Both groups showed statistically significant VAS decreases over time (P<0.009 for dexamethasone and P<0.033 for betamethasone). For ODI, the decrease over time was statistically significant only for the dexamethasone group (P<0.0002 vs. P<0.079 for betamethasone). The improvement was modest at 1 month in the betamethasone group, but was estimated clinically significant at 3 and 6 months as well as at the three visits in the dexamethasone group. No differences on the VAS (p=0.209) and ODI (P=0.181) were found between the two groups at 3 months. At 6 months, improvement of ODI score was at the limit of statistical significance in favour of dexamethasone (P=0.050).

Study	QS	Conclusions
Denis et al. (2015)	HQ (++)	• Pain relief and functional improvement are similar for both dexamethasone and betamethasone at 3 months. • Considering its safety profile, dexamethasone could be considered as first choice for transforaminal LESI

Kennedy et al (2014)

Kennedy et al (2014) (QS:AQ(+)) investigated the difference in pain relief between particulate and non-particulate corticosteroids in 78 patients with radicular pain due to MRI diagnosed HNP. This study used a longer period of assessment, assessing patients at 2 weeks, 3 months and 6 months. Both groups received 1.5mls of injectate. At the 2 week follow-up, both groups showed clinically and statistically significant improvement in pain and functional measures, with a slightly (non-significant) higher level of pain relief with triamcinolone than dexamethasone (43.2 vs. 31.7%). At the 33 and 6 months follow-up there was no difference between the groups. ODI data also improved in each group without reaching a statistically significance difference between groups. Both groups moved from the “severe disability” range (score of 40–60) to the “minimal disability” range (score of 0–20) from baseline to 6 months follow-up. The average number of injections received for each group was 1.6 for dexamethasone and 1.4 for triamcinolone.

Study	QS	Conclusions
Kennedy et al. (2014)	AQ(+)	• Transforaminal LESI are an effective treatment in reducing pain levels in patients with acute radicular pain due to disc herniation, over 6 months • Transforaminal LESI are an effective treatment in improving disability, reducing disability scores (as measured by Oswestry Disability Index scores) in patients with acute radicular pain due to disc herniation over 6 months • Transforaminal LESI are an effective treatment in patients with acute radicular pain due to disc herniation, over 6 months and frequently only require 1 or 2 injections for symptomatic relief. • Dexamethasone appears to possess reasonably similar effectiveness when compared with triamcinolone. However, the dexamethasone group received slightly more injections than the triamcinolone group to achieve the same outcomes.

Koh et al (2015)

Koh et al (2015) (QS:HQ(++)) conducted a randomised, double-blinded, active-comparator controlled study into the effects of combining pulsed radiofrequency (PRF) treatment and transforaminal epidural injection (TFEI) to treat patients with chronic radicular pain caused by lumbar spinal stenosis. They randomly allocated 62 patients to an intervention group (involving FG- transforaminal ESI (2-3ml lidocaine with 20 mg of triamcinolone acetonide) + PRF) and a control group (involving just the FG-transforaminal ESI). Outcome measures included radicular pain intensity, analgesic consumption, physical functioning, global improvement and satisfaction with treatment and adverse events over a 3 month period. Both groups demonstrated significant improvements in NRS pain score and functional capacity (ODI) during the 3-month follow-up period, however, the medication quantification scale did not change significantly from baseline. The number of patients with successful treatment results was higher in the PRF group at 2 months (P = 0.032) and 3 months (P = 0.018), however, there were no significant differences observed in terms of the other outcome variables between the 2 groups.

Study	QS	Conclusions
Koh et al (2015)	HQ (++)	• Lumbar epidural steroid with anaesthetic via transforaminal approach combined with pulsed radiofrequency (PRF) treatment produced better results than lumbar epidural steroid with anaesthetic in reducing pain up to 3 months

Pirbudak et al (2015)

Pirbudak et al (2015) (QS:LQ(-)) investigated the effect of tramadol-only treatment and tramadol + gabapentin treatment in 40 patients who had received a transforaminal LESI with anaesthetic (4 ml, triamcinolone acetonide and 0.25% bupivacaine mixture) for radiculopathy secondary to confirmed NHP of at least 3 months duration. Whilst there was no control group for the transforaminal LESI both groups demonstrated

significant improvement at the 2-week reassessment mark with no between-group differences. Within the groups the VAS scores improved significantly (from 7.05+/-1.7 and 7.1 +/- 1.2, to 1.95 +/-1.27 and 1.15 +/-1.08 respectively), SLR increased (from 43.25^0 (30-60) and 44.50^0 (35–60), to 63.50^0 (30–75) and 60.25^0 (50–70)) and Oswestry Disability Index scores (from 38.00 ± 9.78 and 35.25 ± 9.10 to 26.75 ± 9.63 and 25.00 ± 8.11)

Study	QS	Conclusions
Pirbudak et al. (2015)	LQ(-)	• Transforaminal LESI effective for pain relief in patients with NHP of at least 3 months duration, at 2 weeks • Transforaminal LESI effective for reducing disability scores (as measured by Oswestry Disability Index scores) in patients with NHP of at least 3 months duration, at 2 weeks • Transforaminal LESI effective for improving impairment, as measured by straight leg raise, in patients with NHP of at least 3 months duration, at 2 weeks

3.5 Outcome Measures – Pain and Function - Recommendations

1. The evidence does not support the use of lumbar epidural steroids injections, via the transforaminal approach, for the first line relief of pain or improving disability in patients with radicular symptoms or low back pain

Level B

Level 1

- LESI not effective in reducing need for surgery in short or long term in patients with low back pain (Bicket et al. 2015; SR/MA (AQ+))

Level 1

- Percutaneous adhesiolysis and decompression surgery were more effective than LESI in patients with spinal stenosis (May and Comer 2013; SR (AQ+))
- Discectomy was effective compared to LESI for the short term in patients with radiculopathy due to herniated lumbar disc (Jacobs et al. 2011; SR (AQ+))

RCT

- LESI (interlaminar and transforaminal) no better than oral gabapentin in pain scores at one month and three months. One month after treatment LESI patients had greater reductions in worst leg pain than those treated with gabapentin and were more likely to experience a positive, successful outcome. At three months, there were no significant differences between the two treatments (Cohen et al. 2015; RCT (HQ++))

2. The evidence suggests that the transforaminal approach is effective in reducing pain in patients with radiculopathy, particularly secondary to herniation of nucleus pulposus and particularly in the short term.

Level A

Level 1++

- Transforaminal steroids provide modest analgesic benefit at 3 months in patients with lumbosacral radicular pain secondary to herniated intervertebral discs, but they have no impact on physical disability or incidence of surgery (Bhatia et al. 2016; SR/MA (HQ++))

Level 1+

- Transforaminal LEI with local anaesthetic and steroids, effective for pain relief with lumbar disc herniation in the short term (Manchikanti et al. 2012; SR (HQ++))
- TLESI effective in both short-term and long-term management of radiculopathy pain due to spinal stenosis or lumbar herniation (Benny and Azari 2011 SR (AQ+))
- For lumbar TLESI, the evidence for use in radicular pain was strong for short-term and moderate for long-term improvement in pain and functional outcome (Abdi et al. 2005; SR (AQ+))
- Transforaminal injections are more likely to yield positive results than interlaminar or caudal injections for patients with radiculopathy and low back pain (Cohen et al. 2013; SR (AQ+))
- All approaches to the interlaminar, caudal, and transforaminal epidural space provide long-term relief in 27—56% patients with radiculopathy (Abdi et al. 2005; SR (AQ+))

Level 1

- TLESI produced better pain relief compared with interlaminar LESI in randomised controlled trials in patients with low back pain with lumbosacral radicular pain (Wei et al. 2016; SR (AQ+))
- TLESI with anaesthetic, effective for pain relief with lumbar disc herniation in the long term (Manchikanti et al. 2012; SR (HQ++))

- TLESI with anaesthetic, effective for preventing surgery with lumbar disc herniation (Manchikanti et al. 2012; SR (HQ++))
- TLESI with anaesthetic, effective for pain relief with spinal stenosis in short and long term (Manchikanti et al. 2012; SR (HQ++))
- TLESI effective in reducing pain, restoring function, reducing the need for other health care, and avoiding surgery in patients with lumbar radicular pain caused by contained disc herniations (MacVicar et al. 2013; SR (LQ--))
- TLESI more effective for reducing pain in patients with lumbar herniated disc, compared with spinal stenosis or axial spinal pain. (Cohen et al. 2013; SR (AQ+))
- TLEI effective for reducing pain in patients with spinal stenosis in short-term (Manchikanti et al. 2015; SR (AQ+))
- Bilateral transforaminal injection was more effective than an interlaminar steroid injection in patients with spinal stenosis; (May and Comer 2013; SR (AQ+))
- Transforaminal approaches had better improvement in pain scores (4 months) compared with interlaminar injections. (Bresnahan et al. 2013; SR (A+)).
- TLESI recommended for chronic low back pain (Dagenais et al. 2010; SR(AQ+))
- TLESI recommended as a secondary intervention for low back pain with substantial neurologic involvement (Dagenais et al. 2010; SR(AQ+))
- TLESI have significant effect in relieving chronic pain of lumbar disc herniation and radiculitis with indicated evidence levels of Level II-1 for short-term relief and Level II-2 for long-term relief (Buenaventura et al. 2009; SR (AQ+))

RCT

- TLESIs are an effective treatment in reducing pain levels in patients with acute radicular pain due to disc herniation, over 6 months (Kennedy et al. 2014; RCT (AQ+))
- TLESI are an effective treatment in patients with acute radicular pain due to disc herniation, over 6 months and frequently only require 1 or 2 injections for symptomatic relief (Kennedy et al. 2014; RCT (AQ+))
- TLESI was a useful modality in treating pain secondary to lateral canal spinal stenosis, and the short-term functional outcomes were also improved significantly (Koh et al. 2013; RCT (HQ++))
- TLESI showed limited long-term effects in treating patients with spinal stenosis.(Koh et al 2013; RCT (HQ++))
- TLESI effective for pain relief in patients with NHP of at least 3 months duration, at 2 weeks (Pirbudak et al. 2015; RCT (LQ-))
- TLESI effective for improving impairment, as measured by straight leg raise, in patients with NHP of at least 3 months duration, at 2 weeks (Pirbudak et al. 2015; RCT (LQ-))

3. The evidence suggests that the transforaminal approach is not as effective in reducing disability and improving functional outcomes in patients with radiculopathy, particularly secondary to herniation of nucleus pulposus

Level B

FOR	AGAINST
Level 1++ • Transforaminal steroids provide modest analgesic benefit at 3 months in patients with lumbosacral radicular pain secondary to herniated intervertebral discs, but they have no impact on physical disability or incidence of surgery (Bhatia et al. 2016; SR/MA (HQ++))	
	Level 1+

	• For lumbar TLESI, the evidence for use in radicular pain was strong for short-term and moderate for long-term improvement in pain and functional outcome (Abdi et al. 2005; SR (AQ+))
Level 1 • TLESI not effective for improvement in disability (standardised mean difference in ODI 0). (Quraishi 2012; SR (LQ-)) • transforaminal fluoroscopy guided LESI no more effective compared to interlaminar fluoroscopy guided LESI in functional improvement in patients with radiculopathy secondary to IV disc herniation/degeneration in the long or short term (Chien et al. 2014; SR (HQ++)) • TLESI produced no better functional improvement and Oswestry Disability Index (ODI) score than interlaminar LESI in patients with low back pain with lumbosacral radicular pain (Wei et al. 2016; SR (AQ+))	**Level 1** • TLESI effective in reducing pain, restoring function, reducing the need for other health care, and avoiding surgery in patients with lumbar radicular pain caused by contained disc herniations (MacVicar et al. 2013; SR (LQ--))
	RCT • TLESI are an effective treatment in improving disability, reducing disability scores (as measured by Oswestry Disability Index scores) in patients with acute radicular pain due to disc herniation over 6 months (Kennedy et al. 2014; RCT (AQ+)) • TLESI effective for reducing disability scores (as measured by Oswestry Disability Index scores) in patients with NHP of at least 3 months duration, at 2 weeks (Pirbudak et al. 2015; RCT (LQ-))

4. The evidence suggests that the transforaminal approach is more effective in reducing pain due to radiculopathy compared to other approaches

Level A

Level 1+

- Transforaminal injections are more likely to yield positive results than interlaminar or caudal injections for radiculopathy. (Cohen et al. 2013; SR (AQ+))
- LESI more effective for reducing pain in patients with lumbar herniated disc, compared with spinal stenosis or axial spinal pain. (Cohen et al. 2013; SR (AQ+))

Level 1

- TLESI more effective than interlaminar LESIs (interlaminar LESIs) and caudal LESIs for radicular pain (Roberts et al. 2009; SR (AQ+))
- Bilateral transforaminal injection was more effective than an interlaminar steroid injection in patients with spinal stenosis (May and Comer 2013; SR (AQ+))
- transforaminal approaches had better improvement in pain scores (4 months) compared with interlaminar injections (Bresnahan et al. 2013; SR (AQ+))
- TLESI produced better pain relief compared with interlaminar LESI (Wei et al. 2016; SR (AQ+)).

3.6 Outcome Measures – Pain and Function - By condition

A range of diagnostic criteria were used to identify subjects for the studies included in this review. Table 6 presents the results of the systematic review/randomised controlled trials by diagnostic label

The range of diagnostic labels used reflects a potentially significant source of bias when interpreting the evidence related to the efficacy of lumbar epidural steroid injections. The effectiveness of an intervention such as LESI will depend on the appropriateness of the intervention to the clinical condition. Broad 'symptom-based' diagnostic criteria such as 'radiculopathy' or 'low back pain with radiculopathy' without consideration of the potential causes for the irritation/compression of the nerve make it difficult to consider the clinical applicability of the evidence. Due to the nature of the diagnostic categories presented, it is difficult to identify which groups are mutually exclusive and which patients would necessarily benefit from the intervention.

Table 6: Summary of systematic review/RCT results by condition and approach

Low Back Pain								
	Pain				Functional disability			
	Short Term		Long Term		Short Term		Long Term	
Systematic Reviews								
Bicket et al 2015	N		N					
Fritzler and Sarafini 2011	Y *(6 weeks)*		N		Y *(6 weeks)*		N	
Summary (systematic reviews)	**Y=1**	**N=1**	**Y=0**	**N=2**	**Y=1**	**N=0**	**Y=0**	**N=1**

Radiculopathy								
	Pain				Functional disability			
	Short Term		Long Term		Short Term		Long Term	
Systematic Reviews								
Abdi et al. 2005	Y		Y		Y		Y	
Buenaventura et al. 2009	Y		Y		Y		Y	
MacVicar et al. 2013	Y		Y					
Summary (systematic reviews)	**Y=3**	**N=0**	**Y=3**	**N=0**	**Y=2**	**N=0**	**Y=2**	**N=0**
RCT								
Chun & Park 2015	Y							

Cohen et al. 2015	**Y** *(<3 months)*				**Y** (<3 months)			
Dennis et al. 2015	Y		Y		Y		Y	
Ghai et al. 2014	Y		Y		Y		Y	
Koh et al. 2015	Y *(3 months)*				Y *(3 months)*			
Rados et al. 2013	Y		Y					
RCT Summary	**Y = 5**	**N=0**	**Y=3**	**N=0**	**Y=4**	**N=0**	**Y=2**	**N=0**

Radiculopathy secondary to Herniated Disc								
	Pain				**Functional disability**			
	Short Term		**Long Term**		**Short Term**		**Long Term**	
Systematic Reviews								
Wei et al. 2016 (HNP)	Y				Y			
Bhatia et al. 2016 (HNP)	Y *(3 months)*		N					
Chien et al. 2014 (HNP) *	Y		Y		Y		Y	
Benny and Azari 2011 (HNP)	Y		Y					
Summary (systematic reviews)	**Y=4**	**N=0**	**Y=2**	**N=1**	**Y=2**	N=0	Y=1	N=0
RCT								
Kennedy et al. 2014	Y		Y (6 months)		Y		Y *(6 months)*	
Manchikanti et al. 2014	Y		Y		Y		Y	
Pirbudak et al. 2015	Y *2 Weeks*				Y *2 Weeks*			
Summary (randomised controlled trials)	**Y=3**	**N=0**	**Y=2**	**N=0**	Y=3	N=0	Y=2	N=0

Herniated disc				
	Pain		**Functional disability**	
	Short Term	**Long Term**	**Short Term**	**Long Term**
Systematic Reviews				
Buenaventura et al. 2009	Y	Y	Y	Y

Summary systematic reviews	**Y=1**	**N=0**	**Y=1**	**N=0**	**Y=1**	N=0	**Y=1**	**N=0**

Stenosis								
	Pain				**Functional disability**			
	Short Term		**Long Term**		**Short Term**		**Long Term**	
Systematic Reviews								
May and Comer 2013	N		N		N		N	
Bresnahan et al. 2013	Y		N		Y		N	
Benny and Azari 2011	Y		Y					
Manchikanti et al. 2015	Y							
Summary (systematic reviews)	Y=3	N=1	Y=1	N=2	Y=1	N=1	Y=0	N=2

RCT								
Koh et al. 2013	Y		Y		Y		Y	
Summary (randomised controlled trials)	**Y=1**	**N=0**	**Y=1**	**N=0**	**Y=1**	N=0	**Y=1**	

Recommendations

When considering the evidence according to the diagnostic category:

- For radiculopathy of non-specific causes, the evidence suggests that the optimal approaches for reducing pain and improving functional outcomes are the transforaminal or interlaminar approaches in the short or long term. (Level B)
- For radiculopathy secondary to herniated Disc the evidence suggests that the optimal approach for reducing pain and improving functional outcomes is the transforaminal approach in the short or long term. (Level B)
- For pain due to a herniated disc, the evidence suggests that all approaches are equally effective in the short-term approach for reducing pain and improving functional outcomes with possibly slightly better long term effects with the transforaminal approach. (Level B)

3.7
Outcome Measures – Safety and Risk

This review also sought to synthesise the literature related to complications related to lumbar epidural. A total of 19 cohort studies and 10 case studies were identified and included in this section of the review.

A number of the systematic reviews included in the section on effectiveness of LESI also focussed on the risk of adverse events and complications related to the use of LESI, and have been included in this review. Many of the complications related to lumbar epidurals are similar across all three approaches so have been included in this review. Where specific complications/risks exist for transforaminal approach, these have been presented.

General complications review

Systematic reviews

Koes et al. (1995) reported that in the 12 randomised controlled trials they reviewed no major complications or side effects were reported. Transient minor complaints that were reported included:

- Headache (Serrao et al. 1992: n=8/52 (15%), Beliveau 1971: n=10/45 (22%), Ridley et al 1988: n=1/47 (2%))
- Nausea (Serrao et al. 1992: n=1/52 (2%), Rocco et al. 1989: n=1/49 (2%))
- Irregular periods (Bush and Hillier 1991: n=1/59)
- Pruritis (Rocco et al. 1989: n=1/49)
- Increased sciatic pain (Snoek et al. 1977: n= a few/72)

Four randomised controlled trials reported no side effects and three randomised controlled trials failed to make mention of side effects.

Armon et al. (2007) reported that the most common complication was a transient headache whether or not associated with identifiable dural puncture. More serious complications were several cases of aseptic meningitis, arachnoiditis, and conus medullaris syndrome, typically after multiple subarachnoid injections. Two cases of epidural abscess, one case of bacterial meningitis, and one case of aseptic meningitis were also listed. A retroperitoneal hematoma was reported in one patient on anticoagulant therapy who received a fluoroscopically guided transforaminal injection of steroids (Karppinen et al., 2001). Transient complications have also been encountered during fluoroscopically guided caudal epidural injections, including insomnia, transient non-positional headaches, increased back pain, facial flushing, vasovagal reactions, nausea, and increased leg pain. The role of practitioner experience and radiologic confirmation of needle placement could not be determined based on the reports. The results of the one high-quality study with radiologic confirmed needle placement did not provide a direct comparison of techniques. Therefore, the utility of, or need for, fluoroscopic confirmation of needle placement was unclear from the evidence reviewed by Armon et al. (2007).

Henschke et al. (2010) in their review of the efficacy of injection therapy for chronic low back pain found that in the majority of studies reviewed, no adverse events or side effects associated with treatments were reported. Epidural injections were associated with nausea and headache in some patients; however most trials were small and not designed to evaluate adverse events, so no clear conclusion can be drawn regarding the risks of injection therapy.

Jordan et al. (2011) in their review of interventions for herniated lumbar discs reviewed the adverse events reported in the literature from the use of epidural corticosteroids. They reported that one systematic review of conservative treatment for low back pain (Vroomen et al. 2000) reported no serious adverse effects although 26 subjects of 332 (7.8%) complained of transient headache or transient increase in sciatic pain. One review (DePalma et al., 2005) reported a 1.9% incidence of headache with epidural injections and a retroperitoneal haematoma in one person having anticoagulation treatment in one RCT. One RCT included in their review noted 2 of 43 subjects (5%) reported clinically important adverse effects with LESI, whilst 3 of 42 subjects (7%) reported clinically important adverse effects with placebo (with non-significant differences between the groups). They also noted that headache occurred in two people in each group (5%), and thoracic pain in one subject in the control group (2%).

Epidural hematomas were potentially the most serious of the epidural injection complications and could develop spontaneously even in patients with no evidence of any bleeding tendency, anticoagulation, or traumatic needle insertion. Neurological injuries were an uncommon complication that can occur when performing lumbar epidural steroid injections. Other complications include increased pain, seizures, chemical meningitis, dural puncture, subdural air, pneumocephalus, transient blindness, retinal necrosis, chorioretinopathy, hiccups, flushing, and arterial gas embolism. Side effects related to the administration of steroids are generally attributed either to the chemistry or the pharmacology of the steroids. Finally, radiation exposure was also a potential problem with damage to eyes, skin, and gonads.

Manchikanti et al. (2012a) in their systematic review of the evidence on the effectiveness of transforaminal LESI in managing lumbar spinal pain reported that the most common and worrisome complications, though rare, were related to neural trauma, vascular trauma, intravascular injection, and infection. None of the studies included in their review showed any major complications. Manchikanti et al. (2012a) concluded that most if not all complications could be avoided by careful technique with accurate needle placement, sterile precautions, and a thorough understanding of the relevant anatomy and contrast patterns on fluoroscopic imaging. However, a number of case studies have reported complications including spinal cord injury and infarction and paraplegia following transforaminal injections (Glaser and Falco 2005, Houten and Errico 2002)

Benoist et al. (2012) concluded that concerning safety, LESIs were generally well tolerated and most complications were related to technical problems during the procedure. However, the safety of ESIs should be questioned after the report of several cases of paraplegia complicating the foraminal route, a technique gaining popularity owing to its evidence of efficacy. Although quite exceptional, the seriousness of this adverse event implicates the research of alternative approaches to the foramen and means to detect an eventual arterial injury, as well as the use of a steroid agent with the least tendency to coalesce.

Bui and Bogduk (2013) and MacVicar et al 2013 in their reviews of the effectiveness of CT-Guided transforaminal LESI identified two practice audits of complications (Botwin et al. 2000, Karaman et al. 2011), and five case studies reporting eight cases of catastrophic complications (Houten and Errico 2002, Huntoon and Martin 2004, Somyaji et al. 2005, Glaser and Falco 2005, Kennedy et al. 2009). Both Bui and Bogduk (2013) and MacVicar et al 2013 concluded that "complications" such as headache, postprocedure pain, facial flushing, vasovagal reactions, rash, transient leg weakness, erectile dysfunction, dizziness, increased blood sugar, hypertensive episode, and nausea which have been reported (Botwin et al. 2000, Karaman et al. 2011) do not constitute complications of transforaminal LESI as they are all transient phenomena that might be encountered with any injection involving corticosteroids. Whilst case reports have reported technical problems that occur during transforaminal LESI such as dural puncture (Goodman et al. 2007), or unintended injection into a vein (Furman et al. 2000) or into a disc (Haspeslagh et al. 2004, Cohen et al. 2008, Finn and Case 2005), Bui and Bogduk (2013) and MacVicar et al. 2013 concluded that they do not constitute complications if they do not cause any impairment.

Epstein et al. (2013) reviewed the evidence related to complications arising from interlaminar and transforaminal LESI and identified a range of common risks including, increased neurological deterioration/paralysis/quadriplegia, intravascular injections (7.9-11.6%), cerebrospinal fluid (CSF) fistulas (0.4-6%), persistent positional headaches (28%), arachnoiditis (6-16%), hydrocephalus, air embolism, urinary retention, allergic reactions, intravascular injections (7.9-11.6%), stroke, blindness, neurological deficits/paralysis, hematomas, seizures, and death.

Chien et al. (2014) in their review of the transforaminal versus interlaminar LESI approach reported that despite the advantages for the transforaminal approach, the technique carried certain unique risks. The transforaminal approach has been more often implicated in severe, permanent complications compared to interlaminar LESI, including intravascular injection in up to 23% of lumbar epidural injection cases (Nahm et al. 2010), which can lead to spinal cord infarction and paralysis. Intravascular injection with transforaminal LESI can occur even with the use of digital subtraction angiography or following a negative lidocaine anaesthetic test dose (Chang et al. 2012). The transforaminal approach has been linked to a 12-fold increased risk of intradiscal injection, compared to the interlaminar approach (Candido et al. 2010, Cohen et al.

2008). Additionally, transforaminal LESIs do not decrease the risk of known complications of interlaminar LESI, such as dural and subdural punctures, hematoma formation, cauda equina syndrome (Chien et al. 2014). Chien et al. (2014) concluded that in an individual with lumbosacral radicular pain, the increased risk of complications associated with transforaminal LESI must be weighed against the possibility for superior pain relief and functional outcomes that reduce the rate of spinal surgery, which is itself associated with significant complications.

Cohort studies

Johnson et al. (1999) completed a retrospective cohort study involving 5334 procedures in which epidurography (i.e. the use of fluoroscopy and radiologic contrast material) was used immediately before and after epidural steroid injection, of which 4780 were lumbar, 669 cervical and 40 thoracic epidurals. All injections were performed by one of three experienced procedural neuroradiologists during a 5½-year period. They identified four complications including a significant hypotensive episode, a small dorsal epidural hematoma at the injection site, a severe vasovagal response after injection; and a case of tachycardia. The authors do not provide any information about the site of injection or the approach used in their report

Botwin et al. (2000) in a retrospective review reported complications in 207 patients receiving 322 fluoroscopically guided transforaminal LESI, which included 10 transient non-positional headaches that resolved within 24 hours (3.1%), 8 increased back pain (2.4%), 2 increased leg pain (0.6%), 4 facial flushing (1.2%), 1 vasovagal reaction (0.3%), 1 increased blood sugar (258mg/dL) in an insulin-dependent diabetic (0.3%), and 1 intraoperative hypertension (0.3%). No dural punctures occurred. The incidence of minor complications was 9.6% per injection with no major complications.

Furman et al. (2000) undertook a prospective cohort study evaluating the incidence of vascular penetration during fluoroscopically guided, contrast-enhanced, transforaminal LESI among 761 patients. The overall rate of intravascular injections was 11.2%. There was a statistically significant higher rate of intravascular injections (21.3%) noted with transforaminal LESI performed at S1 (n = 178), compared with those at the lumbar levels (8.1%, n = 583). Using flash or positive blood aspirate to predict intravascular injections was 97.9% specific, but only 44.7% sensitive. The authors concluded that there was a high incidence of intravascular injections in transforaminal ESIs that was significantly increased at S1.

Fitzgibbon et al. (2004) presented a review of the 5,475 claims in the American Society of Anesthesiologists' Closed Claims Project database between 1970 and 1999. This report provided insight into less common major complications associated with LESI. There were 114 claims related to ESIs making up 40% of all invasive pain management claims (Fitzgibbon et al. 2004). The types of complications included nerve injury: (28/114; 25%) Infection: (24/114; 21%), death/brain damage: (9/114; 8%), headache: (20/114; 18%), increased pain, no relief: (10/114; 9%). Nerve injury occurred in 28 of

the 114 claims (14 related to LESI). Six of these resulted in paraplegia, one in quadriplegia. Fitzgibbon et al.'s (2004) analysis demonstrated that injury to the cord was more common in upper lumbar epidural injections. Two cases of spinal cord injury resulting from epidural hematomas following ESI, with both patients having been receiving anticoagulants.

No major neurologic complications (spinal hematomas) were encountered in a series of 1,035 individuals who received 1214 epidural steroid injections while on antiplatelet therapy (Horlocker et al. 2002). Minor complications (blood during needle placement) were encountered in 63 (5.2%), and transient worsening of symptoms or emergence of new neurologic symptoms for more than 24 hours after the injection occurred in 42 (4%) patients with median duration of 3 days and range 1 to 20 days. NSAIDs did not increase the frequency of minor hemorrhagic complications. However, increased age, needle gauge, needle approach, needle insertion at multiple interspaces, number of needle passes, volume of injectant, and accidental dural puncture were all significant risk factors for minor hemorrhagic complications. Whilst the LESI approach that was used was not reported in the paper the authors reported that a midline approach was used in 1124 (93%) and paramedian in 56 (5%) patients, suggesting an interlaminar approach. Fluoroscopic guidance was used in 343 (28%) cases, and contrast injection was performed in 294 (24%) of the treatments. The authors concluded that epidural steroid injection was safe in patients receiving aspirin-like antiplatelet medications. Minor worsening of neurologic function may occur after epidural steroid injection and must be differentiated from etiologies requiring intervention.

Stalcup et al. (2006) presented a retrospective cohort study of 2,217 patients who had undergone selective lumbar nerve root blocks. The authors defined selective lumbar nerve blocks (SLNBs) as injections, performed either under fluoroscopic guidance or computed tomography, into or adjacent to the intervertebral foramen and delivering an anaesthetic and corticosteroid mixture into the immediate vicinity of the nerve root. Minor complications were encountered in 98 of the 1,777 total patient visits, for an overall complication rate of 5.5%. All complications were transient, and no patient suffered lasting harm. There were 1,232 procedures in which the patient received a single injection, and a minor complication was encountered in 62 of these visits. The complication rate approached 5% for all needle-tip positions, which was not statistically different from the overall complication rate. However, there was an increased likelihood of complications in patients undergoing a multiple injection procedure compared to those who had only one injection. The authors concluded that SLNBs performed with fluoroscopic guidance have a low incidence of complications and the specific needle-tip position within or adjacent to the lumbar neural foramen did not appear to be associated with the incidence of complications.

Candido et al. (2010) presented a retrospective review comparing rates of intradiscal injection in fluoroscopy guided transforaminal and interlaminar LESI. A total of 4723 interlaminar ESIs and 2412 transforaminal LESIs were performed over a three-year

period. The study identified 7 intradiscal injections of which 6 were associated with the transforaminal approach (for a rate of 1:402 injections) and 1 was associated with the interlaminar approach (for a rate of 1:4723 injections). Three of the 6 patients had undergone previous lumbar spinal surgery. Four of the 7 injections were done at the L4-5 level, 2 at the L2-3 level, and 1 at the L5-S1 level. None of the patients in this retrospective review sustained an infection. The relative rate of intradiscal injection was approximately 12 times higher after fluoroscopy guided transforaminal compared to fluoroscopy guided interlaminar LESI.

Chang et al. (2011) undertook a retrospective review of the safety of CT-guided steroid injections with air used to localise the epidural space. They reviewed 751 patients who underwent 1000 procedures. Procedures were performed at the L5/S1 levels (75%), L4/5 (15.5%), L3/4 (4.9%), L2/3 (1.3%), L1/2 (0.8%), and T12/L1 (0.1%). Of the 1000 LESI in this review, the authors reported that no immediate or delayed clinically significant complications were reported during a standard 24-hour and 1-week follow-up (99% of patients had 24-hour follow-up, and 93% had 2-week follow-up via phone or office consultation). The authors were clear to point out that only clinically significant complications were reported, although they failed to identify what made a complication clinically significant compared to not clinically significant.

Karaman et al. (2011) assessed the complications of transforaminal LESI prospectively over 1,305 injections in 562 patients over a 5 year period. All of the interventions were performed under fluoroscopic guidance by the same physician using a standardised method, with a follow-up once in the third week. The overall incidence of vascular penetration encountered was 7.4%. Although major complications were not seen, the total rate of all minor complications was 11.5%. Whereas all of the minor complications were transient, the most frequent minor complication was vasovagal reaction (8.7%).

In a retrospective cohort study over a 7-year period, McGrath et al. (2011) reviewed the results of 4,265 injections on 1,857 patients, involving 161 cervical interlaminar injections 123 lumbar interlaminar injections, 17 caudal injections, and 3,964 lumbar transforaminal injections. They identified a lack of major complications and reported 103 minor complications, for an overall complication per injection rate of 2.4%. The most common complications were increased pain (1.1%), pain at the injection site (0.33%), persistent numbness (0.14%), and ''other'' (0.80%). When comparing complications between interlaminar and transforaminal approaches, they reported less common complications with transforaminal injections (0.021%) than for IL injections (0.06%).

Table 7: Rate of complications from 4,265 injections epidural injections
(from McGrath et al. 2011)

Complication	interlaminar	transforaminal
Increased pain	0.021%	0.011%
Numbness	0%	0.0015%

Pain at injection site	0.018%	0.0023%
Other	0.021%	0.0068%
Total	0.06%	0.021%

Manchikanti et al. (2012) presented a prospective evaluation of complications of 10,000 fluoroscopically directed epidural injections of which 39% were caudal epidurals, 23% cervical interlaminar epidurals, 14% lumbar interlaminar epidurals, 13% lumbar transforaminal epidurals, 8% percutaneous adhesiolysis, and 3% thoracic interlaminar epidural procedures. They reported intravenous placement of the needle in 22% of the transforaminal procedures, with other complications including pain during the injection with back pain in 43% of the patients and leg pain in 22% of the patients. Postoperative complications were reported in 34% of the patients including soreness at the injection site (18%), increased pain (5%), muscle spasms (4%), swelling (4%), headache (3%), minor bleeding (2%), dizziness (1%), nausea and vomiting (1%), fever (1%), numbness (1%), and voiding difficulty (1%). With fluoroscopically, guided caudal LESI intravascular placement occurred in 14% of patients. They also reported minor complications in 7% of patients including soreness at the injection site (6%), increased pain (1%), muscle spasms (1%), headache (1%), and nausea and vomiting (1%) (See Table 8).

Table 8: Rate of complications from 10,000 fluoroscopically directed epidural injections
(from Manchikanti et al. 2012)

Complications	Interlaminar	Transforaminal	Caudal/Sacral
	N=1,450	N=1,310	N=3,985
Intravascular injection	0.5%	7.9%	3.1%
Return of blood	0.5%	3.7%	0.7%
Profuse bleeding	0.8%	0.2%	0.3%
Local haematoma	0.28%	0.2%	0.1%
Bruising	0%	0.4%	0.2%
Epidural haematoma	0%	0%	0%
Vasovagal reaction	0%	0.08%	0%
Nerve irritation	0.28%	4.6%	0%
Nerve damage	0%	0%	0%
Spinal Cord Infarct	0%	0%	0%
Disc entry	0%	0.08%	0%
Dural Puncture	0.8%	0%	0%
Headache	0.07%	0%	0%
Infection	0%	0%	0%
Abscess	0%	0%	0%
Facial flushing	0.13%	0.15%	0%
Rate of complications	0.13%-0.8%	0.08%-7.9%	0.1%-3.1%

Plastaras et al. (2015) undertook a retrospective cohort study from a multi-physician clinic of patients who underwent a fluoroscopically guided transforaminal LESI for lumbosacral radicular pain between 2004 and 2007. Complications data was collected using a survey both immediately and at 24 to 72 hours after the injection in 1,295 consecutive patients undergoing 2,025 fluoroscopically guided transforaminal LESI. Immediate complications and delayed complications occurred after 182 (9.2%) and 305 (20.0%) injections, respectively. The most common immediate complications were: vasovagal reaction (4.2%) and interrupted procedure from intravascular flow (1.7%). Common delayed complications included: pain exacerbation (5.0%), injection site soreness (3.9%), headache (3.9%), facial flushing/sweating (1.8%), and insomnia (1.6%). Significant associations were identified between AEs and gender, age, pre-procedure VAS, steroid type, and fluoroscopy time. Trainee involvement in the procedure did not impact the complication rate.

Case studies

Other much less common complications reported in case studies include transient blindness (Young 2002), retinal hemorrhage and necrosis (Browning 2003, Kushner and Olson 1995), serous chorioretinopathy (Pizzimenti and Daniel 2005, Iida et al 2001), persistent recurrent intractable hiccups (McAllister et al. 2005), flushing (Everett et al. 2004, Kim et al. 2010), chemical meningitis (Gutknecht 1987), arachnoiditis (Nelson and Landau 2001), discitis (Yue and Tan 2003) and epidural abscess (Hooten et al. 2004).
When reviewing complications related to LESI they can be divided into 6 major categories.

1. **Neurologic Injury**

Spinal cord damage can occur from needle entry into the cord. Traumatic spinal cord injury has been reported to be more common in patients who received sedation or general anaesthesia, especially in those who were unresponsive during the procedure.

In Fitzgibbon et al.'s (2004) retrospective review of the American Society of Anesthesiologists Closed Claims, nerve injury occurred in 28 of the 114 claims (14 related to LESI). Six of these resulted in paraplegia, one in quadriplegia. Fitzgibbon et al.'s (2004) analysis demonstrated that injury to the cord was more common in upper lumbar epidural injections.

2. **Vascular Insult**

Infarction of the lower spinal cord resulting in paraplegia has also been described following thoracic and lumbar transforaminal injections in a number of case study reports (Kennedy et al. 2009, Glaser and Falco 2005). Injection into the spinal medullary arteries can result in spinal cord infarction, typically in the distribution of the anterior spinal artery; the magnitude and location of the resultant neurologic injury appear to relate to the anatomic location of injection. Spinal cord infarction associated with TF approach is less common than direct spinal cord trauma, according to Fitzgibbon et al. 2004.

Intravascular injection is also possible, but can be prevented by using fluoroscopy (Cannon and Aprill 2000). Previous studies using fluoroscopic confirmation with contrast have shown a rate of 6.4% to 9.2% for the caudal route (White et al. 1980, Renfrew et al. 1991). One multicenter study included 1,219 fluoroscopically guided lumbar spinal injection procedures and found the following rates of intravascular injections: caudal 10.9%, transforaminal 10.8%, and translaminar 1.9 (Sullivan et al. 2000). This study also found that 74% of these vascular injections were not detected by aspiration prior to contrast injection. Another study included 577 transforaminal injections found intravascular injection rates of 8.8% for lumbar levels and 25.2% for the S1 level, with an overall rate of 12.7% (Furman et al. 2000)

All of the corticosteroid suspensions commercially available contain particles large enough to occlude capillaries and arterioles Animal studies have shown that direct injection of particulate steroid into the vertebral artery can result in irreversible posterior circulation strokes similar to those reported in case reports following transforaminal injection of steroid. (Okubadejo et al. 2008). Depot preparations of methylprednisolone, triamcinolone, and betamethasone form particles or aggregates that are larger than red blood cells and could form emboli in terminal vessels in the spinal cord (Bui and Bogduk 2013). Injection of the nonparticulate steroid solution, dexamethasone, resulted in no apparent injury in the same animal model, suggesting preliminary evidence for the safety of this agent.

Embolization has most often been related to the transforaminal approach and has not been implicated as a mechanism for injury following caudal or interlaminar ESIs (Cohen et al. 2013). Although transforaminal injections performed in the lumbar spine carry a much lower risk than in the thoracic or cervical regions, previous surgery has been associated with an increased risk of spinal cord infarct (Houten and Enrico 2002).

Wybier et al. (2009) reported a case series of 12 cases of sudden paraplegia immediately following LESIs since 2002. The clinical pattern was similar in all cases: within a few minutes after the procedures, acute abdominal and leg pain are followed by a complete sensorimotor deficit of the lower limbs. MRI performed a few hours after the procedure was usually normal. In contrast, MRI obtained 24–96hr later disclose a central high-intensity zone of the spinal cord consistent with an acute ischemia. Of the 12 patients reported by Wybier et al. (2009), 8 had previous surgery, and in 10 patients the injection route was foraminal; this route was the only one used in the 4 non-operated patients. The most probable mechanism of this complication is the violation of a radiculomedullary artery with embolization of macroaggregates of steroid, and subsequent deprivation of the arterial supply of the cord. The radiculomedullary artery, also known as Adamkiewicz artery usually arises from the left between T9 and L2. In a minority of individuals, it may arise at a lower level of the lumbar spine. At the level concerned, the nerve root runs in the foramen parallel to the artery, which can be damaged by the needle in the foraminal approach. The high

prevalence of this complication in operated patients may be related to the abundant vasculature and neoangiogenesis of the scar tissue, enhancing the risk of vascular damage.

Karaman et al. (2011) in their retrospective review of 1,305 injections via the transforaminal approach reported an overall incidence of vascular penetration of 7.4%.

The epidemiological evidence shows that CT guidance is not immune to vascular complications (Bui and Bogduk 2013). Of the eight reported cases of spinal cord infarction following lumbar transforaminal injection, five followed CT-guided procedures complications (Houten and Errico 2002, Huntoon and Martin 2004, Somyaji et al. 2005, Kennedy et al. 2009).

Bui and Bogduk (2013) and MacVicar et al. (2013) recommended that to reduce the risk of this complication operators must perform an injection of an adequate volume of contrast medium under continuous, anteroposterior, fluoroscopic imaging, sufficient to ensure that no intraspinal vascular uptake is present. The fluoroscopic field of view should include the spinal canal proximal to the level of injection such that intraspinal arterial uptake may be detected. Other measures recommended include: digital subtraction imaging, the use of low-volume extension tubing to minimise needle movement between the injection of contrast medium and the injection of steroids, and administering a test injection of local anaesthetic before injecting any steroid.

In most cases, there is probably little that can be done to minimise the extent of neurologic dysfunction after a traumatic or embolic event has occurred. High-dose intravenous steroids administered in the hours immediately following traumatic spinal cord injury have been shown to result in a significant reduction in neuronal injury (Hall and Springer 2004)

Intraspinal bleeding is a potentially devastating complication from LESI that can result in paraplegia or quadriplegia. Both epidural and subdural hematomas have been reported following ESIs in patients without coagulopathy or concurrent use of anticoagulants.

The most important risk factor for bleeding is coagulopathy either primary or pharmacological. Anticoagulants and antiplatelet drugs are contraindications to epidural injections of any sort. On the other hand, NSAIDs, do not appear to appreciably increase the risk of epidural bleeding. Horlocker et al. (2002) reported no major hemorrhagic complications among 1035 patients one-third of whom had been taking NSAIDs (134 on aspirin, 249 on other NSAIDs, and 34 on multiple drugs) who underwent 1214 ESIs, of which 80% were lumbar.

In an online survey conducted in 325 respondents (of 2300 surveyed) who perform interventional pain management procedures, nearly 3 times as many thromboembolic complications (n = 162) were reported as were serious bleeding complications (n = 55) (Manchikanti et al. 2012b). Among the thromboembolic events, 153 occurred following discontinuation of anticoagulation therapy, whereas 9 transpired despite antiplatelet therapy being continued. For the bleeding complications, 29 occurred after warfarin or antiplatelet therapy was discontinued, with 26 occurring in the context of continued anticoagulation treatment. These findings suggest that the decision to discontinue anticoagulation therapy for neuraxial injections must be made after careful consideration of the risks and benefits. Because of its location at the distal end of the spinal column, its shallow depth (which enables compression), and the fact that it can easily be accessed with a small gauge needle, the caudal approach might be considered when a LESI is strongly indicated and the risk of discontinuing warfarin or antiplatelet therapy is high.

3. Pharmacologic Effect of Corticosteroids - Hypercorticism and Adrenal Suppression

Theoretical pharmacological complications of corticosteroid administration include suppression of pituitary adrenal axis, hypercorticism, Cushing's syndrome, osteoporosis, avascular necrosis of the bone, steroid myopathy, epidural lipomatosis, weight gain, fluid retention, and hyperglycemia (Parr et al. 2009 and Benyamin et al. 2012).

Tonkovich-Quaranta and Winkler (2000) in their scoping review reported on a range of adverse effects associated with the use of epidural corticosteroids including:

- systemic absorption of the corticosteroid,
- a decrease in plasma cortisol concentrations, and
- suppression of the hypothalamic–pituitary–adrenal axis.

They cited a study by Knight and Burnell (1980) who reported on a series of four patients (out of 181 patients (2.2%)) who experienced adverse effects attributed to epidural steroid injections. The patients had received a total of 240–600 mg of methylprednisolone acetate via epidural catheter over two to three days. At the one-month follow-up, all patients reported adverse effects associated with corticosteroid use. These included facial fattening/swelling, a hump between the shoulder blades, and the appearance of small, raised, scaly lesions on the back. The authors noted that the injections were given on consecutive days and in higher dosages than those used in clinical trials (Knight and Burnell 1980)

The systemic effects resulting from oral or intravenous administration of steroids are rarely observed after epidural injections, however, side effects can result in an identical clinical pattern as Cushing's syndrome as the active corticosteroid, and other depot steroid preparations are slowly released over a period of days to weeks. Case studies

have reported post-LESI effects such as fluid retention and weight gain, facial swelling, buffalo hump, skin bruising, scaly skin lesions, increased blood pressure and congestive heart failure (Stambough et al. 1984, Tuel et al. 1990)

Allergies to any of the medications used can occur, and serious reactions can usually be prevented by questioning patients before the procedure. Side effects induced by corticosteroids are not uncommon. When they occur, the patient typically experiences transient symptoms, including insomnia, facial flushing, a sense of "feeling hot" ("steroid fever"), palpitations, nausea, nonpositional headaches, and a sense of agitation or anxiety. In most instances, these side effects are dose related and transient, usually resolving in the week after the procedure.

Manchikanti (2002) reviewed the potential complications which include complications related to the endocrine system: hyperglycemia or worsening of diabetes; adrenal suppression biologically detected following a series of ESIs performed with short intervals, hypertension with fluid retention and gain of weight.

Burn and Langdon (1974) measured plasma cortisol concentrations before and after epidural injection in a series of 72 outpatients. Patients were given an epidural injection consisting of 10 mL of lidocaine 1.5%, 7 mL of NaCl 0.9%, 1 mL of hydrocortisone acetate (25 mg), and 2 or 4 mL of methylprednisolone (80 or 160 mg). The authors found a statistically significant depression in plasma cortisol concentrations for both methylprednisolone dosages at one week after injection and for the 160mg dose at two weeks after injection. Kay et al. (1994) measured plasma cortisol and adrenocorticotropic hormone (ACTH) concentrations on 14 patients receiving a LESI of triamcinolone acetate 80 mg in 7 mL of lidocaine 1%. Patients received the injections weekly for three weeks. In addition, half the patients were randomised to receive intravenous midazolam 0.07 mg/kg prior to the epidural injection. They found that within 45 minutes of the first epidural injection, the plasma cortisol and ACTH concentrations dropped significantly ($p < 0.05$), and premedication with midazolam accentuated the depression. Plasma concentrations returned to normal within one month of the last injection for the group that did not receive midazolam. For the group that was pre-medicated with midazolam, plasma ACTH and cortisol still showed a statistically significant depression 30 days after the last epidural injection.

Another symptom of hypercorticism is steroid-induced myopathy, which is characterised by progressive proximal muscle weakness increased serum creatinine kinase levels, and a myopathic electromyography and muscle biopsy specimen following a single epidural dose of triamcinolone in a case study by Boonen et al. (1995).

Because severe cases of Cushing syndrome and adrenal suppression have been described after a single, relatively small steroid dose, it is unlikely that this

complication can be avoided in susceptible patients (Cohen et al. 2013). Cohen et al. (2013) reported that the most prudent guiding principle was to use repeated steroid injections only in those who experience significant benefit and to space the injections at long-enough intervals to allow complete recovery of adrenal function. Patients undergoing surgery within a few weeks of receiving deposteroids should be evaluated for adrenal suppression or should receive stress steroid coverage during the perioperative period.

The most commonly used steroids, methylprednisolone acetate, triamcinolone acetamide, and betamethasone acetate and phosphide mixture, have all been shown to be safe at epidural therapeutic doses in both clinical and experimental studies (Cohen et al. 2013)

Based on these studies, Tonkovich-Quaranta and Winkler (2000) recommended that injections of corticosteroids through an epidural catheter should not be given on consecutive days. Waiting one or two weeks between injections does not appear to allow enough time for plasma cortisol and ACTH concentrations to return to normal, and it may be more appropriate to wait one month between doses of epidural corticosteroids.

A decrease in bone marrow density in postmenopausal women was reported in a retrospective study performed in patients who had received a cumulative ESI dose of greater than 120 mg methylprednisolone compared with a control group treated with NSAIDs and muscle relaxants (Kang et al. 2012). In a follow-up study by the same group performed in 352 postmenopausal women who had been treated with ESI, the authors found no association between the incidence of pathological fractures and either the number or total dose of glucocorticoids. (Yi et al. 2012).

4. Altered Glucose Tolerance

Glucocorticoid administration reduces the hypoglycaemic effect of insulin and interferes with blood glucose control in diabetic patients. A prospective cohort study of 30 diabetic patients demonstrated significant changes in blood glucose levels that normalised within 2 days after LESI (Even et al. 2012). The mean blood glucose level before ESI was 160, which increased to 286 immediately after injection. Long-term indices of disease were followed in 9 diabetic patients after a single ESI of 80 mg depo-MPA and were determined to have no effect on glycemic control.

Patients with diabetes receiving ESI should be counselled that blood glucose may increase after intervention, but that the effects should dissipate within 2 days. Glucose levels in diabetic patients should be monitored closely during the first 2 days following any type of steroid injection. Patients need to be informed that adjustment of their insulin dose may be required (Cohen et al. 2013).

5. Dural Puncture

Accidental dural puncture during attempted epidural injection is associated with a headache incidence of greater than 50% (Charsley and Abram 2001). The headache incidence among patients undergoing attempted ESI appears to be much lower, perhaps due to the older patient population, the smaller-gauge needles used, and/or the widespread use of fluoroscopic guidance. In a retrospective cohort study that included 284 IL epidural injections, only 1 post-dural puncture headache was reported, for an overall incidence of 0.004%. (McGrath et al. 2011). Dural puncture may happen with a varying frequency between 2 and 5% (Chazerain 1998, Chou et al. 2009), leading to symptoms of post-dural puncture syndrome including headache, nausea and vertigo, there is a risk of subdural injection of the steroid, its buffers and preservatives carrying a potential neurotoxic effect and a risk of brain thrombophlebitis (Ergan et al. 1997).

Conservative management of post-dural puncture headache includes bed rest, hydration, caffeine, and mild analgesics. Following known dural puncture, an epidural blood patch can quickly and effectively reduce or eliminate the ensuing spinal headache (Cohen et al. 2013).

Direct neurotoxicity caused by the unintentional intrathecal injection of corticosteroid suspensions has been hypothesised to result in arachnoiditis and aseptic meningitis in some individuals. However, the link between intrathecal corticosteroid administration and these neurotoxic syndromes is not at all clear. It is not clear whether a single intrathecal injection is likely to cause serious harm. The reported cases of arachnoiditis were associated with multiple intrathecal injections, and in most cases, there was pre-existing neurologic disease. Arachnoiditis and aseptic meningitis are complications of intrathecal, not epidural, steroid injections. The use of a local anaesthetic test dose and/or fluoroscopy and radiographic contrast are reliable means to prevent unintentional intrathecal administration.

Patients should be instructed to promptly report neurologic changes, new or increasing pain, headache, and fever. A system of night and weekend coverage should be available, and patients should know how to contact the on-call physician. There is a real possibility that if the patient later develops arachnoiditis as a result of ongoing disease or surgery, it may be attributed to the injection. At this time, there is no evidence that epidural injection of steroids, without dural puncture, will produce either aseptic meningitis or arachnoiditis.

Local anaesthetic injection into the subarachnoid, subdural/extra-arachnoid, or extradural spaces may also result in sympathetic block and hypotension. Vasovagal reactions associated with the deep somatic pain of injection are another complication associated with these injections. When predictable, it can be effectively addressed by premedication with atropine. This reaction should be readily recognised with appropriate monitoring and is usually easily managed.

6. Infectious Complications

Any technique that penetrates the skin carries with it the risk of infection, although infectious complications following epidural are rare but can occur. It has been proposed that patients have been exposed to at least a 1-2% risk of infection (probably many go unreported/under-reported), with more serious infections observed in 0.1% of patients, 50% of which involve staphylococcus aureus, resulting in discitis, osteomyelitis, epidural abscess, as well as meningitis according to a literature review by Goodman et al. (2007).

An outbreak of fungal infections of the central nervous system occurred in the United States in late 2012 among patients who received LESI. Kainer et al. (2012) evaluated the outbreak of fungal infections that followed epidural or paraspinal injections of preservative-free MPA from one compounding pharmacy in New England. The median age of the 66 case-patients was 69 years (range, 23-91 years), with the median time from the last epidural injection to the development of symptoms being 18 days (range, 0-56 days). The presenting symptoms included meningitis alone (73%), cauda equina syndrome or focal infection (15%), and posterior circulation stroke, with or without meningitis (12%). At the time of admission, signs and symptoms were headache (in 73% of patients), new-onset or worsening back pain (in 50%), neurologic symptoms such as vertigo (in 48%), nausea (in 39%), and stiff neck (in 29%). A total of 21 patients had laboratory confirmation of Exserohilum rostratum infection, with 1 person developing an Aspergillus fumigatus infection. The risk of infection increased with exposure to a single lot of the compounded drug, older vials, higher administered doses, multiple procedures, female sex, age older than 60 years, and using an IL approach to epidural entry, which is associated with a higher risk of dural puncture. More than 650 cases of fungal infection and 39 deaths were reported. Kainer et al. (2012)

Practitioners involved in the care of these patients were utilising a compounding pharmacy that fell outside the direct regulatory oversight of the US Food and Drug Administration. This compounding pharmacy was preparing large batches of single-use, preservative-free vials of a depot formulation of MPA and marketing and distributing them widely across the United States.

Epidural abscess is a condition that can occur spontaneously, in the absence of injection or instrumentation of the spinal canal. Hooten et al. (2004) in a retrospective review examining the cases of epidural abscess following ESI, reported 14 cases, 2 of which also presented with meningitis. Eight of the cases (67%) exhibited positive blood, CSF, or epidural pus cultures documenting Staphylococcus aureus, suggesting that appropriate antibiotic prophylaxis for these procedures is warranted.

Fitzgibbon et al. (2004) reported infection as a cause for litigation in 24/114 cases involving ESI. There were 12 cases of meningitis, 3 cases of osteomyelitis, and 7 reports of epidural abscess; 2 cases involved multiple infection sites. Among the 7 cases of

epidural abscess, 6 required surgical decompression, and 1 resulted in permanent lower-extremity motor dysfunction. In 1 claim, there were both meningitis and epidural abscess and, in another, a combination of meningitis, abscess, and osteomyelitis.

Meticulous sterile technique with attention to skin preparation should prevent the large majority of infectious complications. Steroid injections should be avoided if there is any active infection. The incidence of infection following ESI is too low to justify routine prophylactic antibiotic use, and there is no data to support the benefit of prophylaxis in immunocompromised patients. The recommendation is that patients undergoing these procedures should receive appropriate pre-procedure prophylactic antibiotics.

Randomised controlled trials

Side effects related to LESI from the randomised controlled trials reviewed in this systematic review are presented in Table 10

Table 10: Side effects related to transforaminal LESI from the randomised controlled trials

	Transforaminal	
	Study	**%**
Adverse events	Friedly et al. 2014	33
Pain at injection site	Denis et al. 2015	9.4
Headache		
Nausea		
Increased lumbar pain	Denis et al. 2015	7.6
Increased radicular pain	Denis et al. 2015	7.6
	Manchikanti et al. 2014	4.6
Flushing	Denis et al. 2015	9.4
Anxiety	Denis et al. 2015	5.7
Vasovagal reaction	Denis et al. 2015	1.9
High blood pressure	Denis et al. 2015	1.9
Hyperglycemia	Denis et al. 2015	1.9
Menometrorrhagia	Denis et al. 2015	11.3
Change of mood	Denis et al. 2015	1.9
Agitation	Denis et al. 2015	3.8
Insomnia	Denis et al. 2015	3.8
Dizziness	Denis et al. 2015	1.9
Nausea/vomiting	Denis et al. 2015	1.9
Delayed menstrual cycle	Denis et al. 2015	1.9
Lower extremity edema	Denis et al. 2015	2%
Headache	Denis et al. 2015	1.9

Postdural puncture headache	Denis et al. 2015	1.9
Skin irritation		
Dural puncture	Manchikanti et al. 2014	4.6
Rate of complications	1.9%-33%	

Recommendations

- Minor complications associated with LESI are not uncommon but rarely require significant medical attention (Level B)
- Major complications associated with LESI are rare (Level B)
- Transforaminal LESIs are associated with a higher incidence of major complications (Level B)

3.8
Outcome Measures – Economic

Across the literature reviewed there has been few cost analyses performed on LESI. Where cost has been included as an outcome measure it is usually as a secondary measure not the primary measure of most research studies. This has serious consequences in terms of sufficient powering of the studies for a definitive finding
In the current era characterised by the need to alter the trajectory of rapidly ascending health care costs, the cost-effectiveness of any intervention has assumed an increasingly important role.

Because of the high costs of surgery, health care utilisation, disability, and lost productivity, any cost-benefit analysis for ESI is to a large extent contingent on reducing alternative health care utilisation (e.g., surgery and health care provider visits) and expediting or enhancing return to work. A number of ways have been suggested to identify cost-benefit from use of LESI. One is to evaluate whether they facilitate return to work, as lost productivity accounts for over half of the economic costs of low back pain, whether they prevent expensive treatments like surgery (Bicket et al. 2015), or calculating the actual costs of the intervention.

In individuals unemployed secondary to low back pain, the likelihood of returning to work declines exponentially with the length of disability with those remaining out of work for more than 3 months unlikely to return to work regardless of the intervention.

Consequently, core domain outcome measures for chronic pain used in studies, often do not even include return to work as a potentially achievable outcome. Cohen et al. (2013) identified a number of studies that have looked at return to work as a secondary outcome. The majority of these clinical trials have failed to report a significant difference between return-to-work rates or missed work days when ESI and control groups are compared. Yet, some randomised controlled trials indicate that in well-selected patients, LESI may improve work status. More patients returned to work in the LESI group than in the control group in several randomised controlled trials (63% vs 25% in Breivik et al (1976), 54% vs 40% in Kraemer et al (1997) and 53% vs 33% in Rogers et al (1992), although all are limited by the small number of participants. In a large-scale (n = 228), double-blind, placebo-controlled cost-effectiveness health care assessment on the efficacy of LESI for sciatica, Price et al (2005) reported no statistically significant difference in the proportion of subjects unable to return to work 1 year after treatment with LESI (24.1% in the treatment group vs 22.2% in the control group), although the mean number of days the treatment group missed work because of radiculopathy declined more than the number of days in the control group (65 vs. 33).

Surgery Sparing

Using surgical intervention as a primary outcome measure of the cost effectiveness of ESI is challenging, however, the ability to prevent surgery is an important outcome measure for ESI, as it is objective (whereas pain is always subjective), reflects sustained and long-term treatment failure, and can dramatically alter cost-utility analyses. The

evidence related to the surgery sparing is unclear. Bicket et al. 2015 in a systematic review on the effectiveness of LESI in reducing the need for surgery reported that there was a small surgery-sparing effect in the short term compared with control injections and reduction in the need for surgery in some patients who would otherwise proceed to surgery. In the long term studies, the surgery –sparing effect of LESI failed to reach statistical significance. As the authors reported, the long-term effectiveness of LESI is limited because of either disease progression of the spine or of the duration of action of the steroid. Also in most controlled studies, LESI were not routinely repeated on an ''as-needed'' basis, as is often done in clinical practice. Randomised controlled trials that allowed for multiple injections were more likely to report positive outcomes than studies that limited the number of injections to one (Roberts et al. 2009).

Cohen et al. (2013) concluded that the evidence for a surgery sparing effect from LESI was conflicting. They reported a randomised controlled trial from Riew et al. (2000) that compared the operative rate in patients with herniated disc or spinal stenosis who were randomised to receive a series of either lumbar transforaminal LESI or epidural bupivacaine (anaesthetic). At follow-up periods ranging between 13 and 28 months, 29% of patients in the treatment group underwent surgery, which favourably compared with a 67% operative rate in the control group. In their subsequent paper when following up the cohort 5 years later most patients who had avoided surgery for the initial year continued to avoid surgery Riew et al. (2006). Radcliff et al 2012 analysed data from the multicenter, randomized SPORT study comparing surgery to nonsurgical treatment for herniated disc, and identified fewer patients who received ESI within 3 months of enrolment expressed a preference for surgery (19% vs. 56%), and a higher percentage crossed over from surgical to nonsurgical management (41% vs. 12%), than those who did not receive ESI. In contrast, the large majority of randomised controlled trials that have included surgery sparing as secondary outcome measures have failed to find a difference in operative rates between ESI and placebo treatments (Cohen et al. 2013).

As identified by Cohen et al. (2013) nearly all of these studies are underpowered to detect a difference and incorporate some degree of bias through patient selection.
With regards to spinal stenosis, the literature reports modest long-term results with surgery for spinal stenosis; QALY cost is $77600 with 62%, or $48112 of the total cost, as direct medical costs. In contrast, caudal epidural injections have shown to have a cost utility of $2155 per QALY with direct medical costs (Manchikanti et al. 2015). While surgery may be essential in severe symptomatic stenosis, for all other conditions conservative management with epidural injections in conjunction with physical therapy modalities and exercise programmes is a cost-effective modality to manage mild to moderate symptomatic central spinal stenosis as well as those patients who have contraindications or are unwilling to undergo surgery. (Manchikanti et al. 2015).

Health care utilisation

Studies evaluating the ability of ESI to reduce health care utilisation as a secondary

outcome measure have yielded conflicting results (Cohen et al. 2013). Karppinen et al. (2001) found no overall difference in healthcare costs between treatment and control groups, although the LESI group had lower medication and therapy costs at 4-week follow-up. Price et al. (2005) in a large review concluded that LESIs do not provide good economic value in terms of the cost per quality-adjusted life year (QALY) for the treatment from the perspective of both the provider and purchaser. Based on the NICE threshold of £30,000 per QALY they concluded that LESIs failed the NICE QALY threshold. However, as the authors warned, the private benefits of short-term pain relief and improved function from LESI may be highly valued by the individual, affecting the ability to transpose these findings to private clinical practice.

Quaraishi et al (2012) reported on an RCT from Karpinnen et al (2001) looking at cost effectiveness related to transforaminal LESI for patients with radiculopathy that found that at the 4-week follow-up period the patients who had received steroid/local anaesthetic injection had utilized fewer therapy visits and fewer drugs resulting in significantly lower costs. However, at all other times, there was no significant cost difference in the groups.

Bresnahan et al. (2013) undertook a study to investigate the Reimbursement amounts related to LESI from their institution, and from the literature. They identified two observational studies that looked at reimbursement from LESI in the USA. Friedly et al. (2007) conducted an observational study that described use trends and cost outcomes of LESI in a Medicare population. They reported rates of lumbar ESI increased 271%, from 1994 to 2001, with a mean number of lumbar injections of 2.5 per patient and that the mean number of days between injections of 110. Over this time reimbursed costs per injection nearly doubled, from $115 to $227, with the total cost of physician professional fees paid by Medicare increasing from $24 million to $175 million.

Manchikanti et al. (2010) used observational data to compare use and charges for ESI in the Medicare population in 1997, 2002, and 2006. All ESI procedures increased 119%, from 1997 to 2006, with the rate of LESI 49% higher in 2006 versus 2002. From 1997 to 2006 the total estimated charges to Medicare during this period grew by 87%, going from $397 million to $744 million. Bresnahan et al. (2013) undertook a study of their own institution and identified 279 individual Medicare beneficiaries who received a total of 404 ESIs over 1 year. A total of 186 patients received a single injection, whereas 63 received 2 injections, 28 received 3 injections, and 2 had 4 injections, with a mean number of days between injections ranging from 43 to 105.2 days. Other frequent service item categories used in relation to an ESI procedure included fluoroscopy (98.76%), iodine low osmolar contrast material (96.04%), anaesthetics (19.55%), and sedatives (16.83%). The mean total payment for technical fees of $505 per episode and $132 for mean total professional fee payments. Stratifying by visit, patients who received 1, 2, 3, or 4 LESI episodes had cumulative, mean total reimbursement amounts (technical and professional fees) of $652, $1260, $1855, and $2403, respectively. They estimated that typical pre-LESI events (i.e. specialist visits

and lumbar MRI without contrast) add approximately $645 payments, in addition to payments for health care use subsequent to the ESI event.

MacVicar et al. (2013) in their systematic review identified that patients who had transforaminal LESI tended to have fewer sick days, fewer resorted to surgery, and twice as many had at least 75% reduction in pain (44% +/- 20% compared with 21% +/- 16%), but statistical significance did not emerge, possibly because of the small sample sizes involved. However, MacVicar et al. (2013) concluded that for those patients with contained herniations, transforaminal LESI was significantly cost-effective at 12 months, achieving a cost-reduction of $12,666 per responder.

This finding was supported by Manchikanti et al. 2012 who concluded that considering the low risk and less expensive nature of the procedure, compared to surgical interventions, transforaminal epidural injections with or without steroids appeared to be cost effective. (Manchikanti et al. 2012)

Recommendations

- The evidence suggests that LESI may present a cost-effective intervention in the short term through reducing other health expenditure, reducing the need for expensive surgery and reducing sick days. Any significant cost effectiveness associated with LESI is dependent on repeat injections on an as needed basis. Level C Recommendation

4. References

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5. Appendices

Appendix 1 - Copies of the SIGN Checklists

SIGN Critical Appraisal Tool for Systematic Reviews and Meta-analyses

SIGN	**Methodology Checklist 1: Systematic Reviews and Meta-analyses** SIGN gratefully acknowledges the permission received from the authors of the AMSTAR tool to base this checklist on their work: *Shea BJ, Grimshaw JM, Wells GA, Boers M, Andersson N, Hamel C,. et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. BMC Medical Research Methodology 2007, **7**:10 doi:10.1186/1471-2288-7-10. Available from http://www.biomedcentral.com/1471-2288/7/10 [cited 10 Sep 2012]*
Study identification (*Include author, title, year of publication, journal title, pages*)	
Guideline topic:	Key Question No:
Before completing this checklist, consider: Is the paper relevant to key question? Analyse using PICO (Patient or Population Intervention Comparison Outcome). IF NO reject. IF YES complete the checklist.	
Checklist completed by:	

Section 1: Internal validity

	In a well conducted systematic review:	***Does this study do it?***	
1.1	The research question is clearly defined and the inclusion/ exclusion criteria must be listed in the paper.	Yes □ **If no reject**	No □
1.2	A comprehensive literature search is carried out.	Yes □ Not applicable □ **If no reject**	No □
1.3	At least two people should have selected studies.	Yes □	No □ Can't say □
1.4	At least two people should have extracted data.	Yes □	No □ Can't say □
1.5	The status of publication was not used as an inclusion criterion.	Yes □	No □
1.6	The excluded studies are listed.	Yes □	No □
1.7	The relevant characteristics of the included studies are provided.	Yes □	No □
1.8	The scientific quality of the included studies was assessed and reported.	Yes □	No □
1.9	Was the scientific quality of the included studies used appropriately?	Yes □	No □

1.10	Appropriate methods are used to combine the individual study findings.	Yes □ Can't say □	No □ Not applicable □
1.11	The likelihood of publication bias was assessed appropriately.	Yes □ Not applicable □	No □
1.12	Conflicts of interest are declared.	Yes □	No □
SECTION 2: OVERALL ASSESSMENT OF THE STUDY			
2.1	What is your overall assessment of the methodological quality of this review?	High quality (++) □ Acceptable (+) □ Low quality (-)□ Unacceptable – reject 0 □	
2.2	Are the results of this study directly applicable to the patient group targeted by this guideline?	Yes □	No □
2.3	**Notes:**		

SIGN Critical Appraisal Tool for Controlled trials

Methodology Checklist 2: Controlled Trials

Study identification (*Include author, title, year of publication, journal title, pages*)

Guideline topic:	Key Question No:	Reviewer:

Before completing this checklist, consider:

1. Is the paper a **randomised controlled trial** or a **controlled clinical trial**? If in doubt, check the study design algorithm available from SIGN and make sure you have the correct checklist. If it is a **controlled clinical trial** questions 1.2, 1.3, and 1.4 are not relevant, and the study cannot be rated higher than 1+
2. Is the paper relevant to key question? Analyse using PICO (Patient or Population Intervention Comparison Outcome). IF NO REJECT (give reason below). IF YES complete the checklist.

Reason for rejection: 1. Paper not relevant to key question ☐ 2. Other reason ☐ (please specify):

SECTION 1: INTERNAL VALIDITY

In a well conducted RCT study…		***Does this study do it?***
1.1	The study addresses an appropriate and clearly focused question.	Yes ☐ No ☐ Can't say ☐
1.2	The assignment of subjects to treatment groups is randomised.	Yes ☐ No ☐ Can't say ☐
1.3	An adequate concealment method is used.	Yes ☐ No ☐ Can't say ☐
1.4	The design keeps subjects and investigators 'blind' about treatment allocation.	Yes ☐ No ☐ Can't say ☐
1.5	The treatment and control groups are similar at the start of the trial.	Yes ☐ No ☐ Can't say □
1.6	The only difference between groups is the treatment under investigation.	Yes ☐ No ☐ Can't say ☐
1.7	All relevant outcomes are measured in a standard, valid and reliable way.	Yes ☐ No ☐ Can't say ☐
1.8	What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?	
1.9	All the subjects are analysed in the groups to which they were randomly allocated (often referred to as intention to treat analysis).	Yes ☐ No ☐ Can't say ☐ Does not apply ☐
1.10	Where the study is carried out at more than one site, results are comparable for all sites.	Yes ☐ No ☐ Can't say ☐ Does not apply ☐

SECTION 2: OVERALL ASSESSMENT OF THE STUDY

2.1	How well was the study done to minimise bias?	High quality (++)☐

	Code as follows:	Acceptable (+)☐ Low quality (-)☐ Unacceptable – reject 0 ☐
2.2	Taking into account clinical considerations, your evaluation of the methodology used, and the statistical power of the study, are you certain that the overall effect is due to the study intervention?	
2.3	Are the results of this study directly applicable to the patient group targeted by this guideline?	
2.4	**Notes.** Summarise the authors' conclusions. Add any comments on your own assessment of the study, and the extent to which it answers your question and mention any areas of uncertainty raised above.	

SIGN Critical Appraisal Tool for Cohort studies

SIGN

Methodology Checklist 3: Cohort studies

Study identification (*Include author, title, year of publication, journal title, pages*)

Guideline topic:	Key Question No:	Reviewer:

Before completing this checklist, consider:

1. Is the paper really a cohort study? If in doubt, check the study design algorithm available from SIGN and make sure you have the correct checklist.
2. Is the paper relevant to key question? Analyse using PICO (Patient or Population Intervention Comparison Outcome). IF NO REJECT (give reason below). IF YES complete the checklist..

Reason for rejection: 1. Paper not relevant to key question ☐ 2. Other reason ☐ (please specify):

Please note that a retrospective study (ie a database or chart study) cannot be rated higher than +.

Section 1: Internal validity

	In a well conducted cohort study:	Does this study do it?	
1.1	The study addresses an appropriate and clearly focused question.[i]	Yes ☐ Can't say ☐	No ☐
	SELECTION OF SUBJECTS		
1.2	The two groups being studied are selected from source populations that are comparable in all respects other than the factor under investigation.[ii]	Yes ☐ Can't say ☐	No ☐ Does not apply ☐
1.3	The study indicates how many of the people asked to take part did so, in each of the groups being studied.[iii]	Yes ☐	No ☐ Does not apply ☐
1.4	The likelihood that some eligible subjects might have the outcome at the time of enrolment is assessed and taken into account in the analysis.[iv]	Yes ☐ Can't say ☐	No ☐ Does not apply ☐
1.5	What percentage of individuals or clusters recruited into each arm of the study dropped out before the study was completed.[v]		
1.6	Comparison is made between full participants and those lost to follow up, by exposure status.[vi]	Yes ☐ Can't say ☐	No ☐ Does not apply ☐

ASSESSMENT

1.7	The outcomes are clearly defined.[vii]	Yes □ Can't say □	No □
1.8	The assessment of outcome is made blind to exposure status. If the study is retrospective this may not be applicable.[viii]	Yes □ Can't say □	No □ Does not apply □
1.9	Where blinding was not possible, there is some recognition that knowledge of exposure status could have influenced the assessment of outcome.[ix]	Yes □ Can't say □	No □ □
1.10	The method of assessment of exposure is reliable.[x]	Yes □ Can't say □	No □
1.11	Evidence from other sources is used to demonstrate that the method of outcome assessment is valid and reliable.[xi]	Yes □ Can't say □	No □ Does not apply□
1.12	Exposure level or prognostic factor is assessed more than once.[xii]	Yes □ Can't say □	No □ Does not apply □
CONFOUNDING			
1.13	The main potential confounders are identified and taken into account in the design and analysis.[xiii]	Yes □ Can't say □	No □
STATISTICAL ANALYSIS			
1.14	Have confidence intervals been provided?[xiv]	Yes □	No □
SECTION 2: OVERALL ASSESSMENT OF THE STUDY			
2.1	How well was the study done to minimise the risk of bias or confounding?[xv]	High quality (++) □ Acceptable (+) □ Unacceptable – reject 0	
2.2	Taking into account clinical considerations, your evaluation of the methodology used, and the statistical power of the study, do you think there is clear evidence of an association between exposure and outcome?	Yes ☐ Can't say ☐	No ☐
2.3	Are the results of this study directly applicable to the patient group targeted in this guideline?	Yes □	No □
2.4	**Notes.** Summarise the authors conclusions. Add any comments on your own assessment of the study, and the extent to which it answers your question and mention any areas of uncertainty raised above.		

Appendix 2: Summary of studies and quality scores for articles included in this review

Author and year	SIGN Score	Approach	Studies (Patient No)	Outcome	Conclusions	Evidence				Grade
						1	2	3	4	
SRs Included in Shamilyan et al.'s (2014) Review										
Novak and Nemeth 2008 *Lumbosacral radiculopathy,*	A(+)	All approaches	11 RCT, 1CCT, 2 Prospective cohort (n=NS)	Pain, function	• There is no evidence to suggest guidelines for frequency and timing of ESIs or to help to define what constitutes the appropriate partial response to trigger a repeat injection.	0	1	1	0	1
Staal et al. 2008 *(SR/MA)* *Subacute and chronic low-back pain (**Radiculopathy excluded)*	HQ (++)	All approaches	7 RCTs (n=101)	Pain, function	• LESI not effective compared to placebo injections for general improvement in the short term	0	1	0	1	1
					• LESI not effective compared to placebo injections for pain relief in the short term	0	1	0	1	1
					• LESI no more effective compared to placebo injections for work disability in the short term	0	1	0	1	1
					• LESI no more effective compared to NSAIDs for pain relief in the short term in post-laminectomy patients	0	1	0	1	1
					• LESI no more effective compared to benzodiazepine for pain relief and general improvement both in the short and intermediate term	0	1	0	1	1
					• LESI no more effective compared to morphine eventually combined with corticosteroids for pain relief in the short and intermediate term in post-laminectomy patients	0	1	0	1	1
Roberts et al. 2009 (SR) *Lumbar Radiculopathy*	A (+)	*Fluoroscopically guided transforaminal epidural*	9 RCTs (n=617)	Pain, function	• TLESI more effective than placebo for treating radicular symptoms from HNP	0	1	0	1	1
					• TLESI effective as a surgery sparing intervention for treating radicular symptoms	0	1	0	1	1
					• TLESI more effective than interlaminar LESIs (interlaminar LESIs) and caudal LESIs for radicular pain	0	1	0	1	1
					• TLESI as effective as a single transforaminal injection of bupivacaine or saline.	0	1	0	1	1

Author and year	Quality	Approach	Studies (patient No)	Outcomes	Conclusions	Grade				Evidence
						1	2	3	4	
Rabinovotch et al. 2009 (SR) *Radicular leg pain and/or low back pain*	A (+)	*All approaches*	15 RCTs, 1 CCT (n=886)	Pain (short term to long term)	• LESI effective in the immediate-term in reducing pain with positive correlation between LESI volume and pain relief: r=0.8027 (p=0.0017).	0	1	1	0	1
					• In the short term, there was a non-statistically significant positive correlation between LESI volume and pain relief: r=0.5019 (p=.168).	0	1	1	0	1
					• In the intermediate term, there was a statistically significant positive correlation between volume and pain relief: r=0.9470 (p=.014).	0	1	1	0	1
					• There was insufficient data to calculate the correlation coefficient in the long-term category.	0	1	0	1	1
					• Irrespective of the medications injected there was a statistically significant difference when comparing the mean effect size where the volume injected was the same between the two groups (mean, standard deviation [SD]: 0.07, -0.26) with those where the volumes were different between comparison groups (mean, SD: 0.81, -0.6),	1	1	1	0	1+
Dagenais et al. 2010 (SR) Acute/chronic LBP +/- radicular referral	A (+)	*Not specified*	10 CG (n=NS)	Neurological improvement	• TLESI recommended for chronic low back pain	0	1	1	0	1
					• LESI recommended as a secondary intervention for low back pain with substantial neurologic involvement	0	1	1	0	1
					• TLESI recommended as a secondary intervention for low back pain with substantial neurologic involvement	0	1	1	0	1
Henschke et al. 2010 (SR) *LBP*	HQ (++)	*All approaches*	2 RCTs (n=88)	Pain	• LESI is no more effective than benzodiazepine injection for pain relief over short to intermediate term.	0	1	0	1	1
					• LESI is no more effective than targeted epidural placement for pain relief over the short to intermediate term.	0	1	0	1	1

Author and year	SIGN Score	Approach	Studies (patient No)	Outcome	Conclusions	Grade				Evidence
						1	2	3	4	
Jordan et al. 2010 (SR) Herniated disc	A(+)	*All approaches*	5 SRs and 5 RCTs (n=NS)	Pain, disability	• LESI effective compared with no LESI at improving limb pain at 2 weeks.	0	1	0	0	1 -
					• LESI no more effective compared with no LESI in reducing limb pain after more than 2 weeks in people with disc herniation	0	1	1	1	1+
					• LESI is no more effective compared with LESI in the longer term at improving disability, or functional outcomes such as straight leg raising and lumbar flexion, in people with disc herniation.	0	1	1	1	1+
					• LESI effective compared with no LESI at increasing subjective global improvement and patient satisfaction in the short term (2 weeks),	0	1	0	1	1
					• LESI not effective compared with no LESI at increasing subjective global improvement and patient satisfaction in the longer term (after 2 weeks) in people with disc herniation.	0	1	0	1	1
					• LESI plus conservative treatment no more effective than conservative treatment at 6 weeks and 6 months for pain scores in people with disc herniation.	0	1	0	1	1
					• LESI plus conservative treatment no more effective than conservative treatment at 6 weeks and 6 months for mobility scores and reducing need for surgery in people with disc herniation	0	1	0	1	1
					• LESI less effective compared with standard discectomy at 1 to 3 months for leg pain or disability in people with lumbar disc herniation	0	1	0	1	1

Author and year	SIGN Score	Approach	Studies (patient No)	Outcome	Conclusions	Grade				Evidence
						1	2	3	4	
Lewis et al. 2011 (SR) Sciatica	HQ (++)	*All approaches*	12 RCTs (n= NS)	Pain and function	• LESI effective in reducing pain and improving functional status compared to inactive control at short-term follow-up (< 6 weeks)	1	1	1	0	1+
					• LESI not effective in global effect compared to inactive control at short-term follow-up	1	1	1	1	1++
					• LESI not effective compared to inactive control for global effect, pain intensity or CSOMs at medium-term follow-up	1	1	1	0	1+
					• LESI not effective compared to inactive control for global effect, pain intensity or CSOMs at long-term follow-up.	1	1	0	1	1+
					• LESI effective compared to usual care for overall recovery and functional status at short-term follow-up, but not for pain intensity.	1	1	1	0	1+
					• LESI not effective compared to usual care at medium-term follow-up for global effect, pain intensity or CSOMs. However, usual care was associated with significantly fewer adverse effects than LESI	1	1	1	1	1++
					• LESI effective compared to non-opioids for reducing pain and improving functional status at short-term follow-up	1	1	0	1	1+
					• LESI not effective compared to non-opioids for global effect or CSOMs at medium-term follow-up or adverse effects.	1	1	0	1	1+
					• LESI not effective compared to chemonucleolysis for the global effect at short-term or medium-term follow-up.	1	1	0	1	1+
					• LESI worse than chemonucleolysis in the number of adverse effects	1	1	0	1	1+
					• LESI effective compared with passive PT for global effect (at medium- and long-term follow-up) and activity restriction for global effect (medium-term follow-up)	1	1	0	1	1+
					• LESI no more effective than acupuncture for pain intensity	1	1	0	1	1+
					• LESI not as effective as disc surgery at reducing pain intensity at medium-term follow-up, but not at long-term follow-up	1	1	0	1	1+

Author and year	SIGN Score	Approach	Studies (patient No)	Outcome	Conclusions	Grade				Evidence
						1	2	3	4	
Benoist et al. 2012 (SR) *Low-back pain with radiculopathy*	LQ (-)	*All approaches*	21 SRs (n=NS)	Pain, function complication	• LESI have a moderate short-term pain relief effect in patients with radiculopathy related to discal herniation	0	0	1	0	1-
					• interlaminar LESIs effective for radiculopathy for short-term pain relief, but limited for long-term pain relief.	0	0	1	0	1-
					• interlaminar LESIs not effective for radiculopathy for long-term pain relief.	0	0	1	1	1
					• Limited evidence for effectiveness of interlaminar LESIs for spinal stenosis	0	0	0	1	2-
					• Effectiveness of Caudal approach for discal pathology was strong for short-term and moderate for long-term pain relief.	0	0	0	1	1-
					• Effectiveness of transforaminal approach was strong for short-term (<6 weeks) and moderate for long-term results (>6 weeks).	0	0	0	1	1-
					• The results were equivalent whether using steroids with local anaesthetic or local anaesthetic alone	0	0	0	1	1-
					• Concerning safety, ESIs are generally well tolerated, and most complications are related to technical problems during the procedure.					
Pinto et al. 2012 *Sciatica*	HQ (++)	*All approaches*	22 RCTs (n=2184)	Pain, disability and functional limitations	• LESI demonstrated effectiveness compared with placebo for leg pain in the short term (mean difference, -6.2 [95% CI, -9.4 to -3.0])	1	1	1	0	1+
					• LESI demonstrated effectiveness compared with placebo for disability in the short term (mean difference, -3.1 [CI,-5.0 to -1.2]).	1	1	1	0	1+
					• LESI did not demonstrate effectiveness compared with placebo for pain or disability over the long term	1	1	1	0	1+
Quraishi 2012 (SR/MA) *Lumbar radiculopathy*	LQ (-)	*Transforaminal*	5 RCTs (n=368)	Pain, disability	TLESI effective for improvement in pain (standardised mean difference in VAS 0.2 in favour of steroid injection),	1	0	0	0	1-
					TLESI not effective for improvement In disability (standardised mean difference in ODI 0).	1	0	0	1	1
					TLESI not more effective compared to transforaminal anaesthetic or saline for improvement In pain or disability at 3 months and 12 months	0	0	0	1	1-

Author and year	SIGN Score	Approach	Studies (patient No)	Outcome	Conclusions	Grade				
						1	2	3	4	
Manchikanti et al. 2012 (SR) *Chronic low back and lower extremity pain of at least 3 months duration*	HQ (++)	*Transforaminal Injections*	13RCTs and 10 Non-RCTs (n=2363)	Pain, functional/psychological status, return to work, complications	• transforaminal LEI with local anesthetic and steroids, effective for pain relief with lumbar disc herniation in long term	0	1	1	0	1
					• transforaminal LEI with local anaesthetic and steroids, effective for pain relief with lumbar disc herniation in short term	0	1	1	1	1+
					• transforaminal LEI with local anaesthetic only effective for pain relief with lumbar disc herniation in short and long term	0	1	1	0	1
					• transforaminal LEI with local anaesthetic and steroids, effective for preventing surgery with lumbar disc herniation	0	1	1	0	1
					• transforaminal LEI with local anaesthetic and steroids, effective for pain relief with spinal stenosis in short term	0	1	1	0	1
					• transforaminal LEI with local anaesthetic and steroids, effective for pain relief with spinal stenosis in long term	0	1	1	0	1
					• The evidence for axial low back pain and post lumbar surgery syndrome is poor, inadequate, limited, or unavailable.					
Choi et al. 2013 (SR/MA) *LBP plus radiculopathy*	HQ (++)	*All approaches*	29 RCTs (n=843)	Pain, functional Improvement in 6-12 months, Need for surgery	• LESI provided significant treatment effect on pain at 6 months of follow-up (weighted mean difference [WMD], −0.41; 95% CI, −0.66 to −0.16), but was no longer statistically significant after adjusting for the baseline pain score (WMD, −0.19; 95% CI, −0.61 to 0.24)	1	1	1	1	1++
					• LESI provided no significant treatment effect on back-specific disability more than a placebo or other procedure	1	1	1	1	1++
					• LESI did not significantly decrease the number of patients who underwent subsequent surgery compared with a placebo or other treatments (relative risk, 1.02; 95% CI, 0.83 to 1.24).	1	1	1	1	1++
Bui and Bogduk 2013 (SR) Radicular pain	LQ (-)	*CT-guided transforaminal*	19 Non-RCT (observational studies) (n=NS)	Pain, Complications	• CT Guided TLESI is no more effective than fluoroscopy-guided injections and is not demonstrably safer.	0	0	0	1	2-
Epstein 2013 (SR) Not specified	R(0)	*Transforaminal*	43 Observational studies (n=NS)	Adverse Events	• Although the benefits for epidural steroid injections may include transient pain relief for those with/ without surgical disease, the multitude of risks attributed to these injections outweighs the benefits.	0	0	0	1	2-

Author and year	SIGN Score	Studies (patient No)	Outcomes	Conclusions	Grade				Evidence
					1	2	3	4	
SRs Not Included in Shamilyan et al.'s (2014) Review *Approach only transforaminal*									
Abdi et al. 2005	A(+)	8 RCTs, 14 cohort studies (transforaminal only)	Pain, functional improvement, psychological status, and return to work.	• For lumbar TLESI the evidence for use in radicular pain was strong for short-term and moderate for long-term improvement in pain and functional outcomes	0	1	1	1	1+
Bhargava et al. 2005 SR Lumbar radiculopathy	LQ(-)	6 Prospective cohort studies	Pain	• All approaches to the interlaminar, caudal, and transforaminal epidural space provide long-term relief in 27—56% patients with radiculopathy.	0	0	0	0	2-
				• Epidural space steroid instillation via the transforaminal approach for the treatment of lumbar radicular pain seemed effective.	0	0	0	0	2-
				• The transforaminal approach seemed to be the best route for delivering medication to the ventral epidural space and/or the dorsal root ganglia.	0	0	0	1	2-
Buenaventura et al. 2009 lumbar (low-back) and sciatica (leg) pain	A(+)	4 RCTs	Pain relief, functional assessment, psychological improvement, return to work, and opioid intake	TLESI have significant effect in relieving chronic pain of lumbar disc herniation and radiculitis with indicated evidence levels of Level II-1 for short-term relief and Level II-2 for long-term relief	0	1	0	1	1
Benny and Azari 2011 (SR) *Radicular back pain*	A(+)	9 RCTs, 4 retrospective and 8 prospective cohort studies (n=1559)	Pain and avoiding surgery	• TLESI effective in both short-term and long term management of radiculopathy due to spinal stenosis or lumbar herniation.	0	1	1	1	1+

Author and year	SIGN Score	Studies (patient No)	Outcomes	Conclusions	Grade				Evidence
					1	2	3	4	

Colimon and Villalobos 2010 SR chronic lower back pain (LBP), radiculopathies associated with discogenic disease, as well as post-laminectomy syndromes.	R(0)	NR	Pain	• Transforaminal approach is indicated for chronic LBP and/or pain in the lower limbs because of HIVD and radiculopathy, spinal stenosis, or failed back surgery syndrome.
				• The level of evidence for the procedure for lumbar pain and lower limb pain is:
				  • Level II-1 for short-term pain relief.
				  • Level II-2 for long-term pain relief.
				• The overall grade of recommendation is 1C for lumbar pain and pain in the lower limb.
					0	0	0	0	1-

Fritzler and Sarafini 2011 (SR) Back pain	LQ (-)	4 RCTs (n=594)	Pain, disability, physical function, rates of return to work, need for future surgery	• LESI effective compared to placebo in reducing disability scores up to 3 weeks and VAS pain scores up to 6 weeks.	0	0	0	1	1-
				• LESI not effective compared to placebo in terms of improved physical function, rates of return to work, or the need for future surgery.	0	0	0	1	1-
				• transforaminal ESIs appear superior to placebo in improving patient satisfaction and pain levels for a minimum of 2 weeks and potentially up to 16 months on average.	0	0	0	1	1-
Bresnahan et al. 2013 (SR) *Lumbar Spinal Stenosis*	A(+)	6 RCTs (n=290) and 2 observational studies (n=279)	Effectiveness evidence (clinical and economic)	• LESI (+/1 anaesthetic) effective compared with control injections in improving walking distance in patients with spinal stenosis in short term	0	1	1	0	1
				• LESI (+/1 anaesthetic) not effective compared with control injections in improving walking distance in patients with spinal stenosis in long-term (>4 months)	0	1	0	1	1
Cohen et al. 2013 (SR) *Radiculopathy, LBP*	A(+)	11 SRs, 8 RCTs (n=691) and 5 Retrospective cohort (n=629)	Effectiveness	• transforaminal injections are more likely to yield positive results than interlaminar or caudal injections,		1	1	1	1+
				• LESI more effective for reducing pain in patients with lumbar herniated disc, compared with spinal stenosis or axial spinal pain.		1	1	1	1+

Author and year	SIGN Score	Studies (patient No)	Outcomes	Conclusions	Grade				Evidence
					1	2	3	4	
MacVicar et al. 2013 (SR) *Radicular pain*	LQ(-)	22 outcome studies, 11 pragmatic trials, and 6 explanatory trials.	Pain	• TLESI effective in reducing pain, restoring function, reducing the need for other health care, and avoiding surgery in patients with lumbar radicular pain caused by contained disc herniations,	0	0	1	0	1
May and Comer 2013 (SR) *Spinal Stenosis*	A(+)	9 RCTs	Pain and Disability	• LESI not effective compared to physical therapy, saline, saline and anaesthetic or anaesthetic injection at long-term follow-up in patients with spinal stenosis;	0	1	1	1	1+
				• Percutaneous adhesiolysis and decompression surgery were more effective than LESI in patients with spinal stenosis;	0	1	0	1	1
				• Bilateral transforaminal injection was more effective than an interlaminar steroid injection in patients with spinal stenosis;	0	1	0	1	1
Bicket et al. 2015 (SR/MA) *LBP*	HQ (++)	26 RCTs in SR, 21 RCTs in M/A (n=3271)	Need for surgery	• LESI not effective in reducing need for surgery in short term	1	1	1	1	1++
				• LESI not effective in reducing need for surgery in long term	1	1	1	1	1++
Chien et al. 2014 (SR) *Lumbosacral radicular pain secondary to IV disc herniation/degeneration*	HQ (++)	5 RCTs and 3 Retrospective cohort studies (n= 506)	Pain relief, functional status	• transforaminal fluoroscopy guided LESI more effective compared to fluoroscopy guided interlaminar LESI in reducing pain in radiculopathy secondary to IV disc herniation/degeneration in the short term	0	1	0	0	1-
				• transforaminal fluoroscopy guided LESI no more effective compared to interlaminar fluoroscopy guided LESI in reducing pain in radiculopathy secondary to IV disc herniation/degeneration in the long term	0	1	0	0	1-
				• transforaminal fluoroscopy guided LESI no more effective compared to interlaminar fluoroscopy guided LESI in functional improvement in patients with radiculopathy secondary to IV disc herniation/degeneration in the long or short term	0	1	0	1	1

Author and year	SIGN Score	Studies (patient No)	Outcomes	Conclusions	Grade				Evidence
					1	2	3	4	
Manchikanti et al. 2015 (systematic review) *Lumbar Central Spinal Stenosis*	A(+)	7 randomised controlled trials(n=460)	Pain, functional status	• transforaminal LEI effective for reducing pain in patients with spinal stenosis in short-term	0	1	0	1	1
				• Caudal and lumbar interlaminar LEI effective for reducing pain in patients with spinal stenosis in long term	0	1	0	1	1
				• LEI with anaesthetic no more effective than LEI with anaesthetic and steroid in long or short term	0	1	1	1	1
Bhatia et al. 2016 systematic review/MA Lumbosacral Radicular Pain from Herniated IVD	HQ(++)	8 randomised controlled trials (n=771)	Pain (1-12 months), disability (ODI RMDQ), psychology QOL	TFE steroids provide modest analgesic benefit at 3 months in patients with lumbosacral radicular pain secondary to herniated intervertebral discs, but they have no impact on physical disability or incidence of surgery	1	1	1	1	1++
Wei et al. 2016 *Low back pain with lumbosacral radicular pain*	HQ(++)	9 randomised controlled trials and 4 Observational studies (n=931)	Pain, functional improvement	Transforaminal LESI produced better pain relief compared with interlaminar LESI in randomised controlled trials, but not in observational studies.	1	1	0	0	1 / 2-
				transforaminal LESI produced no better functional improvement and Oswestry disability index (ODI) score than interlaminar LESI	1	1	0	0	1
				There were no differences between transforaminal and interlaminar LESI in regard to procedure frequency, surgery rate, and ventral epidural spread.	1	1	0	0	1

Appendix 3: Critical appraisals of systematic reviews

Reference (author, year)		Quest													
Study	**Year**	**1.1**	**1.2**	**1.3**	**1.4**	**1.5**	**1.6**	**1.7**	**1.8**	**1.9**	**1.10**	**1.11**	**1.12**	**2.1**	**2.2**
Abdi et al.	**2005**	Y	Y	CS	Y	N	N	Y	Y	Y	N	N	Y	AQ(+)	Y
Benny & Azori	**2011**	Y	N	N	N	N	Y	Y	Y	Y	Y	N	N	AQ(+)	Y
Bhargava et al.	**2005**	Y?	Y	CS	CS	N	N	Y	N	N	NA	NA	N	LQ(-)	Y
Bhatia et al.	**2016**	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	HQ(++)	Y
Bicket et al.	**2015**	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	N	HQ (++)	Y
Bresnahan et al.	**2013**	Y	Y	Y	Y	-	N	Y	Y	Y	CS	N	N	AQ(+)	Y
Buenaventura et al.	**2009**	Y	Y	CS	CS	Y	Y	Y	Y	Y	N	N	Y	AQ(+)	Y
Chien et al.	**2014**	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	N	Y	HQ (++)	Y
Cohen et al.	**2013**	Y	Y	N	N	N	N	Y	Y	Y	Y	N	N	AQ(+)	Y
Colimon & Villalobos	**2010**	N	N	CS	CS	N	N	N	N	N	N	N	N	R(0)	Y
Fritzler & Sarafini	**2011**	Y	N	N	N	N	N	Y	N	N	N	N	N	LQ(-)	Y
Macvicar et al.	**2013**	Y	Y	N	Y	N	Y	N	N	N	Y	N	N	LQ(-)	Y
Manchikanti et al.	**2015**	Y	Y	Y	N	N	Y	Y	Y	Y	Y	N	N	AQ(+)	Y
May & Comer	**2013**	Y	Y	Y	Y	N	N	N	Y	Y	Y	N	Y	AQ(+)	Y
Shamliyan	**2014**	Y	Y	CS	CS	Y	N	Y	Y	Y	NA	N	Y	AQ(+)	Y
Wei et al.	**2016**	Y	Y	Y	Y	N	N	Y	Y	Y	Y	N	Y	AQ(+)	Y

Appendix 4: Critical appraisals of randomised controlled trials

Reference (author, year)		Quest												
Study	**Year**	**1.1**	**1.2**	**1.3**	**1.4**	**1.5**	**1.6**	**1.7**	**1.8**	**1.9**	**1.10**	**2.1**	**2.2**	**2.3**
Chun & Park	2015	Y	Y	Y	Y	Y	Y	Y	6.0%	CS	NA	++	Y	Y
2.4	Injectate at a volume of 8 mL was more effective than injectate at a volume of 3mL for radicular pain in a lumbar transforaminal steroid injection, although both of the injectates contained the same dose of dexamethasone.													
Cohen et al.	2015	Y	Y	Y	Y	Y	Y	Y	49.6%	Y	N	++	Y	Y
2.4	Although epidural steroid injection might provide greater benefit than gabapentin for some outcome measures, the differences are modest and are transient for most people.													
Dennis et al.	2015	Y	Y	Y	Y	Y	Y	Y	17.8%	N	N	++	Y	Y
2.4	According to this study, pain relief and functional improvement are similar for both dexamethasone and betamethasone at 3 months. Considering its safety profile, dexamethasone could be considered as first choice for TFESI. However, given that the study was underpowered, more research is needed to support a recommendation of systematically using dexamethasone in TFESI.													
Friedly et al.	2014	Y	Y	Y	Y	Y	N	Y	3.5%	Y	N	+	Y	Y
2.4	In the treatment of lumbar spinal stenosis, epidural injection of glucocorticoids plus lidocaine offered minimal or no short-term benefit as compared with epidural injection of lidocaine alone.													
Ghai et al.	2014	Y	Y	Y	Y	Y	Y	Y	0.0%	N?	NA	++	Y	Y
2.4	Epidural injection delivered through the PIL approach is equivalent in achieving effective pain relief and functional improvement to the TF approach for the management of low back pain with lumbosacral radicular pain. The PIL approach can be considered a suitable alternative to the TF approach for its equivalent effectiveness, probable better safety profile, and technical ease.													
Kennedy et al.	2014	Y	Y	Y	Y	Y	N	Y	0.0%	N	N	+	Y	Y
2.4	Transforaminal epidural corticosteroid injections are an effective treatment for acute radicular pain due to disc herniation, and frequently only require 1 or 2 injections for symptomatic relief. Dexamethasone appears to possess reasonably similar effectiveness when compared with triamcinolone. However, the dexamethasone group received slightly more injections than the triamcinolone group to achieve the same outcomes.													
Koh et al.	2013	Y	Y	Y	Y	Y	Y?	Y	22.0%	Y	NA	+	Y	Y
2.4	Superior short-term pain relieving efficacy, but limited long-term effects of hypertonic saline, when added to TFEIs.													
Koh et al.	2015	Y	Y	Y	Y	Y	Y	Y	20.9%	Y	NA	++	Y	Y
2.4	The TFEI provided significant short-term pain relief and PRF can be applied in conjunction with TFEI to achieve higher treatment efficacy compared with TFEI alone.													

Reference (author, year)		Quest												
Study	**Year**	**1.1**	**1.2**	**1.3**	**1.4**	**1.5**	**1.6**	**1.7**	**1.8**	**1.9**	**1.10**	**2.1**	**2.2**	**2.3**
Manchikanti et al.	2014	Y	Y	Y	Y	N	Y	Y	26.6%	Y	NA	+	Y	Y
2.4	Transforaminal epidural injections of local anesthetic with or without steroids might be an effective therapy for patients with disc herniation or radiculitis. The present evidence illustrates the lack of superiority of steroids compared with local anesthetic at 2-year follow-up.													
Pirbudak et al.	2015	Y	Y	Y	N	Y	N	Y	0.0%?	N	NA	-	Y	Y
2.4	Similar improvements in VAS, ODI, and SLET values were observed in both groups in the second week. The inflammation markers were not different after treatment, neither within the groups nor between the groups. This study revealed that tramadol + gabapentin treatment was not superior to tramadol treatment													
Rados et al.	2013	Y	Y	N	N	CS	N	Y	8.5%	N	NA?	-	Y	Y
2.4	Steroids are efficient; besides alleviating the overall pain, they also reduce the neuropathic component in chronic lumbar radicular pain, whether it is distributed epidurally by the IL or TF approach.													
Rahimzadeh et al.	2014	Y	Y	Y	Y	Y	N	Y	0.0%?	N	NA	+	Y	Y
2.4	We conclude that adding hyaluronidase to the epidural injectate was effective in the management of chronic low back pain in patients with failed back surgery syndrome demonstrated over a period of 4 weeks.													
Sinofsky et al.	2014	Y	N	N	N	N	CS	Y	7.7%	N	NA	0	Y	Y
2.4	The concordant group demonstrated significantly higher pain reduction as compared to the discordant group. There were no significant differences between the 2 groups in terms of improved function or reduced analgesic requirements. Concordant provocation during interlaminar epidural injection may be a predictor of outcome													
Zhang et al.	2013	Y	Y	Y	N	Y	N	Y	0.0%?	N	NA	+	Y	Y
2.4	In our study, oxygen-ozone nucleolysis provides excellent pain relief in most herniated disc patients who failed to respond to conservative therapy. And there was no significant statistical difference between treatment of injection of oxygenozone combined with steroid and ozone only in the 6 and 12 months follow-up. Therefore, O2–O3 seems to play a role in pain relief, and we suggest the administration of the O2–O3 mixture as a first-choice treatment before recourse to surgery or when surgery is not possible and the addition of epidural steroid infiltration is not required.													

Appendix 5: Critical appraisals of cohort studies examining adverse events

Reference (author, year)		SIGN Item (**Y** = yes, **N** = no, **DNA** = does not apply, **CS** = cannot say, **-** = not reported)																
Study	**Year**	**1.1**	**1.2**	**1.3**	**1.4**	**1.5**	**1.6**	**1.7**	**1.8**	**1.9**	**1.10**	**1.11**	**1.12**	**1.13**	**1.14**	**2.1**	**2.2**	**2.3**
Plastaras et al.	2015	Y	DNA	N	N	-	N	Y	Y	Y	Y	CS	DNA	N	N	LQ(-)	Y	Y
2.4	Fluoroscopically guided lumbosacral TFESI is associated with a similar rate of minor AEs both immediately and 24 to 72 hours after procedure that are typical of other axial corticosteroid injections. Permanent AEs were not found in this sample																	
Schneider et al.	2014	Y	DNA	N	N	-	N	Y	N	N	Y	CS	DNA	N	N	LQ(-)	Y	Y
2.4	Vasovagal reactions have an overall occurrence rate of 3.5% in TFESIs. Although there is a potential for bias, this study does appear to demonstrate that when a trainee is involved in a TFESI, there is nearly twice the rate of vasovagal reaction																	
Qureshi et al.	2013	Y	CS	N	N	-	N	CS	CS	Y	Y	CS	Y	Y	N	LQ(-)	CS	Y
2.4	Blind interlaminar epidural steroid injections are safe when performed with proper technique, monitoring and under recommended sterile precautions. The minor complications are common with this procedure but major complications are rare																	
Kainer et al.	2012	Y	CS	N	N	-	DNA	Y	DNA	Y	Y	Y	N	N	Y	LQ(-)	N	N
2.4	Epidural glucocorticoid injections can lead to localized infection, and fungal pathogens can invade the dura, leading to meningitis and, in some patients, invasion of the posterior circulation vasculature leading to stroke, haemorrhage, or both																	
Kang et al.	2012	Y	Y	N	CS	-	DNA	Y	CS	Y	Y	Y	DNA	Y	N	+	CS	Y
2.4	ESI treatments using less than a total of 200mg triamcinolone had no significant effect on BMD. However, the decrease in BMD of postmenopausal women who received more than 200mg of triamcinolone in one year indicates that ESI involving doses > 200mg/year should be avoided																	
Manchikanti et al.	2012	Y	N	N	N	-	N	CS	CS	N	Y	N	N	N	N	LQ(-)	Y	Y
2.4	Major complications are rare and minor side effects are common																	
Chang et al.	2011	Y	DNA	N	N	-	DNA	CS	N	N	N	N	N	N	N	LQ(-)	N	Y
2.4	The use of air to localize the epidural space in CT-guided ESIs has a high success rate and a very low rate of complications																	
Karaman et al.	2011	Y	DNA	N	N	-	DNA	Y	Y	Y	Y	CS	DNA	N	N	LQ(-)	Y	Y
2.4	The frequency of major complications is pretty rare in transforaminal lumbar epidural steroid injections in expert hands and in the conditions in which safety precautions are taken																	
Candido et al.	2010	Y	Y	N	N	-	DNA	CS	DNA	Y	Y	CS	DNA	N	N	LQ(-)	N	Y
2.4	Our data demonstrate that intradiscal injection is a rare complication during LESI, but occurs more frequently with TFESI than with LESI																	
Trentman et al.	2009	Y	N	N	N	-	DNA	CS	CS	N	CS	DNA	DNA	N	Y	LQ(-)		Y
2.4	The risk of vasovagal reaction is significantly higher for cervical translaminar epidural steroid injections than for lumbar injections																	

Reference (author, year)		SIGN Item (**Y** = yes, **N** = no, **DNA** = does not apply, **CS** = cannot say, **-** = not reported)																
Study	**Year**	**1.1**	**1.2**	**1.3**	**1.4**	**1.5**	**1.6**	**1.7**	**1.8**	**1.9**	**1.10**	**1.11**	**1.12**	**1.13**	**1.14**	**2.1**	**2.2**	**2.3**
McGrath et al.	2011	Y	N	N	N	-	DNA	CS	N	Y	Y	CS	DNA	Y	Y	LQ(-)	Y	Y
2.4	These results suggest that ESIs are a safe and well-tolerated intervention for cervical or lumbar pain and radiculopathy																	
Stalcup et al.	2006	Y	N	Y	N	-	DNA	CS	N	Y	Y	CS	N	N	Y	LQ(-)	CS	Y
2.4	SLNBs performed with fluoroscopic guidance have a low incidence of complications, all of which were minor. The specific needle-tip position within or adjacent to the lumbar neural foramen does not appear to be associated with the incidence of complications																	
Fitzgibbon et al.	2004	Y	N	N	N	-	N	CS	DNA	N	CS	N	DNA	N	N	LQ(-)	N	N
2.4	Brain damage and death were associated with epidural steroid injection only when opioids or local anaesthetics were included																	
Horlocker et al.	2002	Y	N	N	N	-	N	CS	N	Y	Y	CS	N	CS	N	LQ(-)	N	Y
2.4	ESIs are safe in patients receiving aspirin-like antiplatelet medications. However, pain clinic personnel should be aware that minor worsening of neurologic function may occur after ESI and must be differentiated from aetiologies requiring intervention																	
Botwin et al.	2001	Y	Y	Y	N	7.3 %	N	Y	N	Y	Y	CS	N	Y	N	+	Y	Y
2.4	No major complications occurred. The incidence of minor complications was 15.6% per injection. All reactions resolved without morbidity and no patient required hospitalization																	
Botwin et al.	2001 b	Y	N	N	CS	-	DNA	Y	CS	Y	Y	DNA	Y	N	N	LQ(-)	Y	Y
2.4	Average radiation exposure for technicians during these procedures was below the limit of detectability																	
Botwin et al.	2000	Y	Y	DNA	CS	-	DNA	Y	Y	Y	Y	CS	N	CS	N	+	Y	Y
2.4	There were no major complications. The incidence of minor complications was 9.6% per injection. All reactions resolved without morbidity, and no patient required hospitalization																	
Furman et al.	2000	Y	N	N	DNA	-	DNA	CS	DNA	Y	Y	N	N	N	N	LQ(-)	N	Y
2.4	There is a high incidence of intravascular injections in transforaminal ESIs. Fluoroscopically guided procedures without contrast confirmation are instilling medications intravascularly and therefore not into the desired epidural location. This finding confirms the need for not only fluoroscopic guidance but also contrast injection instillation in lumbosacral transforaminal ESIs																	
Johnson et al.	1999	Y	N	N	N	-	N	N	N	CS	Y	N	N	CS	N	LQ(-)	N	Y
2.4	Epidurography followed by therapeutic epidural steroid injection (with or without a local anesthetic) is a safe radiologic procedure that is easily performed by skilled proceduralists on an outpatient basis without intravenous sedation and cardiac monitoring																	

Appendix 6: List of randomised controlled trials within systematic reviews

	Year	Abdi et al.	Benny & Azori	Bhargava et al.	Bhatia et al.	Bicket et al.	Brensnahan et al.	Buenaventura et al.	Chien et al.	Cohen et al.	Colimon & Villalobos	Fritzler et al.	Macvicar et al.	Manchikanti et al.	May & Comer	Shamliyan et al.	Wei et al.	Total References
Lutz et al.	1998	1																**1**
Devulder et al.	1999	1																**1**
Riew et al.	2000	1			1			1										**3**
Karppinen et al.	2001							1										**1**
Karppinen et al.	2001	1			1			1										**3**
Botwin et al.	2002	1																**1**
Vad et al.	2002	1			1			1										**3**
Thomas et al.	2003	1			1													**2**
Butterman	2004	1																**1**
Butterman	2004	1																**1**
Ng et al.	2005				1													**1**
Wilson-Macdonald	2005					1				1				1				**3**
Dreyfuss et al.	2006									1								**1**
Schaufele et al.	2006		1															**1**
Riew et al.	2006		1			1		1		1			1					**5**
Anderberg et al.	2007									1								**1**
Becker et al.	2007									1								**1**
Owlia et al.	2007									1						1		**2**
Jeong et al.	2007		1					1		1			1					**4**
Ackerman & Ahmad	2007		1						1	1			1				1	**5**
Cohen et al.	2008											1						**1**
Manchikanti et al. (a)	2008														1			**1**
Manchikanti et al. (c)	2008									1								**1**
Manchikanti et al. (d)	2008									1								**1**
Rasmussen et al.	2008									1								**1**
Candido et al.	2008								1	1							1	**3**
Fish et al.	2009									1								**1**
Hegihara et al.	2009					1												**1**
Manchikanti et al.	2009														1			**1**
Laiq et al.	2009					1				1								**2**
Sayegh et al.	2009					1				1								**2**
Koc et al.	2009									1				1	1			**3**
Lee et al.	2009		1				1			1				1	1			**5**
Tafazel et al.	2009				1	1				1			1		1			**5**
Gerszten et al.	2010									1								**1**
Huda et al.	2010															1		**1**
Manchikanti et al. (a)	2010									1								**1**
Manchikanti et al. (d)	2010									1								**1**
Park et al.	2010									1			1					**2**

	Year	Abdi et al.	Benny & Azori	Bhargava et al.	Bhatia et al.	Bicket et al.	Brensnahan et al.	Buenaventura et al.	Chien et al.	Cohen et al.	Colimon & Villalobos	Fritzler et al.	Macvicar et al.	Manchikanti et al.	May & Comer	Shamliyan et al.	Wei et al.	Total References
Ghahreman et al.	2010				1	1				1			1					**4**
Datta & Upadhyay	2011															1		**1**
Iversen et al.	2011									1								**1**
Kim et al.	2011									1								**1**
Manchikanti et al.	2011															1		**1**
Park et al.	2011															1		**1**
Gharibo et al.	2011															1	1	**2**
Kang et al.	2011									1						1		**2**
Nam et al.	2011									1				1				**2**
Rados et al.	2011								1	1			1			1	1	**5**
Manchikanti et al. (d)	2012													1				**1**
Manchikanti et al. (e)	2012									1								**1**
Manchikanti et al. (g)	2012									1								**1**
Manchikanti et al. (h)	2012									1								**1**
Brown	2012									1						1		**2**
Cohen et al.	2012					1				1								**2**
Manchikanti et al. (a)	2012									1						1		**2**
Manchikanti et al. (c)	2012									1						1		**2**
Manchikanti et al. (a)	2013															1		**1**
Manchikanti et al. (b)	2013															1		**1**
Gupta et al.	2014																1	**1**
Milburn et al.	2014													1				**1**
Ghai et al.	2014				1									1			1	**3**
Hashemi	2015																1	**1**
Kamble et al.	2015																1	**1**
Rezende et al.	2015																1	**1**
Total References		**9**	**5**	**0**	**8**	**8**	**1**	**6**	**3**	**35**	**0**	**1**	**7**	**7**	**5**	**13**	**9**	**117**

Appendix 7: Data extraction table for randomised controlled trials

Author	Year	Country	Study design	Approach	Steroid	+/- Local Anaesthetic	Outcome Measure	Results	Findings	FUNCTIONAL OUTCOMES: Range of Movement (ROM), Disability, Return To Work (RTW), Quality of Life (QoL), OR other	Safety and Risk	Imaging	Patient and Pathology
Chun & Park	2015	South Korea	Prospective, Active Control RCT	Transforaminal	Dexamethasone	-	VAS @ 4 weeks	The VAS of the high-volume injectate group (DL8) was significantly lower than that of the low-volume injectate group (DL3) (33.3 ± 25 vs. 46.3 ± 25 (p = 0.036)	8 mL was more effective 3mL for radicular pain TFESI; same does of dexamethasone.	DISABILITY: RMDQ @ 4 weeks			66 patients experiencing lumbar radicular pain with a pain intensity of ≥ 40/100 who had been diagnosed with a herniated nucleuspulposus or spinal stenosis after a series of physical, neurologic, and radiologic examinations.
Cohen et al.	2015	USA	Multicentre RCT	Interlaminar & Transforaminal	depomethylprednisolone bupivacaine; gabapentin pills	-	Average leg pain score on a 0-10 NRS @ 1 & 3 months; reduction in analgesic drugs (>20%)	No sig dif @ 1 month: M=3.3(SD = 2.6), change from baseline M=−2.2 (SD 2.4) ESI vs. M=3.7 (SD 2.6) and M= −1.7 (SD 2.6) gabapentin (adjusted difference 0.4 points, 95% CI −0.3 to 1.2; =0.25. No sig dif @ 3 months: M=3.4 (SD 2.7) + M=−2.0 (SD 2.6) ESI vs M= 3.7 (SD 2.8) and M=−1.6 (SD 2.7) gabapentin (adjusted difference 0.3, 95% CI −0.5 to 1.2; P=0.43)	Although epidural steroid injection might provide greater benefit than gabapentin for some outcome measures, the differences are modest and are transient for most people	ROM: Worst leg pain over past week; average & worst back pain DISABILITY: ODI QoL: global perceived effect (measured as no non-rescue interventions + affirmative to following select statements)	The proportion of patients reporting one or more adverse events from the injection was 8% (n=6) in the epidural steroid injection group and 10% (n=7) in the gabapentin group (P=0.75)	MRI	145 people with lumbosacral radicular pain secondary to herniated disc or spinal stenosis for less than four years in duration and in whom leg pain is as severe or more severe than back pain
Dennis et al.	2015	Canada	Double Blind RCT	Transforaminal	Dexamethasone OR betamethasone	+	VAS @ baseline, 1, 3, 6 months	No dif on VAS (as con: (P=0.209) or cat: (>50% (P=0.058) or >75% (P=0.865)) or ODI (P=0.181) @ 3 months. @ 6 months ODI improvement @ sig. limit in favour for dexamethasone (P=0.050).	According to this study, pain relief and functional improvement are similar for both dexamethasone and betamethasone at 3 months. Considering its safety profile, dexamethasone could be considered as first choice for TFESI. However, given that the study was underpowered more research is needed to support a recommendation of systematically using dexamethasone in TFESI.	DISABILITY: ODI @ baseline, 1, 3, 6 months; complications	No serious complications were observed in either group	Fluoroscopy	56 Patients with debilitating radicular pain
Friedly et al.	2014	USA	Double Blind Multisite RCT	Interlaminar & Transforaminal	Lidocaine+/- triamcinolone, betamethasone, dexamethasone, or methylprednisolone	-	10 point NRS for intensity of leg pain	No sig dif between-groups for RMDQ score: (adjusted dif for glucocorticoid-lidocaine group and lidocaine-alone group, −1.0 points; 95% confidence interval [CI], −2.1 to 0.1; P = 0.07) or intensity of leg pain (adjusted difference, −0.2 points; 95% CI, −0.8 to 0.4; P = 0.48) @ 6 weeks	In the treatment of lumbar spinal stenosis, epidural injection of glucocorticoids plus lidocaine offered minimal or no short-term benefit as compared with epidural injection of lidocaine alone.	DISABILITY: RMDQ @ 6 weeks		Fluoroscopic	400 patients who had lumbar central spinal stenosis and moderate-to severe leg pain and disability
Ghai et al.	2014	India	Double Blind, Active Control RCT	Parasagittal Interlaminar OR Transforaminal	Methylprednisolone	-	VAS @ baseline 2 weeks, 1, 2, 3, 6, 9, and 12 months	Effective pain relief (≥ 50% pain relief from baseline on VAS) was observed in 76% (90% CI 60.6 – 88.5%) of patients in the TF group and 78% (90% CI 62.8 – 89.3%) of patients in the PIL (P=1.00) group at 3 months	Epidural injection delivered through the PIL approach is equivalent in achieving effective pain relief and functional improvement to the TF approach for the management of low back pain with lumbosacral radicular pain. The PIL approach can be considered a suitable alternative to the TF approach for its equivalent effectiveness, probable better safety profile, and technical ease.	DISABILITY: MODI @ baseline 2 weeks, 1, 2, 3, 6, 9, and 12 months	No serious complications were observed in either group	C-arm fluoroscopic	62 patients with a diagnosis of CLBP and unilateral lumbosacral radicular pain
Kennedy et al.	2014	USA	Multicentre, Double Blind, Prospective, RCT	Transforaminal	Dexamethasone or triamcinolone	+	NRS @ baseline, 2 weeks, 3, & 6 months	A greater percentage of subjects receiving triamcinolone achieved ≥50% pain relief at 2 weeks than those receiving dexamethasone (43.2 vs 31.7%); however, this did not reach statistical significance and the 95% CIs were overlapping. This trend disappeared by 3 and 6-month follow-up, with greater than 70% of both groups achieving at least 50% pain reduction with no differences between groups.	transforaminal epidural corticosteroid injections are an effective treatment for acute radicular pain due to disc herniation, and frequently only require 1 or 2 injections for symptomatic relief. Dexamethasone appears to possess reasonably similar effectiveness when compared with triamcinolone. However, the dexamethasone group received slightly more injections than the triamcinolone group to achieve the same outcomes.	DISABILITY: ODI @ baseline, 2 weeks, 3, & 6 months		Fluoroscopy	78 consecutive subjects with acute uni-level disc herniation resulting in unilateral radicular pain.

Author	Year	Country	Study design	Approach	Steroid	+/- Local Anaesthetic	Outcome Measure	Results	Findings	FUNCTIONAL OUTCOMES: Range of Movement (ROM), Disability, Return To Work (RTW), Quality of Life (QoL), OR other	Safety and Risk	Imaging	Patient and Pathology
Koh et al.	2015	South Korea	Double Blind, Active Control RCT	Transforaminal	Pulsed radiofrequency + triamcinolone acetonide	+	NRS @ baseline, 1, 2, and 3 months	The number of patients with successful treatment results was higher in the PRF group at 2 months (P = 0.032) and 3 months (P = 0.018). No significant differences were observed in terms of the secondary outcome variables between the 2 groups.	The TFEI provided significant short-term pain relief and PRF can be applied in conjunction with TFEI to achieve higher treatment efficacy compared with TFEI alone	DISABILITY: 10-item ODI @ baseline, 1, 2, and 3 month QoL: MQS + 7-point Likert scale GPE @ baseline, 1, 2, and 3 month	No serious adverse events were noted in either groups	Fluoroscopy	62 patients with Lumbosacral radicular pain lasting ≥12 weeks
Koh et al.	2013	South Korea	Double Blind, Active Control RCT	Transforaminal	Triamcinolone + hypertonic saline or nomal saline	+	NRS @ baseline, 1, 2, 3, 4, and 6 months	In the hypertonic group, there was a statistically significant improvement in the mean pain score compared with the baseline pain score throughout the whole study period (P < 0.001, P = 0.004 at 6 months); in the control group, statistical significance was observed at one (P < 0.001), 2 (P < 0.001), 3 (P < 0.001), and 4 months (P < 0.001). Statistically significant difference between the 2 group at the 2- (P = 0.024) and 3-month (P = 0.012) follow-up.	Superior short-term pain relieving efficacy, but limited long-term effects of hypertonic saline, when added to TFEIs.	DISABILITY: ODI @ baseline, 1, 2, 3, 4, and 6 months	No reports of serious complications during injection, except one patient in the hypertonic group experienced burning pain during injection and declined to participate further in the study	Fluoroscopy	53 patients with chronic lumbosacral radiculopathy secondary to spinal stenosis lasting ≥ 12 weeks
Manchikanti et al.	2014	USA	Double Blind, Active Control RCT	Transforaminal	Lidocaine + sodium chloride OR Lidocaine + betamethasone	+	NRS + Opioid intake @ baseline, 3, 6, 12, 18, and 24 months	At 2 years there was significant improvement in all participants in 65% who received local anaesthetic alone (M= 4.0 ± SD=1.6) and 57% who received local anaesthetic and steroid (M= 4.2 ± SD=1.6)	transforaminal epidural injections of local anesthetic with or without steroids might be an effective therapy for patients with disc herniation or radiculitis. The present evidence illustrates the lack of superiority of steroids compared with local anesthetic at 2-year follow-up.	DISABILITY: ODI @ baseline, 3, 6, 12, 18, and 24 months RTW: Employment Status QoL: Weight changes @ baseline, 3, 6, 12, 18, and 24 months		Fluoroscopy	120 patients with disc herniation and radiculitis.
Pirbudak et al.	2015	Turkey	Prospective, Single Blind, RCT	Transforaminal	Triamcinolone acetonide +bupivacaine	NR	VAS @ baseline and 2 week follow up	VAS @ week 2; no stat. sig. diff. between group T (M=1.95 ± SD=1.27) and group TG (M=1.15 ± SD=1.08) (P > 0.05)	This study revealed that tramadol + gabapentin treatment was not superior to tramadol treatment	ROM: SLET @ baseline and 2 week follow up DISABILITY: ODI @ baseline and 2 week follow up		Fluoroscopy	40 patients with herniated disc-derived acute lumbar radicular pain
Rados et al.	2013	Croatia	Prospective RCT	Interlaminar and Transforaminal	Methylprednisolone + lidocaine	+	PD-Q @ baseline, 2, 4, 6, 12, & 24 weeks.	The trend equation (y = –1.1393x + 25.269) for the TFESI shows a faster recovery than the interlaminar LESI (y = –0.8089x + 26.654). The statistically significant difference in the two groups is proved between the first and the sixth visit (interlaminar LESI, p = 0.014; TFESI, p = 0.001).	Steroids are efficient; besides alleviating the overall pain, they also reduce the neuropathic component in chronic lumbar radicular pain, whether it is distributed epidurally by the IL or TF approach.			Fluoroscopy	64 patients with unilateral chronic lumbar radicular pain.
Rahimzadeh et al.	2014	Iran	Prospective RCT	Transforaminal	Hyaluronidase OR bupivacaine and triamcinolone		VAS @ baseline, 1, 2, 3, 4 weeks; Opioid intake @ baseline, 1, 2, 3, 4 weeks	Pain scores and total analgesic requirement were significantly lower in the HYL group at 2 and 4 weeks after blockade (p < 0.01).	We conclude that adding hyaluronidase to the epidural injectate was effective in the management of chronic low back pain in patients with failed back surgery syndrome demonstrated over a period of 4 weeks	ROM: NRS on movement or static @ baseline, 1, 2, 3, 4 weeks		Fluoroscopy	33 patients with FBSS

Author	Year	Country	Study design	Approach	Steroid	+/- Local Anaesthetic	Outcome Measure	Results	Findings	FUNCTIONAL OUTCOMES: Range of Movement (ROM), Disability, Return To Work (RTW), Quality of Life (QoL), OR other	Safety and Risk	Imaging	Patient and Pathology
Sinofsky et al.	2014	USA	Prospective, Double Blind RCT	Interlaminar	Methylprednisolone	-	Self-rated percentage of pain + daily analgesic consumption.	The concordant group achieved a significant decrease in self-reported pain as compared to the discordant group at 2-week follow-up (61%, t = 2.45, P < 0.01). There were also significantly more patients in the concordant group who reported 75% pain reduction as compared to the discordant group (X = 6.44, df(1), P < 0.05).	The concordant group demonstrated significantly higher pain reduction as compared to the discordant group. There were no significant differences between the 2 groups in terms of improved function or reduced analgesic requirements. Concordant provocation during interlaminar epidural injection may be a predictor of outcome.	ROM: Self-rated changes in functional activity		Fluoroscopy	48 patients with radicular lumbosacral pain.
Zhang et al.	2013	China	Prospective RCT	Intradiscal and intraforaminal	Oxygen-ozone + Betamethasone	+	JOA Score + VAS @ baseline, 3 weeks, 6 & 12 months.	Satisfactory clinical outcomes were obtained in both groups. The reduction of VAS score from baseline to the end of the study was 7.68 to 2.17 and 7.49 to 2.23 in group A and group B respectively and there were remarkable improvements of mean JOA score and recovery rate in every follow-up time in both groups. Furthermore, in 3 weeks follow-up the JOA recovery rate of group B is higher than that of group A, which there was significant different, but there were no significant differences between two groups in 6 and 12 months.	In our study, oxygen-ozone nucleolysis provides excellent pain relief inmost herniated disc patients who failed to respond to conservative therapy. And there was no significant statistical difference between treatment of injection of oxygen-ozone combined with steroid and ozone only in the 6 and 12 months follow-up. Therefore, O2–O3 seems to play a role in pain relief, and we suggest the administration of the O2–O3 mixture as a first-choice treatment before recourse to surgery or when surgery is not possible and the addition of epidural steroid infiltration is not required.		There were no complications	Radiographic	172 consecutive adult patients with low back pain and radicular pain

Appendix 8 - Data extraction for cohort studies examining adverse events

Author	Year	Country	Population	# Injections	Injectate	Approach	Prevalence of Adverse Events	Imaging	Conclusions
Plastaras et al..	2015	United States	Persons (19-89yrs) attending a multiphysician academic Physical Medicine and Rehabilitation clinic between 2004 and 2007	1295	betamethasone or triamcinolone following 1% lidocaine anaesthetic test dose	Lumbosacral transforaminal ESI using the subpedicular transforaminal technique	9.2% experienced immediate (from time of procedure to discharge from clinic visit) adverse events and 20.0% experienced delayed adverse events (24 to 72 hours following procedure). Two immediate adverse events occurred in >1% of procedures: vasocagal episode (4.2%) and intravascular flow that interrupted the procedure (1.7%). Delayed events occuring in >1% of procedures included: pain exacerbations (5.0%), injection site soreness (3.9%), headache (3.9%), facial flushing/sweating (1.8%) and insomnia (1.6%). Five patients required emergency/hospitalisation for low back pain without leg symptoms (n=3), self-limited dizziness - with cardiac history (n=1) and gastroenteritis (n=1).	Fluroscopy	Fluoroscopically guided lumbosacral TFESI is associated with a similar rate of minor AEs both immediately and 24 to 72 hours after procedure that are typical of other axial corticosteroid injections. Permanent AEs were not found in this sample
Correa et al..	2015	Colombia	Persons with chronic radicular pain receiving treatment between July 2010 and December 2011	254	Methylprednisolone	transforaminal lumbar (54.33%), interlaminar lumbar (17.72%), caudal (15.75%), and	One complication was reported for the lumbar transforaminal injection	Fluroscopy	Epidural methylprednisolone is a safe therapeutic option for the treatment of radicular pain

Author	Year	Country	Population	# Injections	Injectate	Approach	Prevalence of Adverse Events	Imaging	Conclusions
						interlaminar cervical (12.20%)			
Schneider et al..	2014	United States	Persons undergoing TFESI at a single acadaemic medical centre between March 2004 and January 2009	4482	Not reported	transforaminal epidural injection (with or without trainee)	Incidence of vasovagal reaction = 2.7% for physician only, 4.9% for trainees	Fluroscopy	Vasovagal reactions have an overall occurrence rate of 3.5% in TFESIs. Although there is a potential for bias, this study does appear to demonstrate that when a trainee is involved in a TFESI, there is nearly twice the rate of vasovagal reaction
Qureshi et al..	2013	Pakistan	Persons undergoing ESI at an interventional pain clinic from July 2009 to November 2012	386	Methylprednisolone acetate with 1% lidocaine	Lumbar (361), Cervical (20), and caudal (5) - using blind approach	For lumbar interlaminar ESI - immediate rections: vasovagal reaction (3.32%), intravascular entry (0.83%), flushing (2.21%), headache (1.1%), transient nerve irritation (0.27%), dural puncture (0.83%), cardiac arrest (0.27%) - delayed - PDPH (0.55% - abbreviation not expanded), bruises (0.83%)	Blind approach	Blind interlaminar epidural steroid injections are safe when performed with proper technique, monitoring and under recommended sterile precautions. The minor complications are common with this procedure but major complications are rare
Kainer et al..	2012	United States	All patients who had undergone epidural or paraspinal glucocorticoid injection procedures at a single	124	Methylprednisolone	Lumbar epidural (110), cervical epidural (12), sacroiliac-	RR of CNS fungal infection for translaminar ESI = 2.5 (95%CI: 1.3 to 4.8) and for use of contaminated methylprednisolone = 6.2 (95%CI: 2.6	Not reported	Epidural glucocorticoid injections can lead to localized infection, and fungal pathogens can invade the dura, leading to

Author	Year	Country	Population	# Injections	Injectate	Approach	Prevalence of Adverse Events	Imaging	Conclusions
			clinic since July 1, 2012, to assess for risk factors for infection. Outcomes included fungal meningitis or nonbacterial and nonviral meningitis of subacute onset, posterior circulation stroke when no cerebrospinal fluid was obtained, or spinal or paraspinal osteomyelitis or epidural abscess at the site of injection			joint (1), other (1)	to 14.5)		meningitis and, in some patients, invasion of the posterior circulation vasculature leading to stroke, haemorrhage, or both
Kang et al..	2012	South Korea	Post menopausal women with lower back pain receiving either medications without ESI or ESI > 4 times with a cumulative triamcinolone dose of >120mg	42 cases	Triamcinolone with 0.5% lidocaine	Lower lumbar	No significant difference in BMD between or within groups from baseline to one-year after treatment.	Not reported	ESI treatments using less than a total of 200mg triamcinolone had no significant effeect on BMD. However, the decrease in BMD of postmenopausal women who received more than 200mg of triamcinolone in one year indicates that ESI involving doses > 200mg/year should be avoided
Manchikanti et al..	2012	United States	Persons undergoing epidural procedures from May 2008 to	1450 lumbar interlaminar epidurals,	Not reported	Caudal epidurals (39%, cervival	**Lumbar interlaminar** = 0.5% Intravascular entry, 0.5% return of blood, 0.8% profuse bleeding, 0.1%	Fluroscopy	Major complications are rare and minor side effects

Author	Year	Country	Population	# Injections	Injectate	Approach	Prevalence of Adverse Events	Imaging	Conclusions
			December 2009 at a specialty referral centre private pain management practice	3985 caudal epidurals, and 1310 transforamina l epidurals		interlaminar epidurals (23%), lumbar interlaminar epidurals (14%), lumber transforamina l epidurals, percutaneous adhesiolysis (8%), thoracic interlaminar epidural	local haematoma, 0.28% transient nerve root irritation, 0.8% dural puncture, 0.07% postlumbar puncture headache, 0.13% facial flushing - **lumbar transforaminal** = 7.9% Intravascular entry, 3.7% return of blood, 0.2% profuse bleeding, 0.2% local haematoma, 0.4% bruising, 0.08% vasovagal reaction, 4.6% transient nerve root irritation, 0.61% jacet joint entry, 0.08% disc entry, 0.15% facial flushing - **caudal epidural** = 3.1% intravascular entry, 0.7% return of blood, 0.3% profuse bleeding, 0.1% local haematoma, 0.2% bruising		are common
Chang et al..	2011	United States	Persons undergoing epidural procedures from May 2008 to December 2009 at a specialty referral centre private pain management practice	751	Betamethasone acetate (91.5% of cases) and methyl prednisolone (4.7% of cases)	Lumbar region	None	CT-imaging	The use of air to localize the epidural space in CT-guided ESIs has a high success rate and a very low rate of complications
Karaman et al..	2011	Turkey	Persons with radiculopathy not responding to first line physiotherapy and medical care, referred to a single hospital-based pain clinic from November 2003 to	1305	Triamcinolone with 0.25% bupivacaine	transforamina l lumbar	Vascular penetration 7.4%, no major complications, minor complications: vasovagal reaction 8.7% and flushing 0.9%	Fluroscopy	The frequency of major complications is pretty rare in transforaminal lumbar epidural steroid injections in expert hands and in the conditions in which safety precautions are taken

Author	Year	Country	Population	# Injections	Injectate	Approach	Prevalence of Adverse Events	Imaging	Conclusions
			December 2008						
Candido et al..	2010	United States	Persons underoing LESI/TFESI at a single academic treatment centre between July 2004 and June 2007	2412 transforaminal and 4723 lumbar	Not reported	transforaminal and interlaminar lumbar	6 for transforaminal ESI and 1 for lumbar ESI	Fluroscopy	Our data demonstrate that intradiscal injection is a rare complication during LESI, but occurs more frequently with TFESI than with LESI
Trentman et al..	2009	United States	Persons undergoing translaminar cervical ESI, matched with those undergoing lumbar ESI, performed between December 1996 and May 2005. Patients who had undergoine previous ESIs were excluded from the study	249	Not reported	Cervical or lumbar ESI	1% in lumbar compared with 8% in cervical ($p<0.001$, 95%CI: 0.04 to 0.12). Multiple logistic regression modeling indicated that the characteristics that were the most strongly associated with the type of procedure were foraminal stenosis, spinal stenosis, use of the sitting position, use of contrast, and use of local anesthesia. The adjusted odds of cervical injection were 14 times higher among patients with vasovagal reaction than among patients without vasovagal reaction ($P = 0.001$, 95%CI: 2.7 to 68). Incidence of adverse effects for lumbar ESIs include blood (1% of procedures), dural puncture (1%), localised pain (10%), paresthesia (13%), and postoperative problems (2%)	Fluroscopy (85% for lumbar and 71% for cervical) and Contrast media (20% for lumbar and 39% for cervical)	The risk of vasovagal reaction is significantly higher for cervical translaminar epidural steroid injections than for lumbar injections

Author	Year	Country	Population	# Injections	Injectate	Approach	Prevalence of Adverse Events	Imaging	Conclusions
McGrath et al..	2011	United States	Persons attending a musculoskeletal physiatry practice between July 2002 and June 2009	4265	Not reported	Lumbar transforaminal (3964), lumbar interlaminar (123), cervical interlaminar (161), and caudal (17)	No major complications. Overall rate of minor complications for TL = 0.021% per injection (IL=0.06%). Minor complications included: increased pain (TF = 0.011% / IL = 0.021%), pain at injection site (TF = 0.0.0023% / IL = 0.018%), persistent numbness (TF = 0.0015% / IL = 0%), and 'other' (TF = 0.0068% / IL = 0.021%). Complications less common in transforaminal injections (2.1%) than in interlaminar (6.0%) (95%CI: 1.7% to 2.6%)	Fluroscopy and contrast media	These results suggest that ESIs are a safe and well-tolerated intervention for cervical or lumbar pain and radiculopathy
Botwin et al..	2000	United States	Persons presenting to a multidisciplinary spine care practice with complaints of lower back and radicular pain dur to herniated nucleus pulposus (HNP) or lumbar spinal stenosis (LSS)	322	Betamethasone acetate or methylprednisolone plus 1% lidocaine	transforaminal	No major complications noted. Incidence of minor complications = 9.6% per injection. Minor complications include: transient nonpositional headaches resolving within 24 hours (3.1%), increased back pain (2.4%), increased leg pain (0.6%), facial flushing (1.2%), vasovagal reaction (0.3%), increased BGL in person receiving insulin therapy for diabetes (0.3%) and intraoperative hypertension (0.3%)	Fluroscopy and contrast media	There were no major complications. The incidence of minor complications was 9.6% per injection. All reactions resolved without morbidity, and no patient required hospitalization
Furman et al..	2000	United States	Persons with either lumbar disc pathology or spinal stenosis receiving treatment with TFESI from March 1998 to July 1999 at a	761	Not reported	Lumbar (583) and S1 transforaminal (178)	Overall rate of intravascular injection = 11.2% (21.3% for TF and 8.1% for L - p<0.001)	Fluroscopy and contrast media	There is a high incidence of intravascular injections in transforaminal ESIs. Fluoroscopically guided procedures without contrast confirmation are

Author	Year	Country	Population	# Injections	Injectate	Approach	Prevalence of Adverse Events	Imaging	Conclusions
			single treatment clinic						instilling medications intravascularly and therefore not into the desired epidural location. This finding confirms the need for not only fluoroscopic guidance but also contrast injection instillation in lumbosacral transforaminal ESIs
Johnson et al..	1999	United States	Persons with back or neck pain with or without radiculopathy, attending a outpatient clinic over a 5.5yr period	5334	Not reported	lumbar (4780), cervical (669), or thoracic (40)	Hypotensive episode (N=1), dorsal epidural haematoma (N=1), vasovagal response (N=1), tachycardia (N=1)	Contrast media	Epidurography followed by therapeutic epidural steroid injection (with or without a local anesthetic) is a safe radiologic procedure that is easily performed by skilled proceduralists on an outpatient basis without intravenous sedation and cardiac monitoring