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Dear Drs. Garrett and Volkar:

The undersigned medical specialty societies, comprising physicians who utilize and/or perform interventional spine procedures to accurately diagnose and treat patients suffering from spine pathologies, would like to take this opportunity to express our strong support for coverage of epidural injections for chronic pain management, and provide a detailed explanation of their importance to Medicare patients' quality of life.

Our societies have a strong record of working to eliminate fraudulent, unproven, and inappropriate procedures. At the same time, we are equally committed to assuring that appropriate, effective, and responsible treatments are preserved.

**Significant relief of radicular neck and back pain, improved quality of life, with restoration of function and return to work, as well as decreased utilization of other healthcare resources** is an outcome that should be readily available to patients covered by Medicare. When epidural injections are performed in a disciplined, responsible manner, they achieve outcomes that are clinically, socially, and economically worthwhile.

#### **SELECTIVE SPINAL NERVE BLOCKS**

Selective spinal nerve blocks (SSNBs) use a small amount of anesthetic injected via a transforaminal approach to anesthetize a specific spinal nerve. SSNBs are diagnostic tools used to evaluate a patient's anatomical level and/or source of radicular pain. They are often used in surgical planning and decision-making.<sup>1</sup>

#### **EPIDURAL STEROID INJECTIONS**

Epidural steroid injections (ESIs) are validated treatments for radicular pain. Many recently published, high profile systematic reviews found that ESIs may be more effective compared to placebo injections in reducing leg pain and disability and were recommended for persistent severe radicular pain, with some studies questioning the advantage of adding steroids to local anesthetic injections.<sup>2-4</sup> These reviews provide excellent information, but have not separately assessed the outcomes of ESIs for different diagnoses and techniques, with goals of identifying patient populations and techniques for which ESIs have a greater likelihood of positive outcomes. Several high-quality systematic reviews have been published that address these issues by reviewing the body of evidence related to cervical and lumbar epidural steroid injections,<sup>5-8</sup> with meticulous stratification by selection criteria and procedural technique. These reviews are attached and present the outcomes

reported in the literature, concluding that effectiveness differs according to how patients are selected and how ESIs are performed.

### **Selection Criteria**

In interventional and surgical spine care, it is imperative to secure an exact diagnosis before proceeding with a specific treatment. Clinical history-taking and physical examination alone have been proven to insufficiently elicit an exact diagnosis, and therefore the proper treatment remains unknown. Advancements in imaging provide substantial insight into anatomic pathology, and together with a history, examination, and sound medical judgment, will lead to a definitive diagnosis.

When assessing the evidence, it is critical to perform subgroup analyses by specific diagnoses. For example, there is no physiologic process beyond systemic effect by which steroids delivered to the epidural space would be expected to relieve axial back pain arising from nociception in the intervertebral discs, facet joints, sacroiliac joints, or supporting musculature. There is ample experimental and clinical evidence that radicular pain has an inflammatory basis and is potentially susceptible to targeted delivery of an anti-inflammatory agent to the interface of neural tissue and the compressive lesion.<sup>9</sup>

Additionally, the identification of the underlying etiologies of pain is essential as different pathologies not only have varying responses to treatment, but also have different natural histories, impacting prognosis. Thus, the time frame of follow-up to determine clinical utility becomes imperative. Some conditions, such as intervertebral disc herniation, can result in debilitating pain, but have an overall favorable natural history. This would be in contrast to neurogenic claudication due to central canal stenosis, which is less likely to resolve spontaneously with time. Thus short-term relief would be very appropriate and expected for pain caused by a disc herniation. To evaluate the long-term effects in this population would be as flawed as evaluating the long-term effectiveness of antibiotics for pneumonia.

### **Procedural Technique**

#### *Image Guidance*

The techniques utilized in the administration of epidural steroids are also critical. Data show that “epidural” injections performed without image guidance may not universally reach the epidural space, even in expert hands.<sup>10-13</sup> Off-target medication delivery may not be efficacious and may be dangerous. Consequently, the FDA Safe Use Initiative on epidural steroid injections recommends use of image guidance for epidural steroid injections if not contraindicated.<sup>14</sup> Imaging should be used when the benefits of reducing the potential for patient harm outweigh the risks of imaging during epidural steroid injections.

#### *Approach/Access/Accuracy*

While image guidance is essential, the technique of delivery is equally important. Different approaches to the epidural space exist and data on the different approaches should not be pooled. Techniques assessed in many studies available for midline interlaminar epidural steroid injection (ILESIs) and caudal injections did not utilize image guidance; and even when performed with image guidance, these procedures may deliver medication distant from the

site of pathology, without certainty that the steroid will reach, or in what concentration it will reach, the target zone in the ventral epidural space. In contrast, transforaminal epidural steroid injection (TFESI) procedures place the needle in direct proximity to the target nerve and verify delivery to that site by observing contrast media flow.<sup>15</sup> Lateral parasagittal ILESI have also been shown to preferentially deliver injectate to the target ventral epidural space.<sup>16</sup> It is not reasonable to combine these different injection techniques in any evaluation of “epidural steroid injections”.

### **General Public Health Concerns**

Some patients may have no other treatment options apart from ESIs. When indicated, conservative care (*e.g.*, physical therapy, chiropractic, medications, *etc.*) has failed. Surgery can be contraindicated due to comorbidities or age, and some patients are adamant that they want to avoid surgery at all costs. Surgery also entails the very real risks of immediate or delayed surgical failure, technical failure, serious infections, permanent paralysis, re-herniations, and subsequent segmental instability requiring fusion. Several authors reported significantly worse outcome of discectomy in those with small, contained disc herniation.<sup>17-19</sup> Some even excluded from surgical consideration patients with small size lumbar disc herniation.<sup>20</sup> Thus, for patients with radicular pain because of a small disc herniation, surgery is far from a guaranteed solution. These are relevant considerations in the broader scope of clinical decision-making between a patient and physician.

Chronic or palliative care is also not always a good option. Opioids and NSAIDs can be contraindicated due to comorbidities, and both may have only short-term and minimal benefits. A large, utilization review, conducted in Denmark, of 2,000 patients who used opioids long-term for chronic pain, found that opioid therapy failed to fulfill any of the treatment goals: pain relief, improved quality of life, or improved functional capacity.<sup>21</sup> Long-term opioid therapy has very real and serious adverse effects, such as physical dependence, tolerance, opioid-induced pain hyperalgesia, addiction, diversion, and abuse; and side effects such as impairment of the immune, endocrine, and reproductive systems.<sup>22-25</sup> Increasing abuse and diversion of prescription opioids have become a serious problem. According to the Centers for Disease Control and Prevention (CDC), from 1999 to 2018, more than 232,000 people died in the United States from overdoses involving prescription opioids. Overdose deaths involving prescription opioids were more than four times higher in 2018 than in 1999.<sup>26</sup>

Regarding NSAIDs, a study in the *New England Journal of Medicine* estimated that at least 103,000 patients are hospitalized per year in the United States for serious gastrointestinal complications due to NSAID use.<sup>27</sup> At an estimated cost of \$15,000 to \$20,000 per hospitalization, the annual direct costs of such complications exceed \$2 billion. This study also estimated that 16,500 NSAID-related deaths occur every year in the United States. This figure is similar to the annual number of deaths from AIDS and considerably greater than the number of deaths from asthma, cervical cancer or Hodgkin's disease. NSAIDs can be considered to be the 15th most common cause of death in the US.

There is no doubt that ESIs are not the panacea for all spinal conditions. There are conditions best treated conservatively and others best treated surgically. ESIs provide a

valuable alternative option for some people. And unlike some medical treatments, which “cure” a problem (*e.g.*, appendectomy), many spinal conditions cannot be cured. Repetitive, palliative treatments can be the only option. The risk-benefit ratio of repeated ESIs can sometimes be preferable to perpetual medication use, or simply living with pain and disability.

### **Outcomes**

A substantial percentage of carefully selected patients will obtain intermediate-term relief from ESIs, and there is moderate evidence that ESI may prevent the need for spine surgery. Some patients require multiple ESIs.

- Approximately 50% of patients will experience 50% relief of cervical radicular pain at 1 month and up to 3 months after cervical transforaminal injection(s) of steroid, which may have surgery-sparing effects.<sup>5</sup>
- For patients with lumbar disc herniation treated with lumbar transforaminal injection(s), high-quality evidence supports that 74% experience at least 50% reduction in pain at 3 months and 64% report relief at six months and one year, likely preventing surgery and allowing the natural history of disc resorption to occur in the majority of patients.<sup>6</sup>
- For patients with lumbar spinal stenosis treated with lumbar transforaminal injection(s), low quality evidence finds that 48% experience at least 50% reduction in pain at 3 months, 43% report relief at 6 months, and 59% report 50% relief at one year.<sup>6</sup>
- For patients with lumbar radicular pain treated with midline lumbar interlaminar ESIs, low quality evidence supports short-term relief of radicular pain due to disc herniation or stenosis.<sup>7</sup>
- For patients with lumbar radicular pain treated with parasagittal interlaminar ESIs, outcomes mirror those seen with the lumbar transforaminal approach.<sup>7</sup>

**In patients diagnosed with radicular pain, Medicare Administrative Contractors should continue to support use of ESIs to achieve such outcomes and ensure that they remain available to Medicare patients.**

The North American Spine Society’s Epidural Steroid Injections and Selective Spinal Nerve Blocks Coverage Policy Recommendations (attached) provides a comprehensive overview of the evidence and recommendations for appropriate use of both procedures.<sup>1</sup> Key recommendations are summarized below:

- Therapeutic ESIs are indicated for the treatment of radicular or referred pain in which 2 of 4 of the following criteria are met:
  - The pain is severe enough to cause a degree of functional and/or vocational impairment or disability.
  - Pain duration of at least 4 weeks, and/or inability to tolerate or failure to respond to 4 weeks of noninvasive care.
  - Objective findings of radiculopathy or sclerotomal referred pain patterns are present and documented on examination.
  - Advanced imaging (CT or MRI) demonstrates a correlative region of nerve involvement.

- Procedures should be performed in accordance with safety guidelines outlined by the MPW (attached).<sup>14</sup>
- For most patients, no more than 4 ESIs would be indicated in a 12-month period. However, there must be some flexibility to allow for special, but not unique, circumstances (*e.g.*, patient presenting to second physician after technically inaccurate ESIs, wrong levels). Additionally, because the CPT code for SSNBs and TFIS is the same, it is reasonable in some cases to allow for up to 4 injections in a 6-month period (*e.g.*, patients with complex multilevel pathology on MRI who want a trial of injection therapy before considering surgery may well end up with 2 ESIs and 2 SSNBs during treatment and work-up).
- Given the explanation above, no more than 4 ESIs and/or SSNBs should be performed in a 6-month period; no more than 6 ESIs and/or SSNBs should be performed in a 12-month period of time regardless of the number of levels involved. However, caution should be exercised to limit the total steroid exposure in the specific period.

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The undersigned societies appreciate the opportunity to provide these comments. The MPW societies would welcome the opportunity to again work with the Medicare Administrative Contractors to revise the coverage criteria included in the LCDs to ensure appropriate access to epidural injections for Medicare patients. If you have any questions or wish to discuss any of our suggestions, please contact Belinda Duszynski, Senior Director of Policy and Practice at the Spine Intervention Society, at [bduszynski@SpineIntervention.org](mailto:bduszynski@SpineIntervention.org).

Sincerely,

American Academy of Pain Medicine

American Academy of Physical Medicine and Rehabilitation

American Society of Anesthesiologists

American Society of Regional Anesthesia and Pain Medicine

North American Neuromodulation Society

North American Spine Society

Spine Intervention Society

*Attachments:*

- Conger A, Cushman DM, Speckman RA, Burnham T, Teramoto M, McCormick ZL. The effectiveness of fluoroscopically guided cervical transforaminal epidural steroid injection for the treatment of radicular pain; a systematic review and meta-analysis. *Pain Med* 2020;21(1):41-54.
- Smith CC, McCormick ZL, Mattie R, MacVicar J, Duszynski B, Stojanovic MP. The effectiveness of lumbar transforaminal injection of steroid for the treatment of radicular pain: a comprehensive review of the published data. *Pain Med* 2020;21(3):472-487.
- Sharma AK, Vorobeychik Y, Wasserman R, Jameson J, Moradian M, Duszynski B, Kennedy DJ; Standards Division of the Spine Intervention Society. The effectiveness and risks of fluoroscopically guided lumbar interlaminar epidural steroid injections: a systematic review with comprehensive analysis of the published data. *Pain Med* 2017;18(2):239-251.
- Cohen SP, Bicket MC, Jamison D, Wilkinson I, Rathmell JP. Epidural steroids: a comprehensive, evidence-based review. *Reg Anesth Pain Med* 2013;38(3):175-200.
- North American Spine Society. Coverage Policy Recommendations: Epidural Steroid Injections and Selective Spinal Nerve Blocks. 2020.
- Rathmell JP, Benzon HT, Dreyfuss P, Huntoon M, Wallace M, Baker R, Riew KD, Rosenquist RW, Aprill C, Rost NS, Buvanendran A, Kreiner DS, Bogduk N, Fourney DR, Fraifeld E, Horn S, Stone J, Vorenkamp K, Lawler G, Summers J, Kloth D, O'Brien D, Tutton S. Safeguards to prevent neurologic complications after epidural steroid injections: consensus opinions from a multidisciplinary working group and national organizations. *Anesthesiology* 2015;122(5):974-84.

## References:

1. North American Spine Society. Coverage Policy Recommendations: Epidural Steroid Injections and Selective Spinal Nerve Blocks. 2020.
2. Oliveira CB, Maher CG, Ferreira ML, Hancock MJ, Oliveira VC, McLachlan AJ, Koes BW, Ferreira PH, Cohen SP, Pinto RZ. Epidural corticosteroid injections for lumbosacral radicular pain. *Cochrane Database Syst Rev* 2020;4(4):CD013577.
3. Foster NE, Anema JR, Cherkin D, Chou R, Cohen SP, Gross DP, Ferreira PH, Fritz JM, Koes BW, Peul W, Turner JA, Maher CG; Lancet Low Back Pain Series Working Group. Prevention and treatment of low back pain: evidence, challenges, and promising directions. *Lancet* 2018;391(10137):2368-2383.
4. Shanthanna H, Busse J, Wang L, Kaushal A, Harsha P, Suzumura EA, Bhardwaj V, Zhou E, Couban R, Paul J, Bhandari M, Thabane L. Addition of corticosteroids to local anaesthetics for chronic non-cancer pain injections: a systematic review and meta-analysis of randomised controlled trials. *Br J Anaesth* 2020;125(5):779-801.
5. Conger A, Cushman DM, Speckman RA, Burnham T, Teramoto M, McCormick ZL. The effectiveness of fluoroscopically guided cervical transforaminal epidural steroid injection for the treatment of radicular pain; a systematic review and meta-analysis. *Pain Med* 2020;21(1):41-54.
6. Smith CC, McCormick ZL, Mattie R, MacVicar J, Duszynski B, Stojanovic MP. The effectiveness of lumbar transforaminal injection of steroid for the treatment of radicular pain: a comprehensive review of the published data. *Pain Med* 2020;21(3):472-487.
7. Sharma AK, Vorobeychik Y, Wasserman R, Jameson J, Moradian M, Duszynski B, Kennedy DJ; Standards Division of the Spine Intervention Society. The effectiveness and risks of fluoroscopically guided lumbar interlaminar epidural steroid injections: a systematic review with comprehensive analysis of the published data. *Pain Med* 2017;18(2):239-251.
8. Cohen SP, Bicket MC, Jamison D, Wilkinson I, Rathmell JP. Epidural steroids: a comprehensive, evidence-based review. *Reg Anesth Pain Med* 2013;38(3):175-200.
9. Mulleman D, Mammou S, Griffoul I, Watier H, Goupille, P. Pathophysiology of disk-related sciatica. I. Evidence supporting a chemical component. *Joint Bone Spine* 2006;73(2):151-8.
10. Sharrock NE. Recordings of, and an anatomical explanation for, false positive loss of resistance during lumbar extradural analgesia. *Br J Anaesth* 1979;51(3):253-8.
11. Bartynski WS, Grahovac SZ, Rothfus WE. Incorrect needle position during lumbar epidural steroid administration: inaccuracy of loss of air pressure resistance and requirement of fluoroscopy and epidurography during needle insertion. *AJNR Am J Neuroradiol* 2005;26(3):502-5.
12. White AH, Derby R, Wynne G. Epidural injections for the diagnosis and treatment of low-back pain. *Spine* 1980;5(1):78-86.
13. Stojanovic MP, Vu TN, Caneris O, Slezak J, Cohen SP, Sang CN. The role of fluoroscopy in cervical epidural steroid injections: an analysis of contrast dispersal patterns. *Spine* 2002;27(5):509-14.
14. Rathmell JP, Benzon HT, Dreyfuss P, Huntoon M, Wallace M, Baker R, Riew KD, Rosenquist RW, Aprill C, Rost NS, Buvanendran A, Kreiner DS, Bogduk N, Fournay DR,

- Fraifeld E, Horn S, Stone J, Vorenkamp K, Lawler G, Summers J, Kloth D, O'Brien D, Tutton S. Safeguards to prevent neurologic complications after epidural steroid injections: consensus opinions from a multidisciplinary working group and national organizations. *Anesthesiology* 2015;122(5):974-84.
15. Ackerman WE, 3rd, Ahmad M. The efficacy of lumbar epidural steroid injections in patients with lumbar disc herniations. *Anesth Analg* 2007;104(5):1217-22
  16. Ghai B, Vadaje KS, Wig J, Dhillon MS. Lateral parasagittal versus midline interlaminar lumbar epidural steroid injection for management of low back pain with lumbosacral radicular pain: a double-blind, randomized study. *Anesth Analg* 2013;117(1):219-27.
  17. Carragee EJ, Han MY, Suen PW, Kim D. Clinical outcomes after lumbar discectomy for sciatica: the effects of fragment type and anular competence. *J Bone Joint Surg Am* 2003;85(1):102-8.
  18. Dewing CB, Provencher MT, Riffenburgh RH, Kerr S, Manos RE. The outcomes of lumbar microdiscectomy in a young, active population: correlation by herniation type and level. *Spine* 2008;33(1):33-8.
  19. Folman Y, Shabat S, Catz A, Gepstein R. Late results of surgery for herniated lumbar disk as related to duration of preoperative symptoms and type of herniation. *Surg Neurol* 2008;70(4):398-401.
  20. Mysliwiec LW, Cholewicki J, Winkelpleck MD, Eis GP. MSU classification for herniated lumbar discs on MRI: toward developing objective criteria for surgical selection. *Eur Spine J* 2010;19(7):1087-93.
  21. Eriksen J, Sjogren P, Bruera E, Ekholm O, Rasmussen NK. Critical issues on opioids in chronic non-cancer pain: an epidemiological study. *Pain* 2006;125:172-9.
  22. Sacerdote P, Manfredi B, Mantegazza P, Panerai AE. Antinociceptive and immunosuppressive effects opiate drugs: a structure-related activity study. *Br J Pharmacol* 1997;121:834-40.
  23. Vallejo R, deLeon-Casasola O, Benyamin R. Opioid therapy and immunosuppression. A review. *Am J Ther* 2004;11:354-65.
  24. Rajagopal A, Vassilopoulou-Sellin R, Palmer JL, Kaur G, Bruera E. Symptomatic hypogonadism in male survivors of cancer with chronic exposure to morphine. *Cancer* 2004;100:851-8.
  25. Mao J. Opioid-induced abnormal pain sensitivity: Implications in clinical opioid therapy. *Pain* 2002;100:213-7.
  26. Wide-ranging online data for epidemiologic research (WONDER). Atlanta, GA: CDC, National Center for Health Statistics; 2020. Available at <http://wonder.cdc.gov>.
  27. Wolfe MM, Lichtenstein DR, Singh G. Gastrointestinal toxicity of nonsteroidal antiinflammatory drugs. *N Engl J Med* 1999;340(24):1888-99.

# The Effectiveness of Fluoroscopically Guided Cervical Transforaminal Epidural Steroid Injection for the Treatment of Radicular Pain; a Systematic Review and Meta-analysis

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## Abstract

**Objective.** Determine the effectiveness of fluoroscopically guided cervical transforaminal epidural steroid injection (CTFESI) for the treatment of radicular pain. **Design.** Systematic review and meta-analysis. **Subjects.** Persons aged  $\geq 18$  years with cervical radicular pain due to disc herniation or degenerative spondylosis. **Comparison.** Sham, placebo procedure, or active standard of care treatment, excluding alternative versions of epidural steroid injection. **Outcomes.** The primary outcome measure was patient-reported improvement in pain of at least 50% from baseline, assessed four or more weeks after the treatment intervention. Secondary outcomes included validated functional assessment tools and avoidance of spinal surgery. **Methods.** Randomized or nonrandomized comparative studies and nonrandomized studies without internal control were included. Three reviewers independently assessed publications in the Medline, PubMed, and Cochrane databases up to July 2018. The Grades of Recommendation, Assessment, Development and Evaluation (GRADE) system was used to evaluate risk of bias and overall quality of evidence. A meta-analysis was conducted for comparative measures of effect and for within-group response rates if applicable. **Results.** There were no studies with an internal comparison group (control group) meeting the review's definition of comparison group. Therefore, comparative measures of effect were not calculated. In cohort studies, pooled response rates were 48% (95% confidence interval [CI] = 34–61%) at one month and 55% (95% CI = 45–64%) at three months. **Conclusions.** Approximately 50% of patients experience  $\geq 50\%$  pain reduction at short- and intermediate-term follow-up after CTFESI. However, the literature is very low quality according the GRADE criteria, primarily due to a lack of studies with placebo/sham or active standard of care control comparison groups.

**Key Words:** Cervical; Transforaminal; Epidural; Steroid; Radiculopathy; Injection

## Introduction

Neck pain is the fourth leading cause of disability, after back pain, depression, and arthralgias [1]. Cervical radiculopathy, a common cause of neck and radiating arm pain, is estimated to affect 83:100 000 individuals annually [2]. Disc herniation and age-related cervical spondylosis are the most common causes of cervical radiculopathy, with the C7, C6, and C8 nerve roots being

most commonly affected, in descending order of frequency [3]. In patients with cervical disc herniations, improvements in pain and function tend to occur within four to six months, and complete recovery occurs in 83% of patients within 24–36 months [4]. Although most cases of cervical radiculopathy eventually resolve, severe pain often prompts physician-directed interventions.

Treatments typically employed to reduce pain associated with cervical radiculopathy include physical therapy, spinal manipulation, spinal traction, anti-inflammatory and neuropathic pain medications, acupuncture, epidural steroid injections, and surgical decompression. Cervical transforaminal epidural steroid injection (CTFESI) is a target-specific treatment for refractory radicular pain. Analgesic mechanisms for epidural steroid administration are hypothesized to include reduction of inflammation at the nerve root, reduction of nociceptive signal transmission from somatic nerves, stabilization of neural membranes, and blockade of C-fiber activity in the dorsal root ganglion [5–7].

CTFESI differs from other routes of epidural access in that corticosteroid is placed directly into the intervertebral foramen, near the cervical nerve root. The theory underpinning this approach is that steroid deposited directly at the location of neural tissue compression or irritation allows for a high concentration (low volume) of corticosteroid to be administered where it will provide the greatest therapeutic effect [8].

## Objectives and Rationale

The present review was performed to systematically review, appraise, and provide a meta-analysis of the published literature on the effectiveness of fluoroscopically guided CTFESI for the treatment of radicular pain compared with sham, placebo, other active treatments, or no treatment, in terms of pain reduction, surgery rates, or disability. The treatment of radicular pain by CTFESI is distinct from the treatment of axial neck pain, which may or may not involve the cervical nerve root(s). Previous rigorous systematic review is limited to literature dated before June 2013, and several new studies have been published since that time [9]. This review is intended to serve as a resource for patients, physicians, regulatory agencies, and third-party payers in order to inform appropriate patient selection and the expected therapeutic value of CTFESI in the management of cervical radicular pain.

## Methods

### Protocol and Registration

This institutional review board–exempt study was registered on PROSPERO (ID: CRD42018106452, 09/19/2018).

### Eligibility Criteria

#### Population

Adults age 18 or older with cervical radicular pain due to disc herniation or degenerative spondylosis were included.

### Intervention

Fluoroscopy guided cervical transforaminal steroid injections. Minimum technical standards for inclusion in this review were taken from recommendations from the *Practice Guidelines for Spinal Diagnostic and Treatment Procedures* [8] and included 1) oblique approach with needle placement parallel to the long access of the intervertebral foramen, targeting the anterior aspect the of superior articular process; 2) utilization of multiplanar fluoroscopy to confirm appropriate needle placement within the foramen; 3) contrast injection and real-time or digital subtraction imaging to exclude intravascular injection. No exclusions were made for needle size, contrast flow patterns, or use of anesthetic test dose. Studies that did not publish at least two fluoroscopic views demonstrating needle placement were only included if the technique was thoroughly described and met the minimum standards above.

### Comparison

Sham, placebo, active treatment, or none. Interlaminar and other routes of epidural entry/methods for epidural steroid administration (such as those not including fluoroscopic guidance) were excluded.

### Outcome

The primary outcome was pain reduction compared with baseline of at least 50% using a validated self-report scale such as the numeric rating scale (NRS). Secondary outcomes were validated functional assessment tools and avoidance of cervical spinal surgery.

### Studies

We included randomized trials and nonrandomized studies including those without an internal control group (single-group studies or case series) with outcomes reported at least four weeks after the treatment intervention. If a study was designed as a randomized trial or nonrandomized comparative study but the comparison group did not meet the definition of a comparison group, the arm or arms meeting this review's intervention criteria were included and considered single-group studies. For example, a randomized trial of fluoroscopic guidance vs computed tomography (CT) guidance during the performance of a CTFESI was treated as a single-arm study, as the CT arm would not meet study inclusion criteria. Case reports, expert opinion, and unpublished data were excluded. No publication date or language restrictions were imposed.

### Information Sources and Search

Clinical outcome studies on the effectiveness of CTFESI specifically for the treatment of radicular pain were obtained by searching the PubMed and Medline databases, using the following search terms: (Radicul\*) AND (cervic\* OR neck OR upper extrem\* OR arm) AND

(transforam\* OR TFESI OR TF). Additionally, the Cochrane databases were searched using the following terms: (epidural OR transforaminal) AND (cerv\*). The searches were designed by DC and performed by AC on July 20, 2018. Literature was also identified from the bibliographies of retrieved publications.

### Study Selection

Two authors (AC and ZM) with formal training in assessment of the medical literature according to principles of evidence-based medicine independently assessed each paper meeting abstract screening criteria. Discrepancies were resolved by consensus discussion in order to reach a final decision regarding study inclusion. Studies were organized by etiology of radicular pain. Etiologic groups included cervical radicular pain due to herniated disc, “spondylotic stenosis” (best interpreted as degenerative foraminal or lateral recess stenosis), or “other” mixed causes of radicular pain. The terms “disc herniation” and “spondylosis” were often used but seldom defined. When described, the term disc herniation mostly commonly referred to displaced disc material impinging on cervical nerve roots. The term “spondylosis” most often referred to degenerative changes causing bony neuroforaminal (NF) or lateral recess stenosis, apart from disc herniation.

### Data Items and Collection

The following information was extracted from each study: 1) bibliographic details including author, year of publication, and location; 2) study inclusion and exclusion criteria; 3) participant characteristics including duration of pain, age, method of diagnosis; 4) etiology of nerve root compression; 5) procedural details (guidance method and technique); 6) injectate composition; and 7) frequency of injection. Additionally, outcome measures were recorded for pain reduction, disability, and surgical rates. Four weeks from the time of the treatment, intervention was considered the minimum duration for clinically meaningful pain relief. Therefore, studies following patients for less than four weeks were excluded from the tabulated sections and figures.

### Risk of Bias and Methodologic Assessment

Three of the four physician authors with formal training in assessment of the medical literature according to principles of evidence-based medicine (AC, RS, and ZM) assessed the risk of bias of the included studies using the GRADE criteria [10]. Discrepancies were resolved by consensus discussion in order to reach a final decision. All included studies were evaluated for appropriate study methodology, procedure techniques, data analysis, and outcome measurement according to the *Guidelines for Composing and Assessing a Paper on Treatment of Pain* [11,12]. Studies were charted according to these methodological characteristics based on an adapted tool from

the Spine Intervention Society’s Evidence-Based Medicine Accreditation Course [13].

### Summary Measures

The principal summary measures were comparative measures of effect (proportion ratio, proportion difference, or number needed to treat) using comparisons of the within-group response rate (proportion of patients reporting  $\geq 50\%$  reduction in pain). The secondary summary measure was the within-group response rate. Recent guidelines have highlighted the benefit of analyzing categorical data to determine the proportion of patients who stand to benefit from an intervention (i.e., responder analysis); in the case of CTFESI, the most commonly used prespecified outcome is  $\geq 50\%$  pain relief [9,12,14]. Studies providing categorical data or raw data, allowing for calculations of success rates (defined as the proportion of patients with a self-reported improvement in pain of at least 50%), were included in tabulated comparisons, whereas studies providing only group mean data were excluded from that portion of the review.

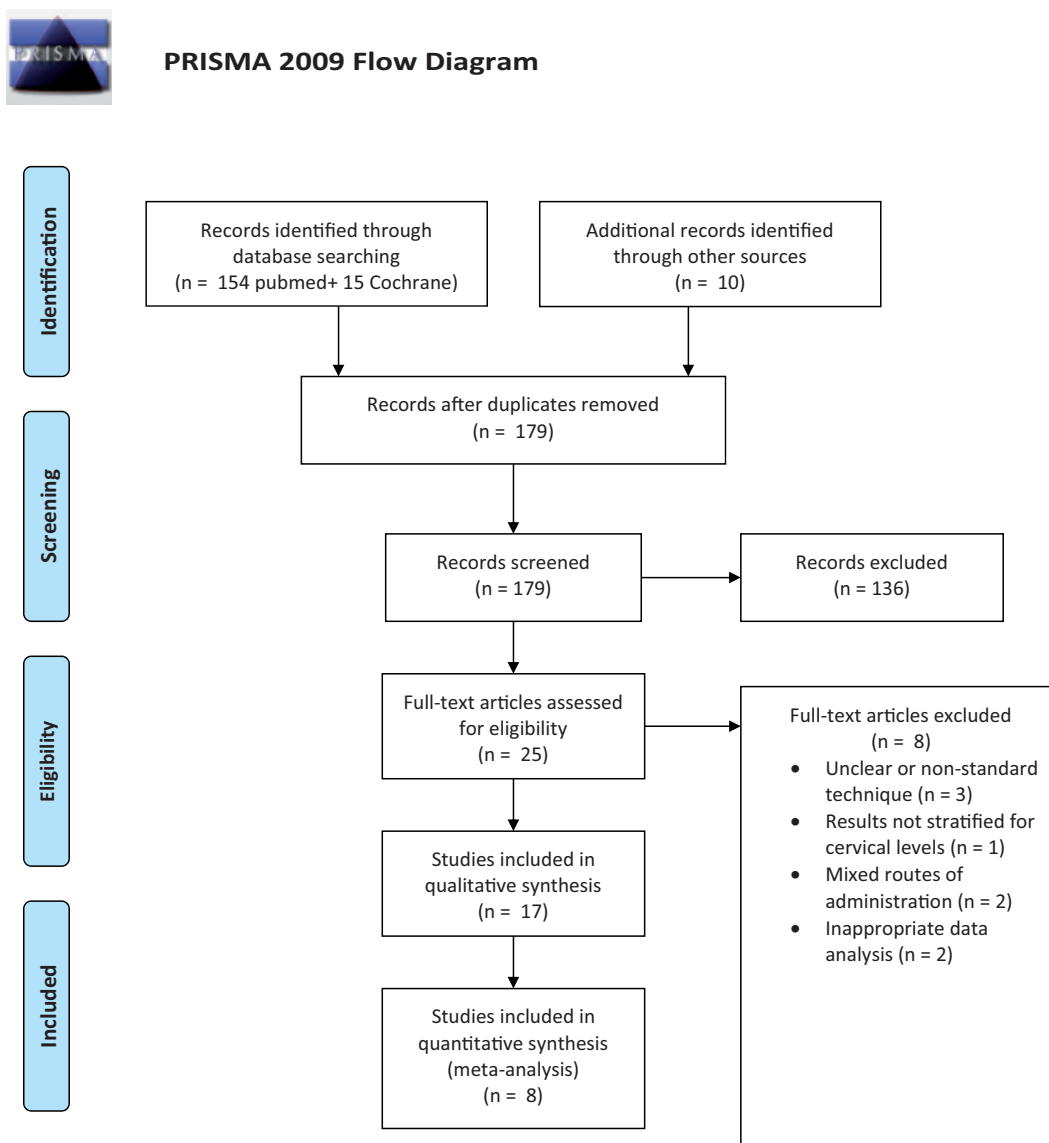
### Synthesis of Results

The data were assessed independent of the conclusions stated by authors of the primary studies with regard to both internal and external validity. Additionally, the quality of evidence relating to the effectiveness of fluoroscopically guided CTFESI was assessed using the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) system [15]. A meta-analysis was then conducted to calculate the proportion of patients achieving  $\geq 50\%$  pain reduction at one month and three months post-treatment, as well as at the two time points combined, separately for groups that received CTFESI with particulate and nonparticulate steroids. Specifically, these proportions were meta-analyzed by calculating the pooled estimate via Freeman-Tukey double arcsine transformation [16] along with an exact confidence interval [17]. The heterogeneity of the studies was observed when analyzing the studies using particulate steroids and all the studies combined, but was not present when analyzing those using nonparticulate steroids, as evaluated by Cochran’s Q and the  $I^2$  statistic [18,19]. Hence, a random-effects model was used for the meta-analysis on the studies using particulate steroids and all the studies combined, whereas a fixed-effects model was used for those using nonparticulate steroids [20,21]. If relative measures of effect could be calculated, inconsistency across studies was evaluated by comparing the direction of effect estimates and the overlap of confidence intervals [22].

## Results

### Study Selection

One hundred seventy-nine publications were identified from the initial query after removal of duplicates. After



**Figure 1.** Flow diagram of identified and included studies.

screening of abstracts for relevant publications, 25 articles were selected for potential inclusion based on population, intervention, comparison, outcome and study design criteria. The full text of these 25 studies was examined in detail; 17 articles were ultimately deemed suitable for inclusion, as shown in the Preferred Reporting in Systematic Reviews and Meta-analysis flow diagram (Figure 1).

The literature search yielded 11 nonrandomized, noncomparative studies (i.e., single-group studies) and six randomized trials that met established inclusion criteria. As none of the trials included a comparison group meeting the review question definition, randomized trial arms meeting the intervention criteria were included and treated as single-group studies. Studies were stratified by etiology of neural compression and are additionally described in Tables 1 and 2.

### Population: Radicular Pain due to Disc Herniation

In 2011, Lee and Lee [23] published an unblinded, single-center randomized controlled trial evaluating outcomes of fluoroscopically guided vs CT-guided CTFESI in patients suffering from cervical radicular pain secondary to single-level paramedian/foraminal disc herniation evident on magnetic resonance imaging (MRI). The study population included persons with pain persisting for at least three months that was unrelieved with oral analgesics and excluded patients with spinal canal stenosis. For this review, the fluoroscopically guided CTFESI treatment arm was included as a single-group study; the data for the CT group were not included in the tabulated section of this review or in the meta-analysis. Sixty-five patients were randomized to fluoroscopic guidance and received an injectate consisting of 5 mg of dexamethasone and 2 mL of 0.5% lidocaine. The primary outcome

**Table 1.** Treatment success rates reported in individual studies; the studies are grouped by inclusion criteria of intervertebral disc herniation vs spondylosis or heterogeneous studies including diagnosis as the etiology of radicular pain

Reference	Definition of Success	Time of Follow-up Assessment	Total No.	Success Rate (95% CI), %
Radicular pain due to cervical disc herniation				
Lee and Lee 2011 [23]	≥50% reduction in NRS	2 mo	65	55 (43–67)
	≥50% improvement in NDI	2 mo		58 (46–70)
Kolstad et al. 2005 [24]	≥50% VAS improvement	6 wk	21	29 (9–48)
	Surgical avoidance	4 mo		24 (6–42)
Costandi et al. 2015 [25]	Surgical avoidance	36 mo	64	70 (57.6–81)
Radicular pain due to spondylosis				
Kim et al. 2018 [26]	≥50% NRS improvement	3 mo	53	70 (57–82)
Persson and Anderberg 2012 [27]	≥50% VAS improvement	3 mo	145	48 (39–56)
Radicular pain of heterogeneous etiology (i.e., herniated discs, “spondylosis,” neuroforaminal stenosis)				
Dreyfuss et al. 2006 [28]	≥50% VAS improvement	1 mo	30	63 (46–81)
Woo and Park 2015 [29]	≥50% NRS improvement	3 mo	30	70 (54–86)
Choi et al. 2015 [30]	≥50% NRS improvement	3 mo	31	65 (49–81)
Klessinger et al. 2014 [31]	≥50% NRS improvement	1 mo	48	35 (22–49)
	Surgical avoidance	1 mo	26	58 (39–77)

CI = confidence interval; NDI = Neck Disability Index; NRS = numeric rating scale; VAS = visual analog scale.

was the proportion of patients achieving ≥50% NRS pain reduction at eight weeks. At this time point, 73% (95% confidence interval [CI] = 60–85%) of the CT arm reported ≥50% improvement in NRS, whereas in the fluoroscopy group 55% (95% CI = 43–67%) of patients reported ≥50% improvement. Regarding function, 58% (95% CI = 46–70%) of patients in the fluoroscopy arm reported ≥40% improvement in Neck Disability Index (NDI), whereas 76% (95% CI = 65–88%) of patients in the CT group reported ≥40% improvement. No information was provided regarding co-interventions.

#### Population: Radicular Pain due to Spondylosis

In 2012, Persson and Anderberg [27] published a prospective single-arm cohort study investigating the effect of a series of three CTFESIs (injectate unspecified) in 145 consecutive patients with cervical radicular pain due to “spondylosis” on MRI who were selected for treatment based on ≥50% reduction in arm pain after a diagnostic selective nerve root block. Seventeen percent of the patients included had prior cervical spine surgery and recurrence of symptoms. Five patients dropped out and were not analyzed by the authors; in accordance with worst-case analysis, these were calculated as treatment failures for the purposes of this review. The primary outcome was the proportion of patients experiencing ≥50% visual analog scale (VAS) reduction in arm pain at 12 weeks. At follow-up, 48% (95% CI = 39–56%) of patients reported ≥50% VAS reduction in arm pain. Ninety-one patients had improved NDI scores, and among responders, NDI scores decreased from an average of  $44 \pm 18.0$  to  $30 \pm 18.3$ . Pain intensity, sleep, and headache improved by the greatest magnitude. No information was provided regarding co-interventions.

In 2018, Kim et al. [26] published a retrospective single-group cohort study of 53 patients with cervical

radicular pain due to foraminal stenosis who received a CTFESI with 20 mg of dexamethasone and 1.5 mL of normal saline. The authors specifically selected patients with “pure foraminal stenosis due to cervical degenerative changes” confirmed by MRI. Twenty-two patients had “nonsevere” NF stenosis (narrowest width of the neural foramen >50% width of extraforaminal nerve root), whereas 31 patients had “severe” NF stenosis (narrowest width of the neural foramen <50%). At three months, 70% (95% CI = 57–82%) of patients reported ≥50% NRS reduction. Notably, there were no significant differences in pain reduction ( $P=0.409$ ) or treatment satisfaction ( $P=0.573$ ) between the severe and nonsevere NF stenosis groups. No information was provided regarding co-interventions.

#### Population: Neural Compression, Mixed Etiologies

In 2006, Dreyfuss et al. [28] conducted a randomized controlled trial of CTFESI with 1 mL of 12.5-mg dexamethasone or 60 mg of triamcinolone diluted with 4% lidocaine for the treatment of cervical radicular pain due to single-level nerve root compression confirmed by MRI or CT scan. Stratification of the etiology of neural compression was not reported. Patients with central stenosis <8 mm were excluded. As each intervention arm met the review criteria for intervention, each arm was treated as a single-group study for the purposes of this review. At four weeks, 60% (95% CI = 35–85%) of the patients in the dexamethasone group reported >50% improvement in pain, whereas 67% (95% CI = 43–91%) of patients in the triamcinolone group reported >50% improvement in pain. Function was measured with the Patient-Specific Functional Scale [34]: 73% (95% CI = 51–96%) of the particulate group regained at least three out of four desired activities of daily living

**Table 2.** Elements of design, methodology, and data analysis that affect study quality, adapted from the Spine Intervention Society evidenced-based medicine course, part I [13]\*

	Diagnosis Clearly Defined and Valid†	Prospective	Uniform Sample Demonstrated	Consecutive Patient Enrollment Reported	Co-interventions Described	Treatment Clearly Defined	Technique Adequately Described
	Minimal Loss to FU (<20%)	Valid Outcome Measures	Independent Outcome Assessment	Real-time Assessment	Categorical Outcome Analysis or Raw Data Available	ITT or Worst-Case Analysis Utilized or No Loss to FU	Outcomes Stratified for Confounders
Dreyfuss et al. 2006 [28]	x	x	x	x		x	x
Lee and Lee 2011 [23]	x	x	x	x		x	x
Woo and Park 2015 [29]	x	x	x	x		x	x
Choi et al. 2015 [30]	x	x	x			x	x
Costandi et al. 2015 [25]	x		x			x	x
Klessinger et al. 2014 [31]	x		x	x		x	x
Kim et al. 2018 [26]	x		x	x		x	x
Kolstad et al. 2005 [24]	x	x				x	x
Persson and Anderberg 2012 [27]	x			x			x
Lin et al. 2006 [32]	x	x					
Lee et al. 2009 [33]	x					x	x
Dreyfuss et al. 2006 [28]	x	x	x	x		x	x
Lee and Lee 2011 [23]	x	x	x	x		x	x
Woo and Park 2015 [29]	x	x	x	x		x	x
Choi et al. 2015 [30]	x	x	x	x		x	x
Costandi et al. 2015 [25]	x	x	x			x	x
Klessinger et al. 2014 [31]	x	x				x	x
Kim et al. 2018 [26]	x	x					
Kolstad et al. 2005 [24]	x	x				x	
Persson and Anderberg 2012 [27]	x			x			x
Lin et al. 2006 [32]	x	x	x				x
Lee et al. 2009 [33]	x					x	x

FU = follow-up; ITT = intent to treat.

\*Studies reporting categorical outcomes for at least one month meeting inclusion criteria for review.

†Etiologic diagnoses of disc herniation, spondylosis, or mixed were accepted so long as patients had clinical evidence of radiculopathy and confirmation of diagnosis with computed tomography or magnetic resonance imaging.

compared with 53% (95% CI = 28–79%) in the nonparticulate group. No information was provided regarding co-interventions.

In 2007, Anderberg et al. [35] conducted a randomized trial comparing CTFESI with 40 mg of methylprednisolone acetate plus 0.5 mL of mepivacaine vs 1 mL of saline and 0.5 mL of mepivacaine for the treatment of painful cervical radiculopathy in 40 patients. All patients had unilateral radicular pain due to “significant degenerative pathology” confirmed by MRI. The cohort had an average symptom duration of 31 months; 7.5% of patients had symptoms for less than six months. Only patients with 50% pain relief from diagnostic selective nerve root block at clinically and radiographically indicated levels were included. At three-week follow-up, a novel questionnaire was utilized to measure pain and function at one, two, and three weeks postinjection. In both the steroid and saline groups (N = 20 each), short-term pain relief was reported by seven patients (35%, 95% CI = 14–56%), but the magnitude of pain reduction was not reported. The authors reported no significant outcome differences between groups. No information was provided regarding possible co-interventions. No results were captured after three weeks; therefore, the data were not included in the tabulated section of this review or in the meta-analysis.

In 2013, Jee et al. [36] conducted a randomized controlled trial of fluoroscopically guided vs ultrasound (US)-guided CTFESI with 10 mg of dexamethasone and 3 mL of 0.5% lidocaine for the treatment of cervical radicular pain due to disc herniation or spinal stenosis. Patients were selected for treatment by “clinical profiles, medical examinations, electromyography tests, or confirmation of herniated disk or spinal stenosis via cervical CT or MRI,” which suggests that advanced imaging may not have been obtained for all patients. The fluoroscopy arm (N = 55) met this review’s definition of intervention and thus was considered a single-group study for the purposes of this review. The visual numeric scale (VNS) for pain and Neck Disability Index (NDI) were the outcomes of interest. Only group mean data were provided. At two weeks, the average baseline VNS of  $6.06 \pm 0.82$  decreased to  $3.17 \pm 0.52$  ( $P < 0.05$ ), and further to  $2.61 \pm 0.42$  ( $P < 0.05$ ) at 12 weeks. At two weeks, the average baseline NDI of  $24.62 \pm 5.77$  decreased to  $17.06 \pm 3.25$ , and further to  $12.40 \pm 2.99$  ( $P < 0.05$ ) at 12 weeks. No information was provided regarding co-interventions. As the proportion of responders could not be calculated (only mean data were provided), the results of this study were not included in the summary tables of this review or in the meta-analysis.

In 2015, Woo and Park [29] conducted a randomized, double-blind controlled trial of CTFESI with 2.5 mg of dexamethasone and 1 mL of 1% lidocaine vs 2.5 mg of dexamethasone and 1 mL of 0.125% lidocaine for the treatment of cervical radicular pain due to foraminal stenosis and/or disc pathology confirmed by MRI. All

patients had failed to respond to “conservative care” (undefined). Fifteen patients were enrolled in each treatment arm and were followed for between six and 12 weeks. After the first injection, patients were followed at two-week intervals for six weeks; those who reported an NRS score  $>3$  following the index CTFESI received a series of three injections at two-week intervals. Categorical data were provided only for the 12-week follow-up. Each intervention arm met criteria for inclusion as a single-group study for the purposes of this review. Together, 70% (95% CI = 54–86%) of patients reported a  $\geq 50\%$  reduction in NRS score.

In 2015, Choi et al. [30] conducted a randomized trial comparing cervical epidural injections with 5 mg of dexamethasone and 2 mL of 0.18% ropivacaine utilizing either a transforaminal route or a modified paramedian interlaminar technique for the treatment of cervical radicular pain due to disc herniation or foraminal stenosis, confirmed by MRI. Notably, patients with moderate or greater neuroforaminal or central stenosis on MRI were excluded. For the purposes of this review, the CTFESI group was considered a single-group study; the data for the modified paramedian interlaminar group were not included in the tabulated section of this review or in the meta-analysis. Of the 31 patients in the CTFESI group, 64.5% (95% CI = 47.8–81.4%) achieved  $\geq 50\%$  NRS reduction at 12 weeks; no other time points were reported. Contrast spread into the anterior epidural space was comparable between groups; vascular contrast patterns occurred less frequently in the modified paramedian interlaminar group. No information was provided regarding possible co-interventions.

In 2008, Kumar and Gowda retrospectively analyzed the outcomes of 33 patients who received CTFESI with 40 mg of triamcinolone and a 1.5-mL mixture of 0.25–0.5% bupivacaine in the treatment of cervical radicular pain due to “cervical disc disease” and/or foraminal stenosis confirmed by MRI [37]. Three patients were lost to follow-up. Only group means were reported. The average preprocedural VAS score (range) was 7.4 (5–10), which decreased to 2.2 (0–7) at six weeks and 2.0 (0–4) at one year. The average NDI score before intervention (range) was 66.9 (44–84), which improved to 31.7 (18–66) at six weeks and 31.1 (16–48) at one year. The reduction at six weeks in VAS scores (95% CI = 4.5–5.8) and the improvement in NDI scores (95% CI = 30.4–40.0) were statistically significant. Outcomes were stratified by disc herniation (N = 12) and cervical spondylosis (N = 21), but no clinically significant differences were demonstrated between these subgroups. No information was provided regarding co-interventions. As only group means were reported, results were not included in the tabulated summary or the meta-analysis.

In 2009, Lee et al. [33] conducted a retrospective single-group cohort study of 159 patients who received either CTFESI with undiluted dexamethasone 10 mg or undiluted triamcinolone 40 mg in the treatment of

cervical radicular pain secondary to disc herniation or NF stenosis due to spondylosis confirmed by MRI or CT scan. The primary outcome was the proportion of patients in whom the treatment was considered “effective.” If the descriptions were “no pain or much improved,” the outcome was classified as “effective,” as opposed to reporting of “slightly improved, same as before, or aggravated.” At an average follow-up (SD) of 15.8 (5) days, 80.4% (95% CI = 73–88%) of patients who received triamcinolone achieved the primary end point of “much improved or absent” pain compared with the 69.4% (95% CI = 58–81%) of patients who received dexamethasone ( $P=0.129$ ). Together, 76% (95% CI = 69–83%) of patients met the authors’ definition of success. No information was provided regarding co-interventions.

In 2012, Chung et al. [38] conducted a retrospective single-group cohort study of 28 consecutive patients who received a CTFESI with 20 mg of triamcinolone with 2 mL of saline and 2 mL of bupivacaine for the treatment of cervical radicular pain due to disc herniation ( $N=9$ ) or spondylosis ( $N=19$ ) confirmed by MRI. After failing to respond to at least two months of “conservative care” (undefined), patients received up to three injections (mean = 2.8) and were assessed at one week and three, six, and 12 months after the final injection. Only group mean data were reported. The average pretreatment VAS score was 7.8. At one week, the average pain score was 3.6, followed by 2.9 at three months and 4.6 at 12 months. Because only group mean data were provided, results were not included in the summary tables of this review or in the meta-analysis.

In 2013, Shakir et al. [39] reported a retrospective cohort study of 441 patients who received CTFESI with 1 mL of 1% lidocaine and either 15 mg dexamethasone or 40 mg triamcinolone for the treatment of cervical radicular pain secondary to a herniated disc or stenosis confirmed by MRI. At four weeks, after an average of 1.91 injections, the mean NRS reduction for the triamcinolone group ( $N=220$ ) was 2.33  $\pm$  2.24 vs 2.38  $\pm$  2.16 in the dexamethasone group ( $N=221$ ,  $P=0.80$ ). Only group mean data were provided. Thirteen percent of records were incomplete, and the authors did not perform a worst-case-scenario analysis. No information was provided regarding co-interventions. As the proportion of responders could not be calculated, results were not included in the summary tables of this review or in the meta-analysis.

In 2013, Ma and Shakir conducted a retrospective single-group study in diabetic and nondiabetic patients who received a CTFESI for cervical radicular pain due to disc herniation or spondylosis confirmed by MRI [40]. Patients received between one and three injections of 1 mL of 1% lidocaine and either 40 mg of triamcinolone or 15 mg of dexamethasone. Only group mean data were reported, with no description of follow-up timeline. No significant differences were observed between the 35

diabetic patients with a mean NRS score (SD) of 6.7 (2.4), who achieved a mean NRS reduction of 2.5 (2.4), and the 294 nondiabetic patients with a baseline NRS of 6.7 (1.8) who achieved a mean NRS reduction of 2.4 (2.2). Fifteen percent of patients were excluded from the analysis. Due to lack of categorical data and a lack of a clear timeline of follow-up, this study was not included in the summary tables of this review or in the meta-analysis.

In 2000 and 2004, Slipman et al. [41,42] published retrospective single-group studies on outcomes after CTFESI performed for patients with atraumatic and traumatic spondylotic cervical radicular pain. In the 2004 study, the authors omitted 40% of the cohort who ultimately underwent surgery as “treatment failures.” At an average follow-up time of 20.7 months, only 20% of patients (95% CI = 0–40%) met the authors’ definition of success (a composite of NRS, employment, medication utilization, and patient satisfaction). Similar issues exist with the 2000 study, so neither could be included for full review.

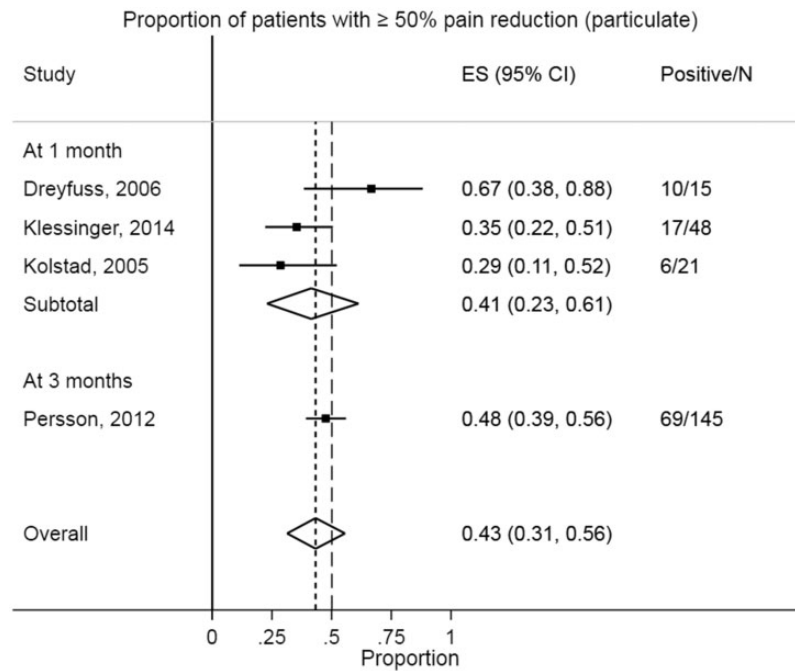
Several other studies could not be included for the following reasons: inadequate description or nonstandard technique [43–45], lack of contrast imaging [43,45], mixed routes of epidural access [46,47], and a retrospective study investigating electrodiagnostic predictors of epidural success that included CTFESI but did not report outcomes separately from lumbar data [48].

### Secondary Outcome: Spinal Surgery

In addition to improvement in pain and function, CTFESI may reduce the rate of surgical treatment. Literature query reviewed four primary studies that included data describing surgical rates after CTFESI; all were noncomparative studies.

### Population: Neural Compression, Mixed Etiologies

In 2005, Kolstad et al. [24] reported outcomes from a prospective noncomparative study examining 21 patients receiving CTFESI with triamcinolone 20 mg (without anesthetic) for the treatment of cervical radicular pain secondary to disc herniation or spondylosis. Cervical spondylosis ( $N=14$ ) or disc herniation ( $N=7$ ) was confirmed with MRI or myelography. All patients had unilateral C6 or C7 radiculopathy, were on a surgical waiting list for planned ACDF, and received two injections spaced apart by two weeks. VAS, Odom’s criteria, and surgical completion were measured at six weeks and four months postinjection. Although only group means were reported, the authors included a table with all data points for participants, allowing for calculation of categorical response rates. At six weeks, 29% (95% CI = 9–48%) experienced a  $\geq 50\%$  reduction in VAS scores for both arm and neck pain. At four months, these same responders (except one) graded their relief of symptoms and



**Figure 2.** Forest plot of the success rates of CTFESI using particulate steroid at one and three months.

satisfaction with treatment as “excellent.” Five of the original 21 participants (24%, 95% CI = 6–42%) canceled their surgeries. Only six participants had symptoms for less than six months, and >50% of participants’ symptom duration exceeded one year. No information was provided regarding possible co-interventions.

In 2014, Klessinger et al. [31] retrospectively analyzed the outcomes and radiographic features of 48 consecutive patients who received CTFESI with 2.5 mg of triamcinolone and bupivacaine for the treatment of cervical radicular pain due to disc herniation or spondylosis confirmed by MRI. At one month, 35.4% (95% CI = 22–49%) of the cohort achieved  $\geq 50\%$  NRS reduction. No clinical or radiologic feature was associated with a successful outcome. Of the 26 patients who were deemed operative candidates, 58% (95% CI = 39–77%) avoided surgery, with no specific timeline provided. Notably, the dose of triamcinolone utilized was unusually low, 6–12% of what has been used in all other published studies utilizing particulate steroid. No information was provided regarding possible co-interventions.

#### Population: Radicular Pain due to Disc Herniation

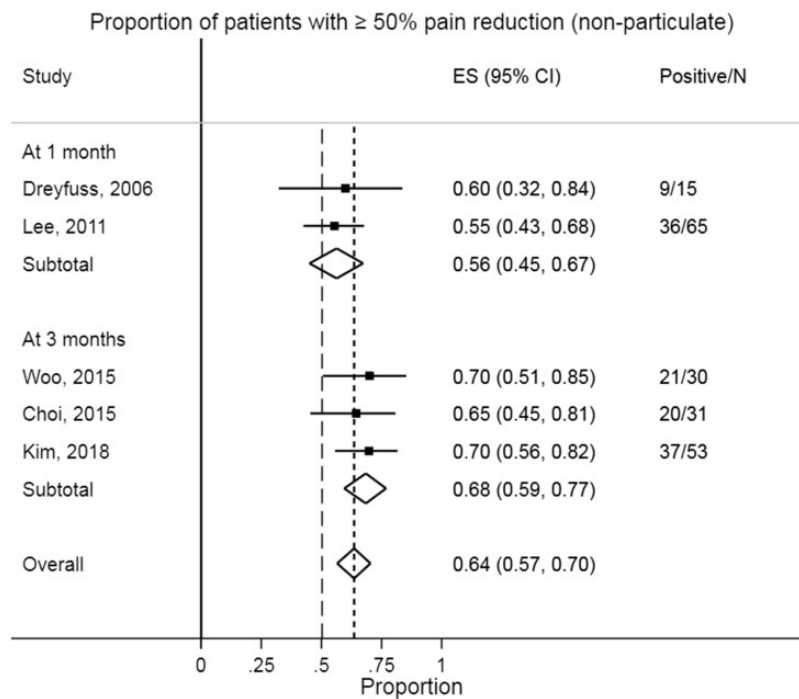
In 2006, Lin et al. [32] retrospectively analyzed the outcomes of 70 surgical candidates with cervical radicular pain due to disc herniation who received CTFESI (injectate unspecified). Disc herniation was confirmed on MRI. All patients had failed to improve with physical therapy and nonsteroidal anti-inflammatory medications and were offered CTFESI while on a surgical waiting list. The primary outcome, surgery avoidance at follow-up (average = 13 months), was achieved in 63% (95% CI = 52–74%) of the cohort, utilizing an average of 1.46

injections. In addition to not specifying the injectate, the authors did not describe the procedural technique, but instead cited a national survey of interventionalists in which multiple approaches were used [49]. Due to these limitations, the study was excluded from the summary tables and meta-analysis.

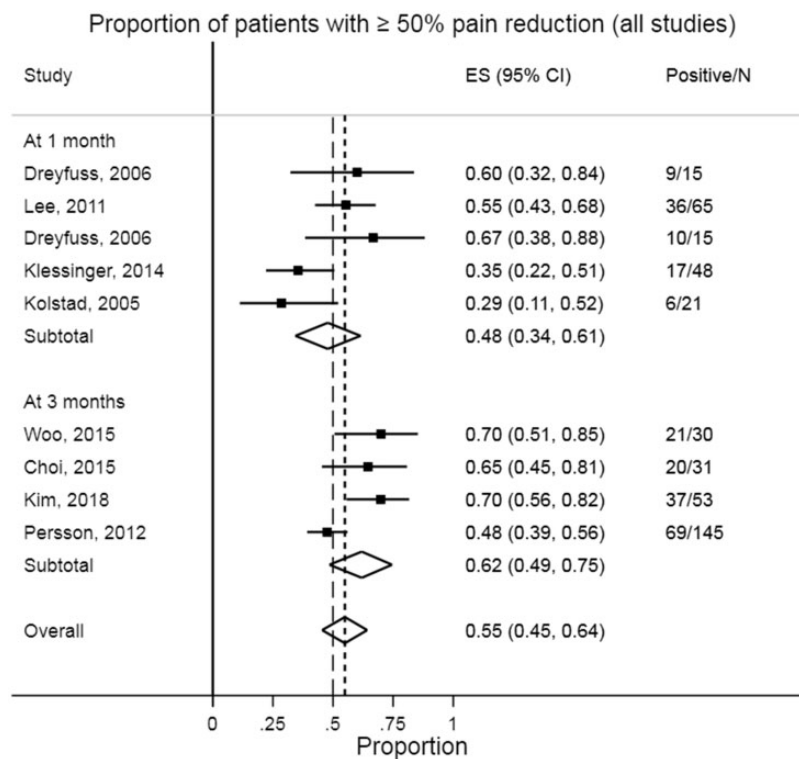
In 2015, Costandi et al. [25] retrospectively analyzed the outcomes of 64 patients with cervical radicular pain due to disc herniation who received CTFESI with 10 mg of dexamethasone and 1 mL of 0.5% bupivacaine. All patients had failed to respond to oral anti-inflammatories and physical therapy for at least eight weeks. At three years, surgery was avoided in 70.3% of the cohort (95% CI = 57.6–81%) utilizing an unspecified number of injections. NRS was measured at undefined time periods; the mean NRS difference before and after injection was 4.4 (95% CI = 3.75–5.10). The mean percent pain reduction was observed at 66% (95% CI = 58%–73%). As only group mean NRS scores were reported, these pain reduction data were not included in the tabulated section of this review or in the meta-analysis.

#### Synthesis of Results

As no studies had an internal comparison group meeting review criteria, a meta-analysis of comparative measures of effect such as a proportion ratio or proportion difference was not possible. A meta-analysis was then conducted in order to calculate the proportion of patients achieving  $\geq 50\%$  pain reduction at short and intermediate time points, as well as at the two time points combined, for groups that received CTFESI with particulate and nonparticulate steroids. Eight studies reported within-group response rates; forest plots describe the



**Figure 3.** Forest plot of the success rates of CTFESI using non-particulate steroid at one and three months.



**Figure 4.** Forest plot of the success rates of CTFESI using both particulate and non-particulate steroid at one and three months.

results for studies utilizing particulate steroids (Figure 2), nonparticulate steroids (Figure 3), and all studies combined (Figure 4). For particulate studies, the reduction in pain scores by  $\geq 50\%$  after CTFESI at one month was estimated at 41% (95% CI = 23–61%), at three months it was 48% (95% CI = 39–56%), and combined it was

43% (95% CI = 31–56%). For nonparticulate studies, reduction in pain scores by  $\geq 50\%$  after CTFESI at one month was estimated at 56% (95% CI = 45–67%), at three months it was 68% (95% CI = 59–77%), and combined it was 64% (95% CI = 57–70%). Together (particulate and nonparticulate studies), reduction in pain

scores by  $\geq 50\%$  after CTFESI at one month was estimated at 48% (95% CI = 34–61%), at three months it was 62% (95% CI = 49–75%), and combined it was 55% (95% CI = 45–64%).

### Adverse Events

No serious adverse events were reported in any study reviewed. Minor side effects included cases of syncope and transient vertigo (N = 3) [35,47], transient dizziness, headache, or facial flushing (N = 14) [23,50], transient dizziness or nystagmus (N = 3) [37], increased pain in the arm or neck (N = 3) [27], and transient Horner syndrome (N = 2) [38].

### Discussion

We report a systematic review of the effectiveness of CTFESI for the treatment of cervical radicular pain, with the first meta-analysis of the responder rate captured in the published literature to date. Although 25 studies have been published involving CTFESI, only 17 of these met inclusion standards for this systematic review. Several studies could not be included due to inadequate description or nonstandard technique [43–45], no utilization of contrast imaging [43,45], mixed routes of epidural access [46,47], and excessive loss to follow-up [41,42]. Of these 17, only 10 utilized validated measurements and provided categorical (or raw) outcome data at or beyond one month. Of these 10 studies, there were no studies with an internal comparison group meeting this review's clinical question. Therefore, no study was able to provide an estimate of a comparative measure of effect such as risk ratio, risk difference, or number needed to treat. No studies meeting inclusion reported the primary outcome beyond three months. Studies have reported outcomes at six and 12 months, but due to inadequate technique description, nonstandard technique, or failure to utilize contrast imaging, these results cannot be generalized to current practice [43–45] but nonetheless have shown success rates of 56% (95% CI = 39–73%) at six months and 38% (95% CI = 21–55%) at one year [43].

Function was inconsistently measured with validated tools in reviewed studies. NDI may improve in up to 58% (95% CI = 46–70%) of patients at two months but was reported categorically only in one study [23].

Although a subgroup analysis of large, well-designed randomized controlled trials (RCTs) involving lumbar transforaminal steroid injections has shown that less severe nerve compression is associated with improved outcomes [51], this pattern has not been established in the cervical spine. In patients with cervical radicular pain due to spondylosis vs disc herniation, no differences in outcomes were noted, either when comparing cohorts targeting just one of these diagnoses or in mixed etiologic studies where outcomes were reported separately (Table 1). Studies stratifying different degrees of NF

stenosis have also shown no differences in outcomes regardless of severity; this may be due to poor interrater agreement in rating foraminal stenosis severity [31].

Several studies challenged traditionally utilized injectates. As seen in Figures 2 and 3, studies utilizing nonparticulate steroids observed higher success rates ( $\geq 50\%$  pain reduction) than those using particulate steroids: 41% and 48% vs 56% and 68% at one and three months, for particulate vs nonparticulate cohorts, respectively. This difference appears to be largely driven by the relatively poor results seen in the presurgical cohorts studied by Klessinger and Kolstad, both of which utilized particulate steroid [24,31]. Dreyfuss et al. [28] published the only head-to-head comparison showing similar effectiveness between nonparticulate and particulate corticosteroid. Although limited literature in the lumbar spine has suggested that low-dose corticosteroids may perform similarly to higher doses [52], no studies have been designed to test this hypothesis, and the differences seen in better performing studies (dexamethasone 2.5 mg and 5 mg) [23,29,30] compared with poorly performing studies (triamcinolone 2.5 mg, 16–24 times lower than doses typically utilized) [24] could also be related patient selection or other factors. One RCT that included patients selected by diagnostic selective nerve root blocks found no intergroup differences at three weeks between local anesthetic plus saline vs local anesthetic and corticosteroid, raising doubts about the short-term benefits of corticosteroid, albeit with substantial methodologic limitations [35]. Determining the ideal concentration and volume of injectate for CTFESI will require high-quality head-to-head RCTs, as single-group observational studies cannot provide these answers.

Surgical avoidance rates were lower in surgery-waitlisted patients (29% at four months, 95% CI = 9–48%) [24] than in patients not yet committed to a surgery waitlist (58%, 95% CI = 39–77%) [31]. The inability of CTFESI to dissuade patients with chronic radiculopathy from an already agreed-upon anterior cervical discectomy and fusion (ACDF) is perhaps unsurprising and may be influenced by factors other than the pain-relieving effects of CTFESI. The ideal study design to conservatively estimate the surgery-sparing value of CTFESI would require all patients to be surgical candidates and to consent to surgery but would provide patients with ongoing management and facilitation of surgical vs nonsurgical decision-making by a clinician who would not perform any procedures, so as to reduce bias to complete or abort surgery after CTFESI. Additionally, issues related to patient expectations and preferences have been observed in large RCTs investigating outcomes of conservative vs operative management of lumbar disc herniation where patients who believed they would have better outcomes with surgery did indeed have better surgical outcomes [53]. Although lower-level evidence, the best-quality study addressing surgical rates after CTFESI was a retrospective cohort study that

reported 70% avoidance at three years (95% CI = 57.6–81%) among patients with cervical radicular pain due to disc herniation [25]. These results approximate the natural history of cervical radiculopathy seen in population-based epidemiologic studies. In a heterogeneous population (22% disc etiology, 68% mixed), Radhakrishnan et al. reported 74% surgery avoidance at a median time of 4.9 years, a strikingly similar rate to that of Costandi et al. at three years and within the 95% confidence interval of Klessinger's study in 2014 [2,25,31]. Interestingly, a recurrence of cervical radiculopathy occurred in 32% of the Radhakrishnan cohort, but only 6% of surgeries occurred after three months, which suggests a more favorable natural history beyond that time point and perhaps strengthens the validity of studies following surgical candidates for shorter durations. Other studies looking specifically at disc herniation reported surgery avoidance around one year in 63% of patients (95% CI = 52–74%) but with unreported injectate or technique [32].

### Quality of Evidence

The GRADE system was used to rate the overall quality of evidence. The evidence relating to both the radicular pain-relieving and surgery-sparing effects of CTFESI was overall rated as very low quality, as it is derived from observational studies or RCTs, which for the purposes of this review's research question were considered observational, single-group studies. In other words, no study had an internal control group meeting this review's definition of a comparison group. This determination suggests that the true treatment effect of CTFESI may differ from the current estimate of effect, and future research may change our current understanding. It is important to understand that although the quality of evidence is very low, this does not imply that CTFESI is ineffective, but rather that the current body of evidence is insufficient to draw strong, precise conclusions, and further study is needed.

### Limitations

There are limitations to the included studies and this review. Individual studies meeting inclusion criteria have been thoroughly reviewed and critically appraised for methodologic rigor and clinical significance. To portray the available data, comparable outcomes have been pooled (Figures 2–4) and relative methodologic quality detailed (Table 2). As can be seen from the latter, the studies reviewed had varying degrees of methodologic rigor irrespective of study design, though there was a trend toward better quality in more recent prospective publications. Notably, no single study reported on co-interventions, and the minority utilized validated functional scales as secondary outcomes. All the observational studies reviewed lacked an internal control. The published RCTs have not used a true placebo/sham or non-CTFESI standard-of-care comparison group.

Instead, all have used an alternative form of cervical epidural steroid injection (such as particulate vs nonparticulate steroid in the injectate or fluoroscopic vs CT guidance). As such, it is not possible to define the treatment effective attributable to steroid injection beyond that of placebo or non-CTFESI standard-of-care treatments. Although these trials offer valuable evidence relating to image guidance and injectate efficacy, comparative effectiveness research is needed to determine how CTFESI compares to other possible interventions, including surgery. In addition to these methodologic limitations, nearly every study reviewed suffers from a small sample size, variably limiting the confidence of treatment effects observed. In the absence of well-designed RCTs, future high-quality observational studies may offer a cost-effective approach to better estimate pain reduction, functional improvement, and surgical avoidance after CTFESI.

The strengths of this review include its narrow research question, thorough literature search, and the individual critical appraisal of all studies meeting inclusion. However, as only one author designed the search terms and only one author extracted the data, relevant articles might have been missed and errors in data collection may have transpired. Readers may consider the a priori exclusion of the RCT control arms to be a limitation of this review. We would like to emphasize that different RCT designs answer different clinical questions, and none has yet provided guidance on the comparative effectiveness of cervical TTFESI. This latter problem reflects the current state of the literature.

### Conclusions

The published evidence suggests that approximately half of patients with cervical radicular pain experience at least 50% pain reduction after CTFESI for up to three months. The evidence for the effectiveness of CTFESI is very low quality according to GRADE criteria, both for pain relief and surgery avoidance. Randomized trials with placebo/sham or non-CTFESI comparison groups are needed to determine the effectiveness and efficacy of CTFESI.

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### References

1. Murray CJL. The state of US health, 1990-2010. *JAMA* 2013;310(6):591–608.
2. Radhakrishnan K, Litchy WJ, O'Fallon WM, Kurland LT. Epidemiology of cervical radiculopathy. A population-based study from Rochester, Minnesota, 1976 through 1990. *Brain* 1994;117(2):325–35.

3. Iyer S, Kim HJ. Cervical radiculopathy. *Curr Rev Musculoskelet Med* 2016;9(3):272–80.
4. Wong JJ, Côté P, Quesnele JJ, Stern PJ, Mior SA. The course and prognostic factors of symptomatic cervical disc herniation with radiculopathy: A systematic review of the literature. *Spine J* 2014;14(8):1781–9.
5. Devor M, Govrin-Lippmann R, Raber P. Corticosteroids suppress ectopic neural discharge originating in experimental neuromas. *Pain* 1985;22(2):127–37.
6. Johansson A, Hao J, Sjölund B. Local corticosteroid application blocks transmission in normal nociceptive C-fibres. *Acta Anaesthesiol Scand* 1990;34(5):335–8.
7. Liberman AC, Druker J, Garcia FA, Holsboer F, Arzt E. Intracellular molecular signaling. *Ann N Y Acad Sci* 2009;1153(1):6–13.
8. Bogduk N. Practice guidelines for spinal diagnostic and treatment procedures. In: Bogduk N, ed. *International Spine Intervention Society*. 2nd ed. San Francisco, CA: International Spine Intervention Society; 2013: p. 272–273.
9. Engel A, King W, Macvicar J. The effectiveness and risks of fluoroscopically guided cervical transforaminal injections of steroids: A systematic review with comprehensive analysis of the published data. *Pain Med* 2014;15(3):386–402.
10. Guyatt GH, Oxman AD, Vist G, et al. GRADE guidelines: 4. Rating the quality of evidence—study limitations (risk of bias). *J Clin Epidemiol* 2011;64(4):407–15.
11. Bogduk N, Kennedy DJ, Vorobeychik Y, Engel A. Guidelines for composing and assessing a paper on treatment of pain. *Pain Med* 2017;18(11):2096–104.
12. McCormick ZL, Vorobeychik Y, Gill JS, et al. Guidelines for composing and assessing a paper on the treatment of pain: A practical application of evidence-based medicine principles to the mint randomized clinical trials. *Pain Med* 2018;19(11):2127–37.
13. Bogduk N. Accreditation Course in Evidence-Based Medicine: Part I: Assessing Studies of Treatment. 2018. Available at: <http://sis.mycrowdwisdom.com/diweb/catalog/item/id/2210314> (accessed November 5 2018).
14. Deyo RA, Dworkin SF, Amtmann D, Andersson G, Borenstein D, Carragee E. Report of the National Institutes of Health Task Force on Research Standards for Chronic Low Back Pain. *Pain Med* 2014;37(7):449–67.
15. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: An emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;336(7650):924–6.
16. Freeman MF, Tukey JW. Transformations related to the angular and the square root. *Ann Math Stat* 1950; 21(4):607–11.
17. Newcombe RG. Two-sided confidence intervals for the single proportion: Comparison of seven methods. *Stat Med* 1998;17(8):857–72.
18. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;327(7414):557–60.
19. Higgins JPT, Thompson SG. Controlling the risk of spurious findings from meta-regression. *Stat Med* 2004;23(11):1663–82.
20. Sutton AJ, Abrams KR, Jones DR, Sheldon TS. *Methods for Meta-Analysis in Medical Research*. Chichester, UK: John Wiley & Sons, Ltd; 2000.
21. Borenstein M, Hedges LV, Higgins JR. *Introduction to Meta-Analysis*. Chichester, UK: John Wiley & Sons, Ltd; 2009.
22. Guyatt G, Oxman AD, Sultan S, et al. GRADE guidelines: 11. Making an overall rating of confidence in effect estimates for a single outcome and for all outcomes. *J Clin Epidemiol* 2013;66(2):151–7.
23. Lee JH, Lee S-H. Comparison of clinical effectiveness of cervical transforaminal steroid injection according to different radiological guidances (C-arm fluoroscopy vs. computed tomography fluoroscopy). *Spine J* 2011;11(5):416–23.
24. Kolstad F, Leivseth G, Nygaard OP. Transforaminal steroid injections in the treatment of cervical radiculopathy. A prospective outcome study. *Acta Neurochir (Wien)* 2005;147(10):1065–70.
25. Costandi SJ, Azer G, Eshraghi Y, et al. Cervical transforaminal epidural steroid injections: Diagnostic and therapeutic value. *Reg Anesth Pain Med* 2015;40(6):674–80.
26. Kim MS, Lee DG, Chang MC. Outcome of transforaminal epidural steroid injection according to severity of cervical foraminal stenosis. *World Neurosurg* 2018;110:e398–403.
27. Persson L, Anderberg L. Repetitive transforaminal steroid injections in cervical radiculopathy: A prospective outcome study including 140 patients. *Evid Based Spine Care J* 2012;3(3):13–20.
28. Dreyfuss P, Baker R, Bogduk N. Comparative effectiveness of cervical transforaminal injections with particulate and nonparticulate corticosteroid preparations for cervical radicular pain. *Pain Med* 2006;7(3):237–42.
29. Woo JH, Park HS. Cervical transforaminal epidural block using low-dose local anesthetic: A prospective, randomized, double-blind study. *Pain Med* 2015;16(1):61–7.
30. Choi E, Nahm FSS, Lee PB. Comparison of contrast flow and clinical effectiveness between a modified paramedian interlaminar approach and transforaminal approach in cervical epidural steroid injection. *Br J Anaesth* 2015;115(5):768–74.
31. Klessinger S, Freund W, Karpel-Massler G, Halatsch ME. Response to transforaminal injection of steroids and correlation to MRI findings in patients with cervical radicular pain or radiculopathy due to disc herniation or spondylosis. *Pain Med* 2014;15(6):929–37.

32. Lin EL, Lieu V, Halevi L, Shamie AN, Wang JC. Cervical epidural steroid injections for symptomatic disc herniations. *J Spinal Disord Tech* 2006;19(3):183–6.
33. Lee JW, Park KW, Chung SK, et al. Cervical transforaminal epidural steroid injection for the management of cervical radiculopathy: A comparative study of particulate versus non-particulate steroids. *Skeletal Radiol* 2009;38(11):1077–82.
34. Westaway MD, Stratford PW, Binkley JM. The patient-specific functional scale: Validation of its use in persons with neck dysfunction. *J Orthop Sport Phys Ther* 1998;27(5):331–8.
35. Anderberg L, Annertz M, Persson L, Brandt L, Säveland H. Transforaminal steroid injections for the treatment of cervical radiculopathy: A prospective and randomised study. *Eur Spine J* 2007;16(3):321–8.
36. Jee H, Lee JH, Kim J, Park KD, Lee WY, Park Y. Ultrasound-guided selective nerve root block versus fluoroscopy-guided transforaminal block for the treatment of radicular pain in the lower cervical spine: A randomized, blinded, controlled study. *Skeletal Radiol* 2013;42(1):69–78.
37. Kumar N, Gowda V. Cervical foraminal selective nerve root block: A ‘two-needle technique’ with results. *Eur Spine J* 2008;17(4):576–84.
38. Chung J, Yim J, Seo H, Kim S, Cho K. The efficacy and persistence of selective nerve root block under fluoroscopic guidance for cervical radiculopathy. *Asian Spine J* 2012;6(4):227–32.
39. Shakir A, Ma V, Mehta B. Comparison of pain score reduction using triamcinolone vs. dexamethasone in cervical transforaminal epidural steroid injections. *Am J Phys Med Rehabil* 2013;92(9):768–75.
40. Ma V, Shakir A. The impact of type 2 diabetes on numeric pain score reduction following cervical transforaminal epidural steroid injections. *Skeletal Radiol* 2013;42(11):1543–7.
41. Slipman CW, Lipetz JS, Jackson HB, Rogers DP, Vresilovic EJ. Therapeutic selective nerve root block in the nonsurgical treatment of atraumatic cervical spondylotic radicular pain: A retrospective analysis with independent clinical review. *Arch Phys Med Rehabil* 2000;81(6):741–6.
42. Slipman CW, Lipetz JS, DePalma MJ, Jackson HB. Therapeutic selective nerve root block in the nonsurgical treatment of traumatically induced cervical spondylotic radicular pain. *Am J Phys Med Rehabil* 2004;83(6):446–54.
43. Vallée J-N, Feydy A, Carlier RY, Mutschler C, Mompont D, Vallée CA. Chronic cervical radiculopathy: Lateral-approach periradicular corticosteroid injection. *Radiology* 2001;218(3):886–92.
44. Wang F, Zhou Q, Xiao L, et al. A randomized comparative study of pulsed radiofrequency treatment with or without selective nerve root block for chronic cervical radicular pain. *Pain Pract* 2017;17(5):589–95.
45. Razzaq AA, O’Brien D, Mathew B, Bartlett R, Taylor D. Efficacy and durability of fluoroscopically guided cervical nerve root block. *Br J Neurosurg* 2007;21(4):365–9.
46. Bush K, Hillier S. Outcome of cervical radiculopathy treated with periradicular/epidural corticosteroid injections: A prospective study with independent clinical review. *Eur Spine J* 1996;5(5):319–25.
47. Lee S-H, Kim K-T, Kim D-H, Lee B-J, Son E-S, Kwack Y-H. Clinical outcomes of cervical radiculopathy following epidural steroid injection: A prospective study with follow-up for more than 2 years. *Spine (Phila Pa 1976)* 2012;37(12):1041–7.
48. McCormick Z, Cushman D, Caldwell M, Marshall B, Ghannad L, Eng C. Does electrodiagnostic confirmation of radiculopathy predict pain reduction after transforaminal epidural steroid injection? A multicenter study. *J Nat Sci* 2015;1(8).
49. Cluff R, Mehio A-K, Cohen SP, Chang Y, Sang CN, Stojanovic MP. The technical aspects of epidural steroid injections: A national survey. *Anesth Analg* 2002;95(2):403–8.
50. Park Y, Ahn JK, Sohn Y, et al. Treatment effects of ultrasound guide selective nerve root block for lower cervical radicular pain: A retrospective study of 1-year follow-up. *Ann Rehabil Med* 2013;37(5):658–67.
51. Ghahreman A, Bogduk N. Predictors of a favorable response to transforaminal injection of steroids in patients with lumbar radicular pain due to disc herniation. *Pain Med* 2011;12(6):871–9.
52. Ahadian FM, McGreevy K, Schulteis G. Lumbar transforaminal epidural dexamethasone: A prospective, randomized, double-blind, dose-response trial. *Reg Anesth Pain Med* 2011;36(6):572–8.
53. Weinstein JN, Tosteson TD, Lurie JD, et al. Surgical vs nonoperative treatment for lumbar disk herniation. *JAMA* 2006;296(20):2441.

## SPINE SECTION

# The Effectiveness of Lumbar Transforaminal Injection of Steroid for the Treatment of Radicular Pain: A Comprehensive Review of the Published Data

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## Abstract

**Objective.** To determine the effectiveness of lumbar transforaminal injection of steroid for the treatment of radicular pain. **Design.** Comprehensive systematic review. **Outcome Measures.** The primary outcome of interest was the proportion of individuals with reduction of pain by  $\geq 50\%$ . Additional outcomes of interest were a more-than-two-point reduction in pain score, patient satisfaction, functional improvement, decreased use of pain medication, and avoidance of spinal surgery. **Results.** For patients with disc herniations, using the criterion of  $\geq 50\%$  reduction in pain, success rates across included studies (range) were 63% (58–68%) at one month, 74% (68–80%) at three months, 64% (59–69%) at six months, and 64% (57–71%) at one year. For patients with lumbar spinal stenosis, success rates across included studies (range) were 49% (43–55%) at one month, 48% (35–61%) at three months, 43% (33–53%) at six months, and 59% (45–73%) at one year, but there was a lack of corroboration from appropriately controlled studies. **Conclusions.** There is strong evidence that lumbar transforaminal injection of steroids is an effective treatment for radicular pain due to disc herniation. There is a lack of high-quality evidence demonstrating their effectiveness for the treatment of radicular pain due to spinal stenosis, though small studies suggest a possible benefit. Lumbar transforaminal injection of nonparticulate steroids is as effective as injections with particulate steroids.

**Key Words:** Lumbar; Radicular pain; Transforaminal; Epidural; Steroid; Injection

## Introduction

Lumbar transforaminal injection of steroid (LTFIS) is a treatment for radicular pain. Steroids are believed to have a therapeutic effect due to their anti-inflammatory properties. This belief is supported by evidence from in vitro studies that show that steroids have a role in decreasing inflammatory mediators such as cytokines and chemokines [1,2]; another study suggests that steroids may provide a stabilizing effect on nociceptive signaling in C-fibers and suppression of ectopic neural discharges [3]. Research has

demonstrated that patients with radicular pain exhibit elevated levels of the neuro-inflammation marker 18kDa translocator protein in both the neuroforamina (containing dorsal root ganglion and nerve roots) and the spinal cord [4], and that epidural injection of steroid may help reduce levels of this neuroinflammatory protein [4].

LTFIS is distinguished from other forms of epidural injections by precise injection of corticosteroid in close proximity to the dorsal root ganglion (DRG) and nerve root using radiographic guidance [5]. The presumption

with this targeted delivery technique is that by placing the steroid in close proximity to the affected nerve root and DRG, the therapeutic effect of this agent will be optimized [5].

The present review was undertaken to provide an update of a 2013 systematic review by MacVicar et al., which evaluated published data through 2012 [6], and to provide practicing physicians with information critical to understanding the appropriate indications, risks, safety precautions, and expected benefits of LTFIS in the management of lumbar radicular pain.

## Methods

The objective of the literature search was to identify data concerning the effectiveness or complications of LTFIS for the treatment of radicular pain. Relevant studies on LTFIS were obtained by searching the PubMed and EMBASE Drugs and Pharmacology databases, using the following terms: lumbar, lumbosacral, transforaminal, epidural, steroids, and injection. Literature was also identified from the bibliographies of retrieved publications. Publications that were not available in English were eliminated, as were articles that did not provide information relevant to the effectiveness or safety of LTFIS.

### Etiology of Radicular Pain

Theoretically, the effectiveness of LTFIS might differ based on the etiologic condition and mechanism(s) causing pain. Studies on the effectiveness of LTFIS were categorized by the diagnosis for which LTFIS was indicated. These diagnostic groups were radicular pain due to disc herniation, radicular pain due to spinal stenosis (including fixed lesions, resulting in central canal, subarticular zone, lateral recess, and neuroforaminal stenosis), and radicular pain due to other diagnoses. The diagnoses were verified by both the descriptions provided by the study authors and the various imaging studies reported in the articles.

### Study Design

For evidence of effectiveness, observational, pragmatic, and explanatory studies were included for review. High-quality observational cohort studies were accepted for review on the grounds that such studies provide *prima facie* evidence of effectiveness. Pragmatic studies were accepted because they 1) demonstrate whether an intervention is more effective than an alternative treatment and 2) provide important information about the effectiveness of the intervention in the same manner as a prospective cohort study. Explanatory trials compare LTFIS with a treatment not expected to have a therapeutic effect; like a cohort study, they provide a measure of the success rate of the index treatment. Explanatory studies also reveal the attributable effect of LTFIS. The attributable effect is the difference in success rates between the index treatment and a sham treatment, which

distinguishes the extent to which the index treatment has a therapeutic effect beyond the nonspecific effects of a sham treatment. Commentaries, essays, editorials, systematic reviews, and other publications that did not provide original data were excluded from success rate calculations.

Publications of original data concerning complications were included regardless of study type. Case reports and studies of treatment were included in order to establish the spectrum, nature, and prevalence of possible complications of LTFIS. Articles that reported complications were analyzed to determine if the complication could plausibly be attributed to LTFIS, and thereafter if it was attributable to technical aspects of the injection or to one of the agents injected. Technical complications were also assessed on whether the procedure had been conducted according to guidelines [5,7].

### Assessment of Methodological Rigor and Appropriateness of Data Analysis

Four reviewers independently assessed publications on the effectiveness of LTFIS for radicular pain. The reviewers were practicing interventional pain physicians who regularly perform LTFIS. Each holds postgraduate qualifications in interventional pain management and has successfully completed formal certificate courses in evidence-based medicine. Studies were included if they met the following criteria: 1) presentation of clinically relevant data on the efficacy or effectiveness of LTFIS for the treatment of radicular pain *and* 2) presentation of valid information based on appropriate procedural technique, study methodology, and data analyses according to the principles of evidence-based medicine [8] or the ability to perform appropriate data analyses from raw published data; *or* 3) report of a complication associated with LTFIS. Studies that did not contain categorical data or the ability to extract categorical data were excluded. Categorical data analysis defines proportions of patients in which prespecified outcomes (e.g.,  $\geq 50\%$  pain relief) are achieved—indicating the success rates of the given treatment. Although group data analysis might suggest that a treatment is statistically effective, it does not reveal how frequently the treatment is successful or the degree to which it is expected to be effective for a given patient [8].

Reviewers also evaluated studies for their intrinsic methodological rigor, assessing various factors critical in the assessment of the quality of studies of pain [8], including whether the study used an acceptable technique for LTFIS, if the sample was representative of a realistic clinical population, if validated outcome measures were used, if  $<20\%$  of patients were lost to follow-up, if the study was controlled for co-interventions, whether there were any conflicts of interest, and whether the diagnostic criteria and assessment tools were valid. Four weeks was considered a minimum threshold for clinically significant

duration of therapeutic effect; studies following patients for less than four weeks postinjection were excluded. Each reviewer provided an appraisal of each paper and discussed conclusions. Elements of data collection methodology were also considered. Prospective studies were considered to be inherently higher quality than retrospective studies with regard to retrieval bias (not all patients are identified and reported). Studies with independent observers were considered to be inherently of higher quality than those without, due to reduced observer and response bias. The results of studies including measures of pain, function, or disability and the use of other health care were considered more convincing than studies reporting only success rates for pain relief. The body of evidence was evaluated using the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) system of appraisal to determine the quality of the evidence of the effectiveness of LTFIS [9]. In essence, the GRADE system asks reviewers to evaluate the body of evidence transparently with consideration not only to study design, but also to attributes that would strengthen or weaken confidence in the estimate of effect. GRADE provides an initial rating of quality based upon the best available evidence that comprises the body of knowledge, then further requires consideration of weaknesses (e.g., risk of bias, indirectness) that merit downgrading and strengths (e.g., large magnitude of effect, dose-response gradient) that would justify upgrading the rating of the quality of the body of evidence. The published data on the effectiveness and safety of LTFIS were taken into account, and overall conclusions were drawn in accordance with the GRADE system. With regard to both study inclusion and GRADE evaluation, disagreements were resolved by consensus decision among the reviewers. For acceptable studies that provided categorical data, the success rates and confidence intervals were calculated.

## Results

**Table 1** shows treatment success rates reported in individual explanatory, pragmatic, and observational studies; the studies are grouped by etiology of radicular pain. **Table 2** presents study-defined definitions of treatment success compared with 50% pain reduction as the definition of treatment success, stratified by study design. The literature search yielded 32 observational cohort studies, nine pragmatic trials, and two explanatory trials that met established inclusion criteria for our review.

### Radicular Pain Due to Disc Herniation

The majority of studies reported on the clinical outcomes of LTFIS for the treatment of radicular pain due to intervertebral disc herniation. The results are grouped by the type of study.

### Observational Cohort Studies

Observational cohort studies that met criteria for inclusion in this review provided evidence on the effectiveness of LTFIS in the treatment of radicular pain caused by lumbar intervertebral disc herniation. Several studies were excluded due to unacceptable study methodology, including inadequate description of LTFIS technique [10], inadequate follow-up [11], or >20% of subjects lost to follow-up [10,12]. One study used a more-than-two-point numeric rating scale (NRS) pain reduction and “at least satisfied with treatment” to define success and reported a success rate of 75% (95% confidence interval [CI] = 64–86%) at two months and 66% (95% CI = 54–78%) at four months [13].

Success, defined as a 50% reduction in radicular pain, was assessed at different time points. As shown in **Table 1**, observational studies have reported statistically similar success rates at given follow-up periods. At one month, success was 60% (95% CI = 48–72%) [32] in one study and 79% (95% CI = 66–92%) in another (**Table 1**) [33]. A different study used an 80% reduction in pain to define success and reported a success rate of 67% (95% CI = 55–79%) at one month [37].

At two months, one study defined success as either a 50% reduction in pain or >40% improvement in Oswestry Disability Index (ODI) score. It reported success in 58% of subjects (95% CI = 54–62%) at two months [39]. Other studies, which defined success as >50% NRS reduction, reported success rates of 57% (95% CI = 50–64%) [38] and 66% (95% CI = 51–81%) [13]. The study by Maus et al. included a large number of subjects and reported a success rate at two months that was consistent with those found in controlled trials [38]. Another study reported success rates of 68% (95% CI = 52–84%), 56% (95% CI = 39–73%), and 59% (95% CI = 42–76%) at two, six, and 12 months, respectively [27].

Successful outcomes (defined by either 50% improvement or >30-mm improvement in visual analog scale [VAS] score) were reported in 56% (95% CI = 43–69%) of subjects at three months [40]. Yet another study, which also followed patients for three months, reported that 53% (95% CI = 38–68%) of patients had a >50% reduction in pain [26].

By the same definition of success, another study found a success rate of 75% (95% CI = 65–85%) at six months [25]. When pain relief was maximally defined as 100% relief at six months, 30% (95% CI = 14–46%) of subjects met success criteria [31].

Observational cohort studies demonstrate that symptoms continue to be improved at the one-year mark. There has been speculation that this may represent regression to the mean or be attributable to a favorable natural history of the disease. An older study that defined success as “at least moderate relief of symptoms” demonstrated a success rate of 73% (95% CI = 57–89%) [24]. Another study reported similar success rates of 73%

**Table 1.** Treatment success rates reported in individual explanatory, pragmatic, and observational studies; the studies are grouped by etiology of radicular pain

References	Definition of Success	Time of Follow-up Assessment	Total No., Success Rate (95% CI)
<b>Radicular pain due to lumbar disc herniation</b>			
<i>Explanatory studies</i>			
Vad et al. 2002 [14] <sup>†</sup>	Patient satisfaction score of “good” or “very good,” ≥5-point RMDQ improvement, and >50% NRS improvement	1 y	Treatment group: 25, 84% (70–98%) Placebo group – saline trigger point injection: 23, 48% (28–68%)
Ghahreman et al. 2010 [15] <sup>†</sup>	≥50% pain reduction on NRS	1 mo 3 mo 6 mo 1 y	28, 54% (36–72%) 28, 39% (21–57%) 28, 32% (15–49%) 28, 25% (9–41%) Placebo group – intramuscular injection of normal saline: 26, 15% (1–29%)
<i>Pragmatic studies</i>			
Karppinen et al. 2001 [16]	>75% relief of leg pain	1 mo 3 mo 6 mo 1 y	80, 41% (29–53%) 80, 38% (26–50%) 80, 30% (20–40%) 80, 38% (26–50%)
Jeong et al. 2007 [17] <sup>‡</sup>	>50% VAS improvement	6 mo	193, 61% (54–68%)
Rados et al. 2011 [18] <sup>†</sup>	>50% VAS improvement	6 mo	32, 63% (46–80%)
Ghai et al. 2014 [19] <sup>†</sup>	≥50% VAS improvement	1 mo 3 mo 6 mo 1 y	30, 63% (46–80%) 30, 77% (62–92%) 30, 77% (62–92%) 30, 77% (62–92%)
Gupta et al. 2014 [20] <sup>†</sup>	≥50% VAS improvement	1 mo 3 mo	20, 80% (62–98%) 20, 90% (77–100%)
Kennedy et al. 2014 [21] <sup>†</sup>	≥50% NRS improvement	3 mo 6 mo	78, 73% (63–83%) 78, 74% (64–84%)
Manchikanti et al. 2014 [22] <sup>†</sup>	≥50% NRS improvement and ≥50% ODI improvement	3 mo 6 mo 1 y 2 y	60, 82% (72–92%) 60, 87% (78–96%) 60, 73% (62–84%) 60, 73% (62–84%)
Pandey et al. 2016 [54] <sup>†</sup>	≥50% improvement of JOA score	1 y	40, 90% (81–99%)
<i>Observational studies</i>			
Weiner and Fraser 1997 [24] <sup>†</sup>	At least “moderate” relief of symptoms	1 y	30, 73% (57–89%)
Lutz et al. 1998 [25] <sup>†</sup>	>50% NRS improvement	6 mo	69, 75% (65–85%)
Viton et al. 1998 [26] <sup>†</sup>	>50% VAS improvement	3 mo	40, 53% (38–68%)
Rosenberg et al. 2002 [27] <sup>†</sup>	>50% NRS improvement	2 mo 6 mo 12 mo	34, 68% (52–84%) 34, 56% (39–73%) 34, 59% (42–76%)
Wang et al. 2002 [28] <sup>†</sup>	Avoidance of surgery	1 y	69, 77% (67–87%)
Schaufele et al. 2006 [29] <sup>†</sup>	Avoidance of surgery	1 y	20, 90% (77–100%)
Yang et al. 2006 [30] <sup>†</sup>	Avoidance of surgery	2 y	21, 67% (47–87%)
Ackerman and Ahmad 2007 [31] <sup>†</sup>	100% pain relief	6 mo	30, 30% (14–46%)
Choi et al. 2007 [32] <sup>†</sup>	>50% VAS improvement and satisfaction score of at least “improved”	1 mo	68, 60% (48–72%)
Lee et al. 2009 [13] <sup>†</sup>	≥2-point NRS improvement and at least “satisfied” with treatment	2 mo 4 mo	59, 75% (64–86%) 59, 66% (54–78%)
Lee et al. 2009 [33] <sup>†</sup>	>50% VAS improvement	1 mo 2 mo	38, 79% (66–92%)* 38, 66% (51–81%)*
Mendoza-Lattes et al. 2009 [34] <sup>†</sup>	Avoidance of surgery	1 y	54, 56% (43–69%)
Manson et al. 2013 [35] <sup>†</sup>	Avoidance of surgery	6 mo	91, 56% (46–66%)
Van Helvoirt et al. 2014 [36] <sup>†</sup>	At least “significantly reduced pain” and avoidance of surgery	1 y	71, 76% (66–86%)
Joswig et al. 2016 [37]	>80% VAS reduction	1 mo	57, 67% (55–79%)
Maus et al. 2016 [38]	≥50 NRS improvement	2 mo	175, 57% (50–64%)
Singh et al. 2016 [39] <sup>†</sup>	>50% NRS improvement or >40% ODI improvement	2 mo	721, 58% (54–62%)

(continued)

Table 1. continued

References	Definition of Success	Time of Follow-up Assessment	Total No., Success Rate (95% CI)
Tecer et al. 2016 [40] <sup>†</sup>	>50% or >30-mm VAS improvement	3 mo	59, 56% (43–69%)
van Helvoirt et al. 2016 [41] <sup>†</sup>	Avoidance of surgery, ≥50% VAS improvement, ≥50% RMDQ improvement, GPE of at least “satisfaction”	1 y	79, 76% (67–85%)
Sariyildiz et al. 2017 [42]	≥50% VAS improvement	1 y	75, 73% (63–83%)
Radicular pain due to spinal stenosis			
Explanatory studies			
None	N/A	N/A	N/A
Pragmatic studies			
Jeong et al. 2007 [17] <sup>†</sup>	>50% VAS improvement	6 mo	46, 57% (43–71%)
Observational studies			
Botwin et al. 2002 [43] <sup>†</sup>	≥50% VAS improvement	1 y	34, 75% (60–90%)
Rosenberg et al. 2002 [27] <sup>†</sup>	>50% NRS improvement	2 mo	26, 54% (35–73%)
		6 mo	26, 19% (4–34%)
		12 mo	26, 35% (17–53%)
Lee et al. 2009 [13] <sup>†</sup>	≥2-point NRS improvement and at least “satisfied” with treatment	2 mo	57, 67% (55–79%)
Lee et al. 2009 [33] <sup>†</sup>	>50% VAS improvement	4 mo	57, 51% (38–64%)
		1 mo	49, 63% (49–77%)*
		2 mo	49, 53% (39–67%)*
Smith et al. 2010 [44] <sup>†</sup>	≥50% VAS improvement	1 mo	19, 32% (11–53%)
Ploumis et al. 2014 [45] <sup>†</sup>	≥50% VAS improvement	6 mo	20, 90% (77–100%)
Park et al. 2015 [46] <sup>†</sup>	>50% NRS improvement	1 mo; 3 mo	30, 70% (54–86%); 30, 43% (25–61%)
Davis et al. 2016 [47] <sup>†</sup>	Avoidance of surgery	2 y	68, 68% (57–79%)
Farooque et al. 2016 [48]	≥50% NRS improvement	1 mo	26, 30% (12–48%)
		3 mo	26, 53% (34–72%)
		6 mo	26, 44% (25–63%)
		2 mo	188, 47% (40–54%)
Maus et al. 2016 [38]	≥50 NRS improvement		
Radicular pain due to failed back surgery syndrome			
Explanatory studies			
None	N/A	N/A	N/A
Pragmatic studies			
None	N/A		
Observational studies			
Rosenberg et al. 2002 [27] <sup>†</sup>	>50% NRS improvement	2 mo	13, 23% (0–46%)
		6 mo	13, 23% (0–46%)
		12 mo	13, 23% (0–46%)
Rahimzadeh et al. 2014 [49] <sup>†</sup>	>50 NRS improvement	1 mo	13, 46% (19–73%)

CI = confidence interval; GPE = global perceived effect; JOA = Japanese Orthopedic Association; LTFIS = lumbar transforaminal injection of steroid; NRS = numeric rating scale; ODI = Oswestry Disability Index; RMDQ = Roland Morris Disability Questionnaire; VAS = visual analog scale.

\*“Small” LTFIS group: 3 mL of injectate.

<sup>†</sup>Multiple LTFIS were allowed.

<sup>‡</sup>Unclear if multiple LTFIS were allowed.

(95% CI = 63–83%) [42], defined by 50% reduction in VAS at one year.

### Pragmatic Studies

There were several studies that did not meet criteria for inclusion in the review. Some studies were excluded because they did not include any categorical data or raw data to allow for calculation of success rates [23,34,50]. Others were excluded due to inadequate description of LTFIS technique [51,52] or inadequate duration of follow-up [53].

There were eight pragmatic studies that provided acceptable data on success rates of LTFIS for disc herniation. Most studies used pain relief as the primary outcome. One study defined success as a 50% improvement in Japanese

Orthopedic Association score and reported a success rate of 90% (95% CI = 81–99%) at one year [54].

Several studies used ≥50% VAS improvement as the definition of success. Studies variously demonstrated success rates at one month of 63% (95% CI = 46–80%) [19] and 80% (95% CI = 62–98%) [20]. At three months, success rates were 77% (95% CI = 62–92%) [19], 73% (95% CI = 63–83%) [21], and 90% (95% CI = 77–100%) [20]. At six months, success rates were 63% (95% CI = 46–80%) [18] and 74% (95% CI = 64–84%) [21].

One study that compared LTFIS with transforaminal epidural injection of saline defined success as 75% relief of leg pain [16,55]. This study has been categorized as a pragmatic study, as epidural injection of any substance

**Table 2.** Total No., success rates, and 95% confidence intervals for study-defined definitions of treatment success vs  $\geq 50\%$  pain reduction as the definition of treatment success, stratified by study design type

Study Design	Discogenic Radicular Pain				Spinal Stenosis-Related Radicular Pain			
	Explanatory	Pragmatic	Observational	All	Explanatory	Pragmatic	Observational	All
All definitions of "success"	28, 54% (36–72%)	130, 53% (44–62%)	1,123, 58% (55–61%)	1,281, 57% (54–60%)	-	-	312, 49% (44–55%)	312, 49% (43–55%)
3 mo defined	28, 39% (21–57%)	268, 67% (61–73%)	158, 59% (51–67%)	454, 65% (61–69%)	-	-	113, 50% (41–59%)	113, 50% (41–59%)
6 mo by study	28, 32% (15–49%)	513, 65% (61–69%)	224, 59% (53–65%)	765, 62% (59–65%)	-	46, 57% (43–71%)	52, 31% (18–44%)	98, 43% (33–53%)
1 y investigators*	53, 53% (40–66%)	170, 58% (51–65%)	432, 73% (69–77%)	655, 67% (63–71%)	-	-	46, 59% (45–73%)	46, 59% (45–73%)
2 y $\geq 50\%$ pain reduction	-	60, 73% (62–84%)	21, 67% (47–87%)	81, 72% (62–82%)	-	-	68, 68% (57–79%)	68, 68% (57–79%)
1 mo	28, 54% (36–72%)	50, 72% (60–84%)	247, 62% (56–68%)	325, 63% (58–68%)	-	-	312, 49% (43–55%)	312, 49% (43–55%)
3 mo	28, 39% (21–57%)	128, 78% (71–85%)	40, 62% (47–77%)	196, 74% (68–80%)	-	-	56, 48% (35–61%)	56, 48% (35–61%)
6 mo	28, 32% (15–49%)	333, 66% (61–71%)	71, 69% (58–80%)	432, 64% (59–69%)	-	46, 57% (43–71%)	52, 31% (18–44%)	98, 43% (33–53%)
1 y	28, 25% (9–41%)	30, 77% (62–92%)	109, 71% (62–80%)	167, 64% (57–71%)	-	-	46, 59% (45–73%)	46, 59% (45–73%)
2 y	-	-	-	-	-	-	-	-

\*Depending on the study, investigators used various definitions of "success," such as improvements in pain or function, positive satisfaction scores, avoidance of surgery, or combinations thereof.

(i.e., steroid, local anesthetic, saline) has the potential to have a therapeutic effect and therefore cannot be considered a placebo. Success rates of 41% (95% CI = 29–53%) at one month, 38% (95% CI = 26–50%) at three months, 30% (95% CI = 20–40%) at six months, and 38% (95% CI = 26–50%) at one year were observed [16].

Other studies incorporated validated functional assessment tools in defining success. One pragmatic study randomized patients to lumbar transforaminal injection of lidocaine and saline or lumbar transforaminal injection of lidocaine and betamethasone (LTFIS) [22]. The study defined success as  $\geq 50\%$  reduction in pain and  $\geq 50\%$  improvement in ODI. For the LTFIS group, success rates were 82% (95% CI = 72–92%) at three months, 87% (95% CI = 78–96%) at six months, 73% (95% CI = 62–84%) at one year, and 73% (95% CI = 62–84%) at two years. The success rates of the LTFIS group were higher than the lidocaine and saline group, though they failed to reach statistical significance [22].

One high-quality pragmatic study on LTFIS for radicular pain due to disc herniation met inclusion criteria and included patients with both LSS and disc herniation, with data stratified by diagnosis [17]. However, because the study did not compare LTFIS with a conventional control treatment, but compared the outcomes of two different techniques of LTFIS, the study is being categorized as providing observational data for the purposes of this review. At six months, 61% (95% CI = 54–68%) experienced a  $\geq 50\%$  reduction in pain on the VAS [17].

### Explanatory Studies

Two explanatory studies met criteria for inclusion [14,15]. Both showed clinically and statistically significant improvement in pain in the LTFIS groups compared with other treatments. A well-designed prospective double-blind randomized controlled trial (RCT) [15] compared the outcomes of 1) transforaminal injection of steroid and local anesthetic (LTFIS), 2) transforaminal injection of local anesthetic alone, 3) transforaminal injection of normal saline, 4) intramuscular injection of steroid, and 5) intramuscular injection of normal saline. Success was defined as  $\geq 50\%$  NRS improvement at one month. A significantly greater proportion of patients treated with LTFIS reported treatment success compared with transforaminal injection of local anesthetic, transforaminal injection of saline, intramuscular steroid injection, or intramuscular saline injection. For the LTFIS group, success rates were 54% (95% CI = 36–72%) at one month, 39% (95% CI = 21–57%) at three months, 32% (95% CI = 15–49%) at six months, and 25% (95% CI = 9–41%) at one year. Significant improvements in function, disability, and reductions in use of other health care were observed in the LTFIS group compared with the other groups (Table 1).

Another RCT compared LTFIS with intramuscular injection of saline [14]. This study used strict criteria of

**Table 3.** Comparative success rates in studies of particulate vs nonparticulate transforaminal injection of steroids

References	Indication	Definition of Success	Time of Follow-up Assessment	Corticosteroids	Success Rate
Park et al. 2010 [107] <sup>†</sup>	Lumbar radicular pain	>50% relief of pain	1 mo	Dexamethasone (7.5 mg) Triamcinolone (40 mg)	36% (23–49%) 100% (93–100%) No significant differences in disability scores
El-Yahouchi et al. 2013 [106]*	Radicular pain with or without radiculopathy	≥50% relief of pain ≥40% RMDQ improvement	2 mo	Dexamethasone (10 mg) Triamcinolone (80 mg) Bethamethasone (12 mg)	Pain: 52.3% (45.9–58.8%) Function: 46.4% (39.9–52.8%) Pain: 45.0% (41.5–48.5%) Function: 41.5% (38.0–45.0%) Pain: 43.6% (40.6–46.6%) Function: 37.2% (34.3–40.1%) Success rates were not significantly different between groups
Kennedy et al. 2014 [21]*	Lumbar radicular pain for disc herniation	≥50% reduction in NRS >50% reduction in ODI	3 mo 6 mo	Dexamethasone (10 mg)  Triamcinolone (40 mg)	3 mo Pain: 73% (59–87%) ODI: 68% (54–82%) 6 mo Pain: 73% (59–87%) ODI: 71% (57–85%) 3 mo Pain: 73% (59–87%) ODI: 68% (53–83%) 6 mo Pain: 76% (62–90%) ODI: 65% (50–80%) No significant differences between groups found for relief of pain, functional improvement, or rates of surgery
Denis et al. 2015 [68]*	Lumbosacral radicular pain	≥50% pain relief	3 mo	Dexamethasone (7.5 mg) Betamethasone (6 mg)	59% (41–77%) 33% (15–51%) No significant differences between mean pain scores at all follow-up points ( <i>P</i> = 0.058)
Kim et al. 2016 [108]*	Excluded from success rate analysis due to grouped diagnoses and inclusion of data from interlaminar injections not separated from LTFIS data	Relative satisfaction	6-mo phone follow-up	Triamcinolone (40 mg) Dexamethasone (10 mg)	Relative satisfaction was significantly better with triamcinolone than with dexamethasone, and the injection-free interval after injection was significantly longer with triamcinolone than with dexamethasone
Bensler et al. 2018 [109] <sup>†</sup>	“Lumbar radiculopathy” without diagnostic criteria	“Better” or “much better” on Patients’ Global Impression of Change scale	1 mo questionnaire	Dexamethasone (4 mg) Triamcinolone (40 mg)	33% (26–40%) 44% (39–49%) Significantly greater improvement in the triamcinolone group ( <i>P</i> = 0.019) More patients reported they were “better” or “much better” in the triamcinolone group

LTFIS = lumbar transforaminal injection of steroid; NRS = numeric rating scale; ODI = Oswestry Disability Index; RMDQ = Roland Morris Disability Questionnaire.

success, including a patient satisfaction score of “good” or “very good,” a five-or-more-point Roland Morris Disability Questionnaire (RMDQ) improvement, and  $\geq 50\%$  NRS improvement. The responder rate was significantly higher in the LTFIS group compared with the intramuscular saline injection group ( $P < 0.005$ ). At one year, the success rate in the LTFIS group was 84% (95% CI = 70–98%). The shortcomings of this study included lack of blinding.

#### **GRADE Assessment of the Evidence: High Quality**

Multiple randomized controlled trials and high-quality observational studies have provided high-quality evidence supporting the effectiveness of LTFIS in reducing pain, improving function, and reducing reliance on other health care in patients with radicular pain due to disc herniation.

#### **Radicular Pain Due to Spinal Stenosis**

Few high-quality studies evaluating LTFIS specifically for radicular pain due to lumbar spinal stenosis (LSS) were encountered; however, a number of cohort and pragmatic studies met criteria for inclusion in this review.

#### **Observational Cohort Studies**

Several studies used pain relief as their primary outcome measure (Table 1). Less convincing definitions of success were used in some studies. These definitions of success included more-than-two-point NRS improvement and a patient satisfaction rating of “at least satisfied.” Using these criteria, success rates were 67% (95% CI = 55–79%) and 51% (95% CI = 38–64%) [13] at two and four months, respectively.

The proportion of patients with a successful outcome, defined as  $\geq 50\%$  reduction in VAS or NRS, was used in several studies. At one month, success rates were reported as 30% (95% CI = 12–48%) [48], 32% (95% CI = 11–53%) [44], 63% (95% CI = 49–77%) [33], and 70% (95% CI = 54–86%) [46]. Two-month success rates were reported as 47% (95% CI = 40–54%) [38], 53% (95% CI = 39–67%) [33], and 54% (95% CI = 35–73%) [27]. At three months, success rates were reported as 43% (95% CI = 25–61%) [46] and 53% (95% CI = 34–72%) [48]. At six months, reported success rates were highly variable, reported as 19% (95% CI = 4–34%) [27], 44% (95% CI = 25–63%) [48], and 90% (77–100%) [45]. Although studies that reported success rates at one year showed a high proportion of successful outcomes, these outcomes are inconsistent and may have been related to other factors such as natural history. Defined as  $\geq 50\%$  NRS improvement, successful outcomes at one year were reported as 35% (95% CI = 17–53%) [27], 75% (95% CI = 60–90%) [43], and 90% (95% CI = 77–100%) [45].

#### **Pragmatic Studies**

Several studies were excluded due to unacceptable study methodology. Two studies were excluded due to lack of categorical data [56,57]. A large pragmatic study concluded that epidural steroids were ineffective for spinal stenosis, but the study failed to control for or provide subgroup analysis of dose or technique (i.e., interlaminar epidural steroid injection or LTFIS) [58]. It is also unclear which patients had radicular pain symptoms vs neurogenic claudication alone, two conditions that likely respond differently to LTFIS.

One high-quality pragmatic study on LTFIS for radicular pain due to LSS met inclusion criteria and included patients with both LSS and disc herniation, with data stratified by diagnosis. However, because the study did not compare LTFIS with a conventional control treatment, but compared the outcomes of two different techniques of LTFIS, the study is being categorized as providing observational data for the purposes of this review. Defining success as a  $\geq 50\%$  VAS reduction in pain, the study demonstrated a success rate of 57% (95% CI = 43–71%) at six months [17].

#### **GRADE Assessment of the Evidence: Low Quality**

With an evidence base consisting of studies with conflicting results related to the effectiveness of LTFIS in the treatment of LSS, the quality of evidence is low in accordance with the GRADE system. Additional studies, controlled for technique and dose and with appropriate subgroup analysis by specific type of stenosis (subarticular, central, foraminal), would assist in determining whether LTFIS is an effective treatment for patients with radicular pain due to lumbar spinal stenosis.

#### **Other Diagnoses**

Some studies evaluated mixed diagnostic categories or evaluated miscellaneous conditions such as radicular pain due to failed back surgery syndrome or epidural lipomatosis.

#### **Observational Cohort Studies**

LTFIS has been used to treat radicular pain in patients with epidural lipomatosis, “mixed radicular pain,” and failed back surgery syndrome, among other etiologies, but evidence on effectiveness is less than convincing because of small sample sizes, short follow-up, or low success rates. Several studies were excluded due to unclear diagnosis or for reporting outcomes of LTFIS for mixed diagnoses. When results were not separated by diagnosis, the studies were omitted from this review [23,59–61]. Others were excluded for not adequately describing technique [62] or for inconsistent follow-up [60]. One study suggested a potential benefit of LTFIS for radicular pain resulting from degenerative lumbar spondylolisthesis, but it was excluded due to the absence of categorical data [63]. Small case series have reported successful relief of

radicular pain from epidural lipomatosis [64,65]. A case series of patients who had persistent radicular pain six months after lumbar discectomy and fusion reported improvement after LTFIS [33]; however, the diagnosis that precipitated the surgery was unclear. One study examined the impact of adding hyaluronidase or saline to LTFIS for patients with the vague diagnosis of “failed back surgery syndrome” [49]. The LTFIS outcomes in this study showed success rates of 46% (95% CI = 19–73%) at four weeks. Another study defined success as a >50% improvement in NRS and reported a success rate of 23% (95% CI = 0–46%), which remained consistent at two, six, and 12 months [27].

**Pragmatic Studies.** No pragmatic studies met inclusion criteria. Several studies were excluded due to unclear diagnoses [66–71]. One study compared response rates to LTFIS among various diagnostic groups (LSS, lumbar disc herniation, postsurgery) and reported that there was no significant difference in response [72]. However, categorical data were not presented separately for each diagnosis; therefore, the study was excluded. Another study evaluating dexamethasone vs betamethasone for mixed diagnoses (LSS and disc herniation) found no difference between the two drugs but was excluded because data were not stratified by diagnosis [68].

**GRADE Assessment of the Evidence: Low Quality.** With low-quality and very limited evidence regarding the effectiveness of LTFIS for radicular pain due to diagnoses other than disc herniation or LSS, the quality of evidence is low in accordance with the GRADE system. Additional studies with appropriate subgroup analysis by specific diagnosis would assist in determining whether LTFIS is an effective treatment for patients with radicular pain due to other diagnoses.

### Dose

Studies have attempted to identify the lowest effective dose of steroid to use in LTFIS. One study, which showed that at one week responses to LTFIS with 10 mg, 20 mg, and 40 mg of triamcinolone were superior to a 5-mg dose, was excluded from analysis due to inadequate duration of follow-up [73]. Another study examined dexamethasone injections of 4 mg, 8 mg, and 12 mg for mixed diagnoses causing “radicular pain” [74]. This study showed no difference among the different doses at 12 weeks; however, accurate conclusions about success rates cannot be drawn due to the diagnostic heterogeneity within the groups of patients. As such, there is currently a lack of high-quality data comparing the relative effectiveness of different steroid doses for LTFIS.

### Predictors of Success

Response rates to LTFIS are variable. Many authors have sought to identify patient characteristics that may

correlate with the success or failure of the procedure. One study suggested that longer duration of pain symptoms before LTFIS for disc herniation may be associated with poorer outcomes, but more evidence is needed to confirm this observation [25]. Another study showed that pain sensitivity questionnaires did not predict outcomes of LTFIS in patients with radicular pain due to LSS, but it was excluded due to the absence of categorical data [75]. Similarly, a study suggests that early response to LTFIS may predict longer duration of effect, but it was also excluded from the review due to lack of categorical data [23]. With regard to radiographic predictors of success, no study followed patients long enough to define the relationship between magnetic resonance imaging (MRI) characteristics of lumbar disc herniations and long-term LTFIS outcomes [32,38,76]. One study reported that the group with the highest proportion of responders at two weeks included those patients whose imaging exhibited grade 3 nerve compression, followed by grade 2, grade 4, and grade 1 [18]. Another study examined whether MRI features (including segmental level, location, and morphological features of disc herniation, cross-sectional area of disc herniation, and grade of nerve root compression) were predictors of success from LTFIS [76]. This study found that the only clinical feature that predicted a successful outcome after LTFIS was low grade of nerve root compression, which predicted a higher rate of success than high-grade nerve root compression. One study correlated positive findings of lumbar radiculopathy on electrodiagnostic studies, with or without active denervation, with a more favorable outcome from LTFIS [77]. The drawbacks of this study include the fact that electrodiagnostic testing may confirm a diagnosis of radiculopathy, but this test is not sensitive to changes in small nerve fibers that mediate nociception in the case of radicular pain without radiculopathy. At this time, available evidence does not support the use of electrodiagnostic testing to select patients for LTFIS. Radicular pain is primarily evaluated by history, physical examination, and diagnostic imaging.

### Surgery-Sparing Effects of LTFIS

Several studies have reported reduced rates of surgery following LTFIS, and several studies have reported successful outcomes from LTFIS when performed on patients who were selected from surgical waiting lists, for whom surgery would have been performed if the procedure was unsuccessful. One well-designed randomized controlled study showed no difference in surgery rates between patients treated with intramuscular steroids and LTFIS, though a higher percentage of patients treated with LTFIS who canceled their surgery reported that they did so because of the beneficial effect of the injection [15]. One study compared transforaminal bupivacaine with LTFIS. At follow-up times of 13 to 24 months, the LTFIS group underwent surgery at a significantly lower rate

[72]. Another study strictly defined success as avoidance of surgery,  $\geq 50\%$  VAS improvement,  $\geq 50\%$  RMDQ improvement, and a patient satisfaction score of at least “satisfaction” [41]. This study reported a success rate of 76% (95% CI = 67–85%) at one year. At six months, one study reported a 56% (95% CI = 46–66%) rate of surgery avoidance [35]. At one year, avoidance of surgery has been reported to vary between 56% and 90% [28,29,36,50]. At two years, 67% (95% CI = 47–87%) [30] and 68% (95% CI = 57–79%) [47] surgery avoidance rates have been reported. The effect of disc morphology on surgery avoidance is unclear, though one study demonstrated a higher rate of surgical avoidance in cases of contained but not extruded disc herniations [16].

### Complications

Reports of unusual transient effects postprocedure include singultus (hiccups) [78], oculomotor nerve palsy [79], and perineal pruritis [80]. Technical problems have also been reported, including dural puncture [81] and unintended injection into a vein [82] or disc [83–86]. None of these cases resulted in permanent effects. The risk of epidural hematoma after LTFIS remains low. There is a report of epidural hematoma secondary to a hemorrhagic facet cyst after LTFIS in a patient who had stopped Plavix and aspirin seven days prior [87]. The implications of this case are unclear.

The most significant complication that has been associated with LTFIS is spinal cord infarction, which has been reported in a total of at least 14 cases [88–94]. All of these cases except one [88] involved the use of particulate steroid. The circumstances of that case of spinal cord injury after LTFIS with preservative-free dexamethasone are vague, and without intraoperative images confirming needle placement, the complication cannot be attributed to the injectate [88]. One theory on the etiology of spinal cord infarction after LTFIS with particulate steroids is that spinal cord infarction may arise when particulate steroids are unintentionally injected into an artery that partially supplies the distal spinal cord, leading to embolic infarction either related to the particulate steroid matter itself or agglutination of red blood cells due to speculation caused by the particulate steroid [95–99]. Animal studies demonstrate that nonparticulate steroid injected directly into the vertebral artery causes no measurable neurologic injury [100]. One caveat is that dexamethasone sodium phosphate combined with ropivacaine may result in crystallization of the solution [101]; therefore, that particular combination of medications should be avoided. Several measures, which are outlined in the 2013 Spine Intervention Society Practice Guidelines, can be adopted to reduce the risk of spinal cord infarction [5]. Injection of contrast medium under real-time fluoroscopy should be performed before injection of steroid in order to detect inadvertent vascular injection and reduce the risk of spinal cord infarction. Other measures that

can be adopted include digital subtraction angiography and a test dose of a rapidly acting local anesthetic [5].

Large studies have continued to support the safety of LTFIS. A study of >14,000 procedures showed no neurologic, hemorrhagic, or infection-related complications, with vasovagal reactions (1.2% of cases) being the most common “side effect” [102]. Other, mostly minor, transient symptoms after LTFIS have included headache, postprocedure pain, facial flushing, rash, leg weakness, erectile dysfunction, dizziness, increased blood sugar, and hypertensive episodes [103–105]. These are temporary phenomena that might be encountered with any injection involving corticosteroids.

### GRADE Assessment of the Evidence of Risks with LTFIS: Very Low Quality

When attempting to apply GRADE to assess the quality of the evidence regarding the risks of LTFIS, it is noted that the published evidence consists of case reports. Accordingly, the body of evidence is of very low quality. With a large study of >14,000 procedures documenting no neurologic, hemorrhagic, or infection-related complications, we have some confidence that the prevalence of complications is very low; however, when they do occur, they can be catastrophic.

### Efficacy of Particulate vs Nonparticulate Steroid

One of the most significant areas of new research addresses the comparative effectiveness of particulate vs nonparticulate steroids used in LTFIS. Interest in this area of study is due to the association between LTFIS and ischemic spinal cord infarction, thought to result from embolization of particulate steroid and/or agglutination of red blood cells in the presence of particulate steroid, with subsequent interruption of arterial supply to the spinal cord.

Given the superior safety profile of nonparticulate steroids, many studies have sought to determine whether LTFIS with nonparticulate steroids is inferior to LTFIS with particulate steroids. Four studies have established that nonparticulate steroids are not inferior to particulate steroids for the treatment of pain attributed to disc herniation [21,68,106,107] (Table 3). One study showed no significant difference in the categorical response rate between LTFIS with triamcinolone (particulate steroid) vs dexamethasone (nonparticulate steroid); at six months, >70% of subjects in both groups achieved  $\geq 50\%$  pain reduction [21]. In that study, a greater number of LTFIS procedures were required in the dexamethasone group compared with the triamcinolone group in order to maintain adequate pain relief during the study period ( $P < 0.05$ ) [21]. A fifth study on radicular pain due to heterogeneous etiologies of LSS and disc herniation also showed noninferiority of nonparticulate steroids, but it was excluded from analysis of success rates due to lack of stratification by diagnosis (Table 3) [108]. There was

only one study that demonstrated superiority of particulate compared with nonparticulate steroid [109]. This study, which used subjective “improvement” as the primary outcome measure, reported a greater-frequency “improvement” in the particulate group at one week and one month following LTFIS. The quality of this study was downgraded due to the imprecision of the diagnostic inclusion parameters.

## Discussion

The focus of the present review was to analyze the published literature on the effectiveness and safety of LTFIS for the treatment of radicular pain in a rigorous and comprehensive manner. To achieve this goal, studies were analyzed only by researchers fully trained and certified in the application of principles of evidence-based medicine. Studies were selected for inclusion using criteria recommended by established guidelines [8,110].

The recommendations for importance of categorical data analyses have been well documented in medical literature. A panel of leading authorities in pain medicine published their recommendations, known as the “Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials” (IMMPACT) guidelines, recommending categorical data analysis (anchor-based methods) over group (mean) data analysis (distribution-based methods) [110]. Although group data may provide a statistical indication that a treatment is effective, they do not provide any information on the proportion of patients in which the treatment is effective, the number of patients for which it is effective, or the degree of effectiveness in a particular patient.

When assessing the level of evidence in accordance with GRADE and stratifying by underlying pathology, trends do emerge. In this review, the authors encountered observational cohort studies, pragmatic RCTs, and explanatory RCTs. The two high-quality explanatory RCTs that examined LTFIS demonstrated that LTFIS is not a placebo and had a significant lasting benefit over sham treatments. Substantial high-quality observational studies further strengthen the conviction that this treatment has an important role in the treatment of radicular pain. The available data establish LTFIS as an effective treatment for radicular pain. Because there is strong evidence from explanatory studies, the quality of evidence is rated as “high” for the effectiveness of LTFIS for the treatment of radicular pain due to intervertebral disc herniation. Without explanatory studies or appropriate justifications to upgrade the level of evidence due to the magnitude of health effect or dose-response gradient, the quality of evidence is rated as “low” for the effectiveness of LTFIS for the treatment of lumbar radicular pain due to spinal stenosis and other diagnoses such as epidural lipomatosis. Some outcome studies suggest that there is a benefit, but there are no corroborating studies or appropriately controlled studies at this time. Although the

quality of evidence is low, this does not indicate that the treatment is ineffective, only that the quality of available evidence in support of LTFIS for these indications is low. The current body of literature does support the conclusion that LTFIS may provide short-term relief of radicular pain related to these diagnoses. An important limitation of the majority of the literature pertaining to spinal stenosis is that the exact nature of “spinal stenosis” was not defined (i.e., central canal, subarticular zone, or neuroforamen). Future studies would be improved by delineating the exact type of stenosis (central, subarticular, or neuroforaminal) and clarifying the distinction between fixed stenosis vs intermittent neurogenic claudication.

The reported surgery-sparing effect of LTFIS is suggested by the evidence, but further study is needed. To confirm that a treatment eliminates the need for surgery, it requires that all patients were destined for surgery and would have had surgery if LTFIS did not work.

LTFIS success rates were higher in patients with a shorter duration of pain, an early positive response to injection, and positive findings of radiculopathy on electromyogram. In terms of radiographic findings, there is little convincing evidence as to whether any MRI disc characteristics predict LTFIS outcomes, though there is some evidence that patients with a low degree of nerve root compression may respond more quickly than patients with a high degree of compression.

The duration of relief after LTFIS is variable. In most of the cases reported in the literature, only one LTFIS treatment was needed for a successful outcome. If the patient’s pain is relieved but returns after a period of time, relief can be achieved again by repeat treatment. However, there are known possible systemic side effects of epidural corticosteroid injections, so injections should be limited to the lowest effective dose and number of injections with an appropriate time interval between injections. Most studies included in our review showed a treatment benefit lasting three to six months, with some studies suggesting a benefit at one or even two years post-injection. The rationale for a one- to two-year benefit from LTFIS is likely related to the favorable natural history of lumbar radicular pain, rather than a one- to two-year effect directly related to the corticosteroid. In addition, many studies were not fully controlled for co-interventions. This includes a possibly significant methodological limitation in studies where several LTFIS procedures were performed in the same patient in between follow-up intervals. Although repeated LTFIS procedures may be justified in some cases for added benefit, performing an additional LTFIS procedure without discrete reporting of when the injection(s) occurred creates a challenge in interpreting the true durability of effect of an individual LTFIS. For patients with disc herniation, LTFIS with nonparticulate steroids are as effective as LTFIS with particulate steroids. Five studies demonstrated that nonparticulate steroids are not inferior to particulate

steroids for treatment of radicular pain attributed to intervertebral disc herniation [21,68,106–108].

In addition, data suggest that LTFIS is a safe procedure. Large studies have continued to support the safety of this procedure, with vasovagal reactions as the most common “complication.” Prior reports of spinal cord infarctions were associated with use of particulate steroid, which is no longer recommended as a firstline medication. Precautions to improve safety have been documented in the literature [5,7,111]. Particulate steroids were most strongly associated with a risk of spinal cord infarction, thought to be the result of arterial embolization by steroid particles. Particles may also form due to crystallization with combinations of ropivacaine and dexamethasone sodium phosphate, so this particular combination should be avoided [101]. Nonparticulate steroids (not mixed with ropivacaine) should be the firstline choice of medication due to their enhanced safety profile, particularly given the fact that multiple studies have shown nonparticulate steroids to be noninferior to particulate steroids.

There are several general limitations to the present review. It is possible that we did not capture all relevant data. Useful data may have been rejected on the basis of not being available in English. Reviewers are also susceptible to confirmation bias, and their assessments can be influenced by their previous experience with and knowledge of a procedure and its effects.

## Conclusions

The published evidence establishes that when appropriate inclusion criteria are applied, LTFIS is an effective treatment for radicular pain due to intervertebral disc herniation. Strong evidence supports this statement. There remains a lack of high-quality evidence demonstrating the effectiveness of LTFIS for the treatment of radicular pain due to spinal stenosis, though the available low-quality data support a possible benefit. There is a paucity of data for miscellaneous conditions such as epidural lipomatosis and failed back surgery syndrome. Published data demonstrate that LTFIS with nonparticulate steroids are not inferior to LTFIS with particulate steroids. Nonparticulate steroids should be the firstline choice of medication due to their enhanced safety profile. More research is needed to identify patient-specific factors that predict the likelihood of a positive response to LTFIS.

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## References

1. Li JY, Xie W, Strong JA, Guo QL, Zhang JM. Mechanical hypersensitivity, sympathetic sprouting, and glial activation are attenuated by local injection of corticosteroid near the lumbar ganglion in a rat model of neuropathic pain. *Reg Anesth Pain Med* 2011;36(1):56–62.
2. Ramesh G, Meisner OC, Philipp MT. Anti-inflammatory effects of dexamethasone and meloxicam on *Borrelia burgdorferi*-induced inflammation in neuronal cultures of dorsal root ganglia and myelinating cells of the peripheral nervous system. *J Neuroinflammation* 2015;12(240).
3. Johansson A, Hao J, Sjolund B. Local corticosteroid application blocks transmission in normal nociceptive C-fibres. *Acta Anaesthesiol Scand* 1990;34(5):335–8.
4. Albrecht DS, Ahmed SU, Kettner NW, Borra RJH, Cohen-Adad J, Deng H. Neuroinflammation of the spinal cord and nerve roots in chronic radicular pain patients. *Pain* 2018;159(5):968–77.
5. SIS Guidelines Book. Lumbar transforaminal access. In: Bogduk N, ed. *Practice Guidelines for Spinal Diagnostic and Treatment Procedures*. 2nd ed. San Francisco: International Spine Intervention Society; 2013:459–538.
6. MacVicar J, King W, Landers MH, Bogduk N. The effectiveness of lumbar transforaminal injection of steroids: A comprehensive review with systematic analysis of the published data. *Pain Med* 2013;14(1):14–28.
7. Rathmell JP, Benzon HT, Dreyfuss P, et al. Safeguards to prevent neurologic complications after epidural steroid injections: Consensus opinions from a multidisciplinary working group and national organizations. *Anesthesiology* 2015;122(5):974–84.
8. Bogduk N, Kennedy DJ, Vorobeychik Y, Engel A. Guidelines for composing and assessing a paper on treatment of pain. *Pain Med* 2017;18:2096–104.
9. Balshem H, Helfand M, Schunemann HJ, et al. GRADE guidelines: 3. Rating the quality of evidence. *J Clin Epidemiol* 2011;64(4):401–6.
10. Lechmann M, Peterson CK, Pfirrmann CWA, Hodler J. Lumbar nerve root injections: A prospective cohort outcomes study comparing age- and gender-matched patients who returned an outcomes-based postal questionnaire with patients who did not return the postal questionnaire. *Skeletal Radiol* 2013;42(10):1429–35.

11. Mallinson PI, Tapping CR, Bartlett R, Maliakal P. Factors that affect the efficacy of fluoroscopically guided selective spinal nerve root block in the treatment of radicular pain: A prospective cohort study. *Can Assoc Radiol J* 2013;64(4):370–5.
12. Shahgholi L, Yost KJ, Carter RE, et al. Correlation of the Patient Reported Outcomes Measurement Information System with legacy outcomes measures in assessment of response to lumbar transforaminal epidural steroid injections. *AJNR Am J Neuroradiol* 2015;36(3):594–9.
13. Lee JH, An JH, Lee SH. Comparison of the effectiveness of interlaminar and bilateral transforaminal epidural steroid injections in treatment of patients with lumbosacral disc herniation and spinal stenosis. *Clin J Pain* 2009;25(3):206–10.
14. Vad VB, Bhat AL, Lutz GE, Cammisa F. Transforaminal epidural steroid injections in lumbosacral radiculopathy: A prospective randomized study. *Spine (Phila Pa 1976)* 2002;27(1):11–6.
15. Ghahreman A, Ferch R, Bogduk N. The efficacy of transforaminal injection of steroids for the treatment of lumbar radicular pain. *Pain Med* 2010;11(8):1149–68.
16. Karppinen J, Ohinmaa A, Malmivaara A, et al. Cost effectiveness of periradicular infiltration for sciatica: Subgroup analysis of a randomized controlled trial. *Spine (Phila Pa 1976)* 2001;26(23):2587–95.
17. Jeong HS, Lee JW, Kim SH, Myung JS, Kim JH, Kang HS. Effectiveness of transforaminal epidural steroid injection by using a preganglionic approach: A prospective randomized controlled study. *Radiology* 2007;245(2):584–90.
18. Rados I, Sakic K, Fingler M, Kapural L. Efficacy of interlaminar vs transforaminal epidural steroid injection for the treatment of chronic unilateral radicular pain: Prospective, randomized study. *Pain Med* 2011;12(9):1316–21.
19. Ghai B, Bansal D, Kay JP, Vadaje KS, Wig J. Transforaminal versus parasagittal interlaminar epidural steroid injection in low back pain with radicular pain: A randomized, double-blind, active-control trial. *Pain Physician* 2014;17(4):277–90.
20. Gupta R, Singh S, Kaur S, Singh K, Aujla K. Correlation between epidurographic contrast flow patterns and clinical effectiveness in chronic lumbar discogenic radicular pain treated with epidural steroid injections via different approaches. *Korean J Pain* 2014;27(4):353–9.
21. Kennedy DJ, Plastaras C, Casey E, et al. Comparative effectiveness of lumbar transforaminal epidural steroid injections with particulate versus nonparticulate corticosteroids for lumbar radicular pain due to intervertebral disc herniation: A prospective, randomized, double-blind trial. *Pain Med* 2014;15(4):548–55.
22. Manchikanti L, Cash KA, Pampati V, Falco FJE. Transforaminal epidural injections in chronic lumbar disc herniation: A randomized, double-blind, active-control trial. *Pain Physician* 2014;17(4):E489–E501.
23. Cyteval C, Fescquet N, Thomas E, Decoux E, Blotman F, Taourel P. Predictive factors of efficacy of periradicular corticosteroid injections for lumbar radiculopathy. *Am J Neuroradiol* 2006;27(5):978–82.
24. Weiner BK, Fraser RD. Foraminal injection for lateral lumbar disc herniation. *J Bone Joint Surg Br* 1997;79(5):804–7.
25. Lutz GE, Vad VB, Wisneski RJ. Fluoroscopic transforaminal lumbar epidural steroids: An outcome study. *Arch Phys Med Rehabil* 1998;79(11):1362–6.
26. Viton JM, Peretti-Viton P, Rubino T, Delarque A, Salamon N. Short-term assessment of periradicular corticosteroid injections in lumbar radiculopathy associated with disc pathology. *Neuroradiology* 1998;40(1):59–62.
27. Rosenberg SK, Grabinsky A, Kooser C, Boswell MV. Effectiveness of transforaminal epidural steroid injections in low back pain: A one year experience. *Pain Physician* 2002;5(3):266–70.
28. Wang JC, Lin E, Brodke DS, Youssef JA. Epidural injections for the treatment of symptomatic lumbar herniated discs. *J Spinal Disord Tech* 2002;15(4):269–72.
29. Schaufele MK, Hatch L, Jones W. Interlaminar versus transforaminal epidural injections for the treatment of symptomatic lumbar intervertebral disc herniations. *Pain Physician* 2006;9(4):361–6.
30. Yang SC, Fu TS, Lai PL, Niu CC, Chen LH, Chen WJ. Transforaminal epidural steroid injection for discectomy candidates: An outcome study with a minimum of two-year follow-up. *Chang Gung Med J* 2006;29(1):93–9.
31. Ackerman WE 3rd, Ahmad M. The efficacy of lumbar epidural steroid injections in patients with lumbar disc herniations. *Anesth Analg* 2007;104(5):1217–22.
32. Choi SJ, Song JS, Kim C, et al. The use of magnetic resonance imaging to predict the clinical outcome of non-surgical treatment for lumbar intervertebral disc herniation. *Korean J Radiol* 2007;8(2):156–63.
33. Lee JH, Moon J, Lee SH. Comparison of effectiveness according to different approaches of epidural steroid injection in lumbosacral herniated disk and spinal stenosis. *J Back Musculoskelet Rehabil* 2009;22(2):83–9.
34. Thomas E, Cyteval C, Abiad L, Picot MC, Taourel P, Blotman F. Efficacy of transforaminal versus interspinous corticosteroid injection in discal radiculalgia—a prospective, randomised, double-blind study. *Clin Rheumatol* 2003;22(4–5):299–304.

35. Manson NA, McKeon MD, Abraham EP. Transforaminal epidural steroid injections prevent the need for surgery in patients with sciatica secondary to lumbar disc herniation: A retrospective case series. *Can J Surg* 2013;56(2):89–96.
36. van Helvoirt H, Apeldoorn AT, Ostelo RW, et al. Transforaminal epidural steroid injections followed by mechanical diagnosis and therapy to prevent surgery for lumbar disc herniation. *Pain Med* 2014;15(7):1100–8.
37. Joswig H, Neff A, Ruppert C, Hildebrandt G, Stienen MN. The value of short-term pain relief in predicting the 1-month outcome of lumbar transforaminal epidural steroid injections. *World Neurosurg* 2017;159(2):291–300.
38. Maus TP, El-Yahouchi CA, Geske JR, et al. Imaging determinants of clinical effectiveness of lumbar transforaminal epidural steroid injections. *Pain Med* 2016;17(12):2176–84.
39. Singh JR, Cardozo E, Christolias GC. The clinical efficacy for two-level transforaminal epidural steroid injections. *PM R* 2017;9(4):377–82.
40. Tecer D, Adiguzel E, Tan AK, Taskaynatan MA. Role of magnetic resonance imaging in ascertaining the success of transforaminal epidural steroid injection for lumbar radicular pain. *Pain Med* 2017;18(4):645–50.
41. van Helvoirt H, Apeldoorn AT, Knol DL, et al. Transforaminal epidural steroid injections influence mechanical diagnosis and therapy (MDT) pain response classification in candidates for lumbar herniated disc surgery. *J Back Musculoskelet Rehabil* 2016;29(2):351–9.
42. Sariyildiz MA, Batmaz I, Yazmalar L, Gunes M, Turan Y. The effectiveness of transforaminal epidural steroid injections on radicular pain, functionality, psychological status and sleep quality in patients with lumbar disc herniation. *J Back Musculoskelet Rehabil* 2017;30(2):265–70.
43. Botwin KP, Gruber RD, Bouchlas CG, et al. Fluoroscopically guided lumbar transformational epidural steroid injections in degenerative lumbar stenosis: An outcome study. *Am J Phys Med Rehabil* 2002;81(12):898–905.
44. Smith CC, Booker T, Schaufele MK, Weiss P. Interlaminar versus transforaminal epidural steroid injections for the treatment of symptomatic lumbar spinal stenosis. *Pain Med* 2010;11(10):1511–5.
45. Ploumis A, Christodoulou P, Wood KB, Varvarousis D, Sarni JL, Beris A. Caudal vs transforaminal epidural steroid injections as short-term (6 months) pain relief in lumbar spinal stenosis patients with sciatica. *Pain Med* 2014;15(3):379–85.
46. Park Y, Lee WY, Ahn JK, Nam HS, Lee KH. Percutaneous adhesiolysis versus transforaminal epidural steroid injection for the treatment of chronic radicular pain caused by lumbar foraminal spinal stenosis: A retrospective comparative study. *Ann Rehabil Med* 2015;39(6):941–9.
47. Davis N, Hourigan P, Clarke A. Transforaminal epidural steroid injection in lumbar spinal stenosis: An observational study with two-year follow-up. *Br J Neurosurg* 2017;31(2):205–8.
48. Farooque M, Salzman MM, Ye Z. Effectiveness of bilateral transforaminal epidural steroid injections in degenerative lumbar spinal stenosis patients with neurogenic claudication: A case series. *PM R* 2017;9(1):26–31.
49. Rahimzadeh P, Sharma V, Imani F, et al. Adjuvant hyaluronidase to epidural steroid improves the quality of analgesia in failed back surgery syndrome: A prospective randomized clinical trial. *Pain Physician* 2014;17(1):E75–82.
50. Mendoza-Lattes S, Weiss A, Found E, Zimmerman B, Gao Y. Comparable effectiveness of caudal vs. transforaminal epidural steroid injections. *Iowa Orthop J* 2009;29:91–6.
51. Karamouzian S, Ebrahimi-Nejad A, Shahsavarani S, Keikhosravi E, Shahba M, Ebrahimi F. Comparison of two methods of epidural steroid injection in the treatment of recurrent lumbar disc herniation. *Asian Spine J* 2014;8(5):646–52.
52. Kawu AA. Epidural steroid injection in patients with lumbosacral radiculopathy in Abuja, Nigeria. *J Neurosci Rural Pract* 2012;3(2):121–5.
53. Kim C, Choi HE, Kang S. Contrast spreading patterns in retrodiscal transforaminal epidural steroid injection. *Ann Rehabil Med* 2012;36(4):474–9.
54. Pandey RA. Efficacy of epidural steroid injection in management of lumbar prolapsed intervertebral disc: A comparison of caudal, transforaminal and interlaminar routes. *J Clin Diagn Res* 2016;10(7):Rc05–11.
55. Karppinen J, Malmivaara A, Kurunlahti M, et al. Periradicular infiltration for sciatica: A randomized controlled trial. *Spine (Phila PA 1976)* 2001;26(9):1059–67.
56. Akuthota V, Hammerich AS, Mintken PE, et al. Effectiveness of physical therapy as an adjunct to epidural steroid injections in the treatment of lumbar spinal stenosis: A pilot randomized controlled trial. *Spine J* 2012;12(9):146S.
57. Park JW, Nam HS, Cho SK, Jung HJ, Lee BJ, Park Y. Kambin's triangle approach of lumbar transforaminal epidural injection with spinal stenosis. *Ann Rehabil Med* 2011;35(6):833–43.
58. Friedly JL, Comstock BA, Turner JA, et al. A randomized trial of epidural glucocorticoid injections for spinal stenosis. *N Engl J Med* 2014;371(1):11–21.
59. Beyaz SG. Comparison of transforaminal and interlaminar epidural steroid injections for the treatment of chronic lumbar pain [in Portuguese]. *Rev Bras Anestesiol* 2017;67(1):21–7.

60. Narozny M, Zanetti M, Boos N. Therapeutic efficacy of selective nerve root blocks in the treatment of lumbar radicular leg pain. *Swiss Med Wkly* 2001; 131(5–6):75–80.
61. Riew KD, Park JB, Cho YS, et al. Nerve root blocks in the treatment of lumbar radicular pain. A minimum five-year follow-up. *J Bone Joint Surg Am* 2006;88(8):1722–5.
62. Sivaganesan A, Chotai S, Parker SL, Asher AL, McGirt MJ, Devin CJ. Predictors of the efficacy of epidural steroid injections for structural lumbar degenerative pathology. *Spine J* 2016;16(8):928–34.
63. Kraiwattanapong C, Wechmongkolgorn S, Chatriyanuyok B, et al. Outcomes of fluoroscopically guided lumbar transforaminal epidural steroid injections in degenerative lumbar spondylolisthesis patients. *Asian Spine J* 2014;8(2):119–28.
64. Botwin KP, Sakalkale DP. Epidural steroid injections in the treatment of symptomatic lumbar spinal stenosis associated with epidural lipomatosis. *Am J Phys Med Rehabil* 2004;83(12):926–30.
65. McCormick Z, Plastaras C. Transforaminal epidural steroid injection in the treatment of lumbosacral radicular pain caused by epidural lipomatosis: A case series and review. *J Back Musculoskelet Rehabil* 2014;27(2):181–90.
66. Byun JM, Park HS, Woo JH, Kim J. The effects of a forceful transforaminal epidural steroid injection on radicular pain: A preliminary study. *Korean J Pain* 2014;27(4):334–8.
67. Chun EH, Park HS. Effect of high-volume injectate in lumbar transforaminal epidural steroid injections: A randomized, active control trial. *Pain Physician* 2015;18(6):519–25.
68. Denis I, Claveau G, Filiatrault M, Fugere F, Fortin L. Randomized double-blind controlled trial comparing the effectiveness of lumbar transforaminal epidural injections of particulate and nonparticulate corticosteroids for lumbosacral radicular pain. *Pain Med* 2015;16(9):1697–708.
69. Manchikanti L, Pakanati RR, Pampati V. Comparison of three routes of epidural steroid injections in low back pain. *Pain Digest* 1999;9:277–85.
70. Ng L, Chaudhary N, Sell P. The efficacy of corticosteroids in periradicular infiltration for chronic radicular pain: A randomized, double-blind, controlled trial. *Spine (Phila Pa 1976)* 2005;30(8):857–62.
71. Tafazal S, Ng L, Chaudhary N, Sell P. Corticosteroids in peri-radicular infiltration for radicular pain: A randomised double blind controlled trial. One year results and subgroup analysis. *Eur Spine J* 2009;18(8):1220–5.
72. Riew KD, Yin Y, Gilula L, et al. The effect of nerve-root injections on the need for operative treatment of lumbar radicular pain. A prospective, randomized, controlled, double-blind study. *J Bone Joint Surg Am* 2000;82-A(11):1589–93.
73. Kang SS, Hwang BM, Son HJ, et al. The dosages of corticosteroid in transforaminal epidural steroid injections for lumbar radicular pain due to a herniated disc. *Pain Physician* 2011;14(4):361–70.
74. Ahadian FM, McGreevy K, Schulteis G. Lumbar transforaminal epidural dexamethasone: A prospective, randomized, double-blind, dose-response trial. *Reg Anesth Pain Med* 2011;36(6):572–8.
75. Kim HJ, Yeom JS, Lee JW, et al. The influence of pain sensitivity on the treatment outcome of transforaminal epidural steroid injection in patients with lumbar spinal stenosis. *Pain Pract* 2014;14(5):405–12.
76. Ghahreman A, Bogduk N. Predictors of a favorable response to transforaminal injection of steroids in patients with lumbar radicular pain due to disc herniation. *Pain Med* 2011;12(6):871–9.
77. McCormick Z, Cushman D, Caldwell M, et al. Does electrodiagnostic confirmation of radiculopathy predict pain reduction after transforaminal epidural steroid injection? A multicenter study. *J Nat Sci* 2015;1(8).
78. Odonkor CA, Smith B, Rivera K, Chhatre A. Persistent singultus associated with lumbar epidural steroid injections in a septuagenarian: A case report and review. *Am J Phys Med Rehabil* 2017;96(1):e1–e4.
79. Gozal YM, Atchley K, Curt BA. Isolated oculomotor nerve palsy after lumbar epidural steroid injection in a diabetic patient. *Surg Neurol Int* 2016; 7(Suppl 42):S1099–s101.
80. El Abd O, Pimentel DC, Amadera JE. Generalized pruritus as an unusual side effect after epidural injection with dexamethasone. *PM R* 2015;7(2):206–9.
81. Goodman BS, Posecion LW, Mallempati S, Bayazitoglu M. Complications and pitfalls of lumbar interlaminar and transforaminal epidural injections. *Curr Rev Musculoskeletal Med* 2008;1(3–4):212–22.
82. Furman MB, O'Brien EM, Zgleszewski TM. Incidence of intravascular penetration in transforaminal lumbosacral epidural steroid injections. *Spine (Phila Pa 1976)* 2000;25(20):2628–32.
83. Cohen SP, Maine DN, Shockey SM, Kudchadkar S, Griffith S. Inadvertent disk injection during transforaminal epidural steroid injection: Steps for prevention and management. *Pain Med* 2008;9(6):688–94.
84. Finn KP, Case JL. Disk entry: A complication of transforaminal epidural injection—a case report. *Arch Phys Med Rehabil* 2005;86(7):1489–91.
85. Haspelslagh S, Van Zundert J, Puylaert M, Heylen R, van Kleef M, Vissers K. Unilateral diagnostic infiltration of lumbar L3 nerve root resulting in an inadvertent discogram: The importance of

- fluoroscopic guidance in interventional pain therapy. *Anesthesiology* 2004;100(4):1019–21.
86. Trinh KH, Gharibo CG, Aydin SM. Inadvertent intradiscal injection with TFESI utilizing Kambin's retrodiscal approach in the treatment of acute lumbar radiculopathy. *Pain Pract* 2016;16(4):E70–3.
  87. Elgafy H, Peters N, Lea JE, Wetzel RM. Hemorrhagic lumbar synovial facet cyst secondary to transforaminal epidural injection: A case report and review of the literature. *World J Orthop* 2016;7(7):452–7.
  88. Gharibo CG, Fakhry M, Diwan S, Kaye AD. Conus medullaris infarction after a right L4 transforaminal epidural steroid injection using dexamethasone. *Pain Physician* 2016;19(8):E1211–e4.
  89. Glaser SE, Falco F. Paraplegia following a thoracolumbar transforaminal epidural steroid injection. *Pain Physician* 2005;8(3):309–14.
  90. Houten JK, Errico TJ. Paraplegia after lumbosacral nerve root block: Report of three cases. *Spine J* 2002;2(1):70–5.
  91. Huntoon MA, Martin DP. Paralysis after transforaminal epidural injection and previous spinal surgery. *Reg Anesth Pain Med* 2004;29(5):494–5.
  92. Kennedy DJ, Dreyfuss P, Aprill CN, Bogduk N. Paraplegia following image-guided transforaminal lumbar spine epidural steroid injection: Two case reports. *Pain Med* 2009;10(8):1389–94.
  93. Somayaji HS, Saifuddin A, Casey AT, Briggs TW. Spinal cord infarction following therapeutic computed tomography-guided left L2 nerve root injection. *Spine (Phila Pa 1976)* 2005;30(4):E106–8.
  94. Tackla RD, Keller JT, Ernst RJ, Farley CW, Bohinski RJ. Conus medullaris syndrome after epidural steroid injection: Case report. *Int J Spine Surg* 2012;6(1):29–33.
  95. Bogduk N. Complications associated with transforaminal injections. In: Neal JM, Rathmell JP, eds. *Complications in Regional Anesthesia and Pain Medicine*. Philadelphia: Saunders Elsevier; 2007:259–65.
  96. Bogduk N. Epidural steroid injection. In: Fishman SM, Ballantyne JC, Rathmell JP, eds. *Bonica's Management of Pain*. 4th ed. Philadelphia, PA: Wolters Kluwer; 2010:1423–37.
  97. Bogduk N, Dreyfuss P, Baker R, Yin W, Landers M, Hammer M. Complications of spinal diagnostic and treatment procedures. *Pain Med* 2008;9(Suppl 1):S11–S34.
  98. Derby R, Lee SH, Date ES, Lee JH, Lee CH. Size and aggregation of corticosteroids used for epidural injections. *Pain Med* 2008;9(2):227–34.
  99. Laemmel E, Segal N, Mirshahi M, et al. Deleterious effects of intra-arterial administration of particulate steroids on microvascular perfusion in a mouse model. *Radiology* 2016;279(3):731–40.
  100. Okubadejo GO, Talcott MR, Schmidt RE, et al. Perils of intravascular methylprednisolone injection into the vertebral artery. An animal study. *J Bone Joint Surg Am* 2008;90(9):1932–8.
  101. Watkins TW, Dupre S, Coucher JR. Ropivacaine and dexamethasone: A potentially dangerous combination for therapeutic pain injections. *J Med Imaging Radiat Oncol* 2015;59(5):571–7.
  102. El-Yahouchi CA, Plastaras CT, Maus TP, et al. Adverse event rates associated with transforaminal and interlaminar epidural steroid injections: A multi-institutional study. *Pain Med* 2016;17(2):239–49.
  103. Botwin KP, Baskin M, Rao S. Adverse effects of fluoroscopically guided interlaminar thoracic epidural steroid injections. *Am J Phys Med Rehabil* 2006;85(1):14–23.
  104. Gunduz OH, Akhlaque U, Sencan S, Celenlioglu AE, Seker A. Contralateral lumbar radicular pain shortly after a transforaminal epidural steroid injection: An unusual sequel. *Am J Phys Med Rehabil* 2014;93(9):834–5.
  105. Karaman H, Kavak GO, Tufek A, Yldrm ZB. The complications of transforaminal lumbar epidural steroid injections. *Spine (Phila Pa 1976)* 2011;36(13):E819–24.
  106. El-Yahouchi C, Geske JR, Carter RE, et al. The noninferiority of the nonparticulate steroid dexamethasone vs the particulate steroids betamethasone and triamcinolone in lumbar transforaminal epidural steroid injections. *Pain Med* 2013;14(11):1650–7.
  107. Park CH, Lee SH, Kim BI. Comparison of the effectiveness of lumbar transforaminal epidural injection with particulate and nonparticulate corticosteroids in lumbar radiating pain. *Pain Med* 2010;11(11):1654–8.
  108. Kim JY, Lee JW, Lee GY, Lee E, Yoon CJ, Kang HS. Comparative effectiveness of lumbar epidural steroid injections using particulate vs. non-particulate steroid: An intra-individual comparative study. *Skeletal Radiol* 2016;45(2):169–76.
  109. Bensler S, Sutter R, Pfirrmann CWA, Peterson CK. Particulate versus non-particulate corticosteroids for transforaminal nerve root blocks: Comparison of outcomes in 494 patients with lumbar radiculopathy. *Eur Radiol* 2018;28(3):946–52.
  110. Dworkin RH, Turk DC, Wyrwich KW, et al. Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. *J Pain* 2008;9(2):105–21.
  111. Kennedy DJ, Levin J, Rosenquist R, et al. Epidural steroid injections are safe and effective: Multisociety letter in support of the safety and effectiveness of epidural steroid injections. *Pain Med* 2015;16(5):833–8.

## Review Article

# The Effectiveness and Risks of Fluoroscopically Guided Lumbar Interlaminar Epidural Steroid Injections: A Systematic Review with Comprehensive Analysis of the Published Data

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Conflicts of interest: None.

## Abstract

**Objective.** To determine the effectiveness and risks of fluoroscopically guided lumbar interlaminar epidural steroid injections.

**Design.** Systematic review of the literature with comprehensive analysis of the published data.

**Interventions.** Three reviewers with formal training in evidence-based medicine searched the literature on fluoroscopically guided lumbar interlaminar epidural steroid injections. A larger team consisting of five reviewers independently assessed the

methodology of studies found and appraised the quality of the evidence presented.

**Outcome Measures.** The primary outcome assessed was pain relief. Other outcomes such as functional improvement, reduction in surgery rate, decreased use of opioids/medications, and complications were noted, if reported. The evidence on each outcome was appraised in accordance with the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) system of evaluating evidence.

**Results.** The search yielded 71 primary publications addressing fluoroscopically guided lumbar interlaminar epidural steroid injections. There were no explanatory studies and all pragmatic studies identified were of low quality, yielding evidence comparable to observational studies.

**Conclusions.** The body of evidence regarding effectiveness of fluoroscopically guided interlaminar epidural steroid injection is of low quality according to GRADE. Studies suggest a lack of effectiveness of fluoroscopically guided lumbar interlaminar epidural steroid injections in treating primarily axial pain regardless of etiology. Most studies on radicular pain due to lumbar disc herniation and stenosis do, however, report statistically significant short-term improvement in pain.

**Key Words.** Image-Guided; Lumbar; Interlaminar; Steroid; Injection

## Introduction

The use of epidural injections for the treatment of spine pathology was described by Evans in 1930 [1]. Traditionally, this procedure was performed using an anatomic landmark-guided, or “blind” technique without fluoroscopic guidance, as described by Barry and

Kendal [2]. However, the lack of image guidance introduces the potential for inaccurate needle placement. Inaccuracy may result in the injectate failing to reach the right level or side, or possibly even worse, the injectate going to undesired locations such as a blood vessel or the subarachnoid space. White et al. found that inaccurate needle placement occurred in 25% to 30% of injections even in the hands of experienced physicians [3,4]. Given that the goal of a spine injection is to deliver an aliquot of medicine to a specific target, the efficacy and safety of this procedure may be contingent upon the accurate delivery of the proposed injectate. The potential complications of intrathecal steroid injections, such as adhesive arachnoiditis, have been well described [5,6]. In addition, despite negative needle aspiration, a significant number of injections following blind needle placement have been proven to be intravascular [4,7].

Once the high rate of inaccurate needle placement associated with blind techniques was elucidated, investigators began exploring use of fluoroscopically guided injections and epidurography to document accurate needle placement before injection of therapeutic substances [8–13]. The first fluoroscopically guided epidural injection was reported in the early 1980s [4]. Today, interlaminar epidural steroid injections are one of the most commonly performed interventions in managing spine pain in the United States [14–23]. The purpose of this review was to identify all publications on fluoroscopically guided lumbar interlaminar epidural steroid injections (L-ILES) and to assess the data with regard to effectiveness based on the underlying pathology, as well as the risks of the procedure so that appropriate use criteria can be developed.

Most reviews to date have indiscriminately combined fluoroscopically guided and non-image-guided L-ILES. Therefore, the purpose of this review was to focus solely on the outcomes and complications reported from fluoroscopically guided L-ILES. Additionally this review attempted to further stratify outcomes based on underlying pathology. The information from this review can be compared to the effectiveness and efficacy data outlined in reviews of other procedures to guide appropriate evidence-based medical decision-making [24].

## Methods

Three investigators, who all have formal training in evidence-based medicine and are members of the Standards Division of the Spine Intervention Society, searched the scientific literature independently for publications on the effectiveness and for any unwanted effects of fluoroscopically guided L-ILES. The literature search was conducted in PubMed using the keywords lumbar, epidural, steroid, injection, radicular pain, radiculopathy, radiculitis, stenosis, and back pain. The searches encompassed all scientific papers published until March 2016. Studies were excluded for the

following reasons: non-English language papers, non-human studies, conference abstracts, case reports (unless they were reports of complications), less than 2 weeks follow-up, and technical considerations as outlined in Table 1. When suitable papers were retrieved, the references of each were perused for relevant citations that had not been identified by the database searches.

Similar to previous systematic reviews done by the Standards Division, studies were sorted based upon their contents, methodology, and study type [24–27]. The papers retrieved by the searches were sorted by each of the investigators into two groups: primary publications (reports of studies that produced original data) and secondary publications (those not producing original data, such as literature reviews, editorials, and letters). The primary publications on the effectiveness of fluoroscopically guided L-ILES were then classified by each of the investigators into three categories termed: observational studies, pragmatic studies, and explanatory studies. Observational studies were defined as those that simply described the outcomes observed after the use of an intervention; note was taken of whether the observational study design was prospective or retrospective, and whether patients were consecutively enrolled. Pragmatic studies were defined as those in which the outcomes of one intervention were compared with those of another intervention expected to have a therapeutic effect. Explanatory studies were defined as those in which the outcomes of an intervention were compared with those of an intervention not expected to have a therapeutic effect. Of special note—many researchers have designed their randomized controlled trials (RCTs) using local anesthetic as a placebo control. However, because there are some data to suggest that local anesthetic may have some therapeutic effect, those studies that compared fluoroscopically guided L-ILES to local anesthetic were considered pragmatic studies in this review [28,29].

The primary papers on effectiveness of fluoroscopically guided L-ILES were then appraised by each of the investigators independently, using an instrument developed by the Society's Standards Division to facilitate reliable assessment of studies of therapeutic effectiveness. The instrument assesses study design and objective; the study population; the intervention under study and any other intervention used for comparison; the outcomes considered and the instruments used to evaluate them; the results reported and the times they were observed after the intervention; any apparent methodological limitations, including non-blinded observers; losses to follow-up; non-consecutive patients; etc. It also records the reviewer's assessment of the paper and the data it reported, with specific attention to any apparent biases or inconsistencies, the precision of estimates of effect (including confidence intervals of data), and any confounding factors. Each reviewer then made a general comment led by the question: "Irrespective of what the authors may or may not have written, does the

**Table 1** Excluded studies

Rationale	References
Technique description; no outcomes assessed	Mehta and Salmon (1985), Fredman et al. (1999), Johnson et al. (1999), Liu et al. (2001), Bartynski et al. (2005), Hameed et al. (2012), Huang and Palmer (2012)
Multiple independent interventions	Gelalis et al. (2009), Dougherty et al. (2004)
Used computed tomography (CT) guidance only	Wagner (2004)
Lack of subgroup analysis (i.e., multiple techniques/approaches, some use of imaging)	Arnhoff et al. (1977), White et al. (1980), Schmid et al. (1999), Simotas et al. (2000), Buttermann (2004 - LDH), Buttermann (2004 - DDD), Kapural et al. (2007), Friedly et al. (2008), Briggs et al. (2010), Tomkins-Lane et al. (2012), Krych et al. (2012), Mandel et al. (2013), Radcliff et al. (2013)
Less than 2 weeks follow-up	Bartynski et al. (2013)
Case Reports (not related to complications)	Aydin et al. (2005), White and Cohen (2007), Shanthanna and Park (2011)
Preliminary results with subsequent publication of complete results	Manchikanti et al. (2010 – Discogenic Pain), Manchikanti et al. (2010 – LDH/radiculitis) Manchikanti et al. (2012 – Stenosis)

study provide valid data on the effectiveness of fluoroscopically guided L-ILESI, and if so, how compelling are those data?"

When the investigators had each completed their independent appraisals of the effectiveness papers, they shared the results of their assessments and discussed any differences of opinion on particular papers until they reached consensus on the value of each paper's contribution to the published evidence of the effectiveness of fluoroscopically guided L-ILESI. The assessments were then appraised by other members of the Society's Standards Division (all also trained in evidence-based medicine).

The resultant body of evidence was analyzed to determine whether it provided evidence of effectiveness using the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) system of evaluating evidence to determine the quality of the evidence. In essence, the GRADE system asks reviewers to transparently evaluate the body of evidence with consideration not only to study design, but attributes that would strengthen or weaken confidence in the estimate of effect. GRADE provides for an initial rating of quality based upon the best available evidence that comprises the evidence base, then further requires consideration of weaknesses (e.g., risk of bias, indirectness) that merit downgrading and strengths (e.g., magnitude of effect, dose response gradient) that would justify upgrading the rating of the quality of the body of evidence.

Since lumbar radicular pain and low back pain are merely symptoms of a variety of conditions that clearly have different natural histories and possibly different responses to interventional therapy, when possible the data were grouped by the underlying spinal pathology

with the focus being intervertebral disc displacement and lumbar spinal stenosis.

Using the same search strategies, the investigators also reviewed studies and reports on the risks of fluoroscopically guided L-ILESI. The information provided in the reports of complications was collated and the resultant body of evidence was evaluated using the GRADE system of appraisal to determine the quality of the evidence for the risks of fluoroscopically guided L-ILESI. The published data on the effectiveness and risks of this procedure were both taken into account, and overall conclusions were drawn in accordance with the GRADE system.

**Results**

A literature search yielded 71 articles on fluoroscopically guided L-ILESI for treatment of lower extremity and/or low back pain due to a variety of etiologies. These articles were assigned into the categories noted in Figure 1. Of the 71 articles, 41 met the established inclusion criteria. There were 27 papers addressing the effectiveness of fluoroscopically guided L-ILESI and 14 publications that discussed aspects of the safety of the procedure and its associated risks.

*Effectiveness*

**Radicular Pain Due to Lumbar Disc Herniation**

*Observational Studies.*

Three small observational studies provide conflicting evidence regarding the effectiveness of fluoroscopically guided L-ILESI in the treatment of radicular pain due to lumbar disc herniation. One study by Ghai et al. was conducted as an RCT, but both treatments studied

were fluoroscopically guided L-ILESI, and differed only with respect to placing the needle midline or parasagittal. Therefore, for present purposes, each arm was considered as an observational study [30].

The study by Furman et al. [31] reported that 23% [1–45%] of 21 patients obtained complete relief of pain at 3 months, and a further 38% [11–64%] obtained at least 50% relief. Ghai et al. reported that 43% [8–67%] of patients achieved at least 50% relief at 6 months [30]. Schaufele et al. did not report success rates, but the mean improvement in leg pain was only 1.4/10 on a visual analog scale (VAS) [32], which is less than half of the minimal clinically important change for lumbar radicular pain in pain for patients with sciatica [33].

#### *Pragmatic Studies.*

Twelve pragmatic studies investigating efficacy of fluoroscopically guided L-ILESI in patients with radicular pain were published between 2007 and 2016. Seven studies compared the effectiveness of the interlaminar approach with either the transforaminal route [34–38] or with both transforaminal and caudal routes [39,40]. Rados et al. [37,38] and Ghai et al. [34] reported improvement in all the outcomes in both groups without a statistically significant difference between them. However, the other studies all demonstrated better effectiveness of the transforaminal route [35,36,39,40].

One RCT compared the effectiveness of L-ILESI with two different steroid preparations (dexamethasone and methylprednisone) and failed to demonstrate a significant difference in outcomes between the two [41]. Another study found similar outcomes of aggregated (both interlaminar and transforaminal) lumbar epidural steroid injections done based on clinical picture compared with one performed based on clinical picture and magnetic resonance imaging (MRI) results [42]. Since all of the above-mentioned pragmatic RCTs failed to demonstrate superiority of L-ILESI over other treatments, the body of evidence provided by these studies in addressing the effectiveness of L-ILESI in treating radicular pain is of low quality, and therefore, comparable to observational studies.

One double-blind pragmatic RCT compared the effectiveness of L-ILESI of local anesthetic with and without steroid in patients with lumbar radicular pain caused by disc herniation and found “potential superiority of steroids” in improving the outcomes at 1-year follow-up [43]. The inclusion/exclusion criteria in this study were well defined. One hundred and twenty patients were randomly assigned to two groups. The subjects were randomized to L-ILESI with 6 ml of 0.5% lidocaine or an L-ILESI of 5 ml of 0.5% lidocaine and 1 ml of betamethasone. The interventional technique was adequately described and the outcome measures included numeric rating scale (NRS), Oswestry Disability Index (ODI), employment status, and reduction in opioid intake. The primary outcome was “significant” improvement defined as

50% or more reduction in pain scores and ODI at 3-month, 6-month, and 12-month follow-ups. Most patients had several (up to five) procedures during the study. Loss to follow-up was 10%. Successful outcomes for those receiving lidocaine only were reported in: 72% [95% (CI): 61–83%] at 3 months, 63% [95% (CI): 51–75%] at 6 months, and 67% (95% CI: 55–79%) at 12 months. For those receiving lidocaine and betamethasone, successful outcomes were reported in: 82% (95% CI: 72–92%) at 3 months, 85% (95% CI: 76–94%) at 6 months, and 85% (95% CI: 76–94%) at 12 months. With overlapping confidence intervals at 3 months and 12 months, the success rates are not statistically significantly different. The NRS scores decreased more in those receiving a corticosteroid compared to the local anesthetic only group ( $P=0.02$ ), and so did the ODI scores ( $P=0.026$ ). Overall, this was a well-designed study with proper randomization and allocation concealment. Intent-to-treat analysis was applied and co-interventions were controlled for. The outcome measures reached minimal clinically important change as demonstrated by categorical data. One potential flaw of this study is that numerous L-ILESI were performed on the same patients and, therefore, the effectiveness of a single procedure remains unknown. The counterargument to that is that many patients, outside of the strictly controlled research settings, often receive more than one L-ILESI a year. Thus, this study may be considered as better representing “the real world”. Another drawback is the choice of a steroid used for epidural injection. Betamethasone is rarely used by pain practitioners because of its high cost and inferior effectiveness as compared with the other steroids commonly used for this intervention [44]. The more egregious flaw, however, concerns the most important categorical outcome of the trial – the success rate of the treatment. Surprisingly, it is not even reported in the article’s abstract but rather mentioned in the results section only. While the 6-month data demonstrate decreased pain and functional improvement with inclusion of steroid, the overlapping 95% confidence intervals at 3 and 12 months suggest the two treatments are equivalent at those timeframes, failing to support the authors’ conclusion of “potential superiority of steroids compared with local anesthetic alone at 1-year follow-up.” However, it is difficult to interpret the data accurately because the authors performed several ESIs on each patient in a rather haphazard fashion. It is possible that before the 6-month follow-up data collection, a greater proportion of patients received the injection more recently compared with the 3- and the 12-month data collection periods. If so, that may explain the inconsistency of the results.

Two pragmatic studies assessed the effectiveness of a parasagittal lumbar interlaminar approach. In 2015, Ghai et al. performed a pragmatic RCT assessing the effectiveness of fluoroscopically guided parasagittal interlaminar injections of local anesthetic with and without steroid for patients with chronic low back pain and

uniradicular pain [45]. At 3 months, 86% of patients in the steroid group reported greater than 50% improvement (90% CI: 73–93%) as compared to 50% in the local anesthetic group (90% CI: 36–64%). Similar results were obtained at 6, 9, and 12 months. This study seems to provide some evidence of greater effectiveness of parasagittal interlaminar epidural steroid injections compared to epidural injections of a local anesthetic. An important confounding factor is the unknown timing of additional injections in relation to the fixed in time follow-up appointments. If some patients received these additional injections close to the follow-up dates they might show much better results skewing the data. Also, the authors chose the unusually broad exclusion criteria, not only excluding patients with large disc herniation but also those with any signs of radiculopathy, thereby rendering the criteria much different from those used in the vast majority of other studies. Hashemi et al. conducted a pragmatic RCT comparing transforaminal and parasagittal injections in patients with radicular pain and found that the success rate, defined as NRS < 3, was not different between the groups [46]. The authors concluded that both techniques were equally effective with 77.3% of parasagittal LESI patients (95% CI: 67–90.5%) and 74.2% of transforaminal LESI patients (95% CI: 62.4–89.4%) gaining success at 2 to 4 weeks. However, a short follow-up in this study tempers the optimism inspired by these positive results.

### Radicular Pain Due to Lumbar Spinal Stenosis

Four observational studies have addressed the effectiveness of fluoroscopically guided L-ILESI for spinal stenosis. Three suggested that short-term improvement could occur, but provide no data on success rates [47–49]. The fourth study found no improvements [50].

In 2014, a pragmatic multicenter, double-blind RCT was published comparing the effectiveness of epidural injections (both transforaminal and interlaminar) containing lidocaine with and without steroids in patients with spinal stenosis [51]. The primary outcome measures were Roland-Morris Disability Questionnaire (RMDQ) and NRS for leg pain at 3 and 6 weeks. The inclusion/exclusion criteria in this study were well-defined and focused on central spinal stenosis. Patients were randomized to two groups: lidocaine 0.25–1%, 1–3mls; and lidocaine 0.25–1%, 1–3mls and 1–3mls of steroid (60–120 mg of triamcinolone or methylprednisolone, 6–12 mg of betamethasone, 8–10 mg dexamethasone). It was a double-blinded study carried out by 26 different physicians. Of the 200 patients in the lidocaine only group, 139 had an interlaminar injection, while 61 received a transforaminal injection, all under fluoroscopic guidance. Of the 200 patients in the lidocaine and steroid group, 143 had an interlaminar injection and 57 had a transforaminal injection, under fluoroscopic guidance. Outcomes were assessed at 3 and 6 weeks. The data were presented as the mean of continuous data for each group. Patients

who received interlaminar injections assigned to glucocorticoids plus lidocaine compared to those assigned to lidocaine alone reported better physical function on the RMDQ and less leg pain at 3 weeks which were statistically significant, but there were no significant differences between the two treatment groups at 6 weeks. The authors concluded that 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. To facilitate recruitment, the study allowed blinded cross over between treatment arms. Of the 200 subjects that initially received steroid and lidocaine, only 60 or 30% (95% CI 24–37%) crossed over; while 90 or 45% (95% CI 38–51%) of the 200 patients treated initially with lidocaine crossed over. It is interesting that there was a statistically significant difference, with more people that only received lidocaine crossing over than those that initially received steroids [52].

This is considered an important study as it mimics clinical practice; however, there are a number of limitations. The inclusion criteria were loose and many patients' pain and disability may not be the result of stenosis. In addition, the variability in both volume (1–6 mls) lidocaine dose and steroid dose and type injected could impact the results and this was not accounted for. No images were included to assess placement or contrast flow patterns. There were multiple physicians involved in performing the procedures. They did not control for or even mention confounding factors such as medication use. Categorical data were not provided, nor were data on some of the more salient outcome measures such as the Swiss Spinal Stenosis Questionnaire. They did not present baseline and post-injection data for each group; rather they provided results only on the between-group differences without adequate subgroup analysis. Therefore, in academic terms, this study might be criticized for not applying uniform, rigorous selection criteria, for not standardizing dosages, for using multiple treating physicians, and for not controlling for co-interventions. However, the practices of the physicians and the patients enrolled reflect what happens in actual clinical practice. So despite the significant limitations mentioned above, this study may be representative of normal clinical practice and appears to support the conclusion that steroids are only minimally more effective than local anesthetic at 3 weeks.

In 2015, another double blind pragmatic RCT was published that compared the effectiveness of an L-ILESI with local anesthetic only to an L-ILESI with local anesthetic and corticosteroid in patients with lumbar radicular pain caused by central spinal stenosis [53]. This study was completed by the same authors as the previously detailed manuscript comparing L-ILESI of lidocaine only to lidocaine and corticosteroid for disc herniations [43]. Outcomes were assessed at baseline and at 3, 6, 12, 18, and 24 months post-treatment, and included NRS and ODI, with success defined as a decrease in either measure by  $\geq 50\%$ . The authors found

that 72% (95% CI: 61–83%) of patients receiving lidocaine and corticosteroid and 73% (95% CI: 62–85%) of patients that received lidocaine only had significant pain relief at 24 months. ODI scores decreased by 75% in both groups at 24 months. The authors concluded that epidural injection of glucocorticoids plus lidocaine offers no benefit as compared with epidural injection of lidocaine alone. However, this study had the same methodological flaws outlined above that permeated the authors' other study [43].

Staats et al. performed a pragmatic RCT comparing the effectiveness of fluoroscopically guided L-ILESI to the MILD (minimally invasive lumbar decompression) procedure in the treatment of spinal stenosis and reported greater improvements in patients' symptoms with the latter treatment [54]. However, the lack of blinding and some other notable shortcomings of this study cast doubts on the relevancy and validity of the presented data. Because the first follow-up in the study was not conducted until after 6 months after each procedure the shorter lasting positive effects of epidural steroid injections might not be registered.

#### Radicular Pain of Unclear Etiology

Two studies were identified that evaluated the effectiveness of fluoroscopically guided L-ILESI in patients with radicular pain of uncertain etiology. A prospective observational study by Burn et al. evaluated 6-month outcomes following L-ILESI or caudal epidural steroid injections in 56 patients with radicular pain resulting from uncertain etiology [55]. Of the 29 patients in the L-ILESI subgroup that received 20 ml of 0.75% lidocaine mixed with 20 mg hydrocortisone and 80 mg of methylprednisolone, 18 [62% [(95% CI: 44–80%)] reported relief of pain from radicular symptoms at 6 months; however, the authors do not quantify the degree or percentage of pain relief. No conclusion can be drawn from this study as the technique is not consistent with standards: large volume was injected at the L3-4 level, two different steroids were used, and some cases were performed using a catheter.

Annaswamy et al. evaluated whether an abnormal needle electromyography (NEE) would predict positive outcomes after L-ILESI [56]. Patients with abnormal NEE experienced better outcomes; however, both groups failed to achieve a minimal clinically important change, reporting less than 2-point reduction on the VAS.

#### Back and/or Leg Pain Due to Unclear or Multiple Etiologies

A 2003 study by Noe and Haynsworth compared the effects of fluoroscopically guided L-ILESI with methylprednisone to betamethasone in patients with low back pain with or without radiculopathy [57]. The 23% loss to

follow-up, absence of categorical data, and results reported only at 4 weeks, limits the obtainable insight into the effectiveness of L-ILESI in treating patients with back and/or leg pain of uncertain etiology.

A pragmatic RCT compared the effectiveness of interlaminar with bilateral transforaminal epidural steroid injections in the treatment of spine pain and pathology in patients with lumbosacral disc herniation or spinal stenosis [58]. Of the patients with stenosis treated with an interlaminar injection, 36% (95% CI: 21–50%), compared with 61% (95% CI: 49–74%) for the transforaminal group, experienced a successful outcome at 2 months, defined as at least a 2-point reduction on the NRS pain scale. For patients with disc herniation, no differences between groups were noted at up to 4 months.

In 2012, Manchikanti et al. performed a pragmatic RCT of 120 patients to assess the effectiveness of fluoroscopically guided lumbar interlaminar injection of local anesthetic with and without steroid in managing chronic low back pain of discogenic origin [59]. Discogenic pain was diagnosed by absence of relief from medial branch blocks or SI joint injection. This is clearly not a validated means of diagnosing "discogenic pain," which resulted in the study being categorized for purposes of this review as providing evidence relative to use of L-ILESI in treating back and/or leg pain of uncertain etiology. In this study, the subjects received either local anesthetic only or a mixture of local anesthetics. Similar to this research groups other studies comparing interlaminar anesthetic to interlaminar anesthetic and corticosteroid in spinal stenosis [49] and disc herniations [42], all subjects improved and no differences were found between the groups in NRS and ODI at 3, 6, and 12-months post enrollment. Unfortunately this paper also contained significant flaws, such as allowing multiple injections for which timing and exact numbers were not adequately controlled, thus limiting the ability to draw real insights and conclusions.

#### Complications and Adverse Effects

In order to accurately report on complications due to fluoroscopically guided L-ILESI, it is imperative to differentiate true reported complications from minor adverse effects. Additionally it is useful to stratify the adverse effects into: generic effects expected of any invasive procedure, those attributable to the agents injected, and technical mishaps peculiar to epidural placement of needles.

True complications following fluoroscopically guided L-ILESI appears to be limited to mostly case reports (see Table 2). In fact a large cohort of over 1,500 consecutive injections revealed no major complications [60]. Further review of the case reports on complications due to fluoroscopically guided L-ILESI revealed several potentially clinically significant complications including: chemical meningitis following inadvertent dural

**Table 2** Adverse effects and complications associated with fluoroscopically guided L-ILESI

Adverse Effects and Complications		
Cause	Complication	Reference
Technique	Dural puncture	Gutknecht (1987)
	Dural puncture	El-Yahchouchi et al. (2015)
	Discitis	Hooten et al. (2006)
	Discitis	Schultz (2008)
	Increase in index pain	McGrath et al. (2011)
	Increase in index pain	El-Yahchouchi et al. (2015)
	Epidural hematoma	Xu et al. (2009)
	Epidural hematoma	Yoo et al. (2009)
	Infection/Inflammation	Chemical meningitis
Epidural abscess		Gotz et al. (2009)
Soft tissue abscess and osteomyelitis		Simopoulos et al. (2008)
Steroid	Transient blindness with permanent vision changes	Young (2002)
	Diabetes mellitus	Young (2002)
	Flushing	Kim et al. (2010)
	Non-positional headache	El-Yahchouchi et al. (2015)
	Sleeplessness	El-Yahchouchi et al. (2015)
Discontinuation of Coumadin	Thromboembolic stroke	Linn et al. (2009)
Unknown mechanism	Paraplegia	Lenoir et al. (2008)
	Vasovagal syncope	Kennedy et al. (2013)
	Vasovagal syncope	El-Yahchouchi et al. (2015)

puncture/intrathecal steroid administration [61], “transient” blindness with retinal hemorrhages on ophthalmologic examination but with permanent vision changes [62], paraplegia [63], soft tissue abscess associated with osteomyelitis [64], epidural abscess [65], and epidural hematoma [66,67].

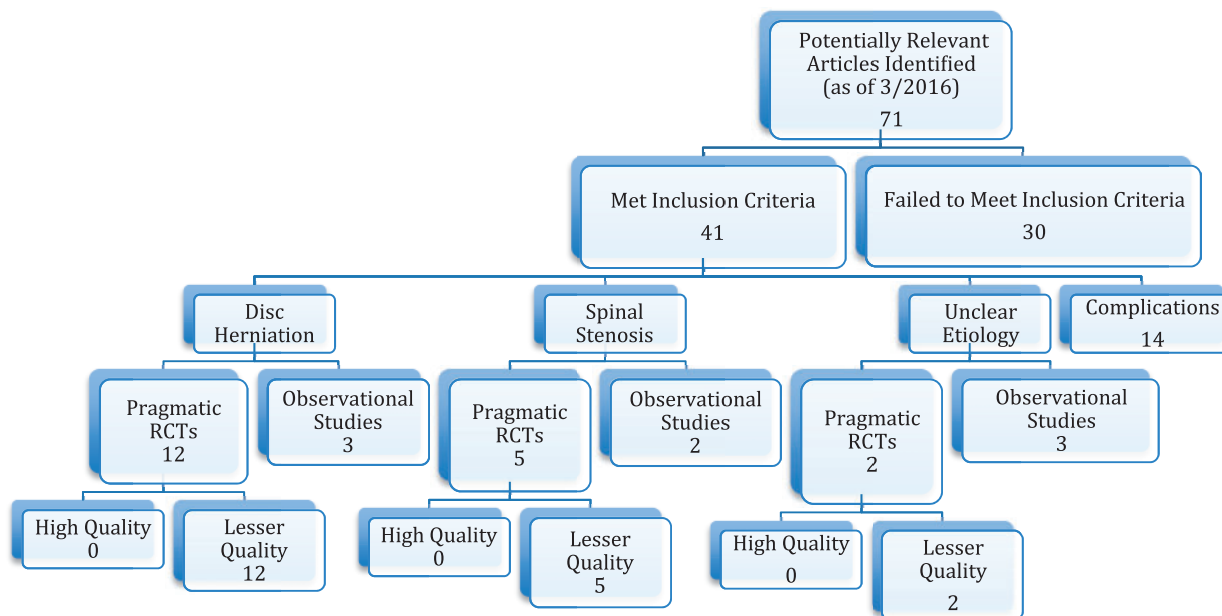
The case report by Young et al. describes a patient that developed transient blindness (20/400 vision bilaterally) with eventual vision improvement to 20/40 (B/L), but who also developed diabetes mellitus, previously not diagnosed, with requirement of insulin on a temporary basis [62]. In regards to the transient blindness, there have been nine previously reported cases with retinal hemorrhages seen on fundoscopic examination [62]. Permanent paraplegia following L1-2 ILESI in a patient with prior L3-4 posterior fusion has been described by Lenoir et al. due to unknown mechanism, possibly through an embolic event due to a variation in the arterial blood supply to the spinal cord, as seen in the transforaminal route [63].

Hooten et al. reported on a patient with L5-S1 discitis with Coagulase negative Staphylococcus post L5-S1 ILEI, requiring complete L5 laminectomy, L5-S1 discectomy, and bilateral medial facetectomies in a 64-year-old with a history of recurrent pulmonary infections [68]. The patient was treated with 6 weeks of IV antibiotics. At 3 months follow-up, the patient reported no lumbosacral spine, radicular lower limb pain, and the patient’s weakness in the lower limbs had improved.

Simopoulos et al. described a soft tissue abscess with osteomyelitis with methicillin-resistant *Staphylococcus Aureus* (MRSA) in an immunocompromised (diabetes mellitus) patient following a second injection in a series of L-ILESIs for radicular pain due to lumbar stenosis [64]. This patient had proper aseptic techniques, but was immunocompromised, and therefore at higher risk of developing an abscess/osteomyelitis. The authors recommended using Chlorhexidine-based solutions when possible, as they may be associated with better skin disinfection for pain procedures in patients with risk factors for immunosuppression.

Linn et al. described an 81-year-old patient who had a history of AFib with previous neuraxial procedures while Coumadin was held per guidelines [69], who developed non-reversible, permanent aphasia and left hemiparesis due to a right middle cerebral artery cerebrovascular accident [70]. While not directly due to the procedure, this complication may have been caused by holding of the anticoagulants in preparation for the procedure. Epidural hematoma has been described in a patient bridged with enoxaparin [66] and in a patient with undiagnosed Idiopathic Thrombocytopenic Purpura [67].

Minor adverse events that are transient in nature and not true complications have also been reported following fluoroscopically guided L-ILESIs. These include: inadvertent disc entry without discitis, flushing, increased or new pain, bleeding, post-injection headache, chest pain, itching/pruritis, weakness, leg cramps, abnormal



**Figure 1** Categorization of potentially relevant articles generated by the literature search.

limb movement, swelling, heart palpitations, diarrhea, night sweats/fevers/chills, muscle spasm, pressure, other back pain, stiffness, numbness, or transient bowel incontinence [60,61,71,72]. Some of these adverse events are due to the mere act of placing a needle and clearly not unique to fluoroscopically guided L-ILESIs. This would include adverse events such as increased pain and vasovagal syncope, both of which have been reported on from large cohorts. Increased pain is one of the most commonly reported adverse events, but in large studies has been found to occur less than 2% of the time [60]. Vasovagal syncope is another well-studied adverse event due to needle placement. One study of 279 consecutive subjects reported 20 [0.7% [(95% CI: 0.5–0.1%)] with transient vasovagal syncope [73], while another larger multi-site study of 1,412 consecutive subjects noted only 3 [0.02% [(95% CI: 0.007–0.06%)] episodes of transient vasovagal syncope [60].

There are also reported effects that are felt to be secondary to the injection of a corticosteroid or other medications. These would therefore not be unique to L-ILESIs and would include: sleeplessness, non-positional headaches, increased blood glucose, facial flushing, adrenal suppression, and allergic reactions [74–78]. Central steroid effects, defined as sleeplessness, flushing and a non-positional headache, have been shown to occur in 2.6% (95% CI: 1.9–3.4%) of patients [60].

Lastly adverse events can also occur due to technical mishaps. In a large cohort, dural punctures have been reported at low rates of 0.2% (95% CI: 0.9–0.6%) [60]. Unintended injection into a disc [68,79] has also been reported in case reports. While dural puncture has been reported from procedures done according to the

Society's standards, intradiscal injections should not occur in correctly performed image-guided procedures.

## Discussion

A systematic review completed by members of the Society's Standards Division earlier this year addressed the effectiveness and risks of blind L-ILESI (in press). The authors of that review determined that there is no role for the routine use of blind L-ILESI in the treatment of spine pathology resulting in pain. They suggested that the evidence should be reviewed to determine whether fluoroscopic guidance results in improved outcomes that would support the use of the interlaminar approach in treating radicular pain, neurogenic claudication, and axial low back pain. Use of fluoroscopy offers several advantages when performing L-ILESI, including: verification of the correct level and side; confirmation, with use of contrast medium, that the injection is accurately placed in the epidural space; and avoidance of intravascular injection. Despite these demonstrated advantages, there have been several systematic reviews undertaken in the past with conflicting results regarding the effectiveness of fluoroscopically guided L-ILESI.

Previous systematic reviews have used traditional methods to assess the evidence, which rely on RCTs but abjure observational studies. These reviews come to very different conclusions regarding the effectiveness of fluoroscopically guided L-ILESI [80–84], but almost all agree that epidural steroid injections provide short-term improvement of radicular pain associated with disc herniation or spinal stenosis. Unlike these previous reviews, the present review employed the GRADE system of appraisal

to determine the quality of the evidence regarding the effectiveness of fluoroscopically guided L-ILESI.

Additionally this review focused on separating the results by the likely underlying pathology, as varying pathologies may have different responses to treatment and they clearly have different natural histories. The disease specific natural history is imperative to consider when discussing the duration of relief. For instance, radicular pain due to a disc herniation typically has a favorable natural history for resolution of pain. This is in stark contrast to neurogenic claudication due to spinal stenosis, which while not generally progressive, does not tend to spontaneously resolve. For those conditions with a favorable natural history, a short duration of relief from a given treatment may be reasonable. The decision to implement the treatment would take the risks and benefits into consideration, in addition to the symptom severity, impact on function, and even total costs including costs of alternative treatments and lost productivity due to inability to work. In the case of radiculopathy due to a disc herniation a short duration of relief that results in less utilization of other health care and a quick return to work may be appropriate. However, a similar short-term effect may be insufficient for a chronic condition such as a spinal stenosis.

When assessing the level of evidence in accordance with GRADE and stratifying by underlying pathology, trends do emerge. For all conditions, the quality of evidence is low in accordance with GRADE. There were no reasons to justify upgrading the evidence for any pathology. To qualify for such an “upgrade” in GRADE methodologically, the evidence provided by observational studies must demonstrate a large magnitude of effect or the presence of a dose-response gradient. Neither of these conditions apply. In addition, many of the studies had several flaws as discussed in detail in the results section.

This low rating in accordance with GRADE is due to the lack of explanatory RCTs for fluoroscopically guided L-ILESI. The literature search yielded twelve pragmatic studies addressing the use of fluoroscopically guided L-ILESI for radicular pain due to herniated disc, and five for spinal stenosis. All of these studies failed to show superiority of L-ILESI to the comparative treatment, with the exception of two studies: one found L-ILESI superior only at 6 months for those with disc herniations [43] and the other showed superiority at up to 12 months [45]. This resulted in the majority of the evidence relative to use of fluoroscopically guided L-ILESI for radicular pain being classified as observational in nature.

While the quality of evidence is low, the body of evidence does support the conclusion that fluoroscopically guided L-ILESI do provide short-term relief of radicular pain from lumbar disc herniation as well as stenosis. As discussed above this may be an appropriate outcome for acute or subacute radicular pain due to a disc herniation, but may be insufficient for those with chronic neurogenic claudication due to spinal stenosis.

There is a body of literature from one research group in the form of multiple RCTs that claim no differences between lumbar interlaminar epidural injection of lidocaine or corticosteroid for several pathologic conditions including spinal stenosis, disc herniations, and pain of unclear etiology. Surprisingly, these patients tended to have similar strong positive response rates regardless of the underlying etiology or substance injected. These studies, while internally consistent, exhibit dissonance with the remainder of the published literature. They also did not control for the number or timing of the multiple injections the subjects received, and utilized a corticosteroid (betamethasone) that has been shown in other studies to be less effective than other corticosteroid preparations [44,57,85]. Due to these considerations it is unclear if these results were due to recurrent methodological flaws, or a lack of effectiveness of betamethasone or even the interlaminar approach.

Several studies have assessed the effectiveness of the parasagittal interlaminar approach compared with either traditional midline L-ILESI or transforaminal injections of steroids [30,34,45,46]. The evidence suggests this technique is significantly more effective than the midline L-ILESI approach in the treatment of radicular pain and possibly of comparable effectiveness to transforaminal injections of steroid for uniradicular pain due to disc herniation.

### *GRADE Assessment of Risks of Fluoroscopically Guided L-ILESI*

When attempting to assess the quality of the evidence on the risks of fluoroscopically guided L-ILESI in accordance with the GRADE system, it is noted that the published evidence consists only of case reports. Accordingly, the body of evidence is of very low quality. That results in very little confidence in the effect estimate and the true effect is likely to be substantially different from the estimate of effect. Readers must be careful not to confuse “evidence of very low quality” with “evidence of little significance” and perhaps go on to dismiss the risks of fluoroscopically guided L-ILESI as too rare to be of concern. The evidence of risks is of very low quality because few cases of serious complications have been published. This may reflect publication bias. There is a tendency for serious complications not to be publicized in papers. Thus, the frequency of complications after fluoroscopically guided L-ILESI is uncertain but when they do occur they can be catastrophic.

### **Conclusion**

There appears to be evidence suggesting a lack of effectiveness of fluoroscopically guided L-ILESI in treating primarily axial pain associated with spinal stenosis or discogenic etiology. Despite the fact that the evidence is of low quality, most studies report significant short-term improvement in radicular pain after fluoroscopically guided L-ILESI in patients with radicular pain due to lumbar disc herniation and stenosis.

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## References

- 1 Evans W. Intracanal epidural injection therapy in the treatment of sciatica. *Lancet* 1930;2:1225–9.
- 2 Barry PJ, Kendall PH. Corticosteroid infiltration of the extradural space. *Ann Phys Med* 1962;6:267–73.
- 3 White AH. Injection techniques for the diagnosis and treatment of low back pain. *Orthop Clin North Am* 1983;14(3):553–67.
- 4 White AH, Derby R, Wynne G. Epidural injections for the diagnosis and treatment of low-back pain. *Spine* 1980;5(1):78–86.
- 5 Abram SE, O'Connor TC. Complications associated with epidural steroid injections. *Reg Anesth* 1996;21(2):149–62.
- 6 Nelson DA. Intraspinal therapy using methylprednisolone acetate. Twenty-three years of clinical controversy. *Spine* 1993;18(2):278–86.
- 7 Renfrew DL, Moore TE, Kathol MH, el-Khoury GY, Lemke JH, Walker CW. Correct placement of epidural steroid injections: Fluoroscopic guidance and contrast administration. *AJNR* 1991;12(5):1003–7.
- 8 Devulder J, Bogaert L, Castille F, Moerman A, Rolly G. Relevance of epidurography and epidural adhesiolysis in chronic failed back surgery patients. *Clin J Pain* 1995;11(2):147–50.
- 9 Du Pen SL, Williams AR, Feldman RK. Epidurograms in the management of patients with long-term epidural catheters. *Reg Anesth* 1996;21(1):61–7.
- 10 el-Khoury GY, Renfrew DL. Percutaneous procedures for the diagnosis and treatment of lower back pain: diskography, facet-joint injection, and epidural injection. *AJR* 1991;157(4):685–91.
- 11 Emery I, Hamilton G. Epidurography using metrizamide an out-patient examination. *Clin Radiol* 1980; 31(6):643–9.
- 12 Hamilton G. Metrizamide epidurography. *J R Soc Med* 1983;76(2):126–30.
- 13 Hatten HP Jr. Metrizamide lumbar epidurography with Seldinger Technique through the sacral notch and selective nerve root injection. *Neuroradiology* 1980;19(1):19–25.
- 14 Armon C, Argoff CE, Samuels J, Backonja MM. Assessment: Use of epidural steroid injections to treat radicular lumbosacral pain: Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology* 2007;68(10):723–9.
- 15 Benyamin RM, Singh V, Parr AT, et al. Systematic review of the effectiveness of cervical epidurals in the management of chronic neck pain. *Pain Physician* 2009;12(1):137–57.
- 16 Buenaventura RM, Datta S, Abdi S, Smith HS. Systematic review of therapeutic lumbar transforaminal epidural steroid injections. *Pain Physician* 2009; 12(1):233–51.
- 17 Chou R, Atlas SJ, Stanos SP, Rosenquist RW. Nonsurgical interventional therapies for low back pain: A review of the evidence for an American Pain Society clinical practice guideline. *Spine* 2009;34(10): 1078–93.
- 18 Conn A, Buenaventura RM, Datta S, Abdi S, Diwan S. Systematic review of caudal epidural injections in the management of chronic low back pain. *Pain Physician* 2009;12(1):109–35.
- 19 Manchikanti L, Boswell MV, Datta S, et al. Comprehensive review of therapeutic interventions in managing chronic spinal pain. *Pain Physician* 2009;12(4):E123–98.
- 20 Manchikanti L, Pampati V, Boswell MV, Smith HS, Hirsch JA. Analysis of the growth of epidural injections and costs in the Medicare population: A comparative evaluation of 1997, 2002, and 2006 data. *Pain Physician* 2010;13(3):199–212.
- 21 Manchikanti L, Singh V, Pampati V, Smith HS, Hirsch JA. Analysis of growth of interventional techniques in managing chronic pain in the Medicare population: A 10-year evaluation from 1997 to 2006. *Pain Physician* 2009;12(1):9–34.
- 22 Parr AT, Diwan S, Abdi S. Lumbar interlaminar epidural injections in managing chronic low back and lower extremity pain: A systematic review. *Pain Physician* 2009;12(1):163–88.

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- 23 Staal JB, de Bie RA, de Vet HC, Hildebrandt J, Nelemans P. Injection therapy for subacute and chronic low back pain: An updated Cochrane review. *Spine* 2009;34(1):49–59.
- 24 MacVicar J, King W, Landers MH, Bogduk N. The effectiveness of lumbar transforaminal injection of steroids: A comprehensive review with systematic analysis of the published data. *Pain Med* 2013;14(1):14–28.
- 25 Engel A, King W, MacVicar J, Standards Division of the International Spine Intervention S. The effectiveness and risks of fluoroscopically guided cervical transforaminal injections of steroids: A systematic review with comprehensive analysis of the published data. *Pain Med* 2014;15(3):386–402.
- 26 King W, Ahmed SU, Baisden J, et al. Diagnosis and treatment of posterior sacroiliac complex pain: A systematic review with comprehensive analysis of the published data. *Pain Med* 2015;16(2):257–65.
- 27 Kreiner DS, MacVicar J, Duszynski B, Nampiarampil DE. The mild(R) procedure: A systematic review of the current literature. *Pain Med* 2014;15(2):196–205.
- 28 Bicket MC, Gupta A, Brown CHt, Cohen SP. Epidural injections for spinal pain: A systematic review and meta-analysis evaluating the “control” injections in randomized controlled trials. *Anesthesiology* 2013;119(4):907–31.
- 29 Tachihara H, Sekiguchi M, Kikuchi S, Konno S. Do corticosteroids produce additional benefit in nerve root infiltration for lumbar disc herniation? *Spine* 2008;33(7):743–7.
- 30 Ghai B, Vadaje KS, Wig J, Dhillon MS. Lateral parasagittal versus midline interlaminar lumbar epidural steroid injection for management of low back pain with lumbosacral radicular pain: A double-blind, randomized study. *Anesth Analg* 2013;117(1):219–27.
- 31 Furman MB, Kothari G, Parikh T, Anderson JG, Khawaja A. Efficacy of fluoroscopically guided, contrast-enhanced lumbosacral interlaminar epidural steroid injections: A pilot study. *Pain Med* 2010;11(9):1328–34.
- 32 Schaufele MK, Hatch L, Jones W. Interlaminar versus transforaminal epidural injections for the treatment of symptomatic lumbar intervertebral disc herniations. *Pain Physician* 2006;9(4):361–6.
- 33 Giraudeau B, Rozenberg S, Valat JP. Assessment of the clinically relevant change in pain for patients with sciatica. *Ann Rheum Dis* 2004;63(9):1180–1.
- 34 Ghai B, Bansal D, Kay JP, Vadaje KS, Wig J. Transforaminal versus parasagittal interlaminar epidural steroid injection in low back pain with radicular pain: A randomized, double-blind, active-control trial. *Pain Physician* 2014;17(4):277–90.
- 35 Gharibo CG, Varlotta GP, Rhame EE, et al. Interlaminar versus transforaminal epidural steroids for the treatment of subacute lumbar radicular pain: A randomized, blinded, prospective outcome study. *Pain Physician* 2011;14(6):499–511.
- 36 Kawu AA. Epidural steroid injection in patients with lumbosacral radiculopathy in Abuja, Nigeria. *J Neurosci Rural Pract* 2012;3(2):121–5.
- 37 Rados I, Sakic K, Fingler M, Kapural L. Efficacy of interlaminar vs transforaminal epidural steroid injection for the treatment of chronic unilateral radicular pain: Prospective, randomized study. *Pain Med* 2011;12(9):1316–21.
- 38 Rados I, Sakic Zdravcevic K, Hrgovic Z. painDETECT questionnaire and lumbar epidural steroid injection for chronic radiculopathy. *Eur Neurol* 2013;69(1):27–32.
- 39 Ackerman WE 3rd, Ahmad M. The efficacy of lumbar epidural steroid injections in patients with lumbar disc herniations. *Anesth Analg* 2007;104(5):1217–22, tables of contents.
- 40 Kamble PC, Sharma A. Outcome of single level disc prolapse treated with transforaminal steroid versus epidural steroid versus caudal steroids. 2016;25(1):217–21.
- 41 Kim D, Brown J. Efficacy and safety of lumbar epidural dexamethasone versus methylprednisolone in the treatment of lumbar radiculopathy: A comparison of soluble versus particulate steroids. *Clin J Pain* 2011;27(6):518–22.
- 42 Cohen SP, Gupta A, Strassels SA, et al. Effect of MRI on treatment results or decision making in patients with lumbosacral radiculopathy referred for epidural steroid injections: A multicenter, randomized controlled trial. *Arch Int Med* 2012;172(2):134–42.
- 43 Manchikanti L, Singh V, Cash KA, Pampati V, Falco FJ. The role of fluoroscopic interlaminar epidural injections in managing chronic pain of lumbar disc herniation or radiculitis: A randomized, double-blind trial. *Pain Pract* 2013;13(7):547–58.
- 44 McCormick Z, Kennedy DJ, Garvan C, et al. Comparison of pain score reduction using

- triamcinolone vs. betamethasone in transforaminal epidural steroid injections for lumbosacral radicular pain. *Am J Phys Med Rehabil* 2015;94(12):1058–64.
- 45 Ghai B, Kumar K, Bansal D, et al. Effectiveness of parasagittal interlaminar epidural local anesthetic with or without steroid in chronic lumbosacral pain: A randomized, double-blind clinical trial. *Pain Physician* 2015;18(3):237–48.
- 46 Hashemi SM, Aryani MR, Momenzadeh S, et al. Comparison of transforaminal and parasagittal epidural steroid injections in patients with radicular low back pain. *Anesthesiol Pain Med* 2015;5(5):e26652.
- 47 Cosgrove JL, Bertolet M, Chase SL, Cosgrove GK. Epidural steroid injections in the treatment of lumbar spinal stenosis efficacy and predictability of successful response. *Am J Phys Med Rehabil* 2011;90(12):1050–5.
- 48 Smith CC, Booker T, Schaufele MK, Weiss P. Interlaminar versus transforaminal epidural steroid injections for the treatment of symptomatic lumbar spinal stenosis. *Pain Med* 2010;11(10):1511–5.
- 49 Koc Z, Ozcakar S, Sivrioglu K, Gurbet A, Kucukoglu S. Effectiveness of physical therapy and epidural steroid injections in lumbar spinal stenosis. *Spine* 2009;34(10):985–9.
- 50 Brown LL. A double-blind, randomized, prospective study of epidural steroid injection vs. the mild(R) procedure in patients with symptomatic lumbar spinal stenosis. *Pain Pract* 2012;12(5):333–41.
- 51 Friedly JL, Comstock BA, Turner JA, et al. A randomized trial of epidural glucocorticoid injections for spinal stenosis. *N Engl J Med* 2014;371(1):11–21.
- 52 Friedly J. *The Utility of Epidural Steroid Injections: Point—Counterpoint*. Boston, MA: AAPM&R Annual Assembly; 2015.
- 53 Manchikanti L, Cash KA, McManus CD, et al. A randomized, double-blind controlled trial of lumbar interlaminar epidural injections in central spinal stenosis: 2-year follow-up. *Pain Physician* 2015;18(1):79–92.
- 54 Staats PS, Benyamin RM. MiDAS ENCORE: Randomized Controlled Clinical Trial Report of 6-Month Results. *Pain Physician* 2016;19(2):25–38.
- 55 Burn JM, Guyer PB, Langdon L. The spread of solutions injected into the epidural space. A study using epidurograms in patients with the lumbosacral syndrome. *Br J Anaesth* 1973;45(4):338–45.
- 56 Annaswamy TM, Bierner SM, Chouteau W, Elliott AC. Needle electromyography predicts outcome after lumbar epidural steroid injection. *Muscle Nerve* 2012;45(3):346–55.
- 57 Noe CE, Haynsworth RF Jr. Comparison of epidural Depo-Medrol vs. aqueous betamethasone in patients with low back pain. *Pain Pract* 2003;3(3):222–5.
- 58 Lee JH, An JH, Lee SH. Comparison of the effectiveness of interlaminar and bilateral transforaminal epidural steroid injections in treatment of patients with lumbosacral disc herniation and spinal stenosis. *Clin J Pain* 2009;25(3):206–10.
- 59 Manchikanti L, Cash KA, McManus CD, Pampati V, Benyamin R. Fluoroscopic lumbar interlaminar epidural injections in managing chronic lumbar axial or discogenic pain. *J Pain Res* 2012;5:301–11.
- 60 El-Yahouchi CA, Plastaras CT, Maus TP, et al. Adverse event rates associated with transforaminal and interlaminar epidural steroid injections: A multi-institutional study. *Pain Med* 2016;17(2):239–47.
- 61 Gutknecht DR. Chemical meningitis following epidural injections of corticosteroids. *Am J Med* 1987;82(3):570.
- 62 Young WF. Transient blindness after lumbar epidural steroid injection: A case report and literature review. *Spine* 2002;27(21):E476–7.
- 63 Lenoir T, Deloin X, Dauzac C, Rillardon L, Guigui P. [Paraplegia after interlaminar epidural steroid injection: A case report]. *Revue De Chirurgie Orthopedique Et Reparatrice De L'appareil Moteur* 2008;94(7):697–701.
- 64 Simopoulos TT, Kraemer JJ, Glazer P, Bajwa ZH. Vertebral osteomyelitis: A potentially catastrophic outcome after lumbar epidural steroid injection. *Pain Physician* 2008;11(5):693–7.
- 65 Gotz F, Lanfermann H, Becker H. [Cervical epidural abscess following lumbar epidural steroid injections]. *Klin Neuroradiol* 2009;19(3):220–6.
- 66 Xu R, Bydon M, Gokaslan ZL, et al. Epidural steroid injection resulting in epidural hematoma in a patient despite strict adherence to anticoagulation guidelines. *J Neurosurg Spine* 2009;11(3):358–64.
- 67 Yoo HS, Park SW, Han JH, et al. Paraplegia caused by an epidural hematoma in a patient with unrecognized chronic idiopathic thrombocytopenic purpura following an epidural steroid injection. *Spine* 2009;34(10):E376–9.

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- 68 Hooten WM, Mizerak A, Carns PE, Huntoon MA. Discitis after lumbar epidural corticosteroid injection: A case report and analysis of the case report literature. *Pain Med* 2006;7(1):46–51.
- 69 Horlocker TT, Wedel DJ, Rowlingson JC, et al. Regional anesthesia in the patient receiving antithrombotic or thrombolytic. Therapy: American Society of Regional Anesthesia and Pain Medicine Evidence-Based Guidelines (Third Edition). *Reg Anesth Pain Med* 2010;35(1):64–101.
- 70 Linn AJ, Desilva C, Peeters-Asdourian C. Thromboembolic stroke: A rare complication associated with peri-procedural management of an epidural steroid injection. *Pain Physician* 2009;12(1):159–62.
- 71 Kim CH, Issa MA, Vaglianti RM. Flushing following interlaminar lumbar epidural steroid injection with dexamethasone. *Pain Physician* 2010;13(5):481–4.
- 72 McGrath JM, Schaefer MP, Malkamaki DM. Incidence and characteristics of complications from epidural steroid injections. *Pain Med* 2011;12(5):726–31.
- 73 Kennedy DJ, Schneider B, Casey E, et al. Vasovagal rates in fluoroscopically guided interventional procedures: A study of over 8,000 injections. *Pain Med* 2013;14(12):1854–9.
- 74 Berthelot JM, Le Goff B, Maugars Y. Side effects of corticosteroid injections: What's new? *Joint Bone Spine* 2013;80(4):363–7.
- 75 Goel AP, Nguyen VH, Hamill-Ruth R. Use of a risk-stratification tool in identification of potential adrenal suppression preceding steroid injection therapy in chronic pain patients. *Pain Med* 2015;16(12):2226–34.
- 76 Gonzalez P, Laker SR, Sullivan W, Harwood JE, Akuthota V. The effects of epidural betamethasone on blood glucose in patients with diabetes mellitus. *PM R* 2009;1(4):340–5.
- 77 Habib G, Jabbour A, Salman J, Hakim G, Haddad H. The effect of epidural methylprednisolone acetate injection on the hypothalamic-pituitary-adrenal axis. *J Clin Anesth* 2013;25(8):629–33.
- 78 Jacobs S, Pullan PT, Potter JM, Shenfield GM. Adrenal suppression following extradural steroids. *Anaesthesia* 1983;38(10):953–6.
- 79 Schultz TE. Inadvertent discogram during epidural steroid injection: A case report. *AANA J* 2008;76(3):189–91.
- 80 Koes BW, Scholten RJ, Mens JM, Bouter LM. Epidural steroid injections for low back pain and sciatica: An updated systematic review of randomized clinical trials. *Pain Digest* 1999;9:241–7.
- 81 Pinto RZ, Maher CG, Ferreira ML, et al. Epidural corticosteroid injections in the management of sciatica: A systematic review and meta-analysis. *Ann Int Med* 2012;157(12):865–77.
- 82 Staal JB, de Bie R, de Vet HC, Hildebrandt J, Nelemans P. Injection therapy for subacute and chronic low-back pain. *Cochrane Database Syst Rev* 2008;3: Cd001824.
- 83 Manchikanti L, Benyamin RM, Falco FJ, Kaye AD, Hirsch JA. Do epidural injections provide short- and long-term relief for lumbar disc herniation? A systematic review. *Clin Orthop Related Res* 2015;473(6):1940–56.
- 84 Manchikanti L, Kaye AD, Manchikanti K, et al. Efficacy of epidural injections in the treatment of lumbar central spinal stenosis: A systematic review. *Anesthesiol Pain Med* 2015;5(1):e23139.
- 85 Stanczak J, Blankenbaker DG, De Smet AA, Fine J. Efficacy of epidural injections of Kenalog and Celestone in the treatment of lower back pain. *AJR* 2003;181(5):1255–8.

# Epidural Steroids

## A Comprehensive, Evidence-Based Review

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**Abstract:** Epidural steroid injections (ESIs) are the most widely utilized pain management procedure in the world, their use supported by more than 45 placebo-controlled studies and dozens of systematic reviews. Despite the extensive literature on the subject, there continues to be considerable controversy surrounding their safety and efficacy. The results of clinical trials and review articles are heavily influenced by specialty, with those done by interventional pain physicians more likely to yield positive findings. Overall, more than half of controlled studies have demonstrated positive findings, suggesting a modest effect size lasting less than 3 months in well-selected individuals. Transforaminal injections are more likely to yield positive results than interlaminar or caudal injections, and subgroup analyses indicate a slightly greater likelihood for a positive response for lumbar herniated disk, compared with spinal stenosis or axial spinal pain. Other factors that may increase the likelihood of a positive outcome in clinical trials include the use of a non-epidural (eg, intramuscular) control group, higher volumes in the treatment group, and the use of depo-steroid. Serious complications are rare following ESIs, provided proper precautions are taken. Although there are no clinical trials comparing different numbers of injections, guidelines suggest that the number of injections should be tailored to individual response, rather than a set series. Most subgroup analyses of controlled studies show no difference in surgical rates between ESI and control patients; however, randomized studies conducted by spine surgeons, in surgically amenable patients with standardized operative criteria, indicate that in some patients the strategic use of ESI may prevent surgery.

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Epidural steroid injections are one of the most commonly performed procedures in medicine. It is a topic that seems to transcend pain medicine, with a domain that extends across multiple specialties and to some extent even outside medicine. Yet, there are few subjects that have generated such intense controversy. Legions of articles have been written on the subject, and, arguably, there may be more research on this treatment

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than for any other interventional therapy in medicine. In fact, so much has been written on the subject that a mythological aura now exists that this is an essential treatment, which makes it even more challenging for patients, and even nonpain physicians, to be able to critically evaluate their effectiveness. The purpose of this article was to provide an evidence-based review on the subject, to include mechanisms of action, efficacy, risks, and cost-effectiveness.

### SEARCH STRATEGY AND LEVELS OF EVIDENCE

Articles included in this review were selected by searches of the PubMed, MEDLINE, EMBASE, and OVID databases from 1953 to February 2013 using various combinations of the search terms “epidural steroid,” “caudal,” “transforaminal,” “selective nerve block,” “selective nerve root block,” “segmental nerve block,” “corticosteroid,” “radiculopathy,” “radicular pain,” “sciatica,” “pain,” “low back,” “lumbar,” “thoracic,” “mid-back,” “cervical,” “neck,” “spinal,” and “spine.” Controlled trials, comparative-effectiveness studies, review articles, and case reports were all considered for inclusion, without language restrictions. The reference lists of all articles were searched for pertinent references that were missed during the initial screening.

Evidence was synthesized, and recommendations were based on a conglomeration of factors including weighted evidence in accordance with the Oxford Centre for Evidence Based Medicine,<sup>1</sup> consensus guidelines when relevant, and perceived bias. Levels of evidence cited in referenced systematic reviews were either based on US Preventive Services Task Force (USPSTF) criteria<sup>2</sup> or, if classified by another scale, conveyed descriptively (eg, fair, good [Table 1]). For comparative-effectiveness studies (ie, type of epidural steroid injection [ESI] and type of corticosteroid), evidence of superiority was described using USPSTF levels of certainty (Table 2).

### HISTORY

The first therapeutic epidural injection was performed in 1885 by neurologist James Leonard Corning,<sup>3</sup> an American-born expatriate. Dr Corning<sup>4</sup> made history by injecting the local anesthetic cocaine between the lower lumbar spinous processes, first in a dog, then in a healthy man to treat “seminal incontinence” and “addiction to masturbation.” Controversy surrounds whether Corning actually injected the solution into the intrathecal space,<sup>5</sup> but because no cerebrospinal fluid was reported, this is widely considered to be the first therapeutic epidural injection.<sup>6</sup>

In 1901, the French physicians Jean-Anthanase Sicard and Ferdinand Cathelin separately described the first use of epidurals to treat radicular pain when they injected dilute solutions of cocaine through the sacral hiatus in patients with intractable sciatica.<sup>7,8</sup> In 1930, Evans<sup>9</sup> reported a 14% success rate with the caudal injection of 40 to 80 mL of solution, with no difference in outcomes noted between local anesthetic and saline. Although the practice of using epidurals to provide surgical anesthesia eventually supplanted its use as a treatment

**TABLE 1.** USPSTF Levels of Evidence<sup>2</sup>

Levels of Evidence	Description
Level I	Evidence obtained from at least 1 properly designed RCT
Level II-1	Evidence obtained from well-designed controlled trials without randomization
Level II-2	Evidence obtained from well-designed cohort or case-control analytic studies, preferably from >1 center or research group
Level II-3	Evidence obtained from multiple time series with or without the intervention; dramatic results in uncontrolled trials might also be regarded as this type of evidence
Level III	Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees

for back pain, the use of caudal<sup>10</sup> and lumbar epidural<sup>11</sup> injections for the treatment of chronic back pain continued to evolve.

The epidural injectate used to treat chronic pain remained a mixture of local anesthetic and saline up to the 1950s<sup>12,13</sup> when the use of corticosteroids to manage lumbar radicular pain was first recorded in 1953 by Lievre et al.<sup>14</sup> In 1961, Goebert et al<sup>15</sup> published a case series of 113 patients suffering from lumbar radiculopathy who were successfully treated with the epidural administration of procaine and hydrocortisone acetate. The first modern controlled trial evaluating ESIs was performed in 1970 by Swerdlow and Sayle-Creer.<sup>16</sup>

## EPIDEMIOLOGY

It is difficult to overestimate the socioeconomic burden posed by spinal pain. The annual cost to treat back pain alone exceeds \$100 billion by some estimates, with more than half due to lost productivity.<sup>17,18</sup> For low back pain (LBP), the most commonly cited lifetime prevalence rates range between 40% and 70%, with an annual prevalence rate ranging between 10% and 30% according to some estimates.<sup>18,19</sup> Among those who develop LBP, approximately 30% will develop either chronic pain or frequent recurrences.<sup>20</sup> In individuals younger than 45 years, back pain is the leading cause of disability.<sup>21</sup>

Neck pain is less well publicized, but also exacts a steep socioeconomic toll. Nearly two-thirds of patients will experience a significant episode of neck pain over the course of their lives, with the annual prevalence around 30%.<sup>22–24</sup> The economic costs of neck pain have not been as well studied as for back pain, but are nevertheless significant and growing.<sup>25,26</sup>

There are various schemes for categorizing chronic pain, with perhaps the most relevant being classification into neuropathic and nociceptive pain, as this affects treatment decisions at nearly every level. For patients with chronic LBP, studies utilizing validated instruments have demonstrated that between 17% and 55% have pain that is primarily neuropathic in nature, with a median of 41%.<sup>27–31</sup> Among neck pain sufferers, no studies have evaluated the proportion of individuals with neuropathic pain, although epidemiological studies suggest an annual incidence of between 1 and 3.5 per 1000 people.<sup>32–34</sup>

Epidural steroid injections are by far the most frequently performed procedures in pain clinics throughout the United States, more than doubling between 2000 and 2008.<sup>35</sup> Although they have historically been utilized for spinal pain of all types, they are widely acknowledged to work better for neuropathic

pain. There have arguably been more reviews and more randomized controlled studies (>45) evaluating ESI for spinal pain than for any other treatment for a single condition. Yet, there continues to be enormous controversy surrounding the short- and long-term efficacy, effectiveness, and, more recently, safety of this treatment.

## MECHANISMS OF ACTION

The mechanisms by which steroids exert their analgesic effects have been debated for many years. Corticosteroids inhibit the enzyme phospholipase A<sub>2</sub>, which catalytically hydrolyzes the bond converting membrane phospholipids into arachidonic acid and lysophospholipids. Phospholipase A<sub>2</sub> is itself an inflammatory mediator present in elevated concentrations in herniated and degenerative intervertebral disks,<sup>36</sup> but its main role is as the rate-limiting factor involved in the production of arachidonic acid, which is the principal substrate for the cyclo-oxygenase and lipo-oxygenase pathways. Metabolism by these pathways results in the formation of the 4 different classes of eicosanoids: prostaglandins, prostacyclins, thromboxanes, and leukotrienes. Prostaglandins, along with these other arachidonic acid byproducts, can cause or exacerbate pain via their inflammatory effects and ability to sensitize peripheral nociceptors.<sup>37</sup> In addition to their anti-inflammatory effects, steroids may inhibit pain via their ability to suppress ectopic discharges from injured nerve fibers<sup>38</sup> and depress conduction in normal unmyelinated C fibers.<sup>39</sup>

**TABLE 2.** USPSTF Levels of Certainty Regarding Net Benefit

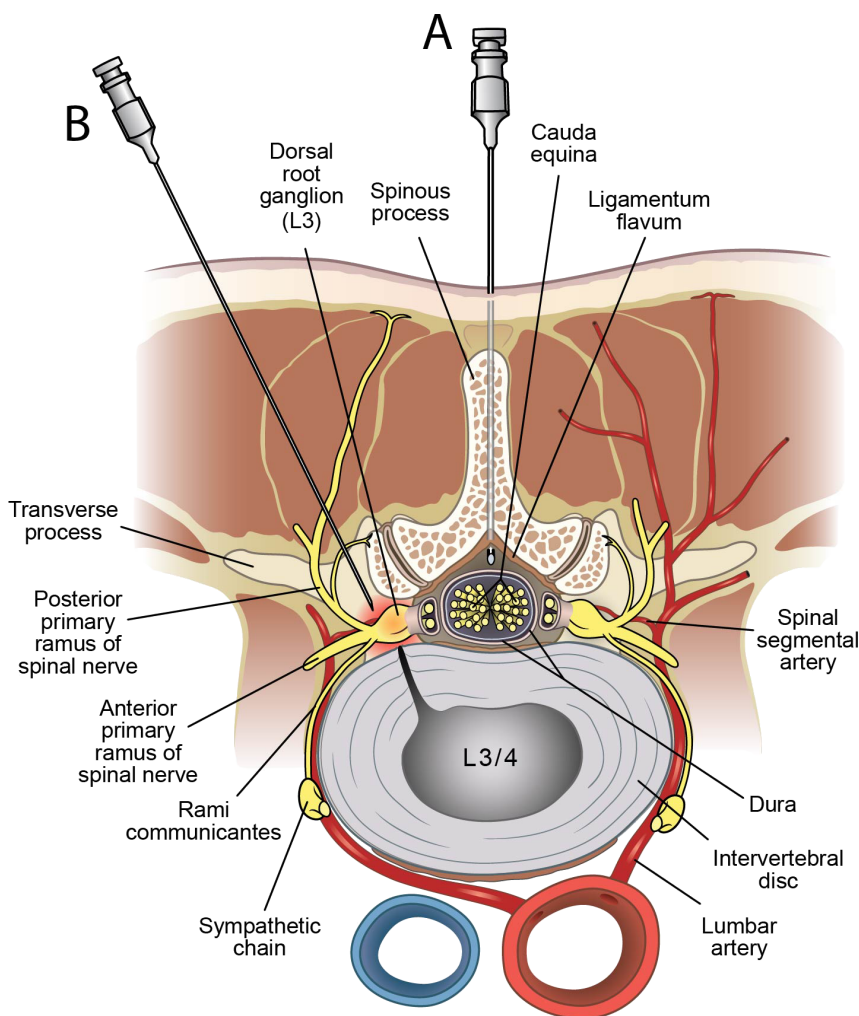
Level of Certainty	Description
High	The available evidence usually includes consistent results from well-designed, well-conducted studies in representative populations. This conclusion is unlikely to be strongly affected by the results of future studies.
Moderate	The available evidence is sufficient to determine the effects of the preventive service on health outcomes, but confidence in the estimate is constrained by such factors as: <ul style="list-style-type: none"> <li>• The number, size, or quality of individual studies</li> <li>• Inconsistency of findings across individual studies</li> <li>• Limited generalizability of findings to routine primary care practice</li> <li>• Lack of coherence in the chain of evidence.</li> </ul> As more information becomes available, the magnitude or direction of the observed effect could change, and this change may be large enough to alter the conclusion.
Low	The available evidence is insufficient to assess effects on health outcomes. Evidence is insufficient because of the following: <ul style="list-style-type: none"> <li>• The limited number or size of studies</li> <li>• Important flaws in study design or methods</li> <li>• Inconsistency of findings across individual studies.</li> <li>• Gaps in the chain of evidence</li> <li>• Findings not generalizable to routine primary care practice</li> <li>• Lack of information on important health outcomes</li> </ul> More information may allow estimation of effects on health outcomes.

Several proposed mechanisms for the beneficial effects do not involve steroids. The injection of local anesthetic can increase blood flow to ischemic nerve roots<sup>40</sup> and, similar to steroids, suppress ectopic discharges from injured neurons and slow or halt nociceptive transmission.<sup>41</sup> Moreover, the administration of saline, local anesthetic, or any nonsteroid solution can exert an analgesic effect via the washout of inflammatory cytokines and the adhesiolysis of scar tissue.<sup>42,43</sup> The effect of nonsteroid solutions was illustrated in a systematic review by Rabinovitch et al,<sup>44</sup> who found a significant correlation between epidural volume and pain relief irrespective of steroid dose in the immediate (<6 weeks;  $r = 0.80$ ,  $P = 0.002$ ) and intermediate-term (3 months to 1 year;  $r = 0.95$ ;  $P = 0.014$ ) and a trend toward significance in the short term (6 weeks to 3 months;  $r = 0.50$ ;  $P = 0.17$ ). When different volumes were used in the treatment and control groups, the effect size for ESI was 0.81, which favorably compared with the effect size when the same volumes were injected (0.07;  $P = 0.001$ ).

### EFFICACY AND TYPE OF INJECTION

The efficacy of ESI in patients is difficult to determine because of the multiple and heterogeneous factors associated

with ESI and their outcome assessment. Differences in injection route, region, control group, injectate characteristics, and patient pathology contribute to variation in outcomes and present challenges in the interpretation of existing studies regarding ESI. Yet, there is a widespread consensus across all specialties that ESI provides at least short-term benefit in well-selected patients. What is less clear is which patients are likely to benefit from the intervention, and whether they provide long-term relief. The conceptual appeal of ESI is that the relief from the procedure will allow the body the time to heal itself, without the long-term sequelae associated with central sensitization.<sup>45</sup> Greater than 70% of patients with radiculopathy will recover within 6 months,<sup>46,47</sup> and a similar proportion will experience resorption of a herniated disk within 1 year of presentation.<sup>48,49</sup> Another rationale for the use of ESI is that the evidence in support of the procedure is more robust (ie, more clinical trials showing benefit), and the risk-benefit ratio more favorable, compared with other treatments. Among randomized clinical trials evaluating surgery for neuropathic LBP and neck pain irrespective of etiology, most demonstrate temporary (ie, 6 months) but not long-term benefit.<sup>50-52</sup> For medications, the evidence is either negative or conflicting at best.<sup>53,54</sup>



**FIGURE 1.** Schematic drawing illustrating L3-4 IL (A) and TF (B) epidural needle placement in relation to anatomical structures in a patient with an L3-4 herniated disk. Adapted with permission from Rathmell.<sup>298</sup>

TABLE 3. Studies Comparing TF, IL, and Caudal ESIs

Study (Year)	Design	Subjects	Interventions	Results	Comments
Ackerman and Ahmad <sup>55</sup> (2007)	Randomized evaluator-blinded	90 Patients with S1 radiculopathy from HNP	TF: 40 mg triamcinolone + 4 mL NS IL: 40 mg triamcinolone + 4 mL NS C: 40 mg triamcinolone + 19 mL NS	TF ESI > IL ESI or caudal ESI at 24 wk	Patients with ventral epidural spread, more common in TF ESI group, had better outcomes
Candido et al <sup>56</sup> (2008)	Randomized	60 Patients with unilateral radiculopathy from HNP and DDD	TF and IL: 80 mg methylprednisolone + 1 mL NS + 1 mL 1% lidocaine	No difference between TF ESI and IL ESI up to 6 mo	Study underpowered
Gharibo et al <sup>57</sup> (2011)	Randomized	42 Patients with unilateral radiculopathy from disk disease <1 y	TF: 40 mg triamcinolone + 1 mL 0.25% bupivacaine IL: 80 mg triamcinolone + 2 mL 0.25% bupivacaine	TF ESI > IL ESI at 2-wk follow-up	Short follow-up period
Kolsi et al <sup>58</sup> (2000)	Randomized	30 Patients with sciatic or femoral neuralgia	TF and IL: 3.75 mg cortivazol + 2 mL 0.5% lidocaine	No difference between TF ESI and IL ESI up to 4 wk	TF ESI > IL ESI for initial mean pain score decrease
Kraemer et al <sup>59</sup> (1997)	Randomized	182 Patients with LBP	TF, IL, and paravertebral injections not described	TF ESI > IL ESI > paravertebral local anesthetic up to 3 mo	Intramuscular steroid injection added in saline group
Lee et al <sup>60</sup> (2009)	Randomized evaluator-blinded	192 Patients with axial LBP due to HNP or SS	TF: 20 mg triamcinolone + 4 mL 0.5% lidocaine IL: 40 mg triamcinolone + 8 mL 0.5% lidocaine	TF ESI > IL ESI up to 4 mo	TF injections received half IL ESI dose on each side. Differences between groups greater for SS patients
Rados et al <sup>61</sup> (2011)	Randomized	64 Patients with chronic unilateral lumbar radiculopathy	TF: 40 mg methylprednisolone + 3 mL 0.5% lidocaine IL: 80 mg methylprednisolone + 8 mL 0.5% lidocaine	No difference between TF ESI and IL ESI through 6 mo	TF ESI contained half the steroid dose and >50% less LA
Thomas et al <sup>62</sup> (2003)	Randomized	31 Patients with lumbosacral radiculopathy from HNP <3 mo	TF and IL: 5 mg dexamethasone in 2-mL solution	TF ESI > IL ESI up to 6 mo	Fluoroscopy used for TF ESI, while IL ESI done blindly
Lee et al <sup>63</sup> (2009)	Retrospective	233 Patients with lumbosacral radiculopathy from SS or HNP	TF small volume: 40 mg triamcinolone + 2 mL 0.5% lidocaine TF large volume: 40 mg triamcinolone + 8 mL 0.5% lidocaine IL: 40 mg triamcinolone + 8 mL 0.5% lidocaine C: 40 mg triamcinolone + 15 mL 0.5% lidocaine	Satisfaction and pain scores: TF ESI and IL ESI > caudal ESI up to 2 mo Function: TF ESI > IL ESI > caudal ESI	Functional benefits of TF ESI more pronounced at 2 wk. Injectate volumes not standardized
Manchikanti et al <sup>64</sup> (1999)	Retrospective case-control	225 Patients with LBP and leg pain	TF: 1.5-3 mg betamethasone + 1 mL 1% lidocaine IL: 120 mg depo-methylprednisolone + 10 mL 0.5% lidocaine, with 80 mg methylprednisolone on subsequent injections C: 80 mg depo-methylprednisolone + 1 mL 0.5% lidocaine	TF ESI and caudal ESI > IL ESI at 1- to 3-mo follow-up, but no difference between groups at 3- to 6- and 6- to 12-mo follow-up	Longer pain duration in caudal ESI group. Variable steroid dose in TF ESI and variable follow-up period

Schaufele et al <sup>65</sup> (2006)	Retrospective case-control	40 Patients with lumbosacral radiculopathy from single-level HNP	TF: 80 mg methylprednisolone + 1–2 mL 2% lidocaine IL: 80 mg methylprednisolone + 2–3 mL 1% lidocaine	TF ESI > IL ESI, variable follow-up period averaging 3 wk	Higher baseline pain scores in IL ESI group. Short follow-up period
Smith et al <sup>66</sup> (2010)	Retrospective case-control	38 Patients with lumbosacral radiculopathy from SS	TF: 80 mg methylprednisolone + 1–2 mL 2% lidocaine IL: 80 mg methylprednisolone + 2–3 mL 2% lidocaine	No difference between TF ESI and IL ESI, variable follow-up averaging 4–6 wk	Study underpowered
Mendoza-Lattes et al <sup>67</sup> (2009)	Retrospective case-control	93 Patients with mostly lower lumbar radiculopathy	Caudal: up to 3 injections of 2 mL of 40 mg/mL depo-methylprednisolone or 3 mL of 6 mg/mL betamethasone Transforaminal: up to 3 injections of a 1:1 solution containing 1.5–2 mL of bupivacaine 0.25% mixed with depo-methylprednisolone or betamethasone	C = TF through 2-y follow-up	16 Patients lost to follow-up. Equivalent rates of surgery between groups. Low volumes used for caudal injections. Included some patients with stenosis and spondylolisthesis

C indicates caudal; LA, local anesthetic; SS, spinal stenosis; DDD, degenerative disk disease.

Epidural steroid injections may be administered via different routes, with the 3 main categories of injection being the transforaminal (TF), interlaminar (IL), and caudal routes (Fig. 1). As shown in Table 3, a majority of studies comparing different routes of injection support the general consensus among practitioners that transforaminal ESI is superior to IL or caudal ESI.<sup>55–67</sup> Transforaminal ESI was superior to IL ESI or caudal in 5 of 8 randomized controlled trials (RCTs) comparing the 2 routes, and 3 of 5 retrospective studies. Studies failing to show benefit included that of Kolsi et al,<sup>58</sup> which nonsignificantly favored TF over IL ESI for initial pain reduction, and that of Candido et al,<sup>56</sup> which was underpowered and used a variation on the classic IL approach.

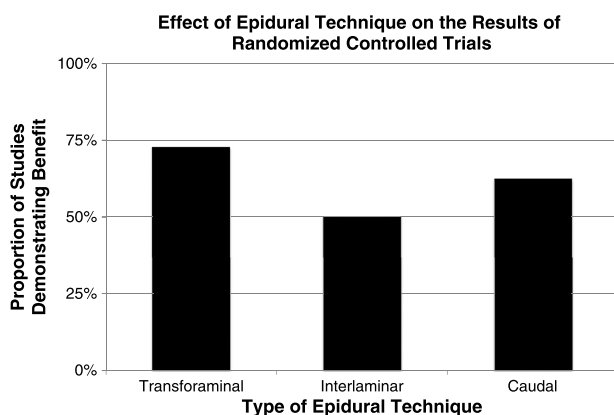
Because the injectate is administered closer to the area of pathology, one might suspect that IL ESIs are more efficacious than caudal ESI. However, a review of randomized clinical trials found that a higher proportion of controlled studies evaluating caudal ESIs were positive than those evaluating IL ESIs (Fig. 2). The likely explanation for this paradoxical phenomenon is that those studies using the caudal route of administration injected higher volumes of solution, which may itself be analgesic.<sup>44</sup> In summary, there is conflicting evidence characterized by a moderate degree of certainty that TF ESIs provide superior benefit to other approaches.<sup>2</sup> For the differences between IL ESI and the caudal approach, the evidence is too scant to draw any conclusions.

The rationale for selection of a particular ESI technique is guided by multiple factors to include radiological evidence of pathology, patient symptoms, previous surgery, demonstrated efficacy, and consideration of possible complications. The distinct advantages and disadvantages of each approach are discussed in the following sections.

### CAUDAL

The sacral hiatus provides the most caudad and direct route of entry to the epidural space and allows for the administration of steroid-based solutions for the treatment of lumbar pathology. Caudal ESIs are less targeted than either TF or IL approach in that the site of injection is not altered according to the level of pathology. Advantages of the caudal approach include a dramatically decreased incidence of dural puncture given the distance from the thecal sac, their safety in postsurgical patients who are at higher risk for both dural puncture and neurological complications related to the intravascular injection of particulate steroids, and possible increased prevalence of ventral epidural spread related to the higher volumes utilized.<sup>68</sup> Meta-analyses have provided conflicting results regarding the role of caudal ESIs in several pain conditions. Several systematic reviews have shown good (level I) evidence for both short- and long-term benefit in managing back and leg pain due to disk herniation, similar (level I) evidence for treating discogenic pain, and less compelling evidence for treating pain associated with spine surgery (level II-2) or spinal stenosis (level II-1).<sup>68–70</sup>

In addition, many practitioners use the caudal route to insert a catheter, which can then be guided up to the targeted area of pathology. When epidural lysis of adhesions is performed, most studies have utilized a caudal catheter-guided approach. In a systematic review by Racz et al,<sup>71</sup> the authors concluded there was strong evidence to support both short- and long-term relief with epidural lysis of adhesions, when repeated interventions are permitted. For lumbar herniated disk, the evidence was moderate for short- and long-term improvement. Of note, most,<sup>72,73</sup> but not all,<sup>74</sup> studies have demonstrated a poor correlation between pain and extent of adhesions. Overall, caudal ESIs are best supported in the treatment of radicular symptoms due to disk



**FIGURE 2.** Effect of epidural technique on the results of randomized controlled trials. 1. Based on all randomized, placebo-controlled studies performed since 1970, as cited in PubMed and EMBASE.<sup>16,99,104,136,137,145,146,166-168,171-182,299-308</sup> 2. Benefit tabulated at initial visit for primary outcome measure.

herniation and previous surgery and carry an extremely low risk of inadvertent dural puncture.

### INTERLAMINAR

Interlaminar ESI can be performed at all levels of the spine and involve passage of a needle through the ligamentum flavum to deliver medication. Similar to caudal ESIs, IL ESIs have been studied extensively regarding their role in radicular pain due to disk herniation, pain due to spinal stenosis, axial back pain in the absence of disk herniation, and failed back surgery syndrome. In addition, IL ESIs have also been studied in pain conditions involving the thoracic and cervical spine. Advantages of this technique include the increased likelihood that injected medication will reach adjacent spinal levels, the ability to treat bilateral pain, and the need for a lower volume of medication when compared with caudal ESIs. Disadvantages include the potential for dural puncture and deposition of medication into the dorsal epidural space, which is more distant from the site of pathology, although 1 prospective study demonstrated a 100% incidence of ventral epidural flow using a parasagittal IL approach.<sup>56</sup>

### Lumbar Interlaminar

Regardless of whether they have excluded studies in which IL ESIs were performed blindly, systematic reviews of IL ESIs in the lumbar region have yielded similar results. On balance, there appears to be good evidence for the treatment of radicular pain due to disk herniation and somewhat weaker evidence for treatment of spinal stenosis, discogenic pain, and postsurgical pain.<sup>75-77</sup> However, there is some diversity in the literature as is evidenced by some reviews that conclude there is good evidence for treating spinal stenosis,<sup>78</sup> whereas others show an unclear benefit for all conditions to include radicular pain.<sup>79,80</sup>

### Thoracic Interlaminar

Pain arising from the thoracic region of the spine is less prevalent than pain in either the neck or low back.<sup>81,82</sup> Thoracic IL ESIs are therefore less commonly performed than either the lumbar or cervical approaches and consequently have been less studied. In addition to spinal pain, there is strong evidence (level I) to support the use of intrathecal steroids for postherpetic neuralgia (PHN), and moderate evidence in favor of the

early use of ESI in acute herpes zoster to prevent PHN.<sup>83</sup> For the latter, a randomized controlled study demonstrated a decreased incidence of PHN in patients with acute zoster who received ESI compared with a control group who received parenteral acyclovir and steroids,<sup>84</sup> whereas a similarly designed study demonstrated a lower incidence at 1 month, but not 3 or 6 months after injection.<sup>85</sup> The sole review on the subject notes the paucity of literature but does report fair evidence for treatment of both pain due to thoracic disk herniation and disk degeneration.<sup>86</sup>

### Cervical Interlaminar

Systematic reviews of cervical IL ESIs have provided mixed evidence for their use in treating cervical radicular pain. Reviews published by the American Society of Interventional Pain Physicians conclude there is good evidence for radiculopathy secondary to a herniated disk (level I), and fair evidence for spinal stenosis, discogenic pain, and failed neck surgery syndrome (level II-1).<sup>87,88</sup> An evidence-informed review by Stout<sup>89</sup> concluded that cervical ESIs are probably effective in the short term, but that definitive evidence is lacking. The author further noted that the evidence is stronger for herniated disk and non-ossesous central stenosis than it is for foraminal or osseous stenosis and that ESI should not be a first-line treatment. Another evidence-informed review by a surgical task force found that cervical ESIs are probably effective for cervical radicular pain in the short term, but that evidence supporting long-term relief is lacking.<sup>90</sup>

Overall, the bulk of recent evidence supports a primary indication for lumbar, thoracic, or cervical IL ESIs of radicular pain due to disk herniation. In the lumbosacral region, the IL approach should be considered in patients with bilateral symptoms or multiple affected spinal levels who have not had spinal surgery. In light of the increased risk for complications stemming from TF ESI performed in the upper lumbar, thoracic, or cervical regions, IL ESI should always be the first-line injection treatment in these areas.

### TRANSFORAMINAL

Similar to IL ESI, the TF epidural approach can be utilized in lumbar, thoracic, and cervical spinal levels, but unlike the IL technique, it can also be performed at sacral levels. The TF injection technique involves the placement of a needle within a neuroforamen, does not require a loss-of-resistance technique, and must be performed with fluoroscopic guidance. The TF approach has several theoretical advantages over other routes of injection in that it is the most target-specific, carries a lower risk of inadvertent dural puncture,<sup>91</sup> and is associated with a greater incidence of ventral epidural spread, especially with placement of the needle in the anterior foramen.<sup>92</sup> However, TF ESIs are also associated with an increased risk profile compared with the caudal and IL approaches. In addition, although there is some evidence for better efficacy compared with caudal and IL ESI,<sup>93</sup> their efficacy in neuropathic spinal pain (NSP) still remains controversial.

### Lumbar Transforaminal

Systematic reviews are hampered by significant heterogeneity but have generally found good evidence supporting short-term relief and mixed evidence in favor of long-term benefit for TF ESIs in treating back pain with radicular symptoms due to disk herniation.<sup>94-96</sup> One recent review found good evidence for the treatment of radicular pain secondary to disk herniation, but only fair or limited evidence for the treatment of spinal

stenosis, postsurgical pain, or axial pain in the absence of disk herniation.<sup>97</sup> Reviews dedicated specifically to either spinal stenosis or postsurgical pain are lacking. Subgroup analyses in several clinical studies have shown either comparable benefit in patients with herniated disk and spinal stenosis<sup>63,98</sup> or only a small benefit in favor of herniated disk.<sup>99</sup> In a comprehensive review by members of the International Spinal Intervention Society (ISIS), the authors concluded that a “substantial proportion” of patients with lumbar radicular pain caused by a contained disk herniation will experience an improvement in pain, function, decreased health care utilization, and a reduced need for surgery following treatment with TF ESI. They found that the evidence was stronger for treating a herniated disk(s) than for spinal stenosis and that the evidence was more compelling when all of the published data were considered than if only a systematic review evaluating RCTs was performed.<sup>100</sup>

### Cervical and Thoracic Transforaminal

The TF approaches to the cervical and thoracic spine are less studied than their lumbar counterpart, and the literature abounds with case reports and reviews detailing the potentially catastrophic complications associated with these approaches.<sup>101–103</sup> Systematic reviews are lacking, and available studies are mostly of the nonrandomized or retrospective variety.

The lone randomized, controlled study for the cervical approach showed positive results in patients with radicular pain, but lacked a pure placebo group.<sup>104</sup> Multiple nonrandomized studies have shown both short-term<sup>105</sup> and long-term benefits with single and repeat injections<sup>106–108</sup> in treating cervical radiculopathy.

Among all injection types, TF thoracic ESIs are the least represented in the literature. One large retrospective study showed a high rate of short-term pain relief (88.5%) but was primarily designed to investigate complication rates and included patients with diverse pain complaints to include disk herniation, spondylosis, spinal stenosis, postsurgical pain, and degenerative disk disease.<sup>109</sup>

Overall, the literature suggests that although the TF approach may be more efficacious than the IL or caudal approaches, the difference in effect size is small. In the cervical, thoracic, and midlumbar to high lumbar regions, the increased risk for catastrophic neurological complications should preclude the use of TF ESI as a first-line treatment.<sup>110,111</sup> In the lumbar region, TF may be considered as a first-line treatment in patients with a history of back surgery who are at increased risk for postdural puncture or who possess focal pathology with correlating unilateral symptoms, although prior surgery may increase the likelihood of intravascular injection.

### EFFECT OF REGION

The region of injection for ESI may influence outcomes, with the 3 primary sites consisting of the cervical, thoracic, and lumbar areas. For cervical ESI, a best-evidence synthesis by Carragee et al<sup>90</sup> found support for short-term improvement of radicular symptoms, whereas a narrative review by Huston<sup>112</sup> concluded that although pathophysiological studies supported the use of cervical ESI, more RCTs were needed to evaluate effectiveness. Since publication of these reviews, 3 RCTs failing to show benefit have been published by the same group of investigators.<sup>113–115</sup> To date, only 1 randomized clinical trial evaluating thoracic ESI has been published, which found no significant difference between epidural steroids and epidural local anesthetic, with both groups demonstrating significant improvement through 12-month follow-up.<sup>116</sup> However, anecdotal

reports suggest comparable benefit for lumbar and cervical procedures.<sup>117</sup>

The lumbar region represents the focus of most of the ESI region-specific literature, with the strength of evidence found in systematic reviews growing over recent years. Some reviews found a lack of evidence to support lumbar ESI due to myriad limitations including poor study quality,<sup>118</sup> poor technical quality of injections,<sup>75</sup> and inclusion of non-ESI injection therapy in the analyses.<sup>80</sup> In contrast, most recent systematic reviews of lumbar ESI report positive findings, from fair to good evidence,<sup>76,96</sup> level 1 evidence,<sup>68</sup> level II-1 and II-2 evidence,<sup>68,94</sup> and moderate evidence.<sup>119</sup>

### EFFECT OF CONTROL GROUP

Efficacy of ESI depends in part on the type of control injection used for comparison. Epidural steroid injection “control groups” in the literature include epidural saline or local anesthetic injections (epidural nonsteroid) and intramuscular or ligamentous injections of corticosteroid, local anesthetic, or saline (nonepidural injection). In indirect comparisons, epidural nonsteroid injections have been demonstrated to provide superior benefit compared with nonepidural injections on at least some outcome measures.<sup>120</sup> This observation is not unique to epidural treatment but is conjectured to be applicable to other therapeutic injections as well.<sup>121</sup> Hence, when a control group consists of epidural nonsteroid injections instead of nonepidural injections (ie, a comparative-effectiveness study), because in essence 2 treatments are being compared (rather than a treatment and a placebo), more patients are needed to detect a difference. This suggests that a large proportion of clinical trials evaluating ESI were underpowered.

### EFFECT OF DOSE AND INJECTATE

Characteristics of the injectate also differ among studies and may impact patient outcome as shown in Table 4. Both the dose and volume of steroid may vary depending on the route of injection, with amounts of each typically increasing as TF, IL, and caudal ESI are performed, respectively. The effect of the dose of steroid for ESI has been examined in 2 randomized studies. In the first study by Owlia et al,<sup>122</sup> an IL ESI dose of 40 mg of methylprednisolone provided a similar reduction in pain with fewer adverse effects compared with 80 mg. A second randomized, double-blind study by Kang et al<sup>123</sup> evaluating the effect of steroid dose during TF 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.

As alluded to earlier, Rabinovitch et al<sup>44</sup> concluded there was an independent, beneficial effect for volume, as the use of higher volumes may result in pain relief in and of itself. A randomized study by Revel et al<sup>124</sup> 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.

### EFFECT OF TYPE OF STEROID

Data evaluating different types of steroid injections are mostly limited to underpowered randomized or retrospective studies comparing particulate to nonparticulate steroids. Among the 3 randomized comparative-effectiveness studies comparing different steroid preparations, 2 reported a nonsignificant benefit in favor of the depo-steroid group,<sup>125,126</sup> with only the largest finding a statistically significant difference for depo-steroids.<sup>127</sup>

**TABLE 4.** Randomized Studies Comparing Different Steroid Mixtures and Approaches for ESI

Study (Year)	Design	Subjects	Interventions	Results
<b>Studies comparing different doses of steroids</b>				
Owlia et al <sup>122</sup> (2007)	Randomized case-matched for age/sex	84 Patients with lumbar radiculopathy from HNP	IL ESI with methylprednisolone 40 mg or 80 mg + 2–4 mL 2% lidocaine	No significant difference between groups for pain improvement. Fewer complications in low-dose group
Kang et al <sup>123</sup> (2011)	Randomized double-blind	160 Patients with lumbar radiculopathy from HNP	Two TF ESI at 1-wk intervals of triamcinolone 5, 10, 20, or 40 mg	Significant pain reduction in all groups except 5 mg after first injection. Nonsignificant trend of better pain reduction with increasing dose after second injection
Revel et al <sup>124</sup> (1996)	Randomized	60 Patients with lumbosacral pain from failed back surgery syndrome	Caudal ESI with either: A. Prednisolone 125 mg in 5 mL alone B. Prednisolone 125 mg in 5 mL + 40 mL normal saline	High-volume injection > low volume for pain reduction at 18 mo
<b>Studies comparing different types of steroids</b>				
Dreyfuss et al <sup>126</sup> (2006)	Randomized	30 Patients with unilateral cervical radiculopathy	TF ESI with 0.75–1 mL 4% lidocaine + either: A: Dexamethasone 12.5 mg B: Triamcinolone 60 mg	Nonsignificant trend favoring particulate steroid
Lee et al <sup>105</sup> (2009)	Retrospective	159 Patients with cervical radiculopathy who failed IL ESI or had previous surgery	TF ESI with either: A: Dexamethasone 10 mg B: Triamcinolone 40 mg	Nonsignificant trend favoring particulate steroid
Kim and Brown <sup>125</sup> (2011)	Randomized single-blind	60 Patients with lumbar radiculopathy ≥6 mo	IL ESI with 10 mL consisting of 2 mL 0.25% bupivacaine + NS + either: A: Dexamethasone 15 mg B: Methylprednisolone 80 mg	Nonsignificant trend favoring particulate steroid
Park et al <sup>127</sup> (2010)	Randomized	106 Patients with lumbar radiculopathy	TF ESI with 1 mL 1% lidocaine + either: A: Dexamethasone 7.5 mg B: Triamcinolone 40 mg	Particulate > nonparticulate steroid for pain reduction
Noe and Haynsworth <sup>128</sup> (2003)	Retrospective	52 Patients with LBP referred for ESI	IL ESI with either: A: Betamethasone 15 mg B: Methylprednisolone 80 mg	Particulate > nonparticulate steroid for pain reduction, improvement in disability
Shakir et al <sup>129</sup> (2013)	Retrospective	441 Patients with cervical radiculopathy	TF ESI with 1 mL of 1% lidocaine + either: A: Dexamethasone 15 mg B: Triamcinolone 40 mg	No difference in pain score reduction between groups
<b>Studies comparing different injection levels</b>				
Jeong et al <sup>98</sup> (2007)	Randomized single-blind	239 Patients with lumbosacral radiculopathy from HNP or SS scheduled for 1 level TF ESI from L1 to S1	TF ESI with 40 mg triamcinolone + 0.5% 0.5 mL Bupivacaine, at either location: A: Ganglionic—at location of exiting nerve root B: Preganglionic—at supra-adjacent intervertebral disk	Nonsignificant trend favoring preganglionic > ganglionic at 1 mo, but no differences at 6-mo follow-up
Lee et al <sup>309</sup> (2006)	Retrospective	33 Patients with lumbar radiculopathy receiving on level TF ESI from L1 to S1	TF ESI with triamcinolone 40 mg + 0.5 mL 0.5% bupivacaine using either A. Conventional approach B. Preganglionic approach (1 level above conventional approach)	Preganglionic TF ESI trends toward but is not significantly better than conventional approach at 2-wk follow-up

SS indicates spinal stenosis.

In the 3 retrospective studies, one found depot steroids was statistically better than non-depo-steroids,<sup>128</sup> one showed a trend toward superiority for depo-steroids over non-depot steroids in patients with cervical radiculopathy,<sup>105</sup> and another found no difference between depo- and non-depo-steroids for cervical TF ESI.<sup>129</sup> In summary, there is conflicting evidence with a low degree of certainty that depo-steroids provide superior relief compared with nondepot steroids.<sup>2</sup>

### EFFECT OF UNDERLYING PATHOLOGY

The efficacy of ESI varies in accordance with the underlying pathology causing NSP. The numerous and diverse conditions that result in spinal pain mandate the use of stringent inclusion criteria for ESI studies to provide clinically meaningful information regarding efficacy, although studies seeking to determine effectiveness may utilize more pragmatic selection criteria that reflect clinical practice. Lumbar herniated nucleus pulposus (HNP) represents the most commonly studied condition, with the most recent and comprehensive systematic reviews demonstrating good<sup>76</sup> and level I<sup>68</sup> evidence supporting the role of ESI, particularly for short-term relief of pain. For intermediate- and long-term benefit (>3 months), the benefit is significantly smaller and may well represent the effect of disease evolution.<sup>130,131</sup> A more limited set of evidence exists for the effectiveness of ESI for other pathology. Some reviews have reported that the evidence for ESI in spinal stenosis is less robust than for herniated disk, but greater than that for failed back surgery syndrome and axial back pain.<sup>97,132,133</sup> However, in clinical studies and subgroup analyses from placebo-controlled trials, some<sup>60,99,134,135</sup> but not all<sup>63,98,136,137</sup> studies have demonstrated better results for herniated disk than spinal stenosis. In a study that sought to identify radiological outcome predictors for cervical ESI, those patients with central stenosis experienced greater benefit than individuals with herniated disk, neuroforaminal stenosis, or nerve root compression.<sup>138</sup>

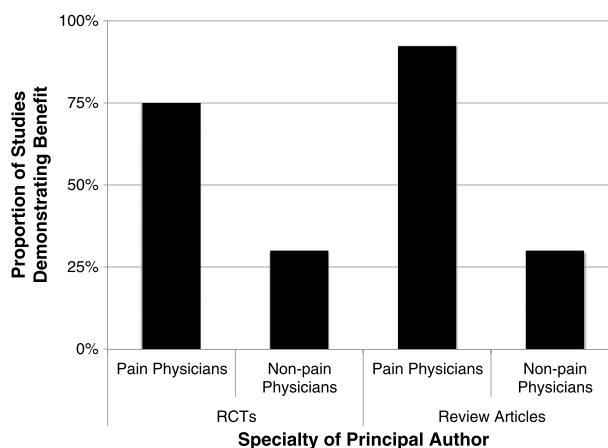
### EFFECT OF SPECIALTY

The influence that the medical specialty of the investigators has in both the interpretation of existing data (ie, systematic reviews) and on the generation of data (ie, results of clinical trials) is extensive. Studies performed by interventionalists are approximately 3 times more likely to report a positive result than those conducted by noninterventionalists. For the evaluation of clinical trials in the form of review articles, the discrepancy is both more pronounced and difficult to reconcile, as different groups evaluating the same data using the same or similar methodological rating schemes have reached different conclusions. There are multiple reasons for these inconsistencies, which include confirmation bias,<sup>139</sup> dissemination bias (ie, publication bias for specialty journals and selective reporting),<sup>140</sup> a better ability of specialists to evaluate selection criteria and technical proficiency, and perhaps even secondary gain (Fig. 3 and Table 5).

### IDEAL NUMBER OF INJECTIONS

There are no clinical trials examining the ideal number of ESI. Numerous guidelines have determined that there is no basis to perform a set series of repeated injections without regard to response, but rather that the number of ESI should be individually tailored to clinical response.<sup>141–143</sup>

Novak and Nemeth<sup>144</sup> performed a literature review in an effort to determine the ideal frequency and timing of ESI. They found that although repeat injections tended to be the norm, there was no evidence to support the practice of a routine series



**FIGURE 3.** Effect of author specialty on the results of randomized controlled trials and systematic review articles.

RCTs based on a search for all randomized, placebo-controlled studies performed since 1970, as cited in PubMed and EMBASE.<sup>16,99,104,136,137,145,146,166–168,171–182,299–308</sup>

Reviews based on a search for all systematic reviews since 2000, as cited in PubMed and EMBASE.<sup>68,69,75–77,80,87,88,90,94–97,118,119,130,131,133,310–314</sup>

Study stratification based on primary author specialty, with anesthesiology or physical medicine and rehabilitation representing pain physicians, and all other specialties representing nonpain physicians. Benefit tabulated at initial visit for primary outcome measure. Percentage of positive ESI studies and review articles stratified by specialty based on first author affiliation. When multiple controlled studies were performed by the same group of authors reported the same results (ie, Manchikanti et al<sup>184,186,191</sup>), only one from each category was counted (eg, 1 negative caudal, 1 negative lumbar IL, and 1 negative cervical IL injection).

of injections. However, the strategic use of repeat injections may enhance outcomes in certain contexts. In a narrative review by Roberts et al,<sup>96</sup> the authors noted that among the 4 level I (randomized controlled) studies evaluated, the 2 that allowed for more than 1 injection reported positive outcomes,<sup>55,136</sup> whereas the 2 studies that limited the number of injections to 1 injection reported negative outcomes.<sup>145,146</sup> The guidelines published by the American Academy of Physical Medicine and Rehabilitation and ISIS both state that if additional injections are warranted, they should be separated by at least a 2-week interval to enable assessment of the full response and to minimize adverse effects such as adrenal suppression.<sup>141,142</sup> In a comprehensive review by MacVicar et al,<sup>100</sup> the authors found that 94% of patients achieve a successful outcome after 1 injection, with only 4% of individuals requiring more than 1 treatment.

### COMPARATIVE-EFFECTIVENESS STUDIES

There have been few comparative-effectiveness studies comparing ESI to other treatments, and only 1 in which patients were purportedly blinded. In an underpowered 6-month study by Koc et al,<sup>147</sup> the authors randomized 29 patients with lumbar spinal stenosis to receive either a high-volume ESI, 2 weeks of physical therapy, or a control group that received no treatment. At follow-up, all groups improved in most measures, with the only statistically significant differences being noted at 2 weeks between the ESI and noninjection groups for pain and function.

In a similar study by Laiq et al,<sup>148</sup> the authors randomized 50 patients with lumbar spinal stenosis to receive either

**TABLE 5.** Review Articles Evaluating ESIs Stratified by Specialty

Study (Year)	Type of Review	Type of Epidural	Primary Author Specialty	Conclusions
Staal et al <sup>80</sup> (2009)	Systematic	Lumbar	Epidemiology	There is limited to moderate evidence that ESIs are not better than placebo or other treatments for pain relief or disability.
Ranquis et al <sup>310</sup> (2010)	Systematic	Perioperative lumbar	Neurosurgery	ESIs reduce postoperative pain and analgesic consumption, and risk of not returning to work, but do not affect quality of life.
Armon et al <sup>131</sup> (2007)	Systematic	Lumbar	Neurology	ESI do not impact function, decrease rate of surgery, or provide pain relief for >3 mo.
Carragee et al <sup>90</sup> (2008)	Systematic	Cervical	Orthopedic surgery	There is support for short-term, but not long-term symptomatic improvement of radicular symptoms with epidural corticosteroids.
Karnezis <sup>311</sup> (2008)	Evidence-based	Lumbar	Orthopedic surgery	Epidural steroid injections may provide only short-term relief from pain in lumbar radiculopathy but have no long-term effect.
Deyo et al <sup>312</sup> (2009)	Narrative	Lumbar	Internal medicine	Increases in expenditures for ESI are not accompanied by improvements in patient outcomes.
Roberts et al <sup>96</sup> (2009)	Systematic	Lumbar	Physical medicine	Fair evidence supporting TF ESIs for treatment of radicular symptoms, good evidence for surgery sparing. Transforaminal ESIs are superior to IL ESI for radicular pain.
Benny and Azan <sup>95</sup> (2011)	Systematic	Lumbar TF	Physical medicine	There is strong evidence for TF ESI for both short-term and long-term relief.
Balagué et al <sup>315</sup> (2012)	Narrative	Lumbar	Rheumatology	Although there are some biological and animal data in favor of corticosteroids for LBP and sciatica, clinical evidence remains scarce. However, ESIs can have some short-term benefit.
Rho and Tang <sup>316</sup> (2011)	Narrative	Lumbar	Physical medicine	There is strong evidence to support the use of TF ESI for radicular pain caused by HNP or spinal stenosis. There is evidence for IL and caudal ESI, but less than for TF ESI.
Quraishi <sup>313</sup> (2012)	Systematic and meta-analysis	Systematic	Surgery	Appropriately performed TF ESI should result in short-term improvement in pain, but not disability. The addition of steroids provides no additional benefit to local anesthetic.
Eckel and Bartynski <sup>317</sup> (2009)	Narrative	Lumbar and cervical	Interventional radiology	Epidural steroid injections are highly effective in a large proportion of patients, including patients with axial pain (neck or LBP), radiculopathy, or spinal stenosis with neurogenic claudication.
Diwan et al <sup>88</sup> (2012)	Systematic	Cervical	Anesthesiology	The evidence is good for cervical ESI for HNP with radiculitis.
Manchikanti et al <sup>97</sup> (2012)	Systematic	Lumbar TF ESI	Anesthesiology	The evidence is good for TF ESI for HNP with radiculitis and fair for spinal stenosis.
Benyamin et al <sup>76</sup> (2012)	Systematic	Lumbar IL	Anesthesiology	The evidence is good for lumbar IL ESI for HNP with radiculitis and fair for spinal stenosis.
Parr et al <sup>69</sup> (2012)	Systematic	Caudal	Anesthesiology	Good evidence for short- and long-term relief for HNP with radiculitis and fair evidence for spinal stenosis, failed back surgery syndrome, or axial pain.
MacVicar et al <sup>100</sup> (2013)	Comprehensive	Lumbar TF ESI	Physical medicine/ISIS	In a substantial proportion of patients with lumbar radicular pain caused by contained disk herniations, lumbar TF injection of corticosteroids is effective in reducing pain, restoring function, reducing the need for other health care, and avoiding surgery.

high-volume ESI or conservative treatment with bed rest, non-steroidal anti-inflammatory drugs (NSAIDs), muscle relaxants, and opioids. Although the steroid group experienced greater pain relief and higher satisfaction scores at 2 weeks and 1 month,

no significant differences were noted at later time points. When evaluating the 1-month data, a significant flaw that needs to be considered is that the conservative group received suboptimal noninterventional treatment, as neither bed rest nor NSAIDs or

muscle relaxants are effective for neuropathic pain.<sup>149</sup> Whereas opioids may provide short-term relief, only a small proportion of individuals will experience long-term benefit.<sup>150</sup>

In the only double-blind, comparative-effectiveness study evaluating ESI, Brown<sup>151</sup> randomized 38 patients with spinal stenosis to receive either ESI or minimally invasive lumbar decompression. Throughout the 12-week follow-up, those patients receiving minimally invasive lumbar decompression experienced greater improvements in neurogenic claudication and disability than those who underwent ESI. Limitations in this study include the questionable effectiveness of blinding and the fact that only a single IL ESI was utilized.

In a randomized, unblinded multicenter study by Gerszten et al<sup>152</sup> performed in 85 patients with radiculopathy, the authors found that percutaneous plasma disk decompression was superior to ESI for pain, function, and quality of life throughout the 2-year follow-up period. However, an inclusion criterion for this study was that all patients already failed a trial with at least 1 ESI. Finally, Buttermann<sup>153</sup> randomized 100 patients with a large herniated disk and radicular symptoms to receive either open discectomy or ESI. Both groups improved, with the decrease in leg pain, but not back pain, reaching statistical significance in favor of the surgery group through 6 months. After 6 months, no differences were noted between groups. Whereas 27 patients who received the ESI crossed over to surgery, 46% did not, suggesting a surgery-sparing effect.

Overall, these findings are consistent with systematic reviews that have found at least moderate evidence for short-term but inconsistent evidence supporting long-term benefit.<sup>90,130,131</sup> Another factor that must be considered when evaluating open-label comparative-effectiveness studies is that the placebo response rate is likely to be significantly higher for injections than it is for noninterventional therapies.<sup>154</sup>

### COST-EFFECTIVENESS

In the current era characterized 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. The cost-effectiveness of any intervention is heavily dependent on utilization patterns and selection criteria. Selecting patients for any interventional procedure characterized by a modest likelihood of success without proper screening (ie, performing ESI on all patients with back pain) is likely to tip any cost-benefit analysis in the direction of costs, while withholding a relatively safe and inexpensive treatment that might facilitate return to work or prevent surgery, can reduce cost-effectiveness. The likelihood of returning to work full-time declines nearly exponentially with time in patients with new onset of back pain with or without radicular pain, and those remaining out of work for more than 3 months are unlikely to return to work regardless of the intervention.<sup>155</sup> Consequently, core domain outcome measures for chronic pain, as identified by a multidisciplinary group of academic, industry, and government-designated specialists, do not even include return to work as a potentially achievable outcome.<sup>156</sup> Because of the high costs of surgery, health care utilization, disability, and lost productivity, any cost-benefit analysis for ESI is to a large extent contingent on reducing alternative health care utilization (eg, surgery and health care provider visits) and expediting or enhancing return to work.

### PREVENTION OF SURGERY

One outcome that can greatly affect the balance of the cost-effectiveness analysis of any intervention is the need for surgery.

Even for neuropathic pain, the surgical rate and the proportion of spine surgeries requiring fusion or instrumentation are higher in the United States than in any other country.<sup>157,158</sup> In large-scale epidemiological studies, a direct correlation between spine surgery rates and ESI has been found,<sup>159</sup> although this is likely attributable to resource utilization patterns.

There has only been 1 randomized study evaluating the ability of ESI to affect surgery rate as a primary outcome.<sup>136</sup> In a double-blind study, an orthopedic spine group compared the operative rate in patients with herniated disk or spinal stenosis who were randomized to receive a series of either lumbar TF ESI or epidural bupivacaine. At follow-up periods ranging between 13 and 28 months, 29% of patients in the treatment group underwent surgery, which favorably compared with a 67% operative rate in the control group. At subsequent 5-year follow-up, most patients who had avoided surgery for the initial year continued to avoid surgery.<sup>160</sup> All 8 patients lost to follow-up at 5 years who had initially avoided surgery received TF ESI, making comparisons at that time interval difficult. In another randomized study by an orthopedic spine group, Rasmussen et al<sup>161</sup> found that that ESI performed after surgery enhanced recovery, decreased hospital stay, and reduced postoperative neurological impairment for up to 2 years following discectomy for HNP, although no difference in reoperation rates was noted. In an analysis of data from the multicenter, randomized SPORT study comparing surgery to nonsurgical treatment for herniated disk, fewer patients who received ESI within 3 months of enrollment 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.<sup>162</sup> For a subgroup analysis performed in patients with spinal stenosis, conflicting findings were noted. Among those patients who received ESI during the first 3 months of enrollment, more patients expressed a preference for nonsurgical treatment (62% vs 33%), and a higher percentage allocated to surgery crossed over to the nonsurgical care (33% vs 11%), than those individuals who were not treated with ESI.<sup>163</sup> However, in the nonsurgical group, more patients who received an ESI crossed over to surgery than those who did not (58% vs 32%). Along with the controlled studies, several uncontrolled studies performed by spine surgeons evaluating surgery as a primary outcome measure have also found a surgery-sparing effect for ESI.<sup>164,165</sup> In contrast, the large majority of randomized controlled studies evaluating surgery rates as a secondary outcome measure failed to find a difference in operative rates between ESI and placebo treatment,<sup>99,137,145,146,166–178</sup> compared with the few that did.<sup>179,180</sup>

The difficulty in evaluating surgery rates as a secondary outcome is that nearly all studies are underpowered to detect a difference and incorporate some degree of bias through patient selection. Many patients who receive ESI are either poor surgical candidates or do not want surgery, so that even an effective treatment may not be able to demonstrate a decrease in surgery rates. Others who are referred from surgery for a temporizing intervention and do have serious surgically amenable pathology may be on a predestined course in which operative treatment is a foregone conclusion. To be able to detect a difference in operative rates and reduce bias, one needs patients with surgically treatable pathology, who are considering surgery but would prefer a less invasive treatment option. The ideal setting to recruit such patients would be a spine surgery center, where the operative criteria can be standardized, and an effective intervention has a reasonable chance to alter the decision-making process. It is not surprising then that the studies suggesting ESI can prevent surgery have been performed by surgeons.

## RETURN TO WORK

There are several obstacles in evaluating return-to-work data, with the major one being the extremely low likelihood of anyone who has been out of work for more than 1 year returning to work full-time. Nevertheless, several investigators have evaluated either return to work or missed work days as a secondary outcome, which in essence means all studies have been underpowered to detect a difference. Not surprisingly, a majority of 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.<sup>146,166,167,178,179</sup> Yet, some studies suggest that in well-selected patients, ESI may improve work status. More patients returned to work in the ESI group than in the control group in several randomized studies (63% vs 25% in Breivik et al,<sup>181</sup> 54% vs 40% in Kraemer et al,<sup>174</sup> and 53% vs 33% in Rogers et al<sup>182</sup>), 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 ESI, Price et al<sup>169</sup> found no significant difference in the proportion of subjects unable to return to work 1 year after treatment (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).

## HEALTHCARE UTILIZATION

Beyond the need for surgery and return to work, further evaluation of health care utilization following ESI results in few direct measurements, and to date, an advanced search of The Cochrane Library yields no relevant economic evaluations of ESI.<sup>183</sup> Investigators looking for a reduction in opioid intake following ESI have met with mixed results, as both ESI and control injections typically result in a decline in analgesic intake.<sup>86</sup> When controlling for diagnosis, randomized comparative-effectiveness studies have found that ESIs reduce opioid intake for within-group but not between-group comparisons in patients suffering from HD with radiculitis,<sup>184,185</sup> failed back surgery syndrome,<sup>114,186</sup> discogenic spine pain,<sup>187,188</sup> and lumbosacral spinal stenosis.<sup>189-191</sup> Studies evaluating the ability of ESI to reduce health care utilization as a secondary outcome measure have also yielded conflicting results. A randomized controlled study by Karppinen et al<sup>146</sup> found no overall difference in health care costs between treatment and control groups, although the steroid group had lower medication and therapy costs at 4-week follow-up. Similar secondary analyses of other controlled studies have found either no difference<sup>166,167,179</sup> or only small, non-significant differences<sup>168</sup> in the utilization of other treatments. The economic analysis of a large, randomized trial by Price and colleagues<sup>169</sup> concluded that ESIs do not provide good economic value in as much as the cost per quality-adjusted life-year for the treatment from the perspective of both the provider and purchaser exceeds the implied thresholds outlined in the National Institute for Health and Clinical Excellence technology appraisal. These findings are consistent with a cost-minimization analysis performed by Straus,<sup>192</sup> which concluded that unlike spinal cord stimulation, ESIs performed under fluoroscopy may not be justified. To date, no studies have directly measured cost utilization outcomes in association with ESI in a controlled fashion. However, extrapolation of an indirect analysis showing that patients with neuropathic pain (44% of whom had radiculopathy) who were managed primarily in pain clinics had significantly fewer emergency room and doctor visits and lower hospitalization costs, compared with those managed by primary care providers or other specialists, suggests that procedural

interventions could reduce health care utilization when appropriately utilized.<sup>193</sup> Further studies aimed at evaluating cost-effectiveness not only for ESIs but also for other procedures are warranted.

## FACTORS ASSOCIATED WITH TREATMENT OUTCOME

### General Factors

In view of the discrepancies between clinical experience and clinical trials, as well as the obstacles faced when designing efficacy studies evaluating ESI, clinicians and researchers have turned their attention toward identifying predictive factors associated with both NSP and ESI outcomes. Although daunting, if NSP patients could be stratified according to phenotypic variables linked to positive (and negative) outcomes following a trial of ESI, treatment could be better tailored to enhance efficacy and cost-effectiveness. A wealth of clinical and experimental data is emerging, but its interpretation remains difficult.

Neuropathic spinal pain is a challenging condition for both primary care providers and specialists in that treatment outcomes are often disappointing,<sup>194,195</sup> even in light of attempts to develop a more focused therapeutic approach.<sup>196,197</sup> Part of this difficulty arises from the general nature of the umbrella term "neuropathic pain," with different recommendations having been issued for different subsets of patients.<sup>198</sup> Even within specific diagnostic categories, substantial predictive variability persists. This variability likely results from the heterogeneity of neuropathic pain mechanisms, concomitant pain generators, and co-existing psychosocial issues.<sup>199</sup>

In patients with NSP, important predictors of outcome include age, measures of disease burden, socioeconomic factors (eg, job satisfaction), and psychopathology. Not only is there a higher risk of developing NSP with increasing age, but older patients tend to experience worse outcomes than their younger counterparts.<sup>200</sup> Proposed explanations for this phenomenon include a greater likelihood of comorbidities, multiple pain generators, and polypharmacy.<sup>201</sup> This effect is independent but amplified by the possible lower degree of efficacy for ESI in spinal stenosis compared with herniated disk.<sup>93,97</sup> Because of the increased risk for adverse pharmacological effects in this cohort, an argument can be made for interventional therapy.

High disease burden is another important marker of poor outcomes in both back and neck pain patients.<sup>202-204</sup> Indirect measurements of increased disease burden include higher baseline pain scores and disability,<sup>149,205</sup> greater use of opioids,<sup>206,207</sup> and a history of failed interventions,<sup>208,209</sup> which have all been shown to be prognosticators of poor outcomes in patients with back and neck pain. Patients with lower levels of education and lack of employment at time of diagnosis may also have worse outcomes than those in higher socioeconomic groups. Along with a lower financial incentive to return to work, it is theorized that patients in lower socioeconomic brackets may also have less access to routine health care surveillance and often present only after a disease process has significantly progressed past the ideal therapeutic window, at which time the likelihood of treatment success has decreased.<sup>210</sup> Many studies have documented a high coprevalence rate of psychopathology with neck and back pain,<sup>211-212</sup> and depression and other forms of psychological distress are negative prognosticators in patients with chronic pain of all types, including NSP.<sup>213-216</sup> In addition to depression, poor coping mechanisms, catastrophization, somatization traits, secondary gain, and the presence of Waddell signs have also been shown to predict treatment failure.<sup>211,216-219</sup>

### Factors Associated With ESI Results

Not surprisingly, disease burden and the presence of co-existing psychosocial stressors have been consistently found to portend negative treatment outcomes after ESI. A study by Jamison et al<sup>220</sup> found the predictors of treatment failure 2 weeks after ESI included a greater number of previous failed treatments, higher analgesic use, unrelenting pain not worsened by activity, and pain increased by coughing. One year after treatment, unemployment secondary to pain, poor response to analgesics, negative straight-leg-raising test, and pain unaffected by activities were associated with negative treatment outcomes. A prospective cohort study by Hopwood and Abram<sup>221</sup> performed in 209 patients who underwent lumbar IL ESI found that constant pain, prolonged duration of pain, smoking, unemployment, sleep dysfunction, psychological distress, and nonradicular pain were associated with treatment failure in univariate analysis. After logistical regression analysis, only prolonged duration, nonradicular pain, lack of employment, and smoking remained significant predictive factors. The negative correlation between symptom duration and treatment response is supported by other studies.<sup>98</sup> A recent study by Kirpalani and Mitra<sup>222</sup> found 70% of opioid-naive patients had a positive outcome after cervical ESI, compared with only 20% in patients on chronic opioid therapy.

Another predictive factor for ESI success is the nature of a patient's symptoms.<sup>87</sup> Systematic reviews<sup>97,132,133</sup> and studies performed in the cervical<sup>223</sup> and lumbar<sup>76</sup> spine have generally found that radicular pain is more responsive than axial pain secondary to mechanical pathology. When broken down by etiology, some studies suggest that a herniated disk may respond better to ESI than neurogenic claudication secondary to spinal stenosis,<sup>60,99,134,135</sup> although this finding is by no means universal.<sup>63,98,136,137</sup>

Even in patients with a particular diagnosis, the severity and subtype of pathology may affect outcome. Among individuals with spinal stenosis, a direct correlation has been found between the severity of pathology and response to treatment.<sup>138,224</sup> In a subgroup analysis of a randomized, placebo-controlled study by Ghahreman and Bogduk<sup>170</sup> performed in patients with herniated

disk, the authors noted an inverse relationship between the degree of nerve root compression on magnetic resonance imaging and the likelihood of a successful outcome. This association was hypothesized to stem from the fact that those with low-grade compression experienced predominantly inflammatory-mediated pain, as opposed to pain due to mechanical compression that is more refractory to treatment. Other studies have yielded mixed results regarding an association between ESI outcomes and the extent of degenerative end-plate spinal changes.<sup>225,226</sup>

Finally, several investigators have sought to identify prognostic factors for ESI based on their preinjection response to standardized sensory testing. In a small study by Schiff and Eisenberg,<sup>227</sup> the authors reported mixed results for the ability of quantitative sensory testing to predict the response to ESI, with a direct correlation being noted between improvement in pain scores and increase in cold sensation threshold but an inverse correlation between pain score improvement and increase in touch and vibration thresholds, mediated by A-beta fibers. Given the expense and time associated with performing baseline quantitative sensory testing, the mixed results do not currently support this practice. In an attempt to find a simpler and more practical means to determine whether intrinsic sensory perception can predict ESI outcome, Cohen et al<sup>228</sup> found a small but statistically significant correlation between the perceived intensity of the pain response to a standardized subcutaneous injection of local anesthetic immediately before a set of ESIs and a person's response to the injections, which persisted through 3-month follow-up. In summary, the weak and often conflicting association between baseline demographic and clinical factors and response to ESI, and the low risks associated with the procedure, make screening out potential candidates with NSP based on phenotypic characteristics impractical at this time (Fig. 4).

### Complications

Complications associated with the epidural administration of corticosteroids are uncommon, but their risk has been highlighted by the recent and devastating outbreak of fungal meningitis

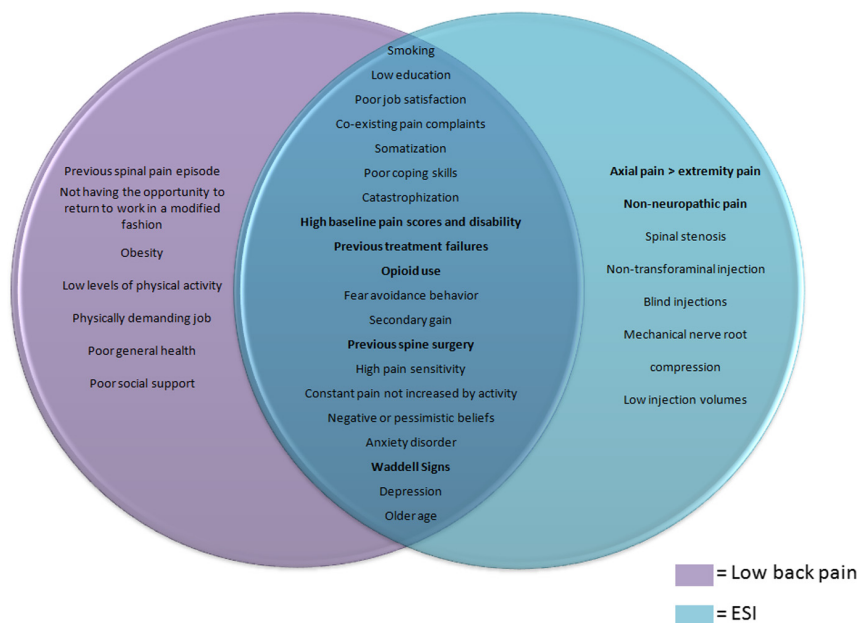


FIGURE 4. Venn diagram depicting predictors of a poor outcome for low back and epidural steroid injections. Characteristics in bold denote major risk factors for negative outcome.

in the United States.<sup>229</sup> Following epidural administration of contaminated steroid, more than 650 cases of fungal infection and 39 deaths were reported in late 2012. There is no mandatory reporting of complications in the United States, and thus the true incidence of serious adverse effects and complications associated with epidural administration of corticosteroids cannot be determined. Despite warnings about the neurotoxic potential of intrathecal injection of corticosteroids,<sup>230</sup> there are few reports of serious complications associated with epidural administration.

A recent retrospective study examined 4265 ESIs performed in 1857 patients over 7 years, which included 161 cervical IL injections, 123 lumbar IL injections, 17 caudal injections, and 3964 lumbar TF injections.<sup>91</sup> No major complications were identified. There were 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%). Complications were less common with TF injections (2.1%) than for IL injections (6.0%). The American Society of Anesthesiologists Closed Claims Study provides some insight into less common major complications, reporting on 114 complications purportedly caused by ESIs that resulted in malpractice litigation.<sup>231</sup> The types of complications cited in that report are shown in Table 6. Complications that have been reported following epidural corticosteroid injections include neurotoxicity, neurologic injury, pharmacological effects of corticosteroids, and other less frequent problems. The aim of this section is to review our current knowledge regarding the complications associated with ESI.

### Neurotoxicity

Direct neurotoxicity caused by the unintentional intrathecal injection of corticosteroid suspensions has been hypothesized 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. Arachnoiditis is an inflammatory condition involving the leptomeninges and the underlying neural structures.<sup>232</sup> Commonly encountered symptoms include constant, burning pain in the lower back and legs; urinary frequency, incontinence; muscle spasms in the back and legs; variable sensory loss; and motor dysfunction. Adhesive arachnoiditis is a severe and often progressive form that is associated with neuropathic pain and neurologic dysfunction. The intrathecal injection of neurotoxic substances can result in arachnoiditis if there is sufficient chemical irritation or inflammation. Aseptic meningitis is a generally benign condition that produces signs of neurological irritation, including burning pain in the legs, headache, meningismus, and in severe cases seizures. Fever and nausea are often reported. Cerebrospinal fluid examination reveals pleocytosis, elevated protein, and decreased glucose. The introduction of nearly any substance, including blood, normal saline, or water, into the subarachnoid space can potentially produce the syndrome.<sup>233</sup>

**TABLE 6.** Outcomes for Malpractice Claims Related to ESIs

Nerve injury: 28
Infection: 24
Death/brain damage: 9
Headache: 20
Increased pain, no relief: 10
Adapted from Fitzgibbon et al <sup>231</sup> (2004)

The first reported cases of arachnoiditis followed neuraxial syphilis or tuberculosis infections. Iatrogenic arachnoiditis was first reported after intrathecal injection of oil-based radiographic contrast agents. Arachnoiditis is most commonly diagnosed among patients who have had multiple prior spinal surgeries, so that identifying the inciting cause is difficult. Arachnoiditis is an uncommon condition, and the symptoms are often difficult to separate from those for which many patients receive ESI. Concern regarding the neurotoxic potential of corticosteroid suspensions arose during treatment of advanced cases of multiple sclerosis (MS) with intrathecal methylprednisolone acetate (MPA). The earliest report of arachnoiditis following intrathecal steroid injections cited 2 cases of adhesive arachnoiditis among a series of 23 patients who received a total of 83 injections of MPA.<sup>234</sup> The author of that report expressed concern that the drug vehicle, polyethylene glycol, could have initiated the inflammatory response. Additional, sporadic case reports have appeared in which individual patients developed arachnoiditis after intrathecal administration of multiple doses of corticosteroids to treat advanced MS.<sup>235,236</sup> A single case of myelographically documented arachnoiditis has been reported following intrathecal MPA treatment for lumbar disk disease<sup>237</sup>; the intrathecal injection occurred in conjunction with inadvertent dural puncture during attempted epidural administration.

Seghal et al<sup>238</sup> documented the occurrence of aseptic meningitis following intrathecal injections of 40 to 200 mg MPA, whereas Goldstein et al<sup>239</sup> were unable to show any cerebrospinal fluid changes or symptoms of meningeal irritation in patients with MS treated with 40 mg MPA. Several cases of aseptic meningitis have also been reported following intrathecal corticosteroid injections.<sup>240–242</sup> One of these cases was severe, producing headache, fever, nausea, bilateral leg pain, and seizures.<sup>240</sup> One case of aseptic meningitis was reported following an epidural injection of MPA.<sup>243</sup> A recent study of intrathecal MPA for PHN failed to find any evidence of either aseptic meningitis or arachnoiditis among 89 patients treated with four 60-mg injections.<sup>244</sup> Patients were followed up for 2 years and underwent diagnostic lumbar punctures and magnetic resonance imaging.

It is difficult to determine which component of the steroid preparation, if any, is neurotoxic. Nelson<sup>230</sup> suggested that polyethylene glycol is the offending agent. This speculation was based on studies demonstrating that concentrations of propylene glycol 78% or greater cause nerve injury.<sup>245,246</sup> The polyethylene glycol preparation used in steroid suspensions is present in concentrations of 2.8% to 3%. Benzon et al<sup>247</sup> studied the acute effects of polyethylene glycol on nerve conduction and found no changes with concentrations of 3% and 10%, slowing of conduction with 20% and 30%, and abolishment of conduction with 40%; the effects were reversible following washout. Benzyl alcohol 0.9% is present in several steroid suspension preparations, including multidose vials of Depo-Medrol brand MPA (Pharmacia & Upjohn, Kalamazoo, Michigan) and Aristocort Intraleonal brand triamcinolone diacetate (American Cyanamid, Madison, New Jersey). Two animal studies reported no or minimal histological changes following the neuraxial injection of the triamcinolone/benzyl alcohol preparation,<sup>248,249</sup> although the clinical relevance of this remains unknown. There have been reports of aseptic meningitis following intracisternal injections of pyrogen-free serum albumen plus 0.9% benzyl alcohol.<sup>250</sup> Following up in these reports, Deland<sup>251</sup> assessed the effects of intracisternal injections of benzyl alcohol 0.9% to 9% in dogs. The highest concentration (10 times the concentration used as a preservative in pharmaceutical agents) produced transient neurological dysfunction related to local anesthetic effects, but there was no evidence of aseptic meningitis at any concentration. Few

histological abnormalities were noted, and those that did occur were observed as frequently in saline controls.

There was considerable public controversy about the risk of arachnoiditis following epidural MPA injection during the 1990s in Australia, prompting many physicians to use Celestone Chronodose (Schering-Plough, Kenilworth, New Jersey) for ESI. This product contains betamethasone 5.7 mg, as betamethasone sodium phosphate 3.9 mg (in solution), and betamethasone acetate 3 mg (in suspension) per milliliter in an aqueous vehicle containing sodium phosphate, sodium phosphate monobasic, disodium edetate, benzalkonium chloride, and water. Despite the absence of both polyethylene glycol and benzyl alcohol in this solution, a study in sheep demonstrated the development of histopathologic changes of arachnoiditis following intrathecal injection of 2 mL or more of this preparation.<sup>252</sup> The product is available in the United States as Celestone Soluspan (Schering-Plough).

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 preexisting neurologic disease. Arachnoiditis and aseptic meningitis are complications of intrathecal, not epidural, steroid injections. The use of a local anesthetic test dose and/or fluoroscopy and radiographic contrast are reliable means to prevent unintentional intrathecal administration. There is no definitive treatment for arachnoiditis or aseptic meningitis, with symptomatic treatment and reassurance being cornerstones of therapy.

### Neurologic Injury

In the Closed Claims Study, nerve injury occurred in 14 patients following ESI.<sup>231</sup> Six of these resulted in paraplegia, one in quadriplegia. Spinal cord damage can occur from needle entry into the cord. In a recent follow-up analysis, the Closed Claims Study Group examined claims associated with procedures conducted at the level of the cervical spine.<sup>253</sup> Injuries related to cervical interventional pain treatment were often severe and related to direct needle trauma to the spinal cord. Traumatic spinal cord injury was more common in patients who received sedation or general anesthesia, especially in those who were unresponsive during the procedure. The majority (59%) of the 64 claims reported in this series were permanent spinal cord injuries related to direct needle trauma to the spinal cord; the most common procedure was epidural injection of corticosteroids. Direct trauma to the spinal cord occurred in association with both the TF and IL routes. Another mechanism of injury is the injection of steroid suspension into a spinal medullary artery with embolization of end arterioles supplying the spinal cord,<sup>254</sup> but this appears to be less common than direct needle trauma to the spinal cord.

The Closed Claims analysis clearly demonstrates that injury to the cord is a significant risk for cervical, thoracic, and upper lumbar epidural injections. Direct needle entry into the cord does not always result in major or permanent neurologic injury. Field et al<sup>255</sup> reported 3 cases of transient neurologic injury that followed otherwise uneventful cervical ESI in awake patients. All 3 patients had large disk herniations that caused effacement of the epidural fat and spinal fluid surrounding the spinal cord at the level of injection. The authors hypothesized that direct injury to the spinal cord or dorsal nerve root could occur even without dural puncture when narrowing or obliteration of the epidural space caused by a large disk herniation displaces the spinal cord posteriorly. More severe neurologic injury occurs if material is injected into the spinal cord, which is more likely to occur in those who are deeply sedated and

unresponsive during the procedure. Two cases of spinal cord injury following cervical ESI were reported by Hodges et al.<sup>256</sup> Both cases used fluoroscopic guidance, both cases were performed at C5-6, and in both cases the patient was heavily sedated with a combination of midazolam and propofol. It was postulated that the patients failed to respond to needle contact with the cord because of sedation. In the Closed Claims analysis, among the patients who underwent cervical procedures and experienced spinal cord injuries, 25% were nonresponsive during the procedure, which was significantly higher than the 5% of patients who underwent cervical procedures and did not have spinal cord injuries.

Catastrophic neurologic injury due to embolization of particulate steroid appears to be most common in association with cervical TF injection. This type of injury was implicated in a fatal case of massive cerebellar injury following a cervical TF injection of triamcinolone acetate.<sup>257</sup> Infarction of the cervical spinal cord resulting in permanent motor and sensory deficits in all extremities following cervical TF injection has also been reported.<sup>254,258</sup> Similarly, infarction of the lower spinal cord resulting in paraplegia has also been described following thoracic and lumbar TF injections.<sup>259,260</sup> All of the corticosteroid suspensions commercially available contain particles large enough to occlude capillaries and arterioles.<sup>261</sup> Injection into the vertebral artery can lead to stroke in the posterior circulation of the brain, with cerebellar infarction, cortical blindness, and in some cases death due to resultant intracranial hypertension. 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. Subsequent study in a pig model has conclusively demonstrated that direct injection of particulate steroid into the vertebral artery results in irreversible posterior circulation strokes similar to those reported in case reports following TF injection of steroid.<sup>262</sup> Injection of the nonparticulate steroid solution dexamethasone resulted in no apparent injury in the same animal model, providing preliminary evidence for the safety of this agent. Embolization has not been implicated as a mechanism for injury following caudal or interlaminar ESIs. Although TF injections performed in the lumbar spine carry a much lower risk than in the thoracic or cervical regions, previous surgery may be associated with an increased risk of spinal cord infarct.<sup>111</sup> Spinal cord infarction associated with TF injection is far less common than direct spinal cord trauma according to the Closed Claims analysis.<sup>253</sup>

In most cases, there is probably little that can be done to minimize the extent of neurologic dysfunction after a traumatic or embolic event has occurred. High-dose intravenous corticosteroid may be of benefit. 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.<sup>263</sup>

### Pharmacologic Effect of Corticosteroids

#### Hypercorticism and Adrenal Suppression

Cushing syndrome is a characteristic pattern of obesity associated with hypertension that results from abnormally high blood levels of cortisol produced by the adrenal cortex. Exogenous administration of glucocorticoids can result in an identical clinical pattern and is frequently called "cushingoid" syndrome. The active corticosteroid in MPA and other depot steroid preparations is slowly released over a period of days to weeks. Common mineralocorticoid effects such as fluid retention and weight gain,

as well as increased blood pressure and congestive heart failure, have been reported after ESI. Cushingoid adverse effects beginning several weeks after ESI have also been reported.<sup>264-266</sup> These can include facial swelling, buffalo hump, skin bruising, and scaly skin lesions.

Jacobs et al<sup>267</sup> documented marked suppression of plasma cortisol levels in 12 patients who each received a single epidural injection of 80 mg MPA. Plasma cortisol and adrenocorticotropic hormone (ACTH) levels were significantly depressed at 1, 7, 14, and 21 days after treatment. The ability of exogenous ACTH to increase plasma cortisol levels was also reduced over a 3-week period. Kay et al<sup>268</sup> sought to determine the adrenal response to a series of 3 weekly epidural injections of 80 mg triamcinolone diacetate and to ascertain whether the preinjection administration of midazolam had any effect. Suppression of serum cortisol and ACTH began within 45 minutes of the initial injection and remained low for 7 days after each of the first 2 injections. At 34 days after the last injection, ACTH and cortisol levels were suppressed only in the group that received midazolam before the procedures.

Another symptom of hypercorticism is steroid-induced myopathy, which is characterized by progressive proximal muscle weakness, increased serum creatinine kinase levels, and a myopathic electromyography and muscle biopsy specimen. This has been reported following a single epidural dose of triamcinolone.<sup>269</sup> All patients who have been taking steroids for long periods develop reversible myofiber atrophy, which should be distinguished from true steroid myopathy.

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. The most prudent guiding principle is 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.

### Altered Glucose Tolerance

Glucocorticoid administration reduces the hypoglycemic effect of insulin and interferes with blood glucose control in diabetic patients.<sup>270</sup> Following injection of depo-steroids, diabetic patients generally experience significant increases in blood glucose levels and insulin requirements for 1 to 2 days after injection. A study of 30 diabetic patients demonstrated significant changes in blood glucose levels that normalized within 2 days after ESI.<sup>271</sup> The mean blood glucose level before ESI was 160, which increased to 286 immediately after injection. There was no correlation between glucose control (Hb<sub>A1c</sub> levels before injection) and response. 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.<sup>272</sup> Patients with diabetes receiving ESI should be counseled 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. Patients with brittle diabetes should consult their internist or endocrinologist before initiating steroid treatment.

### DURAL PUNCTURE

Accidental dural puncture during attempted epidural injection is associated with a headache incidence of greater than 50%.<sup>273</sup>

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 large retrospective analysis that included 284 IL epidural injections, only 1 postdural puncture headache was reported, for an overall incidence of 0.004%.<sup>91</sup> Introduction of air into the subdural or subarachnoid space during attempted epidural needle placement can produce pneumocephalus and an immediate headache that can last up to several days. Although the most common cause of pneumocephalus following ESI is accidental dural puncture resulting in the introduction of air during the loss-of-resistance technique,<sup>274,275</sup> a pneumocephalus headache has been reported after a cervical ESI performed using the hanging-drop technique.<sup>276</sup> In light of the fact that cervical epidural pressures are nearly always positive in the prone position, this is more likely to occur during a cervical ESI performed in the sitting position, in which pressures tend to be negative.<sup>277</sup> There is evidence that the use of a smaller-gauge needle increases the chances of incorrect needle placement,<sup>278</sup> but unlike for epidural anesthesia, the effect of using smaller epidural needles for ESI on the incidence of postdural puncture headache is unknown. Conservative management of postdural puncture headache includes bed rest, hydration, caffeine, and mild analgesics.<sup>279</sup> Following known dural puncture, an epidural blood patch can quickly and effectively reduce or eliminate the ensuing spinal headache.

### BLEEDING COMPLICATIONS

Intraspinal bleeding is a potentially devastating complication that can result in paraplegia or quadriplegia. Back pain and headache may be the presenting complaints. Both epidural<sup>280</sup> and subdural<sup>281</sup> hematomas have been reported following ESIs in patients without coagulopathy or concurrent use of anticoagulants. Benzon et al<sup>282</sup> reported a case of quadriplegia following a cervical ESI in a patient who had been taking clopidogrel and diclofenac. Following surgical decompression, the patient regained upper-extremity function, but his lower extremities remained paralyzed. The earlier Closed Claims Study cites 2 cases of spinal cord injury resulting from epidural hematomas following ESI,<sup>231</sup> with both patients having been receiving anticoagulants. In the subsequent Closed Claims analysis of cervical procedures, Rathmell et al<sup>253</sup> reported 3 cases of epidural hematoma (5% of cervical claims), one of which occurred a month after the procedure and was felt to be unrelated; the use of anticoagulants or coagulopathy was not reported. The most important risk factor for bleeding is coagulopathy—either primary or pharmacological. Anticoagulants and antiplatelet drugs such as clopidogrel are contraindications to epidural injections of any sort. On the other hand, NSAIDs, including aspirin, do not appear to appreciably increase the risk of epidural bleeding. Horlocker et al<sup>283</sup> 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. The only published reports of epidural hematomas resulting in neurologic complications have occurred following cervical injections. Given the rarity of this complication, no conclusions regarding relative risk of cervical versus lumbar epidural injections can be drawn. The discontinuation of medications in patients receiving anti-thrombotic or thrombolytic therapies before ESI is not devoid of risks and should be handled in the same fashion recommended for other regional anesthetics.<sup>284</sup> 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 ( $n = 55$ ).<sup>285</sup> 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, in consultation with a specialist. 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 an ESI is strongly indicated and the risk of discontinuing warfarin or antiplatelet therapy is high.

### INFECTIOUS COMPLICATIONS

Infectious complications following epidural or intra-articular injections are rare. Epidural abscess is a condition that can occur spontaneously, in the absence of injection or instrumentation of the spinal canal. Tang et al<sup>286</sup> reviewed 46 cases of spontaneous epidural abscess and found that 46% occurred in diabetic patients. Common presenting symptoms included paralysis (80%), localized spinal pain (89%), radicular pain (57%), and chills and fever (67%). The erythrocyte sedimentation rate was always elevated, and *Staphylococcus aureus* was the organism isolated in about half the cases. Hooten et al<sup>287</sup> recently performed a literature review examining the cases of epidural abscess following ESI. They found 14 cases, 2 of which also presented with meningitis. A synopsis of the patient characteristics and outcomes for those cases as well as another case<sup>288</sup> not included in that review is shown in Table 7.

Infection was listed in the original Closed Claims Study<sup>231</sup> as a cause for litigation in 24 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. A single case of bacterial diskitis was reported following caudal ESI.<sup>289</sup> This occurred following injection of 120 mg triamcinolone in a 73-year-old woman with mild diabetes mellitus. One month after injection, she returned

with increased back pain. Magnetic resonance imaging revealed L4-5 diskitis and adjacent osteomyelitis. Biopsy culture grew *Pseudomonas aeruginosa*. She was successfully treated with intravenous ciprofloxacin and gentamicin. In the Closed Claims analysis of cervical procedures, infection or abscess was reported in 3 cases (5% of procedures).<sup>253</sup>

Until the recent outbreak associated with contaminated steroids in the United States, fungal infection following ESI was considered to be an extremely rare complication. A case of “torula meningitis” was reported by Shealy<sup>290</sup> more than 40 years ago following an intrathecal injection of MPA. No details of the case, such as the time course after injection or the outcome, were presented. Another case involved the formation of an *Aspergillus* abscess in the spinal canal 6 weeks following the last of 3 ESIs performed in a healthy 31-year-old woman.<sup>291</sup>

An outbreak of fungal infections of the central nervous system occurred in the United States in late 2012 among patients who received ESI with preservative-free MPA prepared by a single compounding pharmacy. 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. As of late December 2012, more than 650 cases of fungal infection and 39 deaths have been reported.<sup>229,292</sup>

Rapid recognition of illness and prompt initiation of therapy are the cornerstones of management for infectious complications. Practitioners involved in the care of these patients were utilizing 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. Numerous reasons appear to have led practitioners to purchase from a compounding pharmacy rather than a pharmaceutical company, including fears of potential patient harm and litigation surrounding use of preservative containing solutions, better availability, and lower costs. The long-term implications of this outbreak are still emerging.

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 are no data to support the benefit of prophylaxis in immunocompromised patients. Routine preprocedure antibiotic administration can lead to the development of resistant strains of pathogens. There is now increasingly widespread antibiotic resistance among strains of *S. aureus*, and patients coming for elective procedures are often carriers of resistant organisms.<sup>293</sup> Most cases of epidural abscess require surgical drainage. Surgical decompression is urgently indicated if there is any neurologic

**TABLE 7.** Characteristics of Cases of Epidural Abscess Following ESIs ( $n = 15$ )

Onset
Within 1 wk: 9
Beyond 1 wk: 6
Patients with diabetes: 5
Injection type
Caudal epidural injection: 1
Lumbar epidural injection: 10
Thoracic epidural injection: 1
Cervical epidural injection: 3
Sequelae
Required laminectomy: 11
Residual motor dysfunction: 5
Deaths: 2

Adapted from Hooten et al<sup>287</sup> and Huang et al<sup>288</sup>

compromise. While waiting for cultures, treatment with antibiotics that cover *S. aureus* and *Staphylococcus epidermidis* is appropriate, as these are the most commonly isolated organisms.<sup>294</sup>

### OTHER ADVERSE EFFECTS AND COMPLICATIONS

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.<sup>295</sup> In a follow-up study by the same group performed in 352 postmenopausal 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.<sup>296</sup>

Vasovagal reactions, with resultant bradycardia, hypotension, nausea, and/or altered consciousness, are fairly common among patients undergoing interventional procedures. The incidence of vasovagal reactions during ESIs was shown to be significantly higher for patients undergoing cervical epidural injections (8%) than for those undergoing lumbar epidurals (1%).<sup>297</sup> In a recent retrospective study conducted by McGrath et al,<sup>91</sup> the most common complications associated with ESI were increased pain (1.1%), pain at injection site (0.33%), and persistent numbness (0.14%). Complications were less common with TF injections (2.1%) than during IL injections (6.0%).

In summary, serious complications from injection of corticosteroid suspensions into the epidural space are uncommon, but complications can be devastating. 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.

### SUMMARY

In summary, ESIs appear to provide some pain relief and functional improvement in well-selected candidates for at least 6 weeks. The evidence for more prolonged benefit or for a surgery-sparing effect is conflicting. Transforaminal ESIs are more effective than other routes of administration, and depo-steroids appear to provide longer pain relief than nondepot formulations. However, the risks associated with the TF administration of depo-steroids in the upper lumbar, thoracic, and cervical regions preclude their use as a first-line treatment. Higher volumes may be associated with better outcomes, and there is some evidence that the epidural injection of nonsteroid solutions may also have analgesic effects. Although comparative-effectiveness studies are lacking, consensus guidelines recommend that the number of ESI be tailored based on individual response, rather than performed as a fixed series. We are of the firm belief that ESIs should continue to be part of a multimodal treatment strategy, but that they be used in a manner based on empirical evidence, rather than done as a rote treatment in any patient with spine pain.

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### REFERENCES

- OCEBM Levels of evidence working group. The Oxford 2011 Levels of Evidence. Oxford Centre for Evidence-Based Medicine. Available at: <http://www.cebm.net/index.aspx?o=5653>. Accessed January 14, 2013.
- Harris R, Helfand M, Woolf S, et al. Methods Work Group, third US Preventive Services Task Force. Current methods of the US Preventives Task Force. *Am J Prev Med*. 2011;20:21–35.
- Corning J. Spinal anaesthesia and local medication of the cord. *N Y Med J*. 1885;42:483–485.
- Corning J. A further contribution on local medication of the spinal cord, with cases. *Med Rec*. 1888;1:291–293.
- Bier A. Versuche uber cocainisierung des ruckenmarkes. *Deut Zeit Chir*. 1899;51:361–369.
- Marx G. The first spinal anesthesia. Who deserves the laurels? *Reg Anesth*. 1994;19:429–430.
- Sicard A. Les injections medicamenteuses extra-durales par voie sacrococcygienne. *Compt Rend Soc De Biol*. 1901;53:396–398.
- Cathelin F. Une nouvelle voie d'injection rachidienne: methode des injections epidurales par le procede du canal sacre-applications a l'homme. *Compt Rend Soc Du Biol*. 1901;53:452–453.
- Evans W. Intrasacral epidural injection in the treatment of sciatica. *Lancet*. 1930;216:1225–1229.
- Viner N. Intractable sciatica—the sacral epidural injection; an effective method of giving relief. *Can Med Assoc J*. 1925;15:630–634.
- Kelman H. Epidural injection therapy for sciatica pain. *Am J Surg*. 1944;64:183–190.
- Davidson J, Robin G. Epidural injections in the lumbosacral syndrome. *Br J Anaesth*. 1961;33:595–598.
- Bresgen C. Uber Ischiassimulation die diagnostische Bedeutung der epiduralen Novocaine-injektion. *Mun med Woch*. 1951;93:934–935.
- Lievre J, Bloch-Michel H, Pean G, et al. L'hydrocortisone en injection locale. *Rev Rhumat Mal Osteoartic*. 1953;20:310–311.
- Goebert H, Jallo S, Gardner W, et al. Painful radiculopathy treated with epidural injections of procaine and hydrocortisone acetate: results in 113 patients. *Curr Res Anesth Analg*. 1961;40:130–134.
- Swerdlow M, Sayle-Creer W. A study of extradural medication in the relief of the lumbosacral syndrome. *Anaesthesia*. 1970;25:341–345.
- Crow W, Willis D. Estimating cost of care for patients with acute low back pain: a retrospective review of patient records. *J Am Osteopath Assoc*. 2009;109:229–233.
- Juniper M, Le T, Mladi D. The epidemiology, economic burden, and pharmacological treatment of chronic low back pain in France, Germany, Italy, Spain and the UK: a literature-based review. *Expert Opin Pharmacother*. 2009;10:2581–2592.
- Hoy D, Bain C, Williams G, et al. A systematic review of the global prevalence of low back pain. *Arthritis Rheum*. 2012;64:2028–2037.
- Henschke N, Maher C, Refshauge K, et al. Prognosis in patients with recent onset low back pain in Australian primary care: inception cohort study. *BMJ*. 2008;337:a171.
- Wolf A, Pflieger B. Burden of major musculoskeletal conditions. *Bull World Health Organ*. 2003;81:646–656.

22. Hogg-Johnson S, van der Velde G, Carroll L, et al. Bone and Joint Decade 2000–2010 Task Force on Neck Pain and Its Associated Disorders: the burden and determinants of neck pain in the general population: results of the Bone and Joint Decade 2000–2010 Task Force on Neck Pain and Its Associated Disorders. *Spine*. 2008;15:S39–S51.
23. Binder A. Neck pain [published online August 4, 2008]. *Clin Evid (Online)*. 2008.
24. Fejer R, Kyvik K, Hartvigsen J. The prevalence of neck pain in the world population: a systematic critical review of the literature. *Eur Spine J*. 2006;15:834–848.
25. Martin B, Turner J, Mirza S, et al. Trends in health care expenditures, utilization, and health status among US adults with spine problems 1997–2006. *Spine*. 2009;34:2077–2084.
26. Martin B, Deyo R, Mirza S, et al. Expenditures and health status among adults with back and neck problems. *JAMA*. 2008;299:656–664.
27. Freynhagen R, Baron R, Gockel U, et al. painDETECT: a new screening questionnaire to identify neuropathic components in patients with back pain. *Curr Med Res Opin*. 2006;22:1911–1920.
28. El Sissi W, Arnaout A, Chaarani M, et al. Prevalence of neuropathic pain among patients with chronic low-back pain in the Arabian Gulf Region assessed using the Leeds assessment of neuropathic symptoms and signs pain scale. *J Int Med Res*. 2010;38:2135–2145.
29. Beith I, Kemp A, Kenyon J, et al. Identifying neuropathic back and leg pain: a cross-sectional study. *Pain*. 2011;152:1511–1516.
30. Kaki A, El-Yaski A, Youseif E. Identifying neuropathic pain among patients with chronic low-back pain: use of the Leeds Assessment of Neuropathic Symptoms and Signs pain scale. *Reg Anesth Pain Med*. 2005;30:422–428.
31. Hassan A, Saleh H, Baroudy Y, et al. Prevalence of neuropathic pain among patients suffering from chronic low back pain in Saudi Arabia. *Saudi Med J*. 2004;25:1986–1990.
32. Salemi G, Savettieri G, Meneghini F, et al. Prevalence of cervical spondylotic radiculopathy: a door-to-door survey in a Sicilian municipality. *Acta Neurol Scand*. 1996;93:184–188.
33. Schoenfeld A, George A, Bader J, Caram P. Incidence and epidemiology of cervical radiculopathy in the United States military: 2000 to 2009. *J Spinal Disord Tech*. 2012;25:17–22.
34. Radhakrishnan K, Litchy W, O'Fallon W, Kurland L. Epidemiology of cervical radiculopathy. A population-based study from Rochester, Minnesota, 1976 through 1990. *Brain*. 1994;117:325–335.
35. Manchikanti L, Pampati V, Falco J, Hirsch J. Growth of spinal interventional pain management techniques: analysis of utilization trends and Medicare expenditures 2000 to 2008 [published online ahead of print July 11, 2012]. *Spine*. 2012.
36. Saal J. The role of inflammation in lumbar pain. *Spine*. 1995;20:1821–1827.
37. Petho G, Reeh P. Sensory and signaling mechanisms of bradykinin, eicosanoids, platelet-activating factor, and nitric oxide in peripheral nociceptors. *Physiol Rev*. 2012;92:1699–1775.
38. Devor M, Govrin-Lippmann R, Raber P. Corticosteroids suppress ectopic neural discharge originating in experimental neuromas. *Pain*. 1985;22:127–137.
39. Johansson A, Hao J, Sjolund B. Local corticosteroid application blocks transmission in normal nociceptive C-fibers. *Acta Anaesthesiol Scand*. 1990;34:335–338.
40. Kobayashi S, Takeno K, Yayama T, et al. Pathomechanisms of sciatica in lumbar disc herniation: effect of periradicular adhesive tissue on electrophysiological values by an intraoperative straight leg raising test. *Spine*. 2010;35:2004–2014.
41. Devor M, Wall P, Catalan N. Systemic lidocaine silences ectopic neuroma and DRG discharge without blocking nerve conduction. *Pain*. 1992;48:261–268.
42. Jacobs L, Vo N, Kang J. Identifying inflammatory targets for the biologic therapies for spinal pain. *PM R*. 2011;3(6 suppl 1):S12–S17.
43. Helm Ii S, Benyamin R, Chopra P, et al. Percutaneous adhesiolysis in the management of chronic low back pain in post lumbar surgery syndrome and spinal stenosis: a systematic review. *Pain Physician*. 2012;15:E435–E462.
44. Rabinovitch D, Peliowski A, Furlan A. Influence of lumbar epidural injection volume on pain relief for radicular leg pain and/or low back pain. *Spine J*. 2009;9:509–517.
45. Brisby H. Pathology and possible mechanisms of nervous system response to disc degeneration. *J Bone Joint Surg Am*. 2006;88(suppl 2):68–71.
46. Mehling W, Gopisetty V, Bartmess E, et al. The prognosis of acute low back pain in primary care in the United States: a 2-year prospective cohort study. *Spine*. 2012;37:678–684.
47. Weber H, Holme I, Amlie E. The natural course of acute sciatica with nerve root symptoms in a double blind placebo controlled trial evaluating the effect of piroxicam. *Spine*. 1993;18:1433–1438.
48. Benoist M. The natural history of lumbar disc herniation and radiculopathy. *Joint Bone Spine*. 2002;69:155–160.
49. Cribb G, Jaffray D, Cassar-Pullicino V. Observations on the natural history of massive disc herniation. *J Bone Joint Surg (Br)*. 2007;89:782–784.
50. Jacobs W, van Tulder M, Arts M, et al. Surgery versus conservative management of sciatica due to a lumbar herniated disc: a systematic review. *Eur Spine J*. 2011;20:513–522.
51. Nikolaidis I, Fouyas I, Sandercock P, Statham P. Surgery for cervical radiculopathy or myelopathy. *Cochrane Database Syst Rev*. 2010;1:CD001466.
52. Kovacs F, Urrutia G, Alarcon J. Surgery versus conservative therapy for symptomatic lumbar spinal stenosis: a systematic review of randomized controlled trials. *Spine*. 2011;36:E1335–E1351.
53. White A, Arnold P, Norvell D, et al. Pharmacologic management of chronic low back pain: synthesis of the evidence. *Spine*. 2011;36:S131–S143.
54. Morlion B. Pharmacotherapy of low back pain: targeting nociceptive and neuropathic pain components. *Curr Med Res Opin*. 2011;27:11–33.
55. Ackerman 3rd W, Ahmad M. The efficacy of lumbar epidural steroid injections in patients with lumbar disc herniations. *Anesth Analg*. 2007;104:1217–1222.
56. Candido K, Raghavendra M, Chinthagada M, et al. A prospective evaluation of iodinated contrast flow patterns with fluoroscopically guided lumbar epidural steroid injections: the lateral parasagittal interlaminar epidural approach versus the transforaminal epidural approach. *Anesth Analg*. 2008;106:638–644.
57. Gharibo C, Varlotta G, Rhame E, et al. Interlaminar versus transforaminal epidural steroids for the treatment of subacute lumbar radicular pain: a randomized, blinded, prospective outcome study. *Pain Physician*. 2011;14:499–511.
58. Kolsi I, Delecrin J, Berthelot J, et al. Efficacy of nerve root versus interspinous injections of glucocorticoids in the treatment of disk-related sciatica. A pilot, prospective, randomized, double-blind study. *Joint Bone Spine*. 2000;67:113–118.
59. Kraemer J, Ludwig J, Bickert U, et al. Lumbar epidural perineural injection: a new technique. *Eur Spine J*. 1997;6:357–361.
60. Lee J, An J, Lee S. Comparison of the effectiveness of interlaminar and bilateral transforaminal epidural steroid injections in treatment of

- patients with lumbosacral disc herniation and spinal stenosis. *Clin J Pain*. 2009;25:206–210.
61. Rados I, Sakic K, Fingler M, et al. Efficacy of interlaminar vs. transforaminal epidural steroid injection for the treatment of chronic unilateral radicular pain: prospective, randomized study. *Pain Med*. 2011;12:1316–1321.
  62. Thomas E, Cyteval C, Abiad L, et al. Efficacy of transforaminal versus interspinous corticosteroid injection in discal radiculalgia: prospective, randomized, double-blind study. *Clin Rheumatol*. 2003;22:299–304.
  63. Lee J, Moon J, Lee S. Comparison of effectiveness according to different approaches of epidural steroid injection in lumbosacral herniated disk and spinal stenosis. *J Back Musculoskelet Rehabil*. 2009;34:83–89.
  64. Manchikanti L, Paganati R, Pampati V. Comparison of three routes of epidural steroid injections in low back pain. *Pain Digest*. 1999;9:277–285.
  65. Schaufele M, Hatch L, Jones W. Interlaminar versus transforaminal epidural injections for the treatment of symptomatic lumbar intervertebral disc herniations. *Pain Physician*. 2006;9:361–366.
  66. Smith C, Booker T, Schaufele M, et al. Interlaminar versus transforaminal epidural steroid injections for the treatment of symptomatic lumbar spinal stenosis. *Pain Med*. 2010;11:1511–1515.
  67. Mendoza-Lattes S, Weiss A, Found E, et al. Comparable effectiveness of caudal vs. trans-foraminal epidural steroid injections. *Iowa Orthop J*. 2009;29:91–96.
  68. Conn A, Buenaventura R, Datta S, et al. Systematic review of caudal epidural injections in the management of chronic low back pain. *Pain Physician*. 2009;12:109–135.
  69. Parr A, Manchikanti L, Hameed H, et al. Caudal epidural injections in the management of chronic low back pain: a systematic appraisal of the literature. *Pain Physician*. 2012;15:E159–E198.
  70. Boswell M, Trescot A, Datta S, et al. Interventional techniques: evidence-based practice guidelines in the management of chronic spinal pain. *Pain Physician*. 2007;10:7–111.
  71. Racz G, Heavner J, Trescot A. Percutaneous lysis of epidural adhesions—evidence for safety and efficacy. *Pain Pract*. 2008;8:277–286.
  72. Almeida D, Prandini M, Awamura Y, et al. Outcome following lumbar disc surgery: the role of fibrosis. *Acta Neurochir (Wien)*. 2008;150:1167–1176.
  73. Rönnerberg K, Lind B, Zoega B, et al. Peridural scar and its relation to clinical outcome: a randomised study on surgically treated lumbar disc herniation patients. *Eur Spine J*. 2008;17:1714–1720.
  74. Ross J, Robertson J, Frederickson R, et al. Association between peridural scar and recurrent radicular pain after lumbar discectomy: magnetic resonance evaluation. ADCON-L European Study Group. *Neurosurgery*. 1996;38:855–863.
  75. Parr A, Diwan S, Abdi S. Lumbar interlaminar epidural injections in managing chronic low back and lower extremity pain: a systematic review. *Pain Physician*. 2009;12:163–188.
  76. Benyamin R, Manchikanti L, Parr A, et al. The effectiveness of lumbar interlaminar epidural injections in the managing chronic low back and lower extremity pain. *Pain Physician*. 2012;15:E363–E404.
  77. Boswell M, Hansen H, Trescot A, Hirsch J. Epidural Steroids in the management of chronic spinal pain. *Pain Physician*. 2003;6:319–334.
  78. Botwin K, Gruber R. Lumbar epidural steroid injections in the patient with lumbar spinal stenosis. *Phys Med Rehabil Clin N Am*. 2003;14:121–141.
  79. Rozenberg S, Dubourg G, Khalifa P, et al. Efficacy of epidural steroids in low back pain and sciatica. A critical appraisal by a French task force of randomized trials. Critical Analysis Group of the French Society of Rheumatology. *Rev Rhum Engl Ed*. 1999;66:79–85.
  80. Staal J, de Bie R, de Vet H, et al. Injection therapy for subacute and chronic low back pain: an updated Cochrane Review. *Spine*. 2009;34:49–59.
  81. Edmond S, Felson D. Prevalence of back symptoms in elders. *J Rheumatol*. 2000;27:220–225.
  82. Cohen S, Gallagher R, Davis S, et al. Spine-area pain in military personnel: a review of epidemiology, etiology, diagnosis, and treatment. *Spine J*. 2012;12:833–842.
  83. Benzon H, Chekka K, Darnule A, et al. Evidence-based case report: the prevention and management of postherpetic neuralgia with emphasis on interventional procedures. *Reg Anesth Pain Med*. 2009;34:514–521.
  84. Pasqualucci A, Pasqualucci V, Galla F, et al. Prevention of postherpetic neuralgia: acyclovir and prednisolone versus epidural local anesthetic and methylprednisolone. *Acta Anaesthesiol Scand*. 2000;44:910–918.
  85. van Wijck A, Opstelten W, Moons K, et al. The PINE study of epidural steroids and local anaesthetics to prevent postherpetic neuralgia: a randomized controlled trial. *Lancet*. 2006;367:219–224.
  86. Benyamin R, Wang V, Vallejo R, et al. A systematic evaluation of thoracic interlaminar epidural injections. *Pain Physician*. 2012;15:E497–E514.
  87. Benyamin R, Singh V, Parr A, et al. Systematic review of the effectiveness of cervical epidurals in the management of chronic neck pain. *Pain Physician*. 2009;12:137–157.
  88. Diwan S, Manchikanti L, Benyamin R, et al. Effectiveness of cervical epidural injections in the management of chronic neck and upper extremity pain. *Pain Physician*. 2012;15:E405–E434.
  89. Stout A. Epidural steroid injections for cervical radiculopathy. *Phys Med Rehabil Clin N Am*. 2011;22:149–159.
  90. Carragee E, Hurwitz E, Cheng I, et al. Treatment of neck pain: injections and surgical interventions: results of the Bone and Joint Decade 2000–2010 Task Force on Neck Pain and Its Associated Disorders. *Spine*. 2008;33:S153–S169.
  91. McGrath J, Schaefer M, Malkamaki D. Incidence and characteristics of complications from epidural steroid injections. *Pain Med*. 2011;12:726–731.
  92. Desai M, Shah B, Sayal P. Epidural contrast flow patterns of transforaminal epidural steroid injections stratified by commonly used final needle-tip position. *Pain Med*. 2011;12:864–870.
  93. Wilkinson I, Cohen S. Epidural steroid injections. *Curr Pain Headache Rep*. 2012;16:50–59.
  94. Buenaventura R, Datta S, Abdi S, Smith H. Systematic review of therapeutic lumbar transforaminal epidural steroid injections. *Pain Physician*. 2009;12:233–251.
  95. Benny B, Azari P. The efficacy of lumbosacral transforaminal epidural steroid injections: a comprehensive literature review. *J Back Musculoskelet Rehabil*. 2011;24:67–76.
  96. Roberts S, Willick S, Rho M, Rittenberg J. Efficacy of lumbosacral transforaminal epidural steroid injections: a systematic review. *PMR*. 2009;1:657–668.
  97. Manchikanti L, Buenaventura R, Manchikanti K, et al. Effectiveness of therapeutic lumbar transforaminal epidural steroid injections in managing lumbar spinal pain. *Pain Physician*. 2012;15:E199–E245.
  98. Jeong H, Lee J, Kim S, et al. Effectiveness of transforaminal epidural steroid injection by using a preganglionic approach. *Radiology*. 2007;245:584–590.
  99. Tafazal S, Ng L, Chaudhary N. Corticosteroids in peri-radicular infiltration for radicular pain: a randomised double blind controlled

- trial. One year results and subgroup analysis. *Eur Spine J*. 2009;18:1220–1225.
100. MacVicar J, King W, Landers M, Bogduk N. The effectiveness of lumbar transforaminal injection of steroids: a comprehensive review with systematic analysis of the published data. *Pain Med*. 2013;14:14–28.
  101. Brouwers P, Kottink E, Simon M, Prevo R. A cervical anterior spinal artery syndrome after diagnostic blockade of the right C6 nerve root. *Pain*. 2001;91:397–399.
  102. Chien G, Candido K, Knezevic N. Digital subtraction angiography does not reliably prevent paraplegia associated with lumbar transforaminal epidural steroid injection. *Pain Physician*. 2012;15:515–523.
  103. Rozin L, Rozin R, Koehler S, et al. Death during transforaminal epidural steroid nerve root block (C7) due to perforation of the left vertebral artery. *Am J Forensic Med Pathol*. 2003;24:351–355.
  104. Anderberg L, Annertz M, Persson L, et al. Transforaminal steroid injections for the treatment of cervical radiculopathy: a prospective and randomised study. *Eur Spine J*. 2007;16:321–328.
  105. Lee J, Park K, Chung S, et al. Cervical transforaminal epidural steroid injection for the management of cervical radiculopathy: a comparative study of particulate versus non-particulate steroids. *Skeletal Radiol*. 2009;38:1077–1082.
  106. Bush K, Hillier S. Outcome of cervical radiculopathy treated with periradicular/epidural corticosteroid injections: a prospective study and independent clinical review. *Eur Spine J*. 1996;5:319–325.
  107. Vallee J, Feydy A, Carlier R, et al. Chronic cervical radiculopathy: lateral approach periradicular corticosteroid injection. *Radiology*. 2001;218:886–892.
  108. Cyteval C, Thomas E, Decoux E, et al. Cervical radiculopathy: open study on percutaneous periradicular foraminal steroid infiltration performed under CT control in 30 patients. *Am J Neuroradiol*. 2004;25:441–445.
  109. Wang A, Pilgram T, Gilula L. Immediate complications and pain relief associated with 296 fluoroscopically guided thoracic foraminal nerve blocks. *Am J Roentgenol*. 2011;197:1410–1416.
  110. Scanlon G, Moeller-Bertram T, Romanowsky S, Wallace M. Cervical transforaminal epidural steroid injections: more dangerous than we think? *Spine*. 2007;32:1249–1256.
  111. Houten J, Errico T. Paraplegia after lumbosacral nerve root block: report of three cases. *Spine J*. 2002;2:70–75.
  112. Huston C. Cervical epidural steroid injections in the management of cervical radiculitis: interlaminar versus transforaminal. A review. *Curr Rev Musculoskelet Med*. 2009;2:30–34.
  113. Manchikanti L, Malla Y, Cash K, et al. Fluoroscopic epidural injections in cervical spinal stenosis: preliminary results of a randomized, double-blind, active control trial. *Pain Physician*. 2012;15:E59–E70.
  114. Manchikanti L, Malla Y, Cash K, et al. Fluoroscopic cervical interlaminar epidural injections in managing chronic pain of cervical postsurgery syndrome: preliminary results of a randomized, double-blind, active control trial. *Pain Physician*. 2012;15:13–25.
  115. Manchikanti L, Cash K, Pampati V, et al. Management of chronic pain of cervical disc herniation and radiculitis with fluoroscopic cervical interlaminar epidural injections. *Int J Med Sci*. 2012;9:424–434.
  116. Manchikanti L, Cash K, McManus C, et al. A preliminary report of a randomized double-blind, active controlled trial of fluoroscopic thoracic interlaminar epidural injections in managing chronic thoracic pain. *Pain Physician*. 2010;13:E357–E369.
  117. Johnson B, Schellhas K, Pollei S. Epidurography and therapeutic epidural injections: technical considerations and experience with 5334 Cases. *AJNR*. 1999;20:697–705.
  118. Nelemans P, deBie R, deVe H, et al. Injection therapy for subacute and chronic benign low back pain. *Spine*. 2001;26:501–515.
  119. DePalma M, Bhargava A, Slipman C. A critical appraisal of the evidence for selective nerve root injection in the treatment of lumbosacral radiculopathy. *Arch Phys Med Rehabil*. 2005;86:1477–1483.
  120. Bicket M, Gupta A, Brown C, Cohen SP. Epidural injections for spinal pain: What constitutes a treatment versus a control. A systematic review and meta-analysis. Accepted with revisions to *Anesthesiology* 3/2013.
  121. Egsmose C, Lund B, Bach Andersen R. Hip joint distension in osteoarthritis. A triple-blind controlled study comparing the effect of intra-articular indoprofen with placebo. *Scand J Rheumatol*. 1984;13:238–242.
  122. Owlia M, Salimzadeh A, Alishiri G, Haghghi A. Comparison of two doses of corticosteroid in epidural steroid injection for lumbar radicular pain. *Singapore Med J*. 2007;48:241–245.
  123. Kang S, Hwang B, Son H, et al. The dosages of corticosteroid in transforaminal epidural steroid injections for lumbar radicular pain due to a herniated disc. *Pain Physician*. 2011;14:361–370.
  124. Revel M, Auleley G, Alaoui S, et al. Forceful epidural injections for the treatment of lumbosacral pain with post-operative lumbar spinal fibrosis. *Rev Rhum Engl Ed*. 1996;63:270–277.
  125. Kim D, Brown J. Efficacy and safety of lumbar epidural dexamethasone versus methylprednisolone in the treatment of lumbar radiculopathy: a comparison of soluble versus particulate steroids. *Clin J Pain*. 2011;27:518–522.
  126. Dreyfuss P, Baker R, Bogduk N. Comparative effectiveness of cervical transforaminal injections with particulate and nonparticulate corticosteroid preparations for cervical radicular pain. *Pain Med*. 2006;7:237–242.
  127. Park C, Lee S, Kim B. Comparison of the effectiveness of lumbar transforaminal epidural injection with particulate and nonparticulate corticosteroids in lumbar radiating pain. *Pain Med*. 2010;11:1654–1658.
  128. Noe C, Haynsworth R Jr. Comparison of epidural Depo-Medrol vs. aqueous betamethasone in patients with low back pain. *Pain Pract*. 2003;3:222–225.
  129. Shakir A, Ma V, Mehta B. Comparison of pain score reduction using triamcinolone vs. dexamethasone in cervical transforaminal epidural steroid injections [published online ahead of print January 30, 2013]. *Am J Phys Med Rehabil*. 2013.
  130. Pinto R, Maher C, Ferreira M, et al. Epidural corticosteroid injections in the management of sciatica: a systematic review and meta-analysis. *Ann Intern Med*. 2012;157:865–877.
  131. Armon C, Argoff C, Samuels J, Backonja M. Assessment: use of epidural steroid injections to treat radicular lumbosacral pain: report of Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology*. 2007;68:723–729.
  132. Stout A. Epidural steroid injections for low back pain. *Phys Med Rehabil Clin N Am*. 2010;21:825–834.
  133. Airaksinen O, Brox J, Cedraschi C, et al. COST B13 Working Group on Guidelines for Chronic Low Back Pain. European guidelines for the management of chronic nonspecific low back pain. *Eur Spine J*. 2006;15(suppl 2):S192–S300.
  134. Kwon J, Lee J, Kim S, et al. Cervical interlaminar epidural steroid injection for neck pain and cervical radiculopathy: effect and prognostic factors. *Skeletal Radiol*. 2007;36:431–436.
  135. Rivest C, Katz J, Ferrante F, et al. Effects of epidural steroid injection on pain due to lumbar spinal stenosis or herniated disks: a prospective study. *Arthritis Care Res*. 1998;11:291–297.
  136. Riew K, Yin Y, Gilula L, et al. The effect of nerve-root injections on the need for operative treatment of lumbar radicular pain. A prospective,

- randomized, controlled, double-blind study. *J Bone Joint Surg Am.* 2000;11:1589–1593.
137. Wilson-MacDonald J, Burt G, Griffin D, et al. Epidural steroid injection for nerve root compression. A randomised, controlled trial. *J Bone Joint Surg Br.* 2005;87:352–355.
  138. Fish D, Kobayashi H, Chang T, Pham Q. MRI prediction of therapeutic response to epidural steroid injection in patients with cervical radiculopathy. *Am J Phys Med Rehabil.* 2009;3:239–246.
  139. Goodyear-Smith F, van Driel M, Arroll B, Del Mar C. Analysis of decisions made in meta-analyses of depression screening and the risk of confirmation bias: a case study. *BMC Med Res Methodol.* 2012;12:76.
  140. Bowden J, Jackson D, Thompson S. Modelling multiple sources of dissemination bias in meta-analysis. *Stat Med.* 2010;29:945–955.
  141. American Academy of Physical Medicine and Rehabilitation. Educational guidelines for interventional spinal procedures. Pauza KJ, editor. Updated and approved in October 2008. Available at: <http://www.aapmr.org/practice/guidelines/Documents/edguidelines.pdf>. Accessed January 14, 2013.
  142. Bogduk N. *Practice Guidelines for Spinal Diagnostic and Treatment Procedures*. San Francisco, CA: International Spinal Intervention Society; 2004.
  143. Manchikanti L, Boswell M, Singh V, et al. Comprehensive evidence-based guidelines for interventional techniques in the management of chronic spinal pain. *Pain Physician.* 2009;12:699–802.
  144. Novak S, Nemeth W. The basis for recommending repeating epidural steroid injections for radicular low back pain: a literature review. *Arch Phys Med Rehabil.* 2008;89:543–552.
  145. Ng L, Chaudhary N, Sell P. The efficacy of corticosteroids in periradicular infiltration for chronic radicular pain: a randomized, double-blind, controlled trial. *Spine.* 2005;30:857–862.
  146. Karppinen J, Malmivaara A, Kurunlahti M, et al. Periradicular infiltration for sciatica: a randomized controlled trial. *Spine.* 2001;26:1059–1067.
  147. Koc Z, Ozcakar S, Sivrioglu K, et al. Effectiveness of physical therapy and epidural steroid injections in lumbar spinal stenosis. *Spine.* 2009;34:985–989.
  148. Laiq N, Khan M, Iqbal M, Khan S. Comparison of epidural steroid injections with conservative management in patients with lumbar radiculopathy. *J Coll Physicians Surg Pak.* 2009;19:539–543.
  149. Cohen S, Argoff C, Carragee E. Management of low back pain. *BMJ.* 2008;337:a2718.
  150. Kuijpers T, van Middelkoop M, Rubinstein S, et al. A systematic review on the effectiveness of pharmacological interventions for chronic non-specific low-back pain. *Eur Spine J.* 2011;20:40–50.
  151. Brown L. A double-blind, randomized, prospective study of epidural steroid injection vs. the MILD(®) procedure in patients with symptomatic lumbar spinal stenosis. *Pain Pract.* 2012;12:333–341.
  152. Gerszten P, Smuck M, Rathmell J, et al. SPINE Study Group. Plasma disc decompression compared with fluoroscopy-guided transforaminal epidural steroid injections for symptomatic contained lumbar disc herniation: a prospective, randomized, controlled trial. *J Neurosurg Spine.* 2010;12:357–371.
  153. Buttermann G. Treatment of lumbar disc herniation: epidural steroid injection compared with discectomy. A prospective, randomized study. *J Bone Joint Surg Am.* 2004;86:670–679.
  154. Kapthuk T, Stason W, Davis R, et al. Sham device v inert pill: randomised controlled trial of two placebo treatments. *BMJ.* 2006;332:391–397.
  155. Teasell R. Compensation and chronic pain. *Clin J Pain.* 2001;17:S46–S64.
  156. Dworkin R, Turk D, Farrar J, et al. Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. *Pain.* 2005;113:9–19.
  157. Deyo R, Gray D, Kreuter W, et al. United States trends in lumbar fusion surgery for degenerative conditions. *Spine.* 2005;30:1441–1445.
  158. Gray D, Deyo R, Kreuter W, et al. Population-based trends in volumes and rates of ambulatory lumbar spine surgery. *Spine.* 2006;31:1957–1963.
  159. Friedly J, Chan L, Deyo R. Geographic variation in epidural steroid injection use in Medicare patients. *J Bone Joint Surg Am.* 2008;90:1730–1737.
  160. Riew K, Park J, Cho Y, et al. Nerve root blocks in the treatment of lumbar radicular pain. A minimum five-year follow-up. *J Bone Joint Surg Am.* 2006;88:1722–1725.
  161. Rasmussen S, Krum-Møller D, Lauridsen L, et al. Epidural steroid following discectomy for herniated lumbar disc reduces neurological impairment and enhances recovery: a randomized study with two-year follow-up. *Spine.* 2008;33:2028–2033.
  162. Radcliff K, Hilibrand A, Lurie J, et al. The impact of epidural steroid injections on the outcomes of patients treated for lumbar disc herniation: a subgroup analysis of the SPORT trial. *J Bone Joint Surg Am.* 2012;94:1353–1358.
  163. Radcliff K, Kepler C, Hilibrand A, et al. Epidural steroid injections are associated with less improvement in the treatment of lumbar spinal stenosis: a subgroup analysis of the SPORT. *Spine.* 2013;38:279–291.
  164. Narozny M, Zanetti M, Boos N. Therapeutic efficacy of selective nerve root blocks in the treatment of lumbar radicular leg pain. *Swiss Med Wkly.* 2001;131:75–80.
  165. Manson N, McKeon M, Abraham E. Transforaminal epidural steroid injections prevent the need for surgery in patients with sciatica secondary to lumbar disc herniation: a retrospective case series. *Can J Surg.* 2013;56:014611–014611.
  166. Arden N, Price C, Reading I, et al. A multicentre randomized controlled trial of epidural corticosteroid injections for sciatica: the WEST study. *Rheumatology.* 2005;44:1399–1406.
  167. Carette S, Leclaire R, Marcoux S, et al. Epidural corticosteroid injections for sciatica due to herniated nucleus pulposus. *N Engl J Med.* 1997;336:1634–1640.
  168. Dilke T, Burry H, Grahame R. Extradural corticosteroid injection in management of lumbar nerve root compression. *Br Med J.* 1973;2:635–637.
  169. Price C, Arden N, Coglán L, et al. Cost-effectiveness and safety of epidural steroids in the management of sciatica. *Health Technol Assess.* 2005;9:1–58.
  170. Ghahreman A, Bogduk N. Predictors of a favorable response to transforaminal injection of steroids in patients with lumbar radicular pain due to disc herniation. *Pain Med.* 2011;12:871–879.
  171. Cuckler J, Bernini P, Wiesel S, et al. The use of epidural steroids in the treatment of lumbar radicular pain. A prospective, randomized, double-blind study. *J Bone Joint Surg Am.* 1985;67:63–66.
  172. Bush K, Hillier S. A controlled study of caudal epidural injections of triamcinolone plus procaine for the management of intractable sciatica. *Spine.* 1991;16:572–575.
  173. Klenerman L, Greenwood R, Davenport H, et al. Lumbar epidural injections in the treatment of sciatica. *Br J Rheumatol.* 1984;23:35–38.
  174. Kraemer J, Ludwig J, Bickert U, et al. Lumbar epidural perineural injection: a new technique. *Eur Spine J.* 1997;6:357–361.
  175. Snoek W, Weber H, Jørgensen B. Double blind evaluation of extradural methyl prednisolone for herniated lumbar discs. *Acta Orthop Scand.* 1977;48:635–641.

176. Mathews J, Mills S, Jenkins V, et al. Back pain and sciatica: controlled trials of manipulation, traction, sclerosant and epidural injections. *Br J Rheumatol*. 1987;26:416–423.
177. Valat J, Giraudeau B, Rozenberg S, et al. Epidural corticosteroid injections for sciatica: a randomized, double blind, controlled clinical trial. *Ann Rheum Dis*. 2003;62:639–643.
178. Cohen S, White R, Kurihara C, et al. Epidural steroids, etanercept or saline in subacute sciatica: a multicenter, randomized trial. *Ann Intern Med*. 2012;156:551–559.
179. Iversen T, Solberg T, Romner B, et al. Effect of caudal epidural steroid or saline injection in chronic lumbar radiculopathy: multicentre, blinded, randomised controlled trial. *BMJ*. 2011;343:d5278.
180. Sayegh F, Kenanidis E, Papavasiliou K, et al. Efficacy of steroid and nonsteroid caudal epidural injections for low back pain and sciatica: a prospective, randomized, double-blind clinical trial. *Spine*. 2009;34:1441–1447.
181. Breivik H, Hesla P, Molnar I, Lind B. Treatment of chronic low back pain and sciatica. Comparison of caudal epidural injections of bupivacaine and methylprednisolone with bupivacaine followed by saline. *Adv Pain Res Ther*. 1976;1:927–932.
182. Rogers P, Nash T, Schiller D, Norman J. Epidural steroids for sciatica. *Pain Clin*. 1992;5:67–72.
183. Gilron I, Johnson A. Economics of chronic pain: how can science guide health policy? *Can J Anesth*. 2010;57:530–538.
184. Manchikanti L, Singh V, Cash K, et al. Preliminary results of randomized, equivalence trial of fluoroscopic caudal epidural injections in managing chronic low back pain: part 2. Disc herniation and radiculitis. *Pain Physician*. 2008;11:801–815.
185. Manchikanti L, Singh V, Falco F, et al. Evaluation of the effectiveness of lumbar interlaminar epidural injections in managing chronic pain of lumbar disc herniation or radiculitis: a randomized, double-blind, controlled trial. *Pain Physician*. 2010;13:343–355.
186. Manchikanti L, Singh V, Cash K, et al. Preliminary results of randomized, equivalence trial of fluoroscopic caudal epidural injections in managing chronic low back pain: part 3. Post surgery syndrome. *Pain Physician*. 2008;11:817–831.
187. Manchikanti L, Cash K, McManus C, et al. Fluoroscopic lumbar interlaminar epidural injections in managing chronic lumbar axial or discogenic pain. *J Pain Res*. 2012;5:301–311.
188. Manchikanti L, Cash K, Pampati V, Malla Y. Fluoroscopic cervical epidural injections in chronic axial or disc-related neck pain without disc herniation, facet joint pain, or radiculitis. *J Pain Res*. 2012;5:227–236.
189. Manchikanti L, Cash K, McManus C, et al. The preliminary results of a comparative effectiveness evaluation of adhesiolysis and caudal epidural injections in managing chronic low back pain secondary to spinal stenosis: a randomized, equivalence controlled trial. *Pain Physician*. 2009;12:E341–E354.
190. Manchikanti L, Cash K, McManus C, et al. Lumbar interlaminar epidural injections in central spinal stenosis: preliminary results of a randomized, double-blind, active control trial. *Pain Physician*. 2012;15:51–63.
191. Manchikanti L, Cash K, McManus C, et al. Results of 2-year follow-up of a randomized, double-blind, controlled trial of fluoroscopic caudal epidural injections in central spinal stenosis. *Pain Physician*. 2012;15:371–384.
192. Straus B. Chronic pain of spinal origin: the costs of intervention. *Spine*. 2002;27:2614–2619.
193. Rodriguez M, Garcia A. A registry of the aetiology and costs of neuropathic pain in pain clinics: results of the registry of aetiologies and costs (REC) in neuropathic pain disorders study. *Clin Drug Investig*. 2007;27:771–782.
194. Dworkin R, O'Connor A, Backonja M, et al. Pharmacologic management of neuropathic pain: evidence based recommendations. *Pain*. 2007;132:237–251.
195. Dworkin R, O'Connor A, Aydtette J, et al. Recommendations for the pharmacological management of neuropathic pain: an overview and literature update. *Mayo Clin Proc*. 2010;85:S3–S14.
196. Finnerup N, Jensen T. Mechanisms of disease: mechanism-based classification of neuropathic pain—a critical analysis. *Nat Clin Pract Neurol*. 2006;2:107–115.
197. Baron R. Mechanisms of disease: neuropathic pain: a clinical perspective. *Nat Clin Pract Neurol*. 2006;2:95–106.
198. Attal N, Cruccu G, Baron R, et al. EFNS guidelines on the pharmacological treatment of neuropathic pain: 2010 revision. *Eur J of Neurol*. 2010;17:1113–1123.
199. Haanpaa M, Backonja M, Bennett M, et al. Assessment of neuropathic pain in primary care. *Am J Med*. 2009;122:S13–S21.
200. Schmader K, Baron R, Haanpaa M, et al. Treatment considerations for elderly and frail patients with neuropathic pain. *Mayo Clin Proc*. 2010;85:S26–S32.
201. Hoving J, de Vet H, Twisk J, et al. Prognostic factors for neck pain in general practice. *Pain*. 2004;110:639–645.
202. Wilkens P, Scheel IB, Grundnes O, et al. Prognostic factors of prolonged disability in patients with chronic low back pain and lumbar degeneration in primary care: a cohort study. *Spine*. 2013;38:65–74.
203. Borghouts J, Koes B, Bouter L. The clinical course and prognostic factors of non-specific neck pain: a systematic review. *Pain*. 1998;77:1–13.
204. Gore D, Sepic S, Gardner G, et al. Neck pain: a long-term follow-up of 205 patients. *Spine*. 1987;12:1–5.
205. Enthoven P, Skargren E, Oberg B. Clinical course in patients seeking primary care for back or neck pain: a prospective 5-year follow-up of outcome and health care consumption with subgroup analysis. *Spine (Phila Pa 1976)*. 2004;29:2458–2465.
206. Webster B, Verma S, Gatchel R. Relationship between early opioid prescribing for acute occupational low back pain and disability duration, medical costs, subsequent surgery and late opioid use. *Spine*. 2007;32:2127–2132.
207. Fillingim R, Doleys D, Edwards R, et al. Clinical characteristics of chronic back pain as a function of gender and oral opioid use. *Spine*. 2003;28:143–150.
208. Chan C, Peng P. Failed back surgery syndrome. *Pain Med*. 2011;12:577–606.
209. Anderson V, Israel Z. Failed back surgery syndrome. *Curr Rev Pain*. 2000;4:105–111.
210. Costa Lda C, Maher C, McAuley J, et al. Prognosis for patients with chronic low back pain: inception cohort study. *BMJ*. 2009;339:b3829.
211. Linton S. A review of psychological risk factors in back and neck pain. *Spine (Phila Pa 1976)*. 2000;25:1148–1156.
212. Bolton J, Humphreys B. The Bournemouth Questionnaire: a short-form comprehensive outcome measure. II. Psychometric properties in neck pain patients. *J Manipulative Physiol Ther*. 2002;25:141–148.
213. Gatchel R, Gardea M. Psychosocial issues: their importance in predicting disability, response to treatment, and search for compensation. *Neurol Clin*. 1999;17:149–166.
214. Pincus T, Burton A, Vogel S, et al. A systematic review of psychosocial factors as predictors of chronicity/disability in prospective cohorts of low back pain. *Spine*. 2002;27:E109–E120.

215. Benjamin S, Barnes D, Berger S, et al. The relationship of chronic pain, mental illness and organic disorders. *Pain*. 1988;32:185–195.
216. Carroll L, Hogg-Johnson S, van der Velde G, et al. Course and prognostic factors for neck pain in the general population: results of the Bone and Joint Decade 2000–2010 Task Force on Neck Pain and Its Associated Disorders. *J Manipulative Physiol Ther*. 2009;32:S87–S96.
217. Rasmussen C, Leboeuf-Yde C, Hestbaek L, et al. Poor outcome in patients with spine-related leg or arm pain who are involved in compensation claims: a prospective study of patients in the secondary care sector. *Scand J Rheumatol*. 2008;37:462–468.
218. den Boer J, Oostendorp R, Beems T, et al. A systematic review of bio-psychosocial risk factors for an unfavourable outcome after lumbar disc surgery. *Eur Spine J*. 2006;15:527–536.
219. Fishbain D, Cole B, Cutler R, et al. A structured evidence-based review on the meaning of nonorganic physical signs: Waddell signs. *Pain Med*. 2003;4:141–181.
220. Jamison R, Vadeboncouer T, Ferrante F. Low back pain patients unresponsive to an epidural steroid injection: identifying predictive factors. *Clin J Pain*. 1991;7:311–317.
221. Hopwood M, Abram S. Factors associated with failure of lumbar steroids. *Reg Anesth*. 1993;18:238–243.
222. Kirpalani D, Mitra R. Is chronic opioid use a negative predictive factor for response to cervical epidural steroid injections? *J Back Musculoskelet Rehabil*. 2011;24:123–127.
223. Ferrante F, Wilson S, Iacobo C, et al. Clinical classification as a predictor of therapeutic outcome after cervical epidural steroid injection. *Spine*. 1993;18:730–736.
224. Kapural L, Mekhail N, Bena J, et al. Value of the magnetic resonance imaging in patients with painful lumbar spinal stenosis (LSS) undergoing lumbar epidural steroid injections. *Clin J Pain*. 2007;23:571–575.
225. Liphofor J, Theodoridis T, Becker G, et al. (Modic) signal alterations of vertebral endplates and their correlation to a minimally invasive treatment of lumbar disc herniation using epidural injections. *Rofo*. 2006;178:1105–1114.
226. Buttermann G. The effect of spinal steroid injections for degenerative disc disease. *Spine J*. 2004;4:495–505.
227. Schiff E, Eisenberg E. Can quantitative sensory testing predict the outcome of epidural steroid injections in sciatica? A preliminary study. *Anesth Analg*. 2003;97:828–832.
228. Cohen S, Mao J, Vu TN, et al. Does pain score in response to a standardized subcutaneous local anesthetic injection predict epidural steroid injection outcomes in patients with lumbosacral radiculopathy? A prospective correlational study. *Pain Med*. 2013;14:327–335.
229. Centers for Disease Control and Prevention, Multistate Fungal Meningitis Outbreak Investigation. Available at: <http://www.cdc.gov/hai/outbreaks/meningitis.html>. Accessed December 31, 2012.
230. Nelson D. Dangers from methylprednisolone acetate therapy by intraspinal injection. *Arch Neurol*. 1988;45:804–806.
231. Fitzgibbon D, Posner K, Caplan R, et al. Chronic pain management: American Society of Anesthesiologists Closed Claims Project. *Anesthesiology*. 2004;100:98–105.
232. Wright M, Denney L. A comprehensive review of spinal arachnoiditis. *Orthop Nurs*. 2003;22:215–219.
233. Bedford T. The effect of injected solutions on the cell count of the cerebrospinal fluid. *Br J Pharmacol*. 1948;3:80–83.
234. Nelson D, Vates T, Thomas R. Complications from intrathecal steroid therapy in patients with multiple sclerosis. *Acta Neurol Scand*. 1973;49:176–188.
235. Bernat J, Sadowski C, Vincent F, et al. Sclerosing spinal pachymeningitis. *J Neurol Neurosurg Psychiatr*. 1976;39:1124–1128.
236. Carta F, Canu C, Datti R, et al. Calcification and ossification of the spinal arachnoid after intrathecal injection of Depo Medrol. *Zentralbl Neurochir*. 1987;48:256–261.
237. Ryan M, Taylor T. Management of lumbar nerve root pain by intrathecal and epidural injection of depot methylprednisolone acetate. *Med J Aust*. 1981;2:532–534.
238. Seghal A, Tweed D, Gardner W, et al. Laboratory studies after intrathecal corticosteroids. *Arch Neurol*. 1963;9:74–78.
239. Goldstein N, McKenzie B, McGuckin W. Changes in cerebrospinal fluid of patients with multiple sclerosis after treatment with intrathecal methylprednisolone acetate: a preliminary report. *Mayo Clin Proc*. 1962;37:657–668.
240. Abram S. The use of epidural steroid injections for the treatment of lumbar radiculopathy. *Anesthesiology*. 1999;91:1937–1941.
241. Gutknecht D. Chemical meningitis following epidural injections of corticosteroids. *Am J Med*. 1987;82:570.
242. Plumb V, Dismukes W. Chemical meningitis related to intrathecal corticosteroid therapy. *South Med J*. 1977;70:1241–1243.
243. Morris J, Konkol K, Longfield R. Chemical meningitis following epidural methylprednisolone injection. *Infect Med*. 1994;11:439–440.
244. Kotani N, Kushikata T, Hashimoto H, et al. Intrathecal methylprednisolone for intractable postherpetic neuralgia. *N Engl J Med*. 2000;343:1514–1519.
245. Margolis G, Hall H, Nowill W. An investigation of efocaine, a long acting anesthetic agent. *Arch Surg*. 1953;61:715–730.
246. Chino N, Awad E, Kottke F. Pathology of propylene glycol administered by perineural and intramuscular injection in rats. *Arch Phys Med Rehabil*. 1974;55:33–38.
247. Benzon H, Gissen A, Strichartz G, et al. The effect of polyethylene glycol on mammalian nerve impulses. *Anesth Analg*. 1987;66:553–559.
248. Delaney T, Rowlingson J, Carron H, et al. Epidural steroid effects on nerves and meninges. *Anesth Analg*. 1980;59:610–614.
249. Abram S, Marsala M, Yaksh T. Analgesic and neurotoxic effects of intrathecal corticosteroids in rats. *Anesthesiology*. 1994;81:1198–1205.
250. Barnes B, Fish M. Chemical meningitis as a complication of isotope cisternography. *Neurology*. 1972;22:83–91.
251. Deland F. Intrathecal toxicity studies with benzyl alcohol. *Toxicol Appl Pharmacol*. 1973;25:153–156.
252. Latham J, Fraser R, Moore R, et al. The pathologic effects of intrathecal betamethasone. *Spine*. 1997;22:1558–1562.
253. Rathmell J, Michna E, Fitzgibbon D, et al. Injury and liability associated with cervical procedures for chronic pain. *Anesthesiology*. 2011;114:918–926.
254. Rathmell J, Aprill C, Bogduk N. Cervical transforaminal injection of steroids. *Anesthesiology*. 2004;100:1595–1600.
255. Field J, Rathmell J, Stephenson J, Katz N. Neuropathic pain following cervical epidural steroid injection. *Anesthesiology*. 2000;93:885–888.
256. Hodges S, Castleberg R, Miller T, et al. Cervical epidural steroid injection with intrinsic spinal cord damage: two case reports. *Spine*. 1998;23:2137–2140.
257. Tiso R, Cutler T, Catania J, et al. Adverse central nervous system sequelae after selective transforaminal block: the role of corticosteroids. *Spine J*. 2004;4:468–474.
258. Baker R, Dreyfuss P, Mercer S, Bogduk N. Cervical transforaminal injection of corticosteroids into a radicular artery: a possible mechanism for spinal cord injury. *Pain*. 2003;103:211–215.
259. Kennedy D, Dreyfuss P, Aprill C, Bogduk N. Paraplegia following image-guided transforaminal lumbar spine epidural steroid injection: two case reports. *Pain Med*. 2009;10:1389–1394.

260. Glaser S, Falco F. Paraplegia following a thoracolumbar transforaminal epidural steroid injection. *Pain Physician*. 2005;8:309–314.
261. Benzon H, Chew T, McCarthy R, et al. Comparison of the particle sizes of different steroids and the effect of dilution: a review of the relative neurotoxicities of the steroids. *Anesthesiology*. 2007;106:331–338.
262. Okubadejo G, Talcott M, Schmidt R, et al. Perils of intravascular methylprednisolone injection into the vertebral artery. An animal study. *J Bone Joint Surg Am*. 2008;90:1932–1938.
263. Hall E, Springer J. Neuroprotection and acute spinal cord injury: a reappraisal. *Neuro Rx*. 2004;1:80–100.
264. Knight C, Burnell J. Systemic side effects of extradural steroids. *Anaesthesia*. 1980;35:593–594.
265. Stambough J, Booth R, Rothman R. Transient hypercorticism after epidural steroid injection. *J Bone Joint Surg*. 1984;66A:1115–1116.
266. Tuel S, Meythaler J, Cross L. Cushing's syndrome from methylprednisolone. *Pain*. 1990;40:81–84.
267. Jacobs S, Pullan P, Potter J, et al. Adrenal suppression following extradural steroids. *Anaesthesia*. 1983;38:953–956.
268. Kay J, Findling J, Raff H. Epidural triamcinolone suppresses the pituitary-adrenal axis in human subjects. *Anesth Analg*. 1994;79:501–505.
269. Boonen S, Van Distel G, Westhovens R, et al. Steroid myopathy induced by epidural triamcinolone injection. *Br J Rheumatol*. 1995;34:385–386.
270. Munck A. Glucocorticoid inhibition of glucose uptake by peripheral tissues: old and new evidence, molecular mechanisms and physiological significance. *Pers Med Biol*. 1971;14:265–269.
271. Even J, Crosby C, Song Y, et al. Effects of epidural steroid injections on blood glucose levels in patients with diabetes mellitus. *Spine*. 2012;37:E46–E50.
272. Zufferey P, Bulliard C, Gremion G, et al. Systemic effects of epidural methylprednisolone injection on glucose tolerance in diabetic patients. *BMC Res Notes*. 2011;4:552.
273. Charsley M, Abram S. The injection of intrathecal normal saline reduces the severity of postdural puncture headache. *Reg Anesth Pain Med*. 2001;26:301–305.
274. Abram S, Cherwenka R. Transient headache immediately following epidural steroid injection. *Anesthesiology*. 1979;50:461–462.
275. Katz J, Lukin R, Bridenbaugh P, et al. Subdural intracranial air: an unusual cause of headache after epidural steroid injection. *Anesthesiology*. 1991;74:615–618.
276. Simopoulos T, Peeters-Asdourian C. Pneumocephalus after cervical epidural steroid injection. *Anesth Analg*. 2001;9:1576–1577.
277. Moon J, Lee P, Nahm F, et al. Cervical epidural pressure measurement: comparison in the prone and sitting positions. *Anesthesiology*. 2010;113:666–671.
278. Liu S, Melmed A, Klos J, et al. Prospective experience with a 20-gauge Tuohy needle for lumbar epidural steroid injections: is confirmation with fluoroscopy necessary? *Reg Anesth Pain Med*. 2001;26:143–146.
279. Harrington B, Schmitt A. Meningeal (postdural) puncture headache, unintentional dural puncture, and the epidural blood patch: a national survey of United States practice. *Reg Anesth Pain Med*. 2009;34:430–437.
280. Williams K, Jackowski A, Evans P. Epidural hematoma requiring surgical decompression following repeated epidural steroid injections for chronic pain. *Pain*. 1990;42:197–199.
281. Reitman C, Watters W. Subdural hematoma after cervical epidural steroid injection. *Spine*. 2002;27:E174–E176.
282. Benzon H, Wong H, Siddiqui T, et al. Caution in performing epidural injections in patients on several antiplatelet drugs. *Anesthesiology*. 1999;91:1558.
283. Horlocker T, Bajwa Z, Zubaira A, et al. Risk assessment of hemorrhagic complications associated with nonsteroidal anti-inflammatory medications in ambulatory pain clinic patients undergoing epidural steroid injection. *Anesth Analg*. 2002;95:1691–1697.
284. Horlocker T, Wedel D, Rowlingson J, et al. Regional anesthesia in the patient receiving antithrombotic or thrombolytic therapy: American Society of Regional Anesthesia and Pain Medicine Evidence-Based Guidelines (Third Edition). *Reg Anesth Pain Med*. 2010;35:64–101.
285. Manchikanti L, Benyamin R, Swicegood J, et al. Assessment of practice patterns of perioperative management of antiplatelet and anticoagulant therapy in interventional pain management. *Pain Physician*. 2012;15:E955–E968.
286. Tang H, Lin H, Liu Y, et al. Spinal epidural abscess—experience with 46 patients and evaluation of prognostic factors. *J Infection*. 2002;45:76–81.
287. Hooten W, Kinney M, Huntoon M. Epidural abscess and meningitis after epidural corticosteroid injection. *Mayo Clin Proc*. 2004;79:682–686.
288. Huang R, Shapiro G, Lim M, et al. Cervical epidural abscess after epidural steroid injection. *Spine*. 2004;29:E7–E9.
289. Yue W, Tan S. Distant skip level discitis and vertebral osteomyelitis after caudal epidural infection: a case report of a rare complication of epidural injections. *Spine*. 2003;28:E209–E211.
290. Shealy C. Dangers of spinal injections without proper diagnosis. *JAMA*. 1966;197:156–158.
291. Saigal G, DonovanPost M, Kozic D. Thoracic intradural *Aspergillus* abscess formation following epidural steroid injection. *Am J Neuroradiol*. 2004;25:642–644.
292. Kainer M, Reagan D, Nguyen D, et al. Fungal infections associated with contaminated methylprednisolone in Tennessee. *N Engl J Med*. 2012;367:2194–2203.
293. Manunga J Jr, Olak J, Rivera C, Martin M. Prevalence of methicillin-resistant *Staphylococcus aureus* in elective surgical patients at a public teaching hospital: an analysis of 1039 patients. *Am Surg*. 2012;78:1096–1099.
294. Rathmell J, Lake T, Ramundo M. Infectious risks of chronic pain treatments: injection therapy, surgical implants, and intradiscal techniques. *Reg Anesth Pain Med*. 2006;31:346–352.
295. Kang S, Hwang B, Son H, et al. Changes in bone mineral density in postmenopausal women treated with epidural steroid injections for lower back pain. *Pain Physician*. 2012;15:229–236.
296. Yi Y, Hwang B, Son H, Cheong I. Low bone mineral density, but not epidural steroid injection, is associated with fracture in postmenopausal women with low back pain. *Pain Physician*. 2012;15:441–449.
297. Trentman T, Rosenfeld D, Seamans D, et al. Vasovagal reactions and other complications of cervical vs. lumbar translaminar epidural steroid injections. *Pain Pract*. 2009;9:59–64.
298. Rathmell J. *Atlas of Image-Guided Intervention in Regional Anesthesia and Pain Medicine*. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2012.
299. Becker C, Heidersdorf S, Drewlo S, et al. Efficacy of epidural perineural injections with autologous conditioned serum for lumbar radicular compression. *Spine*. 2007;32:1803–1808.
300. Beliveau P. A comparison between epidural anaesthesia with and without corticosteroid in the treatment of sciatica. *Rheumatol Phys Med*. 1971;11:40–43.

301. Ghahreman A, Ferch R, Bogduk N. The efficacy of transforaminal injection of steroids for the treatment of lumbar radicular pain. *Pain Med.* 2010;11:1149–1168.
302. Hesla E, Breivik H. Epidural analgesia and epidural steroid injection for treatment of chronic low back pain and sciatica. *Tidsskr Nor Laegeforen.* 1979;99:936–939.
303. Meadeb J, Rozenberg S, Duquesnoy B. Forceful sacrococcygeal injections in the treatment of postdiscectomy sciatica. A controlled study versus glucocorticoid injections. *Joint Bone Spine.* 2001;68:43–49.
304. Nam H, Park Y. Effects of transforaminal injection for degenerative lumbar scoliosis combined with spinal stenosis. *Ann Rehabil Med.* 2011;35:514–523.
305. Ridley M, Kingsley G, Gibson T, Grahame R. Outpatient lumbar epidural corticosteroid injection in the management of sciatica. *Br J Rheumatol.* 1988;27:295–299.
306. Rocco A, Frank E, Kaul A, et al. Epidural steroids, epidural morphine and epidural steroids combined with morphine in the treatment of post-laminectomy syndrome. *Pain.* 1989;36:297–303.
307. Stav A, Ovadia L, Sternberg A, et al. Cervical epidural steroid injection for cervicobrachialgia. *Acta Anaesthesiol Scand.* 1993;37:562–566.
308. Vad V, Bhat A, Lutz G, Cammisa F. Transforaminal epidural steroid injections in lumbosacral radiculopathy: a prospective randomized study. *Spine (Phila Pa 1976).* 2002;27:11–16.
309. Lee J, Kim S, Choi J, et al. Transforaminal epidural steroid injection for lumbosacral radiculopathy: preganglionic versus conventional approach. *Korean J Radiol.* 2006;7:139–144.
310. Ranguis S, Li D, Webster A. Perioperative epidural steroids for lumbar spine surgery in degenerative spinal disease. A review. *J Neurosurg Spine.* 2010;13:45–57.
311. Karnezis I. Minimally invasive therapeutic interventional procedures in the spine: an evidence-based review. *Surg Technol Int.* 2008;17:259–268.
312. Deyo R, Mirza S, Turner J, et al. Overtreating chronic back pain: time to back off? *J Am Board Fam Med.* 2009;22:62–68.
313. Quraishi N. Transforaminal injection of corticosteroids for lumbar radiculopathy: systematic review and meta-analysis. *Eur Spine J.* 2012;21:214–219.
314. Abdi S, Datta S, Trescot A, et al. Epidural steroids in the management of chronic spinal pain: a systematic review. *Pain Physician.* 2007;10:185–212.
315. Balagué F, Piguet V, Dudler J. Steroids for LBP—from rationale to inconvenient truth. *Swiss Med Wkly.* 2012;142:w13566.
316. Rho M, Tang C. The efficacy of lumbar epidural steroid injections: transforaminal, interlaminar and caudal approaches. *Phys Med Rehabil Clin N Am.* 2011;22:139–148.
317. Eckel T, Bartynski W. Epidural steroid injections and selective nerve root blocks. *Tech Vasc Interv Radiol.* 2009;12:11–21.

# Epidural Steroid Injections & Selective Spinal Nerve Blocks

Revised February 2020



DEFINING APPROPRIATE  
COVERAGE POSITIONS



# NASS Coverage Policy Recommendations

## NASS Coverage Committee

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Coverage Policy Recommendations  
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## Introduction

North American Spine Society (NASS) coverage policy recommendations are intended to assist payers and members by proactively defining appropriate coverage positions. Historically, NASS has provided comment on payer coverage policy upon request. However, in considering coverage policies received by the organization, NASS believes proactively examining medical evidence and recommending credible and reasonable positions may be to the benefit of both payers and members in helping achieve consensus on coverage before it becomes a matter of controversy. This coverage recommendation reflects the best available data as of 08/01/18; information and data available after 08/01/18 is thus not reflected in this recommendation and may warrant deviations from this recommendation, if appropriate.

## Methodology

The coverage recommendations put forth by NASS use an evidence-based approach to spinal care when possible. In the absence of strict evidence-based criteria, coverage recommendations reflect the multidisciplinary experience and expertise of the authors in order to reflect reasonable standard practice indications in the United States.

## NASS Coverage Policy Methodology

### Background Information

Epidural steroid injections (ESIs) can be performed via a transforaminal (TF), interlaminar (IL), or caudal approach. Every approach requires the use of fluoroscopic or computerized tomography (CT) guidance to enhance safety and efficacy. However, there are rare or emergent situations where image guidance may be unavailable or pose greater risk than benefit (eg, pregnancy) in which performing a caudal or IL ESI may be appropriate. Insufficient safety and efficacy data exist around ultrasound guidance for any approach to delivering an epidural spinal injection (ESI) for NASS to recommend coverage for this alternative technique.

### Scope and Clinical Indications

**Therapeutic ESIs** are indicated for the treatment of radicular or referred pain (see below\*) in which 2 of 4 of the following criteria are met:

- The pain is severe enough to cause a degree of functional and/or vocational impairment or disability
- Pain duration of at least 4 weeks, and/or inability to tolerate or failure to respond to 4 weeks of noninvasive care (see below\*\*)
- Objective findings of radiculopathy or sclerotomal referred pain pattern are present and documented on examination
- Advanced imaging (CT or magnetic resonance imaging [MRI]) demonstrates a correlative region of nerve involvement

\* Lumbar referred pain is defined by having pain radiating to the buttock and or leg and would include conditions such as neurogenic claudication. Cervical referred pain is defined by having pain radiating into the shoulder, periscapular area and/or upper arm. While these diagnoses clearly include several potential anatomic pain generators, it is a common inclusion criterion for research studies and in clinical practice where the precise pain generator can be in question.<sup>1,2</sup> In these cases, an ESI may offer diagnostic and therapeutic benefits.

\*\* The majority of acute back, neck and radicular pain will improve over 4 weeks. It is therefore reasonable to recommend a trial of less invasive treatments for four weeks for those that have not already demonstrated pain beyond the normal natural history. Appropriate nonsurgical, noninjection treatments should be considered and documented in notes along with a rationale demonstrating that benefits of interventional treatment outweigh risks. Exceptions to waiting 4 weeks exist but should be carefully documented and should be reviewed on a case-by-case basis. These include, but are not limited to:

- At least moderate to severe pain, with functional loss at work and/or home
- Pain unresponsive to outpatient medical management
- Inability to tolerate nonsurgical, noninjection care due to coexisting medical condition(s) (eg, cardiac disease), or severe pain
- Prior successful injection therapy for the same condition that achieved greater than 50% pain relief with documented functional improvement, reduced impairment or decrease in analgesic medication

**Selective spinal nerve blocks (SSNBs)** use a small amount of anesthetic via a transforaminal approach to anesthetize a specific spinal nerve. SSNBs are used to evaluate a patient's anatomical level and/or source of radicular pain. They are often used in surgical planning

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and decision-making. Documentation of pre- and postinjection assessment of the pain to fully document the degree of relief on a visual or numerical analog score (VAS or NAS, respectively) with documentation of objective provocative testing is required.

### Contraindications to ESIs and SSNBs

ESIs and SSNBs are **NOT** indicated in cases that do not fulfill the above criteria. Of note, ESIs are not indicated in the following scenarios:

- **Axial or nonspecific pain without radiating pain (unless it involves a nerve root that does not refer to a limb).**
  - Radiologic abnormalities affecting the nerve roots in the cervical or lumbar spine without concurrent radiating pain, is insufficient to proceed with an ESI
    - ◆ This would include isolated painless symptomology such as “painless-weakness” and painless loss of sensation
  - Caveat: Lesions in the upper lumbar spine (L1 and L2) may have radiating, referred pain whose distribution is limited to the low back, and lesions in the upper cervical spine (C3, C4) may have radiating, referred pain into the periscapular or shoulder region, and thus may be appropriate for an ESI
- **Cancer:**
  - New onset spine pain in patient with a history of cancer, multiple risk factors for cancer, or strong clinical suspicion for cancer in the absence of advanced imaging studies (to rule out local cancer involvement)
  - ESIs may be considered if cancer is ruled out or if the patient's pain is felt to be unrelated to their cancer AND they meet the above criteria or if the epidural is done in coordination with their oncologic treatment
- **Infection:**
  - Localized spine infection or significant systemic infection requiring antibiotic therapy
  - New onset of low back pain and fever without advanced imaging studies, to rule out local infection, in patients with risk factors for infection such as:
    - ◆ History of active intravenous drug use
    - ◆ History of recent or ongoing systemic bacterial or fungal infection
    - ◆ Immunosuppression where reasonable risks exceed benefit
- **Compressive lesions of the spinal cord, conus medullaris or cauda equina**
  - Progressive neurological deficits manifesting as myelopathy, cauda equina syndrome or conus medullaris syndrome are best treated with surgical decompression and are not a primary indication for ESI
- Relative contraindications to the performance of **ESIs and SSNBs** may include coexisting medical conditions such as uncontrolled bleeding disorders, poorly controlled diabetes (if corticosteroids are going to be used), immune system impairment, history of severe allergic reaction to components, etc. In these situations, the risk/benefits of the procedure should be considered in the medical decision-making process.

### Procedural Requirements, Utilization, and Restrictions:

ESIs, regardless of approach or indication, are subject to the following requirements and restrictions:

- Procedures should be done in accordance with the guidelines outlined by the Multisociety Pain Workgroup (MPW).<sup>3</sup>
  - All IL ESIs should be performed using image guidance, with appropriate two-dimensional imaging consisting of an anteroposterior (AP) and either a lateral or contralateral oblique view.
  - To minimize the risk of direct spinal cord injury, IL ESIs should not be performed above C7.
  - ESIs should be performed by injecting contrast medium under real-time fluoroscopy and/or digital subtraction imaging, using an AP view, before injecting any substance that may be hazardous to the patient.
  - A nonparticulate steroid (eg, dexamethasone) should be used for the initial injection for lumbar TF ESIs and used exclusively for all cervical and thoracic TF ESIs.
  - TF ESIs using a particulate steroid is associated with a rare risk of catastrophic neurovascular complications. This risk increases in the upper lumbar, thoracic and cervical spine where the presence of radiculomedullary vessels increase.
  - Situations where particulate steroids could be used in the performance of TF ESIs often involve durability of effect and desire to not repeat procedure. The risks of using particulate steroid in the thoracic and cervical spine likely outweigh the benefits of durability.

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- o Extension tubing is recommended for all TF ESIs for the safety of the provider while injecting contrast under live fluoroscopy, and for the safety of the patient to provide a portal for changing syringes without direct needle manipulation.
- o The ultimate choice of what approach or technique (IL vs TF ESI) to use should be made by the treating physician.
- o IL ESIs can be performed without contrast in patients with documented contraindication to use of contrast (eg, significant history of contrast allergy or anaphylactic reaction).
- o TF ESIs can be performed without contrast in patients with documented contraindication to use, but in these circumstances, particulate steroids are contraindicated, and only preservative-free, nonparticulate steroids should be used.
- ESIs are challenging and come with risk and should only be performed by a well-trained physician that has undergone appropriate medical training.
- Injections are performed independently based on the patient's symptoms and response to prior injections and approach (if performed). There is no role for a routine "series of 3" ESIs.
- If a prior ESI provided no relief, a second ESI is allowed following reassessment of the patient, with documentation of change in injection technique and/or medication used. This post-procedural assessment and the planned procedural modifications should be documented to enhance the chances of a successful outcome.
- No more than 4 ESIs and/or SSNBs should be performed in a 6-month period of time.
- No more than 6 ESIs and/or SSNBs should be performed in a 12-month period of time regardless of the number of levels involved.
- Films that adequately document (minimum of 2 views) final needle position and contrast flow (when used) should be retained and available upon request for tracking outcomes and quality.
- No more than 2 TF ESIs should be performed at a single setting (eg, single level bilaterally or two levels).
- For caudal or IL ESIs, only one level per session may be performed and NOT in conjunction with a TF injection.
- Rarely, referred leg pain is caused by an epidural cyst. It is common that these cysts can be aspirated and ruptured with an intra-articular facet injection. Often, an ESI or SNRB is required to be performed at the same time to maximize durability of relief and treat the associated radiculitis. This procedure is an effective, less risky alternative to surgical decompression.
- Local anesthesia is sufficient for a majority of ESIs. Occasionally minimal to moderate conscious sedation is an appropriate option on a case-by-case basis in consultation with patients who understand the risk benefit ratio. If monitored anesthesia care is utilized, the need for such sedation should be clearly documented in the medical records.

## Rationale

**For radicular pain**, the rationale for coverage is based on high-level evidence and what most practitioners would consider to be accepted practice patterns. Lumbar radicular pain may be caused by a myriad of pathologic conditions including, but not limited to lumbar disc herniation, lumbar stenosis (central or foraminal), lumbar spondylolisthesis, post-operative perineural fibrosis, lumbar facet synovial cysts, or failed low back surgery syndrome. Multiple randomized-controlled trials (RCTs) have demonstrated that lumbar epidural steroid injections (LESIs) are effective in the treatment of lumbar radiculitis caused by disc herniation.<sup>4-10</sup> There is sufficient literature to suggest that a trial of ESIs for radicular pain caused by conditions other than disc herniation is appropriate prior to considering surgical intervention.<sup>11-17</sup>

Similarly, cervical radicular pain may be caused by conditions including, but not limited to, cervical disc herniation, cervical spondylolisthesis, degenerative foraminal or paracentral stenosis, and cervical postsurgery syndrome. When evaluating the literature regarding the use of cervical IL ESI, 8 RCTs support durable improvements in pain and disability for 12 and 24 months for a variety of cervical pathologic conditions. The literature on cervical TF ESIs is limited to observational studies, though benefit, including reduction in surgical intervention has been demonstrated, and the biochemical pathology involved is likely similar to lumbar radicular etiologies.

**For lumbar referred pain**, the rationale for coverage is based on the outcomes from large prospective RCTs<sup>1-2</sup>, and what most practitioners would consider to be accepted practice patterns. Lumbar referred pain is defined as pain radiating to the buttock and/or leg and would clearly include several potential pain conditions such as neurogenic claudication caused by either degenerative or isthmic spinal stenosis. Literature suggests that LESIs are effective in reducing pain in this patient population<sup>16,18,19</sup> though this treatment seems to be less effective in this group than in patients with herniated discs.<sup>20,21</sup> In addition, data show that LESI is equivalent to epidural local anesthetic<sup>1,2,22,23</sup>, likely due to the suppression of neurogenic inflammation by the local anesthetic. It should be noted that epidural injection of local anesthetic has been demonstrated to be more effective than a placebo.<sup>23</sup> Based on these data, it is felt that a trial of LESIs is reasonable prior to the consideration of surgical intervention.

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Other conditions can also cause radiating spine pain. Given the high percentage of radiologic abnormalities in the lumbar spine, the reported variability in pain referral patterns<sup>24</sup>, and the potential diagnostic benefits from an LESI<sup>25</sup>, it is reasonable to pursue injection-based treatments in the diagnostic and treatment pathway for those with radiating lumbar spine pain who have failed conservative care. Large studies that used generic enrollment criteria such as radiating pain have reported both short<sup>1</sup> and long-term<sup>2</sup> positive effects from LESIs, generally with a single injection for several months. This positive effect from a single injection echoes the results from the systematic review by MacVicar et al, who reported that 94% of patients achieved a 50% reduction in pain after only one lumbar TF ESI.<sup>26</sup>



The rationale for the **procedural requirements, utilization and restrictions** is based on the MPW recommendations, which represent the combined efforts of 13 medical societies that focused on the safety of ESIs, as well as what most practitioners would consider to be accepted practice patterns.<sup>3</sup> The recommendations on frequency of injections were in part based on controlled clinical trials.<sup>9,27</sup> These studies found that most patients who respond to ESIs do so with 3 or less injections for a specific episode of back and radicular pain. However, in certain circumstances it is medically appropriate to perform more than 3 injections. Proper documentation of these circumstances and the rationale for the necessity to repeat injections should be noted in the medical records. These circumstances include, but are not limited to:

- The performance of SSNBs for surgical planning after failed ESIs.
- The presence of new injuries after resolution of a prior condition.
- The presence of new injuries after interval surgery since prior ESIs.
- Prior injections were done without fluoroscopy or were inaccurately placed.
- Re-exacerbation of symptoms that responded well to prior ESIs.
- Patients who responded well to prior ESIs that are not surgical candidates due to comorbid medical conditions.

There are a number of reports of complications associated with TF ESIs in the cervical<sup>28,29</sup> and lumbar spine<sup>30-33</sup> that have occurred primarily as a result of intra-arterial injection. The use of live, contrast-enhanced fluoroscopy, digital subtraction imaging, and the use of nonparticulate steroids minimize these risks.<sup>32</sup> Additionally, in the cervical and thoracic spine the risk exists for directly injuring the spinal cord, most commonly during the performance of IL ESI.<sup>34</sup> The use of contrast-enhanced fluoroscopy and judicious use of contralateral oblique viewing minimize these risks.

Because there are potential local and systemic risks with ESIs from both the procedure itself and from the steroids injected, it is reasonable to place limits on the number of injections that should be reasonably administered in a given time. Currently, there is no data to support performing a predetermined “series” of injections. The determination to perform more than one injection should be based on the patient’s response to the prior injection, the approach/location of the injection, the patient’s symptoms, the medications used, and the imaging findings. This evaluation needs to be done via a face-to-face encounter and the reasons for repeating the injection must be clearly documented.





## References

1. Friedly JL, Comstock BA, Turner JA, et al. A randomized trial of epidural glucocorticoid injections for spinal stenosis. *N Engl J Med*. 2014;371(4):390-390. 
2. Friedly JL, Comstock BA, Turner JA, et al. Long-term effects of repeated injections of local anesthetic with or without corticosteroid for lumbar spinal stenosis: a randomized trial. *Arch Phys Med Rehabil*. 2017;98(8).
3. Rathmell JP, Benzon HT, Dreyfuss P, et al. Safeguards to prevent neurologic complications after epidural steroid injections. *Anesthesiology*. 2015;122(5):974-984.
4. Ghahreman A, Ferch R, Bogduk N. The efficacy of transforaminal injection of steroids for the treatment of lumbar radicular pain. *Pain Med*. 2010;11(8):1149-1168.
5. Riew KD, Yin Y, Gilula L, et al. The effect of nerve-root injections on the need for operative treatment of lumbar radicular pain. *J Bone Joint Surg Am*. 2000;82(11):1589-1593.
6. Vad VB, Bhat AL, Lutz GE, Cammisa F. Transforaminal epidural steroid injections in lumbosacral radiculopathy. *Spine*. 2002;27(1):11-15.
7. Ng L, Chaudhary N, Sell P. The efficacy of corticosteroids in periradicular infiltration for chronic radicular pain. *Spine*. 2005;30(8):857-862.
8. Tafazal S, Ng L, Chaudhary N, Sell P. Corticosteroids in peri-radicular infiltration for radicular pain: a randomised double blind controlled trial. One year results and subgroup analysis. *Eur Spine J*. 2009;18(8):1220-1225. 
9. Karppinen J, Malmivaara A, Kurunlahti M, et al. Periradicular infiltration for sciatica: a randomized controlled trial. *Spine*. 2001;26(9):1059-1067.
10. Kennedy DJ, Plastaras C, Casey E, et al. Comparative effectiveness of lumbar transforaminal epidural steroid injections with particulate versus

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- nonparticulate corticosteroids for lumbar radicular pain due to intervertebral disc herniation: a prospective, randomized, double-blind trial. *Pain Med.* 2014;15(4):548-555.
11. Klenerman L, Greenwood R, Davenport HT, White DC, Peskett S. Lumbar epidural injections in the treatment of sciatica. *Rheumatology.* 1984;23(1):35-38.
  12. Iversen T, Solberg TK, Romner B, et al. Effect of caudal epidural steroid or saline injection in chronic lumbar radiculopathy: multicentre, blinded, randomised controlled trial. *Bmj.* 2011;343(sep13 3):d5278-d5278. 
  13. Bush K, Hillier S. A controlled study of caudal epidural injections of triamcinolone plus procaine for the management of intractable sciatica. *Spine.* 1991;16(5):572-575.
  14. Buchner M, Zeifang F, Brocai DR, Schiltenswolf M. Epidural corticosteroid injection in the conservative management of sciatica. *Clin Orthop Relat Res.* 2000;375:149-156.
  15. Maus TP, El-Yahouchi CA, Geske JR, et al. Imaging determinants of clinical effectiveness of lumbar transforaminal epidural steroid injections. *Pain Med.* 2016;17(12):2176-2184.
  16. Botwin KP, Gruber RD, Bouchlas CG, et al. Fluoroscopically guided lumbar transformational epidural steroid injections in degenerative lumbar stenosis: an outcome study. *Am J Phys Med Rehabil.* 2002;81(12):898-905.
  17. Arden NK, Price C, Reading I, et al. A multicentre randomized controlled trial of epidural corticosteroid injections for sciatica: the WEST study. *Rheumatology.* 2005;44(11):1399-1406.
  18. Koc Z, Ozcakar S, Sivrioglu K, Gurbet A, Kucukoglu S. Effectiveness of physical therapy and epidural steroid injections in lumbar spinal stenosis. *Spine.* 2009;34(10):985-989.
  19. Lee JW, Myung JS, Park KW, et al. Fluoroscopically guided caudal epidural steroid injection for management of degenerative lumbar spinal stenosis: short-term and long-term results. *Skeletal Radiol.* 2009;39(7):691-699.
  20. Radcliff K, Kepler C, Hilibrand A, et al. Epidural steroid injections are associated with less improvement in patients with lumbar spinal stenosis. *Spine.* 2013;38(4):279-291. 
  21. Rivest C, Katz JN, Ferrante FM, Jamison RN. Effects of epidural steroid injection on pain due to lumbar spinal stenosis or herniated disks: A prospective study. *Arthritis Care Res.* 1998;11(4):291-297.
  22. Fukusaki M, Kobayashi I, Hara T, Sumikawa K. Symptoms of spinal stenosis do not improve after epidural steroid injection. *Clinical J Pain.* 1998;14(2):148-151.
  23. Bicket MC, Gupta A, Brown CH, Cohen SP. Epidural injections for spinal pain: a systematic review and meta-analysis evaluating the "control" injections in randomized controlled trials. *Anesthesiology.* 2013;119(4):907-931.
  24. Furman MB, Johnson SC. Induced lumbosacral radicular symptom referral patterns: a descriptive study. *Spine J.* 2019 Jan;19(1)163-170.
  25. Lewandowski KU. Successful outcome after outpatient transforaminal decompression for lumbar foraminal and lateral recess stenosis: The positive predictive value of diagnostic epidural steroid injection. *Clin Neurol Neurosurg.* 2018;173:38-45.
  26. Macvicar J, King W, Landers MH, Bogduk N. The effectiveness of lumbar transforaminal injection of steroids: a comprehensive review with systematic analysis of the published data. *Pain Med.* 2013;14(1):14-28.
  27. Ghahreman A, Bogduk N. Predictors of a favorable response to transforaminal injection of steroids in patients with lumbar radicular pain due to disc herniation. *Pain Med.* 2011;12(6):871-879.
  28. Bose B. Quadriplegia following cervical epidural steroid injections: case report and review of the literature. *Spine J.* 2005;5(5):558-63.
  29. Okubadejo G, Talcott M, Schmidt R, et al. Perils of intravascular methylprednisolone injection into the vertebral artery: an animal study. *J Bone Joint Surg Am.* 2005;90(9):1932-8.
  30. Kennedy DJ, Dreyfuss P, Aprill CN, Bogduk N. Paraplegia following image-guided transforaminal lumbar spine epidural steroid injection: two case reports. *Pain Med.* 2009;10(8):1389-1394.
  31. Huntoon M, Martin D. Paralysis after transforaminal epidural injection and previous spinal surgery. *Reg Anesth Pain Med.* 2004;29(5):494-495.
  32. Houten JK, Errico TJ. Paraplegia after lumbosacral nerve root block: report of three cases. *Spine J.* 2002;2(1):70-75.
  33. Wybier M, Gaudart S, Petrover D, Houdart E, Laredo JD. Paraplegia complicating selective steroid injections of the lumbar spine. Report of five cases and review of the literature. *Eur Radiol.* 2009;20(1):181-189.
  34. Rathmell JP, Michna E, Fitzgibbon DR, Stephens LS, Posner KL, Domino KB. Injury and liability associated with cervical procedures for chronic pain. *Anesthesiology.* 2011;114(4):918-926.

## Additional Resources:

- Manchikanti L, Malla Y, Cash KA, McManus CD, Pampati V. Fluoroscopic cervical interlaminar epidural injections in managing chronic pain of cervical postsurgery syndrome: preliminary results of a randomized, double-blind, active control trial. *Pain Phys.* 2012;15(1):13-25. 
- Manchikanti L, Cash K, Pampati V, Wargo BW, Malla Y. Cervical epidural injections in chronic discogenic neck pain without disc herniation or radiculitis: preliminary results of a randomized, double-blind, controlled trial. *Pain Physician.* 2010;13:E265-78. 
- Manchikanti L, Cash K, Pampati V, Wargo, BW, Malla Y. The effectiveness of fluoroscopic cervical interlaminar epidural injections in managing chronic cervical disc herniation and radiculitis: preliminary results of a randomized, double-blind, controlled trial. *Pain Physician* 2010;13:223-36. 
- Manchikanti L, Cash KA, Pampati V, Malla Y. Two-year follow-up results of fluoroscopic cervical epidural injections in chronic axial or discogenic neck pain: a randomized, double-blind, controlled trial. *Int J Med Sci.* 2014;11(4):309-320. 
- McCormick ZL, Nelson A, Bhavne M, et al. A Prospective randomized comparative trial of targeted steroid injection via epidural catheter versus

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standard c7-t1 interlaminar approach for the treatment of unilateral cervical radicular pain. *Reg Anesth Pain Med.* 2017;42(1):82-89.

- Stav A, Ovadia L, Sternberg A, Kaadan M, Weksler N. Cervical epidural steroid injection for cervicobrachialgia. *Acta Anaesthesiol Scand.* 1993;37(6):562-566.
- Pasqualucci A, Varrassi G, Braschi A, et al. Epidural local anesthetic plus corticosteroid for the treatment of cervical brachial radicular pain: single injection versus continuous infusion. *Clin J Pain.* 2007;23(7):551-557.
- Castagnera L, Maurette P, Pointillart V, Vital JM, Erny P, Sénégas J. Long-term results of cervical epidural steroid injection with and without morphine in chronic cervical radicular pain. *Pain.* 1994;58(2):239-243.
- Anderberg L, Annertz M, Persson L, Brandt L, Säveland H. Transforaminal steroid injections for the treatment of cervical radiculopathy: a prospective and randomised study. *Eur Spine J.* 2006;16(3):321-328. 
- Lee JH, Lee SH. Comparison of clinical effectiveness of cervical transforaminal steroid injection according to different radiological guidances (C-arm fluoroscopy vs. computed tomography fluoroscopy). *Spine J.* 2011;11(5):416-423.
- Lee JH, Lee SH. Can repeat injection provide clinical benefit in patients with cervical disc herniation and stenosis when the first epidural injection results only in partial response? *Medicine.* 2016;95(29). 
- Persson L, Anderberg L. Repetitive transforaminal steroid injections in cervical radiculopathy: a prospective outcome study including 140 patients. *Evid Based Spine Care J.* 2013;3(03):13-20. 

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## Comments

Comments regarding the coverage recommendations may be submitted to [coverage@spine.org](mailto:coverage@spine.org) and will be considered in development of future revisions of the work.

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# Safeguards to Prevent Neurologic Complications after Epidural Steroid Injections

## *Consensus Opinions from a Multidisciplinary Working Group and National Organizations*

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### ABSTRACT

**Background:** Epidural corticosteroid injections are a common treatment for radicular pain caused by intervertebral disc herniations, spinal stenosis, and other disorders. Although rare, catastrophic neurologic injuries, including stroke and spinal cord injury, have occurred with these injections.

**Methods:** A collaboration was undertaken between the U.S. Food and Drug Administration Safe Use Initiative, an expert multidisciplinary working group, and 13 specialty stakeholder societies. The goal of this collaboration was to review the existing evidence regarding neurologic complications associated with epidural corticosteroid injections and produce consensus procedural clinical considerations aimed at enhancing the safety of these injections. U.S. Food and Drug Administration Safe Use Initiative representatives helped convene and facilitate meetings without actively participating in the deliberations or decision-making process.

**Results:** Seventeen clinical considerations aimed at improving safety were produced by the stakeholder societies. Specific clinical considerations for performing transforaminal and interlaminar injections, including the use of nonparticulate steroid, anatomic considerations, and use of radiographic guidance are given along with the existing scientific evidence for each clinical consideration.

**Conclusion:** Adherence to specific recommended practices when performing epidural corticosteroid injections should lead to a reduction in the incidence of neurologic injuries. (*ANESTHESIOLOGY* 2015; 122:974–84)

**E**PIDURAL injections of corticosteroids are widely used as a treatment for radicular pain caused by disc herniation and other conditions that affect spinal nerves. These injections are associated with a number of minor complications and side effects, such as exacerbation of pain, vasovagal reaction, headache, and unintentional dural puncture,<sup>1–7</sup> that do not involve any permanent impairment. Of great concern, however, are rare injuries to the central nervous system that occur as a result of epidural

corticosteroid injections. These rare neurologic injuries can be catastrophic and include stroke and spinal cord injury that can result in increased pain, severe permanent disability, or death. An expert working group with facilitation from the U.S. Food and Drug Administration's Safe Use Initiative (SUI) and representatives from leading specialty societies reviewed the existing scientific evidence and assembled consensus clinical considerations aimed at reducing the risk of severe neurologic complications.

This article is featured in "This Month in Anesthesiology," page 1A. Corresponding article on page 964. The preliminary clinical considerations from this working group were presented orally in a panel session titled Transforaminal Epidural Steroid Injections and the Food and Drug Administration Use Initiative that was held during the American Society of Anesthesiologists 2013 Annual Meeting in San Francisco, California, on October 12, 2013, and during a meeting of the Food and Drug Administration Anesthetic and Analgesic Drug Products Advisory Committee held on November 24 and 25, 2014, in Silver Spring, Maryland.

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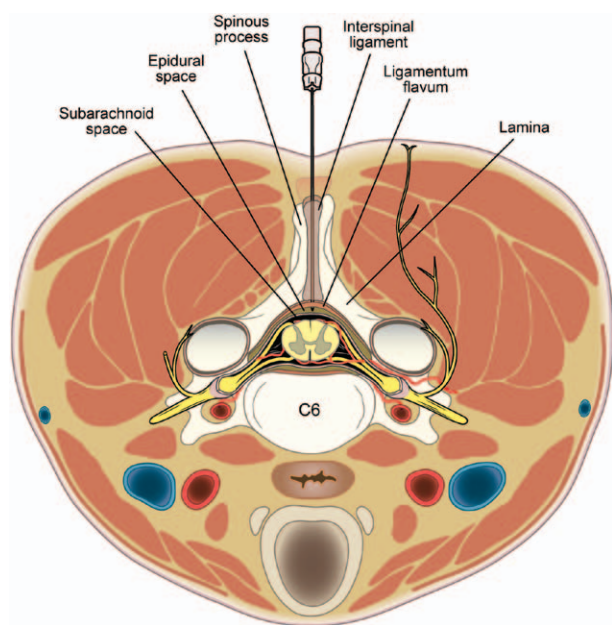
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## Background

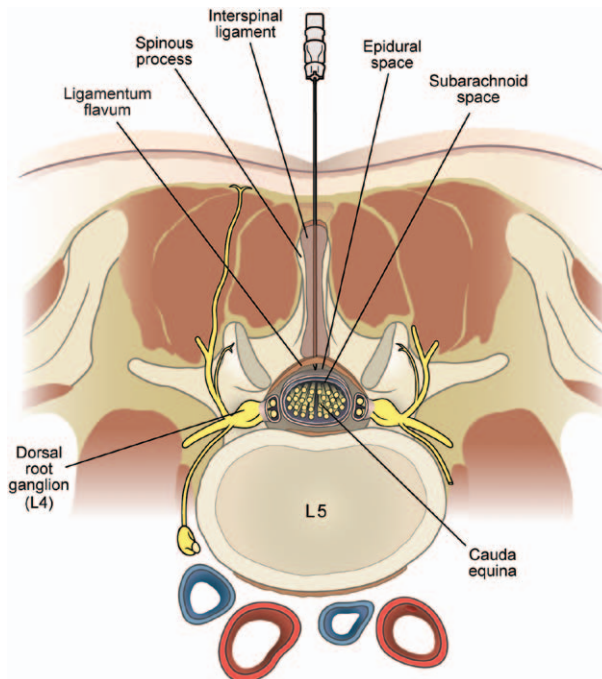
The evidence that neurologic injury is associated with epidural injection of steroids is limited to case reports and reports of closed malpractice claims, and this evidence will be reviewed in the paragraphs that follow. The incidence of these rare complications cannot be calculated from the limited data because there is little information on the numbers of patients undergoing the procedures. The reports show us that these catastrophic injuries do occur, and the number of cases reported in the literature suggests that the risk is not negligible. The most commonly used routes of administration are the interlaminar route, in which the needle is placed between adjacent spinal laminae into the posterior epidural space (figs. 1 and 2), and the transforaminal route, in which the needle is placed in an intervertebral foramen (figs. 3 and 4).

The cardinal neurologic complication of *cervical interlaminar* injections is direct needle injury to the spinal cord (fig. 1). Case reports of such injuries are few in the literature<sup>8</sup>; additional evidence is available from reviews of closed malpractice

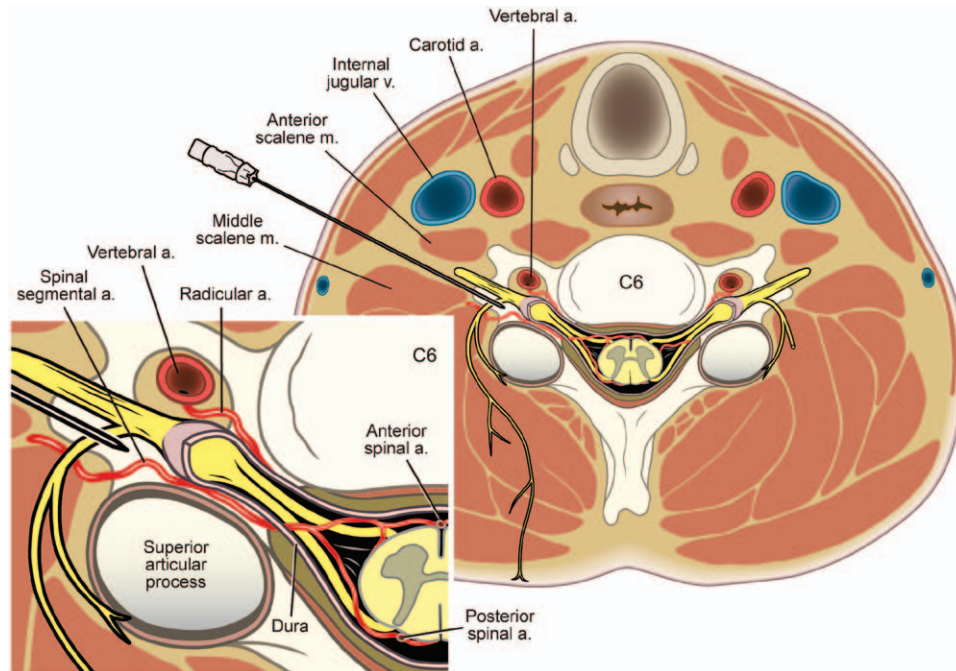
claims. An earlier review of malpractice claims identified 14 cases of spinal cord injury after epidural injection of steroids, among 276 claims relating to chronic pain management between 1970 and 1999.<sup>9</sup> A more recent review looked at malpractice claims between January 1, 2005 and December 31, 2008.<sup>10</sup> Of 294 claims relating to chronic pain management, 64 involved cervical interventions, with 20 cases of direct spinal cord injury. There has also been one report of indirect spinal cord injury, ostensibly due to a transient increase in pressure within the epidural space during injection causing ischemia.<sup>11</sup> Direct spinal cord injury has been reported once after *cervical transforaminal* injections,<sup>12</sup> but the cardinal neurologic complications of this procedure are infarctions of the spinal cord, brainstem, cerebrum, or cerebellum. These have been described in several case reports<sup>13–22</sup> and extended by a survey of 1,340 physicians.<sup>23</sup> A review of closed claims identified nine instances of spinal cord infarction although the overlap with the published case reports could not be determined.<sup>10</sup> Circumstantial evidence, and some direct evidence,



**Fig. 1.** Axial diagram of cervical interlaminar epidural injection. The epidural needle is advanced in the midline between spinous processes and traverses the ligamentum flavum to enter the dorsal epidural space in the midline. The normal cervical epidural space is approximately 3 mm wide (from the ligamentum flavum to the dura mater in the axial plane). Note the proximity of the underlying spinal cord during cervical epidural injection. The most common mechanism of injury during cervical epidural steroid injection performed *via* the interlaminar route is direct needle trauma to the spinal cord. Reproduced, with permission, and modified from original figures, from Rathmell JP: *Atlas of Image Guided Intervention in Regional Anesthesia and Pain Medicine*, 2nd edition. Philadelphia, Lippincott Williams & Wilkins, 2012. Adaptations are themselves works protected by copyright. So in order to publish this adaptation, authorization must be obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.



**Fig. 2.** Axial diagram of interlaminar lumbar epidural injection. The epidural needle is advanced in the midline between adjacent spinous processes to traverse the ligamentum flavum and enter the dorsal epidural space in the midline. The normal epidural space is approximately 4 to 6 mm wide (from the ligamentum flavum to the dura mater in the axial plane). Note the proximity of the underlying cauda equina during lumbar epidural injection. Reproduced, with permission, and modified from original figures, from Rathmell JP: *Atlas of Image Guided Intervention in Regional Anesthesia and Pain Medicine*, 2nd edition. Philadelphia, Lippincott Williams & Wilkins, 2012. Adaptations are themselves works protected by copyright. So in order to publish this adaptation, authorization must be obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.



**Fig. 3.** Axial view of cervical transforaminal injection at the level of C6. The needle has been inserted along the axis of the foramen and is illustrated in final position within the posterior aspect of the foramen. Insertion along this axis avoids the vertebral artery, which lies anterior to the foramen, and the spinal nerve, which lies within the foramen angled anteriorly toward the interscalene groove. Spinal segmental arteries arise from the deep or ascending cervical artery, enter the foramen at variable locations and often course through the foramen, penetrate the dura, and join the anterior or posterior spinal arteries that supply the spinal cord (*inset*). An arterial branch that joins the anterior spinal artery is termed a “spinal segmental” or “spinal medullary” artery. Likewise, arterial branches arise variably from the vertebral artery to supply the nerve root itself (in this illustration, a branch to the nerve root or “radicular” artery is shown); similar branches from the vertebral artery often penetrate the dura to join the anterior or posterior spinal artery. There is great anatomic variation in the vascular supply in this region. The anatomic variant illustrated is shown to demonstrate how a needle can be placed within a small artery that provides critical reinforcing blood supply to the spinal cord during cervical transforaminal injection. Injection of particulate steroid directly into one of these vessels can lead to catastrophic spinal cord injury. Reproduced, with permission, and modified from original figures, from Rathmell JP: *Atlas of Image Guided Intervention in Regional Anesthesia and Pain Medicine*, 2nd edition. Philadelphia, Lippincott Williams & Wilkins, 2012. Adaptations are themselves works protected by copyright. So in order to publish this adaptation, authorization must be obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.

implicates a variety of possible mechanisms for these complications, involving either the vertebral artery or a radicular artery—more precisely termed a radiculomedullary or spinal medullary artery—an artery that reinforces the anterior or posterior spinal artery (fig. 3).<sup>24</sup>

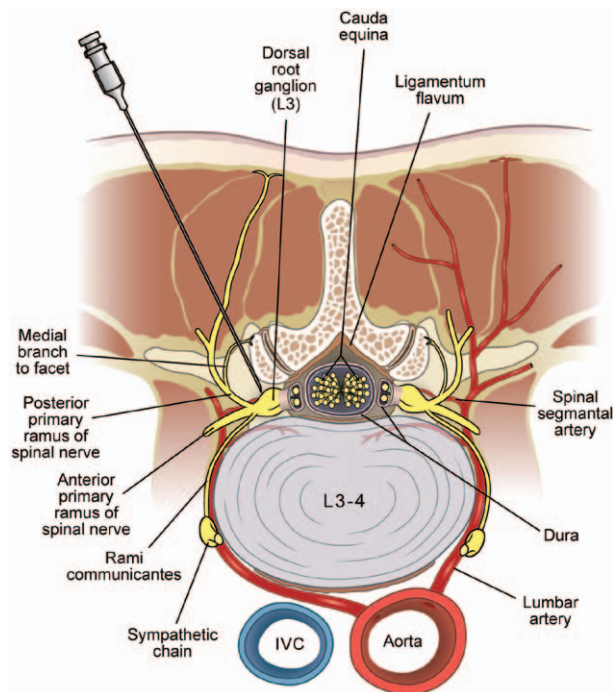
For thoracic and lumbar injections, reports of injuries have been fewer although no less devastating. One case of paraplegia has been reported after a thoracic interlaminar injection of steroids (fig. 2), ostensibly due to direct injury of the spinal cord.<sup>25</sup> In the four cases after lumbar injections,<sup>26–29</sup> the mechanisms of neurologic injury are unclear, but variously may have involved swelling of an unrecognized epidural space-occupying lesion, injury to a radiculomedullary artery, or hematoma.

More extensive is the literature reporting paraplegia after *lumbar transforaminal* injections (fig. 4).<sup>30–37</sup> In all cases, particulate steroids were used, and the suspected mechanism of injury is either injection of steroids into a radiculomedullary artery or spasm of such an artery when perturbed by the needle.

### Anatomy, Laboratory, and Animal Studies

Anatomic studies have shown that the vertebral artery lies in close proximity to needles inserted into the cervical intervertebral foramen, along with other arteries, such as the ascending cervical and deep cervical arteries, which can contribute to the supply of the central nervous system (fig. 3).<sup>38</sup> The diameter of those arteries is sufficient to admit the tip of a needle. In the case of radicular arteries, investigators have captured images of contrast medium injected into cervical radicular arteries in the course of transforaminal injections, showing that it is possible to cannulate these small vessels unintentionally.<sup>24,39</sup>

Laboratory studies have shown that certain steroid preparations contain particles and form aggregates. Methylprednisolone has the largest particles, triamcinolone is intermediate, and betamethasone has the smallest.<sup>15,40,41</sup> These particles or their aggregates can act as emboli if injected into an artery and are of sufficient size to block small terminal arterioles supplying the brain or spinal cord. Dexamethasone does not form particles or aggregates.<sup>40</sup>



**Fig. 4.** Axial view of lumbar transforaminal and selective nerve root injection. The anatomy and proper needle position (axial view) for right L3/L4 transforaminal. IVC = inferior vena cava. Reproduced, with permission, and modified from original figures, from Rathmell JP: *Atlas of Image Guided Intervention in Regional Anesthesia and Pain Medicine*, 2nd edition. Philadelphia, Lippincott Williams & Wilkins, 2012. Adaptations are themselves works protected by copyright. So in order to publish this adaptation, authorization must be obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.

Animal studies have shown that injection of particulate methylprednisolone into the vertebral artery or internal carotid artery can lead to severe neurologic injuries (strokes) similar to those seen in published human case reports.<sup>42,43</sup> Such injuries did not occur after the injection of dexamethasone.

### Possible Mechanisms of Injury

Collectively, these studies suggest that intraarterial injection of particulate steroids is a likely mechanism of spinal or cerebrovascular complications of cervical transforaminal injections. In this regard, it is conspicuous that in virtually all case reports of infarction after cervical transforaminal injection of steroids, particulate steroids were used. In cases where nonparticulate medication was injected, such as lidocaine or contrast (iopamidol), paralysis of the extremities or blindness was temporary.<sup>14,44</sup>

Other potential mechanisms of injury involving the vertebral artery include perforation<sup>45</sup> and traumatic aneurysm caused by penetration with the needle.<sup>22</sup> Direct contact

between an advancing needle and a small artery could theoretically cause spasm of that vessel or create an intimal flap (*i.e.*, dissection).<sup>23,35,40</sup> Direct evidence is lacking for these alternate mechanisms for neurologic injury.

Animal studies have shown that the carrier used in some steroid preparations might be directly toxic to the central nervous system, resulting in injury.<sup>43</sup> A review of the animal studies showed that the concentrations of the preservatives polyethylene glycol and myristyl-gamma-picolinium chloride needed to cause morphologic or nerve conduction changes must be 2 to 10 times the concentrations found in these commercial drug preparations, thus toxicity resulting directly from the low concentrations of preservative appears to be unlikely.<sup>46</sup>

### Role of the Food and Drug Administration Safe Use Initiative

To address concerns related to medication-related risks, the U.S. Food and Drug Administration created its SUI in 2009 to create and facilitate public and private collaborations within the healthcare community.\* The goal of the SUI is to reduce preventable harm by identifying specific, preventable medication risks and developing, implementing, and evaluating cross-sector innovations with partners who are committed to safe medication use. It works with stakeholders to respond to the challenges of managing risks associated with the way medications are used.

Safe Use Initiative facilitated the organization of an expert working group of key stakeholders created to understand the causes of the neurologic injuries associated with epidural steroid injections and devise strategies to mitigate their risk. The working group consisted primarily of experts external to the Food and Drug Administration who have published scientific studies or scholarly works on the topic of epidural steroid injections, and SUI representatives have helped convene and facilitate meetings without actively participating in the deliberations or decision-making process. The working group drafted, discussed, and formulated a set of clinical considerations to minimize the risk of catastrophic neural injury associated with epidural steroid injections, which has resulted in the development of studies and publication of reports to provide guidance to the healthcare community.

### Methods

The SUI convened and facilitated teleconferences conducted by the working group, which drafted, discussed, and formulated a set of clinical considerations designed to minimize the risk of catastrophic neural injury associated with epidural steroid injections. Clinical considerations were formulated with reference to the best available scientific evidence, and when evidence was lacking, expert opinion was sought both within the working group and from leading scientific societies or associations with interest or expertise in the subject of epidural injections. The clinical considerations of the working group primarily considered complications arising from the administration of epidural steroid injections reported in the literature and were designed to

\* FDA's Safe Use Initiative, Collaborating to Reduce Preventable Harm from Medications. Safe Use Final Report. Available at: <http://www.fda.gov/downloads/drugs/drugsafety/ucm188961.pdf>. Accessed January 14, 2015.

reduce harm resulting from one or more putative mechanisms of injury.

Once clinical considerations were drafted, representatives from a number of national pain organizations were invited to review and vote on them. After an initial vote, newer studies were published that provided further guidance on key issues.<sup>47,48</sup> The working group presented findings from these studies to the consulting organizations, which revoted on the clinical considerations based on the new information.

## Results

The representatives of the national organizations overwhelmingly approved all the clinical considerations of the working group, with board approval from their respective societies before rendering their final votes (table 1).

The working group and the advising national organizations unanimously agreed that epidural injections of steroids were rarely associated with serious complications due to injuries of the central nervous system. They agreed that transforaminal injections are associated with a risk of catastrophic neurovascular complications and that particulate steroids appear to be inordinately represented in case reports of these complications.

The representatives unanimously approved the clinical consideration that only nonparticulate steroids should be used in *therapeutic cervical* transforaminal injections. Although the initial use of nonparticulate steroid dexamethasone in *lumbar* transforaminal injections was recommended (11 of 13 votes), the representatives unanimously agreed that there might be instances where particulate steroids could be used in this setting, for example, consideration to use of a particulate steroid might be given if a given patient had failed to improve after an initial treatment with nonparticulate steroid.

Clinical considerations involving technical aspects of the procedures included use of appropriate image-guided views, injection of contrast under real-time fluoroscopy, review of prior imaging studies, use of face mask and sterile gloves, use of extension tubing, and avoidance of heavy sedation.

Three clinical considerations received votes against adoption. Two clinical considerations involved the measures needed to prevent intravascular injection, the representative of one organization felt that digital subtraction imaging (DSI) should be made mandatory when injecting a potentially hazardous substance transforaminally. One clinical consideration that received a negative vote involves the use of extension tubing for transforaminal injections.

Three clinical considerations receive votes of “unable to reach consensus” among the officers, board of directors, or representatives of the organizations. One organization could not reach consensus on the issue of injection of contrast medium under real-time fluoroscopy and/or DSI before cervical transforaminal injections. Two organizations could not reach consensus on two clinical considerations: the initial use of nonparticulate steroid dexamethasone in lumbar transforaminal injections and the performance of interlaminar

injections without contrast in patients with a significant history of contrast allergy or anaphylactic reaction.

## Discussion

Image guidance for all cervical interlaminar injections was recommended to avoid penetration of the spinal cord as a result of improper insertion of the needle. Appropriate lateral or oblique views are essential to gauge depth of needle insertion (fig. 5).<sup>49,50</sup> Relying on loss-of-resistance or on anteroposterior views alone does not protect patients from excessive depth of needle insertion, resulting in the risk that air, saline, or contrast medium might be injected into the spinal cord.

Similar precautions apply for lumbar interlaminar injections. Appropriate lateral or oblique views are required to ensure correct depth of needle insertion, lest the injection be into the subarachnoid space; contrast medium should be used to ensure injection correctly into the epidural space; and particulate steroids are acceptable because there is little risk of intraarterial injection.

The clinical consideration that needle entry for cervical interlaminar injections be performed at C7-T1 was based on reports that at other segmental levels the cervical epidural space is often narrow, making the dural sac and spinal cord more susceptible to penetration and injury.<sup>8,51–53</sup> Based on similar rationale about the close anatomic proximity of the dura mater and spinal cord to the point of needle entry, the clinical consideration was adopted that cervical interlaminar injections should not be undertaken unless inspection of imaging taken before the procedure demonstrates that the epidural space at the segmental level at which the injection will be undertaken is sufficient in size to admit a needle safely. A recent study<sup>54</sup> found that magnetic resonance imaging did not improve treatment outcomes for epidural steroid injections done in patients with a wide range of painful spinal disorders, yet suggested that magnetic resonance imaging may improve outcomes in the subset of patients with radiculopathy. This study did not examine the impact of imaging on safety, nonetheless the authors do emphasize that magnetic resonance imaging can detect rare contraindications to epidural injection, such as spinal metastases and infection.

For cervical procedures in general, irrespective of whether interlaminar or transforaminal injections were performed, analysis of closed claims reveals that having the patient heavily sedated during the procedure or being unresponsive at the time of injection are each significantly associated with an increased risk of spinal cord injury.<sup>10</sup> Furthermore, some 45% of spinal cord injuries were deemed avoidable had suitable precautions been used. There was agreement by all societies that if sedation is used, it should be light enough to allow the patient to communicate pain or other adverse sensations or events during the procedure.

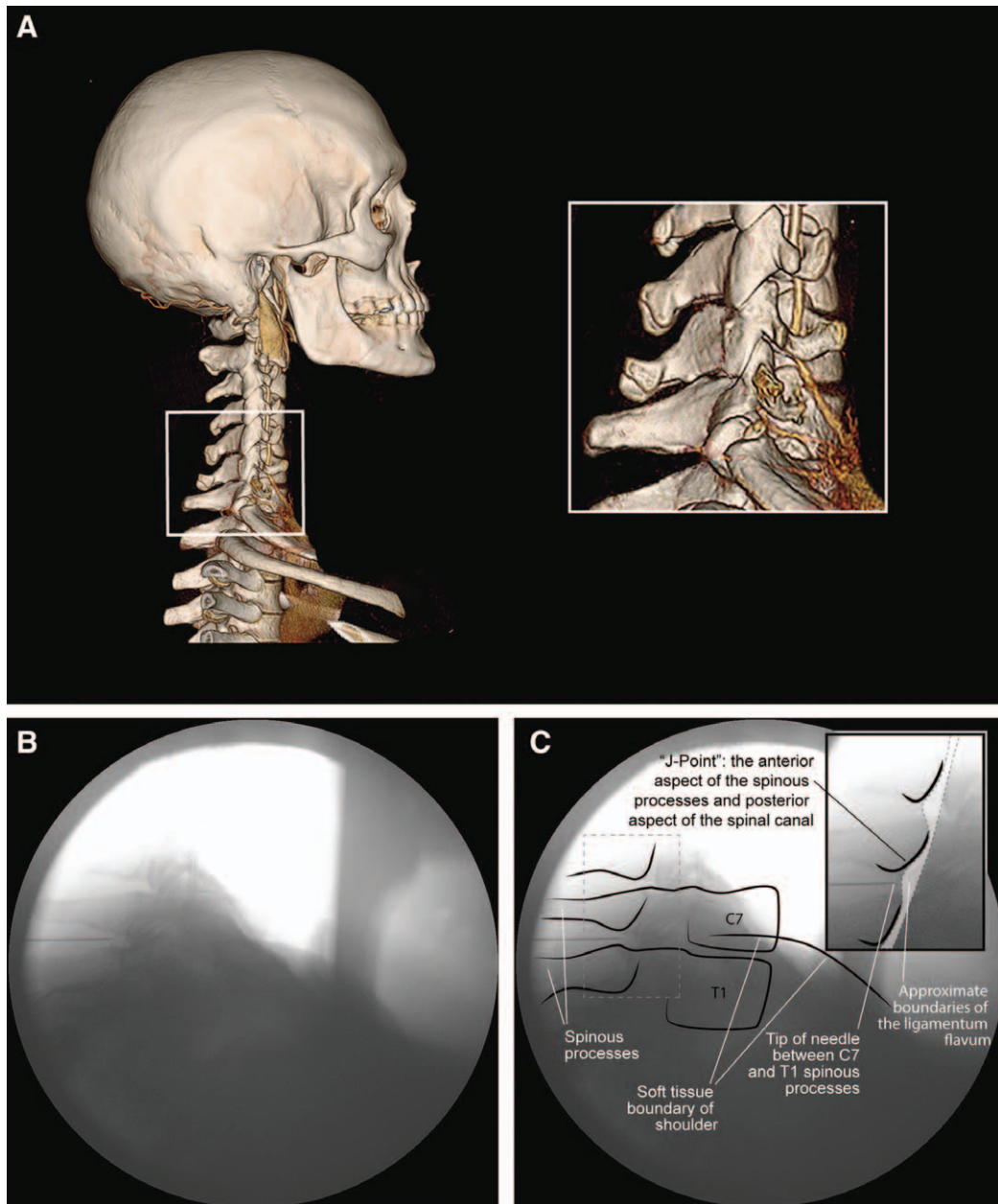
For cervical and lumbar *transforaminal* injections, the cardinal risk is intraarterial injection. Therefore, a test dose of contrast medium is essential to identify unintended entry into an artery *before* any other agent is injected (figs. 6 and 7). Dexamethasone was recommended as the first-line agent for lumbar

**Table 1.** Statements and Clinical Considerations of the Working Group Endorsed by the MultiSpecialty Work Group

Statement/Clinical Consideration	Number of Organizations Agreeing	Number of Organizations Disagreeing	Number of Organizations Unable to Reach Consensus
1. Cervical IL ESIs are associated with a rare risk of catastrophic neurologic injury (fig. 1).	13	0	0
2. TF ESI using particulate steroid is associated with a rare risk of catastrophic neurovascular complications (fig. 3).	13	0	0
3. All cervical IL ESIs should be performed using image guidance, with appropriate AP, lateral, or contralateral oblique views and a test dose of contrast medium (fig. 5).	13	0	0
4. Cervical TF ESIs should be performed by injecting contrast medium under real-time fluoroscopy and/or digital subtraction imaging, using an AP view, before injecting any substance that may be hazardous to the patient (fig. 6).	11	1*	1
5. Cervical IL ESIs are recommended to be performed at C7-T1, but preferably not higher than the C6-C7 level.	13	0	0
6. No cervical IL ESI should be undertaken, at any segmental level, without reviewing, before the procedure, prior imaging studies that show there is adequate epidural space for needle placement at the target level.	13	0	0
7. Particulate steroids should not be used in therapeutic cervical TF injections.	13	0	0
8. All lumbar IL ESIs should be performed using image guidance, with appropriate AP, lateral, or contralateral oblique views and a test dose of contrast medium.	13	0	0
9. Lumbar TF ESIs should be performed by injecting contrast medium under real-time fluoroscopy and/or digital subtraction imaging, using an AP view, before injecting any substance that may be hazardous to the patient (fig. 7).	12	1*	0
10. A nonparticulate steroid (e.g., dexamethasone) should be used for the initial injection in lumbar transforaminal epidural injections.	11	0	2
11. There are situations where particulate steroids could be used in the performance of lumbar TF ESIs.	13	0	0
12. Extension tubing is recommended for all TF ESIs.	12	1	0
13. A face mask and sterile gloves must be worn during the procedure.	13	0	0
14. The ultimate choice of what approach or technique (IL vs. TF ESI) to use should be made by the treating physician by balancing potential risks vs. benefits with each technique for each given patient	13	0	0
15. Cervical and lumbar IL ESIs can be performed without contrast in patients with documented contraindication to use of contrast (e.g., significant history of contrast allergy or anaphylactic reaction)	11	0	2
16. TF ESIs can be performed without contrast in patients with documented contraindication to use, but in these circumstances, particulate steroids are contraindicated and only preservative-free, particulate-free steroids should be used.	13	0	0
17. Moderate-to-heavy sedation is not recommended for ESIs, but if light sedation is used, the patient should remain able to communicate pain or other adverse sensations or events	13	0	0

\* The organization voting against questions 4 and 9 commented, "Digital Subtraction Imaging should be mandatory before injecting a potentially hazardous substance transforaminally."

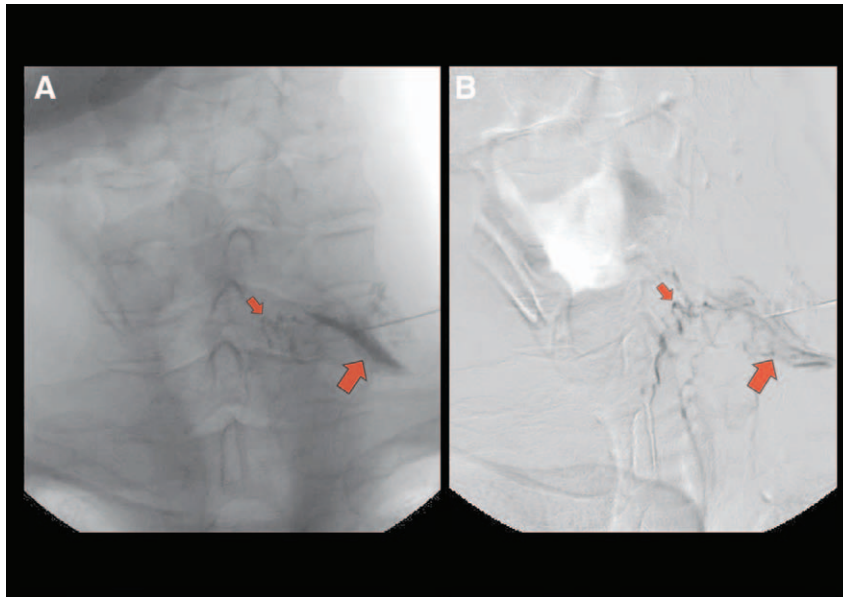
AP = anteroposterior; C6-C7 = the interspace between the sixth and seventh cervical vertebrae; C7-T1 = the interspace between the seventh cervical and first thoracic vertebrae; ESI = epidural steroid injection; IL = interlaminar; TF = transforaminal.



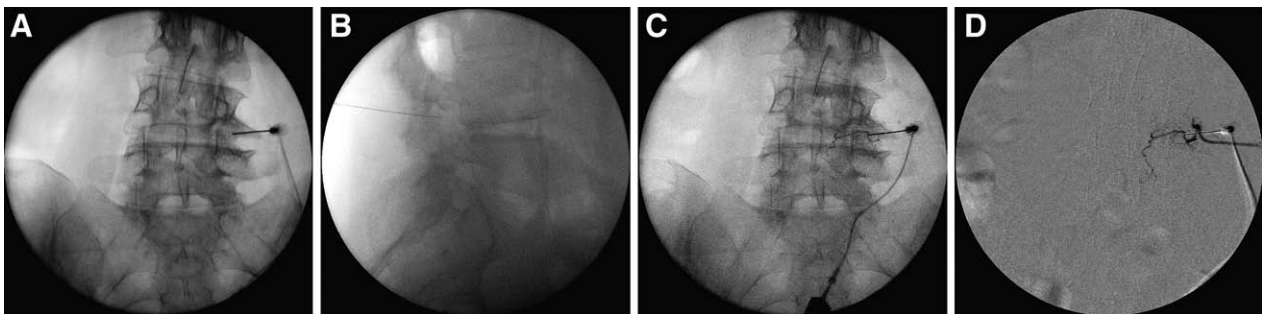
**Fig. 5.** (A) Bony anatomy relevant to cervical interlaminar epidural injection. Three-dimensional reconstruction computed tomography of the cervical spine as viewed in the lateral projection. *Inset* matches the anatomic area in the radiographs shown in *B* and *C*. (B) Lateral radiograph of the cervical spine near the cervicothoracic junction during interlaminar cervical epidural injection. A 22-gauge Touhy needle is in place in the C7/T1 interspace extending toward the dorsal epidural space. (C) Labeled image after injection of radiographic contrast. The anterior most extent of the spinous process and the posterior most extent of the ligamentum flavum and spinal canal coincide with the “J-point” or the point where the inferior margin of the spinous process begins to arc in a cephalad direction, taking the appearance of the letter “J.” The area outlined to the left of the image in the *dashed box* has been enlarged in the *inset* to the right, where the approximate borders of the ligamentum flavum have been outlined. The contrast extends in a linear stripe in a cephalad and caudad direction from the needle tip that outlines the dorsal (posterior) border of the dura mater. Reproduced, with permission, and modified from original figures, from Rathmell JP: *Atlas of Image Guided Intervention in Regional Anesthesia and Pain Medicine*, 2nd edition. Philadelphia, Lippincott Williams & Wilkins, 2012. Adaptations are themselves works protected by copyright. So in order to publish this adaptation, authorization must be obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.

transforaminal injections on two grounds. The first was to avoid particulate steroids, which have been implicated in all cases of severe neurologic complications from this procedure. The

second was that studies have now shown that the effectiveness of dexamethasone is not significantly less than that of particulate steroids.<sup>47,48</sup> Use of dexamethasone as a first-line agent for



**Fig. 6.** Posterior–anterior view of the cervical spine during C7/T1 transforaminal injection, including a digital subtraction sequence after contrast injection. An anteroposterior view of an angiogram obtained after injection of contrast medium before planned transforaminal injection of corticosteroids. (A) Image as seen on fluoroscopy. The needle lies in the left C7/T1 intervertebral foramen. Contrast medium outlines the spinal nerve (*large arrow*). The radicular artery appears as a thin tortuous line of contrast passing medially from the site of injection (*small arrow*). (B) Digital subtraction imaging reveals that the radicular artery (*small arrow*) extends to the midline to join the anterior spinal artery and much of the contrast is located in the correct location surrounding the spinal nerve (*large arrow*). Reprinted from Rathmell JP. *ANESTHESIOLOGY* 2004; 100:1595–600.<sup>24</sup>



**Fig. 7.** Lumbar transforaminal injection and use of digital subtraction to identify intraarterial needle location. (A) Anterior–posterior radiograph of the lumbar spine with the needle is in final position for right L4/L5 transforaminal injection. (B) Lateral radiograph of the lumbar spine with the needle is in final position for right L4/L5 transforaminal injection. (C) Anterior–posterior radiograph of the lumbar spine with the needle is in final position for right L4/L5 transforaminal injection acquired during active injection of radiographic contrast demonstrating intraarterial contrast injection. (D) Same image shown in C as seen using digital subtraction imaging. Reproduced, with permission, and modified from original figures, from Rathmell JP: *Atlas of Image Guided Intervention in Regional Anesthesia and Pain Medicine*, 2nd edition. Philadelphia, Lippincott Williams & Wilkins, 2012. Adaptations are themselves works protected by copyright. So in order to publish this adaptation, authorization must be obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.

lumbar transforaminal is the most controversial clinical consideration the group is putting forward. We acknowledge that there is no direct evidence that nonparticulate steroids are superior to sham injections, and studies that show no difference between particulate and nonparticulate steroids are underpowered.<sup>47,48</sup>

Digital subtraction imaging was endorsed for transforaminal injections on the grounds that it significantly increases the

detection of vascular uptake of contrast medium<sup>55–57</sup> and requires less contrast medium to detect vessels (figs. 6 and 7). One study showed the sensitivity of DSI to be 60% compared with 20% with aspiration.<sup>57</sup> However, the working group acknowledged that DSI was not widely available, not necessarily essential for safety, and increases radiation exposure.<sup>58</sup> Physicians who do not use DSI and rely instead on real-time fluoroscopy must carefully

view the images during the injection of contrast medium, lest the fleeting appearance of a small artery escapes notice.

Extension tubing was recommended so that once a needle had been placed, it would no longer be touched, and risk being dislodged when syringes for successive agents are connected. This practice guards against a needle, shown to be in a safe location by a test dose of contrast medium, being dislodged to an unsafe location when the syringe for steroids is connected. Face masks and gloves were recommended to comply with generally accepted guidelines for aseptic technique.<sup>59</sup>

Topics that have been discussed by some experts but were not considered by the working group include the use of a local anesthetic test dose,<sup>60</sup> placement of the needle at the inferior aspect of the intervertebral foramina instead of the superior "safe triangle,"<sup>61–64</sup> and use of specific needle tip types.<sup>65,66</sup> The working group felt that there were not enough quality publications to discuss these logical but largely untested safeguards. The use of chlorhexidine in alcohol for antisepsis<sup>67</sup> was also omitted in view of the controversy surrounding possible neurotoxicity of the antiseptic solution.<sup>68</sup> Finally, the issue of neuraxial injections in the anticoagulated patient was omitted because the American Society of Regional Anesthesia and Pain Medicine, in collaboration with some national and international organizations, is finalizing guidelines on interventional pain procedures for patients on anticoagulants (Honorio T. Benzon, M.D., Professor of Anesthesiology, Northwestern University Feinberg School of Medicine, Chicago, Illinois, written communication, December 2014).

We acknowledge that catastrophic neurologic injuries can and do occur during epidural steroid injections. The actual incidence is unknown, but epidural steroid injections are common, and reports of these neurologic injuries are uncommon. The purpose of this multidisciplinary effort was to review the available evidence and assemble the best clinical considerations for reducing or eliminating these injuries. Although it is beyond the scope of this effort, it is equally important to closely examine the need for epidural injection in each patient who receives this treatment. The clinical considerations put forth herein are broadly supported by experts from many disciplines and stakeholder national medical organizations. We acknowledge that many of the clinical considerations are nothing more than the logical opinions of a group of experts and many remain untested through rigorous scientific research. Many, if not most of the clinical considerations will never be tested, as the incidence of these rare complications is so low that even large studies including thousands of patients are unlikely to detect meaningful differences after the implementation of the clinical considerations. For now, our hope is that these clinical considerations will help every practitioner who performs epidural injections of steroids to become familiar with the risk of neurologic complications and to adopt the best safeguards to avoid complications and provide the safest care for their patients.

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Spring, Maryland), who worked tirelessly with the working group to convene the meetings necessary to assemble the current set of expert clinical considerations aimed at improving patient safety. The authors also thank the representatives of national organizations (see the appendix for list of all participants), who shared their expertise and served to interface with each of their own organizations as we created the final clinical considerations. The American Society of Interventional Pain Physicians (Paducah, Kentucky) did participate in this project, but left the process voluntarily during our early deliberations; the authors acknowledge their participation, but their inclusion in the list of participants should not be misconstrued as an indication of their support for the final recommendations. This work was assembled through the voluntary efforts of the authors with scheduling and meeting facilitation provided by the U.S. Food and Drug Administration Safe Use Initiative.

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### Competing Interests

Dr. Rathmell is a Director of the American Board of Anesthesiology. Dr. Benzon is a member of the Board of Directors of the American Society of Regional Anesthesia and Pain Medicine. Dr. Dreyfuss is past president of the International Spine Intervention Society. Dr. Huntoon is a member of the Board of Directors of the American Society of Regional Anesthesia and Pain Medicine. Dr. Baker is past president of the North American Spine Society, the past president of the International Spine Intervention Society, and a consultant to Medtronic, Mesoiblast, and Relievent MedSystems. He holds stock in Nocimed and Relievent. Dr. Riew receives royalties from Biomet, Medtronic, and Osprey. He is a stock holder with Amedica, Benvenue, Expanding Orthopedics, Nexgen Spine, Osprey, Paradigm, Spine, Spinal Kinetics, Spineology, Vertiflex, and PSD. He is a board member on the CSRS, KASS, Global Spine Journal, Spine Journal, and AOSpine International. Dr. Rosenquist is past president of the American Society of Regional Anesthesia and Pain Medicine. Dr. Aprill is a founding member of the International Spine Intervention Society. Dr. Buvanendran is a member of the Board of Directors of the American Society of Regional Anesthesia and Pain Medicine. Dr. Bogduk is founding member of the International Spine Intervention Society. The other authors declare no competing interests.

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### References

1. McGrath JM, Schaefer MP, Malkamaki DM: Incidence and characteristics of complications from epidural steroid injections. *Pain Med* 2011; 12:726–31
2. Abbasi A, Malhotra G, Malanga G, Elovic EP, Kahn S: Complications of interlaminar cervical epidural steroid injections: A review of the literature. *Spine (Phila Pa 1976)* 2007; 32:2144–51

3. Schellhas KP, Pollei SR, Johnson BA, Golden MJ, Eklund JA, Pobiell RS: Selective cervical nerve root blockade: Experience with a safe and reliable technique using an anterolateral approach for needle placement. *Am J Neuroradiol* 2007; 28:1909–14
4. Pobiell RS, Schellhas KP, Eklund JA, Golden MJ, Johnson BA, Chopra S, Broadbent P, Myers ME, Shrack K: Selective cervical nerve root blockade: Prospective study of immediate and longer term complications. *Am J Neuroradiol* 2009; 30:507–11
5. Huston CW, Slipman CW, Garvin C: Complications and side effects of cervical and lumbosacral selective nerve root injections. *Arch Phys Med Rehabil* 2005; 86:277–83
6. Ma DJ, Gilula LA, Riew KD: Complications of fluoroscopically guided extraforaminal cervical nerve blocks. An analysis of 1036 injections. *J Bone Joint Surg Am* 2005; 87:1025–30
7. Botwin KP, Gruber RD, Bouchlas CG, Torres-Ramos FM, Freeman TL, Slaten WK: Complications of fluoroscopically guided transforaminal lumbar epidural injections. *Arch Phys Med Rehabil* 2000; 81:1045–50
8. Hodges SD, Castleberg RL, Miller T, Thornburg C: Cervical epidural steroid injection with intrinsic spinal cord damage: Two case reports. *Spine (Phila Pa 1976)* 1998; 23:2137–42
9. Fitzgibbon DR, Posner KL, Domino KB, Caplan RA, Lee LA, Cheney FW; American Society of Anesthesiologists: Chronic pain management: American Society of Anesthesiologists Closed Claims Project. *ANESTHESIOLOGY* 2004; 100:98–105
10. Rathmell JP, Michna E, Fitzgibbon DR, Stephens LS, Posner KL, Domino KB: Injury and liability associated with cervical procedures for chronic pain. *ANESTHESIOLOGY* 2011; 114:918–26
11. Bose B: Quadriplegia following cervical epidural steroid injections: Case report and review of the literature. *Spine J* 2005; 5:558–63
12. Lee JH, Lee JK, Seo BR, Moon SJ, Kim JH, Kim SH: Spinal cord injury produced by direct damage during cervical transforaminal epidural injection. *Reg Anesth Pain Med* 2008; 33:377–9
13. Brouwers PJ, Kottink EJ, Simon MA, Prevo RL: A cervical anterior spinal artery syndrome after diagnostic blockade of the right C6-nerve root. *Pain* 2001; 91:397–9
14. McMillan MR, Crumpton C: Cortical blindness and neurologic injury complicating cervical transforaminal injection for cervical radiculopathy. *ANESTHESIOLOGY* 2003; 99:509–11
15. Tiso RL, Cutler T, Catania JA, Whalen K: Adverse central nervous system sequelae after selective transforaminal block: The role of corticosteroids. *Spine J* 2004; 4:468–74
16. Windsor RE, Storm S, Sugar R, Nagula D: Cervical transforaminal injection: Review of the literature, complications, and a suggested technique. *Pain Physician* 2003; 6:457–65
17. Beckman WA, Mendez RJ, Paine GF, Mazzilli MA: Cerebellar herniation after cervical transforaminal epidural injection. *Reg Anesth Pain Med* 2006; 31:282–5
18. Muro K, O'Shaughnessy B, Ganju A: Infarction of the cervical spinal cord following multilevel transforaminal epidural steroid injection: Case report and review of the literature. *J Spinal Cord Med* 2007; 30:385–8
19. Kim W, Kim JS, Lim SC, Kim YI, Moon DE: Reversible posterior leukoencephalopathy syndrome after cervical transforaminal epidural steroid injection presenting as transient blindness. *Anesth Analg* 2011; 112:967–70
20. Ludwig MA, Burns SP: Spinal cord infarction following cervical transforaminal injection. A case report. *Spine (Phila Pa 1976)* 2005; 30:E266–8
21. Suresh S, Berman J, Connell DA: Cerebellar and brainstem infarction as a complication of CT-guided transforaminal cervical nerve root block. *Skeletal Radiol* 2007; 36:449–52
22. Wallace MA, Fukui MB, Williams RL, Ku A, Baghai P: Complications of cervical selective nerve root blocks performed with fluoroscopic guidance. *Am J Roentgenol* 2007; 188:1218–21
23. Scanlon GC, Moeller-Bertram T, Romanowsky SM, Wallace MS: Cervical transforaminal epidural steroid injections: More dangerous than we think? *Spine (Phila Pa 1976)* 2007; 32:1249–56
24. Rathmell JP, Aprill C, Bogduk N: Cervical transforaminal injection of steroids. *ANESTHESIOLOGY* 2004; 100:1595–600
25. Tripathi M, Nath SS, Gupta RK: Paraplegia after intracord injection during attempted epidural steroid injection in an awake-patient. *Anesth Analg* 2005; 101:1209–11
26. McLain RF, Fry M, Hecht ST: Transient paralysis associated with epidural steroid injection. *J Spinal Disord* 1997; 10:441–4
27. Lenoir T, Deloin X, Dauzac C, Rillardon L, Guigui P: Paraplegia after interlaminar epidural steroid injection: A case report (article in French). *Rev Chir Orthop Reparatrice Appar Mot* 2008; 94:697–701
28. Thefenne L, Dubecq C, Zing E, Rogez D, Soula M, Escobar E, Defuentes G, Lapeyre E, Berets O: A rare case of paraplegia complicating a lumbar epidural infiltration. *Ann Phys Rehabil Med* 2010; 53:575–83
29. Chung JY, Han JH, Kang JM, Lee BJ: Paraplegia after epidural steroid injection. *Anaesth Intensive Care* 2012; 40:1074–6
30. Houten JK, Errico TJ: Paraplegia after lumbosacral nerve root block: Report of three cases. *Spine J* 2002; 2:70–5
31. Huntoon MA, Martin DP: Paralysis after transforaminal epidural injection and previous spinal surgery. *Reg Anesth Pain Med* 2004; 29:494–5
32. Somayaji HS, Saifuddin A, Casey AT, Briggs TW: Spinal cord infarction following therapeutic computed tomography-guided left L2 nerve root injection. *Spine (Phila Pa 1976)* 2005; 30:E106–8
33. Wybier M, Gaudart S, Petrover D, Houdart E, Laredo JD: Paraplegia complicating selective steroid injections of the lumbar spine. Report of five cases and review of the literature. *Eur Radiol* 2010; 20:181–9
34. Lyders EM, Morris PP: A case of spinal cord infarction following lumbar transforaminal epidural steroid injection: MR imaging and angiographic findings. *Am J Neuroradiol* 2009; 30:1691–3
35. Glaser SE, Falco F: Paraplegia following a thoracolumbar transforaminal epidural steroid injection. *Pain Physician* 2005; 8:309–14
36. Kennedy DJ, Dreyfuss P, Aprill CN, Bogduk N: Paraplegia following image-guided transforaminal lumbar spine epidural steroid injection: Two case reports. *Pain Med* 2009; 10:1389–94
37. Chang Chien GC, Candido KD, Knezevic NN: Digital subtraction angiography does not reliably prevent paraplegia associated with lumbar transforaminal epidural steroid injection. *Pain Physician* 2012; 15:515–23
38. Huntoon M: Anatomy of the cervical intervertebral foramina: Vulnerable arteries and ischemic injuries after transforaminal epidural injections. *Pain* 2005; 117:104–11
39. Baker R, Dreyfuss P, Mercer S, Bogduk N: Cervical transforaminal injection of corticosteroids into a radicular artery: A possible mechanism for spinal cord injury. *Pain* 2003; 103:211–5
40. Benzon HT, Chew TL, McCarthy RJ, Benzon HA, Walega DR: Comparison of the particle sizes of different steroids and the effect of dilution: A review of the relative neurotoxicities of the steroids. *ANESTHESIOLOGY* 2007; 106:331–8
41. Derby R, Lee SH, Date ES, Lee JH, Lee CH: Size and aggregation of corticosteroids used for epidural injections. *Pain Med* 2008; 9:227–34
42. Okubadejo GO, Talcott MR, Schmidt RE, Sharma A, Patel AA, Mackey RB, Guarino AH, Moran MJ, Riew KD: Perils of intravascular methylprednisolone injection into the vertebral artery. *J Bone Joint Surg Am* 2008; 90:1932–8
43. Dawley JD, Moeller-Bertram T, Wallace MS, Patel PM: Intra-arterial injection in the rat brain: Evaluation of steroids used for transforaminal epidurals. *Spine (Phila Pa 1976)* 2009; 34:1638–43
44. Karasek M, Bogduk N: Temporary neurologic deficit after cervical transforaminal injection of local anesthetic. *Pain Med* 2004; 5:202–5

45. Rozin L, Rozin R, Koehler SA, Shakir A, Ladham S, Barmada M, Dominick J, Wecht CH: Death during transforaminal epidural steroid nerve root block (C7) due to perforation of the left vertebral artery. *Am J Forensic Med Pathol* 2003; 24:351–5
46. Benzon HT: Compounded steroids for epidural injections: What are the issues? *Anesth Analg* 2013; 117:523–6
47. El-Yahouchi C, Geske JR, Carter RE, Diehn FE, Wald JT, Murthy NS, Kaufman TJ, Thielen KR, Morris JM, Amrami KK, Maus TP: The noninferiority of the nonparticulate steroid dexamethasone and triamcinolone in lumbar transforaminal epidural steroid injections. *Pain Med* 2013; 14:1650–7
48. Kennedy DJ, Plastaras C, Casey E, Visco CJ, Rittenberg JD, Conrad B, Sigler J, Dreyfuss P: Comparative effectiveness of lumbar transforaminal epidural steroid injections with particulate *versus* nonparticulate corticosteroids for lumbar radicular pain due to intervertebral disc herniation: A prospective, randomized, double-blind trial. *Pain Med* 2014; 15:548–55
49. Landers MH, Dreyfuss P, Bogduk N: On the geometry of fluoroscopy views for cervical interlaminar epidural injections. *Pain Med* 2012; 13:58–65
50. Furman MB, Furman M, Jasper NR, Lin HW: Fluoroscopic contralateral oblique view in interlaminar interventions: A technical note. *Pain Med* 2012; 13:1389–96
51. Aldrete JA, Mushin AU, Zapata JC, Ghaly R: Skin to cervical epidural space distances as read from magnetic resonance imaging films: Consideration of the “hump pad.” *J Clin Anesth* 1998; 10:309–13
52. Hogan QH: Epidural anatomy examined by cryomicrotome section. Influence of age, vertebral level, and disease. *Reg Anesth* 1996; 21:395–406
53. Goel A, Pollan JJ: Contrast flow characteristics in the cervical epidural space: An analysis of cervical epidurograms. *Spine (Phila Pa 1976)* 2006; 31:1576–9
54. Cohen SP, Gupta A, Strassels SA, Christo PJ, Erdek MA, Griffith SR, Kurihara C, Buckenmaier CC III, Cornblath D, Vu TN: Effect of MRI on treatment results or decision making in patients with lumbosacral radiculopathy referred for epidural steroid injections: A multicenter, randomized controlled trial. *Arch Intern Med* 2012; 172:134–42
55. McLean JP, Sigler JD, Plastaras CT, Garvan CW, Rittenberg JD: The rate of detection of intravascular injection in cervical transforaminal epidural steroid injections with and without digital subtraction angiography. *PM R* 2009; 1:636–42
56. Hong JH, Kim SY, Huh B, Shin HH: Analysis of inadvertent intradiscal and intravascular injection during lumbar transforaminal epidural steroid injections: A prospective study. *Reg Anesth Pain Med* 2013; 38:520–5
57. Lee MH, Yang KS, Kim YH, Jung HD, Lim SJ, Moon DE: Accuracy of live fluoroscopy to detect intravascular injection during lumbar transforaminal epidural injections. *Korean J Pain* 2010; 23:18–23
58. Maus T, Schueler BA, Leng S, Magnuson D, Magnuson DJ, Diehn FE: Radiation dose incurred in the exclusion of vascular filling in transforaminal epidural steroid injections: Fluoroscopy, digital subtraction angiography, and CT/fluoroscopy. *Pain Med* 2014; 15:1328–33
59. Mangram AJ, Horan TC, Pearson ML, Silver LC, Jarvis WR: Guideline for prevention of surgical site infection, 1999. Centers for Disease Control and Prevention (CDC) Hospital Infection Control Practices Advisory Committee. *Am J Infect Control* 1999; 27:97–132
60. Smuck M, Maxwell MD, Kennedy D, Rittenberg JD, Lansberg MG, Plastaras CT: Utility of the anesthetic test dose to avoid catastrophic injury during cervical transforaminal epidural injections. *Spine J* 2010; 10:857–64
61. Windsor RE, Storm S, Sugar R, Nagula D: Cervical transforaminal injection: Review of the literature, complications, and a suggested technique. *Pain Physician* 2003; 6:457–65
62. Park KD, Lee J, Jee H, Park Y: Kambin triangle *versus* the supraneural approach for the treatment of lumbar radicular pain. *Am J Phys Med Rehabil* 2012; 91:1039–50
63. Atluri S, Glaser SE, Shah RV, Sudarshan G: Needle position analysis in cases of paralysis from transforaminal epidurals: Consider alternative approaches to traditional technique. *Pain Physician* 2013; 16:321–34
64. Murthy NS, Maus TP, Behrns CL: Intraforaminal location of the great radiculomedullary artery (artery of Adamkiewicz): A retrospective review. *Pain Med* 2010; 11:1756–64
65. Heavner JE, Racz GB, Jenigiri B, Lehman T, Day MR: Sharp *versus* blunt needle: A comparative study of penetration of internal structures and bleeding in dogs. *Pain Pract* 2003; 3:226–31
66. Shin J, Kim YC, Lee SC, Kim JH: A comparison of Quincke and Whitacre needles with respect to risk of intravascular uptake in S1 transforaminal epidural steroid injections: A randomized trial of 1376 cases. *Anesth Analg* 2013; 117:1241–7
67. Darouiche RO, Wall MJ Jr, Itani KM, Otterson MF, Webb AL, Carrick MM, Miller HJ, Awad SS, Crosby CT, Mosier MC, Alsharif A, Berger DH: Chlorhexidine-alcohol *versus* povidone-iodine for surgical-site antisepsis. *N Engl J Med* 2010; 362:18–26
68. Sviggum HP, Jacob AK, Arendt KW, Mauermann ML, Horlocker TT, Hebl JR: Neurologic complications after chlorhexidine antisepsis for spinal anesthesia. *Reg Anesth Pain Med* 2012; 37:139–44

## Appendix

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