



1-1-2021

## Epidural Interventions in the Management of Chronic Spinal Pain: American Society of Interventional Pain Physicians (ASIPP) Comprehensive Evidence-Based Guidelines.

Laxmaiah Manchikanti


Nebojsa Nick Knezevic

Annu Navani

Paul J. Christo

Gerard Limerick

Follow this and additional works at: <https://scholarlycommons.pacific.edu/phs-facarticles>

 Part of the [Biochemistry, Biophysics, and Structural Biology Commons](#), [Chemicals and Drugs Commons](#), and the [Pharmacy and Pharmaceutical Sciences Commons](#)  
See next page for additional authors

### Recommended Citation

Manchikanti, L., Knezevic, N. N., Navani, A., Christo, P. J., Limerick, G., Calodney, A. K., Grider, J., Harned, M. E., Cintron, L., Gharibo, C. G., Shah, S., Nampiaparampil, D. E., Candido, K. D., Sooin, A., Kaye, A. D., Kosanovic, R., Magee, T. R., Beall, D. P., Atluri, S., Gupta, M., Helm li, S., Wargo, B. W., Diwan, S., Aydin, S. M., Boswell, M. V., Haney, B. W., Albers, S. L., Latchaw, R., Abd-Elsayed, A., Conn, A., Hansen, H., Simopoulos, T. T., Swicegood, J. R., Bryce, D. A., Singh, V., Abdi, S., Bakshi, S., Buenaventura, R. M., Cabaret, J. A., Jameson, J., Jha, S., Kaye, A. M., Pasupuleti, R., Rajput, K., Sanapati, M. R., Sehgal, N., Trescot, A. M., Racz, G. B., Gupta, S., Sharma, M., Grami, V., Parr, A. T., Knezevic, E., Datta, S., Patel, K. G., Tracy, D. H., Cordner, H. J., Snook, L. T., Benyamin, R. M., & Hirsch, J. A. (2021). Epidural Interventions in the Management of Chronic Spinal Pain: American Society of Interventional Pain Physicians (ASIPP) Comprehensive Evidence-Based Guidelines.. *Pain Physician*, *24*(S1), 27–27.  
<https://scholarlycommons.pacific.edu/phs-facarticles/590>

This Article is brought to you for free and open access by the Thomas J. Long School of Pharmacy at Scholarly Commons. It has been accepted for inclusion in School of Pharmacy Faculty Articles by an authorized administrator of Scholarly Commons. For more information, please contact [mgibney@pacific.edu](mailto:mgibney@pacific.edu).

---

## Authors

Laxmaiah Manchikanti, Nebojsa Nick Knezevic, Annu Navani, Paul J. Christo, Gerard Limerick, Aaron K. Calodney, Jay Grider, Michael E. Harned, Lynn Cintron, Christopher G. Gharibo, Shalini Shah, Devi E. Nampiaparampil, Kenneth D. Candido, Amol Soin, Alan D. Kaye, Radomir Kosanovic, Trevor R. Magee, Douglas P. Beall, Sairam Atluri, Myank Gupta, Standiford Helm li, Bradley W. Wargo, Sudhir Diwan, Steve M. Aydin, Mark V. Boswell, Bill W. Haney, Sheri L. Albers, Richard Latchaw, Alaa Abd-Elseyed, Ann Conn, Hans Hansen, Thomas T. Simopoulos, John R. Swicegood, David A. Bryce, Vijay Singh, Salahadin Abdi, Sanjay Bakshi, Ricardo M. Buenaventura, Joseph A. Cabaret, Jessica Jameson, Sunny Jha, Adam M. Kaye, Ramarao Pasupuleti, Kartic Rajput, Mahendra R. Sanapati, Nalini Sehgal, Andrea M. Trescot, Gabor B. Racz, Sanjeeva Gupta, Manohar Lal Sharma, Vahid Grami, Allan T. Parr, Emilija Knezevic, Sukdeb Datta, Kunj G. Patel, Deborah H. Tracy, Harold J. Cordner, Lee T. Snook, Ramsin M. Benyamin, and Joshua A. Hirsch

## Epidural Guidelines

# Epidural Interventions in the Management of Chronic Spinal Pain: American Society of Interventional Pain Physicians (ASIPP) Comprehensive Evidence-Based Guidelines

Laxmaiah Manchikanti, MD, Nebojsa Nick Knezevic, MD, PhD, Annu Navani, MD, Paul J. Christo, MD, Gerard Limerick, MD, PhD, Aaron K. Calodney, MD, Jay Grider, DO, PhD, Michael E. Harned, MD, Lynn Cintron, MD, Christopher G. Gharibo, MD, Shalini Shah, MD, Devi E. Nampiarampil, MD, Kenneth D Candido, MD, Amol Sooin, MD, Alan D. Kaye, MD, PhD, Radomir Kosanovic, MD, Trevor R. Magee, BS, Douglas P. Beall, MD, Sairam Atluri, MD, Myank Gupta, MD, Standiford Helm II, MD, Bradley W. Wargo, DO, Sudhir Diwan, MD, Steve M. Aydin, DO, Mark V. Boswell, MD, PhD, Bill W. Haney, MD, Sheri L. Albers, DO, Richard Latchaw, MD, Alaa Abd-Elsayed, MD, MPH, Ann Conn, MD, Hans Hansen, MD, Thomas T. Simopoulos, MD, John R. Swicegood, MD, David A. Bryce, MD, Vijay Singh, MD, Salahadin Abdi, MD, Sanjay Bakshi, MD, Ricardo M. Buenaventura, MD, Joseph A. Cabaret, MD, Jessica Jameson, MD, Sunny Jha, MD, Adam M. Kaye, PharmD, Ramarao Pasupuleti, MD, Kartic Rajput, MD, PhD, Mahendra Sanapati, MD, Nalini Sehgal, MD, Andrea M. Trescot, MD, Gabor B. Racz, MD, Sanjeeva Gupta, MD, Manohar Lal Sharma, MBBS, Vahid Grami, MD, Allan T. Parr, MD, Emilija Knezevic, Sukdeb Datta, MD, Kunj G. Patel, MD, Deborah H. Tracy, MD, Harold J. Cordner, MD, Lee T. Snook, MD, Ramsin M. Benyamin, MD, and Joshua A. Hirsch, MD

From: The American Society of  
Interventional Pain Physicians

Author Affiliations can be found on  
pp. S163-S167

Address Correspondence:  
Laxmaiah Manchikanti, MD  
Pain Management Centers of  
America  
67 Lakeview Drive  
Paducah, KY 42001  
E-mail: [drlm@thepainmd.com](mailto:drlm@thepainmd.com)

Conflict of interest: Author  
disclosures are on pp. S163

Manuscript received:  
09/25/2020  
Revised manuscript received:  
11/17/2020  
Accepted for publication:  
11/19/2020

Free full manuscript:  
[www.painphysicianjournal.com](http://www.painphysicianjournal.com)

**Background:** Chronic spinal pain is the most prevalent chronic disease with employment of multiple modes of interventional techniques including epidural interventions. Multiple randomized controlled trials (RCTs), observational studies, systematic reviews, and guidelines have been published. The recent review of the utilization patterns and expenditures show that there has been a decline in utilization of epidural injections with decrease in inflation adjusted costs from 2009 to 2018. The American Society of Interventional Pain Physicians (ASIPP) published guidelines for interventional techniques in 2013, and guidelines for facet joint interventions in 2020. Consequently, these guidelines have been prepared to update previously existing guidelines.

**Objective:** To provide evidence-based guidance in performing therapeutic epidural procedures, including caudal, interlaminar in lumbar, cervical, and thoracic spinal regions, transforaminal in lumbar spine, and percutaneous adhesiolysis in the lumbar spine.

**Methods:** The methodology utilized included the development of objective and key questions with utilization of trustworthy standards. The literature pertaining to all aspects of epidural interventions was viewed with best evidence synthesis of available literature and recommendations were provided.

**Results:** In preparation of the guidelines, extensive literature review was performed. In addition to review of multiple manuscripts in reference to utilization, expenditures, anatomical and pathophysiological considerations, pharmacological and harmful effects of drugs and procedures, for evidence synthesis we have included 47 systematic reviews and 43 RCTs covering all epidural interventions to meet the objectives.

The evidence recommendations are as follows:

**Disc herniation:** Based on relevant, high-quality fluoroscopically guided epidural injections, with or without steroids, and results of previous systematic reviews, the **evidence is Level I**

for caudal epidural injections, lumbar interlaminar epidural injections, lumbar transforaminal epidural injections, and cervical interlaminar epidural injections **with strong recommendation** for long-term effectiveness.

The evidence for percutaneous adhesiolysis in managing disc herniation based on one high-quality, placebo-controlled RCT is **Level II with moderate to strong recommendation** for long-term improvement in patients nonresponsive to conservative management and fluoroscopically guided epidural injections.

For thoracic disc herniation, based on one relevant, high-quality RCT of thoracic epidural with fluoroscopic guidance, with or without steroids, the evidence is **Level II with moderate to strong recommendation** for long-term effectiveness.

**Spinal stenosis:** The evidence based on one high-quality RCT in each category the evidence is **Level III to II** for fluoroscopically guided caudal epidural injections **with moderate to strong recommendation** and **Level II** for fluoroscopically guided lumbar and cervical interlaminar epidural injections **with moderate to strong recommendation** for long-term effectiveness.

The evidence for lumbar transforaminal epidural injections is **Level IV to III with moderate recommendation** with fluoroscopically guided lumbar transforaminal epidural injections for long-term improvement.

The evidence for percutaneous adhesiolysis in lumbar stenosis based on relevant, moderate to high quality RCTs, observational studies, and systematic reviews is **Level II with moderate to strong recommendation** for long-term improvement after failure of conservative management and fluoroscopically guided epidural injections.

**Axial discogenic pain:** The evidence for axial discogenic pain without facet joint pain or sacroiliac joint pain in the lumbar and cervical spine with fluoroscopically guided caudal, lumbar and cervical interlaminar epidural injections, based on one relevant high quality RCT in each category is **Level II with moderate to strong recommendation** for long-term improvement, with or without steroids.

**Post-surgery syndrome:** The evidence for lumbar and cervical post-surgery syndrome based on one relevant, high-quality RCT with fluoroscopic guidance for caudal and cervical interlaminar epidural injections, with or without steroids, is **Level II with moderate to strong recommendation** for long-term improvement.

For percutaneous adhesiolysis, based on multiple moderate to high-quality RCTs and systematic reviews, the evidence is **Level I with strong recommendation** for long-term improvement after failure of conservative management and fluoroscopically guided epidural injections.

**Limitations:** The limitations of these guidelines include a continued paucity of high-quality studies for some techniques and various conditions including spinal stenosis, post-surgery syndrome, and discogenic pain.

**Conclusions:** These epidural intervention guidelines including percutaneous adhesiolysis were prepared with a comprehensive review of the literature with methodologic quality assessment and determination of level of evidence with strength of recommendations.

**Key words:** Chronic spinal pain, interventional techniques, epidural procedures, caudal epidural, lumbar interlaminar epidural, cervical interlaminar epidural, thoracic interlaminar epidural, lumbar transforaminal epidural, percutaneous adhesiolysis

**Disclaimer:** These guidelines are based on the best available evidence and do not constitute inflexible treatment recommendations. Due to the changing body of evidence, this document is not intended to be a “standard of care.” There was no external funding in the preparation of this manuscript.

**Pain Physician 2020: 23:S27-S208**

## 1.0 INTRODUCTION

Chronic spinal pain is the most prevalent chronic disease across the globe, negatively impacting the quality of life (QoL) and function, impacting individuals, their families, communities, businesses, and health systems, and straining the healthcare system as a leading cause of disability adjusted life years. Overall, the impact of chronic pain, of which spinal pain is the major component with low back pain as the leading cause, continues to be disproportionate and enormous.

Chronic persistent spinal pain lasting longer than one year is reported in 25% to 60% of patients (1-38). The prevalence of pain in various spinal regions, while variable, is most present in the low back with 43%, followed by the neck at around 32%, and least in the thoracic spine at 13% (29). Further, most painful conditions increase with age and because there is an increase in multi-morbidity, noncommunicable diseases, and reduced physical activity associated with spinal pain, the global burden related to pain is expected to rise with an increasing global population of 65 years and older, which also applies to the United States (US) (5-8,13,33-38).

The assessments of the impact of spinal pain in the US showed low back pain ranking number 1, neck pain ranking number 3, with musculoskeletal disorders ranking number 2, and depression and anxiety ranking number 4 and 5, among the 30 leading diseases and injuries, contributing to years lived with disability in 2010 (2). In addition, Dieleman et al (39,40) evaluated the economic impact on healthcare in the US and showed an estimated spending of \$134.5 billion in 2016, a 53.5% increase from 2013 or \$87.6 billion spent for managing spinal pain. The costs of other musculoskeletal disorders also increased by 43.5% from \$183.5 billion in 2013 to \$263.3 billion in 2016.

This analysis (40) also showed in 2016, among 154 conditions, low back and neck pain had the highest amount of healthcare spending, of which 57.2% was paid by private insurance, 33.7% paid by public insurance, and 9.2% by out-of-pocket payments. In addition, the same group analyzing the costs (39,40) also performed an economic attribution analysis of healthcare spending attributable to modifiable risk factors in the United States (US) (41). In this analysis, they included behavioral risks, such as smoking and dietary risks; metabolic risks, such as high body mass index (BMI) and high blood pressure; and environmental risks, such as air pollution and occupational carcinogens. This study (41) highlighted that 27% of healthcare spending in the

US in 2016 can be attributed to this broad set of risk factors, with most spending attributable to high BMI, high systolic blood pressure, high fasting plasma glucose, dietary risks, and smoking tobacco.

National health expenditures (42) are projected to grow at an average annual rate of 5.4% from 2019 to 2028 and to represent 19.7% of the gross domestic product (GDP) by the end of the period. Among all major payers, Medicare is expected to experience the fastest spending growth, 7.6% per year, largely because of having the highest projected enrollment growth. In fact, these projected data show that Medicare and Medicaid spending was 37% in 2019 and will grow to 41.6% in 2028. Similarly, federal and other governmental spending was 53.2% in 2019, and will increase to 58% in 2028.

Additionally, healthcare expenditures have been escalating and the financial impact on the US economy is growing with a perfect storm created by COVID-19, the opioid epidemic, issues related to regulations, and lack of reliable, unbiased, evidence-based medicine (43-46). The COVID-19 epidemic resulted in severe access deficits for patients with undertreatment and a lack of treatment for elective care, with severe economic consequences for providers because of reduced reimbursement and increased costs, as well as a severe psychosocial impact, not only on patients, but also on healthcare providers (43-53).

Among multiple modalities of treatments available, epidural injections are one of the most performed procedures in managing spinal pain with or without extremity pain. Epidural injections are utilized in managing pain and disability secondary to herniated discs, spinal stenosis, discogenic pain, and in post-surgery syndrome (7,54-77). Further, in patients with the post-lumbar surgery syndrome and spinal stenosis, percutaneous adhesiolysis is administered frequently for targeted delivery of solutions following the adhesiolysis (7,71-74). Adhesiolysis is also utilized occasionally in managing recalcitrant disc herniation nonresponsive to epidural injections (71). In fact, Best Practices in Pain Management, from the Department of Health and Human Services (HHS) has reviewed the available evidence in pain management and described interventional techniques as part of a continuum prior to surgical interventions and neuromodulation (78,79). Despite their extensive use, discordant conclusions have been brought on by multiple challenges related to the conduct of the randomized controlled trials (RCTs) based on approach (transforaminal, interlaminar, or caudal), control design

(active-controlled versus placebo-controlled), and technical performance with or without fluoroscopy, alternative techniques, and outcome assessments ranging from absolute difference between 2 groups to minimally clinically important difference with assessment of proportion of patients (7,8,54-83).

Discordant conclusions are based on academicians not following the fundamental rules in designing systematic reviews related to inclusion criteria, methodologic quality assessment of the trials or studies, outcome assessments, and perceived intellectual bias with conflicts of interest. In fact, the Institute of Medicine (IOM) (84) has described multiple issues related to the design of the systematic review addressing multiple issues as an example. Multiple systematic reviews have suffered significant bias based on inclusion criteria by converting all active controls to placebos, with conclusions based on inappropriate analysis, leading to invalid results (66-69,74,80-83). IOM extensively described the role of bias and conflicts of interest and the need to minimize the bias and conflicts of interest. IOM defined conflict of interest as, "a set of circumstances that creates the primary interest will be unduly influenced by a secondary interest" (84). Often, primary interests are well-known and disclosed with financial conflicts (even though it is not always the case). However, multiple secondary interests such as pursuit of professional advancement, future funding opportunities and recognition, personal biases, and the desire to do favors for friends and colleagues are often not disclosed. Hidden conflicts of interest have been identified in those with academic interests, but also by taxpayer paid agencies, which advise the policy makers and those preparing reviews for these organizations (74,82,84-87). Major conflicts of interest and inappropriate assessments have been identified by the Cochrane reviews (68,69,88-93). Further, the Institute for Transitional Medicine and Therapeutics (ITMAT) (94) described the confluence (not conflict of interest) in which conflicts of interest represent a complex ecosystem that requires the development of a uniform approach to minimize bias in clinical research across the academic sector. They showed that the conflict of interest is pejorative and that disclosure policies have focused on financial gains only, whereas in academia, the prospect of fame may be even more seductive than fortune. Multiple systematic reviews also have confused facts (verifiable) with their own opinions (judgment based on beliefs and conviction based on personal values), ultimately leading to prejudicial statements – opinions based on insufficient or unexamined evidence.

Recently, Manchikanti et al (93) have published a methodologic review and evidence assessment in guideline preparation in interventional pain management.

The study of the methodologic quality of systematic reviews published in the highest-ranking journals in the field of pain medicine by Riado Minguez et al (95), essentially showed a lack of improvement in the methodological and reporting quality of systematic reviews before or after the publication of A Measurement Tool to Assess Systematic Reviews (AMSTAR) (96), and Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) checklists (97). In this review (95), authors reviewed evidence from multiple journals from Anesthesiology and Pain across the globe, but had not found any systematic reviews to be included from the journal *Pain Medicine*. *Pain Physician* published a large number of systematic reviews of moderate to high-quality.

In another manuscript, Ross et al (98) assessed the methodologic quality of systematic reviews from clinical practice guidelines for the treatment of opioid use disorder and concluded that underperforming areas and AMSTAR included conflicts of interest, funding, and publication bias, whereas in PRISMA, protocol registration and risk of bias are issues of concern. In fact, multiple issues were raised in reference to Cochrane reviews and their discrepancies, which were even less ominous than errors with interventional pain management techniques (89-91). Cochrane reviews have been internationally regarded as one of the leading resources for reliable information on healthcare interventions. Clark et al (89) reported misrepresentation of evidence for vertebroplasty with early interventions in severely affected patients. Clark et al (92) in fact filed a complaint with the Editor in Chief of Cochrane reviews. Clark et al (92) showed that the review did not accurately report the evidence for vertebroplasty in patients with severe symptoms and early fractures. The way the data was presented in the Cochrane review, readers of the review would be unable to discern this information. They alluded to multiple issues with protocol breaches, misreporting of data in the trials, undisclosed conflicts of interest, and faulty risk of bias assessment in the Cochrane review. Kirkham et al (91) analyzed outcome reporting bias (ORB) in trials and concluded that evidence suggests that ORB is a threat to the validity of the evidence base and contributes to research waste. They have also highlighted up-to-date approaches and recommendations for detecting these problems and adjusting the results when performing

sensitivity analysis in systematic reviews. Shah et al (90), in a later publication, assessed ORB in Cochrane systematic reviews in a cross-sectional analysis. They described that discrepancies in outcome reporting (DOR) between protocol and published studies include inclusions of new outcomes, omission of prespecified outcomes, upgrade and downgrade of secondary and primary outcomes, and changes in definitions of prespecified outcomes. Thus, DOR can result in ORB when changes in outcomes occur after knowledge of the results, which essentially has a potential to overestimate treatment effects and underestimate harms at the level of systematic reviews. Their analysis showed that 43%, or 150 of 350, Cochrane review protocol pairings contained DOR. Further, 35%, or 53 of 150, reviews with DOR contained a high risk of ORB, with changes being made after knowledge of results from individual trials. They concluded that the presence of DOR and ORB in Cochrane reviews is of great concern. Obviously, Cochrane review has not identified these issues and has not ascertained to resolve these issues, even though they can do so with simple measures.

This discussion leads to various types of bias in studies in interventional pain management in multiple manuscripts (67,80-82). In fact, Manchikanti et al (81) performed a comparative systematic review and meta-analysis assessing the publication by Chou et al (80), which showed significantly different results when the analysis was performed appropriately. Their conclusion was also not based on scientific evidence, as both local anesthetic and steroids were equally effective. Consequently, they concluded that neither one was effective. Further, Agency for Healthcare Research and Quality (AHRQ) funding has been significantly reduced. The same philosophy was applied by Cochrane review guidance by Pinto et al (67,68) who utilized a similar philosophy with conversion of active control trials with a lack of clinical experience or understanding by the primary authors and lack of disclosures of conflict of interest. These may be added to multiple other deficits of the Cochrane reviews. Another issue is based on the fact that providing pain relief after a single epidural injection, which may last 3 to 13 weeks, the reviewers are assessing their effectiveness for a year, and are also comparing with long-term surgical procedures without any clinical relevance.

Along the same lines, Manchikanti et al (74) analyzed systematic findings of systematic reviews in assessing the effectiveness of percutaneous adhesiolysis in post-lumbar surgery syndrome. The authors (74)

found that a single systematic review by Brito-García et al (87) of 4 randomized trials on this subject at that time, had very low methodologic quality scores on all AMSTAR, PRISMA, and Scottish Intercollegiate Guidelines Network (SIGN) checklist for systematic reviews. The systematic review by Brito-García et al (87) also had numerous deficiencies and improper and inappropriate information. Contrary to the high-profile reviews by Chou et al and others (67,68,80), Lewis et al (99,100) in 2 manuscripts funded by National Health Services (NHS) and Health Technology Assessment Program (HTA) have presented positive results for epidural injections. The systematic review of health technology assessment (99) also utilized an economic model of the clinical effectiveness and cost-effectiveness of management strategies for sciatica, supporting the effectiveness of epidural corticosteroid injections, and disc surgery. In the second manuscript, Lewis et al (100), utilizing a network meta-analysis of comparative clinical effectiveness of management strategies for sciatica with review of 122 relevant studies and 21 treatment strategies showed a statistically significant improvement with epidural injections. In addition, Guo et al (101), in a comparative network meta-analysis to compare the efficacy and tolerability of treatment for sciatica, showed that the epidural steroid with local anesthetic demonstrated superiority over the epidural steroid without local anesthetic and intramuscular steroid. Further, they found subcutaneously injected antitumor necrosis factor- $\alpha$  (anti-TNF- $\alpha$ ) to be superior to the epidural steroid plus anesthetic at reducing pain levels, but the epidural steroids demonstrated superior reductions in the Oswestry Disability Index (ODI) scores, compared to subcutaneous anti-TNF- $\alpha$ . Further, Shanthanna et al (102), in a systematic review and meta-analysis of RCTs in the review of addition of corticosteroids to local anesthetics for chronic noncancer pain injections, after review of 73 trials, concluded that the addition of corticosteroids to local anesthetic has only small benefits and a potential for harm. They found no meaningful improvement in pain scores or the duration of pain relief. They recommended that clinical decisions should consider the potential for harm with steroids and the therapeutic benefit by the local anesthetic alone.

Consequently, despite the availability of numerous systematic reviews (56-77,80-83,102), there have not been guidelines systematically developed in assessing clinical and cost effectiveness of epidural injections, including percutaneous adhesiolysis, in managing spinal pain. The American Society of Interventional Pain Physicians (ASIPP)



guidelines in managing spinal interventional techniques were published in 2013 (7), which included all modalities of treatments in managing spinal pain. Since then, multiple other guidelines have been developed relevant to interventional pain physicians, including facet joint interventions (8), opioid therapy in chronic noncancer pain (6), use of biologics in the management of low back pain (5), antithrombotic guidelines (103), risk mitigation and stratification during COVID-19 for return to interventional pain practice (51), triaging of interventional pain procedures during COVID-19 or related elective surgery restrictions (52), and a position statement on bone marrow concentrate (104). The present guidelines have been developed specifically for epidural interventions, including percutaneous adhesiolysis. Since the US and the world continue to be in the middle of a pandemic, with resurgences, the development of guidelines for epidural procedures is crucial. ASIPP has been at the forefront during COVID-19 pandemic and its influence on interventional pain management with publications related to guidance (51,52), highlighting the value of nonsteroidal injections as steroids were considered as a risk factor for COVID-19 patients (55,58,105-107), value of telemedicine (108,109), influence on technological advances and multiple other aspects including testing and therapeutics (43-45,110-115). The impact of chronic pain has been described by multiple others, with a continuing downturn of revenues and simultaneous increases in expenses (43-53). Consequently, a triad of concurrent epidemics of COVID-19, opioid epidemic, and a regulatory burden with declining reimbursements has created a perfect storm (43) with increasing practice costs, exacerbated by inappropriate evidence-based medicine. Furthermore, the addition of improper evidence-based assessments continues to add to the ongoing storm with inadequate assessments leading to inappropriate conclusions.

The development of these guidelines includes an overview of the current literature regarding the use of epidural injections and percutaneous adhesiolysis procedures in managing spinal pain. These guidelines included evidence-based and evidence-informed strategies utilizing the concepts of efficacy and effectiveness and proper evidence synthesis as described in the literature (5-8,51,52,104,116-126) to avoid conflicts and confluence of interest.

Consequently, ASIPP has undertaken the development of guidelines for epidural interventions, based on a rational and systematic approach to the application of these interventions in managing spinal pain. This is an update of epidural interventions from comprehensive

guidelines published in 2013, which included all spinal interventions (7).

## 2.0 METHODS

### 2.1 Rationale

The National Uniform Claims Committee (NUCC) defines interventional pain management as the discipline of medicine devoted to the diagnosis and treatment of pain related disorders principally with the application of interventional techniques in managing subacute, chronic, persistent, and intractable pain, independently or in conjunction with other modalities of treatment (<https://www.nucc.org>). The Medicare Payment Advisory Commission (MedPAC) defines interventional pain management techniques as minimally invasive procedures including percutaneous precision needle placement of drugs in targeted areas or ablation of targeted nerves; surgical techniques such as laser and endoscopic discectomy; and the placement of intrathecal infusion pumps and spinal cord stimulators for the diagnosis and management of chronic, persistent, or intractable pain (<http://medpac.gov/>).

Chronic spinal pain is a complex and multifactorial disease process with numerous treatment modalities applied in the management of the problem, and the growing social and economic costs continue to influence medical decision-making. Intervertebral discs, facet joints, sacroiliac joints, ligaments, fascia, muscles, and nerve root dura are proven pain generators in the spine (5-8,78,79,127-139). Interventional pain physicians are familiar with various image-guided interventional techniques for the management of spinal pain (5-8).

Many of the causes of spinal pain and other chronic pain conditions are considered to be acute recurrent problems characterized by periods of quiescence punctuated by flare-ups, or chronic diseases, like diabetes or hypertension, requiring long-term treatment with ongoing care. The importance of spinal interventional techniques in managing chronic spinal pain has been established on the basis of advances in imaging, neuroanatomic findings, the development of precision diagnostic and therapeutic injection techniques, and reported nonoperative treatment successes. Many guidelines, systematic reviews, Cochrane Reviews, and other articles pertaining to interventional pain management (IPM) have been published (5-8,54-83). Some of these guidelines, however, are ambiguous and not based on appropriate evidence synthesis, with the inclusion of extensive confluences of interest (66-69,74,80-93,95,97,98,105,140-150). Consequently, these



approaches may not be applicable in managing chronic spinal pain utilizing contemporary IPM.

## 2.2 Objectives

The objective of these guidelines is to provide a rationale and systematic approach to the application of epidural interventions in managing spinal pain. The guidelines are based upon the available evidence concerning the effectiveness and safety in the treatment of spinal pain. The literature shows the value of evidence-based guidelines and the need for appropriate updating of the guidelines to practice with current concepts (5-8,93,116-126).

These guidelines include the description and application of epidural interventions in managing spinal pain due to disc, spinal stenosis and post-surgery syndrome.

## 2.3 Application

While these guidelines may be applied by any specialty, they are specifically intended for use by interventional pain physicians. These guidelines do not constitute inflexible treatment recommendations. It is expected that a clinician will establish a plan of care on a case-by-case basis, considering an individual patient's medical condition, personal needs, and preferences, and the physician's experience. Based on an individual patient's needs, treatment different from that outlined here could be warranted. Consequently, these guidelines do not represent a "standard of care." It is a well-known fact that all treatments are not supported by existing evidence and grading. However, there may be strong clinical support for some interventions.

The goal of these guidelines is to provide patients, practitioners, regulators, and payers, information that may be used to determine whether the available evidence supports the notion of a "standard" for interventional techniques. "Standard" refers to what is applicable to the majority of patients, with a preference for patient convenience and ease of administration without compromising treatment efficacy or morbidity (5-8). It is essential to recognize the difference between "standard" and "standard of care," as utilized as a legal definition (151).

## 2.4 Key Questions

These guidelines focus on the following key questions regarding disc-related and stenotic spinal pain:

1. What is the impact of chronic spinal pain on health-care resources?
2. What are the statistics regarding the trends in utilization of treatment modalities in managing spinal pain?

3. What is the evidence for the structural basis of spinal pain?
4. What is the pathophysiologic basis of epidural interventions in spinal pain?
5. What are the noninterventional diagnostic methods in disc related pathology, spinal stenosis, and post-surgery syndrome?
6. Are the available therapeutic epidural injections and adhesiolysis in managing chronic spinal pain effective?
7. What is the evidence for cost-effectiveness of epidural interventions including adhesiolysis in managing spinal pain?
8. What are the adverse consequences, harms, and related precautions in providing epidural interventions?
9. What are the implications of antithrombotic and anticoagulant therapy and epidural interventions?
10. What are the guidelines for epidural injections and adhesiolysis in managing chronic spinal pain?

## 2.5 Adherence to Trustworthy Standards

In preparation of guidelines for epidural interventions (epidurals and adhesiolysis), the standards from the IOM and the National Guideline Clearinghouse Extent Adherence to Trustworthy Standards (NEATS) were followed (94,118-125). The NEATS instrument was developed and tested as a tool to be used by the trained staff at the AHRQ National Guideline Clearinghouse to provide assessment focused on adherence (119).

### 2.5.1 Disclosure of Guideline Funding Source

Comprehensive evidence-based guidelines for epidural interventions in managing chronic spinal pain were commissioned, prepared, edited, and endorsed by ASIPP without external funding.

### 2.5.2 Disclosure and Management of Financial Conflicts of Interests

Potential conflicts of interest for all panel members within the last 5 years were evaluated prior to the finalizing of these guidelines. Conflicts of interests extended beyond financial relationships, including personal experience, practice patterns, academic interests, and promotions. The panel members with potential conflicts were recused from discussion or preparation of the guidelines in which they had conflicts of interest, and these members agreed not to discuss any aspect of a given guideline with the related industry before data publication.

**2.5.3 Composition of Guideline Development Group**

A panel of experts in managing spinal pain and interventional techniques from various medical fields, convened by ASIPP, reviewed the evidence and formulated recommendations for epidural procedures, including adhesiolysis. Overall, the panel provided a broad representation of academic and nonacademic clinical practitioners with interest and expertise in interventional techniques as applicable to epidural procedures.

**2.6 Evidence Review**

The evidence-based guidelines for epidural interventions were developed utilizing consensus among the panel members after they had reviewed all published literature concerning the use and safety of epidural procedures, including adhesiolysis, in patients with chronic spinal pain. The recommendations have been developed using principles of best evidence synthesis developed by the Cochrane Review, incorporating multiple guidelines modified by ASIPP (152).

**2.6.1 Grading or Rating the Quality or Strength of Evidence**

The grading of evidence is based on RCTs, obser-

vatational studies, and other clinical reports. In addition, systematic reviews and meta-analyses were utilized. The grading of evidence based on ASIPP guidelines is shown in Table 1 (152), whereas Table 2 shows GRADE recommendation grading (125). This grading system specifies levels of scientific evidence and offers an approach to grading the quality of evidence and secondarily the strength of recommendations. AHRQ has recommended a similar approach to the strength of a recommendation (121,125,152).

**2.6.2 Assessment and Recommendations of Benefits and Harms**

These guidelines describe the potential benefits and harms for the interventions and explicitly link the information to specific recommendations.

**2.6.3 Evidence Summary of Recommendations**

Guideline-supporting documents summarize the relevant supporting evidence and link this information to the recommendations.

**2.6.4 Rating or Grading the Strength of Recommendations**

IOM standards demand that for each recommendation, a rating of the strength of the recommendation related to benefits and harms, available evidence, and the confidence in the underlying evidence should be provided. To meet the appropriate standards, the rating schemes recommended by NEATS were utilized as shown in Table 3 (119).

Table 1. Qualitative modified approach to grading of evidence of therapeutic effectiveness studies.

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

Modified from: Manchikanti L, et al. A modified approach to grading of evidence. *Pain Physician* 2014; 17:E319-E325 (152).

Table 2. Recommendation grade.

A	- At least one metaanalysis, systematic review, or RCT rated as 1 + + and directly applicable to the target population or - A systematic review of RCTs or a body of evidence consisting principally of studies rated as 1 + directly applicable to the target population and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2 + + directly applicable to the target population and demonstrating overall consistency of results or - Extrapolated evidence from studies rated as 1 + + or 1 +
C	- A body of evidence including studies rated as 2 + directly applicable to the target population and demonstrating overall consistency of results or - Extrapolated evidence from studies rated as 2 + +
D	- Evidence level 3 or 4 or - Extrapolated evidence from studies rated as 2 +

Source: Harbour R, Miller J. A new system for grading recommendations in evidence based guidelines. *BMJ* 2001; 323:334-336 (125).

Table 3. Guide for strength of recommendations.

Rating for Strength of recommendation	
Strong	There is high confidence that the recommendation reflects best practice. This is based on: a) strong evidence for a true net effect (e.g., benefits exceed harms); b) consistent results, with no minor exceptions; c) minor or no concerns about study quality; and/or d) the extent the panelists' agreement. Other compelling considerations (discussed in the guideline's literature review and analyses) may also warrant a strong recommendation.
Moderate	There is moderate confidence that the recommendations reflects best practice. This is based on: a) good evidence for a true net effect (e.g. benefits exceed harms); b) consistent results, with minor and/or few exceptions; c) minor and/or few concerns about study quality; and/or d) the extent of panelists' agreement. Other compelling considerations (discussed in the guideline's literature review and analyses) may also warrant a moderate recommendation.
Weak	There is some confidence that the recommendation offers the best current guidance for practice. This is based on: a) limited evidence for a true net effect (e.g., benefits exceed harms); b) consistent results, but with important exceptions; c) concerns about study quality; and/or d) the extent of panelists' agreement. Other considerations (discussed in the guideline's literature review and analyses) may also warrant a weak recommendation.

Source: National Guideline Clearinghouse Extent Adherence to Trustworthy Standards (NEATS) instrument (119).

### 2.6.5 Specificity of Recommendations

Evidence and best practices were utilized in forming recommendations for epidural injections and adhesiolysis.

## 2.7 Methodologic Quality and Risk of Bias Assessment

Key recommendations included transparency and reproducibility of judgements, separating risk of bias from other constructs such as applicability and precision, and evaluation of the risk of bias per outcomes.

### 2.7.1 Randomized Controlled Trials

Multiple instruments have been developed over the years to assess the methodological quality, along with bias, in RCTs (153,154). The criteria developed by the Cochrane review editorial board has been used extensively and has been modified over the years. Appendix Table 1 shows Cochrane review criteria (154) and Appendix Table 2 shows criteria developed by interventional pain physicians with a specific item checklist for assessment of RCTs of interventional pain management techniques (153). A third criteria used is based on SIGN (74,155,156) as shown in Appendix Table 3.

While Cochrane criteria is universally accepted and was implemented in several trials, this was not specific for interventional techniques. In contrast, Interventional Pain Management techniques - Quality Appraisal of Reliability and Risk of Bias Assessment (IPM-QRB) was specifically developed for interventional techniques, specifically in patients suffering with chronic spinal pain. This checklist includes various types of criteria, including trial design and guidance report, along with setting, physician, imaging, chronicity of pain, previous treatments, and multiple other appropriate criteria. It has been shown to be more robust than the Cochrane

review criteria and was considered as providing better information than the Cochrane review criteria when compared head-to-head with both Cochrane review criteria and IPM-QRB. Both criteria have been extensively utilized in IPM evidence synthesis.

The literature pertaining to SIGN (74,125,155,156) is not extensive, even though it has been reported in some studies related to interventional techniques (74,155).

#### 2.7.1.1 Scoring IPM-QRB Criteria

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

#### 2.7.1.2 Scoring Cochrane Review Criteria

Utilizing Cochrane review criteria, studies meeting the inclusion criteria with at least 9 of 13 criteria were considered high-quality; 5 to 8 were considered moderate quality. Those meeting criteria of less than 5 were considered as low-quality and were excluded.

#### 2.7.1.3 Scoring SIGN

Methodologic quality assessment of systematic reviews was also conducted utilizing SIGN (74,155,156). The quality assessment was based on 3 options, i.e., those which were designated as ++ (indicated all or most of all standards are met), + (indicated some of the standards are met), and - (indicated all or most of all standards are not met).

### 2.7.2 Nonrandomized Studies

Similar to the checklist for RCTs, Manchikanti et

al (157) developed a comprehensive instrument that is helpful in assessing the methodological quality of nonrandomized trials and is specific to interventional techniques (Appendix Table 4).

IPM checklist with Interventional Pain Management Techniques – Quality Appraisal of Reliability and Risk of Bias Assessment for Nonrandomized Studies (IPM-QRB-NR) has been evaluated in multiple assessments. With the rapid development of RCTs, observational studies are not as frequently used. Further, methodologic quality assessment for these is not utilized.

SIGN also has developed an instrument to assess the methodologic quality and risk of bias assessment in observational studies as shown in Appendix Table 3 (74,125,155,156). In contrast to RCTs, observational studies have not been methodologically assessed as frequently. Further instruments for assessment are also limited.

**2.7.2.1 Scoring For IPM-QRBNR**

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

**2.7.3 Quality Assessment of Systematic Reviews**

Risk of bias and methodological and reporting quality assessment may be performed utilizing 3 tools: AMSTAR, PRISMA, and SIGN.

In the past, we have performed such assessments utilizing all 3 tools; however, it is not only very cumbersome, but also did not provide any meaningful informa-

tion. A low-quality meta-analysis may be high-quality methodologically. To avoid such time issues, we have categorized all the systematic reviews into 3:

1. Low-quality: This category with either a systematic review or meta-analysis, with conversion of studies or moving them into a different category, such as placebo to active control, against the intent of the authors of the original manuscripts, without consent, and without STRONG scientific basis, even though they may be of high, moderate or low methodologic quality based on PRISMA, AMSTAR, or SIGN.
2. Moderate quality: This category included the majority of the systematic reviews, methodologically sound, which followed the appropriate principles without violation of practices, with either a systematic review or meta-analysis with conventional dual-arm analysis only.
3. High-quality: In this category, the systematic reviews, methodologically sound, with the inclusion of appropriate, high-quality principles, with conventional dual-arm meta-analysis and single-arm meta-analysis without violation of standards and keeping the intent of the original manuscripts.

**2.8 External Review**

Guidelines have been subjected to external peer review as per the policies of the publishing journal, *Pain Physician*.

**2.9 Updating Guidelines**

The epidural interventions for chronic spinal pain guidelines will be updated within 5 years or less, based on significant changes in scientific evidence, public policy, or adverse events occurring before January 2026.

**3.0 IMPACT OF CHRONIC SPINAL PAIN ON HEALTH CARE**

Key Question 1: What is the impact of chronic spinal pain on healthcare resources?

The impact of chronic pain continues to be enormous (1-30,39-43,46-50). Figure 1 shows musculoskeletal

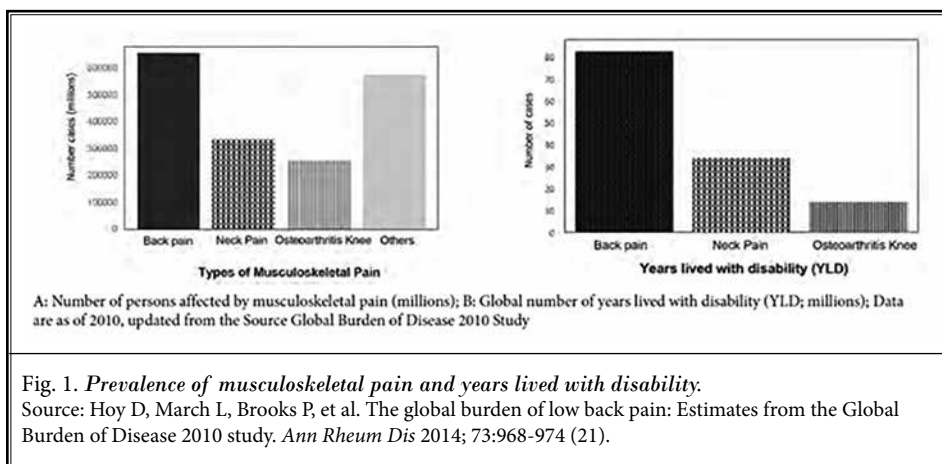


Fig. 1. Prevalence of musculoskeletal pain and years lived with disability. Source: Hoy D, March L, Brooks P, et al. The global burden of low back pain: Estimates from the Global Burden of Disease 2010 study. *Ann Rheum Dis* 2014; 73:968-974 (21).

pain and years lived with disability. Even prior to the COVID-19 pandemic, the annual US expenditures alone, including direct medical costs and lost wages due to chronic pain have been estimated to be higher than those for cancer, heart disease, and diabetes combined (2-7,39-42,104,158-174). As described by Dieleman et al (40), low back and neck pain constitute the number one category of expense in medical

expenditures in the US. In spite of extensive expenditures and multiple measures undertaken to control the expenditures (5-8,39-43,103,104,175-178), with multiplying treatment options, disability continues to escalate (1-8,39,40,103,104,170-174). As shown in Fig. 2, Dieleman et al (40) illustrated the expenses related to musculoskeletal conditions, including back and neck pain, as determined in 2016 based on spending on healthcare in the US.

The prevalence of pain in various spinal regions, is variable, with the highest prevalence in the low back at 43%, followed by the neck at 32%, with the lowest in the thoracic spine at 13% (29). The overall prevalence of low back pain and neck pain over a period of one-year ranged from 22% to 65% with an estimated lifetime occurrence of 84% for low back and neck pain from 20% to 40% with a lifetime prevalence of 67% (3,28-35,103,104,174,179-185). Furthermore, chronic persistent spinal pain may last longer than one-year in as many as 60% of the patients, even after conservative treatment or surgical interventions (1-35,174,179-185).

The prevalence of chronic low back pain is about 23%, with disabling pain in 11% to 12% of the population (183). A systematic review of the clinical course of nonspecific low back pain found that recovery was seen in only 33% of the patients after the first 3 months, whereas after one year after onset, 65% still reported

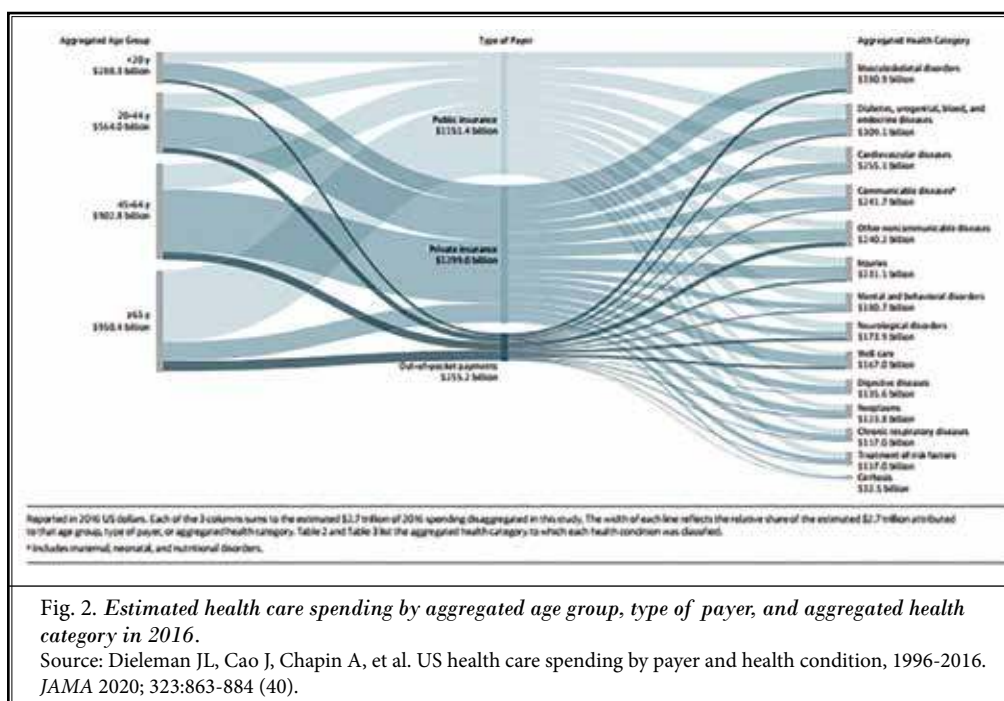


Fig. 2. Estimated health care spending by aggregated age group, type of payer, and aggregated health category in 2016.

Source: Dieleman JL, Cao J, Chapin A, et al. US health care spending by payer and health condition, 1996-2016. *JAMA* 2020; 323:863-884 (40).

pain (185). The 2016 US National Pain Strategy (NPS) (181) placed a focus on those with high impact chronic pain defined as that, "associated with substantial restriction of participation in work, social, and self-care activities for 6 months or more." However, multiple studies have used different algorithms to identify those with high impact chronic pain and to demonstrate significantly higher healthcare costs, lower QoL, depression, and increased absenteeism (180,181,185).

A survey from the CDC (181), in 2016, estimated that 20.4% of US adults, or 50 million, had chronic pain and 8% of US adults, or 19.6 million, had high impact chronic pain, and with higher prevalence associated with advanced age. Age-adjusted prevalences of both chronic pain and high-impact chronic pain were significantly higher among women, adults who had worked previously, but were not currently employed, adults living in or near poverty, and rural residents. Further, the data also showed that non-Hispanic White adults had a significantly higher age-adjusted prevalence of chronic pain than did all other racial and ethnic groups. No significant difference in high impact chronic pain prevalence by race or ethnicity were observed. Among adults aged less than 65 years, prevalences were higher after adjusting for age, for chronic pain, and high impact chronic pain among those with Medicaid and other public healthcare coverage or other insurance



than among adults with private insurance or those who were uninsured. Additionally, among adults aged 65 or greater years, those with both Medicare and Medicaid had higher age-adjusted prevalences of chronic pain and high impact chronic pain than did adults with all other types of coverage, reflecting their disability status, finances, and education.

In fact, a significant proportion of rising morbidity and mortality in midlife among white non-Hispanic Americans in the 21<sup>st</sup> century was attributed to opioid poisonings related to chronic pain and subsequently drug abuse (182) as shown in Figs. 3 and 4.

Freburger et al (35), in assessment of the rising prevalence of chronic low back pain from 1992 to 2006 showed that the prevalence of chronic, impairing low back pain rose significantly over the 14-year interval, from 3.9% in 1992 to 10.2% in 2006. They reported increases for all adult age strata, in men and women, and in white and black races. However, symptom, severity and general health were similar for both years, with some increase in individuals seeking care from a healthcare provider in the past year, increasing from

73.1% to 84%, while the mean number of visits in all providers were similar. They concluded that the prevalence of chronic, impairing low back pain has risen significantly in North Carolina, with continuing high levels of disability and care utilization. They also concluded that a substantial portion of the rise in low back pain care costs over the past 2 decades may be related to the rising prevalence. These studies have not been repeated since then. However, based on the other studies of disability and healthcare costs, the prevalence, as well as disability, may be increasing (2,21,22,36-42,167-173).

Further, Blyth et al (38), in assessing the global burden of musculoskeletal pain, summarized the current understanding of the global burden of musculoskeletal related conditions, applying evidence-based principles generated the prevalence and identified key gaps in the understanding of musculoskeletal pain, with proposals to address these gaps. They identified key long-term drivers of contemporary burden of disease estimates, including age, structure of populations, and their longevity. They identified the escalating growth of treatments, along with harms associated with treatment, including medication-based interventions, notably long-term opioids, nonsteroidal, and steroidal immunosuppressive therapies, and surgical interventions. However, these

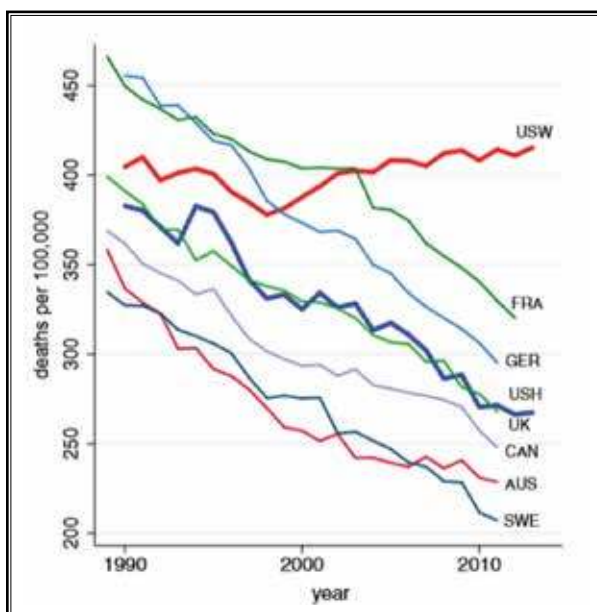


Fig. 3. All-cause mortality, ages 45–54 for US White non-Hispanics (USW), US Hispanics (USH), and six comparison countries: France (FRA), Germany (GER), the United Kingdom (UK), Canada (CAN), Australia (AUS), and Sweden (SWE).

Source: Case A, Deaton A. Rising morbidity and mortality in midlife among white non-Hispanic Americans in the 21<sup>st</sup> century. *Proc Natl Acad Sci USA* 2015; 112:15078-15083 (182).

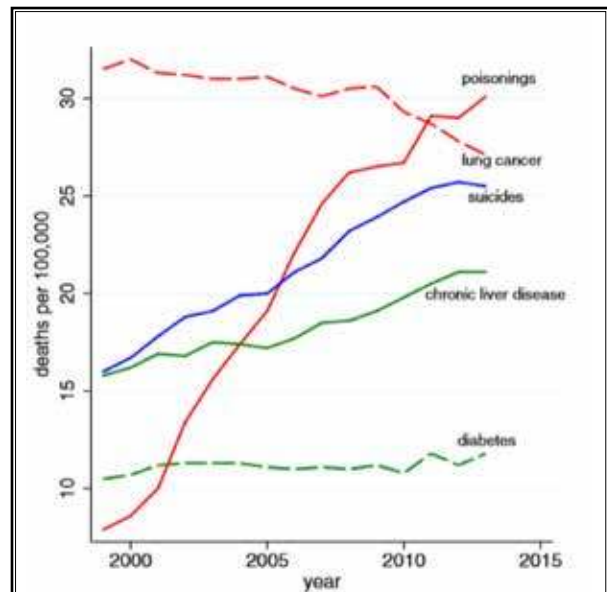


Fig. 4. Mortality by cause, white non-Hispanics ages 45–54. Case A, Deaton A. Rising morbidity and mortality in midlife among white non-Hispanic Americans in the 21<sup>st</sup> century. *Proc Natl Acad Sci USA* 2015; 112:15078-15083 (182).



were not included in their estimated burden. Given the importance of musculoskeletal pain with regard to functional status in older age group, these findings have profound implications for future disability burden and treatments provided to reduce it (20).

A systematic review of the prevalence of musculoskeletal symptoms in the construction industry (37), including back and neck pain, one-year prevalence of low back pain was 51.1% whereas for neck pain it was 24.4 %, and 19.8% for upper back pain. Thus, some prominent authors have indicated that guidelines must be different for developing countries and developed countries in reference to invasive and noninvasive treatments (37,172,174). Chou et al (174) and Acaroğlu et al (37), synthesized recommendations on the use of common elective surgical and interventional procedures for individuals with recommendation of epidural injections, as well as augmentation procedures with formation of clinical care pathways on patient presentation in low- and middle-income communities, contrary to their descriptions of earlier presentations of opposition to these interventions in the US (80,174). In these guidelines, they theorized that epidural steroid injections and vertebral augmentation procedures are less expensive than most surgeries with fewer harms.

Healthcare expenditures have been escalating over the years with estimates of the US healthcare spending reaching \$3.814 trillion in 2019 (42). Furthermore, healthcare expenditures are expected to continue to grow at a rate of 5.4% from 2019 to 2028 (42). Overall, in 2019, cost of healthcare was \$11,597 per person, the cost per person in 2028 will rise to \$17,611. In 2016, low back and neck pain had the highest amount of healthcare spending with an estimated \$134.5 billion with 33.7% of that spent by public insurance. Other musculoskeletal disorders accounted for the second highest amount of healthcare spending of \$129.8 billion, totaling \$264.3 billion (40,41). It appears that expenditures have increased disproportionately with low back and neck pain with the highest healthcare spending, whereas diabetes and ischemic heart disease ranked lower in spending in 2016, a reversal from 2013. However, the calculations of healthcare spending drastically changed in 2020 due to COVID-19. The COVID-19 pandemic not only increased overall healthcare expenditures, but also affected the entire healthcare system with significant increases of costs and reduced access to healthcare (43-53,115).

With increasing prevalence and disability as described above, it is obvious that healthcare expenditures have been escalating and that the financial impact on

the US economy is growing. Additionally, the calculus of healthcare has drastically altered in 2020 and beyond due to COVID-19 catapulted the country into one of the deepest recessions in history, leading to poor health and increase in cardiovascular disease, mental health problems, cognitive dysfunction, and early death that has affected chronic pain patients in numerous ways. The pandemic also resulted in severe economic consequences for providers with reduced reimbursement and increased costs, as well as severe psychosocial impact on healthcare providers (43-53,115). Also, COVID-19 may adversely affect the increasing prevalence of chronic pain, health, anxiety, and behavioral changes (186). In fact, the data shows that 81% of physicians surveyed in July and August of 2020 said that revenue was still lower than pre-pandemic levels. This study also showed increased levels of expenses due to safety practices require use of more personal protective equipment (PPE). Federal financial relief early in the pandemic was somewhat helpful and widely appreciated. However, the core revenue issues these programs were intended to address remain, both in terms of decreased revenue and increased costs. At the same time, practices have been hit with reduced reimbursement (<https://www.cms.gov/medicare/medicare-fee-for-service-payment/physician-feesched>). Furthermore, elective surgeries continue to be reduced by approximately 20% or so and physician burnout among interventional pain physicians is overwhelming as has been reported (44).

Annual healthcare costs for patients with high impact chronic pain (overall and spine-related) (\$14,661 SE: \$814; and \$5,979 SE: \$471, respectively) were significantly higher than in patients with low impact chronic pain (\$6,371 SE: \$557; and \$2,300 SE: \$328) (183). Patients with high impact chronic spinal pain who use opioids are at prevalent at much higher rates than those with low impact chronic pain (48.4% versus 12.4%).

#### **4.0 THE TRENDS IN UTILIZATION OF HEALTHCARE MODALITIES IN MANAGING DISC-RELATED AND SPINAL STENOSIS PAIN**

**Key Question 2: What are the statistics regarding the trends in utilization of treatment modalities in managing spinal pain?**

Overwhelming healthcare costs are a major burden on the economy of the US leading to the implementation of various healthcare reform measures, regulations, and to the imposition of guidelines which have often been based on public policy priorities to reduce healthcare costs. These governmental actions have of-

ten resulted from feigned evidence-based medicine and comparative effectiveness research muddled with conflicts and controversies (5-7,19,22,26,39-46,103,104,166-169,187-264). There has been escalating growth of various modalities for the treatment of spinal pain, including physical therapy, drug therapy, interventional techniques, and surgical interventions.

#### 4.1 Surgery

Ever since the description of the first discectomy to treat disc herniation in 1932 by Mixter, a neurosurgeon, and Barr, an orthopedic surgeon (255), the surgical interventions to treat spinal pain have taken off with evolution of multiple techniques with rapid increase of surgical interventions, raising questions of the effectiveness of surgical treatments (256). Goldthwait and Osgood in 1905 (257), and subsequently in 1929, Dandy (258), an American neurosurgeon, surgically treated 2 patients who complained of back and leg pain. However, in the 1980s, Weber (259) and Hakelius (219) demonstrated significant improvement with nonoperative treatment alone. Thus, the debate about surgical versus nonoperative interventions ensued. Consequently, the Spine Patient Outcomes Research Trial (SPORT) was created to prospectively collect the data (260). In a systematic review by Oster et al (221) of outcomes following 10 year mark of SPORT for intervertebral disc herniation, patients that were likely to cross over to the surgery group had lower incomes, worse baseline symptoms, more baseline disability on the ODI, and were more likely to rate their symptoms as getting worse. In contrast, patients that crossed over to the nonoperative group were older, had higher incomes, were more likely to have upper lumbar disc herniation, less likely to have a positive straight leg raise test, had less pain, better physical function, less disability on ODI, and were more likely to rate their symptoms as getting better (260). They also identified multiple other factors with subgroup analysis, which included level of disc herniation, duration of symptoms, presence of retrolisthesis, patient functional status, effects of previous treatments with epidural steroid injections and opioid medication, outcomes after incidental durotomy, and reoperation rates and associated risks with reoperation. In this assessment, patients who had not received an injection preferred surgery, whereas those who have received injections had a higher rate of crossover to nonsurgical treatment, even though this was confounded by the increased desire to avoid surgery (263). The authors concluded that 4 years and 8 years as treated analysis

showed statistically greater improvements in those patients who were treated surgically. However, the analysis of the RCT cohort failed to show a significant difference based on the intent to principle due to significant patient crossover, which was around 50% (221).

National trends in surgical interventions have been increasing rapidly (202,216,218,220,264,265). Best et al (264) assessed the national surgical trends for intervertebral disc disorders and spinal stenosis between 1994 and 2006. The number of procedures increased from 6.1 to 34.2 for intervertebral disc disorders, and from 0.38 to 3.46 for spinal stenosis per 100,000 population. Yoshihara and Yoneoka (202), in an assessment of national surgical trends of lumbar degenerative disc disease in the U.S. from 2000 to 2009, showed a 2.4-fold population-adjusted increase. Bae et al (227) showed that from 2004 to 2009 there was an increase of spinal fusions for lumbar spinal stenosis from 21.5 % to 31.2%, even though the rate of decompressions decreased from 58.5 % to 49.2%.

Lopez et al (189), in a publication on trends in Medicare utilization and reimbursement for anterior cervical discectomy and fusion, showed an annual increase in procedure volume of 24.2% from 2012 to 2017. Furthermore, hospital reimbursements for cervical spine fusion surgeries without complications or comorbidities experienced nominal and inflation-adjusted increases of 9.5% and 0.7% respectively from \$12,030 in 2012 to \$13,168 in 2017. Similarly, surgeon reimbursements for single level and multilevel anterior cervical discectomy and fusion each nominally decreased from \$958 and \$1,173 in 2012 to \$950 and \$1,138 in 2017.

Reoperation rates for disc herniation and spinal stenosis have been shown to vary from 10 to 23% (227). Overall, 40% of postoperative patients develop postsurgery syndrome or failed back surgery syndrome, requiring further treatment (221,228,265-268). Unfortunately, the numbers of pre- and post-operative patients with disabilities requiring surgical interventions including complex fusions, those patients being treated for failed back surgery syndrome, and patients with refractory chronic low back pain continue to increase (71-74,221-246,265-268).

Overall results of surgical interventions have been lackluster, consequently, post-surgery syndrome, or pain after operative procedures of the spine is observed in a significant proportion of patients (221,228-235,265-268). Fritsch et al (267) reported that epidural fibrosis, recurrent disc herniation, instability, and facet joints were responsible for recurring symptomatology.

Ideally, clinicians should first exhaust all treatment

modalities in the low to moderate risk tier with patients enduring chronic lower back pain before pursuing a surgical intervention. A recent retrospective chart by Kim et al (269) of more than 75 million individuals found that guideline nonadherence in patients with newly diagnosed low back pain (or lower extremity pain) contributed to a substantial amount of economic burden in the US. Interestingly, 38.7% of patients that underwent surgery did not receive conservative management (neither physical therapy or epidural steroid injections) accounting for \$265 million dollars' worth of healthcare expenses in the first 12 months after diagnosis (269). This gap in proper care utilization indicates the need for a more informed perspective regarding high-risk surgical solutions in order to achieve a favorable outcome more effectively.

Multiple investigators have attempted to assess the role of epidural injections in the prevention of surgery for spinal pain in the form of systematic review and meta-analysis of RCTs and retrospective observational series (188,270-278) showing significant, but variable success rate of epidural injections in avoiding surgery ranging as high as 75% response rate. Despite the demonstrated success rate of surgical interventions, the struggle continues in managing patients after surgery (279,280). One of the examples is back pain in surgically treated degenerative lumbar spondylolisthesis (279). Guidelines developed for the use of surgical interventions for the treatment of chronic refractory back pain in degenerative spondylolisthesis have established a poor quality level of evidence and the need for further evidence with studies evaluating primary outcome of back pain in patients with degenerative lumbar spondylolisthesis (281). Bond et al (279) showed improvement in numeric rating scale (NRS) of back pain on average of 2.97 (SD 2.5 points at one year and clinically significant improvement in back pain was observed in 75% of the patients). Even then, 25% of the patients continue to suffer even with minimal criteria used at 30% or so improvement, rather than 50% improvement. It was also shown that rates of imaging in failed back surgery syndrome patients continue to increase, even in patients with spinal cord stimulation (280), driving healthcare costs and indicating lack of response to surgery and also to spinal cord stimulation.

In this context, building on a stepwise strategy stemming from a modest approach such as physical and pharmacological therapy to interventional pain procedures before considering surgery. This strategy allows an additional opportunity to make adjustments to the course of action before escalating care and avoid po-

tentially unnecessary or cost-prohibitive treatment. It is worth noting that constant advancements in new lines of treatment (chemonucleolysis, intradiscal therapies) and regenerative medicine (nerve growth factor, stem cells, plasma therapy) can bridge the gap between conservative and surgical intervention (269). While the results from this novel approach provides encouraging improvements in lower back pain, the limited number of RCTs warrants further study (270). Ultimately, the judicious application of interventional tools in a multidisciplinary healthcare setting has the potential to improve pain outcomes in patients diagnosed with chronic spinal pain.

## 4.2 Interventional Techniques

The use of interventional techniques for the treatment of spinal pain and musculoskeletal disorders increased until 2009, at which point utilization began to decrease (193-200). Recent analysis of growth of utilization of interventional techniques in managing chronic pain in the Medicare population (193) showed an overall decline in utilization of interventional techniques from 2009 to 2018 of 6.7%, with an annual decline of 0.8% per 100,000 fee-for-service (FFS), despite an increase of 0.7% per year of population growth (3.2% of those 65 years or older), and a 3% annual increase in Medicare participation from 2009 to 2018. Further, analysis of utilization patterns of epidural procedures (194) showed epidural procedures have declined at a rate of 20.7% per 100,000 Medicare enrollees from 2009 to 2018, with an annual decline of 2.5%. This analysis (194) also showed a decline in all categories, with an annual decrease of 4.7% for lumbar interlaminar and caudal epidural injections, 4.7% decline for cervical/thoracic transforaminal epidural injections, 1.1% decline for lumbar/sacral transforaminal injections, and 0.4% decline for cervical/thoracic interlaminar epidural injections. Overall declines were higher for lumbar interlaminar epidural injections of 34.9%, compared to lumbar/sacral transforaminal epidural injections of 9.4% (Fig. 5).

The utilization data also shows patterns which continue to fluctuate. As shown in Fig. 6, epidural injections constituted 58% of all procedures in 2000, declining to 39% of overall utilization of interventional techniques in 2018. This graphic display also shows changing patterns of other procedures with increasing facet joint interventions, even though they have plateaued or declined in recent years (193,194). Figure 7 shows that the pattern of utilization of the type of the procedures also has significantly changed. As an example, in the year 2000, lumbar interlaminar epidural injections con-

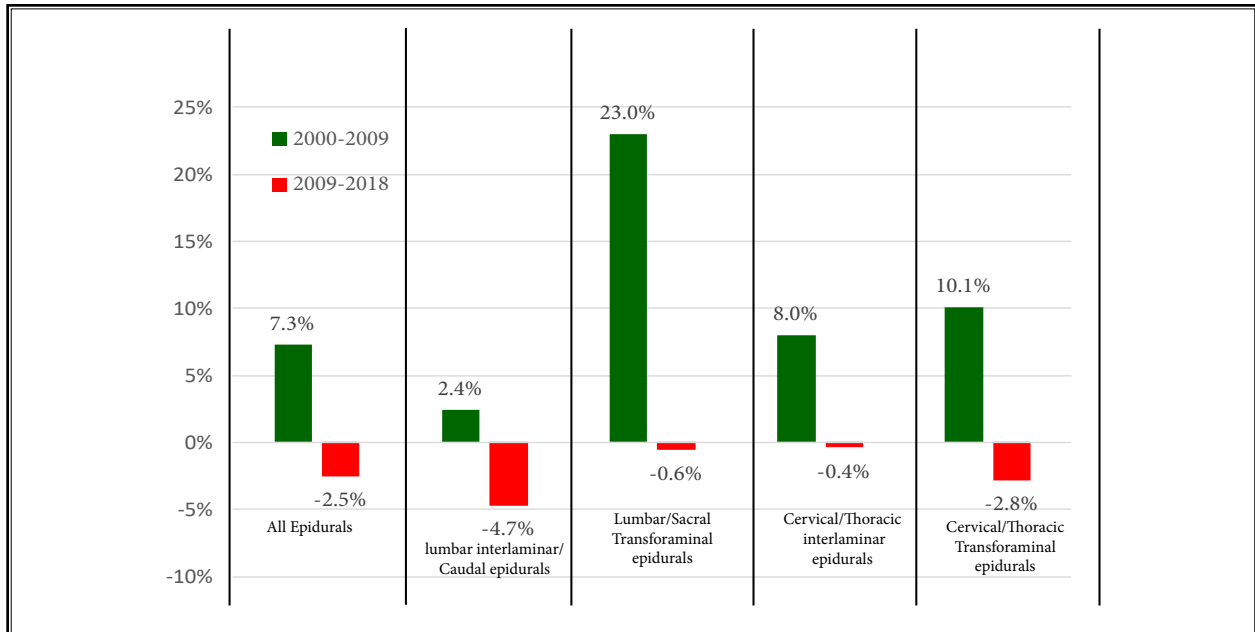


Fig. 5. Frequency of utilization of epidural injections (annual change in the rate) by procedures from 2000 to 2018, in Medicare recipients (194).  
Reproduced with permission from authors and Pain Physician journal.

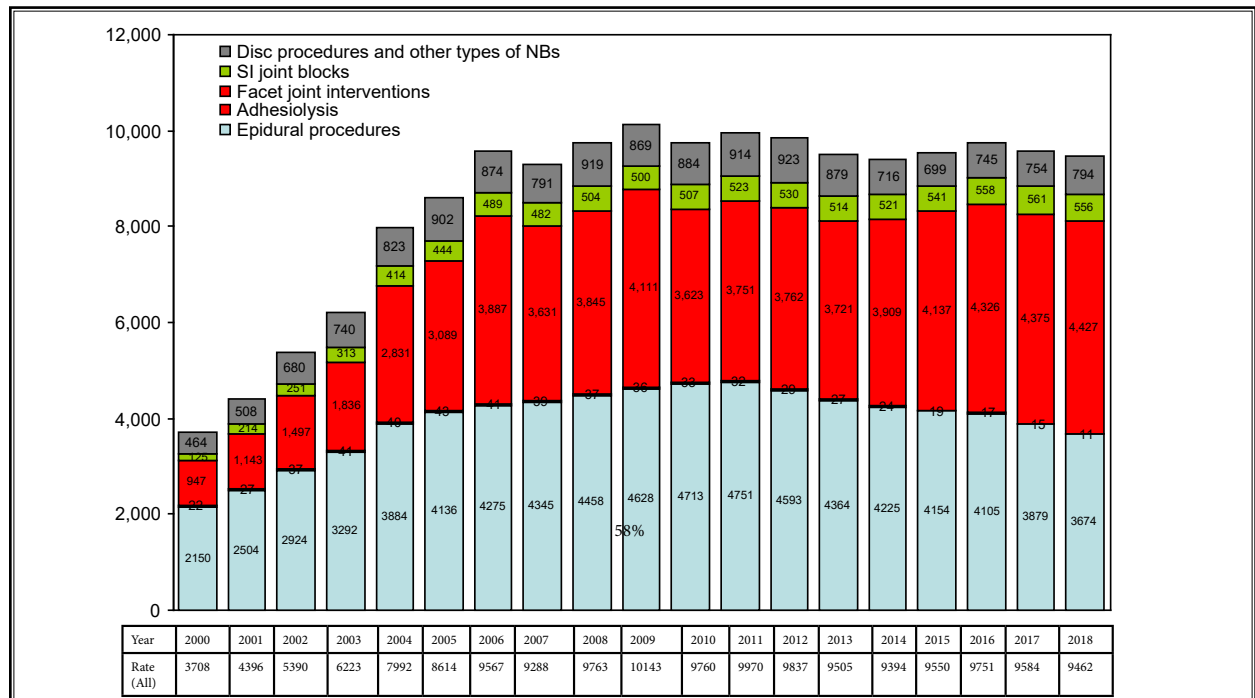


Fig. 6. Distribution of procedural characteristics (rates) by type of procedures from 2000 to 2018 (193,194).  
Reproduced with permission from authors and Pain Physician journal.

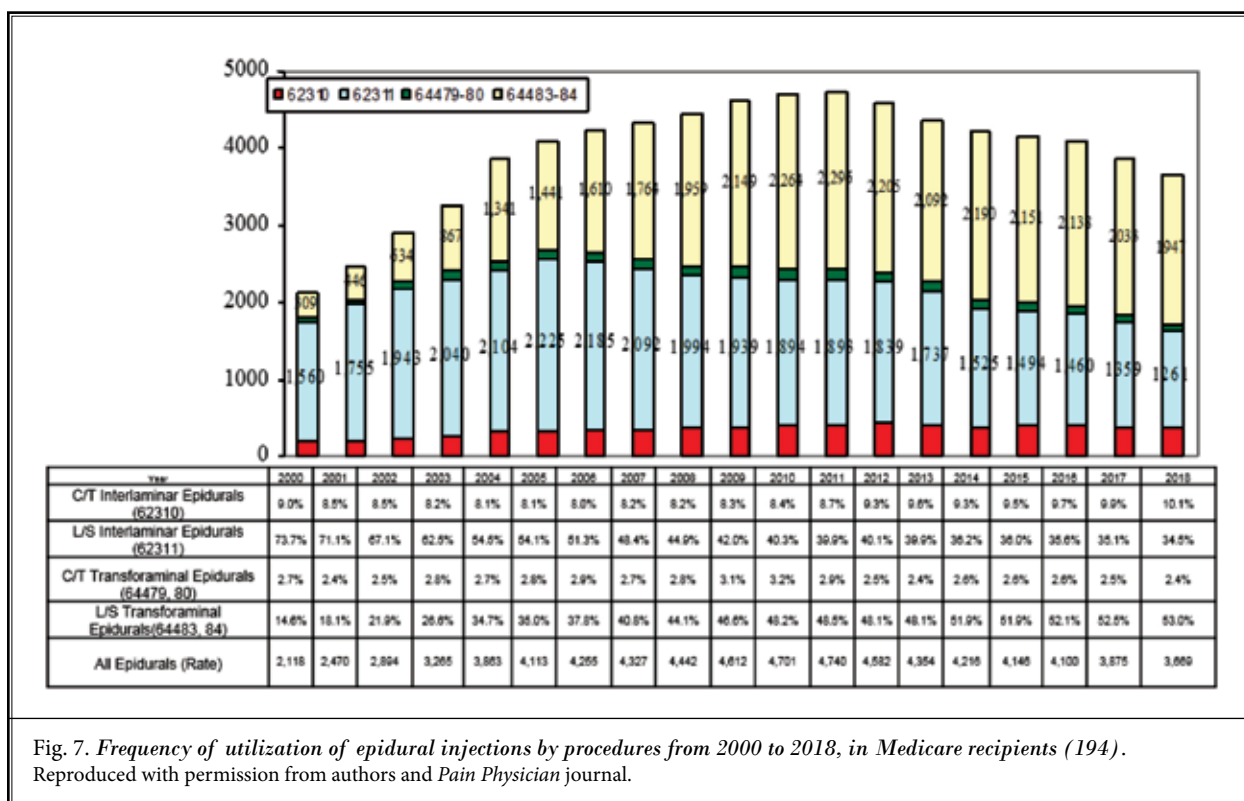


Fig. 7. Frequency of utilization of epidural injections by procedures from 2000 to 2018, in Medicare recipients (194). Reproduced with permission from authors and *Pain Physician* journal.

stituted 73.7% of all epidural procedures, declining to 34.5% in 2018. Similarly, lumbar transforaminal epidural injections constituting 14.6% in 2000, increased to their proportion of utilization to 53%. Cervical interlaminar procedures were 9% in 2000, increasing to 10.1% in 2018 without any significant growth.

Manchikanti et al (282,283) published an analysis of utilization trends and Medicare expenditures of spinal interventional techniques until 2008. The data showed that spinal interventional techniques increased 186.8%, at an annual rate of increase of 14.1% per 100,000 FFS Medicare beneficiaries (283). They showed overall per patient costs were \$1,054.33 in 2000, which increased to \$1,104.57 in 2008. The total approved amounts in FFS population were \$362,347,025 in 2000 compared to \$1,231,180,420 in 2008, a 240% increase for all spinal interventional techniques.

The study of expenditures of epidural procedures in chronic spinal pain in FFS Medicare population from 2009 to 2018 (195) showed a decrease in total expenditures after adjusting to inflation. Inflation adjusted cost per procedure per patient also decreased. However, prior to the inflation, total expenditures increased by 14.6% or an annual increase of 1.5% from \$723,981,594 in 2009 to \$829,987,636 in 2018. Inflation adjusted costs were

\$847,058,465 in 2009 compared to \$829,987,636 in 2018, a reduction of overall 2%. Inflation adjusted cost per patient decreased from \$988.93 in 2009 to \$819.27 in 2018 with a decrease of 17.2% or an annual decline of 2.1%. In addition, inflation adjusted costs per procedure decreased from \$399.77 to \$377.94, with a 5.5% overall reduction or 0.6% annual reduction. The proportion of Medicare patients per 100,000 receiving epidural procedures decreased 9.1% or 1.1% annually. This evaluation also showed overall costs of transforaminal epidurals increased to 27.6% or 2% annually, whereas for lumbar interlaminar and caudal epidural injections cost was reduced 2.7% or 0.3% annually prior to inflation adjustment. The proportion of patients receiving lumbar transforaminal epidural injections reduced 6.5% or at an annual rate of 0.7% compared to lumbar interlaminar and caudal epidural injections, which decreased a total of 33.5% or an annual decline of 4.4% (Fig. 8). Table 4 shows total allowed charges, which also shows specific charges for each type of epidural injection. Table 5 shows characteristics of Medicare beneficiaries and utilization pattern of epidural interventions, whereas Fig. 9 shows epidural procedures and their utilization patterns with number of patients visits and services, all of them showing a decline, specifically services and visits showing

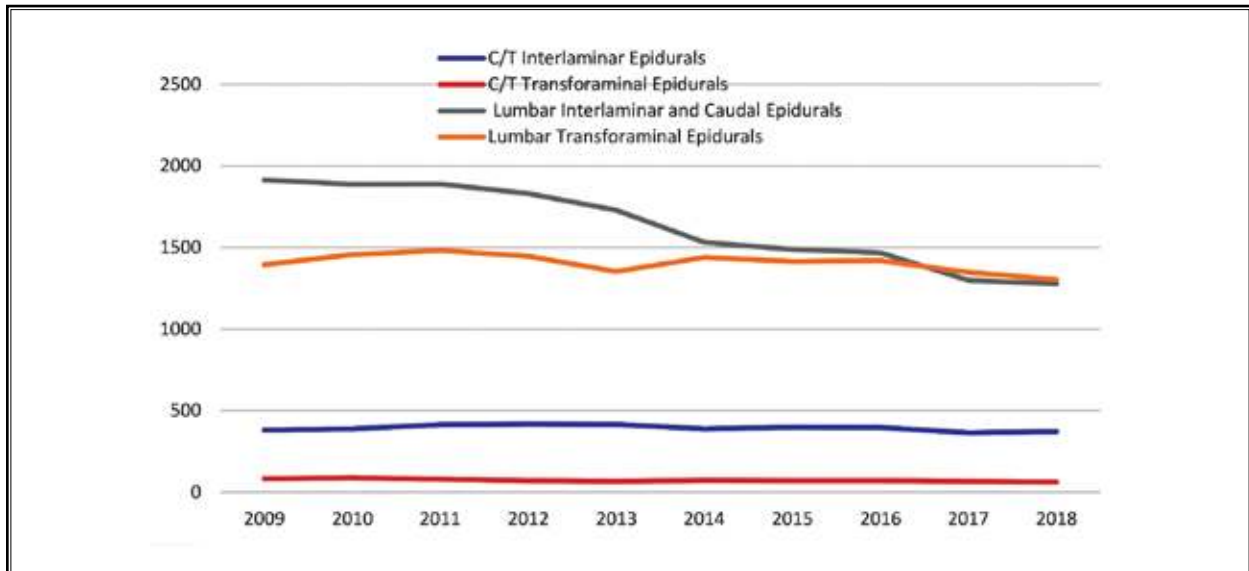


Fig. 8. Frequency of utilizations of epidural injections in the FFS Medicare population per 100,000 participants from 2009-2018 (195).  
Reproduced with permission from authors and *Pain Physician* journal.

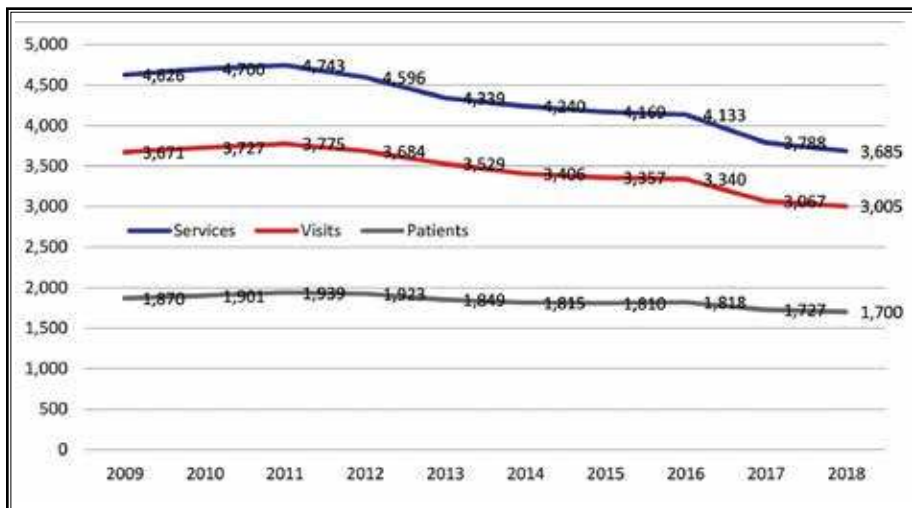


Fig. 9. Epidural procedures rate per 100,000 FFS Medicare population by services, episodes, and patients from 2009-2018 (195).  
Reproduced with permission from authors and *Pain Physician* journal.

### 4.3 Opioids in Spinal Pain

The opioid epidemic has once again taken a central role, adding to new pandemic of COVID-19 with tightened restrictions and worries about increasing COVID risk in opioid-receiving patients, with declining prescriptions for opioids, and finally, recently reported increases of opioid deaths in 2019 and 2020 (46,253). This trend is followed by extensive increases of opioid drug overdoses, with a subsequent increase of 18.2% death rate in year ending from June 2019 to May 2020, due to

a more significant decline than the number of patients receiving epidural procedures. This assessment included only epidural procedures and has not included percutaneous adhesiolysis.

Cost expenditures analysis for facet joint interventions showed increases even after inflation adjustment compared to declines for epidural procedures (284).

COVID-19 pandemic (43-53,79,114,115,253,254,285-302).

Over the years, multiple reviews have been performed in reference to opioid use, overuse, abuse, and a multitude of adverse consequences including opioid-related deaths (5-8,46,103,104,168,213-215,247-254,285-289,303-318). The US drug overdose data of drug-related deaths from 2018 shows an arrest of the escalation and a dip in the curve towards reductions. However, recent



ASIPP Epidural Guidelines

Table 4. Total allowed charges by place of service, by type of procedures.

	2009T	2010T	2011T	2012T	2013T	2014T	2015T	2016T	2017T	2018T	Change	GM
<b>HOPD</b>												
C/T Epidural	\$31,131,829	\$32,928,061	\$39,685,705	\$40,682,055	\$41,850,343	\$47,454,610	\$50,773,324	\$47,001,182	\$36,854,949	\$41,289,652	32.6%	3.2%
L/C Epidural	\$192,894,507	\$197,861,340	\$221,513,807	\$215,692,412	\$221,617,276	\$241,251,024	\$243,323,131	\$212,878,318	\$170,374,971	\$179,685,884	-6.8%	-0.8%
C/T Transforaminal	\$3,763,052	\$6,091,920	\$6,373,754	\$6,452,913	\$6,558,167	\$7,171,305	\$7,291,263	\$7,125,935	\$6,948,418	\$7,074,608	88.0%	7.3%
L Transforaminal	\$109,590,831	\$113,589,353	\$130,736,451	\$133,073,861	\$138,287,242	\$152,914,498	\$154,944,690	\$143,702,101	\$149,454,300	\$153,469,973	40.0%	3.8%
HOPD Total	\$337,380,219	\$350,470,675	\$398,309,716	\$395,901,241	\$408,313,028	\$448,791,436	\$456,332,408	\$410,707,535	\$363,632,638	\$381,520,117	13.1%	1.4%
<b>ASC</b>												
C/T Epidural	\$20,944,665	\$20,554,818	\$22,610,188	\$24,880,313	\$26,015,032	\$26,505,218	\$30,620,749	\$30,150,585	\$24,687,122	\$26,229,326	25.2%	2.5%
L/C Epidural	\$84,308,507	\$81,771,120	\$85,708,087	\$86,834,948	\$86,698,083	\$91,754,133	\$94,117,042	\$88,527,592	\$70,065,234	\$72,014,734	-14.6%	-1.7%
C/T Transforaminal	\$4,717,886	\$5,644,209	\$6,311,051	\$6,774,534	\$6,323,385	\$6,600,849	\$6,314,067	\$6,119,055	\$6,922,032	\$7,026,096	48.9%	4.5%
L Transforaminal	\$106,464,891	\$111,305,376	\$114,568,228	\$124,706,830	\$122,509,658	\$130,994,202	\$137,632,620	\$135,383,957	\$137,634,524	\$137,110,401	28.8%	2.9%
ASC Total	\$216,435,950	\$219,275,523	\$229,197,553	\$243,196,626	\$241,546,158	\$255,854,402	\$268,684,478	\$260,181,189	\$239,308,912	\$242,380,556	12.0%	1.3%
<b>Office</b>												
C/T Epidural	\$12,909,374	\$15,169,815	\$18,346,098	\$20,035,732	\$22,297,572	\$8,938,691	\$20,791,348	\$20,557,918	\$21,048,808	\$22,289,523	72.7%	6.3%
L/C Epidural	\$52,650,996	\$57,527,144	\$64,118,523	\$69,612,045	\$71,012,127	\$29,980,994	\$63,683,884	\$65,040,149	\$66,990,072	\$69,191,026	31.4%	3.1%
C/T Transforaminal	\$7,855,386	\$9,125,096	\$7,159,474	\$5,290,552	\$5,602,389	\$6,794,398	\$6,754,783	\$6,540,584	\$6,046,304	\$5,945,542	-24.3%	-3.0%
L Transforaminal	\$96,749,669	\$112,561,819	\$105,592,099	\$102,101,850	\$100,673,558	\$112,840,227	\$110,666,308	\$111,840,813	\$106,668,313	\$108,660,872	12.3%	1.3%
Office Total	\$170,165,425	\$194,383,874	\$195,216,194	\$197,040,180	\$199,585,646	\$158,554,310	\$201,896,324	\$203,979,464	\$200,753,498	\$206,086,963	21.1%	2.2%
<b>Totals</b>												
C/T Epidural	\$64,985,869	\$68,652,695	\$80,641,991	\$85,598,100	\$90,162,947	\$82,898,518	\$102,185,422	\$97,709,685	\$82,590,879	\$89,808,500	38.2%	3.7%
L/C Epidural	\$329,854,009	\$337,159,604	\$371,340,417	\$372,139,405	\$379,327,486	\$362,986,151	\$401,124,057	\$366,446,059	\$307,430,278	\$320,891,644	-2.7%	-0.3%
C/T Transforaminal	\$16,336,324	\$20,861,225	\$19,844,279	\$18,518,000	\$18,483,941	\$20,566,552	\$20,360,113	\$19,785,574	\$19,916,754	\$20,046,245	22.7%	2.3%
L Transforaminal	\$312,805,391	\$337,456,548	\$350,896,778	\$359,882,542	\$361,470,458	\$396,748,927	\$403,243,618	\$390,926,870	\$393,757,137	\$399,241,246	27.6%	2.7%
Grand Total	\$723,981,594	\$764,130,071	\$822,723,464	\$836,138,047	\$849,444,832	\$863,200,148	\$926,913,210	\$874,868,188	\$803,695,048	\$829,987,636	14.6%	1.5%
Inflation Rate	1.17	1.15	1.12	1.09	1.08	1.06	1.06	1.05	1.02	1	-14.5%	-1.7%
Total inflation-adjusted*	\$847,058,465	\$878,749,582	\$921,450,280	\$911,390,471	\$917,400,419	\$914,992,157	\$982,528,003	\$918,611,597	\$819,768,949	\$829,987,636	-2.0%	-0.2%
Medicare	45,801	46,914	48,300	50,300	51,900	53,500	54,900	56,500	58,000	59,600	30.1%	3.0%
Total Patients	856,540	891,640	936,500	967,080	959,520	971,280	993,960	1,027,120	1,001,700	1,013,080	18.3%	1.9%
per 100,000 Medicare (Inflation Adjustment)	\$1,849,432	\$1,873,107	\$1,907,765	\$1,811,909	\$1,767,631	\$1,710,266	\$1,789,668	\$1,625,861	\$1,413,395	\$1,392,597	-24.7%	-3.1%
Per Medicare Beneficiaries (Inflation Adjustment)	\$18	\$19	\$19	\$18	\$18	\$17	\$18	\$16	\$14	\$14	-24.7%	-3.1%
Per Epidural patient (Inflation Adjustment)	\$988.93	\$985.54	\$983.93	\$942.41	\$956.10	\$942.05	\$988.50	\$894.36	\$818.38	\$819.27	-17.2%	-2.1%

\*Inflation-adjusted and converted to year 2018 values. GM – geometric average. Note: There was about a 16% reduction in payment rates for C/T/L epidural injection in ASC & HOPD settings in 2016 & 2018. In 2014 Payments for ASC & HOPD primary codes increased and removed payments for add-on codes.

Source: Manchikanti L, et al. Declining utilization and inflation-adjusted expenditures for epidural procedures in chronic spinal pain in the Medicare population. *Pain Physician* 2021; 24:1-15 (195).

Table 5. Characteristics of Medicare beneficiaries and utilization pattern of epidural interventional 2009-2018.

	F2009	F2010	F2011	F2012	F2013	F2014	F2015	F2016	F2017	F2018	Change	Rate
U.S. Population	307,006	308,746	311,583	313,874	316,129	318,892	320,897	323,127	326,625	327,167	6.6%	0.7%
≥ 65 years	39,570	40,268	41,370	43,144	44,704	46,179	47,734	49,244	51,055	52,347	32.3%	3.2%
Medicare beneficiaries'	45,801	46,914	48,300	50,300	51,900	53,500	54,900	56,500	58,000	59,600	30.1%	3.0%
≥ 65 years	38,177	38,991	40,000	41,900	43,100	44,600	46,000	47,500	49,200	50,800	33.1%	3.2%
% ≥ 65 years	83.4%	83.1%	82.8%	83.1%	83.0%	83.4%	83.6%	84.1%	84.7%	85.2%	2.3%	0.2%
< 65 years	7,624	7,923	8,300	8,500	8,800	8,900	9,000	9,000	8,900	8,800	15.4%	1.6%
Epidural Services	F2009	F2010	F2011	F2012	F2013	F2014	F2015	F2016	F2017	F2018	Change	Rate
Services (Allowed)	2,118,840	2,205,160	2,290,740	2,311,880	2,251,720	Rate 2,268,300	2,288,520	2,335,000	2,197,300	2,196,100	3.6%	0.4%
Rate	4,626	4,700	4,743	4,596	4,339	4,240	4,169	4,133	3,788	3,685	-20.4%	-2.5%
Episodes	1,727,640	1,793,240	1,866,800	1,894,380	1,849,100	1,836,400	1,851,940	1,895,620	1,785,900	1,798,100	4.1%	0.4%
Rate	3,772	3,822	3,865	3,766	3,563	3,433	3,373	3,355	3,079	3,017	-20.0%	-2.5%
Visits	1,681,200	1,748,660	1,823,380	1,853,120	1,831,420	1,822,260	1,842,720	1,887,260	1,778,580	1,791,200	6.5%	0.7%
Rate	3,671	3,727	3,775	3,684	3,529	3,406	3,357	3,340	3,067	3,005	-18.1%	-2.2%
Patients	856,540	891,640	936,500	967,080	959,520	971,280	993,960	1,027,120	1,001,700	1,013,080	18.3%	1.9%
Rate	1,870	1,901	1,939	1,923	1,849	1,815	1,810	1,818	1,727	1,700	-9.1%	-1.1%
Age groups (Patients)												
≥ 65 Years	686,060	711,020	737,080	756,680	747,640	760,140	783,140	820,060	809,940	832,000	21.3%	2.2%
%	80.1%	79.7%	78.7%	78.2%	77.9%	78.3%	78.8%	79.8%	80.9%	82.1%	2.5%	0.3%
Rate	1,498	1,516	1,526	1,504	1,441	1,421	1,426	1,451	1,396	1,396	-6.8%	-0.8%
<65 Years	170,480	180,620	199,420	210,400	211,880	211,140	210,820	207,060	191,760	181,080	6.2%	0.7%
Rate	372	385	413	418	408	395	384	366	331	304	-18.49%	-2.2%
Episodes by age												
≥ 65	1,365,840	1,413,080	1,452,280	1,466,500	1,421,500	1,421,960	1,446,800	1,501,960	1,433,840	1,466,960	7.4%	0.8%
Rate	2,982	3,012	3,007	2,916	2,739	2,658	2,635	2,658	2,472	2,461	-17.59%	-2.1%
< 65	361,800	380,160	414,520	427,880	427,600	414,440	405,140	393,660	352,060	331,140	-8.5%	-1.0%
Rate	790	810	858	851	824	775	738	697	607	556	-29.79%	-3.8%
Episodes by PLCR												
HOPD	577,100	591,640	618,400	611,780	586,380	584,120	581,020	587,380	538,880	538,200	-6.7%	-0.8%
Rate	1,260	1,261	1,280	1,216	1,130	1,092	1,058	1,040	929	903	-28.39%	-3.6%
ASC	460,740	469,840	501,920	522,560	498,040	502,180	511,920	542,800	508,100	510,360	10.8%	1.1%
Rate	1,006	1,001	1,039	1,039	960	939	932	961	876	856	-14.99%	-1.8%
Office	689,800	731,760	746,480	760,040	764,680	750,100	759,000	765,440	738,920	749,540	8.7%	0.9%
Rate	1,506	1,560	1,546	1,511	1,473	1,402	1,383	1,355	1,274	1,258	-16.59%	-2.0%

Rate: per 100,000 Medicare beneficiaries

Change: Of change from 2009 to 2018, GM – Geometric average. PCPY – Percentage of Change from Previous Year

Source: Manchikanti L, et al. Declining utilization and inflation-adjusted expenditures for epidural procedures in chronic spinal pain in the Medicare population. *Pain Physician* 2021; 24:1-15 (195).

reports by Health Alert Network of CDC Health Advisory (46) showed a significant increase in fatal drug overdoses across the US driven by synthetic opioids before and during the

COVID-19 pandemic. This report showed based on the recent provisional data that approximately 81,230 drug overdose deaths occurred in the US in the 12 months ending in May

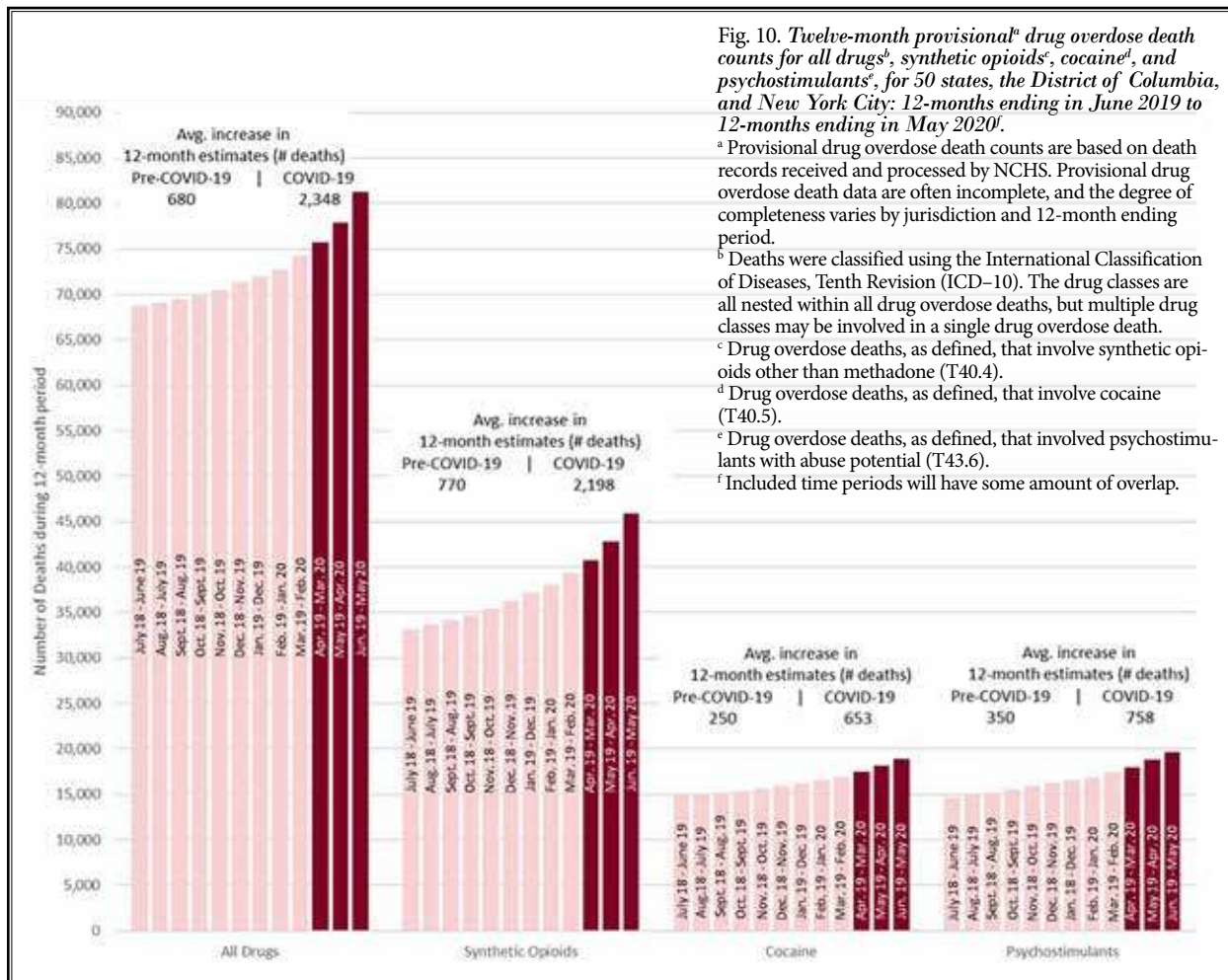


Fig. 10. Twelve-month provisional<sup>a</sup> drug overdose death counts for all drugs<sup>b</sup>, synthetic opioids<sup>c</sup>, cocaine<sup>d</sup>, and psychostimulants<sup>e</sup>, for 50 states, the District of Columbia, and New York City: 12-months ending in June 2019 to 12-months ending in May 2020<sup>f</sup>.

<sup>a</sup> Provisional drug overdose death counts are based on death records received and processed by NCHS. Provisional drug overdose death data are often incomplete, and the degree of completeness varies by jurisdiction and 12-month ending period.

<sup>b</sup> Deaths were classified using the International Classification of Diseases, Tenth Revision (ICD-10). The drug classes are all nested within all drug overdose deaths, but multiple drug classes may be involved in a single drug overdose death.

<sup>c</sup> Drug overdose deaths, as defined, that involve synthetic opioids other than methadone (T40.4).

<sup>d</sup> Drug overdose deaths, as defined, that involve cocaine (T40.5).

<sup>e</sup> Drug overdose deaths, as defined, that involved psychostimulants with abuse potential (T43.6).

<sup>f</sup> Included time periods will have some amount of overlap.

2020, as shown in Fig. 10 (286). Thus, a worsening of the drug overdose epidemic in the US has not only shown a resurgence, but also is the largest number of drug overdoses for a 12-month period ever recorded (46,293). This report is preceded by news of declining 4.1% from 2007 to 2018 (285). However, since then, the number of overdose deaths increased 18.2% from the 12 months ending in June 2019 to the 12 months ending in May 2020 (Fig. 10) (286). Further, increases of the drug overdose deaths ranged more than 20% in 25 states and the District of Columbia, 10% to 19% in 11 states and New York City, and 0% to 9% in 10 states. However, overdose deaths decreased only in 4 states (Appendix Fig. 1).

The CDC report also delved into various issues related to COVID-19. The increases in overdose mortality began in 2019, even before COVID-19 and continued into 2020, exacerbated by the COVID-19 national emergency in the US in March. The acceleration of overdose

deaths due to COVID-19 pandemic was clearly demonstrated (46,49,287-291). Due to the effect of COVID-19, estimates indicate that the largest monthly increases in drug overdose deaths occurred in 12 months ending in May 2020 with 81,230 deaths. Further, the one-month increases were shown to be 2,146 and 3,388 deaths respectively for the 12-month period as shown in Fig. 10. These are the largest monthly increases documented since provisional 12-month estimates began to be calculated in January 2015 (286).

As described earlier in our manuscripts and also supported by overwhelming literature, the primary driver of the increases in overdose deaths continues to be synthetic opioids as shown in Figs. 11 and 12 (285-287,293,294,296,298,303-317). The 12-month count of synthetic opioid deaths increased 38.4% from 12 months ending in June 2019 compared with the 12 months ending in May 2020 (Fig. 10). Of the 38 jurisdic-

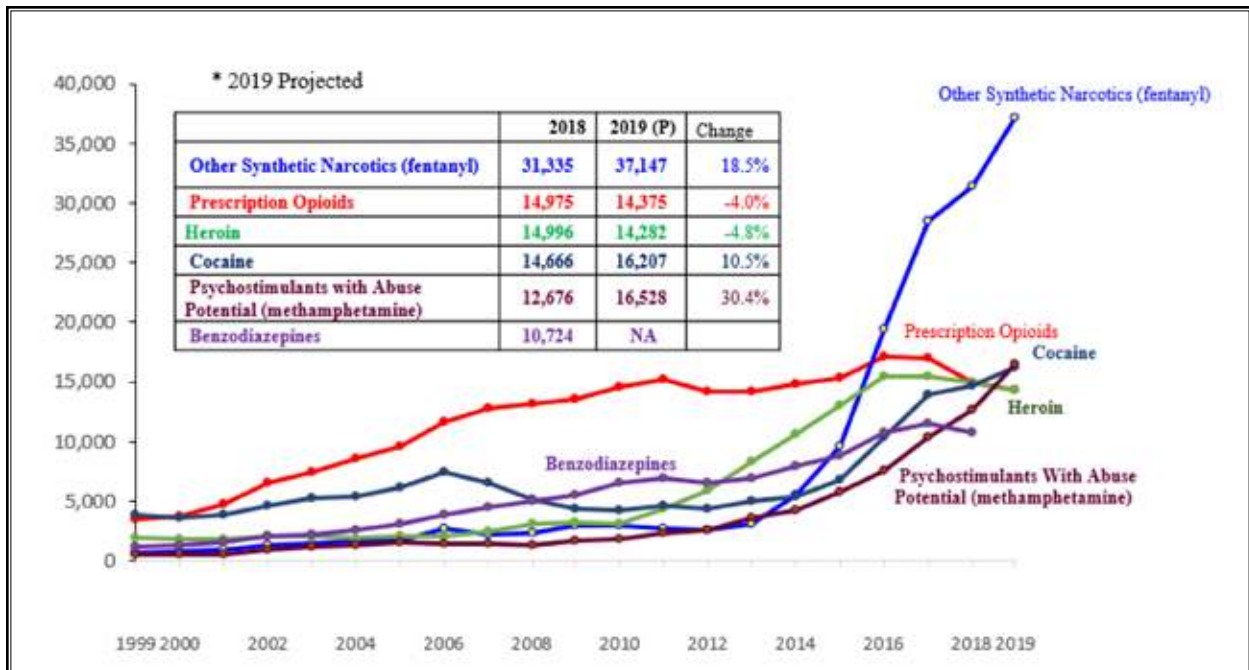


Fig. 11. Number of opioid overdose deaths by category, 1999 to 2019. Source(s): For 1999-2018: National Institute on Drug Abuse. Overdose death rates. May 7, 2020 <https://www.drugabuse.gov/related-topics/trends-statistics/overdose-death-rates> (253,285). For 2019: Ahmad FB, Rossen LM, Sutton P. Provisional drug overdose death counts. National Center for Health Statistics. 2020 (286) <https://www.cdc.gov/nchs/nvss/vsrr/drug-overdose-data.htm>

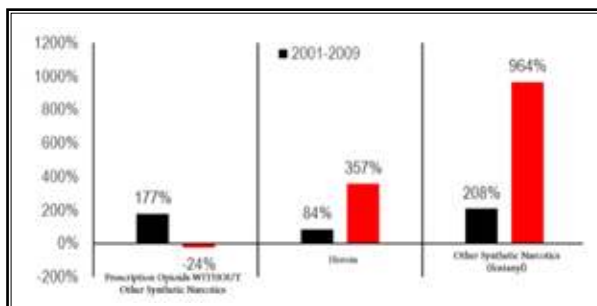


Fig. 12. Quantification of opioid deaths. Source(s): NIDA. Overdose Death Rates. National Institute on Drug Abuse website. <https://www.drugabuse.gov/related-topics/trends-statistics/overdose-death-rates> (285). Reproduced with permission from authors and *Pain Physician* journal

tions, the reports were available for 37, which showed an increase in synthetic opioid overdose deaths (286). In these reports, 18 jurisdictions reported increases greater than 50%, 11 reported increase of 25% to 45%, 7 reported increases of 10% to 24%, only one reported an increase of less than 10%, as shown in Appendix Fig. 2 (46). Once again, it also has been confirmed by these

jurisdictional reports and state and local health department reports that an increase in synthetic involved opioid deaths is primarily linked to illicit manufactured fentanyl (287,293,294,296). Fentanyl deaths have been concentrated in the 28 states east of the Mississippi river, where the heroin market has primarily been dominated by white powder heroin (296,297). In contrast, states west of the Mississippi river have seen the largest increases in synthetic opioid deaths occurring in 10 western states with a 98% increase. This is consistent with large increases in illicitly manufactured fentanyl availability in western states (288) and increases in fentanyl positivity in clinical toxicology drugs tested in the west after the COVID-19 pandemic (289). However, synthetic opioid overdose deaths have increased substantially in multiple other regions including 12 southern states and the District of Columbia (35.4%), 6 midwestern states (32.1%), and 8 northeastern states and New York City (21.1%), as shown in Appendix Fig. 2.

Apart from heroin and synthetic fentanyl, overdose deaths involving cocaine increased by 26.5% during this period as shown in Fig. 10 (46). In addition, data have shown that recent increases in overdose deaths involving cocaine are primarily related to overdose

deaths and involved both cocaine and synthetic opioids (primarily illicitly manufactured fentanyl) (290), but also illicitly manufactured heroin (295).

Similar to synthetic opioids and cocaine, overdose deaths involving psychostimulants, such as methamphetamine have been increasing with and without synthetic opioid co-use and at a rate faster than overdose deaths involving cocaine (290). Thus, provisional 12-month counts of overdose deaths involving psychostimulants in the US increased by 34.8% from the 12 months ending in June 2019 compared to the 12 months ending in May 2020. This leads to striking statistics that the number of deaths involving psychostimulants now exceeds the number of cocaine involved deaths as shown in Fig. 10 and 11. As CDC data shows, these increases are consistent with the increased availability of methamphetamine in the illicit drug supply and increases in the methamphetamine related treatment admissions (46,288,292).

Based on the CDC report, they have distanced from calling the opioid epidemic and opioid deaths and

called it driven by synthetic opioids, confirming the appropriate name, illicit drug epidemic or synthetic opioid epidemic. The previous reports also showed a decline of overdose death rates of 14.5% for prescription opioids from 2017 to 2018. Furthermore, the provisions data from 2018 to 2019 showed a 4.2% decrease of prescription opioid deaths with total deaths of 14,347 in 2019. However, the CDC report has not shown prescription related opioid deaths in the present report (46). Consequently, prescription opioid deaths seem to be declining below the levels of cocaine, heroin, and maybe even methamphetamine. The lower numbers may be achieved if methadone deaths are separated from prescription opioids, as methadone may be obtained by multiple means with only a small proportion from prescription opioids for management of chronic pain (Fig. 11 and Table 6). During COVID-19, opioid prescriptions and morphine milligram equivalent (MME) doses also have significantly decreased and are expected to decrease further. Prescription opioid related deaths with inclusion of methadone were 14,375 in 2019, whereas,

Table 6. National drug overdose (od) deaths, 2000-2018

	2000	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019 (R)	2019 (P)
Total Overdose Deaths	17,415	38,329	41,340	41,502	43,982	47,055	52,404	63,632	70,237	67,367	71,364	71,987
Any Opioid <sup>1</sup> (T40.0-T40.4, T40.6)	8,407	21,088	22,784	23,164	25,050	28,647	33,091	42,249	47,600	46,802	50,343	50,806
Prescription Opioids <sup>2</sup> (T40.2-T40.3)	3,785	14,583	15,140	14,240	14,145	14,838	15,281	17,087	17,029	14,975	14,252	14,375
Prescription Opioids AND Other Synthetic Narcotics	167	939	889	861	1,015	1,489	2,263	4,055	5,444	5,417	NA	NA
Prescription Opioids WITHOUT Other Synthetic Narcotics	3,618	13,644	14,251	13,379	13,130	13,349	13,018	13,032	11,585	9,558	NA	NA
Other Synthetic Narcotics (fentanyl) <sup>3</sup> (T40.4), other than methadone	782	3,007	2,666	2,628	3,105	5,544	9,580	19,413	28,466	31,335	36,733	37,147
Heroin <sup>4</sup> (T40.1)	1,842	3,036	4,397	5,925	8,257	10,574	12,989	15,469	15,482	14,996	14,157	14,282
Cocaine <sup>5</sup> (T40.5)	3,544	4,183	4,681	4,404	4,944	5,415	6,784	10,375	13,942	14,666	16,071	16,207
Psychostimulants With Abuse Potential (methamphetamine) <sup>6</sup> (T43.6)	578	1,854	2,266	2,635	3,627	4,298	5,716	7,542	10,333	12,676	16,356	16,528
Benzodiazepines <sup>7</sup> (T42.4)	1,298	6,497	6,872	6,524	6,973	7,945	8,791	10,684	11,537	10,724	NA	NA

R – Reported; P – Predicted values

Source for 2000 to 2018: <https://www.drugabuse.gov/drug-topics/trends-statistics/overdose-death-rates>

For 2019: <https://www.cdc.gov/nchs/nvss/vsrr/drug-overdose-data.htm> (data based on 12/6/2020)



excluding methadone these deaths were 12,084 with 2,787 deaths attributed to methadone. Methadone is obtained from multitude of sources with prescription methadone contributing to a small proportion of the deaths or a minority of deaths. It is also worrisome that stricter regulations, lack of access to prescription opioids during COVID-19 epidemic may be fueling the illicit drug market. Thus, previous postulations that if we can control overdose deaths related to heroin and synthetic opioids, the opioid epidemic will be resolved, may be fine-tuned to state if we control illicit drug epidemic and maintain access to appropriate opioid prescriptions.

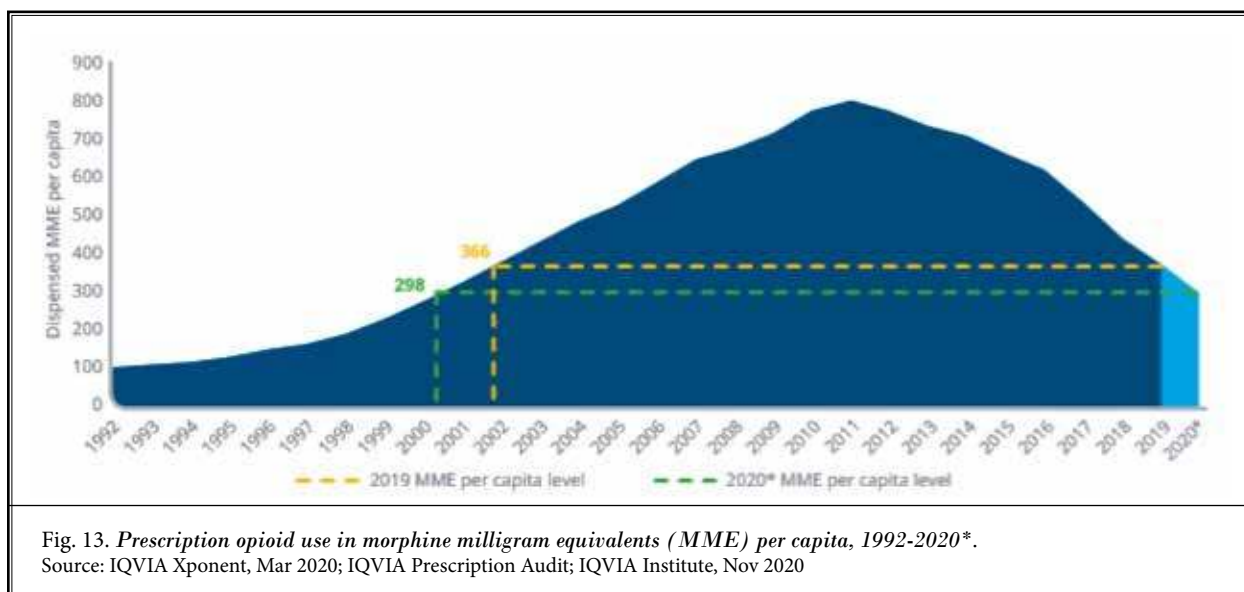
In reviewing the prescription trends in the US, multiple reports over the years have captivated the country with most attention paid to the opioid epidemic, which changed this year in the face of COVID-19 pandemic. Patients with chronic pain and addiction have been affected by disruptions to life and healthcare during COVID. Prescription opioid trends in the US published by IQVIA Institute (313) in December 2020, showed that prescription opioid use in the US continues to decline rapidly, with only 100 billion MME expected to be dispensed in 2020. This is a 60% decline from 246 billion MME dispensed at the peak of opioid prescribing in 2011 as shown in Fig. 13 and Appendix Fig. 3. Reports also highlighted that between 2019 and 2020, there is an expected 17.1% decline in MME, including the effects of disruptions from the COVID-19 pandemic, marking the ninth consecutive year of declines and the third year of double-digit change. Prescription opioid

use was approximately 16 pills or 134 MME per adult Americans in 1992, and rose to a peak of 55 pills or 790 MME in 2011. This use has since declined by 54% to 29 pills and 366 MME per capita in 2019, though population growth has been 5.4% since 2011.

In 2020, the projected decline in MME per capita is 17.1%, meaning prescription opioid use will reach mid 2000 levels. This represents a 20 years cycle, marked by 11 years of gains and 9 years of reductions. Consequently, by the end of 2020, MME per capita is expected to drop to 298, nearing the levels seen in 2000, which was 270 MME per capita (Fig. 13) (313).

Even though overall prescriptions have seen a significant reduction, Medicare Part D prescriptions have increased by 2% since 2011, rising from 53 million prescriptions to 54 million in 2019. The Medicare Part D share of prescriptions has increased from 21% to 35% over the same timeframe, as the over 65 population has increased by 31% and seniors often require more procedures and also suffer with multiple degenerative conditions resulting in larger number of opioid prescriptions. Even then, compared to 2019, prescriptions have declined 17% from 66 million in 2014; however, prescriptions for commercial patients declined by 51%, even though commercial prescriptions still comprised the largest share of prescription opioids, with 48% of the volume in 2019 down from 58% in 2011.

Overall, these decreases in volume and dosage along with redistribution among the populations have been driven by changes in clinical usage, regulatory





and reimbursement policies, and progressively more restrictive legislation enacted since 2012, and finally the guidelines from the CDC. Multitude of these legislations including National All Schedules Prescription Electronic Reporting (NASPER) Act have resulted in prescription drug monitoring programs in all states which facilitates decrease in inappropriate prescriptions (286,296,303,314-328).

Manchikanti et al (303) described various issues related to the opioid epidemic and pointed out the tragic failures of the current systems to control opioid misuse. Thus, multiple factors propagated the epidemic, starting with the fifth vital sign pain movement together with a confluence of interest and a failure of oversight from the opioid industry, which was largely responsible for the epidemic. Multiple confluences of interests were reported, including promotion of opioids based on inadequate evidence with advocacy from Portenoy and Foley (329). Further fuel was added with the establishment of pain as the fifth vital sign, which was embraced by multiple organizations and it was essentially forced on hospitals and other healthcare professionals in assessing pain relief and quality improvement (6,303). Further contributing issues were the medical boards themselves. Most of the guidelines although allegedly written for appropriate opioid use, were essentially promoting excessive use and abuse patterns, as they were developed by the opioid industry with confluence of interest. Further, multiple failures in the oversight of opioid manufacturing, distribution, diversion and import, in addition to medical necessity and appropriate monitoring of opioid prescriptions fueled the epidemic (303).

It is difficult to point out the reasons for the explosion of the fentanyl epidemic, along with increases in the usage of heroin, as well as cocaine, as shown in Figs. 10 to 12 (46,285,286,303-305,308). The significant movement to control the opioid epidemic in the US was initiated with prescription drug monitoring programs, state regulations curbing opioid prescriptions, and increasing the focus on education. Overall federal spending increased 128% from 2017 to 2018 with the major increases in federal spending due to treatment and recovery programs with costs ranging from approximately \$599 million to 2.1 billion (286,314). Overall, total opioid spending increased from \$3.3 billion in 2007 to \$7.4 billion in 2018 in the US (286).

#### **4.4 Noninterventional Techniques in Managing Spinal Pain**

There are many noninvasive or noninterventional techniques for managing spine pain including medica-

tions, exercise programs, physical therapy, acupuncture, massage, transcutaneous electrical nerve stimulation (TENS), biofeedback therapy and chiropractic treatments.

##### **4.4.1 Medications**

Nonopioid medications for treating low back pain include nonsteroidal anti-inflammatory drugs (NSAIDs), antidepressants and acetaminophen (330). Multiple systematic reviews evaluated recent randomized trials of medication treatment for patients with low back pain (331-334).

In the treatment of patients with acute low back pain with NSAIDs, there was a high certainty that these medications were more effective than placebo for improving disability and a moderate certainty that they were more effective at providing short-term pain reduction. There was a low degree of certainty that NSAIDs were better than placebo in regards to global improvement and there was no difference in short-term pain reduction when comparing the selective COX-2 inhibitors to nonselective NSAIDs. There was also a negligible difference in the rate of adverse events in patients using either NSAIDs or COX-2 inhibitors for acute low back pain.

In the treatment of chronic nonspecific low back pain, 6 of the 13 trials showed that NSAIDs were significantly more effective than placebo for pain relief and are slightly more effective at improving the patients' disability. This systematic review by Enthoven et al (332) showed no difference in efficacy between the different NSAIDs, which included both selective and nonselective NSAIDs and because the inclusion of RCTs that were at low risk of bias there was an overall reduction in the differences between the NSAIDs and placebos. Also due to the small sample sizes, there could be no conclusion regarding the occurrence of adverse events or whether NSAIDs are safe for long-term use.

When examining the evidence for the treatment of low back pain with acetaminophen, one recent systematic review concluded that there was insufficient evidence to assess the efficacy of acetaminophen in patients with low back pain (331). Another review focusing on the treatment of chronic low back pain with medication concluded that there was no significant difference between a NSAID (diflunisal) and acetaminophen for pain relief in patients with low back pain.

Other medications used to treat low back pain include antiepileptics and antidepressants. A recent systematic review analyzed both classes of medications and concluded that one type of antiepileptic (topiramate) was both safe and effective agent in the treatment of chronic

Table 7. Systematic reviews of exercise programs for the treatment of low back pain.

Treatment	Author, Year	Number and Type of Studies	Results Number of patients	Conclusions
Exercise	Saragiotto et al, 2016 (335)	29 RCTs	<p>There is low to moderate quality evidence that MCE is effective for improving pain at short, intermediate and long-term follow-up with medium effect sizes (long-term, MD -12.97; 95% CI -18.51 to -7.42) when compared to minimal intervention.</p> <p>There was also a clinically important difference for function and global impression of recovery compared with minimal intervention.</p> <p>There is very low to low-quality evidence that MCE is clinically more effective than exercise and electro-physical agents for pain, disability, global impression of recovery and QoL with medium to large effect sizes (pain at short-term, MD -30.18; 95% CI -35.32 to -25.05).</p> <p>Total patient number – 2,431</p>	<p>There is very low to moderate quality evidence that MCE has a clinically important effect compared with a minimal intervention for chronic low back pain.</p> <p>There is very low to low-quality evidence that MCE has a clinically important effect compared with exercise plus electro-physical agents.</p> <p>There is moderate to high-quality evidence that MCE provides similar outcomes to manual therapies and low to moderate quality evidence that it provides similar outcomes to other forms of exercises.</p> <p>Overall, MCE is not superior to other forms of exercise</p>
	Byström et al, 2013 (336)	<p>16 RCTs (n = 1933) 80% with chronic LBP</p> <p>The review included studies of subacute duration (4 to 12 weeks) and of chronic duration &gt; 6 months)</p> <p>Short-term (6 weeks to 4 months), intermediate term (4 to 8 months) and long-term (8 to 15 months)</p>	<p>1. Motor control exercises vs general exercise (n = 741) 7 trials</p> <ul style="list-style-type: none"> <li>• Short-term (6 trials, WMD -7.80 on 0 to 100 scale, 95% CI -10.95 to -4.65)</li> <li>• Intermediate term (3 trials, WMD -6.06, 95% CI -10.94 to -1.18)</li> <li>• Effects were not statistically significant at long-term (4 trials, WMD -3.10, 95% CI -7.03 to 0.83)</li> </ul> <p>2. Motor control exercises vs minimal intervention (n = 541; 3 trials)</p> <ul style="list-style-type: none"> <li>• MCE was also associated with better function:</li> <li>• Short-term (6 trials, WMD -4.65 on 0 to 100 scale, 95% CI -6.20 to -3.11)</li> <li>• Long-term (3 trials, WMD -4.72, 95% CI -8.81 to -0.63).</li> </ul> <p>3. Motor control exercises vs multimodal physical therapy (n = 499) 4 trials</p> <p>In CLBP, MCE was associated with lower pain scores versus minimal intervention:</p> <ul style="list-style-type: none"> <li>• Short-term (WMD -12.48 on a 0 to 100 scale, 95% CI -19.04 to -5.93)</li> <li>• Intermediate term (WMD -10.18, 95% CI -16.64 to -3.72)</li> <li>• Long-term (WMD -13.32 95% CI -19.75 to -6.90)</li> </ul> <p>4. MCE vs other components of that intervention (n = 152) 2 trials</p> <p>MCE was also associated with better function:</p> <ul style="list-style-type: none"> <li>• -Short-term (3 trials WMD -9.00 on 0 to 100 scale, 95% CI -15.28 to -2.73)</li> <li>• Intermediate term (2 trials WMD -5.62, 95% CI -10.46 to -0.77)</li> <li>• Long-term (2 trials, WMD -6.64, 95% CI -11.72 to -1.57)</li> </ul>	<p>For CLBP, motor control exercises was associated with lower pain intensity versus general exercise:</p>

MCE = motor control exercise; RCTs = randomized controlled trials; MD = mean difference; N = number; LBP = low back pain; CLBP = chronic low back pain; WMD = weighted mean difference; CI = confidence interval

low back pain and produced significantly positive changes in pain sensitivity, patient disability, health-related QoL, and weight loss (334). The review also concluded that antidepressants had a statistically significant improvement in

low back pain when compared to placebo in patients being treated for chronic low back pain. The antidepressant medications, however, were also associated with significantly more side effects when compared to placebo (334).

#### 4.4.2 Exercise Programs

Exercise has typically been viewed as a moderately effective treatment for chronic low back pain but there is no clear evidence that indicates one form of exercise is more effective than another. Most of the current exercise recommendations are based upon motor control exercise (MCE) that focuses on establishing and maintaining core muscle strength (Table 7).

Of the 45 RCTs presented evaluating MCE on low back pain, there was supportive evidence that this treatment was associated with better pain control and patient function than minimal intervention (335,336). There was low to moderate evidence that MCE was clinically more important than minimal intervention for treating chronic low back pain and that it provided similar outcomes to other forms of exercise (335). This was found regardless of whether the pain scores were measured at short, medium or long-term follow-ups (335). There was very low or low-quality of evidence that MCE had a more clinically important effect than electro-physical agents (EPA) and moderate to high-quality of evidence that MCE provided similar outcomes to other types of exercises. Overall, it was concluded that MCE was not superior to other forms of exercise.

When comparing the results of MCE on patients with mostly chronic low back pain and evaluating different follow-up times to compare MCE with general exercise, minimal intervention, multimodal physical therapy and other forms of intervention it was found that MCE was associated with lower pain intensity than general exercise in the short and intermediate term but not in the long-term (336). It was found that MCE was associated with better function at all follow-up time points. As in previous systematic reviews, MCE was associated with lower pain scores and better function compared to minimal intervention at all follow-up time points (335,336).

#### 4.4.3 Physical Therapy and Multidisciplinary Rehabilitation

The goal of physical therapy is to improve pain and increase function to prevent unnecessary disability and to keep the patient's low back pain from worsening. Physical therapy and multidisciplinary biopsychosocial rehabilitation (MBR) include a number of different treatment strategies such as exercise, rest, stretching, tai chi, yoga, massage, spinal manipulation and other treatments. In patients with chronic low back pain, physical therapy with exercise approach is a first line treatment that is routinely utilized.

Of the 83 studies with 8,816 patients evaluating physical therapy and rehabilitation interventions to treat patients with chronic low back pain, it was found that exercise therapy improved pain intensity, disability and long-term function when compared to nonexercise conventional care and behavioral therapy was effective for decreasing pain intensity compared to no treatment in the short-term (337). Multidisciplinary treatment was also found to be effective at reducing pain intensity and disability at short-term follow-up compared to no treatment (337). The evidence from the RCTs showed low-quality evidence for the efficacy of exercise therapy compared to conventional care and low-quality evidence for the efficacy of behavioral therapy compared to no treatment (337). There was moderate evidence for the effectiveness of multidisciplinary treatment compared to no treatment or other active treatments in reducing pain in the short-term. The authors concluded that there was an insufficient amount of data to draw firm conclusions on the clinical effect of back schools, low-level laser therapy, patient education, massage, traction, superficial heat/cold, and lumbar supports for chronic low back pain.

In a systematic review of 41 RCTs, Kamper et al (338) found that MBR improves pain and disability more than conventional care in the short and long-term but there is no evidence that it improves work outcomes in the short or long-term. The authors also found that MBR improves pain and disability more than no MBR in the short-term and there is additional evidence that MBR improves pain, disability, and work outcomes more than physical treatments in the short and long-term (338).

#### 4.4.4 Acupuncture

In treating low back pain, patients may seek alternative medical approaches to address their low back pain. One of the most common treatments among the alternative approaches is acupuncture. Despite the fact that it is interventional and invasive, it is included in this section. Acupuncture is a very old medical treatment that originated in the Far East and has gained increasing interest in the west as a treatment for low back pain (339). Despite the increasing popularity of acupuncture, the effectiveness is often disputed and many systematic reviews and meta-analyses have investigated its effectiveness (340,341). Recently, three clinical practice guidelines have also been published with differing recommendations on the treatment of low back pain with acupuncture (342-344). Given these inconsistencies, the recent systematic reviews and meta-analyses are very

important for providing a systematic assessment of the strength and completeness of the current evidence. In 16 systematic reviews of over 35,000 patients with acute low back pain, evidence shows acupuncture is better at relieving pain than sham treatments but the evidence was somewhat inconsistent (340). In addition to providing substantive pain relief, this review showed that acupuncture had a positive effect on improving patients' function. The summary of this systematic review showed that in patients with chronic low back pain, the evidence demonstrated that acupuncture consistently provides short-term pain relief and functional improvements when compared to no treatment or acupuncture and another conventional treatment (340). Seven of the systematic reviews were of varying quality but showed that acupuncture produces more pain relief and functional improvement than no treatment at short-term follow-up. Five systematic reviews found that acupuncture used in addition to conventional therapy provided short-term improvements in pain and function in the treatment of patients with chronic low back pain (340).

In another meta-analysis of 25 studies with over 6,200 patients, acupuncture had a clinically meaningful reduction in pain when compared to sham treatments and an improvement in function immediately after the treatment when compared to other patients either not receiving treatment or receiving conventional therapies (341). When acupuncture was compared to medications including NSAIDs, muscle relaxants, and analgesics as well as conventional treatments, there were statistically significant differences between the control groups and the patients receiving acupuncture (341). Although acupuncture improved pain and function immediately after intervention and more than no treatment, sham or medications (NSAIDs, muscle relaxants or analgesics), the differences were small.

Patients who received acupuncture in addition to conventional treatment had greater pain relief and improved function directly following the intervention and at the time of follow-up compared to those who received conventional treatment only (341). This meta-analysis also reviewed electroacupuncture and found that this technique resulted in significantly less pain and improved activity immediately after the intervention compared to the control group (341).

#### **4.4.5 Massage**

Massage has been traditionally thought to improve symptoms by providing pain relief through physical and mental relaxation and by increased the threshold of pain by the release of endorphins (345). The thought

behind the mechanism of pain relief is that massaging a certain area stimulates large nerve fibers that have an inhibitory effect on T-cells and pain relief follows (346). Massage may also have an effect on the autonomic nervous system by shifting it from a state of sympathetic response to a state of parasympathetic response or vice versa (347). The mechanism between massage and symptom relief is not fully understood but there are numerous trials and some literature reviews and systemic meta-analyses that investigate the efficacy of massage (348,349).

In a meta-analysis by Farber et al (348), the quality of evidence was found to be low to very low primarily because of risk of bias and imprecision. They found that for acute low back pain, massage was better than inactive controls in the short-term for pain but not for function. It was also determined that for patients with subacute and chronic low back pain, massage was better than inactive treatments for pain and function in the short-term but not in the long-term. The analysis also showed that when compared to active controls, massage was better for pain both in the short-term and at long-term follow-up. Functional improvement was found in patients with sub-acute and chronic low back pain as compared with inactive controls, but only at the short-term follow-up.

The review by Furlan et al (349) included 8 of 13 articles with a high risk of bias. In two of the studies, massage was superior to producing pain and functional improvements at short and long-term follow-ups. Eight studies showed that massage was similar to exercises, and better than joint mobilization, relaxation therapy, physical therapy, acupuncture, and self-care education for decreasing symptoms when compared to other active treatments. When positive effects of massage were present, the duration of these effects was one year after the end of treatment. Two studies showed that acupuncture massage gave rise to better results than Swedish massage and another trial concluded that Thai massage produces similar results to Swedish massage. Overall, there was moderate evidence of short and long-term improvement in pain and function with massage as compared with sham or other treatments but the differences in degree of improvement are small. The review showed that massage might be beneficial for patients with subacute and chronic low back pain, especially when combined with exercises and education.

#### **4.4.6 Transcutaneous Electrical Nerve Stimulation (TENS)**

Despite the common usage of TENS for pain man-

agement, evidence for its effectiveness is not conclusive. Due to this lack of optimal evidence TENS is not a treatment that is typically covered by insurance and is often restricted for use in RCTs. Previous health technology assessments and society led meta-analyses have found no benefit for TENS in patients with chronic pain (350,351). Some have criticized the recent society meta-analysis for a paucity of RCTs and the fact that the assessment did not compare the effectiveness of TENS with other nerve stimulation therapies (NSTs).

Studies comparing exercise therapy to passive therapies such as TENS, low-level laser therapy, ultrasound, thermal therapy, and ultrasound found no statistically significant difference between the exercise therapy and the other therapies, including TENS, but there was some serious limitations and inconsistencies in this low-quality evidence (337). Two studies comparing TENS with acupuncture or percutaneous electrical nerve stimulation (PENS) found that TENS was better for controlling pain but three studies comparing the same modalities found that PENS and acupuncture were better for controlling pain in the short-term (337). The evidence quality was very low in showing that PENS and acupuncture are better than TENS at providing short-term pain relief. Another study compared TENS to a new biphasic TENS in regards to pain and functional outcomes and found no difference. Five other studies comparing TENS with sham TENS or PENS found no significant difference between the groups. Only one study showed a significant benefit of TENS for pain relief compared to sham at short-term follow-up. All of this comparison data comparing TENS to PENS and sham was of low-quality.

Overall, the meta-analysis by van Middlekoop (337) found no difference between TENS and other treatments in regard to pain or functional outcomes when TENS was compared to other active interventions. The authors also noted that the findings of the Cochrane review from Khadilkar et al, when compared to their meta-analysis, were very similar in that they both conclude that TENS is not supported in the management of chronic low back pain (337,352).

A meta-analysis from Wu et al (353) showed the efficacy of TENS was similar to that of controls for providing pain relief and that other types of NSTs were more effective than TENS for providing pain relief. The only benefit they found for TENS was that it was better than control treatment in improving functional disability in the short-term (353).

The overall results of the Wu et al meta-analysis of RCTs comparing the effectiveness of TENS to controls

and other NSTs suggest that TENS does not improve symptoms of lower back pain, but could offer short-term improvement of functional disability (353).

#### **4.4.7 Chiropractic Treatments**

The efficacy of spinal manipulative therapy (SMT) for treating chronic low back pain is debated and the recommendations for use are heterogeneous. In some health systems SMT is treated as a first line option, but in others it is most often recommended along with other spinal treatments or not recommended at all (354,355). There is also at least one recent review of guidelines that suggests that SMT should be considered as a second-tier treatment option after exercise and behavior therapy (356).

In most reviews, SMT is considered to represent any manual treatment of the spine. Mobilizations of the spine are typically low velocity or passive movement techniques as opposed to manipulation which uses a high velocity thrust applied to a synovial joint near the end of the range of motion (357). This thrust often produces an audible pop or crack that results from cavitation of the joint.

There are many theories as to the mechanism of action of SMT and most of the hypotheses can be separated into neurophysiological and biomechanical categories (358,359). The biomechanical theory proposes that SMT acts on a spinal lesion to reduce the mechanical stresses and the neurophysiological theory suggests that SMT affects the primary afferent neurons from the paraspinal musculature and the neurons that control pain processing (360,361).

In a Cochrane review by Rubinstein et al (362), the authors found that there was moderate quality evidence indicating that SMT was no different than other treatments for short-term pain relief but that it produced a small improvement in function. They also found high-quality evidence that indicated that SMT had a small positive effect for short-term pain relief and small to moderate positive effects for improvement in function when compared to other nonrecommended therapies (362). These results were similar for intermediate and long-term outcomes. One study with a low risk of selection bias found no increased risk of adverse events associated with SMT. Most of the adverse events seen with SMT were transient and of mild to moderate severity (362). Overall, the authors found that SMT produces similar clinical results when compared to recommended therapies for patients with chronic low back pain and seemed to be better than



nonrecommended interventions for improvement of short-term function.

Coulter et al (184) published the results of a systematic review and meta-analysis of manipulation and mobilization for treating chronic low back pain which was composed of 51 trials meeting the inclusion criteria, and 9 trials with 1,176 patients with sufficient data were included in the meta-analysis. They concluded that there is moderate quality evidence that manipulation and mobilization are likely to reduce pain and improve function for patients with chronic low back pain. In addition, they concluded that manipulation appears to produce a larger effect than mobilization, even though both therapies appear safe and that multimodal programs may be a promising option.

Coulter et al (171) also performed a systematic review and meta-analysis for an appropriateness panel for manipulation and mobilization for treating chronic nonspecific neck pain. They included 47 randomized trials with low risk of bias, including 4,460 patients with nonspecific chronic neck pain. They concluded that studies published since January 2000 provide low-moderate quality evidence that various types of manipulation and/or mobilization will reduce pain and improve function for chronic nonspecific neck pain compared to other interventions. Further, it appears that multimodal approaches, in which multiple treatment approaches are integrated, might have the greatest potential impact. The studies comparing to no treatment or sham were mostly testing the effect of a single dose, which may or may not be helpful in clinical practice. They also hypothesized that given the low rate of serious adverse events, other types of studies with much larger sample sizes would be required to fully describe the safety of manipulation and/or mobilization for nonspecific chronic neck pain.

Rothberg and Friedman (363) in a systematic review of complementary therapies in addition to medication for patients with nonchronic, nonradicular low back pain concluded that available evidence does not support the use of spinal manipulation or excessive therapy in addition to standard medical therapy. They also concluded that there was insufficient evidence to determine if yoga or massage was beneficial. However, this study was criticized (364) for not including any studies beyond 2009 and there were multiple RCTs which were available for inclusion during the publication of this systematic review.

Sherbourne et al (365) from RAND Corporation also described coping and management techniques used

by chronic low back pain patients receiving treatment from chiropractors. The results showed that respondents reported using an average 9 coping behaviors in the prior 6 months. Persons with chronic low back pain were proactive in their coping strategies and frequently used self-care coping strategies like those provided by chiropractors in patient education. Along similar lines, in another manuscript from RAND Corporation (366), the results showed that 79% of the sample gave positive responses to the time spent with the provider item and a majority of the patients rated their provider at the top of the scale. The results also showed that more chiropractic patients reported always getting answers to questions the same day and always seen within 15 minutes of their appointment.

Overall, these experiences provide information to interventional pain physicians and also the importance of multimodal treatment, including chiropractic treatment apart from physical therapy, exercise program, and drug therapy.

#### **4.4.8 Biofeedback Therapy**

Behavioral and psychological treatments have been shown to be effective in the treatment of chronic pain by decreasing pain and improving function, but reducing psychological distress (365). There is some evidence that psychological treatments are more effective than medication and physical therapy in the short-term (366).

Biofeedback is a psychological treatment that may be performed independently or as an adjunctive therapy along with physical therapy or cognitive behavioral therapy (CBT). During biofeedback treatments, patients receive sensory information about physiological processes from their central nervous system (CNS) such as respiratory rate, heart rate, or muscle tension. Biofeedback teaches the patient to self-regulate their physiological processes with the assistance of the biofeedback information (366,367). The goals of the biofeedback sessions are to teach the patient to consciously reduce muscle tension or to positively affect their own coping mechanism.

There are different types of biofeedback treatments including electromyographic, heart rate variability and respiratory biofeedback with electromyographic biofeedback being the most common. There has been no obvious mechanism of action for biofeedback in the treatment of chronic low back pain; however, the benefits of biofeedback have been shown in a number of different chronic pain conditions (368). In previous meta-analyses, biofeedback has been shown to be more effective than cognitive behavioral therapy and physical

therapy (369,370). It has been difficult to establish conclusions on the efficacy of biofeedback therapy due to the heterogeneity of the biofeedback treatments and the common practice of including this treatment with others as an additive treatment.

Sielski et al (370) in a meta-analysis included an evaluation of controlled and uncontrolled chronic back pain studies that included biofeedback, to evaluate short-term and long-term effects of biofeedback on pain. This meta-analysis focused on manuscripts that reported standalone biofeedback as a treatment or comprising at least one-fourth of the total treatment (370). The goal was to determine the efficacy of biofeedback compared to different control groups and to identify important components of the treatment effects. The authors found that biofeedback resulted in a significant small-to-medium reduction of pain that was durable out to an eight-month follow-up and that it was also effective in reducing depression, disability and muscle tension (370). Biofeedback was also found to improve the patients' cognitive coping skills and these results remained stable at follow-up. The moderator analyses showed that longer biofeedback treatments were more effective for decreasing disability and that a greater proportion of biofeedback in the overall treatment strategy was more effective for reducing depression. They concluded that biofeedback treatment can be used as a standalone therapy or as an adjunctive intervention and can produce improvement on various pain-related outcomes both in the short-term and in the long-term.

## 5.0 STRUCTURAL BASIS OF SPINAL PAIN

### Key Question 3: What is the evidence for structural basis of spinal pain?

Chronic spinal pain is a complex and multifactorial phenomenon. Consequently, the high prevalence of chronic spinal pain, the numerous modalities of treatments applied in management of the problem, and the growing social and economic costs continue to influence medical decision-making. Despite its commonality, both in primary care and tertiary care, it is often difficult to reach a definite diagnosis of the origin of spinal pain. Interventional techniques are based on the philosophy of a neurophysiologic basis, in that when present, a structural origin of pain is important with or without coexisting psychosocial abnormalities and comorbid conditions. A major source of exponential growth in treatment modalities is the inherent difficulty in obtaining an accurate diagnosis. In the search of a diagnosis, an inaccurate or incorrect diagnosis, may lead not only

to expensive diagnostic ventures, but to treatment failures resulting in wasted healthcare dollars, and diversion of essential healthcare resources. Fundamental to proper treatment is an accurate diagnosis, which is based on the reliability of the test used to make the diagnosis. There are no universally accepted gold standards for the diagnosis of spinal pain, regardless of the suspected source (127-139,164,165,188,192,371-383). The majority of pain problems are not related to an easily identifiable cause. In addition, chronic pain may be confused with chronic pain syndrome, which is defined as a complex pain condition with physical, psychological, emotional, and social components (7,384). Chronic pain and chronic pain syndrome often appear similar, and at times may coexist.

Epidural interventions including multiple types of epidural procedures and percutaneous epidural adhesiolysis are administered in disc-related pathology including disc herniation, disc protrusion, discogenic pain, spinal stenosis, and radiculitis.

### 5.1 Lumbar Disc-Related Pathology, Spinal Stenosis, Post-surgery Syndrome

Chronic, persistent low back, lower extremity pain, and radicular pain may be secondary to disc herniation, disc disruption, disc degeneration, spinal stenosis, or post-lumbar surgery syndrome resulting in disc-related pain with or without radiculitis.

#### 5.1.1 Lumbar Disc-Related Degeneration

The spine is composed of five lumbar vertebrae and, between them, intervertebral discs which together constitute one quarter of the total length of the spine (385). In a healthy back, the intervertebral discs, being 70-80% aqueous, are soft and compressive to preserve spinal movements, absorb shock impact, and distribute axial and torsional forces (386-388). Through the normal process of aging, the inner nucleus pulposus of the discs becomes replaced with fibrocartilage as the proteoglycan, water, and noncollagenous protein concentrations decrease, and the collagen concentration increases (389,390). This loss of fluid due to dropped oncotic pressure in the discs makes them thinner and less flexible, hindering their function (386-388). Cartilaginous endplate erosion contributes to disc degeneration by compromising the flow of oxygen and nutrients to the discs (388,391-393). Endplate defects, which may result from disc degeneration or trauma, can stimulate nociceptors within the discs (394-396).

Another age-related mechanism of disc degen-

eration is the formation of small tears into the outer annulus fibrosis of the discs. This may be worsened by injury from daily activities and sports. This leads to disc space collapse and disc resorption as the nucleus pulposus streams out through the tears, causing the disks to bulge, protrude or rupture, leading to herniated discs. Herniated material may also contain cartilaginous endplate, fragmented apophyseal bone and annular tissue (397-399). The resulting instability may lead to abnormal micro-motions, causing tension and irritation in the surrounding structures. The loss of disc height can lead to abnormal loading of apophyseal joints, which may in turn cause osteoarthritic changes (400). The space between vertebrae becoming narrower may lead to the production of osteophytes, which in rare cases apply pressure on the spinal cord or spinal nerve roots, further worsening pain and nerve function (401).

Herniated lumbar disc is a displacement of disc material (nucleus pulposus or annulus fibrosis) beyond the intervertebral disc space. Over the past 78 years, voluminous literature has been published describing the epidemiology, diagnosis, and numerous treatment modalities for herniated disc pain, following the description of disc herniation by Mixter and Barr in 1934 (255). However, magnetic resonance imaging (MRI) findings of a herniated disc are not always accompanied by clinical symptoms (402). The prevalence of a symptomatic herniated lumbar disc is about 1% to 3% (402) with the highest prevalence among people aged 30 to 50 years (403), with a man to woman ratio of 2:1 (404). In individuals aged 25 to 55 years, about 95% of herniated discs occur at the lower lumbar spine (L4/5 and L5/S1 level); disc herniation above this level is more common in people aged over 55 years (405,406). Lumbar disc displacement may present as internal disc disruption, disc prolapse, disc protrusion, disc extrusion, disc herniation, or simply discogenic pain. The estimated prevalence of lumbar radiculopathy or sciatica has been described as 9.8 per 1,000 cases (407,408). It has been estimated that lumbar disc herniation occurs in 30% of the population at some time in their lifetime. Studies also have shown that sciatic symptoms may be present from 1.6% in the general population to 43% in select working populations in the US (408-411). Additionally, spontaneous resorption or regression of lumbar disc herniation has been reported in multiple assessments. Zhong et al (412), in a systematic review published in 2017 reported incidence of spontaneous resorption was 66.66%. The incidence in the United Kingdom was 82.94%, and in Japan was 62.58%. On the other end of the spectrum,

Chiu et al (413) found a rate of spontaneous regression of 96% for disc sequestration, 70% for disc extrusion, 41% for disc protrusion, and 13% for disc bulging. They also showed the rate of complete resolution of disc herniation was 43% for sequestered discs and 15% for extruded discs. Wang et al (414) performed a systematic review and meta-analysis and also discussed multiple systematic reviews performed. Overall, they showed an incidence of regression of 63% among nonsurgically treated symptomatic lumbar disc herniation patients. By discussing multiple studies, they showed that there was no significant regression before 4 months and after 10.5 months to be the ideal time to find regression after the onset. The highest incidence rate (IR) of 96% was documented by Lee et al (415) with an average follow-up of 341 days. Ahn et al (416) also reported an IR of 69% with an average follow-up time of 8.5 months. Others (417-421) reported an IR of 62% to 64%. Wang et al (414) described that the follow-up time of the 6 studies with IRs of approximately 63% ranged from 8.5 to 12.9 months with an average of 10.5 months. Furthermore, a multitude of conservative managements including epidural injections have been shown to be effective in managing chronic disc herniation (7,55-57,60-65). One study looking at alternative and integrative therapy showed positive long-term results of lumbar disc herniation patients receiving nonsurgical, complementary, and alternative medicine treatments with favorable results and high satisfaction rates. Lumbar radiculopathy secondary to disc herniation resolves spontaneously in 23% to 48% of patients, but up to 30% to 70% will still have pronounced symptoms after one year, with 5% to 15% of patients undergoing surgery (409,422). Even though first described by Wirshow in 1857, the pathophysiology and the mechanism of pain due to disc herniation remain controversial (423,424).

The intervertebral disc has been implicated as a source of spinal pain based on decades of pre-clinical, clinical, and epidemiological research, though the precise mechanisms continue to be debated as the literature evolves (7,127,129,130,136,138,139,371,423,424). Further, based on controlled evaluations, lumbar intervertebral discs showed the prevalence of internal disc disruption in 39% of a younger cohort of patients following injury (128), and 42% in a heterogeneous population comprised of all age groups and all types of low back pain (425). Further, in a study that sought to determine the prevalence of discogenic pain without assessing internal disc disruption, the reported prevalence rate was 26% (137).

Disc herniation may cause mechanical compression or inflammation. The normal intervertebral disc is avascular and aneural, except for the outer third of the annulus fibrosus. Maintaining a dynamic equilibrium between the synthesis and degradation of the extracellular matrix is pivotal in intervertebral disc homeostasis, but degeneration of the extracellular matrix occurs in patients with low back pain. Ingrowth of nociceptive neural fiber into deeper parts of the degenerated intervertebral disc is considered as one of the most widely accepted pathophysiological mechanisms related to chronic discogenic pain (426,427). Disc inflammation may promote axonal growth of afferent fibers innervating the disc by secreting pro-inflammatory mediators, such as tumor necrosis factor (TNF) and interleukin 6 (IL-6) as disc degeneration proceeds (428-432). In addition, nerve growth factor (NGF) is known to be a trophic growth factor for sympathetic and sensory nerve cells and to stimulate their differentiation, growth, maintenance, and survival (433). Further, it also has been shown that NGF also shows a hyperalgesic property by sensitizing and sprouting sensory nerve fibers in painful pathologic conditions (434,435). It has also been proposed that actions of NGF in painful intervertebral disc not only sensitize the sensory neuron, but also stimulate the peripheral nociceptive sensory neurons to grow into the intervertebral disc tissue where the extracellular matrix is degenerated in most cases (420). Inflammatory involvement has been extensively described (127,427-437). Consequently, the proposed etiologies and radiculitis may be summarized to include neural compression with dysfunction, vascular compromise, inflammation, and biochemical influences. Risbud and Shapiro (438) described the pathophysiology of disc degeneration and pain showing that in the inflammatory milieu neurogenic factors, in particular NGF and brain-derived neurotrophic factor (BDNF) generated by the disc and immune cells along with a multitude of other factors including TNF and IL-6. Phospholipase A-2 induces an expression of pain associated with cation channels in the dorsal root ganglia (DRG). Risbud and Shapiro (438) also showed that disc degeneration is characterized by 3 distinct, but overlapping phases in which cytokines play a central role with an initiating event resulting in phenotypic changes in production of cytokines and chemokines by both the nucleus pulposus and annulus fibrosus cells in the first phase, followed by further application of the inflammatory response by infiltrating immunocytes, as well as neovascularization and nerve ingrowth into the structurally deficient disc tissues in

the second phase. In the final phase, nerve endings are sensitized and the modulation of DRG pain channel activities are altered by inflammatory mediators and neurotrophins resulting in pain. Further, Olmarker et al (439,440) also showed that spinal nerve roots, when compressed, exhibited interneural edema, deprived nutritional supply (439) and loss of amplitude of nerve conduction (440). In fact, these experimental findings were confirmed by Kuslich et al (130), who reported that noncompressed nerve roots did not reproduce the patients' pain when stimulated intraoperatively in awake surgical patients. Consequently, epidural procedures are suited in managing chronic lumbar disc herniation, with a natural history of radicular pain showing a favorable prognosis (55-65,70,71,75,76,436). Disc regression or resorption have been shown to be most favorable in disc sequestration (96%), disc extrusion (70%), and disc protrusion (40%); however, it was only 13% in disc bulging (413). Saal et al (420) reported that 90% of the patients showed good to excellent outcomes and 92% had achieved return to work status with nonoperative treatment of disc extrusions.

### **5.1.2 Lumbar Spinal Stenosis**

Spinal stenosis is the result of abnormal narrowing of the spinal canal, lateral recess or the intervertebral foramina, resulting in pressure on the spinal cord or nerve roots (441,442). The two lower motion segments (L3-L4 and L4-L5) are the most commonly affected related to being more vulnerable to rotatory strains (443). Spinal stenosis may develop by a combination of chronic mechanical compression and cord instability. Along with ischemia, these factors may lead to neurologic symptoms or claudication (444-451). Some common causes of spinal stenosis include disc-related degeneration, osteophyte formation, herniated discs, arthritis, ligament or facet joint hypertrophy, epidural fat deposition, spinal tumors, and traumas (447-451). Adult degenerative scoliosis and degenerative spondylolisthesis may lead to instability and facet hypertrophy, resulting in stenosis (441-444).

Lumbar spinal stenosis is a common source of back and leg pain, and often involves weakness and numbness (441-443). More severe cases may present with neurological symptoms such as radiculopathy, myelopathy or cauda equina syndrome. Permanent numbness or paralysis can result from a long-term compression of spinal nerves or of the spinal cord. Lumbar spinal stenosis is the most common cause of spinal surgery in patients over 65 years old (441-444).

The prevalence of lumbar spinal stenosis increases with age, and is approximately 19.4% among individuals aged 60-69 years old (442,452). Nonetheless, it may develop earlier due to injury or congenital factors (442). The rate of progression over time is variable, and may not always exhibit symptoms. Some studies report that approximately half of patients remain clinically stable, while a quarter worsen or improve (399,453,454). The symptoms of spinal stenosis may significantly affect patients' mobility, functional autonomy and performance in routine tasks (451).

The pathophysiologic mechanism is similar to disc herniation, even though the mechanical component is more significant with narrowing of the spinal canal or the intervertebral foramen resulting in either neurogenic claudication or radiculitis. Epidural injections have been shown to be effective in managing lumbar spinal stenosis in multiple RCTs and systematic reviews (7,55,58,60,65,70,77,81,83). In addition, spinal stenosis patients have been shown to respond to percutaneous adhesiolysis (72-74).

### **5.1.3 Lumbar Post-surgery Syndrome**

Pain and disability in the low back and lower extremities following lumbar spine surgery has been hypothesized to be secondary to multiple causes including epidural fibrosis, sacroiliac joint pain, disc herniation, discogenic pain, spinal stenosis, arachnoiditis, and facet joint pain, along with inappropriate surgery (7,72-74,221,228,265-267,269,277,455-477). Failed back surgery syndrome was defined by the International Association for the Study of Pain (IASP) as a phenomenon of persistent or recurrent pain, mainly in the lower back or legs, even after previously anatomically successful surgeries (478). The review of literature of recurrent pain after lumbar discectomy for lumbar disc herniation, in patients under the age of 70 years, showed frequent or recurrent leg pain in 5% to 36% of patients 2 years after the operation (477,479). Some literature also has shown occurrence rates variable from 10% to 40% (73,476,479,480). Even though the ongoing debate continues in reference to epidural fibrosis and its effect on multiple pain problems or lack thereof, debate continues without an end (458,459,460,481,482). Nevertheless, Ross et al (460) showed that patients with extensive epidural fibrosis were 3.2 times more likely to experience recurrent radicular pain than those with less scarring. Electrophysiological evidence of neurologic disturbances caused by peridural scar formation was shown in experimental studies (464). Various additional

abnormalities including mechanical tethering of nerve roots secondary to epidural fibrosis in the vertebral canal (465,466), disturbances in blood flow (467), and expression of proinflammatory cytokines causing irritation of exposed dorsal root ganglion and triggering painful responses have been described (468). In addition, osteopontin has been shown to play a major role in the formation of epidural fibrosis and a mark-up DRG response to peridural scar formation (461). Additional experimental evidence has implicated paraspinal muscle spasms, tail contracture, pain behaviors, tactile allodynia, epidural and perineural scarring, and nerve root adherence to the underlying discs and pedicle in animal models (469).

Wound healing after tissue injury involves 4 major coordinated and regulated steps: hemostasis, inflammation, proliferation, and remodeling. Different factors can interfere with these steps, causing improper or impaired wound healing (473). Central to this is an increased inflammatory response with recruitment of polymorphonuclear neutrophils to the injury site. These cells help in the clearance of pathogens and foreign particles, but also lead to tissue injury with generation of reactive oxygen species (ROS) (483), excessive migration of fibroblasts and collagen deposition. Thus, excessive scarring and adhesion formation occurs and can be exacerbated by pathological process such as infection, inflammation, and hematoma formation (484). Numerous strategies have been tested to reduce adhesion formation post spinal surgery; however, there have not been any therapeutic breakthroughs to achieve this goal (473).

Consequently, in post-lumbar surgery syndrome, a multitude of pathophysiologic bases have been described including recurrent disc herniation, scarring and entrapment of the nerve roots and discogenic pain. These can be addressed with epidural interventions, either with epidural injections or percutaneous adhesiolysis. Multiple RCTs and systematic reviews have been performed with caudal epidural injections, as well as percutaneous adhesiolysis in post-lumbar surgery syndrome (56,58,60,72-74).

### **5.2 Cervical Disc-Related Pathology, Spinal Stenosis, Post-Surgery Syndrome**

Chronic, persistent neck and upper extremity pain and radicular pain may be secondary to disc herniation, discogenic pain, spondylosis, spinal stenosis, or post cervical surgery syndrome resulting in disc related pain with or without radiculitis.



### 5.2.1 Cervical Disc-Related Pathology

Intervertebral disc-related pain can be caused by structural abnormalities, such as disc degeneration and disc herniation, and biochemical effects such as inflammation (7,134,436).

Disc degeneration can be broadly classified into 2 categories: internal disruption and herniation (485). Internal disruption refers to a pathway that ends with derangement of the internal nucleus pulposus and/or annular fibers with little or no external deformation (486). Initially, repetitive microtrauma slowly causes the formation of small circumferential micro fissures. These concentric fissures coalesce over time to cause formation of radial fissures that extend from the inner, gelatinous nucleus pulposus to the outer third of the annulus fibrosus (487). While the nucleus pulposus of each disc is not innervated, the outer annulus fibrosus is innervated anteriorly by the vertebral nerve and posterolaterally by the sinuvertebral nerve (488). Therefore, when the radial fissures invade the annulus, it is thought that they may become a source of discogenic pain (489,490). However, it should be noted that annular fissure tears can also be found in asymptomatic individuals.

Recent studies on the etiology of discogenic pain have demonstrated that inflammatory cytokines such as TNF- $\alpha$ , IL-1  $\alpha/\beta$ , IL-2, IL-4, IL-6, IL-8, IL-10, IL-17, IL-20, and IFN- $\gamma$  are secreted by cells in degenerative discs (491). The expression of these cytokines has multiple effects. In particular, IL-1 $\beta$  has been found to increase NGF expression and TNF- $\alpha$  has been associated with up-regulation of substance P (492). Further, levels of NGF and TNF- $\alpha$  have been found to be increased in painful discs (493). The increased presence of NGF in the disc is thought to contribute to discogenic pain by causing infiltration of nerve fibers into otherwise aneural tissue (492). Additionally, the increase in cytokine expression causes chemokine production, which, in turn, leads to recruitment of T-cells, B-cells, macrophages and mast cells. These cells cause matrix degradation and continue to amplify the inflammatory cascade (438,491).

The incidence of cervical disc herniation, however, is less common than lumbar disc herniations (134,436,494-500). The cervical disc herniation is a common source of cervical radiculopathy. The incidence of cervical disc herniations has been reported from Rochester, Minnesota, with the annual incidence as 18.6 per 100,000 or 0.186% with incidence peaking in the sixth decade of life (501). However, the etiology of cervical spine disc herniation is multifactorial (497,502,503). The proposed risk factors include male gender, present cigarette smoking, heavy

lifting, and frequent driving or occupation involving driving (497,502,503). Further, evidence also shows that incidence of cervical disc herniation is higher in professional drivers, army aviators, and those who operate vibrating equipment (497,503). In addition, a study reported that history of physical exercise or trauma preceded the onset of symptoms in 14.8% of cases (501).

The mechanical compression on the nerve root that is being irritated by the herniated disc material is an important factor in the production of neck and upper extremity pain. The mechanical, chemical, and inflammatory components produce ischemic neuropathy related to the alteration of blood flow patterns or defects in the neuronal transport mechanism of the nerve root itself. Radicular pain may occur in the absence of nerve root compression secondary to nucleus pulposus extrusion or inflammatory reaction to the chemicals.

Multiple studies have shown the unique properties of spinal nerves and inflammatory mechanisms, explaining various mechanisms other than mechanical compression and compression affecting dorsal root ganglion (7,134,436,498,504-520). In fact, herniated cervical intervertebral discs have been shown to produce metalloproteinases, nitric oxide, interleukin-6, and prostaglandin E2 (505). These substances are considered to be potential irritants of spinal nerves or inflammation.

Cervical radiculopathy is a pathologic process that involves neurophysiologic dysfunction of the nerve root (521-523). This syndrome is characterized by myotomal weakness, paresthesias, sensory disturbances and depressed muscle stretch reflexes, all of which are sequelae of a hypofunctional nerve root (485). In cervical radiculopathy, the hypofunctional nerve root is the result of nerve root compression. Direct nerve compression causes a conduction block and interruption of axonal flow, as well as hypoxia and all of its associated effects (523).

Most often, the cervical nerve root injury present in cervical radiculopathy is caused by intervertebral disc herniation (524). This mechanism of injury was first described by Semmes and Murphey in 1943 (525). Since that time, numerous studies have demonstrated that cervical disc abnormalities are often present in asymptomatic individuals (526-529). Why can a cervical disc herniation cause radiculopathy in one patient, while another patient with a similar herniation may be asymptomatic? The reasons for this difference are not completely clear. However, it is thought that an inflammatory response to the cervical disc herniation is responsible for initiating the neurophysiologic dysfunction characteristic of

cervical radiculopathy (505-507,530,531). This theory is supported by evidence that nerve root inflammation, in the absence of frank compression may continue to cause disruptions in nerve root physiology (532). Inflammatory mediators may be secreted from a degenerated or herniated nucleus pulposus (491-493,523,533). Additionally, the gradient of compression may also play a significant role in determining whether or not a disk herniation becomes symptomatic (534).

Spondylitic changes represent the second most common cause of cervical radiculopathy. Spondylosis is an umbrella term, which covers the degenerative changes that develop in the spine over time: ligamentous hypertrophy, hyperostosis, disk degeneration, and facet and/or uncovertebral joint arthropathy (535). Hypertrophy of the facet or uncovertebral joints may cause stenosis of the intervertebral foramina and subsequent nerve root compression (535,536). Osteophytes may also compress the adjacent nerve root. Other less common, but noteworthy causes of cervical radiculopathy include facet joint cysts, nerve tumors (e.g., schwannomas), fibroproliferation, hematomas, and trauma (523,537,538).

The course and prognosis of cervical disc herniation has been studied in multiple manuscripts (500,501,539). A systematic review of the literature of the course and prognostic factors of symptomatic cervical disc herniation with radiculopathy (500) concluded that most patients with symptomatic cervical spine disc herniation with radiculopathy recovered. In addition, a clinical guideline (540) for the diagnosis and treatment cervical radiculopathy from degenerative disorders concluded that signs and symptoms of degenerative disorders of the cervical spine resulting in radiculopathy will be self-limited and will resolve spontaneously over a variable length of time without specific treatment. In another manuscript (539), it was shown that in the natural history of cervical radiculopathy, 43% of the patients had no further symptoms after a few months, 29% had only mild or intermittent symptoms, and only 27% had disabling pain. The authors of the large epidemiologic prevalence study from Rochester, Minnesota (501) over a 5-year follow-up period showed that 31.7% of patients with symptomatic cervical radiculopathy showed symptoms recurrence, with only 26% needing surgical intervention for intractable pain, sensory deficit or objective weakness (501).

Based on the pathophysiology of cervical disc degeneration, disc herniation, and resultant radiculopathy, multiple investigators have shown the effectiveness of cervical epidural injections in managing neck and upper extremity pain (55,58,60,64,70,76).

### **5.2.2 Cervical Spondylosis**

Degenerative changes of the cervical spine reach a prevalence of nearly 95% by age 65. These changes are associated with disc protrusion, neuroforaminal narrowing, and spinal cord contour changes in up to 78% of asymptomatic individuals (539-541).

Spondylosis is a chronic degenerative condition of the cervical spine associated with the formation of osteophytes and compression of the spinal cord. Spondylosis refers to degenerative changes of the spine involving the intervertebral discs, uncovertebral joints of Luschka, facet joints, ligaments, and connective tissue of the cervical vertebrae. Degenerative changes of the cervical spine are seen in approximately 10% of individuals by age 25 and in 95% by age 65. The levels most commonly affected by both disc herniation and chronic spondylosis are C6/C7, followed by C5/C6 as these are the cervical segments where the most extension and flexion occurs.

In most symptomatic cases, spondylosis is associated with aging and with compression of the spinal cord, producing either central or neuroforaminal stenosis in patients older than 55 (542).

Cervical spondylotic myelopathy refers to clinically evident spinal cord dysfunction with the presence of long-track signs due to compression of the spinal cord. Weakness or stiffness in the legs with unsteady gait, together with weakness or clumsiness in the hands, is pathognomonic of cervical spondylotic myelopathy. The progression of weakness may be gradual in some patients or sudden in others following minor trauma. Some patients may complain of hesitancy on urination, even though loss of sphincter control or urinary incontinence is rare and considered a late sign of myelopathy.

Cervical epidural injections, specifically in radiculopathy, are known to be helpful in managing cervical spondylosis. There are no specific studies conducted for this purpose. However, the mechanism is similar to spinal stenosis and disc herniation. Consequently, epidural injections fit the pathophysiological basis for epidural interventions. Epidural steroid injections are not routinely recommended in those patients who go on to develop spondylotic myelopathy.

### **5.2.3 Cervical Spinal Stenosis**

Cervical spinal stenosis is a common disease that results in considerable morbidity and disability (543-546). Degenerative change is the most common cause of cervical stenosis and can be due to disc herniation, osteophyte formation, or a combination of both, namely disc-osteophyte complex (547).

The normal AP diameter of the mid-cervical spinal canal is approximately 17-18 mm (548). Based on a large cadaveric study, cervical stenosis, or narrowing of the central cervical canal has an estimated US population prevalence of 4.9% (549). Cervical stenosis may be congenital, in which case it is secondary to short pedicles and bony abnormalities of the lateral masses and laminae (550). More frequently, however, cervical stenosis is acquired--the result of cervical spondylosis. The pathway to acquired cervical stenosis begins with gradual degeneration of the cervical intervertebral discs. As the discs degenerate and shrink, they pull away from the vertebral endplates, causing instability of the spinal segments. This instability may lead to hypertrophy and/or calcification of the ligamentum flavum and/or posterior longitudinal ligament, hypertrophy of the facet and/or uncovertebral joints and the formation of cysts on the joints and ligaments (551).

Tandem spinal stenosis is a degenerative disease that describes a double stenotic lesion involving the cervical and lumbar spine (546,552-555). Historically, tandem spinal stenosis accounts for between 5% and 60% of all cases of stenosis (546). However, cervical spinal stenosis is less common than lumbar spinal stenosis. Asymptomatic stenosis in the cervical and thoracic spines of patients with symptomatic lumbar stenosis has been reported in 23.9% in the cervical spine and 24.3% in the thoracic spine, with 12.1% with combined radiologic cervical and thoracic stenosis in addition to their symptomatic lumbar stenosis or triple stenosis (554). With increasing age, a large proportion of the population exhibits radiological signs of discopathy or spondylosis, leading to constriction of the spinal canal (543).

Cervical spinal stenosis may also cause myelopathy, which is broadly defined as a symptomatic dysfunction of the cervical spinal cord caused by compressive etiologies (543,545,546,555-557). However, cervical myelopathy can occur because of cord compression resulting from one of several physiological factors including spondylolysis/congenital stenosis, disc herniation, ossification of the posterior longitudinal ligament, hypertrophy of the ligamentum flavum, and degenerative subluxation. For the past 4 decades, there have been several attempts to correlate the clinical severity of spinal stenosis with the degree of spinal cord compression on MRI (556-561). However, no methodology has been validated. In a recent manuscript, Karpova et al (545) assessed the reliability of quantitative MRI methods in the assessment of spinal canal stenosis and cord compression in cervical myelopathy. They concluded that the measurements of maximum ca-

nal compromise, maximum spinal cord compression, and compression ratio were reliable and correlated well with the clinical severity of cervical myelopathy.

Based on the pathophysiologic basis of cervical spinal stenosis, cervical epidural injections have been shown to be effective and are indicated (55,58,60,64,70,76).

#### **5.2.4 Cervical Post-surgery Syndrome**

Cervical post-surgery syndrome represents a cluster of symptoms following cervical spine surgery wherein the expectations of the patient and spine surgeon are not met. Animal models of post-lumbar laminectomy syndrome demonstrated paraspinal muscle spasms, tail contractures, pain behaviors, tactile allodynia, epidural and perineural scarring, and nerve root adherence to the underlying disc and pedicle (457,458,461,464,467-477). It also has been postulated that there may be a final common pathway with all the described etiologies, which results in peripheral and central facilitation potentiated by inflammatory and nerve injury mechanisms.

In a recent manuscript, Seichi et al (562) explored the mechanism of post-operative axial neck pain which is a common complication (563-574) even though neurological recovery after laminoplasty is appropriate (566-568). They described that even though multiple factors, including surgical trauma to the posterior cervical muscles and the period of external immobilization, have been suggested as causative factors for the development of pain (563-572), the precise mechanism underlying the development of post-operative axial pain remains unclear (564). They described that post-operative axial pain is multifactorial in nature with soft tissue injuries, such as those that occur due to intraoperative damage of the posterior extensor musculature, are considered to be a major mechanical factor in the development of post-operative axial pain (573,574). In addition to muscle damage, nerve tissue injuries sustained during surgery also have been suggested as a causative factor of post-operative axial pain (563,564).

Based on the above pathophysiologic basis, epidural interventions are performed in the cervical spine with appropriate outcomes (55,58,60,64,70,76).

#### **5.3 Thoracic Disc-Related Pathology, Spinal Stenosis, Post-surgery Syndrome**

Thoracic disc related pathology, spinal stenosis, and post-surgery syndrome produce symptoms related to thoracic pain and radiculitis (7,135,546,575-580).

### 5.3.1 Thoracic Disc Related Pathology

Thoracic discogenic pain is a much less frequent occurrence than cervical/lumbar discogenic pain. When considering the biomechanics of the spine, this is not surprising because the cervical and lumbar regions support more of the weight of the axial skeleton than the thoracic and sacral regions (581). Additionally, the coronal orientation of the thoracic zygapophyseal joints makes them more stable than those found in the cervical and lumbar spine (582). The presence of the ribs also provides additional stability to the thoracic vertebra. As a result, the intervertebral discs in the thoracic spine are less prone to degenerative changes than those in the cervical and lumbar regions. However, when thoracic discogenic pain does occur, it is typically the result of the same degenerative pathway that takes place in cervical and lumbar discs. Also, in similar fashion to the cervical and lumbar spine, thoracic disc herniations may be found in asymptomatic patients. It is important to note that the cord/canal ratio in the thoracic spine is 40%, compared to 25% in the cervical spine (583). Moreover, due to its tenuous blood supply, the thoracic spine is particularly susceptible to ischemic damage. Therefore, when thoracic disc herniations do lead to myelopathy, it is typically more severe than in the cervical and lumbar spine.

Thoracic disc herniation is rare, with an estimate preference of 1 per million people or 0.0001%, constituting a small proportion of overall disc herniations of 40 to 50 per 100,000 population or 0.04% to 0.05% (584). Consequently, as expected, surgical procedures in the thoracic spine make up only 0.15% to 4% of the procedures for disc herniation (585). Thoracic disc herniations are associated with progression, dominated by the risk of medullary compression; however, surgery for thoracic disc herniation has a poor reputation because of its technical difficulties and the risk of potentially serious hard to treat complications (579).

Presence of asymptomatic stenosis has been estimated 11% to 37%. Thoracic disc herniation is most common in adults 30 to 50 years of age (579). Thoracic disc herniations are located below T7-T8 in 75% of the cases. Further, T11 to T12 disc is the most vulnerable because of greater mobility and posterior longitudinal ligament weakness at this level. Only 4% of thoracic disc herniations are located above T3-T4. The cases of thoracic disc herniations complicating proximal junctional syndrome have been reported after the thoracolumbar fusion (586). Thoracic disc herniations frequently calcify or ossify (584). However, spontaneous regression of

thoracic disc herniations with or without calcification or ossification have been reported (587). Thoracic disc herniations have been reported to be more common in Scheuermann's disease and also have been found in 3% to 37% with a history of trauma.

The herniated disc can be very large in volume. In fact, thoracic disc herniation is labeled as 'giant' when it occupies more than 40% of medullary canal on computed tomography (CT) scan or MRI (585). The volume and calcified nature of herniation increases the risk of intradural extension due to erosion and progressive thinning of the dura, even though intradural extension is only present in 0.26% to 0.3% of all herniated discs, whereas it is present in 15% to 70% of joint calcified thoracic disc herniations.

The majority of patients may not present with radicular pain. Some may present only with thoracic pain. The mechanism of radicular pain is similar to cervical and lumbar spinal pain with mechanical compression and inflammation.

Thoracic discs also have been shown to be the cause of pain without disc herniation, mostly axial pain.

Based on pathophysiology of discogenic or radicular pain, epidural interventions are effective in post-surgery syndrome. However, there is only one RCT available in the literature (588) included in systematic reviews (55,58,60). Nevertheless, based on the response to discogenic pain in the lumbar and cervical spine, it appears appropriate when medical necessity arises and indications are met.

### 5.3.2 Thoracic Spinal Stenosis

Thoracic spinal stenosis is a relatively rare disease characterized by narrow spinal canal and compression of the spinal cord and/or nerve root (580). In a systematic review, Chen et al (580) showed the results with diagnosis of ossification of the posterior longitudinal ligament (OPLL) in 18.7%, ossification of the ligamentum flavum (OLF) in 41.5% of the patients, and 7.4% were shown to have both OPLL and OLF. In addition, 32.4% were with thoracic disc herniation producing spinal stenosis. Thoracic OPLL occurred mostly at the middle thoracic spine (43.4%), while OLF predominantly occurred at the lower thoracic spine (63.1%). Thoracic disc herniation was mainly localized in the middle (46%) and lower thoracic (50.3%) spine. Tandem spinal stenosis was observed in 52.1% with accompanying cervical diseases and 35.9% with lumbar diseases.

Even though thoracic myelopathy caused by spinal stenosis is less common than that of cervical and lum-

bar disease (588). The outcomes are poor if surgery is performed (589). Multiple factors responsible for poor prognosis have been described including tenuous blood supply to the thoracic spinal cord (590,591), natural kyphotic curve of the thoracic spine which limits backward movement of the spinal cord, especially during ventral compression. Also, thoracic spinal stenosis is a degenerative disease that progresses slowly and can be asymptomatic for a long time, resulting in irreversible neurological damage due to delayed diagnosis (592-595). Finally, the multifactorial nature (589,596-598) of the disease involving many pathologic changes and a combination of multiple factors and co-existence of other spinal pathologies frequently leads to misdiagnosis and incorrect treatment (599). Consequently, even though options are poor, early diagnosis and optimal treatment are recommended.

Based on the pathophysiologic basis, epidural injections are indicated with all the appropriate precautions if medical necessity and appropriate indications are present, based on the results in lumbar and cervical spine (7,55,58,60,65,70,77,81,83).

### 5.3.3 Thoracic Post-surgery Syndrome

Post thoracic surgery syndrome is rare compared to lumbar or cervical post-surgery syndromes due to the fact that surgical interventions constitute only a small proportion of overall surgical interventions for disc herniations for spinal stenosis. Even then, early diagnosis and appropriate management has been recommended (599). Surgical interventions are offered for managing disc herniation, as well as thoracic spinal stenosis and spondylosis. Meanwhile, thoracic surgical interventions are performed for scoliosis and other congenital deformities (575,600-603).

Epidural interventions are performed less frequently than in the lumbar and cervical spine for disc herniation, spinal stenosis, and discogenic pain; however, for thoracic post-surgery syndrome these procedures must only be performed if there is appropriate access available below the surgical level or with catheterization with or without adhesiolysis.

## 6.0 PATHOPHYSIOLOGIC BASIS OF EPIDURAL INTERVENTIONS

### Key Question 4: What is the pathophysiologic basis of epidural interventions in spinal pain?

Multiple therapeutic spinal interventional techniques are applied in managing chronic spinal pain. The rationale includes the commonality and complexity of

spinal pain problems and ability of diagnostic blocks to identify sources of chronic spinal pain. The degenerative processes of the spine and the origin of spinal pain are complex without consistent correlation of radiographic changes to the clinical picture and prognosis. The effectiveness of a large variety of therapeutic interventions used to manage chronic spinal pain has not been demonstrated conclusively (7). In fact, Best Practices in Pain Management from the HHS, has reviewed the available evidence in pain management and described interventional techniques as part of a continuum prior to surgical interventions and neuromodulation (78,79). Among multiple therapeutic interventional techniques with available evidence that are commonly applied are epidural injections including adhesiolysis.

Epidural injections have been in existence since the first descriptions of caudal epidural with local anesthetic for low back pain in 1901, as described by Sicard (604), Cathelin (605), and Pasquier and Leri (606). It is also important to note that Sicard (604,607,608) administered an epidural injection with local anesthetic only and reported several weeks of improvement. He acquired the reputation as the "pain doctor" for treating patients from all over France (607,608). Consequently, epidural injections during the first 50 years were limited to local anesthetic alone (102,609-611), until reports of administration of steroids through sacral nerve root by Robecchi and Capra (612) and Lievre et al (613) in the early 1950s.

Epidural injections are performed with an interlaminar or transforaminal approach in the lumbar, cervical, or thoracic spine. Caudal procedures are performed for lumbosacral disorders. Caudal and interlaminar epidurals have been the common procedures, but more recently, transforaminal epidural injections, specifically in the lumbosacral spine, have been reversing the trend (194,195). The caudal approach is the earliest described technique delivering the medication into the lumbar epidural space from the sacral hiatus, requiring larger volumes of medication in order to reach the target site (7,611,614). It is considered the safest and easiest technique. With the interlaminar approach, the medication is delivered more commonly into the posterior epidural space, but often into the ventral epidural space, specifically with paramedian or parasagittal techniques (614-617).

In the lumbar transforaminal approach, the needle is inserted close to the nerve root, either superiorly or inferiorly, described as supraneural or infraneural approaches (7,614,618-623). However, the supraneural



approach, classically described as the safe triangle approach, has been associated with a multitude of complications (621-624). Consequently, multiple infraneural approaches have been described (618-625). The major described advantage of transforaminal epidural injection appears to be the anatomical position and accurate needle placement to enhance the effectiveness of epidural injection, even though safety is questionable with the supraneural approach when using particulate steroids. When performed under fluoroscopic guidance, superiority of any of the techniques has not been demonstrated conclusively in the lumbar spine.

In reference to thoracic and cervical transforaminal epidural injections, these have been associated with a multitude of complications (626-633).

Percutaneous epidural adhesiolysis, also known as epidural neuroplasty, neurolysis, or lysis of epidural adhesions is an interventional pain management technique that has emerged over approximately the last 30 years (634). The procedure is performed utilizing a reinforced catheter with mechanical adhesiolysis and with injection of multiple fluids. The goals of this procedure are not only to break down fibrous adhesions that may prevent free movement of structures in the intervertebral foramina and in the bony intervertebral canal, but also to remove any barriers or scars that prevent application of medication to structures believed to be the source of pain, and to provide targeted application of local anesthetics, corticosteroids, and other agents (72-76).

## **6.1 Mechanism of Action Local Anesthetics and Steroids**

Several manuscripts have been published evaluating the role of steroids and local anesthetics for epidural injections. In a neural blockade, the rationale for injecting local anesthetic is to block sensory signals. Even though they are often used for diagnostic purposes and believed to provide a temporary effect in acute pain, when used in chronic pain, they provide long-term relief very much beyond its pharmacological duration of action due to a decrease in sensitization and various other mechanisms (7,8,102,609,610). In clinical practice, steroids are typically combined with local anesthetics, with hopes of prolonging the duration of pain relief (56-58,60,61,102).

The rationale for neuraxial steroid use is primarily based on the benefits of neural blockade, which include pain relief that outlasts by hours, days, and sometimes weeks. Neural blockade effectiveness is based on the

postulation that it alters or interrupts nociceptive input, reflex mechanism of the afferent limb, self-sustaining activity of the neuronal pools in the neuroaxis, and the pattern of central neuronal activities (55-62). Consequently, the pharmacological and physical actions of corticosteroids, along with local anesthetics have been the basis of such explanations.

### **6.1.1 Steroids**

Corticosteroids in neuraxial blockade have been postulated to reduce inflammation, either by inhibiting the synthesis or release of a number of proinflammatory substances, or by causing a reversible local anesthetic effect (55-62). There are several modes of action of corticosteroids including membrane stabilization, inhibition of neural peptide synthesis or action, blockade of phospholipase A2 activity, local anesthetic effect, prolonged suppression of ongoing neuronal discharge, and suppression of sensitization of dorsal-horn neurons (102,635-646). Corticosteroids inhibit phospholipase A2, which converts membrane phospholipids into arachidonic acid and lysophospholipids (639,641,647). It is further followed by conversion to proinflammatory eicosanoids, including prostaglandins, thromboxanes, and leukotrienes. Pain is exacerbated and peripheral nociceptors are sensitized by inflammatory mediators. Thus, corticosteroids not only provide antiinflammatory effects, but also inhibit ectopic discharges from nerve fibers (641). Despite extensive use, there is no evidence that steroid injections are disease-modifying agents with a direct effect on pain generation or transmission, with an exception of inflammatory conditions such as rheumatoid arthritis (102). Further, there are no studies demonstrating the anti-inflammatory role of steroids or differentiation of inflammatory radiculopathies from noninflammatory radiculopathies (54,56-59,639). During the search for confirmation of the anti-inflammatory effect of steroids in epidural injections, multiple explanations relied on inflammatory component in lumbosacral radiculopathy. The first evidence suggesting inflammation in patients with radiculopathy was published in 1981 (642). Ryan and Taylor (642) examined samples of cerebral spinal fluid during administration of intrathecal and epidural injections, and theorized that inflammation was a critical component of radicular pain, and that intraspinal steroids were likely to be most effective when this inflammation was still acute, before the pathology had progressed to nerve root fibrosis or axonal death. This led to the classification of 2 categories of radiculopathy, compressive and inflammatory.

Lindahl and Rexed (648) described inflammation, edema, and proliferative or degenerative changes in biopsy samples from the posterior nerve roots of patients undergoing laminectomy. In lumbar disc herniation and radiculopathic pattern of symptoms, consideration for a primary biochemical inducement of pain over a mechanical mechanism is a contemporary topic of spinal research. Even then, the exact pathomechanism by which a degenerative intervertebral disc leads to neural inflammation and pain had not been determined. Using modern techniques of chemical analysis, biochemical markers which participate in the degenerative cascade and possibly with onset of pain (649) can be identified. While, Scuderi et al (649) were unable to identify the presence of inflammatory peptides in the epidural lavage of patients with symptomatic radicular pain due to herniated disc disease, de Souza Grava et al (650) indicated that specific cytokines released during the inflammatory process induced by the herniated intervertebral disc play a fundamental role in the development of mechanical and thermal hyperalgesia and that the maintenance of this inflammation may be the most important point for the chronification of the pain. In addition, Shamji et al (651) concluded that there was evidence of altered gait in a model of noncompressive disc herniation with radiculopathy in a rat model. However, systematic inflammation was absent, but mechanical allodynia, local inflammation, and autoreactive immune activation were observed. Cuéllar et al (652) also developed an animal model for the study of biochemical changes that occur in the epidural space after intervertebral disc herniation. The performed epidural lavage in 48 rats after L5 dorsal root ganglion exposure to autologous nucleus pulposus illustrating nucleus pulposus causing the elevation of IL-6, TNF- $\alpha$ , and IFN- $\gamma$  - all attenuated by IFN- $\gamma$  blockade. However, Brisby et al (653) showed inconclusive results after the assessment of proinflammatory cytokines in cerebrospinal fluid and serum in 39 patients with disc herniation and sciatica. They (653) showed that concentrations of IL-8 in cerebrospinal fluid were increased in 12 out of 39 patients, and these increased levels of IL-8 correlated to a short duration of pain and to more pronounced herniation with normal concentrations of IL-1 $\beta$ , IL-6, IFN- $\gamma$ , and TNF- $\alpha$  in cerebrospinal fluid and serum in almost all patients with lumbar disc herniation. However, they were unable to demonstrate any relationship between IL-8 concentrations in cerebrospinal fluid and pain intensity, positive neurological findings, or a positive straight leg raising test.

Thus, the role of various chemicals and inflammation has been extensively investigated with discogenic pathol-

ogy and radicular pain. The complex mechanism of discogenic pain includes chemical nociception leading to low back pain with or without disc herniation (7,134-136,654-658). The research in animals has shown upregulation of various pain regulated molecules, such as calcitonin gene related peptide and Substance P, in the dorsal root ganglions neurons innervating degenerated intervertebral discs (7,657-659). In fact, in recent years epidural TNF- $\alpha$  inhibitory injections have been utilized to treat lumbar radiculitis rather than epidural steroid injections (7,659-667).

In earlier studies, Berg (668) and Green (669) observed a consistent reduction in the swelling of involved nerve roots coincidental with improvement in the patient's sciatic symptoms with steroid administration. Thus, it is postulated that corticosteroids reduce inflammation either by inhibiting the synthesis or release of a number of pro-inflammatory substances or by causing a reversible local anesthetic effect (514,638,641,644,646,670-683). The various modes of action of corticosteroids include membrane stabilization, inhibition of neural peptide synthesis or action, blockade of phospholipase A2 activity, prolonged suppression of ongoing neuronal discharge, and suppression of sensitization of dorsal horn neurons.

Epidural injections of betamethasone in a model of lumbar radiculopathy showed a significant effect on thermal hyperalgesia, while the administration of intravenous methylprednisolone significantly reduced the nerve root injury produced by epidural application of autologous nucleus pulposus in a pig experimental model (635-638,643-645). Another study concluded that lipopolysaccharide accelerated the process of herniated intervertebral disc resorption, whereas high-dose steroids suppressed the process (644). Research studying the effects of local methylprednisolone on pain in a nerve injury model by inducing peripheral mononeuropathy showed that the heat hyperalgesia and mechano-allodynia, but not mechano-hyperalgesia were depressed in the animals receiving corticosteroids; however, not in those treated with saline, with the effect remaining during the 11 day test period (645). The effects of systemic methylprednisolone on acute nociception and on pain behavior in hyperalgesia were studied in normal and neuropathic rats (646). The results showed that chronic steroid treatment prevented the development of neuropathic edema and completely blocked neurogenic extravasation; however, the findings also showed that corticosteroids did not affect nociceptive thresholds in normal or neuropathic hyperalgesic rats.

Ever since the descriptions of Hollander et al (647)

in 1951, enthusiasm erupted with the temporary improvement of symptoms in many cases, but it was also tempered by warnings of the possibility of increasing the damage in joints subjected to excessive use in periods of freedom from symptoms. Their early publication in 1951 (684) also noted that the results of treatment of the knee have been more encouraging than those of treatment of other joints, presumably because of the ease with which injection of the knee joint can be accomplished.

### 6.1.2 Local Anesthetics

Local anesthetics have been used ever since the discovery of the medicinal properties of cocaine, long before the compound was brought to Europe for its local anesthetic properties to be discovered (56-58,102). Based on this foundation, regional anesthesia developed into interventional pain management. In 1899, Tuffer (685) described therapeutic nerve blocks in pain management using spinal injections of cocaine to control pain from sarcoma of the leg. In 1903, Cushing described pain relief with nerve blocks (686), along with reports of trigeminal alcohol blockade (687).

The development of caudal epidural injections for pain management began in 1901 (604-608) and interlaminar epidural injections in 1933 by Dogliotti (688).

The effectiveness of local anesthetics in chronic pain is based on anti-inflammatory actions and the alteration of multiple pathophysiologic mechanisms including noxious peripheral stimulation, excess nociception resulting in the sensitization of the pain pathways, and excess the release of neurotransmitters causing complex central responses including hyperalgesia or wind-up, resulting in an increase in nociceptive sensitization of the nervous system, and phenotype changes which are also considered as part of the neuronal plasticity (55-58,102,689-699). Sato et al (691) showed the prolonged analgesic effect of epidural ropivacaine in a rat model of neuropathic pain. Along those same lines, Tachihara et al (692) provided evidence that there is a lack of additional benefit with nerve root infiltration for lumbar disc herniation by the addition of steroids to lidocaine.

## 7.0 DIAGNOSIS OF DISC-RELATED PATHOLOGY, SPINAL STENOSIS, AND RADICULITIS

### Key Question 5: What are the noninterventional diagnostic methods in disc related pathology, spinal stenosis, and post-surgery syndrome?

Spinal pain is one of the most common chronic pain conditions. Intervertebral discs, facet joints, sacroiliac joints, ligaments, fascia, muscle and nerve root dura have

been shown to be capable of transmitting pain in the spine with resulting symptoms of axial and extremity pain.

Disc herniation and spinal stenosis are diagnosed with physical examination, radiological assessment, and neurophysiological assessment. For chronic axial pain without disc herniation or radiculitis, the precision diagnostic blocks applied include facet joint nerve blocks, provocation discography, and sacroiliac joint blocks, and to a lesser extent, lumbosacral selective nerve root blocks or transforaminal epidural injections in the diagnosis of difficult radicular pain syndromes.

## 7.1 Lumbar Spine

### 7.1.1 History and Physical Examination

The assessment of differential diagnoses is based on history, and physical examination which includes neurological examination, motor examination, sensory examination, reflex examination, and application of provocative maneuvers including straight leg raising test, crossed straight leg raising test, bowstring sign, and slump test. Deyo et al (700) showed that sciatica was highly sensitive for a clinically important herniated disc, as was old age for spinal stenosis and compression fractures. Subjective symptoms of numbness are considered reasonably sensitive (0.76), but not specific (0.33) as a sign of radiculopathy (136,701). Objective signs of numbness are reasonably sensitive, although numbness is not specific as a sign of radiculopathy.

The sensory examination should cover the bilateral lower extremities to evaluate for all dermatomal or more diffuse sensory loss as seen in the peripheral neuropathies with a stocking distribution of loss. Dermatomes may define the area of skin innervated by a single nerve root or peripheral nerve. A simple sensory examination involves testing for sensation for 3 dermatomes in the lower extremity, L4, L5, and S1. Sensation may be evaluated using many different modalities, including vibration, proprioception, temperature, light touch, and pin prick (702). The sensitivity and specificity of the sensory examination in the diagnosis of lumbar disc herniation has been described to range from 16% to 66% for sensitivity, and 51% to 86% for the specificity (702).

Radiation of pain needs to be carefully interpreted. Somatic referred pain is mostly in the buttock or lower extremity with any type of pain generators in the lumbar spine and should not be confused with radicular pain. The cardinal distinctions lie in the quality of pain and its behavior. Table 8 shows the differences between radicular and somatic pain.

Rubinstein and van Tulder (703) in a best evidence review of diagnostic procedures for neck and low back pain, showed that a number of factors can be identified which can assist the clinician in identifying sciatica due to disc herniation or serious pathology. However, they were unable to show any evidence based on history leading to a diagnosis not related to radicular pain. A neurologic and musculoskeletal examination may assist in the diagnosis of radiculopathy or radicular pain with identification of disc herniation at various levels. Figure 14 illustrates the clinical features of posterolateral lumbar intervertebral disc herniation. Straight leg raising or cross straight leg raising and motor examination may be crucial in the assessment of disc herniation. Table 9 shows the diagnostic features for various levels of nerve root involvement.

Radiculitis, radicular pain, or radiculopathy may be seen not only with herniation of the nucleus pulposus, but, also with central and foraminal spinal stenosis, nerve root entrapment in the lateral recess, and other causes such as spondylolisthesis, spondylolysis, facet joint cysts, and epidural fibrosis, internal disc disruption, or discogenic pain without involvement of other structures.

The presence of radiating pain needs careful evaluation and interpretation. Somatic type pain referred into the buttock and lower extremity can be expected with any of the pain generators of the lumbar spine. Determining the difference between referred pain and radicular pain is critical to arriving at the correct diagnosis and treatment plan (7). Anatomically, somatic/referred pain sources arise from the posterior segments or elements of the spine while radicular pain arises from the anterior segments. Typically, the presenting

Table 8. Features of somatic and radicular pain.

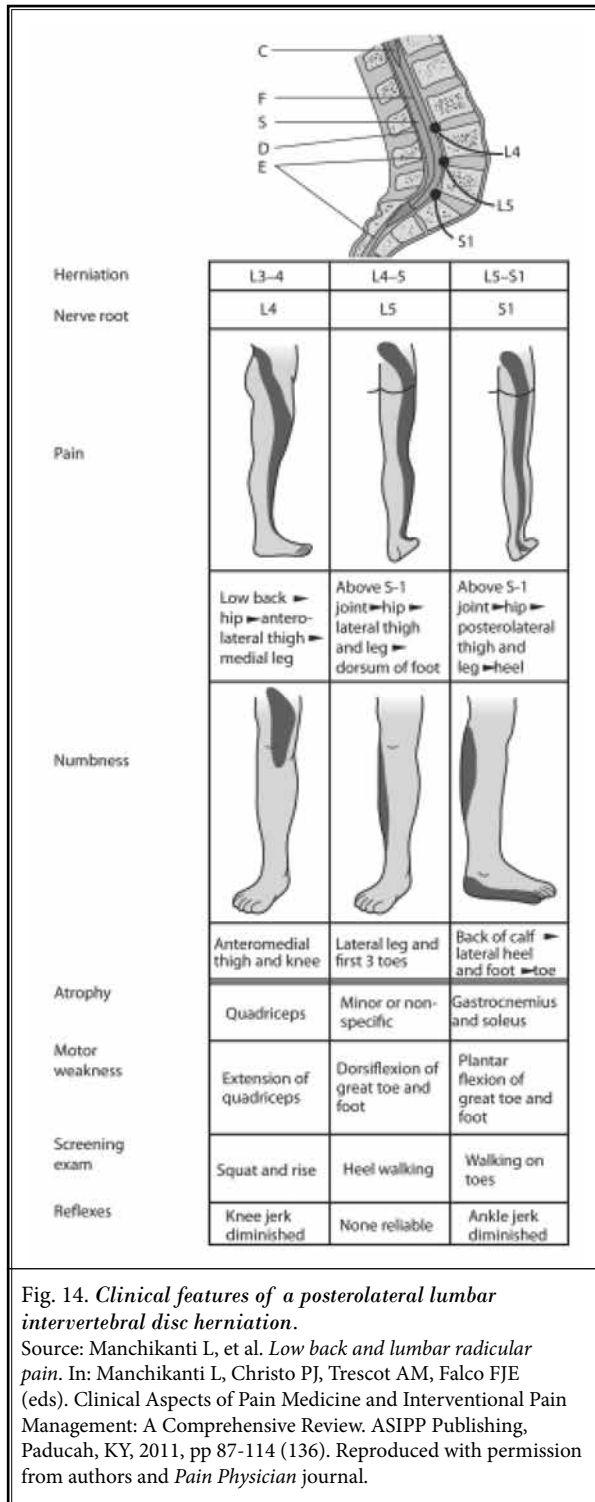
	Somatic or Referred Pain	Radicular Pain
Segment Causes	Posterior segment or element	Anterior segment
	Facet joint pain	Disk herniation
	Sacroiliac joint pain	Annular tear
	Myofascial syndrome	Spinal stenosis
	Internal disk disruption	
Symptoms		
Quality	Dull, aching, deep	Sharp, shooting, lancinating
	Like an expanding pressure	Like an electrical shock
	Poorly localized	
	Back worse than leg	Leg worse than back
	No paresthesia	Paresthesia present
	Covers a wide area	Well defined and localized
	No radicular or shooting pain	Radicular distribution
Modification	Worse with extension	Worse with flexion
	Better with flexion	Better with extension
	No radicular pattern	Radicular pattern
Radiation	Low back to hip, thigh, groin	Follows nerve root distribution
	Radiation below knee unusual	Radiation below knee common
	Quasisegmental	Radicular pattern
Signs		
Sensory Alteration	Uncommon	Probably
Motor Changes	Only subjective weakness	Objective weakness
	Atrophy rare	Atrophy possibly present
Reflex Changes	None	Commonly described, but seen only occasionally
Straight Leg Raises	Only low back pain	Reproduction of leg pain
	No root tension signs	Positive root tensions signs

Source: Manchikanti L, et al. Low back and lumbar radicular pain. In: Manchikanti L, Christo PJ, Trescot AM, Falco FJE (eds). *Clinical Aspects of Pain Medicine and Interventional Pain Management: A Comprehensive Review*. ASIPP Publishing, Paducah, KY, 2011, pp 87-114 (136).

Table 9. Diagnostic features for various levels of nerve root involvement.

Herniation	Nerve Root	Pain	Numbness	Atrophy	Motor Weakness	Screening Examination	Reflexes
L3-4	L4	Low back; hip; anterolateral thigh, medial leg	Anteromedial thigh and knee	Quadriceps	Extension of quadriceps	Squat and rise	Knee jerk diminished
L4-5	L5	Above S1 joint; hip; lateral thigh and leg; dorsum of foot	Lateral leg and first 3 toes	Minor or nonspecific	Dorsiflexion of great toe and foot	Heel walking	None reliable
L5-S1	S1	Above S1 joint; hip; posterolateral and thigh leg; heel	Back of calf; lateral heel and foot; toe	Gastrocnemius and soleus	Plantar flexion of great toe and foot	Walking on toes	Ankle jerk diminished

Source: Manchikanti L, et al. Low back and lumbar radicular pain. In: Manchikanti L, Christo PJ, Trescot AM, Falco FJE (eds). *Clinical Aspects of Pain Medicine and Interventional Pain Management: A Comprehensive Review*. ASIPP Publishing, Paducah, KY, 2011, pp 87-114 (136).



with radicular pain. Finally, finding on examination with somatic/referred pain will typically be without sensory, motor or reflex changes while the opposite is true for radicular pain (Table 8) (7).

Physical examination for lumbar radiculopathy related to disc herniation in patients with low back pain often provides inaccurate and incomplete information. In a Cochrane database systematic review (704), the conclusion of 16 cohort studies and 3 case-controlled studies, the authors concluded that in isolation diagnostic performance of most physical tests (scoliosis, paresis or muscle weakness, muscle wasting, impaired reflexes, sensory deficits) was poor. Some tests (forward flexion, hyperextension test, and slump test) performed slightly better, but the number of studies was small. Most studies assessed the straight leg raising test. The results in surgical populations were variable compared to those with imaging. In surgical populations, characterized by a high prevalence of disc herniation (58% to 98%), the straight leg raise showed high sensitivity (pooled estimate 0.92, 95% CI: 0.87 to 0.95) with widely varying specificity (0.10 to 1.00, pooled estimate 0.28, 95% CI: 0.18 to 0.40). However, results of studies using imaging showed more heterogeneity and poorer sensitivity. The crossed straight leg raise showed high specificity of 0.90 with consistently low sensitivity (0.28). Tawa et al (705) in a 2017 systematic review of accuracy of clinical neurological examination in diagnosing lumbo-sacral radiculopathy, with inclusion of 12 studies assessed neurological examination. The diagnostic performance of sensory testing using MRI as a reference standard demonstrated a sensitivity of 0.61 and a specificity of 0.63. Motor tests sensitivity was poor to moderate, ranging from 0.13 to 0.61. They showed that generally, the diagnostic performance of reflex testing was notably good with specificity ranging from 0.60 to 0.93 and sensitivity ranging from 0.14 to 0.67. They also showed that the straight leg raise test recorded a mean sensitivity of 0.84 and specificity of 0.78. Bellier et al (706) assessed a range of the different nerve root movements in cadavers to identify them during a passive straight leg raise. They concluded that the lumbo-sacral nerve roots in the spinal canal region move statistically significantly in response to the clinically applied straight leg raise test, except for L2 root during the left straight leg raise. This movement was symmetric and greater when a bilateral straight leg raise was applied. The anatomical results correlated with those observed empirically in clinical practice. Thus, the results may be variable with multiple observers. In an older study assessing the sensitivity and specificity of the slump and straight raising test in patients with lumbar disc herniation (707), the authors concluded that the

symptoms of somatic or referred pain will be a deep dull ache, while lightning like, sharp shooting pain is found



slump test might be used more frequently as a sensitive physical examination tool in patients with symptoms of lumbar disc herniations. However, they also concluded that moving to its high specificity; the straight leg raise may especially help identify patients who have herniations with root compression requiring surgery. In this study, the results found that the slump test was more sensitive 0.84 than the straight leg raise 0.52 in patients with lumbar disc herniations; however, straight leg raise was found to be a simply more specific test 0.89 than the slump test 0.83.

As mentioned above, central spinal stenosis can present with radiculitis, however, it will more typically present much differently than radiculopathy secondary to disc herniation. This clinical presentation will typically feature neurogenic claudication type symptoms. These patients will have little pain at rest or while sitting, however, upon standing and walking the patient will report heaviness in the legs, sensation of the legs going numb, and even the onset of low back pain. Classically, these symptoms are consistent and reproducible with the distance ambulated, relieved by forward flexion, recumbency or sitting. Lateral recess stenosis and resultant nerve impingement in the foramen will present with or without back pain and leg pain radiating into the ankle or toes. Diagnosis of the other conditions mentioned require radiologic evaluation. Certainly, radiologic evaluation can help to differentiate different types of spinal stenosis from a lumbar disc herniation, as well as conditions of the spine, which can result in radicular pain (7).

Lateral recess stenosis with nerve entrapment mostly presents without low back pain and rare muscle weakness. The pain may radiate into the ankle and occasionally into toes. Further, radiologic examination often differentiates it from lumbar radiculopathy from disc herniation.

The correlation of symptoms with MRI findings was assessed by Albert et al (708) in a cross-sectional diagnostic accuracy study of adult patients with radicular leg pain with positive neurological signs (average 2.8 signs – hypoalgesia, diminished reflexes, muscle weakness, positive straight leg raise test). They studied 93 patients with their pain charts and MRI correlation in an MRI confirmed single-level radiculopathy. The results show a wide overlap in pain patterns from compromised L5 and S1 nerve roots, but some distinguished features. The pain patterns had approximately 50% to 80% overlap with published dermatomes. However, clinicians were unable to determine with any accuracy above chance whether an individual pain drawing was from a person

with a compromised L5 or S1 nerve root, and use of composite pain drawings did not improve that accuracy.

As shown in Table 9, motor weakness may present at all levels. Lumbar radiculopathy is usually characterized by weakness affecting 2 or more muscles from the same spinal segment, but different peripheral nerves (186). Thus, an L5 radiculopathy may affect both the dorsal flexors of the foot and toes (peroneal nerve) and abduction of the hip (superior gluteal nerve). Consequently, strength examination should include the assessment of hip flexors L1 to L3, quadriceps L2 to L4, tibialis anterior L4 to L5, extensor hallucis longus L5, and the gastrocnemius – soleus (S1).

The sensitivity and specificity of muscle strength testing in patients with lumbar radiculopathy has been evaluated. Kerr et al (709) demonstrated reduced ankle dorsiflexion in 54%, in plantar flexion 13% of those with lumbar disc protrusions from L4 to S1 with an overall specificity of 89%. Multiple studies have shown sensitivity as low as 20%, whereas, specificity as high as 99%.

### **7.1.2 Imaging**

In managing low back pain, basic imaging with plain films and advanced imaging with CT scan and MRI are utilized. Due to its greater resolution of soft tissues and interosseous tissues, MRI is considered superior to CT scan for the demonstration of condition such as nerve tumors, cysts, infection, and other disorders. However, CT scan is superior to MRI in the demonstration of bone and the preferred modality for diagnosing of complex fractures or deformities. However, the studies show that sensitivity and specificity for plain CT, CT myelography, and MRI are the same, with an approximate sensitivity of 0.90 and specificity of 0.70 (710,711). Further, a positive and negative predictive value of 0.82 is also the same for all 3 modalities.

Studies in asymptomatic volunteers have shown a high prevalence of disc abnormalities with a herniated nucleus pulposus in 20% of individuals younger than 40 years and in 27% of individuals older than 40 years on CT scan (711). MRI findings showed disc bulges and disc herniations with increasing frequency with age, with a high prevalence of asymptomatic disc herniations (712,713). Further, a positive relationship with symptoms and disc herniation has been shown in some cases even though it was not universal (714). The grading of lumbar disc herniation and nerve root compression (715) and interobserver and intraobserver variability in MRI evaluation of patients with suspected disc herniation continues to be debated (716).

**7.1.3 Electrodiagnostic Studies**

The utility of electrophysiologic studies has been based on the ability to objectify abnormalities of nerve conduction resulting from radiculopathy and to identify the particular segment. Andersson and colleagues (717) in a consensus summary on the diagnosis and treatment of lumbar disc herniation concluded that, “although neurophysiological testing is frequently used to diagnose patients with radiculopathy associated with disc herniation, these tests are not clinically necessary to confirm the presence of radiculopathy.” However, neurophysiologic testing might be appropriate when the clinical situation is less clearly delineated and for differentiation of disc herniation from other neurologic disorders, such as neuropathy or peripheral nerve entrapment.

**7.2 Cervical Spine**

**7.2.1 History and Physical Examination**

Cervical spine pain is a common clinical condition affecting activities of daily living and QoL in people around the world. It can manifest as neck pain as well as pain in the shoulder, trapezius, scapular areas as well as the upper

extremities. The distinguishing features of cervical radicular pain and somatic referred pain are illustrated in Table 10 (7). The cervical pain secondary to the disc can extend to the upper back and head and is associated with referred pain into the upper extremity. In the patients where disc and facet related conditions co-exist, the differentiation due to the overlapping symptoms can be challenging. Radicular pain is most likely to travel below the elbow, and somatic referred pain is most often limited to above the elbow, but radicular pain may be restricted to the upper back or shoulder girdle, and somatic pain may radiate below the elbow (134,373). In contrast to the lumbar spine, paresthesia is considered to be more valid than the distribution of pain. The distribution of paresthesia in the hand is also considered more valid than the distribution of paresthesia in the forearm. In addition, paresthesia, with or without pain, occurs in 90% of patients with surgically proven radiculopathy due to disc prolapse (498,718). Approximately 45% of patients are unable to localize the paresthesia to a distinct region; and they present with diffuse, nondermatomal symptoms. In general, paresthesia affecting the thumb or index finger is attributed to the C6 dermatome; the middle finger, with or without involvement of the index finger, is assigned to the C7 dermatome; and the little finger is assigned to the C8 dermatome (Fig. 15) (7).

Assessment of pain in the cervical region is based on a patient’s history and an extensive physical examination which includes a neurological examination; motor examination; sensory examination; reflex assessment; application of provocative maneuvers, including Spurling’s neck compression test, shoulder abduction test, neck distraction test, Lhermitte sign, Hoffman sign, and Addison’s test (719).

Table 11 shows the signs and symptoms of nerve root compression in the cervical region (7,314). Rubinstein and van Tulder (703), in a best evidence review, showed that a positive Spurling’s, traction/neck distraction, and Valsalva can be

Table 10. Distinguishing features of cervical radicular pain and somatic referred pain.

	Somatic Pain	Radicular Pain
Causes	Facet joint pain Myofascial syndrome Discogenic pain	Disc herniation Annular tear Spinal stenosis
Symptoms Quality	Deep Aching Poorly localized Neck worse than arm No paresthesia Covers a wide area No radicular or shooting pain	Sharp Shooting Well localized Arm worse than neck Paresthesia are very reliable Well defined area Radicular distribution
Modification	Worse with extension Better with flexion No radicular pattern	Worse with flexion Better with extension Radicular pattern
Radiation	Neck to head, shoulder blades, upper back, radiation below elbow – unusual, no radicular pain	Follows nerve root distribution, radiation below elbow common, radicular and shooting pain
Signs		
Sensory alterations	Uncommon	Probable
Motor changes	Only subjective weakness Atrophy is rare	Objective weakness Atrophy may be present
Reflex changes	None	Commonly expressed but seen occasionally

Source: Manchikanti L, et al. Neck and cervical radicular pain. In: Manchikanti L, Christo PJ, Trescot AM, Falco FJE (eds). *Clinical Aspects of Pain Medicine and Interventional Pain Management: A Comprehensive Review*. ASIPP Publishing, Paducah, KY, 2011, pp 35-60 (134).

used to establish a diagnosis of cervical radiculopathy. In a systematic review, the same authors found that no single provocative test had both a high sensitivity and high specificity (720). The Spurling's test, neck traction test (lifting the head and relieving pain), and Valsalva maneuver were found to be highly specific.

The other existing literature appears to support the high specificity, but indicates low sensitivity, and good to fair inter-examiner reliability for Spurling neck compression test, the neck distraction test, and shoulder abduction (relief test) (721). For Hoffman's sign, the existing literature does not address inter-examiner reliability, but appears to indicate fair sensitivity and fair to good specificity (719). Numbness in the upper limb is a reasonably reliable sign (722), even though it is not a universal feature in patients with radiculopathy. The prevalence rate of numbness has varied significantly from 24% to 48%, and 60% to as high as 86% (723). Numbness is most often seen in the C6 and C7 dermatomes, indicating the most frequent involvement of these nerve roots. The predictive validity of numbness was calculated to be 0.7. Consequently, Wainner and Gill (724) stated that with regard to cervical radiculopathy, many investigators believe that, "given the paucity of evidence, the true value of the clinical examination is unknown at this time."

Along the same lines, in a manuscript published in 2018, Thoomes et al (373) described the findings of a systematic review examining the value of physical tests in diagnosing cervical radiculopathy. They identified 5 diagnostic accuracy studies; however, only Spurling's test was evaluated in more than one study, showing a high specificity ranging from 0.89 to 1.00, with sensitivity ranging from 0.38 to 0.97. They also showed that no studies were found that assessed the diagnostic accuracy of widely used neurological tests such as key muscle strength, tendon reflex-

es, and sensory impairments. They concluded that there is limited evidence for the accuracy of physical examina-

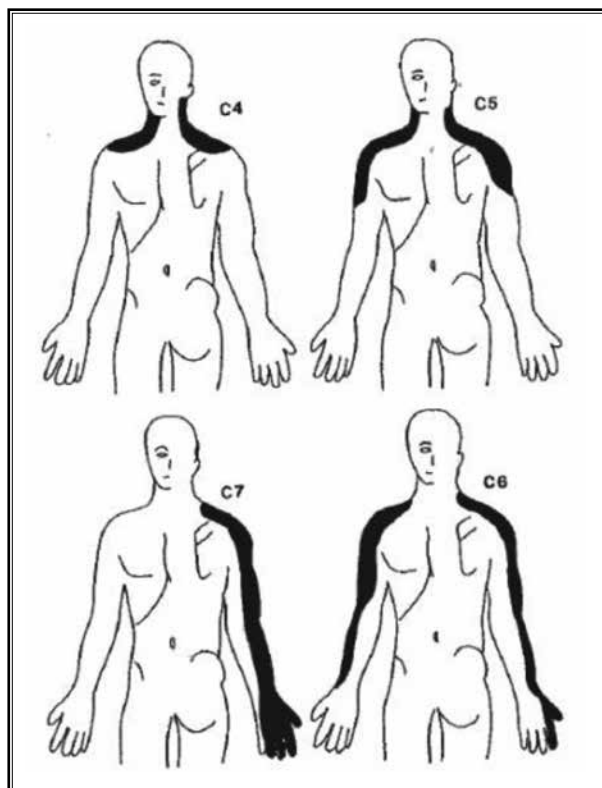


Fig. 15. Dermatome distribution of C4, C5, C6, C7 spinal nerves.

Source: Manchikanti L, et al. Neck and cervical radicular pain. In: Manchikanti L, Christo PJ, Trescot AM, Falco FJE (eds). *Clinical Aspects of Pain Medicine and Interventional Pain Management: A Comprehensive Review*. ASIPP Publishing, Paducah, KY, 2011, pp 35-60 (134). Reproduced with permission from authors and *Pain Physician* journal.

Table 11. Signs and symptoms of nerve root compression of the cervical region.

Root Involvement	Location of Lesion	Referred Pain	Motor Dysfunction	Sensory Dysfunction	Reflex Changes
C5	C4/5	Shoulder and upper arm	Shoulder muscles (deltoid-supraspinatus-infraspinatus) ↓ abduction and external rotation	↓ Upper and lateral aspect of the shoulder	↓ Biceps reflex
C6	C5/6	Radial aspect of forearm	Biceps and brachialis muscles ↓ flexion of the elbow and supination	Radial aspect of forearm	↓ Thumb reflex and brachioradialis reflex
C7	C6/7	Dorsal aspect of forearm	Triceps muscle ↓ extension of the elbow	↓ Index and middle digits	↓ Triceps reflex
C8	C7/T1	Ulnar aspect of forearm	Intrinsics of the hand ↓ adduction and abduction	↓ Ring and little digits	No change

Source: Manchikanti L, et al. Neck and cervical radicular pain. In: Manchikanti L, Christo PJ, Trescot AM, Falco FJE (eds). *Clinical Aspects of Pain Medicine and Interventional Pain Management: A Comprehensive Review*. ASIPP Publishing, Paducah, KY, 2011, pp 35-60 (134).

tion tests for the diagnosis of cervical radiculopathy. They further stated that when consistent with patient history, clinicians may use a combination of Spurling's, axial traction, and an arm squeeze test to increase the likelihood of a cervical radiculopathy, whereas as a combined result of 4 negative neurodynamic tests (upper limb, neurodynamic test, arm squeeze test, shoulder abduction (relief) test, and traction-distraction test) and an arm squeeze test could be used to rule out the disorder.

### **7.2.2 Imaging**

In reference to imaging, Rubinstein and van Tulder (703), in a best evidence review of diagnostic procedures for neck and low back pain, concluded that in patients 50 years of age or older, plain spinal radiography together with standard laboratory tests are highly accurate in identifying the underlying systemic disease; however, plain radiography is not a valuable tool for nonspecific neck pain. They also showed that no systematic reviews were identified which examined the diagnostic accuracy of diagnostic imaging in those with neck pain.

When applicable, the American College of Radiology recommends a cervical spine series of x-rays as an initial study including lateral, anteroposterior, and oblique views. Disc-space narrowing, subchondral sclerosis, and osteophyte formation can be evaluated on lateral views. Attention to comparing disc height at one level to adjacent levels as well as foraminal stenosis can be pertinent in some cases (725,726). CT imaging may be required to visualize C7 adequately. Flexion and extension and lateral bending films can be used to diagnose instability.

Based on the above discussion, plain radiography is not of much significant use in neck pain or radiculopathy. Myelography is an invasive and stressful investigation. This can show the deformations produced by intradural, dural, and some extradural lesions of the cervical vertebral canal. However, it does not demonstrate a lesion directly, and it demonstrates those affecting the lateral reaches of the cervical spine nerves poorly, if at all (727). Conventional CT scan provides axial images, in which the lateral reaches of the intervertebral foramina can be seen. CT myelography is considered to be an accurate and reliable test and has proven to be superior to myelography in the diagnosis of cervical disc protrusions; however, it is an expensive and invasive test. MRI is the choice of imaging in the modern era, replacing myelography, CT scan, and CT myelography. MRI is considered to be as accurate as CT myelography for detecting cervical nerve root com-

pression, even though it may be slightly inferior for detecting bony impingement of nerve roots (545,728). As observed with MRI, the prevalence of numerous abnormalities of the cervical spine in asymptomatic individuals is a concern (546,728,729). Boden et al (526) demonstrated in a study of asymptomatic subjects, 10% of patients under age 40 had disc herniations, and in patients over 40, 20% have foraminal stenosis and 8% had disc herniations. Hence, a diagnosis of cervical radicular pain is considered definite only after careful evaluation and corroboration of history, physical examination, imaging, electrodiagnostic and in some cases, diagnostic injectional studies.

### **7.2.3 Neurophysiologic Testing**

Neurophysiologic testing with electromyography and nerve conduction studies offers no advantage in radiculopathy. However, they are of significant value in the identification and differentiation of cervical radiculopathy with a peripheral lesion (549,730,731). According to Narayanaswami et al (730), the specificity of EMG for diagnosing radiculopathy has been reported to be 77%, while average sensitivity is 73%. This review further noted the sensitivity lower, 40% for mild to moderate radiculopathy and higher, 80% moderate to severe radiculopathy. The diagnosis changed in only 2/60 cases with the addition of clinical information. Intra-rater reproducibility was 80%, 87% for radiculopathy and 73% for normal studies. Inter-rater agreement was 63%, 70% for radiculopathy and 53% for normal studies. Inter-rater agreement for denervation was 90% and re-innervation was only 60%. They further noted the 2 to 3-week delay in the onset of the positive sharp waves and fibrillation potentials could yield falsely negative results done at onset of radiculopathy. In their 2011 clinical guidelines, the North American Spine Society notes insufficient evidence to make a recommendation for or against the use of electromyography for patients in whom the diagnosis of cervical radiculopathy is unclear after clinical examination and MRI (540).

The most common causes of cervical nerve root compression are cervical spondylosis, disc degeneration, disc herniation, and spinal stenosis. However, numerous other causes exist. Radiculopathy is a shooting, radiating pain that extends into the hand, or with paresthesia in forearm and hand, accompanied by objective neurologic signs with sensory loss, objective motor weakness, or hyporeflexia. In difficult cases, without radicular symptoms, diagnostic interventions applied include very rarely selective nerve root blocks, associated with high

risk, and more commonly, cervical provocation discography. Thus, for these guidelines cervical nerve root blocks have not been assessed.

In most cases, cervical disc herniation, spinal stenosis, radiculitis, and symptomatic spondylosis are diagnosed by imaging and neurophysiologic testing. However, when there is no correlation between radiologic pathology and clinical assessment, cervical provocation discography and cervical selective nerve root blocks have been recommended (127,732,733).

## 7.3 Thoracic Spine

### 7.3.1 History and Physical Examination

Assessment is based on history, physical examination, neurological examination, and imaging. Quite often it is difficult to identify the differences between somatic and radicular pain which is more complex in the thoracic spine than lumbar or cervical spine in that symptoms are similar in various conditions in the thoracic spine based on the description of neurological myotomes and dermatomes in multiple reviews and textbooks. Neurological assessment includes tone, coordination, proprioception, and abdominal and lower limb reflexes. As it is well known, the plantar reflex is particularly important in assessing spinal cord function. Dura mater signs include neck flexion and the slump test (135).

### 7.3.2 Imaging

In reference to imaging, age-related changes are extremely common in the thoracic spine in asymptomatic subjects. The great majority of patients with radiologic osteoarthritis are asymptomatic. A high prevalence of anatomic irregularities has been found in asymptomatic patients (734,735). Even though plain radiograph is the most common imaging technique, it does not satisfy the objective of identification of the cause of the pain and there is concern that plain radiographs are not sensitive enough to exclude disease. CT myelography is an alternative investigation in patients who have contraindications to MRI (736). MRI though commonly utilized, raises concerns that it is too sensitive, thus giving rise to false-positive findings. In most instances, it can reliably distinguish infection, fracture, and tumor (726).

### 7.3.3 Neurophysiologic Testing

The utility of electrophysiologic/electrodiagnostic studies have been based on the ability to objectify abnormalities of nerve conduction and electromyography

resulting from radiculopathy and to identify the particular segment.

Although the majority of patients who are diagnosed with thoracic spine pain due to the previously mentioned conditions, may undergo conservative modalities and treatments (737). These may also include noninvasive interventions, and are based on diagnostic imaging, as well as in some cases noninvasive diagnostic interventions (737).

In the cases of patients where further diagnostic procedures, separate from imaging need to be performed, may require diagnostic interventions with provocation discography to identify discogenic pain and/or controlled diagnostic facet joint nerve blocks to diagnose or eliminate facet joint pain (737).

## 8.0 THERAPEUTIC EPIDURAL INTERVENTIONS

### Key Question 6: Are the available therapeutic epidural injections and adhesiolysis in managing chronic spinal pain effective?

Epidural interventions are provided through caudal, interlaminar, and transforaminal approaches. Percutaneous adhesiolysis is provided through caudal, interlaminar and transforaminal approaches in the lumbar spine. Inherent variations, differences, advantages, and disadvantages applicable to all epidural interventions, including percutaneous adhesiolysis, with assessment of effectiveness and outcomes, all of the procedures are considered as separate entities. Furthermore, response is also considered separate, along with indications for various pathological conditions (disc herniation and/or radiculitis, central spinal stenosis, foraminal stenosis, post-surgery syndrome, and discogenic pain without disc herniation) which are variable. Consequently, outcomes are assessed based on pathology for each approach.

### 8.1 Evidence Review and Synthesis

Methodology is described in Section 2. Briefly, identification of systematic reviews and studies for the review, which included relevant RCTs and observational studies when indicated with description of appropriate outcomes and follow-up was performed. All the studies, including systematic reviews, RCTs, and observational studies must have included the primary outcome parameter of pain relief and other secondary outcomes such as functional status improvement. Short-term relief was considered as less than 6 months of improvement in pain and function, whereas at least one year of pain relief with improvement in functional status was considered as long-term improvement.





ing the efficacy and tolerability of the treatments for sciatica, concluded that epidural steroid was recommended as a good intervention due to superiority in reducing ODI. Further, in this manuscript, they also identified intravenous and subcutaneous anti-TNF- $\alpha$  as the optimal treatment for both acute and chronic sciatica patients.

Lewis et al (99,100) in a systematic review and network meta-analysis of comparative clinical effectiveness of management strategies for sciatica, including surgical interventions, concluded that this was the first manuscript comparing many different strategies for sciatica in the same systematic review and meta-analysis. Their findings supported the effectiveness of epidural injections in the same line as disc surgery and nonopioid medication.

Lee et al (753) comparing the nonsurgical treatments for patients with radicular pain from lumbosacral disc herniation concluded that epidural injection was strongly recommended with high degree of evidence and transforaminal approach was more strongly recommended than caudal approach.

Cho et al (155) also performed a systematic review of treatment outcomes for patients with failed back surgery syndrome and concluded that percutaneous adhesiolysis provided better improvement than spinal cord stimulation. Cho et al showed in this review significant evidence for both percutaneous adhesiolysis and spinal cord stimulation with a recommendation of Level A for epidural adhesiolysis for 6 to 12 months of pain relief and functional improvement and Level B for spinal cord stimulation.

Among the 47 systematic reviews, 3 systematic reviews addressed the questions related to placebo and active-control agents (56-58).

A single systematic review of high-quality by Manchikanti et al (56) evaluated if epidural injection of sodium chloride solution was a true placebo or it is an active control agent. In this systematic review, they also performed conventional dual arm and a single arm analysis. In this analysis, they used 20% improvement from baseline pain scores or disability as clinically significant parameter, even though in all other reviews, they used 50% improvement in pain and disability as the criterion standard. They included 8 trials meeting inclusion criteria, with 2 trials utilizing fluoroscopic imaging and one study utilizing ultrasound. With dual arm meta-analysis, there was no significant difference between epidural sodium chloride solution and epidural steroids with sodium chloride solution. However, with single arm analysis, both epidural saline and epidural steroids with saline were effective in reducing 20% of pain; however, only reducing disability scores by 10% to 12%. The authors concluded that both epidural saline

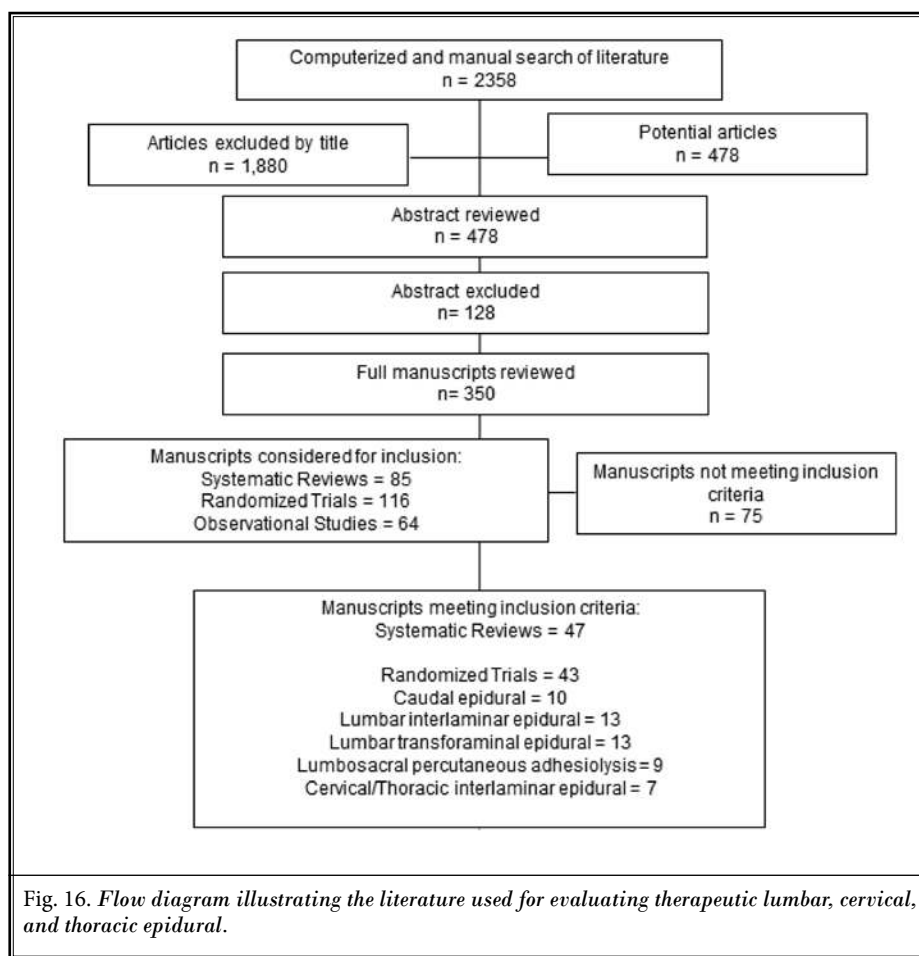


Fig. 16. Flow diagram illustrating the literature used for evaluating therapeutic lumbar, cervical, and thoracic epidural.

and epidural steroids with saline showed effect beyond placebo with strong evidence, that neither epidural saline, nor epidural steroids with saline or placebo and that both are effective.

One such systematic review and meta-analysis by Manchikanti et al (57) assessed the effectiveness of epidural bupivacaine, with or without steroids, administered for low back and lower extremity pain. It included 4 independent studies; one on interlaminar approach and three on transforaminal epidural injections, all of which were ranked as high-quality based on Cochrane review criteria and IPM-QRB criteria. In this review also, the authors utilized a conventional dual arm and single arm meta-analysis showing significant effectiveness of both bupivacaine and bupivacaine with steroids with a single arm analysis, even though both of them were similar with dual arm analysis. The review concluded that epidurally administered bupivacaine acts as an active agent rather than a placebo (Level I evidence), and that bupivacaine administered alone was almost equally effective as when administered with steroids (Level II evidence). These findings clearly show that local anesthetic is not a placebo and the approach in all the active-controlled trials with local anesthetic converting into placebo-controlled with conclusion of local anesthetics as ineffective leads to inappropriate conclusions and misinformation (67-69,80).

A similar systematic review and meta-analysis by Knezevic et al (58) of high-quality investigated the evidence supporting the effectiveness of epidural lidocaine, with or without steroids, in managing spinal pain. In this analysis, the authors utilized extensive methodologic quality assessment criteria, along with conventional dual arm and single arm meta-analysis. Of the 15 manuscripts meeting the inclusion criteria, 4 addressed caudal epidural injections, 2 lumbar transforaminal injections and 5 lumbar interlaminar epidural injections. The results showed similar improvements in pain and function with the epidural administration of lidocaine alone or with steroids, both for short-and long-term (Level II evidence). This study also once again demonstrated that utilizing single arm analysis clear effect of each modality was demonstrated with lidocaine, as well as lidocaine with steroids. It is inappropriate to judge that lidocaine is a placebo. They also showed lack of publication bias. Consequently, both had similar effectiveness, but translated into lack of effectiveness of any modality with negative conclusions. Once again, this study clearly shows that local anesthetic lidocaine is not placebo and it is inappropriate assessments performed

provides erroneous conclusions and misinformation.

Similar to the above manuscripts, a systematic review and meta-analysis by Lee et al (61), which was of moderate quality, assessed the effectiveness of epidural injections consisting of local anesthetic or saline with or without steroids for the management of lumbosacral disc herniation. The qualitative study included 14 manuscripts, and the quantitative study included 13 manuscripts. The included studies were considered as high-quality, but the evidence was deemed moderate due to inconsistencies and lack of single arm analysis. The study found that the addition of steroids to local anesthetic or saline provided better effectiveness compared to injections of local anesthetics or saline without steroid, at 6-month follow-up to one year, with no significant differences after one year.

Mesregah et al (64), in a moderate quality review, also evaluated the clinical effectiveness of interlaminar epidural injections of local anesthetic with or without steroids for managing chronic pain utilizing 4 studies available meeting inclusion criteria, they showed the addition of steroids to anesthetic injected was not associated with better pain and functional score outcomes compared with anesthetic injected alone in patients with chronic neck pain based on conventional dual arm analysis. Overall, the conclusions are similar to other systematic reviews shown above indicating local anesthetic lidocaine is not a placebo. Such conclusions are misleading and are misinformation.

Zhao et al (65) in a systematic review and conventional meta-analysis of moderate quality confirmed the similar effects associated with lidocaine alone versus in combination with steroids in the management of lumbar disc herniation and lumbar central spinal stenosis with the inclusion of 7 trials. These results again confirm the impressions shown above.

Bicket et al (66) in a moderate quality systematic review and meta-analysis evaluating the "control" injections in RCTs included 43 studies with 3,641 patients. Under the control injections, they included sodium chloride solution, as well as local anesthetic solutions. Nevertheless, they concluded that epidural nonsteroid injections may provide improved benefit compared with nonepidural injections on some measures. However, they have not performed a single arm analysis. They also have not utilized appropriate methodologic criteria. In addition, they utilized manuscripts which included epidural injections performed without fluoroscopy. Even then, in other manuscripts published by Cochrane review (68,69), one of the senior authors of the above

manuscript (66) as a coauthor claimed that due to lack of effectiveness of local anesthetics, they were considered as placebo, providing conflicting and contradicting information, leading to inappropriate conclusions and misinformation to communities in general.

Manchikanti et al (76) in a moderate quality review also published a comparison of efficacy of saline, local anesthetics, and steroids in epidural and facet joint injections for the management of spinal pain in a systematic review of RCTs; however, without meta-analysis. They included a total of 13 trials. They showed the effectiveness of local anesthetic alone and local anesthetic with steroids to be equally effective except in lumbar disc herniation, where the superiority of local anesthetic with steroids was demonstrated in short-term follow-up, whereas there was no difference with long-term follow-up.

Shanthanna et al (102) in an extensive high-quality systematic review and meta-analysis of RCTs assessed the effectiveness of the addition of corticosteroids to local anesthetics for chronic noncancer pain injections. They included 71 trials and reached the conclusion that addition of corticosteroids to local anesthetics has only small benefits and a potential for harm. They further concluded that injection of local anesthetic alone could be therapeutic, beyond being diagnostic. They recommended that a shared decision based on patient preferences should be considered and high doses must be avoided, along with a series of steroid injections.

Multiple systematic reviews were conducted assessing the effectiveness beyond comparison of local anesthetic alone or local anesthetic with steroids. Among these, 2 moderate quality systematic reviews (60,76) assessed multiple spinal regions. The description of the manuscript by Manchikanti et al (76) is provided above. The results applied to multiple spinal regions. Similarly, Kaye et al (60) assessed the efficacy of epidural injections in managing chronic spinal pain utilizing a best evidence synthesis with assessment of multiple spinal regions. This systematic review was performed, however, without meta-analysis. It was considered as a moderate quality publication. In this review, they included 52 RCTs with a placebo control or an active control design meeting inclusion criteria. The results showed that the evidence in managing lumbar disc herniation or radiculitis was Level II for long-term improvement, either with caudal, interlaminar, or transforaminal epidural injections with no significant differences among the groups. The evidence was Level II for long-term management of cervical disc herniation with interlaminar epidural

injections. The evidence was Level II to III in managing thoracic disc herniation with an interlaminar approach. The evidence was Level II for caudal and lumbar interlaminar epidural injections with Level III evidence for lumbar transforaminal epidural injections for lumbar spinal stenosis. The evidence was Level III for cervical spinal stenosis management with interlaminar epidural injection. They also showed evidence of Level II for axial or discogenic pain without facet arthropathy or disc herniation treated with caudal or lumbar interlaminar epidural injections in the lumbar region, whereas it was Level III in the cervical region treated with cervical interlaminar epidural injections. The evidence for post-lumbar surgery syndrome was Level II with caudal epidural injections and for post cervical surgery syndrome. It was Level III with cervical interlaminar epidural injections.

Among the multiple systematic reviews available, the majority were conducted in the lumbar spine. In addition, systematic reviews included prevention of surgery with epidural injection administration, comparisons between steroids (particulate vs. nonparticulate steroids), the role of etanercept, and comparative analysis of techniques.

Lee et al (62) conducted a systematic review of 27 studies to compare the benefits of transforaminal versus interlaminar epidural injections in patients with lumbosacral disc herniation in this moderate quality systematic review. Despite the low-grade evidence due to the inconsistency and imprecision of the included studies, the authors reported more favorable, though not significant, outcomes for the transforaminal epidural for short-term (2 weeks to 1 month) and long-term (4 to 6 months) pain reduction, as well as short- and long-term functional improvement.

Similar to the above review, Lee et al (63), in a moderate quality systematic review and meta-analysis, compared clinical efficacy of transforaminal and caudal epidural steroid injection in lumbar and lumbosacral disc herniation. In this assessment, they utilized 6 studies, showing 4 articles supporting the superiority of transforaminal epidural injection over caudal epidural injection, one article showed no significant difference, and one article supported the superiority of caudal epidural steroid injection to transforaminal epidural injection. Even though they concluded that meta-analysis showing short- and long-term trends towards better clinical efficacy with transforaminal epidural injections than caudal epidural injections, there was no statistical significance, and the evidence level was low because of inconsistencies and imprecisions.

Manchikanti et al (75) performed a moderate quality systematic review without meta-analysis assessing short and long-term relief for lumbar disc herniation. With literature search up to June 2013, they included 23 RCTs of high and moderate methodologic quality for analysis. The results showed that evidence for the efficacy of all 3 approaches for epidural injection under fluoroscopy was strong for short-term (less than 6 months) and moderate for long-term (greater than 6 months) based on the Cochrane rating system with 5 levels of evidence best evidence synthesis.

Manchikanti et al (81) performed a comparative systematic review and meta-analysis assessing epidural injections for lumbar radiculopathy and spinal stenosis in response to a publication by Chou et al (80). Chou et al converted all active-controlled trials into placebo-control with inappropriate conclusions as others (67-69). In a high-quality comparative systematic review and meta-analysis, Manchikanti et al (81) included 39 RCTs with 9 placebo-controlled trials evaluating epidural corticosteroid injections, either with sodium chloride solution injection or bupivacaine compared to placebo injections. In addition, they used 12 studies comparing local anesthetic alone to local anesthetic with steroids. They also performed a meta-analysis of 5 studies utilizing sodium chloride or bupivacaine with steroid showing lack of efficacy. A comparison of lidocaine to lidocaine with steroids in 7 studies showed significant effectiveness from baseline to long-term follow-up periods. Meta-analysis showed a similar effectiveness for pain and function without noninferiority of lidocaine compared to lidocaine with steroids at 3 months and 12 months. This review highlighted the differences between appropriate and inappropriate analysis and reviewers of systematic reviews downgrading the manuscripts without appropriate information and most importantly, utilizing lidocaine as a placebo.

Manchikanti et al (77) in a moderate quality systematic review assessed the efficacy of epidural injections in the treatment of lumbar central spinal stenosis. With assessment through 2014, the author showed Level II evidence for long-term improvement for caudal and lumbar interlaminar epidural injections, whereas they showed Level III evidence for transforaminal epidural injections for short-term improvement only. They also concluded that the interlaminar approach appears to be superior to the caudal approach and the caudal approach appears to be superior to the transforaminal approach.

Bhatia et al (754) in a moderate quality systematic review and meta-analysis assessed the effectiveness of

transforaminal epidural steroid injections for treating lumbosacral radicular pain from herniated intervertebral discs. They included 8 RCTs. They concluded that transforaminal epidural steroids provide modest analgesic benefit at 3 months in patients with lumbosacral radicular pain secondary to herniated intervertebral discs, but they have no impact on physical disability or incidence of surgery. There was a high degree of heterogeneity among the publications.

Liu et al (752) evaluated the effectiveness of transforaminal versus caudal routes for epidural steroid injections in managing lumbosacral radicular pain, in a moderate quality systematic review and meta-analysis in 2016. They utilized 6 prospective and 2 retrospective studies involving 664 patients. They concluded that both transforaminal and caudal approaches are effective in reducing pain and improving functional scores, and they also demonstrated similar effectiveness in the management of lumbosacral radicular pain, in contrast to Lee et al (63).

Meng et al (750) evaluated epidural injections with or without steroids in managing chronic low back pain secondary to lumbar spinal stenosis in a low-quality systematic review. Overall, they included 13 RCTs; however, some of them were duplicates. They concluded that both epidural injections with steroids or with local anesthetic alone provided significant pain relief and functional improvement in managing chronic low back pain secondary to lumbar spinal stenosis, and the inclusion of steroids confers no advantage compared to local anesthetic alone. This is another manuscript emphasizing that lidocaine is not a placebo.

Sharma et al (743) assessed the effectiveness and risks of fluoroscopically guided lumbar interlaminar epidural steroid injections in a systematic review with comprehensive analysis of published data in a low-quality systematic review. They assessed 71 primary studies. They reported that there were no explanatory or placebo-controlled studies and all pragmatic studies identified were of low-quality, yielding evidence comparable to observational studies. However, they have not performed methodologic quality analysis and also inappropriately assessed the RCTs converting them into active-controlled RCTs. Nevertheless, they concluded that the body of evidence regarding the effectiveness of fluoroscopically guided interlaminar epidural steroid injections is of low-quality. They also concluded that studies suggested a lack of effectiveness of fluoroscopically guided lumbar interlaminar epidural steroid injections in treating primarily axial pain, regardless of etiology.



They further commented that most studies on radicular pain due to lumbar disc herniation and stenosis do, however, report statistically significant short-term improvement in pain. Their analysis and conclusions are rather confusing and indicates their clear bias towards transforaminal epidural injections.

Smith et al (742) described transforaminal injections of steroids for treatment of radicular pain performed a comprehensive review of the published data. However, they considered it to be a comprehensive systematic review; however, it appears to be a narrative review or very low-quality systematic review. They concluded that there was strong evidence that lumbar transforaminal epidural injection of steroids is an effective treatment for radicular pain due to disc herniation. There is 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. They also made a statement that lumbar transforaminal injection of nonparticulate steroids is as effective as injection with particulate steroids. Apart from lack of methodologic quality assessment and lack of meta-analysis, their bias is clear in favor of transforaminal epidural injections.

The same group of authors from the Spine Intervention Society (SIS) performed a systematic review with comprehensive analysis of the published data of the effectiveness and risks of nonimage guided lumbar interlaminar epidural steroid injections. With inclusion of a large number of publications (92), they concluded that in patients with lumbar radicular pain secondary to disc herniation or neurogenic claudication due to spinal stenosis, nonimage guided lumbar interlaminar epidural steroid injections appear to have clinical effectiveness limited to short-term pain relief. Therefore, in a contemporary medical practice, these procedures should be restricted to the rare settings where fluoroscopy is not available. However, these results are similar to the results they published with fluoroscopy guided lumbar interlaminar epidural steroid injections (743) raising multiple questions of their own biases.

Zhai et al (738) evaluated epidural injections with or without steroid in managing chronic low back and lower extremity pain with a meta-analysis of RCTs in a low-quality assessment. The authors utilized multiple duplicates and have not performed single arm analysis. Nevertheless, this meta-analysis confirms that epidural injections of local anesthetic with or without steroids have beneficial but similar effects in the treatment of patients with chronic low back and lower extremity pain.

Yang et al (739) assessed epidural steroid injection versus conservative treatment for patients with lumbosacral radicular pain with a meta-analysis of RCTs in a moderate quality publication. With the inclusion of 6 RCTs, they concluded that the use of epidural steroid injections is more effective for alleviating lumbosacral radicular pain than conservative treatment in terms of short-term and intermediate-term. In addition, the patients also reported more successful outcomes after receiving epidural steroid injections when compared to conservative treatment. However, this effect was not maintained at long-term follow-up.

Wei et al (740) published comparison of transforaminal versus interlaminar epidural steroid injections in low back pain with lumbosacral radicular pain in a moderate quality meta-analysis of the literature in 2016. They included 931 patients from 9 RCTs and 4 observational studies. They concluded that transforaminal epidural steroid injection to manage low back pain provided superior short-term pain relief and equal functional improvement when compared to interlaminar epidural injection. There was no statistically significant difference between groups with regard to procedure, frequency, surgery rate, and ventral epidural spread.

Pairuchvej et al (744) performed a systematic review and meta-analysis of moderate quality comparing short and mid-term outcomes of lumbar transforaminal epidural injections with preganglionic and postganglionic approach in lumbosacral radiculopathy published in 2018. They concluded that postganglionic epidural steroid injection has a statistically significant higher chance of effectiveness when compared to preganglionic epidural steroid injection. They concluded that in terms of pain scores and complications, there were no statistically significant differences between the 2 groups. The results were generally homogenous and with little publication bias, they believed that these should be generalizable. Due to multiple complications related to transforaminal epidural injections with particulate steroids, infraneural and supraneural approaches have been suggested. Preganglionic refers to supraneural approach and postganglionic refers to infraneural approach.

Manchikanti et al (70) performed a systematic review without meta-analysis for epidural injections to assess if they provide long-term relief of neck and upper extremity pain. They included 7 manuscripts meeting inclusion criteria. Of these, 4 assessed the role of interlaminar epidural injections for managing disc herniation or radiculitis, and 3 assessed these injections for managing central spinal stenosis, discogenic pain without facet

joint pain, and post-surgery syndrome. They concluded that with qualitative best evidence synthesis, there is Level II evidence for the efficacy of cervical interlaminar epidural injections with local anesthetic with or without steroids, based on at least one high-quality relevant RCT in each category for disc herniation, discogenic pain without facet joint pain, central spinal stenosis, and post-surgery syndrome.

In contrast to the mostly positive systematic reviews, 2 systematic reviews with one update (67,69,80) have shown lack of effectiveness of epidural steroids. They all showed lack of effectiveness of epidural steroids. The common denominator being conversion of active-controlled trials into placebo-controlled trials and considering local anesthetic as placebo. They also have additional issues with their publications, including conflicts of interest, publication bias, and inappropriate data synthesis. Manchikanti et al (81) performed a comparative analysis of Chou et al's publication (80) which also applies to other systematic reviews showing their deficiencies and providing contrary results.

Bui and Bogduk (749) performed a systematic review of the effectiveness of CT guided, lumbar transforaminal injection of steroids in a low-quality systematic review. They were only able to include 4 studies with success rate being reported between 34% and 62%. They concluded that evidence-base for CT guided lumbar transforaminal injection of steroids is meager. Further, this intervention is not more effective than fluoroscopically guided injection and is not demonstrably safer. The authors also commented that with using techniques of "As Low As Reasonably Achievable" (ALARA) fluoroscopy times are 5 times less than that of low dose CT protocol and 18 to 40 times less than a standard CT protocol.

Chang Chien et al (615) in a systematic review of comparative studies for lumbosacral radicular pain of transforaminal versus interlaminar approaches to epidural steroid injections, in a low-quality systematic review without meta-analysis utilized 5 prospective studies with 249 patients. Their results showed that only in short-term the results were in favor of transforaminal with 15% difference compared to interlaminar epidural injections for pain relief. However, there was no difference at 1 or 6 months. They concluded that both transforaminal epidural steroid injections and interlaminar epidural steroid injections are effective in reducing pain and improving functional scores. In addition, transforaminal epidural steroid injections provided nonclinically significant superiority to interlaminar epidural steroid injections only at 2-week follow-up. Further, based on 2

studies, interlaminar epidural steroid injection provided nonclinically significant superiority to transforaminal epidural injections in function improvement.

Arirachakaran et al (756) assessed comparative outcomes of epidural steroids versus placebo after lumbar discectomy in lumbar disc herniation in a systematic review and meta-analysis of RCTs of moderate quality. They included a total of 12 studies and analyzed the pooled data with 9 studies having undergone conventional discectomy and 3 studies having undergone minimally invasive surgery discectomy, with a total of 1,006 patients. They concluded that there were no significant differences in reference to morphine consumption and hospital stay or complications between the 2 groups. This systematic review is a very unusual review and the studies they included are also extremely unusual. Epidural steroids are not recommended following the surgery in the immediate intraoperative period. This manuscript provides an opportunity to discourage such usage.

Jing et al (667) assessed efficacy and safety of etanercept in the treatment of sciatica in a systematic review and meta-analysis which was of moderate quality. They concluded that etanercept treatment was associated with a significantly reduced pain in leg and back compared to placebo and may possibly improve leg pain relief compared to steroids, but failed to improve ODI. They also concluded that etanercept should be recommended for sciatica with caution because of heterogeneity. However, the drug is not approved or available in the US for epidural usage purposes.

Three systematic reviews were performed assessing particulate and nonparticulate steroids in epidural injections (745,747,748).

Feeley et al (747) performed a systematic review and meta-analysis of moderate quality assessing particulate and nonparticulate steroids in spinal epidurals. They concluded that particulate steroids were not demonstrably better in relieving pain compared to their nonparticulate counterparts. These conclusions are based on 4 studies with 300 participants.

Mehta et al (745) in a systematic review of moderate quality assessed efficacy of particulate versus nonparticulate corticosteroids in epidural injections. From inclusion of multiple heterogenic studies, they concluded that there was no statistically significant difference in terms of pain reduction or improved functional outcome between when performing cervical transforaminal epidural injection, whereas lumbar radiculopathy due to stenosis or disc herniation, transforaminal epidural using particulate versus nonparticulate was equivocal

in reducing pain and improving function. Consequently, the authors recommended nonparticulate steroids.

Makkar et al (748) published a systematic review and meta-analysis of the current literature of particulate and nonparticulate steroids for transforaminal epidural injections. In this analysis, they included 7 studies comprising 3,542 patients in the particulate group and 856 patients in the nonparticulate group. The results showed better improvement with Visual Analog Scale (VAS) by 0.53 in the particulate group compared to the nonparticulate group. However, nonparticulate group had a larger proportion of patients with more than 50% pain relief than the particulate group. They concluded that since the use of particulate steroids seems to be associated with slightly better VAS scores only, clinicians need to weigh their clinical relevance in light of complications and US Food and Drug Administration (FDA) recommendations on the use of particulate steroids. However, FDA recommendation is for all types of steroids. Consequently, it appears that all 3 studies show there was no significant difference; however, all 3 systematic reviews included cervical transforaminal epidural injections, even though Makkar et al (748) included predominantly lumbar transforaminal epidural injections. Considering that local anesthetics alone are equally effective to particulate steroids in most instances, these differences are minimal, specifically with clinical relevance.

Helm et al (83) in a recent publication evaluated transforaminal epidural steroid injections in a systematic review and meta-analysis, which was of high-quality. In this analysis, they included 18 RCTs with 11 trials evaluating radicular pain due to disc herniation. They also performed single arm meta-analysis in addition to conventional dual arm analysis. They showed Level I evidence for use of transforaminal epidural injections for radicular pain from disc herniations. However, the evidence was Level IV for central stenosis, failed back surgery syndrome, and Level V for radicular pain from foraminal stenosis and for axial pain.

There have been multiple publications of systematic reviews with percutaneous adhesiolysis. The effectiveness of percutaneous adhesiolysis for managing chronic pain due to lumbar central spinal stenosis was examined in a high-quality systematic review and meta-analysis (9 studies) by Manchikanti et al (73). The authors found Level II evidence for both the short- and long-term improvement in pain and function in response to the intervention. The authors in this manuscript also utilized conventional dual and single arm meta-analysis illustrating effectiveness with both types of analysis.

Another high-quality systematic review and meta-analysis by Manchikanti et al (72) looked at the efficacy of percutaneous adhesiolysis in the treatment of chronic refractory lower back and lower extremity pain due to post-laminectomy surgery syndrome. Their analysis included 4 systematic reviews and 4 RCTs. All but one systematic review, which was deemed low-quality, demonstrated Level I evidence for the efficacy of percutaneous adhesiolysis in this patient population.

Manchikanti et al (74) in a systematic analysis of findings of reviews looked at various systematic reviews performed on the subject of percutaneous adhesiolysis and determined that except for a few of them, one particular systematic review by Brito-García et al (87) was inappropriately performed. Manchikanti et al (74) in this manuscript also reexamined the evidence and performed the systematic review of 4 RCTs utilized in the previous systematic reviews and concluded that there was Level I evidence for percutaneous adhesiolysis based on significant evidence from published RCTs and 3 of the 4 systematic reviews in post-lumbar surgery syndrome.

Systematic reviews were also performed to assess surgery sparing effect of epidural injections, both in lumbar spine and cervical spine. Bicket et al (271) in a review of 26 randomized controlled studies with meta-analysis showed that patients receiving epidural steroid injections were less likely to undergo surgery than those who received control treatment, providing moderate evidence. The results also showed that evidence suggested that between one-third and half of patients considering surgery who undergo epidural steroid injection can avoid surgery; however, with low level of evidence.

Koltsov et al (272) in assessment of incidence and risk factors of subsequent surgery in patients receiving lumbar epidural steroid injections showed that within 6 months, 12.5% of epidural steroid injection patients underwent lumbar surgery, whereas by one year, 16.9% had surgery, and by 5 years, 26.1% had surgery. The authors concluded that in the long-term, more than one out of every 4 patients undergoing epidural steroid injection for lumbar herniation or stenosis subsequently had surgery, and nearly one of 6 had surgery within the first year. While the authors attempted to present a negative view because of surgical orientation, avoiding surgery in 76% of the patients, specifically on a long-term basis, is considered phenomenal. These authors also started with the negative connotation that up to 30% of patients had surgery within one to 2 years following lumbar epidural steroid injection and up to 49% had surgery within 5 years (273-277), with roughly half

of patients requiring a second epidural steroid injection to achieve their surgery-sparing results (273,274,278) implying that one epidural steroid injection must provide total relief, similar to surgery, or better. Further, all the studies assessing these factors also misunderstand active-controlled trials to placebo-controlled trials as do Cochrane reviews and other academicians.

In contrast, in the cervical spine, Kleimeyer et al (188) from the department of orthopedic surgery, in the assessment of cervical epidural steroid injections and the incidence of subsequent surgery, showed that within 6 months of cervical epidural steroid injections, 11.2% of patients underwent surgery, increasing to 14.5% by one year, and 22.3% by 5 years. Overall, they concluded that following cervical epidural steroid injections, over 1 in 5 patients underwent surgery within 5 years, showing 75% response rate as in lumbar spine, again which will be considered as excellent improvement and outcomes.

### 8.3 Randomized Controlled Trials

Based on extensive search criteria, numerous manuscripts were identified and considered for inclusion. Of the 180 manuscripts of epidural interventions, including adhesiolysis trials, identified, multiple trials were excluded for not meeting inclusion criteria. Only studies performed under fluoroscopic guidance with a minimum of 6 months follow-up were included. Subsequently, 43 trials and 2 observational studies were included. Only fluoroscopic guided procedures were utilized, based on philosophy that fluoroscopy provides the best results as described in the literature and also preferred method from Centers for Medicare and Medicaid Services (CMS), and other medical policies. While ultrasound is evolving, it continues to be in infancy with comparative studies. Further, 6-month follow-up as minimum was utilized as it indicates long-term follow-up of the patients with epidural injections, mostly multiple procedures, rather than expecting a single procedures and expecting to last on a long-term basis. It becomes difficult to extrapolate the short-term results to long-term; consequently, 6-month follow-up was utilized. Further, multiple manuscripts which have been excluded from the inclusion have been listed with description of characteristic features in manuscripts by Kaye et al (60) and Knezevic et al (58). Knezevic et al (58) also showed lack of publication bias.

#### 8.3.1 Methodological Quality Assessment

A methodological quality assessment of the RCTs meeting inclusion criteria was carried out utilizing Cochrane review criteria (154) and IPM-QRB criteria (153)

as shown in Appendix Tables 2 and 3. Nonrandomized studies were assessed utilizing IPM-QRBNR (157) as shown in Appendix Table 4.

### 8.4 Caudal Epidural Injections

Thirty-three studies examined caudal epidural injections for effectiveness (757-789). Following the application of our criteria for inclusion, 10 RCTs (765-770,779,783,784,786) met the inclusion criteria with procedures being performed under fluoroscopic guidance and with a minimum of 6 months of follow-up, with publication of appropriate outcome parameters (765-770,779,783,784,786). Twenty-three studies were excluded due to many of them being performed without fluoroscopy, and some studies describing short-term outcomes or inadequate reporting. Multiple studies published at various intervals were utilized as one study with the final publication. Consequently, multiple studies utilized in previous systematic reviews failed to meet the inclusion criteria (56,57,67,69,75-77). Using Cochrane and IPM-QRB criteria, 6 of the 10 studies were determined to be high-quality (762,765-767,770,784) and 4 of 10 were determined to be moderate quality (769,779,783,786). Appendix Table 5 shows methodologic quality assessment utilizing Cochrane review criteria, Appendix Table 6 shows methodologic quality assessment utilizing IPM-QRB criteria and Table 12 shows descriptive characteristics of caudal epidural injections.

Manchikanti et al conducted 4 studies (762,765-767). They used an identical protocol in each study: an active control design with a 2-year follow-up. These studies evaluated the efficacy of epidural injections in 2 groups: one group received a local anesthetic only and the other group received a local anesthetic with a steroid. In these 4 studies, a total of 480 patients were evaluated for one of the following conditions: lumbar disc herniation; lumbar discogenic pain without facet joint or sacroiliac joint pain; lumbar central spinal stenosis; and lumbar post-surgery syndrome.

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

Table 12. Characteristics of fluoroscopic randomized trials of caudal epidural injections.

Study Characteristics Methodological Quality Scoring	Participants and Interventions	Outcome Measures	Pain Relief and Function						Results			Comments
			3 mos.	6 mos.	12 mos.	24 mos.	Short-term ≥ 6 mos	Long Term		24 mos.		
								> 6 mos.	≥ 12 mos.			
Manchikanti et al, 2012 (765) RA, AC, F Disc herniation or radiculopathy Quality Scores: Cochrane = 12/13 IPM-QRB = 44/48	Total = 120 Lidocaine = 60 Lidocaine with steroids = 60 Lidocaine vs lidocaine mixed with steroid Number of injections = 1 to 5	NRS, ODI, employment status, opioid intake Responsive category was defined as at least 3 weeks of significant improvement with the first 2 procedures. Significant improvement: 50% improvement in pain and function.	Overall: LA 62% vs LA with steroid 72% Responsive: LA 77% vs LA with steroid 80%	Overall: LA 72% vs LA with steroid 73% Responsive: LA 87% vs LA with steroid 86%	Overall: LA 67% vs LA with steroid 72% Responsive: LA 85% vs LA with steroid 84%	Overall: LA 60% vs LA with steroid 65% Responsive: LA 77% vs LA with steroid 76%	Lidocaine & lidocaine with steroid effective	Lidocaine & lidocaine with steroid effective	Lidocaine & lidocaine with steroid effective	<ul style="list-style-type: none"> <li>• Positive double-blind randomized trial with superiority of steroids with average pain relief for steroids. Overall improvement with local anesthetic alone or with steroids was similar.</li> <li>• Nonresponsive patients were also similar with 13 and 10 in local anesthetic only and with steroids group.</li> <li>• Over a period of 2 years, on average, a total of 5-6 injections were provided.</li> </ul>		
Manchikanti et al, 2012 (767) RA, AC, F Central spinal stenosis Quality Scores: Cochrane = 12/13 IPM-QRB = 44/48	Total = 100 Lidocaine + steroid = 50 Lidocaine 0.5% vs. lidocaine mixed with steroid. Average number of injections = 5 to 6 for 2 years	NRS, ODI, employment status, opioid intake Responsive category was defined as at least 3 weeks of significant improvement with the first 2 procedures. Significant improvement: 50% improvement in pain and function.	Overall: LA 58% vs LA with steroid 48% Responsive: LA 78% vs. LA with steroid 65%	Overall: LA 54% vs LA with steroid 50% Responsive: LA 73% vs. LA with steroid 68%	Overall: LA 44% vs LA with steroid 46% Responsive: LA 54% vs. LA with steroid 62%	Overall: LA 38% vs LA with steroid 44% Responsive: LA 51% vs LA with steroid 57%	Both treatments effective	Both treatments effective	Both treatments effective	<ul style="list-style-type: none"> <li>• Double-blind design in a practical setting.</li> <li>• Similar results with local anesthetic or with local anesthetic and steroids.</li> <li>• Nonresponsive patients: local anesthetic = 13, steroids = 13.</li> <li>• A total of 5-6 injections on average were provided over a period of 2 years; compared to all patients with significant improvement of 38% in local anesthetic group, 44% in steroid group.</li> </ul>		



Table 12 (con't). Characteristics of fluoroscopic randomized trials of caudal epidural injections.

Study Characteristics Methodological Quality Scoring	Participants and Interventions	Outcome Measures	Pain Relief and Function					Results			Comments
			3 mos.	6 mos.	12 mos.	24 mos.	Short-term ≥ 6 mos	Long Term > 6 mos.	≥ 12 mos.	24 mos.	
<p>Manchikanti et al, 2012 (762) RA, AC, F Axial or discogenic Quality Scores: Cochrane = 12/13 IPM-QRB = 44/48</p>	<p>Total = 120 Lidocaine = 60 Lidocaine with steroids = 60 Lidocaine vs. Lidocaine mixed with steroid Average number of injections = 5 to 6 for 2 years</p>	<p>NRS pain scale, ODI, employment status, opioid intake Responsive category was defined as at least 3 weeks of significant improvement with the first 2 procedures. Significant improvement: 50% improvement in pain and function.</p>	<p>Overall: LA 60% vs LA with steroid 72% Responsive: LA 87% vs LA with steroid 88%</p>	<p>Overall: LA 62% vs LA with steroid 72% Responsive: LA 89% vs. LA with steroid 93%</p>	<p>Overall: LA 56% vs LA with steroid 68% Responsive: LA 84% vs. LA with steroid 85%</p>	<p>Overall: LA 54% vs LA with steroid 60% Responsive: LA 84% vs LA with steroid 73%</p>	<p>P</p>	<p>P</p>	<p>P</p>	<ul style="list-style-type: none"> <li>Positive randomized double-blind trial with similar results with local anesthetic or with local anesthetic and steroids.</li> <li>There was an inordinately high proportion of patients failing to respond initially in both groups, 23 in local anesthetic group, and 19 in steroid group.</li> <li>On average, a total of 5-6 injections were provided over a period of 2 years.</li> </ul>	
<p>Manchikanti et al, 2012 (766) RA, AC, F Post-surgery syndrome Quality Scores: Cochrane = 12/13 IPM-QRB = 44/48</p>	<p>Total = 140 Lidocaine = 70 Lidocaine + steroid = 70 Lidocaine vs. lidocaine mixed with non-particulate betamethasone Average number of injections = 5 to 6 for 2 years</p>	<p>NRS, ODI, employment status, opioid intake Responsive category was defined as at least 3 weeks of significant improvement with the first 2 procedures. Significant improvement: 50% improvement in pain and function.</p>	<p>Overall: LA 56% vs LA with steroid 54% Responsive: LA 76% vs. LA with steroid 67%</p>	<p>Overall: LA 56% vs LA with steroid 61% Responsive: LA 74% vs. LA with steroid 78%</p>	<p>Overall: LA 53% vs LA with steroid 59% Responsive: LA 70% vs. LA with steroid 75%</p>	<p>Overall: LA 47% vs LA with steroid 58% Responsive: LA 62% vs LA with steroid 69%</p>	<p>P</p>	<p>P</p>	<p>P</p>	<ul style="list-style-type: none"> <li>Positive results with local anesthetics with or without steroids.</li> <li>Similar results with local anesthetic or with local anesthetic and steroids.</li> <li>Nonresponsive patients: local anesthetic = 17, steroids = 15.</li> <li>On average, 5-6 injections were provided over a period of 2 years; compared to all patients with significant improvement of 47% in local anesthetic group, 58% in steroid group.</li> </ul>	

Table 12 (con't). Characteristics of fluoroscopic randomized trials of caudal epidural injections.

Study Characteristics Methodological Quality Scoring	Participants and Interventions	Outcome Measures	Pain Relief and Function					Results			Comments	
			3 mos.	6 mos.	12 mos.	24 mos.	Short-term ≥ 6 mos	Long Term > 6 mos.	≥ 12 mos.	24 mos.		
Ackerman & Ahmad, 2007 (783) RA, AC, F Disc herniation or radiculopathy Quality Scores: Cochrane = 8/13 IPM-QRB = 25/48	Total = 90 Caudal = 30 Interlaminar = 30 Transforaminal = 30 Methylprednisolone + saline Number of injections = 1 to 3	Numeric pain score (0 - 10), rating of pain relief, ODI, BDI, contrast dispersion pattern Follow-up: 24 weeks	Caudal = 57% Interlaminar = 60% Transforaminal = 83%	Caudal = 57% Interlaminar = 60% Transforaminal = 83%	N/A	N/A	N/A	Effective in all arms	Effective in all arms	N/A	N/A	Positive mid-term results in a relatively small trial.
Dashfield et al, 2005 (784) RA, AC, F Disc herniation or radiculopathy Quality Scores: Cochrane = 10/13 IPM-QRB = 33/48	Total = 60 Caudal = 30 Endoscopy = 30 Lidocaine with triamcinolone Number of injections = 1	Pain relief, SF-MPQ, HADS scores	SI	SI	N/A	N/A	Lidocaine with triamcinolone effective	Lidocaine with triamcinolone effective	N/A	N/A	N/A	Positive mid-term results in a relatively small trial.
Murakibhavi & Khemka, 2011 (786) RA, NTC, F Disc herniation or radiculopathy Quality Scores: Cochrane = 8/13 IPM-QRB = 27/48	Group A = 50 control conservative management Group B = 52 caudal epidural with lidocaine and methylprednisolone Total = 102 patients Conservative management or caudal epidural steroid injections	VAS, ODI, BDI, NPI	Group A = 32% Group B = 92%	Group A = 24% Group B = 86%	N/A	N/A	Steroids effective	Steroids effective	N/A	N/A	N/A	Positive short-term results, with methylprednisolone and lidocaine.
Kamble et al, 2016 (770) RA, AC, F Single level disc prolapse Quality Scores: Cochrane = 9/13 IPM-QRB = 32/48	Transforaminal = 30 Number of injections = 1-3 Interlaminar = 30 Number of injections = 1-3 Caudal = 30 Number of injections = 1-3	VAS, ODI	N/A	Transforaminal = VAS baseline 7.1 ± 0.7 to 2.6 ± 0.7 ODI = 37.7 ± 2.83 to 16.8 ± 2.53 Interlaminar = VAS baseline 7.0 ± 0.7 to 3.4 ± 1.4 ODI = 36.9 ± 2.82 to 21.4 ± 6.08 Caudal = VAS baseline 7.2 ± 0.6 to 3.5 ± 1.0 ODI = 38.3 ± 2.78 to 21.9 ± 3.35	N/A	N/A	All 3 techniques were effective	N/A	N/A	N/A	N/A	While all 3 techniques were effective, transforaminal group showed superiority. However, there was no difference between caudal and interlaminar approaches.

Table 12 (con't). Characteristics of fluoroscopic randomized trials of caudal epidural injections.

Study Characteristics Methodological Quality Scoring	Participants and Interventions	Outcome Measures	Pain Relief and Function					Results			Comments
			3 mos.	6 mos.	12 mos.	24 mos.	Short-term ≥ 6 mos	Long Term			
								> 6 mos.	≥ 12 mos.	24 mos.	
<p>Pandey, 2016 (769) RA, AC, F Disc prolapse Quality Scores: Cochrane = 8/13 IPM-QRB = 29/48</p>	<p>Total = 140 patients Caudal = 82 Transforaminal = 40 Interlaminar = 18 All were treated with steroid and local anesthetic with or without sodium chloride solution</p>	<p>JOA score</p>	<p>N/A</p>	<p>JOA scores Caudal = baseline 15.39 to 24.02 Effectiveness = 74.3% Transforaminal = baseline 15.57 to 26.55 Effectiveness = 90% Interlaminar = baseline 15.33 to 25</p>	<p>N/A</p>	<p>P</p>	<p>P</p>	<p>N/A</p>	<p>In comparing caudal epidural with interlaminar and transforaminal, authors showed response in 74.3% with caudal route, 77.7% with interlaminar, and 90% with transforaminal approach. Overall results are positive. There is no significant difference between caudal and interlaminar; however, transforaminal appears to be superior.</p>		
<p>Singh et al, 2017 (779) RA, AC, F Single level prolapsed lumbar intervertebral disc Quality Scores: Cochrane = 8/13 IPM-QRB = 30/48</p>	<p>Number of patients = 80 Caudal with steroids group = 40 2 mL of methylprednisolone, 80 mg along with lignocaine 2% diluted in 20 mL of normal saline 3 caudal epidural injections were given at an interval of 3 weeks irrespective of previous epidural injection effect SRNB = 40 A single injection of 2 mL of methylprednisolone, 80 mg, mixed with 5 mL of lignocaine 2%</p>	<p>VAS, ODI &amp; significant pain relief of 50%</p>	<p>VAS Caudal vs. SNRB = 61.5% vs. 55.5% ODI decreased caudal vs. SNRB = 64.6% vs. 52.8%</p>	<p>VAS Caudal vs. SNRB = 59.6% vs. 52.9% ODI decreased caudal vs. SNRB = 65.1% vs. 48.6%</p>	<p>N/A</p>	<p>Caudal epidural superior to SNRB with steroids</p>	<p>Caudal epidural superior to SNRB with steroids</p>	<p>Caudal epidural superior to SNRB with steroids</p>	<p>Positive short-term and long-term relief in both caudal and SNRB; however, relief in the caudal group was superior. However, this study suffered with multiple limitations of 3 caudal epidural injections compared to one SNRB and high volumes of injections, which are clinically inappropriate in both caudal and SNRB groups.</p>		

Source: Manchikanti L, et al. Assessment of methodologic quality of randomized trials of interventional techniques: Development of an interventional pain management specific instrument. *Pain Physician* 2014; 17:E263-E290 (153).

RA = Randomized; AC = Active Control; F = Fluoroscopy; NRS = Numeric Rating Scale; ODI = Oswestry Disability Index; IPM-QRB = Interventional Pain Management techniques - Quality Appraisal of Reliability and Risk of Bias Assessment; LA = local anesthetic; BDI = Beck Depression Inventory; SF-MPQ = Short-Form McGill Pain Questionnaire; HADS = Hospital Anxiety and Depression Scale; NTC = No treatment control; VAS = Visual Analog Scale; NPI = Numerical Pain Intensity; JOA = Japanese Orthopaedic Association; SNRB = selective nerve root block; SI = significant improvement; NA = Not Applicable; P = Positive; N = negative

Responsive group patients in all 4 studies had superior outcomes; however, it should be noted that none of the studies had a placebo control. But each study only enrolled patients with chronic pain, and homogeneity was maintained because the patients in each study had a similar diagnosis. Each study established the efficacy of local anesthetic with steroid for the pathology treated; in addition, the patients in the disc herniation study had a higher quality of pain relief at 6 and 12 months. The mechanisms of action of local anesthetics and steroids have an abundance of experimental and clinical evidence (55-58,102,604-608,689-699). Further, there have been previous descriptions concerning the effectiveness of sodium chloride injected into the epidural space and joint spaces (76,436,698).

Among the newer studies published in 2017, Singh et al (779), in a prospective randomized assessment, studied transforaminal epidural injections versus caudal epidural injections for single level prolapsed lumbar intervertebral disc. In this study, they utilized 80 patients with 40 patients in each group. Both groups received steroids and local anesthetic; however, there was significant difference in the volumes, which were rather high. Patients in the caudal group received 2 mL of methylprednisolone (80 mg) with 10 mL of lignocaine 2% diluted in 20 mL of normal saline. Further, a total of 3 caudal epidural injections were given at intervals irrespective of previous epidural injection effect. However, transforaminals were given by a single injection of 2 mL of methylprednisolone 80 mg mixed with 5 mL of lignocaine (7 mL total), a high volume, using a supraneural technique. For the outcomes, they utilized pain relief as well as ODI. More importantly, they assessed the patients with more than 50% relief. In the transforaminal group, pain was reduced by more than 50% until 6 months, while in the caudal group, more than 50% reduction of pain was maintained until one year. The reduction in ODI in the transforaminal group was 52.8% until 3 months, 48.6% until 6 months, and 46.7% at one year, while in the caudal group, the improvement was 64.6%, 65.1% and 65.4% at corresponding follow-up periods. They concluded that caudal epidural was more effective or superior to transforaminal, with an increased ease of administration.

Pandey (769) assessed the efficacy of epidural steroid injection in the management of lumbar prolapsed intervertebral disc in comparative evaluation with caudal, interlaminar, and transforaminal approaches. They included a total of 140 patients with randomization into 3 groups with 80 patients utilizing the caudal approach,

40 patients by transforaminal approach, and 8 patients by interlaminar approach using a simple randomization; however, this randomization is not uniform. Utilizing Japanese Orthopaedic Association (JOA) scores they calculated the improvement at 6 months and one-year and effectiveness of the medication for each route. Their results showed that one-year after injecting the steroid, all three routes were found to be effective in improving JOA scores with caudal route showing improvement in 74.3%, interlaminar showing improvement in 77.7%, and transforaminal route in 90%. They also showed that the transforaminal route was significantly more effective than the caudal and interlaminar at both 6 months and one-year after injection. No significant differences were seen between the caudal and interlaminar approaches. The limitations of this study include unequal randomization and lack of data showing significant improvement.

Kamble et al (770) studied 90 patients randomized to 3 groups with approaches of caudal, interlaminar, and transforaminal with randomization with 30 patients in each group in a single level disc prolapse patients confirmed by MRI. They followed the patients for 12 months and the results were compared using change in VAS score and ODI; however, they presented only 6 month results. Their results showed the change in pain scores were statistically different at 1 and 6 month intervals such that a higher change was observed by the transforaminal route as compared to the other two. There was no difference in change of scores between the interlaminar and caudal routes. For ODI scores, a greater change was seen in delivery at all times, as compared to the other 2. There was no difference in change of scores between the interlaminar and caudal routes at any time of the assessment. The VAS scores changed from 7.1 to 2.6 at 6-month follow-up in the transforaminal group compared to 7.0 to 3.4 in the interlaminar group, and 7.2 to 3.5 in the caudal group. Similarly, ODI scores changed from 37.7 to 16.8 in the transforaminal group compared to 36.9 to 21.4 in the interlaminar group and 38.3 to 21.9 in the caudal group. Overall, these findings showed positive results. However, as shown above, positive results with transforaminal were superior. It should be noted that the 12-month results were not published and also 50% relief was not assessed.

Among the older studies, Ackerman and Ahmad (783) compared the efficacy of caudal epidural injections with lumbar interlaminar and transforaminal epidural injections. This was a relatively small study showing the superiority of both lumbar interlaminar and

transforaminal epidural injections over caudal epidural injections. The authors utilized both local anesthetic and steroids.

Dashfield et al (784) assessed and compared caudal epidural steroid injections with targeted steroid placement during spinal endoscopy for chronic sciatica. Their study showed that epidural injections without passage of endoscopy equipment was superior.

Murakibhavi and Khemka (786) compared caudal epidural steroid injections in a RCT of disc herniation with conservative treatment measures which included medication as well as physiotherapy, whereas the intervention group received caudal epidural steroid injections with 20 mL of normal saline, 2 mL of 2% preservative-free lidocaine, and 2 mL or 80 mg of triamcinolone acetate. The authors showed complete long-term relief in 86% of the patients in the caudal epidural group compared to 24% in the conservative management group. This was a moderate quality trial, without blinding, comparing conservative modalities to epidural injections.

Among the excluded studies, there was only one study by Iversen et al (785), utilizing a placebo design, however, without fluoroscopy, but with ultrasound and injection of steroid without local anesthetic. The study was highly deficient in multiple aspects with substantial criticism advanced (790-792). This study illustrates numerous flaws. As a first concern, the selection criteria are overtly broad. A significant proportion of patients ( $n = 17$ ) did not even have to undergo randomization because their symptoms improved between assessment and randomization indicating the inclusion of short-term or subacute pain. In addition, after the randomization, 5 patients had spontaneous improvement before the first injection. A large proportion of patients were excluded due to neurologic compression, including cauda equina syndrome. They also attributed most of their results to natural course. Patient selection appears to be quite inappropriate. In chronic pain settings with long-lasting pain, patients undergoing various modalities of treatments would already have responded to a natural course or placebo effect. Further, while MRI was utilized as the criteria for disc herniation, ultimately the authors included clinically proven radiculopathy for inclusion criteria. Multiple flaws with the procedure include ultrasound identification of caudal epidural space, which the authors claim is appropriate for caudal even though they concede it was not appropriate for transforaminal. Ultrasound identification is not appropriate for either caudal or for transforaminal. Further, the injection was

not only nontargeted with an unproven technique, namely ultrasound, but also included large volumes of sodium chloride solution without local anesthetics and relatively small volumes of triamcinolone. It also appears, somewhat surprising, that only 17 patients of the 345 declined to participate in the study, even though it is a placebo-control study.

Sayegh et al (782) studied patients with either acute or subacute sciatica. This randomized controlled study reported significant improvement for those receiving local anesthetic alone or with steroids. However, they reported that adding steroids provided a superior outcome because the onset of relief was faster, longer lasting, and of a higher quality.

Park et al (773) studied the role of caudal epidural steroid injection for the treatment of unilateral lower lumbar radicular pain utilizing a single-blinded randomized design comparing ultrasound-guided versus fluoroscopy-guided procedures. They included a total of 110 patients with 55 patients in each group. In a short-term follow-up of 12 weeks, they showed improvement with pain and function in both groups.

Revel et al (787) studied forceful epidural injections for the treatment of lumbosciatic pain with postoperative lumbar spine fibrosis. They included 60 patients with persistent or recurrent lumbosciatic pain after surgery and with epidural fibrosis. This was a moderate quality study with positive results.

Datta and Upadhyay (776) compared 3 different steroid agents for treatment of low back pain through caudal approach with allocation of patients into 4 groups with one group receiving local anesthetic alone (bupivacaine), whereas 3 groups received 3 types of steroids utilizing bupivacaine and with total dose equivalent to 210 mg of methylprednisolone or 3 injections with methylprednisolone acetate, triamcinolone acetate, or betamethasone acetate. All injections were administered with 10 to 15 mL volume of 0.125% bupivacaine alone or bupivacaine mixed with 80 mg of methylprednisolone, 80 mg of triamcinolone, or 15 mg of dexamethasone. The procedures were performed blindly without fluoroscopy and a significant proportion of patients had disc herniations at L3/4, either individually or in combination, in the majority of the patients (the level at which caudal epidural has poor spread pattern), specifically when performed without fluoroscopy. VAS improved the most in the methylprednisolone and triamcinolone groups from baseline scores of 7.4 to 4.9 in the methylprednisolone group and 4.8 in the triamcinolone group. In contrast, the dexamethasone



group improved from 7.3 to 5.2 and local anesthetic alone group improved from 7.2 to 6.18. These results in a short-term follow-up show that methylprednisolone and triamcinolone with local anesthetic in rather high doses were more effective than high dose dexamethasone and bupivacaine alone. Thus, the results show that there is significant improvement with steroids when local anesthetics are added.

Huda et al (789), utilizing a blind approach, assessed 70 patients. They compared methylprednisolone or triamcinolone mixed with bupivacaine and normal saline with a total of 20 mL volume. In the methylprednisolone group, at the end of 6 months, 68.5% of the patients reported improvement, whereas improvement was seen in 40% of the patients in the triamcinolone group. The results are impressive considering that patients received only one injection of steroid with bupivacaine.

#### **8.4.1. Evidence Synthesis**

Based on the available studies, qualitative and quantitative analysis were performed. Qualitative analysis data was derived from the data from this assessment. Quantitative analysis data was derived from a multitude of previous systematic reviews, which included conventional dual-arm analysis and single-arm analysis.

In the present assessment, there were 2 RCTs (769,770) comparing caudal, interlaminar and transforaminal groups in managing disc herniation. In both studies, caudal and interlaminar epidurals were equivalent, whereas transforaminal was shown to be somewhat superior. In contrast, Ackerman and Ahmad (783), which was included in this analysis, showed superiority of both lumbar interlaminar and transforaminal epidural injections over caudal epidural injections. It must be noted that this was a very small study.

However, Singh et al (779) compared selective nerve root blocks and caudal epidural injection for single level prolapsed lumbar intervertebral disc in a prospective randomized study. They showed significantly better improvement with caudal epidural injections at 6 months and one year. They utilized 3 caudal epidural injections compared to one transforaminal epidural injection. Consequently, the value of this study and results in reference to superiority are questionable, even though they show that both approaches are effective.

In the present review, there were no studies meeting inclusion criteria with placebo control. All of the studies meeting inclusion criteria were of an active control nature. Four studies by Manchikanti et al presented 2-year relief with positive response in disc herniation,

central spinal stenosis, axial or discogenic pain, and post-lumbar surgery syndrome.

Overall, 7 studies provided the results of caudal epidural injections in disc herniation (765,769,770,779,783,784,786). All of them were judged to be positive. Consequently, the evidence for caudal epidural injections in disc herniation, with inclusion of 7 relevant medium to high-quality studies is Level I with strong recommendation. Comparative studies of caudal, interlaminar, and transforaminal show equal effectiveness of caudal and interlaminar. However, superiority of transforaminal epidural injections was demonstrated in two studies (769,770). Thus, based on relevant studies, there is Level III evidence that transforaminal are superior to caudal epidural injections and Level III evidence that caudal epidural injections are equivalent to lumbar interlaminar epidural injections.

The evidence for central spinal stenosis is Level III to II based on a single RCT (767), which is an active control, with inclusion of 100 patients with 24-month follow-up with moderate to strong recommendation in select patients.

The evidence for axial or discogenic pain after elimination of facet joint pain and sacroiliac joint pain is Level II based on one active control RCT (762) with inclusion of 120 patients and a 2-year follow-up with moderate to strong recommendation.

For post-surgery syndrome, based on one high-quality relevant RCT (766), the evidence is Level II with moderate to strong recommendation.

Cost utility analysis was also favorable for caudal epidural injections in all 4 conditions studied, namely, disc herniation, central spinal stenosis, post-lumbar surgery syndrome, and axial discogenic pain (795). The cost utility analysis showed cost for one-year quality-adjusted life year (QALY) of \$2,172.50 for direct costs and \$3,627.24 for total cost with addition of indirect costs. There was no significant difference among the groups; however, among various conditions, for disc herniation total cost was \$3,682.35 per one-year QALY. For axial or discogenic pain after ruling out the facet joint and sacroiliac joint pain, it was \$3,567.42, spinal stenosis it was \$3,598.85, and for post-surgery syndrome it was \$3,658.43 for one-year QALY.

Multiple systematic reviews have assessed the role of caudal epidural injections with or without steroids in managing pain in the lumbar spine for various conditions, including disc herniation, discogenic pain without disc herniation, central spinal stenosis, and post-surgery syndrome. Only a few systematic reviews focused on

analyzing the evidence for caudal epidural injections, either alone or comparatively. Manchikanti et al (75-77,81) and Kaye et al (60) evaluated caudal epidural injections separately and in combination with interlaminar and transforaminal epidural injections in the lumbar spine. All of these studies uniformly showed the effectiveness of caudal epidural injections and basically included the same studies.

In addition, Lee et al (63), compared the clinical efficacy of transforaminal and caudal epidural steroid injections in a systematic review utilizing 6 studies showing somewhat the superiority of transforaminal epidural injections over caudal epidural injection in 4 articles, with one article showing no significant difference, and one article supporting the superiority of caudal epidural steroid injection to transforaminal epidural injection. Their conclusion was towards better clinical efficacy with transforaminal epidural injections. However, there was no statistical significance and the evidence was low because of inconsistencies and imprecisions. Consequently, the clinical relevance is not determined.

Manchikanti et al compared caudal epidural studies with interlaminar and transforaminal epidural studies (614,793,794). In one of those studies (614), they compared the efficacy of caudal, interlaminar, and transforaminal epidural injections in managing lumbar disc herniation by looking at whether one method was superior to the other. They included 3 RCTs with 120 patients in each trial with 60 patients receiving local anesthetic only and 60 patients in each trial receiving local anesthetic with steroids. Analysis showed similar efficacy for caudal, interlaminar, and transforaminal approaches in managing chronic pain and disability from disc herniation. While there were differences in relief patterns, they were not statistically significant. At 12 months, significant improvement (considered as at least 50% pain relief and improvement in ODI scores for function from baseline) of 72% was shown in the caudal group, 85% in the interlaminar group, and 57% in the transforaminal group. However, further analysis with only responsive patients showed 84% improvement in the caudal group, 86% in the interlaminar group, and 73% in the transforaminal group. Overall, there was no significant difference between groups. However, it appears that interlaminar may be somewhat better than caudal.

Manchikanti et al (793) also compared the effectiveness of caudal epidural with lumbar interlaminar epidural in central spinal stenosis. Similar to the above study, they derived the data from 2 previously published

RCTs. Results showed significant improvement in patients suffering with chronic lumbar spinal stenosis with caudal and interlaminar epidural approaches up to 2 years. However, the interlaminar group showed significant difference between caudal and interlaminar with interlaminar being superior to caudal in spinal stenosis.

Manchikanti et al (794) also studied the difference between caudal and lumbar interlaminar injections in chronic lumbar axial discogenic pain. They utilized 2 RCTs from each group. In this assessment, the lumbar interlaminar approach was shown to be superior to the caudal approach. The primary outcome measure, with significant improvement being defined as pain relief and functional status improvement of at least 50% from baseline, was reported at 20-month follow-up in 72% who received local anesthetic only utilizing the lumbar interlaminar approach and 54% who received local anesthetic only utilizing a caudal approach. Further, in patients receiving local anesthetic with a steroid, the response rate was 67% of those who had a lumbar interlaminar approach and 68% of those who had a caudal approach at 12 months. Consequently, they concluded that the response was significantly better in the lumbar interlaminar group who received local anesthetic only, 77% versus 56% at 12 months, and 72% versus 54% at 24 months.

### 8.5 Lumbar Interlaminar Epidural Injections

Lumbar interlaminar epidural injections were studied for effectiveness in 53 studies (617,769,770,783,796-843). Of the 53 studies considered for inclusion, only 13 RCTs met inclusion criteria. (617,769,770,783,797,799,801,804,817,818,821,823,843). Appendix Table 7 shows Cochrane review criteria assessment results, whereas, Appendix Table 8 shows criteria by IPM-QRB. Table 13 shows characteristic features of fluoroscopic RCTs of lumbar interlaminar epidural injections. Using both Cochrane and IPM-QRB criteria, 10 studies (617,770,797,799,801,804,817,821,823,843) were rated high, while 4 were rated moderate quality (769,783,818).

Manchikanti et al conducted 3 of these studies (797,799,801). They used an identical protocol in each study: an active control design with a 2-year follow-up. These studies evaluated the efficacy of epidural injections in 2 groups: one group received a local anesthetic only and the other group received a local anesthetic with a steroid. In these 3 studies, a total of 360 patients were evaluated for one of the following conditions: lumbar disc herniation; lumbar discogenic pain without facet joint or sacroiliac joint pain; and lumbar central

Table 13. Characteristics of fluoroscopic randomized controlled trials of lumbar interlaminar epidural injections.

Study Characteristics Methodological Quality Scoring	Participants and Interventions	Outcome Measures	Pain Relief and Function					Results			Comment(s)
			3 mos.	6 mos.	12 mos.	24 mos.	Short-term ≤ 6 mos.	Long-Term			
								> 6 mos.	≥ 12 mos.	24 mos.	
<p>Manchikanti et al, 2014 (797) RA, AC, F Disc herniation or radiculopathy Quality Scores: Cochrane = 11/13 IPM-QRB = 44/48</p>	<p>Total = 120 Local anesthetic = 60 Local anesthetic and steroids = 60 Xylocaine or Lidocaine with non-particulate Celestone Average number of injections = 5 to 6 for 2 years</p>	<p>NRS, ODI, employment status, opioid intake, significant improvement 50% or greater of ODI scores Responsive category was defined as at least 3 weeks of significant improvement with the first 2 procedures. Significant improvement: 50% improvement in pain and function.</p>	<p>Overall: Lidocaine 72% vs. lidocaine with steroid 82% Responsive: Lidocaine 86% vs. lidocaine with steroid 83%</p>	<p>Overall: Lidocaine 63% vs. lidocaine with steroid 85% Responsive: Lidocaine 76% vs. lidocaine with steroid 86%</p>	<p>Overall: Lidocaine 67% vs. lidocaine with steroid 85% Responsive: Lidocaine 80% vs. lidocaine with steroid 86%</p>	<p>Overall: Lidocaine 60% vs. lidocaine with steroid 70% Responsive: Lidocaine 72% vs. lidocaine with steroid 71%</p>	<p>Both treatments are effective</p>	<p>Both treatments are effective</p>	<p>Both treatments are effective</p>	<p>Both treatments are effective</p>	<ul style="list-style-type: none"> <li>Positive randomized trial with long-term follow-up.</li> <li>Overall, similar results with local anesthetic or with local anesthetics and steroids with significant improvement.</li> <li>Steroids were superior at 6 months with pain relief and 12 months with functional status</li> <li>A significantly higher proportion of patients non-responsive to the first 2 injections in the local anesthetic group 10 vs one.</li> <li>On average, a total of 5-6 injections were provided over a period of 2 years.</li> </ul>
<p>Ghai et al, 2015 (804) RA, DB, AC, F Disc herniation or radiculopathy Quality Scores: Cochrane = 10/13 IPM-QRB = 39/48</p>	<p>Total = 69 Lidocaine = 34 Lidocaine + methylprednisolone = 35 Local anesthetic group: 8 mL of 0.5% lidocaine Lidocaine + methylprednisolone: 6 mL of 0.5% lidocaine mixed with 80 mg (2 mL) of methylprednisolone acetate Average procedures: 2</p>	<p>NRS and functional disability using Modified Oswestry Disability Questionnaire Follow-up: 1 year</p>	<p>Lidocaine: 50% Lidocaine with methylprednisolone: 86%</p>	<p>Lidocaine: 56% Lidocaine with methylprednisolone: 86%</p>	<p>Lidocaine: 59% Lidocaine with methylprednisolone: 89%</p>	<p>N/A</p>	<p>Both arms effective. Steroids superior</p>	<p>Both arms effective. Steroids superior</p>	<p>Both arms effective. Steroids superior</p>	<p>N/A</p>	<p>This active control trial with a long-term follow-up comparing lidocaine alone with lidocaine with methylprednisolone showed similar results after 3 months, even though quality of relief was superior in the local anesthetic with steroid group.</p>

Table 13 (con't). Characteristics of fluoroscopic randomized controlled trials of lumbar interlaminar epidural injections.

Study Characteristics Methodological Quality Scoring	Participants and Interventions	Outcome Measures	Pain Relief and Function				Results			Comment(s)
			3 mos.	6 mos.	12 mos.	24 mos.	Short-term ≤ 6 mos.	Long-Term > 6 mos.	≥ 12 mos.	
Manchikanti et al 2015 (799) RA, AC, F Central spinal stenosis Quality Scores: Cochrane = 11/13 IPM-QRB = 43/48	Total = 120 Local anesthetics = 60 Local anesthetics and steroids = 60 Lidocaine alone or with Celestone Average number of injections = 5 to 6 for 2 years	NRS, ODI, employment status, opioid intake Responsive was defined as those patients responding with at least 3 weeks of improvement with the first 2 procedures. Significant improvement: 50% improvement in pain and function.	Overall: LA 83% vs LA with steroid 77% Responsive: LA 90% vs LA with steroid 86%	Overall: LA 72% vs LA with steroid 75% Responsive: LA 78% vs LA with steroid 83%	Overall: LA 77% vs LA with steroid 67% Responsive: LA 84% vs LA with steroid 71%	Overall: LA 72% vs LA with steroid 73% Responsive: LA 84% vs LA with steroid 85%	Both treatments effective	Both treatments effective	Both treatments effective	<ul style="list-style-type: none"> <li>Positive results in a large active control trial.</li> <li>Both local anesthetic alone or with steroids were effective with no significant difference between the groups.</li> <li>On average, a total of 5-6 injections were administered over a period of 2 years.</li> </ul>
Ökmen & Ökmen 2017 (817) RA, AC, F Disc herniation Quality Scores: Cochrane = 12/13 IPM-QRB = 40/48	Total = 120 Epidural bupivacaine 0.25%, 10 mL = 60 Epidural bupivacaine 0.25%, 10 mL + 40 mg of methylprednisolone = 60 Procedures administered at L4-5 under fluoroscopic guidance Number of injections = 1-2	VAS, ODI Follow-up: 1 to 12 months	Significantly better results in epidural bupivacaine and steroid group Both groups showed significant improvement from baseline, more significant in the steroid group than bupivacaine alone group.	Significantly better results in epidural bupivacaine and steroid group Both groups showed significant improvement from baseline, more significant in the steroid group than bupivacaine alone group.	Significantly better results in epidural bupivacaine and steroid group Both groups showed significant improvement from baseline, more significant in the steroid group than bupivacaine alone group.	N/A	Bupivacaine steroids superior	Bupivacaine steroids superior	N/A	<ul style="list-style-type: none"> <li>Positive results for both epidural bupivacaine and epidural bupivacaine with steroids.</li> <li>Significant improvement in epidural bupivacaine and steroid group from baseline with pain and function, as well as ODI compared to bupivacaine.</li> </ul>
Friedly et al, 2014 (278,818) RA, AC, F Central and foraminal spinal stenosis Quality Scores: Cochrane = 8/13 IPM-QRB = 30/48	Total = 400 Lidocaine Group: Interlaminar = 139 Transforaminal = 61 Glucocorticoids plus Lidocaine Group: Interlaminar = 143 Transforaminal = 57 Lidocaine alone or glucocorticoid plus lidocaine Variable doses	NRS, RMDQ	Significant improvement. At 3 weeks and 6 weeks RMDQ scores were significantly less in glucocorticoid-lidocaine group compared to lidocaine group. Leg pain was also significantly less in the steroid group compared to lidocaine alone group.	No significant differences or improvement in observational study	No significant differences or improvement in observational study	N/A	Both treatments effective with superiority of steroid with lidocaine	None	None	<ul style="list-style-type: none"> <li>Large trial with flawed design and assessment with positive results at 3 months. Even though based on flawed analysis it shows negative results. Multiple flaws include not only the design and analysis of the data, but patient selection, technical considerations, and inherent bias.</li> <li>Follow-up observational study has not provided additional information.</li> </ul>

Table 13 (con't). Characteristics of fluoroscopic randomized controlled trials of lumbar interlaminar epidural injections.

Study Characteristics Methodological Quality Scoring	Participants and Interventions	Outcome Measures	Pain Relief and Function						Results			Comment(s)
			3 mos.	6 mos.	12 mos.	24 mos.	Short-term ≤ 6 mos.		Long-Term			
							> 6 mos.	≥ 12 mos.	24 mos.			
Manchikanti et al, 2013 (801) RA, AC, F Axial or discogenic Quality Scores: Cochrane = 11/13 IPM-QRB = 44/48	Total = 120 Local anesthetics = 60 Local anesthetics and steroids = 60 Lidocaine alone or with Celestone Average number of injections = 5 to 6 for 2 years	NRS, ODI, employment status, opioid intake Responsive was defined as those patients responding with at least 3 weeks of improvement with the first 2 procedures. Significant improvement: 50% improvement in pain and function.	Overall: LA 83% vs LA with steroid 77% Responsive: LA 90% vs LA with steroid 86%	Overall: LA 72% vs LA with steroid 75% Responsive: LA 78% vs LA with steroid 83%	Overall: LA 77% vs LA with steroid 67% Responsive: LA 84% vs LA with steroid 71%	Overall: LA 72% vs LA with steroid 67% Responsive: LA 78% vs LA with steroid 70%	P	P	P	P	<ul style="list-style-type: none"> <li>Positive results in a large active control trial.</li> <li>Both local anesthetic alone or with steroids were effective with no significant difference between the groups.</li> <li>On average, a total of 5-6 injections were administered over a period of 2 years.</li> </ul>	
Ackerman & Ahmad, 2007 (783) RA, AC, F Disc herniation or radiculopathy Quality Scores: Cochrane = 8/13 IPM-QRB = 25/48	Total = 90 Caudal = 30 Interlaminar = 30 Transforaminal = 30 Methylprednisolone + saline Number of injections = 1 to 3	Numeric pain score (0 - 10), rating of pain relief, ODI, BDI, contrast dispersion pattern Follow-up: 24 weeks	Caudal = 57% Interlaminar = 60% Transforaminal = 83%	Caudal = 57% Interlaminar = 60% Transforaminal = 83%	N/A	N/A	Effective in all arms	Effective in all arms	Effective in all arms	N/A	<ul style="list-style-type: none"> <li>Positive mid-term results in a relatively small trial.</li> <li>Shows effectiveness of steroids with all approaches with superiority of transforaminal</li> </ul>	
Rados et al, 2011 (821) RA, AC, F Disc herniation or radiculopathy Quality Scores: Cochrane = 9/13 IPM-QRB = 30/48	Total = 64 IL = 32 TF = 32 Lidocaine with methylprednisolone Number of injections = 1 to 3	VAS, ODI, 50% pain relief Follow-up: 6 months	N/A	Interlaminar lidocaine with methylprednisolone = 53% Transforaminal lidocaine with methylprednisolone = 63%	N/A	N/A	Effective with both approaches	N/A	N/A	N/A	<ul style="list-style-type: none"> <li>Positive results with short follow-up period in comparison of 2 approaches with lidocaine with methylprednisolone</li> </ul>	
Ghai et al, 2014 (617) RA, AC, F Disc herniation or radiculopathy Quality Scores: Cochrane = 10/13 IPM-QRB = 42/48	Total = 62 Parasagittal interlaminar = 32 Transforaminal = 30 2 mL of methylprednisolone (80 mg) mixed with 2 mL of normal saline for both PIL and transforaminal groups Number of epidural steroid injections: Transforaminal group: 60 PIL group: 58 Average procedures: 2	Visual analog scale, Oswestry Disability questionnaire, significant improvement, greater than 50% pain relief from baseline, Patient Global Impression	PIL group: 78% Transforaminal group: 77%	PIL group: 75% Transforaminal group: 77%	PIL group: 69% Transforaminal group: 77%	N/A	Effectiveness in both arms	Effectiveness in both arms	Effectiveness in both arms	N/A	This is relatively small active control trial with a long-term follow-up assessing the role of parasagittal interlaminar epidural injections and transforaminal epidural injections showing equal improvement with steroids without local anesthetic.	



Table 13 (con't). Characteristics of fluoroscopic randomized controlled trials of lumbar interlaminar epidural injections.

Study Characteristics Methodological Quality Scoring	Participants and Interventions	Outcome Measures	Pain Relief and Function				Results			Comment(s)
			3 mos.	6 mos.	12 mos.	24 mos.	Short-term ≤ 6 mos.	Long-Term > 6 mos.	≥ 12 mos.	
Candido et al, 2013 (843) RA, AC, F Disc herniation or radiculopathy Quality Scores: Cochrane = 10/13 IPM-QRB = 37/48	106 patients Midline interlaminar = 53 Parasagittal interlaminar = 53 120 mg methylprednisolone with 2 mL of 0.5% lidocaine Number of Injections: Not available	Pain relief, disability, NRS, ODI, use of opioid medication Follow-up: 12 months	ODI Midline = 36% Parasagittal = 51% Pain: Midline = 29% Parasagittal = 50%	ODI Midline = 21% Parasagittal = 55% Pain: Midline = 29% Parasagittal = 53%	ODI Midline = 15% Parasagittal = 56% Pain: Midline = 28% Parasagittal = 55%	N/A	Parasagittal superior	Parasagittal superior	N/A	<ul style="list-style-type: none"> <li>The authors showed significant evidence that parasagittal approach with injection of local anesthetic and steroids was superior to midline approach of interlaminar epidural injections.</li> <li>This study shows combination of methylprednisolone with lidocaine was superior administered with a parasagittal approach compared to midline approach.</li> </ul>
Amr, 2011 (823) RA, AC, F Disc herniation or radiculopathy Quality Scores: Cochrane = 12/13 IPM-QRB = 38/48	Total = 200 Local anesthetic + steroid = 100 Local anesthetic + steroid + ketamine = 100 Triamcinolone plus preservative free ketamine and 0.9% saline Number of injections = 1	Pain scores, Oswestry low back pain disability questionnaire	Significant improvement in ketamine group	Significant improvement in ketamine group	Significant improvement in ketamine group	N/A	Effective with addition of ketamine to bupivacaine and triamcinolone	Effective with addition of ketamine to bupivacaine and triamcinolone	N/A	<ul style="list-style-type: none"> <li>Positive randomized trial for ketamine with long-term follow-up with ketamine with local anesthetic and steroid.</li> </ul>
Kamble et al, 2016 (770) RA, AC, F Single level disc prolapse Quality Scores: Cochrane = 9/13 IPM-QRB = 32/48	Transforaminal = 30 Number of injections = 1-3 Interlaminar = 30 Number of injections = 1-3 Caudal = 30 Number of injections = 1-3	VAS, ODI	N/A	Transforaminal = VAS baseline 7.1 ± 0.7 to 2.6 ± 0.7 ODI = 37.7 ± 2.83 to 16.8 ± 2.53 Interlaminar = VAS baseline 7.0 ± 0.7 to 3.4 ± 1.4 ODI = 36.9 ± 2.82 to 21.4 ± 6.08 Caudal = VAS baseline 7.2 ± 0.6 to 3.5 ± 1.0. ODI = 38.3 ± 2.78 to 21.9 ± 3.35	N/A	N/A	All 3 techniques were effective	N/A	While all 3 techniques were effective, transforaminal group showed superiority. However, there was no difference between caudal and interlaminar approaches.	

Table 13 (con't). Characteristics of fluoroscopic randomized controlled trials of lumbar interlaminar epidural injections.

Study Characteristics Methodological Quality Scoring	Participants and Interventions	Outcome Measures	Pain Relief and Function				Results			Comment(s)
			3 mos.	6 mos.	12 mos.	24 mos.	Short-term ≤ 6 mos.	Long-Term		
								> 6 mos.	≥ 12 mos.	
Pandey; 2016 (769) RA, AC, F Disc prolapse Quality Scores: Cochrane = 8/13 IPM-QRB = 29/48	Total = 140 patients Caudal = 82 Transforaminal = 40 Interlaminar = 18 All were treated with steroid and local anesthetic with or without sodium chloride solution	JOA score	N/A	JOA scores Caudal = baseline 15.39 to 24.02 Effectiveness = 74.3% Transforaminal = baseline 15.57 to 26.55 Effectiveness = 90% Interlaminar = baseline 15.33 to 24.72 Effectiveness = 77.7%	N/A	P	P	P	In comparing caudal epidural with interlaminar and transforaminal, authors showed response in 74.3% with caudal route, 77.7% with interlaminar, and 90% with transforaminal approach. Overall results are positive. There is no significant difference between caudal and interlaminar; however, transforaminal appears to be superior.	

RA = Randomized; AC = Active Control; F = Fluoroscopy; DB = Double-Blind; P = Positive; N = Negative; NA = Not Applicable; NRS = Numeric Rating Scale; ODI = Oswestry Disability Index; VAS = Visual Analog Scale; PIL = Parasagittal Interlaminar; RMDQ = Roland Morris Disability Questionnaire; JOA = Japanese Orthopaedic Association; IPM-QRB = Interventional Pain Management techniques - Quality Appraisal of Reliability and Risk of Bias Assessment

spinal stenosis. Similar outcomes were seen in 60% to 84% of the patients in these studies. Both Cochrane and IPM-QRB rated these studies as high-quality (10 of 12 and either 43 or 44 of 48, respectively).

These studies divided patients into responsive and nonresponsive groups. A patient was considered responsive if a 50% improvement in pain and function was achieved in the first 3 weeks with the initial 2 injections. Nonresponsive patients in each pathology studied were: interlaminar injections of local anesthetic only - 10 with disc herniation, 5 with discogenic pain, and 9 with central stenosis; local anesthetic with steroids—1 with disc herniation, 6 with discogenic pain, and 7 with central stenosis. These results show that there were many in the nonresponsive local anesthetic disc herniation group, but no differences were noted between the subgroups in the other pathologies studied. Also, the addition of steroids to the local anesthetic appears to result in superior outcomes for pain at 6 months and functional status at 12 months for those with disc herniation (797). Patients who do not respond to local anesthetic alone for disc herniation may achieve a better outcome with the addition of steroids. Of interest is the fact that none of these studies had a placebo group.

Two studies were conducted by Ghai et al (617,804). In the first study (617), they compared parasagittal interlaminar and transforaminal epidural steroid injections without local anesthetic in 62 patients. The results showed significant improvement at 3 months, 6 months, and 12 months in 78%, 75%, 69% of patients in the parasagittal interlaminar group compared to 77%, 77%, 77% in the transforaminal epidural group. This was a relatively small active control trial with a long-term follow-up assessing the role of parasagittal interlaminar epidural injections and transforaminal epidural injections, showing equal improvement with steroids without local anesthetic. In the second study, Ghai et al (617) compared local anesthetic alone with local anesthetic with steroids in disc herniation or radiculitis. In an active-control trial of 34 patients in the local anesthetic group and 35 in the local anesthetic with steroid group, they administered 8 mL of local anesthetic of 0.5% lidocaine, or 6 mL of local anesthetic with steroid of 80 mg of methylprednisolone. The re-

sults showed effectiveness in both groups at the end of 12 months. There was a superiority of steroids at the 3-month assessment; however, this dissipated over time.

Ökmen and Ökmen (817) published a randomized, blinded, prospective study of efficacy of interlaminar epidural steroid administration in multilevel intervertebral disc disease with chronic low back pain in 2017. Their inclusion criteria were low back pain of more than 6 months, pain unresponsive to conservative treatment methods, presence of MRI findings, disc bulge and protrusion for the definite diagnosis of lumbar disc pathology, the presence of nerve root compression symptoms, and VAS above 5. They also had significant exclusion criteria. They studied 98 patients with injection of 10 mL of 0.25% bupivacaine in 50 patients and bupivacaine and steroid in 48 patients receiving 10 mL of 0.25% bupivacaine in addition to 40 mg of methylprednisolone with all procedures performed at L4/5 intervertebral space in prone position under the guidance of C-arm fluoroscopy. They treated patients with a second epidural injection if they did not exhibit 50% reduction in VAS score on day 15. Results showed a statistically significant difference between the groups in the VAS and ODI scores measured at 3, 6, and 12 months between the groups less than 0.05. The VAS and ODI scores were higher in the local anesthetic group compared with the steroid group at all time points. They also showed that patients requiring a second injection did not show any significant difference between the groups. Overall, this is a well-designed study and showed effectiveness of local anesthetic mixed with steroids. Further, this is the first study utilizing the interlaminar approach showing effectiveness of mixture with bupivacaine in contrast to lidocaine (58,759,762,765,797,799,801).

Friedly et al (278,818) conducted a large study with a poor and complicated design, which was not practical, with high volume glucocorticoid steroid injection, but low volume lidocaine alone injections. They provided interlaminar epidural injections with lidocaine of 1-3 mL, 0.5% to 1%, whereas either interlaminar or transforaminal epidural injections with 1-3 mL of 0.25% to 1% of lidocaine. In addition to this, glucocorticoid was added in rather high doses in the group for glucocorticoid as much as 60-120 mg of triamcinolone, 6-12 mg of betamethasone, and 60-120 mg of methylprednisolone. There was no equivalency in these doses. Administrations were highly variable based on practice patterns. There was a total of 200 patients in each group. However, the interlaminar approach with lidocaine alone was 139 compared to 143 in the groups with steroids and

61 had transforaminal lidocaine alone, whereas 57 had transforaminal lidocaine with glucocorticoids with extremely high doses. The study period lasted 6 weeks. The authors failed to assess the most common parameter, i.e., 50% improvement, with pain and physical function and the proportion of the patients. After 6 weeks, the analysis was performed. without separation of interlaminar and transforaminal and with a large crossover of the patients. Thus, it became an observational study. Further, repeat injections were very infrequent. During the first 6 weeks, only 76 patients (38%) in lidocaine alone group, and 80 patients (40%) in corticosteroid plus lidocaine group received a second injection. None of them received 3 injections (818). It is not a practical approach. In addition, during 6 to 12 weeks, 91 patients (47.2%) in the lidocaine alone group received one injection and 26 patients (13.5%) received 2 injections, while none received 3 or more. During the same period, in the corticosteroid and lidocaine groups, 67 patients (34.7%) received one injection and 28 or 14.5% received 2 injections. Finally, from 12 weeks to 12 months, over 66% did not receive any additional injections (278). Only 12, or 6.6%, in the lidocaine alone group, and 16.4%, or 31, in the corticosteroid plus lidocaine group received one additional injection, while 12.6% and 13.8%, with lidocaine alone or lidocaine with steroids, respectively, received 3 or more injections. Overall, very few patients received more than 3 injections. This is not a common practice. Generally, responsive patients receive one injection once in 3 months, that is at least 4 injections if they are not responding in the therapeutic phase, and 2 to judge in the diagnostic phase. Further, analysis was not very clear. There was no analysis performed using the proportion of patients obtaining 50% or greater relief. Further, there was no analysis separately provided for lumbar interlaminar epidural injections compared to transforaminal epidural injections. They also reported significant side effects because of the high dose of steroids in the steroid group. Based on the strictest criteria, this manuscript did not meet inclusion criteria. However, to avoid criticism, this manuscript was utilized in the analysis, which essentially showed similar effectiveness with lidocaine alone or lidocaine with steroids and significant effectiveness from baseline to follow-up periods utilizing mean improvement with leg pain intensity and disability index. Overall, despite a multitude of issues related to the study, this can be considered to be a positive study which shows lidocaine alone is also effective, similar to with steroids, and also provides basis that it is not a placebo. Finally, their conclusion

was that epidural injections of corticosteroid plus lidocaine offered no benefit from 6 weeks to 12 months beyond that of injection of lidocaine alone. Further, they also opined that repeated injections of either type offered no additional long-term benefit if injection in the first 6 weeks did not improve pain. While this was affirmed by Manchikanti et al in multiple manuscripts (759,762,765,797,799,801,844), lack of effectiveness was contradictory. If they consider a 2-point change in leg pain intensity as a significant difference and their results showed that leg pain intensity was reduced by a minimum of  $2.2 \pm 2.9$  to  $2.9 \pm 3.1$ , the study presented a successful outcome rather than a lack of outcome with similar effects of lidocaine alone and lidocaine with steroids. This study also received extensive importance being published in the *New England Journal of Medicine* and also AHRQ funded. However, it also received substantial criticism in a full manuscript publication (844) and letters to the editor (845-848).

Candido et al (843) assessed the correlation of pain relief with concordant pressure paresthesia during parasagittal interlaminar lumbar epidural injections with local anesthetic alone or with local anesthetic and steroids with 53 patients randomized to each group. Patients were administered 120 mg of methylprednisolone acetate, combined with preservative free lidocaine, and normal saline with a total volume of 4 mL. They showed effectiveness of steroid mixed with local anesthetic with lateral parasagittal interlaminar approaches in 55% of the patients at one-year follow-up with pain and function. The results were superior in the parasagittal group with pain relief, disability, and opioid intake.

Pandey (769) studied a comparison of caudal, transforaminal, and interlaminar routes in a randomized trial. However, the number of patients were unevenly distributed with 82 patients treated by the caudal route, 40 by the transforaminal route, and 18 by the interlaminar route. One of the disadvantages in this study is disproportionate randomization with a small proportion of patients in the transforaminal group showing significant improvement and therefore may not be statistically or clinically significant. Outcome scores were calculated at 6 month and one year and the effectiveness of medication was calculated for each route. All patients were treated with methylprednisolone 80 mg in 2 mL. The steroid was mixed with normal saline, 26 mL, plus 2% xylocaine 2 mL for the caudal route, 2% xylocaine 4 mL for the interlaminar route, 2% xylocaine 1 mL for the transforaminal route. However, the volume was high for caudal route procedures. The

results showed, at one year, average JOA scores of 15.39 baseline changing to 24.02 for caudal, 15.57 to 26.55 for transforaminal, whereas for interlaminar, it was 15.33 to 24.72. The rate of improvement was 50% to 100% in 74% of the patients in the caudal group, 78% in the interlaminar group, and 90% in the transforaminal group. Analysis showed significantly more effectiveness of transforaminal than caudal and interlaminar routes at both 6 months and one year after injection. However, no significant difference was seen between the caudal and interlaminar routes. The manuscript did not provide the number of injections in any of the groups.

Kamble et al (770) in an RCT of comparison of transforaminal epidural, lumbar interlaminar epidural, and caudal epidural steroids included 90 patients with 30 patients in each group. Even though the manuscript stated that all patients were followed up to 12 months and the results were compared using change in VAS and ODI, the published results, in fact, were only up to 6 months. In the transforaminal group, the patients were given 40 mg of triamcinolone acetate with 1 mL of bupivacaine and 2 mL of lignocaine at each level. For the interlaminar epidural injections, they provided 40 mg of triamcinolone acetate with 1 mL of bupivacaine and 1 mL of lignocaine in a dilution of 10 mL of normal saline. Similarly, for caudal epidural injections, they injected 40 mg of triamcinolone acetate with 1 mL of bupivacaine and 2 mL of lignocaine in a dilution of 10 mL of normal saline. A maximum of 3 injections were used per patient with a minimum interval of 2 weeks between subsequent injections. The results showed significant change at 6-month follow-up of VAS for transforaminal from  $7.1 \pm 0.7$  to  $2.6 \pm 0.7$ , and for interlaminar from  $7.0 \pm 0.7$  to  $3.4 \pm 1.4$ . For caudal, the VAS was  $7.2 \pm 0.6$  at baseline, which reduced to  $3.5 \pm 1.0$ . Two patients in the transforaminal group and 3 patients in each of the interlaminar and caudal groups underwent surgical intervention with a change from 6.672% to 10%. It would have been interesting to see their results at one year; however, these were not available. There was no significant difference between interlaminar and caudal epidural steroids. However, transforaminal was judged to be superior for both short and long-term as compared to interlaminar and caudal epidural steroid injections for a single level disc prolapse.

Ackerman and Ahmad (783) compared caudal, interlaminar, and transforaminal epidural injections. They reported similar efficacy for caudal and transforaminal injections, but superiority for transforaminal in mid-term results in a small, moderate-quality trial.

In a study that received widespread attention, but failed to meet inclusion criteria, Carette et al (827) reported that at 3 months neither normal saline nor saline with depo-methylprednisolone injected in the lumbar epidural spine was effective, despite some initial improvement reported with the saline and steroid injection. Their methodology and conclusions have been criticized (849-852).

### 8.5.1 Evidence Synthesis

Based on the available studies, qualitative and quantitative analysis was performed. Qualitative analysis data was derived from the data from this assessment. Quantitative analysis data was derived from a multitude of previous systematic reviews, which included conventional dual-arm analysis and single-arm analysis. Of the 13 studies included in this assessment (278,617,769,770,783,797,799,801,804,817,818,821,823,843), there were no placebo-controlled trials meeting the inclusion criteria. Among these, 4 studies assessed the role of epidural procedures with local anesthetic with or without steroid (797,804,817,823). One study (799) exclusively included central spinal stenosis with interlaminar epidural injections with local anesthetic with or without steroids. One study (801) was performed in axial or discogenic pain with local anesthetics or local anesthetics with steroids in axial or discogenic pain after eliminating facet joint pain, as well as sacroiliac joint pain. Eight of the 14 studies were comparative analysis with interlaminar compared to transforaminal epidural injections (617,769,770,783,818,821,823,843). Among these, 3 studies (769,770,783) studied and compared all 3 modalities including caudal, interlaminar, and transforaminal epidural injections. Four (278,617,818,821,843) compared interlaminar with transforaminal epidural injections. All of them included disc herniation patients except for Friedly et al (278,818), including only patients suffering with spinal stenosis. All the studies evaluating disc herniation without other modality of treatment showed positive results. One of these studies had 24-month follow-up and all others had at least one year follow-up. While all the studies utilized lidocaine with or without steroids, Ökmen and Ökmen (817) utilized bupivacaine instead of lidocaine. The comparative studies showed generally superiority of transforaminal epidural injections over interlaminar epidural injections in managing disc herniation. With central stenosis, overall, 3 studies were identified. The first study by Manchikanti et al provided a 24-month follow-up with 120 patients in a randomization of 60 patients in each group showing positive results at 24 months with repeat injections.

Friedly et al (818) showed inconclusive results in a poorly designed and performed trial despite its publication in *New England Journal of Medicine* and AHRQ funding.

Based on these high and moderate quality studies, the level of evidence is Level I for disc herniation with strong recommendation, Level II for spinal stenosis with moderate to strong recommendation, Level II for axial or discogenic pain with moderate to strong recommendation.

Multiple systematic reviews have been performed assessing lumbar interlaminar epidural injections. The focus has been either on transforaminal or lumbar interlaminar epidural injections. Overall, the results have been positive except in reviews of inappropriate analysis. Manchikanti et al (75-77,81), Knezevic et al (58), and Kaye et al (60) performed analysis separating into caudal, interlaminar, and transforaminal epidural injections with evidence levels of I to II based on the RCTs.

Appropriately performed cost utility analysis also showed lumbar interlaminar epidural injections to be cost effective within the range of multiple interventional techniques and significantly better than surgical interventions at 2-year follow-up (853). However, inappropriately performed cost utility analysis showed lack of cost effectiveness (854). Manchikanti et al (853) performed cost utility analysis of lumbar interlaminar epidural in the treatment of lumbar disc herniation, central spinal stenosis, and axial or discogenic low back pain in 360 patients with 3 RCTs, with a total estimated cost including direct and indirect costs of \$3,425 for disc herniation, \$3,527 for axial or discogenic pain without disc herniation, \$2,961 for central spinal stenosis, and an overall average cost for lumbar interlaminar epidural injections of \$3,301 respectively.

### 8.6 Lumbar Transforaminal Epidural Injections

Lumbar transforaminal epidural injections' effectiveness were evaluated in 43 studies (273-276,617,618,660,662-664,666,699,700,783,820,821,855-881). After application of inclusion criteria with fluoroscopic guidance, 6-month follow-up with reporting of appropriate outcomes, 13 RCTs met inclusion criteria (273,276,617,769,770,783,818,821,856,857,860,879,881). Methodologic quality assessment was performed utilizing Cochrane review criteria as shown in Appendix Table 9 and IPM-QRB criteria as shown in Appendix Table 10. Table 14 shows the descriptive characteristic features of included studies. Evaluation with both Cochrane and IPM-QRB criteria, 9 were high-quality (273,276,617,770,821,856,857,860,881), and 5 were moderate-quality (769,770,783,818,879).



Table 14. Characteristics of fluoroscopic randomized controlled trials of lumbar transforaminal epidural injections.

Study Characteristics Methodological Quality Scoring	Participants and Interventions	Outcome Measures	Pain Relief and Function						Results			Comment(s)
			3 mos.	6 mos.	12 mos.	24 mos.	Short-term ≤ 6 mos.	Long-Term				
								> 6 mos.	≥ 12 mos.	24 mos.		
Karppinen et al, 2001 (856) RA, PC, F Disc herniation or radiculopathy Quality Scores: Cochrane = 13/13 IPM-QRB = 34/48	Total=160 Methylprednisolone-bupivacaine = 80 Saline = 80 Sodium chloride solution, or methylprednisolone (40 mg) and bupivacaine (5 mg) Number of injections = 1	VAS, ODI, Nottingham Health Profile, cost, physical examination Follow-up: 12 months with only initial procedures	A significant treatment effect in favor of saline treatment for back pain.	The treatment effects in both leg pain and back pain favored the saline treatment.	There were no treatment effects in favor of either treatment.	N/A	Lack of effectiveness of steroid with bupivacaine	Lack of effectiveness of steroid with bupivacaine	N/A	<ul style="list-style-type: none"> <li>An ineffective or inappropriate placebo design, without applicable results.</li> <li>Overall saline appears to have been superior at 3 months and 6 months, but no significant difference at one year between both groups.</li> <li>Leg pain decreased on average by 65% in both groups.</li> <li>Surgery was avoided in the majority of the patients with 18 patients in the steroid group and 15 in the saline group undergoing surgery.</li> </ul>		
Manchikanti et al, 2014 (860) RA, AC, F Disc herniation or radiculopathy Quality Scores: Cochrane = 11/13 IPM-QRB = 44/48	Total = 120 Lidocaine with steroids = 60 Lidocaine vs lidocaine mixed with steroid with infraneural approach Average number of injections = 5 to 6 for 2 years	NRS pain scale, ODI, employment status, opioid intake Responsive category was defined as at least 3 weeks of significant improvement with the first 2 procedures. Significant improvement: 50% improvement in pain and function.	Overall: LA 75% vs LA with steroid 67% Responsive: LA 90% vs LA with steroid 82%	Overall: LA 73% vs LA with steroid 67% Responsive LA 88% vs LA with steroid 87%	Overall: LA 75% vs LA with steroid 57% Responsive LA 92% vs LA with steroid 73%	Overall: LA 65% vs LA with steroid 57% Responsive LA 80% vs LA with steroid 73%	Effectiveness in both groups. Lidocaine alone or with steroids effective.	Effectiveness in both groups. Lidocaine alone or with steroids effective.	<ul style="list-style-type: none"> <li>Similar results with local anesthetic or with local anesthetic and steroids.</li> <li>Nonresponsive patients: local anesthetic = 11, steroids = 15.</li> <li>Local anesthetics were somewhat superior, though not statistically significant.</li> <li>On average, a total of 5-6 injections were administered over a period of 2 years.</li> </ul>			
Riew et al, 2000 & 2006 (275,276) RA, AC, F Disc herniation or radiculopathy Quality Scores: Cochrane = 9/13 IPM-QRB = 32/48	Total = 55 Bupivacaine alone (1 mL, 0.25%) = 27 Bupivacaine (1 mL, 0.25%) with steroid (1 mL betamethasone) = 28 Number of injections = 1-4	Need for operative treatment, North American Spine Society Questionnaire Follow-up: 1 months to 28 months	71% of steroid group chose not to have surgery and 33% of bupivacaine group chose not to have surgery	71% of steroid group chose not to have surgery and 33% of bupivacaine group chose not to have surgery	71% of steroid group chose not to have surgery and 33% of bupivacaine group chose not to have surgery	N/A	P	P	N/A	<ul style="list-style-type: none"> <li>Epidural bupivacaine with steroids was significantly more effective than transforaminal bupivacaine with steroids was significantly more effective than epidural bupivacaine alone in avoiding surgery.</li> </ul>		

Table 14 cont. Characteristics of fluoroscopic randomized controlled trials of lumbar transforaminal epidural injections.

Study Characteristics Methodological Quality Scoring	Participants and Interventions	Outcome Measures	Pain Relief and Function						Results			Comment(s)
			3 mos.	6 mos.	12 mos.	24 mos.	Short-term ≤ 6 mos.	Long-Term				
								> 6 mos.	≥ 12 mos.	24 mos.		
Tatazal et al, 2009 (881) RA, AC, F Disc herniation or radiculopathy and spinal stenosis Quality Scores: Cochrane = 11/13 IPM-QRB = 32/48	Total: 150 patients Lumbar disc herniation: 76 Local anesthetic = 34 Local anesthetic with steroid = 42 Local anesthetic group: Injection of 2 mL of 0.25% bupivacaine with steroid group: Injection of 2 mL of 0.25% bupivacaine and 40 mg of methylprednisolone. Bupivacaine only: Lumbar disc herniation: 34 Foraminal stenosis: 25 Bupivacaine with steroids Lumbar disc herniation: 42 Foraminal stenosis: 23 Number of injections = 1 to 3	VAS, ODI, LBOS Avoidance of surgery Outcomes: 12 weeks 1 year for surgery Excellent outcome	ODI: LA 13.8 ± 3.7 versus LA with steroid 13.6 ± 3.1 VAS leg pain: LA 24.3 ± 5.5 versus LA with steroid 27.46 ± 4.7	N/A	Disc herniation group showed greater reduction in the ODI with a mean change of 15 points from baseline of 46.6 in the bupivacaine only group and 43.4 in bupivacaine and steroid group. There was a mean change in the VAS of 26 mm in the disc prolapse group.	N/A	Excellent to good outcomes in 54% Bupivacaine alone and bupivacaine with steroid are both effective	N/A	The requirements for treatments were the same in local anesthetic alone group or local anesthetic with steroids. Overall surgery rates was 18%, the surgery rate was 22% in the bupivacaine only group and 14% in the bupivacaine and steroid group.	N/A	• There was no significant difference between both groups. Surgery was avoided in both groups. • Corticosteroid addition to local anesthetic failed to provide any additional benefit when compared to local anesthetic injection alone.	
Vad et al, 2002 (879) RA, AC, F Disc herniation or radiculopathy Quality Scores: Cochrane = 5/13 IPM-QRB = 16/48	Total: 50 patients Transforaminal: 25 Trigger point injections: 25 Transforaminal injections were performed by safe triangle approach or sacral foramen injection utilizing contrast followed by 1.5 mL of betamethasone acetate 9 mg and 1.5 mL of 2% preservative free Xylocaine. Trigger point injections were performed with 3 mL of normal saline	Outcome measures included visual numeric score, Roland-Morris score, finger to floor distance, and patient satisfaction score. Outcomes were measured at 3 weeks, 6 weeks, 3 months, 6 months, and 12 months.	In transforaminal group 84% showed improvement in trigger point injection group 48% showed improvement	In transforaminal group 84% showed improvement in trigger point injection group 48% showed improvement	In transforaminal group 84% showed improvement in trigger point injection group 48% showed improvement.	N/A	Transforaminal steroids with lidocaine effective	Transforaminal steroids with lidocaine effective	Transforaminal steroids with lidocaine effective	N/A	This is a randomized trial, but randomization was by patient choice with patients receiving either a high dose transforaminal epidural steroid injection or saline trigger point injection. Study yielded positive results for transforaminal epidural injections at one-year follow-up.	

Table 14 con't. Characteristics of fluoroscopic randomized controlled trials of lumbar transforaminal epidural injections.

Study Characteristics Methodological Quality Scoring	Participants and Interventions	Outcome Measures	Pain Relief and Function					Results			Comment(s)	
			3 mos.	6 mos.	12 mos.	24 mos.	Short-term ≤ 6 mos.	Long-Term > 6 mos.	≥ 12 mos.	24 mos.		
Akerman & Ahmad, 2007 (783) RA, AC, F Disc herniation or radiculopathy Quality Scores: Cochrane = 8/13 IPM-QRB = 25/48	Total=90 Caudal = 30 Interlaminar = 30 Transforaminal = 30 Steroid and saline with local anesthetic injections = 1 to 3	Numeric pain score (0 - 10), rating of pain relief, ODI, BDI, contrast dispersion pattern Follow-up: 24 weeks	Caudal = 57% Interlaminar = 60% Transforaminal = 83%	Caudal = 57% Interlaminar = 60% Transforaminal = 83%	N/A	N/A	N/A	Effective in all arms	Effective in all arms	N/A	N/A	<ul style="list-style-type: none"> <li>Positive mid-term results in a relatively small trial.</li> <li>Shows effectiveness of steroids with all approaches with superiority of transforaminal</li> </ul>
Rados et al, 2011 (821) RA, AC, F Disc herniation or radiculopathy Quality Scores: Cochrane = 9/13 IPM-QRB = 30/48	Total=64 Interlaminar = 32 Transforaminal = 32 Lidocaine with methylprednisolone Number of injections = 1 to 3	VAS, ODI, 50% pain relief Follow-up: 6 months	N/A	N/A	N/A	N/A	N/A	Effective with both approaches	Effective with both approaches	N/A	N/A	<ul style="list-style-type: none"> <li>Positive results with short follow-up period in comparison of 2 approaches with lidocaine with methylprednisolone</li> </ul>
Jeong et al, 2007 (857) RA, AC, F Disc herniation or radiculopathy Quality Scores: Cochrane = 10/13 IPM-QRB = 31/48	Total=193 Ganglionic = 104 Preganglionic = 89 0.5 mL of bupivacaine hydrochloride and 40 mg of 1 mL of triamcinolone Number of injections = 1	VAS Follow-up: 7-30 days 6 months	Preganglionic = 88.4% Ganglionic = 70.9%	Preganglionic = 60.4% Ganglionic = 67.2%	N/A	N/A	Both approaches effective	Both approaches effective	Both approaches effective	N/A	N/A	Moderate quality study with mid-term positive results.
Ghai et al, 2014 (617) RA, DB, AC, F Disc herniation or radiculopathy Quality Scores: Cochrane = 10/13 IPM-QRB = 42/48	Total = 62 Parasagittal interlaminar = 32 Transforaminal = 30 2 mL of methylprednisolone (80 mg) mixed with 2 mL of normal saline for both PIL and transforaminal groups Number of epidural steroid injections: Transforaminal group: 60 PIL group: 58 Average procedures: 2	Visual analog scale, Oswestry Disability questionnaire, significant improvement, greater than 50% pain relief from baseline, Patient Global Impression	PIL group: 78% Transforaminal group: 77%	PIL group: 75% Transforaminal group: 77%	PIL group: 69% Transforaminal group: 77%	N/A	Effectiveness in both arms	Effectiveness in both arms	Effectiveness in both arms	N/A	N/A	This relatively small active control trial with a long-term follow-up assessed the role of parasagittal interlaminar epidural injections and transforaminal epidural injections showing equal improvement with steroids without local anesthetic.

Table 14 con't. Characteristics of fluoroscopic randomized controlled trials of lumbar transforaminal epidural injections.

Study Characteristics Methodological Quality Scoring	Participants and Interventions	Outcome Measures	Pain Relief and Function				Results			Comment(s)
			3 mos.	6 mos.	12 mos.	24 mos.	Short-term ≤ 6 mos.	Long-Term > 6 mos.	≥ 12 mos.	
Friedly et al., 2014 & 2017 (278,818) RA, AC, F Spinal stenosis Quality Scores: Cochrane = 8/13 IPM-QRB = 30/48	Total = 400 Lidocaine Group: Interlaminar = 139 Transforaminal = 61 Glucocorticoids plus lidocaine Group: Interlaminar = 143 Transforaminal = 57 Lidocaine alone or glucocorticoid plus lidocaine Variable doses	NRS, RMDQ Follow-up: 6 weeks	Significant improvement. At 3 weeks and 6 weeks RMDQ scores were significantly less in glucocorticoid-lidocaine group compared to lidocaine group. Leg pain was also significantly less in the steroid group compared to lidocaine alone group.	No significant differences or improvement in observational study	N/A	Both treatments effective	Neither treatment was effective	Neither treatment was effective	N/A	Large trial with flawed design and assessment with positive results at 3 months. Even though based on flawed analysis it shows negative results. Multiple flaws include not only the design and analysis of the data, but patient selection, technical considerations, and inherent bias.
Kennedy et al., 2014 (273) RA, AC, F Disc herniation or radiculopathy Quality Scores: Cochrane = 10/13 IPM-QRB = 30/48	Total patients = 78 Dexamethasone 15 mg or 1.5 mL = 41 patients Triamcinolone 60 mg or 1.5 mL = 37 patients Number of Injections: 1 to 3	NRS, ODI, at least 50% reduction in pain and disability scores	Dexamethasone group 73% reduction in pain scores, 68% reduction in ODI scores Triamcinolone group 73% reduction in pain scores, 68% reduction in ODI scores	N/A	N/A	Both drugs effective	Both drugs effective	N/A	N/A	<ul style="list-style-type: none"> <li>This is one of the studies showing effectiveness of steroids without local anesthetic.</li> <li>Relatively small study with short-term follow-up only</li> </ul>
Kamble et al., 2016 (770) RA, AC, F Single level disc prolapse Quality Scores: Cochrane = 9/13 IPM-QRB = 32/48	Transforaminal = 30 Number of injections = 1-3 Interlaminar = 30 Number of injections = 1-3 Caudal = 30 Number of injections = 1-3	VAS, ODI	Transforaminal = VAS baseline 7.1 ± 0.7 to 2.6 ± 0.7 ODI = 37.7 ± 2.83 to 16.8 ± 2.53 Interlaminar = VAS baseline 7.0 ± 0.7 to 3.4 ± 1.4 ODI = 36.9 ± 2.82 to 21.4 ± 6.08 Caudal = VAS baseline 7.2 ± 0.6 to 3.5 ± 1.0. ODI = 38.3 ± 2.78 to 21.9 ± 3.35	N/A	N/A	All 3 techniques were effective; however, transforaminal group showed superiority. There was no difference between caudal and interlaminar approaches	N/A	N/A	N/A	While all 3 techniques were effective, transforaminal group showed superiority. However, there was no difference between caudal and interlaminar approaches.

Table 14 con't. Characteristics of fluoroscopic randomized controlled trials of lumbar transforaminal epidural injections.

Study Characteristics Methodological Quality Scoring	Participants and Interventions	Outcome Measures	Pain Relief and Function				Results			Comment(s)
			3 mos.	6 mos.	12 mos.	24 mos.	Short-term ≤ 6 mos.	Long-Term		
								> 6 mos.	≥ 12 mos.	
Pandey, 2016 (769) RA, AC, F Disc prolapse Quality Scores: Cochrane = 8/13 IPM-QRB = 29/48	Total = 140 patients Caudal = 82 Transforaminal = 40 Interlaminar = 18 All were treated with steroid and local anesthetic with or without sodium chloride solution	JOA score	N/A	JOA scores Caudal = baseline 15.39 to 24.30 Transforaminal = baseline 15.57 to 26.65 Interlaminar = baseline 15.33 to 25	JOA scores Caudal = baseline 15.39 to 24.02 Effectiveness = 74.3% Transforaminal = baseline 15.57 to 26.55 Effectiveness = 90% Interlaminar = baseline 15.33 to 24.72 Effectiveness = 77.7%	P	P	P	In comparing caudal epidural with interlaminar and transforaminal, authors showed response in 74.3% with caudal route, 77.7% with interlaminar, and 90% with transforaminal approach. Overall results are positive. There is no significant difference between caudal and interlaminar; however, transforaminal appears to be superior.	

RA = Randomized; AC = Active Control; F = Fluoroscopy; PC = Placebo Control; DB = Double-Blind; P = Positive; N = Negative; NA = Not Applicable; LA = local anesthetic; IPM-QRB = Interventional Pain Management techniques -- Quality Appraisal of Reliability and Risk of Bias Assessment; NRS = Numeric Rating Scale; ODI = Oswestry Disability Index; VAS = Visual Analog Scale; LBOS = Low Back Outcome Score; PIL = Parasagittal Interlaminar; RMDQ = Roland Morris Disability Questionnaire; JOA = Japanese Orthopaedic Association; BDI = Beck Depression Inventory

Karppinen et al (856) conducted a high-quality study as graded by both Cochrane and IPM-QRB criteria. Their study looked at the efficacy of a single injection of either sodium chloride solution or local anesthetic with steroid. They followed patients for up to one year. Patients who received sodium chloride fared better at 3 months and 6 months, but there was no significant difference at one year. However, in a subgroup analysis (882), they reported that in patients who had disc protrusions, local anesthetic with steroid had a better efficacy than just sodium chloride. There has been significant related criticism (883,884). In addition, Karppinen et al (882) also calculated cost effectiveness of periradicular infiltration for sciatica based on subgroup analysis of an RCT. Obviously, these types of assessments never yield appropriate cost effectiveness results.

Manchikanti et al (860) conducted an active control trial that followed 120 patients for 2 years. They used an infraneural approach, injecting either local anesthetic alone or local anesthetic with steroid. At the end of the 2-year study period, 65% of those who received local anesthetic alone and 57% who received local anesthetic with steroid had significant improvement in all measured categories: pain intensity, function, and medication reduction. A subcategory analysis of patients who responded to the treatment—determined as those who had at least a 50% improvement in pain and function for 3 weeks with the first 2 injections—reported that 80% of those who received local anesthetic alone saw improvement and 73% of those who received local anesthetic with steroid saw improvement.

Tafazal et al (881) conducted a study on spinal stenosis and disc herniation treated either with local anesthetic alone or local anesthetic with steroid. Only disc herniation inclusion criteria were met. Superior results were reported for sciatica with similar efficacy for local anesthetic alone and local anesthetic with steroid.

Cohen et al (876), in a seemingly flawless study, assessed epidural steroid injections compared to gabapentin for lumbosacral radicular pain. However, the study had numerous flaws including using a safe triangle approach when injecting particulate steroids, a flawed design and analysis of the data, and an inordinately high proportion of patients who withdrew from the study even at the 3-month follow-up (632,633,885,886). Consequently, the study was excluded. The inclusion criteria were also extremely weak with some patients who had less than 3 months of pain and some who had 3 to 6 months. The gabapentin dosage was higher than usually administered in clinical settings at 1800 to 3600 mg



per day without proven efficacy (211). Overall, this trial showed no significant improvement in either group.

Ghahreman et al's (274) follow-up period was even shorter - only one month. Their study was also small but included multiple arms. Consequently, the study was excluded. They reported that local anesthetic with steroids was vastly superior to local anesthetic alone: 54% improvement versus only a 7% improvement. This study also had an arm that received a true placebo—sodium chloride solution injected away from the nerve root. They reported a lack of efficacy for this placebo, but when one study arm was injected with sodium chloride into the source of pain, there was a significant effect, though not as great as local anesthetic with steroids.

In a small study by Riew et al (275,276), patients with disc herniation were injected either with local anesthetic alone or local anesthetic with steroid. Their outcome measure was avoidance of surgery; 33% of those in the local anesthetic alone group and 71% in the local anesthetic with steroid group avoided surgery. While both treatments were deemed effective, local anesthetic with steroid was deemed superior.

The remaining trials were of an active control nature with Vad et al (879) comparing transforaminal epidural injections with local anesthetic with steroid with trigger point injections, demonstrating an overwhelming superiority for transforaminal epidural injections; however, this was a moderate quality trial, barely meeting inclusion criteria. Ackerman and Ahmad (783) compared caudal, interlaminar, and transforaminal approaches which showed transforaminal to be superior to interlaminar and caudal; however, this was a small trial with only a 6-month follow-up; it was also of moderate quality. Jeong et al (857) compared a ganglionic and pre-ganglionic approach in a large population; however, with only a 6-month follow-up, no significant difference was shown between pre-ganglionic and ganglionic approaches. Similarly, Park et al (618) assessed the role of transforaminal epidural injections using a supraneural approach, otherwise known as a safe triangle approach, comparing it to the Kambin triangle approach. This was a relatively small study showing no significant difference between both approaches at 3 months, not included in evidence synthesis. Rados et al (821) and Ghai et al (617) compared interlaminar epidural injections with transforaminal, while Rados et al (821) utilized a standard epidural injection technique; Ghai et al (617) utilized a parasagittal interlaminar approach. Rados et al (821) showed the superiority of transforaminal in a small study and they (617) showed

no significant difference with a parasagittal approach compared to a transforaminal approach.

As described in the section on interlaminar epidural injections, Friedly et al (818) conducted an inappropriate and flawed assessment combining lumbar interlaminar epidural injections with lumbar transforaminal epidural injections. There were multiple flaws in the design as well as the analysis leading to an inappropriate interpretation and conclusions (844).

In one trial (273), transforaminal epidural injections were compared with particulate versus nonparticulate corticosteroids. Comparative effectiveness of transforaminal with particulate versus nonparticulate corticosteroid showed effectiveness of triamcinolone and dexamethasone with pain relief and improvement in functional status up to 6 months, without clear differences between groups.

Among the newer studies (769,770), Pandey (769) assessed the efficacy of epidural steroid injection in management of lumbar prolapsed intervertebral disc in comparative evaluation with caudal, interlaminar, and transforaminal approaches. They included a total of 140 patients with randomization into 3 groups with 80 patients using the caudal approach, 40 patients by the transforaminal approach, and 8 patients with interlaminar approach by a simple randomization; however, this randomization is not uniform. Utilizing JOA scores they calculated the improvement at 6 months and one-year and effectiveness of the medication for each route. Their results showed that one-year after injecting the steroid, all three routes were found to be effective in improving JOA scores with caudal route showing improvement in 74.3%, interlaminar showing improvement in 77.7%, and transforaminal route in 90%. They also showed that the transforaminal route was significantly more effective than caudal and interlaminar at both 6 months and one-year after injection. No significant differences were seen between the caudal and interlaminar approaches. The limitations of this study include unequal randomization and lack of data showing significant improvement.

Kamble et al (770) studied 90 patients randomized to 3 groups with approaches of caudal, interlaminar, and transforaminal with randomization with 30 patients in each group in a single level disc prolapse patients confirmed by MRI. They followed the patients for 12 months and the results were compared using change in VAS score and ODI; however, they presented only 6-month results. Their results showed the change in pain scores were statistically different at 1- and 6-month intervals such as that a higher change was observed by trans-

foraminal route as compared to the other two. There was no difference in the change of scores between interlaminar and caudal routes. For ODI scores, a greater change was seen in transforaminal at all times as compared to the other 2. There was no difference in change of scores between interlaminar and caudal route at any time of the assessment. The VAS scores changed from 7.1 to 2.6 at 6-month follow-up in the transforaminal group compared to 7.0 to 3.4 in the interlaminar group, and 7.2 to 3.5 in the caudal group. Similarly, ODI scores changed from 37.7 to 16.8 in the transforaminal group compared to 36.9 to 21.4 in the interlaminar group and 38.3 to 21.9 in the caudal group. Overall, these results showed positive results; however, as shown above, positive results with transforaminal being superior, but the 12-month results were not published and also 50% relief criteria was not performed.

While the studies considered here concentrated on steroids, there is also significant literature on tumor necrosis factor alpha (TNF- $\alpha$ ) inhibitors (660,662,666,861,863,865,887-890).

Freeman et al (863) performed a randomized, double-blind, placebo-controlled trial of transforaminal epidural TNF- $\alpha$  for the treatment of symptomatic lumbar disc herniation. They included 49 subjects with lumbosacral radicular pain secondary to lumbar disc herniation and treated them with either TNF- $\alpha$  or placebo. Inclusion criteria were lumbosacral radicular pain secondary to lumbar disc herniation and an average leg pain intensity of 5/10 or more. Patients received 2 transforaminal epidural injections, 2 weeks apart, and were assessed for efficacy up to 26 weeks for the second injection. The primary outcome measure was the change in mean daily worst leg pain. They utilized multiple outcome measures. The results showed transforaminal epidural injection was carried out with the injection of 2 mL of injectate. The injectate was variable, ranging from 0.5 mg, 2.5, 12.5 mg of etanercept, and placebo. Essentially, there were 12 patients in each group, except for 2.5 mg of etanercept group, where there were 13 patients. The results showed that 43 of the 49 randomized patients completed the study. Patients receiving 0.5 mg of etanercept showed a clinically and statistically significant reduction in mean daily worst leg pain compared with the placebo cohort from 2 to 26 weeks for both the per protocol population and the intention-to-treat analysis. Fifty percent of these subjects reported 100% reduction in worst leg pain at 4 weeks post treatment compared with 0% subjects in the placebo cohort. Improvement in all secondary outcomes were also observed in the 0.5

mg etanercept cohort. The overall incidence of adverse events was similar in placebo and all etanercept cohorts. Improvement was seen in all groups; however, the best results were obtained in 0.5 mg etanercept group, rather surprisingly.

Dagar et al (865) in a study of transforaminal epidural etanercept followed the patients for 2 months with injection of 2 transforaminal epidural injections of etanercept, 2 mg, 2 weeks apart, assessing the efficacy up to 3 months after the second injection. Results showed 31 of 33 enrolled patients completed the study and showed clinically and statistically significant reduction in VAS for leg pain and back pain and ODI.

Cohen et al (660) performed transforaminal epidural injection of etanercept with 3 groups of 6 patients who received etanercept in escalating doses. Two patients in each group received sham saline injection. They also conducted concurrent animal studies to assess the histologic changes and functional deficits in beagle dogs treated with perineural transforaminal etanercept. Clonidine was safety tested extensively, and only after these studies demonstrated no histological damage or neurologic deficits, open-label and prospective trials conducted, ultimately resulting in the FDA approval for epidural administration in cancer neuropathic pain (887,888). After the initial phase of this epidural etanercept study the authors were advised of the need for investigational new drug requirement for nonfood drug administration approved drugs for neuraxial administration. The human study was temporarily halted until the patients who had been studied to date received MRI showing absence of pathology, and screening MRI procedures were then mandated for subsequent patients. Since then, multiple other studies have been conducted. Cohen et al (660) did not show a dose response relationship with increasing doses of the active agents as others. However, this aspect is troubling because the mechanism of binding and inactivation of TNF- $\alpha$  suggests that there should be a dose response. There was very little difference in ODI numerical improvement, particularly in the higher dose etanercept group as compared to saline.

Other studies included intravenous administration of etanercept (662). Some included short-term follow-up, whereas a few other studies included intravenous administration. Okoro et al (662) in a 3-month follow-up with intravenous administration concluded that small numbers of trial participants limited the statistical analysis; however, they also concluded that the trend appears to show no benefit to the use of

etanercept over placebo in the pharmacological treatment of sciatica. Korhonen et al (664), also administering intravenous, with one-year follow-up showed the long-term results of this randomized trial did not support the use of TNF- $\alpha$  compared with placebo for lumbar radicular pain. A further study in a subgroup of patients, especially in the presence of Modic changes, appears to be warranted. Ohtori et al (666) studied transforaminal approach and provided only 2 weeks of follow-up, comparing with dexamethasone. They concluded that epidural administration with only 2 weeks of administration TNF- $\alpha$  inhibitor into the spinal nerve produced pain relief.

Wei et al (861) compared lidocaine with steroids and lidocaine with TNF- $\alpha$  inhibitor in the treatment of lumbar stenosis. In this RCT, they included 30 patients in each group and also followed them through 6 months. Overall results showed significant improvement in patients receiving lidocaine and TNF- $\alpha$  inhibitor with VAS and the disability index. There was no significant difference in the groups with lidocaine with steroids (Diprosan) or lidocaine only groups.

Overall, it appears that TNF- $\alpha$  inhibitor drugs may have an effect in lumbar radicular pain. In an editorial, Huntoon (887) reviewed pre-clinical and clinical evidence of TNF- $\alpha$  inhibitor. It appears that there may be a role for TNF- $\alpha$  blockers in managing radicular pain. The risk may be that the FDA has a Black Box Warning placed in May 2008, because of the potential for several adverse occurrences. Thus, the use of etanercept must be weighed against these risks (anaphylaxis, immune deficiency, sepsis, tuberculosis, reactivation or novel infection), and the rare possibility of lymphoma. To understand the true incidence of infections of the neuraxis would likely require thousands of applications of these drugs over many years to compare them to steroids (887). Further, the high incidence of radicular pain worldwide mandates a safe therapy, because of the potential for high incidence of sciatica worldwide and also high incidence of high prevalence of epidural injections in the elderly which mandates a safe therapy. Thus, many trials have to be shown to be safe and effective. Huntoon (887) raised the possibilities of issues related to inadvertent injection into a radicular artery. The authors thus far do not comment on these issues. Further, all of them utilized supraneural approach, which is prone to causing intraarterial injections. Consequently, it is strongly cautioned against attempting to inject etanercept until further studies have been performed. In addition, cost is also a major factor.

### **8.6.1 Evidence Synthesis**

The evidence was synthesized based on qualitative and quantitative analysis. Qualitative analysis was performed based on present assessment, whereas quantitative analysis was utilized from previous systematic reviews, which included conventional dual-arm and single-arm analysis in multiple manuscripts. In this analysis, with the inclusion of 13 RCTs (273,275,617,769,770,783,818,821,856,857,860,879,881), there was only one RCT utilizing sodium chloride solution (856), which was considered as placebo even though there are a multitude of questions in relation to injecting sodium chloride solution over an active structure (56). The remaining were all active-controlled trials. Consequently, a total of 12 of 13 studies focused on disc herniation with transforaminal epidural injections. Friedly et al (278,818) studied central and foraminal spinal stenosis. Other studies were comparative analysis between lumbar interlaminar and transforaminal epidural injections or caudal, interlaminar, and transforaminal epidural injections or preganglionic and postganglionic approaches or comparative analysis among the drugs with dexamethasone and triamcinolone (273,617,843) and all 3 approaches were utilized (699,700,783). In disc herniation, among the 5 RCTs included, the only trial which is considered as placebo-controlled has shown lack of effectiveness even though in subgroup analysis, they felt it was effective and also they performed cost utility analysis. The remaining 4 trials (275,860,879,881) showed positive results. The larger studies by Manchikanti et al with 120 patients and 24-month follow-up showed positive results at 24 months (860). However, these results were not superior to interlaminar epidural injections or caudal epidural injections (614). Tafazal et al (881) in studying 150 patients with radiculitis secondary to disc herniation or spinal stenosis showed positive results with no significant difference with local anesthetic alone or with local anesthetic and steroid. Vad et al (879) in a moderate quality study showed positive results with a 12-month follow-up in 50 patients receiving transforaminal epidural injections. Further, multiple other studies comparing interlaminar and transforaminal in disc herniation also showed positive results (617,699,700,783,841,857). The quantitative analysis and previous systematic reviews also showed positive evidence. Consequently, the evidence for transforaminal epidural injections in lumbar disc herniation is Level I with strong recommendation.

Riew et al (275) in a small study of 55 patients utilized bupivacaine alone or bupivacaine with steroids to assess the avoidance of surgery. They showed that 71%

of the steroid group chose not to have surgery and 33% of bupivacaine group not to have surgery. Overall, bupivacaine with steroids were effective even though bupivacaine alone was not effective.

For spinal stenosis, Friedly et al (818) performed a poorly designed and executed study with negative results for transforaminal epidural injections. Tafazal et al (881) also studied spinal stenosis, along with disc herniation in a total of 150 patients with 64 patients with spinal stenosis. They also showed positive results with local anesthetic, as well as steroids. However, there was no significant difference between steroid and local anesthetic. Consequently, the level of evidence is Level IV to III with moderate recommendation of transforaminal epidural injections in managing central spinal stenosis.

One study (273) also evaluated the role of dexamethasone versus triamcinolone showing equivocal results in a relatively small study without local anesthetic. One study (857) compared ganglionic and preganglionic approaches with a 6-month follow-up showing the effectiveness of both approaches. The studies comparing interlaminar epidural injections with transforaminal (617,699,700,783,821) showed either equivalent improvement or superiority of transforaminal epidural injections in managing disc herniation. Thus, overall evidence is Level III with moderate to weak recommendation for transforaminal epidural injections for disc herniation over lumbar interlaminar or caudal epidural approaches.

Multiple systematic reviews also have been performed assessing lumbar transforaminal epidural injections. Overall, the results have been positive except in reviews with inappropriate analysis.

### 8.7 Percutaneous Adhesiolysis

Literature search for percutaneous adhesiolysis in the lumbar spine yielded a total of 29 studies (891-919) and 9 RCTs (891-901) meeting inclusion criteria.

For this analysis, we also utilized observational studies for post-lumbar central spinal stenosis (908,910). There were 6 RCTs of post-surgery syndrome (893,894,896-899,901), 2 RCTs of spinal stenosis (891,892,900), and only one RCT assessing disc herniation (895). Appendix Table 11 shows Cochrane review criteria for RCTs. Appendix Table 12 shows IPM-QRB criteria for RCTs, whereas Appendix Table 13 shows IPM-QRBNR for nonrandomized or observational studies. Table 15 shows characteristic features of various randomized and nonrandomized studies in assessing effectiveness data.

Manchikanti et al (72) performed a systematic

review and meta-analysis of the effectiveness of percutaneous adhesiolysis in managing post-lumbar surgery syndrome and showed Level I or strong evidence with inclusion of 6 RCTs (893,894,896,897,901,902) and 4 observational studies (903-906), with 7 of the studies providing results of at least 12 months of follow-up. All of the studies included in the analysis showed positive results. The randomized trials assessing response rate based on significant improvement of 50% pain relief and functional status have shown 70% (893,894) and 72% (897) of the patients with significant improvement at 1-year follow-up, and 88% at 2-year follow-up (893,894). Other studies also have shown significant improvement (903,906). Meta-analysis also showed significant improvement with percutaneous adhesiolysis in comparison with epidural injections and with a single-arm meta-analysis for the active control studies.

Manchikanti et al (73) also performed a systematic review and meta-analysis with inclusion of 2 RCTs (891,892,900) and 4 observational studies (892,908-910) with Level II or moderate evidence in the systematic review and meta-analysis. The primary outcome or hard endpoint was the proportion of patients with 50% pain relief and improvement in functionality, whereas secondary outcome measures, or soft endpoints, were pain relief and/or improvement in functionality. The positive results were observed from all the studies included in this analysis, even though balloon inflated catheters showed superior results compared to catheter adhesiolysis. Among the randomized trials, one randomized trial (891,892) assessing response rate based on significant improvement of 50% pain relief and functional status has shown a success rate of 76% at 12 months, compared to 4% in the caudal epidural group. The second RCT (900) with only 6-month followup available comparing catheter-based adhesiolysis with inflatable balloon catheter showed superior results with the balloon inflatable catheter. Further, among the observational studies, one study followed the patients for 24 months with a 71% improvement rate. Surprisingly enough, in this systematic review, superior results were observed in appropriately conducted long-term studies (891,892). Single arm meta-analysis also showed significant improvement from baseline with 38% improvement of pain relief and 30% improvement of functional status overall combining all the studies. Further, the available data shows superior results when significant improvement was utilized as the primary outcome parameter at 12 months as well as 24 months in over 70% of the patients. All the studies had at least 12 months of appropriate outcomes available.

Table 15. Effectiveness of percutaneous adhesiolysis assessed by randomized controlled trials and observational studies.

Study Characteristics Methodological Quality Scoring	Participants and Interventions	Outcome Measures	Pain Relief and Function					Results			Comment(s)
			3 mos.	6 mos.	12 mos.	24 mos.	Short-term ≤ 6 mos.	Long-Term			
								> 6 mos.	≥ 12 mos.	24 mos.	
<b>LUMBAR POST-SURGERY SYNDROME</b>											
Manchikanti et al, 2009, 2012 (893,894) RA, AC, DB Post-lumbar surgery syndrome Quality Scores: Cochrane: 11/13 IPM-QRR: 42/48	Total = 120 Percutaneous adhesiolysis = 60 Caudal epidural = 60 - Percutaneous adhesiolysis with lidocaine, betamethasone and 10% hypertonic solution; - Caudal epidural injection with lidocaine, betamethasone and 0.9% NaCl solution	NRS, ODI, employment status, opioid intake	78% in adhesiolysis group experienced >50% relief compared to 23% in control group	73% in adhesiolysis group experienced >50% relief compared to 7% in control group	70% in adhesiolysis group experienced >50% relief compared to 5% in control group	82% in adhesiolysis group vs. 5% in caudal group	P	P	P	P	Short- and long-term effectiveness of adhesiolysis on post-lumbar surgery syndrome
Chan-jing et al, 2012 (896) RA, AC, DB Post-lumbar surgery syndrome Quality Scores: Cochrane: 12/13 IPM-QRR: 34/48	Total = 76 Percutaneous adhesiolysis = 38 Epidural injection = 38 - Percutaneous adhesiolysis with saline and dexamethasone; - Epidural injection of dexamethasone	VAS, McNabb lumbar disease evaluation, opioid use	NA	Intervention group VAS score >3 VAS points lower than baseline, control group VAS score <1 point lower than baseline	NA	NA	P	NA	NA	NA	Short-term effectiveness of adhesiolysis in patients with failed back surgery syndrome
Manchikanti et al, 2004 (897) RA, PC, DB Predominantly post-surgery syndrome Quality Scores: Cochrane: 12/13 IPM-QRR: 37/48	Total = 75 Control with normal saline = 25 Adhesiolysis with normal saline = 25 Adhesiolysis with hypertonic saline = 25 - One-day adhesiolysis with 0.9% saline and local anesthetic and steroid; - One-day adhesiolysis with 10% saline and local anesthetic and steroid; - Epidural injection with local anesthetic, steroid and 0.9% saline	VAS, ODI, employment status, opioid intake, range of motion, psychological evaluation by P-3	72% of 10% saline group, 64% of 0.9% group and 0% of control group had >50% pain relief	72% of 10% saline group, 60% of 0.9% group and 0% of control group had >50% pain relief	72% of 10% saline group, 60% of 0.9% group and 0% of control group had >50% pain relief	NA	P	P	P	NA	Short- and long-term effectiveness and equivalency between normal and hypertonic saline adhesiolysis in chronic low back pain
Veielmann et al, 2006 (898) RA, AC Post-surgery syndrome and disc prolapse Quality Scores: Cochrane: 8/13 IPM-QRR: 30/48	Total = 99 Adhesiolysis = 47 Physiotherapy = 52 - One-day adhesiolysis with 10% saline, ropivacaine and triamcinolone; - Physical therapy 99 patients with chronic low back pain and sciatica based on disc protrusion/prolapse or failed back surgery	VAS, ODI, GHS, use of analgesics	Mean improvement of the adhesiolysis group was >50% in VAS and >40% in ODI. Physical therapy group had ~10% relief	Mean improvement of the adhesiolysis group was >50% in VAS and >40% in ODI. Physical therapy group had ~10% relief	Mean improvement of the adhesiolysis group was >50% in VAS and >40% in ODI. Physical therapy group had ~10% relief	NA	P	P	P	NA	Short and long-term effectiveness of adhesiolysis over physiotherapy in patients with sciatica



Table 15 (con't). Effectiveness of percutaneous adhesiolysis assessed by randomized controlled trials and observational studies.

Study Characteristics Methodological Quality Scoring	Participants and Interventions	Outcome Measures	Pain Relief and Function					Results			Comment(s)									
			3 mos.	6 mos.	12 mos.	24 mos.	Short-term ≤ 6 mos.	Long-Term												
Heavner et al, 1999 (899) RA, DB Post-surgery syndrome and disc prolapse Quality Scores: Cochrane: 10/13 IPM-QRB: 23/48	Total = 59 Group I (hypertonic saline plus hyaluronidase) = 17 Group II (hypertonic saline) = 15 Group III (isotonic saline) = 17 Group IV (isotonic saline plus hyaluronidase) = 10 3-day adhesiolysis with either 0.9% or 10% saline and with or without hyaluronidase	SEM, VAS for back, right leg, and left leg pain	About 50% of subjects had more than 10/100 improvement in VAS	About 50% of subjects had more than 10/100 improvement in VAS	About 50% of subjects had more than 10/100 improvement in VAS	NA	P	P	P	NA	NA	NA	Short- and long-term effectiveness and equivalency between adhesiolysis groups with 0.9% and 10% saline and with or without hyaluronidase in patients with low back pain and radiculopathy							
Akbas et al, 2018 (901) RA, AC Post-lumbar surgery syndrome Quality Scores: Cochrane: 9/13 IPM-QRB: 35/48	60 patients 3 groups: Caudal = 20 S1 foraminal = 20 L5 transforaminal = 20 All patients underwent placement of 16 gauge RX Coude needle in the Rac2 catheter with 3 approaches along with adhesiolysis. They also received exercises with neural flossing 3-4 times daily for 3 months.	VAS, ODI 1 month, 3 months, 6 months after the procedure	Significant improvement was seen with pain and functional status with reduction in scores with all 3 approaches with no significant differences between the approaches.	Significant improvement was seen with pain and functional status with reduction in scores with all 3 approaches with no significant differences between the approaches.	Significant improvement was seen with pain and functional status with reduction in scores with all 3 approaches with no significant differences between the approaches.	NA	P	P	P	NA	NA	The 3 approaches result in the same outcome with regard to pain relief and complication rate. Adhesiolysis is an effective technique in managing post-lumbar surgery syndrome pain.								
<b>LUMBAR SPINAL STENOSIS</b>																				
Manchikanti et al, 2009, 2013 (891,892) Central spinal stenosis RA, AC Quality Scores: Cochrane: 11/13 IPM-QRB: 36/48	Total = 50 Percutaneous adhesiolysis = 25 Additional 45 patients followed for 2 years in adhesiolysis group Caudal epidural = 25 - Percutaneous adhesiolysis with lidocaine, 10% NaCl solution and betamethasone; - Caudal epidural injection with catheterization, lidocaine, normal NaCl solution and betamethasone	NRS, ODI, opioid intake, employment status	80% of adhesiolysis had >50% relief vs 28% for caudal	80% of adhesiolysis had >50% relief vs 12% for caudal	76% of adhesiolysis had >50% relief (3.5 average injections) vs 4% for caudal	71% of patients in adhesiolysis group only	P	P	P	P	P	Short- and long-term effectiveness of adhesiolysis on chronic intractable pain secondary to lumbar central spinal stenosis								

Table 15 (cont). Effectiveness of percutaneous adhesiolysis assessed by randomized controlled trials and observational studies.

Study Characteristics Methodological Quality Scoring	Participants and Interventions	Outcome Measures	Pain Relief and Function						Results			Comment(s)	
			3 mos.	6 mos.	12 mos.	24 mos.	Short-term ≤ 6 mos.	Long-Term	> 6 mos.	≥ 12 mos.	24 mos.		
Karm et al, 2018 (900) RA, AC, DB Refractory central lumbar spinal stenosis who suffered from chronic lower back pain and/or lumbar radicular pain Quality Scores: Cochrane: 11/13 IPM-QRB: 34/48	Total = 44 Balloon adhesiolysis = 24 Balloon-less adhesiolysis = 20 2-day percutaneous adhesiolysis with inflatable balloon catheter or balloon-less catheter	NRS, ODI, GPES, MQS	Successful response of 40% in balloon-less group and 58% in inflatable balloon group	Successful response of 25% in balloon-less group and 58% in inflatable balloon group	NA	NA	NA	NA	N = (balloon-less), P = (inflatable balloon)	NA	NA	NA	Negative study for adhesiolysis with balloon-less catheter, positive study for inflatable balloon catheter on chronic lower back pain and/or lumbar radicular pain
Choi et al, 2016 (908) Single arm, prospective observational study Severe spinal stenosis Quality Score: IPM-QRBNR = 28/48	61 patients Adhesiolysis with a single combined treatment with balloon inflatable catheter ZiNeu.	NRS, ODI measures at 1, 3, 6, and 12 months, 30% or more than 2-point reduction in NRS	61%	57%	36%	NA	NA	P	P	P	NA	NA	Patients with severe stenosis and also significant proportion of patients with foraminal stenosis, 31% were included. There was large number of patients missing followup at end of one-year. Improvement of 30% or NRS of 2 considered
Choi et al, 2013 (910) Retrospective assessment Post-lumbar surgery syndrome or spinal stenosis Quality Score: IPM-QRBNR = 24/48	78 patients studied with percutaneous adhesiolysis with caudal approach. Following appropriate adhesiolysis, 5 mL of 0.25% ropivacaine containing 1,500 units or hyaluronidase was injected in the recovery room. 6 mL of 10% sodium chloride solution was injected. Following this, 2 mL of 0.9% sodium chloride solution containing 40 mg of triamcinolone was injected.	Pain relief. Assessment of proportion of patients based on severity of the stenosis.	51.1% successful response	49% successful response	NA	NA	NA	P	NA	NA	NA	NA	Small retrospective assessment in 78 patients with positive results with a single treatment in 51% of the patients at 3 months and 49% of the patients at 6 months. Authors also included a large number of patients with previous surgery of 37% of the patients. They also included 33% with foraminal stenosis. In addition severe stenosis was seen in 13% of the patients and root compression in 46% of the patients providing somewhat mixed results.

Table 15 (con't). Effectiveness of percutaneous adhesiolysis assessed by randomized controlled trials and observational studies.

Study Characteristics Methodological Quality Scoring	Participants and Interventions	Outcome Measures	Pain Relief and Function					Results			Comment(s)
			3 mos.	6 mos.	12 mos.	24 mos.	Short-term ≤ 6 mos.	Long-Term			
								> 6 mos.	≥ 12 mos.	24 mos.	
DISC HERNIATION											
Gerdemeyer et al, 2013 (895) RA, PC, DB Chronic lumbar radicular pain lasting longer than 4 months Quality Scores: Cochrane: 13/13 IPM-QRB 44/48	Total = 90 Percutaneous adhesiolysis = 46 Placebo = 44 - Percutaneous adhesiolysis with steroids and 10% saline solution; - Placebo (no spinal canal insertion, saline solution)	ODI, VAS	26/45 of treated group had >50% improvement in ODI compared to 7/42 of placebo group	31/42 of treated group had >50% improvement in ODI compared to 4/37 of placebo group	28/31 of treated group had >50% improvement in ODI compared to 9/26 of placebo group	NA	P	P	P	NA	Short- and long-term effectiveness of adhesiolysis on chronic lumbar radicular pain Most relevant placebo-controlled trial

RA = randomized; DB = double-blind; AC = active control; PC = placebo-controlled; P = positive; N = negative; NA = not applicable; NRS = Numeric Rating Scale; ODI = Oswestry disability index; VAS = Visual Analog Scale; GHS = Gerbershagen score; SEM = Short Form McGill Pain Questionnaire; GPES = Global Perceived Effect of Satisfaction; MQS = Medication Quantification Scale III; IPM-QRB = Interventional Pain Management techniques - Quality Appraisal of Reliability and Risk of Bias Assessment; IPM-QRBNR = Interventional Pain Management Techniques - Quality Appraisal of Reliability and Risk of Bias Assessment for Nonrandomized Studies

In reference to disc herniation, multiple studies have been performed; however, there has been only one high-quality randomized, double-blind, placebo-controlled trial (895). Other studies (897-899) also included a small number of patients with disc herniation. None of the observational studies met inclusion criteria.

Gerdemeyer et al (895) performed the trial in patients with chronic radicular pain lasting longer than 4 months, which failed to respond to conservative treatment. After screening 381 patients, 90 patients were enrolled. They were randomly assigned to receive either percutaneous neurolysis or placebo with concealed allocation. The primary outcome measure was differences in percentage of change of ODI scores 3 months after intervention. Secondary outcome measures were difference in percent change of ODI scores and VAS at 6 and 12 months after intervention and success rates defined as at least 50% reduction in ODI and VAS scores (mean change from baseline) at 3, 6, and 12 months after treatment. With strict criteria, they also used extensive statistical analysis. The methodology included a 3-day lysis procedure in both groups. The lysis procedure was performed with adhesiolysis and following the placement of the catheter with injection of 10 mL of 0.25% bupivacaine through the catheter followed by 10 mL of preservative free saline containing 150 units per mL of hyaluronidase, saline (10 mL 10%) containing 40 mg of triamcinolone being injected slowly along with 2 mL of 0.25% bupivacaine. The catheter was left in place and on each of the next 2 days, 10 mL of 0.25% bupivacaine was injected through the catheter, followed by the slow injection of 10 mL of 10% saline and 2 mL of 0.25% bupivacaine, then the catheter was removed. In the placebo group, however, a needle and catheter were inserted, similar to lysis group, except the needle was intentionally inserted so it did not enter the spinal canal and the catheter was inserted into the subcutaneous tissues overlying the effected level. Each patient received through the catheter 10 mL of preservative free saline on each of the next 2 days, then the catheter was removed. Subsequent to the 3 injection series, all subjects were prescribed physical therapy with no activity restrictions. Patients were provided with rescue medication of paracetamol. The results showed the ODI and VAS scores, as well as the success for ODI versus VAS were significantly better at 3, 6, and 12 months in the lysis group versus the control group. The ODI in the lysis group improved 55.3 ± 11.6 to 26.4 ± 10.8 after 3 months. The placebo group improved from 55.4 ± 11.5 to 41.8 ± 14.6. In addition, VAS improved 6.7 ± 1.1 to 2.9

$\pm 1.9$  in the active group and from  $6.7 \pm 1.1$  to  $4.8 \pm 2.2$  after placebo. Twelve-month follow-up showed further improvement and the differences were significant. The main advantages of this study have been that they truly utilized a placebo response by placing the catheter subcutaneously without entering the spinal canal. Twelve-month outcomes showed 50% improvement in VAS in 69% of patients in the placebo group and 94% of the patients in the lysis group, whereas, ODI greater than 50% improvement was seen in 35% of the patients in the placebo group and 90% of the patients in the lysis group with significant differences as shown in Table 16.

### 8.7.1 Evidence Synthesis

Evidence synthesis in this manuscript was derived from qualitative and quantitative analysis. Qualitative analysis was performed based on the present assessment, whereas quantitative analysis was utilized from previous systematic reviews, which included conventional dual-arm and single-arm analysis in multiple manuscripts. In the present analysis 6 RCTs assessed the role of adhesiolysis in post-lumbar surgery syndrome (893,894,896-899,901). All studies were subjected to

conventional dual-arm and single-arm analysis by Manchikanti et al (72). There was one study with 2-year follow-up (893,894) showing short-term and long-term effectiveness of adhesiolysis on post-lumbar surgery syndrome in 82% of the patients in the adhesiolysis group with multiple procedures. The 5 RCTs assessed patients for one-year (893,894,897,898,899,901), and all of them showed positive results with short-term and long-term improvement. One trial (896) provided only 6 month relief showing short-term improvement. Thus, evidence for lumbar post-surgery syndrome is Level I with strong recommendation.

In spinal stenosis, percutaneous adhesiolysis was studied in 2 RCTs (891,892,900) and 2 observational studies (908,910). A single study (891,892) showed positive results with 71% of patients responding in adhesiolysis group at 24-month follow-up. The results were 76% at end of one-year with significant improvement with average procedures of 6.4 per 2 years. The second RCT (900) compared balloon adhesiolysis with percutaneous adhesiolysis in 44 patients. They showed successful adhesiolysis in inflatable balloon group, consequently this study is considered as negative for percutaneous adhesiolysis and positive for balloon adhesiolysis. Another observational study with a single-arm (908), also showed adhesiolysis with a single combined treatment of balloon inflated catheter with positive results. The study had a small number of patients and also several patients were missing. The second retrospective (910) assessment which included patients with spinal stenosis as well as post-lumbar surgery syndrome showed 45% successful response at 6 months in 78 patients considered as positive. Thus, the level of evidence is considered as Level II with moderate to strong recommendation based on lack of other available treatments.

For chronic recalcitrant disc herniation, there is one high-quality RCT as described here (895). Other randomized trials also utilized a small proportion of patients with chronic disc herniation (897-899). Overall the results have been positive in all the studies, consequently, the level of evidence is II with moderate to strong recommendation in patients with chronic disc herniation failing to respond to conservative modalities including epidural injections.

Cost utility analysis by Manchikanti et al (920) assessing post-lumbar surgery syndrome and lumbar central spinal stenosis with percutaneous adhesiolysis showed direct costs of \$2,652 for post-lumbar surgery syndrome and \$2,649 for lumbar central spinal stenosis for one-year QALY. Overall costs for one-year QALY were \$4,428.84 for post-lumbar surgery syndrome and

Table 16. Follow-up data 3, 6, and 12 months after intervention.

Outcome of primary criteria 3 months after intervention			
	Placebo group	Lysis group	P-value
ODI	41.8 $\pm$ 14.6	26.4 $\pm$ 10.8	< 0.01 **
VAS	4.8 $\pm$ 2.2	2.9 $\pm$ 1.9	< 0.01 **
> 50% improvement ODI	7/42 (17%)	26/45 (58%)	< 0.01 **
> 50% improvement VAS	12/42 (29%)	31/45 (69%)	< 0.01 **
Outcome of primary criteria 6 months after intervention			
ODI	37.3 $\pm$ 13.1	11.9 $\pm$ 8.7	< 0.01 **
VAS	3.8 $\pm$ 1.6	1.4 $\pm$ 0.9	< 0.01 **
> 50% improvement ODI	4/37 (11%)	31/42 (74%)	< 0.01 **
>50% improvement VAS	14/36 (39%)	32/42 (76%)	= 0.01 **
Outcome of primary criteria 12 months after intervention			
ODI	30.7 $\pm$ 14.2	9.6 $\pm$ 9.3	< 0.01 **
VAS	2.8 $\pm$ 1.5	1.2 $\pm$ 1.0	< 0.01 **
> 50% improvement ODI	9/26 (35%)	28/31 (90%)	< 0.01 **
> 50% improvement VAS	18/26 (69%)	29/31 (94%)	< 0.032 **

\*\* indicate significance  $P < 0.05$

ODI = Oswestry disability index; VAS = Visual Analog Scale  
Adapted and modified with permission from: Gerdesmeyer L, et al. Percutaneous epidural lysis of adhesions in chronic lumbar radicular pain: A randomized, double-blind, placebo-controlled trial. *Pain Physician* 2013;16:185-196 (895).

\$4,423.83 for lumbar central spinal stenosis, which included direct and indirect costs.

As described earlier, Manchikanti et al (72) performed a conventional dual-arm and a single-arm meta-analysis in post-lumbar surgery syndrome showing significant improvement in pain relief and ODI scores. Similarly, Manchikanti et al (73) in a systematic review and meta-analysis of spinal stenosis showed the results of single-arm analysis with significant improvement with percutaneous adhesiolysis.

### 8.8 Cervical and Thoracic Interlaminar Epidural Injections

For this analysis, cervical and thoracic interlaminar epidural injections were combined based on the recommendation of CMS and the American Medical Association (AMA) Current Procedural Terminology (CPT) Committee as a single region and due to the lack of multiple studies in the thoracic region. Our search criteria yielded a total of 22 studies (588,921-941) meeting the initial inclusion criteria. However, with elimination of nonfluoroscopic guided treatments and also short-term follow-ups, a total of 7 RCTs were included in the analysis with 6 trials in the cervical spine (922,924,925,927,932,941), and one trial in the thoracic spine (588). We also included 2 observational studies (937,940) in the cervical spine with long-term follow-up. Appendix Table 14 shows Cochrane criteria, Appendix Table 15 shows IPM-QRB criteria for RCTs, whereas Table 17 shows descriptive characteristics of cervical and thoracic interlaminar epidural injections.

Seven randomized trials (588,922,924,925,927,932,941) and 2 observational studies (937,940) met the inclusion criteria. Cochrane and IPM-QRB criteria graded 6 of the RCTs to be of high-quality (588,922,924,925,927,941) and one of them to be of moderate quality (932).

Manchikanti et al conducted 4 active control studies in the cervical spine (922,924,925,927) and one (588) in the thoracic spine. These studies enrolled 416 patients in the cervical spine and 110 patients in the thoracic spine and examined the use of local anesthetic alone or local anesthetic with steroid for the following etiologies: disc herniation, discogenic pain without facet joint pain, central spinal stenosis, and post-surgery syndrome. Only one study (925) had a minimum one-year follow-up and the other 4 had a 2-year follow-up. Both Cochrane and IPM-QRB criteria graded all of them as high-quality.

All 5 of these studies found there to be similar results for the efficacy of the 2 injectates in each etiology. These studies analyzed outcomes based on subgroups

that were either responsive or nonresponsive to the treatment that was received. A responsive patient was one who received at least 3 weeks of 50% improvement with the first 2 treatments. Responsive group patients in all etiologies had superior outcomes. All the studies showed positive results achieving 68% to 80% pain relief with functional status improvement.

McCormick et al (941) published a prospective randomized comparative trial of targeted steroid injection via epidural catheter compared to standard interlaminar approach for the treatment of unilateral cervical radicular pain at C5-6 with 76 participants. The criteria were rather strict with radicular pain, MRI pathology, consistent with clinical symptoms and signs, a numeric pain score of 4 or higher, nonresponsiveness of conservative therapy, but utilized 4-week duration of pain as the inclusion criteria. Procedures were performed under fluoroscopic guidance with injection of 2 mL of triamcinolone acetate 40 mg/mL diluted in 1 mL of 1% preservative free lidocaine. They had multiple primary and secondary outcome measures including pain relief, NDI, and pain disability index, along with Global Impression of Change, daily morphine equivalent, and medication quantification scale (MQS) III scores. At one-month follow-up in the catheter and standard epidural injection groups, 26 or 72% and 23 or 60% of the participants reported 50% or greater NRS reductions and a similar number reported improvement in NDI. The authors did not report 50% pain relief beyond one-month; however, other parameters showed at 3 months and 6 months significant reductions in pain from the baseline of 6 to 2.5 at 3 months, 2 at 6 months in the standard group; whereas, it was 7 and 2 at 3 months, and 2 at 6 months in the targeted catheter group. NDI scores also improved from 21 to 15.5 at 3 months and 8 at 6 months in the standard intervention group compared to a baseline of 19 with changes of 10.5 and 7.5 at 3 months and 6 months in the targeted catheter group. It appeared that both were effective, however, the targeted group tended to do better. Further, they also reported that there was a trend of lower incidence of cervical spine surgery in the targeted group during the 6-month follow-up.

Cohen et al (932) performed a double-blind RCT assessing a conservative management group that received medication and physical therapy with an epidural injection group that received steroid alone and with a combination group that received epidural steroids as well as conservative management. The study may be criticized for various flaws in the design as well as its analysis with a large number of noncompliant patients; it appears that patients may have done better around 3 months



Table 17. Characteristics of fluoroscopic cervical/thoracic interlaminar epidural injections.

Study Characteristics Methodological Quality Scoring	Participants and Interventions	Outcome Measures	Pain Relief and Function					Results			Comment(s)
			3 mos.	6 mos.	12 mos.	24 mos.	Short-term ≤ 6 mos.	Long-term > 6 mos.	≥ 12 mos.	24 mos.	
Manchikanti et al 2013 (922) RA, AC, DB, F Cervical disc herniation or radiculopathy Quality Scores: Cochrane = 12/13 IPM-QRB = 43/48	Total = 120 Local anesthetic = 60 Local anesthetic with steroids = 60 Local anesthetic or with Celestone Average number of injections = 5 to 6 for 2 years	NRS, NDI, employment status, opioid intake Significant improvement > 50% pain relief and > 50% functional status improvement	Overall: LA 83% vs LA with steroid 70% Responsive: LA 91% vs LA with steroid 84%	Overall: LA 82% vs LA with steroid 73% Responsive: LA 91% vs LA with steroid 86%	Overall: LA 72% vs LA with steroid 68% Responsive: LA 77% vs LA with steroid 82%	Overall: LA 72% vs LA with steroid 68% Responsive: LA 77% vs LA with steroid 80%	P	P	P	P	<ul style="list-style-type: none"> <li>Positive results in a randomized large trial performed under fluoroscopy with long-term follow-up.</li> <li>Similar results with local anesthetic or with local anesthetic and steroids.</li> <li>Overall, a total of 5-6 injections were administered over a period of 2 years.</li> </ul>
McComnick et al. 2017 (941) RA, SB, AC, F Unilateral cervical radicular pain C5-C6 Quality Scores: Cochrane = 10/13 IPM-QRB = 37/48	Total = 76 Standard interlaminar epidural injection at C5-C6 = 40 Targeted cervical interlaminar epidural steroid injections = 36 Injectate was 2 mL of triamcinolone acetate (80 mg) diluted in 1 mL of 1% preservative free lidocaine in both groups.	NRS, ONDI, PDI, MPQ, PGIC, DME, MQS	NRS standard group: Baseline: 6 3 months: 2.5 NRS targeted catheter group: Baseline: 7 3 months: 2 ONDI standard group: Baseline: 21 3 months: 15.5 ONDI targeted group: Baseline: 19 3 months: 10.5	NRS standard group: 6 months: 2 NRS targeted catheter group: 6 months: 2 ONDI standard group: 6 months: 8 ONDI targeted group: 6 months: 7.5	NA	NA	P	NA	NA	<p>This is a prospective randomized comparative trial of standard interlaminar epidural injection compared to targeted steroid injection via epidural catheter approach in unilateral cervical radicular pain showing effectiveness of both modalities and no significant difference noted between the modalities. The relief with one injection lasted almost 6 months in responsive patients, which is unusual based on the other studies.</p>	
Cohen et al. 2014 (932) RA, AC, F Cervical disc herniation or radiculopathy Quality Scores: Cochrane = 6/13 IPM-QRB = 24/48	Total = 169 Conservative treatment group = 59 (medical therapy and physical modalities) Epidural steroid injection group = 58 (3 mL of solution containing 60 mg of depo-methylprednisolone and normal saline) Combination therapy group = 55 (epidural steroid injection and gabapentin and physical modalities)	Within group changes and between group changes, pain, NRS, NDI	Positive outcome: Conservative group: 26.8% Epidural group: 36.7% Combination therapy group: 56.9%	Positive outcome: Conservative group: 23.6% Epidural group: 25.5% Combination therapy group: 44%	NA	NA	U	NA	NA	<ul style="list-style-type: none"> <li>Undetermined results at 3 months for epidural steroid injection without local anesthetic combined with conservative management, with borderline response in 36.7% at 3 months and 25.5% at 6 months with epidural injections.</li> <li>This trial included acute and chronic pain patients. Number of injections provided is not shown. Local anesthetic was not utilized. There was a large number of patients who were not compliant in conservative and combination groups.</li> </ul>	

Table 17 (con't). Characteristics of fluoroscopic cervical/thoracic interlaminar epidural injections.

Study Characteristics Methodological Quality Scoring	Participants and Interventions	Outcome Measures	Pain Relief and Function					Results			Comment(s)
			3 mos.	6 mos.	12 mos.	24 mos.	Short-term ≤ 6 mos.	Long-Term			
								> 6 mos.	≥ 12 mos.	24 mos.	
<p>Manchikanti et al, 2012 (925)                      RA, AC, F                      Cervical spinal stenosis                      Quality Scores:                      Cochrane = 11/13                      IPM-QRB = 42/48</p>	<p>Total = 60                      Local anesthetic only = 30                      Local anesthetic with steroids = 30                      Celestone                      Average number of injections = 3 to 4 for 1 year</p>	<p>NRS, NDI, employment status, opioid intake                      Significant improvement &gt; 50% pain relief and &gt; 50% functional status improvement                      Responsive was defined as those patients responding with at least 3 weeks of improvement with the first 2 procedures.</p>	<p>Overall:                      LA 77% vs LA with steroid 87%                      Responsive: LA 79% vs LA with steroid 82%</p>	<p>Overall:                      LA 87% vs LA with steroid 80%                      Responsive: LA 79% vs LA with steroid 92%</p>	<p>Overall:                      LA 73% vs LA with steroid 70%                      Responsive: LA 90% vs LA with steroid 89%</p>	<p>NA</p>	<p>P</p>	<p>P</p>	<p>P</p>	<p>NA</p>	<ul style="list-style-type: none"> <li>•Preliminary results of a large randomized trial performed under fluoroscopy with positive results.</li> <li>•Similar results with local anesthetic or with local anesthetic and steroids.</li> <li>•Overall, 3-4 injections were provided over a period of 1 year.</li> </ul>
<p>Manchikanti et al 2014 (924)                      RA, DB, AC, F                      Cervical axial or discogenic                      Quality Scores:                      Cochrane = 11/13                      IPM-QRB = 44/48</p>	<p>Total = 120                      Local anesthetic only = 60                      Local anesthetic with steroids = 60                      Celestone                      Average number of injections = 5 to 6 for 2 years</p>	<p>NRS, NDI, opioid intake, employment, changes in weight                      Significant improvement &gt; 50% pain relief and &gt; 50% functional status improvement</p>	<p>Overall:                      LA 68% vs LA with steroid 77%                      Responsive: LA 75% vs LA with steroid 82%</p>	<p>Overall:                      LA 67% vs LA with steroid 73%                      Responsive: LA 73% vs LA with steroid 79%</p>	<p>Overall:                      LA 72% vs LA with steroid 68%                      Responsive: LA 78% vs LA with steroid 83%</p>	<p>Overall:                      LA 73% vs LA with steroid 70%                      Responsive: LA 78% vs LA with steroid 75%</p>	<p>P</p>	<p>P</p>	<p>P</p>	<p>P</p>	<ul style="list-style-type: none"> <li>•Positive results of a large RCT performed under fluoroscopy.</li> <li>•Similar results with local anesthetic or with local anesthetic and steroids.</li> <li>•A total of 5-6 injections on average were provided over a period of 2 years.</li> </ul>
<p>Manchikanti et al, 2018 (927)                      RA, AC, F                      Cervical post-surgery syndrome                      Quality Scores:                      Cochrane = 11/13                      IPM-QRB = 42/48</p>	<p>Total = 116                      Local anesthetic only = 58                      Local anesthetic with steroids = 58                      Celestone                      Average number of injections = 5 to 6 for 2 years</p>	<p>NRS, NDI, employment status, opioid intake                      Significant improvement &gt; 50% pain relief and &gt; 50% functional status improvement                      Responsive was defined as those patients responding with at least 3 weeks of improvement with the first 2 procedures.</p>	<p>NA</p>	<p>Overall:                      LA 69% vs LA with steroid 74%                      Responsive: LA 74% vs LA with steroid 81%</p>	<p>Overall:                      LA 74% vs LA with steroid 69%                      Responsive: LA 79% vs LA with steroid 81%</p>	<p>Overall:                      LA 69% vs LA with steroid 71%                      Responsive: LA 74% vs LA with steroid 79%</p>	<p>P</p>	<p>P</p>	<p>P</p>	<p>P</p>	<ul style="list-style-type: none"> <li>•An active-control trial conducted with fluoroscopy with positive results.</li> <li>•Similar results with local anesthetic or with local anesthetic and steroids.</li> <li>•On average, 3-4 injections were provided during one-year and 5-6 injections for 2 years.</li> </ul>

Table 17. Characteristics of fluoroscopic cervical/thoracic interlaminar epidural injections.

Study Characteristics Methodological Quality Scoring	Participants and Interventions	Outcome Measures	Pain Relief and Function					Results			Comment(s)
			3 mos.	6 mos.	12 mos.	24 mos.	Short-term ≤ 6 mos.	Long-Term			
								> 6 mos.	≥ 12 mos.	24 mos.	
Manchikanti et al, 2014 (588) RA, AC, DB, F Thoracic pain Quality Scores: Cochrane = 11/13 IPM-QRB = 43/48	Total = 110 Local anesthetic only = 55 Local anesthetic with steroids = 55 6 mL of local anesthetic only or 6 mL of local anesthetic with 6 mg of nonparticulate betamethasone Average number of injections = 5 - 6 for 2 years	NRS, ODI, employment status, opioid intake Significant improvement > 50% pain relief and > 50% functional status improvement	Overall: LA 78% vs LA with steroid 82% Responsive: LA 88% vs LA with steroid 86%	Overall: LA 74% vs LA with steroid 84% Responsive: LA 84% vs LA with steroid 90%	Overall: LA 71% vs LA with steroid 84% Responsive: LA 80% vs LA with steroid 90%	Overall: LA 71% vs LA with steroid 80% Responsive: LA 80% vs LA with steroid 86%	P	P	P	P	<ul style="list-style-type: none"> <li>• First large randomized trial with active control design and long-term follow-up.</li> <li>• Similar results with local anesthetic or with local anesthetic and steroids.</li> <li>• On average, 5-6 total procedures were performed over a period of 2 years.</li> </ul>
Joswig et al, 2018 (937) R, F Cervical disc herniation	Total = 45 Injectate: 0.5% bupivacaine 1 mL mixed with 40 mg of triamcinolone	VAS, NDI	66.7% responded with pain relief and improvement in disability scores	NA	36 of 45 responded, 7 patients received a second injection and 6 of them responded with one of them be lost to follow-up	NA	P	P	NA	<p>This is a study to assess the safety of a second interlaminar epidural injection in the cervical spine. Results are rather amazing that majority of the patients had one-year relief and only 7 of 45 patients required a second injection. However, authors injected 0.5% bupivacaine, which is considered unsafe if subarachnoid leakage or injection happened in advertently.</p>	
Bevaz & Eman, 2013 (940) R, F Cervical pain syndrome	Total: 65 Discal pathology = 26 Degenerative pathology = 38 Spinal stenosis = 9 Injectate = a total of 5 mL of 80 mg of triamcinolone acetoinide with 3 mL of bupivacaine 0.25%	NRS	Satisfaction scores were average 3.3 ± 0.9 80% of patients were classified as perfect or good satisfaction	Satisfaction scores were average 3.3 ± 0.9 80% of patients were classified as perfect or good satisfaction	Satisfaction scores were average 3.3 ± 0.9 80% of patients were classified as perfect or good satisfaction	NA	P	P	NA	<p>This study was a fluoroscopy guided cervical interlaminar steroid injection; however, bupivacaine was injected which is not an appropriate injection for cervical epidural injections which may lead to substantial complications even though they have not reported any complications. Overall, the response was good with positive results.</p>	

RA = Randomized; AC = Active Control; F = Fluoroscopy; DB = Double-Blind; SB = Single Blind; R = Retrospective; P = Positive; N = Negative; NA = Not Applicable; U = Unclear; LA = local anesthetic; IPM-QRB = Interventional Pain Management techniques -- Quality Appraisal of Reliability and Risk of Bias Assessment; NRS = Numeric Rating Scale; NDI = Neck Disability Index; ONDI = Oswestry Neck Disability Index; PDI = Pain Disability Index; MPQ = McGill Pain Questionnaire; PGIC = Patient Global Impression of Change; DME = daily morphine equivalents; MQS = Medication Quantification Scale III scores

(942). Thus, the results of this trial are considered undetermined. Further, the authors did not provide information on the number of injections.

Multiple observational studies are available; however, there were only 2 studies meeting inclusion criteria performed under fluoroscopic guidance (937,940). Joswig et al (937) evaluated the role of repeat epidural steroid injections for cervical disc herniation. They performed cervical epidural injections with the interlaminar approach in 45 patients for cervical disc herniation. They showed 30 of them responded and 15 showed lack of response. Among these, 8 of them underwent surgery, while 7 of them received a second injection. The initial response lasted for 12 months and a subsequent second injection response also lasted 12 months in almost all patients with one patient being lost to follow-up. The relief is somewhat superior to previous studies. Further, they also injected 0.5% bupivacaine with steroid mixture of 2 mL, which we considered as a risky technique in the cervical spine due to the potential for subarachnoid leakage of the fluid or subarachnoid puncture utilizing subarachnoid injection.

The second study was by Beyaz and Eman (940) utilizing fluoroscopically guided cervical interlaminar steroid injections in patients with cervical pain syndromes. They used various types of conditions in their study including disc herniation, degenerative disc disease, and cervical spinal stenosis. Only 9 patients had stenosis and 26 patients had discal pathology, all others had degenerative pathology among the 65 patients included in the study. In this study, the authors injected a total of 5 mL of 80 mg of triamcinolone acetonide with 3 mL of bupivacaine 0.25% into the epidural space similar to the other study which is considered to be risky in the US. They reported significant improvement in pain scores from before the injection to 12-month follow-up. Overall, 51 patients or 80% had perfect/good scores. They reported no complications in the study.

Among the older studies, which were not included in this analysis, but were included in the other previous analysis, Castagnera et al (929), Stav et al (930), and Pasqualucci et al (931) were utilized due to lack of multiple randomized trials, meeting appropriate inclusion criteria of 50 patients. The patients included were 24 by Castagnera et al (929), 42 by Stav et al (930), and 40 by Pasqualucci et al (931). Overall, all 3 trials showed positive results either comparing local anesthetic with steroids or steroid plus morphine (929) with steroid plus morphine showing positive results. Stav et al (930) compared local anesthetic with steroids to intramuscular steroid and the epidural local anesthetic with steroids injection group

showed positive results. Pasqualucci et al (931) assessed bupivacaine with methylprednisolone acetate, comparing single versus continuous infusion groups with significant improvement in both groups, with the continuous improvement group showing better results.

## 8.9 Evidence Synthesis

Qualitative analysis was performed and quantitative analysis was obtained from previously published studies (58,64).

The evidence synthesis based on the present review of the available literature shows there were 3 RCTs (922,932,941) studying cervical disc herniation. One of the 2 observational studies focused on cervical disc herniation (937). Among these studies, Manchikanti et al (922) studied 120 patients with a 24-month follow-up with multiple procedures performed as pain returned with a total of 5-6 procedures per 2 years. They showed significant improvement at 2-year follow-up with 72% utilizing local anesthetics and 68% utilizing local anesthetic and steroids with significant improvement in pain and function. However, in the responsive group, it was 77% with local anesthetic and 80% with local anesthetic and steroids. In a recent study, McCormick et al (941) studied 76 patients and compared the standard interlaminar epidural injection with targeted cervical interlaminar epidural steroid injection with 40 and 36 patients in each group providing a 6-month follow-up. This study showed positive results. Cohen et al (932) compared a conservative treatment group with 59 medical therapy patients, an epidural injection group with 58 patients and a combination therapy group with 55 patients where they administered epidural steroid injection and pharmacotherapy with gabapentin and physical modalities. They showed that 57% with positive relief the combination therapy group at 3 months and 44% at 6 months. Combination therapy with various components, along with drug therapy and a structured exercise program or other physical interventions is the common practice. Consequently, this can be judged as a positive study. The observational report also showed positive results in 45 patients (937). However, they used 0.5% bupivacaine 1 mL mixed with 40 mg of triamcinolone. Bupivacaine is not recommended for cervical epidural injections due to its untoward effects in case of leakage or subarachnoid puncture. Thus, overall the evidence is Level I with strong recommendation for interlaminar epidural injections in managing disc herniation.

In the assessment for spinal stenosis, a single RCT by Manchikanti et al (925) utilizing 60 patients with one-

year follow-up showed positive results in 73% with local anesthetic and 70% with local anesthetic and steroids. However, in the responsive group, overall significant improvement was higher with 90% in the local anesthetic group versus 89% in the local anesthetic with steroids, with overall 3 to 4 injections during the whole year. One of the observational studies also included cervical spinal stenosis patients. However, these numbers were extremely low. Consequently, this does not provide any additional evidence. Thus, based on one relevant high-quality RCT (925), the evidence is Level II with moderate to strong recommendation.

For axial discogenic pain or patients without facet joint pain, a single study with 120 patients by Manchikanti et al (924) with 2-year follow-up showed positive results in overall groups in 73% with local anesthetic and 70% with local anesthetic and steroids. However, the response was better with 78% with local anesthetic versus 75% with steroids at the end of 2 years with 5 to 6 cervical epidural procedures over a period of 2 years. Thus, based on one relevant high-quality RCT, evidence is Level II with moderate to strong recommendation.

In cervical post-surgery syndrome, there was only one RCT (927) with inclusion of 116 patients with 58 patients in each group with either local anesthetic or local anesthetic with steroids with 24-month follow-up showing in all-inclusive patients, significant improvement in 69% in the local anesthetic group and 71% in the local anesthetic with steroid group. However, in the responsive groups, positive response with local anesthetic was 74% versus local anesthetic with steroid in 79%. Similar to other studies by this group, repeat injections were performed 3 to 4 during the first year and a total of 5 to 6 over a period of 2 years. Consequently, the evidence is Level II to I with moderate to strong recommendation.

For thoracic pain, there was only one RCT by Manchikanti et al (588) with 110 patients with 55 patients in each group with the inclusion of all types of thoracic pain patients. At 24-month follow-up, the results showed 71% improvement with local anesthetic only and 80% improvement with local anesthetic with steroid when all patients were considered. However, the response was better if responsive patients were considered with 80% utilizing local anesthetic alone versus 86% with local anesthetic and steroids with 5 to 6 total procedures during a period of 2 years.

The evidence for thoracic epidural injections is Level II with moderate to strong recommendation.

However, in the present review, the addition of steroids may provide better improvement in the cervical

spine based on RCTs and observational studies considering various issues with local anesthetic administration in the cervical spine. It may be appropriate to avoid local anesthetics except in certain circumstances with extreme caution.

Cost utility analysis also was performed for cervical epidural injections and thoracic epidural injections (943,944). In the assessment of the cost utility in cervical disc herniation, post-surgery syndrome, or discogenic pain, utilizing 2-year data, with 356 patients, average cost including direct costs and indirect costs was \$3,785.89 per one-year improvement in QOL (943). The cost was somewhat higher for axial discogenic pain at \$4,028.55, compared to disc herniation at \$3,475.38 and post-surgery syndrome at \$3,856. Evaluation of cost utility of the thoracic interlaminar epidural injections (944) showed with a 2-year follow-up with one-year QOL improvement including direct and indirect costs of \$3,245; however, in only responsive participants it was \$3,148.73. In this study, the authors also calculated cost utility in 10 nonresponsive participants, which was \$45,440 per one-year improvement in QoL. This emphasizes the fact that is inappropriate to use patients in nonresponsive studies or negative studies for cost utility analysis.

Multiple systematic reviews performed in the past (58,60,64,70) have shown significant improvement with or without steroids with significant evidence levels. Kaye et al (60) showed Level II evidence for long-term management of cervical disc herniation with interlaminar epidural injection. The evidence is Level II to III in managing thoracic pain, and cervical spinal stenosis, cervical discogenic axial pain, and cervical post-surgery syndrome. Mesregah et al (64) showed the addition of steroids to anesthetic injectate was not associated with better pain and functional score outcomes compared with anesthetic agent alone in patients with chronic neck pain. Knezevic et al (58) also showed no significant difference between local anesthetic alone compared to local anesthetic with steroids.

## 8.10 Summary of Evidence

Analysis of summary of evidence for disc herniation, spinal stenosis, discogenic pain, and post-surgery syndrome is presented based on the present review of the evidence in conjunction with appropriately performed systematic reviews published in the literature.

### 8.10.1 Disc Herniation

#### 8.10.1.1 Caudal

For caudal epidural injections in managing disc



herniation with multiple relevant, moderate to high-quality fluoroscopically guided epidural injections with or without steroids trials, and results of previous systematic reviews, the evidence is Level I with strong recommendation for long-term effectiveness.

#### **8.10.1.2 Lumbar Interlaminar**

For lumbar interlaminar epidural injections with multiple relevant moderate to high-quality fluoroscopically guided epidural injections with or without steroids trials, and relevant previous systematic reviews, the evidence is Level I with strong recommendation for long-term effectiveness.

#### **8.10.1.3 Lumbar Transforaminal**

For lumbar transforaminal epidural injections with inclusion of multiple moderate to high-quality RCTs of fluoroscopic transforaminal epidural injections with or without steroids, and inclusion of findings of relevant previous systematic reviews, the evidence is Level I with strong recommendation for long-term effectiveness.

The evidence shows no significant difference between caudal and interlaminar epidural injections, whereas, the evidence also shows some superiority of transforaminal epidural injections over caudal and interlaminar epidural injections in achieving long-term improvement with epidural injections.

#### **8.10.1.4 Percutaneous Adhesiolysis**

Based on the present assessment with one relevant high-quality, placebo-controlled, RCT, the evidence is Level II with moderate to strong recommendation for long-term effectiveness for percutaneous adhesiolysis in patients nonresponsive to conservative management and fluoroscopically guided epidural injections.

#### **8.10.1.5 Cervical Interlaminar**

In the cervical spine, for managing cervical disc herniation, based on relevant moderate to high-quality RCTs and published systematic reviews, fluoroscopically guided cervical interlaminar epidural injections, show evidence is Level I with strong recommendation for long-term effectiveness.

#### **8.10.1.6 Thoracic Interlaminar**

In the thoracic spine, for thoracic disc herniation, based on one relevant high-quality RCT using fluoroscopic guidance with or without steroids and previously published systematic reviews, the evidence is Level II with moderate to strong recommendation for long-term effectiveness.

### **8.10.2 Spinal Stenosis**

#### **8.10.2.1 Caudal**

For lumbar central spinal stenosis, the evidence based on present assessment and previously available systematic reviews, based on one high-quality RCT, the evidence is Level III to II with moderate to strong recommendation for long-term improvement with fluoroscopically guided caudal epidural injections.

#### **8.10.2.2 Lumbar Interlaminar**

For lumbar central spinal stenosis, with evidence synthesis with inclusion of relevant moderate to high RCTs and previously published systematic reviews, the evidence is Level II with moderate to strong recommendation with fluoroscopically guided lumbar interlaminar epidural injections for long-term improvement.

#### **8.10.2.3 Lumbar Transforaminal**

For lumbar spinal stenosis, based on the present analysis of moderate to high-quality RCTs and previously available systematic reviews, the evidence is Level IV to III with moderate recommendation with fluoroscopically guided lumbar transforaminal epidural injections for long-term improvement.

#### **8.10.2.4 Percutaneous Adhesiolysis**

The evidence of percutaneous adhesiolysis in lumbar spinal stenosis with present evidence synthesis with relevant, moderate to high-quality RCTs, observational studies and systematic reviews, is Level II with moderate to strong recommendation for long-term improvement after failure of conservative management and fluoroscopically guided epidural injections.

#### **8.10.2.5 Cervical Interlaminar**

For cervical spinal stenosis, based on present evidence synthesis with one high-quality RCT and previously published systematic reviews, the evidence is Level II with moderate to strong recommendation for fluoroscopically guided cervical interlaminar epidural injections with long-term improvement.

### **8.10.3 Axial Discogenic Pain**

#### **8.10.3.1 Caudal**

The evidence for lumbar axial discogenic pain without facet joint pain or sacroiliac joint pain is Level II with

moderate to strong recommendation for caudal epidural injections based on one fluoroscopically guided high-quality RCT for long-term effectiveness.

#### 8.10.3.2 Lumbar Interlaminar

Based on one high-quality RCT with long-term follow-up and previous systematic reviews, the evidence is Level II for discogenic pain after exclusion of facet joint pain and sacroiliac joint pain with moderate to strong recommendation for fluoroscopically guided lumbar interlaminar epidural injections with or without steroids for long-term effectiveness.

#### 8.10.3.3 Cervical Interlaminar

Based on the present evidence synthesis with one relevant high-quality RCT with long-term follow-up, with fluoroscopically guided cervical interlaminar epidural injection with or without steroids, the evidence is Level II with moderate to strong recommendation for long-term effectiveness.

### 8.10.4 Post-surgery Syndrome

#### 8.10.4.1 Caudal

The present evidence synthesis based on one relevant high-quality RCT with long-term improvement and previously performed systematic reviews, the evidence is Level II with moderate to strong recommendation with fluoroscopically guided caudal epidural injections with or without steroids for long-term effectiveness.

#### 8.10.4.2 Cervical Interlaminar

The present evidence synthesis based on one relevant high-quality RCT with long-term improvement and previously performed systematic reviews, the evidence is Level II to I with moderate to strong recommendation with fluoroscopically guided cervical interlaminar epidural injections with or without steroids for long-term effectiveness.

#### 8.10.4.3 Percutaneous Adhesiolysis

Based on present evidence synthesis with multiple moderate to high-quality RCTs in conjunction with previously published systematic reviews, the evidence for percutaneous adhesiolysis in managing post-lumbar surgery syndrome is Level I with strong recommendation for long-term improvement after failure of conservative management and fluoroscopically guided epidural injections.

## 9.0 COST UTILITY ANALYSIS FOR EPIDURAL INTERVENTIONS

### Key Question 7: What is the evidence for cost effectiveness of epidural interventions including percutaneous adhesiolysis in managing chronic spinal pain?

To understand the cost utility of epidural interventions, it is crucial to focus on the origins and relevance of healthcare costs and the multiple means to reduce the impact on healthcare without affecting access to quality care and patient choices. Over the years, cost utility analysis has taken an important pivotal role in the provision of value-based healthcare with consideration of high-quality healthcare in conjunction with either increasing the access or at least not curtailing it (175-178,945-952). The economic impact of spinal pain is described in Section 3.

The data available from cost utility or cost effectiveness analysis provides policymakers and providers with knowledge to compare treatment strategies and to choose appropriate resource allocation with optimization of relative priorities among various interventions (951). While it is simple and easy to calculate the direct costs of an intervention, it is often difficult to assess indirect costs, specifically in interventional pain management (795,853,943,944,953,954). Consequently, indirect measures are utilized in measuring the overall costs.

Over the years, multiple cost utility or cost effectiveness studies have been performed in the US. Despite this knowledge, healthcare costs in managing spinal pain only continue to escalate with increasing disability. However, based on the Affordable Care Act (ACA), cost effectiveness is not utilized as a basis for coverage or other analysis in the US (175,176,955-958). Thus, indirect measures are utilized based on the utilization and overall costs to the governmental programs, whereas private insurers routinely utilize cost utility analysis in their policy developments. In contrast, in other countries with universal healthcare, such as the United Kingdom, cost effectiveness and cost utility analysis are often utilized as the basis for coverage (959). In the United Kingdom, these assessments are based on health technology assessment guidance. However, even though in principle the US does not consider cost utility analysis for coverage, in action the importance of high-quality with low expenses has been stressed with numerous public policy decisions including the ACA, physician quality reporting systems (PQRS), value-based payment (VBP) systems, merit-based incentive payment systems (MIPS), and accountable interventional pain management (945,956-958).

### 9.1 Cost Effectiveness or Cost Utility Analysis

The purpose of cost utility analysis in health economics is to estimate the ratio between the cost of a health-related intervention and the benefit it produces in terms of numbers of years lived in full health by the beneficiaries. Thus, it is considered as a special case of cost-effective analysis, and both of the terms are often used interchangeably. In the scenario of cost utility analysis, cost is measured in monetary units; however, in cost benefit analysis, benefits do not have to be expressed in monetary terms. Among the earlier publications, Kepler et al (946) showed that one-year cost of QoL gained was less than \$100,000 in only 45% of the studies assessed. In a similar study by Indrakanti et al (947), a greater value was demonstrated on studies of nonoperative treatments while comparing surgical interventions. They showed highly variable costs for QALY, ranging from \$304 to \$579,527, with a median cost of \$13,000.

Dagenais et al (951,952,960) assessed the cost of illness and cost utility studies in the US and internationally and their role in informed decision-making concerning interventions for low back pain. In their assessment of cost of illness studies (951,952,960,961), they provided a breakdown on direct costs. The largest proportion of direct medical costs for low back pain was spent on physical therapy (17%) and inpatient services (17%), followed by pharmacy (13%) and primary care (13%). In their assessment of the role of cost utility evaluations (951), their results showed most studies were from the United Kingdom and were published 3 years prior to their publication in 2009.

The results have been highly variable for surgical interventions versus nonsurgical interventions, specifically in relation to calculation of direct and indirect expenses. Multiple studies comparing surgical interventions with nonsurgical interventions showed mixed results with surgical care with a significant incremental benefit by some, with others showing lack of advantage of surgical care. In fact, the most quoted cost utility analysis comes from the data from SPORT study. Tosteson et al (962) showed cost effectiveness of surgical treatment for lumbar disc herniation at \$69,403 per QALY for the general population, and \$34,355 for the Medicare population per QALY. They also studied cost effectiveness of spinal stenosis surgeries (963). In this assessment (963), the results showed cost effectiveness of spinal stenosis at \$77,600 per QALY gained, with \$115,600 per QALY gained for degenerative spondylolisthesis. Cost effectiveness

analysis of posterior cervical fusion for degenerative spondylolisthesis showed a \$20,547 per QALY in one study (374). Anterior cervical discectomy and fusion in obese patients was cost effective at \$52,816. Further, anterior cervical discectomy and fusion in obese patients was cost effective at QALY of \$68,070 compared to nonobese patients at \$52,816 QALY, which was not significantly different between the 2 (374).

Multiple studies also have been published on nonsurgical therapies, including epidural injections as an inclusion therapy of various modalities, or individual monotherapy (964-971). However, these studies were more extensive in the lumbar spine than the cervical spine.

### 9.2 Physical Therapy and Chiropractic

In studies performed with physical therapy in managing low back pain, specified as nonspecific in origin, the incremental cost effectiveness of \$4,594 per QALY was shown with physical therapy (964). However, a favorable cost utility of \$2,216 per QALY for spinal stabilization physiotherapy was demonstrated with individualized physiotherapy (965). Other data also exists in relation to physiotherapy compared to advice alone, which showed cost effectiveness of physiotherapy in low back pain of 6 weeks duration, at a cost utility of \$6,379 per QALY (966). In another study, cost effectiveness of primary care management, with or without early physical therapy for acute low back pain (967), showed better QoL in patients receiving early physical therapy after one year, even though costs were higher, further calculating data in this study (967). The incremental cost effectiveness ratio was \$32,058 per QALY. These results have been stressed despite the costs to initiate early physical therapy to reduce the risk of extensive advanced imaging or other invasive procedures for low back pain (968-971). Physical therapy is also extensively recommended for strengthening purposes prior to surgical interventions, or in conjunction with other modalities of treatments, leading to structured exercise program, and also after surgical interventions.

The evidence is minimal for the long-term effectiveness of physical therapy as an individual modality, or even in conjunction with other modalities; however, it may contribute to faster recovery in multidisciplinary management (971-975). Adogwa et al (976,977), showed the average cost per patient utilizing therapy to be \$4,010, with 67% of patients with lumbar spinal stenosis undergoing physical therapy, most commonly combined

with other medical management. Physical therapy costs also include repeat therapy, need for additional durable medical equipment such as lumbosacral arthrosis, TENS units, and electronic stimulation units. Patient's failure in compliance with continuing to do home exercises after being discharged may also account for suboptimal outcomes (973). Lilly et al (978) nonoperative described assessment of nonoperative management strategies in a herniated lumbar disc population, showing positive results. Among the total of 278,000 patients with intervertebral disc herniation, 97% were successfully managed with nonoperative treatments, while 3% failed maximal nonoperative therapy (MNT) and underwent a lumbar microdiscectomy. The treatments included physical therapy, as well as other modalities.

Analysis of complementary and alternative medical treatments, including chiropractic management for cost effectiveness compared to no treatment, a placebo, physical therapy, or usual care in reducing pain immediately or at short-term after initiation of the treatment, showed significantly greater effectiveness of complementary and alternative medical treatments (171,184,979-984). Alternative treatments have increased substantially over the years reaching into a multibillion-dollar industry. In 2007, a total cost of over \$33 billion was spent out-of-pocket on visits to complementary and alternative medicine practitioners, and purchases of products, classes, and materials (981). The estimates in 2020 show that complementary and alternative medicine market may be worth over \$296 billion by 2027. Thus, patients with spinal pain spend considerable amounts out-of-pocket for medical massage, acupuncture, Chinese medicine, and over-the-counter (OTC) and durable medical equipment. These costs are often not measurable.

Clinical and cost effectiveness of chiropractic treatments have been studied in multiple investigations. Coutler et al (184) in a systematic review and meta-analysis, which included 51 trials and 9 trials utilized for meta-analysis, showed moderate quality evidence that manipulation and mobilization are likely to reduce pain and improve function for patients with chronic low back pain. Herman et al (982) assessed multiple nonpharmacological interventions for cost effectiveness than usual care. Utilizing a Marko model, the results showed that from this societal perspective, all but 2 of the therapies were cost effective at less than \$50,000 per QALY for typical patient mix and most were cost saving. From the payer perspective, fewer were cost saving, but the same number were cost effective. Assuming all patients in the model have high impact chronic pain increases, the ef-

fectiveness and cost effectiveness of most, but not all, therapies indicating that substantial benefits are possible in subpopulations. Coutler et al (171) showed the effectiveness of manipulation and mobilization for treating chronic nonspecific neck pain. Hays et al (983) assessed group and individual level change on health-related QoL in chiropractic patients with chronic low back or neck pain in a 3-month longitudinal study, which is rather short-term. However, they showed that chiropractic care was associated with significant group-level improvement in health-related QoL over time, especially in pain. Only a minority of the individuals in the sample got significantly better. They concluded that this study suggested some benefits of chiropractic on functioning and well-being of patients with low back and neck pain.

Leininger et al (980) published a manuscript on the cost effectiveness of spinal manipulative therapy, supervised exercise and home exercise in 241 older adults with chronic mechanical neck pain. Results showed the authors in this manuscript assessed the cost effectiveness of home exercises with advice (HEA), SMT plus HEA and supervised rehabilitative exercise (SRE) plus HEA. Total costs for SMT plus HEA were 5% lower than HEA and 47% lower than SRE plus HEA. SMT plus HEA resulted in a greater reduction of neck pain over the year relative to HEA. Differences in disability and QALY's favored SMT plus HEA. The authors showed that the probability that adding SMT to HEA is cost effectiveness at willingness to pay thresholds of \$50,000 to \$200,000 per QALY gained ranges from 0.75 to 0.81. The results also showed that if adopting a healthcare perspective, cost for SMT plus HEA were 66% higher than HEA, resulting in an incremental cost-effectiveness ratio (ICER) of \$55,975 per QALY gained.

### 9.3 NonSurgical Treatments Compared to Surgical Treatments

Evidence for the effectiveness of the interventional techniques has been demonstrated and may be variable due to multiple reasons, including the specialists assessing the cost utility providing the least effectiveness of 5% for nonoperative treatments, and not applying the actual costs and QoL improvement for interventions (976-978,985-991). While the cost of nonsurgical treatment may seem extensive, surgical treatments have additional costs associated with risks of complications, including costs of repeat operations and cost of care of failed surgical interventions. A significant proportion of the patients undergoing interventional pain management techniques have already undergone surgical inter-

ventions on multiple occasions or surgical interventions are not feasible.

Adogwa et al (977) performed a 5-year cost analysis of long-term cost of maximum nonoperative treatments in patients with symptomatic lumbar stenosis or spondylolisthesis that ultimately required surgery. They assessed a total of 4,133 eligible patients from 498,000 (0.8%), undergoing one, 2, or 3-level posterior lumbar instrumented fusion. A significant portion of patients had comorbid factors with 20.8% smokers, 44.5% with Type 2 diabetes mellitus, and 38.2% with obesity. They showed the maximum nonoperative treatments utilization as 66.7% used NSAIDs, 84.4% used opioids, 58.6% used muscle relaxants, 65.5% received lumbar epidural steroid injections, 66.6% attended physical therapy or occupation therapy, and 25% attended chiropractic management. They showed total direct costs associated with all MNT prior to index fusion of \$4,010 on nonoperative treatments per patient. Overall, 45.5% of the cost was on epidural injections, followed by 18% for NSAIDs, and 14.2% for opioid costs. Surprisingly in this assessment, PT-OT with a greater number of patients attending had lesser costs compared to chiropractic visits. However, these patients were continuously active within the insurance system for at least 5 years before lumbar fusion. In utilizing cost utility, authors have ignored the fact that these patients have been active and have responded to the treatments with improvement in quality of life. They also ignored the fact of costs, not only for surgical intervention, but indirect costs, along with follow-up care, failed surgery with returning to the same modalities of treatments, including spinal cord stimulation or intrathecal infusion systems and repeat surgery.

Cummins et al (991) assessing cost and utilization of nonoperative therapy for chronic back pain studied 1,411 patients within the SPORT. They analyzed the nonoperative treatment patients with intervertebral disc herniation, spinal stenosis, and degenerative spondylolisthesis with stenosis received prior to enrollment. With regards to patients with either spinal stenosis or degenerative spondylolisthesis, they determined that prior opioid use occurred in 29% and 27% of patients, OTC medication use in 31% and 27%, chiropractic treatment in 33% and 26%, and emergency department presentation in 7% and 4%. However, more importantly, 70% of the patients with spinal stenosis or degenerative spondylolisthesis with stenosis, 70% of the patients received preoperative physical therapy, 55% to 60% had received injections, and 50% to 60% used anti-inflammatory medication.

Daffner et al (992) retrospectively analyzed 30,709

patients by identifying the charges involved in the conservative management of lumbar disc herniation eventually requiring discectomy in the 90 days preoperatively. The average cost per patient over this time period was \$3,445, with 32% of this total coming from charges for injections, 31% from diagnostic imaging, 13% from outpatient visits, 11% from physical therapy visits, 2% from chiropractic visits, and other expenses less than 2%. In this analysis, they also included both diagnostic as well as therapeutic charges.

Tosteson et al (993) in a study comparing surgical treatment of spinal stenosis without degenerative spondylolisthesis also published the nonsurgical care and cost effectiveness. The analysis included 634 participants with stenosis and 601 participants with degenerative spondylolisthesis with associated stenosis. Of these, 62% of the participants with stenosis and 61% of participants with degenerative spondylolisthesis had surgery. Total adjusted mean nonoperative care costs were similar. Diagnostic tests were reported more frequently among those treated surgically. For either disease groups, epidural or trigger point use was higher among patients treated nonoperatively. Among patients with stenosis, 45% were nonoperative management and 30% were surgery recipients, whereas it was 46% for nonoperative management and 29% for surgery recipients for degenerative spondylolisthesis with stenosis. Opioid use was higher among those receiving surgery in both groups, 71% surgery recipients and 35% in the nonoperative management group. The total costs for nonoperative management for spinal stenosis were \$13,359, whereas they were \$16,046 for degenerative spondylolisthesis with spinal stenosis, which included total direct and indirect costs. In contrast, for surgical interventions, they were \$26,222 versus \$42,081 for degenerative spondylolisthesis with spinal stenosis. Cost effectiveness was 1.37 and 1.33 for nonoperative management and it was 1.54 and 1.55 for surgical interventions for spinal stenosis and degenerative spondylolisthesis with spinal stenosis. While there seems to be not much difference in the calculated cost effectiveness for QALY, they described that cost utility was better for surgical interventions. With stenosis surgery, improved health with a QALY gain was 0.17, at a cost of \$77,600, ranging from \$49,600 to \$120,000 per QALY gained. For degenerative spondylolisthesis, QALY gain was 0.23 at a cost of \$115,600, ranging from \$90,800 to \$144,900 per QALY gained.

Tosteson et al (962,963) also assessed cost effectiveness of surgical versus nonoperative treatment for lum-



bar disc herniation over a period of 2 years. This analysis showed total costs of \$27,341 for surgery for disc herniation in a commercial population and \$20,150 in a Medicare population. For nonoperative care, the costs were \$13,135. The mean cost per QALY gained for surgery was \$69,403 in the general population and \$34,355 for the Medicare population over a 2-year period. Tosteson et al (993), in another manuscript, provided the data on comparative effectiveness evidence from SPORT comparing surgical versus nonoperative care for spinal stenosis, degenerative spondylolisthesis, and intervertebral disc herniation. They showed that cost per QALY gained decreased for spinal stenosis from \$77,600 at 2 years to \$59,400 at 4 years, for degenerative spondylolisthesis, costs decreased from \$115,600 to \$64,300 and for intervertebral disc herniation, from \$34,355 to \$20,600.

The same group, with Lurie as the first author (994), published the 8-year results of the SPORT for disc herniation. In this analysis, they showed that patients undergoing surgical intervention continued to do better than nonoperative treatment. The results after 10 years also showed continuing improvement in the results (995).

Spinal cord stimulators were assessed for cost utility in multiple studies (996-998) in the management of chronic pain of failed back surgery syndrome, complex regional pain syndrome (CRPS), peripheral arterial disease (PAD), and refractory and angina pectoris. Kumar et al (996) showed cost utility at Canadian dollars (CAD) \$9,293, CAD \$11,216, CAD \$93,050, and CAD \$99,084 for failed back surgery syndrome, CRPS, PAD, and refractory angina pectoris, respectively, per QALY gained.

Taylor et al (997) demonstrated that the incremental cost effectiveness of spinal cord stimulation compared with conventional medical management was £5,624 per QALY, with an 89% probability that spinal cord stimulation is cost effective at a willingness to pay the threshold of £20,000. They also showed that compared with reoperation, the incremental cost effectiveness of spinal cord stimulation was £6,392 per QALY, with an 82% probability of cost effectiveness at the £20,000 threshold.

However, Hollingworth et al (998) in an analysis of the cost effectiveness of spinal cord stimulation for failed back surgery syndrome in a workers' compensation population showed that the mean medical cost per spinal cord stimulation patient over 24 months was \$52,091, which was \$17,291 higher than the pain clinic group and \$28,128 higher than in the usual care group.

#### 9.4 Cost Utility of Epidural Injections

Cost utility or cost effectiveness analysis of epidural interventions was published in multiple manuscripts as a single modality (795,853,854,943,944,953,954,999). Earlier investigations and some more recent investigations have utilized inaccurate methodology, extrapolating from patients who have failed to respond to epidural injections (854,999,1000). Often it is difficult to understand methodologies showing inappropriate results with inappropriate calculation of the economic impact of treatments (961). Dagenais et al (989) described cases with high income and disproportionately excessive charges for treatments received, showing a nonoperative cost of \$53,595 for one attack of acute radiculitis, with each transforaminal epidural injection costing \$2,500. Inappropriate analysis in interventional pain management appears to be a common phenomenon.

Price et al (854), in an RCT of clinical and cost utility analysis, showed interlaminar epidural injections with inappropriate design of the study. They based their results on improvement at 3 weeks in one patient, based on the trial protocol of £16,816 to £23,963, depending on the number of epidural steroid injections needed to treat. They also showed that if only one epidural was provided, the total charge to purchasers to improve one patient at 3 weeks was £7,936 to £11,306. Obviously, not only was the RCT flawed, but also the cost utility analysis and all the inferences drawn on this study. It was performed without fluoroscopic guidance and has not been included in many systematic reviews or guidelines.

Whynes et al (999) evaluated a small number of patients modeling resource use and data from other studies. They studied 39 patients over a period of 13 weeks showing the QALY gain. They showed mean cost of an injection was £219, with a cost quality ratio of 2 injections, amounting to £8,975 per QALY gained. They also concluded that when provided in an outpatient setting, epidural steroid injections are short-term, but nevertheless, cost effective means of managing chronic LBP. However, this study is faced with extensive criticism due to a small number of patients and data extrapolation from 3 weeks of relief.

Carreon et al (1000) assessed in their surgical practice from June 2012 to July 2013 if appropriate outcome parameters were available. Their results showed that of the 421 patients who had received lumbar epidural steroid injections, 323 patients, or 77%, had data available with EQ-5D, 145 patients, or

45%, had a QALY gain at a cost of \$62,175 per QALY gained (mean 0.117), 127, or 40%, had a loss in QALY (mean 0.120), and 51 patients, or 15%, had no change in QALY. Many of them were precluded from surgery. The cost utility per QALY gained was at \$62,175. The assessment is very crude. There is significant bias as patients may be seeing the surgeon to obtain surgical intervention. Further, since these are surgical referrals, they may have already failed epidural injections with expectation of surgical interventions with high levels of placebo experience and potential lack of medical necessity. However, it is not acceptable in the US to perform these procedures in Medicare patients without documentation of adequate relief. They also showed in some cases, patients have received 6 procedures per year, which is unusually high. Consequently, the results of this study are unreliable for any type of clinical utility.

Multiple studies were performed by Manchikanti et al (795,853,920,943,944) including: caudal, lumbar, cervical, and thoracic interlaminar epidural injections, and lumbosacral percutaneous adhesiolysis.

A cost utility analysis of fluoroscopic caudal epidural injections with or without steroids (795) was performed based on 4 RCTs with lumbar disc herniation, axial discogenic LBP, central spinal stenosis, and post-lumbar surgery syndrome (765,766-768). A total of 480 patients were studied with 120 patients in each disc herniation and discogenic pain group, 140 patients in the post-surgery syndrome, and 100 patients in the spinal stenosis group, with utilization of 2-year data outcomes with calculation of 2-year data of cost utility analysis as shown in Fig. 17 and Table 18. Significant improvement was seen in all groups of patients with local anesthetic only or with steroids except for the spinal stenosis group at 12 months and 24 months. The average cost for improvement of one-year quality of life, with inclusion of direct costs and indirect costs were \$3,628 with caudal epidural injections. There were no differences among the costs in each category (Table 18).

Cost utility analysis of lumbar interlaminar epidural injections (853) in the treatment of lumbar disc herniation, central spinal stenosis, and axial discogenic low back pain was assessed in 360 patients utilizing the data from 3 RCTs (797,799,801). As shown in Fig. 18, there was significant improvement clinically ranging from 65% to 73% at 2-year follow up. As shown in Table 19, the total estimated cost including procedural costs, costs of medical and other indirect costs

for one-year improvement in QoL was shown to be \$3,301 overall.

Response from RCTs was also performed in patients receiving cervical interlaminar epidural injections in the treatment of cervical disc herniation, post-surgery syndrome, or discogenic pain (943) as shown in Fig. 19. The results showed positive response in 71% of the patients receiving cervical epidural injections with local anesthetic alone or with steroids at 24 months. There was no difference between 6-month follow up, 12-month follow up, and 24-month follow up. The average costs, including direct and indirect costs, were \$3,785.89 for one-year improvement in QoL (Table 20).

Cost utility of thoracic interlaminar epidurals was also evaluated (944). A single RCT with a 2-year follow-up of clinical effectiveness was utilized. This study showed significant improvement in these patients (Fig. 20). This study included 110 patients with a 2-year follow-up (588). Methodology was similar to the other studies by Manchikanti et al. Cost utility analysis showed direct procedural cost of \$1,943.19, whereas total estimated cost per QALY was \$3,245.12 (Table 21).

Cost utility of percutaneous adhesiolysis was performed (920) in post-lumbar surgery syndrome and central spinal stenosis in the lumbar spine utilizing 2 RCTs (893,894).

The results of 2 RCTs of low back pain (891-894) with 60 and 70 patients over a 2-year follow-up with the actual reimbursement data showed direct cost expenses of \$2,652 for post-lumbar surgery syndrome and \$2,649 for lumbar central spinal canal stenosis. With the addition of 67% for indirect costs, the total cost for one-year quality of improvement is \$4,429 for post-lumbar surgery syndrome and \$4,424 for lumbar central spinal stenosis (920). Figure 21 and Table 22 show the outcomes and cost utility analysis of percutaneous adhesiolysis.

Figure 22 shows ranges of cost utility analysis in various commonly utilized procedures in the US. Thus, the costs of epidural injections are within the range. Further, the costs utility with one-year improvement of all interventional pain management techniques, except for spinal cord stimulation, were below \$5,000. Appropriately performed studies show cost effectiveness, whereas, inappropriate inclusion criteria and studies favoring surgery show lack of effectiveness.

In addition to the procedures on the spine, cost utility shows that it is lower than many other chronic diseases. Tosteson et al (963) in their manuscript de-

scribed that spinal stenosis fusion surgery at a cost of \$115,600 per QALY improvement may be considered as too expensive. In another manuscript (995), they also summarized the evidence from the SPORT by addressing outcomes and costs for 3 types of spine problems. Their results showed that after 4-year follow-up, patients with 3 spine conditions that may be treated sur-

gically or nonoperatively, have systematic differences in value endpoints. The average surgical patient enjoys better health outcomes and higher treatment satisfaction but incurs higher costs. However, for those who are not candidates for surgical interventions and those who are opposed to surgery or their medical status contraindicates surgery, treatment with epidural in-

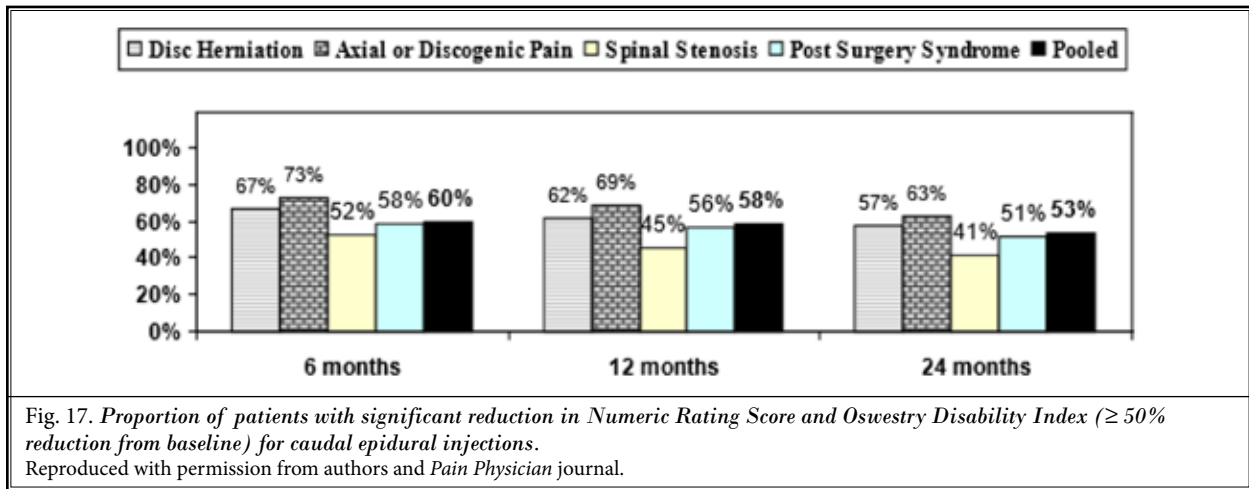


Table 18. Analysis of cost effectiveness of caudal epidural injections in managing pain and disability of disc herniation, discogenic pain, spinal stenosis, and post surgery syndrome in 480 patients.

	Disc Herniation	Axial or Discogenic Pain	Spinal Stenosis	Post Surgery Syndrome	Total
Number of patients	120	120	100	140	480
Total number of procedures for 2 years	601	647	400	696	2344
Number of treatments for 2 years per patient (mean) ± SD	5.0 ± 2.55	5.4 ± 2.63	4.0 ± 2.57	5.0 ± 2.76	4.9 ± 2.67
Number of weeks with significant improvement for all patients in the study in weeks for 2 years	6294	7254	4305	7096	24949
Significant improvement in weeks per procedure (mean) ± SEM	9.4 ± 7.23	10.7 ± 8.25	9.7 ± 13.54	8.4 ± 6.14	9.5 ± 8.92
Number of weeks with significant improvement per patient for 2 years	52.5 ± 38.46	60.4 ± 37.71	43.1 ± 41.52	50.7 ± 38.71	52.0 ± 39.33
<b>Total Cost (\$)</b>					
Physician	\$74,761.00	\$81,729.00	\$45,944.00	\$88,776.00	\$291,210.00
Facility	\$192,225.00	\$216,268.00	\$132,468.00	\$210,168.00	\$751,129.00
Total	\$266,986.00	\$297,997.00	\$178,412.00	\$298,944.00	\$1,042,339.00
<b>Cost per procedure (\$)</b>					
Physician	\$124.40	\$126.30	\$115.10	\$127.60	\$124.30
Facility	\$319.80	\$334.30	\$332.00	\$302.00	\$320.60
Total	\$444.20	\$460.60	\$447.10	\$429.50	\$444.90
Cost per 1-week QALY (\$)	\$42.42	\$41.08	\$41.44	\$42.13	\$41.78
Cost per 1-year QALY (\$)	\$2,205.79	\$2,136.18	\$2,155.03	\$2,190.68	\$2,172.50
Cost per 2-year QALY (\$)	\$4,411.59	\$4,272.36	\$4,310.07	\$4,381.37	\$4,344.99
Average Total cost per patient for 2 years	\$2,225.00	\$2,483.00	\$1,784.00	\$2,135.00	\$2,172.00

terventions seems appropriate. They also showed that longer follow-up periods after the surgery at 4 years and 10 years, cost effectiveness per QALY improved significantly (962,994).

Further, the epidural interventions may avoid the surgery in a significant portion of patients (188,271-274,278) providing better value.

## 10.0 COMPLICATIONS AND SIDE EFFECTS OF EPIDURAL INTERVENTIONS

**Key Question 8: What are the adverse consequences and harms and related precautions in providing epidural procedures?**

Complications related to epidural injections are rare, but can be serious and devastating, specifically in cervical spine (623,866,1001-1038). They are usually

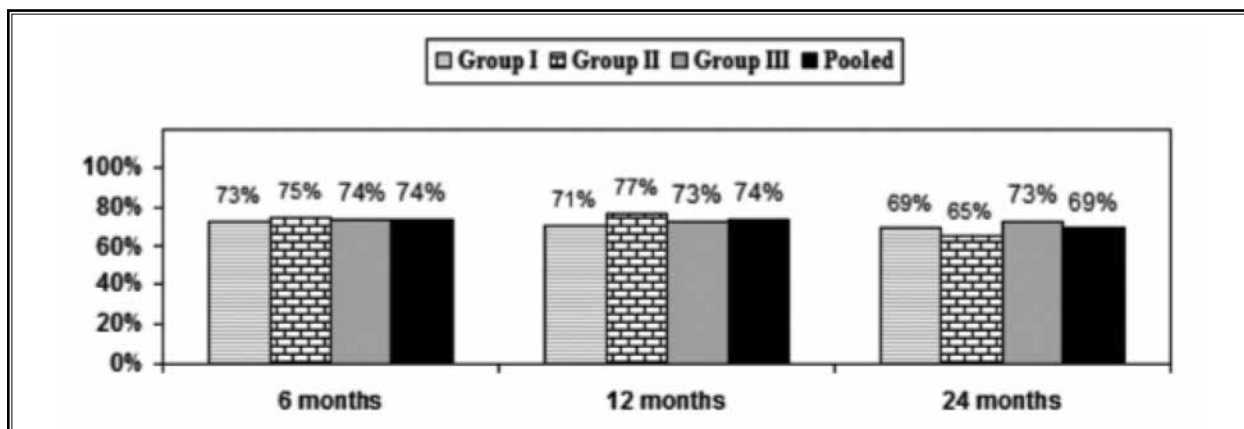


Fig. 18. Proportion of patients with significant reduction in Numeric Rating Score and Oswestry Disability Index ( $\geq 50\%$  reduction from baseline) with lumbar interlaminar epidural injections. Reproduced with permission from authors and Pain Physician journal.

Table 19. Cost utility analysis of lumbar interlaminar epidural injections in managing pain and disability of disc herniation, discogenic pain, and spinal stenosis.

	Disc Herniation	Discogenic Pain	Spinal Stenosis	Total
Number of patients	120	120	120	360
Total number of procedures for 2 years	682	714	644	2040
Number of treatments for 2 years per patient (mean) $\pm$ SD	5.7 $\pm$ 2.5	6.0 $\pm$ 2.5	5.4 $\pm$ 2.6	5.7 $\pm$ 2.6
Number of weeks with significant improvement for all patients in the study in weeks	7667	7900	8074	23641
Significant improvement in weeks per procedure (mean) $\pm$ SD	10.8 $\pm$ 5.7	10.5 $\pm$ 5.9	13.2 $\pm$ 12.7	11.5 $\pm$ 8.8
Direct procedural costs without drug costs (\$)				
Physician	\$85,443	\$93,250	\$66,342	\$245,036
Facility	\$216,942	\$227,649	\$208,994	\$653,585
Total	\$302,385	\$320,899	\$275,336	\$898,620
Direct costs per procedure (\$)				
Physician	\$125.28	\$130.60	\$103.02	\$120.12
Facility	\$318.10	\$318.84	\$324.52	\$320.38
Total	\$443.38	\$449.44	\$427.54	\$440.50
Average total direct costs per patient in 2 years	\$2,519.88	\$2,674.16	\$2,294.47	\$2496.17
Direct procedural improvement in quality of life (\$)	\$2,050.87	\$2,112.25	\$1,773.28	\$1,976.58
Indirect costs including drug costs for 1-year improvement in quality of life (\$)	\$1,374.08	\$1,791.68	\$1,188.10	\$1,324.31
Total estimated costs including procedural costs, costs of medicine and other indirect costs for 1-year improvement in quality of life (\$)	\$3,425	\$3,527	\$2,961	\$3,301

Total costs (\$) for one-year improvement of quality of life

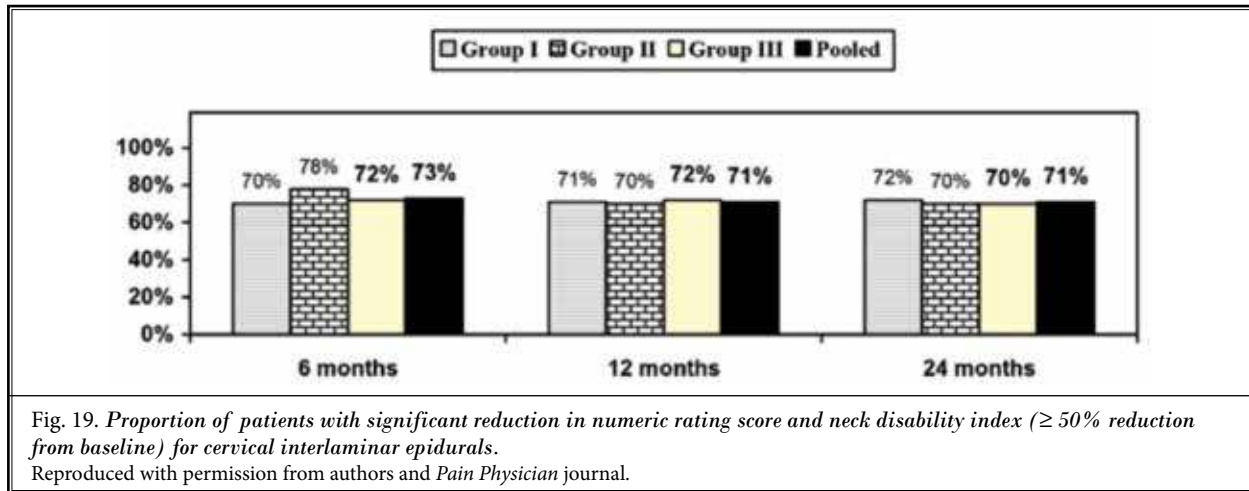


Table 20. Analysis of cost effectiveness of cervical epidural injections in managing pain and disability of disc herniation, discogenic pain, and post surgery syndrome.

	Group I Discogenic Pain	Group II Disc Herniation	Group III Post surgery Syndrome	Pooled
Number of patients	120	120	116	356
Total number of procedures for 2 years	689	654	627	1971
Number of treatments for 2 years per patient (mean ) $\pm$ SD	5.7 + 2.4	5.4 + 2.7	5.4 + 2.6	5.5 + 2.5
Number of weeks with significant improvement for all patients in the study in weeks	8,093	7,900	7,254	23,247
Average total relief in two year per patient				
Significant improvement in weeks per procedure (mean ) $\pm$ SD	11.6 + 7.7	12.6 + 12.0	11.4 + 8.6	11.9 + 9.6
Total Cost (\$)				
Physician	\$89,321	\$95,130	\$82,162	\$266,614
Facility	\$286,117	\$221,033	\$239,971	\$747,121
Total	\$375,439	\$316,163	\$322,133	\$1,013,735
Cost per procedure (\$)				
Physician	\$129.64	\$145.46	\$131.04	\$135.27
Facility	\$415.26	\$337.97	\$382.73	\$379.06
Total	\$544.90	\$483.43	\$513.77	\$514.33
Average total direct costs per patient in 2 years	\$3,128.66	\$2,634.69	\$2,777.01	\$2,847.57
Direct procedural improvement in quality of life (\$) per one year	\$2,412.31	\$2,081.07	\$2,309.20	\$2,267.57
Indirect costs including drug costs for 1-year improvement in quality of life (\$)	\$1,616.25	\$1,394.32	\$1,547.16	\$1,519.27
Total estimated costs including procedural costs, costs of medicine and other indirect costs for 1-year improvement in quality of life (\$)	\$4,028.55	\$3,475.38	\$3,856.36	\$3,785.89

All the payments based 2018 allowed rates  
 SD = standard deviation

related to either the needle placement or drug activity. Medical-legal analysis has revealed the causes of injury are multifactorial, involving aspects of technical execution, clinical judgment, communication with the patient and other medical providers, and documentation (1019).

Interventional pain management physicians approach the epidural space by a caudal, transforaminal, or interlaminar technique. Transforaminal epidurals have been associated with more adverse events after injection of corticosteroids. This is due to an inadvertent injection into or mechanical damage of the critical vasculatures



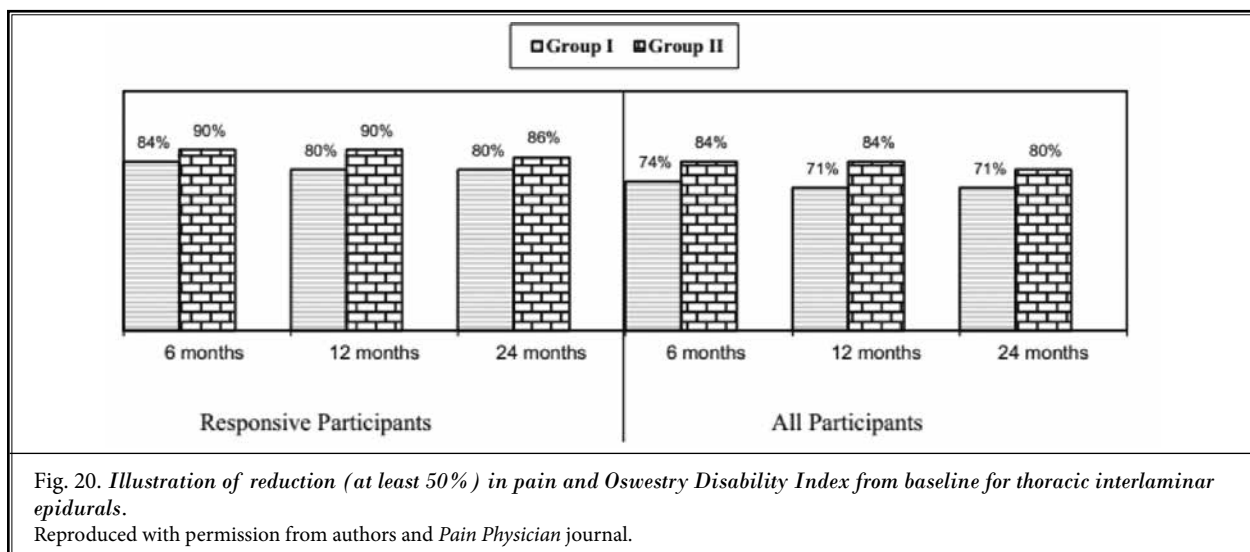


Table 21. Analysis of cost-utility of thoracic epidural injections.

	Responsive Participants	Nonresponsive Participants	All Participants
Number of patients	100	10	110
Total number of procedures for 2 years	586	20	606
Number of treatments for 2 years per patient (mean ± SD)	5.9 ± 2.3	2.0 ± 0.8	5.5 ± 2.5
Number of weeks with significant improvement for all patients in the study in weeks	7879	18	7897
Average total relief in 2 years per patient	78.8 ± 25.6	1.8 ± 2.1	71.8 ± 3302
Significant improvement in weeks per procedure (mean ± SD)	13.6 ± 10.1	0.9 ± 1.1	13.2 ± 10.2
<b>Total cost</b>			
Physician	\$66,765.68	\$2252.75	\$69,018.43
Facility	\$218,918.99	\$7165.98	\$226,084.97
Total	\$285,684.67	\$9418.73	\$295,103.40
<b>Cost per procedure (\$)</b>			
Physician	\$11.93	\$112.64	\$113.89
Facility	\$373.58	\$358.30	\$373.08
Total	\$487.52	\$470.94	\$486.97
Average total direct costs per patient in 2 years	\$2856.85	\$941.87	\$2682.76
Direct procedural improvement in quality of life (\$) per 1 year	\$1885.47	\$27,209.66	\$1943.19
Indirect costs including drug costs for 1-year improvement in quality of life (\$)	\$1263.54	\$18,230.47	\$1301.93
Total estimated costs including procedural costs, costs of medicine and other indirect costs for 1-year improvement in quality of life (\$)	\$3148.73	\$45,440.13	\$3245.12

All the payments based 2018 allowed rates

that supply the brain or spinal cord when injectates are administered via this approach (886,1020,1021).

Caudal epidural steroid injections have been thought to be a safer approach for treating pain in lumbar stenosis. However, there are reports of rare neurological deficits that are transient or permanent. These

include cauda equina syndrome in patients with spinal stenosis, spinal infarction, chemo toxicity, vascular-occlusion, and epidural hematoma (1020,1022).

Cervical and lumbar interlaminar epidural steroid injection and transforaminal epidural steroid injection are 2 distinct approaches that attempt to deliver medication

to the irritated nerve roots. The transforaminal epidural steroid injection allows for a more direct approach into the anterolateral neuroforaminal space where inflammation due to a posterolateral disc displacement commonly resides. Transforaminal epidural spread of corticosteroid has been associated with improved pain and functional outcome improvements, although the evidence has been refuted in some of the literature.

In the last decade, the use of epidural steroid injections has come under scrutiny. In 2011, the label for tri-

amcinolone was updated, warning against epidural use. In April 2014, the FDA issued a warning that epidural steroid injections can cause "rare but serious adverse events, including loss of vision, stroke, paralysis, and death," mainly based on case reports of direct spinal cord injury and of infarctions related to cervical transforaminal placement of particulate steroids, although the FDA warning and package insert revisions covered all steroids including dexamethasone (1039). In the FDA's risk assessment between 1997 and 2014, a total of 90

serious and sometimes fatal neurologic events were reported to the FDA Adverse Event Reporting System (FAERS), including cases of paraplegia, quadriplegia, spinal cord infarction, and stroke. Further, compounded glucocorticoids used in epidural injections also have been associated with fungal meningitis (1040-1049), but cases involving contaminated products were not included in the case series under consideration. However, potential causes of various adverse events including multiple

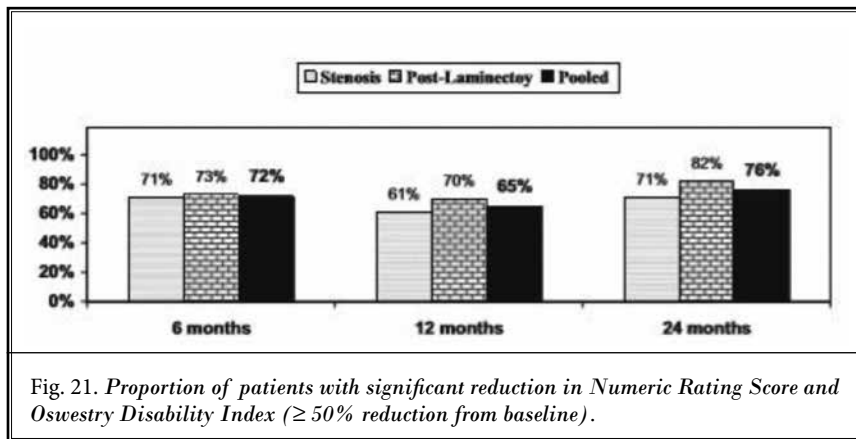
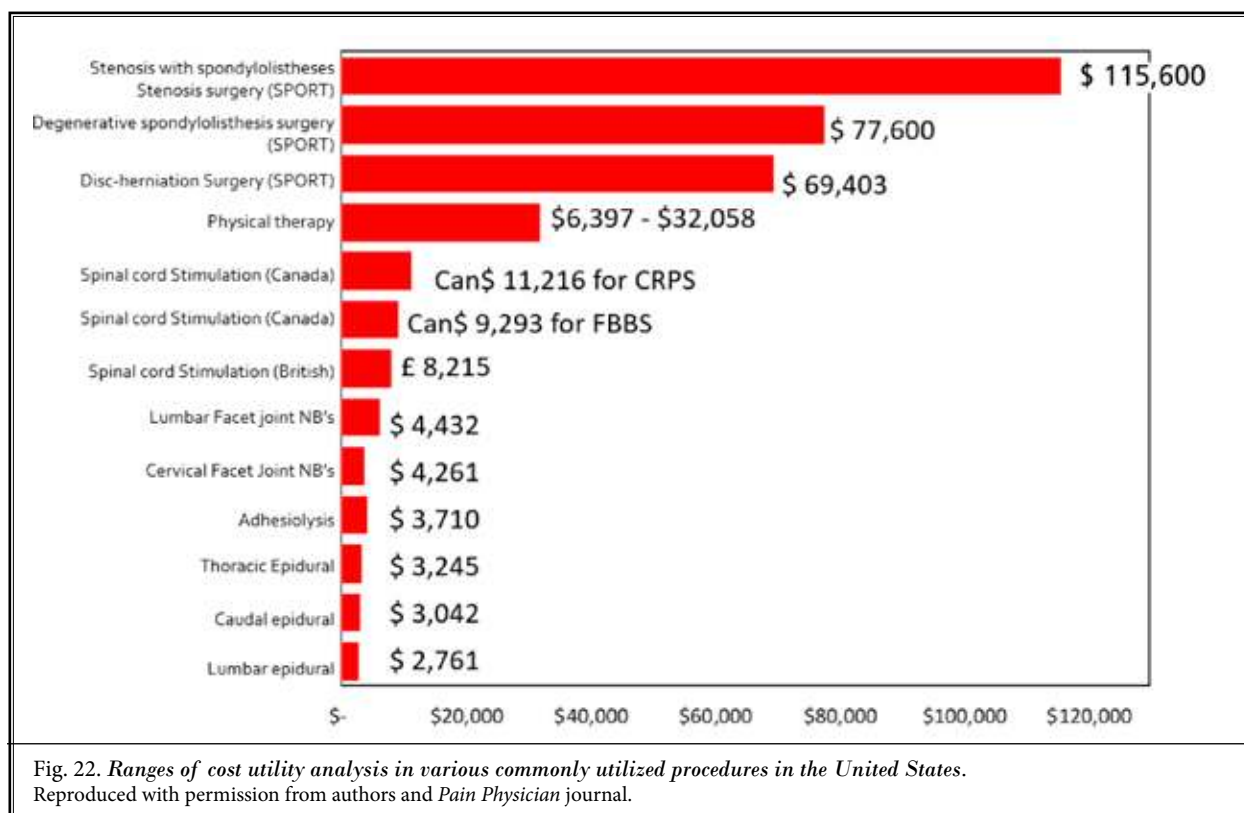


Fig. 21. Proportion of patients with significant reduction in Numeric Rating Score and Oswestry Disability Index ( $\geq 50\%$  reduction from baseline).

Table 22. Analysis of cost-effectiveness of percutaneous adhesiolysis injections in managing pain and disability of lumbar spinal stenosis and postsurgery syndrome.

	Spinal Stenosis	Postsurgery Syndrome	Total
Number of patients	70	60	130
Total number of procedures for 2 years	397	385	782
Number of treatments for 2 years per patient (mean $\pm$ SD)	5.7 $\pm$ 2.73	6.4 $\pm$ 2.32	6.0 $\pm$ 2.56
Number of weeks with significant improvement for all patients in the study in weeks	4,979	4,704	9,686
Significant improvement in weeks per procedure (mean $\pm$ SD)	13.2 $\pm$ 12.6	11.7 $\pm$ 2.97	12.5 $\pm$ 9.47
Total cost (\$)			
Physician	87,082	83,112	170,140
Facility	166,891	156,529	323,420
Total	253,919	239,641	493,560
Cost per procedure (\$)			
Physician	219.21	215.88	217.57
Facility	420.38	406.56	413.58
Total	639.59	622.44	631.15
Cost for 1-week improvement in quality of life	51.00	50.94	50.96
Cost for 1-year improvement in quality of life	2,652	2,649	2,650
Cost for 2-year improvement in quality of life	5,304	5,298	5,299
Average total cost per patient for 2 years	3,627	3,994	3,797

\$ is adjusted to 2012



causes and those involving technique related problems such as intrathecal injection, epidural hematoma, direct spinal cord injury, and embolic infarction after inadvertent intra-arterial injection. The FDA sought to determine the central question regarding the role of glucocorticoids themselves in these adverse events (1050).

Inadvertent vascular mechanical or occlusive injury is believed to be the leading cause of the infarctions. This may be due to intravascular injection of particulate steroids, arterial injury, dissection, dislodgement of plaque causing embolism, or arterial muscle spasm. The embolization path is believed to start through the periradicular arteries, which exit the neural foramen and accompany the nerve to the spinal cord. Although most complications have been seen with particulate steroid and cervical spine transforaminal epidural steroid injections, case reports of spinal infarction have been seen with nonparticulate lumbar steroid injections such as dexamethasone as well (1021).

Transforaminal epidural steroid injections are associated with other complications as well. Transforaminal epidural steroid injections, compared to interlaminar epidural steroid injections, are associated with an increased risk of intradiscal injection (1025,1026). Ad-

ditionally, transforaminal epidural steroid injections do not decrease the risk of known complications of interlaminar epidural steroid injections, such as dural and subdural punctures, hematoma formation, and cauda equina syndrome (1021,1022). Although complications are rare, they can be catastrophic, and the implementation of safety guidelines based on common practice has been attempted. The FDA convened a panel of experts, including pain medicine experts, to determine specific techniques of this procedure that may reduce potential harm, but evidence was lacking, and consensus was not reached on all the items (632,1039). Consequently, the Multisociety Pain Workgroup (MPW), without inclusion of the ASIPP, approved multiple safeguards to prevent neurologic complications after epidural steroid injections (632); however, there were many issues involved. Consequently, it was opposed by ASIPP (1039). Following this, ASIPP also petitioned the FDA asking them to prevent the safeguards from being mandatory and also requested them to remove the safety warning (1051). However, the FDA denied the request to remove the safety warning or limiting to cervical transforaminal epidural injections, but agreed with the second item that safeguards were not required (1050).

As described by Racoosin et al (1050) in the assessment of the risk from the FDA in reference to serious neurologic events after epidural corticosteroid injection, they emphasized the fact that even though inadvertent intra-arterial injection is one mechanism for serious neurologic events, there were other potential causes. They quoted a study by the American Society of Anesthesiologists (ASA) Closed Claims Project showing that in cases of cervical procedures for chronic pain that led to malpractice claims, direct needle trauma to a nerve or the spinal cord was the most common procedure related event. Further, this study (1052) found that of the cervical epidural procedures that were associated with spinal cord injury, two-thirds were performed with an interlaminar approach and one-third with the transforaminal approach (1052). The FDA also clarified that the recently published clinical consideration for healthcare providers (1050) recommendations came from the working group, not the agency, as had been requested by the ASIPP petition (1051). Consequently, the class warning published in 2014 for all injectable glucocorticoid products labels carrying, "serious neurologic events, some resulting in death, have been reported with epidural injection of corticosteroids" and the safety and that the "safety and effectiveness of epidural administration of corticosteroids have not been established and corticosteroids are not approved for this use (1050)." In their final determination, the FDA determined that the class warning was warranted based on its analysis of FAERS cases and reports in the medical literature of serious neurological events. Further, the warning did not distinguish any difference in the risk associated with the various injection approaches, locations of spinal injections, or glucocorticoid formulation, because the data suggested that each approach, location, and formulation was associated with some risk of neurologic injury. At the same time, they have not approved or mandated the safeguards recommended by MPW.

Epidural steroid injections are associated with a number of minor complications and side effects, such as exacerbation of pain, vasovagal reaction, and steroid side effects such as facial flushing and hyperglycemia, which do not involve any permanent impairment (55,1027,1027). Of great concern however, are the rare but major complications such as epidural abscess, discitis, and hematoma formation, radiculo-medullary artery injury due to needle or injection with particulate steroids, spinal cord infarction, stroke and spinal cord injury that can result in severe permanent disability, paralysis, or death (7).

Other complications include extra epidural placement with subcutaneous injection; subdural injection, dural puncture with post-lumbar puncture headache (more common in interlaminar lumbar epidurals), nerve damage, intracranial air injection or increased intracranial pressure; and pulmonary embolism. Less common complications include transient blindness (1029), retinal hemorrhage and necrosis (1030,1031), spinal cord infarct by caudal (1006), placement of needle into filum terminale (1005), serous chorioretinopathy (1032,1033), persistent recurrent intractable hiccups (1034), pneumocephalus (1009), chemical meningitis (1035), arachnoiditis (1037), and discitis (1036).

Recommendations have been made to limit or avoid the use of epidural steroid injections of corticosteroids in high-risk patients, such as the elderly, during the COVID-19 pandemic (1053). Steroid distancing has also been advocated as a result (55). Additionally, ASIPP has issued guidelines on evidence-based risk mitigation and stratification during COVID-19 for return to interventional pain practice as well as triaging interventional pain procedures during COVID-19 or related elective surgery restrictions that risk and acuity stratify epidural steroid injections (51,52).

Apart from COVID-19 issues, steroids continue to present with multiple problems including vascular embolism related to particulate steroids when utilizing transforaminal epidural injections. These are seen with particulate steroids such as triamcinolone or dexamethasone. In contrast, betamethasone, which is a smaller particulate steroid, shows less prevalence of the side effects and lesser suppression of glucocorticoid synthesis, leading to fewer complications (55).

### 10.1 Side Effects of Steroids

The pharmacokinetics of corticosteroids continues to be complex. With intramuscular administration, absorption of the water-soluble sodium phosphate and sodium succinate source is rapid, whereas the rate of absorption of lipid soluble acetate and acetonide is much slower (1054-1058). The subject of interest for this discussion is the role of systematic absorption of epidural steroids, which has been explored in multiple reports. Janicki et al (1057) reported pharmacokinetic analysis of methylprednisolone after epidural administration in rabbits, with only traces of methylprednisolone being detected at 6 and 12 hours after administration of the highest epidural dose of the drug (5 mg/kg). Further, plasma methylprednisolone doses at all sampling times for the epidural doses of 2.5 and 1.25 mg/kg were also

not detectable. Jacobs et al (1055) have also reported being unable to detect methylprednisolone in blood samples. Friedly et al (1058) in a study of the systemic effects of epidural steroid injections for spinal stenosis showed that of the 200 patients receiving corticosteroid, 32 patients or 20.3% experienced cortisol reduction at 3 weeks of  $\geq 50\%$  compared with 10 patients (6.7%) treated with lidocaine only. The effect on 3-week cortisol changes did not differ by patient level characteristics. They also showed that those treated with methylprednisolone or triamcinolone had an average 3-week cortisol reduction of 41% and 41.6% from baseline, respectively. Further comparison with patients treated with betamethasone or dexamethasone, found no significant changes with cortisol and they were similar to lidocaine alone. They concluded that the higher rates of cortisol suppression at 3 weeks in those receiving epidural corticosteroid injections, particularly with longer acting insoluble corticosteroid formulations, are consistent with sustained systemic absorption of corticosteroid. Hooten et al (1059) showed that terminal elimination half-life of lumbar epidurally administered triamcinolone in a noncompartmental analysis was 523 hours (almost 22 days), and the peak triamcinolone concentration of 4.1 ng/mL was detected within 24 hours after administration. This elimination half-life after lumbar epidural administration is much longer than the elimination half-life of intravenous administration and is likely explained by the suspension and re-distribution of the depo preparation within the epidural fat and the epidural anatomy (1060).

Risk of reductions in bone density have been reported in high dose steroids (1061-1064), though lower doses were potentially safe. Symptomatic hypothalamic-pituitary-adrenal (HPA) suppression has been reported occasionally. Abdul et al (1063) in 2017 reported that, after one epidural injection of 80 mg of methylprednisolone, 87% of patients exhibited HPA axis suppression at day 7 post-injection, 43% at day 14, and 7% at day 28. Habib et al (1064) in 2013, found a dose dependent effect in a study examining the magnitude and duration of this suppression after a single epidural injection of methylprednisolone. Eighty-six percent of the patients who received an 80 mg dose were reported to have laboratory confirmed HPA axis suppression one week post-injection compared to 53% of those receiving a 40 mg dose; 20% of all participants had continued suppression at 4 weeks post-injection. Steroid solubility is a factor in endocrine influence; longer-acting agents (triamcinolone and methylprednisolone) have been found to suppress corti-

sol production for a longer duration than more soluble agents (dexamethasone and betamethasone) (1058).

Corticosteroids have anti-inflammatory effects; they reduce pain related to inflammation by down-regulation of the immune function as well as reduction of inflammatory cells and mediators (lymphocytes, macrophages, and mast cells) (1065,1066). Although it has not been directly studied, the endocrine disruption from a single epidural steroid injection suggests similar systemic effects on immune response. The use of systemic corticosteroids can adversely affect the innate (immediate) immune response by impairing the ability of neutrophils to migrate to infection sites as well as macrophage and monocyte function. The adaptive immune response (which leads to immunological memory) is also negatively affected by corticosteroids, as the capability of plasma cells to produce immunoglobulins IgG and IgA is reduced by 10 to 20% after exposure. Injection therapy plausibly has similar effects to the oral administration effects described in the literature.

Consequently, adverse immune influences of corticosteroids during an influenza infection is of increased concern for those prescribed or injected with corticosteroids, with specific concern during the current COVID-19 pandemic. Meta-analysis of orally administered corticosteroid versus placebo demonstrates an increased risk of influenza infection within the steroid group. One study found a dose-dependent relationship for infection risk, showing a relative risk of 1.5 with low doses of steroids and a relative risk greater than 8 with doses above 40 mg/day (1067). In another study, rheumatoid arthritis patients taking oral prednisone had relative risks ranging from 1.4 ( $< 5$  mg/day dose) to 2.3 ( $> 10$  mg/day dose) for hospitalization due to pneumonia compared to rheumatoid arthritis patients not taking oral prednisone (1068). Although data for single-dose exposure to corticosteroids is limited, early evidence is provided in a report on an observational cohort from the Mayo Clinic. Over five influenza seasons, an increased incidence of influenza infection was associated with steroid injection compared to no injection (1069). There are currently no studies specifically examining the relationship between corticosteroid injections and COVID-19, however, the findings presented here raise concern for a potential relationship.

Thus, the literature surrounding infrequent adverse effects of epidural corticosteroids continues to accumulate (1070-1072), with alterations in blood glucose levels among patients with diabetes (1073,1074), and prolonged effects on the HPA axis (1075). Further, it has also been reported that systemic side effects are common with



long-term administration of steroids (1058,1076,1077). Lamer et al (1070) in a study of 8 patients also assessed serum triamcinolone levels following cervical interlaminar epidural injection. Data of the pharmacokinetics showed peak triamcinolone concentration (C max) of 5.4 ng/mL median value within 22.1 hours (T max) of administration. The terminal elimination half-life was 219 hours, the median value. They also compared the results of this study with the previous study of lumbar interlaminar epidural injections (1059) and showed similar patterns. This comparison also showed that while the pharmacokinetic profile is similar, the T max is earlier and T ½ is shorter for the cervical compared to the lumbar epidural steroid injection. In similar lines with other investigators, recently, Sim et al (105) assessed the relationship between epidural steroid dose and separation of HPA access. In the analysis of 30 patients with administration of triam-

cinolone, either 40 mg or 20 mg, they showed that 40 mg triamcinolone group showed longer HPA separation,  $19.7 \pm 3.1$  days compared to triamcinolone 20 mg group ( $8.0 \pm 2.4$  days) and the recovery rate of triamcinolone 40 mg group was lower than that of 20 mg group with a significant difference ( $P$  value  $> 0.015$ ) as shown in Fig. 23.

In another manuscript, Chon and Moon (1078) reported that in all subjects who received epidural steroid injections with triamcinolone acetate, 40 mg were suppressed temporarily but were restored after a mean of  $19.9 \pm 6.8$  days.

The data also shows that intravenous triamcinolone acetonide pharmacokinetics using the soluble form have been previously determined, demonstrating a half-life of approximately 1.5 to 2 hours (1079-1080). However, in contrast to intravenous administration, intra-articular knee injection of a suspension of acetonide showed

vastly different results wherein triamcinolone acetonide was detected in serum for more than 2 weeks and the half-life ranged from 77 to 446 hours (1081). Thus, it is crucial to understand the different mechanisms of short-acting and long-acting drugs, along with particulate sizes. It is also hypothesized that there is less sequestration of particulate steroids in the cervical epidural space, consequently with faster absorption. Table 23 shows the profile of commonly used epidural steroids based on the data derived from multiple sources (1054-1056,1076,1082-1084). Table 24

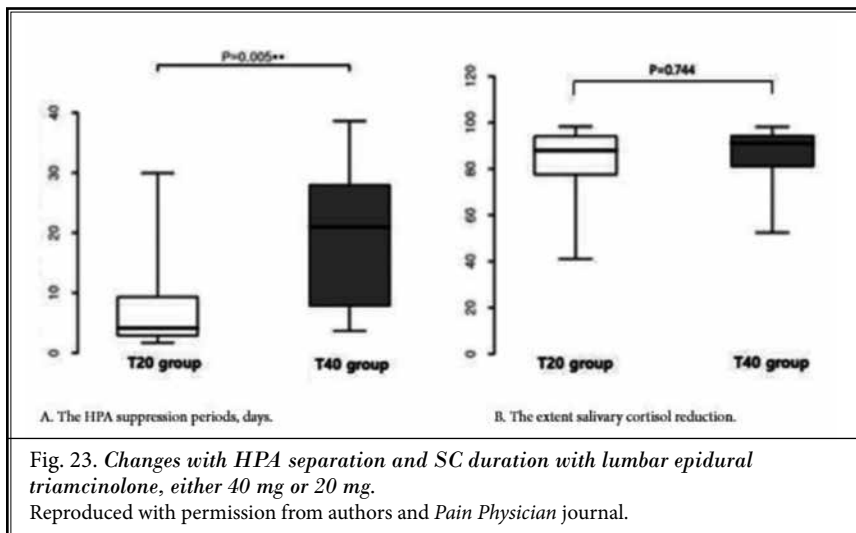


Fig. 23. Changes with HPA separation and SC duration with lumbar epidural triamcinolone, either 40 mg or 20 mg. Reproduced with permission from authors and Pain Physician journal.

Table 23. Profile of commonly used epidural steroids.

Drug	Equivalent Dose	Epidural Dose	Anti-inflammatory Potency	Sodium Retention Capacity	Duration of Adrenal Suppression		
					IM	Single Epidural	Three Epidurals
Hydrocortisone	20 mg	NA	1	1	NA	NA	NA
Depomethylprednisolone (Depo-Medrol)	4 mg	40-80 mg	5	0.5	1-6 weeks	1-3 weeks	NA
Triamcinolone acetonide (Kenalog)	4 mg	40-80 mg	5	0	2-6 weeks	3-5 weeks	2-3 months
Betamethasone (Celestone Soluspan)	0.6 mg	6-12 mg	25	0	1-2 weeks	NA	NA

NA = not applicable

Data adapted and modified from: McEvoy et al (1054), Jacobs et al (1055), Kay et al (1056), Hsu et al (1076), Mikhail et al (1083,1084), and Schimmer and Parker (1082).

Table 24. Formulations of commonly used epidural steroids.

Amount of steroid	Depo-Medrol Methylprednisolone			Aristocort Triamcinolone Diacetate	Kenalog Triamcinolone Diacetate	Celestone Betamethasone
	20 mg/mL	40 mg/mL	80 mg/mL	40 mg/mL	40 mg/mL	6 mg/mL
Polyethylene glycol 3350	29.5	29.1	28.2	30	--	--
Polysorbate 80	1.97	1.94	1.88	2	0.4	--
Benzyl alcohol	6.9	6.8	6.59	--	--	3.4
Dibasic sodium phosphate	9.3	9.16	8.8	9	9	--
Edetate disodium	--	--	--	--	--	7.1
Edetate disodium	--	--	--	--	--	0.1
Benzalkonium chloride	--	--	--	--	--	0.2

shows formulations of commonly used epidural steroids. Dexamethasone is not being discussed since it is a nonparticulate and short-acting steroid with the least side effects, but it is associated with some side effects.

Overall, systemic side effects are significant with the influence of corticosteroids on the metabolism of carbohydrates, fats, proteins, and purine. They can also affect electrolyte and water balance and may affect the functions of the CNS and of the cardiovascular, renal, endocrine, reproductive, and immune systems, as well as the bones and muscles (1077). Long-term effects may be caused directly by excess glucocorticoid in the circulation or indirectly through suppression of the HPA. It is also common that patients presenting to interventional pain management may be taking long-term steroids for multiple medical problems and also may be receiving intra-articular steroid injections.

The specific effects on the immune system are especially worrisome during the COVID-19 pandemic. While there are no data available with regard to the effects of epidural administration of glucocorticoids on the immune system, there are data available regarding systemic administration with high dose glucocorticoid therapy, equivalent to doses of 40 mg or more of prednisone per day. With high doses, there is an immediate risk of infection due to inhibition of phagocyte cell function, which abates after completion of therapy (1085). In patients with rheumatoid arthritis, acute effects of 1 gm of intravenous methylprednisolone showed development of leukopenia within 2 hours of the dose, which peaked at 6 hours, and resolved by 24 hours. In addition, doses of less than 40 mg, considered as low to moderate, have been shown to reduce T lymphocytes with delayed hypersensitivity responses. With long-term low dose

usage, some inhibition of immune responses may increase with the duration of therapy (1086). Multiple issues related to vaccination have been discussed in the past (1087-1089); however, not specifically with the COVID-19 virus. Considering the literature, short-term therapy with low dose within appropriate duration of 6 to 13 weeks may not have any significant effect. The Advisory Committee on Immunization Practices (ACIP) (1090) and the CDC (1091) advise to defer live vaccinations for at least one month after discontinuation of high dose systemically absorbed glucocorticoid therapy administered for 14 days.

## 10.2 Side Effects of Local Anesthetics

Historically, the use of procaine was extensively utilized following cocaine; however, the introduction of lidocaine in 1948 and bupivacaine, which was introduced in 1963, has been extensively used outside of the epidural space with lidocaine also used for intra-articular injections in chronic pain management. The mechanism of action of intravenous lidocaine in neuropathic pain cannot be explained by blockade of voltage-gated Na<sup>+</sup> channels alone. The clinical effects include reduction of spontaneous pain, allodynia, and hyperalgesia. Further, local anesthetic infusions have been utilized in various types of pain providing longer term relief than the expected duration of the local anesthetic (1092). Local anesthetics also have systemic and local toxic effects. Systemic toxicity relates to the relatively narrow difference between therapeutic plasma levels and toxic levels (1093). Peak plasma levels are determined by the dose and rate of systemic absorption. The genes controlling the subunit of Na<sup>+</sup> channels give rise to different pharmacological and biophysiological profiles of Na<sup>+</sup> channels through the body (1092). Overall, levobupivacaine

has lower systemic toxicity than other amides because of its lower affinity for cardiac channels (1094). Intra-articular local anesthetics may cause chondrotoxicity; however, chondrotoxicity is worse with bupivacaine or mepivacaine. While methemoglobinemia is a major issue with prilocaine, benzocaine and lidocaine can also cause methemoglobinemia (1095,1096).

Local anesthetic toxicity affects 2 organs that inherently are less tolerant of anaerobic metabolism, the heart and brain. Cardiac toxicity is mostly related to accidental intravascular injection, leading to the conduction disturbances, contractile dysfunction, and ventricular arrhythmias that are seen in local anesthetic induced cardiac toxicity (1097). More importantly, for interventional pain physicians, the incidence of cardiac toxicity increases with bupivacaine, a longer acting anesthetic. Bupivacaine blocks inactive sodium channels during the cardiac potential at a concentration of 0.2 mcg. Bupivacaine binding is described as “fast-in, slow-out” fashion as it binds very quickly to a large portion of sodium channels during the cardiac action potential, but releases from the channel slowly during diastole, resulting in a large proportion of medication accumulating at 60 to 150 beats per minute. Local anesthetic toxicity may become a serious issue, even though adverse effects are rare. From minor symptoms to major cardiac or CNS effects, local anesthetic system toxicity is an important consequence in interventional pain management. The epidemiology of local anesthetic toxicity has been reported from zero events to 25 per 10,000 nerve blocks. One study reported seizures of 79 of 10,000 brachial plexus block procedures (1098,1099).

Lidocaine at 5 to 10 mcg/mL will also result in a substantial sodium channel blockade during cardiac action potential. However, in contrast to bupivacaine, lidocaine follows the “fast-in, fast-out” principle, meaning it releases from sodium channels rapidly during diastole. This allows for a quick recovery, and reduced incidence of cardiac toxicity even compared to bupivacaine. Consequently, during a cardiac arrest, it may be crucial to continue resuscitation measures until bupivacaine is completely released. CNS changes include agitation, confusion, dizziness, drowsiness, dysphoria, auditory changes, tinnitus, perioral numbness, metallic taste, and dysarthria. Without adequate recognition and treatment, these signs as symptoms can progress to seizures, respiratory arrest, and/or coma.

Historically, local anesthetic literature suggests

that cardiac toxicity is often presented after antecedent CNS toxicity (1097). However, with more potent local anesthetics, cardiac toxicity may precede CNS toxicity. Lidocaine was utilized far more frequently than bupivacaine. Subarachnoid blockade with bupivacaine may turn out to be a disaster, specifically in the cervical spine. Consequently, injections of bupivacaine in the cervical or thoracic spine is contraindicated. Even then, lidocaine is also injected in extremely low concentrations of 0.5%. In the cervical spine, one must still be careful with appropriate visualization of the epidural space without any subdural or subarachnoid filling. Failure to follow basic principles can result in respiratory arrest, as well as cardiac arrest.

### 10.3 Radiation Safety

Other complications of epidural interventions include radiation exposure, when guided under fluoroscopy. This is a potential problem with damage to eyes, skin, and reproductive organs (1100-1104).

The ALARA principle should be respected when x-ray is used because excessive radiation to a patient or a physician can cause radiation injury or a stochastic effect such as neoplasm and genetic mutation (1104).

Radiation exposure used in pain procedures is related to factors such as the skill of the operator, the distance of the operator from the patient, the orientation of the operator’s head, the distance of the image detector from the patient, the beam collimation, the tube configuration, the tube voltage and filtration, and the complexity of the procedure (1102).

Fortunately, most studies regarding radiation exposure during fluoroscopy-guided pain interventions have concluded that exposure levels are below the yearly limit established by the International Commission on Radiological Protection (ICRP). However, exposure to low levels of ionizing radiation over the long-term cannot be accurately predicted. These long-term, low-level ionizing radiation exposures may not acutely destroy cells, but may lead to cell damage and genetic mutations that can lead to sequelae years later (1103).

### 10.4 Complications of Lysis of Adhesions and Neuroplasty

Lysis of adhesion was first introduced into the lexicon of interventional pain medicine techniques in 1989 (1105). Since that introduction, the procedure has grown in acceptance and application to include epiduroscopy and transforaminal approaches to the

relief of pain secondary to adhesions (911,1105). While the procedure was initially introduced in the lumbar space, the application of the concept has expanded for use in the thoracic and cervical spine as well (1106,1107). The complications that associated with the procedure are well defined and include well described procedure-related issues with neuraxial access and intervention such as post procedure discomfort, dural puncture/tears and post-dural puncture headache, infection, nerve injury, transient neurologic syndrome, to the more rare and higher clinical impact adverse events such as seizure, visual impairment, neurogenic bladder, cauda equina syndrome, and contrast-induced rhabdomyolysis (7,1105-1108).

Reviewing more recent literature, to date, no studies evaluating lysis of adhesions or neuroplasty in the cervical spine have evaluated complications or complication rates. The studies performed in this region have only evaluated effectiveness (1106). One randomized, double blinded, pilot study compared mechanical lysis of adhesions with chemical lysis using corticosteroid and hyaluronidase in the lumbar spine (911). This study suggested an improved outcome with steroid + hyaluronidase with regard at six months and one year but no complication rate was noted (1109). A recent study evaluated neuroplasty in 430 consecutive patients with single level lumbar disc herniation demonstrating a tendency in the treatment group to avoid need for decompressive surgery (911). Again, in this study, the complication rate was not mentioned. Including the Marchesini report (1110), 22 complications were reported in 246 subjects with no lasting sequela though several of the transient symptoms were ominous in nature upon presentation.

## **11.0 IMPLICATIONS ANTITHROMBOTIC AND ANTICOAGULANT THERAPY**

**Key Question 9: What are the implications of antithrombotic and anticoagulant therapy and epidural interventions?**

Implications of antithrombotic and anticoagulant therapy during interventional procedures has been updated and multiple guidelines have been developed by various organizations (103,1111-1113). The use of prescription medications to manage thrombosis risk and the ease of availability of OTC and herbal products that mediate or modulate the coagulation cascade is increasing (103,1111-1127). Interventional pain physicians frequently encounter the challenge of the potential risk of bleeding or thrombosis in perioperative

management of the patients receiving antithrombotic and anticoagulant therapy (1031,1122,1126,1128-1150). Modulation of anticoagulant and antithrombotic therapy during performance of interventional techniques is one of the major clinical decisions often made without precise evidence-based literature to support existing opinions (103,1122,1126,1128-1150). Leading causes of morbidity and mortality worldwide include cardiovascular and cerebrovascular disease (1113,1114,1118,1121,1151-1154). Additionally, one of the leading causes of disability and functional impairment across the globe is chronic persistent pain (3-7,39,40,168,196-200,303). Therefore, the overlap between chronic persistent pain and cardiovascular disease has a synergistic impact on physical and psychological health, affecting the performance of social responsibilities, including work and family life. Antithrombotic therapy has a clear evidence-based foundation with a favorable risk-benefit profile for prevention and management of cardiovascular disease, including limiting the present and future burden of cardiac or cerebrovascular infarcts (103,1112-1114,1127,1155-1168). A significant portion of patients with established cerebrovascular, cardiovascular, or peripheral vascular disease who are receiving antithrombotic therapy, are commonly in need of interventional pain management.

Based on published guidelines, derived by clinical case reports and consensus, a large subset of clinicians report stopping antiplatelet therapy and consider this concept as a standard of care (103,1126,1130,1133,1135,1169-1175). Although the overall incidence of bleeding complications and epidural hematoma in the nonobstetric epidural literature has been reduced, the incidence has been higher with procedures involving cervical and thoracic spine in interventional procedures and is growing, with or without anticoagulant therapy (103,1128-1138,1148-1150,1176-1195). Of note, the clinical literature reports of incidences of epidural hematoma cases accompanying interventional techniques and neuraxial techniques are increasing rapidly (103,1126,1128,1138,1150,1196-1212). While some reports indicate a decreasing incidence of bleeding complications related to neuraxial techniques (1209), multiple studies have been performed assessing the prevalence and risks related to bleeding complications and epidural hematoma with neuraxial procedures, specifically epidural injections (103,1126,1128-1138,1146,1147,1150,1204-1212). In

fact, anticoagulants have been described to cause the most serious adverse events in the US. According to the CDC, in the US in 2011, 48% of the US population were taking a prescription medicine in any given month, and 11% were taking 5 or more prescribed medicines. The FDA estimated that the number of reports it receives represents only the tip of the "iceberg" (1213). Among the healthcare providers and patients, anticoagulant drugs, Warfarin and dabigatran, were on the top (1213).

Significant risks of withdrawing antiplatelet therapy include cardiovascular, cerebrovascular, and peripheral vascular thrombosis. In addition, the risks are higher in chronic pain patients as chronic psychosocial stress causes a hypercoagulable state, as reflected by increased procoagulant molecular fibrinogen (or coagulation factor 7), reduced fibrinolytic capacity and increased platelet activity (103,1111,1212,1214,1215). Stress has been shown to affect coagulation activity via an influence on the regulation of genes coding for coagulation and fibrinolysis molecules (1215) with increase in hormonal levels (1216-1218) and an underlying surge of catecholamine and cortisol induced hypercoagulability (1218). A prior systematic review and meta-analysis explored the hazards of discontinuing or altering aspirin regimens among patients at risk for coronary artery disease (1157). Importantly, in patients at moderate to high risk for coronary artery disease, withdrawal or noncompliance with aspirin therapy was associated with 3-fold higher risk of major adverse cardiac events and the risk was magnified in patients with coronary stents. The findings support the recommendation that aspirin discontinuation in this patient population should be advocated only under circumstances where the risk of adverse outcomes caused by bleeding risk clearly outweighs that of catastrophic atherothrombotic events. These findings have been confirmed in later studies (1158-1165,1212). Conversely, recently published large-scale evidence (1123-1125) shows lack of benefit of aspirin for primary prevention of cardiovascular events, but aspirin therapy is associated with increased bleeding episodes. Thus, current evidence suggests that the risks of coronary events related to patients abstaining from their antiplatelet medications during the perioperative period are more serious when compared to the risks of continuing antiplatelet therapy through the perioperative period.

Multiple publications (103,1129,1130,1138,1142,1204,1207) have also supported the concept of con-

tinuing antiplatelet/anticoagulant agents in patients undergoing various interventional pain procedures in light of identical complication rates as compared to the patients who stop taking these for a particular recommended period. It should be noted that there are only a few clinical reports of an epidural hematoma available in patients undergoing interventional therapies for chronic pain, which included patients both continuing and discontinuing antithrombotic therapy.

### 11.1 Prevalence and Risk Assessment of Studies

Multiple studies have been published assessing the prevalence, as well as the risk of bleeding with interventional techniques (1128-1131,1134,1137,1138,1146-1150). In a survey of practice patterns among interventional pain physicians in 2012, Manchikanti et al (1128) showed that the majority of physicians discontinued antithrombotic agents; however, this study also showed that there were a significantly higher number of complications related to thromboembolic events of a total of 162 compared to hemorrhagic complications of a total of 55 in this population.

In a prospective evaluation of bleeding risks for interventional techniques in chronic pain, Manchikanti et al (1129) assessed the rates of adverse events in patients undergoing interventional techniques on antithrombotic therapy with cessation or without cessation and compared them to a group of patients without antithrombotic therapy. While the results showed differences in milder complications, there were no reports of hemorrhagic complications requiring any type of treatment. In this assessment, the authors studied all types of procedures with 1,227 of 1,831 continuing aspirin compared to 604 of 1,831 discontinuing them. Similarly, they also studied 100 patients on clopidogrel with continuation, whereas, 226 patients were discontinued. Further, there were 128 patients with aspirin and other agents with continuation and 151 were discontinued. The procedures performed included cervical epidural injections with continued aspirin in 249 patients, thoracic epidural in 30 patients, lumbar interlaminar epidural in 128 patients, lumbar transforaminal in 144 patients, whereas 528 patients for caudal epidural injections, and 148 for percutaneous adhesiolysis. In reference to clopidogrel, it was continued in 10 patients undergoing cervical epidural, one patient with thoracic epidural,



14 patients with lumbar epidural, 44 patients with caudal epidurals, 10 with lumbar transforaminal epidural, and 21 with percutaneous adhesiolysis. There were a large number of facet joint interventions and other treatments.

Warner et al (1150) in a manuscript describing bleeding and neurological complications in 58,000 interventional pain procedures showed that preprocedural aspirin or nonsteroidal anti-inflammatory drug therapy was prevalent in 17,825 procedures or 30.7% of the procedures without significant bleeding complications. Out of total of 58,066 procedures performed in the study, 22.4% of the procedures were performed with perioperative administration of aspirin within 7 days, 12.1% of the patients with administration of nonsteroidal anti-inflammatory drugs within 7 days, 1.6% of clopidogrel within 7 days. The study also included 3,880 lumbar epidural injections, 304 thoracic interlaminar injections with a large number of epidural injections with over 50% of the epidural injections not assigned to a region. They concluded that bleeding complications were rare in patients undergoing low or intermediate risk pain procedures even in the presence of antiplatelet medication.

Lagerkranser (1148), and Lagerkranser and Lindquist (1149) have published an extensive review of neuraxial blocks and spinal hematoma in 2 parts from 1994 to 2015 covering demographics, risk factors, diagnosis, treatment, and outcome. They also considered previous reviews published in 1992, 1994, and 1996 case reviews, analyzing 29, 61, and 51 cases of spinal hematoma after neuraxial blocks, respectively, between 1906 and 1996, in 147 manuscripts (1149). In managing chronic pain with epidural injections, they identified 21 hematomas, 17 (5 cervical, 4 thoracic, and 8 lumbar) after epidural injections, and 4 after percutaneous application of spinal cord stimulators. However, they did not identify the number of patients developing hematoma with appropriate cessation of antithrombotic therapy based on recommended guidelines. Overall, they showed that 37% of the patients who were not on antihemostatic drugs, whereas 63% were on antihemostatic drugs with 47 of the cases, receiving more than one antihemostatic drug, and 12 receiving 3 such drugs. Further, they also had 6 reports which were indeterminate. Consequently, the number of patients without antithrombotic therapy, but with hematoma formation seems to be almost 40%.

Lagerkranser (1148) showed that an annual average of 7.5 published cases of spinal hematoma in the years 1994 to 2015, compared to an average of only 2.5 case reports per year from 1976 to 1993. They also identified that there has been a transition from a male to female dominance among patients suffering from post-neuraxial blockade and spinal hematoma particularly among the elderly women. They identified bloody tap at the introduction of a neuraxial needle or catheter as a major risk factor, but multiple attempts to reach the spinal canal do not seem to increase the risk of spinal hematoma. Their results also showed that 80% of the patients developing spinal hematoma had severe neurological symptoms with paresis or paralysis. When compared over time, outcomes have improved significantly (1148). The results showed that among patients subjected to surgical evacuation of the hematoma, outcomes were best if surgery was performed within 12 hours from the first sign of motor dysfunction. However, even patients operated on after more than 24 hours had relatively favorable outcomes. Further, outcomes after surgical evacuation of the epidural hematoma were satisfactory, compared to subdural hematoma, which had poor outcomes. They recommended that suspicion of spinal hematoma calls for the consultation of a surgeon without delay. MRI was the recommended diagnostic tool. Surgical evacuation within 12 hours from the sign of motor dysfunction seems to lead to the best outcome, even though many patients operated on as late as after more than 24 hours did regain full motor function (1148).

Appendix Table 16 describes the studies assessing the risk of thrombosis and bleeding with interventional pain management techniques. All but 2 studies in this assessment are related to performing interventional techniques without cessation of antithrombotic therapy (1128-1131,1134,1136-1138,1145,1147). Only one study (1128) was related to an online physician survey and study of spinal hematoma with neuraxial blocks. Among all the studies, only 2 studies included epidural injections (1129,1138). All others have performed a large portion of procedures with low risk or intermediate risk including transforaminal epidural injections.

A systematic review of risks and benefits of seizing or continuing anticoagulant medication for image-guided procedures for spine pain by Smith et al (1130), including 14 manuscripts assessing the role of antithrombotics in interventional pain management.

They showed that procedures involving interlaminar access carry a nonzero risk of hemorrhagic complications, regardless of whether anticoagulants are seized or continued. For other procedures, hemorrhagic complications have not been reported, and case series indicate that they are safe when performed in patients who continue anticoagulants. Among the reports they reviewed, 3 of them reported the adverse effects of seizing anticoagulants, with serious consequences, including death. They concluded that other than for interlaminar procedures, the evidence does not support the view that anticoagulant and antiplatelet medication must be seized before image-guided spine pain procedures.

Thus, based on the evidence presented from reviews and primary studies, it appears that there is no significant difference whether antithrombotic therapy is discontinued or continued in reference to the bleeding. A majority of the authors have studied intermediate and low risk procedures without the inclusion of epidural injections. The only one study reviewing spinal cord stimulation also showed lack of increased risk with continuation of aspirin and other NSAIDs. Consequently, cessation of anticoagulant medication is recommended only for interlaminar epidural injections in consultation with the patient and other healthcare providers managing antithrombotic medications, instead of seizing by providing them with mandatory instructions to stop for 7 to 10 days, or even longer.

### 11.2 Reports of Thromboembolic Events

There have been multiple reports of thromboembolic events with the discontinuation of antithrombotics and anticoagulants prior to performance of interventional procedures. Manchikanti et al (1128)

in an assessment of practice patterns of perioperative management of antiplatelet and anticoagulant therapy in interventional pain management reported 162 thromboembolic events compared to 55 serious bleeding complications from epidural hematomas. This study showed thromboembolic events were 3 times more frequent than bleeding complications. Further, they also showed bleeding complications from epidural hematomas were similar whether antiplatelet therapy was continued or discontinued with an occurrence of 26 versus 29 respectively; in this survey the sample sizes were not provided. Consequently, it is difficult to assess the exact risk of bleeding complications and similarly thromboembolic events. Endres et al (1138) reported 9 patients with thromboembolic events after cessation of anticoagulant therapy out of 1,626 procedures. These complications included 2 deaths 5 strokes, one pulmonary embolism, and one myocardial infarction in patients when anticoagulants were stopped; however, they have not reported any bleeding complications in patients where anticoagulants were continued. Kumar et al (1219) reported a case of pulmonary embolism after discontinuation of warfarin during a spinal cord stimulation trial. Linn et al (1220) also reported right middle cerebral artery infarction with persistent left hemiparesis, neglect and dysarthria with L5-S1 epidural steroid injection after discontinuation of warfarin for 9 days preprocedure. Manchikanti et al (1204) in providing 2 case reports and a literature review described 2 cases of thromboembolic complications with cessation of antithrombotic therapy. Table 25 shows reported thromboembolic and cardiovascular complications related to discontinuation of antiplatelet or anticoagulation therapy.

Table 25. *Thromboembolic and cardiovascular complications related to discontinuation of antiplatelet or anticoagulation therapy.*

Study	Type of study	Complications
Endres et al (1138)	Observational report of interventional techniques	<ul style="list-style-type: none"> <li>• 2 patients died</li> <li>• 5 suffered strokes</li> <li>• 1 suffered pulmonary embolism</li> <li>• 1 suffered myocardial infarction</li> </ul>
Kumar et al (1219)	Case report of dorsal column stimulator trial	<ul style="list-style-type: none"> <li>• Pulmonary embolism without lasting complications</li> </ul>
Linn et al (1220)	Case report of L5/S1 epidural steroid injection	<ul style="list-style-type: none"> <li>• Right middle cerebral artery infarction with persistent left hemiparesis, neglect, and dysarthria</li> </ul>
Manchikanti et al (1128)	Online survey	<ul style="list-style-type: none"> <li>• Reports of epidural hematoma: 55</li> <li>• Reports of thromboembolic complications: 162</li> </ul>
Manchikanti et al (1204)	Case report and literature review of interventional techniques	<ul style="list-style-type: none"> <li>• 2 cases of thromboembolic complications with cessation of antithrombotic therapy.</li> </ul>

### 11.3 Case Reports of Bleeding Complications

There were multiple case reports discovered citing epidural hematoma in patients with or without continued antithrombotic therapy during an interventional technique (1196-1204,1210,1221-1242).

Multiple reports of bleeding and epidural hematoma associated with interventional techniques in patients without antithrombotic therapy have been published (1176-1178,1180,1181,1183-1194,1202,1204,1207,1208-1222,1225,1227,1231,1233,1234,1238,1240,1242-1249), whereas several reports of bleeding in patients with discontinued antithrombotic therapy also have been published (1196,1199-1201,1204,1205,1210,1223,1228-1230,1232). Reports of bleeding complications and epidural hematoma in patients with continuation of antiplatelet therapy with interventional techniques also have been published. Multiple reports of bleeding complications with continuation of anticoagulant therapy during interventional techniques were identified (1197-1199,1202,1203,1224,1239,1241).

Figures 24-26 show summary reports of several epidural hematomas with epidural injections, acupuncture and dry needling, and spinal cord stimulation lead placement in patients without antithrombotic therapy, with antithrombotic therapy withheld for an appropriate duration, and with antithrombotic therapy continued. A total of 46 epidural hematomas were described in 43 case reports. There were 23 in the cervical spine, 8 in the thoracic spine, and 15 in the lumbar spine. Of these, 21 patients were not on antiplatelet therapy, 9 patients had their antithrombotic therapy discontinued, 14 continued antithrombotic therapy, and 2 cases were due to fish oil and one case of ketorolac and paroxetine. Further, as shown in Fig. 26, epidural injections were responsible for 33 cases of hematomas, 7 cases were secondary to acupuncture or dry needling and 6 were related to spinal cord stimulation. There was one case report of caudal epidural injection with cilostazol (1241), and in one case report, we were unable to obtain full manuscript (1246). Cases of chronic subdural hematoma and cases of abdominal hematomas were not included.

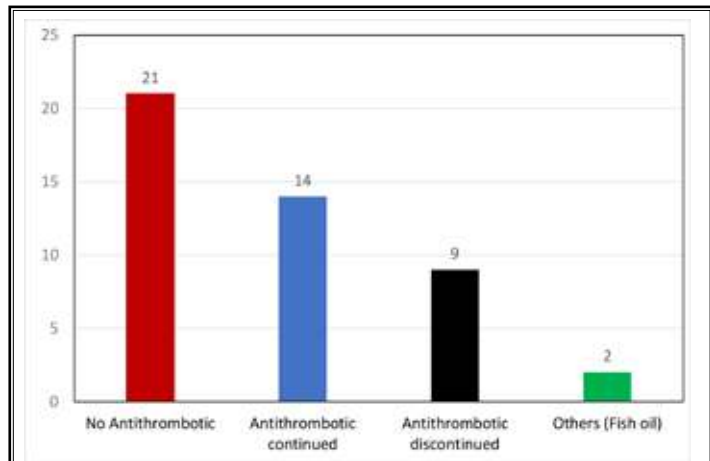


Fig. 24. Epidural hematoma incidence based on presence or absence of anticoagulant/antiplatelet therapy following administration of epidural injections.

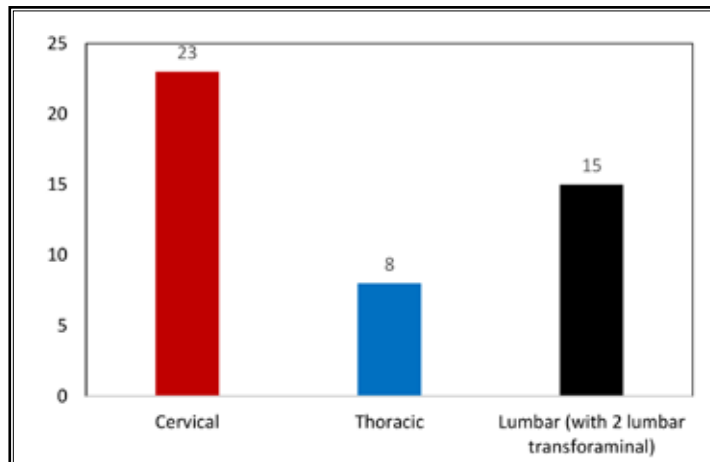


Fig. 25. Epidural hematoma incidence based on spinal regions

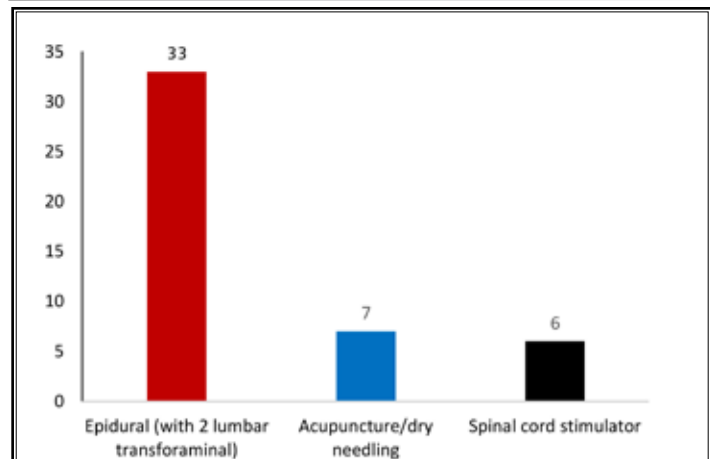


Fig. 26. Epidural hematoma cases reported based type of procedure

**11.4 Guidelines and Recommendations**

Guidelines and recommendations were based on risk stratification, pharmacology of antithrombotics and anticoagulants, and the application of available evidence.

**11.4.1 Risk Stratification**

Interventional techniques performed in the spine and other regions for chronic cancer and noncancer pain patients face variable risks depending on anticoagulant or antithrombotic therapy, age, anatomy, the specific region of interest, and obesity. Consequently, various authors have described procedural classifications according to the potential risk for serious bleeding.

Raj et al (1250) stratified risk scores based on technique related bleeding risk and patient-related bleeding risk factors. This risk classification took various factors into consideration including a sharp or blunt needle, as well as the use of fluoroscopy and lack of fluoroscopy.

Breivik et al (1133), in a comprehensive topical review of reducing risk of spinal hematoma from spinal epidural and pain procedures, based their recommendations on an extensive review of 166 case reports published from 1994 through 2015 (1148,1149), phar-

macology of drugs, and available clinical evidence relating to complications whether the antithrombotics were continued or discontinued.

Narouze et al (1111) provided guidance for interventional spine and pain procedures in patients on antiplatelet and anticoagulant medications. They provided an extensive review of the literature, considered pharmacology, and current literature with development of risk stratification.

Deer et al (1112) provided recommendations on bleeding and coagulation management in neurostimulation devices. They also provided bleeding risk stratifications for neuromodulation procedures. Their classification showed spinal cord stimulation trial and implant, dorsal root ganglion stimulation, and intrathecal catheter and pump implant as high to intermediate risk neuromodulation procedures. Further, they classified deep brain stimulation and motor cord stimulation as high-risk neuromodulation procedures. This is in contrast to other guidance where spinal cord stimulation trial and implant, dorsal root ganglion stimulation, and intrathecal catheter and pump implant are considered as high risk.

Oprea et al (1126) published risk stratification, perioperative, and periprocedural management of patients receiving anticoagulant therapy based on

Table 26. Classification of interventional techniques based on the potential risk for bleeding.

Low-Risk Procedures	Intermediate-Risk Procedures*	High-Risk Procedures*
1. Trigger point and muscular injections (including piriformis injection) 2. Peripheral joints 3. Peripheral nerve blocks 4. Sacroiliac joint and ligament injections and nerve blocks 5. Caudal epidural injections 6. Ganglion impar blocks	1. Facet joint interventions (intra-articular injections, nerve blocks and radiofrequency neurotomy) 2. Lumbar transforaminal epidural injections at L4, L5, S1 3. Lumbar intradiscal procedures 4. Hypogastric plexus blocks 5. Lumbar sympathetic blocks 6. Peripheral nerve stimulation trial and implant 7. Pocket revision and implantable pulse regenerator/ intrathecal pump replacement 8. Caudal percutaneous adhesiolysis 9. Lumbar percutaneous disc decompression (L4/5 or below) 10. Lumbar vertebral augmentation (below L4) 11. Intervertebral spinous prosthesis 12. Lumbar discography	1. Cervical, thoracic, and lumbar interlaminar epidurals 2. Cervical, thoracic and lumbar above L3 transforaminal epidural injections 3. Spinal cord stimulator trial and implant 4. Percutaneous adhesiolysis with interlaminar or transforaminal approach 5. Percutaneous disc decompression (above L4/5) 6. Sympathetic blocks (stellate ganglion; thoracic splanchnic, celiac plexus) 7. Thoracic and cervical intradiscal procedures 8. Vertebral augmentation, lumbar (above L4), thoracic and cervical 9. Intrathecal catheter and pump implant 10. Interspinous prosthesis and MILD*

\*Patients with high risk of bleeding (e.g., old age, history of bleeding tendency, concurrent uses of other anticoagulants/antiplatelets, liver cirrhosis or advanced liver disease, and advanced renal disease) undergoing low or intermediate-risk procedures should be treated as intermediate or high risk, respectively.

Source: Kaye AD, et al. Responsible, safe, and effective use of antithrombotics and anticoagulants in patients undergoing interventional techniques: American Society of Interventional Pain Physicians (ASIPP) guidelines. *Pain Physician* 2019; 22:S75-S128 (103).

bleeding risk for each procedure, pharmacology, and evidence of the risk of the development of bleeding complications as well as thromboembolic risks.

Lagerkranser (1148), and Lagerkranser and Lindquist (1149), published an extensive review of neuraxial blocks and spinal hematoma with review of 100 case reports published from 1994 to 2015 with demographics and risk factors, as well as diagnosis, treatment, and outcomes. They described multiple risk factors related to hemostasis, elderly females, and spinal disorders and complicated blocks, especially spinal stenosis and “bloody taps,” whereas multiple attempts do not seem to increase the risk of bleeding. Further, they conceded that in a large number of cases, no risk factor was reported.

Multiple factors and the available literature in reference to the adverse consequences of anticoagulant and antithrombotic therapy with interventional techniques were utilized in developing risk stratification. The following classification for interventional techniques has been developed (Table 26) (103,1126,1128-1136,1148,1149,1239,1250). The classification describes low risk, intermediate risk, and high-risk procedures. However, based on comorbid medical conditions and other risk factors of coagulopathies and concurrent use of other anticoagulants and antiplatelets, the procedural risk classification may be changed from low risk to intermediate, and intermediate to high risk.

Of all the low risk procedures as shown in Table 26, the caudal epidural injection was the only one which has reported an epidural hematoma with continuation of cilostazol (1241). This is extremely unusual and probably coincidental. Consequently, with caudal epidural injections and other low risk procedures, antithrombotic and anticoagulant therapy may be continued with the appropriate guidelines.

Intermediate risk procedures include multiple procedures performed, constituting a great proportion of the procedural prevalence. This risk stratification is somewhat different from the one proposed by American Society of Regional Anesthesia and Pain Medicine (ASRA) (1111). Justifiably, we have included caudal percutaneous adhesiolysis into intermediate risk procedures as there have not been any case reports. Further, lumbar transforaminal epidural injections at L4, L5, S1, and sympathetic blocks have been included in these categories due to 2 case reports of lumbar transforaminals resulting in hematoma without antithrombotic therapy and 2 case reports of sympathetic blocks. Lumbar interlaminar epidural

injections performed between L5 and S1 are included in the intermediate risk procedures; whereas, procedures performed at L4-5 and at higher levels are included in the high risk procedures. A majority of the lumbar epidural hematomas developed despite the discontinuation of antithrombotic therapy, and these were performed above the L5-S1 interspace. If epidural hematoma develops at L5-S1 it will have significantly higher space availability to be asymptomatic and to be managed conservatively.

The high-risk procedures include the majority of the procedures performed in the cervical and thoracic spine. These guidelines are in contrast to ASRA guidelines with the inclusion of cervical, thoracic, and lumbar due to the available literature and potential issues related to epidural hematoma requiring surgical exploration and spinal cord damage.

### **11.5 Pharmacologic Aspects and Hemostasis Monitoring**

The main categories of antithrombotics and anticoagulants are described as; platelet inhibitors, interfering with platelet aggregation (clumping) and thrombus formation; anticoagulants interfering with formation of the clotting, thereby reducing fibrin formation and preventing clots from forming and expanding; and fibrinolytics interfering with the final clot.

Monitoring of hemostasis is performed with multiple standard tests including platelet count, activated partial thromboplastin time (APTTa), and international normalized ratio (INR) (1133). A normal INR is considered as 0.9 to 1.2. Consequently, for epidural injections, an INR of less than 1.5 is ideal for high risk and moderate risk procedures, and less than 1.8-2.00 is ideal for low risk procedures.

Additional advanced hemostatic tests for monitoring of hemostasis include multiple viscoelastic tests like thromboelastography or thromboelastometry extensively used to evaluate liver disease (1251). However, this parameter has been studied for safe epidural catheter removal with the conclusion that the tests were not well validated in this context and there were frequent false negative test results (1252,1253). Even then, a clearly abnormal curve indicates deranged hemostasis and must be taken seriously (1253,1254).

#### **11.5.1 NSAIDs and Aspirin**

NSAIDs inhibit cyclooxygenase enzymes COX1 and COX2, which inhibit prostaglandin production to decrease the inflammatory response. Thus, NSAIDs



Table 27. Characteristics of aspirin and NSAIDs.

	Aspirin or acetylsalicylic acid (Oral Low Dose)	NSAIDs
Target	COX -1 irreversible	COX-1 reversible, COX-2
Time to peak effect	0.5 hours	Varies
Plasma Half Life	0.5 hours	Variable from 1 to 72 hours
Renal elimination	+	+
Time to 50% recovery of platelet function	3 days	1 day
Hours to C-Max	0.5 hours	~0.5 hours
Metabolism	Hepatic	Hepatic
Bioavailability	60%	50-95%
Antithrombotic effect	++	+

NSAID = non-steroidal anti-inflammatory drug; COX = cyclo-oxygenase

Rating of antithrombotic effect and renal elimination: (+) = insignificant; + = low; ++ = moderate; +++ = pronounced; ++++ = high.

Source: Kaye AD, et al. Responsible, safe, and effective use of antithrombotics and anticoagulants in patients undergoing interventional techniques: American Society of Interventional Pain Physicians (ASIPP) guidelines. *Pain Physician* 2019; 22:S75-S128 (103).

have analgesic effects and are used for minimizing pain. Thromboxane A2 is produced via COX1 enzyme activity, which is a potent thrombus activator. Aspirin is an irreversible inhibitor of COX1 and has significant clinical benefits for preventing thrombus formation. In response to aspirin, more prostacyclin is produced by endothelial cells, but there is no additional thromboxane made as there are no nuclei in platelets, thus, there is a greater percent of prostacyclin to thromboxane, thinning the blood. Elevated bleeding risk is a concern for a small portion of patients, but adverse effects are rare. Prostacyclin (PGI2) synthesis from vascular endothelial cells is dependent on COX2 and has anti-platelet effects. High doses of aspirin reduce PGI2 production which can abolish the anti-platelet effect of low dose aspirin. Low-dose aspirin anti-platelet effects last for 7-10 days, as bone marrow directed platelet renewal is required for clotting to resume. Low-dose aspirin therapy is well established to reduce the risk of cardiovascular events in patients with acute coronary syndromes, cerebral infarct, or occlusive vascular disease (1255). However, recently published large scale evidence (1121,1123-1125) shows a lack of benefit with aspirin for the primary prevention of cardiovascular events, while it does increase the risk of bleeding.

Table 27 shows pharmacokinetic and pharmacodynamic characteristics of aspirin and NSAIDs. Time to 50% recovery of platelet function with aspirin is shown as 3 days (1133). Antiplatelet function of irreversible inhibitors is dependent mainly on platelet regeneration than drug half-life.

For other NSAIDs, unlike aspirin, the platelet effects of these drugs are directly related to systemic plasma drug concentrations and influenced by the pharmacokinetic clearance of these medications. It takes approximately 5 half-lives for systematic elimination. Recommendations (103,1111,1112) have been revised for aspirin, whether to continue or discontinue in the perioperative period for interventional pain procedures. Decision-making is based on the reason for aspirin utilization, a multitude of risk factors including vascular anatomy surrounding the target area, degree of the invasiveness of the procedure, and potential sequelae associated with perioperative bleeding. Thus, aspirin for primary prophylaxis can be stopped without any hesitation. The major consideration in withholding aspirin is the thromboembolic risk. Based on the available evidence, it appears that aspirin discontinuation for 4 days may be sufficient. In contrast, for nonsteroid anti-inflammatory agents, recommended discontinuation by ASRA is one day for diclofenac, ibuprofen, and Ketorolac. Recommended discontinuation time is 2 days for etodolac and indomethacin. Discontinuation is about 4 days for meloxicam and Naprosyn, 6 days for Nabumetone, and 10 days for piroxicam and Oxaprozin. However, the evidence for stopping NSAIDs agents other than aspirin seems to be very limited. Stopping these drugs may become a practical issue and patients may not like it to stop all the drugs and complain of significantly more pain. Consequently, based on the available, very limited, evidence, the clinician may continue or discontinue. In reference to ketorolac, this is used

Table 28. Comparative pharmacokinetics/pharmacodynamics of ADP-receptor inhibitors.

	Clopidogrel (Plavix®)	Prasugrel (Effient®)	Ticlopidine (Ticlid®)	Ticagrelor (Brilinta®)
Target	P2Y12ADP	P2Y12ADP	P2Y12ADP, also inhibits liver CYP2C19 and CYP2B6	P2Y12ADP
Antithrombotic activity	++	+++	++	++++
Time to Cmax	3-7 days	3-5 days	8-11 days	2-4 hours
Time to peak effect	4 hours to 4 days	1 hour	3-5 days	2.5 hours
CYP metabolism	CYP1A2, CYP2B6, CYP2C9, CYP2C19 and CYP3A4/5	CYP450-mediated (primarily CYP3A4 and CYP2B6)	Cytochromes P450	CYP3A4
Bioavailability	> 50%	≥ 79%	> 80%	36%
Protein binding	94-98%	Active metabolite: ~98%	98%	>99.7%
Plasma half-life	7-8 hours (inactive metabolite)	~7 hours (range 2 hours to 15 hours)	12 hours (single dose) 4-5 days (repeated dose)	7 hours (ticagrelor), 8.5 hours (active metabolite AR-C124910XX)
Renal elimination	50% kidney, 46% biliary	Urine (~68% inactive metabolites); feces (27% inactive metabolites)	Renal and fecal	Biliary
Time to 50% recovery of platelet function	3 days	3 days	6 days	1.5 days

CYP = cytochrome P450

Source: Kaye AD, et al. Responsible, safe, and effective use of antithrombotics and anticoagulants in patients undergoing interventional techniques: American Society of Interventional Pain Physicians (ASIPP) guidelines. *Pain Physician* 2019; 22:S75-S128 (103).

intraoperatively or postoperatively. Consequently, it is not advisable to administer ketorolac to patients during or after epidural injections.

### 11.5.2 Adenosine Diphosphate Receptor Inhibitors

Adenosine diphosphate (ADP)-receptor inhibitors inhibit platelet aggregation. The drugs in this category utilized for clinical applications include Clopidogrel (Plavix®), Prasugrel (Effient®), Ticlopidine (Ticlid®), and Ticagrelor (Brilinta®). Table 28 shows comparative pharmacokinetics and pharmacodynamics of ADP-receptor inhibitors.

Clopidogrel is the prototypical thienopyridine drug that inhibits the P2Y12 receptor. The P2Y12 receptor is activated by ADP binding and promotes platelet aggregation. Depending on the dosage schedule, the maximal platelet aggregation inhibitory effects of clopidogrel are reached within 3 to 7 days. After discontinuation, recovery of platelet inhibition occurs 50% after 3 days and full recovery after one week (1256). Eighty percent of subjects demonstrated normal platelet aggregation by the 4th day (1256). Other studies have demonstrated the recovery of platelet function after the cessation of aspirin in volunteers in surgical patients after 3 days in volunteers and within 4-6 days in surgical patients (1257). In this study, by day 6 all of the subjects had

restored platelet aggregation to at least 85% of the baseline level.

Ticlopidine also belongs to the thienopyridine group and is maximally aggregated after 8 to 11 days of a 500 mg per day dosage schedule. After withdrawal of 72 hours, there is still a lingering effect as there is an irreversible inhibition of platelet function (1258). Prasugrel acts by antagonizing ADP at the platelet's purine receptors, and aggregation is thus noncompetitively and irreversibly inhibited.

Prasugrel, or Effient, has significantly higher irreversible antiplatelet activity compared to clopidogrel with time to peak effect of one hour. Thus, administration of the first dose results in around half of the platelets being inhibited within the first hour of taking this medication. Following three to five days of therapy, the steady-state inhibition of platelet aggregation reaches around 70% (1259). As a prodrug, prasugrel is rapidly metabolized to active and inactive metabolites. These metabolites have varying elimination rates, although the active metabolites have an elimination half-life of 7 hours, with a wide range of 2-15 hours (1260).

Lastly, a distinct ADP-receptor inhibitor is Ticagrelor, which directly inhibits P2Y12 receptors (1259-1263). While Ticagrelor is metabolized to active metabolites, the original compound is responsible for the majority of the

inhibitory effects (1262,1263). A notable advantage of Ticagrelor is rapid effect, with peak platelet inhibition after 2 to 4 hours of intake (1264). These medications undergo hepatic conversion to active metabolites, which are then eliminated by the kidneys (1265). In addition, glycoprotein IIB/IIIA receptors are less activated, causing a reduction in fibrinogen fixation and platelet crosslinking.

ADP inhibitors were described as responsible for the formation of an epidural hematoma after central neuraxial blockade in 2.5% of 160 cases or 4 cases. In the present assessment, clopidogrel either in combination with aspirin or ticlopidine was utilized in a total of 3 cases, with 2 cases being discontinued appropriately and one case it was continued. Thus, ADP inhibitors with reports available for only one or 2 drugs showed any relevance in 8% of the cases with only one case or 2.6% of cases where it was continued and in 5% of the cases it was discontinued. This is similar to the reports from Lagerkranser et al (1148).

#### **11.5.3 Phosphodiesterase (PDE) Inhibitors**

Phosphodiesterase inhibitors include Cilostazol (Plental®) and Dipyridamole (Persantine®). These medications selectively inhibit phosphodiesterase, which leads to an increase in intracellular cyclic adenosine monophosphate (cAMP) and subsequent reversible inhibition of platelet aggregation (1266). Additionally, Dipyridamole blocks thromboxane synthase, the thromboxane receptor, and the cellular reuptake of adenosine into platelets, red blood cells, and endothelial cells. This results in increased adenosine in the extracellular space and inhibition of formation of cytokines and proliferation of smooth muscle cells. Absorption of Dipyridamole occurs in the gastrointestinal tract and is pH dependent. Gastric acid suppressors and proton pump inhibitors inhibit absorption, which can be prevented via buffered additives added to the medication (1267). An additional advantage of Cilostazol is inhibition of PDE3A, which is selective to vascular smooth muscle cells and results in vasodilatation. Cilostazol is administered at 100 mg twice daily and reaches maximum plasma levels after three hours. It is eliminated via hepatic metabolism and is excreted in the urine (1268). Thus, cilostazol is contraindicated in those with severe renal insufficiency. For interventional procedures, phosphodiesterase inhibitors have been considered as safe to continue. However, risk may increase with the addition of aspirin. Limited data exists evaluating the risk of perioperative surgical bleeding with cilostazol (1270) and no standard perioperative guidelines are available (1269). Further, if the medication is discontinued, at 50 hours (approximately 5 half-lives), less than 5% of the drug remains in plasma and improve-

ments in platelet aggregation have been demonstrated, despite continuous prior dosing (1270).

There is a single case report of bleeding complications associated with an interventional technique (1241). In this case report, the patient underwent a caudal epidural injection developing an epidural hematoma extending from L2 through S1 with concomitant central canal compromise, severe at L2-3 and L3-4 levels. This patient had received, in the past, lumbar interlaminar epidural injection without any side effects. Emergency decompression laminectomy was carried out with the patient making full recovery. This is the only case report in interventional techniques. Cilostazol alone without aspirin is recommended to be continued during interventional techniques. Lagerkranser et al (1148) also reported 2 cases of phosphatase inhibitors with dipyridamole with an incidence of 1.3% in 160 cases. Overall cilostazol is considered as a low risk drug and its continuation is appropriate.

#### **11.5.4 Glycoprotein GPIIb/IIIa Inhibitors**

A final common component of platelet aggregation is the glycoprotein IIb/IIIa receptor. Specialized medications inhibit this receptor, potentially inhibiting platelet aggregation while being reversible (1220).

Abciximab (ReoPro®) is a Fab fragment of a humanized monoclonal antibody directed against the GPIIb receptor. Abciximab inhibits over 80% of ADP-induced platelet aggregation and is given via IV administration. Additionally, thrombin generation is inhibited by Abciximab, which quickly binds to platelets with high affinity.

Eptifibatid (Integrilin®) is a cyclic peptide inhibitor of the fibrinogen binding site on the GPIIb receptor. Tirofiban (Aggrastat®) is an additional glycoprotein IIb/IIIa receptor inhibitor, reaching maximum efficacy after 4 hours of administration, with 50-80% inhibition of platelet aggregation (1271). Platelet function normalizes 8 to 24 h after stopping the IV infusion.

There were no case reports secondary to the development of epidural hematoma in patients receiving glycoprotein IIB/IIIA. Additionally, it appears that these drugs are not commonly used for prevention of thromboembolic activity.

#### **11.5.5 Low-Molecular Weight Heparin**

Low molecular weight heparins (LMWHs) inhibit the coagulation cascade via binding to antithrombin, which leads to a conformational change of antithrombin, which accelerates inhibition of factor Xa. LMWH has advantages: relatively high bioavailability, longer half-life, and ability for use once per day. Maximum efficacy levels are observed

after 3-4 hours post subcutaneous administration, and elimination occurs after 4-6 hours in those with normal renal function (1272). High molecular weight heparins (HMWH) catalyze the inhibition of clotting factors IXa, Xa and thrombin by greatly enhancing antithrombin III activity, by causing a conformational change in ATIII exposing its reactive site. Testing is required to determine the dose effect on coagulation via partial thromboplastin time (PTT). HMWH is not absorbed by GI tract due to its large molecular weight, therefore IV or SC injection must be used. The short half-life of (HMWH approximately 1h) means frequent injections or continuous infusion, and it is thus not considered suitable in an outpatient setting.

Low molecular weight heparin is one of the commonly used drugs and has been implicated in multiple cases of epidural hematoma. Lagerkranser et al (1148) showed low molecular weight heparin being responsible for the highest number of cases in 31% of the reports. Our reports also show 2 cases of warfarin with bridging with LMWH being responsible for epidural hematoma (1229,1230), both in the lumbar spine.

### 11.5.6 Warfarin

Oral anticoagulants inhibit the synthesis of vitamin K-dependent clotting factors, which are factor II, VII, IX, and X. Warfarin blocks the gamma-carboxylation of glutamate residues in prothrombin and factors VII, IX, and X. This results in biologically inactive coagulation factor molecules. Vitamin K epoxide reductase is the enzyme that catalyzes the carboxylation reaction. Therapeutic doses of warfarin inhibit vitamin K epoxide reductase, which prevents the reductive metabolism of the inactive vitamin K epoxide to its active hydroquinone form. Synthesis is the primary target of oral anticoagulants (warfarin), therefore the effects of these medications are not apparent until previously-existing clotting factor turnover has occurred. Factor half-lives vary, from factor VII at 6-8 hours to factor II at 50-80 hours (1273). Thus, it has a slow onset of action (8-12 hours) as existing clotting factors must be depleted, and the maximal effect occurs 3-5 days after administration. Warfarin is monitored by PT and INR, which is a normalized ratio of the patient's PT to that of a control sample (1273). Age, female gender, and preexisting medical conditions such as hepatic, cardiac, and renal disease modify the patient's response to warfarin. Asian patients, for example, have higher sensitivity to warfarin and require lower doses than those patients of European descent (1273). Dietary changes may alter the patient's clotting ability, and those on Warfarin are advised to avoid grapefruit and cranberry products, eat a consistent amount of leafy greens and

other high vitamin K containing foods and are advised to limit herbal supplement intake of garlic, ginger, ginkgo biloba, ginseng, and fish oil. Warfarin may be reversed with administration of vitamin K, which is associated with multiple side effects.

Warfarin is one of the most common drugs utilized in patients undergoing interventional techniques. Multiple complications have been reported with case reports of epidural hematoma in patients with warfarin, despite being stopped per the guidelines.

Lagerkranser et al (1148) reported warfarin contributing to spinal hematoma in 11% of the cases. They showed cases of warfarin which were stopped appropriately with 2 of them also receiving enoxaparin with a similar incidence of around 10%.

### 11.5.7 Direct Thrombin Inhibitors

Direct thrombin inhibitors include Dabigatran (Pradaxa®), Argatroban (Acova™), Bivalirudin (Angio-max®), Lepirudin (Refludan®), Desirudin (IPRIVASK®), and Hirudin as shown in Table 29. Of all the direct thrombin inhibitors, Dabigatran may be reversed by Idarucizumab (Praxbind®), which was approved in 2015.

Dabigatran etexilate is an oral anticoagulant and is a prodrug that is converted to dabigatran in the plasma. After an oral dose, the peak effect is reached within 2 to four hours, and plasma half-life is 13 hours on average (1274). Dabigatran dose recommendations depend on renal efficacy in the patient receiving the medication. In those with a creatinine clearance of greater than 30mL/minute, 150 mg is taken orally twice daily. For patients with lower creatinine clearance, 75mg twice daily is recommended. Dabigatran's function is via factor inhibition and not clotting factor depletion, thus, the administration of clotting factors is anticipated to be less effective in reversing the effects of dabigatran. Dabigatran is mostly cleared by the kidneys. In those with normal kidney function, dabigatran is excreted in 1-2 days post-discontinuation. This also depends on renal sufficiency of the patient taking the medication. There is one case report with epidural hematoma despite its discontinuation for 7 days prior to interventional techniques (1215). Lagerkranser et al (1148) also reported on a case of spinal hematoma out of 160 cases.

Argatroban is a small molecule direct thrombin inhibitor that is administered intravenously. It reaches steady-state plasma concentrations in 1-3 hours and is metabolized via the liver. It has a half-life of 50 minutes and is monitored by PTT. As it is metabolized hepatically, it is a viable alternative for Dabigatran, which is metabolized renally (1275).

Table 29. Comparative pharmacokinetics/pharmacodynamics of direct thrombin inhibitor.

	<b>Dabigatran (Pradaxa)</b>	<b>Argatroban (Acova)</b>	<b>Bivalirudin (Angiomax)</b>	<b>Lepirudin (Refludan)</b>	<b>Desirudin (IPRIVASK)</b>	<b>Hirudin</b>
Target	Direct thrombin inhibitor	Direct thrombin inhibitor	Reversible direct thrombin inhibitor	Direct thrombin inhibitor	Direct thrombin inhibitor	Naturally occurring peptide anticoagulant
Time to Cmax	2-4 hours	1-3 hours	2 minutes	4 hours	1-3 hours	3 hours
Time to peak effect	0.5 – 2 hours	2 hours	15 min	0.5-2 hours	2 hours	3-4 hours
Metabolism	Metabolized via conjugation into 4 acyl glucuronides, not mediated by CYP450	CYP3A4	Proteolytic cleavage	Lepirudin is thought to be metabolized by release of amino acids via catabolic hydrolysis of the parent drug	Metabolized by stepwise degradation from the C-terminus possibly catalyzed by carboxypeptidase(s) such as carboxypeptidase A	Proteolytic cleavage
Bioavailability	3-7%(Oral)	100% IV	100% IV application only	100% (injection or infusion)	100%	100% IV
Protein binding	35%	54%	no	n/a	n/a	n/a
Plasma half-life	13 hours	50 minutes	~25 minutes in patients with normal renal function	1.3 hours	2-3 hours	80 minutes
Renal elimination	80% urine	Liver	Yes	Yes	Yes	Renal, about 48% (35% unchanged)
Linear PK	Yes	Yes	Yes	Yes	Yes	Yes
Time to 50% recovery of thrombin function	12 hours	2 hours	0.5 hours	1.5 hours	2 hours	2 hours
Reversal agents	Praxbind	NA	NA	NA	NA	NA

CYP = cytochrome P450; IV = intravenous

Source: Kaye AD, et al. Responsible, safe, and effective use of antithrombotics and anticoagulants in patients undergoing interventional techniques: American Society of Interventional Pain Physicians (ASIPP) guidelines. *Pain Physician* 2019; 22:S75-S128 (103).

Bivalirudin works by binding specifically to the catalytic site, in addition to the anion-binding exosite of circulating and clot-bound thrombin. Bivalirudin is cleared by the kidney and thus is dose-dependent on overall renal function. It has as a half-life of 25 minutes in those with normal renal function, but this may be doubled in those with severe renal insufficiency (1276).

Desirudin is a subcutaneously administered direct thrombin inhibitor and is indicated for the prevention of venous thromboembolism after total joint replacement. It is recommended that dosage adjustment and aPTT be monitored in patients with moderate-to-severe renal impairment. After intravenous administration, desirudin is removed rapidly via the renal system, with 90% of the dose removed from the plasma within 2 hours. Plasma concentrations decline with a mean half-life of 2-3 hours. Subcutaneous administration demonstrates a half-life of 2 hours (1277).

Hirudin has specific activity on fibrinogen and binds

to and inhibits only activated thrombin, making it an extremely potent direct thrombin inhibitor. Thus, hirudin dissolves the formation of clots and thrombi and has therapeutic value in coagulation disorders. It is also able to act on complexed thrombin and does not alter other serum protein function or activity (1278). Hirudin has a half-life of 2-3 hours and is monitored by a PTT, allowing close titration over a wide range of anticoagulative clinical desires. Activated clotting time (ACT) and prothrombin time (PT) are insensitive for monitoring hirudin.

#### 11.5.8 Direct Factor Xa Inhibitors

Direct factor Xa inhibitors such as Rivaroxaban (Xarelto®) have been commonly used in the US (Table 30). Of multiple Xa inhibitors available, apixaban (Eliquis) and rivaroxaban (Xarelto®) can be reversed by Andexanet alfa (Andexxa®), a coagulation factor Xa (recombinant), which has been approved by the FDA for the urgent reversal of the anticoagulant effect in 2018 (1279).



Table 30. Comparative pharmacokinetics/pharmacodynamics of direct factor Xa inhibitor.

	<b>Apixaban (Eliquis)</b>	<b>Rivaroxaban (Xarelto)</b>	<b>Edoxaban (Savaysa, Lixiana)</b>	<b>Betrixaban (Bevyxxa)</b>	<b>Fondaparinux (Arixtra)</b>
Target	Xa	Xa	Xa	Xa	Xa
Time to Cmax	1-3 hours	2-4 hours	1-2 hours	3-4 hours	2 hours
Time to peak effect	3-4 hours	2-4 hours	1-2 hours	3-4 hours	2-3 hours
CYP Metabolism	15%	32%	NR	NR	n/a
Bioavailability	66%	80%	>45%	34%	100%
Transporter	P-gp	P-gp/BCRP	P-gp	P-gp	P-gp
Protein binding	87%	>90%	55%	60%	94%
Plasma Half-life	8-15 hours	9-13 hours	8-10 hours	37 hours	17-21 hours
Renal elimination	25%	33%	35%	< 1%	100%
Linear PK	Yes	No	Yes	n/a	Yes
Time to 50% recovery of Xa	12 hours	12 hours	12 hours	19-27 hours	12 hours
Reversal AGENTS	Andexxa	Andexxa	NA	NA	NA

BCRP = breast cancer resistance protein; CYP = cytochrome P450; NR – not reported; P-gp = P-glycoprotein

Source: Kaye AD, et al. Responsible, safe, and effective use of antithrombotics and anticoagulants in patients undergoing interventional techniques: American Society of Interventional Pain Physicians (ASIPP) guidelines. *Pain Physician* 2019; 22:S75-S128 (103).

Rivaroxaban (Xarelto®) has dual renal and hepatic clearance, with around one-third of the drug being active with each route of metabolism. This dual route of clearance makes accumulation less likely than other medications that are solely hepatically or renally cleared. Rivaroxaban is orally administered and has a half-life of 5.7 to 9.2 hours. Plasma protein binding of rivaroxaban is 92-95%. One third of the absorbed dose is excreted in the urine, and two-thirds of the dose is excreted as an inactive metabolite in the feces and urine. Rivaroxaban has the potential for drug interactions with medications that are P-glycoprotein inhibitors and those metabolized by CYP3A4 (1280).

Apixaban (Eliquis®) is a specific factor Xa inhibitor like its counterpart, rivaroxaban. It is rapidly absorbed and reaches peak concentrations in 1-2 hours (1281,1282). Apixaban has an oral availability of 45% and has a relatively complex elimination pathway with both direct renal and intestinal excretion, with the latter being the majority (1282,1283). Edoxaban (Savaysa® or Lixiana®) was approved for the prevention of venous thromboembolisms following lower limb orthopedic surgery in 2011 and is an oral direct factor Xa inhibitor that inhibits free factor A and prothrombinase activity. It has also been approved for the prevention of stroke and systemic embolism. Peak plasma concentrations are reached 1.5 hours after oral administration, and it has an elimination half-life of 10-14 hours when taken at 60mg once daily. It is excreted via both hepatic and

renal systems (1284). It is orally available, and not removed by dialysis.

Betrixaban (Bevyxxa®) is a potent oral factor Xa inhibitor that recently received FDA approval. It has exemplified promising results, as it has low hERG affinity and has reduced bleeding risk and prevented thromboembolism in clinical trials for orthopedic knee surgery (1285-1287). Betrixaban has the smallest percent of renal clearance, is INR/PTT insensitive, and has minimal liver metabolism. Another selective factor Xa inhibitor, Fondaparinux (Arixtra®) is 100% bioavailable and achieves maximum concentration in 1.7 hours of administration (1288). Its extended half-life of 17 to 21 hours allows once-daily dosing (1289).

There were no case reports in the present assessment; however, Lagerkranser et al (1148) showed 2 cases of spinal hematoma with rivaroxaban yielding 1.3% prevalence among 160 cases developing spinal hematoma.

### 11.5.9 Thrombolytic Agents

Fibrinolysis is caused by thrombolytic agents via conversion of plasminogen and thrombi to plasmin to destroy clots. These “clot busters” such as recombinant tissue-type plasminogen activator (tPA), streptokinase, urokinase, tenecteplase, and reteplase are enzymes that have effects on both circulating and tissue type plasminogen. The half-life of these thrombolytic drugs is generally a few hours, but the inhibition of plasmino-

gen and fibrinogen may last for up to 27 hours after administration (1290).

There were no reports of epidural hematoma development in patients receiving thrombolytic agents in our analysis; however, Lagerkranser et al (1148) reported 4 cases or 2.5% in the review of 160 cases of spinal hematoma. Among the miscellaneous agents, Chien et al (1198) reported a case of epidural hematoma in a patient receiving fluoxetine, fish oil, and vitamin E. There was also another case report by Jenkie et al (1203) with fish oil and the development of cervical epidural hematoma leading to surgical intervention for decompression. Lagerkranser et al (1148) also reported one patient on selective serotonin receptor inhibitor of 160 cases.

#### **11.5.10 Cannabis (THC and CBD)**

Cannabis is a genus of plants of the Cannabaceae family and contains more than 500 compounds - 120 cannabinoids and 80 biologically active chemical compounds (1291-1293). Cannabis interacts with the endocannabinoid system, composed of a network of receptors (CB1 and CB2), signaling molecules, and enzymes. Two common compounds found in cannabis are  $\Delta$ -9-tetrahydrocannabinol (THC) and cannabidiol (CBD), available as oral solid and semisolid dosage forms, oils, topicals, and transdermal patches. However, because medical cannabis is not regulated, exact doses and contents of CBD:THC are unknown. Daily doses are highly variable, generally, they should not exceed THC daily dose-equivalent of 30 mg/day (1294). THC and CBD provide differential effect with the THC eliciting psychoactive effects with medical benefits particularly for neurological disorders (1295,1296), whereas CBD can help to moderate and subdue psychosis-inducing effects of THC (1297). While they have shown benefit to some extent for neurodegenerative disorders such as multiple sclerosis, glaucoma, food intake disorders, involuntary motor disorders, schizophrenia, and sleep conditions, they have been used frequently in chronic pain legally or illegally. Thus, patients on THC and CBD may present for interventional techniques. Side effects of cannabis and anticoagulant or antiplatelet agents has been described. Cannabis has the potential to interfere with the effectiveness of multiple antithrombotic and anticoagulant agents and may cause antithrombotic effects. Greger et al (1291) published a review of cannabis and interactions with anticoagulant and antiplatelet agents. With metabolism of THC and CBD, primarily by the hepatic P450 enzymatic pathway and UPD-glucuronosyltransferase (UGT), the interactions are proposed (1298-1301). Case

reports with increased INR in patients on warfarin with smoking THC have been described (1302-1305). Cannabis may also alter concentrations of direct-acting oral coagulants including rivaroxaban, dabigatran, and edoxaban (1306-1309). CBD also may impact the metabolism of direct acting oral anticoagulants leading to increased concentrations (1310). Interactions have been reported with clopidogrel with cannabis as it has been shown to inhibit CYP2C19 and enzyme responsible for converting clopidogrel to its active metabolite (1311,1312).

The current knowledge is limited in reference to the effects on interventional techniques. While interactions with warfarin may be monitored with INR, interactions with other drugs is more difficult. There have not been any reports of epidural hematoma associated with THC or CBD; however, there have been suggestions of withholding cannabis and CBD for 5 days prior to high-risk interventional procedures.

#### **11.5.11 Omega-3 Fatty Acids and Vitamin E**

Vitamin E is a fat-soluble plasma antioxidant, composed naturally of 4 tocopherols ( $\alpha$ ,  $\beta$ ,  $\gamma$ , and  $\delta$ ) and 4 tocotrienols. Vitamin E is most commonly utilized as a dietary supplement. As an antioxidant, vitamin E has been promoted as a therapeutic agent in cardiovascular disease. Platelet aggregation is abnormally increased in patients with cardiovascular disease to modulate platelet aggregation. Vitamin E has been shown in animal and human studies to normalize the bioactivity of nitric oxide, but the precise mechanism of action is unknown (1313,1314). Vitamin E has been shown to attenuate platelet aggregation and delay thrombus formation by a decrease in free radical generation, as well as an increase in endogenous superoxide dismutase and nitric oxide synthase expression and activity (1315-1317). However, *in vivo* reports have been less convincing. Even then, it is a common practice to advise patients preparing for surgical procedures or epidural injections to temporarily refrain from the use of vitamin E, along with other antiplatelet agents. Several studies have convincingly shown that coagulation (PT, PTT, bleeding time) is not affected by the dietary supplementation of vitamin E (1318-1320). A study by Dereska et al (1313) investigated the effect of vitamin E supplementation on platelet aggregation, coagulation profile, and bleeding time in healthy individuals. In this experiment with 42 healthy volunteers with a 2 week abstinence period from the use of antiplatelet agents, followed by determination of baseline platelet aggregation properties and coagulation studies, patients were given moderate

dose vitamin E (800 IU of dl- $\alpha$ -tocopherol acetate) for 14 days with reevaluation of platelet aggregation and coagulation profile. The results showed that dietary supplementation with moderate dosage of synthetic vitamin E did not significantly prolong bleeding or platelet aggregation in vivo. The effect of vitamin E on platelet aggregation in vitro does not appear to be reproducible in vivo. Therefore, they concluded that, perioperative discontinuation of vitamin E may not be necessary. Even though vitamin E has been discontinued commonly, specifically prior to interlaminar epidural procedures, similar to aspirin and antithrombotics, there have not been any case reports of epidural hematoma with either with any of the interventional procedures, including spinal cord stimulation.

Similar to vitamin E, fish oil or omega-3 fatty acids have been used as dietary supplements. Fish oil has been used to treat a number of conditions, which include asthma, diabetes mellitus, rheumatoid arthritis, inflammatory bowel disease, systemic lupus erythematosus, hyperlipidemia, and cardiovascular disease. In patients who take fish oil supplements, the omega-3 fatty acids compete for incorporation into the platelet cell membranes, thereby increasing the ratio of omega-3 fatty acids. These effects translate to increases in bleeding time and a reduction in ADP, collagen, and epinephrine-induced platelet aggregation in patients taking omega-3 fatty acid supplements (1321,1322). Begtrup et al (1322) performed a systematic review and showed there was no impact of fish oil supplements on bleeding risk. In this review, they identified 52 publications with 32 publications on healthy subjects and 20 publications on patients undergoing surgery. They concluded that fish oil supplements reduced platelet aggregation in healthy subjects. However, this biochemical effect was not reflected in increased bleeding risk during or after surgery evaluated in RCTs. Consequently, this systematic review did not support the need for discontinuation of fish oil supplements prior to surgery or other invasive procedures. Two case reports have been published with cervical epidural hematomas following cervical epidural injection (1176,1203). These 2 case reports do not confirm that fish oil is the causative agent; however, it is essential to exert significant caution.

#### **11.5.12 Selective Serotonin-Norepinephrine Reuptake Inhibitors (SSRIs)**

Selective serotonin reuptake inhibitors (SSRIs) have also been implicated in alteration of bleeding since serotonin is an integral component in the hemostatic

cascade. It is released from dense intercellular granules and acts as a platelet agonist causing activation and recruitment of additional platelets. This antiplatelet effect may explain why bleeding and bruising (1206) and possibly even treatment of acute coronary syndrome has been reported for patients taking SSRIs (1323,1324). Consequently, SSRIs have been shown to have significant effect on platelet aggregation and thus primary hemostasis (1323-1326). SSRIs deplete serotonin in platelets, decreasing platelet binding affinity, and platelet secretion (1327,1328). Paroxetine has been shown to decrease intraplatelet serotonin concentration by 83% and inhibit platelet plug formation as reflected by a 32% prolongation of closure time (1329).

Auerbach et al (1330) in a multicenter retrospective study conducted to examine the perioperative use of SSRIs, analyzing more than 500,000 patients. The results showed that patients receiving SSRIs had increased risk for adverse events, including higher odds of bleeding (1330). Thus, there is a potential for SSRIs to be causative of bleeding with epidural injections; however, their significance as a single factor is not known.

#### **11.5.13 Herbal/Alternative Therapies**

Garlic has a dose-dependent effect on bleeding, as it contains a compound called ajoene. Derived from allicin, the compound that provides garlic's flavor, ajoene inhibits granule release and fibrinogen binding and additionally inhibits aggregation of platelets via a variety of mechanisms. Prostacyclin, forskolin, indomethacin, and dipyridamole are all altered via ajoenes inhibition of granule release (1331,1332). Ginkgo Biloba has been used for thousands of years, and its mechanism is not entirely understood. Ginkgo is thought to antagonize platelet activating factor (PAF) and collagen leading to inhibition of platelet aggregation, resulting in several reports of spontaneous bleeding. Flavonol glycosides and terpene glycosides have been suggested to be the chemical compounds responsible for the increased bleeding events after intake of this medication (1333,1334). Ginseng is commonly used and reduces the effect of warfarin, declining peak INR levels. Ginsenosides are the major active ingredient of ginseng, and possibly induce cytochrome P450 enzymes to increase the metabolism of Warfarin and thus reduce its effect (1335).

#### **11.6 Recommendations**

Table 31 shows guidelines for antithrombotic medication management during interventional spine procedures. This table also shows comparisons of ASIPP and

Table 31. Guidelines for antithrombotic medication management and spinal procedures (risk stratification described in Table 13).

Medication	Time to Wait After Last Dose of Medication Before Low Risk Interventional Techniques Are Performed (Caudal Epidural)		Time to Wait After Last Dose of Medication Before Moderate Risk Interventional Techniques Are Performed (Lumbar Transforaminal)		Time to Wait After Last Dose of Medication Before High Risk Interventional Techniques Are Performed (Cervical, Thoracic, and Lumbar interlaminar Epidural)		Timing of Therapy restoration or Restarting	
	ASIPP	ASRA (IIII)	ASIPP	ASRA (IIII)	ASIPP	ASRA (IIII)	ASIPP	ASRA (IIII)
NSAIDS (COX 1) (COX 2)	May continue or stop 1-10 days due to lack of protective effect	Stop 1-10 days due to lack of protective effect	May continue or stop 1-10 days due to lack of protective effect	Stop 1-10 days due to lack of protective effect	May continue or stop 1-10 days due to lack of protective effect	Stop 1-10 days due to lack of protective effect	24 hours	24 hours
THC/CBD	May continue or stop 1-10 days	NA	May continue or stop 1-10 days	NA	Stop for 5 days	NA	24 hours	NA
Aspirin								
Low-Dose Aspirin	Continue or may stop for 3 days	Stop for 4 days	Continue or may stop for 3 days	Stop for 4 days	Stop for 5 days	Stop for 6 days	24 hours	24 hours
High Dose Aspirin	Continue or may stop for 3 days	Stop for 4 days	Continue or may stop for 3 days	Stop for 4 days	Stop for 5 days	Stop for 6 days	24 hours	24 hours
Antiplatelet Agents (Phosphodiesterase Inhibitors)								
Dipyridamole (Persantine)	May continue	May continue	May continue	May continue	May continue or stop for 2 days	Stop for 2 days	12 hours	12 hours
Cilostazol (Pletal)	May continue	May continue	May continue	May continue	May continue or stop for 2 days	Stop for 2 days	12 hours	12 hours
Aggrenox (dipyridamole plus aspirin)	May continue	Stop for 4 days	May continue	Stop for 4 days	Stop for 5 days	Stop for 6 days	24 hours	24 hours
Platelet Aggregation Inhibitors								
Clopidogrel (Plavix)	May continue	May continue	May continue or stop for 5 days	Stop for 7 days	Stop for 5 days	Stop for 7 days	12 hours	12 hours
Prasugrel (Effient)	May continue	May continue	May continue or stop for 6 days	Stop for 7-10 days	Stop for 6 days	Stop for 7-10 days	24 hours	24 hours
Ticlopidine (Ticlid)	May continue	NA	May continue or stop for 7 days	NA	Stop for 7-10 days	NA	24 hours	24 hours
Ticagrelor (Brilinta)	May continue	Continue	May continue or stop for 3 days	NA	Stop for 3-5 days	Stop for 5-10 days	24 hours	24 hours
Vitamin K Antagonists								
Warfarin	May stop for 2 days INR ≤ 3.0	INR < 3.0	Stop for 2-5 days INR ≤ 2	Stop for 5 days INR normalize	Stop for 2-5 days INR ≤ 1.5	Stop for 5 days INR normalize	24 hours	24 hours

Table 31 (cont.). Guidelines for antithrombotic medication management and spinal procedures (risk stratification described in Table 13).

Medication	Time to Wait After Last Dose of Medication Before Low Risk Interventional Techniques Are Performed		Time to Wait After Last Dose of Medication Before Moderate Risk Interventional Techniques Are Performed		Time to Wait After Last Dose of Medication Before High Risk Interventional Techniques Are Performed		Timing of Therapy restoration or Restarting	
	ASIPP	ASRA (IIII)	ASIPP	ASRA (IIII)	ASIPP	ASRA (IIII)	ASIPP	ASRA (IIII)
<b>Thrombin Inhibitors</b>								
Dabigatran (Pradaxa)	May continue or stop for 2 days	May continue or stop for 2 days	Stop for 4-5 days 6 days - renal	Stop for 4-5 days 6 days - renal	Stop for 4-5 days 6 days - renal	Stop for 4-5 days 6 days - renal	24 hours	24 hours
<b>Anti-Xa Agents</b>								
Apixaban (Eliquis)	May continue or stop for 2 days	May continue or stop for 2 days	Stop for 3-5 days	Stop for 3-5 days	Stop for 3-5 days	Stop for 3-5 days	24 hours	24 hours
Rivaroxaban (Xarelto)	May continue or stop for 1 day	May continue or stop for 1 day	Stop for 2 days	Stop for 3 days	Stop for 2 days	Stop for 3 days	24 hours	24 hours
Edoxaban (Savaysa, Lixiana)	May continue or stop for 1 day	NA	Stop for 3 days	NA	Stop for 3 days	NA	24 hours	24 hours
<b>Heparins</b>								
Heparin (treatment) - IV	Discontinue for 4 hours	Discontinue for 4 hours	Discontinue for 4 hours	Discontinue for 4 hours	Discontinue for 4 hours	Discontinue for 4 hours	24 hours	24 hours
Heparin (treatment) - SC	Discontinue for 8-10 hours	Discontinue for 8-10 hours	Discontinue for 8-10 hours	Discontinue for 8-10 hours	Discontinue for 8-10 hours	Discontinue for 8-10 hours	24 hours	24 hours
Low Molecular Weight Heparin	Discontinue for 24 hours	Discontinue for 24 hours	Discontinue for 24 hours	Discontinue for 24 hours	Discontinue for 24 hours	Discontinue for 24 hours	24 hours	24 hours
<b>Thrombolytic Agents</b>								
TPA, Streptokinase, Alteplase, Reteplase	May continue	May continue	Stop for 2 days	Stop for 2 days	Stop for 2 days	Stop for 2 days	24 hours	24 hours
<b>GPIIb/IIIa Inhibitors</b>								
Abciximab (ReoPro)	May continue	May continue	Stop for 1-2 days	Stop for 2-5 days	Stop for 1-2 days	Stop for 2-5 days	8-12 hours	8-12 hours
Eptifibatid (Integrilin)	May continue	May continue	Stop for 8 hours	Stop for 8-24 hours	Stop for 8 hours	Stop for 8-24 hours	8-12 hours	8-12 hours
Tirofiban (Aggrastat)	May continue	May continue	Stop for 8 hours	Stop for 8-24 hours	Stop for 8 hours	Stop for 8-24 hours	8-12 hours	8-12 hours
<b>Miscellaneous</b>								
Fondaparinux (Arixtra)	May continue	May continue	Stop for 4 days	Stop for 4 days	Stop for 4 days	Stop for 4 days	8-12 hours	8-12 hours



ASRA guidelines. These recommendations differ from our previously published guidelines, as well as from ASRA guidelines based on the present analysis of the evidence.

General recommendations based on ASRA guidelines (1111) are to discontinue the drugs for 5 half-lives; however, the exception to the 5 half-life recommendation should occur in individuals with hepatic dysfunction, and renal dysfunction including nephrotic syndrome.

## 12.0 GUIDELINES FOR THERAPEUTIC EPIDURAL INTERVENTIONS

These guidelines for the delivery of therapeutic epidural interventions provide an algorithmic approach based on the best available evidence on the epidemiology of various identifiable sources of chronic spinal pain, specifically epidural interventions. This approach is designed to promote the efficient use of interventional pain management techniques based on the best available evidence. However, this may not be applicable in each and every patient. The purpose of the described approach is to provide a disciplined approach to the use of spinal interventional techniques in managing spinal pain. This approach includes evaluation, diagnostic, and therapeutic approaches, which in turn avoid unnecessary care, as well as poorly documented practices.

This algorithmic approach does not dictate the standard of care – these are guidelines. Furthermore, with space constraints, details of comprehensive initial evaluations and all the findings are not provided. Only relevant descriptions are provided.

### 12.1 Documentation Requirements

Documentation is to provide evidence of information. Documentation includes evaluation and management services, procedural services, and billing and coding. While the purpose of documentation is to provide information, it reflects the competency and character of the physician (7,504,1336-1339).

Medical necessity requires appropriate diagnosis and coding by the International Classification of Diseases, 10th Revision, (ICD-10-CM) to justify services rendered and indicates the severity of a patient's condition (1340). The Balanced Budget Act (HR 2015, Section 4317) requires all physicians to provide diagnostic information for all Medicare/Medicaid patients starting from January 1, 1998 (1340-1343). Medical necessity is defined in numerous ways (1344,1345). The Centers for Medicare and Medicaid Services (CMS) (1342,1343) defines medical necessity as follows: “. . .no payment may be made under part A or part B for any expense incurred for items or services which . . .are not reasonable

and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member.”

Further, reasonable and necessary are defined as follows (1342):

- Service must be:
- Safe and effective
- Not experimental or investigational Appropriate, including the duration and frequency that is considered appropriate for the service in terms of whether it is:
  - Furnished in accordance with accepted standards of medical practice for the diagnosis or treatment of the patient's condition or to improve the patient's function
  - Furnished in a setting appropriate to the patient's medical needs and condition
  - Ordered and/or furnished by qualified personnel
  - One that meets, but does not exceed, the patient's medical need
  - At least as beneficial as an existing and available medically appropriate alternative.

### 12.1.1 Elements of Documentation

Federal, state, third party payer, and managed care plans rely heavily on provider documentation when assessing the claims for various parameters. These include:

- Was the billed service actually rendered or provided to the patient?
- Was the level of service or extent of the service accurately reported?
- Was the service or procedure medically necessary?
- Was the claim sent to the correct primary insurer for the service or procedure performed?

### 12.1.2 Types of Documentation

Documentation includes evaluation and management services and interventional techniques. Documentation for spinal interventional techniques may vary based on whether the procedure was performed in a facility setting such as hospital outpatient department or ambulatory surgery center versus in a physician's office.

#### 12.1.2.1 Documentation of Interventional Procedures

All spinal interventional techniques are considered surgical procedures.

Documentation requirements are as follows:

- History and physical.
- Indications and medical necessity.

- Intra-operative procedural description.
- Post-operative monitoring and ambulation.
- Discharge/disposition.

**12.1.2.2 History and Physical**

The physician’s history should include the following elements:

- Documentation of the signs and symptoms warranting the interventional procedure.
- A listing of the patient’s current medications including dosages, route, and frequency of admission.
  - Any existing co-morbid conditions and previous surgeries.
  - Documentation of any social history or conditions which would have an impact on the patient’s care upon discharge from the facility following the procedure.

The physician’s physical examination should not only reflect the relevance of the interventional procedure, but also the type of anesthesia planned. Generally, for interventional techniques, if no anesthesia is to be administered, the physical examination is limited to the assessment of the patient’s mental status and an examination specific to the proposed procedure, including any co-morbid conditions.

However, if intravenous sedation or any other type of anesthesia is planned, the physical examination should also include documentation of the results of an auscultatory examination of the heart and lungs, and an assessment and written statement about the patient’s general health, in addition to the assessment of mental status and an examination specific to the proposed procedure and any co-morbid conditions.

**12.1.2.3 Documentation of Indications and Medical Necessity**

Medical necessity must be established for each and every procedure and encounter (1337,1338,1342). General documentation requirements for all spinal interventional techniques for indications and medical necessity are as follows:

1. Complete initial evaluation including history and physical examination.
2. Physiological and functional assessment, as necessary and feasible.
3. Definition of indications and medical necessity, as follows:
  - Suspected organic problem.

- Nonresponsiveness to conservative modalities of treatment.
- Pain and disability of moderate-to-severe degree.
- No evidence of contraindications such as severe spinal stenosis resulting in intraspinal obstruction, infection, or predominantly psychogenic pain.
- Responsiveness to prior interventions with improvement in physical and functional status for repeat blocks or other interventions.
- Repeating interventions only upon return of pain and deterioration in functional status.

**12.1.2.4 Procedural Documentation**

This includes a description of the procedure, post-operative monitoring, and discharge/disposition (1338) (Table 32).

**12.2 Comprehensive Algorithm**

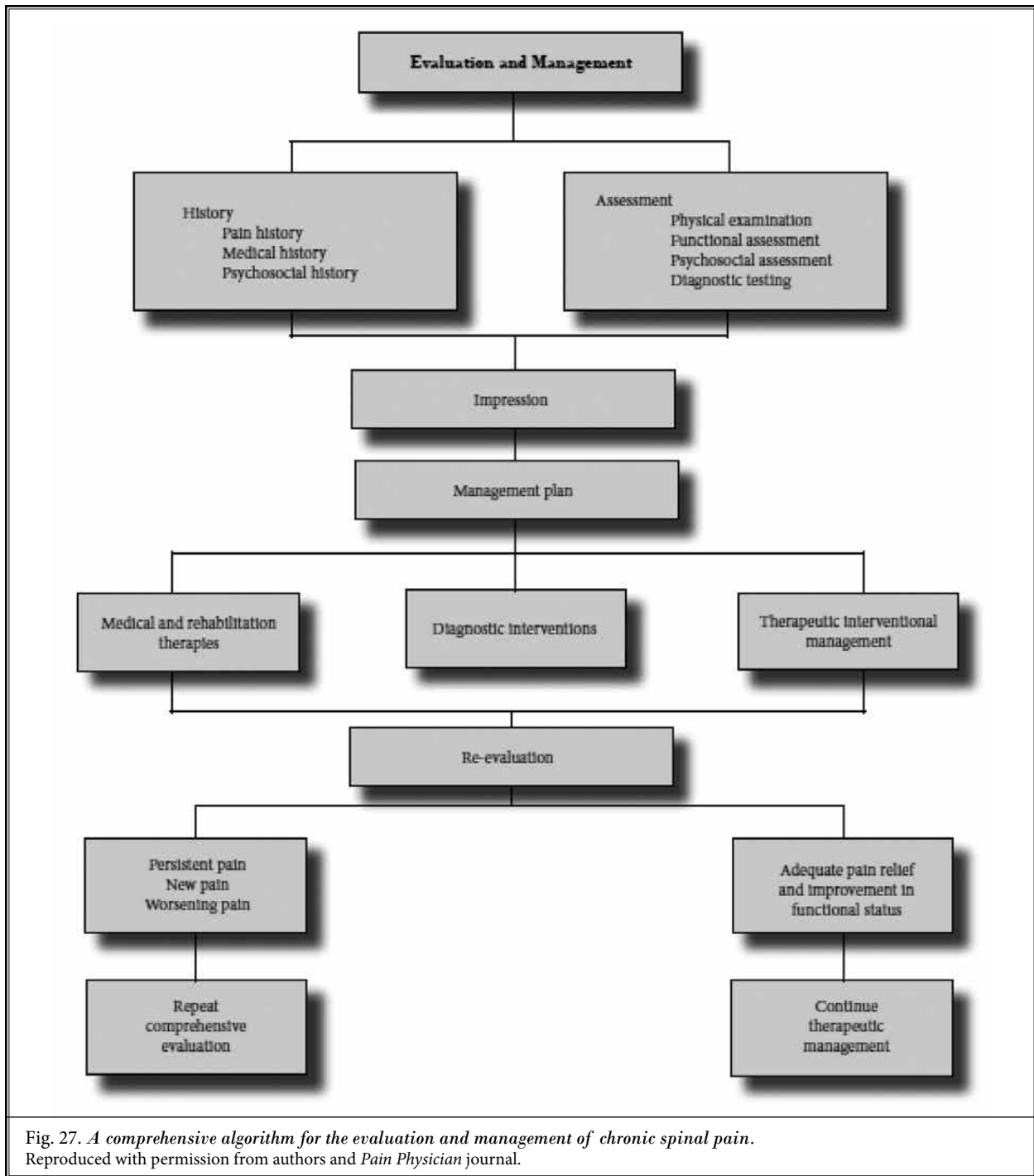
Figure 27 illustrates an algorithmic approach for the evaluation and management of a chronic pain patient (7). Appropriate history, physical examination, and medical decision-making are essential to the provision of appropriate documentation and patient care. Not covered in this algorithm are socioeconomic issues and psychosocial factors that may be important in the clinical decision-making process. A comprehensive and complete evaluation will assist in complying with regulations, providing appropriate care, and fulfilling an algorithmic approach.

**12.3 Lumbar Epidural Interventions**

Based on the comprehensive review of literature and available evidence, there is Level I evidence with a

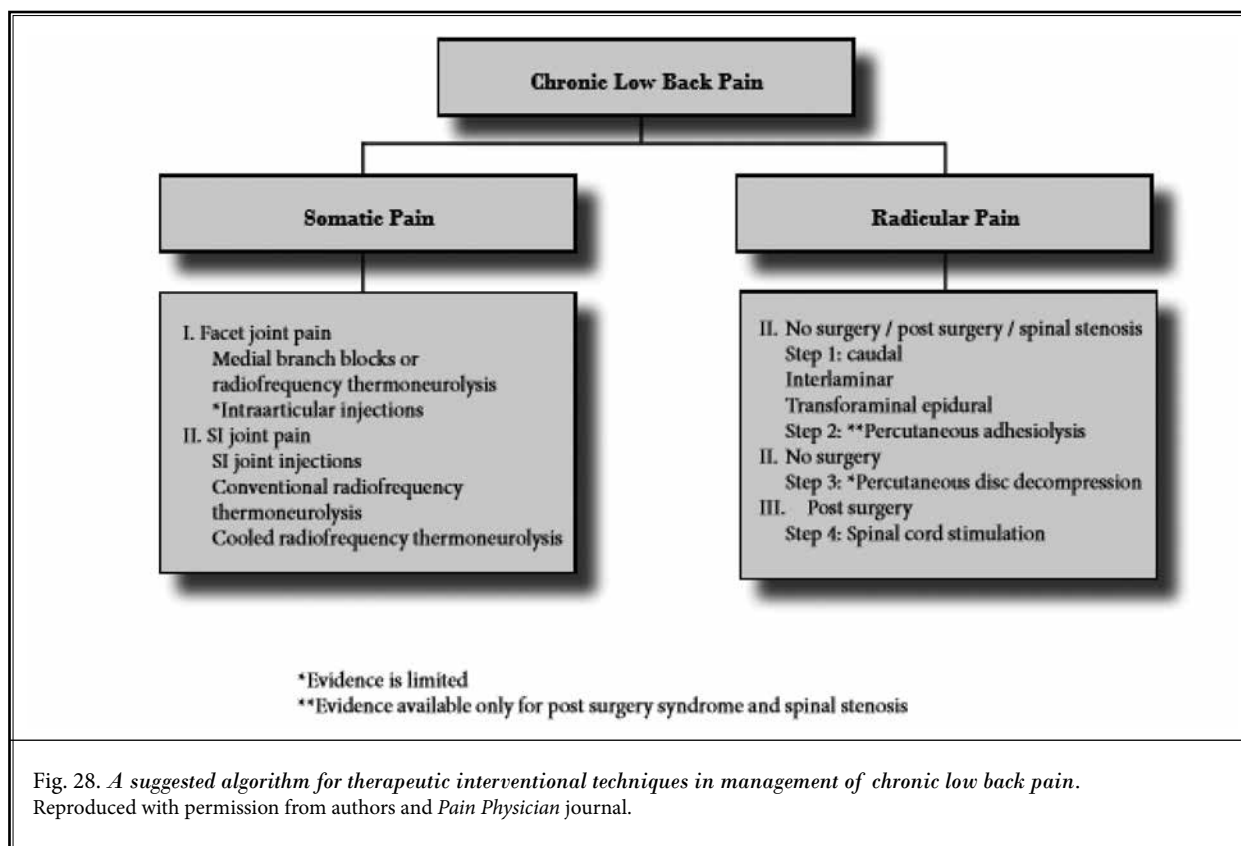
Table 32. *Procedural documentation guidelines for interventional techniques.*

<ol style="list-style-type: none"> <li>1. History and physical</li> <li>2. Indications and medical necessity</li> <li>3. Description of the procedure                     <ul style="list-style-type: none"> <li>Consent</li> <li>Monitoring</li> <li>Sedation</li> <li>Positioning</li> <li>Site preparation</li> <li>Fluoroscopy</li> <li>Drugs utilized</li> <li>Needle placement</li> <li>Complications</li> </ul> </li> <li>4. Post-operative monitoring</li> <li>5. Discharge and instructions</li> </ol>
---



strong recommendation for caudal epidural injections, lumbar interlaminar epidural injections, and lumbar transforaminal epidural injections in managing radicular pain or disc herniation. Additionally, the evidence is

Level III to II with a moderate to strong recommendation for caudal, Level II for lumbar interlaminar epidural injections with moderate to strong recommendation in managing spinal stenosis. The level of evidence is IV to



III with moderate recommendation for lumbar transforaminal epidurals in managing lumbar spinal stenosis. The evidence for post-surgery syndrome is Level II with a moderate to strong recommendation for caudal epidural injections. The evidence for axial discogenic pain is Level II with moderate to strong recommendation for caudal and lumbar interlaminar epidural injections. The evidence assessment is based on contemporary practice in interventional pain management settings for all the procedures performed under fluoroscopy (Fig. 28).

In patients with post-lumbar surgery syndrome, spinal stenosis, and recalcitrant stenosis after failure to respond to fluoroscopically directed epidural injections, percutaneous adhesiolysis is considered (72-76,895). Based on the current literature, the evidence is Level I with a strong recommendation for percutaneous adhesiolysis in managing post-lumbar surgery syndrome and Level II with a moderate to strong recommendation in managing lumbar spinal stenosis and recalcitrant disc herniation with chronic low back and/or lower extremity pain nonresponsive to conservative modalities including fluoroscopically directed epidural injections.

The next step in the radicular pain algorithm is implantable therapy with spinal cord stimulation or implantable infusion systems. Spine cord stimulation is recommended to the patient population for whom all other appropriate medical options have been tried without sufficient improvement in pain control.

#### 12.4 Cervical Epidural Procedures

The current evidence for cervical interlaminar epidural injections in disc herniation is Level I with strong recommendation. The evidence in discogenic pain and spinal stenosis is Level II with moderate to strong recommendation and Level II to I with moderate to strong recommendation for post-surgery syndrome (Fig. 29).

#### 12.5 Thoracic Epidural Procedures

Disc protrusions and herniations are much less common in the thoracic spine than the lumbar or cervical spine. Nonetheless, very few patients who present with thoracic radiculitis, post-surgery syndrome, spinal stenosis, and radiculitis without disc protrusion, and patients

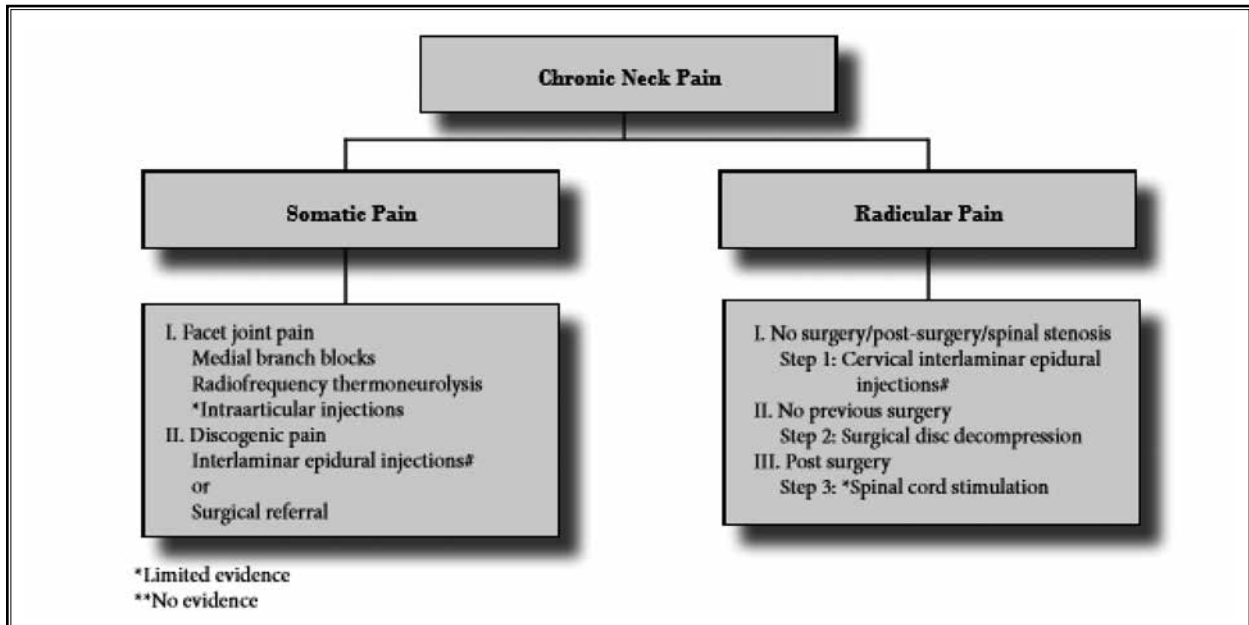


Fig. 29. A suggested algorithm for therapeutic interventional techniques in management of chronic low back pain. Reproduced with permission from authors and Pain Physician journal.

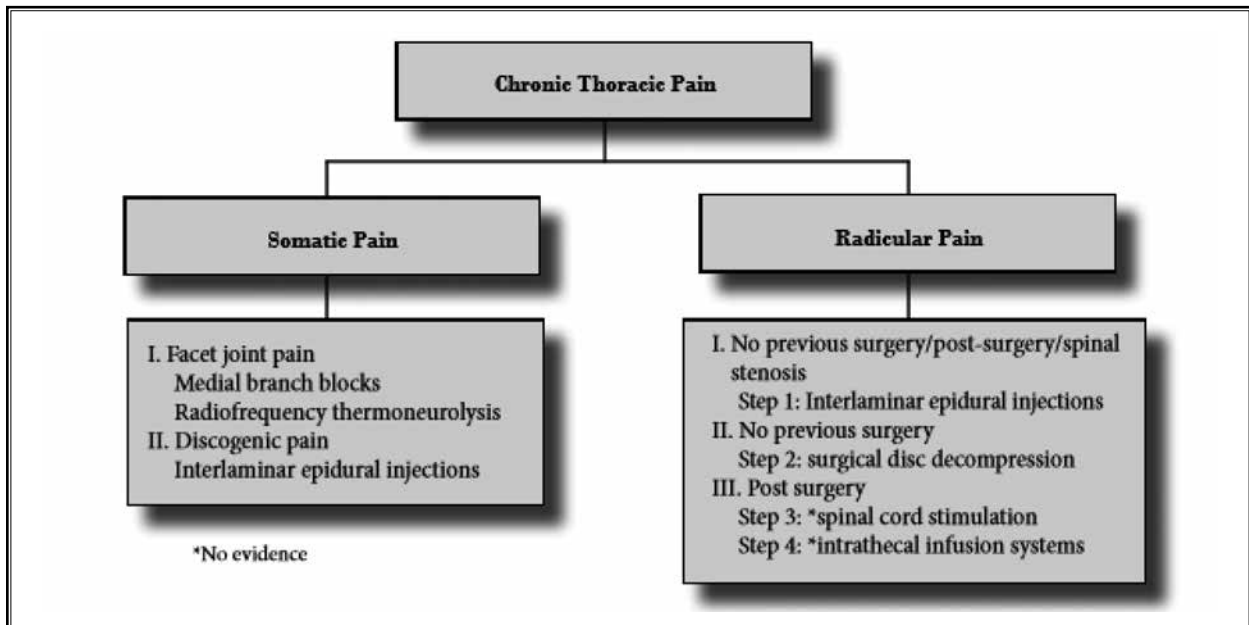


Fig. 30. A suggested algorithm for therapeutic interventional techniques in the management of chronic thoracic pain. Reproduced with permission from authors and Pain Physician journal.

failing to show evidence of facet joint pain are candidates for epidural injections (Fig. 30). Epidural injections are most commonly provided through an interlaminar route

rather than transforaminal which is associated with high risk. Thoracic interlaminar epidural injections show Level II evidence with moderate to strong recommendation.



## 12.6 Therapeutic Lumbar Epidural Interventions

Epidural procedures are applied in the cervical, thoracic, and lumbosacral regions. While these include diagnostic, as well as therapeutic interventions, these therapeutic and diagnostic interventions hold much less importance for epidural procedures rather than diagnostic facet joint interventions.

The indications, frequency, and total number of interventions have been considered important issues, even though debated and poorly addressed. These are based on flawed assumptions from nonexistent evidence. Over the years, some authors have recommended one injection for diagnostic as well as therapeutic purposes. Some have preached 3 injections in a series irrespective of a patient's progress or lack thereof; whereas, others suggest 3 injections followed by a repeat course of 3 injections after 3-, 6-, or 12-month intervals. There are also proponents who propose that an unlimited number of injections with no established goals or parameters should be available. A limitation of 3 mg per kilogram of body weight of steroid or 210 mg per year in an average person and a lifetime dose of 420 mg of steroid also have been advocated; however, with no scientific basis. The comprehensive review of the literature in preparation of these guidelines and review of all the systematic reviews has not shown any basis for the above reported assumptions and limitations. The administration must be based solely on patients' response, safety profile of the drug, experience of the patient, and pharmacological and chemical properties such as duration of action and suppression of adrenals (55). Further, multiple well controlled trials have illustrated no significant difference with local anesthetic alone, or in combination with local anesthetic and steroids (58).

Side effects of steroids are significant based on the complex pharmacokinetics and systemic absorption of epidurally administered steroids which has been explored in multiple reports. Friedly et al (1058) assessed systemic of epidural steroid injections for spinal stenosis in 200 patients receiving corticosteroids, with 32 patients (20.3%) experiencing cortisol reduction at 3 weeks of greater than 50% compared with 10 patients (6.7%) treated with lidocaine only. The effect on a 3-week cortisol changes did not differ by patient level characteristic. Further, those patients who were treated with methylprednisolone or triamcinolone had an average 3-week cortisol reduction of 41% and 41.6% from baseline respectively. In addition, patients treated with betamethasone or dexamethasone, found no significant changes with cortisol that they were similar to lidocaine alone. Hooten et al (1059) showed tri-

amcinolone concentrations almost 22 days. Multiple others have described HPA axis suppression (1075) and other side effects with increase in blood glucose levels along with adverse immune influence leading to influenza infections with specific concerns during COVID (1061-1064). In a dose dependant evaluation, Habib et al (1064) in 2013, examined the magnitude and duration of the suppression of a single epidural injection of methylprednisolone. Eighty-six percent of the patients who received 80 mg dose were reported to have laboratory confirmed HPA axis suppression one week post injection compared to 53% of those receiving 40 mg dose. Further, 20% of all participants had continued suppression at 4 weeks post injection.

Thus, the frequency may be based on the type of injectate with no significant effect with local anesthetics with potential repeat of injection therapy if necessary after a 2 week waiting period, for dexamethasone and betamethasone of 2 to 4 weeks and for methylprednisolone and triamcinolone 4 weeks and 4 to 6 weeks based on the dosage.

Manchikanti et al performed multiple randomized controlled trials with inclusion of over 12,000 patients with local anesthetic alone or with steroids utilizing a low dose betamethasone (i.e., 6 mg) has not reported any complications.

During COVID-19 pandemic it may be crucial to follow these rules from the CDC, as well as guidance from multiple organizations including ASIPP (51,52,55,58).

### 12.6.1 Lumbar Epidural Injections

Lumbar epidural injections include caudal, interlaminar, and transforaminal. Common indications are as follows:

- Chronic low back and/or lower extremity pain of at least 3 months duration which has failed to respond or poorly responded to noninterventional and non-surgical conservative management resulting from:
  - Disc herniation/lumbar radiculitis: (evidence – Level I with strong recommendation for caudal, interlaminar, and transforaminal)
  - Lumbar spinal stenosis: (evidence – Level II for caudal with moderate to strong recommendation, Level II for lumbar interlaminar with moderate to strong recommendation and Level IV to III with moderate recommendation for lumbar transforaminal)
  - Post-lumbar surgery syndrome: (evidence – Level II for caudal with moderate to strong recommendation)
  - Axial or discogenic low back pain without facet

joint or sacroiliac joint pain or disc herniation: (evidence – Level II for caudal and lumbar interlaminar with moderate to strong recommendation)

- Moderate to severe pain causing functional disability.
- Lumbar interlaminar may be performed in post-surgery syndrome only if the access to the epidural space is obtained outside the scar (caudal and transforaminal are preferred modalities).
- Acute proven disc herniation with radiculitis with disabling pain or to avoid surgical intervention, herpes zoster, post herpetic neuralgia, CRPS I and II, epidural injections may be performed at physician discretion without above requirements.

### 12.6.2 Cervical Epidural

While cervical epidural injections may be administered either by the interlaminar or transforaminal approach, only the interlaminar approach has been studied with appropriate indications and effectiveness. Further, cervical transforaminal epidural injections are associated with high risk. Common indications for cervical interlaminar epidurals are as follows:|

- Chronic neck and/or upper extremity pain of at least 3 months duration which has failed to respond or poorly responded to noninterventional and nonsurgical conservative management resulting from:
  - Disc herniation/cervical radiculitis (evidence – Level I with strong recommendation)
  - Cervical spinal stenosis (evidence – Level II with moderate to strong recommendation)
  - Post cervical surgery syndrome (evidence – Level II to I with moderate to strong recommendation)
  - Axial or discogenic pain without facet joint pathology or disc herniation (evidence – Level II with moderate to strong recommendation)
- Intermittent or continuous pain causing functional disability.
- Acute proven disc herniation with radiculitis with disabling pain or to avoid surgical intervention, herpes zoster, post herpetic neuralgia, CRPS I and II, epidural injections may be performed at physician discretion without above requirements.

### 12.6.3 Thoracic Epidural

Thoracic epidural injections may be performed either with an interlaminar approach or a transforaminal approach. The literature is scant in reference to thoracic epidural injections, with Level II evidence. Consequently, only interlaminar epidural injections are described herewith. Common indications are as follows:

- Chronic mid back or upper back pain of at least 3 months duration which has failed to respond or poorly responded to noninterventional and nonsurgical conservative management resulting from:
  - Thoracic disc herniation/radiculitis
  - Thoracic spinal stenosis
  - Thoracic post-surgery syndrome
  - Axial or discogenic pain without facet joint pathology or disc herniation
  - Moderate to severe pain causing functional disability.
- Acute proven disc herniation with radiculitis with disabling pain or to avoid surgical intervention, herpes zoster, post herpetic neuralgia, CRPS I and II, epidural injections may be performed at physician discretion without above requirements.

### 12.7 Frequency of Epidural Procedures

- Guidelines of frequency of interventions apply to epidural injections caudal, interlaminar, and transforaminal.
- In the diagnostic phase, a patient may receive 2 procedures at intervals of no sooner than 2 weeks, preferably 4-6 weeks based on the type and dosage of steroid used.
- In the therapeutic phase (after the diagnostic phase is completed), the suggested frequency of interventional techniques should be 2½ to 3 months or longer between each injection, provided that > 50% relief is obtained for 2½ to 3 months, not exceeding 4 per year, per region.
- If neural blockade is applied for different regions, they may be performed at intervals of no sooner than one week and preferably 2 weeks for most types of procedures. The therapeutic frequency may remain at intervals of at least 2 months for each region. It is further suggested that all regions be treated at the same time, provided all procedures can be performed safely.
- In the treatment or therapeutic phase, the epidural injections should be repeated only as necessary according to medical necessity criteria, and it is suggested that these be limited to a maximum of 4 times per year.
- Cervical and thoracic regions are considered as one region and lumbar and sacral are considered as one region.

### 12.8 Percutaneous Adhesiolysis

At the present time, the evidence is available for

percutaneous adhesiolysis in the lumbar region only utilizing a caudal approach. Evidence for the cervical and thoracic regions and transforaminal approach in the lumbar region is only emerging. Common indications for percutaneous adhesiolysis with a caudal approach in lumbar region are as follows:

- Chronic low back and/or lower extremity pain of at least 6 months duration which failed to respond to or poorly responded to noninterventional and nonsurgical conservative management and fluoroscopically directed epidural injections secondary to:
  - Post-surgery syndrome (evidence – Level I with strong recommendation).
  - Central spinal stenosis (evidence – Level II with moderate to strong recommendation)
  - Disc herniation/radiculitis/severe degenerative disc disease (evidence – Level II with moderate to strong recommendation)
- Intermittent or continuous pain causing functional disability.

### 12.8.1 Frequency of Interventions

- The number of procedures is preferably limited to:
  - 2 interventions per year, with a 3-day protocol
  - 4 interventions per year, with a one-day protocol.

### Acknowledgments

The authors wish to thank Bert Fellows, MA, Director Emeritus of Psychological Services at Pain Management Centers of Paducah, for manuscript review and Tonie M. Hatton and Diane E. Neihoff, transcriptionists, for their assistance in preparation of this manuscript. We would like to thank the editorial board of Pain Physician for review and criticism in improving the manuscript.

### Disclosures

Dr. Christo reports personal fees from Y- MABs, GSK Healthcare, and Eli Lilly outside the submitted work.

Dr. Calodney is a consultant for Medtronic, Stryker, Nevro, and Boston Scientific outside the submitted work.

Dr. Grider is on the Scientific Board of Intralink Spine outside the submitted work.

Dr. Harned receives and unrestricted fellow education grant from Medtronic and research support from Nevro outside the submitted work.

Dr. Shah is a consultant for Masimo Corporation, Allergan Inc., and SPR Therapeutics outside the submitted work.

Dr. Soin is the founder and CEO of Soin Neuroscience, which is developing a spinal cord stimulator to treat spinal pain and has a patent for Soin Neuroscience, Jan One, and Avanos and patent pending for Soin Therapeutics outside the submitted work.

Dr. Beall is a consultant for Medtronic, Spineology, Merit Medical, Lilly, Johnson & Johnson, SpinTech, Imaging3, IZI, Medlantis, Techlamed, Consultant, Peterson Enterprises, Medical Metrics, Radius Pharmaceuticals, Avanos, Vertiflex, Sollis Pharmaceuticals, Simplify Medical, Stryker, Lenoss Medical, Spine BioPharma, Piramal, ReGelTec, Nanofuse, and Talosix; has received a research funding grant from Medtronic, SpinTech, Medical Metrics, Avanos, Relievent, Vertiflex, Stryker, Sollis Pharmaceuticals, Simplify Medical, Lenoss Medical, Spine BioPharma, and Vivex; is on the Advisory Board for Medtronic, Imaging3, ReGelTec, Nanofuse, Talosix, and Vivex; is a Board Member for SpinTech and Nocimed; is a stockholder with Artio, Sophiris, Eleven Biotherapeutics, Radius Pharmaceuticals, Flow Forward, Lenoss Medical and Spine BioPharma; editorial support for Thieme, Springer, and Humana; and is on the Speakers' Bureau for Eli Lilly, Radius Pharmaceuticals, Stryker, Medtronic, Vivex, Vertiflex, Merit, Medlantis, Avanos, and Piramal outside the submitted work.

Dr. Abd-Elseyed is a consultant of Medtronic and Avanos outside the submitted work.

Dr. Benjamin is a paid consultant for Medtronic Inc. outside the submitted work.

Dr. Nampiarampil is a speaker for AbbVie outside the submitted work.

Dr. Hirsch is a consultant for Medtronic and Senior Affiliate Research Fellow at the Neiman Policy Institute outside the submitted work.

### Author Affiliations

Laxmaiah Manchikanti, MD

Dr. Manchikanti is Co-Director, Pain Management Centers of America, Clinical Professor, Anesthesiology and Perioperative Medicine, University of Louisville, Louisville, KY, and Professor of Anesthesiology-Research, Department of Anesthesiology, School of Medicine, LSU Health Sciences Center, New Orleans and Shreveport, LA, USA  
 drlm@thepainmd.com

Nebojsa Nick Knezevic, MD, PhD

Dr. Knezevic is Vice Chair for Research and Education; Department of Anesthesiology; Advocate Illinois Masonic Medical Center, Chicago, IL, and Clinical Professor of Anesthesiology and Clinical Professor of Surgery, College of Medicine, University of Illinois, Chicago, IL, USA

nick.knezevic@gmail.com

Annu Navani, MD

Dr. Navani is Medical Director, Comprehensive Spine & Sports Center, and Advisor, Le Reve Regenerative Wellness, Campbell, CA, USA

anavani@cssctr.com

Paul J. Christo, MD

Professor, Division of Pain Medicine, Department of Anesthesiology and Critical Care Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, USA

pchristo@jhmi.edu

Gerard Limerick, MD, PhD

Dr. Limerick, Interventional Pain Fellow, Department of Anesthesiology and Critical Care Medicine, Division of Pain Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, USA

glimeri1@jhmi.edu

Aaron K. Calodney, MD

Dr. Calodney is Director of Clinical Research, Precision Spine Care, Tyler, TX and Department of Anesthesiology, Louisiana State University, Shreveport, LA, USA

aaroncalodney@me.com

Jay S. Grider, DO, PhD

Dr. Grider, Professor, Department of Anesthesiology, University of Kentucky, Lexington, KY, USA

jsgrid2@email.uky.edu

Michael E. Harned, MD

Dr. Harned is Professor, Department of Anesthesiology, University of Kentucky, Lexington, KY, USA

meharn2@email.uky.edu

Lynn Cintron, MD

Dr. Cintron, Adjunct Associate Clinical Professor, Dept. of Anesthesiology and Perioperative Care, University of California, Irvine School of Medicine, Irvine, CA, USA

drlynncintron@gmail.com

Christopher G. Gharibo, MD

Dr. Gharibo is Medical Director of Pain Medicine, NYU Langone Health, Professor of Anesthesiology, Peri-Operative Care & Pain Medicine, and Professor of Orthopedics, NYU Grossman School of Medicine, New York, NY, USA.

cgharibo@usa.net

Shalini Shah, MD

Dr. Shah is Associate Professor, Vice-Chair, Department of Anesthesiology, and Enterprise Director, Pain Services, University of California Irvine, Orange, CA, USA

shahshalini@gmail.com

Devi E. Nampiaparampil, MD

Dr. Nampiaparampil is Medical Director, Metropolis Pain Medicine, and Associate Professor, Dept. of Rehabilitation Medicine, Grossman NYU School of Medicine, New York, NY.

devichechi@gmail.com

Kenneth D. Candido, MD

Dr. Candido is Chairman, Department of Anesthesiology, Advocate Illinois Masonic Medical Center and Professor of Clinical Anesthesia and Clinical Surgery, University of Illinois College of Medicine, Chicago, IL, USA

kdcandido1@gmail.com; kdcandido@yahoo.com

Amol Soin, MD

Dr. Soin is Medical Director, Ohio Pain Clinic, and Clinical Assistant Professor of Surgery at Wright State University, Dayton, OH, USA.

drsoin@gmail.com

Alan D. Kaye, MD, PhD

Dr. Kaye is Professor, Pain Fellowship Director, Provost, Chief Academic Officer, Vice Chancellor of Academic Affairs, Departments of Anesthesiology and Pharmacology, Toxicology, and Neurosciences, LSU Health Sciences Center, Shreveport, Ochsner Shreveport Hospital and Pain Clinic Feist-Wieller Cancer Center, Shreveport, LA, USA

akaye@lsuhsc.edu, alankaye44@hotmail.com

Radomir Kosanovic, MD

Dr. Kosanovic is an Interventional Pain and Spine Fellow at the Pain Management Centers of America, Paducah, KY, USA.

rkosanovic@pmcoa.us

Trevor R. Magee, BS

Mr. Magee, Clinical Radiology of Oklahoma, Edmond, OK, USA

trevor.magee@ou.edu

Douglas P. Beall, MD

Dr. Beall, Department of Spine Intervention, Summit Medical Center, Edmond, OK, USA

db@clinrad.org

Sairam Atluri, MD  
Dr. Atluri is Medical Director, Tri-State Spine Care Institute, Cincinnati, OH, USA  
saialturi@gmail.com

Myank Gupta, MD  
Dr. Gupta is President & CEO, Principal Investigator, Kansas Pain Management & Neuroscience Research Center, LLC, Overland Park, KS, and Adjunct Clinical Assistant Professor, Anesthesiology and Pain Medicine, Kansas City University of Medicine and Biosciences, Kansas City, MO, USA  
mayankempire@yahoo.com; mayank.g@kansaspain-management.com

Standiford Helm II, MD  
Dr. Helm is Medical Director, The Helm Center for Pain Management, Laguna Woods, CA, USA  
drhelm@thehelmcenter.com

Bradley W. Wargo, DO  
Dr. Wargo, Interventional Pain Management, Cross-town Back & Pain Institute-OrthoSouth, Memphis, TN, and Adjunct Clinical Associate Professor, Kansas Health Science Center School of Medicine, Wichita, KS, USA  
drbwargo@gmail.com

Sudhir Diwan, MD  
Dr. Diwan is President, Advanced Spine on Park Avenue, and Associate Clinical Professor, Albert Einstein College of Medicine, New York, NY, USA  
sudhir.diwan63@gmail.com

Steve M. Aydin, DO  
Dr. Aydin is Clinical Assistant Professor of PMR, Zucker School of Medicine at Hofstra Northwell Health, Manhasset, NY, USA and Chief of PMR and Interventional Pain Management, Kayal Orthopaedic Center, PC, Paramus, NJ, USA  
steve.aydin@gmail.com

Mark V. Boswell, MD, PhD  
Dr. Boswell is Professor and Chairman, Pain Medicine, Department of Anesthesiology, University of Toledo College of Medicine and Life Sciences, Toledo, OH, USA  
mark.boswell2@utoledo.edu; mvboswell01@gmail.com

Bill W. Haney, MD  
Dr. Haney is an interventional pain physician, Pain

Management Centers of America, Louisville, KY, USA  
docbillhaney@gmail.com

Sheri L. Albers, DO  
Dr. Albers, Director of Research, Radiology Research and Consultation, Sacramento, CA, USA  
Sla2oz@aol.com

Richard E. Latchaw, MD  
Dr. Latchaw, Neuroradiology Section, Dept. of Radiology, University of California at Davis Health System, Sacramento, CA, USA  
relatchaw@aol.com

Alaa Abd-Elseyed, MD  
Dr. Abd-Elseyed is Medical Director, UW Health Pain Services, and Associate Professor, Anesthesiology, University of Wisconsin School of Medicine and Public Health, Madison, WI, USA  
alaawny@hotmail.com; abdelseyed@wisc.edu

Ann Conn, MD  
Dr. Conn is staff physician, Advanced Pain Institute, Covington, LA, USA  
annconn@gmail.com

Hans Hansen, MD  
Dr. Hansen is Director & CEO, Pain Relief Centers, Conover, NC, USA  
hhansen@painreliefcenters.com

Thomas T. Simopoulos, MD  
Dr. Simopoulos is Division Chief, Arnold Warfield Pain Management Center, Department of Anesthesiology, Critical Care and Pain Medicine, Co-Director of the Spine Center, Beth Israel Deaconess Medical Center, and Assistant Professor, Harvard Medical School, Boston, MA, USA  
tsimopou@bidmc.harvard.edu

John R. Swicegood, MD  
Dr. Swicegood is Medical Director, Advanced Interventional Pain and Diagnostics of Western Arkansas, Fort Smith, AR, USA  
swice99@gmail.com

David A. Bryce, MD  
Dr. Bryce is a staff physician, Meriter-Unity Point Hospital, Madison, WI, USA  
tonys09@gmail.com



Vijay Singh, MD  
Dr. Singh is Medical Director, Spine Pain Diagnostics Associates, Niagara, WI  
vj@wmpnet.net

Salahadin Abdi, MD  
Dr. Abdi is Tenured Professor and Chair, Department of Pain Medicine, Helen Buchanan & Stanley Joseph Seeger Endowed Research Professor, University of Texas, MD Anderson Cancer Center, Houston, TX, USA.  
SAbdi@mdanderson.org

Sanjay Bakshi, MD  
Dr. Bakshi is an interventional pain management physician at Lenox Hill Hospital, New York, NY, USA  
drbakshi58@gmail.com

Ricardo M. Buenaventura, MD  
Dr. Buenaventura is Medical Director, Pain Relief of Dayton, Centerville, OH, and Clinical Associate Professor, Department of Surgery & Internal Medicine, Wright State University School of Medicine, Dayton, OH, USA.  
dr.rbuena@gmail.com

Joseph A. Cabaret, MD  
Dr. Cabaret is founder & CEO, Genesis Pain Specialists, Camarillo, CA, USA  
jcab@mac.com

Jessica Jameson, MD  
Dr. Jameson, Physician Owner, Axis Spine Center, Coeur d'Alene, ID, USA  
j.jameson@axisspinecenter.com

Sunny Jha, MD, MS  
Dr. Jha, Department of Anesthesiology, Houston Methodist Hospital, Houston, TX, USA  
sunnyjha@gmail.com

Adam M. Kaye, PharmD, FASCP, FCPhA  
Dr. AM Kaye is Clinical Professor of Pharmacy, Department of Pharmacy Practice, Thomas J. Long School of Pharmacy and Health Sciences, University of the Pacific, Stockton, CA, USA  
akaye@pacific.edu

Ramarao Pasupuleti, MD  
Dr. Pasupuleti is Medical Director, Center for Pain Management, Bowling Green, KY, USA.  
rampasupuleti@yahoo.com

Kartic Rajput, MD, PhD  
Dr. Rajput is an Interventional Pain Physician, Gould Medical Group, Stockton, CA, USA  
drkartic@gmail.com

Mahendra R. Sanapati, MD  
Dr. Sanapati is Co-Director, Pain Management Centers of America, Evansville, IN, and Assistant Professor of Anesthesiology and Research, School of Medicine, LSU Health Sciences Center, New Orleans, LA, USA  
msanapati@gmail.com

Nalini Sehgal, MD  
Dr. Sehgal is Professor, Chair, Division of Rehabilitation Medicine, Vice Chair Department of Orthopedics & Rehabilitation and Program Director, Multidisciplinary Pain Medicine Fellowship, University of Wisconsin School of Medicine & Public Health, UW Health, Madison, WI, USA  
Sehgal@rehab.wisc.edu

Andrea M. Trescot, MD  
Dr. Trescot, Florida Pain Relief Group (PPOA), Orange Park, FL, USA  
drtrescot@gmail.com

Gabor B. Racz, MD  
Dr. Racz, Texas Tech University Health Sciences Center, Lubbock, TX, and Professor and Chairman Emeritus, Dept. of Anesthesiology, Clinical Appointment, Preston Surgery Center, Frisco, TX, USA  
gbracz@yahoo.com

Sanjeeva Gupta, MD, Dip. NB, FRCA, FIPP, FFPMRCA  
Dr. Gupta is a Consultant in Pain Medicine and Anesthesia, Department of Anesthesia, Pain Medicine and Intensive Care, Bradford Teaching Hospital NHS Foundation Trust, Bradford Royal Infirmary, Bradford, UK  
sgupta6502@aol.com

Manohar Lal Sharma, MBBS, FRCA, FFPMRCA, MSc  
Pain Management  
Mr. Sharma is a Consultant in Pain Medicine, Department of Pain Medicine, The Walton Centre NHS Foundation Trust, and Honorary Senior Lecturer, University of Liverpool, Foundation Building, Brownlow Hill, Liverpool, England, United Kingdom.  
manoharpain@yahoo.co.uk; manohar.sharma@thewaltoncentre.nhs.uk; manohar.sharma@nhs.net

Vahid Grami, MD, MPH  
Dr. Grami is an Associate Physician in Anesthesiology and Pain Medicine Department at Geisinger Medical Center, Danville, PA, USA  
vgrami1@geisinger.edu

Allan T. Parr, MD  
Dr. Parr is Medical Director, Premier Pain Center, Covington, LA, USA  
alparr@alparr.com

Emilija Knezevic  
Ms. Knezevic is a student at University of Illinois at Urbana-Champaign, College of Liberal Arts and Sciences, Champaign, IL, USA  
ekneze2@illinois.edu

Sukdeb Datta, MD  
Dr. Datta is Medical Director, Datta Endoscopic Back Surgery and Pain Center and Professorial Lecturer, Department of Anesthesiology, Mount Sinai School of Medicine, New York, NY, USA  
sdattamd@gmail.com

Kunj G. Patel, MD  
Dr. Patel is Medical Director, Center for Regenerative and Interventional Spine and Sports Pain, St. Louis, MO, USA  
kunj.patel@gmail.com

Deborah H. Tracy, MD  
Dr. Tracy, Interventional Pain Management Physician, HCA Oak Hill Hospital, Board Chair, Brooksville, FL, USA  
tracypain@tampabay.rr.com

Harold J. Cordner, MD  
Dr. Cordner, Florida Pain Management Associates, Sebastian, FL; and Associate Clinical Professor Florida State University College of Medicine, Tallahassee, FL, USA  
gassdoc@aol.com

Lee T. Snook, MD  
Dr. Snook is Medical Director of Metropolitan Pain Management Consultants, Inc., Sacramento, CA, USA  
LSnook@pain-mPMC.com

Ramsin M. Benyamin, MD  
Dr. Benyamin is Medical Director, Millennium Pain Center, Bloomington, IL, Clinical Assistant Professor of Surgery, College of Medicine, University of Illinois, Urbana-Champaign, IL, Department of Psychology, Illinois Wesleyan University, and Stimgenics LLC, Bloomington, IL, USA  
RBenyamin@treatingpain.com

Joshua A. Hirsch, MD  
Dr. Hirsch is Vice Chair and Service Line Chief of Neurointerventional Radiology, Chief of Neurointerventional Spine, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA  
jahirsch@mgh.harvard.edu

Appendix tables and figures available at [www.painphysicianjournal.com](http://www.painphysicianjournal.com)

## REFERENCES

- GBD 2017 DALYs and HALE Collaborators. Global, regional, and national disability-adjusted life years (DALYs) for 359 diseases and injuries and healthy life expectancy (HALE) for 195 countries and territories, 1990-2017: A systematic analysis for the Global Burden of Disease Study 2017. *Lancet* 2018; 392: 1859-1922.
- U.S. Burden of Disease Collaborators. The state of US health, 1990 – 2010: Burden of diseases, injuries, and risk factors. *JAMA* 2013; 310:591-608.
- Hoy DG, Bain C, Williams G, et al. A systematic review of the global prevalence of low back pain. *Arthritis Rheum* 2012; 64:2028-2037.
- Hoy DG, Protani M, De R, Buchbinder R. The epidemiology of neck pain. *Best Pract Res Clin Rheumatol* 2010; 24:783-792.
- Navani A, Manchikanti L, Albers SL, et al. Responsible, safe, and effective use of biologics in the management of low back pain: American Society of Interventional Pain Physicians (ASIPP) guidelines. *Pain Physician* 2019; 22:S1-S74.
- Manchikanti L, Kaye AM, Knezevic NN, et al. Responsible, safe, and effective prescription of opioids for chronic non-cancer pain: American Society of Interventional Pain Physicians (ASIPP) guidelines. *Pain Physician* 2017; 20: S3-S92.
- Manchikanti L, Abdi S, Atluri S, et al. An update of comprehensive evidence-based guidelines for interventional techniques of chronic spinal pain: Part II: Guidance and recommendations. *Pain Physician* 2013; 16:S49-S283.
- Manchikanti L, Kaye AD, Soin A, et al. Comprehensive evidence-based guidelines for facet joint interventions in the management of chronic spinal pain: American Society of Interventional Pain Physicians (ASIPP) guidelines. *Pain Physician* 2020; 23:S1-S127.

9. Shmigel A, Foley R, Ibrahim H. Epidemiology of chronic low back pain in us adults: Data from the 2009-2010 national health and nutrition examination survey. *Arthritis Care Res (Hoboken)* 2016; 68:1688-1694.
10. Husky MM, Ferdous Farin F, Compagnone P, Fermanian C, Kovess-Masfety V. Chronic back pain and its association with quality of life in a large French population survey. *Health Qual Life Outcomes* 2018; 16:195.
11. Wettstein M, Eich W, Bieber C, Tesarz J. Pain intensity, disability, and quality of life in patients with chronic low back pain: Does age matter? *Pain Med* 2019; 20:464-475.
12. Dutmer AL, Schiphorst Preuper HR, Soer R, et al. Personal and societal impact of low back pain: The Groningen spine cohort. *Spine (Phila Pa 1976)* 2019; 44:E1443-E1451.
13. Manchikanti L, Singh V, Falco FJE, Benyamin RM, Hirsch JA. Epidemiology of low back pain in adults. *Neuromodulation* 2014; 17:3-10.
14. Roberts SB, Calligeros K, Tsirikos Al. Evaluation and management of paediatric and adolescent back pain: Epidemiology, presentation, investigation, and clinical management: A narrative review. *J Back Musculoskeletal Rehabil* 2019; 32:955-988.
15. Johansson MS, Jensen Stochkendahl M, Hartvigsen J, Boyle E, Cassidy JD. Incidence and prognosis of mid-back pain in the general population: A systematic review. *Eur J Pain* 2017; 21:20-28.
16. Umer W, Antwi-Afari MF, Li H, Szeto GPY, Wong AYL. The prevalence of musculoskeletal symptoms in the construction industry: A systematic review and meta-analysis. *Int Arch Occup Environ Health* 2018; 91:125-144.
17. Jun D, Zoe M, Johnston V, O'Leary S. Physical risk factors for developing non-specific neck pain in office workers: A systematic review and meta-analysis. *Int Arch Occup Environ Health* 2017; 90:373-410.
18. Osborn R, Doty MM, Moulds D, Sarnak DO, Shah A. Older Americans were sicker and faced more financial barriers to health care than counterparts in other countries. *Health Aff (Millwood)* 2017; 36:2123-2132.
19. Institute of Medicine (IOM). *Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research*. The National Academies Press, Washington, DC, June 29, 2011. Accessed 11/10/2020. [www.nap.edu/catalog/13172/relieving-pain-in-america-a-blueprint-for-transforming-prevention-care](http://www.nap.edu/catalog/13172/relieving-pain-in-america-a-blueprint-for-transforming-prevention-care)
20. Blyth FM, Noguchi N. Chronic musculoskeletal pain and its impact on older people. *Best Pract Res Clin Rheumatol* 2017; 31:160-168.
21. Hoy D, March L, Brooks P, et al. The global burden of low back pain: Estimates from the Global Burden of Disease 2010 study. *Ann Rheum Dis* 2014; 73:968-974.
22. Mokdad AH, Ballestros K, Echko M, et al. US Burden of Disease Collaborators, The state of US health, 1990-2016: Burden of diseases, injuries, and risk factors among US states. *JAMA* 2018; 319:1444-1472.
23. Bansal D, Asrar MM, Ghai B, Pushpendra D. Prevalence and impact of low back pain in a community-based population in northern India. *Pain Physician* 2020; 23:E389-E398.
24. Smith HJ, Taubman SB, Clark LL. A burden and prevalence analysis of chronic pain by distinct case definitions among active Duty U.S. military service members, 2018. *Pain Physician* 2020; 23:E429-E440.
25. Abdelgadir J, Ong EW, Abdalla SM, et al. Demographic factors associated with patient-reported outcome measures in pain management. *Pain Physician* 2020; 23:17-24.
26. Cassidy JD, Carroll LJ, Côté P. The Saskatchewan Health and Back Pain Survey. The prevalence of low back pain and related disability in Saskatchewan adults. *Spine (Phila Pa 1976)* 1998; 23:1860-1867.
27. Bressler HB, Keyes WJ, Rochon PA, Badley E. The prevalence of low back pain in the elderly. A systematic review of the literature. *Spine (Phila Pa 1976)* 1999; 24:1813-1819.
28. Côté P, Cassidy JD, Carroll L. The Saskatchewan Health and Back Pain Survey. The prevalence of neck pain and related disability in Saskatchewan adults. *Spine (Phila Pa 1976)* 1998; 23:1689-1698.
29. Leboeuf-Yde C, Nielsen J, Kyvik KO, Fejer R, Hartvigsen J. Pain in the lumbar, thoracic or cervical regions: Do age or gender matter? A population-based study of 34,902 Danish twins 20-71 years of age. *BMC Musculoskelet Disord* 2009; 10:39.
30. Mills SEE, Nicolson KP, Smith BH. Chronic pain: A review of its epidemiology and associated factors in population-based studies. *Br J Anaesth* 2019; 123:e273-e283.
31. King S, Chambers CT, Huguet A, et al. The epidemiology of chronic pain in children and adolescents revisited: A systematic review. *Pain* 2011; 152:2729-2738.
32. Jarvik JG, Gold LS, Tan K, et al. Long-term outcomes of a large, prospective observational cohort of older adults with back pain. *Spine J* 2018; 18:1540-1551.
33. Loney PL, Stratford PW. The prevalence of low back pain in adults: A methodological review of the literature. *Phys Ther* 1999; 79:384-396.
34. Fejer R, Kyvik KO, 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.
35. Freburger JK, Holmes GM, Agans RP, et al. The rising prevalence of chronic low back pain. *Arch Intern Med* 2009; 169:251-258.
36. World Health Organization. World report on ageing and health. World Health Organization, Geneva 2015.
37. Acaroğlu E, Nordin M, Randhawa K, et al. The global spine care initiative: A summary of guidelines on invasive interventions for the management of persistent and disabling spinal pain in low- and middle-income communities. *Eur Spine J* 2018; 27:870-878.
38. Blyth FM, Briggs AM, Schneider CH, Hoy DG, March LM. The global burden of musculoskeletal pain-where to from here? *Am J Public Health* 2019; 109:35-40.
39. Dieleman JL, Baral R, Birger M, et al. US spending on personal health care and public health, 1996-2013. *JAMA* 2016; 316:2627-2646.
40. Dieleman JL, Cao J, Chapin A, et al. US health care spending by payer and health condition, 1996-2016. *JAMA* 2020; 323:863-884.
41. Bolnick HJ, Bui AL, Bulchis A, et al. Health-care spending attributable to modifiable risk factors in the USA: An economic attribution analysis. *Lancet Public Health* 2020; 5:e525-e535.
42. Keehan SP, Cuckler GA, Poisal JA, et al. National Health Expenditure Projections, 2019-28: Expected rebound in prices drives rising spending growth. *Health Aff (Millwood)* 2020; 39:704-714.
43. Manchikanti L, Vanaparthi R, Atluri S, Sachdeva H, Kaye AD, Hirsch JA. Concurrent public health emergencies in the US: COVID-19 and the opioid epidemic with hampered access to

- chronic pain management: A review. *Pain Ther* 2020; in press.
44. Jha SS, Shah S, Calderon MD, Soin A, Manchikanti L. The effect of COVID-19 on interventional pain management practices: A physician burnout survey. *Pain Physician* 2020; 23:S271-S282.
  45. Gharaei H, Diwan S. COVID-19 pandemic: Implications on interventional pain practice—a narrative review. *Pain Physician* 2020; 23:S311-S318.
  46. Centers for Disease Control and Prevention. Increase in fatal drug overdoses across the United States driven by synthetic opioids before and during the COVID-19 pandemic. *CDC Health Alert Network*, December 17, 2020. Accessed 12/30/2020  
[https://emergency.cdc.gov/han/2020/han00438.asp?ACSTrackingID=USCDC\\_511-44961&ACSTrackingLabel=HAN%20438%20-%20General%20Public&deliveryName=USCDC\\_511-DM44961](https://emergency.cdc.gov/han/2020/han00438.asp?ACSTrackingID=USCDC_511-44961&ACSTrackingLabel=HAN%20438%20-%20General%20Public&deliveryName=USCDC_511-DM44961)
  47. American Medical Association. COVID-19 physician practice financial impact survey results. Accessed 11/3/2020.  
[www.ama-assn.org/practice-management/sustainability/covid-19-physician-practice-financial-impact-survey-results](http://www.ama-assn.org/practice-management/sustainability/covid-19-physician-practice-financial-impact-survey-results)
  48. Lyu W, Wehby GL. Shelter-in-place orders reduced COVID-19 mortality and reduced the rate of growth in hospitalizations. *Health Aff (Millwood)* 2020; 39:1615-1623.
  49. Eccleston C, Blyth FM, Dear BF, et al. Managing patients with chronic pain during the COVID-19 outbreak: Considerations for the rapid introduction of remotely supported (eHealth) pain management services. *Pain* 2020; 161:889-893.
  50. Chang HY, Daubresse M, Kruszewski SP, Alexander GC. Prevalence and treatment of pain in EDs in the United States, 2000 to 2010. *Am J Emerg Med* 2014; 32:421-431.
  51. Shah S, Diwan S, Soin A, et al. Evidence-based risk mitigation and stratification during covid-19 for return to interventional pain practice: American Society of Interventional Pain Physicians (ASIPP) Guidelines. *Pain Physician* 2020; 23:S161-S182.
  52. Gharibo C, Sharma A, Soin A, et al. Triaging interventional pain procedures during COVID-19 or related elective surgery restrictions: Evidence-informed guidance from the American Society of Interventional Pain Physicians (ASIPP). *Pain Physician* 2020; 23:S183-S204.
  53. Gorski D. The Great Barrington Declaration: COVID-19 deniers follow the path laid down by creationists, HIV/AIDS denialists, and climate science deniers. *Science-Based Medicine*, October 12, 2020. Accessed 11/23/2020  
<https://sciencebasedmedicine.org/great-barrington-declaration>
  54. Bogduk N. Epidural steroids. *Spine (Phila Pa 1976)* 1995; 20:845-848.
  55. Manchikanti L, Kosanovic R, Vanaparthy R, et al. Steroid distancing in interventional pain management during COVID-19 and beyond: Safe, effective and practical approach. *Pain Physician* 2020; 23:S319-S350.
  56. Manchikanti L, Knezevic NN, Sanapati J, et al. Is epidural injection of sodium chloride solution a true placebo or an active control agent? A systematic review and meta-analysis. *Pain Physician* 2021; 24:41-59.
  57. Manchikanti L, Knezevic NN, Parr A, Kaye AD, Sanapati M, Hirsch JA. Does epidural bupivacaine with or without steroids provide long-term relief? A systematic review and meta-analysis. *Curr Pain Headache Rep* 2020; 24:26.
  58. Knezevic N, Manchikanti L, Urits I, et al. Lack of superiority of epidural injections with lidocaine with steroids compared to without steroids in spinal pain: A systematic review and meta-analysis. *Pain Physician* 2020; 23:S239-S270.
  59. Bogduk N, Christophidis N, Cherry D, et al. Epidural use of steroids in the management of back pain. Report of working party on epidural use of steroids in the management of back pain. National Health and Medical Research Council Commonwealth of Australia, Canberra 1994, pp 1-76.
  60. Kaye AD, Manchikanti L, Abdi S, et al. Efficacy of epidural injections in managing chronic spinal pain: A best evidence synthesis. *Pain Physician* 2015; 18:E939-E1004.
  61. Lee JH, Kim DH, Kim DH, et al. Comparison of clinical efficacy of epidural injection with or without steroid in lumbosacral disc herniation: A systematic review and meta-analysis. *Pain Physician* 2018; 21:449-468.
  62. Lee JH, Shin KS, Park SJ, et al. Comparison of clinical efficacy between transforaminal and interlaminar epidural injections in lumbosacral disc herniation: A systematic review and meta-analysis. *Pain Physician* 2018; 21:433-448.
  63. Lee JH, Shin KH, Bahk SJ, et al. Comparison of clinical efficacy of transforaminal and caudal epidural steroid injection in lumbar and lumbosacral disc herniation: A systematic review and meta-analysis. *Spine J* 2018; 18:2343-2353.
  64. Mesregah MK, Feng W, Huang WH, et al. Clinical effectiveness of interlaminar epidural injections of local anesthetic with or without steroids for managing chronic neck pain: A systematic review and meta-analysis. *Pain Physician* 2020; 23:335-348.
  65. Zhao W, Wang Y, Wu J, et al. Long-term outcomes of epidurals with lidocaine with or without steroids for lumbar disc herniation and spinal stenosis: A meta-analysis. *Pain Physician* 2020; 23:365-374.
  66. Bicket M, 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; 119:907-931.
  67. Pinto RZ, Maher CG, Ferreira ML, et al. Epidural corticosteroid injections in the management of sciatica: A systematic review and meta-analysis. *Ann Intern Med* 2012; 157:865-877.
  68. Oliveira CB, Maher CG, Ferreira ML, et al. Epidural corticosteroid injections for lumbosacral radicular pain. *Cochrane Database Syst Rev* 2020; 4:CD013577.
  69. Oliveira CB, Maher CG, Ferreira ML, et al. Epidural corticosteroid injections for sciatica: An abridged Cochrane systematic review and meta-analysis. *Spine (Phila Pa 1976)* 2020; 45:E1405-E1415.
  70. Manchikanti L, Nampiaparampil DE, Candido KD, et al. Do cervical epidural injections provide long-term relief in neck and upper extremity pain? A systematic review. *Pain Physician* 2015; 18:39-60.
  71. Helm II S, Racz GB, Gerdesmeyer L, et al. Percutaneous and endoscopic adhesiolysis in managing low back and lower extremity pain: A systematic review and meta-analysis. *Pain Physician* 2016; 19:E245-E282.
  72. Manchikanti L, Knezevic NN, Sanapati SP, Sanapati MR, Kaye AD, Hirsch JA. Is percutaneous adhesiolysis effective in managing chronic low back and lower extremity pain in post-surgery syndrome: A systematic review and meta-analysis. *Curr Pain Headache Rep* 2020; 24:30.
  73. Manchikanti L, Knezevic NN, Sanapati

- MR, Boswell MV, Kaye AD, Hirsch JA. Effectiveness of percutaneous adhesiolysis in managing chronic central lumbar spinal stenosis: A systematic review and meta-analysis. *Pain Physician* 2019; 22:E523-E550.
74. Manchikanti L, Soin A, Boswell MV, Kaye AD, Sanapati M, Hirsch JA. Effectiveness of percutaneous adhesiolysis in post lumbar surgery syndrome: A systematic analysis of findings of systematic reviews. *Pain Physician* 2019; 22:307-322.
  75. 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 Relat Res* 2015; 473:1940-1956.
  76. Manchikanti L, Nampiaparampil DE, Manchikanti KN, et al. Comparison of the efficacy of saline, local anesthetics, and steroids in epidural and facet joint injections for the management of spinal pain: A systematic review of randomized controlled trials. *Surg Neurol Int* 2015; 6:S194-S235.
  77. Manchikanti L, Kaye AD, Manchikanti KN, Boswell MV, Pampati V, Hirsch JA. Efficacy of epidural injections in the treatment of lumbar central spinal stenosis: A systematic review. *Anesth Pain Med* 2015; 5:e23139.
  78. U.S. Department of Health and Human Services. Pain Management Best Practices Inter-Agency Task Force. Final Report on Pain Management Best Practices: Updates, Gaps, Inconsistencies, and Recommendations. May 9, 2019. Accessed 11/3/2020. [www.hhs.gov/ash/advisory-committees/pain/reports/index.html](http://www.hhs.gov/ash/advisory-committees/pain/reports/index.html)
  79. Manchikanti L, Singh V, Kaye AD, Hirsch JA. Lessons for better pain management in the future: Learning from the past. *Pain Ther* 2020; 9:373-391.
  80. Chou R, Hashimoto R, Friedly JL, et al. Epidural corticosteroid injections for radiculopathy and spinal stenosis: A systematic review and meta-analysis. *Ann Intern Med* 2015; 163:373-381.
  81. Manchikanti L, Knezevic NN, Boswell MV, Kaye AD, Hirsch JA. Epidural injections for lumbar radiculopathy and spinal stenosis: A comparative systematic review and meta-analysis. *Pain Physician* 2016; 19:E365-E410.
  82. Boswell MV, Manchikanti L. Appropriate design and methodologic quality assessment, clinically relevant outcomes are essential to determine the role of epidural corticosteroid injections. Commentary RE: Chou R, et al. Epidural corticosteroid injections for radiculopathy and spinal stenosis: A systematic review and meta-analysis. *Ann Intern Med* 2015; 163:373-381. *Evid Based Med* 2016; 21:89.
  83. Helm II S, Harmon PC, Noe C, et al. Transforaminal epidural steroid injections. A systematic review and meta-analysis of efficacy and safety. *Pain Physician* 2021; 24:S209-S232.
  84. Eden J, Levit L, Berg A, Morton S (eds); Committee on Standards for Systematic Reviews of Comparative Effectiveness Research; Institute of Medicine. Finding What Works in Health Care. Standards for Systematic Reviews. The National Academies Press, Washington, DC, 2011. Accessed 11/3/2020. [www.nap.edu/catalog/13059/finding-what-works-in-health-carestandards-for-systematic-reviews](http://www.nap.edu/catalog/13059/finding-what-works-in-health-carestandards-for-systematic-reviews)
  85. Chou R, Atlas SJ, Loeser JD, Rosenquist RW, Stanos SP. Guideline warfare over interventional therapies for low back pain: Can we raise the level of discourse? *J Pain* 2011; 12:833-839.
  86. Manchikanti L, Benyamin RM, Falco FJE, Caraway DL, Datta S, Hirsch JA. Guidelines warfare over interventional techniques: Is there a lack of discourse or straw man? *Pain Physician* 2012; 15:E1-E26.
  87. Brito-García N, García-Pérez L, Kovacs FM, et al. Efficacy, effectiveness, safety, and cost effectiveness of epidural adhesiolysis for treating failed back surgery syndrome. A systematic review. *Pain Med* 2019; 20: 692-706.
  88. Beall DP, Tutton SM, Murphy K, Olan W, Warner C, Test JB. Analysis of reporting bias in vertebral augmentation. *Pain Physician* 2017; 20:E1081-E1090.
  89. Clark W, Bird P, Diamond T, Gonski P, Gebiski V. Cochrane vertebroplasty review misrepresented evidence for vertebroplasty with early intervention in severely affected patients. *BMJ Evid Based Med* 2020; 25:85-89.
  90. Shah K, Egan G, Huan LN, Kirkham J, Reid E, Tejani AM. Outcome reporting bias in Cochrane systematic reviews: A cross-sectional analysis. *BMJ Open* 2020; 10:e032497.
  91. Kirkham JJ, Altman DG, Chan AW, Gamble C, Dwan KM, Williamson PR. Outcome reporting bias in trials: A methodological approach for assessment and adjustment in systematic reviews. *BMJ* 2018; 362:k3802.
  92. Clark W, Diamond T, Bird P, et al. Letter to the editor RE: Percutaneous vertebroplasty for osteoporotic vertebral compression fracture. *Cochrane Database Syst Rev* 2018; 4:CD006349.
  93. Manchikanti L, Atluri S, Boswell MV, et al. Methodology for evidence synthesis and development of comprehensive evidence-based guidelines for interventional techniques in chronic spinal pain. *Pain Physician* 2021; 24:S1-S26.
  94. Cappola AR, FitzGerald GA. Confluence, not conflict of interest: Name change necessary. *JAMA* 2015; 314:1791-1792.
  95. Riado Minguez D, Kowalski M, Vallve Odena M, et al. Methodological and reporting quality of systematic reviews published in the highest ranking journals in the field of pain. *Anesth Analg* 2017; 125:1348-1354.
  96. A Measurement Tool to Assess Systematic Reviews (AMSTAR). Accessed 12/18/2020 <https://amstar.ca/>
  97. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med* 2009; 151:264-269, W64.
  98. Ross A, Rankin J, Beaman J, et al. Methodological quality of systematic reviews referenced in clinical practice guidelines for the treatment of opioid use disorder. *PLoS One* 2017; 12:e0181927.
  99. Lewis R, Williams N, Matar HE, et al. The clinical effectiveness and cost effectiveness of management strategies for sciatica: Systematic review and economic model. *Health Technol Assess* 2011; 15:1-578.
  100. Lewis RA, Williams NH, Sutton AJ, et al. Comparative clinical effectiveness of management strategies for sciatica: Systematic review and network meta-analyses. *Spine J* 2015; 15:1461-1477.
  101. Guo JR, Jin XJ, Shen HC, et al. A comparison of the efficacy and tolerability of the treatments for sciatica: A network meta-analysis. *Ann Pharmacother* 2017; 51:1041-1052.
  102. Shanthanna H, Busse J, Wang L, et al. 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; 125:779-801.
  103. Kaye AD, Manchikanti L, Novitch MB, et al. Responsible, safe, and effective use of antithrombotics and anticoagulants in patients undergoing



- interventional techniques: American Society of Interventional Pain Physicians (ASIPP) guidelines. *Pain Physician* 2019; 22:S75-S128.
104. Manchikanti L, Centeno CJ, Atluri S, et al. Bone marrow concentrate (BMC) therapy in musculoskeletal disorders: Evidence-based policy position statement of American Society of Interventional Pain Physicians (ASIPP). *Pain Physician* 2020; 23:E85-E131.
  105. Sim SE, Hong HJ, Roh K, Seo J, Moon HS. Relationship between epidural steroid dose and suppression of hypothalamus-pituitary-adrenal axis. *Pain Physician* 2020; 23:S283-S294.
  106. Ercalik T, Kilic M. Efficacy of intradiscal ozone therapy with or without perforaminal steroid injection on lumbar disc herniation: A double-blinded controlled study. *Pain Physician* 2020; 23:477-484.
  107. Scemama P, Farah F, Mann G, Margulis R, Gritsenko K, Shaparin N. Considerations for epidural blood patch and other postdural puncture headache treatments in patients with COVID-19. *Pain Physician* 2020; 23:S305-S310.
  108. Schwartz R, Urits I, Yazdi C, Kaye AD, Viswanath O. Incorporating telemedicine into interventional pain practices during the COVID-19 pandemic. *Pain Physician* 2020; 23:S455-S456.
  109. Wahezi SE, Duarte RV, Yerra S, et al. Telemedicine during COVID-19 and beyond: A practical guide and best practices multidisciplinary approach for the orthopedic and neurologic pain physical examination. *Pain Physician* 2020; 23:S205-S238.
  110. Mahajan A, Manchikanti L. Value and validity of coronavirus antibody testing. *Pain Physician* 2020; 23:S381-S390.
  111. Atluri S, Manocha V, Boddu N, et al. Safety and effectiveness of intravascular mesenchymal stem cells to treat organ failure and possible application in COVID-19 complications. *Pain Physician* 2020; 23:S391-S420.
  112. Kaye RJ. Overview of stem cell therapy for acute respiratory distress syndrome with focus on COVID 19. *Pain Physician* 2020; 23:S421-S432.
  113. Shah S, Diwan S, Kohan L, et al. The technological impact of COVID-19 on the future of education and health care delivery. *Pain Physician* 2020; 23:S367-S380.
  114. Puntillo F, Giglio M, Brienza N, et al. Impact of COVID-19 pandemic on chronic pain management: Looking for the best way to deliver care. *Best Pract Res Clin Anaesthesiol* 2020; 34:529-537.
  115. Zhang M, Zheng H, Wang J. Considerations when COVID-19 pandemic collides opioid crisis: What we should know? *J Anes Perio Manag* 2020; 4:009
  116. Graham R, Mancher M, Wolman DM, Greenfield S, Steinberg E (eds); Committee on Standards for Developing Trustworthy Clinical Practice Guidelines; Institute of Medicine. *Clinical Practice Guidelines We Can Trust*. The National Academies Press, Washington, DC, 2011.
  117. Argyriou C, Georgiadis GS, Georgarakos EI, et al. Applying evidence-based medicine in actual clinical practice: Can we bridge the gap? A Review of the Literature. *Hellenic J Cardiol* 2015; 56:373-378.
  118. Choi SJ, Jeong WK, Jo AJ, et al. Methodology for developing evidence-based clinical imaging guidelines: Joint Recommendations by Korean Society of Radiology and National Evidence-Based Healthcare Collaborating Agency. *Korean J Radiol* 2017; 18:208-216.
  119. National Guideline Clearinghouse Extent Adherence to Trustworthy Standards (NEATS) instrument. Accessed 11/3/2020. [www.ncbi.nlm.nih.gov/pubmedhealth/PMH0079458/](http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0079458/)
  120. Fehlings MG, Nater A. Development and implementation of guidelines in neurosurgery. *Neurosurg Clin N Am* 2015; 26:271-282.
  121. Harris RP, Helfand M, Woolf SH, et al; Methods Work Group, Third US Preventive Services Task Force. Current methods of the US Preventive Services Task Force. *Am J Prevent Med* 2001; 20:21-35.
  122. Murad MH. Clinical Practice Guidelines: A Primer on development and dissemination. *Mayo Clin Proc* 2017; 92:423-433.
  123. Becker M, Neugebauer EA, Eikermann M. Partial updating of clinical practice guidelines often makes more sense than full updating: A systematic review on methods and the development of an updating procedure. *J Clin Epidemiol* 2014; 67:33-45.
  124. Wu JS, Wong RK, Lloyd NS, Johnston M, Bezjak A, Whelan T; Supportive Care Guidelines Group of Cancer Care Ontario. Radiotherapy fractionation for the palliation of uncomplicated painful bone metastases - An evidence-based practice guideline. *BMC Cancer* 2004; 4:71.
  125. Harbour R, Miller J. A new system for grading recommendations in evidence based guidelines. *BMJ* 2001; 323:334-336.
  126. Maas ET, van Dongen JM, Juch JNS, et al. Randomized controlled trials reflected clinical practice when comparing the course of low back pain symptoms in similar populations. *J Clin Epidemiol* 2019; 116:122-132.
  127. Manchikanti L, Soin A, Benyamin RM, et al. An update of the systematic appraisal of the accuracy and utility of discography in chronic spinal pain. *Pain Physician* 2018; 21:91-110.
  128. Simopoulos TT, Manchikanti L, Gupta S, et al. Systematic review of the diagnostic accuracy and therapeutic effectiveness of sacroiliac joint interventions. *Pain Physician* 2015; 18:E713-E756.
  129. Bogduk N. Low back pain. In: *Clinical Anatomy of the Lumbar Spine and Sacrum*. 4th edition. Churchill Livingstone, New York, 2005, pp 183-216.
  130. Kuslich SD, Ulstrom CL, Michael CJ. The tissue origin of low back pain and sciatica: A report of pain response to tissue stimulation during operation on the lumbar spine using local anesthesia. *Orthop Clin North Am* 1991; 22:181-187.
  131. Bogduk N, McGuirk B. *Medical Management of Acute and Chronic Low Back Pain. An Evidence-Based Approach: Pain Research and Clinical Management*. Elsevier Science BV, Amsterdam, 2002.
  132. Bogduk N, McGuirk B. *Management of Acute and Chronic Neck Pain. An Evidence-Based Approach*. Elsevier, Edinburgh, 2006.
  133. Spitzer WO, LeBlanc FE, Dupuis M. Scientific approach to the assessment and management of activity-related spinal disorders: A monograph for clinicians. Report of Quebec Task Force on Spinal Disorders. *Spine (Phila Pa 1976)* 1987; 12:S1-59.
  134. Manchikanti L, Falco FJE, Benyamin RM. Neck and cervical radicular pain. In: Manchikanti L, Christo PJ, Trescot AM, Falco FJE (eds). *Clinical Aspects of Pain Medicine and Interventional Pain Management: A Comprehensive Review*. ASIPP Publishing, Paducah, KY, 2011, pp 35-60.
  135. Manchikanti L, Singh V, Datta S. Thoracic and chest wall pain and radicular pain. In: Manchikanti L, Christo PJ, Trescot AM, Falco FJE (eds). *Clinical Aspects of Pain Medicine and Interventional Pain*

- Management: A Comprehensive Review.* ASIPP Publishing, Paducah, KY, 2011, pp 61-86.
136. Manchikanti L, Hirsch JA, Datta S, Falco FJE. Low back and lumbar radicular pain. In: Manchikanti L, Christo PJ, Trescot AM, Falco FJE (eds). *Clinical Aspects of Pain Medicine and Interventional Pain Management: A Comprehensive Review.* ASIPP Publishing, Paducah, KY, 2011, pp 87-114.
  137. Manchikanti L, Singh V, Pampati V, et al. Evaluation of the relative contributions of various structures in chronic low back pain. *Pain Physician* 2001; 4:308-316.
  138. Schwarzer AC, Aprill CN, Derby R, Fortin J, Kine G, Bogduk N. The prevalence and clinical features of internal disc disruption in patients with chronic low back pain. *Spine (Phila Pa 1976)* 1995; 20:1878-1883.
  139. Yin W, Bogduk N. The nature of neck pain in a private pain clinic in the United States. *Pain Med* 2008; 9:196-203.
  140. Greenhalgh T, Howick J, Maskrey N; Evidence Based Medicine Renaissance Group. Evidence based medicine: A movement in crisis? *BMJ* 2014; 348:g3725.
  141. Gudala K, Bansal D, Vatte R, Ghai B, Schifano F, Boya C. High prevalence of neuropathic pain component in patients with low back pain: Evidence from metaanalysis. *Pain Physician* 2017; 20:343-352.
  142. Rysavy M. Evidence-based medicine: A science of uncertainty and an art of probability. *Virtual Mentor* 2013; 15:4-8.
  143. Hickey S, Roberts H. Evidence based medicine: Neither good evidence nor good medicine. *Orthomolecular Medicine News Service*, December 7, 2011. Accessed 12/18/2020. [www.orthomolecular.org/resources/omns/v07n15.shtml](http://www.orthomolecular.org/resources/omns/v07n15.shtml)
  144. Every-Palmer S, Howick J. How evidence-based medicine is failing due to biased trials and selective publication. *J Eval Clin Pract* 2014; 20:908-914.
  145. Reichman OH, Origitano TC, Anderson DE, Duckworth EA. Lies, damned lies, and statistics: A neurosurgical perspective on the international randomized trial of extracranial to intracranial arterial bypass surgery. *J Stroke Cerebrovasc Dis* 2009; 18:389-397.
  146. Mercuri M, Baigrie B, Upshur REG. Going from evidence to recommendations: Can GRADE get us there? *J Eval Clin Pract* 2018; 24:1232-1239.
  147. Howick J. The evidence-based medicine renaissance: Holy grail or poisoned chalice? *BMC Blog Network*, July 3, 2014. Accessed 12/18/2020. <https://blogs.biomedcentral.com/on-medicine/2014/07/03/the-evidence-based-medicine-renaissance-holy-grail-or-poisoned-chalice/>
  148. Packer M. Are meta-analyses a form of medical fake news? Thoughts about how they should contribute to medical science and practice. *Circulation* 2017; 136:2097-2099.
  149. Foroutan F, Guyatt G, Alba AC, Ross H. Meta-analysis: mistake or milestone in medicine? *Heart* 2018; 104:1559-1561.
  150. Mercuri M, Gafni A. The evolution of GRADE (Part 2): Still searching for a theoretical and/or empirical basis for the GRADE framework. *J Eval Clin Pract* 2018; 24:1211-1222.
  151. Butterworth JF 4th, Rathmell JP. Standard care, standards for care, or standard of care? *Anesthesiology* 2010; 112:277-278.
  152. Manchikanti L, Falco FJE, Benyamin RM, Kaye AD, Boswell MV, Hirsch JA. A modified approach to grading of evidence. *Pain Physician* 2014; 17:E319-E325.
  153. Manchikanti L, Hirsch JA, Cohen SP, et al. Assessment of methodologic quality of randomized trials of interventional techniques: Development of an interventional pain management specific instrument. *Pain Physician* 2014; 17:E263-E290.
  154. Furlan AD, Malmivaara A, Chou R, et al; Editorial Board of the Cochrane Back, Neck Group. 2015 updated method guideline for systematic reviews in the Cochrane Back and Neck Group. *Spine (Phila Pa 1976)* 2015; 40:1660-1673.
  155. Cho JH, Lee JH, Song KS, et al. Treatment outcomes for patients with failed back surgery. *Pain Physician* 2017; 20:E29-E43.
  156. Baird AG, Lawrence JR. Guidelines: is bigger better? A review of SIGN guidelines. *BMJ Open* 2014; 4:e004278.
  157. Manchikanti L, Hirsch JA, Heavner JE, et al. Development of an interventional pain management specific instrument for methodologic quality assessment of nonrandomized studies of interventional techniques. *Pain Physician* 2014; 17:E291-E317.
  158. Wilson F, Ardern CL, Hartvigsen J, et al. Prevalence and risk factors for back pain in sports: A systematic review with meta-analysis. *Br J Sports Med* 2020 Oct 19 [Online ahead of print].
  159. Stubbs B, Koyanagi A, Thompson T, et al. The epidemiology of back pain and its relationship with depression, psychosis, anxiety, sleep disturbances, and stress sensitivity: Data from 43 low- and middle-income countries. *Gen Hosp Psychiatry* 2016; 43:63-70.
  160. Taylor JB, Goode AP, George SZ, Cook CE. Incidence and risk factors for first-time incident low back pain: A systematic review and meta-analysis. *Spine J* 2014; 14:2299-2319.
  161. Lang J, Ochsmann E, Kraus T, Lang JW. Psychosocial work stressors as antecedents of musculoskeletal problems: A systematic review and meta-analysis of stability-adjusted longitudinal studies. *Soc Sci Med* 2012; 75:1163-1174.
  162. Karran EL, Grant AR, Moseley GL. Low back pain and the social determinants of health: A systematic review and narrative synthesis. *Pain* 2020; 161:2476-2493.
  163. Heuch I, Heuch I, Hagen K, Storheim K, Zwart JA. Associations between the number of children, age at childbirths and prevalence of chronic low back pain: The Nord-Trøndelag Health Study. *BMC Public Health* 2020; 20:1556.
  164. Levin DC, Parker L, Palit CD, Rao VM. After nearly a decade of rapid growth, use and complexity of imaging declined, 2008-14. *Health Aff (Millwood)* 2017; 36:663-670.
  165. Liechty A, Tsang S, Turkheimer E, Duncan GE. Association between low back pain and body mass index in adult twins: An analysis of monozygotic and dizygotic twins of the Washington State Twin Registry. *Spine J* 2020; 20:1805-1815.
  166. U.S. Burden of Disease Collaborators, Mokdad AH, Ballestros K, Echkol M, et al. The State of US Health, 1990-2016: Burden of diseases, injuries, and risk factors among US states. *JAMA* 2018; 319:1444-1472.
  167. Gaskin DJ, Richard P. The economic costs of pain in the United States. *J Pain* 2012; 13:715-724.
  168. Manchikanti L, Atluri S, Candido KD, et al. Zohydro™ approval by Food and Drug Administration: Controversial or frightening? *Pain Physician* 2014; 17:E437-E450.
  169. Martin BI, Turner JA, Mirza SK, Lee MJ, Comstock BA, Deyo RA. Trends in health care expenditures, utilization, and health status among US adults with spine problems, 1997-2006. *Spine (Phila Pa 1976)* 2009; 34:2077-2084.

170. Dagenais S, Gay RE, Tricco AC, Freeman MD, Mayer JM. NASS contemporary concepts in spine care: Spinal manipulation therapy for acute low back pain. *Spine J* 2010; 10:918-940.
171. Coulter ID, Crawford C, Vernon H, et al. Manipulation and mobilization for treating chronic nonspecific neck pain: A systematic review and meta-analysis for an appropriateness panel. *Pain Physician* 2019; 22:E55-E70.
172. Chou R, Côté P, Randhawa K, et al. The global spine care initiative: Applying evidence-based guidelines on the non-invasive management of back and neck pain to low- and middle-income communities. *Eur Spine J* 2018; 27:851-860.
173. Briggs AM, Cross MJ, Hoy DG, et al. Musculoskeletal health conditions represent a global threat to healthy aging: A report for the 2015 World Health Organization World Report on Ageing and Health. *Gerontologist* 2016; 56:S243-S255.
174. Chou R, Hashimoto R, Friedly J, et al. Pain Management Injection Therapies for Low Back Pain. Technology Assessment Report ESIBo813. (Prepared by the Pacific Northwest Evidence-based Practice Center under Contract No. HHS 290-2012-00014-1.) Rockville, MD: Agency for Healthcare Research and Quality; July 10, 2015.
175. Manchikanti L, Helm S 2nd, Benyamin RM, et al. A critical analysis of Obamacare: Affordable care or insurance for many and coverage for few? *Pain Physician* 2017; 20:111-138.
176. Obama B. United States health care reform: Progress to date and next steps. *JAMA* 2016; 316:525-532.
177. Cannon MF. Is Obamacare harming quality? (Part 1). *Health Affairs Blog*, January 4, 2018. Accessed 12/18/2020. [www.healthaffairs.org/doi/10.1377/hblog20180103.261091/full/](http://www.healthaffairs.org/doi/10.1377/hblog20180103.261091/full/)
178. Blumenthal D, Collins SR, Fowler EJ. The Affordable Care Act at 10 Years - Its coverage and access provisions. *N Engl J Med* 2020; 382:963-969.
179. Herman PM, Whitley MD, Ryan GW, Hurwitz EL, Coulter ID. The impact of patient preferences and costs on the appropriateness of spinal manipulation and mobilization for chronic low back pain and chronic neck pain. *BMC Musculoskelet Disord* 2019; 20:519.
180. Office of the Assistant Secretary for Health. National Pain Strategy. Washington, DC: US Department of Health and Human Services; Accessed November 9, 2017 2016.
181. Dahlhamer J, Lucas J, Zelaya C, et al. Prevalence of chronic pain and high-impact chronic pain among adults - United States, 2016. *MMWR Morb Mortal Wkly Rep* 2018; 67:1001-1006.
182. Case A, Deaton A. Rising morbidity and mortality in midlife among white non-Hispanic Americans in the 21st century. *Proc Natl Acad Sci USA* 2015; 112:15078-15083.
183. Balague F, Mannion AF, Pellise F, Cedraschi C. Non-specific low back pain. *Lancet* 2012; 379:482-491.
184. Coulter ID, Crawford C, Hurwitz EL, et al. Manipulation and mobilization for treating chronic low back pain: A systematic review and meta-analysis. *Spine J* 2018; 18:866-879.
185. Itz CJ, Geurts JW, van Kleef M, Nelemans P. Clinical course of non-specific low back pain: A systematic review of prospective cohort studies set in primary care. *Eur J Pain* 2013; 17:5-15.
186. Clauw DJ, Häuser W, Cohen SP, Fitzcharles MA. Considering the potential for an increase in chronic pain after the COVID-19 pandemic. *Pain* 2020; 161:1694-1697.
187. Pennings JS, Khan I, Hills JM, Coronado RA, Devin CJ, Archer KR. Classifying chronic opioid use before spine surgery: Comparison of self-report and prescription drug monitoring program (PDMP) reporting. *Spine J* 2020; 20:1795-1797.
188. Kleimeyer JP, Koltsov JCB, Smuck MW, Wood KB, Cheng I, Hu SS. Cervical epidural steroid injections: Incidence and determinants of subsequent surgery. *Spine J* 2020; 20:1729-1736.
189. Lopez CD, Boddapati V, Lombardi JM, et al. Recent trends in Medicare utilization and reimbursement for anterior cervical discectomy and fusion. *Spine J* 2020; 20:1737-1743.
190. Labaran L, Bell J, Puvanesarajah V, et al. Demographic trends in paddle lead spinal cord stimulator placement: Private insurance and Medicare beneficiaries. *Neurospine* 2020; 17:384-389.
191. Elsamadicy AA, Farber SH, Yang S, et al. Impact of insurance provider on overall costs in failed back surgery syndrome: A cost study of 122,827 patients. *Neuromodulation* 2017; 20:354-360.
192. Han JL, Murphy KR, Hussaini SMQ, et al. Explantation rates and healthcare resource utilization in spinal cord stimulation. *Neuromodulation* 2017; 20:331-339.
193. Manchikanti L, Sanapati MR, Pampati V, Boswell MV, Kaye AD, Hirsch JA. Update on reversal and decline of growth of utilization of interventional techniques in managing chronic pain in the Medicare population from 2000 to 2018. *Pain Physician* 2019; 22:521-536.
194. Manchikanti L, Sanapati MR, Soin A, et al. An updated analysis of utilization of epidural procedures in managing chronic pain in the Medicare population from 2000 to 2018. *Pain Physician* 2020; 23:111-126.
195. Manchikanti L, Pampati V, Soin A, Sanapati MR, Kaye AD, Hirsch JA. Declining utilization and inflation-adjusted expenditures for epidural procedures in chronic spinal pain in the Medicare population. *Pain Physician* 2021; 24:1-15.
196. Manchikanti L, Kosanovic R, Pampati V, Kaye AD. Declining utilization patterns of percutaneous adhesiolysis procedures in the fee-for-service (FFS) Medicare population. *Pain Physician*; 2021; 24:17-29.
197. Manchikanti L, Manchikanti MV, Vanaparthi R, Kosanovic R, Pampati V. Utilization patterns of sacroiliac joint injections from 2000 to 2018 in fee-for-service Medicare population. *Pain Physician* 2020; 23:439-450.
198. Manchikanti L, Soin A, Mann DP, et al. Utilization patterns of facet joint interventions in managing spinal pain: A retrospective cohort study in the US fee-for-service Medicare population. *Curr Pain Headache Rep* 2019; 23:73.
199. Manchikanti L, Sanapati MR, Pampati V, et al. Update of utilization patterns of facet joint interventions in managing spinal pain from 2000 to 2018 in the US fee-for-service Medicare population. *Pain Physician* 2020; 23:E133-E149.
200. Manchikanti L, Soin A, Mann DP, Bakshi S, Pampati V, Hirsch JA. Comparative analysis of utilization of epidural procedures in managing chronic pain in the Medicare population: Pre and post Affordable Care Act. *Spine (Phila Pa 1976)* 2019; 44:220-232.
201. Manchikanti L, Sanapati J, Pampati V, Kaye AD, Hirsch JA. Utilization of vertebral augmentation procedures in the United States: A comparative analysis in medicare fee-for-service population pre- and post-2009 trials. *Curr Pain Headache Rep* 2020; 24:22.
202. Yoshihara H, Yoneoka D. National trends in the surgical treatment for

- lumbar degenerative disc disease: United States, 2000 to 2009. *Spine J* 2015; 15:265-271.
203. Becker A, Held H, Redaelli M, et al. Low back pain in primary care: Costs of care and prediction of future health care utilization. *Spine (Phila Pa 1976)* 2010; 35:1714-1720.
  204. Konstantinou K, Dunn KM, Ogollah R, et al. Prognosis of sciatica and back-related leg pain in primary care: The ATLAS cohort. *Spine J* 2018; 18:1030-1040.
  205. Leavitt SB. NSAID dangers may limit pain-relief options. *Pain-Topics News/Research UPDATES*, March 14, 2010.
  206. Graves JM, Fulton-Kehoe D, Jarvik JG, Franklin GM. Health care utilization and costs associated with adherence to clinical practice guidelines for early magnetic resonance imaging among workers with acute occupational low back pain. *Health Serv Res* 2014; 49:645-665.
  207. Gingras MA, Lieu A, Papillon-Ferland L, Lee TC, McDonald EG. Retrospective cohort study of the prevalence of off-label gabapentinoid prescriptions in hospitalized medical patients. *J Hosp Med* 2019; 14:E1-E4.
  208. U.S. Food and Drug Administration. FDA warns about serious breathing problems with seizure and nerve pain medications gabapentin (Neurontin, Gralise, Horizant) and pregabalin (Lyrica, Lyrica CR) when used with CNS depressants or in patients with lung problems. December 19, 2019. Accessed 12/18/2020.  
[www.fda.gov/drugs/drug-safety-and-availability/fda-warns-about-serious-breathing-problems-seizure-and-nerve-pain-medicines-gabapentin-neurontin](http://www.fda.gov/drugs/drug-safety-and-availability/fda-warns-about-serious-breathing-problems-seizure-and-nerve-pain-medicines-gabapentin-neurontin)
  209. O'Gara T, Kemper KJ, Birkedal J, Curl W, Miller N, Abadie B. Survey of conventional and complementary and alternative therapy in patients with low back pain. *J Surg Orthop Adv* 2016; 25:27-33.
  210. Karvelas DA, Rundell SD, Friedly JL, et al. Subsequent health-care utilization associated with early physical therapy for new episodes of low back pain in older adults. *Spine J* 2017; 17:380-389.
  211. Moore A, Wiffen P, Kalso E. Antiepileptic drugs for neuropathic pain and fibromyalgia. *JAMA* 2014; 312:182-183.
  212. Sclafani JA, Constantin A, Ho PS, Akuthota V, Chan L. Descriptive analysis of spinal neuroaxial injections, surgical interventions, and physical therapy utilization for degenerative lumbar spondylolisthesis within Medicare beneficiaries from 2000 to 2011. *Spine (Phila Pa 1976)* 2017; 42:240-246.
  213. Chou R, Hartung D, Turner J, et al. Opioid Treatments for Chronic Pain. Comparative Effectiveness Review, No. 229. AHRQ Publication No. 20-EHC011. Rockville, MD: Agency for Healthcare Research and Quality. April 2020.
  214. McDonagh MS, Selph SS, Buckley DI, et al. Nonopioid Pharmacologic Treatments for Chronic Pain. Comparative Effectiveness Review, No. 228. AHRQ Publication No. 20-EHC010. Rockville, MD: Agency for Healthcare Research and Quality. April 2020.
  215. Skelly AC, Chou R, Dettori JR, et al. Noninvasive Nonpharmacological Treatment for Chronic Pain: A Systematic Review Update. Comparative Effectiveness Review, No. 227. AHRQ Publication No. 20-EHC009. Rockville, MD: Agency for Healthcare Research and Quality. April 2020.
  216. Pannell WC, Savin DD, Scott TP, Wang JC, Daubs MD. Trends in the surgical treatment of lumbar spine disease in the United States. *Spine J* 2015; 15:1719-1727.
  217. Kronemyer B. For osteoarthritis, NSAIDs linked to negative clinical outcomes and higher costs. *Pain Med News*, November 12, 2020. Accessed 12/18/2020.  
[www.painmedicineneews.com/Clinical-Pain-Medicine/Article/11-20/For-Osteoarthritis-NSAIDs-Linked-to-Negative-Clinical-Outcomes-and-Higher-costs/61097?sub=&en=true&id=Uo80924635](http://www.painmedicineneews.com/Clinical-Pain-Medicine/Article/11-20/For-Osteoarthritis-NSAIDs-Linked-to-Negative-Clinical-Outcomes-and-Higher-costs/61097?sub=&en=true&id=Uo80924635)
  218. Al Jammal OM, Delavar A, Maguire KR, et al. National trends in the surgical management of lumbar spinal stenosis in adult spinal deformity patients. *Spine (Phila Pa 1976)* 2019; 44:E1369-E1378.
  219. Hakelius A. Prognosis in sciatica. A clinical follow-up of surgical and non-surgical treatment. *Acta Orthop Scand Suppl* 1970; 129:1-76.
  220. Jain N, Phillips FM, Shimer AL, Khan SN. Surgeon reimbursement relative to hospital payments for spinal fusion: Trends from 10-year Medicare analysis. *Spine (Phila Pa 1976)* 2018; 43:720-731.
  221. Oster BA, Kikanloo SR, Levine NL, Lian J, Cho W. Systematic review of outcomes following 10-year mark of Spine Patient Outcomes Research Trial for intervertebral disc herniation. *Spine (Phila Pa 1976)* 2020; 45:825-831.
  222. Raad M, Reidler JS, El Dafrawy MH, et al. US regional variations in rates, outcomes, and costs of spinal arthrodesis for lumbar spinal stenosis in working adults aged 40-65 years. *J Neurosurg Spine* 2018; 30:83-90.
  223. Rajaei SS, Kanim LE, Bae HW. National trends in revision spinal fusion in the USA: Patient characteristics and complications. *Bone Joint J* 2014; 96-B:807-816.
  224. Machado GC, Maher CG, Ferreira PH, et al. Trends, complications, and costs for hospital admission and surgery for lumbar spinal stenosis. *Spine (Phila Pa 1976)* 2017; 42:1737-1743.
  225. Rajaei SS, Bae HW, Kanim LE, Delamarter RB. Spinal fusion in the United States: Analysis of trends from 1998 to 2008. *Spine (Phila Pa 1976)* 2012; 37:67-76.
  226. Lad SP, Babu R, Ugiliweneza B, Patil CG, Boakye M. Surgery for spinal stenosis: Long-term reoperation rates, health care cost, and impact of instrumentation. *Spine (Phila Pa 1976)* 2014; 39:978-987.
  227. Bae HW, Rajaei SS, Kanim LE. Nationwide trends in the surgical management of lumbar spinal stenosis. *Spine (Phila Pa 1976)* 2013; 38:916-926.
  228. McGirt MJ, Ambrossi GL, Dato G, et al. Recurrent disc herniation and long-term back pain after primary lumbar discectomy: Review of outcomes reported for limited versus aggressive disc removal. *Neurosurgery* 2009; 64:338-344; discussion 344-345.
  229. Schofferman J, Reynolds J, Herzog R, Covington E, Dreyfuss P, O'Neill C. Failed back surgery: Etiology and diagnostic evaluation. *Spine J* 2003; 3:400-403.
  230. Slipman CW, Shin CH, Patel RK, et al. Etiologies of failed back surgery syndrome. *Pain Med* 2002; 3:200-214.
  231. Burton CV, Kirkaldy-Willis WH, Yong-Hing K, Heithoff KB. Causes of failure of surgery on the lumbar spine. *Clin Orthop Relat Res* 1981; 157:191-199.
  232. Waguespack A, Schofferman J, Slosar P, Reynolds J. Etiology of long-term failures of lumbar spine surgery. *Pain Med* 2002; 3:18-22.
  233. Katz V, Schofferman J, Reynolds J. The sacroiliac joint: A potential cause of pain after lumbar fusion to the sacrum. *J Spinal Disord Tech* 2003; 16:96-99.
  234. DePalma MJ, Ketchum JM, Saullo TR. Etiology of chronic low back pain in patients having undergone lumbar fusion. *Pain Med* 2011; 12:732-739.
  235. DePalma MJ, Ketchum JM, Saullo TR, Laplante BL. Is the history of a surgical discectomy related to the source of chronic low back pain? *Pain Physician* 2012; 15:E1-E6.
  236. Abd-Elseyed A, Fischer M, Dimbert J,



- Fiala KJ. Prescription drugs and the US workforce: Results from a National Safety Council Survey. *Pain Physician* 2020; 23:1-6.
237. Pan M, Li Q, Li S, et al. Percutaneous endoscopic lumbar discectomy: Indications and complications. *Pain Physician* 2020; 23:49-56.
238. Chen C, Fan P, Huang L, Zhen H, Liu L, Wang Y. Percutaneous endoscopic lumbar discectomy as an emergent surgery for cauda equina syndrome caused by lumbar disc herniation. *Pain Physician* 2020; 23:E259-E264.
239. Yun DJ, Park SJ, Lee SH. Open lumbar microdiscectomy and posterolateral endoscopic lumbar discectomy for antero- and retrospondylolisthesis. *Pain Physician* 2020; 23:393-404.
240. Xin Z, Kong W, Cai M, et al. Translaminar osseous channel-assisted full-endoscopic flavectomy decompression of thoracic myelopathy caused by ossification of the ligamentum flavum: Surgical technique and results. *Pain Physician* 2020; 23:E475-E486.
241. Wu PF, Li YW, Wang B, Jiang B, Tu ZM, Lv GH. Posterior cervical foraminotomy via full-endoscopic versus microendoscopic approach for radiculopathy: A systematic review and meta-analysis. *Pain Physician* 2019; 22:41-52.
242. Avellanal M, Diaz-Reganon G, Orts A, Gonzalez-Montero L, Riquelme I. Transforaminal epiduroscopy in patients with failed back surgery syndrome. *Pain Physician* 2019; 22:89-95.
243. Lin CY, Chang CC, Chen YJ, et al. New strategy for minimally invasive endoscopic surgery to treat infectious spondylodiscitis in the thoracolumbar spine. *Pain Physician* 2019; 22:281-293.
244. Ahn Y, Lee SG, Son S, Keum HJ. Transforaminal endoscopic lumbar discectomy versus open lumbar microdiscectomy: A comparative cohort study with a 5-year follow-up. *Pain Physician* 2019; 22:295-304.
245. Mao Y, Li Y, Cui X. Percutaneous endoscopic debridement and drainage for spinal infection: Systemic review and meta-analysis. *Pain Physician* 2019; 22:323-330.
246. Li Z, Chen L, Li B, Wei J. Efficacy and safety of surgical interventions for treating multilevel cervical spondylotic myelopathy via anterior approach: A network meta-analysis. *Pain Physician* 2019; 22:E275-E286.
247. Manders L, Abd-Elseyed A. Mandatory review of prescription drug monitoring program before issuance of a controlled substance results in overall reduction of prescriptions including opioids and benzodiazepines. *Pain Physician* 2020; 23:299-304.
248. Sanger N, Bhatt M, Singhal N, et al. Adverse outcomes associated with prescription opioids for acute low back pain: A systematic review and meta-analysis. *Pain Physician* 2019; 22:119-138.
249. Moride Y, Lemieux-Uresandi D, Castillon G, et al. A systematic review of interventions and programs targeting appropriate prescribing of opioids. *Pain Physician* 2019; 22:229-240.
250. Alexander JC, Silge J, Jones S, Joshi GP. Evaluation of opioid prescribing habits based on analysis of a state prescription drug monitoring program. *Pain Physician* 2019; 22:E425-E433.
251. Wertli MM, Held U, Signorell A, Steurer J, Blozik E, Burgstaller JM. Opioid prescription in Switzerland: Appropriate comedication use in cancer and noncancer pain. *Pain Physician* 2019; 22:537-548.
252. Iannaccone F, Nielson P, Adigun H, Kaufman A. What are future pain physicians learning? A survey of opioid prescribing practices among US pain fellowship programs. *Pain Physician* 2019; 22:549-554.
253. Wilson N, Kariisa M, Seth P, Smith H 4th, Davis NL. Drug and opioid-involved overdose deaths - United States, 2017-2018. *MMWR Morb Mortal Wkly Rep* 2020; 69:290-297.
254. Gladden RM, O'Donnell J, Mattson CL, Seth P. Changes in opioid-involved overdose deaths by opioid type and presence of benzodiazepines, cocaine, and methamphetamine — 25 States, July–December 2017 to January–June 2018. *MMWR Morb Mortal Wkly Rep* 2019; 68:737-744.
255. Mixer WJ, Barr JS. Rupture of the intervertebral disc with involvement of the spinal canal. *N Eng J Med* 1934; 211:210-215.
256. Truumees E. A history of lumbar disc herniation from Hippocrates to the 1990s. *Clin Orthop Relat Res* 2015; 473:1885-1895.
257. Goldthwait JE, Osgood RB. A consideration of the pelvic articulations from an anatomical. *Pathol Clin Standpoint* 1905; 152:593-601.
258. Dandy WE. Loose cartilage from intervertebral disk simulating tumor of the spinal cord. By Walter E. Dandy, 1929. *Clin Orthop Relat Res* 1989; 4-8.
259. Weber H. Lumbar disc herniation. A controlled, prospective study with ten years of observation. *Spine (Phila Pa 1976)* 1983; 8:131-140.
260. Weinstein JN, Tosteson TD, Lurie JD, et al. Surgical vs nonoperative treatment for lumbar disk herniation: The Spine Patient Outcomes Research Trial (SPORT): A randomized trial. *JAMA* 2006; 296:2441-2450.
261. Goh BC, Striano BM, Lopez WY, et al. Laminoplasty versus laminectomy and fusion for cervical spondylotic myelopathy: A cost analysis. *Spine J* 2020; 20:1770-1775.
262. Herman PM, Broten N, Lavelle TA, Sorbero ME, Coulter ID. Health care costs and opioid use associated with high-impact chronic spinal pain in the United States. *Spine (Phila Pa 1976)* 2019; 44:1154-1161.
263. Radcliff K, Hilibrand A, Lurie JD, 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.
264. Best MJ, Buller LT, Eismont FJ. National trends in ambulatory surgery for intervertebral disc disorders and spinal stenosis: A 12-year analysis of the national surveys of ambulatory surgery. *Spine (Phila Pa 1976)* 2015; 40:1703-1711.
265. Machado GC, Witzleb AJ, Fritsch C, Maher CG, Ferreira PH, Ferreira ML. Patients with sciatica still experience pain and disability 5 years after surgery: A systematic review with meta-analysis of cohort studies. *Eur J Pain* 2016; 20:1700-1709.
266. Fritsch CG, Ferreira ML, Maher CG, et al. The clinical course of pain and disability following surgery for spinal stenosis: A systematic review and meta-analysis of cohort studies. *Eur Spine J* 2017; 26:324-335.
267. Fritsch EW, Heisel J, Rupp S. The failed back surgery syndrome: Reasons, intraoperative findings, and long-term results: A report of 182 operative treatments. *Spine (Phila Pa 1976)* 1996; 21:626-633.
268. Parker SL, Mendenhall SK, Godil SS, et al. Incidence of low back pain after lumbar discectomy for herniated disc and its effect on patient-reported outcomes. *Clin Orthop Relat Res* 2015; 473:1988-1999.
269. Kim LH, Vail D, Azad TD, et al. Expenditures and health care utilization among adults with newly diagnosed low back and lower extremity pain. *JAMA Netw Open* 2019; 2:e193676.



270. Sanapati J, Manchikanti L, Atluri S, et al. Do regenerative medicine therapies provide long-term relief in chronic low back pain: A systematic review and meta-analysis. *Pain Physician* 2018; 21:515-540.
271. Bicket MC, Horowitz JM, Benzon HT, Cohen SP. Epidural injections in prevention of surgery for spinal pain: Systematic review and meta-analysis of randomized controlled trials. *Spine J* 2015; 15:348-362.
272. Koltsov JCB, Smuck MW, Zigel A, et al. Lumbar epidural steroid injections for herniation and stenosis: Incidence and risk factors of subsequent surgery. *Spine J* 2019; 19:199-205.
273. Kennedy D, Plataras 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; 15:548-555.
274. 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.
275. 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; 82:1589-1593.
276. Riew D, 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; 88:1722-1725.
277. Waddell G, Kummel EG, Lotto WN, Graham JD, Hall H, McCulloch JA. Failed lumbar disc surgery and repeat surgery following industrial injury. *J Bone Joint Surg Am* 1979; 61:201-207.
278. 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; 98:1499-1507.
279. Bond M, Evaniew N, Bailey CS, et al. Back pain in surgically treated degenerative lumbar spondylolisthesis: What can we tell our patients? *Spine J* 2020; 20:1940-1947.
280. Farber SH, Han JL, Petraglia Iii FW, et al. Increasing rates of imaging in failed back surgery syndrome patients: Implications for spinal cord stimulation. *Pain Physician* 2017; 20:E969-E977.
281. Eck JC, Sharan A, Ghogawala Z, et al. Guideline update for the performance of fusion procedures for degenerative disease of the lumbar spine. Part 7: Lumbar fusion for intractable low-back pain without stenosis or spondylolisthesis. *J Neurosurg Spine* 2014; 21:42-47.
282. 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; 13:199-212.
283. Manchikanti L, Pampati V, Falco FJE, Hirsch JA. Growth of spinal interventional pain management techniques: Analysis of utilization trends and Medicare expenditures 2000 to 2008. *Spine (Phila Pa 1976)* 2013; 38:157-168.
284. Manchikanti L, Pampati V, Soin A, et al. Trends of expenditures and utilization of facet joint interventions in fee-for-service (FFS) Medicare population from 2009-2018. *Pain Physician* 2020; 23:S129-S147.
285. NIDA. Overdose Death Rates. National Institute on Drug Abuse website. Accessed 11/25/2020. [www.drugabuse.gov/drug-topics/trends-statistics/overdose-death-rates](http://www.drugabuse.gov/drug-topics/trends-statistics/overdose-death-rates)
286. Ahmad FB, Rossen LM, Sutton P. Provisional drug overdose death counts. National Center for Health Statistics. 2020. Accessed 11/10/2020. [www.cdc.gov/nchs/nvss/vsrr/drug-overdose-data.htm](http://www.cdc.gov/nchs/nvss/vsrr/drug-overdose-data.htm)
287. American Medical Association. Opioid Task Force 2020 Progress Report. Physicians' progress toward ending the nation's drug overdose and death epidemic. Accessed 12/16/2020. [www.ama-assn.org/system/files/2020-07/opioid-task-force-progress-report.pdf](http://www.ama-assn.org/system/files/2020-07/opioid-task-force-progress-report.pdf)
288. Drug Enforcement Administration, Diversion Control Division. National Forensic Laboratory Information System: NFLIS-Drug 2019 Midyear Report. 2020. Springfield, VA: U.S. Drug Enforcement Administration.
289. Wainwright JJ, Mikre M, Whitley P, et al. Analysis of drug test results before and after the US declaration of a national emergency concerning the COVID-19 outbreak. *JAMA* 2020; 324:1674-1677.
290. Kariisa M, Scholl L, Wilson N, Seth P, Hoots B. Drug overdose deaths involving cocaine and psychostimulants with abuse potential—United States, 2003–2017. *MMWR Morb Mortal Wkly Rep* 2019; 68:388-395.
291. Becker WC, Fiellin DA. When epidemics collide: Coronavirus disease 2019 (COVID-19) and the opioid crisis. *Ann Intern Med* 2020; 173:59-60.
292. Jones CM, Olsen EO, O'Donnell J, Mustaquim D. Resurgent methamphetamine use at treatment admission in the United States, 2008-2017. *Am J Public Health* 2020; 110:509-516.
293. Jalal H, Buchanich JM, Roberts MS, Balmert LC, Zhang K, Burke DS. Changing dynamics of the drug overdose epidemic in the United States from 1979 through 2016. *Science* 2018; 361:eaau1184.
294. Shover CL, Falasinnu TO, Dwyer CL, et al. Steep increases in fentanyl-related mortality west of the Mississippi River: Recent evidence from county and state surveillance. *Drug Alcohol Depend* 2020; 216:108314.
295. Centers for Disease Control and Prevention. HIV Infection, risk, prevention, and testing behaviors among persons who inject drugs—National HIV Behavioral Surveillance: Injection drug use, 20 U.S. cities, 2015. HIV Surveillance Special Report 18. Revised edition.
296. Hedegaard H, Bastian BA, Trinidad JP, Spencer MR, Warner M. Regional differences in the drugs most frequently involved in drug overdose deaths: United States, 2017. National Vital Statistics Reports; vol 68 no 12. Hyattsville, MD: National Center for Health Statistics. 2019.
297. O'Donnell J, Gladden RM, Mattson CL, Hunter CT, Davis NL. Vital signs: Characteristics of Drug overdose deaths involving opioids and stimulants — 24 States and the District of Columbia, January–June 2019. *MMWR Morb Mortal Wkly Rep* 2020; 69:1189-1197.
298. Heath C, Sommerfield A, von Ungern-Sternberg BS. Resilience strategies to manage psychological distress among healthcare workers during the COVID-19 pandemic: A narrative review. *Anaesthesia* 2020; 10:1364-1371.
299. Dubey MJ, Ghosh R, Chatterjee S, Biswas P, Chatterjee S, Dubey S. COVID-19 and

- addiction. *Diabetes Metab Syndr* 2020; 14:817-823.
300. Alexander GC, Stoller KB, Haffajee RL, Saloner B. An epidemic in the midst of a pandemic: Opioid use disorder and COVID-19. *Ann Intern Med* 2020; 3:57-58.
  301. Dubey S, Biswas P, Ghosh R, et al. Psychosocial impact of COVID-19. *Diabetes Metab Syndr* 2020; 14:779-788.
  302. Yakusheva O, van den Broek-Altenburg EV, Brekke G, Atherly A. The cure is not worse than the disease – A humanitarian perspective. *SSRN*, July 10, 2020. Accessed 12/18/2020. [https://papers.ssrn.com/sol3/papers.cfm?abstract\\_id=3638575](https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3638575)
  303. Manchikanti L, Sanapati J, Benyamin RM, Atluri S, Kaye AD, Hirsch JA. Reframing the prevention strategies of the opioid crisis: Focusing on prescription opioids, fentanyl, and heroin epidemic. *Pain Physician* 2018; 21:309-326.
  304. Fischer B, Jones W, Vojtila L, Kurdyak P. Patterns, changes, and trends in prescription opioid dispensing in Canada, 2005-2016. *Pain Physician* 2018; 21:219-228.
  305. Singer JA. Stop calling it an opioid crisis – it's a heroin and fentanyl crisis. *Cato Institute*, January 9, 2018. Accessed 12/18/2020. [www.cato.org/blog/stop-calling-it-opioid-crisis-its-heroin-fentanyl-crisis?cs\\_referral=yes](http://www.cato.org/blog/stop-calling-it-opioid-crisis-its-heroin-fentanyl-crisis?cs_referral=yes)
  306. National Institute on Drug Abuse. Overdose death rates. August 2018. Accessed 12/18/2020. [www.drugabuse.gov/related-topics/trends-statistics/overdose-death-rates](http://www.drugabuse.gov/related-topics/trends-statistics/overdose-death-rates)
  307. United States Drug Enforcement Administration. DEA proposes reduction to amount of controlled substances to be manufactured in 2018. August 4, 2017. Accessed 12/18/2020. [www.dea.gov/divisions/hq/2017/hq080417.shtml](http://www.dea.gov/divisions/hq/2017/hq080417.shtml)
  308. Schuchat A, Houry D, Guy GP Jr. New data on opioid use and prescribing in the United States. *JAMA* 2017; 318:425-426.
  309. Centers for Disease Control and Prevention. 2018 Annual Surveillance Report of Drug-Related Risks and Outcomes — United States. Surveillance Special Report. Centers for Disease Control and Prevention, U.S. Department of Health and Human Services. Published August 31, 2018. Accessed 12/14/2020. [www.cdc.gov/drugoverdose/pdf/pubs/2018-cdc-drug-surveillance-report.pdf](http://www.cdc.gov/drugoverdose/pdf/pubs/2018-cdc-drug-surveillance-report.pdf)
  310. Seth P, Rudd RA, Noonan RK, Haegerich TM. Quantifying the epidemic of prescription opioid overdose deaths. *Am J Public Health* 2018; 108:500-502.
  311. IQVIA Institute for Human Data Science Study. Medicine use and spending in the U.S. A review of 2018 and outlook for 2023. May 2019. Accessed 11/3/2020. [www.iqvia.com/insights/the-iqvia-institute/reports/medicine-use-and-spending-in-the-us-a-review-of-2018-and-outlook-to-2023](http://www.iqvia.com/insights/the-iqvia-institute/reports/medicine-use-and-spending-in-the-us-a-review-of-2018-and-outlook-to-2023)
  312. IQVIA™ Institute for Human Data Science Releases 2019 Medicines Report on U.S. Drug Consumption; U.S. Rx Opioid Volume Declined 17% in 2018 – Largest Single-Year Drop Ever Recorded. Accessed 12/16/2020. [www.iqvia.com/newsroom/2019/05/iqvia-institute-for-human-data-science-releases-2019-medicines-report-on-us-drug-consumption-us-rx-o](http://www.iqvia.com/newsroom/2019/05/iqvia-institute-for-human-data-science-releases-2019-medicines-report-on-us-drug-consumption-us-rx-o)
  313. IQVIA Institute for Human Data Science. Prescription opioids trends in the United States: Measuring and understanding progress in the opioid crisis. Accessed 12/30/2020 [www.iqvia.com/insights/the-iqvia-institute/reports/prescription-opioid-trends-in-the-united-states](http://www.iqvia.com/insights/the-iqvia-institute/reports/prescription-opioid-trends-in-the-united-states)
  314. Tracking federal funding to combat the opioid crisis. March 2019. Accessed 11/10/2020. <https://bipartisanpolicy.org/wp-content/uploads/2019/03/Tracking-Federal-Funding-to-Combat-the-Opioid-Crisis.pdf>
  315. Gostin LO, Hodge JG, Noe SA. Reframing the opioid epidemic as a national emergency. *JAMA* 2017; 318:1539-1540.
  316. Volkow ND, Collins FS. The role of science in the opioid crisis. *N Engl J Med* 2017; 377:1798.
  317. Kolodny A, Frieden TR. Ten steps the federal government should take now to reverse the opioid addiction epidemic. *JAMA* 2017; 318:1537-1538.
  318. Bonnie RJ, Kesselheim AS, Clark DJ. Both urgency and balance needed in addressing opioid epidemic: A report from the National Academies of Sciences, Engineering, and Medicine. *JAMA* 2017; 318:423-424.
  319. Pergolizzi JV Jr, Raffa RB, LeQuang JA. The Centers for Disease Control and Prevention opioid guidelines: Potential for unintended consequences and will they be abused? *J Clin Pharm Ther* 2016; 41:592-593.
  320. Bao Y, Pan Y, Taylor A, et al. Prescription drug monitoring programs are associated with sustained reductions in opioid prescribing by physicians. *Health Aff (Millwood)* 2016; 35:1045-1051.
  321. Bao Y, Wen K, Johnson P, et al. Assessing the impact of state policies for prescription drug monitoring programs on high-risk opioid prescriptions. *Health Aff (Millwood)* 2018; 37:1596-1604.
  322. Dowell D, Haegerich TM, Chou R. CDC guideline for prescribing opioids for chronic pain—United States, 2016. *MMWR Recomm Rep* 2016; 65:1-49.
  323. HHS guide for clinicians on the appropriate dosage reduction or discontinuation of long-term opioid analgesics. Accessed 11/3/2020. [www.hhs.gov/opioids/sites/default/files/2019-10/Dosage\\_Reduction\\_Discontinuation.pdf](http://www.hhs.gov/opioids/sites/default/files/2019-10/Dosage_Reduction_Discontinuation.pdf)
  324. Prescribing policies: States confront opioid overdose epidemic. Accessed 11/3/2020. [www.ncsl.org/research/health/prescribingpolicies-states-confront-opioidoverdose-epidemic.aspx](http://www.ncsl.org/research/health/prescribingpolicies-states-confront-opioidoverdose-epidemic.aspx)
  325. Kertesz SG, Gordon AJ. A crisis of opioids and the limits of prescription control: United States. *Addiction* 2019; 114:169-180.
  326. U.S. Department of Health and Human Services Office of Inspector General. Medicare Part D Beneficiaries at Serious Risk of Opioid Misuse or Overdose: A Closer Look. May 4, 2020. Accessed 11/3/2020. <https://oig.hhs.gov/oei/reports/oei-02-19-00130.asp>
  327. Gever J. HHS: Don't withdraw opioids suddenly – Department issues guideline on tapering and discontinuation. *MedPage Today*, October 10, 2019.
  328. Dowell D, Haegerich TM, Chou R. No shortcuts to safer opioid prescribing. *N Engl J Med* 2019; 380:2285-2287.
  329. Portenoy RK, Foley KM. Chronic use of opioid analgesics in non-malignant pain: Report of 38 cases. *Pain* 1986; 25:171-186.
  330. Chou R, Deyo R, Friedly J, et al. Noninvasive Treatments for Low Back Pain [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2016 Feb. Report No.: 16-EHC004-EF. PMID: 26985522.
  331. Davies RA, Maher CG, Hancock MJ. A systematic review of paracetamol for

- non-specific low back pain. *Eur Spine J* 2008; 17:1423-1430.
332. Enthoven WT, Roelofs PD, Deyo RA, van Tulder MW, Koes BW. Non-steroidal anti-inflammatory drugs for chronic low back pain. *Cochrane Database Syst Rev* 2016; 2:CD012087.
333. van der Gaag WH, Roelofs PD, Enthoven WT, van Tulder MW, Koes BW. Non-steroidal anti-inflammatory drugs for acute low back pain. *Cochrane Database Syst Rev* 2020; 4:CD013581.
334. Chung JW, Zeng Y, Wong TK. Drug therapy for the treatment of chronic nonspecific low back pain: Systematic review and meta-analysis. *Pain Physician* 2013; 16:E685-E704.
335. Saragiotto BT, Maher CG, Yamato TP, et al. Motor control exercise for chronic non-specific low-back pain. *Cochrane Database Syst Rev* 2016; 1:CD012004.
336. Byström MG, Rasmussen-Barr E, Grooten WJ. Motor control exercises reduces pain and disability in chronic and recurrent low back pain: A meta-analysis. *Spine (Phila Pa 1976)* 2013; 38:E350-E358.
337. van Middelkoop M, Rubinstein SM, Kuijpers T, et al. A systematic review on the effectiveness of physical and rehabilitation interventions for chronic non-specific low back pain. *Eur Spine J* 2011; 20:19-39.
338. Kamper SJ, Apeldoorn AT, Chiarotto A, et al. Multidisciplinary biopsychosocial rehabilitation for chronic low back pain. *Cochrane Database Syst Rev* 2014; 9:CD000963.
339. Sherman KJ, Cherkin DC, Connelly MT, et al. Complementary and alternative medical therapies for chronic low back pain: What treatments are patients willing to try? *BMC Complement Altern Med* 2004 Jul 19; 4:9.
340. Liu L, Skinner M, McDonough S, Mabire L, Baxter GD. Acupuncture for low back pain: An overview of systematic reviews. *Evid Based Complement Alternat Med* 2015; 2015:328196.
341. Lam M, Galvin R, Curry P. Effectiveness of acupuncture for nonspecific chronic low back pain: A systematic review and meta-analysis. *Spine (Phila Pa 1976)* 2013; 38:2124-2138.
342. Airaksinen O, Brox JI, Cedraschi C, et al. Chapter 4. European guidelines for the management of chronic nonspecific low back pain. *Eur Spine J* 2006; 15:S192-S300.
343. National Collaborating Centre for Primary Care (UK). Low Back Pain: Early Management of Persistent Non-specific Low Back Pain [Internet]. London, Royal College of General Practitioners (UK), May 2009.
344. Chou R, Qaseem A, Snow V, et al. Diagnosis and treatment of low back pain: A joint clinical practice guideline from the American College of Physicians and the American Pain Society. *Ann Intern Med* 2007; 147:478-491.
345. Ernst E. Massage therapy for low back pain: A systematic review. *J Pain Symptom Manage* 1999; 17:65-69.
346. Melzack R, Wall PD. *The Challenge of Pain*, 2nd ed. Penguin Books, London, 1996.
347. Moyer CA, Rounds J, Hannum JW. A meta-analysis of massage therapy research. *Psychol Bull* 2004; 130:3-18.
348. Farber K, Wieland LS. Massage for low-back Pain. *Explore (NY)* 2016; 12:215-217.
349. Furlan AD, Imamura M, Dryden T, Irvin E. Massage for low back pain: An updated systematic review within the framework of the Cochrane Back Review Group. *Spine (Phila Pa 1976)* 2009; 34:1669-1684.
350. Reeve J, Corabian P. *Transcutaneous Electrical Nerve Stimulation (TENS) and Pain Management*. Ottawa, Ontario, Canada: Canadian Coordinating Office for Health Technology Assessment (CCOHTA), 1995.
351. Dubinsky RM, Miyasaki J. Assessment: Efficacy of transcutaneous electric nerve stimulation in the treatment of pain in neurologic disorders (an evidence-based review): Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology* 2010; 74:173-176.
352. Khadilkar A, Milne S, Brosseau L, et al. Transcutaneous electrical nerve stimulation (TENS) for chronic low-back pain. *Cochrane Database Syst Rev* 2005 3:CD003008.
353. Wu LC, Weng PW, Chen CH, Huang YY, Tsuang YH, Chiang CJ. Literature review and meta-analysis of transcutaneous electrical nerve stimulation in treating chronic back pain. *Reg Anesth Pain Med* 2018; 43:425-433.
354. Qaseem A, Wilt TJ, McLean RM, Forciea MA, Clinical Guidelines Committee of the American College of Physicians. Noninvasive treatments for acute, subacute, and chronic low back pain: A clinical practice guideline from the American College of Physicians. *Ann Intern Med* 2017; 166:514-530.
355. Bons SCS, Borg MAJP, Van den Donk M, et al. NHG guideline for aspecific low-back pain, 2017. Accessed 12/7/2020. <https://richtlijnen.nhg.org/standaarden/aspecificke-lagerugpijn#volledige-tekst>
356. Foster NE, Anema JR, Cherkin D, et al; Lancet Low Back Pain Series Working Group. Prevention and treatment of low back pain: Evidence, challenges, and promising directions. *Lancet* 2018; 391:2368-2383.
357. Sandoz R. The significance of the manipulative crack and of other articular noises. *Ann Swiss Chiro Assoc* 1969; 4:47-68.
358. Bialosky JE, Bishop MD, Robinson ME, Zeppieri G Jr, George SZ. Spinal manipulative therapy has an immediate effect on thermal pain sensitivity in people with low back pain: A randomized controlled trial. *Phys Ther* 2009; 89:1292-1303.
359. Fryer G. Integrating osteopathic approaches based on biopsychosocial therapeutic mechanisms. Part 1: The mechanisms. *Int J Osteopath Med* 2017; 25:30-41.
360. Xia T, Long CR, Vining RD, et al. Association of lumbar spine stiffness and flexion-relaxation phenomenon with patient-reported outcomes in adults with chronic low back pain - a single-arm clinical trial investigating the effects of thrust spinal manipulation. *BMC Complement Altern Med* 2017; 17:303.
361. Bialosky JE, Bishop MD, Price DD, Robinson ME, George SZ. The mechanisms of manual therapy in the treatment of musculoskeletal pain: A comprehensive model. *Man Ther* 2009; 14:531-538.
362. Rubinstein SM, de Zoete A, van Middelkoop M, Assendelft WJJ, de Boer MR, van Tulder MW. Benefits and harms of spinal manipulative therapy for the treatment of chronic low back pain: A systematic review and meta-analysis of randomised controlled trials. *BMJ* 2019; 364:l689.
363. Rothberg S, Friedman BW. Complementary therapies in addition to medication for patients with nonchronic, nonradicular low back pain: A systematic review. *Am J Emerg Med* 2017; 35:55-61.
364. Bronson MA, Smith DL, Tuchin P. Spinal manipulation is beneficial for nonchronic low back pain. *Am J Emerg Med* 2017; 35:1576-1577.
365. Sherbourne CD, Ryan GW, Whitley MD, et al. Coping and management

- techniques used by chronic low back pain patients receiving treatment from chiropractors. *J Manipulative Physiol Ther* 2019; 42:582-593.
366. Hays RD, Sherbourne CD, Spritzer KL, et al. Experiences With chiropractic care for patients with low back or neck pain. *J Patient Exp* 2020; 7:357-364.
367. Schwartz NM, Schwartz MS. Definitions of biofeedback and applied psychophysiology. In: Schwartz MS, Andrasik F (eds). *Biofeedback: A Practitioner's Guide*, vol. 3. Guilford Press, New York, 2003 pp 27-42.
368. Flor H, Birbaumer N. Comparison of the efficacy of electromyographic biofeedback, cognitive-behavioural therapy, and conservative medical interventions in the treatment of chronic musculoskeletal pain. *J Consult Clin Psychol* 1993; 61:653-658.
369. Magnusson, Chow DH, Diamandopoulos Z, Pope MH. Motor control learning in chronic low back pain. *Spine (Phila Pa 1976)* 2008; 33:E532-E538.
370. Sielski R, Rief W, Glombiewski JA. Efficacy of biofeedback in chronic back pain: A meta-analysis. *Int J Behav Med* 2017; 24:25-41.
371. Wolfer L, Derby R, Lee JE, Lee SH. Systematic review of lumbar provocation discography in asymptomatic subjects with a meta-analysis of false-positive rates. *Pain Physician* 2008; 11:513-538.
372. Shambrook J, McNee P, Harris EC, et al. Clinical presentation of low back pain and association with risk factors according to findings on magnetic resonance imaging. *Pain* 2011; 152:1659-1665.
373. Thoomes EJ, van Geest S, van der Windt DA, et al. Value of physical tests in diagnosing cervical radiculopathy: A systematic review. *Spine J* 2018; 18:179-189.
374. Chotai S, Sielatycki JA, Parker SL, et al. Effect of obesity on cost per quality-adjusted life years gained following anterior cervical discectomy and fusion in elective degenerative pathology. *Spine J* 2016; 16:1342-1350.
375. McNee P, Shambrook J, Harris EC, et al. Predictors of long-term pain and disability in patients with low back pain investigated by magnetic resonance imaging: A longitudinal study. *BMC Musculoskelet Disord* 2011; 12:234.
376. Chou R, Qaseem A, Owens DK, Shekelle P; Clinical Guidelines Committee of the American College of Physicians. Diagnostic imaging for low back pain: Advice for high-value health care from the American College of Physicians. *Ann Intern Med* 2011; 154:181-189.
377. Lurie JD. What diagnostic tests are useful for low back pain? *Best Pract Res Clin Rheumatol* 2005; 19:557-575.
378. King W, Lau P, Lees R, Bogduk N. The validity of manual examination in assessing patients with neck pain. *Spine J* 2007; 7:22-26.
379. Jordan A, Mehlsen J, Ostergaard K. A comparison of physical characteristics between patients seeking treatment for neck pain and age-matched healthy people. *J Manipulative Physiol Ther* 1997; 20:468-475.
380. Wainner RS, Fritz JM, Irrgang JJ, Boninger ML, Delitto A, Allison S. Reliability and diagnostic accuracy of the clinical examination and patient self-report measures for cervical radiculopathy. *Spine (Phila Pa 1976)* 2003; 28:52-62.
381. Cheung KM, Samartzis D, Karppinen J, Luk KD. Are "patterns" of lumbar disc degeneration associated with low back pain?: New insights based on skipped level disc pathology. *Spine (Phila Pa 1976)* 2012; 37:E430-E438.
382. Kalichman L, Kim DH, Li L, Guermazi A, Hunter DJ. Computed tomography-evaluated features of spinal degeneration: Prevalence, intercorrelation, and association with self-reported low back pain. *Spine J* 2010; 10:200-208.
383. de Schepper EI, Damen J, van Meurs JB, et al. The association between lumbar disc degeneration and low back pain: The influence of age, gender, and individual radiographic features. *Spine (Phila Pa 1976)* 2010; 35:531-536.
384. Manchikanti L, Singh V, Datta S, Cohen SP, Hirsch JA. Comprehensive review of epidemiology, scope, and impact of spinal pain. *Pain Physician* 2009; 12:E35-E70.
385. Waxenbaum JA, Reddy V, Futterman B. Anatomy, back, intervertebral discs. 2020 Aug 10. In: StatPearls [Internet]. Treasure Island (FL), StatPearls Publishing, 2020 Jan.
386. Vlaeyen JWS, Maher CG, Wiech K, et al. Low back pain. *Nat Rev Dis Primers* 2018;4:52.
387. Kepler CK, Ponnappan RK, Tannoury CA, Risbud MV, Anderson DG. The molecular basis of intervertebral disc degeneration. *Spine J* 2013; 13:318-330.
388. Raj PP. Intervertebral disc: Anatomy-physiology-pathophysiology-treatment. *Pain Pract* 2008; 8:18-44.
389. Pearce RH, Grimmer BJ, Adams ME. Degeneration and the chemical composition of the human lumbar intervertebral disc. *J Orthop Res* 1987; 5:198-205.
390. Oichi T, Taniguchi Y, Oshima Y, Tanaka S, Saito T. Pathomechanism of intervertebral disc degeneration. *JOR Spine* 2020; 3:e1076.
391. Holm S, Maroudas A, Urban JP, Selstam G, Nachemson A. Nutrition of the intervertebral disc: Solute transport and metabolism. *Connect Tissue Res* 1981; 8:101-119.
392. Fasset DR, Kurd MF, Vaccaro AR. Biologic solutions for degenerative disk disease. *J Spinal Disord Tech* 2009; 22:297-308.
393. Huang YC, Urban JP, Luk KD. Intervertebral disc regeneration: Do nutrients lead the way? *Nat Rev Rheumatol* 2014; 10:561-566.
394. Wang Y, Videman T, Battie MC. ISSLS prize winner: Lumbar vertebral endplate lesions: Associations with disc degeneration and back pain history. *Spine (Phila Pa 1976)* 2012; 37:1490-1496.
395. Wang Y, Videman T, Battie MC. Lumbar vertebral endplate lesions: Prevalence, classification, and association with age. *Spine (Phila Pa 1976)* 2012; 37:1432-1439.
396. McNally DS, Shackelford IM, Goodship AE, Mulholland RC. In vivo stress measurement can predict pain on discography. *Spine (Phila Pa 1976)* 1996; 21:2580-2587.
397. Wade KR, Robertson PA, Thambyah A, Broom ND. How healthy discs herniate: A biomechanical and microstructural study investigating the combined effects of compression rate and flexion. *Spine (Phila Pa 1976)* 2014; 39:1018-1028.
398. Guterl CC, See EY, Blanquer SB, et al. Challenges and strategies in the repair of ruptured annulus fibrosus. *Eur Cell Mater* 2013; 25:1-21.
399. Genevay S, Atlas SJ. Lumbar spinal stenosis. *Best Pract Res Clin Rheumatol* 2010; 24:253-265.
400. Adams MA, Dolan P, Hutton WC, Porter RW. Diurnal changes in spinal mechanics and their clinical significance. *J Bone Joint Surg Br* 1990;72:266-270.
401. Liyew WA. Clinical presentations of lumbar disc degeneration and lumbosacral nerve lesions. *Int J Rheumatol* 2020; 2020:2919625.
402. Andersson G. Epidemiology of spinal disorders. In: Frymoyer JW, et al. (eds).



- The Adult Spine: Principles and Practice*. Raven Press, New York, 1997, pp 93-141.
403. Heliövaara M. *Epidemiology of Sciatica and Herniated Lumbar Intervertebral Disc*. The Social Insurance Institution, Helsinki, 1988.
  404. Postacchini F, Cinotti G. Etiopathogenesis. In: Postacchini F (ed). *Lumbar Disc Herniation*. Spring-Verlag, New York, 1999, pp 151-164.
  405. Friberg S, Hirsch C. Anatomical and clinical studies on lumbar disc degeneration. *Acta Orthop Scand* 1949; 19:222-242.
  406. Schultz A, Andersson G, Ortengren R, Haderspeck K, Nachemson A. Loads on the lumbar spine. Validation of a biomechanical analysis by measurements of intradiscal pressures and myoelectric signals. *J Bone Joint Surg Am* 1982; 64:713-720.
  407. Savettieri G, Salemi G, Rocca WA, Meneghini F, et al. Prevalence of lumbosacral radiculopathy in two Sicilian municipalities. Sicilian Neuro-Epidemiologic Study (SNES) Group. *Acta Neurol Scand* 1996; 93:464-469.
  408. Konstantinou K, Dunn KM. Sciatica: Review of epidemiological studies and prevalence estimates. *Spine (Phila Pa 1976)* 2008; 33:2464-2472.
  409. Ilyas H, Savage J. Lumbar disk herniation and SPORT: A Review of the literature. *Clin Spine Surg* 2018; 31:366-372.
  410. Chen BL, Guo JB, Zhang HW, et al. Surgical versus non-operative treatment for lumbar disc herniation: A systematic review and meta-analysis. *Clin Rehabil* 2018; 32:146-160.
  411. Shin JS, Lee J, Lee YJ, et al. Long-term course of alternative and integrative therapy for lumbar disc herniation and risk factors for surgery: A prospective observational 5-year follow-up study. *Spine (Phila Pa 1976)* 2016; 41:E955-E963.
  412. Zhong M, Liu JT, Jiang H, et al. Incidence of spontaneous resorption of lumbar disc herniation: A meta-analysis. *Pain Physician* 2017; 20:E45-E52.
  413. Chiu CC, Chuang TY, Chang KH, Wu CH, Lin PW, Hsu WY. The probability of spontaneous regression of lumbar herniated disc: A systematic review. *Clin Rehabil* 2015; 29:184-195.
  414. Wang Y, Dai G, Jiang L, et al. The incidence of regression after the non-surgical treatment of symptomatic lumbar disc herniation: A systematic review and meta-analysis. *BMC Musculoskelet Disord* 2020; 21:530.
  415. Lee J, Shin JS, Lee YJ, et al. Long-term course and predictive factors associated with disc resorption in lumbar disc herniation patients. *J Neurol Sci* 2017; 381:278.
  416. Ahn SH, Ahn MW, Byun WM. Effect of the transligamentous extension of lumbar disc herniations on their regression and the clinical outcome of sciatica. *Spine (Phila Pa 1976)* 2000; 25:475-480.
  417. Delauche-Cavallier MC, Budet C, Laredo JD, et al. Lumbar disc herniation: Computed tomography scan changes after conservative treatment of nerve root compression. *Spine (Phila Pa 1976)* 1992; 17:927-933.
  418. Bozzao A, Gallucci M, Masciocchi C, Aprile I, Barile A, Passariello R. Lumbar disk herniation: MR imaging assessment of natural history in patients treated without surgery. *Radiology* 1992; 185:135-141.
  419. Komori H, Shinomiya K, Nakai O, Yamaura I, Takeda S, Furuya K. The natural history of herniated nucleus pulposus with radiculopathy. *Spine (Phila Pa 1976)* 1996; 21:225-229.
  420. Saal JA, Saal JS, Herzog RJ. The natural history of lumbar intervertebral disc extrusions treated nonoperatively. *Spine (Phila Pa 1976)* 1990; 15:683-686.
  421. Bush K, Cowan N, Katz DE, Gishen P. The natural history of sciatica associated with disc pathology. A prospective study with clinical and independent radiologic follow-up. *Spine (Phila Pa 1976)* 1992; 17:1205-1212.
  422. Hahne AJ, Ford JJ, McMeeken JM. Conservative management of lumbar disc herniation with associated radiculopathy: A systematic review. *Spine (Phila Pa 1976)* 2010; 35:E488-E504.
  423. Buy X, Gangi A. Percutaneous treatment of intervertebral disc herniation. *Semin Intervent Radiol* 2010; 27:148-159.
  424. Castro I, Santos DP, Christoph Dde H, Landeiro JA. The history of spinal surgery for disc disease: An illustrated timeline. *Arq Neuropsiquiatr* 2005; 63:701-706.
  425. DePalma MJ, Ketchum JM, Saullo T. What is the source of chronic low back pain and does age play a role? *Pain Med* 2011; 12:224-233.
  426. Liu Q, Jin L, Mahon BH, Chordia MD, Shen FH, Li X. Novel treatment of neuroinflammation against low back pain by soluble fullerol nanoparticles. *Spine (Phila Pa 1976)* 2013; 38:1443-1451.
  427. Alimasi W, Sawaji Y, Endo K, et al. Regulation of nerve growth factor by anti-inflammatory drugs, a steroid, and a selective cyclooxygenase 2 inhibitor in human intervertebral disc cells stimulated with interleukin-1. *Spine (Phila Pa 1976)* 2013; 38:1466-1472.
  428. Koerner JD, Markova DZ, Schroeder GD, et al. The effect of substance P on an intervertebral disc rat organ culture model. *Spine (Phila Pa 1976)* 2016; 41:1851-1859.
  429. Golish SR, Hanna LS, Bowser RP, Montesano PX, Carragee EJ, Scuderi GJ. Outcome of lumbar epidural steroid injection is predicted by assay of a complex of fibronectin and aggrecan from epidural lavage. *Spine (Phila Pa 1976)* 2011; 36:1464-1469.
  430. Moon HJ, Kim JH, Lee HS, et al. Annulus fibrosus cells interact with neuron-like cells to modulate production of growth factors and cytokines in symptomatic disc degeneration. *Spine (Phila Pa 1976)* 2012; 37:2-9.
  431. Inoue G, Ohtori S, Aoki Y, et al. Exposure of the nucleus pulposus to the outside of the anulus fibrosus induces nerve injury and regeneration of the afferent fibers innervating the lumbar intervertebral discs in rats. *Spine (Phila Pa 1976)* 2006; 31:1433-1438.
  432. McCarron RF, Wimpee MW, Hudkins PG, Laros GS. The inflammatory effect of nucleus pulposus. A possible element in the pathogenesis of low-back pain. *Spine (Phila Pa 1976)* 1987; 12:760-764.
  433. Levi-Montalcini R. The nerve growth factor 35 years later. *Science* 1987; 237:1154-1162.
  434. Woolf CJ, Ma QP, Allchorne A, et al. Peripheral cell types contributing to the hyperalgesic action of nerve growth factor in inflammation. *J Neurosci* 1996; 16:2716-2723.
  435. Micera A, Vigneti E, Pickholtz D, et al. Nerve growth factor displays stimulatory effects on human skin and lung fibroblasts, demonstrating a direct role for this factor in tissue repair. *Proc Natl Acad Sci USA* 2001; 98:6162-6167.
  436. Manchikanti L, Hirsch JA. Clinical management of radicular pain. *Expert Rev Neurother* 2015; 15:681-693.
  437. Kreiner DS, Hwang SW, Easa JE, et al. An evidence-based clinical guideline for the diagnosis and treatment of lumbar disc herniation with radiculopathy. *Spine J* 2014; 14:180-191.
  438. Risbud MV, Shapiro IM. Role of cytokines in intervertebral disc degeneration: Pain and disc content. *Nat Rev Rheumatol* 2014; 10: 44-56.
  439. Olmarker K, Rydevik B, Hansson T, et



- al. Compression-induced changes of the nutritional supply to the porcine cauda equina. *J Spinal Disord Tech* 1990; 3:25-29.
440. Olmarker K, Holm S, Rydevik B. Importance of compression onset rate for the degree of impairment of impulse propagation in experimental compression injury of the porcine cauda equina. *Spine (Phila Pa 1976)* 1990; 15:416-419.
441. Haig AJ, Tomkins CC. Diagnosis and management of lumbar spinal stenosis. *JAMA* 2010; 303:71-72.
442. Kalichman L, Cole R, Kim DH, et al. Spinal stenosis prevalence and association with symptoms: The Framingham Study. *Spine J* 2009; 9:545-550.
443. Deer T, Sayed D, Michels J, Josephson Y, Li S, Calodney AK. A review of lumbar spinal stenosis with intermittent neurogenic claudication: Disease and diagnosis. *Pain Med* 2019; 20:S32-S44.
444. Kovacs FM, Urrútia G, Alarcón JD. Surgery versus conservative treatment for symptomatic lumbar spinal stenosis: A systematic review of randomized controlled trials. *Spine (Phila Pa 1976)* 2011; 36:E1335-E1351.
445. Andreisek G, Deyo RA, Jarvik JG, Porchet F, Winklhofer SF, Steurer J; LSOS working group. Consensus conference on core radiological parameters to describe lumbar stenosis - an initiative for structured reporting. *Eur Radiol* 2014; 24:3224-3232.
446. Yuan S, Zou Y, Li Y, Chen M, Yue Y. A clinically relevant MRI grading system for lumbar central canal stenosis. *Clin Imaging* 2016; 40:1140-1145.
447. Burgstaller JM, Schöffler PJ, Buhmann JM, et al; LSOS Study Group. Is there an association between pain and magnetic resonance imaging parameters in patients with lumbar spinal stenosis? *Spine (Phila Pa 1976)* 2016; 41:E1053-E1062.
448. Lønne G, Ødegård B, Johnsen LG, Solberg TK, Kvistad KA, Nygaard ØP. MRI evaluation of lumbar spinal stenosis: Is a rapid visual assessment as good as area measurement? *Eur Spine J* 2014; 23:1320-1324.
449. Schroeder GD, Kurd MF, Vaccaro AR. Lumbar spinal stenosis: How is it classified? *J Am Acad Orthop Surg* 2016; 24:843-852.
450. Takenaka H, Sugiura H, Kamiya M, et al. Predictors of walking ability after surgery for lumbar spinal canal stenosis: A prospective study. *Spine J* 2019; 19:1824-1831.
451. Lurie J, Tomkins-Lane C. Management of lumbar spinal stenosis. *BMJ* 2016; 352:h6234.
452. Yabuki S, Fukumori N, Takegami M, et al. Prevalence of lumbar spinal stenosis, using the diagnostic support tool, and correlated factors in Japan: A population-based study. *J Orthop Sci* 2013; 18:893-900.
453. Johnsson KE, Rosen I, Uden A. The natural course of lumbar spinal stenosis. *Clin Orthop Relat Res* 1992:82-86.
454. Cowley P. Neuroimaging of spinal canal stenosis. *Magn Reson Imaging Clin N Am* 2016; 24:523-539.
455. Osterman H, Sund R, Seitsalo S, Keskimäki I. Risk of multiple reoperations after lumbar discectomy: A population-based study. *Spine (Phila Pa 1976)* 2003; 28:621-627.
456. Law JD, Lehman RAW, Kirsch WM. Reoperation after lumbar intervertebral disc surgery. *J Neurosurg* 1978; 48:259-263.
457. Einhaus SL, Robertson JT, Dohan FC Jr, Wujek JR, Ahmad S. Reduction of peridural fibrosis after lumbar laminotomy and discectomy in dogs by a resorbable gel (ADCON-L). *Spine (Phila Pa 1976)* 1997; 22:1440-1446.
458. Vogelsang JP, Finkenstaedt M, Vogelsang M, Markakis E. Recurrent pain after lumbar discectomy: The diagnostic value of peridural scar on MRI. *Eur Spine J* 1999; 8:475-479.
459. BenDebba M, Augustus van Alphen H, Long DM. Association between peridural scar and activity-related pain after lumbar discectomy. *Neurol Res* 1999; 21:S37-S42.
460. Ross JS, Robertson JT, Frederickson RC, et al. Association between peridural scar and recurrent radicular pain after lumbar discectomy: Magnetic resonance evaluation. *Neurosurgery* 1996; 38:855-863.
461. Brzezicki G, Jankowski R, Blok T, et al. Postlaminectomy osteopontin expression and associated neurophysiological findings in rat peridural scar model. *Spine (Phila Pa 1976)* 2011; 36:378-385.
462. 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.
463. Almeida DB, Prandini MN, Awamura Y, et al. Outcome following lumbar disc surgery: The role of fibrosis. *Acta Neurochir (Wien)* 2008; 150:1167-1176.
464. Jou IM, Tai TW, Tsai CL, Tsai TM, Yung WS, Jung YC. Spinal somatosensory evoked potential to evaluate neurophysiologic changes associated with postlaminotomy fibrosis: An experimental study. *Spine (Phila Pa 1976)* 2007; 32:2111-2118.
465. Alkalay RN, Kim DH, Urry DW, Xu J, Parker TM, Glazer PA. Prevention of postlaminectomy epidural fibrosis using bioelastic materials. *Spine (Phila Pa 1976)* 2003; 28:1659-1665.
466. Ozer AF, Oktenoglu T, Sasani M, et al. Preserving the ligamentum flavum in lumbar discectomy: A new technique that prevents scar tissue formation in the first 6 months post surgery. *Neurosurgery* 2006; 59:ONS126-ONS133.
467. Cooper RG, Freemont AJ, Hoyland JA, et al. Herniated intervertebral disc-associated periradicular fibrosis and vascular abnormalities occur without inflammatory cell infiltration. *Spine (Phila Pa 1976)* 1995; 20:591-598.
468. Schimizzi AL, Massie JB, Murphy M, et al. High-molecular-weight hyaluronan inhibits macrophage proliferation and cytokine release in the early wound of a preclinical postlaminectomy rat model. *Spine J* 2006; 6:550-556.
469. Massie JB, Huang B, Malkmus S, et al. A preclinical post laminectomy rat model mimics the human post laminectomy syndrome. *J Neurosci Methods* 2004; 137:283-289.
470. Massie JB, Schimizzi AL, Huang B, Kim CW, Garfin SR, Akeson WH. Topical high molecular weight hyaluronan reduces radicular pain post laminectomy in a rat model. *Spine J* 2005; 5:494-502.
471. Harrington JF, Messier AA, Hoffman L, Yu E, Dykhuizen M, Barker K. Physiological and behavioral evidence for focal nociception induced by epidural glutamate infusion in rats. *Spine (Phila Pa 1976)* 2005; 30:606-612.
472. Kim KD, Wang JC, Robertson DP, et al. Reduction of leg pain and lower-extremity weakness for 1 year with Oxiplex/SP gel following laminectomy, laminotomy, and discectomy. *Neurosurg Focus* 2004; 17:ECP1.
473. VEDIAPPAN RS, Mascarenhas A, Nguyen-Hoang A, et al. Prevention of peridural adhesions in spinal surgery: Assessing safety and efficacy of Chitogel with Deferiprone in a sheep model. *J Clin Neurosci* 2020; 72:378-385.
474. Puvanesarajah V, Nourbakhsh A,

- Hassanzadeh H, Shimer AL, Shen FH, Singla A. Readmission rates, reasons, and risk factors in elderly patients treated with lumbar fusion for degenerative pathology. *Spine (Phila Pa 1976)* 2016; 41:1933-1938.
475. Wang H, Sun W, Fu D, Shen Y, Chen YY, Wang LL. Update on biomaterials for prevention of epidural adhesion after lumbar laminectomy. *J Orthop Translat* 2018; 13:41-49.
476. Daniell JR, Osti OL. Failed back surgery syndrome: A review article. *Asian Spine J*. 2018; 12:372-379.
477. Thomson S. Failed back surgery syndrome – definition, epidemiology, and demographics. *Br J Pain* 2013; 7:56-59.
478. Merskey H, Bogduk N. Task Force on Taxonomy of the International Association for the Study of Pain. Classification of chronic pain: Descriptions of chronic pain syndromes and definition of pain terms. 2nd ed. Seattle: IASP Press; 1994.
479. Skolasky RL, Wegener ST, Maggard AM, Riely LH 3rd. The impact of reduction of pain after lumbar spine surgery: The relationship between changes in pain and physical function and disability. *Spine (Phila Pa 1976)* 2014; 39:1426-1432.
480. Chan CW, Peng P. Failed back surgery syndrome. *Pain Med* 2011; 12:577-606.
481. Bosscher HA, Heavner JE. Incidence and severity of epidural fibrosis after back surgery: An endoscopic study. *Pain Pract* 2010; 10:18-24.
482. Haq I, Cruz-Almeida Y, Siqueira EB, Norenberg M, Green BA, Levi AD. Postoperative fibrosis after surgical treatment of the porcine spinal cord: A comparison of dural substitutes. Invited submission from the Joint Section Meeting on Disorders of the Spine and Peripheral Nerves, March 2004. *J Neurosurg Spine* 2005; 2:50-54.
483. Fujii J, Kurahashi T, Konno T, Homma T, Iuchi Y. Oxidative stress as a potential causal factor for autoimmune hemolytic anemia and systemic lupus erythematosus. *World J Nephrol* 2015; 4:213-222.
484. Mohi Eldin MM, Abdel Razeq NM. Epidural fibrosis after lumbar disc surgery: Prevention and outcome evaluation. *Asian Spine J* 2015; 9:370-385.
485. Cifu DX. *Braddom's Physical Medicine & Rehabilitation*. 5th ed. Elsevier, Philadelphia, PA, 2015, pp 687-709.
486. Crock HV. A reappraisal of intervertebral disc lesions. *Med J Aust* 1970; 1:983-989.
487. Yu SW, Haughton VM, Sether LA, Wagner M. Comparison of MR and diskography in detecting radial tears of the annulus: A postmortem study. *AJNR Am J Neuroradiol* 1989; 10:1077-1081.
488. Bogduk N, Windsor M, Inglis A. The innervation of the cervical intervertebral discs. *Spine (Phila Pa 1976)* 1988; 13:2-8.
489. Rabischong P, Louis R, Vignaud J, Massare C. The intervertebral disk. *Anat Clin* 1978; 1:55-64.
490. Whitecloud TS 3rd, Seago RA. Cervical discogenic syndrome. Results of operative intervention in patients with positive discography. *Spine (Phila Pa 1976)* 1987; 12:313-316.
491. Navone SE, Marfia G, Giannoni A, et al. Inflammatory mediators and signalling pathways controlling intervertebral disc degeneration. *Histol Histopathol* 2017; 32:523-542.
492. Peng B, DePalma MJ. Cervical disc degeneration and neck pain. *J Pain Res* 2018; 11:2853-2857.
493. García-Cosamalón J, del Valle ME, Calavia MG, et al. Intervertebral disc, sensory nerves and neurotrophins: Who is who in discogenic pain? *J Anat* 2010; 217:1-15.
494. Okada E, Matsumoto M, Ichihara D, et al. Aging of the cervical spine in healthy volunteers: A 10-year longitudinal magnetic resonance imaging study. *Spine (Phila Pa 1976)* 2009; 34:706-712.
495. Lunsford LD, Bissonette DJ, Jannetta PJ, Sheptak PE, Zorub DS. Anterior surgery for cervical disc disease: Part 1: Treatment of lateral cervical disc herniation in 253 cases. *J Neurosurg* 1980; 53:1-11.
496. O'Laioire S, Thomas D. Spinal cord compression due to prolapse of cervical intervertebral disc. *J Neurosurg* 1983; 59:847-853.
497. Kelsey JL, Githens PB, Walter SD, et al. An epidemiological study of acute prolapsed cervical intervertebral disc. *J Bone Joint Surg Am* 1984; 66:907-914.
498. Bogduk N. Pathology. In: *Medical Management of Acute Cervical Radicular Pain: An Evidence-Based Approach*. 1st Edition. Cambridge Press, Newcastle, 1999, pp 13-18.
499. Grodzinski B, Durham R, Mowforth O, Stubbs D, Kotter MRN, Davies BM. The effect of ageing on presentation, management and outcomes in degenerative cervical myelopathy: A systematic review. *Age Ageing* 2020 [Epub ahead of print].
500. 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; 14:1781-1789.
501. 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; 117:325.
502. Jensen MV, Tüchsen F, Orhede E. Prolapsed cervical intervertebral disc in male professional drivers in Denmark, 1981-1990. A longitudinal study of hospitalizations. *Spine (Phila Pa 1976)* 1996; 21:2352-2355.
503. Mason KT, Harper JP, Shannon SG. Herniated nucleus pulposus: Rates and outcomes among U.S. Army aviators. *Aviat Space Environ Med* 1996; 67:338-340.
504. Manchikanti L, Boswell MV, Singh V, et al. Comprehensive review of neurophysiologic basis and diagnostic interventions in managing chronic spinal pain. *Pain Physician* 2009; 12:E71-E120.
505. Kang JD, Georgescu HI, McIntyre-Larkin L, Stefanovic-Racic M, Evans CH. Herniated cervical intervertebral discs spontaneously produce matrix metalloproteinases, nitric oxide, interleukin-6 and prostaglandin E2. *Spine (Phila Pa 1976)* 1995; 22:2373-2378.
506. Kang JD, Stefanovic-Racic M, McIntyre LA, Georgescu HI, Evans CH. Toward a biochemical understanding of human intervertebral disc degeneration and herniation. Contributions of nitric oxide, interleukins, prostaglandin E2, and matrix metalloproteinases. *Spine (Phila Pa 1976)* 1997; 22:1065-1073.
507. Furusawa N, Baba H, Miyoshi N, et al. Herniation of cervical intervertebral disc: Immunohistochemical examination and measurement of nitric oxide production. *Spine (Phila Pa 1976)* 2001; 26:1110-1116.
508. Rothman SM, Ma LH, Whiteside GT, Winkelstein BA. Inflammatory cytokine and chemokine expression is differentially modulated acutely in the dorsal root ganglion in response to different nerve root compressions. *Spine (Phila Pa 1976)* 2011; 36:197-202.
509. DeLeo JA, Yezierski RP. The role of neuroinflammation and neuroimmune activation in persistent pain. *Pain* 2001; 90:1-6.
510. Rutkowski MD, DeLeo JA. The role of cytokines in the initiation and maintenance of chronic pain. *Drug News Perspect* 2002; 15:626-632.

511. McMahon SB, Cafferty WB, Marchand F. Immune and glial cell factors as pain mediators and modulators. *Exp Neurol* 2005; 192:444-462.
512. Aloisi F. Immune function of microglia. *Glia* 2001; 36:165-179.
513. Eskes C, Juillerat-Jeanneret L, Leuba G, Honnegger P, Monnet-Tschudi F. Involvement of microglia-neuron interactions in the tumor necrosis factor- $\alpha$  release, microglial activation, and neurodegeneration induced by trimethyltin. *J Neurosci Res* 2003; 71:583-590.
514. Hashizume H, DeLeo JA, Colburn RW, Weinstein JN. Spinal glial activation and cytokine expression after lumbar root injury in the rat. *Spine (Phila Pa 1976)* 2000; 25:1206-1217.
515. Sweitzer S, Martin D, DeLeo JA. Intrathecal interleukin-1 receptor antagonist in combination with soluble tumor necrosis factor receptor exhibits an anti-allodynic action in a rat model of neuropathic pain. *Neuroscience* 2001; 103:529-539.
516. DeLeo JA, Winkelstein BA. Physiology of chronic spinal pain syndromes: From animal models to biomechanics. *Spine (Phila Pa 1976)* 2002; 27:2526-2537.
517. Flatters SJ, Fox AJ, Dickenson AH. Spinal interleukin-6 (IL-6) inhibits nociceptive transmission following neuropathy. *Brain Res* 2003; 984:54-62.
518. Aschner M. Astrocytes as mediators of immune and inflammatory responses in the CNS. *Neurotoxicology* 1998; 19:269-281.
519. Sommer C, Kress M. Recent findings on how proinflammatory cytokines cause pain: Peripheral mechanisms in inflammatory and neuropathic hyperalgesia. *Neurosci Lett* 2004; 361:184-187.
520. Siivola SM, Levoska S, Tervonen O, Ilkko E, Vanharanta H, Keinänen-Kiukaanniemi S. MRI changes of cervical spine in asymptomatic and symptomatic young adults. *Eur Spine J* 2002; 11:358-363.
521. Ellenberg MR, Honet JC, Treanor WJ. Cervical radiculopathy. *Arch Phys Med Rehabil* 1994; 75:342-352.
522. Woods BI, Hilibrand AS. Cervical radiculopathy: Epidemiology, etiology, diagnosis, and treatment. *J Spinal Disord Tech* 2015; 28:E251-E259.
523. Rhee JM, Yoon T, Riew KD. Cervical radiculopathy. *J Am Acad Orthop Surg* 2007; 15:486-494.
524. Hunt WE MC. Management of cervical radiculopathy. *Clin Neurosurg* 1986; 33:485-502.
525. Semmes RE, Murphey F. The syndrome of unilateral rupture of the sixth cervical intervertebral disk: With compression of the seventh cervical nerve root a report of four cases with symptoms simulating coronary disease. *J Am Med Assoc* 1943; 121:1209-1214.
526. Boden SD, McCowin PR, Davis DO, Dina TS, Mark AS, Wiesel S. Abnormal magnetic-resonance scans of the cervical spine in asymptomatic subjects. A prospective investigation. *J Bone Joint Surgery Am* 1990; 72:1178-1184.
527. Matsumoto M, Fujimura Y, Suzuki N, et al. MRI of cervical intervertebral discs in asymptomatic subjects. *J Bone Joint Surgery Br* 1998; 80:19-24.
528. McRae DL. Asymptomatic intervertebral disc protrusions. *Acta Radiol* 1956; 46:9-27.
529. Teresi LM, Lufkin RB, Reicher MA, et al. Asymptomatic degenerative disk disease and spondylosis of the cervical spine: MR imaging. *Radiology* 1987; 164:83-88.
530. Fakhoury J, Dowling TJ. *Cervical Degenerative Disc Disease*. In: StatPearls [Internet]. StatPearls Publishing, Treasure Island, FL, 2020.
531. Kang KC, Lee HS, Lee JH. Cervical radiculopathy focus on characteristics and differential diagnosis. *Asian Spine J* 2020; 14:921-930.
532. Olmarker K, Rydevik B, Nordborg C. Autologous nucleus pulposus induces neurophysiologic and histologic changes in porcine cauda equina nerve roots. *Spine (Phila Pa 1976)* 1993; 18:1425-1432.
533. Crette S FM. Cervical radiculopathy. *N Engl J Med* 2005; 353:392-399.
534. Rydevik B, Brown MD, Lundborg G. Pathoanatomy and pathophysiology of nerve root compression. *Spine (Phila Pa 1976)* 1984; 9:7-15.
535. Yu YL, E Woo, Huang CY. Cervical spondylitic myelopathy and radiculopathy. *Acta Neurol Scand* 1987; 75:367-373.
536. Slipman CW, Chow DW, Isaac Z, et al. An evidence-based algorithmic approach to cervical spinal disorders. *Crit Rev Phys Rehab Med* 2001; 13:18.
537. Lunardi P, Acqui M, Ricci G, Agrillo A, Ferrante L. Cervical synovial cysts: Case report and review of the literature. *Eur Spine J* 1999; 8:232-237.
538. Polston D. Cervical radiculopathy. *Neurol Clin* 2007; 25:373-385.
539. Lees F, Turner JW. Natural history and prognosis of cervical spondylosis. *Br Med J* 1963; 2:1607-1610.
540. Bono CM, Ghiselli G, Gilbert TJ, et al; North American Spine Society. An evidence-based clinical guideline for the diagnosis and treatment of cervical radiculopathy from degenerative disorders. *Spine J* 2011; 11:64-72.
541. Garfin SR. Cervical degenerative disorders: Etiology, presentation, and imaging studies. *Instr Course Lect* 2000; 49:335-338.
542. Truumees E, Herkowitz HN. Cervical spondylotic myelopathy and radiculopathy. *Instr Course Lect* 2009; 49:339-360.
543. Meyer F, Börm W, Thorné C. Degenerative cervical spinal stenosis: Current strategies in diagnosis and treatment. *Dtsch Arztebl Int* 2008; 105:366-372.
544. Morishita Y, Naito M, Hymanson H, Miyazaki M, Wu G, Wang JC. The relationship between the cervical spinal canal diameter and the pathological changes in the cervical spine. *Eur Spine J* 2009; 18:877-883.
545. Karpova A, Arun R, Davis AM, et al. Reliability of quantitative magnetic resonance imaging methods in the assessment of spinal canal stenosis and cord compression in cervical myelopathy. *Spine (Phila Pa 1976)* 2013; 38:245-252.
546. Overley SC, Kim JS, Gogel BA, Merrill RK, Hecht AC. Tandem spinal stenosis: A systematic review. *JBJS Rev* 2017; 5:E2.
547. Crette S, Fehlings MG. Clinical practice. Cervical radiculopathy. *N Engl J Med* 2005; 353:392-399.
548. Wolf BS, Khilnani M, Malis L. The sagittal diameter of the bony cervical spinal canal and its significance in cervical spondylosis. *J Mt Sinai Hosp N Y* 1956; 23:283-292.
549. Lee MJ, Cassinelli EH, Riew KD. Prevalence of cervical spine stenosis. *J Bone Joint Surg Am* 2007; 89:376-380.
550. Miyazaki M, Takita C, Yoshiwa T, Itonaga I, Tsumura H. Morphological analysis of the cervical pedicles, lateral masses, and laminae in developmental canal stenosis. *Spine (Phila Pa 1976)* 2010; 35:E1381-E1385.
551. Hug A, Hähnel S, Weidner N. Diagnostik und konservative Therapie zervikaler und lumbaler Spinalkanalstenosen [Diagnostics and conservative treatment of cervical and lumbar spinal stenosis].

- Nervenarzt* 2018; 89:620-631.
552. McCormick WE, Steinmetz MP, Benzel EC. Cervical spondylotic myelopathy: Make the difficult diagnosis, then refer for surgery. *Cleve Clin J Med* 2003; 70:899-904.
553. Kikuike K, Miyamoto K, Hosoe H, Shimizu K. One-staged combined cervical and lumbar decompression for patients with tandem spinal stenosis on cervical and lumbar spine: Analyses of clinical outcomes with minimum 3 years followup. *J Spinal Disord Tech* 2009; 22:593-601.
554. Park MS, Moon SH, Kim TH, et al. Asymptomatic stenosis in the cervical and thoracic spines of patients with symptomatic lumbar stenosis. *Global Spine J* 2015; 5:366-371.
555. Hu PP, Yu M, Liu XG, Liu ZJ, Jiang L. Surgeries for patients with tandem spinal stenosis in cervical and thoracic spine: Combined or staged surgeries? *World Neurosurg* 2017; 107:115-123.
556. Montgomery DM, Brower RS. Cervical spondylotic myelopathy. Clinical syndrome and natural history. *Orthop Clin North Am* 1992; 23:487-493.
557. Cadotte DW, Karpova A, Fehlings MG. Cervical spondylotic myelopathy: Surgical outcomes in the elderly. *Int J Clin Rheumatol* 2010; 5:327-337.
558. Houten JK, Cooper PR. Laminectomy and posterior cervical plating for multilevel cervical spondylotic myelopathy and ossification of the posterior longitudinal ligament: Effects on cervical alignment, spinal cord compression, and neurological outcome. *Neurosurg* 2003; 52:1081-1087.
559. Singh A, Crockard HA, Platts A, Stevens J. Clinical and radiological correlates of severity and surgery-related outcome in cervical spondylosis. *J Neurosurg* 2001; 94:189-198.
560. Yukawa Y, Kato F, Yoshihara H, Yanase M, Ito K. MR T2 image classification in cervical compression myelopathy: Predictor of surgical outcomes. *Spine (Phila Pa 1976)* 2007; 32:1675-1678.
561. Fernández de Rota JJ, Meschian S, Fernández de Rota A, Urbano V, Baron M. Cervical spondylotic myelopathy due to chronic compression: The role of signal intensity changes in magnetic resonance images. *J Neurosurg Spine* 2007; 6:17-22.
562. Seichi A, Kimura A, Higashi T, et al. Localization of the medial branches of the cervical dorsal rami during cervical laminoplasty. *Spine (Phila Pa 1976)* 2012; 37:E1603-E1606.
563. Hosono N, Yonenobu K, Ono K. Neck and shoulder pain after laminoplasty. A noticeable complication. *Spine (Phila Pa 1976)* 1996; 21:1969-1973.
564. Wang S, Jiang S, Jiang L, Dai LY. Axial pain after posterior cervical spine surgery: A systematic review. *Eur Spine L* 2011; 20:185-194.
565. Saita K, Hishino Y, Kikkawa I, Ishii T, Lee JH. Complaint of nuchal pain following cervical laminoplasty. *J Musculoskeletal Res* 1999; 3:253-258.
566. Seichi A, Takeshita K, Ohishi I, et al. Long-term results of double-door laminoplasty for cervical stenotic myelopathy. *Spine (Phila Pa 1976)* 2001; 26:479-487.
567. Kimura A, Seichi A, Inoue H, Hoshino Y. Long-term results of double-door laminoplasty using hydroxyapatite spacers in patients with compressive cervical myelopathy. *Eur Spine J* 2011; 20:1560-1566.
568. Chiba K, Ogawa Y, Ishii K, et al. Long-term results of expansive open-door laminoplasty for cervical myelopathy-average 14-year follow-up study. *Spine (Phila Pa 1976)* 2006; 31:2998-3005.
569. Wagner SC, Formby PM, Kang DG, et al. Persistent axial neck pain after cervical disc arthroplasty: A radiographic analysis. *Spine J* 2016; 16:851-856.
570. Lin JH, Chien LN, Tsai WL, Chen LY, Hsieh YC, Chiang YH. Reoperation rates of anterior cervical discectomy and fusion versus posterior laminoplasty for multilevel cervical degenerative diseases: A population-based cohort study in Taiwan. *Spine J* 2016; 16:1428-1436.
571. Tracey RW, Kang DG, Cody JP, Wagner SC, Rosner MK, Lehman RA Jr. Outcomes of single-level cervical disc arthroplasty versus anterior cervical discectomy and fusion. *J Clin Neurosci* 2014; 21:1905-1908.
572. Brenke C, Scharf J, Schmieder K, Barth M. High prevalence of heterotopic ossification after cervical disc arthroplasty: Outcome and intraoperative findings following explantation of 22 cervical disc prostheses. *J Neurosurg Spine* 2012; 17:141-146.
573. Takeuchi K, Yokoyama T, Aburakawa S, et al. Axial symptoms after cervical laminoplasty with C3 laminectomy compared with conventional C3-C7 laminoplasty. A modified laminoplasty preserving the semispinalis cervicis inserted into axis. *Spine (Phila Pa 1976)* 2005; 30:2544-2549.
574. Kato M, Nakamura H, Konishi S, et al. Effect of preserving paraspinous muscles on postoperative axial pain in the selective cervical laminoplasty. *Spine (Phila Pa 1976)* 2008; 33:E455-E459.
575. Amand N, Regan JJ. Video-assisted thoracoscopic surgery for thoracic disc disease: Classification and outcome study of 100 consecutive cases with a 2-year minimum follow-up period. *Spine (Phila Pa 1976)* 2002; 27:871-879.
576. Williams MP, Cherryman GR, Husband JE. Significance of thoracic disc herniation demonstrated by MR imaging. *J Comput Assist Tomogr* 1989; 13:211-214.
577. Awaad EE, Martin DW, Smith KR Jr. Asymptomatic versus symptomatic herniated thoracic discs: Their frequency and characteristics as detected by computed tomography after myelography. *Neurosurgery* 1991; 28:180-186.
578. Dietze DD, Fessler RG. Thoracic disc herniations. *Neurosurg Clin North Am* 1993; 4:75-90.
579. Court C, Mansour E, Bouthors C. Thoracic disc herniation: Surgical treatment. *Orthop Traumatol Surg Res* 2018; 104:S31-S40.
580. Chen G, Fan T, Yang X, Sun C, Fan D, Chen Z. The prevalence and clinical characteristics of thoracic spinal stenosis: A systematic review. *Eur Spine J* 2020; 29:2164-2172.
581. Liu Z, Duan Y, Rong X, Wang B, Chen H, Liu H. Variation of facet joint orientation and tropism in lumbar degenerative spondylolisthesis and disc herniation at L4-L5: A systematic review and meta-analysis. *Clin Neurol Neurosurg* 2017; 161:41-447.
582. Fogwe DT, Petrone B, Mesfin FB. Thoracic Discogenic Syndrome. 2020 Nov 1. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 Jan.
583. Palumbo MA, Hilibrand AS, Hart RA, Bohlman HH. Surgical treatment of thoracic spinal stenosis: A 2- to 9-year follow-up. *Spine (Phila Pa 1976)*. 2001; 26:558-566.
584. Quint U, Bordon G, Preissl I, Sanner C, Rosenthal D. Thoracoscopic treatment for single level symptomatic thoracic disc herniation: A prospective followed cohort study in a group of 167 consecutive cases. *Eur Spine J* 2012; 21:637-645.
585. Hott JS, Feiz-Erfan I, Kenny K, Dickman



- CA. Surgical management of giant herniated thoracic discs: Analysis of 20 cases. *J Neurosurg Spine* 2005; 3:191-197.
586. Kim YJ, Bridwell KH, Lenke LG, Rhim S, Cheh G. Sagittal thoracic decompression following long adult lumbar spinal instrumentation and fusion to L5 or S1: Causes, prevalence, and risk factor analysis. *Spine (Phila Pa 1976)* 2006; 31:2359-2366.
587. Sari H, Misirlioglu TO, Palamar D. Regression of a symptomatic thoracic disc herniation with a calcified intervertebral disc component. *Acta Orthop Traumatol Turc* 2016; 50:698-701.
588. Manchikanti L, Cash KA, McManus CD, Pampati V, Benyamin RM. Thoracic interlaminar epidural injections in managing chronic thoracic pain: A randomized, double-blind, controlled trial with a 2-year follow-up. *Pain Physician* 2014; 17:E327-E338.
589. Barnett GH, Hardy RW, Little JR, Bay JW, Sybert GW. Thoracic spinal canal stenosis. *J Neurosurg* 1987; 66:338-344.
590. Domisse GF. The blood supply of the spinal cord. A critical vascular zone in spinal surgery. *J Bone Joint Surg Br* 1974; 56:225-235.
591. Lazorthes G, Gouaze A, Zadeh JO, Santini JJ, Lazorthes Y, Burdin P. Arterial vascularization of the spinal cord. Recent studies of the anastomotic substitution pathways. *J Neurosurg* 1971; 35:253-262.
592. Li Z, Ren D, Zhao Y, et al. Clinical characteristics and surgical outcome of thoracic myelopathy caused by ossification of the ligamentum flavum: A retrospective analysis of 85 cases. *Spinal Cord* 2016; 54:188-196.
593. Yu S, Wu D, Li F, Hou T. Surgical results and prognostic factors for thoracic myelopathy caused by ossification of ligamentum flavum: posterior surgery by laminectomy. *Acta Neurochir (Wien)* 2013; 155:1169-1177.
594. Aizawa T, Sato T, Sasaki H, et al. Results of surgical treatment for thoracic myelopathy: Minimum 2-year follow-up study in 132 patients. *J Neurosurg Spine* 2007; 7:13-20.
595. Garry JP. A rare case of thoracic spinal stenosis in a white male. *Current Sports Med Rep* 2018; 17:13-15.
596. Bajwa NS, Toy JO, Ahn NU. Establishment of parameters for congenital thoracic stenosis: A study of 700 postmortem specimens. *Clin Orthop Relat Res* 2012; 470:3195-3201.
597. Zhu Q, Qian M, Xiao J, Wu Z, Wang Y, Zhang J. Myelopathy due to calcified meningiomas of the thoracic spine: Minimum 3-year follow-up after surgical treatment. *J Neurosurg Spine* 2013; 18:436-442.
598. Pettigrew DB, Fessler RD, Farley CW, et al. Spinal cord intramedullary pressure in thoracic scoliotic deformity: A cadaveric study. *Spine (Phila Pa 1976)* 2015; 40:E242-E247.
599. Takeuchi A, Miyamoto K, Hosoe H, Shimizu K. Thoracic paraplegia due to missed thoracic compressive lesions after lumbar spinal decompression surgery - Report of three cases. *J Neurosurg* 2004; 100:71-74.
600. Mulier S, Debois V. Thoracic disc herniations: Transthoracic, lateral, or posterolateral approach? A review. *Surg Neurol* 1998; 49:599-606.
601. Kim SI, Ha KY, Lee JW, Kim YH. Prevalence and related clinical factors of thoracic ossification of the ligamentum flavum—a computed tomography-based cross-sectional study. *Spine J* 2018; 18:551-557.
602. Munigangaiah S, Maleki F, McCabe JP. Multilevel spinal stenosis at cervical, thoracic and lumbar spine: A clinical report. *Joint Bone Spine* 2012; 79:417-418.
603. Zhao BL, Ji C, Jiang JJ, Yin RF. Clinical effectiveness of treatment of combined upper thoracic spinal stenosis and multilevel cervical spinal stenosis with different posterior decompression surgeries. *Int J Surg* 2018; 55:220-223.
604. Sicard MA. Les injections medicamenteuse extradurales par voie saracoccygiene. *Comptes Rendus des Seances de la Societe de Biologie et de ses Filiales (Paris)* 1901; 53:452-453.
605. Cathelin F. Une nouvelle voie d'injection rachidienne: methode des injections epidurales par le procede du canal sacre - applications à l'homme. *Compt Rend Soc de Biol* 1901; 53:452-453.
606. Pasquier NM, Leri D. Injection intra-et extradurales de cocaine a dose minime dans le traitement de la sciaticque. *Bull Gen Ther* 1901; 142:196.
607. Ter Meulen BC, Weinstein H, Ostelo R, Koehler PJ. The epidural treatment of sciatica: Its origin and evolution. *Eur Neurol* 2016; 75:58-64.
608. Steimlé R, Jean A, Sicard (1872-1929). *J Neurol* 2013; 260:1946-1947.
609. Cyriax J. Epidural local anaesthesia. In: *Textbook of Orthopaedic Medicine*. Vol 1, 8th ed. Harcourt Publishers, New York, 1982, pp 310-27.
610. Evans W. Intracanal epidural injection in the treatment of sciatica. *Lancet* 1930; 2:1225-1229.
611. Singh V, Manchikanti L. Role of caudal epidural injections in the management of chronic low back pain. *Pain Physician* 2002; 5:133-148.
612. Robecchi A, Capra R. Hydrocortisone (compound F); first clinical experiments in the field of rheumatology. *Minerva Med* 1952; 98:1259-1263.
613. Lievre JA, Bloch-Mechel H, Pean G. L'hydrocortisone en injection locale. *Rev Rhum* 1953; 20:310-311.
614. Manchikanti L, Singh V, Pampati V, Falco FJE, Hirsch JA. Comparison of the efficacy of caudal, interlaminar, and transforaminal epidural injections in managing lumbar disc herniation: Is one method superior to the other? *Korean J Pain* 2015; 28:11-21.
615. Chang Chien GC, Knezevic NN, McCormick Z, Chu SK, Trescott AM, Candido KD. Transforaminal versus interlaminar approaches to epidural steroid injections: A systematic review of comparative studies for lumbosacral radicular pain. *Pain Physician* 2014; 17:E509-E524.
616. Candido KD, Raghavendra MS, Chinthagada M, Badiie S, Trepashko DW. 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.
617. 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; 17:277-290.
618. 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; 91:1039-1050.
619. Maadawy AAE, Mazy A, Adrosy MEMME, El-Mitwalli AA, Naby AMAE, Gomma M. A comparative study between interlaminar nerve root targeted epidural versus infraneural transforaminal epidural steroids for treatment of intervertebral disc herniation. *Saudi J Anaesth* 2018; 12:599-605.
620. Arici T, Kurçaloğlu M, Eyiğor C, Uyar M. Transforaminal epidural steroid injection and infraneural approach. *Agri* 2019; 31:104-106.
621. Levi D, Horn S, Corcoran S. The incidence of intradiscal, intrathecal,



- and intravascular flow during the performance of retrodiscal (infraneural) approach for lumbar transforaminal epidural steroid injections. *Pain Med* 2016; 17:1416-1422.
622. Munjupong S, Kumnerdee W. Effect of supraneural transforaminal epidural steroid injection combined with caudal epidural steroid injection with catheter in chronic radicular pain management: Double blinded randomized controlled trial. *F1000Res* 2020; 9:634.
623. Atluri S, Glaser SE, Shah RV, Sudarshan G. Needle position analysis in cases of paralysis from transforaminal epidurals: Consider alternative approaches to traditional techniques. *Pain Physician* 2013; 16:321-334.
624. Glaser SE, Falco FJE. Paraplegia following a thoracolumbar transforaminal epidural steroid injection. *Pain Physician* 2005; 8:309-314.
625. Simon JI, McAuliffe M, Parekh NN, Petrolla J, Furman MB. Intravascular penetration following lumbar transforaminal epidural injections using the infraneural technique. *Pain Med* 2015; 16:1647-1649.
626. Ludwig MA, Burns SP. Spinal cord infarction following cervical transforaminal epidural injection: A case report. *Spine (Phila Pa 1976)* 2005; 30:E266-E268.
627. Beckman WA, Mendez RJ, Paine GF, Mazzilli MA. Cerebellar herniation after cervical transforaminal epidural injection. *Reg Anesth Pain Med* 2006; 31:282-285.
628. Wallace MA, Fukui MB, Williams RL, Ku A, Baghai P. Complications of cervical selective nerve root blocks performed with fluoroscopic guidance. *AJR Am J Roentgenol* 2007; 188:1218-1221.
629. Rozin L, Rozin R, Koehler SA, 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.
630. 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; 91:397-399.
631. U.S. Food and Drug Administration. Drug Safety Communications. FDA Drug Safety Communication: FDA requires label changes to warn of rare but serious neurologic problems after epidural corticosteroid injections for pain, April 23, 2014. Accessed 11/23/2020. [www.fda.gov/downloads/Drugs/DrugSafety/UCM394286.pdf](http://www.fda.gov/downloads/Drugs/DrugSafety/UCM394286.pdf)
632. 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; 122:974-984.
633. Manchikanti L, Candido KD, Singh V, et al. Epidural steroid warning controversy still dogging FDA. *Pain Physician* 2014; 17:E451-E474.
634. Manchikanti L, Bakhit CE. Percutaneous lysis of epidural adhesions. *Pain Physician* 2000; 3:46-64.
635. Nicol GD, Klingberg DK, Vasko MR. Prostaglandin E2 enhances calcium conductance and stimulates release of substance P in avian sensory neurons. *J Neurosci* 1992; 12:1917-1927.
636. Coderre T. Contribution of protein kinase C to central sensitization and persistent pain following tissue injury. *Neurosci Lett* 1992; 140:181-184.
637. Hayashi N, Weinstein JN, Meller ST, et al. The effect of epidural injection of betamethasone or bupivacaine in a rat model of lumbar radiculopathy. *Spine (Phila Pa 1976)* 1998; 23:877-885.
638. Lee HM, Weinstein JN, Meller ST, et al. The role of steroids and their effects on phospholipase A2. An animal model of radiculopathy. *Spine (Phila Pa 1976)* 1998; 23:1191-1196.
639. Manchikanti L. Role of neuraxial steroids in interventional pain management. *Pain Physician* 2002; 5:182-199.
640. Goppelt-Strube M. Molecular mechanisms involved in the regulation of prostaglandin biosynthesis by glucocorticoids. *Biochem Pharmacol* 1997; 53:1389-1395.
641. Devor M, Govrin-Lippmann R, Raber P. Corticosteroids suppress ectopic neural discharge originating in experimental neuromas. *Pain* 1985; 22:127-137.
642. Ryan MD, Taylor TKF. Management of lumbar nerve root pain. *Med J Aust* 1981; 2:532-534.
643. Olmarker K, Byrod G, Cornefjord M, et al. Effects of methylprednisolone on nucleus pulposus-induced nerve root injury. *Spine (Phila Pa 1976)* 1994; 19:1803-1808.
644. Minamide A, Tamaki T, Hashizume H, et al. Effects of steroids and lipopolysaccharide on spontaneous resorption of herniated intervertebral discs. An experience study in the rabbit. *Spine (Phila Pa 1976)* 1998; 23:870-876.
645. Johansson A, Bennett GJ. Effect of local methylprednisolone on pain in a nerve injury model. A pilot study. *Reg Anesth* 1997; 22:59-65.
646. Kingery WS, Castellote JM, Maze M. Methylprednisolone prevents the development of autotomy and neuropathic edema in rats, but has no effect on nociceptive thresholds. *Pain* 1999; 80:555-566.
647. Hollander JL, Stoner EK, Brown EM Jr, DeMoor P. Joint temperature measurement in the evaluation of anti-arthritis agents. *J Clin Invest* 1951; 30:701-706.
648. Lindahl O, Rexed B. Histological changes in spinal nerve roots of operated cases of sciatica. *Acta Orthop Scand* 1950; 20:215-225.
649. Scuderi GJ, Brusovanik GV, Anderson DG, et al. Cytokine assay of the epidural space lavage in patients with lumbar intervertebral disk herniation and radiculopathy. *J Spinal Disord Tech* 2006; 19:266-269. Erratum in: *J Spinal Disord Tech* 2006; 19:463.
650. de Souza Grava AL, Ferrari LF, Defino HL. Cytokine inhibition and time-related influence of inflammatory stimuli on the hyperalgesia induced by the nucleus pulposus. *Eur Spine J* 2012; 21:537-545.
651. Shamji MF, Allen KD, So S, et al. Gait abnormalities and inflammatory cytokines in an autologous nucleus pulposus model of radiculopathy. *Spine (Phila Pa 1976)* 2009; 34:648-654.
652. Cuéllar JM, Borges PM, Cuéllar VG, Yoo A, Scuderi GJ, Yeomans DC. Cytokine expression in the epidural space: A model of noncompressive disc herniation-induced inflammation. *Spine (Phila Pa 1976)* 2013; 38:17-23.
653. Brisby H, Olmarker K, Larsson K, Nutu M, Rydevik B. Proinflammatory cytokines in cerebrospinal fluid and serum in patients with disc herniation and sciatica. *Eur Spine J* 2002; 11:62-66.
654. O'Neill CW, Kurgansky ME, Derby R, Ryan DP. Disc stimulation and patterns of referred pain. *Spine (Phila Pa 1976)* 2002; 27:2776-2781.
655. Crock HV. Isolated lumbar disc resorption as a cause of nerve root canal stenosis. *Clin Orthop* 1976; 115:109-115.
656. Holm S, Holm AK, Ekstrom L, Karladani A, Hansson T. Experimental disc degeneration due to endplate injury. *J Spinal Disord Tech* 2004; 17:64-71.
657. Aoki Y, Ohtori S, Ino H, et al. Disc inflammation potentially promotes axonal regeneration of dorsal root ganglion neurons innervating lumbar intervertebral disc in rats. *Spine (Phila Pa*

- 1976) 2004; 29:2621-2626.
658. Hayashi Y, Ohtori S, Yamashita M, et al. Direct single injection of p38 mitogen-activated protein kinase inhibitor does not affect calcitonin gene-related peptide expression in dorsal root ganglion neurons innervating punctured discs in rats. *Spine (Phila Pa 1976)* 2009; 34:2843-2847.
659. Kim NR, Lee JW, Jun SR, et al. Effects of epidural TNF- $\alpha$  inhibitor injection: Analysis of the pathological changes in a rat model of chronic compression of the dorsal root ganglion. *Skeletal Radiol* 2012; 41:539-545.
660. Cohen SP, Bogduk N, Dragovich A, et al. Randomized, double-blind, placebo-controlled, dose-response, and preclinical safety study of transforaminal epidural etanercept for the treatment of sciatica. *Anesthesiology* 2009; 110:1116-1126.
661. Tobinick E, Davoodifar S. Efficacy of etanercept delivered by perispinal administration for chronic back and/or neck disc-related pain: A study of clinical observations in 143 patients. *Curr Med Res Opin* 2004; 20:1075-1085.
662. Okoro T, Tafazal SI, Longworth S, Sell PJ. Tumor necrosis alpha-blocking agent (etanercept): A triple blind randomized controlled trial of its use in treatment of sciatica. *J Spinal Disord Tech* 2010; 23:74-77.
663. Genevay S, Viatte S, Finckh A, Zufferey P, Balagué F, Gabay C. Adalimumab in severe and acute sciatica: A multicenter, randomized, double-blind, placebo-controlled trial. *Arthritis Rheum* 2010; 62:2339-2346.
664. Korhonen T, Karppinen J, Paimela L, et al. The treatment of disc-herniation-induced sciatica with infliximab: One-year follow-up results of FIRST II, a randomized controlled trial. *Spine (Phila Pa 1976)* 2006; 31:2759-2766.
665. Cohen SP, Wenzell D, Hurley RW, et al. A double-blind, placebo-controlled, dose response pilot study evaluating intradiscal etanercept in patients with chronic discogenic low back pain or lumbosacral radiculopathy. *Anesthesiology* 2007; 107:99-105.
666. Ohtori S, Miyagi M, Eguchi Y, et al. Epidural administration of spinal nerves with the tumor necrosis factor-alpha inhibitor, etanercept, compared with dexamethasone for treatment of sciatica in patients with lumbar spinal stenosis: A prospective randomized study. *Spine (Phila Pa 1976)* 2012; 37:439-444.
667. Jing S, Yang C, Zhang X, Wen S, Li Y. Efficacy and safety of etanercept in the treatment of sciatica: A systematic review and meta-analysis. *J Clin Neurosci* 2017; 44:69-74.
668. Berg A. Clinical and myelographic studies of conservatively treated cases of lumbar intervertebral disc protrusion. *Acta Chir Scand* 1953; 104:124-129.
669. Green LN. Dexamethasone in the management of symptoms due to herniated lumbar disc. *J Neurol Neurosurg Psychiatry* 1975; 38:1211-1217.
670. 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 34:1638-1643.
671. Fowler RJ, Blackwell GJ. Anti-inflammatory steroid induced biosynthesis of a phospholipase A2 inhibitor which prevents prostaglandin generation. *Nature* 1979; 278:456-459.
672. Svensson CI, Lucas KK, Hua XY, Powell HC, Dennis EA, Yaksh TL. Spinal phospholipase A2 in inflammatory hyperalgesia: Role of the small, secretory phospholipase A2. *Neuroscience* 2005; 133:543-553.
673. Hua SY, Chen YZ. Membrane receptor-mediated electrophysiological effects of glucocorticoid on mammalian neurons. *Endocrinology* 1989; 124:687-691.
674. Johansson A, Hao J, Sjolund B. Local corticosteroid application blocks transmission in normal nociceptor C fibers. *Acta Anaesthesiol Scand* 1990; 34:335-338.
675. Hayashi N, Weinstein JN, Meller ST, Lee HM, Spratt KF, Gebhart GF. The effect of epidural injection of betamethasone or bupivacaine in a rat model of lumbar radiculopathy. *Spine (Phila Pa 1976)* 1998; 23:877-885.
676. Minamide A, Hashizume H, Yoshida M, Kawakami M, Hayashi N, Tamaki T. Effects of basic fibroblast growth factor on spontaneous resorption of herniated intervertebral discs. An experimental study in the rabbit. *Spine (Phila Pa 1976)* 1999; 24:940-945.
677. Minamide A, Tamaki T, Hashizume H, Yoshida M, Kawakami M, Hayashi N. Effects of steroid and lipopolysaccharide on spontaneous resorption of herniated intervertebral discs. An experimental study in the rabbit. *Spine (Phila Pa 1976)* 1998; 23:870-876.
678. Hasegawa T, An HS, Inufusa A, Mikawa Y, Watanabe R. The effect of age on inflammatory responses and nerve root injuries after lumbar disc herniation: an experimental study in a canine model. *Spine (Phila Pa 1976)* 2000; 25:937-940.
679. Lundin A, Magnuson A, Axelsson K, Nilsson O, Samuelsson L. Corticosteroids preoperatively diminishes damage to the C-fibers in microscopic lumbar disc surgery. *Spine (Phila Pa 1976)* 2005; 30:2362-2367.
680. Byrod G, Otani K, Brisby H, Rydevik B, Olmarker K. Methylprednisolone reduces the early vascular permeability increase in spinal nerve roots induced by epidural nucleus pulposus application. *J Orthop Res* 2000; 18:983-987.
681. Kartha S, Weisshaar CL, Philips BH, Winkelstein BA. Pre-treatment with meloxicam prevents the spinal inflammation and oxidative stress in DRG neurons that accompany painful cervical radiculopathy. *Neuroscience* 2018; 388:393-404.
682. Kawakami M, Tamaki T, Hayashi N, Hashizume H, Nishi H. Possible mechanism of painful radiculopathy in lumbar disc herniation. *Clin Orthop Relat Res* 1998; 351:241-251.
683. Hasegawa T, An HS, Inufusa A, Mikawa Y, Watanabe R. The effect of age on inflammatory responses and nerve root injuries after lumbar disc herniation: an experimental study in a canine model. *Spine (Phila Pa 1976)* 2000; 25:937-940.
684. Hollander JL, Moore R. Studies in osteo-arthritis using intra-articular temperature response to injection of hydrocortisone acetate and prednisone. *Ann Rheum Dis* 1956; 15:320-326.
685. Tuffer T. Anesthésie medullaire chirurgicale par injection sousarachnoïdienne lombaire de cocaine; technique et résultats. *Semaine Médicale* 1900; 20:167.
686. Cushing H. On the avoidance of shock in major amputations by cocainization of large nerve-trunks preliminary to their division. *Ann Surg* 1902; 36:321.
687. Schloesser H. Heilung periphärer Reizzustände sensibler und motorischer Nerven. *Klin Monatsbl Augenheilkd* 1903; 41:255.
688. Dogliotti AM. Segmental peridural anesthesia. *Am J Surg* 1933; 20:107-118.
689. Manchikanti L, Kosanovic R, Cash KA, et al. Assessment of prevalence of cervical facet joint pain with diagnostic cervical medial branch blocks: Analysis based on chronic pain model. *Pain Physician* 2020; 23:531-540.
690. Manchikanti L, Kosanovic R, Pampati

- V, et al. Low back pain and diagnostic lumbar facet joint nerve blocks: Assessment of prevalence, false-positive rates, and a philosophical paradigm shift from an acute to a chronic pain model. *Pain Physician* 2020; 23:519-530.
691. Sato C, Sakai A, Ikeda Y, Suzuki H, Sakamoto A. The prolonged analgesic effect of epidural ropivacaine in a rat model of neuropathic pain. *Anesth Analg* 2008; 106:313-320.
692. Tachihara H, Sekiguchi M, Kikuchi S, Konno S. Do corticosteroids produce additional benefit in nerve root infiltration for lumbar disc herniation. *Spine (Phila Pa 1976)* 2008; 33:743-747.
693. Mao J, Chen LL. Systemic lidocaine for neuropathic pain relief. *Pain* 2000; 87:7-17.
694. Ferrante FM, Paggioli J, Cherukuri S, Arthru GR. The analgesic response to intravenous lidocaine in the treatment of neuropathic pain. *Anesth Analg* 1996; 82:91-97.
695. Lavoie PA, Khazen T, Filion PR. Mechanisms of the inhibition of fast axonal transport by local anesthetics. *Neuropharmacology* 1989; 28:175-181.
696. Bisby MA. Inhibition of axonal transport in nerves chronically treated with local anesthetics. *Exp Neurol* 1975; 47:481-489.
697. Pasqualucci A. Experimental and clinical studies about the preemptive analgesia with local anesthetics. Possible reasons of the failure. *Minerva Anesthesiol* 1998; 64:445-457.
698. Arner S, Lindblom U, Meyerson BA, Molander C. Prolonged relief of neuralgia after regional anesthetic block. A call for further experimental and systematic clinical studies. *Pain* 1990; 43:287-297.
699. Hamaya C, Barr T, Strichartz GR. Multiple inhibitory mechanisms of lidocaine on bradykinin receptor activity in model sensory neurons. *Reg Anesth Pain Med* 2018; 43:605-612.
700. Deyo RA, Rainville J, Kent DL. What can the history and physical examination tell us about low back pain? *JAMA* 1992; 268:760-765.
701. Andersson GB, Deyo RA. History and physical examination in patients with herniated lumbar discs. *Spine (Phila Pa 1976)* 1996; 21:105-185.
702. Solomon J, Nadler SF, Press J. Physical examination of the lumbar spine. In: Malanga GA, Nadler SF (eds). *Musculoskeletal Physical Examination: An Evidence-Based Approach*. Elsevier Mosby, Philadelphia, pp 189-226.
703. Rubinstein SM, van Tulder M. A best-evidence review of diagnostic procedures for neck and low-back pain. *Best Pract Res Clin Rheumatol* 2008; 22:471-482.
704. van der Windt DA, Simons E, Riphagen II, et al. Physical examination for lumbar radiculopathy due to disc herniation in patients with low-back pain. *Cochrane Database Syst Rev* 2010; 2:CD007431.
705. Tawa N, Rhoda A, Diener I. Accuracy of clinical neurological examination in diagnosing lumbo-sacral radiculopathy: A systematic literature review. *BMC Musculoskelet Disord* 2017; 18:93.
706. Bellier A, Latreche A, Tissot L, Robert Y, Chaffanjon P, Palombi O. Movements of the lumbo-sacral nerve roots in the spinal canal induced by straight leg raising test: An anatomical study. *Surg Radiol Anat* 2018; 40:1223-1230.
707. Majlesi J, Togay H, Unalan H, Toprak S. The sensitivity and specificity of the Slump and the Straight Leg Raising tests in patients with lumbar disc herniation. *J Clin Rheumatol* 2008; 14:87-91.
708. Albert HB, Hansen JK, Søggaard H, Kent P. Where do patients with MRI-confirmed single-level radiculopathy experience pain, and what is the clinical interpretability of these pain patterns? A cross-sectional diagnostic accuracy study. *Chiropr Man Therap* 2019; 27:50.
709. Kerr RS, Cadoux-Hudson TA, Adams CB. The value of accurate clinical assessment in the surgical management of the lumbar disc protrusion. *J Neurol Neurosurg Psychiatry* 1988; 51:169-173.
710. Thornbury JR, Fryback DG, Turski PA, et al. Discussed nerve compression in patients with acute low back pain: Diagnosis with MR, CT myelography, and plain CT. *Radiology* 1993; 186:731-738.
711. Wiesel SW, Tsourmas N, Feffer HL, et al. A study of computer-assisted tomography: I: The incidence of positive CAT scans in an asymptomatic group of patients. *Spine (Phila Pa 1976)* 1984; 9:549-551.
712. Boden SD, Davis DO, Dina TS, et al. Abnormal magnetic resonance scans of the lumbar spine in asymptomatic subjects. *J Bone Joint Surg Am* 1990; 72:403-408.
713. Jensen MC, Bran-Zawadzki MN, Obuchowski N, et al. Magnetic resonance imaging of the lumbar spine in people without back pain. *N Engl J Med* 1994; 331:69-73.
714. Bogduk N, Govind J. Imaging. In: *Medical Management of Acute Lumbar Radicular Pain: An Evidence-Based Approach*. Cambridge Press, Newcastle, 1999, pp 43-51.
715. Li Y, Fredrickson V, Resnick DK. How should we grade lumbar disc herniation and nerve root compression? A systematic review. *Clin Orthop Relat Res* 2015; 473:1896-1902.
716. Hajiahmadi S, Shayganfar A, Askari M, Ebrahimian S. Interobserver and intraobserver variability in magnetic resonance imaging evaluation of patients with suspected disc herniation. *Heliyon* 2020; 6:e05201.
717. Andersson GB, Brown MD, Dvorak J, et al. Consensus summary on the diagnosis and treatment of lumbar disc herniation. *Spine (Phila Pa 1976)* 1996; 21:75S-78S.
718. Jensen RK, Kongsted A, Kjaer P, Koes B. Diagnosis and treatment of sciatica. *BMJ* 2019; 367:l6273.
719. Malanga GA, Landes P, Nadler SF. Provocative tests in cervical spine examination: Historical basis and scientific analyses. *Pain Physician* 2003; 6:199-205.
720. Rubenstein S, Pool J, Tulder M, Riphagen I, deVet H. A systematic review of the diagnostic accuracy of provocative tests of the neck for diagnosing cervical radiculopathy. *Eur Spine J* 2007; 16:307-319.
721. Bogduk N. Clinical Features. In: *Medical Management of Acute Cervical Radicular Pain: An Evidence-Based Approach*. 1st Edition. Cambridge Press, Newcastle, 1999, pp 19-34.
722. Bogduk N. Physical Examination. In: *Medical Management of Acute Cervical Radicular Pain: An Evidence-Based Approach*. 1st Edition. Cambridge Press, Newcastle, 1999, pp 35-50.
723. Heckmann JG, Lang CJG, Zöbelien I, Laumer R, Druschky A, Neundörfer B. Herniated cervical intervertebral discs with radiculopathy: An outcome study of conservatively or surgically treated patients. *J Spinal Disord* 1999; 12:396-401.
724. Wainner RS, Gill H. Diagnosis and nonoperative management of cervical radiculopathy. *J Orthop Sports Phys Ther* 200; 30:728-744.
725. Noe C, Racz G. Cervical radicular pain. In: Khelemsky Y, Malhotra A, Gritsenko K, (eds). *Academic Pain Medicine: A Practical Guide to Rotation, Fellowship, and Beyond*. Springer, New York, 2019, pp 211-218.

726. American College of Radiology. ACR Appropriateness Criteria. Chronic neck pain. Accessed 12/08/2020. <https://acsearch.acr.org/docs/69426/Narrative/>
727. Bogduk N. Imaging. In: *Medical Management of Acute Cervical Radicular Pain: An Evidence-Based Approach*. 1st Edition. Cambridge Press, Newcastle, 1999, pp 61-66.
728. Modic MT, Masaryk TJ, Mulopulos GP, Bundschuh C, Han JS, Bohlman H. Cervical radiculopathy: Prospective evaluation with surface coil MR imaging, CT with metrizamide, and metrizamide myelography. *Radiology* 1986; 161:753-759.
729. Wang XR, Kwok TCY, Griffith JF, Man Yu BW, Leung JCS, Wang YXJ. Prevalence of cervical spine degenerative changes in elderly population and its weak association with aging, neck pain, and osteoporosis. *Ann Transl Med* 2019; 7:486.
730. Narayanaswami P, Geisbush T, Jones L, Weiss M, Mozaffar T, Rutkove S. Confirmation bias and specificity of electromyography for radiculopathy. *Neurology* 2015; 84:164.
731. Bokshan SL, DePasse JM, Eltorai AE, Paxton ES, Green A, Daniels AH. An evidence-based approach to differentiating the cause of shoulder and cervical spine pain. *Am J Med* 2016; 129:913-918.
732. Onyewu O, Manchikanti L, Singh V, et al. An update of the appraisal of the accuracy and utility of cervical discography in chronic neck pain. *Pain Physician* 2012; 15:E777-E806.
733. Malhotra G, Abbasi A, Rhee M. Complications of transforaminal cervical epidural steroid injections. *Spine (Phila Pa 1976)* 2009; 34:731-739.
734. Madhugiri VS, Gundamaneni SK, Yadav AK, Sasidharan GM, Roopesh Kumar VR, Shankar Ganesh CV. Intradural thoracic disc presenting with radiculopathy. *Neurol India* 2012; 60:257-259.
735. Mankin JM, Hecht S, Thomas WB. Agreement between T2 and haste sequences in the evaluation of thoracolumbar intervertebral disc disease in dogs. *Vet Radiol Ultrasound* 2012; 53:162-166.
736. Matsumoto M, Okada E, Ichihara D, et al. Age-related changes of thoracic and cervical intervertebral discs in asymptomatic subjects. *Spine (Phila Pa 1976)* 2010; 35:1359-1364.
737. Wood KB, Garvey TA, Gundry C, Heithoff KB. Magnetic resonance imaging of the thoracic spine. Evaluation of asymptomatic individuals. *J Bone Joint Surg Am* 1995; 77:1631-1638.
738. Zhai J, Zhang L, Li M, et al. Epidural injection with or without steroid in managing chronic low back and lower extremity pain: A meta-analysis of ten randomized controlled trials. *Int J Clin Exp Med* 2015; 8:8304-8316.
739. Yang S, Kim W, Kong HH, Do KH, Choi KH. Epidural steroid injection versus conservative treatment for patients with lumbosacral radicular pain: A meta-analysis of randomized controlled trials. *Medicine (Baltimore)* 2020; 99:e21283.
740. Wei G, Liang J, Chen B, et al. Comparison of transforaminal versus interlaminar epidural steroid injection in low back pain with lumbosacral radicular pain: A meta-analysis of the literature. *Int Orthop* 2016; 40:2533-2545.
741. Vorobeychik Y, Sharma A, Smith CC, et al. The effectiveness and risks of non-image-guided lumbar interlaminar epidural steroid injections: A systematic review with comprehensive analysis of the published data. *Pain Med* 2016; 17:2185-2202.
742. 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; 21:472-487.
743. Sharma AK, Vorobeychik Y, Wasserman R, et al. 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; 18:239-251.
744. Pairuchvej S, Arirachakaran A, Keorochana G, et al. The short and midterm outcomes of lumbar transforaminal epidural injection with preganglionic and postganglionic approach in lumbosacral radiculopathy: A systematic review and meta-analysis. *Neurosurg Rev* 2018; 41:909-916.
745. Mehta P, Syrop I, Singh JR, Kirschner J. Systematic review of the efficacy of particulate versus nonparticulate corticosteroids in epidural injections. *PM R* 2017; 9:502-512.
746. Bensler S, Sutter R, Pfirrmann CWA, Peterson CK. Is there a difference in treatment outcomes between epidural injections with particulate versus non-particulate steroids? *Eur Radiol* 2017; 27:1505-1511.
747. Feeley IH, Healy EF, Noel J, Kiely PJ, Murphy TM. Particulate and non-particulate steroids in spinal epidurals: A systematic review and meta-analysis. *Eur Spine J* 2017; 26:336-344.
748. Makkar JK, Singh PM, Jain D, Goudra B. Particulate vs non-particulate steroids for transforaminal epidural steroid injections: Systematic review and meta-analysis of the current literature. *Pain Physician* 2016; 19:327-340.
749. Bui J, Bogduk N. A systematic review of the effectiveness of CT-guided, lumbar transforaminal injection of steroids. *Pain Med* 2013; 14:1860-1865.
750. Meng H, Fei Q, Wang B, et al. Epidural injections with or without steroids in managing chronic low back pain secondary to lumbar spinal stenosis: A meta-analysis of 13 randomized controlled trials. *Drug Des Devel Ther* 2015; 9:4657-4667.
751. Liu K, Liu P, Liu R, Wu X, Cai M. Steroid for epidural injection in spinal stenosis: A systematic review and meta-analysis. *Drug Des Devel Ther* 2015; 9:707-716.
752. Liu J, Zhou H, Lu L, et al. The effectiveness of transforaminal versus caudal routes for epidural steroid injections in managing lumbosacral radicular pain: A systematic review and meta-analysis. *Medicine (Baltimore)* 2016; 95:e3373.
753. Lee JH, Choi KH, Kang S, et al. Nonsurgical treatments for patients with radicular pain from lumbosacral disc herniation. *Spine J* 2019; 19:1478-1489.
754. Bhatia A, Flamer D, Shah PS, Cohen SP. Transforaminal epidural steroid injections for treating lumbosacral radicular pain from herniated intervertebral discs: A systematic review and meta-analysis. *Anesth Analg* 2016; 122:857-870.
755. 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; 21:41-54.
756. Arirachakaran A, Siripaiboonkij M, Pairuchvej S, et al. Comparative outcomes of epidural steroids versus placebo after lumbar discectomy in lumbar disc herniation: A systematic review and meta-analysis of randomized controlled trials. *Eur J Orthop Surg Traumatol* 2018; 28:1589-1599.
757. Manchikanti L, Cash KA, McManus



- CD, Pampati V, Smith HS. Preliminary results of a randomized, equivalence trial of fluoroscopic caudal epidural injections in managing chronic low back pain: Part 1--Discogenic pain without disc herniation or radiculitis. *Pain Physician* 2008; 11:785-800.
758. Manchikanti L, Singh V, Cash KA, Pampati V, Damron KS, Boswell MV. Preliminary results of a 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.
759. Manchikanti L, Singh V, Cash KA, Pampati V, Datta S. Preliminary results of a 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.
760. Manchikanti L, Cash KA, McManus CD, Pampati V, Abdi S. Preliminary results of a randomized, equivalence trial of fluoroscopic caudal epidural injections in managing chronic low back pain: Part 4--Spinal stenosis. *Pain Physician* 2008; 11:833-848.
761. Manchikanti L, Singh V, Cash KA, Pampati V, Damron KS, Boswell MV. A randomized, controlled, double-blind trial of fluoroscopic caudal epidural injections in the treatment of lumbar disc herniation and radiculitis. *Spine (Phila Pa 1976)* 2011; 36:1897-1905.
762. Manchikanti L, Cash KA, McManus CD, Pampati V, Smith HS. One year results of a randomized, double-blind, active controlled trial of fluoroscopic caudal epidural injections with or without steroids in managing chronic discogenic low back pain without disc herniation or radiculitis. *Pain Physician* 2011; 14:25-36.
763. Manchikanti L, Singh V, Cash KA, Pampati V, Datta S. Management of pain of post lumbar surgery syndrome: One-year results of a randomized, double-blind, active controlled trial of fluoroscopic caudal epidural injections. *Pain Physician* 2010; 13:509-521.
764. Manchikanti L, Cash KA, McManus CD, Pampati V, Fellows B. Fluoroscopic caudal epidural injections with or without steroids in managing pain of lumbar spinal stenosis: One-year results of randomized, double-blind, active-controlled trial. *J Spinal Disord Tech* 2012; 25:226-234.
765. Manchikanti L, Singh V, Cash KA, Pampati V, Damron KS, Boswell MV. Effect of fluoroscopically guided caudal epidural steroid or local anesthetic injections in the treatment of lumbar disc herniation and radiculitis: A randomized, controlled, double blind trial with a two-year follow-up. *Pain Physician* 2012; 15:273-286.
766. Manchikanti L, Singh V, Cash KA, Pampati V, Datta S. Fluoroscopic caudal epidural injections in managing post lumbar surgery syndrome: Two-year results of a randomized, double-blind, active-control trial. *Int J Med Sci* 2012; 9:582-591.
767. Manchikanti L, Cash KA, McManus CD, Pampati V, Fellows B. 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.
768. Zahaar MS. The value of caudal epidural steroids in the treatment of lumbar neural compression syndromes. *J Neurol Orthop Med Surg* 1991; 12:181-184.
769. 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:RC05-11.
770. Kamble PC, Sharma A, Singh V, Natraj B, Devani D, Khapane V. Outcome of single level disc prolapse treated with transforaminal steroid versus epidural steroid versus caudal steroids. *Eur Spine J* 2016; 25:217-221.
771. Yin M, Mo W, Wu H, et al. Efficacy of caudal epidural steroid injection with targeted indwelling catheter and manipulation in managing patients with lumbar disk herniation and radiculopathy: A prospective, randomized, single-blind controlled trial. *World Neurosurg* 2018; 114:e29-e34.
772. Akkaya T, Ozkan D, Kertmen H, Sekerci Z. Caudal epidural steroid injections in postlaminectomy patients: Comparison of ultrasonography and fluoroscopy. *Turk Neurosurg* 2017; 27:420-425.
773. Park Y, Lee JH, Park KD, Ahn JK, Park J, Jee H. Ultrasound-guided vs. fluoroscopy-guided caudal epidural steroid injection for the treatment of unilateral lower lumbar radicular pain: A prospective, randomized, single-blind clinical study. *Am J Phys Med Rehabil* 2013; 92:575-586.
774. Cervera-Irímia J, Tomé-Bermejo F. Caudal epidural steroid injection in the treatment of chronic discogenic low back pain. Comparative, prospective and randomized study. *Rev Esp Cir Ortop Traumatol* 2013; 57:324-332.
775. Nandi J, Chowdhery A. A randomized controlled clinical trial to determine the effectiveness of caudal epidural steroid injection in lumbosacral sciatica. *J Clin Diagn Res* 2017; 11:RC04-RC08.
776. Datta R, Upadhyay KK. A randomized clinical trial of three different steroid agents for treatment of low backache through the caudal route. *Med J Armed Forces India* 2011; 67:25-33.
777. McCahon RA, Ravenscroft A, Hodgkinson V, Evley R, Hardman J. A pilot study of the dose-response of caudal methylprednisolone with levobupivacaine in chronic lower back pain. *Anaesthesia* 2011; 66:595-603.
778. McGregor AH, Anjarwalla NK, Stambach T. Does the method of injection alter the outcome of epidural injections? *J Spinal Disord* 2001; 14:507-510.
779. Singh S, Kumar S, Chahal G, Verma R. Selective nerve root blocks vs. caudal epidural injection for single level prolapsed lumbar intervertebral disc - A prospective randomized study. *J Clin Orthop Trauma* 2017; 8:142-147.
780. Czarski Z. Treatment of sciatica with hydrocortisone and Novocaine injections into the sacral hiatus. *Przeegl Lek* 1965; 21:511-513.
781. Breivik H, Hesla PE, 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. In: Bonica JJ, Albe-Fessard D, (eds). *Advances in Pain Research and Therapy*. Raven Press, New York, 1976, pp 927-932.
782. Sayegh FE, Kenanidis EI, Papavasiliou KA, Potoupnis ME, Kirkos JM, Kapetanos GA. Efficacy of steroid and nonsteroid caudal epidural injections for low back pain and sciatica: A prospective, randomized, double-blind clinical trial. *Spine (Phila Pa 1976)* 2009; 34:1441-1447.
783. Ackerman WE 3rd, Ahmad M. The efficacy of lumbar epidural steroid injections in patients with lumbar disc herniations. *Anesth Analg* 2007; 104:1217-1222.
784. Dashfield A, Taylor M, Cleaver J, Farrow D. Comparison of caudal steroid epidural with targeted steroid placement during spinal endoscopy for chronic sciatica: A prospective, randomized, double-blind trial. *Br J Anaesth* 2005; 94:514-519.
785. 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:d5278.
786. Murakibhavi VG, Khemka AG. Caudal epidural steroid injection: A randomized controlled trial. *Evid Based Spine Care J* 2011; 2:19-26.
787. Revel M, Auleley GR, 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.
788. Yousef AA, EL-Deen AS, Al-Deeb AE. The role of adding hyaluronidase to fluoroscopically guided caudal steroid and hypertonic saline injection in patients with failed back surgery syndrome: A prospective, double-blinded, randomized study. *Pain Pract* 2010; 10:548-553.
789. Huda N, Bansal P, Gupta SM, Ruhela A, Rehman M, Afzal M. The efficacy of epidural depo-methylprednisolone and triamcinolone acetate in relieving the symptoms of lumbar canal stenosis: A comparative study. *J Clin Diagn Res* 2010; 4:2843-2847.
790. Gupta S, Ward S, Munglani R, Sharma M. Letter to the Editor RE: Iversen T, et al. Effect of caudal epidural steroid or saline injection in chronic lumbar radiculopathy: Multicentre, blinded, randomised controlled trial. *BMJ* 2011;343:d5278. Careful patient selection, fluoroscopy and contrast injection are needed for effective spinal injections. Published online 9/26/2011. Author's reply: Published online 9/29/2011.
791. Saripanidis S. Letter to the Editor RE: Iversen T, et al. Re: Effect of caudal epidural steroid or saline injection in chronic lumbar radiculopathy: Multicentre, blinded, randomised controlled trial. *BMJ* 2011;343:d5278. Gate control pain modulation theory invalidates the control group used in this research. Published online 10/8/2011.
792. Yland MJ. Letter to the Editor Re: Iversen T, et al. Re: Effect of caudal epidural steroid or saline injection in chronic lumbar radiculopathy: Multicentre, blinded, randomised controlled trial. *BMJ* 2011; 343:d5278. Published online 11/19/2011. Author's reply: Published online 9/29/2011.
793. Manchikanti L, Falco FJE, Pampati V, Hirsch JA. Lumbar interlaminar epidural injections are superior to caudal epidural injections in managing lumbar central spinal stenosis. *Pain Physician* 2014; 17:E691-E702.
794. Manchikanti L, Pampati V, Benyamin RM, Boswell MV. Analysis of efficacy differences between caudal and lumbar interlaminar epidural injections in chronic lumbar axial discogenic pain: Local anesthetic alone vs. local combined with steroids. *Int J Med Sci* 2015; 12:214-222.
795. Manchikanti L, Falco FJE, Pampati V, Cash KA, Benyamin RM, Hirsch JA. Cost utility analysis of caudal epidural injections in the treatment of lumbar disc herniation, axial or discogenic low back pain, central spinal stenosis, and post lumbar surgery syndrome. *Pain Physician* 2013; 16:E129-E143.
796. Manchikanti L, Singh V, Cash KA, Pampati V, Falco FJE. 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; 13:547-558.
797. Manchikanti L, Singh V, Cash KA, Pampati V, Falco FJE. A randomized, double blind, active-control trial of the effectiveness of lumbar interlaminar epidural injections in disc herniation. *Pain Physician* 2014; 17:E61-E74.
798. Manchikanti L, Cash KA, McManus CD, Damron KS, Pampati V, Falco FJ. Lumbar interlaminar epidural injections in central spinal stenosis: Preliminary results of a randomized, double-blind, active control trial. *Pain Physician* 2012; 15:51-63.
799. Manchikanti L, Cash KA, McManus CD, Damron KS, Pampati V, Falco FJE. A randomized, double-blind controlled trial of lumbar interlaminar epidural injections in central spinal stenosis: 2-year follow-up. *Pain Physician* 2015; 18:79-92.
800. Manchikanti L, Cash KA, McManus CD, Pampati V, Benyamin RM. Preliminary results of a randomized, double-blind, controlled trial of fluoroscopic lumbar interlaminar epidural injections in managing chronic lumbar discogenic pain without disc herniation or radiculitis. *Pain Physician* 2010; 13:E279-E292.
801. Manchikanti L, Cash KA, McManus CD, Pampati V, Benyamin RM. A randomized, double-blind, active-controlled trial of fluoroscopic lumbar interlaminar epidural injections in chronic axial or discogenic low back pain: Results of a 2-year follow-up. *Pain Physician* 2013; 16:E491-E504.
802. Makkar JK, Gourav KKP, Jain K, et al. Transforaminal versus lateral parasagittal versus midline interlaminar lumbar epidural steroid injection for management of unilateral radicular lumbar pain: A randomized double-blind trial. *Pain Physician* 2019; 22:561-573.
803. Hammerich A, Whitman J, Mintken P, et al. Effectiveness of physical therapy combined with epidural steroid injection for individuals with lumbar spinal stenosis: A randomized parallel-group trial. *Arch Phys Med Rehabil* 2019; 100:797-810.
804. Ghai B, Kumar K, Bansal D, Dhatt SS, Kanukula R, Batra YK. Effectiveness of parasagittal interlaminar epidural local anesthetic with or without steroid in chronic lumbosacral pain: A randomized, double-blind clinical trial. *Pain Physician* 2015; 18:237-248.
805. Koc Z, Ozcakar S, Sivrioglu K, Gurbet A, Kucukoglu S. Effectiveness of physical therapy and epidural steroid injections in lumbar spinal stenosis. *Spine (Phila Pa 1976)* 2009; 34:985-989.
806. Laiq N, Khan MN, Iqbal MJ, Khan S. Comparison of epidural steroid injections with conservative management in patients with lumbar radiculopathy. *J Coll Physicians Surg Pak* 2009; 19:539-543.
807. Mathews JA, Mills SB, Jenkins VM, et al. Back pain and sciatica: Controlled trials of manipulation, traction, sclerosant and epidural injection. *Br J Rheumatol* 1987; 26:416-423.
808. Hesla PE, Breivik H. Epidural analgesia and epidural steroid injection for treatment of chronic low back pain and sciatica. *Tidsskr Nor Laegeforen* 1979; 99:936-939.
809. Evans I, Logina I, Vanags I, Borgeat A. Ultrasound versus fluoroscopic-guided epidural steroid injections in patients with degenerative spinal diseases: A prospective, randomised study. *Eur J Anaesthesiol* 2015; 32:262-268.
810. 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.
811. Rogers P, Nash T, Schiller D, Norman J. Epidural steroids for sciatica. *Pain Clin* 1992; 5:67-72.
812. Cuckler JM, Bernini PA, Wiesel SW, Booth RE Jr, Rothman RH, Pickens GT. The use of epidural steroid in the treatment of radicular pain. *J Bone Joint Surg* 1985; 67:63-66.
813. Ridley MG, Kingsley GH, Gibson T, Grahame R. Outpatient lumbar

- epidural corticosteroid injection in the management of sciatica. *Br J Rheumatol* 1988; 27:295-299.
814. Klenerman L, Greenwood R, Davenport HT, White DC, Peskett S. Lumbar epidural injections in the treatment of sciatica. *Br J Rheumatol* 1984; 23:35-38.
815. Valat JP, Giraudeau B, Rozenberg S, et al. Epidural corticosteroid injections for sciatica: A randomised, double blind, controlled clinical trial. *Ann Rheum Dis* 2003; 62:639-643.
816. Bronfort G, Evans RL, Maiers M, Anderson AV. Spinal manipulation, epidural injections, and self-care for sciatica: A pilot study for a randomized clinical trial. *J Manipulative Physiol Ther* 2004; 27:503-508.
817. Ökmen K, Ökmen BM. The efficacy of interlaminar epidural steroid administration in multilevel intervertebral disc disease with chronic low back pain: A randomized, blinded, prospective study. *Spine J* 2017; 17:168-174.
818. Friedly JL, Comstock BA, Turner JA, et al. A randomized trial of epidural glucocorticoid injections for spinal stenosis. *N Engl J Med* 2014; 371:11-21.
819. Kraemer J, Ludwig J, Bickert U, Owczarek V, Traupe M. Lumbar epidural perineural injection: A new technique. *Eur Spine J* 1997; 6:357-361.
820. 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; 25:206-210.
821. 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; 12:1316-1321.
822. 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.
823. Amr YM. Effect of addition of epidural ketamine to steroid in lumbar radiculitis: One-year follow-up. *Pain Physician* 2011; 14:475-481.
824. Dilke TF, Burry HC, Grahame R. Extradural corticosteroid injection in the management of lumbar nerve root compression. *Br Med J* 1973; 2:635-637.
825. Pirbudak L, Karakurum G, Oner U, Gulec A, Karadasli H. Epidural corticosteroid injection and amitriptyline for the treatment of chronic low back pain associated with radiculopathy. *Pain Clinic* 2003; 15:247-253.
826. Arden NK, Price C, Reading I, et al; WEST Study Group. A multicentre randomized controlled trial of epidural corticosteroid injections for sciatica: The WEST study. *Rheumatology (Oxford)* 2005; 44:1399-1406.
827. 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.
828. Wilson-MacDonald J, Burt G, Griffin D, Glynn C. Epidural steroid injection for nerve root compression: A randomized, controlled trial. *J Bone Joint Surg Br* 2005; 87:352-355.
829. Fukusaki M, Kobayashi I, Hara T, Sumikawa K. Symptoms of spinal stenosis do not improve after epidural steroid injection. *Clin J Pain* 1998; 14:148-151.
830. Snoek W, Weber H, Jorgensen B. Double-blind evaluation of extradural methylprednisolone for herniated lumbar disc. *Acta Orthop Scand* 1977; 48:635-641.
831. Gelalis ID, Arnaoutoglou E, Pakos EE, et al. Effect of interlaminar epidural steroid injection in acute and subacute pain due to lumbar disk herniation: A randomized comparison of 2 different protocols. *Open Orthop J* 2009; 3:121-124.
832. 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; 117:219-227.
833. Borghi B, Aurini L, White PF, et al. Long-lasting beneficial effects of periradicular injection of meloxicam for treating chronic low back pain and sciatica. *Minerva Anestesiol* 2013; 79:370-378.
834. 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; 8:119-128.
835. Serrao JM, Marks RL, Morley SJ, Goodchild CS. Intrathecal midazolam for the treatment of chronic mechanical low back pain: A controlled comparison with epidural steroid in a pilot study. *Pain* 1992; 48:5-12.
836. Rocco AG, Frank E, Kaul AF, Lipson SJ, Gallo JP. Epidural steroids, epidural morphine and epidural steroids combined with morphine in the treatment of post-laminectomy syndrome. *Pain* 1989; 36:297-303.
837. Price CM, Rogers PD, Prosser AS, Arden NK. Comparison of the caudal and lumbar approaches to the epidural space. *Ann Rheum Dis* 2000; 59:879-882.
838. Mobaleghi J, Allahdini F, Nasserli K, et al. Comparing the effects of epidural methylprednisolone acetate injected in patients with pain due to lumbar spinal stenosis or herniated disks: A prospective study. *Int J Gen Med* 2011; 4:875-878.
839. Gharibo C, Varlotta GP, Rhame EE, Liu EC, Bendo JA, Perloff MD. 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.
840. Helliwell M, Robertson J, Ellis R. Outpatient treatment of low back pain and sciatica by a single extradural corticosteroid injection. *Br J Clin Pract* 1985; 39:228-231.
841. Cocelli LP, Karakurum G, Cebesoy O, Karadasli H, Oner U. Clinical comparison of effectiveness of epidural triamcinolone and betamethasone in discal radiculalgia: A prospective, randomized study. *J Musculo Pain* 2009; 17:281-286.
842. Buttermann GR. The effect of spinal steroid injections for degenerative disc disease. *Spine J* 2004; 4:495-505.
843. Candido KD, Rana MV, Sauer R, et al. Concordant pressure paresthesia during interlaminar lumbar epidural steroid injections correlates with pain relief in patients with unilateral radicular pain. *Pain Physician* 2013; 16:497-511.
844. Manchikanti L, Candido KD, Kaye AD, et al. Randomized trial of epidural injections for spinal stenosis published in the New England Journal of Medicine: Further confusion without clarification. *Pain Physician* 2014; 17:E475-E487.
845. Andersson GB. Epidural glucocorticoid injections in patients with lumbar spinal stenosis. *N Engl J Med* 2014; 371:75-76.
846. Wang M, Serak J, Chi J. Epidural steroid injections for spinal stenosis. *Neurosurgery* 2014; 75:N16.
847. Engel AJ, Scott Kreiner D, Stojanovic MP. Finding an answer: Comments on a randomized trial of epidural glucocorticoid injections for lumbar

- spinal stenosis. *Pain Med* 2017; 18:204-210.
848. von Keudell A, Sadoghi P. A response to the New England Journal of Medicine article: A randomized trial of epidural glucocorticoid injections for spinal stenosis. *J Spinal Disord Tech* 2015; 28:76.
849. Manning DC, Hopwood MB. Corticosteroid injections for sciatica. *N Engl J Med* 1997; 337:1242; author reply 1242-1243.
850. Orlando MP, Sherman MO. Corticosteroid injections for sciatica. *N Engl J Med* 1997; 337:1242; author reply 1242-1243.
851. Raza K. Corticosteroid injections for sciatica. *N Engl J Med* 1997; 337:1241; author reply 1242-1243.
852. Gillies JH, Ward JH, Griesdale DE. Corticosteroid injections for sciatica. *N Engl J Med* 1997; 337:1242; author reply 1242-1243.
853. Manchikanti L, Pampati V, Benyamin RM, Hirsch JA. Cost utility analysis of lumbar interlaminar epidural injections in the treatment of lumbar disc herniation, central spinal stenosis, and axial or discogenic low back pain. *Pain Physician* 2017; 20:219-228.
854. Price C, Arden N, Coglán L, Rogers P. Cost-effectiveness and safety of epidural steroids in the management of sciatica. *Health Technol Assess* 2005; 9:1-58.
855. 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.
856. Karppinen J, Malmivaara A, Kurunlahti M, et al. Periradicular infiltration for sciatica: A randomized controlled trial. *Spine (Phila Pa 1976)* 2001; 26:1059-1067.
857. 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; 245:584-590.
858. 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; 30:857-862.
859. 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; 11:1654-1658.
860. 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:E489-E501.
861. Wei P, Xu Y, Yao Q, Wang L. Randomized trial of 3-drug combination for lumbar nerve root epidural injections with a TNF- $\alpha$  inhibitor in treatment of lumbar stenosis. *Br J Neurosurg* 2020; 34:168-171.
862. Denis I, Claveau G, Filiatrault M, Fugère 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; 16:1697-1708.
863. Freeman BJ, Ludbrook GL, Hall S, et al. Randomized, double-blind, placebo-controlled, trial of transforaminal epidural etanercept for the treatment of symptomatic lumbar disc herniation. *Spine (Phila Pa 1976)* 2013; 38:1986-1994.
864. Gupta AK, Mital VK, Azmi RU. Observations of the management of lumbosacral syndromes (sciatica) by epidural saline. *J Indian Med Assoc* 1970; 54:194-196.
865. Dagar A, Kumar R, Kashyap A, Prabhat V, Lal H, Kumar L. Transforaminal epidural etanercept for the treatment of prolapsed lumbar intervertebral disc induced sciatica. *J Clin Orthop Trauma* 2017; 8:148-152.
866. Cohen SP, White RL, Kurihara C, et al. Epidural steroids, etanercept, or saline in subacute sciatica: A multicenter, randomized trial. *Ann Intern Med* 2012; 156:551-559.
867. Gerszten PC, Smuck M, Rathmell JP, 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.
868. Burgher AH, Hoelzer BC, Schroeder DR, Wilson GA, Huntoon MA. Transforaminal epidural clonidine versus corticosteroid for acute lumbosacral radiculopathy due to intervertebral disc herniation. *Spine (Phila Pa 1976)* 2011; 36:E293-E300.
869. Park CH, Lee SH, Park HS. Lumbar retrodiscal versus post-ganglionic transforaminal epidural steroid injection for the treatment of lumbar intervertebral disc herniations. *Pain Physician* 2011; 14:353-360.
870. 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; 22:299-304.
871. He Y, Chen L, Xu Z, Wang J, Liu B. Lumbar transforaminal epidural block for treatment of low back pain with radicular pain. *Nan Fang Yi Ke Da Xue Xue Bao* 2020; 40:1804-1809.
872. 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; 14:361-370.
873. Gallucci M, Limbucci N, Zugaro L, et al. Sciatica: Treatment with intradiscal and intraforaminal injections of steroid and oxygen-ozone versus steroid only. *Radiology* 2007; 242:907-913.
874. Ahadian FM, McGreevy K, Schulteis G. Lumbar transforaminal epidural dexamethasone: A prospective, randomized, double-blind, dose-response trial. *Reg Anesth Pain Med* 2011; 36:572-578.
875. Buttermann GR. Treatment of lumbar disc herniation: epidural steroid injection compared with discectomy: A prospective, randomized study. *J Bone Joint Surg Am* 2004; 86:670-679.
876. Cohen SP, Hanling S, Bicket MC, et al. Epidural steroid injections compared with gabapentin for lumbosacral radicular pain: Multicenter randomized double blind comparative efficacy study. *BMJ* 2015; 350:h1748.
877. Becker C, Heidersdorf S, Drewlo S, de Rodriguez SZ, Krämer J, Willburger RE. Efficacy of epidural perineural injections with autologous conditioned serum for lumbar radicular compression: An investigator-initiated, prospective, double-blind, reference controlled study. *Spine (Phila Pa 1976)* 2007; 32:1803-1808.
878. Kolsi I, Delecrin J, Berthelot JM, Thomas L, Prost A, Maugars Y. 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.
879. Vad VB, Bhat AL, Lutz GE, Cammisa F. Transforaminal epidural steroid injections in lumbosacral radiculopathy:

- A prospective randomized study. *Spine (Phila Pa 1976)* 2002; 27:11-16.
880. Koh WU, Choi SS, Park SY, et al. Transforaminal hypertonic saline for the treatment of lumbar lateral canal stenosis: A double-blinded, randomized, active-control trial. *Pain Physician* 2013; 16:197-211.
881. 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; 18:1220-1225.
882. 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; 26:2587-2595.
883. Manchikanti L, Singh V. Periradicular infiltration for sciatica. *Spine (Phila Pa 1976)* 2002; 27:335-336.
884. Patel N. RE: Karppinen J, et al. Periradicular infiltration for sciatica. A randomized controlled trial. *Spine* 26, 1059-1067:2001. *Spine (Phila Pa 1976)* 2002; 27:1588-1589; author reply 1588-1589.
885. Manchikanti L, Boswell MV, Kaye AD, Hirsch JA. Letter to the Editor RE: Cohen SP, Hanling S, Bicket MC, et al. Epidural steroid injections compared with gabapentin for lumbosacral radicular pain: multicenter randomized double blind comparative efficacy study. *BMJ* 2015;350:h1748. *BMJ* Published online first 12 May 2015.
886. Manchikanti L, Hirsch JA. Neurological complications associated with epidural steroid injections. *Curr Pain Headache Rep* 2015; 19:482.
887. Huntoon MA. Etanercept: An epidural steroid alternative for minimally invasive treatment of radiculitis. *Anesthesiology* 2009; 110:967-969.
888. Eisenach JC, Dewan DM, Rose JC, Angelo JM. Epidural clonidine produces antinociception, but not hypotension, in sheep. *Anesthesiology* 1987; 66:496-501.
889. Okada SK, Siegel NJ. Risk of serious infections and malignancies with anti-TNF antibody therapy in rheumatoid arthritis. *JAMA* 2006; 296: 2201-2202.
890. Bongartz T, Sutton AJ, Sweeting MJ, Buchan I, Matteson EL, Montori V. Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: Systematic review and meta-analysis of rare harmful effects in randomized controlled trials. *JAMA* 2006; 295:2275-2285. Erratum in: *JAMA* 2006; 295:2482.
891. Manchikanti L, Cash KA, McManus CD, Pampati V, Singh V, Benyamin R. 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.
892. Manchikanti L, Cash KA, McManus CD, Pampati V. Assessment of effectiveness of percutaneous adhesiolysis in managing chronic low back pain secondary to lumbar central spinal canal stenosis. *Int J Med Sci* 2013; 10:50-59.
893. Manchikanti L, Singh V, Cash KA, Pampati V, Datta S. A comparative effectiveness evaluation of percutaneous adhesiolysis and epidural steroid injections in managing lumbar post surgery syndrome: A randomized, equivalence controlled trial. *Pain Physician* 2009;12:E355-E368.
894. Manchikanti L, Singh V, Cash KA, Pampati V, Datta S. Assessment of effectiveness of percutaneous adhesiolysis and caudal epidural injections in managing lumbar post surgery syndrome: A 2-year follow-up of randomized, controlled trial. *J Pain Res* 2012; 5:597-608.
895. Gerdesmeyer L, Wagenpfeil S, Birkenmaier C, et al. Percutaneous epidural lysis of adhesions in chronic lumbar radicular pain: A randomized, double-blind, placebo-controlled trial. *Pain Physician* 2013;16:185-196.
896. Chun-jing H, Hao-xiong N, Jia-xiang N. The application of percutaneous lysis of epidural adhesions in patients with failed back surgery syndrome. *Acta Cir Bras* 2012;27:357-362.
897. Manchikanti L, Rivera JJ, Pampati V, et al. One-day lumbar epidural adhesiolysis and hypertonic saline neurolysis in treatment of chronic low back pain: A randomized, double-blind trial. *Pain Physician* 2004; 7:177-186.
898. Veihelmann A, Devens C, Trouillier H, Birkenmaier C, Gerdesmeyer L, Refior HJ. Epidural neuroplasty versus physiotherapy to relieve pain in patients with sciatica: A prospective randomized blinded clinical trial. *J Orthop Sci* 2006;11:365-369.
899. Heavner JE, Racz GB, Raj P. Percutaneous epidural neuroplasty: Prospective evaluation of 0.9% NaCl versus 10% NaCl with or without hyaluronidase. *Reg Anesth Pain Med* 1999; 24:202-207.
900. Karm MH, Choi SS, Kim DH, et al. Percutaneous epidural adhesiolysis using inflatable balloon catheter and balloon-less catheter in central lumbar spinal stenosis with neurogenic claudication: A randomized controlled trial. *Pain Physician* 2018; 21:593-606.
901. Akbas M, Elawamy AR, Salem HH, Fouad AZ, Abbas NA, Dagistan G. Comparison of 3 approaches to percutaneous epidural adhesiolysis and neuroplasty in post lumbar surgery syndrome. *Pain Physician* 2018; 21:E501-E508.
902. Hossieni B, Dadkhah P, Moradi S, Hashemi SM, Safdari F. The results of treating failed back surgery syndrome by adhesiolysis: comparing the one- and three-day protocols. *Anesth Pain Med* 2017; 7:e60271.
903. Manchikanti L, Pampati V, Fellows B, Rivera JJ, Beyer CD, Damron KS. Role of one day epidural adhesiolysis in management of chronic low back pain: A randomized clinical trial. *Pain Physician* 2001; 4:153-166.
904. Lee JH, Lee SH. Clinical effectiveness of percutaneous adhesiolysis versus transforaminal epidural steroid injection in patients with postlumbar surgery syndrome. *Reg Anesth Pain Med* 2014; 39:214-218.
905. Fabris LK, Suput A, Gusic N, Mamontov P. Epidural adhesiolysis in the management of chronic low back pain in failed back surgery syndrome and in lumbar radicular pain: First year of experience at Pula General Hospital, Pula, Croatia – A randomized trial. *Acta Med Croatica* 2019; 73:57-65.
906. Manchikanti L, Pampati V, Bakht CE, Pakanati RR. Non-endoscopic and endoscopic adhesiolysis in post lumbar laminectomy syndrome: A one-year outcome study and cost effectiveness analysis. *Pain Physician* 1999; 2:52-58.
907. Moon SH, Lee JI, Cho HS, Shin JW, Koh WU. Factors for predicting favorable outcome of percutaneous epidural adhesiolysis for lumbar disc herniation. *Pain Res Manag* 2017; 2017:1494538.
908. Choi SS, Lee JH, Kim D, et al. Effectiveness and factors associated with epidural decompression and adhesiolysis using a balloon-inflatable catheter in chronic lumbar spinal stenosis: 1-year follow-up. *Pain Med* 2016; 17:476-487.
909. Lee JH, Lee SH. Clinical effectiveness of percutaneous adhesiolysis and predictive factors of treatment efficacy in patients with lumbosacral spinal



- stenosis. *Pain Med* 2013; 14:1497-1504.
910. Choi E, Nahm FS, Lee PB. Evaluation of prognostic predictors of percutaneous adhesiolysis using a Racz catheter for post lumbar surgery syndrome or spinal stenosis. *Pain Physician* 2013; 16:E531-E536.
  911. Cho PG, Ji GY, Yoon YS, Shin DA. Clinical effectiveness of percutaneous epidural neuroplasty according to the type of surgical level lumbar disc herniation: A 12 month follow up study. *J Korean Neurosurg Soc* 2019; 62:681-690.
  912. Moon SH, Park JY, Cho SS, et al. Comparative effectiveness of percutaneous epidural adhesiolysis for different sacrum types in patients with chronic pain due to lumbar disc herniation: A propensity score matching analysis. *Medicine (Baltimore)* 2016; 95:e4647.
  913. Taheri A, Khajenasiri AR, Nazemian Yazdi NA, Safari S, Sadeghi J, Hatami M. Clinical evaluation of percutaneous caudal epidural adhesiolysis with the Racz technique for low back pain due to contained disc herniation. *Anesth Pain Med* 2016; 6:e26749.
  914. Cho S, Park HS. Percutaneous epidural adhesiolysis with epidural steroid injection: A non-inferiority test of non-particulate steroids versus particulate steroids. *Pain Med* 2016; 17:1612-1619.
  915. Park SH, Ji GY, Cho PG, et al. Clinical significance of epidurography contrast patterns after adhesiolysis during lumbar percutaneous epidural neuroplasty. *Pain Res Manag* 2018; 2018:6268045.
  916. Choi EJ, Yoo YJ, Lee PB, Kim YC, Lee SC, Moon JY. A retrospective study to evaluate the effect of concentration of hypertonic saline on efficacy and safety of epidural adhesiolysis. *Anesth Analg* 2017; 124:2021-2029.
  917. Lee F, Jamison DE, Hurley RW, Cohen SP. Epidural lysis of adhesions. *Korean J Pain* 2014; 27:3-15.
  918. Tuijpp SJ, Van Zundert J, De Vooght P, et al. Does the use of epiduroscopic lysis of adhesions reduce the need for spinal cord stimulation in failed back surgery syndrome? A short-term pilot study. *Pain Pract* 2018; 18:839-844.
  919. Lee SE, Joe HB, Park JH, et al. Distribution range of cervical interlaminar epidural injections: A comparative study with 2.5 mL, 5 mL, and 10 mL of contrast. *Pain Physician* 2013; 16:155-164.
  920. Manchikanti L, Helm S II, Pampati V, Racz GB. Cost utility analysis of percutaneous adhesiolysis in managing pain of post-lumbar surgery syndrome and lumbar central spinal stenosis. *Pain Pract* 2015; 15:414-422.
  921. Manchikanti L, Cash KA, Pampati V, Wargo BW, Malla Y. Management of chronic pain of cervical disc herniation and radiculitis with fluoroscopic cervical interlaminar epidural injections. *Int J Med Sci* 2012; 9:424-434.
  922. Manchikanti L, Cash KA, Pampati V, Wargo BW, Malla Y. A randomized, double-blind, active control trial of fluoroscopic cervical interlaminar epidural injections in chronic pain of cervical disc herniation: Results of a 2-year follow-up. *Pain Physician* 2013; 16:465-478.
  923. Manchikanti L, Cash KA, 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.
  924. 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; 11:309-320.
  925. Manchikanti L, Malla Y, Cash KA, McManus CD, Pampati V. Fluoroscopic epidural injections in cervical spinal stenosis: Preliminary results of a randomized, double-blind, active control trial. *Pain Physician* 2012; 15:E59-E70.
  926. Manchikanti L, Malla Y, Cash KA, McManus CD, Pampati V. Fluoroscopic cervical interlaminar epidural injections in managing chronic pain of cervical post-surgery syndrome: Preliminary results of a randomized, double-blind active control trial. *Pain Physician* 2012; 15:13-26.
  927. Manchikanti L, Malla Y, Cash KA, Pampati V, Hirsch JA. Comparison of effectiveness for fluoroscopic cervical interlaminar epidural injections with or without steroid in cervical post-surgery syndrome. *Korean J Pain* 2018; 31:277-288.
  928. Manchikanti L, Cash KA, McManus CD, Pampati V, Benyamin RM. 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.
  929. Castagnera L, Maurette P, Pointillart V, Vital JM, Erny P, Senegas J. Long-term results of cervical epidural steroid injection with and without morphine in chronic cervical radicular pain. *Pain* 1994; 58:239-243.
  930. Stav A, Ovadia L, Sternberg A, Kaadan M, Weksler N. Cervical epidural steroid injection for cervicobrachialgia. *Acta Anaesthesiol Scand* 1993; 37:562-566.
  931. 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; 23:551-557.
  932. Cohen SP, Hayek S, Semenov Y, et al. Epidural steroid injections, conservative treatment, or combination treatment for cervical radicular pain: A multicenter, randomized, comparative-effectiveness study. *Anesthesiology* 2014; 121:1045-1055.
  933. Hashizume K, Fujiwara A, Watanabe K, Kamihara M, Iwasaki S, Yamagami H. A prospective comparison of CT-epidurogram between th1-transforaminal epidural injection and th1/2-parasagittal interlaminar epidural injection for cervical upper limb pain. *Pain Physician* 2019; 22:165-176.
  934. Clark R, Doyle M, Sybrowsky C, Rosenquist R. Epidural steroid injections for the treatment of cervical radiculopathy in elite wrestlers: Case series and literature review. *Iowa Orthop J* 2012; 32:207-214.
  935. Amrhein TJ, Bozdogan E, Vekaria S, et al. Cross-sectional CT assessment of the extent of injectate spread at CT fluoroscopy-guided cervical epidural interlaminar steroid injections. *Radiology* 2019; 292:723-729.
  936. Yoon JY, Kwon JW, Yoon YC, Lee J. Cervical interlaminar epidural steroid injection for unilateral cervical radiculopathy: Comparison of midline and paramedian approaches for efficacy. *Korean J Radiol* 2015; 16:604-612.
  937. Joswig H, Neff A, Ruppert C, Hildebrandt G, Stienen MN. Repeat epidural steroid injections for radicular pain due to lumbar or cervical disc herniation: What happens after 'salvage treatment'? *Bone Joint J* 2018; 100-B:1364-1371.
  938. Hong JH, Jung SW. Analysis of epidural waveform for cervical epidural steroid injections confirmed with fluoroscopy. *Medicine (Baltimore)* 2018; 97:e0202.
  939. Hashemi M, Dadkhah P, Taheri M, Dehghan K, Valizadeh R. Cervical epidural steroid injection: Parasagittal versus midline approach in patients with unilateral cervical radicular pain;



- A randomized clinical trial. *Bull Emerg Trauma* 2019; 7:137-143.
940. Beyaz SG, Eman A. Fluoroscopy guided cervical interlaminar steroid injections in patients with cervical pain syndromes: A retrospective study. *J Back Musculoskelet Rehabil* 2013; 26:85-91.
941. McCormick ZL, Nelson A, Bhavne M, et al. A prospective randomized comparative trial of targeted steroid injection via epidural catheter versus standard C7-T1 interlaminar approach for the treatment of unilateral cervical radicular pain. *Reg Anesth Pain Med* 2017; 42:82-89.
942. Manchikanti L, Benyamin RM, Hirsch JA. Inappropriate trial of cervical epidural injections. Letter to the Editor RE: Cohen SP et al. Epidural steroid injections, conservative treatment, or combination treatment for cervical radicular pain: A multicenter, randomized, comparative-effectiveness study. *Anesthesiology* 2014; 121:1045-1055. *Anesthesiology* 2015; 122:1441-1442.
943. Manchikanti L, Pampati V, Parr III A, et al. Cervical interlaminar epidural injections in the treatment of cervical disc herniation, post surgery syndrome, or discogenic pain: Cost utility analysis from randomized trials. *Pain Physician* 2019; 22:421-431.
944. Manchikanti L, Pampati V, Sanapati SP, Sanapati MR, Kaye AD, Hirsch JA. Evaluation of cost-utility of thoracic interlaminar epidural injections. *Curr Pain Headache Rep* 2020; 24:5.
945. Manchikanti L, Helm II S, Singh V, Hirsch JA. Accountable interventional pain management: A collaboration among practitioners, patients, payers, and government. *Pain Physician* 2013; 16:E635-E670.
946. Kepler CK, Wilkinson SM, Radcliff KE, et al. Cost-utility analysis in spine care: A systematic review. *Spine J* 2012; 12:676-690.
947. Indrakanti SS, Weber MH, Takemoto SK, et al. Value-based care in the management of spinal disorders: A systematic review of cost-utility analysis. *Clin Orthop Relat Res* 2012; 470:1106-1123.
948. Critchlow S, Hirst M, Akehurst R, et al. A systematic review of cost-effectiveness modeling of pharmaceutical therapies in neuropathic pain: Variation in practice, key challenges, and recommendations for the future. *J Med Econ* 2017; 20:129-139.
949. Selden TM, Lipton BJ, Decker SL. Medicaid expansion and marketplace eligibility both increased coverage, with trade-offs in access, affordability. *Health Aff (Millwood)* 2017; 36:2069-2077.
950. Peterson MA. The ACA a decade in: Resilience, impact, and vulnerabilities. *J Health Polit Policy Law* 2020; 45:595-608.
951. Dagenais S, Roffey DM, Wai EK, Haldeman S, Caro J. Can cost utility evaluations inform decision making about interventions for low back pain? *Spine J* 2009; 9:944-957.
952. Dagenais S, Haldeman S, Polatin PB. It is time for physicians to embrace cost-effectiveness and cost utility analysis research in the treatment of spinal pain. *Spine J* 2005; 5:357-360.
953. Manchikanti L, Pampati V, Kaye AD, Hirsch JA. Cost utility analysis of cervical therapeutic medial branch blocks in managing chronic neck pain. *Int J Med Sci* 2017; 14:1307-1316.
954. Manchikanti L, Pampati V, Kaye AD, Hirsch JA. Therapeutic lumbar facet joint nerve blocks in the treatment of chronic low back pain: Cost utility analysis based on a randomized controlled trial. *Korean J Pain* 2018; 31:27-38.
955. Manchikanti L, Hirsch JA. Regulatory burdens of the Affordable Care Act. *Harvard Health Policy Rev* 2012; 13:9-12.
956. Hirsch JA, Schaefer PW, Romero JM, Rabinov JD, Sanelli PC, Manchikanti L. Comparative effectiveness research. *AJNR Am J Neuroradiol* 2014; 35:1677-1680.
957. Manchikanti L, Hammer M, Benyamin RM, Hirsch JA. Physician Quality Reporting System (PQRS) for interventional pain management practices: Challenges and opportunities. *Pain Physician* 2016; 19:E15-E32.
958. Manchikanti L, Helm II S, Calodney AK, Hirsch JA. Merit-based incentive payment system: meaningful changes in the final rule brings cautious optimism. *Pain Physician* 2017; 20:E1-E12.
959. National Institute for Health and Care Excellence. Low back pain and sciatica in over 16s: Assessment and management. Invasive treatments. NICE guideline NG59. Methods, evidence and recommendations, 2016. Accessed 11/10/2020. [www.nice.org.uk/guidance/ng59/evidence/full-guideline-invasive-treatments-pdf-2726157998](http://www.nice.org.uk/guidance/ng59/evidence/full-guideline-invasive-treatments-pdf-2726157998)
960. Dagenais S, Caro J, Haldeman S. A systematic review of low back pain cost of illness studies in the United States and internationally. *Spine J* 2008; 8:8-20.
961. Dagenais S, Haldeman S. Commentary: Laboring to understand the economic impact of spinal disorders. *Spine J* 2012; 12:1119-1121.
962. Tosteson AN, Skinner JS, Tosteson TD, et al. The cost effectiveness of surgical versus nonoperative treatment for lumbar disc herniation over two years: Evidence from the Spine Patient Outcomes Research Trial (SPORT). *Spine (Phila Pa 1976)* 2008; 33:2108-2115.
963. Tosteson AN, Lurie JD, Tosteson TD, et al; SPORT Investigators. Surgical treatment of spinal stenosis with and without degenerative spondylolisthesis: Cost-effectiveness after 2 years. *Ann Intern Med* 2008; 149:845-853.
964. Whitehurst DG, Lewis M, Yao GL, et al. A brief pain management program compared with physical therapy for low back pain: results from an economic analysis alongside a randomized clinical trial. *Arthritis Rheum* 2007; 57:466-473.
965. Johnson RE, Jones GT, Wiles NJ, et al. Active exercise, education, and cognitive behavioral therapy for persistent disabling low back pain: A randomized controlled trial. *Spine (Phila Pa 1976)* 2007; 32:1578-1585.
966. Rivero-Arias O, Gray A, Frost H, Lamb SE, Stewart-Brown S. Cost-utility analysis of physiotherapy treatment compared with physiotherapy advice in low back pain. *Spine (Phila Pa 1976)* 2006; 31:1381-1387.
967. Fritz JM, Kim M, Magel JS, Asche CV. Cost-effectiveness of primary care management with or without early physical therapy for acute low back pain: Economic evaluation of a randomized clinical trial. *Spine (Phila Pa 1976)* 2017; 42:285-290.
968. Fritz JM, Brennan GP, Hunter SJ, Magel JS. Initial management decisions after a new consultation for low back pain: implications of the usage of physical therapy for subsequent health care costs and utilization. *Arch Phys Med Rehabil* 2013; 94:808-816.
969. Fritz JM, Childs JD, Wainner RS, Flynn TW. Primary care referral of patients with low back pain to physical therapy: Impact on future health care utilization and costs. *Spine (Phila Pa 1976)* 2012; 37:2114-2121.
970. Childs JD, Fritz JM, Wu SS, et al. Implications of early and guideline adherent physical therapy for low back pain on utilization and costs. *BMC Health Serv Res* 2015; 15:150.
971. Macedo LG, Hum A, Kuleba L, et al. Physical therapy interventions for degenerative lumbar spinal stenosis: A systematic review. *Phys Ther* 2013; 93:12:1646-1660.

972. Ammendolia C, Stuber K, de Bruin LK, et al. Nonoperative treatment of lumbar spinal stenosis with neurogenic claudication: A systematic review. *Spine (Phila Pa 1976)* 2012; 37(10):E609-E616.
973. Bove AM, Lynch AD, Ammendolia C, Schneider M. Patients' experience with nonsurgical treatment for lumbar spinal stenosis: A qualitative study. *Spine J* 2018; 18(4):639-647.
974. Mo Z, Zhang R, Chang M, Tang S. Exercise therapy versus surgery for lumbar spinal stenosis: A systematic review and meta-analysis. *Pak J Med Sci* 2018; 34(4):879-885.
975. Ma XL, Zhao XW, Ma JX, Li F, Wang Y, Lu B. Effectiveness of surgery versus conservative treatment for lumbar spinal stenosis: A system review and meta-analysis of randomized controlled trials. *Int J Surg* 2017; 44(3):29-338.
976. Adogwa O, Davison MA, Lilly DT, et al. A 2-year cost analysis of maximum nonoperative treatments in patients with symptomatic lumbar stenosis or spondylolisthesis that ultimately required surgery. *Global Spine J* 2019; 9(4):424-433.
977. Adogwa O, Davison MA, Vuong VD, et al. Long-term costs of maximum nonoperative treatments in patients with symptomatic lumbar stenosis or spondylolisthesis that ultimately required surgery: A 5-year cost analysis. *Spine (Phila Pa 1976)* 2019; 44(4):424-430.
978. Lilly DT, Davison MA, Eldridge CM, et al. An assessment of nonoperative management strategies in a herniated lumbar disc population: Successes versus failures. *Global Spine J* 2020; 7(2):192568220936217.
979. Furlan AD, Yazdi F, Tsertsvadze A, et al. A systematic review and meta-analysis of efficacy, cost-effectiveness, and safety of selected complementary and alternative medicine for neck and low-back pain. *Evid Based Complement Alternat Med* 2012; 2012:953139.
980. Leininger B, McDonough C, Evans R, Tosteson T, Tosteson AN, Bronfort G. Cost-effectiveness of spinal manipulative therapy, supervised exercise, and home exercise for older adults with chronic neck pain. *Spine J* 2016; 16(12):1292-1304.
981. Nahin RL, Barnes PM, Stussman BJ, Bloom B. Costs of complementary and alternative medicine (CAM) and frequency of visits to CAM practitioners: United States. *National Health Statistics Reports* 2009; 18:1-4.
982. Herman PM, Lavelle TA, Sorbero ME, Hurwitz EL, Coulter ID. Are nonpharmacologic interventions for chronic low back pain more cost effective than usual care? Proof of concept results from a Markov model. *Spine (Phila Pa 1976)* 2019; 44(14):1456-1464.
983. Hays RD, Spritzer KL, Sherbourne CD, Ryan GW, Coulter ID. Group and individual-level change on health-related quality of life in chiropractic patients with chronic low back or neck pain. *Spine (Phila Pa 1976)* 2019; 44(6):647-651.
984. Complementary & alternative medicine market worth \$296.3 billion by 2027. *Grand View Research*, March 2020. Accessed 12/23/2020.  
www.grandviewresearch.com/press-release/global-alternative-complementary-medicine-therapies-market
985. Cairns K, Deer T, Sayed D, van Noort K, Liang K. Cost-effectiveness and safety of interspinous process decompression (Superion). *Pain Med* 2019; 20(2):S2-S8.
986. Davison MA, Lilly DT, Eldridge CM, Singh R, Bagley C, Adogwa O. Regional differences in prolonged non-operative therapy utilization prior to primary ACDF surgery. *J Clin Neurosci* 2020; 80(1):143-151.
987. Aichmair A, Burgstaller JM, Schwenkglenks M, et al. Cost-effectiveness of conservative versus surgical treatment strategies of lumbar spinal stenosis in the Swiss setting: Analysis of the prospective multicenter Lumbar Stenosis Outcome Study (LSOS). *Eur Spine J* 2017; 26(2):501-509.
988. Driessen MT, Lin CW, van Tulder MW. Cost-effectiveness of conservative treatments for neck pain: A systematic review on economic evaluations. *Eur Spine J* 2012; 21(14):1441-1450.
989. Dagenais S, Moher D. Re: Hurwitz EL, Morgenstern H, Vassilaki M, Chiang LM. Frequency and clinical predictors of adverse reactions to chiropractic care in the UCLA neck pain study. *Spine* 2005; 30(14):1477-84. *Spine (Phila Pa 1976)* 2006; 31(2):53.
990. Parker SL, Godil SS, Mendenhall SK, Zuckerman SL, Shau DN, McGirt MJ. Two-year comprehensive medical management of degenerative lumbar spine disease (lumbar spondylolisthesis, stenosis, or disc herniation): A value analysis of cost, pain, disability, and quality of life. *J Neurosurg Spine* 2014; 21(2):143-149.
991. Cummins J, Lurie JD, Tosteson TD, et al. Descriptive epidemiology and prior healthcare utilization of patients in the Spine Patient Outcomes Research Trial's (SPORT) three observational cohorts: Disc herniation, spinal stenosis, and degenerative spondylolisthesis. *Spine (Phila Pa 1976)* 2006; 31(8):806-814.
992. Daffner SD, Hymanson HJ, Wang JC. Cost and use of conservative management of lumbar disc herniation before surgical discectomy. *Spine J* 2010; 10(4):463-468.
993. Tosteson AN, Tosteson TD, Lurie JD, et al. Comparative effectiveness evidence from the spine patient outcomes research trial: Surgical versus nonoperative care for spinal stenosis, degenerative spondylolisthesis, and intervertebral disc herniation. *Spine (Phila Pa 1976)* 2011; 36(20):2061-2068.
994. Lurie JD, Tosteson TD, Tosteson AN, et al. Surgical versus nonoperative treatment for lumbar disc herniation: Eight-year results for the spine patient outcomes research trial. *Spine (Phila Pa 1976)* 2014; 39(3):3-16. Erratum in: *Spine (Phila Pa 1976)* 2015; 40:E59.
995. Weinstein JN, Tosteson AN, Tosteson TD, et al. The SPORT value compass: Do the extra costs of undergoing spine surgery produce better health benefits? *Med Care* 2014; 52(10):1055-1063. Erratum in: *Med Care* 2015; 53:386.
996. Kumar K, Rizvi S. Cost-effectiveness of spinal cord stimulation therapy in management of chronic pain. *Pain Med* 2013; 14(16):1631-1649.
997. Taylor RS, Ryan J, O'Donnell R, Eldabe S, Kumar K, North RB. The cost-effectiveness of spinal cord stimulation in the treatment of failed back surgery syndrome. *Clin J Pain* 2010; 26(4):463-469.
998. Hollingworth W, Turner JA, Welton NJ, Comstock BA, Deyo RA. Costs and cost-effectiveness of spinal cord stimulation (SCS) for failed back surgery syndrome: An observational study in a workers' compensation population. *Spine (Phila Pa 1976)* 2011; 36(20):2076-2083.
999. Whynes DK, McCahon RA, Ravenscroft A, Hardman J. Cost effectiveness of epidural steroid injections to manage chronic lower back pain. *BMC Anesthesiol* 2012; 12:26.
1000. Carreon LY, Bratcher KR, Ammous F, Glassman SD. Cost-effectiveness of lumbar epidural steroid injections. *Spine (Phila Pa 1976)* 2018; 43(3):35-40.
1001. Schreiber AL, McDonald BP, Kia F, Fried GW. Cervical epidural steroid injections

- and spinal cord injuries. *Spine J* 2016; 16:1163-1166.
1002. Chang A, Wang D. Complications of fluoroscopically guided cervical interlaminar epidural steroid injections. *Curr Pain Headache Rep* 2020; 24:63.
  1003. Palmer E. Management of cervical epidural hematoma after cervical epidural steroid injection using a catheter technique. *Pain Med* 2020; 21:1301-1302.
  1004. Yu HH, Van Steyn P, Drayer NJ, Jackson KL, Kang DG. Is cervical epidural steroid injection safe and efficacious for the treatment of cervical radiculopathy? *Clin Spine Surg* 2020; 33:92-94.
  1005. Ramsook RR, Spinner D, Doshi RR. Filum terminale needle placement during caudal epidural steroid injection. *Pain Med* 2017; 18:1464-1466.
  1006. Wang G, Liang J, Jia Z, Wan L, Yang M. Spinal cord infarction caused by sacral canal epidural steroid injection: A case report. *Medicine (Baltimore)* 2018; 97:e0111.
  1007. Amoretti N, Baqué J, Litrico S, Stacoffe N, Palmer W. Serious neurological complication resulting from inadvertent intradiscal injection during fluoroscopically guided interlaminar epidural steroid injection. *Cardiovasc Intervent Radiol* 2019; 42:775-778.
  1008. Yürük D, Yılmaz A, Özgencil GE, Aşık İ. Acute rhabdomyolysis following epidural steroid injection: An unusual complication in a patient with low back pain. *Agri* 2019; 31:150-152.
  1009. Chacko J, Levis K, Hahn B. Pneumocephalus after epidural injection. *J Emerg Med* 2018; 54:e45-e47.
  1010. Redon S, Laksiri N, Doche E, Hirtz C, Brun G, Donnet A. Stroke after spontaneous intracranial hypotension: Not a single mechanism. Case report and review of literature. *J Clin Neurosci* 2020; 74:253-255.
  1011. Stolzenberg DS, Koehler, III PJ, Teng J, Simon JI. Inadvertent discogram during lumbar interlaminar epidural steroid injection. *PMCR* 2020; 4:103-110.
  1012. Boudier-Revéret M, Chang MC. Segmental spinal myoclonus after a cervical transforaminal epidural steroid injection. *Am J Phys Med Rehabil* 2020; 99:e128-e130.
  1013. Han HJ, Wook KJ, Ho JJ. Intramedullary pneumorrhachis following a cervical epidural steroid injection. *Neurochirurgie* 2020; S0028-3770: 30403-30403.
  1014. Orduna-Valls JM, Cedeno DL, Nebreda-Clavo C, et al. Microscopic study of injectable steroids: Effects of postmixing time on particle aggregation. *Pain Physician* 2020; 23:E417-E424.
  1015. Schaaf S, Huang W, Perera S, et al. Association of protein and genetic biomarkers with response to lumbar epidural steroid injections in subjects with axial low back pain. *Am J Phys Med Rehabil* 2020. Epub ahead of print.
  1016. Koo J, Cho KT. Pneumocephalus and chemical meningitis after inadvertent dural puncture during lumbar epidural injection. *Korean J Neurotrauma* 2020; 16:67-72.
  1017. Smuck M, Paulus S, Patel A, Demirjian R, Ith MA, Kennedy DJ. Differential rates of inadvertent intravascular injection during lumbar transforaminal epidural injections using blunt-tip, pencil-point, and catheter-extension needles. *Pain Med* 2015; 16:2084-2089.
  1018. Kreitz TM, Mangan J, Schroeder GD, et al. Do preoperative epidural steroid injections increase the risk of infection after lumbar spine surgery? *Spine (Phila Pa 1976)* 2021; 46:E197-E202.
  1019. Abrecht CR, Saba R, Greenberg P, Rathmell JR, Urman RU. A contemporary medicolegal analysis of outpatient interventional pain procedures: 2009-2016. *Anesth Analg* 2019; 129:255-262.
  1020. Wibowo HA, Rhatomy S. Cauda equina syndrome after caudal epidural sacral injection in severe lumbar spinal stenosis: Case report. *Int J Surg Case Rep* 2020; 77:12-14.
  1021. 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:E1211-E1214.
  1022. Seo YT, Kong HH, Lee GJ, Bang HJ. Persistent cauda equina syndrome after caudal epidural injection under severe spinal stenosis: A case report. *J Pain Res* 2017; 10:1425-1429.
  1023. Richard K, Waggoner G, Donnan M, Ayesu K, Madruga M, Carlan SJ. Epidural steroid injection-induced pancreatitis: A case report. *Am J Case Rep* 2020; 21:e921241.
  1024. Amrhein TJ, Parivash SN, Gray L, Kranz PG. Incidence of inadvertent dural puncture during CT fluoroscopy-guided interlaminar epidural corticosteroid injections in the cervical spine: An analysis of 974 cases. *AJR Am J Roentgenol* 2017; 209:656-661.
  1025. 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:E70-E73.
  1026. Plastaras CT, Casey E, Goodman BS, Chou L, Roth D, Rittenberg J. Inadvertent intradiscal contrast flow during lumbar transforaminal epidural steroid injections: A case series examining the prevalence of intradiscal injection as well as potential associated factors and adverse events. *Pain Med* 2010; 11:1765-1773.
  1027. Everett CR, Baskin MN, Novoseletsky D, Speech D, Patel R. Flushing as a side effect following lumbar transforaminal epidural steroid injection. *Pain Physician* 2004; 7:427-429.
  1028. Kim CH, Issa MA, Vaglianti RM. Flushing following interlaminar lumbar epidural steroid injection with dexamethasone. *Pain Physician* 2010; 13:481-484.
  1029. Young WF. Transient blindness after lumbar epidural steroid injection: A case report and literature review. *Spine (Phila Pa 1976)* 2002; 27:E476-E477.
  1030. Browning DJ. Acute retinal necrosis following epidural steroid injections. *Am J Ophthalmol* 2003; 136:192-194.
  1031. Kusher FH, Olson JC. Retinal hemorrhage as a consequence of epidural steroid injection. *Arch Ophthalmol* 1995; 113:309-313.
  1032. Iida T, Spaide RF, Negrao SG, Carvalho CA, Yannuzzi LA. Central serous chorioretinopathy after epidural corticosteroid injection. *Am J Ophthalmol* 2001; 132:423-425.
  1033. Pizzimenti JJ, Daniel KP. Central serous chorioretinopathy after epidural steroids. *Pharmacotherapy* 2005; 25:1141-1146.
  1034. McAllister RK, McDavid AJ, Meyer TA, Bittenbinder TM. Recurrent persistent hiccups after epidural steroid injection and analgesia with bupivacaine. *Anesth Analg* 2005; 100:1834-1836.
  1035. Gutknecht DR. Chemical meningitis following epidural injections of corticosteroids (Letter). *Am J Med* 1987; 82:570.
  1036. Yue WM, Tan SB. Distant skip level discitis and vertebral osteomyelitis after caudal epidural injection: A case report of a rare complication of epidural injections. *Spine (Phila Pa 1976)* 2003; 28:E209-E211.
  1037. Nelson DA, Landau WM. Intraspinal steroids: History, efficacy, accidentality, and controversy with review of United States Food and Drug Administration

- reports. *J Neurol Neurosurg Psychiatry* 2001; 70:433-443.
1038. Brunasso L, Basile L, Gerardo Iacopino D, et al. All that glitters is not gold: A spinal epidural empyema following epidural steroid injection. *Surg Neurol Int* 2020; 11:240.
1039. Manchikanti L, Falco FJE, Benyamin RM, Gharibo CG, Candido KD, Hirsch JA. Epidural steroid injections safety recommendations by the Multi-Society Pain Workgroup (MPW): More regulations without evidence or clarification. *Pain Physician* 2014; 17:E575-E588.
1040. Dorratoltaj N, O'Dell ML, Bordwine P, Kerkering TM, Redican KJ, Abbas KM. Epidemiological Effectiveness and cost of a fungal meningitis outbreak response in New River Valley, Virginia: Local health department and clinical perspectives. *Disaster Med Public Health Prep* 2018; 12:38-46.
1041. Kainer MA, Reagan DR, Nguyen DB, et al; Tennessee Fungal Meningitis Investigation Team. Fungal infections associated with contaminated methylprednisolone in Tennessee. *N Engl J Med* 2012; 367:2194-2203.
1042. Moudgal V, Singal B, Kauffman CA, et al. Spinal and paraspinal fungal infections associated with contaminated methylprednisolone injections. *Open Forum Infect Dis* 2014; 1:ofu022.
1043. Manchikanti L, Benyamin RM. Key safety considerations when administering epidural steroid injections. *Pain Manag* 2015; 5:261-272.
1044. Chiller TM, Roy M, Nguyen D, et al; Multistate Fungal Infection Clinical Investigation Team. Clinical findings for fungal infections caused by methylprednisolone injections. *N Engl J Med* 2013; 369:1610-1619.
1045. Lyons JL, Gireesh ED, Trivedi JB, et al. Fatal exserohilum meningitis and central nervous system vasculitis after cervical epidural methylprednisolone injection. *Ann Intern Med* 2012; 157:835-836.
1046. Kleinfeld K, Jones P, Riebau D, et al. Vascular complications of fungal meningitis attributed to injections of contaminated methylprednisolone acetate. *JAMA Neurol* 2013; 70:1173-1176.
1047. Centers for Disease Control and Prevention (CDC). Spinal and paraspinal infections associated with contaminated methylprednisolone acetate injections - Michigan, 2012-2013. *MMWR Morb Mortal Wkly Rep* 2013; 62:377-381.
1048. Renfrow JJ, Frenkel MB, Hsu W. Fungal contamination of methylprednisolone causing recurrent lumbosacral intradural abscess. *Emerg Infect Dis* 2017; 23:552-553.
1049. Centers for Disease Control and Prevention (CDC). Multistate outbreak of fungal infection associated with injection of methylprednisolone acetate solution from a single compounding pharmacy - United States, 2012. *MMWR Morb Mortal Wkly Rep* 2012; 61:839-842.
1050. Racoosin JA, Seymour SM, Cascio L, Gill R. Serious neurologic events after epidural glucocorticoid injection--the FDA's risk assessment. *N Engl J Med* 2015; 373:2299-2301.
1051. Letter to Division of Dockets Management, Food and Drug Administration, Department of Health and Human Services, from American Society of Interventional Pain Physicians RE FDA Citizens Petition, September 3, 2014.
1052. Rathmell JP, Michna E, Fitzgibbon DR, Stephens LS, Posner KL, Domino KB. Injury and liability associated with cervical procedures for chronic pain. *Anesthesiology* 2011; 114:918-926.
1053. Shanthanna H, Cohen SP, Strand N, et al. Recommendations on chronic pain practice during the COVID-19 Pandemic: A joint statement by American Society of Regional Anesthesia and Pain Medicine (ASRA) and European Society of Regional Anesthesia and Pain Therapy (ESRA). Accessed 12/8/2020. [www.asra.com/page/2903/recommendations-on-chronic-pain-practice-during-the-covid-19-pandemic](http://www.asra.com/page/2903/recommendations-on-chronic-pain-practice-during-the-covid-19-pandemic)
1054. McEvoy GK, Litvak K, Welsh OH, et al. AHFS 99 Drug Information. Bethesda, American Society of Health-System Pharmacists, 1999, pp 2636-2662.
1055. Jacobs A, Pullan PT, Potter JM, et al. Adrenal suppression following extradural steroids. *Anaesthesia* 1983; 38:953-956.
1056. Kay JK, Findling JW, Raff H. Epidural triamcinolone suppresses the pituitary adrenal axis in human subjects. *Anesth Analg* 1994; 79:501-505.
1057. Janicki PK, Johnson B, Parris WC. Pharmacokinetic analysis of plasma methylprednisolone after administration in rabbits. *Proceedings of the American Society of Regional Anesthesia*, Annual Meeting, 1995, p 7.
1058. Friedly JL, Comstock BA, Heagerty PJ, et al. Systemic effects of epidural steroid injections for spinal stenosis. *Pain* 2018; 159:876-883.
1059. Hooten WM, Nicholson WT, Gazelka HM, Reid JM, Moeschler SM, Lamer TJ. Serum triamcinolone levels following interlaminar epidural injection. *Reg Anesth Pain Med* 2016; 41:75-79.
1060. Yanez JA, Remsberg CM, Sayre CL, Forrest ML, Davies NM. Flipflop pharmacokinetics--delivering a reversal of disposition: challenges and opportunities during drug development. *Ther Deliv* 2011; 2:643-672.
1061. Kim M, Yang YH, Son HJ. Effect of medications and epidural steroid injections on fractures in postmenopausal women with osteoporosis. *Medicine (Baltimore)* 2019; 98:e16080.
1062. Kerezoudis P, Rinaldo L, Alvi MA, et al. The effect of epidural steroid injections on bone mineral density and vertebral fracture risk: A Systematic review and critical appraisal of current literature. *Pain Med* 2018; 19:569-579.
1063. Abdul AJ, Ghai B, Bansal D, Sachdeva N, Bhansali A, Dhatt SS. Hypothalamic pituitary adrenocortical axis suppression following a single epidural injection of methylprednisolone acetate. *Pain Physician* 2017; 20:E991-E1001.
1064. 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; 25:629-633.
1065. Barnett J, Bernacki MN, Kainer JL, Smith HN, Zaharoff AM, Subramanian SK. The effects of regenerative injection therapy compared to corticosteroids for the treatment of lateral epicondylitis: A systematic review and meta-analysis. *Arch Physiother* 2019; 9:12.
1066. MacMahon PJ, Eustace SJ, Kavanagh EC. Injectable corticosteroid and local anesthetic preparations: A review for radiologists. *Radiology* 2009; 252:647-661.
1067. Ginzler E, Diamond H, Kaplan D, Weiner M, Schlesinger M, Seleznick M. Computer analysis of factors influencing frequency of infection in systemic lupus erythematosus. *Arthritis Rheum* 1978; 21:37-44.
1068. Wolfe F, Caplan L, Michaud K. Treatment for rheumatoid arthritis and the risk of hospitalization for pneumonia: Associations with prednisone, disease modifying antirheumatic drugs, and anti-tumor necrosis factor therapy. *Arthritis Rheum* 2006; 54:628-634.
1069. Sytsma TT, Greenlund LK, Greenlund LS. Joint corticosteroid injection



- associated with increased influenza risk. *Mayo Clin Proc Innov Qual Outcomes* 2018; 2:194-198.
1070. Lamer TJ, Dickson RR, Gazelka HM, et al. Serum triamcinolone levels following cervical interlaminar epidural injection. *Pain Res Manag* 2018; 2018:8474127.
1071. Hagan JB, Erickson D, Singh RJ. Triamcinolone acetonide induced secondary adrenal insufficiency related to impaired CYP3A4 metabolism by coadministration of nefazodone. *Pain Med* 2010; 11:1132-1135.
1072. Song Y, Schroeder JR, Bush LM. Iatrogenic cushing syndrome and secondary adrenal insufficiency related to concomitant triamcinolone and ritonavir administration: A case report and review. *J Int Assoc Provid AIDS Care* 2013; 13:511-514.
1073. Even JL, Crosby CG, Song Y, McGirt MJ, Devin CJ. Effects of epidural steroid injections on blood glucose levels in patients with diabetes mellitus. *Spine (Phila Pa 1976)* 2012; 37:E46-E50.
1074. Zufferey P, Bulliard C, Gremion G, Saugy M, So A. Systemic effects of epidural methylprednisolone injection on glucose tolerance in diabetic patients. *BMC Res Notes* 2011; 4:552.
1075. Elston MS, Conaglen HM, Hughes C, Meyer-Rochow GY, Conaglen JV. Duration of cortisol suppression following a single dose of dexamethasone in healthy volunteers: A randomised double-blind placebo-controlled trial. *Anaesth Intensive Care* 2013; 41:596-601.
1076. Hsu D, Fu P, Gyermek L, Tan C. Comparison of plasma cortisol and ACTH profile after a single lumbar epidural dose of triamcinolone 40 mg, 80 mg respectively in low back pain patients. *Anesth Analg* 1996; 82:S191.
1077. King W, Miller DC, Smith CC; Spine Intervention Society's Patient Safety Committee. Systemic effects of epidural corticosteroid injection. *Pain Med* 2018; 19:404-405.
1078. Chon JY, Moon HS. Salivary cortisol concentration changes after epidural steroid injection. *Pain Physician* 2012; 15:461-466.
1079. Derendorf H, Hochhaus G, Rohatagi S, et al. Pharmacokinetics of triamcinolone acetonide after intravenous, oral, and inhaled administration. *J Clin Pharmacol* 1995; 35:302-305.
1080. Mollmann H, Rohdewald P, Schmidt EW, Salomon V, Derendorf H. Pharmacokinetics of triamcinolone acetonide and its phosphate ester. *Eur J Clin Pharmacol* 1985; 29:85-89.
1081. Beer PM, Bakri SJ, Singh RJ, Liu W, Peters GB, Miller M. Intraocular concentration and pharmacokinetics of triamcinolone acetonide after a single intravitreal injection. *Ophthalmology* 2003; 110:681-686.
1082. Schimmer BP, Parker KL. Adrenocorticotrophic hormone; adrenocortical steroids and their synthetic analogs; inhibitors of the synthesis and actions of adrenocortical hormones. In: Brunton LL, Lazo JS, Parker KL (eds). *The Pharmacological Basis of Therapeutics*, 11th ed, McGraw Hill, New York p 1587-1612.
1083. Mikhail GR, Sweet LC, Mellinger RC. Parenteral long-acting corticosteroid effect on hypothalamic pituitary adrenal function. *Ann Allergy* 1973; 31:337-343.
1084. Mikhail GR, Livingood CS, Mellinger RC, et al. Effect of long-acting parenteral corticosteroids on adrenal function. *Arch Dermatol* 1969; 100:263-268.
1085. Haynes BF, Fauci AS. The differential effect of in vivo hydrocortisone on the kinetics of subpopulations of human peripheral blood thymus-derived lymphocytes. *J Clin Invest* 1978; 61:703-707.
1086. Dixon WG, Abrahamowicz M, Beauchamp ME, et al. Immediate and delayed impact of oral glucocorticoid therapy on risk of serious infection in older patients with rheumatoid arthritis: A nested case-control analysis. *Ann Rheum Dis* 2012; 71:1128-1133.
1087. Lahood N, Emerson SS, Kumar P, Sorensen RU. Antibody levels and response to pneumococcal vaccine in steroid-dependent asthma. *Ann Allergy* 1993; 70:289-294.
1088. Kubiet MA, Gonzalez-Rothi RJ, Cottey R, Bender BS. Serum antibody response to influenza vaccine in pulmonary patients receiving corticosteroids. *Chest* 1996; 110:367-370.
1089. Herron A, Dettleff G, Hixon B, et al. Influenza vaccination in patients with rheumatic diseases. Safety and efficacy. *JAMA* 1979; 242:53-56.
1090. General recommendations on immunization. Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR*, January 28, 2011, Vol. 60, No. 2.
1091. U.S. Centers for Disease Control and Prevention. How CDC is making COVID-19 vaccine recommendations. December 2020. Accessed 12/10/2020 [www.cdc.gov/coronavirus/2019-ncov/vaccines/recommendations-process.html](http://www.cdc.gov/coronavirus/2019-ncov/vaccines/recommendations-process.html)
1092. Hermanns H, Hollmann MW, Stevens MF, et al. Molecular mechanisms of action of systemic lidocaine in acute and chronic pain: A narrative review. *Br J Anaesth* 2019; 123:335-349.
1093. Taylor A, McLeod G. Basic pharmacology of local anesthetics. *BJA Education* 2020; 20:34-41.
1094. El-Boghdady K, Pawa A, Chin KJ. Local anesthetic systemic toxicity: Current perspectives. *Local Reg Anesth* 2018; 11:35-44.
1095. Christie LE, Picard J, Weinberg GL. Local anaesthetic systemic toxicity. Continuing education in anaesthesia. *Crit Car Pain* 2015; 15:136-142.
1096. Guay J. Methemoglobinemia related to local anesthetics: A summary of 242 episodes. *Anesth Analg* 2009; 108:837-845.
1097. Mahajan A, Derian A. Local anesthetic toxicity. In: *StatPearls*. StatPearls Publishing, Treasure Island, FL, 2020.
1098. Neal JM, Woodward CM, Harrison TK. The American Society of Regional Anesthesia and Pain Medicine checklist for managing local anesthetic systemic toxicity: 2017 version. *Reg Anesth Pain Med* 2018; 43:150-153.
1099. Neal JM, Barrington MJ, Fettiplace MR, et al. The Third American Society of Regional Anesthesia and Pain Medicine Practice Advisory on Local Anesthetic Systemic Toxicity: Executive Summary 2017. *Reg Anesth Pain Med* 2018; 43:113-123.
1100. Manchikanti L, Cash KA, Moss TL, Rivera JJ, Pampati V. Risk of whole body radiation exposure and protective measures in fluoroscopically guided interventional techniques: A prospective evaluation. *BMC Anesthesiol* 2003; 3:2.
1101. Kim WJ, Yoo SH, Park HS. Evaluation of protective equipment for the reduction of radiation exposure to physicians performing fluoroscopically guided lumbar transforaminal epidural steroid injections: A randomized controlled trial. *Medicine (Baltimore)* 2020; 99:e21424.
1102. Kelly R, McMahon A, Hegarty D. Ionizing radiation dose exposure to the ocular region of pain physicians during C-arm guided pain interventions. *Pain Physician* 2018; 21:E523-E532.
1103. Choi EJ, Go G, Ki Han W, Lee PB. Radiation exposure to the eyes and thyroid during C-arm fluoroscopy-guided cervical epidural injections is far below the safety limit. *Korean J Pain*



- 2020; 33:73-80.
1104. Jones AK, Balter S, Rauch P, Wagner LK. Medical imaging using ionizing radiation: Optimization of dose and image quality in fluoroscopy. *Med Phys* 2014; 41:014301.
1105. Racz GB, Heavner JE. Introduction to Lysis of Adhesions. In: Racz GB, Noe CE (eds) *Techniques of Neurolysis*. Springer International, Switzerland, 2016.
1106. Han YJ, Lee MN, Cho MJ, Park HJ, Moon DE, Kim YH. Contrast runoff correlates with the clinical outcome of cervical epidural neuroplasty using a Racz catheter. *Pain Physician* 2016; 19:E1035-E1040.
1107. Racz GB, Heavner JE, Trescot A. Percutaneous lysis of epidural adhesions--Evidence for safety and efficacy. *Pain Pract* 2008; 8:277-86. Erratum in: *Pain Pract* 2009; 9:244.
1108. Manchikanti L, Pampati V, Bakhit CE, Pakanati RR. Non-endoscopic and endoscopic adhesiolysis in post-lumbar laminectomy syndrome: A one-year outcome study and cost effectiveness analysis. *Pain Physician* 1999; 2:52-58.
1109. Rapčan R, Kočan L, Mláka J, et al. A randomized, multicenter, double-blind, parallel pilot study assessing the effect of mechanical adhesiolysis vs adhesiolysis with corticosteroid and hyaluronidase administration into the epidural space during epiduroscopy. *Pain Med* 2018; 19:1436-1444.
1110. Marchesini M, Flaviano E, Belini V, Baciarello M, et al. Complication of epiduroscopy: A brief review and case report. *Korean J Pain* 2018; 31:296-304.
1111. Narouze S, Benzon HT, Provenzano D, et al. Interventional spine and pain procedures in patients on antiplatelet and anticoagulant medications (Second Edition): Guidelines from the American Society of Regional Anesthesia and Pain Medicine, the European Society of Regional Anaesthesia and Pain Therapy, the American Academy of Pain Medicine, the International Neuromodulation Society, the North American Neuromodulation Society, and the World Institute of Pain. *Reg Anesth Pain Med* 2018; 43:225-262.
1112. Deer TR, Narouze S, Provenzano DA, et al. The Neurostimulation Appropriateness Consensus Committee (NACC): Recommendations on bleeding and coagulation management in neurostimulation devices. *Neuromodulation* 2017; 20:51-62.
1113. Jenkins AT, Kantorovich A, Burman L. Contemporary use of oral antithrombotic agents: Focus on dual and triple therapeutic approaches. *Pharmacotherapy* 2017; 37:1545-1564.
1114. Colonna P, Andreotti F, Ageno W, Pengo V, Marchionni N. Clinical conundrums in antithrombotic therapy management: A Delphi Consensus panel. *Int J Cardiol* 2017; 249:249-256.
1115. Levine GN, Bates ER, Bittl JA, et al. 2016 ACC/AHA guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease. *J Am Coll Cardiol* 2016; 68:1082-1115.
1116. Zhao Q, Zhu Y, Xu Z, et al. Effect of ticagrelor plus aspirin, ticagrelor alone, or aspirin alone on saphenous vein graft patency 1 year after coronary artery bypass grafting: A randomized clinical trial. *JAMA* 2018; 319:1677-1686.
1117. Johnston SC, Easton JD, Farrant M, et al. Clopidogrel and aspirin in acute ischemic stroke and high-risk TIA. *N Engl J Med* 2018; 379:215-225.
1118. Lenzer J. Anticoagulants cause the most serious adverse events, finds US analysis. *BMJ* 2012; 344:e3989.
1119. Roule V, Blanchart K, Humbert X, et al. Antithrombotic therapy for ACS in elderly patients. *Cardiovasc Drugs Ther* 2017; 31:609-618.
1120. Proietti M, Romanazzi I, Romiti GF, Farcomeni A, Lip GYH. Real-world use of Apixaban for stroke prevention in atrial fibrillation: A systematic review and meta-analysis. *Stroke* 2018; 49:98-106.
1121. Gerstein NS, Albrechtsen CL, Mercado N, Cigarroa JE, Schulman PM. A comprehensive update on aspirin management during noncardiac surgery. *Anesth Analg* 2020; 131:1111-1123.
1122. Goes R, Muskens IS, Smith TR, Mekary RA, Broekman mL, Moojen WA. Risk of aspirin continuation in spinal surgery: A systematic review and meta-analysis. *Spine J* 2017; 17:1939-1946.
1123. McNeil JJ, Wolfe R, Woods RL, et al. Effect of aspirin on cardiovascular events and bleeding in the healthy elderly. *N Engl J Med* 2018; 379:1509-1518.
1124. McNeil JJ, Woods RL, Nelson MR, et al. Effect of aspirin on disability-free survival in the healthy elderly. *N Engl J Med* 2018; 379:1499-1508.
1125. Ridker PM. Should aspirin be used for primary prevention in the post-statin era? *N Engl J Med* 2018; 379:1572-1574.
1126. Oprea AD, Noto CJ, Halaszynski TM. Risk stratification, perioperative and periprocedural management of the patient receiving anticoagulant therapy. *J Clin Anesth* 2016; 34:586-599.
1127. Hart RG, Sharma M, Mundl H, et al. Rivaroxaban for stroke prevention after embolic stroke of undetermined source. *N Engl J Med* 2018; 378:2191-2201.
1128. Manchikanti L, Benyamin RM, Swicegood JR, et al. Assessment of practice patterns of perioperative management of antiplatelet and anticoagulant therapy in interventional pain management. *Pain Physician* 2012; 15:E955-E968.
1129. Manchikanti L, Malla Y, Wargo BW, et al. A prospective evaluation of bleeding risk of interventional techniques in chronic pain. *Pain Physician* 2011; 14:317-329.
1130. Smith CC, Schneider B, McCormick ZL, et al. Risks and benefits of ceasing or continuing anticoagulant medication for image-guided procedures for spine pain: A systematic review. *Pain Med* 2018; 19:438-448.
1131. Moeschler SM, Warner NS, Lamer TJ, et al. Bleeding complications in patients undergoing percutaneous spinal cord stimulator trials and implantations. *Pain Med* 2016; 17:2076-2081.
1132. LaVallee J, Royer R, Smith G. Prevalence of bleeding complications following ultrasound-guided botulinum toxin injections in patients on anticoagulation or antiplatelet therapy. *PM R* 2017; 9:1217-1224.
1133. Breivik H, Norum H, Fenger-Eriksen C, et al. Reducing risk of spinal haematoma from spinal and epidural pain procedures. *Scand J Pain* 2018; 18:129-150.
1134. Horlocker TT, Bajwa ZH, Ashraf Z, et al. Risk assessment of hemorrhagic complications associated with nonsteroidal antiinflammatory medications in ambulatory pain clinic patients undergoing epidural steroid injection. *Anesth Analg* 2002; 95:1691-1697.
1135. Ahmed SU, Tonidandel W, Trella J, Martin NM, Chang Y. Peri-procedural protocols for interventional pain management techniques: A survey of US pain centers. *Pain Physician* 2005; 8:181-185.
1136. McCormick ZL, Popescu A, Smith C; Spine Intervention Society's Patient Safety Committee. Fact finders for patient safety: Risk of bleeding with nonaspirin nonsteroidal anti-inflammatory drugs before spine procedures. *Pain Med* 2018; 19:2322-2323.
1137. Petraglia FW 3rd, Farber SH, Gramer

- R, et al. The incidence of spinal cord injury in implantation of percutaneous and paddle electrodes for spinal cord stimulation. *Neuromodulation* 2016; 19:85-90.
1138. Andres S, Shufelt A, Bogduk N. The risks of continuing or discontinuing anticoagulants for patients undergoing common interventional pain procedures. *Pain Med* 2017; 18:403-409.
1139. Selak V, Kerr A, Poppe K, et al. Annual risk of major bleeding among persons without cardiovascular disease not receiving antiplatelet therapy. *JAMA* 2018; 319:2507-2520.
1140. Chen LW, Yin HL. A literature review of antithrombotic and anticoagulating agents on sexual function. *Andrologia* 2017; 49:10.
1141. Sáez-Alcaide LM, Sola-Martín C, Molinero-Mourelle P, Paredes-Rodríguez V, Zarrias-Caballero C, Hernández-Vallejo G. Dental management in patients with antiplatelet therapy: A systematic review. *J Clin Exp Dent* 2017; 9:e1044-e1050.
1142. Kent TL, Custer PL. Bleeding complications in both anticoagulated and nonanticoagulated surgical patients. *Ophthalmic Plast Reconstr Surg* 2013; 29:113-117.
1143. Veitch AM. Endoscopy in patients on antiplatelet agents and anticoagulants. *Curr Treat Options Gastroenterol* 2017; 15:256-267.
1144. Baron TH, Kamath PS, McBane RD. Management of antithrombotic therapy in patients undergoing invasive procedures. *N Engl J Med* 2013; 368:2113-2124.
1145. Lucijanic M, Ziga S, Grgurevic I. Comment to: "Management and outcome of gastrointestinal bleeding in patients taking oral anticoagulants or antiplatelet drugs". *J Gastroenterol* 2017; 52:1075-1076.
1146. Goodman BS, House LM, Vallabhaneni S, Mallempati S, Willey MR, Smith MT. Anticoagulant and antiplatelet management for spinal procedures: A prospective, descriptive study and interpretation of guidelines. *Pain Med* 2017; 18:1218-1224.
1147. van Helmond N, Day W, Chapman KB. Continuing anti-thrombotic medication during low-to-intermediate risk spinal procedures: A retrospective evaluation. *Pain Physician* 2017; 20:437-443.
1148. Lagerkranser M. Neuraxial blocks and spinal haematoma: Review of 166 case reports published 1994-2015. Part 1: Demographics and risk-factors. *Scand J Pain* 2017; 15:118-129.
1149. Lagerkranser M, Lindquist C. Neuraxial blocks and spinal haematoma: Review of 166 cases published 1994 - 2015. Part 2: diagnosis, treatment, and outcome. *Scand J Pain* 2017; 15:130-136.
1150. Warner NS, Hooten WM, Warner MA, et al. Bleeding and neurologic complications in 58,000 interventional pain procedures. *Reg Anesth Pain Med* 2017; 42:782-787.
1151. Andrade JG, Macle L, Nattel S, Verma A, Cairns J. Contemporary atrial fibrillation management: A comparison of the current AHA/ACC/HRS, CCS, and ESC guidelines. *Can J Cardiol* 2017; 33:965-976.
1152. Steinberg BA, Washam JB. Appropriate dosing of nonvitamin K antagonist oral anticoagulants for stroke prevention in atrial fibrillation. *Trends Cardiovasc Med* 2017; 27:567-572.
1153. Erath JW, Hohnloser SH. Anticoagulation in atrial fibrillation: Current evidence and guideline recommendations. *Herz* 2018; 43:2-10.
1154. CDC, NCHS. Underlying Cause of Death 1999-2013 on CDC WONDER Online Database, released 2015. Data are from the Multiple Cause of Death Files, 1999-2013, as compiled from data provided by the 57 vital statistics jurisdictions through the Vital Statistics Cooperative Program.
1155. Becattini C, Franco L, Agnelli G. Risk of death in patients with major bleedings while on treatment with oral anticoagulants. *Int J Cardiol* 2017; 235:200.
1156. Melmed KR, Lyden P, Gellada N, Moheet A. Intracerebral hemorrhagic expansion occurs in patients using non-vitamin K Antagonist oral anticoagulants comparable with patients using warfarin. *J Stroke Cerebrovasc Dis* 2017; 26:1874-1882.
1157. Biondi-Zoccai GG, Lotrionte M, Agostoni P, et al. A systematic review and meta-analysis on the hazards of discontinuing or not adhering to aspirin among 50,279 patients at risk for coronary artery disease. *Eur Heart J* 2006; 27:2667-2674.
1158. Gurbel PA, Bliden KP, Hiatt BL, O'Connor CM. Clopidogrel for coronary stenting: Response variability, drug resistance, and the effect of pretreatment platelet reactivity. *Circulation* 2003; 107:2908-2913.
1159. Cerrato E, D'Ascenzo F, Biondi-Zoccai GG, Abbate A. Dual antiplatelet therapy after drug-eluting stent implantation: when is "enough" enough? *J Cardiovasc Pharmacol* 2014; 64:38-40.
1160. Zullo A, Hassan C, Radaelli F. Gastrointestinal endoscopy in patients on anticoagulant therapy and antiplatelet agents. *Ann Gastroenterol* 2017; 30:7-14.
1161. Saia F. Surgery after drug-eluting stent implantation: it's not all doom and gloom! *J Thorac Dis* 2017; 9:E373-E377.
1162. Huynh K. Pharmacotherapy: Aspirin discontinuation increases risk of cardiovascular events. *Nat Rev Cardiol* 2017; 14:696-697.
1163. Luni FK, Riaz H, Khan AR, et al. Clinical outcomes associated with per-operative discontinuation of aspirin in patients with coronary artery disease: A systematic review and meta-analysis. *Catheter Cardiovasc Interv* 2017; 89:1168-1175.
1164. Hastings S, Myles PS, McIlroy DR. Aspirin and coronary artery surgery: An updated meta-analysis. *Br J Anaesth* 2016; 116:716-717.
1165. Ho PM, Peterson ED, Wang L, et al. Incidence of death and acute myocardial infarction associated with stopping clopidogrel after acute coronary syndrome. *JAMA* 2008; 299:532-539. Erratum in: *JAMA* 2008; 299:2390.
1166. Marso SP, Amin AP, House JA, et al. Association between use of bleeding avoidance strategies and risk of periprocedural bleeding among patients undergoing percutaneous coronary intervention. *JAMA* 2010; 303:2156-2164.
1167. Sprigg N, Gray LJ, England T, et al. A randomised controlled trial of triple antiplatelet therapy (aspirin, clopidogrel and dipyridamole) in the secondary prevention of stroke: Safety, tolerability and feasibility. *PLoS One* 2008; 3:e2852.
1168. Walker CW, Dawley CA, Fletcher SF. Aspirin combined with clopidogrel (Plavix) decreases cardiovascular events in patients with acute coronary syndrome. *Am Fam Physician* 2007; 76:1643-1645.
1169. Bellini M, Barbieri M. Coagulation management in epidural steroid injection. *Anaesthesiol Intensive Ther* 2014; 46:195-199.
1170. Gogarten W, Van Aken H, Buttner J, Riess H, Wulf H, Buerkle H. Neuraxial blockade and thromboembolism prophylaxis/antithrombotic therapy: Revised recommendations of the German Society of Anaesthesiology

- and Intensive Care. *Anaesth Intensivmed* 2003; 44:218-230.
1171. Llau JV, de Andrés J, Gomar C, Gómez A, Hidalgo F, Sahagún J, Torres LM. Drugs that alter hemostasis and regional anesthetic techniques: Safety guidelines. Consensus Conference. *Rev Esp Anesthesiol Reanim* 2001; 48:270-278.
1172. Bugada D, Massimo A, Nicola Z, Antonio B, Battista B, Paolo G. Regional anesthesia and anticoagulant drugs: A survey of current Italian practice. *Eur J Pain Suppl* 2011; 5:335-343.
1173. Gogarten W, Buerkle H, Van Aken H. The use of concomitant antiplatelet drugs during neuraxial anesthesia is contraindicated in Germany. *Reg Anesth Pain Med* 2003; 28:585-586; author reply 586.
1174. Llau Pitarch JV, De Andrés Ibáñez J, Gomar Sancho C, Gómez Luque Z, Hidalgo Martínez F, Torres Morera LM. Hemostasis-altering drugs and techniques for regional anesthesia and analgesia: Safety recommendations. *Rev Esp Anesthesiol Reanim* 2005; 52:248-250.
1175. Kozek-Langenecker SA, Fries D, Gütl M, et al. Locoregional anesthesia and coagulation inhibitors. Recommendations of the Task Force on Perioperative Coagulation of the Austrian Society for Anesthesiology and Intensive Care Medicine. *Anaesthesist* 2005; 54:476-484.
1176. Beasley D, Goree JH. Cervical epidural hematoma following interlaminar epidural steroid injection via the contralateral oblique view in patient taking omega-3 fatty acids. *Reg Anesth Pain Med* 2019; 44:253-255.
1177. Karri J, Chien G, Polson G, McDaniel S, Glaser S. Case of an epidural hematoma following a lumbar epidural steroid injection in a patient taking aspirin and duloxetine. *PMCR* 2020; 4:121-126.
1178. Petro J, Asgerally A, Simopoulos T, Urits I, Aner M. Diagnosis and spontaneous resolution of an epidural hematoma in a patient presenting after cervical epidural steroid injection. *IPM Reports* 2018; 2:213-219.
1179. Yland MJ. Letter to Editor. Risk of spinal cord injury with interlaminar cervical epidural steroid injections, related to the dorsal muscular artery, and retrograde flow. *IPM Reports* 2019; 3:193-194.
1180. Noori S, Laufer I, Gulati A. Acute epidural hematoma occurring after removal of percutaneous spinal cord stimulator trial leads in a cancer patient with chronic thrombocytopenia: A case report. *IPM Reports* 2018; 2:27-33.
1181. Lam CM, Monroe BR, Novosat T. Spontaneous resolution of presumed acute epidural hematoma formation after lumbar epidural steroid injection. *IPM Reports* 2017; 1:157-161.
1182. Candido KD. Epidural hematoma formation following neuraxial interventional pain management procedures. Have we even begun to comprehend the mechanisms and risk factors? *IPM Reports* 2017; 1:7-10.
1183. Sanders RA, Bendel MA, Moeschler SM, Mauck WD. Epidural hematoma following interlaminar epidural injection in patient taking Aspirin. *Reg Anesth Pain Med* 2018; 43:310-312.
1184. Sawaya C, Sawaya R. Central nervous system bleeding after a lumbar puncture: Still an ongoing complication. *Am J Case Rep* 2018; 19:1103-1107.
1185. De Cassai A, Correale C, Sandei L. Neuraxial and perineural bleeding after neuraxial techniques: an overview of the last year. *Eurasian J Med* 2020; 52:211-216.
1186. Khan TW, Yacoub A. Pitfalls in interventional pain medicine: Hyponatremia after DDAVP for a patient with Von Willebrand Disease undergoing an epidural steroid injection. *Case Rep Anesthesiol* 2017; 2017:6467090.
1187. Banik RK, Chen Chen CC. Spinal epidural hematoma after interlaminar cervical epidural steroid injection. *Anesthesiology* 2019; 131:1342-1343.
1188. Mehta N. Intracranial hemorrhage and pneumocephaly after cervical epidural injection. *Clin Pract Cases Emerg Med* 2019; 3:369-371.
1189. Kim SI, Lee DH, Kim SH, Cho YH. Spinal epidural hematoma occurring at a distance from the transforaminal epidural injection site: A case report. *Medicine (Baltimore)* 2019; 98:e16654.
1190. Gungor S, Aiyer R. Epidural hematoma development contralateral to dura after lumbar transforaminal epidural steroid injection. *Pain Manag* 2017; 7:367-375.
1191. Zhang B, Chen J, Zou N, et al. Spontaneous resolution and complete recovery of spontaneous cervical epidural hematoma: Report of two cases and literature review. *Neurochirurgie* 2019; 65:27-31.
1192. Teles P, Correia JP, Pappamikail L, et al. A spontaneous cervical epidural hematoma mimicking a stroke - A case report. *Surg Neurol Int* 2020; 11:157.
1193. Emamhadi M, Ghadarjani S, Alijani B, et al. Spontaneous cervical epidural hematoma with stroke manifestations. *Asian J Neurosurg* 2019; 14:286-288.
1194. Mohamed EH, Dsouza LB, Elnabawy WA, Bashir K, Elmoheen A. Acute spinal extradural hematoma and cord compression: Case report and a literature review. *Cureus* 2020; 12:e11603.
1195. Gallice M, Rouberol F, Albaladejo P, et al. Managing antithrombotic therapy in vitreoretinal surgery. *J Fr Ophthalmol* 2015; 38:61-73.
1196. Benyamin RM, Vallejo R, Wang V, Kumar N, Cedeno DL, Tamrazi A. Acute epidural hematoma formation in cervical spine after interlaminar epidural steroid injection despite discontinuation of clopidogrel. *Reg Anesth Pain Med* 2016; 41:398-401.
1197. Buvanendran A, Young AC. Spinal epidural hematoma after spinal cord stimulator trial lead placement in a patient taking aspirin. *Reg Anesth Pain Med* 2014; 39:70-72.
1198. Chien GC, McCormick Z, Araujo M, Candido KD. The potential contributing effect of ketorolac and fluoxetine to a spinal epidural hematoma following a cervical interlaminar epidural steroid injection: A case report and narrative review. *Pain Physician* 2014; 17:E385-E395.
1199. Giberson CE, Barbosa J, Brooks ES, et al. Epidural hematomas after removal of percutaneous spinal cord stimulator trial leads: Two case reports. *Reg Anesth Pain Med* 2014; 39:73-77.
1200. Page J, Moisi M, Oskouian RJ. Lumbar epidural hematoma following interlaminar fluoroscopically guided epidural steroid injection. *Reg Anesth Pain Med* 2016; 41:402-404.
1201. Swicegood J, Manchikanti L, Benyamin R, Hirsch J. A report of acute thoracic epidural hematoma after interlaminar epidural injection. *IPM Reports* 2017; 1:33-38.
1202. Swicegood J, Manchikanti L, Benyamin R, Hirsch J. Two cases of acute epidural hematoma formation after cervical interlaminar epidural steroid injections. *IPM Reports* 2017; 1:27-32.
1203. Jenkie E, Benyamin R, Manchikanti L. Fish oil as a potential contributor to epidural hematoma following cervical epidural steroid injection: A case report and focused literature review. *IPM Reports* 2017; 1:19-26.
1204. Manchikanti L, Malla Y, Benyamin R, Hirsch J. Prevalence of epidural hematoma following cervical epidural injections in interventional pain management settings: Literature review

- with two case reports. *IPM Reports* 2017; 1:11-17.
1205. Kim SH, Han YJ, Kim YH, Lee JM, Kim YM, Park HJ. Spontaneous absorption of a lumbar epidural hematoma after interlaminar epidural steroid injection in a patient with spinal stenosis: Close observation as a treatment strategy. *Chin Med J (Engl)* 2018; 131:117-118.
1206. Castro VM, Gallagher PJ, Clements CC, et al. Incident user cohort study of risk for gastrointestinal bleed and stroke in individuals with major depressive disorder treated with antidepressants. *BMJ Open* 2012; 2:e000544.
1207. Manchikanti L, Gruber TJ, Prabhakar H, Hirsch JA. Acute epidural hematoma following a cervical epidural injection in a patient without bleeding risk. *IPM Reports* 2018; 2:119-126.
1208. Berrigan WA, Whitehair C, Zorowitz R. Acute spinal epidural hematoma as a complication of dry needling: A case report. *PM R* 2019; 11:313-316.
1209. Cameron CM, Scott DA, McDonald WM, Davies MJ. A review of neuraxial epidural morbidity: Experience of more than 8,000 cases at a single teaching hospital. *Anesthesiology* 2007; 106:997-1002.
1210. Caputo AM, Gottfried ON, Nimjee SM, Brown CR, Michael KW, Richardson WJ. Spinal epidural hematoma following epidural steroid injection in a patient treated with dabigatran: A case report. *JBJS Case Connect* 2013; 3:e64.
1211. Warner NS, Moeschler SM, Warner MA, et al. Bleeding complications in patients undergoing celiac plexus block. *Reg Anesth Pain Med* 2016; 41:488-493.
1212. Lagerkranser M, Johnsson H, Ljungström KG. Management of thrombocyte inhibitors prior to surgery. Too early withdrawal can result in severe risks for the patient. *Lakartidningen* 2008; 105:2188-2189.
1213. Lenzer J. Anticoagulants cause the most serious adverse events, finds US analysis. *BMJ* 2012; 344:e3989.
1214. Gould MK, Garcia DA, Wren SM, et al. Prevention of VTE in nonorthopedic surgical patients: Antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest* 2012; 141:e227S-e277S.
1215. Falck-Ytter Y, Francis CW, Johanson NA, et al. Prevention of VTE in orthopedic surgery patients: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest* 2012; 141:e278S-e325S.
1216. ACCP-NHLBI national conference on antithrombotic therapy. American College of Chest Physicians and the National Heart, Lung and Blood Institute. *Chest* 1986; 89:1S-106S.
1217. Guyatt GH, Akl EA, Crowther M, Schünemann HJ, Gutterman DD, Lewis SZ. Introduction to the ninth edition: Antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest* 2012; 141:485-52S.
1218. Eikelboom JW, Hirsh J, Spencer FA, Baglin TP, Weitz JI. Antiplatelet drugs: Antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest* 2012; 141:e89S-e119S.
1219. Kumar V, Turakhia PB, Wunnava MS. Pulmonary embolism during dorsal column stimulator (DCS) trial. *Reg Anesth Pain Med* 2013; 38 (abstract only).
1220. Linn AJ, Desilva C, Peeters-Asdourian C. Thromboembolic stroke: A rare complication associated with periprocedural management of an epidural steroid injection. *Pain Physician* 2009; 12:159-162.
1221. Yoo HS, Park SW, Han JH, Chung JY, Yi JW, Kang JM, Lee BJ, Kim DO. Paraplegia caused by an epidural hematoma in a patient with unrecognized chronic idiopathic thrombocytopenic purpura following an epidural steroid injection. *Spine (Phila Pa 1976)* 2009; 34:E376-E379.
1222. Desai MJ, Dua S. Perineural hematoma following lumbar transforaminal steroid injection causing acute-on-chronic lumbar radiculopathy: A case report. *Pain Pract* 2014; 14:271-277.
1223. Shanthanna H, Park J. Acute epidural haematoma following epidural steroid injection in a patient with spinal stenosis. *Anaesthesia* 2011; 66:837-839.
1224. Williams KN, Jackowski A, Evans PJ. Epidural haematoma requiring surgical decompression following repeated cervical epidural steroid injections for chronic pain. *Pain* 1990; 42:197-199.
1225. Ghaly RF. Recovery after high-dose methylprednisolone and delayed evacuation: A case of spinal epidural hematoma. *J Neurosurg Anesthesiol* 2001; 13:323-328.
1226. Weller RS, Gerancher JC, Crews JC, Wade KL. Extensive retroperitoneal hematoma without neurologic deficit in two patients who underwent lumbar plexus block and were later anticoagulated. *Anesthesiology* 2003; 98:581-585.
1227. Stoll A, Sanchez M. Epidural hematoma after epidural block: Implications for its use in pain management. *Surg Neurol* 2002; 57:235-240.
1228. Chiravuri S, Wasserman R, Chawla A, Haider N. Subdural hematoma following spinal cord stimulator implant. *Pain Physician* 2008; 11:97-101.
1229. Xu R, Bydon M, Gokaslan ZL, Wolinsky JP, Witham TF, Bydon A. Epidural steroid injection resulting in epidural hematoma in a patient despite strict adherence to anticoagulation guidelines. *J Neurosurg Spine* 2009; 11:358-364.
1230. Ain RJ, Vance MB. Epidural hematoma after epidural steroid injection in a patient withholding enoxaparin per guidelines. *Anesthesiology* 2005; 102:701-703.
1231. Lee JH, Lee H, Jo DJ. An acute cervical epidural hematoma as a complication of dry needling. *Spine (Phila Pa 1976)* 2011; 36:E891-E893.
1232. Reitman CA, Watters W 3rd. Subdural hematoma after cervical epidural steroid injection. *Spine (Phila Pa 1976)* 2002; 27:E174-E176.
1233. Eftekhari B, Ketabchi E, Ghodsi M, Esmaeili B. Lumbar epidural hematoma due to lumbar acupuncture. *Neurol India* 2005; 53:245-246.
1234. Ozdemir O, Calisaneller T, Yildirim E, Altinors N. Acute intracranial subdural hematoma after epidural steroid injection: A case report. *J Manipulative Physiol Ther* 2007; 30:536-538.
1235. Chen JC, Chen Y, Lin SM, Yang HJ, Su CF, Tseng SH. Acute spinal epidural hematoma after acupuncture. *J Trauma* 2006; 60:414-416.
1236. Lee JY, Nassr A, Ponnappan RK. Epidural hematoma causing paraplegia after a fluoroscopically guided cervical nerve-root injection. A case report. *J Bone Joint Surg Am* 2007; 89:2037-2039.
1237. Bose B. Quadriplegia following cervical epidural steroid injections: Case report and review of the literature. *Spine J* 2005; 5:558-563.
1238. Domenicucci M, Marruzzo D, Pesce A, Raco A, Missori P. Acute spinal epidural hematoma after acupuncture: Personal case and literature review. *World Neurosurg* 2017; 102:695.e11-695.e14.
1239. Maier C, Gleim M, Weiss T, Stachetzki U, Nicolas V, Zenz M. Severe bleeding



- following lumbar sympathetic blockade in two patients under medication with irreversible platelet aggregation inhibitors. *Anesthesiology* 2002; 97:740-743.
1240. Keane JR, Ahmadi J, Gruen P. Spinal epidural hematoma with subarachnoid hemorrhage caused by acupuncture. *AJNR Am J Neuroradiol* 1993; 14:365-366.
1241. Choi JJ, Chang YJ, Jung WS, Lee KC, Kim JH, Jo YY. Discordant lumbar epidural hematoma after caudal steroid injection: A case report (CARE-compliant). *Medicine (Baltimore)* 2017; 96:e7127.
1242. Kim M, Park KS. Intracranial chronic subdural hematoma presenting with intractable headache after cervical epidural steroid injection. *J Korean Neurosurg Soc* 2015; 58:144-146.
1243. Takawira N, Han RJ, Nguyen TQ, Gaines JD, Han TH. Spinal cord stimulator and epidural haematoma. *BJA* 2012; 109:649-650.
1244. Kloss BT, Sullivan AM, Rodriguez E. Epidural hematoma following spinal cord stimulator implant. *Int J Emerg Med* 2010; 3:483-484.
1245. Smith CC, Lin JL, Shokat M, Dosanjh SS, Casthely D. A report of paraparesis following spinal cord stimulator trial, implantation and revision. *Pain Physician* 2010; 13:357-363.
1246. Santiago FM, Santiago J, Prieto M, et al. Dorsal epidural hematoma after implantation of a dorsal nerve stimulator. *Rev Esp Anestesiol Reanim* 2005; 52:440-441.
1247. Nam KH, Hwa Choi CH, Yang MS, Kang DW. Spinal epidural hematoma after pain control procedure. *J Korean Neurosurg Soc* 2010; 48:281-284.
1248. Chen CY, Liu GC, Sheu RS, Huang CL. Bacterial meningitis and lumbar epidural hematoma due to lumbar acupuncture: A case report. *Kaohsiung J Med Sci* 1997; 13:328-331.
1249. Dehaene S, Biesemans J, Van Boxem K, Vidts W, Sterken J, Van Zundert J. Post-dural puncture headache evolving to a subdural hematoma: A case report. *Pain Pract* 2021; 21:83-87.
1250. Raj PP, Shah RV, Kaye AD, Denaro S, Hoover JM. Bleeding risk in interventional pain practice: Assessment, management, and review of the literature. *Pain Physician* 2004; 7:3-51.
1251. Mallett SV. Clinical utility of viscoelastic tests of coagulation (TEG/ROTEM) in patients with liver disease and during liver transplantation. *Semin Thromb Hemost* 2015; 41:527-537.
1252. Thomas O, Rein H, Strandberg K, Schott U. Coagulative safety of epidural catheters after major upper gastrointestinal surgery: Advanced and routine coagulation analysis in 38 patients. *Perioper Med (Lond)* 2016; 5:28.
1253. Thomas OD. Haemostatic safety in epidural analgesia. Lund: Lund University, Faculty of Medicine, Doctoral Dissertation Series 2016:117. Accessed 12/14/2020.  
[http://portal.research.lu.se/portal/files/15557976/Haemostatic\\_safety\\_in\\_epidural\\_analgesia\\_minus\\_manus.pdf](http://portal.research.lu.se/portal/files/15557976/Haemostatic_safety_in_epidural_analgesia_minus_manus.pdf)
1254. Forkin KT, Colquhoun DA, Nemerlut EC, Huffmeyer JL. The coagulation profile of end-stage liver disease and considerations for intraoperative management. *Anesth Analg* 2018; 126:46-61.
1255. Patrono C, Baigent C, Hirsh J, Roth G; Physicians American College of Chest Physicians. Antiplatelet drugs: American College of Chest Physicians evidence-based clinical practice guidelines (8th Edition). *Chest* 2008; 133:199S-233S.
1256. Moshfegh K, Redondo M, Julmy F, et al. Antiplatelet effects of clopidogrel compared with aspirin after myocardial infarction: Enhanced inhibitory effects of combination therapy. *J Am Coll Cardiol* 2000; 36:699-705.
1257. Kolber MR, Korownyk C. An aspirin a day? Aspirin use across a spectrum of risk: Cardiovascular disease, cancers and bleeds. *Expert Opin Pharmacother* 2014; 15:153-157.
1258. Onyeji CO, Tessier PR, Nightingale CH, Vallee F, Nicolau DP. Pharmacokinetics of ticlopidine in the rabbit. *J Pharm Pharmacol* 1999; 51:393-396.
1259. Baker WL, White CM. Role of prasugrel, a novel P2Y<sub>12</sub> receptor antagonist, in the management of acute coronary syndromes. *Am J Cardiovasc Drugs* 2009; 9:213-229.
1260. Brandt JT, Close SL, Iturria SJ, et al. Common polymorphisms of CYP2C19 and CYP2C9 affect the pharmacokinetic and pharmacodynamic response to clopidogrel but not prasugrel. *J Thromb Haemost* 2007; 5:2429-2436.
1261. Gu X, Fu X, Wang Y, et al. Comparison of ticagrelor and high-dose clopidogrel on the platelet functions in patients with inadequate response to clopidogrel. *Am J Cardiovasc Dis* 2017; 7:1-8.
1262. Teng R. Ticagrelor: Pharmacokinetic, pharmacodynamic and pharmacogenetic profile: An update. *Clin Pharmacokinet* 2015; 54:1125-1138.
1263. Teng R, Oliver S, Hayes MA, Butler K. Absorption, distribution, metabolism, and excretion of ticagrelor in healthy subjects. *Drug Metab Dispos* 2010; 38:1514-1521.
1264. Gurbel PA, Bliden KP, Butler K, et al. Randomized double-blind assessment of the ONSET and OFFSET of the antiplatelet effects of ticagrelor versus clopidogrel in patients with stable coronary artery disease: The ONSET/OFFSET study. *Circulation* 2009; 120:2577-2585.
1265. Weber AA, Schrör K. Pharmacology of ticlopidine and clopidogrel in comparison with acetylsalicylic acid. *Internist (Berl)* 1997; 38:1115-1120.
1266. Schror K. The pharmacology of cilostazol. *Diabetes Obes Metab* 2002; 4:S14-S19.
1267. Russell TL, Berardi RR, Barnett JL, O'Sullivan TL, Wagner JG, Dressman JB. pH-related changes in the absorption of dipyridamole in the elderly. *Pharm Res* 1994; 11:136-143.
1268. Woo SK, Kang WK, Kwon KI. Pharmacokinetic and pharmacodynamic modeling of the antiplatelet and cardiovascular effects of cilostazol in healthy humans. *Clin Pharmacol Ther* 2002; 71:246-252.
1269. Lee K, Kim JY, Yoo BS, Yoon J, Hong MK, Ahn MS, Choe H, Lee SH. Cilostazol augments the inhibition of platelet aggregation in clopidogrel low-responders. *J Thromb Haemost* 2010; 8:2577-2579.
1270. Ikeda Y, Kikuchi M, Murakami H, et al. Comparison of the inhibitory effects of cilostazol, acetylsalicylic acid and ticlopidine on platelet functions ex vivo. Randomized, double-blind crossover study. *Arzneimittelforschung* 1987; 37:563-566.
1271. Collier BS. Anti-GPIIb/IIIa drugs: Current strategies and future directions. *Thromb Haemost* 2001; 86:427-443.
1272. Horlocker TT, Heit JA. Low molecular weight heparin: Biochemistry, pharmacology, perioperative prophylaxis regimens, and guidelines for regional anesthetic management. *Anesth Analg* 1997; 85:874-885.
1273. Ansell J, Hirsh J, Hylek E, et al. Pharmacology and management of the vitamin K antagonists: American College of Chest Physicians evidence-





1310. Zhu HJ, Wang JS, Markowitz JS, et al. Characterization of Pglycoprotein inhibition by major cannabinoids from marijuana. *J Pharmacol Exp Ther* 2006; 317:850-857.
1311. Qian Y, Gurley BJ, Markowitz JS. The potential for pharmacokinetic interactions between cannabis products and conventional medications. *J Clin Psychopharm* 2019; 39: 462-471.
1312. Jiang R, Yamaori S, Okamoto Y, et al. Cannabidiol is a potent inhibitor of the catalytic activity of cytochrome P4502C19. *Drug Metab Pharmacokin* 2013; 28:332-338.
1313. Dereska NH, McLemore EC, Tessier DJ, Bash DS, Brophy CM. Short-term, moderate dosage Vitamin E supplementation may have no effect on platelet aggregation, coagulation profile, and bleeding time in healthy individuals. *J Surg Res* 2006; 132:121-129.
1314. Duffy S, Vita JA, Keaney JF Jr. Antioxidants and endothelial function. *Heart Failure* 1999; 15:135.
1315. Li D, Saldeen T, Romeo F, Mehta JL. Different isoforms of tocopherols enhance nitric oxide synthase phosphorylation and inhibit human platelet aggregation and lipid peroxidation: implications in therapy with vitamin E. *J Cardiovasc Pharmacol Ther* 2001; 6:155-161.
1316. Saldeen T, Li D, Mehta JL. Differential effects of alpha- and gamma-tocopherol on low-density lipoprotein oxidation, superoxide activity, platelet aggregation and arterial thrombogenesis. *J Am Coll Cardiol* 1999; 34:1208-1215. Erratum in: *J Am Coll Cardiol* 2000; 35:263.
1317. Li D, Saldeen T, Romeo F, Mehta JL. Relative effects of alpha- and gamma-tocopherol on low-density lipoprotein oxidation and superoxide dismutase and nitric oxide synthase activity and protein expression in rats. *J Cardiovasc Pharmacol Ther* 1999; 4:219-226.
1318. Bakaltcheva I, Gyimah D, Reid T. Effects of alpha-tocopherol on platelets and the coagulation system. *Platelets* 2001; 12:389-394.
1319. Stampfer MJ, Jakubowski JA, Faigel D, Vaillancourt R, Deykin D. Vitamin E supplementation effect on human platelet function, arachidonic acid metabolism, and plasma prostacyclin levels. *Am J Clin Nutr* 1988; 47:700-706.
1320. Morinobu T, Ban R, Yoshikawa S, Murata T, Tamai H. The safety of high-dose vitamin E supplementation in healthy Japanese male adults. *J Nutr Sci Vitaminol (Tokyo)* 2002; 48:6-9.
1321. Busti AJ. *The mechanism for how omega-3 fatty acids (fish oil) could increase the risk of bleeding.* *EBM Consult, Last Reviewed October 2015. Accessed 1/7/2021.* [www.ebmconsult.com/articles/fish-oil-omega-3-fatty-acids-EPA-DHA-Lovaza-platelet-inhibition-bleeding-risk-mechanism](http://www.ebmconsult.com/articles/fish-oil-omega-3-fatty-acids-EPA-DHA-Lovaza-platelet-inhibition-bleeding-risk-mechanism)
1322. Begtrup KM, Krag AE, Hvas AM. No impact of fish oil supplements on bleeding risk: A systematic review. *Dan Med J* 2017; 64:A5366.
1323. Schlienger RG, Meier CR. Effect of selective serotonin reuptake inhibitors on platelet activation: Can they prevent acute myocardial infarction? *Am J Cardiovasc Drugs* 2003; 3:149-162.
1324. Maurer-Spurrej E. Serotonin reuptake inhibitors and cardiovascular diseases: A platelet connection. *Cell Mol Life Sci* 2005; 62:159-170.
1325. Li N, Wallén NH, Ladjevardi M, Hjendahl P. Effects of serotonin on platelet activation in whole blood. *Blood Coagul Fibrinolysis* 1997; 8:517-523.
1326. De Abajo FJ. Effects of selective serotonin reuptake inhibitors on platelet function: Mechanisms, clinical outcomes and implications for use in elderly patients. *Drugs Aging* 2011; 28:345-367.
1327. Sewnath ME, van Hillegersberg R, Koopman MM, Levi MM, Gouma DJ. Increased perioperative blood loss during treatment with paroxetine. *Ned Tijdschr Geneesk* 2002; 146:1800-1802.
1328. Turner MS, May DB, Arthur RR, Xiong GL. Clinical impact of selective serotonin reuptake inhibitors therapy with bleeding risks. *J Intern Med* 2007; 261:205-213.
1329. Hergovich N, Aigner M, Eichler HG, Entlicher J, Drucker C, Jilma B. Paroxetine decreases platelet serotonin storage and platelet function in human beings. *Clin Pharmacol Ther* 2000; 68:435-442.
1330. Auerbach AD, Vittinghoff E, Maselli J, Pekow PS, Young JQ, Lindenauer PK. Perioperative use of selective serotonin reuptake inhibitors and risks for adverse outcomes of surgery. *JAMA Intern Med* 2013; 173:1075-1081.
1331. Srivastava KC. Evidence for the mechanism by which garlic inhibits platelet aggregation. *Prostaglandins Leukot Med* 1986; 22:313-321.
1332. Rendu F, Daveloose D, Debouzy JC, et al. Ajoene, the antiplatelet compound derived from garlic, specifically inhibits platelet release reaction by affecting the plasma membrane internal microviscosity. *Biochem Pharmacol* 1989; 38:1321-1328.
1333. Biber A. Pharmacokinetics of ginkgo biloba extracts. *Pharmacopsychiatry* 2003; 36:S32-S37.
1334. Koch E. Inhibition of platelet activating factor (PAF)-induced aggregation of human thrombocytes by ginkgolides: Considerations on possible bleeding complications after oral intake of Ginkgo biloba extracts. *Phytomedicine* 2005; 12:1016.
1335. Teng CM, Kuo SC, Ko FN, et al. Antiplatelet actions of panaxynol and ginsenosides isolated from ginseng. *Biochim Biophys Acta* 1989; 990:315-320.
1336. Manchikanti L, Helm S, Singh V, et al. An algorithmic approach for clinical management of chronic spinal pain. *Pain Physician* 2009; 12:E225-E264.
1337. Manchikanti L, Singh V, Hirsch JA. Compliance and documentation for interventional techniques. In: Manchikanti L, Kaye AD, Falco FJE, Hirsch JA (eds). *Essentials of Interventional Techniques in Managing Chronic Spinal Pain*. Springer, New York, NY, 2018, pp 35-40.
1338. Manchikanti L, Singh V, Hirsch JA. Documentation for interventional techniques: In-office, ASC, and HOPD. In: Manchikanti L (ed). *Essentials of Practice Management: Billing, Coding, and Compliance in Interventional Pain Management*. ASIPP Publishing, Paducah, KY, 2012, pp 181-198.
1339. Centers for Medicare and Medicaid Services. COVID-19 vaccine policies and guidance. Accessed 1.18.2021. [www.cms.gov/covidvax](http://www.cms.gov/covidvax)
1340. ICD-10-CM 2021: The Complete Official Codebook. 1st edition. American Medical Association, Chicago, 2020.
1341. H.R. 2015. Balanced Budget Act of 1997. P.L. 105-33, August 5, 1997.
1342. Medicare Program Integrity Manual. Chapter 13 – Local Coverage Determinations. Accessed 01/19/2020. [www.cms.gov/Regulations-and-Guidance/Guidance/Manuals/downloads/pim83c13.pdf](http://www.cms.gov/Regulations-and-Guidance/Guidance/Manuals/downloads/pim83c13.pdf)
1343. Social Security Act Section 1862(a) (1) (A). Accessed 01/19/2020. [www.ssa.gov/OP\\_Home/ssact/title18/1862.htm](http://www.ssa.gov/OP_Home/ssact/title18/1862.htm)
1344. Quinn C. Issues of medical necessity. A medical director's guide to good faith adjudication. *Am J Managed Care* 1997; 3:883-888.
1345. Garner BA (ed). *Black's Law Dictionary*. 11th Edition. Thomson Reuters, St. Paul, 2019.



## ASIPP Epidural Guidelines

Appendix Table 1. Sources of risk of bias from Cochrane Review collaboration.

Bias Domain	Source of Bias		Possible Answers
Selection	(1) Was the method of randomization adequate?	<p>A random (unpredictable) assignment sequence. Examples of adequate methods are coin toss (for studies with 2 groups), rolling a dice (for studies with 2 or more groups), drawing of balls of different colors, drawing of ballots with the study group labels from a dark bag, computer-generated random sequence, preordered sealed envelopes, sequentially-ordered vials, telephone call to a central office, and preordered list of treatment assignments.</p> <p>Examples of inadequate methods are: alternation, birth date, social insurance/security number, date in which they are invited to participate in the study, and hospital registration number.</p>	Yes/No/Unsure
Selection	(2) Was the treatment allocation concealed?	Assignment generated by an independent person not responsible for determining the eligibility of the patients. This person has no information about the persons included in the trial and has no influence on the assignment sequence or on the decision about eligibility of the patient.	Yes/No/Unsure
Performance	(3) Was the patient blinded to the intervention?	Index and control groups are indistinguishable for the patients or if the success of blinding was tested among the patients and it was successful.	Yes/No/Unsure
Performance	(4) Was the care provider blinded to the intervention?	Index and control groups are indistinguishable for the care providers or if the success of blinding was tested among the care providers and it was successful.	Yes/No/Unsure
Detection	(5) Was the outcome assessor blinded to the intervention?	<p>Adequacy of blinding should be assessed for each primary outcome separately. This item should be scored “yes” if the success of blinding was tested among the outcome assessors and it was successful or:</p> <ul style="list-style-type: none"> <li>• for patient-reported outcomes in which the patient is the outcome assessor (e.g., pain, disability): the blinding procedure is adequate for outcome assessors if participant blinding is scored “yes”</li> <li>• for outcome criteria assessed during scheduled visit and that supposes a contact between participants and outcome assessors (e.g., clinical examination): the blinding procedure is adequate if patients are blinded, and the treatment or adverse effects of the treatment cannot be noticed during clinical examination</li> <li>• for outcome criteria that do not suppose a contact with participants (e.g., radiography, magnetic resonance imaging): the blinding procedure is adequate if the treatment or adverse effects of the treatment cannot be noticed when assessing the main outcome</li> <li>• for outcome criteria that are clinical or therapeutic events that will be determined by the interaction between patients and care providers (e.g., cointerventions, hospitalization length, treatment failure), in which the care provider is the outcome assessor: the blinding procedure is adequate for outcome assessors if item “4” (caregivers) is scored “yes”</li> <li>• for outcome criteria that are assessed from data of the medical forms: the blinding procedure is adequate if the treatment or adverse effects of the treatment cannot be noticed on the extracted data</li> </ul>	Yes/No/Unsure
Attrition	(6) Was the drop-out rate described and acceptable?	The number of participants who were included in the study but did not complete the observation period or were not included in the analysis must be described and reasons given. If the percentage of withdrawals and drop-outs does not exceed 20% for short-term follow-up and 30% for long-term follow-up and does not lead to substantial bias a “yes” is scored (N.B. these percentages are arbitrary, not supported by literature).	Yes/No/Unsure
Attrition	(7) Were all randomized participants analyzed in the group to which they were allocated?	All randomized patients are reported/analyzed in the group they were allocated to by randomization for the most important moments of effect measurement (minus missing values) irrespective of noncompliance and cointerventions.	Yes/No/Unsure
Reporting	(8) Are reports of the study free of suggestion of selective outcome reporting?	All the results from all prespecified outcomes have been adequately reported in the published report of the trial. This information is either obtained by comparing the protocol and the report, or in the absence of the protocol, assessing that the published report includes enough information to make this judgment.	Yes/No/Unsure

Appendix Table 1 (con't). Sources of risk of bias from Cochrane Review collaboration.

Bias Domain	Source of Bias		Possible Answers
Selection	(1) Was the method of randomization adequate?	A random (unpredictable) assignment sequence. Examples of adequate methods are coin toss (for studies with 2 groups), rolling a dice (for studies with 2 or more groups), drawing of balls of different colors, drawing of ballots with the study group labels from a dark bag, computer-generated random sequence, preordered sealed envelopes, sequentially-ordered vials, telephone call to a central office, and preordered list of treatment assignments.	Yes/No/Unsure
		Examples of inadequate methods are: alternation, birth date, social insurance/security number, date in which they are invited to participate in the study, and hospital registration number.	
Selection	(2) Was the treatment allocation concealed?	Assignment generated by an independent person not responsible for determining the eligibility of the patients. This person has no information about the persons included in the trial and has no influence on the assignment sequence or on the decision about eligibility of the patient.	Yes/No/Unsure
Performance	(3) Was the patient blinded to the intervention?	Index and control groups are indistinguishable for the patients or if the success of blinding was tested among the patients and it was successful.	Yes/No/Unsure
Performance	(4) Was the care provider blinded to the intervention?	Index and control groups are indistinguishable for the care providers or if the success of blinding was tested among the care providers and it was successful.	Yes/No/Unsure
Detection	(5) Was the outcome assessor blinded to the intervention?	Adequacy of blinding should be assessed for each primary outcome separately. This item should be scored "yes" if the success of blinding was tested among the outcome assessors and it was successful or:	Yes/No/Unsure
		<ul style="list-style-type: none"> <li>for patient-reported outcomes in which the patient is the outcome assessor (e.g., pain, disability): the blinding procedure is adequate for outcome assessors if participant blinding is scored "yes"</li> </ul>	
		<ul style="list-style-type: none"> <li>for outcome criteria assessed during scheduled visit and that supposes a contact between participants and outcome assessors (e.g., clinical examination): the blinding procedure is adequate if patients are blinded, and the treatment or adverse effects of the treatment cannot be noticed during clinical examination</li> </ul>	
		<ul style="list-style-type: none"> <li>for outcome criteria that do not suppose a contact with participants (e.g., radiography, magnetic resonance imaging): the blinding procedure is adequate if the treatment or adverse effects of the treatment cannot be noticed when assessing the main outcome</li> </ul>	
		<ul style="list-style-type: none"> <li>for outcome criteria that are clinical or therapeutic events that will be determined by the interaction between patients and care providers (e.g., cointerventions, hospitalization length, treatment failure), in which the care provider is the outcome assessor: the blinding procedure is adequate for outcome assessors if item "4" (caregivers) is scored "yes"</li> </ul>	
Attrition	(6) Was the drop-out rate described and acceptable?	The number of participants who were included in the study but did not complete the observation period or were not included in the analysis must be described and reasons given. If the percentage of withdrawals and drop-outs does not exceed 20% for short-term follow-up and 30% for long-term follow-up and does not lead to substantial bias a "yes" is scored (N.B. these percentages are arbitrary, not supported by literature).	Yes/No/Unsure
Attrition	(7) Were all randomized participants analyzed in the group to which they were allocated?	All randomized patients are reported/analyzed in the group they were allocated to by randomization for the most important moments of effect measurement (minus missing values) irrespective of noncompliance and cointerventions.	Yes/No/Unsure
Reporting	(8) Are reports of the study free of suggestion of selective outcome reporting?	All the results from all prespecified outcomes have been adequately reported in the published report of the trial. This information is either obtained by comparing the protocol and the report, or in the absence of the protocol, assessing that the published report includes enough information to make this judgment.	Yes/No/Unsure



Appendix Table 1 (con't). Sources of risk of bias from Cochrane Review collaboration.

Bias Domain	Source of Bias		Possible Answers
Selection	(9) Were the groups similar at baseline regarding the most important prognostic indicators?	Groups have to be similar at baseline regarding demographic factors, duration and severity of complaints, percentage of patients with neurological symptoms, and value of main outcome measure(s).	Yes/No/Unsure
Performance	(10) Were cointerventions avoided or similar?	If there were no cointerventions or they were similar between the index and control groups.	Yes/No/Unsure
Performance	(11) Was the compliance acceptable in all groups?	The reviewer determines if the compliance with the interventions is acceptable, based on the reported intensity, duration, number and frequency of sessions for both the index intervention and control intervention(s). For example, physiotherapy treatment is usually administered for several sessions; therefore it is necessary to assess how many sessions each patient attended. For single-session interventions (e.g., surgery), this item is irrelevant.	Yes/No/Unsure
Detection	(12) Was the timing of the outcome assessment similar in all groups?	Timing of outcome assessment should be identical for all intervention groups and for all primary outcome measures.	Yes/No/Unsure
Other	(13) Are other sources of potential bias unlikely?	<p>Other types of biases. For example:</p> <ul style="list-style-type: none"> <li>When the outcome measures were not valid. There should be evidence from a previous or present scientific study that the primary outcome can be considered valid in the context of the present.</li> <li>Industry-sponsored trials. The conflict of interest (COI) statement should explicitly state that the researchers have had full possession of the trial process from planning to reporting without funders with potential COI having any possibility to interfere in the process. If, for example, the statistical analyses have been done by a funder with a potential COI, usually "unsure" is scored.</li> </ul>	Yes/No/Unsure

Source: Furlan AD, et al; Editorial Board of the Cochrane Back, Neck Group. 2015 updated method guideline for systematic reviews in the Cochrane Back and Neck Group. *Spine (Phila Pa 1976)* 2015; 40:1660-1673 (154).

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

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

## ASIPP Epidural Guidelines

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

		Scoring
	> 6 months	2
9.	Previous Treatments	
	Conservative management including drug therapy, exercise therapy, physical therapy, etc.	
	Were not utilized	0
	Were utilized sporadically in some patients	1
	Were utilized in all patients	2
10.	Duration of Follow-up with Appropriate Interventions	
	Less than 3 months or 12 weeks for epidural or facet joint procedures, etc. and 6 months for intradiscal procedures and implantables	0
	3 to 6 months for epidural or facet joint procedures, etc., or 1 year for intradiscal procedures or implantables	1
	6 months to 17 months for epidurals or facet joint procedures, etc., and 2 years or longer for discal procedures and implantables	2
	18 months or longer for epidurals and facet joint procedures, etc., or 5 years or longer for discal procedures and implantables	3
IV.	OUTCOMES	
11.	Outcomes Assessment Criteria for Significant Improvement	
	No descriptions of outcomes OR < 20% change in pain rating or functional status	0
	Pain rating with a decrease of 2 or more points or more than 20% reduction OR functional status improvement of more than 20%	1
	Pain rating with decrease of $\geq 2$ points AND $\geq 20\%$ change or functional status improvement of 20%	2
	Pain rating with a decrease of 3 or more points or more than 50% reduction OR functional status improvement with a 50% or 40% reduction in disability score	2
	Significant improvement with pain and function $\geq 50\%$ or 3 points and 40% reduction in disability scores	4
12.	Analysis of all Randomized Participants in the Groups	
	Not performed	0
	Performed without intent-to-treat analysis without inclusion of all randomized participants	1
	All participants included with or without intent-to-treat analysis	2
13.	Description of Drop Out Rate	
	No description of dropouts, despite reporting of incomplete data or $\geq 20\%$ withdrawal	0
	Less than 20% withdrawal in one year in any group	1
	Less than 30% withdrawal at 2 years in any group	2
14.	Similarity of Groups at Baseline for Important Prognostic Indicators	
	Groups dissimilar with significant influence on outcomes with or without appropriate randomization and allocation	0
	Groups dissimilar without influence on outcomes despite appropriate randomization and allocation	1
	Groups similar with appropriate randomization and allocation	2
15.	Role of Co-Interventions	
	Co-interventions were provided but were not similar in the majority of participants	0
	No co-interventions or similar co-interventions were provided in the majority of the participants	1
V.	RANDOMIZATION	
16.	Method of Randomization	
	Quasi randomized or poorly randomized or not described	0

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

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

Appendix Table 3. Degree of evidence as described by SIGN.

1++	- High-quality meta-analysis and systematic review conducted by randomized clinical trials - RCTs with a very low risk of bias
1+	- Well-designed meta-analysis and systematic review conducted by randomized or non-randomized clinical trials - Randomized or non-randomized clinical trials with a low risk of bias
1-	- Meta analysis and systematic review conducted by randomized or non-randomized clinical trials - Randomized or non-randomized clinical trials with a high risk of bias
2++	High-quality systematic review conducted by a patient control study, cohort study, or diagnosis analytic study - High-quality patient control study, cohort study, or diagnosis analytic study of very low risk of confounding, bias or contingency, or a high possibility of cause and effect relationship
2+	- High-quality patient control study, cohort study, or diagnosis analytic study of the low risk of a confounding, bias or contingency, or the normal possibility of a cause and effect relationship
2-	- Patient control study, cohort study, or diagnosis analytic study of the high risk of a confounding bias or contingency, or the low possibility of a cause and effect relationship
3	- Non-analytic studies, e.g., before-and-after study, case series, case report
4	- Expert opinion

Source: Harbour R, Miller J. A new system for grading recommendations in evidence based guidelines. *BMJ* 2001; 323:334-336 (125).



Appendix Table 4. *IPM checklist for assessment of nonrandomized or observational studies of IPM techniques utilizing IPM-QRBNR.*

		Scoring
I.	STUDY DESIGN AND GUIDANCE REPORTING	
1.	STROBE or TREND Guidance	
	Case Report/Case Series	0
	Study designed without any guidance	1
	Study designed with minimal criteria and reporting with or without guidance	2
	Study designed with moderately significant criteria or implies it was based on STROBE or TREND without clear description or the study was conducted before 2011 or similar criteria utilized with study conducted before 2011	3
	Designed with high level criteria or explicitly uses STROBE or TREND with identification of criteria or conducted prior to 2011	4
II.	DESIGN FACTORS	
2.	Study Design and Type	
	Case report or series (uncontrolled – longitudinal)	0
	Retrospective cohort or cross-sectional study	1
	Prospective cohort case-control study	2
	Prospective case control study	3
	Prospective, controlled, nonrandomized	4
3.	Setting/Physician	
	General setting with no specialty affiliation and general physician	0
	Specialty of anesthesia/PMR/neurology, etc.	1
	Interventional pain management with interventional pain management physician	2
4.	Imaging	
	Blind procedures	0
	Ultrasound	1
	CT	2
	Fluoro	3
5.	Sample Size	
	Less than 100 participants without appropriate sample size determination	0
	At least 100 participants in the study without appropriate sample size determination	1
	Sample size calculation with less than 50 patients in each group	2
	Appropriate sample size calculation with at least 50 patients in each group	3
	Appropriate sample size calculation with 100 patients in each group	4
6.	Statistical Methodology	
	None	0
	Some statistics	1
	Appropriate	2
III.	PATIENT FACTORS	
7.	Inclusiveness of Population	
7a.	For epidural procedures:	
	Poorly identified mixed population	1
	Poorly identified mixed population with large sample ( $\geq 200$ )	2
	Clearly identified mixed population	3
	Disorders specific trials (i.e. well defined spinal stenosis and disc herniation, disorder specific, disc herniation or spinal stenosis or post-surgery syndrome)	4
7b.	For facet or sacroiliac joint interventions:	

## ASIPP Epidural Guidelines

Appendix Table 4. *IPM checklist for assessment of nonrandomized or observational studies of IPM techniques utilizing IPM-QRBNR. (continued)*

		Scoring
	No specific selection criteria	1
	No diagnostic blocks based on clinical symptomatology	2
	Selection with single diagnostic blocks	3
	Selection with placebo or dual diagnostic blocks	4
8.	Duration of Pain	
	Less than 3 months	0
	3 to 6 months	1
	> 6 months	2
9.	Previous Treatments	
	Conservative management including drug therapy, exercise therapy, physical therapy, etc.	
	Were not utilized	0
	Were utilized sporadically in some patients	1
	Were utilized in all patients	2
10.	Duration of Follow-up with Appropriate Interventions	
	Less than 3 months or less for epidural or facet joint procedures, etc., and 6 months for intradiscal procedures and implantables	1
	3-6 months for epidural or facet joint procedures, etc., or one year for intradiscal procedures or implantables	2
	6-12 months for epidurals or facet joint procedures, etc., and 2 years or longer for discal procedures and implantables	3
	18 months or longer for epidurals and facet joint procedures, etc., or 5 years or longer for discal procedures and implantables	4
IV.	OUTCOMES	
11.	Outcomes Assessment Criteria for Significant Improvement	
	No descriptions of outcomes OR < 20% change in pain rating or functional status	0
	Pain rating with a decrease of 2 or more points or more than 20% reduction OR functional status improvement of more than 20%	1
	Pain rating with decrease of $\geq 2$ points AND $\geq 20\%$ change or functional status improvement of 20%	2
	Pain rating with a decrease of 3 or more points or more than 50% reduction OR functional status improvement with a 50% or 40% reduction in disability score	2
	Significant improvement with pain and function $\geq 50\%$ or 3 points and 40% reduction in disability scores	4
12.	Description of Drop Out Rate	
	No description despite reporting of incomplete data or more than 30% withdrawal	0
	Less than 30% withdrawal in one year in any group	1
	Less than 40% withdrawal at 2 years in any group	2
13.	Similarity of Groups at Baseline for Important Prognostic Indicators	
	No groups or groups dissimilar with significant influence on outcomes	0
	Groups dissimilar without significant influence on outcomes	1
	Groups similar	2
14.	Role of Co-Interventions	
	Dissimilar co-interventions or similar co-interventions in some of the participants	1
	No co-interventions or similar co-interventions in majority of the participants	2

Appendix Table 4. *IPM checklist for assessment of nonrandomized or observational studies of IPM techniques utilizing IPM-QRBNR. (continued)*

		Scoring
V.	ASSIGNMENT	
15.	Method of Assignment of Participants	
	Case report/case series or selective assignment based on outcomes or retrospective evaluation based on clinical criteria	1
	Prospective study with inclusion without specific criteria	2
	Retrospective method with inclusion of all participants or random selection of retrospective data	3
	Prospective, well-defined assignment of methodology and inclusion criteria (quasi randomization, matching, stratification, etc.)	4
VI.	CONFLICTS OF INTEREST	
16.	Funding and Sponsorship	
	Trial included industry employees with or without proper disclosure	-3
	Industry employees involved; high levels of funding with remunerations by industry or an organization funded with conflicts	-3
	Industry or organizational funding with reimbursement of expenses with some involvement or no information available	0
	Industry or organization funding of expenses without involvement	1
	Funding by internal resources only	2
	Governmental funding without conflict such as NIH, NHS, AHRQ	3
TOTAL MAXIMUM		48

Source: Manchikanti L, et al. Development of an interventional pain management specific instrument for methodologic quality assessment of non-randomized studies of interventional techniques. *Pain Physician* 2014; 17:E291-E317 (157).

Appendix Table 5. Methodological quality assessment of fluoroscopic randomized trials of caudal epidural injections utilizing Cochrane review criteria.

	Manchikanti et al (765)	Ackerman & Ahmad (783)	Dashfield et al (784)	Murakibhavi & Khemka (786)	Manchikanti et al (767)	Manchikanti et al (762)	Manchikanti et al (766)	Kamble et al (770)	Pandey (769)	Singh et al (779)
Randomization adequate	Y	N	Y	Y	Y	Y	Y	Y	N	N
Concealed treatment allocation	Y	N	Y	N	Y	Y	Y	Y	N	N
Patient blinded	Y	N	Y	Y	Y	Y	Y	Y	N	N
Care provider blinded	Y	N	N	N	Y	Y	Y	N	N	N
Outcome assessor blinded	N	N	N	N	N	N	N	Y	N	N
Drop-out rate described	Y	Y	Y	Y	Y	Y	Y	N	Y	Y
All randomized participants analyzed in the group	Y	Y	Y	Y	Y	Y	Y	N	Y	Y
Reports of the study free of suggestion of selective outcome reporting	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Groups similar at baseline regarding most important prognostic indicators	Y	Y	Y	N	Y	Y	Y	Y	Y	Y
Co-interventions avoided or similar	Y	Y	N	N	Y	Y	Y	Y	Y	Y
Compliance acceptable in all group	Y	Y	Y	Y	Y	Y	Y	U	Y	Y
Time of outcome assessment in all groups similar	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Are other sources of potential bias not likely	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
SCORE	12/13	8/13	10/13	8/13	12/13	12/13	12/13	9/13	8/13	8/13

Y = Yes; N = No; U = Unclear  
 Source: Furlan AD, et al; Editorial Board of the Cochrane Back, Neck Group. 2015 updated method guideline for systematic reviews in the Cochrane Back and Neck Group. *Spine (Phila Pa 1976)* 2015; 40:1660-1673 (154).

Appendix Table 6. Methodologic quality assessment of randomized trials of caudal epidural injections utilizing IPM-QRB.

	Singh et al (779)	Manchikanti et al (765)	Ackerman & Ahmad (783)	Dashfield et al (784)	Murakibhavi & Khemka (786)	Manchikanti et al (767)	Manchikanti et al (762)	Manchikanti et al (766)	Pandey (769)	Kamble et al (770)
<b>I. TRIAL DESIGN AND GUIDANCE REPORTING</b>										
1.	1	3	0	1	2	3	3	3	0	0
<b>II. DESIGN FACTORS</b>										
2.	2	2	2	2	2	2	2	2	2	2
3.	2	2	2	2	1	2	2	2	2	2
4.	3	3	3	3	3	3	3	3	2	2
5.	2	3	1	1	2	3	3	3	1	2
6.	1	1	1	1	1	1	1	1	1	1
<b>III. PATIENT FACTORS</b>										
7.	2	2	2	1	2	2	2	2	2	2
8.	2	2	1	2	1	2	2	2	2	1
9.	2	2	0	0	0	2	2	2	2	2
10.	1	3	2	2	1	3	3	3	2	1
<b>IV. OUTCOMES</b>										
11.	2	4	1	2	4	4	4	4	2	2
12.	2	2	2	2	2	2	2	2	2	2
13.	2	2	2	2	2	2	2	2	2	0
14.	1	1	1	1	0	1	1	1	1	1
15.	1	1	1	1	0	1	1	1	1	1
<b>V. RANDOMIZATION</b>										
16.	0	2	0	2	0	2	2	2	0	2
<b>VI. ALLOCATION CONCEALMENT</b>										
17.	0	2	0	2	2	2	2	2	0	2
<b>VII. BLINDING</b>										
18.	0	1	0	1	1	1	1	1	0	1
19.	0	1	0	0	0	1	1	1	0	0
20.	0	0	0	0	0	0	0	0	0	1
<b>VIII. CONFLICTS OF INTEREST</b>										
21.	2	2	1	2	0	2	2	2	2	2
22.	2	3	3	3	1	3	3	3	3	3
<b>TOTAL</b>	<b>30</b>	<b>44</b>	<b>25</b>	<b>33</b>	<b>27</b>	<b>44</b>	<b>44</b>	<b>44</b>	<b>29</b>	<b>32</b>

Source: Manchikanti L, et al. Assessment of methodologic quality of randomized trials of interventional techniques: Development of an interventional pain management specific instrument. *Pain Physician* 2014; 17:E263-E290 (153).



Appendix Table 7. Methodological quality assessment of randomized trials assessing fluoroscopic lumbar interlaminar epidural injections utilizing Cochrane review criteria.

	Ackerman & Ahmad (783)	Rados et al (821)	Amr (823)	Manchikanti et al (799)	Manchikanti et al (801)	Manchikanti et al (797)	Friedly et al (273,318)	Ghai et al (617)	Ghai et al (804)	Candido et al (843)	Ökmen and Ökmen (817)	Kamble et al (770)	Pandey (769)
Randomization adequate	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N
Concealed treatment allocation	N	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N
Patient blinded	N	N	Y	Y	Y	Y	N	N	Y	N	Y	Y	N
Care provider blinded	N	N	Y	Y	Y	Y	N	N	N	N	Y	N	N
Outcome assessor blinded	N	N	Y	N	N	N	N	N	N	N	Y	Y	N
Drop-out rate described	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	N	Y
All randomized participants analyzed in the group	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	N	N	Y
Reports of the study free of suggestion of selective outcome reporting	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y
Groups similar at baseline regarding most important prognostic indicators	Y	Y	Y	N	N	N	Y	Y	Y	Y	Y	Y	Y
Co-interventions avoided or similar	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Compliance acceptable in all group	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	U	Y
Time of outcome assessment in all groups similar	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Are other sources of potential bias not likely	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y
SCORE	8/13	9/13	12/13	11/13	11/13	11/13	8/13	10/13	10/13	10/13	12/13	9/13	8/13

Y = Yes; N = No; U = Unclear  
 Source: Furlan AD, et al; Editorial Board of the Cochrane Back, Neck Group. 2015 updated method guideline for systematic reviews in the Cochrane Back and Neck Group. *Spine (Phila Pa 1976)* 2015; 40:1660-1673 (154).

Appendix Table 8. Methodologic quality assessment of randomized trials assessing fluoroscopic lumbar interlaminar epidural injections utilizing IPM-QRB.

		Ackerman & Ahmad (783)	Rados et al (821)	Amr (823)	Manchikanti et al (799)	Manchikanti et al (801)	Manchikanti et al (797)
I.	TRIAL DESIGN AND GUIDANCE REPORTING						
1.	CONSORT or SPIRIT	0	2	2	3	3	3
II.	DESIGN FACTORS						
2.	Type and Design of Trial	2	2	2	2	2	2
3.	Setting/Physician	2	3	3	2	2	2
4.	Imaging	3	3	3	3	3	3
5.	Sample Size	1	1	3	3	3	3
6.	Statistical Methodology	1	1	1	1	1	1
III.	PATIENT FACTORS						
7.	Inclusiveness of Population	2	1	2	2	2	2
8.	Duration of Pain	1	2	2	2	2	2
9.	Previous Treatments	0	0	2	2	2	2
10.	Duration of Follow-up with Appropriate Interventions	2	2	3	3	3	3
IV.	OUTCOMES						
11.	Outcomes Assessment Criteria for Significant Improvement	1	2	2	4	4	4
12.	Analysis of all Randomized Participants in the Groups	2	2	1	2	2	2
13.	Description of Drop Out Rate	2	2	2	2	2	2
14.	Similarity of Groups at Baseline for Important Prognostic Indicators	1	2	2	0	1	1
15.	Role of Co-Interventions	1	1	1	1	1	1
V.	RANDOMIZATION						
16.	Method of Randomization	0	2	2	2	2	2
VI.	ALLOCATION CONCEALMENT						
17.	Concealed Treatment Allocation	0	0	2	2	2	2
VII.	BLINDING						
18.	Patient Blinding	0	0	1	1	1	1
19.	Care Provider Blinding	0	0	1	1	1	1
20.	Outcome Assessor Blinding	0	0	1	0	0	0
VIII.	CONFLICTS OF INTEREST						
21.	Funding and Sponsorship	1	0	0	2	2	2
22.	Conflicts of Interest	3	2	0	3	3	3
TOTAL		25	30	38	43	44	44

Source: Manchikanti L, et al. Assessment of methodologic quality of randomized trials of interventional techniques: Development of an interventional pain management specific instrument. *Pain Physician* 2014; 17:E263-E290 (153).

Appendix Table 8 (cont.). *Methodologic quality assessment of randomized trials assessing fluoroscopic lumbar interlaminar epidural injections utilizing IPM-QRB.*

		Friedly et al (278,818)	Ghai et al (617)	Ghai et al (804)	Candido et al (843)	Ökmen and Ökmen (817)	Pandey (769)	Kamble et al (770)
I.	TRIAL DESIGN AND GUIDANCE REPORTING							
1.	CONSORT or SPIRIT	3	3	3	2	2	0	0
II.	DESIGN FACTORS							
2.	Type and Design of Trial	2	2	2	2	2	2	2
3.	Setting/Physician	2	2	2	2	2	2	2
4.	Imaging	3	3	3	3	3	2	2
5.	Sample Size	3	2	2	2	3	1	2
6.	Statistical Methodology	0	1	1	1	1	1	1
III.	PATIENT FACTORS							
7.	Inclusiveness of Population	1	2	2	2	2	2	2
8.	Duration of Pain	1	2	1	1	2	2	1
9.	Previous Treatments	1	2	1	2	2	2	2
10.	Duration of Follow-up with Appropriate Interventions	0	3	3	2	2	2	1
IV.	OUTCOMES							
11.	Outcomes Assessment Criteria for Significant Improvement	0	4	4	2	2	2	2
12.	Analysis of all Randomized Participants in the Groups	2	2	2	2	1	2	2
13.	Description of Drop Out Rate	2	2	0	2	2	2	0
14.	Similarity of Groups at Baseline for Important Prognostic Indicators	2	2	2	2	2	1	1
15.	Role of Co-Interventions	0	1	1	1	1	1	1
V.	RANDOMIZATION							
16.	Method of Randomization	2	2	2	2	2	0	2
VI.	ALLOCATION CONCEALMENT							
17.	Concealed Treatment Allocation	2	2	2	2	2	0	2
VII.	BLINDING							
18.	Patient Blinding	0	0	1	0	1	0	1
19.	Care Provider Blinding	0	0	0	0	0	0	0
20.	Outcome Assessor Blinding	0	0	0	0	1	0	1
VIII.	CONFLICTS OF INTEREST							
21.	Funding and Sponsorship	3	2	2	2	2	2	2
22.	Conflicts of Interest	1	3	3	3	3	3	3
TOTAL		30	42	39	37	40	29	32

Source: Manchikanti L, et al. Assessment of methodologic quality of randomized trials of interventional techniques: Development of an interventional pain management specific instrument. *Pain Physician* 2014; 17:E263-E290 (153).

Appendix Table 9. Methodological quality assessment of randomized trials of fluoroscopic transforaminal epidural injections utilizing Cochrane review criteria.

	Ackerman & Ahmad (763)	Rados et al (821)	Karppinen et al (856)	Jeong et al (857)	Riew et al (275,276)	Tafazal et al (881)	Vad et al (879)	Manchikanti et al (860)	Friedly et al (278,818)	Chai et al (617)	Kennedy et al (273)	Kamble et al (770)	Pandey (769)
Randomization adequate	N	Y	Y	U	U	Y	U	Y	Y	Y	Y	Y	N
Concealed treatment allocation	N	N	Y	U	U	Y	N	Y	Y	Y	Y	Y	N
Patient blinded	N	N	Y	Y	Y	Y	N	Y	N	N	N	Y	N
Care provider blinded	N	N	Y	N	N	Y	N	Y	N	N	N	N	N
Outcome assessor blinded	N	N	Y	Y	Y	N	U	N	N	N	N	Y	N
Drop-out rate described	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	N	Y
All randomized participants analyzed in the group	Y	Y	Y	Y	Y	N	N	Y	Y	Y	Y	N	Y
Reports of the study free of suggestion of selective outcome reporting	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y
Groups similar at baseline regarding most important prognostic indicators	Y	Y	Y	Y	U	Y	Y	N	Y	Y	Y	Y	Y
Co-interventions avoided or similar	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Compliance acceptable in all group	Y	Y	Y	Y	Y	Y	U	Y	Y	Y	Y	U	Y
Time of outcome assessment in all groups similar	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Are other sources of potential bias not likely	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y
SCORE	8/13	9/13	13/13	10/13	9/13	11/13	5/13	11/13	8/13	10/13	10/13	9/13	8/13

Y = Yes; N = No; U = Unclear  
 Source: Furlan AD, et al; Editorial Board of the Cochrane Back, Neck Group. 2015 updated method guideline for systematic reviews in the Cochrane Back and Neck Group. *Spine (Phila Pa 1976)* 2015; 40:1660-1673 (154).

ASIPP Epidural Guidelines

Appendix Table 10. *Methodologic quality assessment of randomized trials of fluoroscopic transforaminal epidural injections utilizing IPM-QRB.*

		Ackerman & Ahmad (783)	Rados et al (821)	Karppinen et al (856)	Jeong et al (857)	Riew et al (275,276)	Tafazal et al (881)	Vad et al (879)
I.	TRIAL DESIGN AND GUIDANCE REPORTING							
1.	CONSORT or SPIRIT	0	2	2	2	1	2	1
II.	DESIGN FACTORS							
2.	Type and Design of Trial	2	2	2	2	2	2	2
3.	Setting/Physician	2	3	1	1	1	1	1
4.	Imaging	3	3	3	3	3	3	2
5.	Sample Size	1	1	3	3	2	1	1
6.	Statistical Methodology	1	1	1	1	1	1	1
III.	PATIENT FACTORS							
7.	Inclusiveness of Population	2	1	2	1	2	1	2
8.	Duration of Pain	1	2	0	0	1	1	0
9.	Previous Treatments	0	0	0	0	2	2	0
10.	Duration of Follow-up with Appropriate Interventions	2	2	1	2	2	1	1
IV.	OUTCOMES							
11.	Outcomes Assessment Criteria for Significant Improvement	1	2	2	2	1	2	2
12.	Analysis of all Randomized Participants in the Groups	2	2	2	2	2	1	0
13.	Description of Drop Out Rate	2	2	1	2	2	1	0
14.	Similarity of Groups at Baseline for Important Prognostic Indicators	1	2	2	2	2	1	0
15.	Role of Co-Interventions	1	1	0	1	0	1	1
V.	RANDOMIZATION							
16.	Method of Randomization	0	2	2	1	1	2	0
VI.	ALLOCATION CONCEALMENT							
17.	Concealed Treatment Allocation	0	0	2	0	0	2	0
VII.	BLINDING							
18.	Patient Blinding	0	0	1	1	1	1	0
19.	Care Provider Blinding	0	0	1	0	1	1	0
20.	Outcome Assessor Blinding	0	0	1	1	0	0	0
VIII.	CONFLICTS OF INTEREST							
21.	Funding and Sponsorship	1	0	2	2	2	2	0
22.	Conflicts of Interest	3	2	3	2	3	3	2
TOTAL		25	30	34	31	32	32	16



Appendix Table 10 (cont.). Methodologic quality assessment of randomized trials of fluoroscopic transforaminal epidural injections utilizing IPM-QRB.

		Manchikanti et al (860)	Friedly et al (278,818)	Ghai et al (617)	Kennedy et al (273)	Pandey (769)	Kamble et al (770)
<b>I.</b>	<b>TRIAL DESIGN AND GUIDANCE REPORTING</b>						
1.	CONSORT or SPIRIT	3	3	3	3	0	0
<b>II.</b>	<b>DESIGN FACTORS</b>						
2.	Type and Design of Trial	2	2	2	2	2	2
3.	Setting/Physician	2	2	2	2	2	2
4.	Imaging	3	3	3	3	2	2
5.	Sample Size	3	3	2	2	1	2
6.	Statistical Methodology	1	0	1	1	1	1
<b>III.</b>	<b>PATIENT FACTORS</b>						
7.	Inclusiveness of Population	2	1	2	2	2	2
8.	Duration of Pain	2	1	2	0	2	1
9.	Previous Treatments	2	1	2	2	2	2
10.	Duration of Follow-up with Appropriate Interventions	3	0	3	1	2	1
<b>IV.</b>	<b>OUTCOMES</b>						
11.	Outcomes Assessment Criteria for Significant Improvement	4	0	4	2	2	2
12.	Analysis of all Randomized Participants in the Groups	2	2	2	2	2	2
13.	Description of Drop Out Rate	2	2	2	1	2	0
14.	Similarity of Groups at Baseline for Important Prognostic Indicators	1	2	2	2	1	1
15.	Role of Co-Interventions	1	0	1	1	1	1
<b>V.</b>	<b>RANDOMIZATION</b>						
16.	Method of Randomization	2	2	2	2	0	2
<b>VI.</b>							
17.	Concealed Treatment Allocation	2	2	2	2	0	2
<b>VII.</b>	<b>BLINDING</b>						
18.	Patient Blinding	1	0	0	0	0	1
19.	Care Provider Blinding	1	0	0	0	0	0
20.	Outcome Assessor Blinding	0	0	0	0	0	1
<b>VIII.</b>	<b>CONFLICTS OF INTEREST</b>						
21.	Funding and Sponsorship	2	3	2	0	2	2
22.	Conflicts of Interest	3	1	3	0	3	3
<b>TOTAL</b>		<b>44</b>	<b>30</b>	<b>42</b>	<b>30</b>	<b>29</b>	<b>32</b>

Source: Manchikanti L, et al. Assessment of methodologic quality of randomized trials of interventional techniques: Development of an interventional pain management specific instrument. *Pain Physician* 2014; 17:E263-E290 (153).

Appendix Table 11. *Methodological quality assessment of randomized trials of percutaneous adhesiolysis procedures utilizing Cochrane review criteria.*

	Chun-jing et al (896)	Manchikanti et al (893,894)	Heavner et al (899)	Manchikanti et al (897)	Akbas et al (901)	Gerdsmeyer et al (895)	Manchikanti et al (891,892)	Veihelmann et al (898)	Karm et al (900)
Randomization adequate	Y	Y	U	Y	Y	Y	Y	Y	Y
Concealed treatment allocation	Y	Y	U	Y	Y	Y	Y	Y	Y
Patient blinded	Y	Y	Y	Y	N	Y	Y	N	Y
Care provider blinded	N	N	N	N	N	Y	N	N	N
Outcome assessor blinded	Y	U	Y	Y	NA	Y	N	Y	N
Drop-out rate described	Y	Y	Y	Y	Y	Y	Y	U	Y
All randomized participants analyzed in the group	Y	Y	Y	Y	Y	Y	Y	Y	Y
Reports of the study free of suggestion of selective outcome reporting	Y	Y	Y	Y	Y	Y	Y	Y	Y
Groups similar at baseline regarding most important prognostic indicators	Y	Y	Y	Y	Y	Y	Y	U	Y
Co-interventions avoided or similar	Y	Y	Y	Y	Y	Y	Y	N	Y
Compliance acceptable in all group	Y	Y	Y	Y	Y	Y	Y	Y	Y
Time of outcome assessment in all groups similar	Y	Y	Y	Y	Y	Y	Y	Y	Y
Are other sources of potential bias not likely	Y	Y	Y	Y	Y	Y	Y	Y	Y
SCORE	12/13	11/13	10/13	12/13	9/13	13/13	11/13	8/13	11/13

Y = Yes; N = No; U = Unclear

Source: Furlan AD, et al; Editorial Board of the Cochrane Back, Neck Group. 2015 updated method guideline for systematic reviews in the Cochrane Back and Neck Group. *Spine (Phila Pa 1976)* 2015; 40:1660-1673 (154).

Appendix Table 12. Methodologic quality assessment of randomized trials of percutaneous adhesiolysis procedures utilizing IPM-QRB.

	Chun-jing et al (896)	Manchikanti et al (893,894)	Heavner et al (899)	Manchikanti et al (897)	Akbas et al (901)	Gerdesmeyer et al (895)	Manchikanti et al (891,892)	Veihelmann et al (898)	Karm et al (900)
<b>I. TRIAL DESIGN AND GUIDANCE REPORTING</b>									
1.	0	3	0	3	2	3	2	0	2
<b>II. DESIGN FACTORS</b>									
2.	2	2	2	2	2	3	2	2	2
3.	1	2	2	2	2	2	2	1	2
4.	3	3	3	3	3	3	3	3	3
5.	2	3	0	2	2	2	2	2	1
6.	1	1	1	1	1	1	1	1	1
<b>III. PATIENT FACTORS</b>									
7.	2	2	1	1	2	2	2	2	2
8.	1	2	2	2	2	2	2	2	2
9.	2	2	2	2	2	2	2	2	2
10.	1	2	2	2	1	2	2	2	2
<b>IV. OUTCOMES</b>									
11.	2	4	0	2	2	4	4	4	2
12.	2	2	1	2	2	2	1	1	1
13.	1	1	0	1	0	1	1	0	1
14.	2	2	2	2	2	2	1	1	1
15.	1	1	1	1	1	1	1	1	1
<b>V. RANDOMIZATION</b>									
16.	2	2	0	2	2	2	2	1	2
<b>VI. ALLOCATION CONCEALMENT</b>									
17.	2	2	1	1	2	2	1	1	2
<b>VII. BLINDING</b>									
18.	1	1	1	1	0	1	1	0	1
19.	0	0	0	0	0	1	0	0	0
20.	1	0	0	1	0	1	0	1	0
<b>VIII. CONFLICTS OF INTEREST</b>									
21.	2	2	2	2	2	2	2	2	2
22.	3	3	0	3	3	3	2	1	2
TOTAL	34	42	23	37	35	44	36	30	34

Source: Manchikanti L, et al. Assessment of methodologic quality of randomized trials of interventional techniques: Development of an interventional pain management specific instrument. *Pain Physician* 2014; 17:E263-E290 (153).

Appendix Table 13. *Assessment of nonrandomized or observational studies of percutaneous adhesiolysis procedures in lumbar spinal stenosis meeting inclusion criteria utilizing IPM-QRBNR.*

		<b>Choi et al (908)</b>	<b>Choi et al (910)</b>
I.	STUDY DESIGN AND GUIDANCE REPORTING		
1.	STROBE or TREND GUIDANCE	2	2
II.	DESIGN FACTORS		
2.	Study Design and Type	3	2
3.	Setting/Physician	2	2
4.	Imaging	3	3
5.	Sample Size	0	0
6.	Statistical Methodology	2	2
III.	PATIENT FACTORS		
7.	Inclusiveness of Population	2	0
8.	Duration of Pain	2	2
9.	Previous Treatments	2	2
10.	Duration of Follow-up with Appropriate Interventions	2	1
IV.	OUTCOMES		
11.	Outcomes Assessment Criteria for Significant Improvement	2	2
12.	Description of Drop Out Rate	0	1
13.	Similarity of Groups at Baseline for Important Prognostic Indicators	0	0
14.	Role of Co-Interventions	2	2
V.	ASSIGNMENT		
15.	Method of Assignment of Participants	2	0
VI.	CONFLICTS OF INTEREST		
16.	Funding and Sponsorship	2	2
TOTAL		28	24

Source: Manchikanti L, et al. Development of an interventional pain management specific instrument for methodologic quality assessment of nonrandomized studies of interventional techniques. *Pain Physician* 2014; 17:E291-E317 (157).

Appendix Table 14. *Methodological quality assessment of randomized trials assessing fluoroscopic cervical/thoracic interlaminar epidural injections utilizing Cochrane review criteria.*

	<b>Manchikanti et al (922)</b>	<b>Manchikanti et al (924)</b>	<b>Manchikanti et al (925)</b>	<b>Manchikanti et al (927)</b>	<b>Manchikanti et al (588)</b>	<b>Cohen et al (932)</b>	<b>McCormick et al (941)</b>
Randomization adequate	Y	Y	Y	Y	Y	Y	Y
Concealed treatment allocation	Y	Y	Y	Y	Y	N	Y
Patient blinded	Y	Y	Y	Y	Y	N	N
Care provider blinded	Y	Y	Y	Y	Y	N	N
Outcome assessor blinded	N	N	N	N	N	N	N
Drop-out rate described	Y	Y	Y	Y	Y	Y	Y
All randomized participants analyzed in the group	Y	Y	Y	Y	Y	N	Y
Reports of the study free of suggestion of selective outcome reporting	Y	Y	Y	Y	Y	Y	Y
Groups similar at baseline regarding most important prognostic indicators	Y	N	N	N	N	Y	Y
Co-interventions avoided or similar	Y	Y	Y	Y	Y	Y	Y
Compliance acceptable in all group	Y	Y	Y	Y	Y	N	Y
Time of outcome assessment in all groups similar	Y	Y	Y	Y	Y	Y	Y
Are other sources of potential bias not likely	Y	Y	Y	Y	Y	N	Y
SCORE	12/13	11/13	11/13	11/13	11/13	6/13	10/13

Y = Yes; N = No; U = Unclear

Source: Furlan AD, Malmivaara A, Chou R, et al; Editorial Board of the Cochrane Back, Neck Group. 2015 updated method guideline for systematic reviews in the Cochrane Back and Neck Group. *Spine (Phila Pa 1976)* 2015; 40:1660-1673 (154).



ASIPP Epidural Guidelines

Appendix Table 15. *Methodologic quality assessment of randomized trials assessing fluoroscopic cervical/thoracic interlaminar epidural injections utilizing IPM-QRB.*

		Manchikanti et al (922)	Manchikanti et al (924)	Manchikanti et al (925)	Manchikanti et al (927)	Cohen et al (932)	McCormick et al (941)	Manchikanti et al (588)
I.	TRIAL DESIGN AND GUIDANCE REPORTING							
1.	CONSORT or SPIRIT	3	3	3	3	3	3	3
II.	DESIGN FACTORS							
2.	Type and Design of Trial	2	2	2	2	2	2	2
3.	Setting/Physician	2	2	2	2	2	2	2
4.	Imaging	3	3	3	3	3	3	3
5.	Sample Size	3	3	2	2	3	2	3
6.	Statistical Methodology	1	1	1	1	1	1	1
III.	PATIENT FACTORS							
7.	Inclusiveness of Population	2	2	2	2	2	2	2
8.	Duration of Pain	2	2	2	2	0	0	2
9.	Previous Treatments	2	2	2	2	0	2	2
10.	Duration of Follow-up with Appropriate Interventions	3	3	2	2	1	1	3
IV.	OUTCOMES							
11.	Outcomes Assessment Criteria for Significant Improvement	4	4	4	4	0	2	4
12.	Analysis of all Randomized Participants in the Groups	2	2	2	2	0	2	2
13.	Description of Drop Out Rate	2	2	2	2	2	2	2
14.	Similarity of Groups at Baseline for Important Prognostic Indicators	0	1	1	1	1	2	0
15.	Role of Co-Interventions	1	1	1	1	0	1	1
V.	RANDOMIZATION							
16.	Method of Randomization	2	2	2	2	2	2	2
VI.	ALLOCATION CONCEALMENT							
17.	Concealed Treatment Allocation	2	2	2	2	0	2	2
VII.	BLINDING							
18.	Patient Blinding	1	1	1	1	0	1	1
19.	Care Provider Blinding	1	1	1	1	0	0	1
20.	Outcome Assessor Blinding	0	0	0	0	0	0	0
VIII.	CONFLICTS OF INTEREST							
21.	Funding and Sponsorship	2	2	2	2	1	2	2
22.	Conflicts of Interest	3	3	3	3	1	3	3
TOTAL		43	44	42	42	24	37	43

Source: Manchikanti L, et al. Assessment of methodologic quality of randomized trials of interventional techniques: Development of an interventional pain management specific instrument. *Pain Physician* 2014; 17:E263-E290 (153).

Appendix Table 16. *Studies assessing the risk of thrombosis and bleeding with interventional pain management techniques.*

Study/Year	Methods	Results	Conclusions by the Study Authors	Author Conclusions of the Review
Manchikanti et al, 2012 (1128)	An online physician survey of antithrombotics with complications with or without discontinuation of various antithrombotics and anticoagulants.	The results illustrated an overwhelming pattern of discontinuing antiplatelet and warfarin therapy as well as aspirin and other NSAIDs prior to performing interventional pain management techniques. However, thromboembolic complications were 3 times more prevalent than epidural hematomas (162 versus 55 events).	The authors concluded that clinicians must balance the risks of thromboembolism and bleeding in each patient prior to the routine discontinuation of antiplatelet therapy.	This study essentially shows that even though there is no evidence of increased risk of epidural hematoma, the majority of physicians discontinue antiplatelet therapy despite increased risk of thromboembolic complications.
Manchikanti et al, 2011 (1129)	The prospective evaluation of measurable outcomes of intravascular entry of the needle, bruising, local bleeding, profuse bleeding, local hematoma, oozing, and postoperative soreness.	In this study, one-quarter (3,087) of patient encounters undergoing interventional pain management procedures, were on antithrombotic therapy. Antithrombotic therapy was continued in 55% of the patients or 1,711 encounters, whereas, it was discontinued in 45% of the patients or 1,376 encounters.  There was no difference in significant side effect rate with or without continuation of antithrombotic therapy.	Of the 1,831 patients receiving aspirin 604 discontinued and 1,227 continued and all of them received epidural injections including cervical, thoracic, lumbar interlaminar, and caudal epidural injections. Of the total 326 patients undergoing epidural injections on clopidogrel 226 discontinued and 100 continued with patients undergoing all types of epidural injections including cervical, thoracic, and lumbar interlaminar epidural injections. However, for cervical epidural injections a large proportion discontinued (67) versus continued (10).  There was no clinical or statistical difference in any of the major aspects of bleeding.	This study essentially showed that there is no significant difference in bleeding patterns whether antithrombotic agents are continued or discontinued except for warfarin with no fatal incidents in a large proportion of patients.
Moeschler et al, 2016 (1131)	A total of 642 percutaneous SCS procedures were performed on 421 unique patients, including 346 SCS trials, 255 SCS implantations, and 41 revision surgeries. Patients had received aspirin or NSAIDs within 7 days of needle placement for 101 procedures (15.7%).	They performed 642 percutaneous spinal cord stimulation procedures, trial, revision, or implantation in 421 patients. No major bleeding complications. They have performed 101 procedures on patients who had taken aspirin or NSAIDs within 7 days of procedure. There were no bleeding or neurological complications identified in this cohort.	Although the incidence of epidural hematoma is low, the development of bleeding complications following SCS lead placement can be devastating. In the present investigation, we identified no cases of epidural hematoma following percutaneous SCS lead placement, including more than 100 patients receiving aspirin or NSAIDs. Future investigations with larger numbers are needed to better define the relationships between periprocedural aspirin and NSAID utilization and bleeding complications.	Even though authors have shown no complications with continuation of NSAIDs or aspirin within 7 days in approximately 16% of the patients, the study consists of a small number of patients.  Further, this agrees with older guidance of continuation of NSAIDs and aspirin in the perioperative period, even though it is contradictory to more recent guidelines (1111).
Petraglia et al, 2016 (1137)	Of the 8,326 patients meeting inclusion criteria receiving spinal cord stimulation, 5,458 were percutaneous and 2,868 were paddle leads. The overall incidence of spinal cord injury was 177 or 2.13% with percutaneous lead placement contributing to 128 or 2.35% incidences versus paddle leads contributing to 49 or 1.71% incidence.	Of the 8,326 patients meeting inclusion criteria receiving spinal cord stimulation, 5,458 were percutaneous and 2,868 were paddle leads. The overall incidence of spinal cord injury was 177 or 2.13% with percutaneous lead placement contributing to 128 or 2.35% incidences versus paddle leads contributing to 49 or 1.71% incidence.	Authors concluded that this study showed overall a low incidence supporting that SCS is a safe procedure.	This is a large database in the United States; however, the study was up from 2000 to 2009. There seems to be exponential increase of spinal cord stimulator placements since 2009; consequently, this data may not reflect present literature.

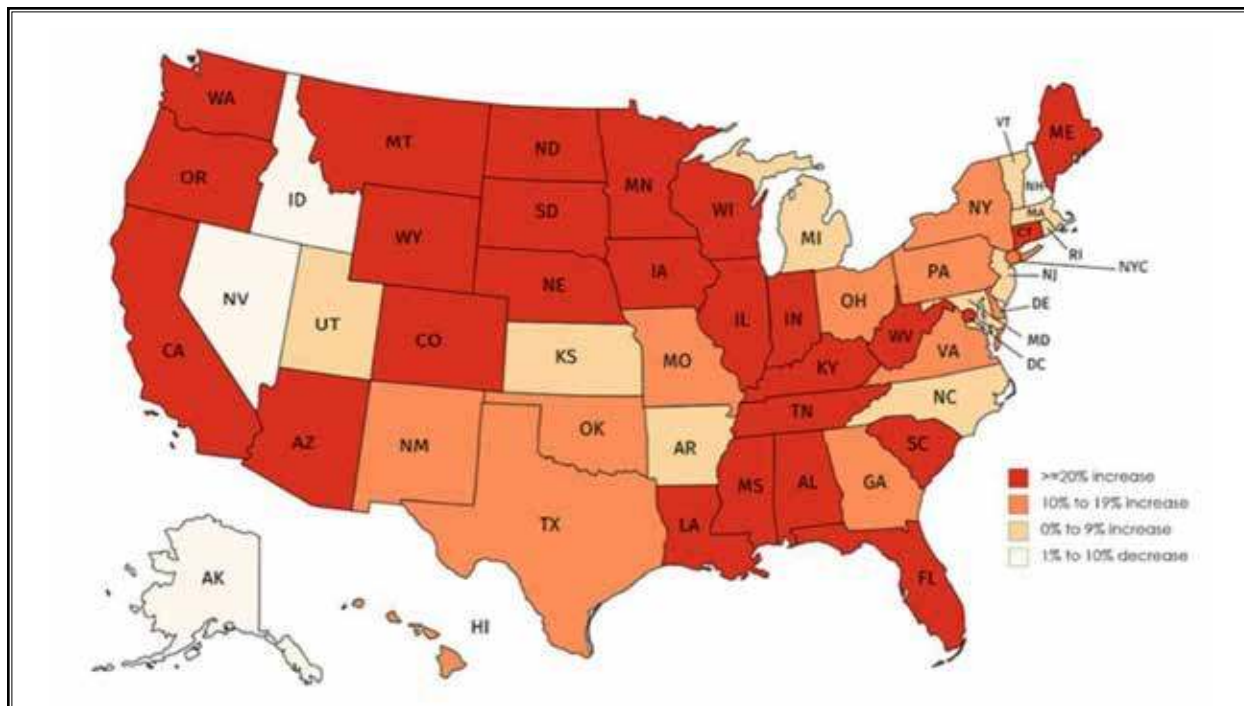
Appendix Table 16 (con't). *Studies assessing the risk of thrombosis and bleeding with interventional pain management techniques.*

Study/Year	Methods	Results	Conclusions by the Study Authors	Author Conclusions of the Review
Endres et al, 2017 (1138)	The study was performed as an observational study in a private practice in which some partners continued anticoagulants while other partners routinely discontinued anticoagulants. They studied 4,766 procedures in which anticoagulants were continued and 2,296 procedures in which anticoagulants were discontinued.	No complications attributable to anticoagulants were encountered in 4,766 procedures in which anticoagulants were continued; however, in 2,296 procedures in which anticoagulants were discontinued, according to the guidelines, 9 patients suffered serious morbidity, including 2 deaths.	Lumbar transforaminal epidural injections, lumbar facet joint nerve blocks, trigger point injections, and sacroiliac joint blocks appear to be safe in patients who continue anticoagulants. In patients discontinuing anticoagulants, serious complications are observed in a low proportion of patients with 0.2%.	This is an observational study in a large number of patients; however, interlaminar epidural injections or other high risk procedures were not included.  Further, authors conclusions are appropriate correlating with other conclusions that risk of serious complications of discontinuing anticoagulant therapy, even though this risk is low at 0.2%.
Warner et al, 2017 (1150)	Retrospective cohort of adult patients undergoing low and intermediate risk pain procedures were assessed from 2005 through 2014 at a single academic tertiary care center.  A total of 58,066 procedures were performed on 24,590 patients. Antiplaquet therapy included preprocedural aspirin or nonsteroidal antiinflammatory drug therapy in 17,825 procedures comprising of 30.7%.	The study included 3,880 lumbar epidural injections, 304 thoracic interlaminar injections with a large number of epidural injections with over 50% unassigned to a region.  22% of the patients received aspirin within 7 days, 12% of the patients received nonsteroidal antiinflammatory drugs within 7 days, 2% clopidogrel within 7 days, and Coumadin within 7 days in 3% of the patients. They also maintained INR of 1.0.	Authors concluded that bleeding complications are rare in patients undergoing low or intermediate pain procedures, even in the presence of antiplatelet medications.	Authors studied low and intermediate risk procedures in patients on nonsteroidal antiinflammatory agents including aspirin. Of these, 22% of the patients received aspirin within 7 days.  The study also included 3,880 lumbar epidural injections, 304 thoracic interlaminar injections with a large number of epidural injections with over 50% of the epidural injections not assigned to a region.
Goodman et al, 2017 (1146)	A prospective descriptive evaluation of patients undergoing interventional pain procedures on various antiplatelet and anticoagulant agents at a single interventional physiatry practice.	Overall incidence of spinal epidural hematoma for all procedures studied was one in 4,047 procedures (0.02%, 95% CI ¼ 0.00–0.15%). No thromboembolic events (myocardial infarction, cerebrovascular accident, or critical limb ischemia) were observed within 24–48 hours after spinal injection for all patients in the study.	Continuation of clopidogrel or warfarin for lumbar transforaminal epidural and posterior-approach facet joint injections may be reasonable. Interlaminar injections carry greater bleeding risk and merit consideration of holding anticoagulant/antiplatelet agents.	Authors have not provided any conclusive evidence if one procedure is safer to perform than the other while patient continues the anti-thrombotic agents.
van Helmond et al, 2017 (1147)	Retrospective review of the safety of low to intermediate risk spine procedures in patients with continued antithrombotic therapy.	Authors identified 490 patients of total of 2,204 patients on antithrombotic medications which included aspirin, P2Y12 inhibitors, warfarin, heparin, factor Xa inhibitors, and dipyridamole. The procedures included facet joint nerve blocks and facet joint radiofrequency in all spine regions and sacroiliac joint injections.	Authors concluded that there were no hemorrhagic complications in performing these procedures and they were safe.	The results are in a small number of patients with low risk and intermediate risk procedures of facet joint interventions and sacroiliac joint interventions without inclusion of high risk procedures of interlaminar epidural injections.

Appendix Table 16 (con't). *Studies assessing the risk of thrombosis and bleeding with interventional pain management techniques.*

Study/Year	Methods	Results	Conclusions by the Study Authors	Author Conclusions of the Review
Horlocker et al, 2002 (1134)	A prospective study of 1,214 epidural steroid injections in ambulatory pain centers. 32% of the patients were receiving nonsteroidal antiinflammatory agents including 34 patients on multiple medications. Aspirin was the most common NSAID and was noted by 158 patients including 140 patients on 325 mg or less per day.	There were no major hemorrhage complications with spinal hematomas. NSAIDs did not increase the frequency of minor hemorrhagic complications. Increased age, needle gauge, needle approach, needle insertion at multiple interspaces, number of needle passes, volume of injectate, and accidental dural puncture were all significant risk factors for minor hemorrhagic complications.	Authors concluded that epidural steroid injection is safe in patients receiving aspirin-like antiplatelet medications. Minor worsening of neurologic function may occur after epidural steroid injection and must be differentiated from etiologies requiring interventions.	The results of this study strongly show that discontinuation of antiplatelet therapy and continued therapy with Aspirin was not essential and is not associated with major hemorrhagic complications.
Lagerkranser et al 2017 (1148,1149)	Authors in these 2 manuscripts studied neuraxial blocks and spinal hematoma with review of 166 case reports published from 1994 to 2015 with descriptions of demographics, risk factors, diagnosis, treatment, and outcomes.  They utilized extensive search criteria in various languages across the globe. They also compared the previous reports published in 1992, 1994, and 1996.  37% of patients with hematoma were not receiving antithrombotic therapy.	They identified 166 case reports on spinal hematoma after central neuraxial blockade during the years between 1994 and 2015. The annual number of case reports published during this period almost tripled compared with the 2 preceding decades.  Authors identified 21 cases of hematoma from epidural injections with 17 after steroid injections, 5 in cervical, 4 in thoracic, and 8 in lumbar regions. They also identified 4 after percutaneous application of spinal cord stimulators.  The authors identified spinal stenosis as the most common spinal disease, which was identified as the most common of all spinal diseases in 14 cases with spinal disease reported in 37 cases of 166 cases.	Authors concluded that anti-hemostatic drugs, heparins in particular, are still major risk factors for developing spinal bleeding. Other risk factors were hemostatic and spinal disorders and complicated blocks, especially bloody taps, whereas multiple attempts did not seem to increase the risk of bleeding.  They recommended that suspicion of spinal hematoma calls for the consultation of surgeon without delay. MRI was the recommended diagnostic tool. Surgical evacuation within 12 hours from the sign of motor dysfunction seems to lead to the best outcome, even though many patients operated as late as after more than 24 hours did regain full motor function.	This report is an extensive review of epidural hematoma of all origins, specifically of epidural injections for chronic pain with a prevalence of 21 cases of hematomas and 3 cases hematoma after spinal cord stimulation.  Hematomas were identified in 37% of patients without antithrombotic therapy.  Significant information is provided in this review indicating the risk of bloody taps, and prompt surgical intervention to improve outcomes.  Limitations include lack of assessment after appropriate cessation of antithrombotic therapy.

NSAIDs= nonsteroidal anti-inflammatory drugs; SCS = spinal cord stimulator; MRI = magnetic resonance imaging  
Source: Kaye AD, et al. Responsible, safe, and effective use of antithrombotics and anticoagulants in patients undergoing interventional techniques: American Society of Interventional Pain Physicians (ASIPP) guidelines. *Pain Physician* 2019; 22:S75-S128 (103).



Appendix Fig. 1. *Percentage change in 12-months ending provisional<sup>a</sup> data on all fatal drug overdoses<sup>b</sup>, 50 states, the District of Columbia, and New York City: Overdose deaths from 12-months ending in June 2019 to 12-months ending in May 2020<sup>c</sup>.*

<sup>a</sup> Provisional drug overdose death counts are based on death records received and processed by NCHS. Provisional drug overdose death data are often incomplete, and the degree of completeness varies by jurisdiction and 12-month ending period. Consequently, the numbers of drug overdose deaths are underestimated based on provisional data relative to final data and are subject to random variation. Provisional data are based on available records that meet certain data quality criteria at the time of analysis and may not include all deaths that occurred during a given time period. Therefore, they should not be considered comparable with final data and are subject to change. The counts used in this analysis are the “predicted” values. Predicted provisional counts represent estimates of the number of deaths adjusted for incomplete reporting.

<sup>b</sup> Deaths were classified using the International Classification of Diseases, Tenth Revision (ICD–10). Drug overdose deaths were identified using underlying cause-of-death codes X40–X44, X60–X64, X85, and Y10–Y14.

<sup>c</sup> Included time periods will have some amount of overlap. For example, the 12-months ending in June 2019 (i.e., July 2018 to June 2019) includes deaths occurring in June 2019, which is also included separately in 12-months ending in May 2020 (i.e., June 2019 to May 2020).



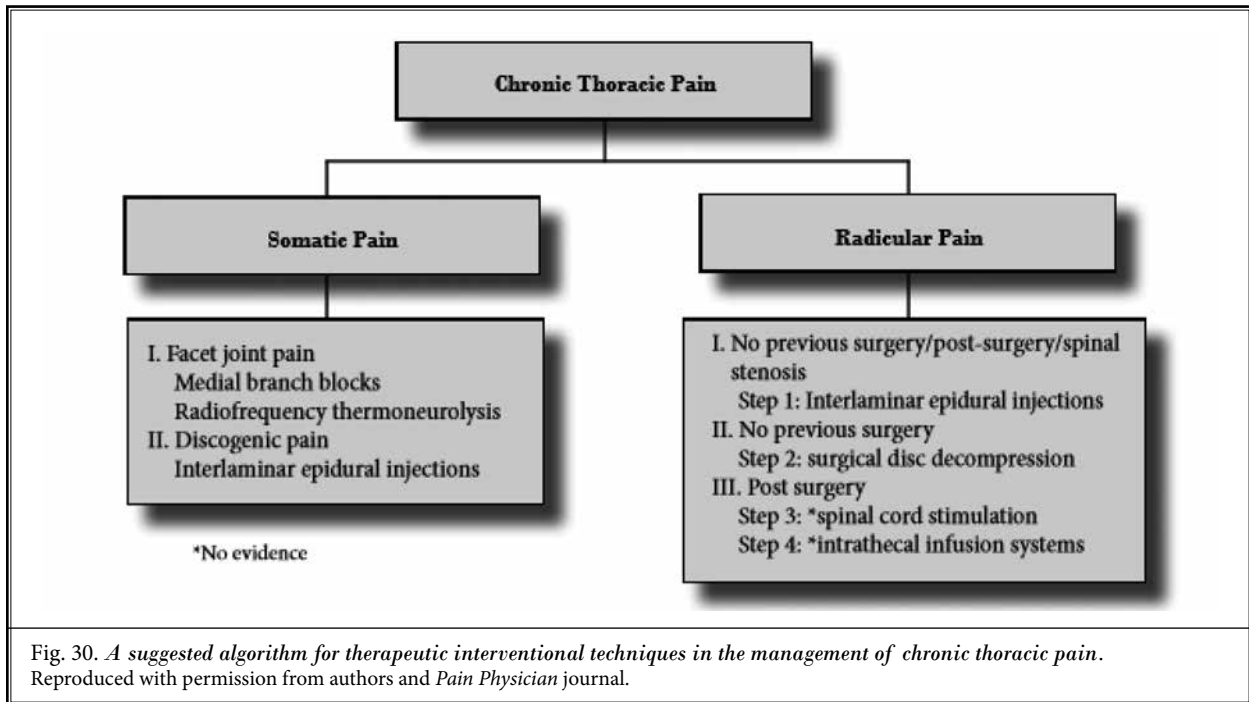
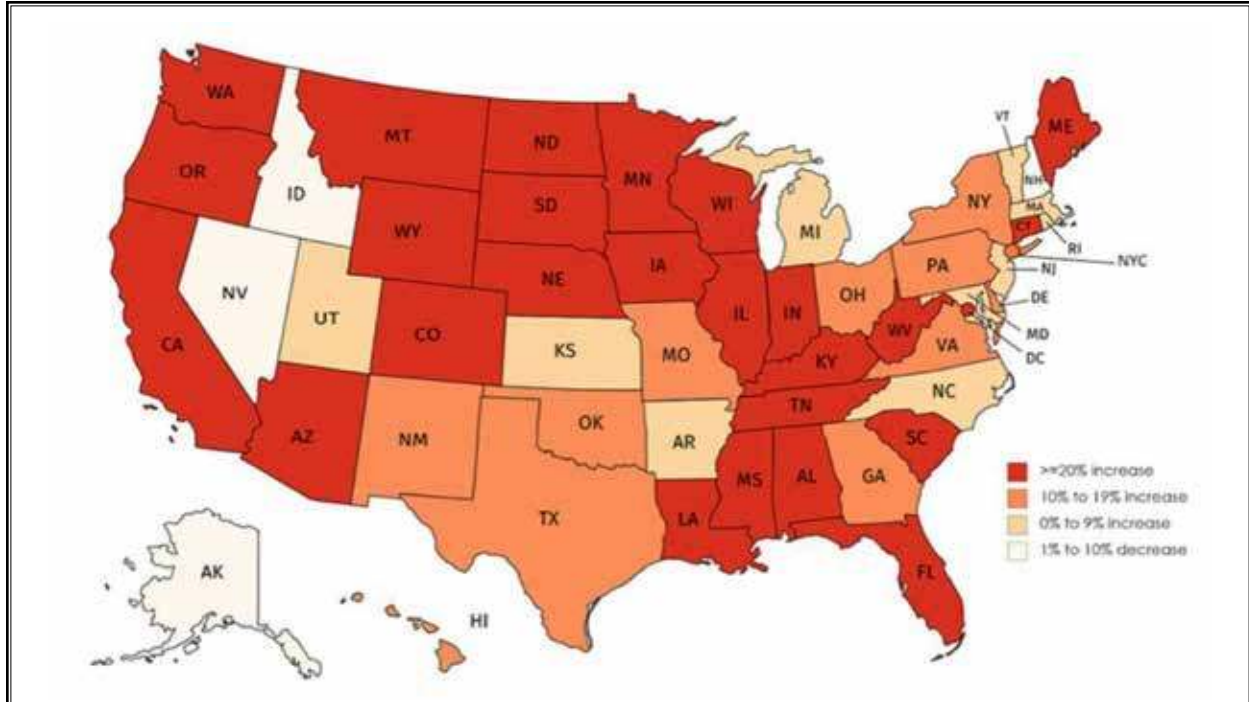


Fig. 30. A suggested algorithm for therapeutic interventional techniques in the management of chronic thoracic pain. Reproduced with permission from authors and Pain Physician journal.



Appendix Fig. 1. *Percentage change in 12-months ending provisional<sup>a</sup> data on all fatal drug overdoses<sup>b</sup>, 50 states, the District of Columbia, and New York City: Overdose deaths from 12-months ending in June 2019 to 12-months ending in May 2020<sup>c</sup>.*

<sup>a</sup> Provisional drug overdose death counts are based on death records received and processed by NCHS. Provisional drug overdose death data are often incomplete, and the degree of completeness varies by jurisdiction and 12-month ending period. Consequently, the numbers of drug overdose deaths are underestimated based on provisional data relative to final data and are subject to random variation. Provisional data are based on available records that meet certain data quality criteria at the time of analysis and may not include all deaths that occurred during a given time period. Therefore, they should not be considered comparable with final data and are subject to change. The counts used in this analysis are the “predicted” values. Predicted provisional counts represent estimates of the number of deaths adjusted for incomplete reporting.

<sup>b</sup> Deaths were classified using the International Classification of Diseases, Tenth Revision (ICD–10). Drug overdose deaths were identified using underlying cause-of-death codes X40–X44, X60–X64, X85, and Y10–Y14.

<sup>c</sup> Included time periods will have some amount of overlap. For example, the 12-months ending in June 2019 (i.e., July 2018 to June 2019) includes deaths occurring in June 2019, which is also included separately in 12-months ending in May 2020 (i.e., June 2019 to May 2020).