

January 14, 2016

Josh Morse, MPH
Health Technology Assessment Program Director
Washington State Health Care Authority
626 8th Avenue SE
P.O. Box 45502
Olympia, WA 98504-5502

Submitted via e-mail: shtap@hca.wa.gov

Dear Mr. Morse:

Representatives of 15 medical specialty societies, comprising physicians who utilize and/or perform spinal injection procedures to accurately diagnose and treat patients suffering from spine pathologies, have convened to review and comment on the draft report from the Washington State Health Care Authority's (WA HCA) Health Technology Assessment Program's re-review of spinal injections. These medical specialty societies share a common goal with the WA HCA: identifying spinal injections that provide value to the patient and society through measurable improvements in pain and physical functioning with no or minimal adverse events.

We extend to the committee an offer to provide national and international expert input as a resource for this process. We are fully cognizant of the issues of cost-containment, overutilization and inappropriate utilization, and therefore also wish to bring into focus which interventions are effective when treating the various causes of back and neck pain. We have concerns, however, that because of the questions posed, along with the review's inclusion/exclusion criteria, the report will not assist in making such determinations. In fact, the report's conclusions may lead to egregious denial of access to these procedures for many patients suffering from spine pathology.

In the spirit of transparency, it is imperative that the WA HCA request the authors of the report carefully consider all comments received during the public comment period, and require that a document outlining all comments and how they have been addressed be made publicly available with the final report. We trust that due consideration will be given to our comments and that the report will be revised to ensure that all of the highest quality evidence is addressed in order to provide an accurate assessment of the procedures reviewed.

Our primary concerns fall into these main categories:

- Topic Selection
- Report Development Methodology
 - Absence of Peer-Review Process
- Evidence Base Restriction to Randomized Controlled Trials (RCTs)
- Inadequate Subgroup Analyses for Each Question
 - Specific Diagnoses
 - Image Guidance
 - Approach/Access/Accuracy
- Statistical Analysis: Inappropriate Weight to Continuous (Mean) Data

- Accuracy of Data Presentation and Conclusions
- General Public Health Concerns

Topic Selection

We question the decision to re-review the entire field of spinal injections based upon publication of one new study by Friedly *et al.* (1) and a U.S. Food and Drug Administration (FDA) initiative to assess the risks of epidural steroid injections. (2) In regards to the former, this clinical study did not pertain to the majority of spine pathologies, including: lumbar foraminal or lateral recess stenosis, lumbar disc herniations and radicular pain, facet or sacroiliac joint pain, or any cervical or thoracic pathology. Thus, there is no basis for a re-review of the efficacy concerning these conditions and their associated treatments, nor is there new evidence that would warrant a reversal of the coverage decisions made by the WA HCA Health Technology Clinical Committee (HTCC) in 2011.

In regards to the FDA initiative, similar to nearly all medical treatments, there are known potential risks with epidural steroid injections. The most serious and lasting complications include spinal cord infarction or direct injury, brainstem and brain infarction, and spinal nerve root injury. The FDA's concerns were raised on the basis of case reports – low quality evidence inappropriate for formulating practice recommendations. These reports were published prior to the 2011 WA HCA review of spinal injections, and were therefore considered in the 2011 WA HCA report's safety discussion. In fact, the only new data available are from large studies showing safety of spinal injections. A recently published multi-institutional study examined more than 16, 500 consecutive epidural injections performed in accordance with evidence-based guidelines in all spine segments with no major adverse events. (3)

An expert working group with facilitation from the FDA's Safe Use Initiative (SUI) and representatives from leading specialty societies reviewed the existing scientific evidence and assembled consensus clinical considerations aimed at reducing the risk of severe neurologic complications. (4) The working group and the advising national organizations unanimously agreed that epidural injections of steroids were rarely associated with serious complications due to injuries of the central nervous system. They agreed that transforaminal injections are associated with a risk of catastrophic neurovascular complications and that particulate steroids appear to be inordinately represented in case reports of these complications. The representatives unanimously approved the clinical consideration that only non-particulate steroids should be used in therapeutic cervical transforaminal injections. Although use of non-particulate steroid dexamethasone as a first-line injectate in lumbar transforaminal injections was recommended, the representatives unanimously agreed that there might be instances where particulate steroids could be used in this setting (e.g., a patient fails to improve after an initial treatment with non-particulate steroid). Clinical considerations involving technical aspects of the procedures included the necessary use of appropriate image-guided views, injection of contrast under real-time fluoroscopy, review of prior imaging studies, use of facemask and sterile gloves, use of extension tubing, and avoidance of heavy sedation. Spinal injections should not be abandoned due to a very low risk of neurologic injury, particularly when appropriate measures can and should be utilized to substantially mitigate risks. Ultimately, the FDA has not modified the Black Box warning or limited use of corticosteroid for epidural steroid injections. (5)

Report Development Methodology

Spectrum Research is a for-profit company that has been contracted to perform at least 14 separate health technology assessments for the state of Washington. Given the established financial relationship between the two parties, and potential for reciprocity in the form of ongoing contracts which could be construed as a conflict of interest, at the very least the report itself should disclose this relationship between the two parties.

The WA HCA website indicates that clinical experts may be consulted at various points throughout the HTA process. The clinical experts serving in any advisory role for the review must be intimately familiar with the intricacies of proper patient selection and study design, technical 'nuances' of proper injection techniques, and the utility of various outcome measures. The process for selecting these experts needs to be rational and transparent. Experts should be highly regarded among their peers in the field of interventional pain management. While the report indicates that a number of experts in various fields participated in this review, the lack of transparency about their names, expertise, and level of involvement is of concern. Involvement of individuals with subject-specific clinical expertise in the development of the report is critical.

Washington State law RCW 70.14.110 states that the HTCC's decision cannot differ from Medicare or expert guidelines unless there is substantial evidence that their coverage decisions are wrong. Despite this requirement, the report failed to outline Medicare's coverage policies (e.g. Noridian's local coverage determinations on spinal injection procedures) or review expert guidelines published by the national medical societies vested in these treatments, such as those providing these comments. It would be prudent for the HTCC to review these policies and guidelines, as they would provide assistance in determining coverage decisions, and it is necessary to ensure that state law is followed.

Based on that state law, to restrict access to spinal injections, the burden of proof thus lies with the HTCC to prove these interventions are no better than placebo. Of the 142 conclusions reached, only two were based on high quality evidence, and these pertained to epidural steroid injections compared with epidural injections of local anesthetic in the treatment of one condition, lumbar central stenosis. (6) Only three conclusions were based on moderate quality evidence. There are 137 conclusions with low or insufficient evidence. When interpreting these conclusions, it is imperative that "low quality evidence" is not equated to "low treatment efficacy".

Absence of Peer Review Process

According to the report, "the information in this assessment is intended to assist health care decision makers, clinicians, patients and policy makers in making sound evidence-based decisions that may improve the quality and cost-effectiveness of health care services." Peer-reviewed journals are meant to serve this purpose, as their editors are clinical and research experts who review manuscripts and approve publications only of the highest quality and ensure the absence of bias. It is of great concern that this technology assessment, which has bypassed the typical peer-review process by clinical experts, will be used to inform decisions that will potentially affect the care of millions of patients in the United States.

Evidence Base Restriction to Randomized Controlled Trials (RCTs)

Evidence-based medicine seeks to identify the "current best evidence", including clinical evidence, in making patient care decisions. (7) With a restriction to randomized controlled trials (RCTs) as the sole evidence to address questions of efficacy, the report ignores the **best available** evidence.

The exclusion of high quality observational studies of clinical effectiveness removes important information and context from a synthesis of the literature. (7-9) In the recently published systematic review of long-term opioid therapy for chronic pain, Chou *et al.* highlighted the importance of observational studies in situations where RCTs fail to adequately assess effectiveness with consideration to important factors, such as type of pain and patient characteristics. (10,11) "Observational studies could also help address a number of these research questions, but should be specifically designed to evaluate patients with chronic pain prescribed long-term opioid therapy and appropriately measure and address potential confounders." (10)

Recent methodology literature suggests that effect estimates from high quality observational trials do not differ significantly from RCTs. (9) Many of the RCTs that met the inclusion criteria established by the authors of this report include patients selected only by symptoms or in whom image guidance has not been utilized. These failings, further discussed below, make such trials irrelevant to current clinical practice and not unexpectedly show poor outcomes. Comparing non-image guided (blind) injections to injections performed in accordance with evidence-based guidelines (12) that achieve precise needle placement at a 1 - 2mm target zone in three-dimensional space with confirmation of medication distribution by real-time observation of contrast flow has no validity. There are very few RCTs that utilize current practice standards. Hence, examination of recently published large observational studies adds important information that is more relevant to current standards of practice.

There is no mandate by the WA HCA to limit technology assessments to RCTs. The choice to limit the review to RCTs was purposeful and inconsistent with prominent ideology regarding evidence-based medicine. (7) Evidence-based medicine involves identifying the best available evidence with which to answer clinical questions. An observational trial with appropriately selected patients and treatment indications, accurate and current treatment techniques, and appropriate outcome measures and time frames is far more relevant than an RCT with good randomization and blinding, but improper patient and treatment indications, antiquated or poor treatment technique, and weaker outcome measures.

If all RCTs are analyzed as equals, simply because they have good randomization and low risk of bias, this does a great disservice to the scientific gains and practice improvements that the field of spine medicine has achieved in the last several decades. As an analogy, consider a hypothetical review of RCTs involving chemotherapy for breast cancer, spanning several decades of research, in which all of the studies were considered equivalent and pooled data were utilized. The efficacy of current diagnostic and treatment paradigms would appear erroneously poor, despite the clear gains this field has achieved in recent decades and years.

Purposefully preventing a comprehensive and unrestricted evidence-based review is a great disservice to all stakeholders, as the review will come to erroneous conclusions, and the HTCC could egregiously deny access to procedures that truly can be beneficial. The ramifications of this cannot be understated. Patients could be left to suffer in pain; become dependent on risky and expensive medications; seek unnecessary, risky, and expensive surgeries; utilize additional health care resources; miss more work and incur time-loss payments and/or loss of taxable income; and other far-reaching consequences.

Inadequate Subgroup Analyses for Each Question:

Specific Diagnosis

We commend the authors of the report on making an attempt to define appropriate subgroups/diagnoses; however, the categories implemented (e.g. lumbar radiculopathy due to disc pathology and/or foraminal narrowing, lumbar radiculopathy attributed to multiple causes) represent a mixed bag of anatomic diagnoses, clinical syndromes without defined pathology, and inappropriate grouping of distinct diagnoses. The categories fail to adequately represent the way anatomic pathology and clinical presentation of symptoms are evaluated both clinically and in the literature.

In the fields of interventional spine injections and surgery, it is imperative to secure an exact diagnosis before proceeding with a specific treatment. Clinical history-taking and physical examination alone have been proven to insufficiently elicit an exact diagnosis, and therefore the proper treatment remains unknown. Advancements in imaging provide substantial insight into anatomic pathology, and together with a history, examination, and sound medical judgment, will lead to a definitive diagnosis. Only then can a specific spinal intervention be offered and performed. Despite this necessity, several of the RCTs that met inclusion criteria for this report did not require advanced imaging to secure a diagnosis. Some of these trials are older studies that either did not have such advanced imaging at their disposal or were performed at a time when standard of care did not require imaging.

It is critical to perform subgroup analyses by specific diagnoses. For example, there is no physiologic process beyond systemic effect by which steroids delivered to the epidural space would be expected to relieve axial back pain arising from nociception in the intervertebral discs, facet joints, sacroiliac joints, or supporting musculature. There is ample experimental and clinical evidence that radicular pain has an inflammatory basis and is potentially susceptible to targeted delivery of an anti-inflammatory agent to the interface of neural tissue and the compressive lesion. (13) For this reason, it is imperative that studies included in the assessment have diagnostic specificity, with correlative imaging findings as a requirement for inclusion.

As an analogy, consider a hypothetical systematic review of prescription medication for the treatment of cough, a common symptom like low back pain. Studies may show beneficial effects from antibiotics in a group of patients with bacterial pneumonia, a specific diagnosis, whereas pooled data from heterogeneous groups of patients with cough– including viral bronchitis, chemical pneumonitis, asthma, lung cancer, *etc.* – would produce different effects. If these pooled effects showed that many different medications had minimal impact on cough from various sources, would we abandon prescription antibiotics for pneumonia?

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

antibiotics for pneumonia given the largely favorable natural history, or should we state antibiotics are ineffective because all subjects were better at 1 year follow-up? Similarly, should we withhold pain medications from patients with fractures or after orthopedic surgery, as these conditions only result in pain and have favorable natural histories?

Image Guidance

The techniques utilized in the administration of epidural steroids are also critical. The authors of the report acknowledge that the use of image guidance was reported in only two of the studies of interlaminar epidural steroids for lumbar radiculopathy. However, they fail to separately analyze results based upon use of image guidance. Furthermore, while they state that image guidance is often used to improve accuracy of medication delivery, they do not acknowledge the impact of image guidance on outcomes. Data show that “epidural” injections performed without image guidance may not universally reach the epidural space, even in expert hands. (14-16) Off-target medication delivery may not be efficacious and may be dangerous. The report directly contradicts the FDA Safe Use Initiative on epidural steroid injections that demands image guidance. (4) To suggest to patients and physicians that epidural steroid injections do not require image guidance may create a significant potential for patient harm.

Approach/Access/Accuracy

While image guidance is essential, the technique of delivery is equally important. As with image guidance, the authors acknowledge that different approaches to the epidural space exist. While data are presented by different approach in the tables, the text and conclusions pool results from the various approaches together. Many midline interlaminar epidural steroid injection (ILESIs) and caudal injection studies suffer from the lack of image guidance; and even when performed with image guidance, these procedures may deliver medication distant from the site of pathology, without certainty that the steroid will reach, or in what concentration it will reach, the target zone in the ventral epidural space. In contrast, transforaminal epidural steroid injection (TFESI) procedures place the needle in direct proximity to the target nerve and verify delivery to that site by observing contrast media flow. (17) Recently described lateral parasagittal ILESIs have also been shown to preferentially deliver injectate to the target ventral epidural space. (18) It is not reasonable to combine these different injection techniques in an evaluation of “epidural steroid injections”.

Many studies have shown that technically accurate injections will produce better outcomes. The only way to control for technical accuracy in a clinical trial is with blinded analysis of all procedure images and contrast media spread by independent reviewers. This has not been done in any of the studies included in the current report.

Statistical Analysis: Inappropriate Weight to Continuous (Mean) Data

Many of the included RCTs report only continuous data as a comparison between group means in reference to a minimum clinically important difference. However, pain and functional disability treatment responses are rarely normally distributed. Rather, responses are often bimodal, with segregation into responder and non-responder populations. Group means will thus conceal a clinically significant response in the responders. Categorical outcomes that define the proportion of patients reaching a predefined responder status are critical to meaningful interpretation, as noted in the recent NIH Task Force recommendations on research standards for chronic low back pain. (19) Given the importance of relying on categorical data, acknowledged by the report’s authors, it is disappointing that the categorical data from the Ghahremani, *et al.* study were not

included in the review. (20) When categorical data are available, they should be acknowledged and greater weight should be applied to these results than studies with mean data.

Accuracy and Transparency of Data Presentation and Conclusions

The stated aim of the report was to, “systematically review, critically appraise, analyze, and synthesize research evidence evaluating the efficacy, comparative efficacy, and safety of spinal injections in adults with subacute or chronic spinal pain.” Of the 142 conclusions reached, only five were rated “high quality”. This extensive document can only say very few things with any amount of certainty. One certain conclusion is that there is no difference between epidural steroid and epidural anesthetic in achieving short-term pain relief in the treatment of lumbar stenosis. It is unfortunate if this entire report was commissioned to make this one recommendation based on the “new literature” identified, namely the LESS trial by Friedly, *et al.* (1) Surprisingly, two of the other recommendations graded “moderate” or higher are in support of intra-articular facet steroid injections. This is despite a relative dearth of evidence in support of this procedure.

This is in stark contrast to a number of high quality peer-reviewed systematic reviews on similar topics that have been able to arrive at significant conclusions. In the author’s literature search for such reviews, they failed to identify arguably the best reviews on epidural steroid injections for lumbar and cervical radicular pain by MacVicar, *et al.* and Engel, *et al.* respectively. (21-23)

The tabulation of grading appears to give a semblance of transparency in the evaluation of a group of studies, but these data tables are far from transparent. Some examples of issues with the tables include the following:

- The individual papers comprising the sub-analysis for each subject in each table are not cited. Without appropriate referencing, it appears that RCTs may have been missing from the analyses in several tables. For transparency sake, it is critical to identify the studies.
- A uniform definition of the various outcomes has not been provided across all tables. Successful outcomes should be clearly defined for all categories in all tables.
- There are inconsistent analyses across categories by duration of follow-up (e.g. combining intermediate and long-term in some categories and not others).
- There is not uniformity in the tables for reporting all outcomes data at each time point. It appears the authors have arbitrarily selected outcomes and time points as was seen fit, rather than uniformly listing studies in all categories.
- If evaluating facetogenic pain, the data presentation should be comprehensive.
- It is unclear why sacroiliac pain is omitted from Table 1.
- There is obviously a risk differential between cervical and lumbar interventions, the types of interventions, and the injectates utilized. The grading of studies in Table 3 does not take this into account, but lumps them altogether.
- Transparency is required in delineating how the authors have reached the conclusions. “ESI for disc and foraminal compression” simply states “no significant difference” and “low quality evidence”. Without additional explanation, the assessment appears arbitrary.

Meaningful conclusions cannot be derived without re-analyzing the data after excluding all RCTs in which no confirmatory imaging was done or reported, no fluoroscopic guidance was used (most old studies), and no caudal epidural steroid injections were allowed. This analysis should also

stratify results of each treatment by diagnosis [e.g. TFESI for acute/subacute pain, TFESI for acute single-level HNP, TFESI for low-to-moderate grade compression, *etc.*].

General Public Health Concerns

A systematic review of a specific topic is not required to take into consideration a plethora of other factors that are prudent when a physician and patient decide to pursue a treatment. On the other hand, a committee making coverage decisions does need to consider the bigger picture. Some patients may have no other options apart from spinal injections. Implicit in this discussion of spinal injections is that conservative care (e.g. physical therapy, chiropractic, medications, *etc.*) has failed. Surgery can be contraindicated due to comorbidities or age, and some patients are adamant that they want to avoid surgery at all costs. Surgery also entails the very real risks of immediate or delayed surgical failure, technical failure, serious infections, permanent paralysis, re-herniations, and subsequent segmental instability requiring fusion. Several authors reported significantly worse outcome of discectomy in those with small, contained disc herniation. (24-26) Some even excluded from surgical consideration patients with small size lumbar disc herniation. (27) Thus, for patients with radicular pain because of a small disc herniation, surgery is far from a guaranteed solution. These are relevant considerations in the broader scope of clinical decision-making between a patient and physician.

Chronic or palliative care is also not always a good option. Opioids and NSAIDs can be contraindicated due to comorbidities, and both may have only short-term and minimal benefits. A large, utilization review, conducted in Denmark, of 2,000 patients who used opioids long-term for chronic pain, found that opioid therapy failed to fulfill any of the treatment goals: pain relief, improved quality of life, or improved functional capacity. (28) Long-term opioid therapy has very real and serious adverse effects, such as physical dependence, tolerance, opioid-induced pain hyperalgesia, addiction, diversion, and abuse; and side effects such as impairment of the immune, endocrine, and reproductive systems. (29-32) Increasing abuse and diversion of prescription opioids have become a serious problem. According to the Centers for Disease Control and Prevention (CDC), during 2014, 28,647 (61%) drug overdose deaths involved some type of opioid, including heroin. Prescription opioids killed 19,000. (33)

Regarding NSAIDs, a study in the *New England Journal of Medicine* estimated that at least 103,000 patients are hospitalized per year in the United States for serious gastrointestinal complications due to NSAID use. (34) At an estimated cost of \$15,000 to \$20,000 per hospitalization, the annual direct costs of such complications exceed \$2 billion. This study also estimated that 16,500 NSAID-related deaths occur every year in the United States. This figure is similar to the annual number of deaths from AIDS and considerably greater than the number of deaths from asthma, cervical cancer or Hodgkin's disease. NSAIDs can be considered to be the 15th most common cause of death in the US.

There is no doubt that spinal injections are not the panacea for all spinal conditions. There are conditions best treated conservatively and others best treated surgically. Spinal injections provide a valuable alternative option for some people. And unlike some medical treatments, which “cure” a problem (e.g. appendectomy), many spinal conditions cannot be cured. Repetitive, palliative treatments can be the only option. The risk-benefit ratio of repeated spinal injections can sometimes be preferable to perpetual medication use, or simply living with pain and disability.

Summary

It is imperative to recognize that study methodology is meaningless unless the procedures being assessed are performed on appropriately selected patients with appropriate indications using accurate and current technique. An RCT with sound randomization, excellent blinding, and no losses to follow-up is of no value if the patients did not have the condition under investigation and/or the therapeutic procedure was not conducted accurately. Stratification of studies by appropriate patient selection and acceptable, technical performance of the procedures is critically important and must be considered in parallel with, or even precede, evaluation of study design in assigning value to a study. Because the methodological limitations outlined above, the current draft of the report does not adequately address the key questions posed and is not a satisfactory reference for the topic.

Thank you for considering our comments, which are offered in the spirit of collaboration to ensure an accurate assessment of injection procedures that can be effective tools in the treatment of appropriately selected patients. If you have any questions or wish to discuss our comments, please contact Belinda Duszynski, Senior Director of Policy and Practice at the Spine Intervention Society, at bduszynski@spinalinjection.org.

Sincerely,

American Association of Neurological Surgeons

American Academy of Pain Medicine

American Academy of Physical Medicine and Rehabilitation

American College of Radiology

American Pain Society

American Society of Anesthesiologists

American Society of Neuroradiology

American Society of Regional Anesthesia and Pain Medicine

American Society of Spine Radiology

Congress of Neurological Surgeons

North American Neuromodulation Society

North American Spine Society

Society of Interventional Radiology

Spine Intervention Society

Washington State Association of Neurological Surgeons

References:

1. Friedly JL, Comstock BA, Turner JA, et al. A randomized trial of epidural glucocorticoid injections for spinal stenosis. *N Engl J Med* 2014;371:11-21.
2. 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. <http://www.fda.gov/Drugs/DrugSafety/ucm394280.htm>
3. El-Yahouchi CA, Plastaras CT, Maus TP, Carr CM, McCormick ZL, Geske JR, Smuck M, Pingree MJ, Kennedy DJ. Adverse event rates associated with transforaminal and interlaminar epidural steroid injections: A multi-institutional study. *Pain Med*. 2015 Nov 23. [Epub ahead of print]
4. Rathmell JP, Benzon HT, Dreyfuss P, Huntoon M, Wallace M, Baker R, Riew KD, Rosenquist RW, April C, Rost NS, Buvanendran A, Kreiner DS, Bogduk N, Fournery DR, Fraifeld E, Horn S, Stone J, Vorenkamp K, Lawler G, Summers J, Kloth D, O'Brien D, Tutton S. Safeguards to prevent neurologic complications after epidural steroid injections: consensus opinions from a

multidisciplinary working group and national organizations. *Anesthesiology*. 2015 May;122(5):974-84.

5. 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 Dec 10;373(24):2299-301.
6. Bicket MC, Gupta A, Brown CH, Cohen SP. Epidural injections for spinal pain: a systematic review and meta-analysis evaluating the "control" injections in randomized controlled trials. *Anesthesiology* 2013;119:907-31.
7. Sackett, D. L., Rosenberg, W. M. C., Gray, J. A. M., Haynes, R. B. & Richardson, W. S. Evidence based medicine: what it is and what it isn't. *BMJ* 1996;312,71-72.
8. Concato, J., Shah, N. & Horwitz, R. I. Randomized, controlled trials, observational studies, and the hierarchy of research designs. *NEJM* 2000;342:1887-1892.
9. Anglemeyer A, Horvath HT, Bero L. Healthcare outcomes assessed with observational study designs compared with those assessed in randomized trials. *Cochrane Database Syst Rev*. 2014 Apr 29;4:MR000034.
10. Chou R, Deyo R, Devine B, Hansen R, Sullivan S, Jarvik JG, et al. The Effectiveness and Risks of Long-Term Opioid Treatment of Chronic Pain. Evidence report/technology assessment no. 218. (Prepared by the Pacific Northwest Evidence-based Practice Center under contract no. 290-2012-00014-I). AHRQ publication no. 14-E005-EF. Rockville, MD: Agency for Healthcare Research and Quality; 2014.
11. Chou R, Turner JA, Devine EB, Hansen RN, Sullivan SD, Blazina I, Dana T, Bougatsos C, Deyo RA. The effectiveness and risks of long-term opioid therapy for chronic pain: a systematic review for a National Institutes of Health Pathways to Prevention Workshop. *Ann Intern Med*. 2015 Feb 17;162(4):276-86.
12. Bogduk N ed. Practice guidelines for spinal diagnostic and treatment procedures. 2nd edition. International Spine Intervention Society. San Francisco, USA 2013.
13. Mulleman D, Mammou S, Griffoul I, Watier H, Goupille, P. Pathophysiology of disk-related sciatica. I. Evidence supporting a chemical component. *Joint Bone Spine* 2006;73(2):151-8.
14. Sharrock NE. Recordings of, and an anatomical explanation for, false positive loss of resistance during lumbar extradural analgesia. *Br J Anaesth*. 1979 Mar;51(3):253-8.
15. Bartynski WS, Grahovac SZ, Rothfus WE. Incorrect needle position during lumbar epidural steroid administration: inaccuracy of loss of air pressure resistance and requirement of fluoroscopy and epidurography during needle insertion. *AJNR Am J Neuroradiol* 2005; 26 (3): 502-5.
16. White AH, Derby R, Wynne G. Epidural injections for the diagnosis and treatment of low-back pain. *Spine (Phila Pa 1976)* 1980 Jan-Feb; 5 (1): 78-86.
17. Ackerman WE, 3rd, Ahmad M. The efficacy of lumbar epidural steroid injections in patients with lumbar disc herniations. *Anesth Analg*. 2007 May;104(5):1217-22
18. Ghai B, Vadaje KS, Wig J, Dhillon MS. Lateral parasagittal versus midline interlaminar lumbar epidural steroid injection for management of low back pain with lumbosacral radicular pain: a double-blind, randomized study. *Anesth Analg* 2013; 117 (1): 219-27.
19. Deyo RA, Dworkin SF, Amtmann D, Andersson G, Borenstein D, Carragee E, Carrino J, Chou R, Cook K, DeLitto A, Goertz C, Khalsa P, Loeser J, Mackey S, Panagis J, Rainville J, Tosteson T, Turk D, Korff MV, Weiner DK. Report of the NIH Task Force on research standards for chronic low back pain. *Pain Med* 2014; 15 (8): 1249-67.
20. Ghahreman A, Ferch R, Bogduk N. The efficacy of transforaminal injection of steroids for the treatment of lumbar radicular pain. *Pain Med* 2010;11(8):1149-68.

21. MacVicar J, King W, Landers MH, Bogduk N. The effectiveness of lumbar transforaminal injections of steroids: a comprehensive review with systematic analysis of the published data. *Pain Med* 2013; 14: 14-28.
22. Engel A, King W, MacVicar J. The effectiveness and risks of fluoroscopically-guided cervical transforaminal injections of steroids: a systematic review with comprehensive analysis of the published data. *Pain Med* 2014; 15: 386-402.
23. Cohen SP, Bicket MC, Jamison D, Wilkinson I, Rathmell JP. Epidural steroids: a comprehensive, evidence-based review. *Reg Anesth Pain Med*. 2013 May-Jun;38(3):175-200.
24. Carragee EJ, Han MY, Suen PW, Kim D. Clinical outcomes after lumbar discectomy for sciatica: The effects of fragment type and anular competence. *J Bone Joint Surg Am* 2003;85(1):102-8.
25. Dewing CB, Provencher MT, Riffenburgh RH, Kerr S, Manos RE. The outcomes of lumbar microdiscectomy in a young, active population: Correlation by herniation type and level. *Spine (Phila Pa 1976)* 2008;33(1):33-8.
26. Folman Y, Shabat S, Catz A, Gepstein R. Late results of surgery for herniated lumbar disk as related to duration of preoperative symptoms and type of herniation. *Surg Neurol* 2008;70(4):398-401.
27. Mysliwiec LW, Cholewicki J, Winkelpolek MD, Eis GP. MSU classification for herniated lumbar discs on MRI: Toward developing objective criteria for surgical selection. *Eur Spine J* 2010;19(7):1087-93.
28. Eriksen J, Sjogren P, Bruera E, Ekholm O, Rasmussen NK. Critical issues on opioids in chronic non-cancer pain: An epidemiological study. *Pain* 2006;125:172-9.
29. Sacerdote P, Manfredi B, Mantegazza P, Panerai AE. Antinociceptive and immunosuppressive effects opiate drugs: A structure-related activity study. *Br J Pharmacol* 1997;121:834-40.
30. Vallejo R, deLeon-Casasola O, Benyamin R. Opioid therapy and immunosuppression. A review. *Am J Ther* 2004;11:354-65.
31. Rajagopal A, Vassilopoulou-Sellin R, Palmer JL, Kaur G, Bruera E. Symptomatic hypogonadism in male survivors of cancer with chronic exposure to morphine. *Cancer* 2004;100:851-8.
32. Mao J. Opioid-induced abnormal pain sensitivity: Implications in clinical opioid therapy. *Pain* 2002;100:213-7.
33. Rudd RA, Aleshire N, Zibbell JE, Gladden RM. Increases in drug and opioid overdose deaths - United States, 2000-2014. *MMWR Morb Mortal Wkly Rep*. 2016 Jan 1;64:1378-82.
34. Wolfe MM, Lichtenstein DR, Singh G. Gastrointestinal toxicity of nonsteroidal antiinflammatory drugs. *N Engl J Med*. 1999 Jun 17;340(24):1888-99.