WASHINGTON STATE HEALTH CARE AUTHORITY

Peer Review, Public and Washington State Agency Comments and Responses for Spinal Injections

Health Technology Assessment

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Provided by:

Spectrum Research, Inc.

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1. Spectrum Research Response to Peer Review Comments

No comments were received from the Washington State Agency.

Portions of both letters of peer review were copied below in order for the reader to easily identify the text to which we responded. The entirety of the peer reviewers' letters may be found in section 3.

Response to Janna Friedly, M.D., University of Washington/ Harborview Medical Center

Portions of the peer review were copied below in order for the reader to easily identify the text to which we responded. The entirety of the peer review letter

Background comments:

1. *Comment:* One recent higher quality RCT (Ghahreman et al, 2010)[3] of epidural steroid injections for herniated disc associated with radiculopathy was not included in the review, but should be considered when evaluating the literature on epidural steroid injections.

   Response: The RCT meets our inclusion criteria; the study was published in August 2010, and therefore falls within the dates of our literature search. Thus the study has been added to the report.

2. *Comment:* It is stated that diabetes mellitus is a contraindication to steroid injections. There are currently no published evidence-based guidelines regarding steroid injections and diabetes… Cut-offs of blood glucoses of 200 on the day of injection are commonly used; however there is no standard of care regarding this issue and little evidence to support this practice.

   Response: We removed diabetes mellitus from the section on contraindications.

Report objectives and key questions comments:

1. *Comment:* …the available data to adequately answer these [key] questions is lacking in the literature (particularly for key questions 3 and 4). The lack of high quality research to address these questions limits the ability to answer the questions about cost effectiveness and efficacy in subgroups in a clinically meaningful way and in order to direct healthcare policy and coverage decisions.

   Response: The availability of high quality research is addressed in the strength of evidence for each key question. For key questions 3 and 4, we found the strength of evidence for our conclusions to be Low or Very low (See Tables 25-26 in report).

2. *Comment:* …one of the challenges when considering this body of literature is determining the appropriate control or placebo to use for comparison. There

are many different possible options, and in the literature there is quite a bit of variability in terms of control interventions chosen. …There are valid arguments for comparison to any number of "control" interventions, but it has to be recognized that each comparison answers a slightly different question related to the comparative effectiveness of epidural steroid injections.

Response: We agree, and structured the outcomes for key question 1 in the same manner as was done in the American Pain Society Evidence Report (Chou et al, 2009)[1]. That is, we separated the studies by spinal injection type, indication, and comparator.

3. *Comment:* There is a trend in medicine to consider trials in which both groups (treatment and placebo) improve, but to the same degree, as "positive" evidence of treatment efficacy. Appropriately, Chou, et al. in Appendix G, partially address this flawed logic and point out that if both arms of a randomized, controlled trial improve to an equal degree, one has not demonstrated that the treatment is more effective than no treatment at all. In addition, even if one concludes (inappropriately) that the treatment and the placebo are both effective, why not treat patients with the placebo and eliminate the added risks of the steroid medication? There are a number of reasons "placebo" treatments found to be effective in randomized, controlled trials are not effective treatments in actual clinical practice. There are inherent biases in trials that contribute to a "placebo effect" in addition to the physiologic responses (i e. stress reduction, relaxation, etc) typically considered the "placebo effect." These biases include the Hawthorne effect (or observer bias) and the related cheerleader effect (encouragement and attention received by participating in a study from research coordinators and study personnel), regression to the mean (people with high levels of pain, particularly chronic pain, will tend to improve and regress towards the mean) as well as a ritual effect of having interventions and follow-ups associated with the study itself. These biases are phenomena of clinical studies and will not translate to clinical practice – this is why "placebos" are much less effective in actual clinical practice than in clinical trials.

   Response: We agree, and considered an outcome "positive" only if there was a statistically meaningful improvement in the treatment (spinal injection) group compared with the control group. While there are numerous theoretical reasons as to why placebo treatments may be more effective in RCTs than in actual clinical practice, RCTs are widely considered to provide the highest quality evidence regarding the efficacy of a given treatment.

Methods comments:

1. *Comment:* When determining the strength of evidence (SoE), three factors are taken into account: the quality of the studies, the quantity of the data and the consistency of the findings. One challenge with the spinal injection literature is that there are large numbers of extremely poorly conducted RCTs that are considered level II evidence. It is important to heavily weight the quality of how

trials are conducted as conclusions drawn from an RCT can be just as suspect as those drawn from case series or case reports. In the case of the spinal injection literature, large volumes of poorly conducted studies (still considered level IIb) that have consistent (yet inaccurate or unreliable) findings are being published in a single journal. Given this, the authors of this HTA conclude that the strength of evidence regarding injection efficacy is elevated to "moderate" rather than "low" for many of the injections included in this report (including interlaminar or caudal injections for LBP without radiculopathy, interlaminar or caudal injections for spinal stenosis, FBSS and for ESI vs. adhesiolysis). In this HTA, the authors correctly concluded that each of these studies was negative (if conclusions can be drawn at all), as each group – treatment and control had equal improvement. As mentioned earlier, demonstrating equal improvement in treatment and control/placebo arms does not demonstrate treatment efficacy. However, I will take this a step further and argue that none of these studies should be used to weight the SoE at all in terms of quality, quantity or consistency – "positive" or "negative" - given the poor methodology and intrinsic biases in the studies that render their conclusions irrelevant to the discussion of effectiveness of spinal injections. What we are left with is "low" quality evidence for every category of injection and indication with the exception of lumbar transforaminal steroid injections for disc herniation with radiculopathy.

Response: The strength of evidence regarding injection efficacy was downgraded (rather than elevated) for the injections mentioned above due to limitations in the study quality (ie., the majority of the studies were lower-quality as is mentioned by the reviewer).

2. *Comment:* … One key study published recently was not included in this report and deserves consideration (Ghahreman et al, 2010)[3].
   Response: We agree; this study has been added to the report.

Results comments:

1. *Comment:* Given the gaps in the literature, there is insufficient data to draw conclusions for key questions 1 and 4 with the exception of the efficacy of lumbar transforaminal epidural steroid injections for herniated disc with radiculopathy.

   Response: Again, the quality of the research available is addressed in the strength of evidence of the conclusions for each key question.

2. *Comment:* Key question #2 is reasonably well answered – although one could argue that safety data is best drawn from large registries rather than from randomized, controlled trials in which inclusion, exclusion criteria as well as procedures are highly controlled. It is not uncommon to observe more adverse events and complications when procedures are applied to actual clinical practice – particularly when there are not clear guidelines or there is variability in the

patient population and technique of procedure (for example, fluoroscopy use, type and amount of steroid, number of injections, etc).

Response: We agree that safety data are best obtained from large observational studies rather than from RCTs; we reported the complications from both the RCTs included in key question 1 as well as observational studies with at least 100 patients. We did not identify any large registry studies relevant to the topic.

3. *Comment:* (Key question 2) As previously mentioned, additional research is needed to fully understand the safety issues related to epidural steroid injections in people with diabetes. In addition, it should be mentioned that adrenal suppression may occur for up to 30 days following epidural steroid injection. The incidence and the clinical implications of this adrenal suppression are currently unknown, particularly in higher risk populations.

   Response: This information was added to section 4.2.6 of the final report.

Response to Laxmaiah Manchikanti, M.D., University of Louisville/ Pain Management Center of Paducah

Preface comments:

1. *Comment:*I was surprised to see that the report was available to the general public even before it was available to peer reviewers. I understand that the purpose of the peer review is to ensure that the objectives were met; the methods and analysis are consistent with good methodology; that the conclusions are reasonably based on the data and analysis; and that the report is objective.

   Response: The draft report is published on the HTA website and is open for public comments for an approximately two week period; it is during this time that we make the report available to our peer reviewers for comment. Following this period, we respond to the public comments and peer reviewers and simultaneously make changes to the report where needed. The final report thus incorporates the peer reviews.

2. *Comment:*…if contributing to a specialty is considered to be a conflict of interest as you have stated, I have numerous conflicts of interest being the founder of the American Society of Interventional Pain Physicians (ASIPP), working on various aspects of interventional pain management including specialty designation, CAC representation, NASPER, and various other activities. Further, I'm also an active practitioner of interventional pain management. Finally, I continue to be the Chairman of the Board and the Chief Executive Officer of ASIPP, which

o
m ith Rosenquist for pro, and myself for con for the APS guidelines.

Response: Contributing to a specialty in itself is not considered to be a conflict of interest. However, we are required to provide any potential conflict of interest for the studies included in the report and therefore are obligated to fully disclose your leadership roles with ASIPP and SIMPS (as well as the goals and financial support of these organizations, which could be perceived as potential conflicts of interest) to the HTCC committee.

Introduction comments:

1. *Comment:*… the lifetime prevalence of spinal pain has been reported as 54% to 80% (reference provided). Studies of the prevalence of low back pain and neck pain and its impact in general have shown 23% of patients reporting Grade II to IV low back pain with high pain intensity and disability versus 15% with neck pain. Age-related prevalence of persistent pain has been described to be more common in the elderly associated with functional limitations and difficulty in performing daily life activities. Chronic persistent low back and neck pain is seen in 25% to 60% of patients one year or longer after the initial episode. Above all, the increasing prevalence of low back pain has not been mentioned. Freburger et al (5) illustrated the rising prevalence of chronic low back pain following an evaluation of North Carolina households conducted in 1992 and repeated in 2006. The results showed increasing prevalence of chronic impairing low back pain over a 14-year interval from 3.9% in 1999 to 10.2% in 2006. Overall prevalence of low back pain increased by 162%, with increases of 226% in non-Hispanic blacks, and 219% in the 45 to 54-year old age group. The increases were approximately 320% in females aged 21 to 34 and 293% in males aged 45 to 54. Overall, the annual increase has been estimated at 11.6.

   Response: In section 2.1, we modified the statement to indicate that the lifetime prevalence of back pain is 75-80% in accordance with the reference you provided.

Background comments:

2.1 The condition

1. *Comment:* The description of the condition (section 2.1) seems to be limited to low back pain only, while the report states spinal injections.

   Response: The RCTs included in this report that evaluated cervical spinal injections included patients with neck pain with or without disc herniation or

radiculitis, or with neck pain of facet joint origin. These indications were included in this section.

2.3 Mechanism of action

2. *Comment:* The reviewers … do not describe the mechanism of action of other agents (besides steroids) utilized including local anesthetics, sodium chloride solution, and placebo itself in the same detail as they have described the mechanism of action of steroids. The authors also have not described any mechanical aspects of epidural and facet joint injections and nerve blocks, including the needle placement, adhesiolysis, dilution of toxic substances, and mechanical effects.

   Response: We did not discuss the mechanism of action of local anesthetic, saline, or placebo as these typically serve as the control treatments. The mechanisms of action of the different types of spinal injections were not discussed, as the report was designed to address whether these treatments are effective. The injection procedures for epidural, facet joint, intradiscal, and sacroiliac joint injections are described in section 2.4. Studies reporting on adhesiolysis were beyond the scope of this report.

2.4 Injection procedures

3. *Comment:* With regards to epidural injections, I'm not quite certain that 3 approaches are described by McLain et al.

   *Response:*McLain reviews the caudal, interlaminar, and transforaminal routes for epidural steroid injections. The full article can be accessed for free: http://www.ccjm.org/content/71/12/961.long

4. *Comment:* For lumbar or cervical facet joint blocks, all therapeutic facet joint interventions including radiofrequency neurotomy are indicated in patients with a positive response to controlled local anesthetic blocks, rather than only facet joint nerve blocks.

   Response: The scope of this report does not extend to facet joint interventions such as radiofrequency neurotomy.

2.5 – 2.6 Indications and contraindications

5. *Comment*: I'm not quite certain McLain et al have described the indications … [and] contraindications.

   Response: McLain reviews the indications and contraindications for epidural steroid injections. The full article can be accessed for free: http://www.ccjm.org/content/71/12/961.long

2.9 Previous systematic reviews/ technology assessments

6. *Comment:* This document appears to be an extension of Chou and Huffman's clinical guidelines for APS. However, these guidelines are only for managing low back pain.

   Response: The Chou/APS evidence review was used as the basis for evaluating the literature available on lumbar spine injections only.

7. *Comment:* Chou and Huffman's guidelines have been criticized [references provided]. As shown further in the document, Chou has responded with a critique of our critique. Neither the critique of the critique, nor the response from us, has been published. As I understand, the critique has been accepted for publication. We are preparing a response. I am quite certain the reviewers of this document, along with Chou, would agree that there are 3 sides to the truth, and just because you believe something, that doesn't make it the truth. At least one should listen to explanations from other sides. There is substantial validity to the critical reviews published. Chou, in his critique to the critique letter, exhibits anger without appropriately answering important questions regarding the exclusion of multiple manuscripts, inadequate search results, continued financial conflicts of interest, or the lack of information on the members participating in the review which has been provided for the first time in this document – though it remains incomplete.

   Response: We included a summary of your critique of the Chou/APS evidence report (section 3.2.2 and Appendix F) and have provided space in the report for responses by both Chou (Appendix G) and yourself (in the form of the peer review).

8. *Comment:* Multiple mistakes with regards to association with other organizations are brushed off as typographical errors.

   Response: We are not clear which portion of our report you are referring to; no mention of typographical errors in regards to association with other organizations was made in section 2.9.

9. *Comment:* Consequently, the authors of this document should consider carefully and cautiously before including the results of Chou and Huffman. This activity essentially invalidates this entire review and paints a picture with one brush stroke of bias with conflicts of interest. This is not a justification for any principles of evidence-based medicine.

   Response: We critically appraised the methodology used in the Chou/APS evidence report in section 3.2.2.

10. *Comment:* Table 2: The overview of previous systematic reviews of spinal injections includes multiple manuscripts of previous systematic reviews of

spinal injections. The first manuscript illustrated by Manchikanti et al is not a separate systematic review, but is a compilation of other systematic reviews.

Response: We are not clear about this comment, as this article (Manchikanti 2009; Comprehensive review of therapeutic interventions in managing chronic spinal pain) reviews RCTs (for example, Table 5 on page E136 in the article) as well as systematic reviews.

11. *Comment:* Comments about overlap in studies by therapy group are not well understood.

    Response: This was a misunderstanding on our part; this comment has been deleted.

12. *Comment:* The second manuscript by Levin is also not a systematic review.

    Response: This article uses methodology consistent with a systematic review of RCTs (all prospective double-blind randomized placebo-controlled trials published between 1973 and 2007 were sought using "extensive" Pubmed searches; the authors "reviewed [these articles] with strict interpretation of their results." Furthermore, the article reaches "evidence-based conclusions".

13. *Comment:* The manuscripts by Hall et al do not appear to be systematic reviews.

    Response: The manuscripts by Hall were designed to be systematic reviews; the authors sought RCTs, observational studies, and systematic reviews and evaluated the quality of evidence using GRADE:
    http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2908004/?tool=pubmed
    http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2907975/?tool=pubmed

14. All others [systematic reviews] appear to be appropriate except the Canadian Agency for Drugs and Technologies in Health and Kirpalani's manuscript.

    Response: It is appropriate to include the Canadian Agency for Drugs and Technologies in Health in this section as this report is a health technology assessment. www.cadth.ca/media/pdf/I3003_tr_**Facet_Joint_Injection**s_e.pdf

    While the search methodology used in Kirpalani's review appears to have been systematic in nature, we agree that this was not clearly a systematic review and the reference has been removed from Table 2.

2.10 Medicare and representative private insurer coverage policies

15. *Comment:* This provides a comprehensive list of coverage policies. However, there may be some errors related to the coverage, specifically with regards to diagnostic facet joint nerve blocks.

Response: It is not clear which policy or policies you are referring to with regards to errors in the coverage of diagnostic facet joint nerve blocks. All coverage policies were copied directly from their sources.

The evidence comments:

3.1 Methods of the systematic literature review

1. *Comment:* My concern is related, once again, to the carry forward of Chou and Huffman's previous work. Inasmuch as Chou is a co-author of this document, and it is probably prepared on similar grounds, and is also an *a priori* decision of non-coverage for any of the procedures, it must be stated that Chou and Huffman's review is met with multiple deficiencies as illustrated previously. By doing so, you may be inadvertently accepting the results of a controversial guideline. No one is quite certain if any of the other authors, except for Huffman, were involved in any of the analyses. Whether it is admitted or not, this review is not going to stand alone in a vacuum as a methodologic document; it will be applied clinically and change the entire practice of interventional pain management.

   Response: We critically appraised the methodology used in the Chou/APS evidence report in section 3.2.2 and in general found the methodology to be high quality. In addition, the methodology was generally consistent with that typically used in health technology assessments done for the State of Washington. Therefore, we determined that the Chou/APS evidence report would be appropriate to use as a basis for the lumbar portion of our report.

3.1.1 Inclusion/exclusion criteria

2. *Comment:*Most of the criteria appear appropriate except for the comparator. The studies that compared spinal injections to placebo (saline/water and/or local anesthetic) injections or to non-placebo controls were included. These criteria and the statements areboth inaccurate. The misunderstandings are not only limited to the researchers and the methodologists, but also clinicians such as Levin. There are numerous difficulties related to placebo groups and interventional techniques. Thus, an active control study utilizing local anesthetics is considered appropriate. However, local anesthetic is not a placebo… [see full peer review for additional text]Thus, this has to be changed. Otherwise, the entire document will not have any value and we will continue to argue about the appropriateness of this document. The solution is that all local anesthetic injections should be considered as active controls and extreme caution must be utilized in evaluating the response to either sodium chloride solution or water or any other solution injected into closed spaces.

   Response: We considered studies to be placebo controlled if they used injections of saline/water and/or local anestheticas has been done by other authors[1, 5, 8]. Nevertheless, the results of all studies, including those that used local anesthetic

as a control, are reported both in the text and in Appendix L; the reader may draw conclusions from the raw data if desired.

3. *Comment: …*it is essential to focus on … other aspects wherein positive and negative effects may be seen either with placebo or active agents

   Response: We considered an outcome "positive" only if there was a statistically meaningful improvement in the treatment (spinal injection) group compared with the control group. Focusing on changes in treatment effect for each group rather than comparing the outcomes of the treatment to the control group negates the power of the comparative (randomized) study (please also refer to Appendix G of the report under "ASIPP Methods").

3.1.4 Study quality assessment: level of evidence (LoE) evaluation

4. *Comment:* Further, the definition of different levels of evidence for articles on therapy and prognosis describes that there should be a follow-up rate of 80%, and patients followed long enough for outcomes to occur; however, unfortunately, most of the studies which are considered as positive in this review and Chou and Huffman's review are short-term follow-ups. If this is considered as criteria, it would eliminate many of the studies from consideration. Obviously, only the studies with follow-ups of one year or at least 6 months would be considered appropriate.

   Response: This report was designed to address both the short-and long-term outcomes following spinal injections. For more information, please see the Washington State Health Care Authority HTA Program Draft Key Questions, which is available at the following site: http://www.hta.hca.wa.gov/spinal_injections.html

5. *Comment:* The follow-up may be appropriate at the 60% or 70% level considering the variables involved in these interventions. Adequate flexibility must also be given to the fact that these are chronic pain patients and are being monitored for over one to two years. It appears that the authors would like 100% of the criteria met for a good quality randomized controlled trial (RCT). However, this is not the case with all other reviews.

   If one meets the 80% criteria, that should be considered to be of good quality. Obviously, using this criteria, if the study violates 20% of the criteria, whether it is based on inability to understand, inability to obtain information, or bias, the study will be judged automatically as poor quality or IIb, even if it is conducted according to CONSORT guidelines. Thus, the inclusion criteria may be tied to a follow-up duration of 6 months or one year with greater than 30% to 40% dropout rate as an essential factor and meeting the 80% criteria should be considered as good quality whereas less than 50% should be considered as poor.

Response: The rate of follow-up is important when determining the internal validity of a study. Only a 0% rate of loss to follow-up would ensure no possible entry of bias at this juncture of a study. However, this is unrealistic in most trials. Some have suggested that <5% loss leads to little bias, while >20% poses serious threats to validity [Sackett DL, Richardson WS, Rosenberg W, Haynes RB. Evidence-based medicine: how to practice and teach EBM. New York: Churchill Livingstone, 1997].The problem with lost to follow-up relates to the fact that often those lost to follow-up have different prognoses from those who are not lost. The reason that some are lost to follow-up may be that they had an adverse outcome (worse pain and or function) or because they were doing well and therefore did not return for follow-up. If an RCT meets all quality criteria outlined in Appendix D except follow-up of 80%, it would be considered an LoE IIa, or moderate quality RCT. RCTs are considered poor quality (LoE IIb) only if they violated two or more criteria for a good quality RCT.

3.2 Quality of literature available

3.2.2 Critical appraisal of randomized controlled trials

6. *Comment:* Once again, I'm lost with the purpose of this evaluation. It should be independent of the evidence report as performed by Chou and Huffman. Numerous deficiencies of this evaluation have been evaluated and listed (13,14). Even Chou's reply to the critique does not address most of the issues, essentially brushing them off. If a systematic review's search misses multiple manuscripts, continues to utilize so-called typographical errors for approximately one to two years after the final publication, information has been provided to the media, fails to publish the names of involved authors and the number of authors who withdrew that are pain physicians, and fails to contact authors for clarification, then that type of review should not be considered and followed. Further, at best, if the same philosophy has been utilized, this review can be considered as an update of Chou and Huffman's guidelines.

   Response: As previously stated, the methodology Chou/APS evidence report was generally consistent with that typically used in health technology assessments done for the State of Washington. Therefore, we determined that the Chou/APS evidence report would be appropriate to use as a basis for the lumbar portion of our report (see section 3.1 in the report for more details).

7. *Comment:* Without bias, with the exception of Chou, at least 2 authors of this manuscript should look at the deficiencies of Chou and Huffman's guidelines and critical appraisal of the literature review and bias.

   Response: Two reviewers (RH and JD) critically appraised the Chou/APS evidence report as well as each RCT; section 3.2.2 reflects the conclusion of both reviewers. Any disagreement between reviewers was discussed until an agreement was reached.

Lumbar epidural injections

8. *Comment:* Under Lumbar Epidural Injections, this review considered 11 studies receiving a level of evidence of IIb as illustrated in Appendix E, which is considered to be of poor quality. Of these, 8 have been described as published by Manchikanti et al since 2008 in the evaluation of the efficacy of lumbar epidural steroid injections (43-50). The authors characterized all these 8 RCTs since 2008 as similar. However, these are not similar. These may be similar in methodology, etc., but they are not all about lumbar epidural injections. Four manuscripts evaluated caudal epidural injections (43,46-48) in various types of low back disorders – disc herniation or radiculitis, discogenic pain without radiculitis or facet joint pain, spinal stenosis, post lumbar surgery syndrome. Two manuscripts evaluated lumbar interlaminar injections (44,50) either in disc herniation and radiculitis or discogenic pain without disc herniation, radiculitis, or facet joint pain. The other 2 manuscripts evaluated percutaneous adhesiolysis either in post lumbar surgery syndrome or spinal stenosis (45,49). Thus, these are different articles evaluating separate conditions employing multiple techniques. These manuscripts must be evaluated separately and the evidence should be assessed separately.

   *Response:*Even though there were differences in the diagnoses and injection approaches, because the methodology was so similar in these studies, we wrote one summary to describe the methodology for ease of reading. However, each study was individually evaluated regarding the quality of the methodology (see Appendix E).

9. *Comment:* All of the 4 caudal studies (43,46-48) were preliminary reports. The text clearly discusses the drawbacks of every preliminary report. Of further note, for all of these 4 studies, a one-year follow-up of each study will soon be published.

   Response: While the studies may be preliminary, they met our inclusion criteria and were thus included to provide the best and most up to date evidence on spinal injections.

Manchikanti (2008) (part 2)

10. *Comment:* In reference to the manuscript evaluating caudal epidural injections in disc herniation and radiculitis (47) allocation concealment and intention-to-treat were shown to be negative or absent. However, the manuscript on page 804 describes allocation concealment, which shows that the operating room nurse assisting with the procedure randomized the patients and prepared their drugs appropriately. Allocation was concealed from not only the physician, but also all other nursing personnel. Thus, participants and those administering the interventions were blinded to group assignment. The blinding was assured by mixing the patients with other patients receiving routine treatment and not informing the physician performing the procedure of the inclusion of the patients in the study. Further, all the patients for one-year follow-up were selected by the statistician not participating in the provision of patient care. The

unblinding results were not disclosed to either the treating physician or other participants or patients. Thus, allocation concealment was appropriate and the nature of blinding was not interrupted.

Response: Concealment is different than blinding. Concealment is the technique of ensuring that implementation of the random allocation sequence occurs without foreknowledge of treatment assignment. Concealment shields those who enroll patients into a study from knowing the upcoming assignments. The decision to include or exclude a patient into a trial should be made in ignorance of the upcoming assignment because knowledge of the next assignment could influence whether a patient is included or excluded based on perceived prognosis.Although the physicians performing the injections were blinded to the treatment assignment and study participation status of each patient, no information was given as to how concealment of patient allocation was ensured prior to the procedure. Regarding blinding, credit was given (see also Appendix E).

11. Methodologic quality assessment also shows that intention-to-treat analysis was not performed. In fact, on page 805, it clearly describes that intention-to-treat analysis was performed. Consequently, this should be a positive or plus (+).

    Response: Credit was not given for intention-to-treat analysis as patients who crossed over to the other treatment for subsequent injections could do so only after unblinding and hence withdrawal from the study. For credit to be given, data must be analyzed according to the treatment assigned even if patients crossed over and received the other treatment. If patients are not analyzed in this way, the randomized allocation of the patients is negated. Thus, for credit to be given in this study, patients who received the other treatment would not have been withdrawn from the study and would have been analyzed according to the allocated treatment.

12. *Comment:* Under Other Methods, Implementation, there is a negative for cointerventions applied equally. Cointerventions were applied equally. There were no differences in the cointerventions. In fact, there were no specific cointerventions except for their activity, return to work, continued exercise program, which was applied to all patients equally. Thus, this should also be a positive.

    Response: Credit was not given because additional treatments received by patients (i.e., physical therapy, occupational therapy, bracing, etc.) were not reported (except for opioid usage). For credit, data must be provided that demonstrates, for example, that there were no differences in the use of physical therapy between treatment groups as differences in use of this therapy might influence study outcomes.

13. *Comment:* The next issue with this manuscript is with regards to complete follow-up of greater than 80%. While I have recommended that this should be reduced to 70% or lower and have also taken into consideration the issues of placebo injections and long-term follow-up, as shown on page 807, based on the number of treatments provided, lack of follow-up was found in 11 of 126 occasions in Group I (8.7%) or 6 of 42 patients (14.3%); whereas it was 8 of 126 occasions (6.3%) in Group II with 5 of 42 (12%). In an extreme scenario, if you consider one-year follow-up and 6 patients missing at 12 months it would be 14.3% in Group I and in Group II, it was only 5 of 42 patients or 12%. Thus, at all points, the follow-up was present in more than 80% according to your own criteria. Thus, it should be positive.

    Response: For all studies, the rate of complete follow-up was calculated based on the number of patients randomized. In this case, 120 patients were randomized, and complete follow-up was available for 68% of patients at 3 months and 62% of patients at 12 months.

14. *Comment:* Sample size also showed negative. According to the calculations, the sample size required prior to conducting the study was 40 participants. We have included 42 participants in this preliminary analysis, thus it should be positive.

    Response: Credit has been given since a power calculation was done to determine the sample size (and at least as many patients were included per treatment group).

15. *Comment:* The authors have attempted to control for all the confounding factors. We do not see any deficiencies in these aspects, thus, these should be also positive or plus (+).

    Response: There were potentially meaningful difference in some baseline characteristics, such as patient weight, at baseline between groups that were not controlled or adjusted for.

Manchikanti (2008) (part 1)

16. *Comment:* The study evaluating effectiveness of caudal epidurals in discogenic pain without disc herniation or radiculitis or facet joint pain (46), or reference 114, was not appropriately characterized in this review. Allocation concealment with implementation and blinding was appropriately performed as described above for manuscript (47), or reference 128; thus, this should be a positive evaluation. Further, intention-to-treat analysis also was given a negative evaluation; however, this was performed and described appropriately on page 789; thus, this should change to positive.Cointerventions were applied equally to all and this has been described extensively as above; thus, this should be positive.Complete follow-up of over 80% was also applicable as shown on page 789. The data were available in the majority of the included patients. Intent-to-treat analysis was performed due to non-available data on 10 occasions in Group

I on a total of 7 patients, and on 5 occasions on 3 patients with Group II. Based on the number of treatments provided, lack of follow-up was found in 10 of 108 occasions (9.3%) in Group I, or 7 of 36 patients (19.4%), whereas it was 5 of 108 occasions (4.6%) in Group II with 3 of 36 patients (8.3%). Thus, the 80% criteria was met and this should be positive

*Response:*The rationale for giving credit or not giving credit for various points in the critical appraisal are outlined in section 3.2.3; please also see the responses to comments #10–13 above, which are applicable to this study.

17. *Comment:* Another issue is with regards to sample size. The sample size determinations are illustrated on page 789. Based on the evaluation, it required 26 patients in each group of the trial. We have included in this analysis 36 patients in each group. Thus, the sample size criteria have been met even after considering missed patients resulting in a 20% withdrawal rate.

    Response: Credit has been given since a power calculation was done to determine the sample size (and at least as many patients were included per treatment group).

Manchikanti (2008) (part 4)

18. *Comment:* The next study utilized in the methodology assessment was preliminary results in spinal stenosis (43), or reference 111. This study has taken a pattern similar to the one described above. In contrast to the methodologic quality assessors, allocation concealment was provided as described on page 837 along with implementation and blinding. This was appropriate, thus, it should be positive. Intention-to-treat analysis was considered as negative; however, this was positive as you see from the description on page 837, similar to the above manuscript. Once again there was a negative assignment for cointerventions applied. The cointerventions were applied equally to all patients, thus this should be positive. With regards to complete follow-up of over 80%, based on the number of follow-up periods, lack of follow-up was found in 13 of 60 occasions (9.3%) in Group I, or 7 of 20 patients; whereas it was 13 of 60 occasions in Group II with 5 of 20. Thus, if you consider the number of patients, you may be accurate; however, these should be considered with number of follow-up points rather than number of patients at one certain level. Once again, I reiterate that follow-up of over 80% is an extremely high standard to meet. Based on the number of treatments provided, lack of follow-up was found in 10 of the 108 occasions (9.3%) in Group I, or 7 of 36 patients (19.4%); whereas it was 5 of 108 (4.6%) occasions in Group II with 3 of 36 patients (8.3%) at least one time. Thus, even though I do not agree with 80% complete follow-up criteria, it does meet this criteria.

    Response: The rationale for giving credit or not giving credit for various points in the critical appraisal are outlined in section 3.2.3; please also see the responses to comments #10–13 above, which are applicable to this study. Credit has been

given since a power calculation was done to determine the sample size (and at least as many patients were included per treatment group).

Manchikanti (2008) (part 3)

19. *Comment:* The fourth study in reference to caudal epidural injections of Manchikanti et al (48), or reference 129, evaluated the role of caudal epidural injections in post lumbar surgery syndrome. The reviewers showed deficiencies with allocation concealment and intention-to-treat analysis with reference to study design. Allocation concealment was appropriate as described for the earlier studies, along with implementation and blinding; thus this should be changed to positive. Further, intention-to-treat analysis was also provided appropriately on page 821 of the manuscript; thus this would be positive. Under Other Methods, Implementation, the reviewers showed the cointerventions applied equally, complete follow-up of 80% or greater and adequate sample size as negative attributes to the trial. However, cointerventions were applied equally to all patients as illustrated earlier. However, we concede that the follow-up was present only in 65% of patients at the end of one-year; thus, this can continue to be negative under the present criteria. However, adequate sample size explanation was shown on page 820 which required 18 patients in each group. Consequently, we utilized 20 patients; thus, the sample size would be appropriate. It should be positive.

    Response:Response: The rationale for giving credit or not giving credit for various points in the critical appraisal are outlined in section 3.2.3; please also see the responses to comments #10–13 above, which are applicable to this study. Credit has been given since a power calculation was done to determine the sample size (and at least as many patients were included per treatment group).

Manchikanti (2010) (Preliminary results…)

20. *Comment:* The study by Manchikanti et al (44), or reference 112, evaluating the effectiveness of lumbar interlaminar epidural injections in managing chronic lumbar discogenic pain without disc herniation, radiculitis, or facet joint pain was provided with a IIb Level of Evidence. Under the study design, there was an issue with allocation concealment; however, allocation concealment was performed appropriately as described on page E282, along with implementation and blinding (masking). Thus, this should be rated positive. Under Other Methods, Implementation, the negative points were for cointerventions applied equally, complete follow-up of 80% or more, adequate sample size, and controlling for possible confounding. Cointerventions were applied equally as in all other studies as described earlier for caudal epidural injections. With regards to complete follow-up of 80% or greater, as shown on page E283 and Figure 1 on E284, based on the number of treatments provided, lack of follow-up was found in 8 of the 135 occasions (6%) in Group I or 4 of 35 patients (11%); whereas it was 11 of 132 occasion (8%) in Group II with 7 of 35 patients (20%). Thus, this

does meet the criteria of 80%, consequently this has to be changed to be positive. Sample size determination is provided on page E282. The sample size is estimated to be 55 patients in each group, however, since this is a preliminary study there were 35 patients included in each group. Controlling for possible confounding was rated negatively. This should be changed to positive. There were no issues with confounding to affect the results. The numeric rating scores were higher in Group I, though slightly; however, it will not affect the results because the evaluation was performed with baseline to follow-up periods rather than the change in the effect size between 2 treatment groups. Thus, it would be positive.

Response: The rationale for giving credit or not giving credit for various points in the critical appraisal are outlined in section 3.2.3; please also see the responses to comments #10–13 above, which are applicable to this study. Credit has been given since a power calculation was done to determine the sample size (and at least as many patients were included per treatment group). Regarding controlling for possible confounding, credit was not given as the statistically meaningful differences in the baseline pain scores, duration of pain, and weight of patients between groups were not controlled for in the analysis of the results.

Manchikanti (2010) (Evaluation of the effectiveness…)

21. *Comment:* The second manuscript concerning lumbar epidural injections relates to the management of lumbar disc herniation or radiculitis with lumbar interlaminar epidural injections (50), or reference 132. The reviewers in applying the methodologic quality criteria for this manuscript again question the allocation concealment; however, the allocation concealment, implementation, and blinding were appropriately performed. Thus, this should be changed to positive. Under Other Methods, Implementation, the reviewers question the application of cointerventions, complete follow-up of 80%, and controlling for possible confounding. Cointerventions were applied equally to both groups, thus this should be changed to positive. Complete follow-up of over 80% was also illustrated appropriately as follows: the complete follow-up of 80% or more patients, based on the number of treatments provided, lack of follow-up was found in 13 of 137 occasions in Group I (9%), or 7 of 35 patients (20%); whereas it was 5 of 146 occasions in Group II (3%) with 3 of 35 patients (9%). Thus, 80% of the patients were followed. With regards to the confounding factors, the differences appeared in the numeric pain rating scores and with patients with mode of onset of pain; however, these should have not affected the results. This has been described in the text; thus, this should be positive.

    Response: The rationale for giving credit or not giving credit for various points in the critical appraisal are outlined in section 3.2.3; please also see the responses to comments #10–13 above, which are applicable to this study.Regarding controlling for possible confounding, there were potentially meaningful difference in some baseline characteristics, such as sex distribution, at baseline between groups that were not controlled or adjusted for.

Manchikanti (2009) (The preliminary results…) and Manchikanti (2009) (A comparative effectiveness…) (and Manchikanti (2004) (One day…) (in the Chou/APS evidence report)

22. *Comment:* In reference to the adhesiolysis studies (45) or reference 113, (49) or reference 130, it is inappropriate to include them with the epidural studies. Chou's argument has been that in the study (51), or reference 127[6] (Manchikanti 2004 (One day…)), caudal epidural injections were administered. However, they were administered as a control group after they had failed fluoroscopically directed epidural injections.

    Response: These studies met our inclusion criteria as the control group was treated with epidural injections. It would be inappropriate to lump the conclusions from these studies with those from other studies (ie., epidural injections of steroids versus saline), and we therefore reached separate conclusions for these studies. Although these studies use epidural injections as the control treatment, they still provide the highest level of evidence available on the efficacy of epidural steroid injections compared with adhesiolysis and were thus included in the report.

23. *Comment:* Further, the authors have misunderstood the nature of relief and suggested that the group had no significant relief. However, just because the group of patients failed to respond with significant pain relief above 50%, that does not rule out that they have not experienced any relief at all. A significant proportion of patients in this study (51), or reference 127[6] (Manchikanti 2004 (One day…)), had relief at one-month (i.e., 50% or more).

    Response: While patients in the epidural injections group may have experienced some pain relief, they had statistically meaningfully lower rates of significant pain relief (defined as pain relief ≥ 50%) compared with either of the adhesiolysis groups. We were unable to identify one-month pain relief data in the study; at three months statistically fewer patients in the epidural steroid injection group had pain relief of at least 50% compared with either of the two adhesiolysis groups (0% versus 64% versus 72%; $P < .001$) (Figure 4 in study[6]).

24. *Comment:* Both of the studies (45) or reference 113, and (49) or reference 130, should meet all the criteria. The methodologic quality assessment misunderstood some of the aspects. Allocation concealment was maintained along with blinding. Only the physician at the time of the performance of the procedure knew whether patients were in the control group or the intervention group. Even then, allocation concealment was appropriately maintained as none of the other personnel were aware of the allocation. Further, intention-to-treat analysis was also utilized in both studies. It was clearly illustrated. In the section Other, Methods Implementation, deficiencies were noted for both studies with regards to cointerventions, complete follow-up of 80%, and controlling for

possible confounding. Cointerventions were applied equally to all groups and potential confounding was controlled and addressed in both groups in both studies. Complete follow-up of 80% or more is a difficult issue in this case because of the patients essentially receiving no significant effect from the control intervention and subsequently withdrawing from the treatment. That is the only way we can recruit patients. If we say that they cannot withdraw, we will not have any recruitment at all; thus, both of these studies would meet Level of Evidence of I, or in a worst case scenario, IIa.

Response: The rationale for giving credit or not giving credit for various points in the critical appraisal are outlined in section 3.2.3; please also see the responses to comments #10–13 above, which are applicable to this study.Regarding controlling for possible confounding, there were potentially meaningful difference in some baseline characteristics, such as sex distribution, at baseline between groups that were not controlled or adjusted for. Regarding controlling for possible confounding, credit was not given in Manchikanti (2009) (A comparative effectiveness…) asthere were potentially meaningful difference in some baseline characteristics, such as opioid use, at baseline between groups that were not controlled or adjusted for.

Sayegh (2009)

25. *Comment:* On the evaluation of Sayegh et al (52), or reference 172, though the blind caudal epidural injections followed all of the appropriate principles, they did not describe random sequence generation; however, it appears that they maintained allocation concealment. Thus, the study should meet the criteria of Level of Evidence of IIa with only one negative element. It would have been worthwhile to contact the authors for any questions related to this study.

    Response: No information was given in this study regarding the method of randomization or the method by which concealment/blinding of allocation was ensured.

Peng (2010)

26. *Comment:* Peng et al (55), or reference 157, describes intradiscal injection. I do not believe there is any relevance for this study to be included here.

    Response: This report was designed to evaluate the following types of spinal injections: epidural injections, facet joint injections, medial branch blocks, sacroiliac joint injections, and intradiscal injections. For more information, please see the Washington State Health Care Authority HTA Program Draft Key Questions, which is available at the following site:
    http://www.hta.hca.wa.gov/spinal_injections.html
    The study by Peng meets the inclusion criteria and evaluates the effectiveness of intradiscal injections.

Other studies as summarized in the Chou/APS evidence report (2009)

27. *Comment:* With regards to the caudal epidural injections, it may be worthwhile considering Dashfield et al (56), which meets appropriate criteria receiving a high quality assessment. However, whether through inaccuracy or through lack of understanding, this continues to be utilized under the category of endoscopic adhesiolysis, but not for caudal epidural injections. The study should be utilized for caudal epidural injections as it is an active control trial wherein the active control happens to be more effective than the intervention. Even Chou and Huffman have given it a reasonably high rating of 7 of 11 on their methodologic quality assessment.

    Response: This study compared different approaches of epidural steroid injections; its results have been summarized in section 4.3.1 (Different approaches for administering lumbar epidural steroids in patients) as follows: "One higher-quality trial found no difference in outcomes comparing the caudal approach versus targeted steroid placement during spinal endoscopy in patients with radicular back pain, with needle placement confirmed by fluoroscopy for both methods."

28. *Comment:* The next study is related to Ackerman and Ahmad (57), or reference 2, which failed to meet inclusion criteria for ASIPP systematic reviews and guidelines due to less than 6 months of follow-up. However, Chou and Huffman considered this as a high-quality study with methodologic quality assessment of 9 of 11; this should be considered for evaluation not only for caudal, but also for interlaminar as well as transforaminal epidural injections – an active-control trial.

    Response: This study also compared different approaches of epidural steroid injections; its results have been summarized in section 4.3.1 (Different approaches for administering lumbar epidural steroids in patients) as follows: "The transforaminal approach was found to be superior to both the interlaminar and caudal approaches in one higher-quality trial."

29. *Comment:* For transforaminal epidural injections, the studies of Karppinen et al (58,59), Riew et al (60,61), Jeong (62), Ng (63), and Ackerman and Ahmad (57) should be reevaluated which I believe yield good evidence.

    Response: These studies were included as part of the Chou/APS evidence report:
    - Karpinnen (2001): transforaminal epidural steroid versus saline injections (section 4.1.2 and the corresponding table (Table 9)): this study reported mixed short-term results and negative long-term results.
    - Riew (2000): transforaminal epidural steroid versus local anesthetic injections (section 4.1.2 and the corresponding table (Table 9)): this study reported positive long-term results.

- Jeong (2007) compared different transforaminal approaches of epidural steroid injections (at the exiting nerve root versus the supraadjacent intravertebral disc level), however the results were not summarized in the section evaluating different approaches for administering epidural steroids in the Chou report because both were groups were considered transforaminal approaches.
- Ng (2005): since the publication of the Chou/APS evidence report, the authors published an updated version of this study, which was included in section 4.1.2 (Tafazal 2009).
- Ackerman and Ahmad: this study was addressed in the response to comment #31, above.

30. *Comment:* In relation to adhesiolysis, both studies of post laminectomy syndrome show positive results (49,51). In addition, the spinal stenosis study also shows positive results, though preliminary and emerging (45).

    Response: Manchikanti (2009) (49) (A comparative effectiveness…) reported statistically higher (worse) pain scores for patients treated with epidural injections compared with adhesiolysis at three months (section 4.1.3, Table 10, Appendix L). The outcomes of Manchikanti (2004) (One day…) (51) were discussed in our response to comment 26, above. The outcomes of Manchikanti (2009) (The preliminary results…) (45) were also negative, as patients treated with epidural injections had statistically worse mean pain and ODI scores than those who were treated with adhesiolysis (section 4.1.3, Table 10, Appendix L).

Lumbar facet joint interventions
Manchikanti (2010) (Evaluation of lumbar facet…)

31. *Comment:* In this evaluation, only one RCT was identified and utilized for the evaluation of lumbar facet joint injections after Chou's criteria (64), or reference 131. The methodologic quality assessment criteria in reference to study design question the allocation concealment and intention-to-treat analysis with negative evaluation. However, allocation concealment was described on page 127 of the manuscript, along with implementation and blinding; thus, these should be positive. Further, intention-to-treat analysis was also described rather extensively on page 127 and sensitivity analysis for pain rating scores for intention-to-treat analysis methodology was also described on page 129. Thus, this should also be judged positive. Under Other Methods, Implementation, the reviewers question the application of cointerventions and adequate sample size. Cointerventions were applied equally to both groups. This has been illustrated in the manuscript; thus, this would be positive. The next issue relates to adequate sample size. The sample size determination and justification was provided on page 126. There were no randomized trials available to base the calculation of sample size; thus, we took the sample size of 60, which probably is 3 to 4 times the normal.

Response: The rationale for giving credit or not giving credit for various points in the critical appraisal are outlined in section 3.2.3; please also see the responses to comments #10–13 above, which are applicable to this study.Regarding adequate sample size, credit was not given since no power calculation was done to determine the sample size.

32. *Comment:* There have been substantial misunderstandings and discussions with regards to Nath et al's manuscript (65). This manuscript needs to be re-evaluated. In fact, this was the only study which met inclusion criteria by Datta et al (66). It is unfortunate that Chou and Huffman included multiple inappropriate studies to force the evidence into the negative category.

    Response: The study by Nath et al[7] evaluated radiofrequency neurotomy, which was one of our exclusion critieria (see Table 4 in report). Thus, this study is not within the scope of this report.

33. *Comment:* Of the multiple other studies Chou and Huffman have included, Van Wijk et al (69), and multiple other studies did not meet inclusion criteria by others due to numerous deficiencies (69-74). … [references 76-78 in the peer review were also cited in this discussion]

    Response: As noted in the response to comment #35 above, these studies are beyond the scope of this report as they evaluated radiofrequency neurotomy.

Cervical epidural interventions
Manchikanti (2010) (The effectiveness of fluoroscopic…)

34. *Comment:* Manchikanti et al (80), or reference 121, evaluated the effectiveness of fluoroscopic cervical interlaminar epidural injections in managing chronic cervical disc herniation and radiculitis and was a report of preliminary results. The reviewers questioned the study design of this manuscript with allocation concealment and intention-to-treat analysis providing negative results. Allocation concealment was described appropriately, along with implementation and blinding; just like the other manuscripts in the lumbar region, on page 226 it was applied appropriately; thus, the rating needs to be changed to positive. The next issue relates to intention-to-treat analysis. This was also described on page 226 appropriately and sensitivity analysis was also carried out prior to applying the methodology. This requires a change to positive. Under Other Methods, Implementation, questions were raised with regards to cointerventions, complete follow-up, and adequate sample size. Cointerventions, as described earlier, and in the manuscript in detail, were applied equally to both groups; thus, this should be judged positive. Complete follow-up of 80% or higher was also described on page 226 of the manuscript. Based on the number of treatments provided, lack of follow-up was found in 2 of 105 occasions in Group I (2%), or 1 of 35 patients (3%); 3 of 105 occasions in Group II (3%) with 2 of 35 patients (6%). Thus, this meets and exceeds the criteria described by the review

authors. In reference to adequate sample size, sample size determination was described on page 225 with a requirement of 55 patients in each group; however, because this is a preliminary study, only 35 patients were included; thus, considering the results of various other included studies, this sample size should be considered adequate.

Response: The rationale for giving credit or not giving credit for various points in the critical appraisal are outlined in section 3.2.3; please also see the responses to comments #10–13 above, which are applicable to this study.Regarding adequate sample size, credit has not been given: although a power calculation was done to determine adequate sample size, not as many patients were included per treatment group as required by the calculation.

Manchikanti (2010) (Cervical epidural…)

35. *Comment:* The second study was also by Manchikanti et al (80), or reference 120, evaluating the role of cervical epidural injections in patients with discogenic neck pain without disc herniation, radiculitis, or facet joint pain. The review authors for this study claimed deficiencies in the study design's allocation concealment and intention-to-treat analysis. Both have been described extensively above and in the particular manuscript also; thus, both should be appropriately changed to positive. Under the Other Methods, Implementation, the review authors claim deficiencies with cointerventions, complete follow-up, and adequate sample size. Cointerventions were applied to both groups, thus there should not be any questions about this issue, and it should be positive. With regards to complete follow-up of 80% or more patients, as illustrated on page E268, based on the number of treatments provided, lack of follow-up was found in 2 of 105 occasions in Group I (2%) or 1 of the 35 patients (3%); whereas it was 3 of 105 occasions (3%) or 2 of 35 patients (6%) in Group II. Thus, this meets and exceeds the required criteria. The next question relates to adequate sample size, which was provided with a negative impression. The sample size determination is illustrated on page E268. Even though there are not studies available, we have utilized the worst case scenario situation, and utilized a sample size of 55 patients; we utilized 35 patients in each group for the preliminary analysis. Thus, it does meet the sample size criteria.

    Response: The rationale for giving credit or not giving credit for various points in the critical appraisal are outlined in section 3.2.3; please also see the responses to comments #10–13 above, which are applicable to this study.Regarding adequate sample size, credit has not been given: although a power calculation was done to determine adequate sample size, not as many patients were included per treatment group as required by the calculation.

Cervical facet joint interventions

Manchikanti (2008) (Cervical medial branch blocks…)

36. *Comment:* The cervical medial branch blocks one year and 2-year follow-ups were described by Manchikanti et al (82,83), or references 133 and 122. The

review authors provided deficiencies in the study design in reference to the allocation concealment, which has been clearly described, along with implementation and blinding; thus, this rating needs to be changed to a positive or plus (+). Under Other Methods, Implementation, the review authors questioned cointerventions application and adequate sample size. Cointerventions were applied equally to all groups. Adequate sample size was determined based on previous studies, which was very low, thus we utilized a 60 patient sample size. This should meet the criteria for sample size.

Response: The rationale for giving credit or not giving credit for various points in the critical appraisal are outlined in section 3.2.3; please also see the responses to comments #10–13 above, which are applicable to this study.Regarding adequate sample size, credit has not been given as no power calculation was done to determine adequate sample size.

Length of follow-up and percent of patients followed

37. *Comment:* Once again, this varies based on the number of patients included in the study. These are all addressed in individual manuscripts. It is inaccurate to report that none of the studies had complete follow-up of 80% or more. This is a miscalculation; please look at the calculations, and revise them as described. This is what is called review bias which may not be overcome.

    Response: As described above (see response to comment #13), we calculated the rate of complete follow-up for all studies based on the number of patients randomized. Calculations for follow-up rates may be found for all the RCTs included in our analysis in the top of the third column in the tables in Appendices L–P.

The evidence comments:

4.1.1 Lumbar interlaminar or caudal epidural injections versus placebo

1. *Comment:* Regarding the opioid issues, it should be clear if the participants were on high dose opioid or low dose opioids and how long they had been on opioids.

Response: These data are available in Appendices L–P.

2. *Comment:* With regards to employment, employment needs to be carefully looked at and defined in discrete employable categories and if the study is a placebo control or active control.

Response: All studies were described as either placebo or non-placebo (active) controlled. Regarding employment, we reported the total percent of patients eligible for employment who were employed (either part or full-time). We only reported the data this way as there were ≤ 16 patients eligible for employment in each study and subdividing the results into part- and full-time employment

would have yielded very small (generally < 10 patients) study groups. Specific patient numbers for employment data are available in Appendices L–P.

3. *Comment:* Table 5 shows pain and function outcomes. It is of course, a summarization which is based on misunderstanding the various issues involved and misapplication of the methodologic quality assessment. One of the issues related to all the evaluations, whether it is epidural or facet joints, either in the cervical spine or lumbar spine, appears to be that the reviewers have utilized the philosophy that the difference between 2 groups is the effect. However, in active control groups, this is inappropriate, since there are no placebo control groups. Most of the evaluated studies used local anesthetic as the control. Further, in radiofrequency neurotomy, when a local anesthetic is injected over medial branches, that is not considered to be a placebo even though radiofrequency was not applied.

Response: These issues have been previously discussed. We considered an outcome "positive" only if there was a statistically meaningful improvement in the treatment (spinal injection) group compared with the control group. Focusing on changes in treatment effect for each group rather than comparing the outcomes of the treatment to the control group negates the power of the comparative (randomized) study (please also refer to Appendix G of the report under "ASIPP Methods"). Radiofrequency neurotomy was not within the scope of the report.

References

1. Chou R, Huffman LH. Guideline for the evaluation and management of low back pain: evidence review for the American Pain Society; http://www.ampainsoc.org/pub/cp_guidelines.htm. 2009.
2. Ghahreman A, Ferch R, Bogduk N. The efficacy of transforaminal injection of steroids for the treatment of lumbar radicular pain. Pain Med 2010;11:1149-68.
3. 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;7:177-86.
4. Nath S, Nath CA, Pettersson K. Percutaneous lumbar zygapophysial (Facet) joint neurotomy using radiofrequency current, in the management of chronic low back pain: a randomized double-blind trial. Spine (Phila Pa 1976) 2008;33:1291-7; discussion 8.

2. Spectrum Research Response to Public Comments

Letters to the editor/HTCC are included below. None were critical appraisals of the draft report.

3. Peer Reviews

Janna Friedly, M.D., University of Washington/ Harborview Medical Center

OVERALL Comments

In general, I found this report to be of high quality in terms of the presentation, organization and for the most part in terms of the methodology and content of the findings. This is an extremely difficult body of literature to review and summarize and the authors did a commendable job synthesizing the existing data into meaningful conclusions. I will focus my review on several methodological issues and new data that I feel should be addressed by this report.

INTRODUCTION Comments

The topic of effectiveness, safety and cost effectiveness of spinal injections for neck and back pain conditions is extremely important. As described in this report, these types of injections are being used with increasing frequency, but significant questions still remain in terms of effectiveness, particularly in certain subgroups of patients. In the current healthcare climate, with rising healthcare costs and increasing emphasis on comparative effectiveness, this type of assessment is very clinically relevant and has appreciable public policy implications.

BACKGROUND Comments

The literature review presented is adequate and covers the essential topics. The authors used the Chou et al. systematic review as a base for the literature review to answer the key questions in this report. Of note, one recent higher quality randomized clinical trial (RCT) (Ghahreman, et al., 2010[2]) of epidural steroid injections for herniated disc associated with radiculopathy was not included in this review, but should be considered when evaluating the literature on epidural steroid injections.

One small clarification regarding the indications and contraindications for spinal injections should be noted. In this report, it is stated (section 2.6) that diabetes mellitus is a contraindication to steroid injections. There are currently no published evidence-based guidelines regarding steroid injections and diabetes. There are some limited studies that suggest that blood sugars will increase following spinal injections[9, 10]. However, the clinical implications of this are currently unknown. There is quite a bit of variability in the actual clinical practice of performing injections in people with diabetes mellitus. Cut-offs of blood glucoses of 200 on the day of injection are commonly used; however there is no standard of care regarding this issue and little evidence to support this practice. This issue is particularly important given the

demographics of spinal stenosis and degenerative spine disorders and further research is needed to clarify the recommendations for steroid injections in patients with diabetes.

REPORT OBJECTIVES & KEY QUESTIONS Comments

The key questions addressed in this report include:

1. What is the evidence of efficacy and effectiveness of spinal injections?
2. What is the evidence of the safety of spinal injections?
3. What is the evidence that spinal injections have differential efficacy or safety issues in sub-populations?
4. What is the evidence of cost implications and cost-effectiveness of spinal injections?

These broad questions are appropriate to address relevant policy and clinical issues; however the available data to adequately answer these questions is lacking in the literature (particularly for key questions 3 and 4). The lack of high quality research to address these questions limits the ability to answer the questions about cost effectiveness and efficacy in subgroups in a clinically meaningful way and in order to direct healthcare policy and coverage decisions.

A review of the body of literature on spinal injections quickly shows the reasons it is so difficult to summarize. To start, there is a plethora of patient characteristics (acute vs. chronic pain, pathologic/etiologic diagnosis, psychosocial factors, etc), intervention characteristics (approach and technique, dosage, frequency and number of injections), comparators and outcomes to assess. For example, one of the challenges when considering this body of literature is determining the appropriate control or placebo to use for comparison. There are many different possible options, and in the literature there is quite a bit of variability in terms of control interventions chosen. For example, should epidural steroid injections be compared to the effectiveness of epidural injections of local anesthetic or saline; or should they be compared with injections of steroid, anesthetic, saline outside of the epidural space; or should they be compared with other commonly used treatment for pain such as physical therapy, acupuncture, chiropractic care, massage, exercise, oral medications or surgery? There are valid arguments for comparison to any number of "control" interventions, but it has to be recognized that each comparison answers a slightly different question related to the comparative effectiveness of epidural steroid injections.

There is a trend in medicine to consider trials in which both groups (treatment and placebo) improve, but to the same degree, as "positive" evidence of treatment efficacy. Appropriately, Chou, et al. in Appendix G, partially address this flawed logic and point out that if both arms of a randomized, controlled trial improve to an equal degree, one has not demonstrated that the treatment is more effective than no treatment at all. In addition, even if one concludes (inappropriately) that the treatment and the placebo are both effective, why not treat patients with the placebo and eliminate the added risks of the steroid medication? There are a number of reasons "placebo" treatments found to be effective in randomized, controlled trials are not effective treatments in actual clinical practice. There are inherent biases in trials that contribute to a "placebo effect" in addition to the physiologic responses (i e. stress reduction, relaxation, etc) typically considered the "placebo effect." These biases include the Hawthorne effect (or observer bias) and the related cheerleader effect (encouragement and attention received by

participating in a study from research coordinators and study personnel), regression to the mean (people with high levels of pain, particularly chronic pain, will tend to improve and regress towards the mean) as well as a ritual effect of having interventions and follow-ups associated with the study itself. These biases are phenomena of clinical studies and will not translate to clinical practice – this is why "placebos" are much less effective in actual clinical practice than in clinical trials.

Unfortunately, the literature on spinal injections has been flooded with poor quality studies and numerous systematic reviews of the same primary studies that have contributed to the confusion about the effectiveness of spinal injections. Given the complexity of the problem of "pain", i.e. the variety of ways to classify patient characteristics, the interventions, comparators and outcomes coupled with the lack of high quality research, it becomes very challenging to draw any concrete conclusions about the overall effectiveness of epidural steroid injections.

METHODS Comments

The methods used for identifying studies and evaluating the evidence were appropriate. Using level of evidence (LoE) ratings to assess the quality of the studies is helpful, although the majority of the studies available are classified as IIb studies or randomized, controlled trials of poor quality. When determining the strength of evidence (SoE), three factors are taken into account: the quality of the studies, the quantity of the data and the consistency of the findings. One challenge with the spinal injection literature is that there are large numbers of extremely poorly conducted RCTs that are considered level II evidence. It is important to heavily weight the quality of how trials are conducted as conclusions drawn from an RCT can be just as suspect as those drawn from case series or case reports. In the case of the spinal injection literature, large volumes of poorly conducted studies (still considered level IIb) that have consistent (yet inaccurate or unreliable) findings are being published in a single journal. Given this, the authors of this HTA conclude that the strength of evidence regarding injection efficacy is elevated to "moderate" rather than "low" for many of the injections included in this report (including interlaminar or caudal injections for LBP without radiculopathy, interlaminar or caudal injections for spinal stenosis, FBSS and for ESI vs. adhesiolysis). In this HTA, the authors correctly concluded that each of these studies was negative (if conclusions can be drawn at all), as each group – treatment and control had equal improvement. As mentioned earlier, demonstrating equal improvement in treatment and control/placebo arms does not demonstrate treatment efficacy. However, I will take this a step further and argue that none of these studies should be used to weight the SoE at all in terms of quality, quantity or consistency – "positive" or "negative" - given the poor methodology and intrinsic biases in the studies that render their conclusions irrelevant to the discussion of effectiveness of spinal injections. What we are left with is "low" quality evidence for every category of injection and indication with the exception of lumbar transforaminal steroid injections for disc herniation with radiculopathy.

As mentioned, one key study published recently was not included in this report and deserves consideration (Ghahreman, et al, 2010[2]). This was a higher quality RCT (level IIa if only considering up to the primary outcome and level IIb for longer term outcomes given insufficient sample size for a five arm study and loss to follow-up). This study of lumbar transforaminal

epidural steroid injections for herniated disc with radiculopathy demonstrated improvement of pain and function at least until the primary outcome of 4 weeks.

RESULTS Comments

Given the gaps in the literature, there is insufficient data to draw conclusions for key questions 1 and 4 with the exception of the efficacy of lumbar transforaminal epidural steroid injections for herniated disc with radiculopathy.

Key question #2 is reasonably well answered – although one could argue that safety data is best drawn from large registries rather than from randomized, controlled trials in which inclusion, exclusion criteria as well as procedures are highly controlled. It is not uncommon to observe more adverse events and complications when procedures are applied to actual clinical practice – particularly when there are not clear guidelines or there is variability in the patient population and technique of procedure (for example, fluoroscopy use, type and amount of steroid, number of injections, etc). As previously mentioned, additional research is needed to fully understand the safety issues related to epidural steroid injections in people with diabetes. In addition, it should be mentioned that adrenal suppression may occur for up to 30 days following epidural steroid injection[4, 9, 10]. The incidence and the clinical implications of this adrenal suppression are currently unknown, particularly in higher risk populations.

Key question #3 addresses whether or not there are subgroups of patients for which the evidence of efficacy varies. This report concludes that there is no data to suggest differences in efficacy based on diagnosis. Again, I would argue that with the addition of the Ghahreman study, there is at least moderate evidence that epidural steroid injections are more effective in people with herniated disc and radiculopathy than a variety of placebo injections in the short-term. Further data is needed to determine if there are any differences between other subgroups of diagnoses as well as ethnicities.

In terms of key question #4, there is certainly a need for additional high quality data on cost effectiveness. The reality is that the treatment of pain has become an increasingly expensive endeavor without significant population level changes in health outcomes. Over the last 20 years, it has become routine to order advanced imaging and to perform a variety of relatively expensive treatments for pain. In fact, a medical specialty "Interventional Pain" has been created and is blossoming. The costs of any of these treatments for spine related pain will only be offset if they lead to a significant reduction in subsequent surgery rates, improved return to work and reduction in subsequent health care utilization of other high cost services. This clearly has not been demonstrated with epidural steroid injections as the authors conclude ("very low" strength of evidence).

QUALITY OF REPORT

Overall, I found this report to be of superior quality and the authors should be commended on tackling such a broad and difficult topic as well as they have done. The results of this report clearly demonstrate the need for high quality, unbiased research to answer a number of questions

related to the efficacy of spinal injections. With the exception of transforaminal epidural steroid injections for herniated disc with radiculopathy, it is difficult to conclude much from the current body of research evidence regarding the efficacy and cost-effectiveness of epidural steroid injections in the short or long term.

Quality Of the Report
(Click in the gray box to make your selection)
Superior ☒
Good ☐
Fair ☐
Poor ☐

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November 24, 2010

Robin Hashimoto, PhD
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Subject: Spinal Injections HTA for Washington State-Peer Review

Dr. Hashimoto:

Thank you for allowing me to provide peer review for the Spinal Injections Health Technology Assessment for Washington State prepared by Spectrum Research, Inc., co-authored by Hashimoto, Raich, Ecker, Henrikson, Wallace,Dettori, and Chou.

As per your instructions, I chose not to use the form. However, I was surprised to see that the report was available to the general public even before it was available to peer reviewers. I understand that the purpose of the peer review is to ensure that the objectives were met; the methods and analysis are consistent with good methodology; that the conclusions are reasonably based on the data and analysis; and that the report is objective.

As you have shown in your report, I have co-authored criticism of the American Pain Society (APS) Guidelines Part 1 and Part 2. Also, we are preparing a letter to Chou addressing his critique of our critique, which appears in this document. Further, if contributing to a specialty is considered to be a conflict of interest as you have stated, I have numerous conflicts of interest being the founder of the American Society of Interventional Pain Physicians (ASIPP), working on various aspects of interventional pain management including specialty designation, CAC representation, NASPER, and various other activities. Further, I'm also an active practitioner of interventional pain management. Finally, I continue to be the Chairman of the Board and the Chief Executive Officer of ASIPP, which represents interventional pain physicians, and the Society of Interventional Pain Management Surgery Centers (SIPMS), which represents surgery centers focusing on the performance of interventional pain management techniques. I have also participated in discussions with Chou at the Annual Meeting of ASIPP on June 26, 2010. I am also scheduled to discuss the APS guidelines at the AAPM meeting with Rosenquist for pro, and myself for con for the APSguidelines.

1.0 INTRODUCTION

1.1 Overview of the Topic

The overview of the topic appears to be adequate. However, 2 of the 3 references utilized (1-3) are from 2003 and 2004. The third reference is a webMD reference, not an epidemiologic study, or a review. As illustrated in a comprehensive review (4), the lifetime prevalence of spinal pain has been reported as 54% to 80%. Studies of the prevalence of low back pain and neck pain and its impact in general have shown 23% of patients reporting Grade II to IV low back pain with high pain intensity and disability versus 15% with neck pain. Age-related prevalence of persistent pain has been described to be more common in the elderly associated with functional limitations and difficulty in performing daily life activities. Chronic persistent low back and neck pain is seen in 25% to 60% of patients one year or longer after the initial episode.

Above all, the increasing prevalence of low back pain has not been mentioned. Freburger et al (5) illustrated the rising prevalence of chronic low back pain following an evaluation of North Carolina households conducted in 1992 and repeated in 2006. The results showed increasing prevalence of chronic impairing low back pain over a 14-year interval from 3.9% in 1999 to 10.2% in 2006. Overall prevalence of low back pain increased by 162%, with increases of 226% in non-Hispanic blacks, and 219% in the 45 to 54-year old age group. The increases were approximately 320% in females aged 21 to 34 and 293% in males aged 45 to 54. Overall, the annual increase has been estimated at 11.6%.

There are also other publications which show increases in all types of interventional techniques, along with OIG studies (6-9).

1.2 Key Questions

The key questions are appropriate.

1.3 Outcomes Assessed

Outcomes assessed are appropriate.

2. BACKGROUND

2.1 The Condition

The description of the condition seems to be limited to low back pain only, while the report states spinal injections. Otherwise, the descriptions are appropriate.

2.2 The Technology and its Comparators

Comparators

Once again the reviewers use a 2004 manuscript which is not widely utilized. There are multiple manuscripts evaluating the structural basis of spinal pain. While it is admitted that the pathogenesis and mechanisms of chronic back pain remain challenging, many of them are known depending upon individual philosophy of methodology or assessment.

Spinal Injections

The comment provided above with the increase in interventional techniques applies here also (6-9).

2.3 Mechanism of Action

The reviewers described the mechanism of action of steroids; however, it appears that they do not describe the mechanism of action of other agents utilized including local anesthetics, sodium chloride solution, and placebo itself in the same detail as they have described the mechanism of action of steroids.However, they do provide some important aspects. The mechanism of action of local anesthetics in general, and long-acting effectiveness, have been discussed extensively in multiple manuscripts,as I also mention in Section 3.1.1.

The authors also have not described any mechanical aspects of epidural and facet joint injectionsand nerve blocks, including the needle placement, adhesiolysis, dilution of toxic substances, and mechanical effects.

2.4 Injection Procedures

Epidural Injections

With regards to epidural injections, I'm not quite certain that 3 approaches are described by McLain et al (10). It is surprising that the authors have chosen to utilize multiple web references, which have neither peer review nor accountability.

Facet Joint Injections

With regard to facet joint injections, the authors may want to mention the controversy regarding 50% or 100% relief. Two manuscripts illustrating the validity of controlled diagnostic facet joint nerve blocks with 80% relief have been published (11,12).

Intradiscal injection of corticosteroids is not a procedure performed frequently or even recognized.

2.5 Indications

I'm not quite certain McLain et al have described the indications (10).

For lumbar or cervical facet joint blocks, all therapeutic facet joint interventions including radiofrequency neurotomy are indicated in patients with a positive response to controlled local anesthetic blocks, rather than only facet joint nerve blocks.

There are no accepted indications for intradiscal injection.

2.6 Contraindications

Once again, contraindications illustrate McLain et al (10) as a reference. Otherwise the section appears to be appropriate.

2.7 Potential Complications and Harms

The descriptions are appropriate.

2.8 Clinical Guidelines

The illustrations of these guidelines are appropriate.

2.9 Previous Systematic Reviews/Technology Assessments

This document appears to be an extension of Chou and Huffman's clinical guidelines for APS. However, these guidelines are only for managing low back pain. Chou and Huffman's guidelines have been criticized (13,14). As shown further in the document, Chou has responded with a critique of our critique. Neither the critique of the critique, nor the response from us, has been published. As I understand, the critique has been accepted for publication. We are preparing a response. I am quite certain the reviewers of this document, along with Chou, would agree that there are 3 sides to the truth, and just because you believe something, that doesn't make it the truth. At least one should listen to explanations from other sides. There is substantial validity to the critical reviews published. Chou, in his critique to the critique letter, exhibits anger without appropriately answering important questions regarding the exclusion of multiple manuscripts, inadequate search results, continued financial conflicts of interest, or the lack of information on the members participating in the review which has been provided for the first time in this document – though it remains incomplete.

Multiple mistakes with regards to association with other organizations are brushed off as typographical errors.

Consequently, the authors of this document should consider carefully and cautiously before including the results of Chou and Huffman. This activity essentially invalidates this entire review and paints a picture with one brush stroke of bias with conflicts of interest. This is not a justification for any principles of evidence-based medicine. Another issue, which will be utilized further on in the discussion, is that the criteria for this review are separate or different from Chou and Huffman's criteria. It would be easy to brush off and get angry; however, a logical explanation is essential.

Table 2: The overview of previous systematic reviews of spinal injections includes multiple manuscripts of previous systematic reviews of spinal injections. The first manuscript illustrated by Manchikanti et al is not a separate systematic review, but is a compilation of other systematic reviews. Comments about overlap in studies by therapy group are not well understood. The second manuscript by Levin is also not a systematic review.

The manuscripts by Hall et al do not appear to be systematic reviews, and the search does not appear to be systematic reviews. All others appear to be appropriate except the Canadian Agency for Drugs and Technologies in Health and Kirpalani's manuscript.

2.10 Medicare and Representative Private Insurer Coverage Policies

This provides a comprehensive list of coverage policies. However, there may be some errors related to the coverage, specifically with regards to diagnostic facet joint nerve blocks.

3.0 THE EVIDENCE

3.1 The Methods of the Systematic Literature Review

My concern is related, once again, to the carry forward of Chou and Huffman's previous work. Inasmuch as Chou is a co-author of this document, and it is probably prepared on similar grounds, and is also an*a priori* decision of non-coverage for any of the procedures,it must be stated that Chou and Huffman's review is met with multiple deficiencies as illustrated previously. By doing so, you may be inadvertently accepting the results of a controversial guideline. No one is quite certain if any of the other authors, except for Huffman, were involved in any of the analyses. Whether it is admitted or not, this review is not

going to stand alone in a vacuum as a methodologic document;it will be applied clinically and change the entire practice of interventional pain management.

As you well know, we all should remember that the actual value of any evidence is relative to the application in which it will be used, and the circumstances in, and agents for whom such evidence may or may not have relevance. Thus, evidence-based practice or medicine must evolve through a methodological, rational accumulation, analysis, and understanding of the evidentiary knowledge that can be applied in the clinical setting. It may be unusual for methodologists to understand that it is difficult to practice evidence-based medicine.Thus, evidence-based medicine must be seen as an integration of the best research evidence coupled with patients' circumstances and values to arrive at clinical decisions for a distinctive approach to patient care.

Evidence-based medicine involves 2 fundamental principles. I know I am talking to experts. First, scientific evidence alone is never sufficient to make a clinical decision; these evaluations do not function in a vacuum. Decision-makers must always consider the patient's values when evaluating the benefits, risks, and burdens associated with any or all treatment strategies. Second, while evidence-based medicine is a hierarchy of informational value(s) to guide clinical decision-making, this hierarchy is not absolute and must reflect how different types and levels of evidence can be relative to, and inform the calculus of, circumstance(s), agents, and the consequences of decisions and actions.

As you well know, the 4 basic contingencies that define evidence-based practice are: the patient's problem, the medical literature, a critical appraisal of the available evidence, and, finally,the integration of the final body of evidence with all aspects and context of the clinical circumstances in order to facilitate the decisional process that determines the best clinical care of each patient. In general, all definitions of evidence-based medicine involve 3 critical, overarching processes:

- First, evidence-based practice involves the ongoing systematic review of the "science" to support the clinical decisional process of diagnostic and treatment planning that is relevant to clinicians and that is necessary for resolving clinical and personal equipoise, and informing patient consent.
- Second, evidence-based practice involves the integration of such scientific knowledge with the clinician's training and practical experience.
- Third, evidence-based practice should involve the active participation of patients in making decisions about their care.

Thus, it is essential and the responsibility of all involved to develop clinical guidelines and definethe body of evidence regarding safety, effectiveness, appropriate indications, cost-effectiveness, and other attributes of medical care. However, if special interests twist their interpretations to drive an agenda and develop guidelines based on personal biases and not on science and the best care for the patient, such guidelines have no relevance in clinical practice. Further, researchers, clinicians, professional organizations, and government should recognize that the value of evidence is only as good as the type of evidence reviewed, the methodology utilized, the knowledge and experience of the reviewers, and many other factors, including bias, self-interest, and economics. A formal set of rules must complement medical training and common sense for clinicians to interpret the results of clinical research effectively. However, having knowledge of evidence-based practice tools (methodology) does not make one qualified to develop guidelines. Knowing the tools of evidence-based practice methodology is necessary, but not sufficient, for delivering a higher quality of patient care. The clinical guidelines panels must incorporate not only the methodologists, but also the clinicians who actually practice medicine and are experts in the techniques being reviewed. This is echoed in recent correspondence from Congress to the Secretary of the Department of Health and Human Services.

It is essential that the authors of the review follow the methodology, which they have established, and also has been standardized rather than continue to modify the methodology.

3.1.1 Inclusion/Exclusion Criteria

Most of the criteria appear appropriate except for the comparator. The studies that compared spinal injections to placebo (saline/water and/or local anesthetic) injections or to non-placebo controls were included. These criteria and the statements areboth inaccurate. The misunderstandings are not only limited to the researchers and the methodologists, but also clinicians such as Levin. There are numerous difficulties related to placebo groups and interventional techniques. Thus, an active control study utilizing local anesthetics is considered appropriate. However, local anesthetic is not a placebo.

By definition, the placebo effect is a physiological and/or psychological reaction to an inactive substance or an inactive procedure. Consequently, placebo effect represents a key interphase between physiology, psychology, and patient care (15-17). Justifiably or not, in recent years, evidence-based specialists have devoted significantly more attention to placebo effect, particularly as it relates to the experience of analgesia. However, what methodologists are forgetting is that the desire for reduced pain predicts placebo analgesia and that placebo analgesia can be mediated by endogenous opioids. Consequently, understanding predictors of placebo analgesia is important, as treatment for chronic pain can benefit from clinically meaningful placebo effects. Similarly, it is essential for clinicians and methodologists to understand nocebo effects.

In contrast to placebo, nocebo represents a phenomenon opposite that of placebo analgesia, characteristically considered to be a worsening or consistent lack of change of symptoms after the administration of some agent known to be effective – hyperalgesia (16,17). However, nocebo effects in interventional pain management have not been carefully distinguished from drug-induced hyperalgesia, tachyphylaxis, tolerance, and/or progression of the underlying organic pathology causing increased pain and diminished sensitivity to a particular pharmacologic agent or procedure.

Multiple personality variables, including optimism and pessimism of not only the patient, but also the referring physician, family, and the investigators themselves, may produce or alter placebo analgesia, or even induce nocebo effect. There is research showing that dispositional optimism indicates that, when faced with adversity, optimism is associated with active, behavioral, and mental coping. Further research also shows that optimists often shift their focus away from adversity to the more positive features of the situation – especially when dealing with adversity that is out of their control. It may not be surprising to know that in a study of breast cancer patients, optimistic early-stage patients found greater benefits in their experience with cancer than pessimistic patients. In addition, among individuals recovering from coronary artery bypass surgery, it was found that optimists were more likely to focus on their recovery and less likely to dwell on their post-surgery negative effect than pessimists (18). In addition, laboratory studies indicate that optimists display an intentional bias for positive stimuli (19-21) and are more likely than pessimists to cognitively elaborate on, and be persuaded by positively framed messages (22). Thus, one can argue that a treatment's failure is a nocebo effect in a controlled situation, the opposite of the placebo effect. For example, in a study in patients undergoing interventional procedures, sodium chloride solution, midazolam, and fentanyl produced placebo effects in 13% to 15%, 15% to 20%, and 18% to 30% of the patients respectively (16). However, surprisingly a nocebo effect was seen in 5% to 8% of the patients in the sodium chloride group, 8% of the patients in the midazolam group, and 3% to 8% of the patients in the fentanyl group. Consequently, it is essential to focus on not only the methodological

aspects, but also other aspects wherein positive and negative effects may be seen either with placebo or active agents in 13% to 30% of patients (16).

Designing a placebo study in interventional techniques is an extremely difficult venture. Many believe that comparing the impact of an intervention with the natural course of the disease in a randomized, blinded fashion can only be achieved when the comparator group receives a placebo. This placebo, in the case of interventional treatment would be a sham intervention, and represents the first obstacle for RCTs in interventional pain management. During the patient information session, the clinician must inform the patient about the potential risks and benefits of the treatment that will be studied, but the clinician also must explain to the patient that he or she may have perhaps a 50% chance of receiving an intervention with no active component. Considering that interventional pain management techniques are only offered when conservative treatment fails, researchers face a patient population that has a highly pronounced wish for improvement and is often reluctant to accept the potential receipt of a placebo therapy. This results in a high rate of patients' refusal to participate in a study and subsequent withdrawals if they do participate. Similarly, the referring physician may negatively influence the inclusion rate. Both factors essentially compromise the inclusion rate of patients very seriously to an extent that the study may have to be cancelled or cannot be performed. This effect is seen not only with placebo controlled trials, but also with active-controlled trials. Further, the effect will not actually reveal the true effect of the lack of treatment since all patients who are suffering with chronic pain are not enrolled in the study,and are not receiving the same attention, evaluation, explanation, and so-called placebo treatment. Finally, one must design a TRUE placebo study.

Very few studies have applied true placebo or so-called sham interventions. Many of those claiming to be placebo-controlled are actually active interventions with injection of active agents. True placebo would only be injection of an inactive agent into an inactive location away from the epidural space or facet joint nerves, or facet joints themselves. As you are well aware, even the injections of sodium chloride solution and dextrose have been shown to yield different results (23). The experimental and clinical findings from the investigations of the electrophysiological effects of 0.9% sodium chloride and dextrose 5% in water solution have illustrated multiple variations of neural stimulation. The potential inaccuracy created by 0.9% sodium chloride solution versus 5% dextrose has been described in the literature (23-25). Further, injection of sodium chloride either into the disc, facet joint, or paraspinal muscles produces similar, yet variable results (25,26). There are also studies showing the lack of inertness of sodium chloride solution when injected into a closed space (27,28). Sodium chloride itself has been injected to treat low back pain and sciatica (28).

In addition to the injection of placebo, placement of the needle itself and injection of any solution with adhesiolysis effects and neurolytic effects of needle and various solutions injected, along with mechanical pressure, and dilution of inflammatory substances, also play a substantial role in understanding the placebo effect or its lack thereof.

Clinical aspects as well as placebo and nocebo have to be taken into consideration. The rules which apply for oral medications may not apply whenever there is an intervention. Even if local anesthetic is considered to be a placebo or even if the placebo actually helps, it may be worthwhile to provide patients with such a placebo treatment for them to improve. Otherwise, the patients who have been with long-term chronic pain may continue to suffer. Also, when evaluating a placebo effect, one should consider the role of repeat interventions over a period of as long a time as 2 years or so with continued positive results in a high percentage of the patients similar to the other intervention.

Local anesthetics also have been described to provide short to long-term symptomatic relief based on various mechanisms (29-33), including suppression of nociceptive discharge, the block of axonal transport (33), the blockade of the sympathetic reflex arc (31), blockade of sensitization, anti-

inflammatory effect (34), and axonal transport blockade of nerve fibers (32,33). The long-lasting effect of local anesthetics has also been demonstrated in multiple studies (29-36). Further, no additional benefit was demonstrated by using corticosteroids in rat experimentation with nerve root infiltration with either local anesthetic alone, or with local anesthetic and steroids (37). This has led to the postulation that corticosteroids may be unnecessary for nerve root blocks.

Thus, this has to be changed. Otherwise, the entire document will not have any value and we will continue to argue about the appropriateness of this document. The solution is that all local anesthetic injections should be considered as active controls and extreme caution must be utilized in evaluating the response to either sodium chloride solution or water or any other solution injected into closed spaces.

In Table 4: In the summary of inclusion and exclusion criteria under publication, it states that studies published only in the English language in peer-reviewed journals are included. However, there has been significant criticism in the past for not including other language studies. As a peer reviewer, I do not have any comments on this issue. I believe it is appropriate to utilize only English language studies published in peer-reviewed journals.

3.1.2 Data Sources and Search Strategy

Excellent search strategy; however, the only disadvantage, once again, is the issue of taking the information from Chou and Huffman and carrying it forward.

3.1.3 Data Extraction

Appropriate except continuation of APS/Chou evidence reports.

3.1.4 Study Quality Assessment: Level of Evidence (LoE) Evaluation

The quality criteria described in Appendix D are appropriate. Further, the definition of different levels of evidence for articles on therapy and prognosis describes that there should be a follow-up rate of 80%, and patients followed long enough for outcomes to occur; however, unfortunately, most of the studies which are considered as positive in this review and Chou and Huffman's review are short-term follow-ups. If this is considered as criteria, it would eliminate many of the studies from consideration. Obviously, only the studies with follow-ups of one year or at least 6 months would be considered appropriate.

The follow-up may be appropriate at the 60% or 70% level considering the variables involved in these interventions. Adequate flexibility must also be given to the fact that these are chronic pain patients and are being monitored for over one to two years. It appears that the authors would like 100% of the criteria met for a good quality randomized controlled trial (RCT). However, this is not the case with all other reviews. If one meets the 80% criteria, that should be considered to be of good quality. Obviously, using this criteria, if the study violates 20% of the criteria, whether it is based on inability to understand, inability to obtain information, or bias, the study will be judged automatically as poor quality or IIb, even if it is conducted according to CONSORT guidelines.

Thus, the inclusion criteria may be tied to a follow-up duration of 6 months or one year with greater than 30% to 40% dropout rate as an essential factor and meeting the 80% criteria should be considered as good quality whereas less than 50% should be considered as poor quality.

If the same criteria are applied, the majority of the opioid trials included in Chou and Huffman's opioid guidelines synthesis (38) will not meet criteria as most of them have more than 50% withdrawal rate, except in cases where there was an enrichment protocol. Further, the best studies in the literature from the

SPORT trial also show similar deficiencies. Weinstein et al (39) in surgical versus non-operative treatment for lumbar disc herniation, found that the randomized cohort showed enrollment of 245 patients assigned to the surgery, but only 187 patients had data available at 2-year follow-up, whereas 256 were assigned for non-operative care; 191 patients had available data analysis at 2-year follow-up (25% withdrawal rate). In the observational cohort (40), in the surgical group, of the 521 patients choosing surgery, the data were available in only 429 patients at 2-year follow-up with a 17.7% withdrawal rate. At 4-year follow-up (41), the number of patients available for follow-up declined to 149 and 150 from 245 and 256 respectively in the randomized group, and from 521 to 342 in the observational study. Similar issues have been faced in surgical versus non-operative treatment for lumbar spinal stenosis (42) with data available in 92 of the 138 patients randomized to surgery, and 96 of 151 randomized to non-surgical treatment. Similar effects were seen in the observational cohort.

Even though the effect size is not related to the quality of assessment, I request the authors of this assessment to review the multiple manuscripts describing this (39-42) and others if desired. These manuscripts show differences in baseline characteristics of the patients. Further, the effect size is minimal in multiple studies. Consequently, all the studies may be considered negative and of low quality.

Finally, application of these stringent criteria which were not even existent at the time of the studies performed may not serve any purpose.Thus, the best service may be provided by existing CONSORT guidelines at the time when the studies were designed/performed, rather than individually developed, ever-changing guidelines.

3.2 Quality of Literature Available

3.2.1 Quality of Studies Retained

3.2.2 Critical Appraisal of Systematic Reviews

Once again, I'm lost with the purpose of this evaluation. It should be independent of the evidence report as performed by Chou and Huffman. Numerous deficiencies of this evaluation have been evaluated and listed (13,14). Even Chou's reply to the critique does not address most of the issues, essentially brushing them off. If a systematic review's search misses multiple manuscripts, continues to utilize so-called typographical errors for approximately one to two years after the final publication, information has been provided to the media, fails to publish the names of involved authors and the number of authors who withdrew that are pain physicians, and fails to contact authors for clarification, then that type of review should not be considered and followed. Further, at best, if the same philosophy has been utilized, this review can be considered as an update of Chou and Huffman's guidelines.

3.2.3 Critical Appraisal of Randomized Controlled Trials

Without bias, with the exception of Chou, at least 2 authors of this manuscript should look at the deficiencies of Chou and Huffman's guidelines and critical appraisal of the literature review and bias.

Lumbar Epidural Injections

Under Lumbar Epidural Injections, this review considered 11 studies receiving a level of evidence of IIb as illustrated in Appendix E, which is considered to be of poor quality. Of these, 8 have been described as published by Manchikanti et al since 2008 in the evaluation of the efficacy of lumbar epidural steroid injections (43-50). The authors characterized all these 8 RCTs since 2008 as similar. However, these are not similar. These may be similar in methodology, etc., but they are not all about lumbar epidural injections.

Four manuscripts evaluated caudal epidural injections (43,46-48) in various types of low back disorders – disc herniation or radiculitis, discogenic pain without radiculitis or facet joint pain, spinal stenosis, post lumbar surgery syndrome. Two manuscripts evaluated lumbar interlaminar injections (44,50) either in disc herniation and radiculitis or discogenic pain without disc herniation, radiculitis, or facet joint pain. The other 2 manuscripts evaluated percutaneous adhesiolysis either in post lumbar surgery syndrome or spinal stenosis (45,49). Thus, these are different articles evaluating separate conditions employing multiple techniques.

These manuscripts must be evaluated separately and the evidence should be assessed separately.

All of the 4 caudal studies (43,46-48) were preliminary reports. The text clearly discusses the drawbacks of every preliminary report.

Of further note, for all of these 4 studies, a one-year follow-up of each study will soon be published.

In reference to the manuscript evaluating caudal epidural injections in disc herniation and radiculitis (47), or reference 128, allocation concealment and intention-to-treat were shown to be negative or absent. However, the manuscript on page 804 describes allocation concealment, which shows that the operating room nurse assisting with the procedure randomized the patients and prepared their drugs appropriately. Allocation was concealed from not only the physician, but also all other nursing personnel. Thus, participants and those administering the interventions were blinded to group assignment. The blinding was assured by mixing the patients with other patients receiving routine treatment and not informing the physician performing the procedure of the inclusion of the patients in the study. Further, all the patients for one-year follow-up were selected by the statistician not participating in the provision of patient care. The unblinding results were not disclosed to either the treating physician or other participants or patients. Thus, allocation concealment was appropriate and the nature of blinding was not interrupted.

Methodologic quality assessment also shows that intention-to-treat analysis was not performed. In fact, on page 805, it clearly describes that intention-to-treat analysis was performed. Consequently, this should be a positive or plus (+).

Under Other Methods, Implementation, there is a negative for cointerventions applied equally. Cointerventions were applied equally. There were no differences in the cointerventions. In fact, there were no specific cointerventions except for their activity, return to work, continued exercise program, which was applied to all patients equally. Thus, this should also be a positive.

The next issue with this manuscript is with regards to complete follow-up of greater than 80%. While I have recommended that this should be reduced to 70% or lower and have also taken into consideration the issues of placebo injections and long-term follow-up, as shown on page 807, based on the number of treatments provided, lack of follow-up was found in 11 of 126 occasions in Group I (8.7%) or 6 of 42 patients (14.3%); whereas it was 8 of 126 occasions (6.3%) in Group II with 5 of 42 (12%). In an extreme scenario, if you consider one-year follow-up and 6 patients missing at 12 months it would be 14.3% in Group I and in Group II, it was only 5 of 42 patients or 12%. Thus, at all points, the follow-up was present in more than 80% according to your own criteria. Thus, it should be positive.

Sample size also showed negative. According to the calculations, the sample size required prior to conducting the study was 40 participants. We have included 42 participants in this preliminary analysis, thus it should be positive.

The authors have attempted to control for all the confounding factors. We do not see any deficiencies in these aspects, thus, these should be also positive or plus (+).

Consequently if the criteria are changed appropriately, the study will be Level of Evidence I.

The study evaluating effectiveness of caudal epidurals in discogenic pain without disc herniation or radiculitis or facet joint pain (46), or reference 114, was not appropriately characterized in this review. Allocation concealment with implementation and blinding was appropriately performed as described above for manuscript (47), or reference 128; thus, this should be a positive evaluation. Further, intention-to-treat analysis also was given a negative evaluation; however, this was performed and described appropriately on page789; thus, this should change to positive.

Under Other Methods,Implementation, there were negative assessments for cointerventions applied equally, complete follow-up of over 80%, and adequate sample size. Cointerventions were applied equally to all and this has been described extensively as above; thus, this should be positive.

Complete follow-up of over 80% was also applicable as shown on page 789. The data were available in the majority of the included patients. Intent-to-treat analysis was performed due to non-available data on 10 occasions in Group I on a total of 7 patients, and on 5 occasions on 3 patients with Group II. Based on the number of treatments provided, lack of follow-up was found in 10 of 108 occasions (9.3%) in Group I, or 7 of 36 patients (19.4%), whereas it was 5 of 108 occasions (4.6%) in Group II with 3 of 36 patients (8.3%). Thus, the 80% criteria was met and this should be positive.

Another issue is with regards to sample size. The sample size determinations are illustrated on page 789. Based on the evaluation, it required 26 patients in each group of the trial. We have included in this analysis 36 patients in each group. Thus, the sample size criteria have been met even after considering missed patients resulting in a 20% withdrawal rate.

Thus, this manuscript will be Level of Evidence I if the criteria are followed appropriately.

The next study utilized in the methodology assessment was preliminary results in spinal stenosis (43), or reference 111. This study has taken a pattern similar to the one described above. In contrast to the methodologic quality assessors, allocation concealment was provided as described on page 837 along with implementation and blinding. This was appropriate, thus, it should be positive.

Intention-to-treat analysis was considered as negative; however, this was positive as you see from the description on page 837, similar to the above manuscript.

Once again there was a negative assignment for cointerventions applied. The cointerventions were applied equally to all patients, thus this should be positive.

With regards to complete follow-up of over 80%, based on the number of follow-up periods, lack of follow-up was found in 13 of 60 occasions (9.3%) in Group I, or 7 of 20 patients; whereas it was 13 of 60 occasions in Group II with 5 of 20.Thus, if you consider the number of patients, you may be accurate; however, these should be considered with number of follow-up points rather than number of patients at one certain level. Once again, I reiterate that follow-up of over 80% is an extremely high standard to meet.

With regards to the adequate sample size, a negative was provided; however, this was also inaccurate. Sample size was determined to be 18 patients in each group and there were 20 patients; thus, even the preliminary analysis would meet sample size criteria. The methodologic quality assessors have provided

positive rating for controlling for possible confounding, thus, the rating for this manuscript would change to Level of Evidence I.

Based on the number of treatments provided, lack of follow-up was found in 10 of the 108 occasions (9.3%) in Group I, or 7 of 36 patients (19.4%); whereas it was 5 of 108 (4.6%) occasions in Group II with 3 of 36 patients (8.3%) at least one time. Thus, even though I do not agree with 80% complete follow-up criteria, it does meet this criteria.

Consequently, based on the above, applying the same criteria utilized in this evaluation, it lacks only one item; thus, the Level of Evidence would at least be IIa.

The fourth study in reference to caudal epidural injections of Manchikanti et al (48), or reference 129, evaluated the role of caudal epidural injections in post lumbar surgery syndrome. The reviewers showed deficiencies with allocation concealment and intention-to-treat analysis with reference to study design. Allocation concealment was appropriate as described for the earlier studies, along with implementation and blinding; thus this should be changed to positive. Further, intention-to-treat analysis was also provided appropriately on page 821 of the manuscript; thus this would be positive.

Under Other Methods,Implementation, the reviewers showed the cointerventions applied equally, complete follow-up of 80% or greater and adequate sample size as negative attributes to the trial. However, cointerventions were applied equally to all patients as illustrated earlier. However, we concede that the follow-up was present only in 65% of patients at the end of one-year; thus, this can continue to be negative under the present criteria.However, adequate sample size explanation was shown on page 820 which required 18 patients in each group. Consequently, we utilized 20 patients; thus, the sample size would be appropriate.It should be positive.

Based on the revised ratings and using the criteria of this present review, the Level of Evidence for this study would be IIa.

The next methodologic quality assessment pertains to lumbar interlaminar epidural injections studies (44,50), or references 112 and 132.

The study by Manchikanti et al (44), or reference 112, evaluating the effectiveness of lumbar interlaminar epidural injections in managing chronic lumbar discogenic pain without disc herniation, radiculitis, or facet joint pain was provided with a IIb Level of Evidence. Under the study design, there was an issue with allocation concealment; however, allocation concealment was performed appropriately as described on page E282, along with implementation and blinding (masking). Thus, this should be rated positive.

Under Other Methods,Implementation, the negative points were for cointerventions applied equally, complete follow-up of 80% or more, adequate sample size, and controlling for possible confounding. Cointerventions were applied equally as in all other studies as described earlier for caudal epidural injections. With regards to complete follow-up of 80% or greater, as shown on page E283 and Figure 1 on E284, based on the number of treatments provided, lack of follow-up was found in 8 of the 135 occasions (6%) in Group I or 4 of 35 patients (11%); whereas it was 11 of 132 occasion (8%) in Group II with 7 of 35 patients (20%). Thus, this does meet the criteria of 80%, consequently this has to be changed to be positive. Sample size determination is provided on page E282. The sample size is estimated to be 55 patients in each group, however, since this is a preliminary study there were 35 patients included in each group.

Controlling for possible confounding was rated negatively.This should be changed to positive. There were no issues with confounding to affect the results. The numeric rating scores were higher in Group I, though

slightly; however, it will not affect the results because the evaluation was performed with baseline to follow-up periods rather than the change in the effect size between 2 treatment groups. Thus, it would be positive.

Consequently, based on the present strict criteria utilized, the manuscript should be rated as IIa in a worst case scenario.

The second manuscript concerning lumbar epidural injections relates to the management of lumbar disc herniation or radiculitis with lumbar interlaminar epidural injections (50), or reference 132. The reviewers in applying the methodologic quality criteria for this manuscript again question the allocation concealment; however, the allocation concealment, implementation, and blinding were appropriately performed.Thus, this should be changed to positive.

Under Other Methods,Implementation, the reviewers question the application of cointerventions, complete follow-up of 80%, and controlling for possible confounding. Cointerventions were applied equally to both groups, thus this should be changed to positive. Complete follow-up of over 80% was also illustrated appropriately as follows:the complete follow-up of 80% or more patients, based on the number of treatments provided, lack of follow-up was found in 13 of 137 occasions in Group I (9%), or 7 of 35 patients (20%); whereas it was 5 of 146 occasions in Group II (3%) with 3 of 35 patients (9%). Thus, 80% of the patients were followed.

With regards to the confounding factors, the differences appeared in the numeric pain rating scores and with patients with mode of onset of pain; however, these should have not affected the results. This has been described in the text; thus, this should be positive.

Consequently, considering all the factors, the Level of Evidence is either level I or IIa.

In reference to the adhesiolysis studies (45) or reference 113, (49) or reference 130, it is inappropriate to include them with the epidural studies. Chou’s argument has been that in the study (51), or reference 127, caudal epidural injections were administered.However, they were administered as a control group after they had failed fluoroscopically directed epidural injections. Chou and Huffman also argued that in our previous study (51), or reference 127, we made the selection criteria very strict.We would have thought that using strict selection criteria would meet your academic standards rather than face criticism. Further, the authors have misunderstood the nature of relief and suggested that the group had no significant relief.However, just because the group of patients failed to respond with significant pain relief above 50%,that does not rule out that they have not experienced any relief at all. A significant proportion of patients in this study (51), or reference 127, had relief at one-month (i.e., 50% or more).Both of the studies (45) or reference 113, and (49) or reference 130, should meet all the criteria. The methodologic quality assessment misunderstood some of the aspects. Allocation concealment was maintained along with blinding.Only the physician at the time of the performance of the procedure knew whether patients were in the control group or the intervention group. Even then, allocation concealment was appropriately maintained as none of the other personnel were aware of the allocation. Further, intention-to-treat analysis was also utilized in both studies. It was clearly illustrated.

In the section Other,Methods Implementation, deficiencies were noted for both studies with regards to cointerventions, complete follow-up of 80%, and controlling for possible confounding. Cointerventions were applied equally to all groups and potential confounding was controlled and addressed in both groups in both studies. Complete follow-up of 80% or more is a difficult issue in this case because of the patients essentially receiving no significant effect from the control intervention and subsequently withdrawing from the treatment.That is the only way we can recruit patients. If we say that they cannot withdraw, we

will not have any recruitment at all; thus, both of these studies would meet Level of Evidence of I, or in a worst case scenario,IIa.

On the evaluation of Sayegh et al (52), or reference 172, though the blind caudal epidural injections followed all of the appropriate principles, they did not describe random sequence generation;however, it appears that they maintained allocation concealment.Thus, the study should meet the criteria of Level of Evidence of IIa with only one negative element. It would have been worthwhile to contact the authors for any questions related to this study.

Tafazal et al (53), or reference 193, described transforaminal epidural injection. We had no access to this manuscript. Thus, I am unable to comment. I have no comments on Koc et al (54), or reference 96, as this does not even meet inclusion criteria in any of the other evaluations.

Peng et al (55), or reference 157, describes intradiscal injection. I do not believe there is any relevance for this study to be included here.

With regards to the caudal epidural injections, it may be worthwhile considering Dashfield et al (56), which meets appropriate criteria receiving a high quality assessment.However, whether through inaccuracy or through lack of understanding, this continues to be utilized under the category of endoscopic adhesiolysis, but not for caudal epidural injections. The study should be utilized for caudal epidural injections as it is an active control trial wherein the active control happens to be more effective than the intervention. Even Chou and Huffman have given it a reasonably high rating of 7 of 11 on their methodologic quality assessment. The next study is related to Ackerman and Ahmad (57),or reference 2, which failed to meet inclusion criteria for ASIPP systematic reviews and guidelines due to less than 6 months of follow-up. However, Chou and Huffman considered this as a high-quality study with methodologic quality assessment of 9 of 11; this should be considered for evaluation not only for caudal, but also for interlaminar as well as transforaminal epidural injections – an active-control trial.

Thus, applying the proper evidence and utilizing only the new studies (42,47,51,52), of which 3 of them were fluoroscopically directed, there is positive evidence for caudal epidural steroid injections in managing low back and lower extremity pain secondary to lumbar disc herniation and radiculitis. Of the 4 studies, only 2 of them provided follow-up over a period of 6 months. Thus, all 4 are positive for follow-up of less than 6 months, whereas 2 studies with one-year follow-up are also positive for one-year follow-up. However, for low back pain of disc origin without radicular pain, disc herniation, or facet joint pain; lumbar central spinal stenosis; and post lumbar surgery syndrome, the effectiveness is based on only one study in each condition in recent years with performance of the procedures under fluoroscopy and one-year follow-up.

For lumbar interlaminar epidural injections, the evidence is based on only the studies by Manchikanti et al (44,50) which were performed under fluoroscopy with one-year follow-up for only disc herniation and radiculitis; and low back pain of discogenic origin without disc herniation, radiculitis, or facet joint pain.

For transforaminal epidural injections, the studies of Karppinen et al (58,59), Riew et al(60,61), Jeong (62), Ng (63), and Ackerman and Ahmad (57) should be reevaluated which I believe yield good evidence.

In relation to adhesiolysis, both studies of post laminectomy syndrome show positive results (49,51). In addition, the spinal stenosis study also shows positive results, though preliminary and emerging (45). Thus, the evidence must be positive for post lumbar surgery syndrome for adhesiolysis with positive but a lower evidence for spinal stenosis.

Lumbar Facet Joint Interventions

The next descriptions are related to lumbar facet interventions. In this evaluation, only one RCT was identified and utilized for the evaluation of lumbar facet joint injections after Chou's criteria (64), or reference 131. The methodologic quality assessment criteria in reference to study design question the allocation concealment and intention-to-treat analysis with negative evaluation. However, allocation concealment was described on page 127 of the manuscript, along with implementation and blinding; thus, these should be positive. Further, intention-to-treat analysis was also described rather extensively on page 127 and sensitivity analysis for pain rating scores for intention-to-treat analysis methodology was also described on page 129.Thus, this should also be judged positive.

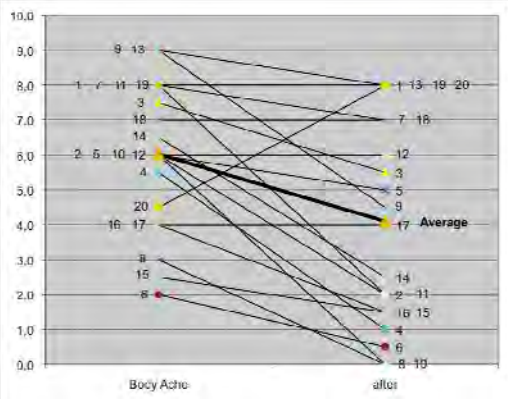
Under Other Methods,Implementation, the reviewers question the application of cointerventions and adequate sample size. Cointerventions were applied equally to both groups. This has been illustrated in the manuscript; thus, this would be positive.

The next issue relates to adequate sample size. The sample size determination and justification was provided on page 126. There were no randomized trials available to base the calculation of sample size; thus, we took the sample size of 60, which probably is 3 to 4 times the normal. As the reviewers are aware, multiple sample sizes have been less than 20 patients per group; thus, this is adequate. Consequently, the rating should be a Level of Evidence of I, or in a worst case scenario, IIa.

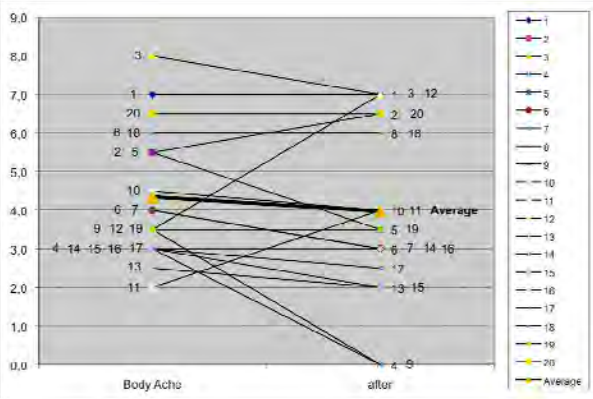
There have been substantial misunderstandings and discussions with regards to Nath et al's manuscript (65). This manuscript needs to be re-evaluated. In fact, this was the only study which met inclusion criteria by Datta et al (66). It is unfortunate that Chou and Huffman included multiple inappropriate studies to force the evidence into the negative category. Further, Chou and Huffman found multiple deficiencies with this study which was previously considered one of the best studies in the literature except for lack of long-term follow-up. Obviously the data generated by this manuscript was misinterpreted. Chou and Huffman (67) reported the final scores in both groups were identical and there was no change in low back pain. This is in contrast to the manuscript which clearly states and showed clear and distinct differences between both groups in all aspects. The intervention group with radiofrequency neurotomy showed statistically significant improvement, not only in back and leg pain, but also back and hip movement as well as sacroiliac joint pain. There was also significant improvement in quality of life variables, global perception of improvement, and generalized pain in the intervention group with radiofrequency neurotomy. Chou et al also utilized conflicting numbers in the study at different places in their document, either 40 or 60, with the actual number being 40. Chou and Huffman also missed the fundamental and basic fact that it was an active control study with needle placement, as well as local anesthetic injection over the nerve. The major criticism of Chou has been that "the sham control group (which had higher baseline scores) had greater potential to experience improvement from baseline" and this was the comment he made in the letter to *Pain Physician*.However, this was not the criticism provided in the manuscripts published earlier. Further, this criticism has not beensubstantiated as there was no sham group. Both groups were active, one was active with local anesthetic injection, the second one with radiofrequency neurotomy. It also has not been substantiated as the subject of whether patients with more pain are easier to treat successfully, when compared to those with less pain. This has never been studied. In fact, the converse may well be true. The individual patient data as graphs for the baseline and outcome measures for generalized pain, back pain and leg pain and global perception of improvement from Nath et al is illustrated here. The graphs illustrate no bias. It was not as if patient's in the intervention group, with more severe pain responded to treatment better or more often than patients with less severe pain; however, patients with all degrees of severity responded. Further, patients with the most severe pain, more often contributed to failures than did patients with less severe pain.

Generalised Pain

Interventionwith radiofrequency neurotomy

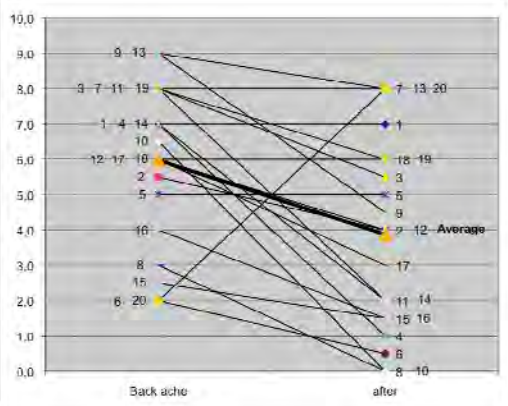


Control with local anesthetic injection and sham lesioning

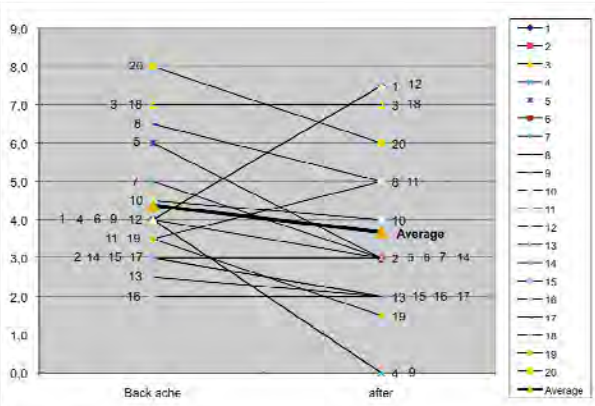


Back Pain

Interventionwith radiofrequency neurotomy

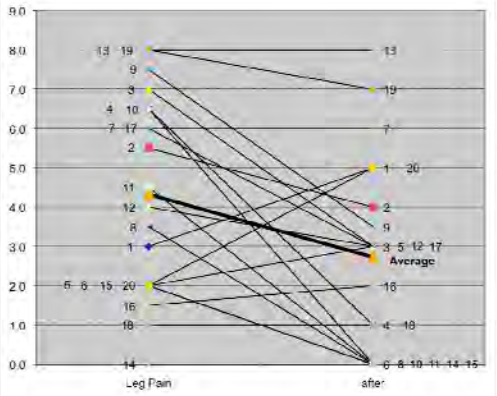


Control with local anesthetic injection and sham lesioning

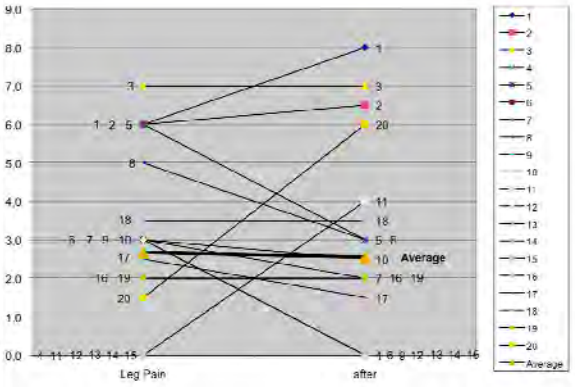


Leg Pain

Interventionwith radiofrequency neurotomy

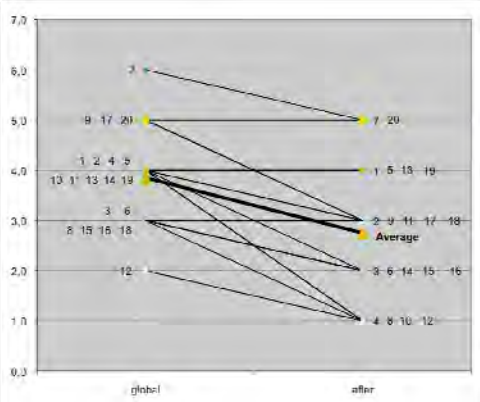


Control with local anesthetic injection and sham lesioning

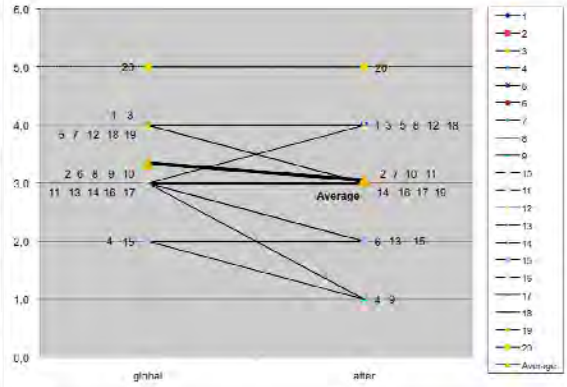


Global improvement

Interventionwith radiofrequency neurotomy



Control with local anesthetic injection and sham lesioning



Not only did Chou and Huffman faileto contact Nath, they continue to change their argument with regards to Nath et al's manuscript, which has been described as an appropriate manuscript (68).

Of the multiple other studies Chou and Huffman have included, Van Wijk et al (69), and multiple other studies did not meet inclusion criteria by others due to numerous deficiencies (69-74). Chou continues to deny the fact that these procedures were not performed appropriately; obviously the quality of the procedure does not mean anything for methodologists according to him. Of most interest is Leclaire et al (70) who randomly assigned patients to receive either radiofrequency neurotomy under fluoroscopic guidance (N=36) or the same procedure without denervation (so called sham procedure – but trulynot a sham – but an active control) (N=34). The authors concluded that, although radiofrequency ablation might provide short-term improvement in functional disability, the efficacy of the treatment has not been established. This study (70) used diagnostic nerve blocks to identify affected locations. The Leclaire study invited criticism because it failed to define the study population and had inappropriate diagnostic criteria with intraarticular injections to identify patients for radiofrequency neurotomy. Patients were evaluated with a single diagnostic block with 50% pain relief as the criterion standard. They considered any relief of

one-day duration during a seven-day period following a single diagnostic intraarticular injection as significant. Such an effect could be the result of many factors, including natural sequence. Thus, any results or conclusions based on this study would be erroneous. Interesting enough, Gauci (75) requested from the authors of the study an explanation on precisely what medical assessment groups should interpret from the study's results.

Leclaire et al (76), in a recent letter to the editor of Pain Practice, acknowledged multiple deficiencies in their study; many consider this a retraction of their manuscript. They elaborated that the results of their research have been interpreted by the UK's National Institute for Health and Clinical Evidence (NICE) as evidence that radiofrequency neurotomy is ineffective as a treatment for low back pain; they are of the opinion this is an inappropriate use of the conclusions of their study given that the authors themselves have serious reservations about their own study. Further, they described contemporary reviews that rejected their study did so with a dated approach and so were inappropriate or invalidated (66,77). They also acknowledged the value of controlled local anesthetic blocks and false-positive rates. They stated that if they repeated their study today, they would use controlled medial branch blocks as the primary inclusion criteria to correctly identify patients with pain originating from the lumbar zygapophysial joints. They discussed needle positioning and lesioning. Their final conclusion was that the study should be viewed as a precursor to more effective diagnostic and therapeutic strategies in the management of zygapophysial joint pain and must be interpreted only in its historical context of what methodology has been shown to be invalid. Further, they stated that only selection criteria based on controlled medial branch blocks with high grade relief consistent with the physiologic effects of the anesthetic and an appropriate multiplanar fluoroscopic radiofrequency neurotomy technique should be used to produce valid studies on this treatment for chronic low back pain.

It is very interesting that Leclaire is the second author of the manuscript published by Carette et al (27), which is considered as a standard for negative response and also for positive response with sodium chloride solution injected into a closed space.

Other studies including Van Wijk (69) also had multiple deficiencies (62,78) of their own results.

Based on this evaluation, lumbar facet joint nerve blocks are presented with positive evidence if it is appropriately evaluated and the low quality and inappropriate studies from Chou and Huffman are excluded.

In reference to radiofrequency neurotomy with all the criticism apart, Nath's study is ideal and it should be included as high quality with positive results.However, this is not a sham controlled study, it is an active control study. The same applies to Leclaire's study which has been used negatively to affect the evidence synthesis even though the authors have agreed that that should not be done.

Sacroiliac Joint Injection

No comment.

Lumbar Intradiscal Injections

No comments. The study provided here is relevant.

Cervical Epidural Injections

The reviewers describe 3 studies (79-81), or references 120, 121, and 189, which were identified and received a Level of Evidence grade of IIb as illustrated in Appendix E. Two of them happened to be by Manchikanti et al (79,80), or references 120 and 121. Manchikanti et al (80), or reference 121, evaluated the effectiveness of fluoroscopic cervical interlaminar epidural injections in managing chronic cervical disc herniation and radiculitis and was a report of preliminary results. The reviewers questioned the study design of this manuscript with allocation concealment and intention-to-treat analysis providing negative results. Allocation concealment was described appropriately, along with implementation and blinding;just like the other manuscripts in the lumbar region, on page 226 it was applied appropriately; thus, the rating needs to be changed to positive. The next issue relates to intention-to-treat analysis. This was also described on page 226 appropriately and sensitivity analysis was also carried out prior to applying the methodology. This requires a change to positive.

Under Other Methods,Implementation, questions were raised with regards to cointerventions, complete follow-up, and adequate sample size. Cointerventions, as described earlier, and in the manuscript in detail, were applied equally to both groups; thus, this should be judged positive. Complete follow-up of 80% or higher was also described on page 226 of the manuscript. Based on the number of treatments provided, lack of follow-up was found in 2 of 105 occasions in Group I (2%), or 1 of 35 patients (3%); 3 of 105 occasions in Group II (3%) with 2 of 35 patients (6%). Thus, this meets and exceeds the criteria described by the review authors. In reference to adequate sample size, sample size determination was described on page 225 with a requirement of 55 patients in each group; however, because this is a preliminary study, only 35 patients were included; thus, considering the results of various other included studies, this sample size should be considered adequate.

Consequently, the study would achieve a Level of Evidence of I, or in a worst case scenario, IIa.

The second study was also by Manchikanti et al (80), or reference 120, evaluating the role of cervical epidural injections in patients with discogenic neck pain without disc herniation, radiculitis, or facet joint pain. The review authors for this study claimed deficiencies in the study design's allocation concealment and intention-to-treat analysis. Both have been described extensively above and in the particular manuscript also; thus, both should be appropriately changed to positive.

Under the Other Methods, Implementation, the review authors claim deficiencies with cointerventions, complete follow-up, and adequate sample size. Cointerventions were applied to both groups, thus there should not be any questions about this issue, and it should be positive. With regards to complete follow-up of 80% or more patients, as illustrated on page E268, based on the number of treatments provided, lack of follow-up was found in 2 of 105 occasions in Group I (2%) or 1 of the 35 patients (3%); whereas it was 3 of 105 occasions (3%) or 2 of 35 patients (6%) in Group II. Thus, this meets and exceeds the required criteria. The next question relates to adequate sample size, which was provided with a negative impression. The sample size determination is illustrated on page E268. Even though there are not studies available, we have utilized the worst case scenario situation, and utilized a sample size of 55 patients; we utilized 35 patients in each group for the preliminary analysis. Thus, it does meet the sample size criteria.

Consequently, the Level of Evidence is I or in a worst case scenario, IIa.

The evaluation of Stav et al (81), or reference 189, appears appropriate.

Cervical Facet Joint Interventions

The authors identified 2 RCTs, both of which were rated as a Level of Evidence Grade IIb. These included 2 studies by Manchikanti et al, which were published as 2 reports of the same trial (82,83), or references 133 and 122. The other manuscript was of Barnsley et al (84), or reference 15.

The cervical medial branch blocks one year and 2-year follow-ups were described by Manchikanti et al (82,83), or references 133 and 122. The review authors provided deficiencies in the study design in reference to the allocation concealment, which has been clearly described, along with implementation and blinding; thus, this rating needs to be changed to a positive or plus (+). Under Other Methods,Implementation, the review authors questioned cointerventions application and adequate sample size. Cointerventions were applied equally to all groups. Adequate sample size was determined based on previous studies, which was very low, thus we utilized a 60 patient sample size. This should meet the criteria for sample size.

Consequently, the Level of Evidence grading for this study is level I, or in a worst case scenario, IIa.

Barnsley et al (84), or reference 15, seems to have been evaluated appropriately.

With reference to cervical facet joint interventions, there is positive evidence for medial branch blocks and radiofrequency neurotomy with negative evidence for cervical intraarticular injections.

With regards to other issues and comments, we have described in detail the issues related to Manchikanti et al's studies.

Randomization and Concealment Allocation

This is addressed in each manuscript. This has been described according to CONSORT guidelines in each manuscript.

Intention-to-Treat

Intention-to-treat analysis was given in all the studies. Each manuscript has described appropriately how many patients were unblinded and withdrawn.

Blinding

The investigator recording the patient outcomes was also blinded. All major outcomes of patients are reported, so are all other studies related to the spine and the interventions.

Cointerventions

These have been addressed and they were all similar cointerventions.

Length of Follow-up and Percent of Patients Followed

Once again, this varies based on the number of patients included in the study. These are all addressed in individual manuscripts. It is inaccurate to report that none of the studies had complete follow-up of 80% or more. This is a miscalculation; please look at the calculations, and revise them as described. This is what is called review bias which may not be overcome.

Confounding

Confounding was controlledin all the studies. The four studies which had statistical differences between study groups at baseline were not influenced by these factors.

Conflict of Interest

We have provided appropriate information on conflict of interest. Everything is available on the websites, and I have also provided this in the beginning.

4.0 RESULTS

4.1 Key Question 1. What is the evidence of efficacy and effectiveness of spinal injections?

4.1.1 Lumbar interlaminar or caudal epidural injections versus placebo (saline/water and/or local anesthetic controls).

These results are affected because of inappropriate evidence synthesis, methodologic quality assessment, and misunderstanding of the role of placebo as described earlier. If these issues are appropriately addressed, the results will be different in most of the aspects.

Regarding the opioid issues,it should be clear if the participants were on high dose opioid or low dose opioids and how long they had been on opioids.

With regards to employment, employment needs to be carefully looked at and defined in discrete employable categories and if the study is a placebo control or active control.

Table 5 shows pain and function outcomes. It is of course,a summarization which is based on misunderstanding the various issues involved and misapplication of the methodologic quality assessment.

One of the issues related to all the evaluations, whether it is epidural or facet joints, either in the cervical spine or lumbar spine, appears to be that the reviewers have utilized the philosophy that the difference between 2 groups is the effect.However, in active control groups, this is inappropriate, since there are no placebo control groups. Most of the evaluated studies used local anesthetic as the control. Further, in radiofrequency neurotomy, when a local anesthetic is injected over medial branches, that is not considered to bea placebo even though radiofrequency was not applied.

Finally, with regards to Chou’s rebuttal, you have not heard from the authors of this criticism yet. He may be legitimate in some of the minor aspects. Even then, his guidelines have been prepared carelessly without appropriate application of the standards of evidence-based medicine.

As an additional point, Rubinstein and van Tulder et al (85), who are well-known for their evidence-based medicine principles and their research, have published a best-evidence review of diagnostic procedures for neck and low back pain. They have provided very low evidence for many tests, but they provided moderate to strong evidence for diagnostic facet joint blocks. Their conclusion was that there was strong evidence for the diagnostic accuracy of facet joint blocks in evaluating spinal pain, and moderate evidence for transforaminal epidural injections, as well as sacroiliac joint injections for diagnostic purposes.

Finally, the authors of this review, Chou and Huffman, and all others concerned with systematic reviews, evidence synthesis, and recommendation of guidelines, should reveal their connections to each other, to

insurance agencies, their income basis, and the funding received, including the amount paid for the guidelines and to each individual.It should simply state that there were no conflicts of interest; accusing others of conflicts of interest on the same issues is not fair. Obviously, the review authors are paid for this evaluation and so are Chou and Huffman and others. Piecemeal declaration of conflicts or lack thereof, is inappropriate unless there is a misunderstanding.

In summary, you have asked me to perform this review to ensure that the objectives were met (I have to say they were not met); that the methods and analysis are consistent with good methodology (I must state that the methods and analysis are not consistent with good methodology and are biased); that the conclusions are reasonably based on the data and analysis (I must add that the conclusions may be reasonable based on the analysis, but they are not accurate); and that the report is objective (I must disagree with the objectivity of the report).

Thank you again for providing this opportunity to participate in this evaluation. If you have any questions please feel free to contact me.

Sincerely,

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"Man spends his life in reasoning on the past, in complaining of the present, in fearing future." *Antoine Rivarol*

"There is no limit to what a man can do or where he can go if he doesn't mind who gets the credit." *Ronald Reagan*

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4. Public Comments

Alan Chen, MD

I am writing to express my opinion on the indication and purpose for this procedure that has limited evidence for any long term benefit compared to no injection.

The important thing to note is that there is evidence that acute pain from lumbar disc herniations causing a radiculopathy will in 61% of cases improve enough over the course of 3 to 6 months to avoid the need for surgery. This is with conservative treatment to control pain and restore function using PT, pain medications, and ESIs.

The role of an ESI is to help these patients afford the opportunity to "ride out" this acute pain period and give the opportunity for natural healing to take place so that surgery may be avoided. The evidence for short term efficacy is clear for ESIs, and is indicated if the pain (despite more conservative options of PT, NSAIDS, pain meds) is still incapaciating and preventing the patient to perform ADLs (activites of daily living).

In my opinion, ESIs are NOT indicated for chronic radiculopathies, as these do not typically improve over time. A chronic radiculopathy that has not changed in quality over the course of at least 6 months has a reduced chance of improving. At this point, surgical options should be considered.

Without ESIs, the costs for L and I will increase tremendously because of time loss payments, ER visits, and a significant increase in number of spine surgeries that patients will opt for...simply because there will be no other option to control their pain. In addition, although pain is subjective, acute pain needs to be treated under L and I...these patients are typically incapacitated initially, and opiates, NSAIDs, are insufficient...to the point where the patient would go to the ER.

The same is true for cervical and thoracic ESIs...and whether an ESI is performed foraminally or interlaminarly.

If you would like to discuss this further with me, please feel free to call me at 425-306-8403.

Alan Chen, MD
Interventional Physiatrist
Cascade Orthopaedics
Auburn, WA

Ghislaine Robert, MD

I'm a sports medicine physician and I highly recommend that we have the option to send our L&I compensation patients for spinal injections.
The natural evolution of most disk disease is to eventually either fuse or become asymptomatic. The spine injections have a strong place when the symptoms are severe and the patient is unable to perform his job. They are not a cure but they help the patient to be more functional and less in pain. If we remove them from the options of treatment, I assure you that you will end up paying a lot more surgeries.

Respectfully submitted

--
Dr Ghislaine Robert MD
LMCC, CCFP, FCMF
Dip Sport Med (CASM)

Michael Gofeld, MD, FIPP

UW Medicine
DIVISION OF
PAIN MEDICINE

WE ARE COMMITTED TO PREDICT, DIAGNOSE AND PREVENT PAIN FROM BECOMING A DISABLING DISEASE

November 21, 2010

Health Technology Assessment

RE: Spinal Injections Draft Evidence Report

Dear HTA Committee Members,

I read the draft evidence report with great interest. Notwithstanding importance of key questions of efficacy and effectiveness, safety and cost-effectiveness, I believe HTA has no mandate to open this discussion.

According to HTA website, "the primary purpose of HTA is to ensure **medical treatments and services** paid for with state health care dollars are safe and proven to work". However, "spinal injections" are merely a **drug delivery route**. There is no specific technology used, but simply a needle, a syringe and a medication. Same medications (corticosteroids and local anesthetic) *are extensively used in general medical practice. In fact, oral and parenteral corticosteroids* are routinely prescribed in primary care setting, despite clear recommendation against it published by a US government sponsored guideline committee (1). Notably there is no such definite opinion ever issued regarding epidural route of steroid administration. The evidence is similar to presented in the current draft, i.e. randomized controlled studies found no or short-term benefit of oral or parenteral corticosteroids in treatment of sciatica (2-5). The goal of epidurally administered corticosteroids is not a long-term benefit. If there is a situation of an acute sciatica, the injection may abort painful debilitating illness and allow faster functional recovery. When the situation is chronic, injectional therapy is a palliation and no long-term benefit is likely to be achieved. The whole discussion of side effects and complications is irrelevant as well. Any subcutaneous and intramuscular injection may result in complications including vasovagal syncope, infection, bleeding, etc. The rate of neurological complications is extremely low and predominantly related to suboptimal technique or agents' choice.
I assert that the question of the intraarticular facet injections is yet, again, about a route of administration and cannot be assessed as a technology. Moreover, spinal facet joints are skeletal articulations and in this respect injections into them are not different from other intraarticular injections (e.g. knee, shoulder).
Quoting again HTA website, "Health Technology is a *broad term that includes: medical / surgical devices and procedures; medical equipment; and diagnostic tests. Health technologies range from simple items to complex tools or treatments..*", I call the committee members to withdraw the current draft and refrain from assessing topics unrelated to medical technology.

Respectfully,

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Regence

Regence does not disagree with the critical appraisal of the scientific evidence related to spinal injections.

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Multi-specialty national medical society comments

November 24, 2010

Brian R. Budenholzer, MD, FAAFP
Chair
Washington State Health Technology Committee
P.O. Box 42712
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Dear Dr. Budenholzer,

The undersigned national medical societies, would like to submit our consensus comments to the Washington State Health Technology Clinical Committee (HTCC) in response to Spectrum Research's vendor report ("Report") on the subject of spinal injections. Our organizations represent a broad spectrum of spine care specialists, who perform spinal injections in order to improve the quality of life for our patients.

Among our members are the clinicians and academicians whose published literature provides the seminal references upon which the practice of evidence-based interventional spine care is based. Our organizations have a long record of work dedicated to eliminating fraudulent, unproven and inappropriate procedures; while assuring that appropriate, effective and responsible practices are preserved, so that patients are not deprived of reasonable and effective diagnostic and therapeutic options. As such, we are cognizant of the complexity of the task facing the Committee.

We would like to offer the Committee additional information, beyond that referenced in the Report. Our goal is not to dissect the Report and engage in academic discussions, but to offer our collective expertise in order to help the Committee reach a determination that is fair, humane, and socially responsible, while remaining accountable to the evidence. To that end, we are submitting a series of appendices that address concepts and procedures of concern to us and our patients.

We extend to the committee an offer to provide national and international expert input and expertise as a resource in this process. If we may answer any questions or provide any

assistance please feel free to contact Margaret Klys, Director of Health Policy at the International Spine Intervention Society (ISIS) at mklys@spinalinjection.org or 708-505-9416. Additionally, staff contact information for all the undersigned societies is attached in Appendix A.

Sincerely,

James T. Rutka, MD, PhD, President
American Association of Neurological Surgeons

Gregory W. Petermann, MD, President
American Society of Spine Radiology

Eduardo M. Fraifeld, MD, President
American Academy of Pain Medicine

Christopher C. Getch, MD, President
Congress of Neurological Surgeons

Michael F. Lupinacci, MD, President
American Academy
of Physical Medicine & Rehabilitation

Way Yin, MD, President
International Spine Intervention Society

Robert K. Zeman, MD
Chair, Carrier Advisory Committee Network
American College of Radiology

Gregory Przybylski, MD, President
North American Spine Society

Mark Warner, President
American Society of Anesthesiologists

James F. Benenati, MD, President
Society of Interventional Radiology

Patrick A. Turski, MD,
Chair, Clinical Practice Committee
American Society of Neuroradiology

I. CONTEXT

Low back pain is a distinctly different condition from lumbar radicular pain (previously known as "sciatica"). Similarly, neck pain is distinctly different from cervical radicular pain. The evidence-base for low back pain – encompassing mechanisms, causes, investigation, and treatment, is entirely different from the evidence base for lumbar radicular pain. The same applies for neck pain and cervical radicular pain.

The causes of acute and chronic low back pain can be elusive and difficult to determine, but the causes of radicular pain are often plainly evident. The most common cause of radicular pain is disc herniation, causing neuroforaminal or lateral recess stenosis.

The lesions that cause most acute radicular pain are demonstrable and their pathophysiology is potentially reversible. The presence of demonstrable pathology causing acute radicular pain means that the conventional approaches for the management of chronic back pain cannot – and should not – be applied to the management of acute radicular pain.

Patients with acute cervical or lumbar radicular pain have few legitimate "conservative" therapeutic options. They may benefit from natural history, but those with persistent pain face surgery as the only recognized option. Yet spine surgery is costly and not without risks.

Multidisciplinary pain management is not appropriate for acute radicular pain. Patients with radicular pain do not have an adjustment disorder; nor are they failing to cope with an undefinable source of pain. They have potentially reversible lesions.

Traditional "conservative care" options (*e.g.* physical therapy, chiropractic manipulation, NSAIDs, traction, *etc.*) although commonly accepted as reasonable, have not been definitely proven to be of benefit for those with radicular pain.

Opioids are often used as a palliative measure for patients awaiting surgery, and failure to benefit from opioids is used as an indication for surgery. However, there is no evidence that they are effective in the long term. They neither remove the lesion nor inhibit its pathophysiology.

For the above stated reasons, patients with radicular pain face an anguishing dilemma. This dilemma should be shared by those who direct their care, or who pay for it. No drug stops radicular pain. No form of conservative care reliably reduces radicular pain let alone stops it. Patients with acute radicular pain can choose conservative and pharmacologic care while natural history runs its course, but those with persistent radicular pain will have exhausted these options. Surgery looms as the only commonly perceived alternative.

It is in this context that the use of therapeutic spinal injections has arisen. Injections offer two virtues: they can stop the pain, and they can reduce the need for surgery.

II. LIMITATIONS

Conscientious and responsible practitioners do not wish to be party to the undisciplined and profligate use of ineffective procedures. Ideally, the use of any procedure should be predicated on clinical indications that have been validated by quantitative research. However, in some situations, the indications are ambiguous or irregular, ***because the necessary research has not yet been conducted.*** At other times, irresponsible practitioners disregard either the evidence or common sense and abuse procedures. They perform a procedure because it can be done or paid for and not because the patient is likely to benefit.

In these latter circumstances it is not the procedure that is at fault; but rather the behavior of practitioners that is irresponsible. ***Prohibiting a procedure on these grounds may eliminate irresponsible behavior, but in doing so, disenfranchises responsible practitioners and limits effective treatment options for patients.*** This may result in a situation in which access to an effective procedure is removed in favor of unsupported care options or shunting patients to riskier and more costly interventions.

Ideally, procedures should be allowed – or paid for – only if they are performed for appropriate indications. A particular example includes the various forms of epidural injections. These injections should be performed primarily for patients with a history, physical examination and imaging studies consistent with a diagnosis of radicular pain.

Therapeutic injections may need to be repeated, in order to reinstate the relief previously obtained. In such cases, administrators have often sought some magic number of injections that are clinically indicated and should be allowed. This is frequently artificial and may not ultimately be helpful. Responsible practitioners repeat treatments only if they have previously benefitted patients. Therefore the indication for repeat treatment becomes a demonstrated and documented benefit from previous treatment. Some insurers have already adopted such a principle for judging justification for repeat treatment.

Guiding practice by imposing clinically sensible and socially responsible limitations shifts the burden. The patients of responsible practitioners are not denied care. Having defined limitations converts the abuse of "clinical freedom" to one of an act of fraud.

III. RECORDS

Procedures may be abused in at least two ways. Neither constitutes responsible practice. As long as it remains possible for unscrupulous practitioners to continue abuses, the reputations of the procedures and responsible practitioners are maligned.

A practitioner may claim to perform a procedure – the name of the procedure appears on the procedure report or billing form. Yet there is no guarantee that the procedure billed has either been performed, or performed correctly. A needle might be placed and medication delivered, but not in the correct location, either deliberately or through ignorance. Such behavior disadvantages the patient and raises costs associated with the procedure.

Radiographic images obtained at the time a procedure is performed and subsequently maintained in the medical record provide a means of quality control. In most cases, both diagnostic and therapeutic spinal injection procedures are performed under radiographic guidance in order to maximize safety and efficacy. It is physically possible to retain radiographic records of the procedure in the medical record. Radiographic images in concert with medical records outlining the indications for the procedures provide a ready means of identifying both proper patient selection and proper technique.

The International Spine Intervention Society has published widely recognized guidelines addressing the technical performance of spinal injection procedures. [1]

Reference

1. Bogduk N (ed.). Practice Guidelines for Spinal Diagnostic and Treatment Procedures. San Francisco: International Spine Intervention Society, 2004.

IV. THERAPEUTIC EPIDURAL INJECTIONS

There are a variety of approaches to "epidural" injections which are ***not*** the same. They differ in technique, objectives and evidence-base.

Traditionally, epidural injections were performed "blind", *i.e.* without radiographic guidance. In the case of most epidurals performed for anesthesia, postoperative analgesia, and labor analgesia, this is still the case. Therapeutic agents were delivered in the vicinity of the purported pathology, but there was no guarantee that the agents actually reached the pathology. Spread of injectate in the epidural space is unpredictable. Injections using the caudal route, for example, are delivered even more remotely from lumbar pathology than injections using the interlaminar route. Several studies have shown that "blind" injections often fail to even enter the epidural space, especially in the hands of inexperienced providers. According to various studies, "blind" caudal injections fail to reach the epidural space in up to 35% of cases [1-4], and "blind" interlaminar injections fail to do so in up to 17% of cases [1,5-7]. This failure may contribute to the lack of efficacy of "blind" injections in some cases.

Interlaminar injections are commonly performed with fluoroscopic or CT guidance. Fluoroscopy allows direct visualization of the needle location followed by injection of a test-dose of contrast medium. This test-dose shows that the injection is in the epidural space and neither intrathecal nor intravascular. In addition, the test-dose demonstrates that the injectate spreads to the site of the target pathology. If inappropriate spread is observed, it allows the practitioner to reposition the needle to obtain optimal injectate spread.

Fluoroscopically-guided, *transforaminal* injections were developed in order to increase the accuracy of injections epidural injections and improve spread of the injectate to the anterior epidural space. Instead of relying on injectate to flow from the dorsal epidural space to the target nerve and its pathology, transforaminal injections deliberately deliver the injectate directly to the target nerve where it exits the neuroforamen.

In the presence of substantially different techniques, *data on the efficacy of different epidural injection procedures cannot legitimately be aggregated*. Previous reviews have erroneously done so, and created a false impression regarding the overall efficacy of therapeutic epidural injections. [8]

In order to develop the most accurate conclusions, the evidence on efficacy must be stratified according to the technique used and the conditions for which they were utilized. For example, low back pain is a different condition from lumbar radicular pain and cervical radicular pain is different from lumbar radicular pain.

If the evidence for efficacy is stratified according to the indication for treatment, the various procedures fall into three categories:

- as having explicit evidence of *no* efficacy
- as *lacking* evidence of efficacy
- as *having* evidence of efficacy.

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V. THERAPEUTIC EPIDURAL INJECTIONS USING THE "BLIND" LUMBAR INTERLAMINAR TECHNIQUE

For the relief of *radicular pain* in the lower limb, several studies have variously shown that:

Epidural injection of corticosteroids using the "blind" interlaminar route is either:

- no more effective than sham injections
  - at 30 days [1] at 35 days [2], or two months [3] after treatment.
- no more effective than:
  - an epidural injection of local anesthetic alone [3] or
  - an epidural injection of normal saline [5], or
  - an intramuscular injection of steroids [6].

Some studies have shown that "blind" interlaminar epidural injection of steroids achieves slightly greater reduction of pain at 20 days [2] or three weeks [7] after treatment, but differences from control were extinguished thereafter.

At 35 days after "blind" interlaminar epidural steroid treatment, the NNT for "any relief of pain" is 100 [2]. (This means that 100 patients would need to be treated before one could be claimed to have benefited from the specific effects of the treatment.)

These data refute any worthwhile contention of lasting benefit from "blind" therapeutic lumbar interlaminar injections of steroids. They do not constitute a definitive treatment for lumbar radicular pain. They do not constitute a valid alternative treatment for lumbar radicular pain.

However, the data do support the possible use of "blind" lumbar interlaminar injection of steroids as a short-term, temporizing, or brief palliative, intervention for patients with radicular pain who are awaiting definitive treatment, such as surgery, within two or three weeks or in whom sufficient relief is obtained to allow the patient to await the outcome of the natural course of the disease with less discomfort.

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VI. LUMBAR TRANSFORAMINAL INJECTIONS OF STEROIDS

INDICATIONS

The sole indication for lumbar transforaminal injection of steroids is lumbar or sacral radicular pain.

ADVANTAGES

This procedure was developed to improve the accuracy of steroid injections. Transforaminal injection affords several real advantages over the procedures that it replaces:

- The needle is placed directly against the target nerve.
- A test injection of contrast medium ensures that the intended medication flows directly and accurately along the affected nerve.
- A test injection of contrast medium allows aberrant injections to be identified and corrected before medication is administered.
- In particular, a test injection of contrast medium viewed under live fluoroscopy guards against unwanted injection into the thecal sac or into radicular or medullary arteries.

EFFICACY

The use of fluoroscopically-guided, transforaminal injections of steroids was heralded by an observational study that enrolled 30 patients who were on a waiting list for surgery [1]. Following treatment, 47% obtained complete relief of pain that endured for at least 12 months, and only 20% ultimately required surgery.

A subsequent, observational study reported that 52 out of 69 patients (75%) obtained greater than 50% relief of the pain, at follow-up times of between 28 and 144 weeks [2]. Other, observational studies echoed these outcomes [3,4].

For the purposes of interpreting the controlled trials that followed, these observational studies identified *three critical properties of the treatment that are pertinent to the interpretation of controlled trials*:

- First, either or both of two outcome measures can be used; transforaminal injections of steroids may reduce the need for surgery and/or relieve pain.
- Secondly, transforaminal injections of steroids are not universally successful; they work in only a proportion of cases.
- The third feature is that patients may require up to three injections in order to achieve the optimal effect, with 2.1 injections being the representative average [3,4].

Two controlled trials compared transforaminal injection of steroids with transforaminal injection of local anesthetic. Both found no differences in outcome [5,6,7]. In both cases, however, continuous data and group statistics were used to assess outcomes; sub-group analysis to identify patients who responded was not undertaken, and treatment was limited to a single injection.

These two negative studies have been outnumbered by subsequent positive studies.

One study showed that transforaminal injections of steroids were more often effective than paraspinal injections of normal saline for the relief of pain [8]. Although encouraging, the results of this study are not compelling because the two treatments were different in the method of execution and, therefore, did not control for the same placebo factors.

Another study compared transforaminal injections of steroids with conventional interlaminar injection of steroids [9]. No differences in outcome were evident at six days after treatment, but by 30 days, and at 6 months after treatment, those patients treated with transforaminal injections showed, statistically significant, greater improvements in pain and function relating to work and leisure. Other, less rigorous studies have corroborated this superiority [10,11,12].

One controlled trial [13] used *avoidance of surgery as the outcome measure*. It found that only 8 of 28 patients (29%) required surgery after treatment with transforaminal injections of betamethasone, compared with 18 out of 27 patients (67%) treated with transforaminal injections of bupivacaine. A later publication reported a five-year follow-up of these patients, which showed that the outcome was enduring [14].

A recent, controlled trial addressed several of the deficiencies and ambiguities of previous studies. It aimed to determine whether the route of injection and the agent injected were crucial [15]. It compared the efficacy of transforaminal injection of steroids, with the efficacy of transforaminal injection of local anesthetic, transforaminal injection of normal saline, intramuscular steroids, and intramuscular normal saline. It used a categorical outcome measure: the proportion of patients who obtained at least 50% relief of pain coupled with restoration of function, and substantial reduction of the need for other health care. It also measured the reduction in surgery. All patients were surgical candidates. The study found that transforaminal injection of normal saline, transforaminal injection of local anesthetic, intramuscular injection of steroids, and intramuscular injection of normal saline were all successful in similar proportions of patients [15]. Collectively, these interventions had a success rate of 15%. In contrast, transforaminal injection of steroids was effective in 54% of cases. All patients who were relieved of their pain were restored to normal or near normal function, and reduced their need for other health care interventions to simple exercises or over the counter medications [15]. All patients who had previously required opioids ceased opioids. The use of surgery was reduced to 30%. These outcomes were not evident when group statistics were used, because only a proportion of patients benefitted. Under those conditions, the outcomes of patients who benefit are camouflaged by the outcomes of those who do not, when group statistics are used. The efficacy of transforaminal injection of steroids appears only if and when categorical outcomes are used. Doing so reveals patients who clearly benefit from the treatment.

Further analysis has revealed that the response to transforaminal injection of steroids is primarily affected by the nature of the disc herniation responsible for the pain [16]. The success rate of transforaminal injection of steroids rises to 75% in patients with minor degrees of nerve root compression, but is only 26% in patients with high grade compression. Consequently, for evaluation of transforaminal injection of steroids, outcomes need to be stratified according to the nature and severity of the causative pathology.

SYNOPSIS

- Transforaminal injections of steroids benefits only a proportion of patients with lumbar radicular pain, but when successful,
- **Transforaminal injections of steroids:**
  - **reduce pain**
  - **restore function**

- **substantially reduce the need for other health care**
- **reduce the need for surgery**
- **are equally effective for acute or persistent pain**

CONTEXT

Patients with lumbosacral radicular pain have few options. Conservative care is no more effective than natural history. No drugs can relieve their pain. Prior to the development of transforaminal epidural steroid injection, surgery has been the most common option.

SAFETY

Transforaminal injection of steroids is potentially hazardous if not performed meticulously and by physicians who are experts in fluoroscopically guided-spinal interventions. Spinal cord injury can occur if injection into a medullary artery is not recognized during the injection of contrast medium, and if particulate steroids are injected into that artery [17].

No complications have been recorded in any of the controlled trials, and none have been reported when operators have followed prescribed guidelines for the conduct of the procedure [18].

COST

A head-to-head cost-effectiveness comparison of transforaminal injection of steroids with surgery has not been conducted. Therefore, formal evidence of cost-effectiveness is not available. However, *prima facie*, transforaminal injections of steroids would be cost-effective if their success rate was greater than the ratio between the cost of injection therapy and the cost of surgery. *At present, the cost of surgery is at least 10 times the cost of injection, and a success rate of 50% would allow up to five repetitions of treatment to match the outcomes of surgery, before cost-effectiveness would be challenged.*

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VII. ACCURACY AND SAFETY OF CERVICAL INTERLAMINAR EPIDURAL INJECTIONS OF STEROIDS

When performed "blind" (*i.e.* without radiographic image guidance), cervical interlaminar epidural steroid injection relies on the operator either using a hanging drop technique or experiencing a loss of resistance to identify entry into the epidural space. However these techniques are not completely reliable. When judged against subsequent fluoroscopy and epidurography, loss of resistance had a false-positive rate of 53% for entry into the epidural space [1]. Even with second and third attempts, successful placement was achieved in only 75% of cases [1].

On the other hand, using fluoroscopic guidance for cervical interlaminar epidural steroid injection with injection of a small amount of contrast medium under AP and lateral and/or oblique imaging improves the accuracy of needle placement[1]. For reasons of both safety and accuracy the vast majority of cervical interlaminar epidural injections in the private sector are performed with fluoroscopic guidance and subsequent confirmation of entry into the epidural space with contrast injection [2].

The risk of spinal cord injury is least at segmental levels where the dura is furthest away from the ligamentum flavum, *i.e.* where the epidural space is "largest", typically at C6-7 and C7-T1 [3]. Therefore, it is recommended that injections be performed only at these segmental levels to minimize risk of dural puncture or spinal cord trauma[4,5]. From these levels, injected material flows adequately to other segments that may be the source of the patient's symptoms [6,7]. The adequacy of the epidural space at the level of the proposed injection must be assessed before the procedure using MRI [8].

Live, multiplanar high quality fluoroscopic imaging should be used to ensure accurate and safe depth of needle placement for cervical interlaminar epidural injections [6,10,11]. As with any spinal injection procedure, cervical interlaminar injection of steroids is potentially hazardous if not performed meticulously and by physicians who are experts in fluoroscopically guided-spinal interventions.

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VIII. CERVICAL INTERLAMINAR EPIDURAL INJECTIONS OF STEROIDS

Indication

Cervical interlaminar epidural injections of steroids are a treatment for cervical radicular pain. Radicular pain caused by central spinal stenosis, herniated intervertebal discs and multilevel cervical spondylosis is most likely to respond to this treatment [1-4].

Efficacy

Observational studies attest to success rates ranging from 38% at one month to 78% at one year, after a single epidural steroid injection [5-16]; but these studies did not control for non-specific effects. A prospective, randomized, controlled has accounted for such effects [17]. Its features were:

- 50 initial patients with cervical radiculopathy, mean duration 15 months;
- 25 subjects treated with 1-3 cervical interlaminar epidural injections of steroids, using 80 mg methylprednisolone and 5 cc of 1% lidocaine, or
- 17 subjects treated with 1-3 posterior cervical intramuscular (IM) injections of the same medications performed every 2 weeks.
- If there was no improvement from the first injection further injections were not performed.
- Mean number of injections was 2.5 in both groups.
- At one week, 76% of patients in the epidural steroid group had good/very good improvement (≥50% decrease of VAS) compared with 35.5% in the IM group.
- At 1 year 68% of the epidural steroid group at good/very good relief (≥50% decrease of VAS) compared with 11.8% of the IM group.
- Higher grade pain relief (≥75%) was seen in 56% of the epidural steroid group compared with 5.9% of the IM injection group.
- At 1 year, range of motion improved, analgesic use was reduced and the capacity to work significantly improved in the epidural group compared with the IM injection group.

This study demonstrates that the *route of administration* of corticosteroid (epidural) is *pivotal* to the therapeutic effect of cervical epidural injection of steroids, and that the responses achieved cannot be attributed to systemic effects of steroids or to non-specific factors. The evidence attests to a number needed to treat (NNT) of 2, for the outcomes of either at least 50% relief at one year, or at least 75% relief at one year. ***No other treatment for cervical radicular pain rivals such outcomes.***

Although the literature is limited to one randomized controlled trial, that study is overwhelmingly positive, and ***no study has refuted*** the efficacy of cervical interlaminar epidural injections of steroids.

Context

No drugs stop cervical radicular pain. No conservative therapy has been shown to be effective.

Cervical interlaminar epidural injections of steroids are the only alternative to surgery for patients with cervical radicular pain.

Cost-effectiveness

No studies have formally addressed the cost-effectiveness of cervical interlaminar injections of steroids. Although this is a deficiency in the literature, it does not constitute evidence that cervical interlaminar injections of steroids are not cost-effective.

The ideal study would be prospective, with patients randomized to undergo injection therapy or surgery, with costs calculated and adjusted for quality of life years gained. Such a study would be both costly and difficult to mount and complete. Cervical radicular pain is not a common condition.[8] It would take a long time, with multiple centers, to recruit the numbers of subjects required and willing to participate.

In principle, however, cervical interlaminar epidural injections of steroids would be cost-effective if their success rate was greater than the ratio between the cost of treatment with injections and the cost of treatment with surgery. ***At present, the costs of surgery exceed those of injection by a factor of at least 10. The success rate of injection (59%) would allow at least five repetitions of treatment to match the success of surgery.***

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IX. SACROILIAC INTRA-ARTICULAR INJECTIONS OF STEROIDS

INDICATIONS

Intraarticular injections of steroids into the sacroiliac joint have been used to treat two separate and distinct conditions:

- Sacroiliitis in patients with seronegative spondylarthropathies, and
- Idiopathic pain from the sacroiliac joint: so-called mechanical sacroiliac joint pain.

The evidence for these two entities differs in certain respects.

SACROILIITIS

The prevalence of sacroiliitis is unknown, but it is a recognized rheumatologic entity. It can be diagnosed by medical imaging demonstrating inflammation of the affected joint.

Ten, prospective, observational studies have shown benefit for sacroiliac joint injections in patients with seronegative spondyloathropathy. This benefit ranges from a minimum of a 60% success at one month to a 92% success rate at 10 months post-injection [1-9].

Two, controlled studies have demonstrated that the responses to injections of steroids cannot be dismissed as a placebo effect. ***No study has refuted the efficacy of injection of steroids.***

In one study[10], 10 patients with seronegative spondylarthropathy were randomized to receive a unilateral, periarticular injection of corticosteroid and anesthetic, while 10 were treated with an injection of saline and local anesthetic. At 2 months, there was a 48% mean reduction in pain scores in the corticosteroid group versus only a 4% mean reduction in the control group ($p=0.02$).

In the other study [11], 13 joints in 10 patients were treated with fluoroscopically-guided intraarticular injections. Six joints were injected with corticosteroid, and seven were treated with placebo injections using normal saline. At 1 month, 5 of the 6 injections with corticosteroid provided greater than 70% relief of pain, compared with none of the 7 placebo injections ($P < 0.05$). The use of NSAIDs and oral corticosteroids was decreased by 14% in the placebo group but by 50% in the corticosteroid group. Patients from the placebo group and patients from the corticosteroid group who failed or relapsed were treated a second time with injections of steroids. At 1 month, 85.7% were assessed as having a good result, 62% at 3 months, and 58% at 6 months.

SACROILIAC JOINT PAIN

Using either anatomic or physiologic controls, diagnostic blocks demonstrate that amongst patients with chronic low back pain, the source of their pain can be traced to one or the other of their sacroiliac joints in 13–19% of cases [12,13]. In patients with persistent pain after lumbosacral arthrodesis, single (uncontrolled) intraarticular blocks suggest a prevalence of SIJ of 32%. [14,15]

Seven retrospective descriptive studies of sacroiliac intraarticular injection of steroids have reported success rates that vary considerably with respect to the proportion of patients obtaining relief of pain and the duration of that response [14,16-21].

One, prospective observational study selected for treatment 39 patients who obtained greater than 75% relief of pain following controlled, intraarticular, diagnostic blocks of the joint to be

treated [22]. Twenty-six patients (66.7%) experienced ≥50% pain reduction for more than 6 weeks after the intraarticular injection of corticosteroid, with the mean duration of pain reduction in these responders of 36.8 weeks. Significant reductions were also seen in the modified Oswestry Disability Index. Univariate analysis revealed that treatment failure was significantly associated with a history of lumbar/lumbosacral fusion: 42% of patients with a history of lumbar/lumbosacral fusion experienced a long-lasting pain relief, whereas 78% patients with no history of lumbar/lumbosacral fusion experienced a long-lasting pain relief.

There have been no controlled trials of intraarticular injections of steroids for mechanical sacroiliac joint pain. The only related literature is a randomized controlled trial of periarticular injections of steroids [23].

Patients were selected on the basis of clinical signs [23]. Diagnostic blocks were not used to establish a diagnosis of sacroiliac joint pain. Thirteen patients were treated with a periarticular injection of corticosteroid and anesthetic, while 11 patients received isotonic sodium chloride and lidocaine. A one month, the median decrease in pain scores was 74% in the corticosteroid group, but only 25% in the control group. The study concluded that a periarticular injection of corticosteroid may be effective in the treatment of pain in the region of the SIJ in non-spondylarthropathic patients.

COMPLICATIONS

There are no published reports of any substantial complications related to sacroiliac joint injections.

CONTEXT

For the treatment of seronegative sacroiliitis, the controlled studies were necessarily small because of the rarity of the condition being treated. Nevertheless, one study [11] showed worthwhile and lasting benefit from a simple intervention. ***No other treatment is available for seronegative sacroiliitis and no other has either been tested or proven.*** Without the option of intraarticular steroids, affected patients face the prospect of perpetual drug therapy using agents with known toxic effects when used long-term, with little prospect for relief of their pain.

For the treatment of so-called mechanical sacroiliac joint pain, an academic and moral dilemma arises. Patients with sacroiliac joint pain can be identified, using controlled diagnostic blocks. They are not patients with back pain of unknown or uncertain origin. They have a definite and detectable source of pain. For such patients, no drug has shown to effectively and reliably relieve their pain and no conservative treatment has been shown to be effective. Some surgeons offer arthrodesis as a speculative therapy, but no compelling evidence of effectiveness is available. Furthermore, conventional arthrodesis is a massive and destructive undertaking, requiring extirpation of the posterior ligaments of the joint and their replacement with bone graft and insertion of metallic hardware.

The literature on intraarticular injection of steroids for sacroiliac joint pain is far from compelling. The results from observational studies are not consistent, and controlled studies have not refuted non-specific effects of treatment.

Under these circumstances, sacroiliac joint pain cannot be sustained as an outright indication for treatment with intraarticular injection of steroids. However, such injections might be endorsed with limitations.

Intraarticular steroids could be opportunistically injected in the course of diagnostic blocks of the joint, at the discretion of the operator. This addition would be at no cost to the payor. However, in the event that the patient clearly benefits, repeat injections could be endorsed and reimbursed. The definition of benefit would be sufficient relief of pain so as to restore function, reduce the use of other health care, and return to work if applicable, for a period of at least three months.

Under those conditions, the indication for intraarticular injection of steroids would be previous, documented benefit from an intraarticular injection of steroids.

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APPENDIX A

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