

Spinal Injections Re-Review

Draft Key Questions: Public Comment & Response

October 13, 2015

Health Technology Assessment Program (HTA)

Washington State Health Care Authority

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Response to Public Comments

Spectrum Research is an independent vendor contracted to produce evidence assessment reports for the Washington HTA program. For transparency, all comments received during the public comment periods are included in this response document. Comments related to program decisions, process, or other matters not pertaining to the evidence report are acknowledged through inclusion only.

This document responds to comments from the following parties:

Key Questions

- Brandon Messerli, DO
- Belinda Duszynski, Senior Director of Policy and Practice, Representing a multiple professional societies
- Arthur S. Watanabe, MD, President of the Washington Society of Interventional Pain Physicians Spinal Diagnostics and Laxmaiah Manchikanti, MD, Chairman of the Board and Chief Executive Officer, ASIPP and SIPMS (comments contained in email with attachment of Letter to the Editor by Laxmaiah Mandhikanti, MD, to the Annals of Internal Medicine)

Specific responses pertaining to comments are included in Table 1 below. Complete comments submitted are attached following responses.

Comment	Response
Brandon Messerli, DO	
1. There are two primary concerns with the proposed key questions: that it is contrary to HTA policy to re-review the entire scope of spine injections for “back pain” based on limited new evidence published since the 2011 evidence review.	<p><i>Thank you for your comments.</i></p> <p><i>This topic was identified for re-review based on publication of an FDA warning and a new RCT comparing epidural steroid injections to a non-steroid containing placebo in subjects with spinal stenosis. The updated review will include an updated literature search for the whole scope of the original review to ensure the update review is current.</i></p>
2. Sole utilization of RCTs is a corruption of evidence based medicine.	<p><i>Thank you for your comments</i></p> <p><i>Well-conducted RCTs remain the standard for evaluating the efficacy of an intervention. Comparative observational studies with concurrent controls can be helpful in certain situations when the outcome is “hard” and quantitative, (e.g., evaluating death). However, they are susceptible to selection bias and confounding, and have been shown to overestimate the effectiveness of a treatment, especially one based on subjective outcomes. When ample RCTs are available, these studies are used to provide the highest level of evidence. When there is a lack of RCTs to provide evidence on efficacy, we look for comparative observational studies with concurrent controls as the next best level of evidence. Since this is a re-review, we know that there are ample RCTs on this topic evaluating the efficacy of spinal injections. For these reasons we do not agree that this is a corruption of evidence based medicine. Note that observational studies can be useful in evaluating harms. We will use them to answer KQ2 on safety.</i></p>
Belinda Duszynski	
1. The background information provided begins with the assertion that, “Approximately 90% of low back pain is of the nonspecific type, and a similar majority of neck pain is nonspecific.” There is no reference cited to support this statement, and this is not substantiated in clinical practice.	<p><i>Thank you for your comments</i></p> <p><i>We modified the statement in the introduction to read: “In most patients reporting low back pain (>85%), symptoms cannot reliably be attributed to a specific spinal disease or pathology” and added a reference for this statement (Chou R, Qaseem A, Owens DK, et al. Diagnostic imaging for</i></p>

	Comment	Response
		<p><i>low back pain: advice for high-value health care from the American College of Physicians. Ann Intern Med. 2011;154(3):181-9.) Note that guidelines from the American College of Physicians and others state that most low back pain cannot reliably be attributed to a specific source of low back pain. Additionally, because of the lack of a reference standard for specific causes of non-radicular low back pain, the accuracy of diagnostic injections procedures for diagnosis of specific sources of low back pain is unknown.</i></p>
2.	<p>Evidence Base Restriction to Randomized Controlled Trials (RCTs). With a restriction to randomized controlled trials (RCTs) as the sole evidence to address questions of efficacy, the ensuing report will ignore the best available evidence. (emphasis in bold from the Letter's author)</p>	<p><i>Thank you for your comments</i></p> <p><i>Well-conducted RCTs remain the standard for evaluating the efficacy of an intervention. Comparative observational studies with concurrent controls can be helpful in certain situations when the outcome is "hard" and quantitative, (e.g., evaluating death). However, they are susceptible to selection bias and confounding, and have been shown to overestimate the effectiveness of a treatment, especially one based on subjective outcomes. When ample RCTs are available, these studies are used to provide the highest level of evidence. When there is a lack of RCTs to provide evidence on efficacy, we look for comparative observational studies with concurrent controls as the next best level of evidence. Since this is a re-review, we know that there are ample RCTs on this topic evaluating the efficacy of spinal injections. For these reasons we do not agree that the best available evidence will be ignored. Note that observational studies can be useful in evaluating harms. We will use them to answer KQ2 on safety.</i></p>
3.	Subgroups	<p><i>See specifics in the answer to KQ3</i></p>
4.	Importance of categorical, not continuous data	<p><i>We will report categorical data when provided by the published studies. This is not limited by our PICO.</i></p>
5.	<p>Comment on KQ1: Suggest that Question 1 is not needed. Question 3 should be the only question relative to efficacy and effectiveness. Assess the evidence by</p>	<p><i>Thank you for your comments</i></p> <p><i>Subgroups mentioned will be included in KQ3. Please see answers to KQ3 below for details.</i></p>

Comment	Response
<p>diagnosis, use of image guidance, and approach, relying on the best available literature, not restricting to RCTs of heterogeneous patient populations. Aggregating multiple procedures, or heterogeneous techniques of a class of procedures, is useless. If retaining Question 1, add considerations of:</p> <ul style="list-style-type: none"> • Prevention of spine surgery • Use of epidurals in conjunction with other modalities (evidence of synergy; e.g. mechanical diagnosis and treatment---based physical therapy) • Analgesic medication use, separately from opioid use • Subgroup analysis by diagnoses • Subgroup analysis by use of image guidance • Subgroup analysis by approach/access 	
<p>6. Question 2: What is the evidence of the safety of spinal injections? Add considerations of:</p> <ul style="list-style-type: none"> • This question must take into consideration comparison of the risks of spine surgery, the typical alternative treatment option in patients properly selected for spine injection. • This question must also take into consideration comparison of the risks of pharmacologic treatment of persisting spine pain, particularly treatment with opioid analgesics. • Careful consideration when addressing this question must separate adverse event rates in the context of adherence to society guidelines vs. the rate of adverse events when injections are performed without such rigor. In particular, serious irreversible complications have yet to be reported in most spinal injections performed in accordance with Spine Intervention Society Guidelines. (21---23) • Subgroup analysis by diagnoses • Subgroup analysis by use of image guidance • Subgroup analysis by approach/access • Case reports provide no insight into the frequency of adverse events. 	<p><i>Thank you for your comments</i></p> <p><i>The safety of spinal injections will be compared with the safety of the comparative treatment. In studies comparing injections with surgery, the risks reported in the surgical group will be the comparison. The same for pharmacologic treatment.</i></p> <p><i>Subgroups mentioned (including use of particulate vs. non-particulate steroids as recommended by the referenced guidelines) will be included in KQ3. Please see answers to KQ3 below for details. The ability to draw conclusions from analyses of subgroups will be dependent on the frequency of the harm reported. It is anticipated that in most cases, the numbers to stratify by subgroups will be too small. Nevertheless, see comments below in KQ3.</i></p> <p><i>While case reports cannot provide incidence data, they can inform with respect to the types and severity of harms.</i></p>

	Comment	Response
7.	<p>Question 3: What is the evidence that spinal injections have differential efficacy or safety issues in subpopulations?</p> <p>Consideration (d) indicates “diagnosis or time elapsed from fracture” – suggest (d) should be “diagnosis” and another consideration should be “subacute or chronic nature of condition”</p> <p>Include all considerations listed in Question 1, along with:</p> <ul style="list-style-type: none"> • Prevention of spine surgery • Use of epidurals in conjunction with other modalities (evidence of synergy; e.g. mechanical diagnosis and treatment---based physical therapy) • Analgesic medication use, separately from opioid use • Subgroup analysis by use of image guidance • Subgroup analysis by approach/access 	<p><i>We specifically added the following to the list of subgroups that will be considered:</i></p> <ul style="list-style-type: none"> • <i>Duration of pain,</i> • <i>Type of steroid (particulate, non-particulate),</i> • <i>Use of imaging guidance,</i> • <i>Route of administration (e.g., for epidural injections interlaminar, transforaminal, or caudal injections; for facet injections intra-articular, extra-articular (per-capsular) or medial branch injections)</i> <p>Note:</p> <ol style="list-style-type: none"> 1. <i>“Diagnosis or time elapsed from fracture” should simply be “diagnosis.”</i> 2. <i>The first and third bullets relate to outcomes, not subgroups. Prevention of surgery has been added as an outcome of interest in the PICO table, as has non-analgesic medication.</i>
8.	<p>Question 4: What is the evidence of cost implications and cost---effectiveness of spinal injections?</p> <ul style="list-style-type: none"> • Cost---comparison of spinal injection treatment paired with other conservative measures (e.g., PT, oral analgesics) to spinal surgery paired with other conservative measures (e.g., PT, oral analgesics) must specifically be addressed given that this is the typically realistic clinical picture. • Comparisons to individual competing therapies: physical therapy, NSAIDs, opioids, surgery: this inevitably requires an assessment of their clinical effectiveness, where such data exist. • Subgroup analysis by diagnoses • Subgroup analysis by use of image guidance • Subgroup analysis by approach/access 	<p><i>As with safety, the cost of spinal injections will be compared with the cost of the comparative treatment. For example, in cost effectiveness studies comparing injections with surgery, the cost effectiveness comparison will be between the surgical group and the injection group. The same for pharmacologic and other conservative methods of treatment.</i></p>

Comment		Response
Arthur S. Watanabe, MD and Laxmaiah Manchikanti, MD		
1.	<ol style="list-style-type: none"> 1. Financial Conflicts of Interest and Intellectual Bias 2. Inappropriate and Illogical Conversion of Active-Controlled Trials to Placebo-Controlled Trials 3. Biased, Pre-Possessed, Intellectually Biased Methodological Quality Assessment 4. Utilization of Inappropriate Outcome Parameters 5. Analytic Methods 6. Composition of Panel 	<p><i>Thank you for your comments. No change to key questions.</i></p> <p><i>The purpose of the WA HTA program is to ensure that treatments purchased with state health care dollars are safe and proven to work. Reviews are conducted by contracted technology assessment centers.</i></p> <p><i>Comments related to the AHRQ review titled "Pain Management Injection Therapies for Low Back Pain" do not pertain to the current WA HTA report. We welcome your review and comments on the draft report when it's published.</i></p>

September 15, 2015

Dorothy Frost Teeter, Director
Washington State Health Care Authority
626 8th Avenue SE
P.O. Box 45502
Olympia, WA 98504-5502

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

Dear Ms. Teeter:

As a licensed physician in the state of Washington, I would like to comment on the Washington State Health Care Authority's re-review of spinal injections via the Health Technology Assessment program. There are two primary concerns with the proposed key questions: that it is contrary to HTA policy to re-review the entire scope of spine injections for "back pain" based on limited new evidence published since the 2011 evidence review, and that it is contrary to HTA policy to limit evidence reviews for questions #1 and #3 to randomized controlled trials.

HTA policy states that "previous determinations are considered for review at least once every 18 months, based on whether new evidence may change the previous determination." The Lumbar Epidurals for Spinal Stenosis (LESS) trial (Friedly, Bresnahan, et al), is a valid reason to re-review ESI for the indication of central spinal stenosis, but is not a valid reason to re-review ESI for all other conditions, nor non-epidural spine interventions. As an analogy, if the HTA were considering coverage of SGLT2 inhibitors for diabetes mellitus type 2, and there was new evidence regarding its efficacy, this should prompt a re-review of the efficacy of SGLT2 inhibitors, not a re-review of the efficacy of all other diabetic pharmacological treatments such as insulin, biguanides, and sulfonylureas. *For these reasons, this re-review must be limited to the efficacy of ESI for central spinal stenosis.*

The FDA's Drug Safety Communication of April 2014 regarding ESI safety did not constitute "new evidence"; rather, it was a warning to the public, and a reminder to providers, of the risks of ESI. If one were to consider it "new evidence" from the viewpoint of the HTA, this would be a valid reason to prompt a re-review of the safety of ESI. However, it is not a valid reason to re-review the safety of non-epidural spine interventions, nor the efficacy or clinical effectiveness of ESI. As an analogy, if the HTA were considering coverage of SGLT2 inhibitors for diabetes mellitus type 2, and there were new safety concerns regarding the rate of urinary tract infections as an adverse effect, this should prompt a re-review of the safety profile of SGLT2 inhibitors, not a re-review of the safety or efficacy of all other diabetic pharmacological treatments such as insulin, biguanides, and sulfonylureas. *For these reasons, this re-review must be limited to the safety of ESI.*

If there are other original prospective clinical studies, published since the HTA review in 2011, that have examined the efficacy, clinical effectiveness, or safety of other interventional spine injections, these studies need to be reported as the justification for a re-review of the evidence for the respective category of spine injections. *The inclusion of topics for re-review must not be arbitrary, and the decision-making process must be transparent.*

In the Executive Summary of the August 2015 HTA Process Evaluation, it states "The HCA Director contracts with independent TACs to complete a systematic, evidence-based assessment of each technology ... the assessment must give the greatest weight to evidence determined to be the most valid and reliable, based on objective factors, and shall include consideration of safety, health outcomes, and cost data submitted by state agencies, as well as evidence submitted by an interested party." It does not state that only RCTs will be considered. In the 2011 HTA analysis of spine injections, Spectrum took the proverbial high ground by their decision to solely utilize RCTs. This is a corruption of evidence based medicine, which demands the utilization of the best available evidence, not only RCTs. This is exemplified by Sackett, who stated: "Evidence based medicine is not restricted to randomized trials and meta-analyses.

It involves tracking down the best external evidence with which to answer our clinical questions." HTA reviews for many other topics of clinical effectiveness have included nonRCTs in their analyses. There may be significant variability, within the pool of evidence vendors working with the HTA, in the evidence vendor's decision of whether or not to include nonRCTs. This variability is unacceptable. The exclusion of high quality observational studies of clinical effectiveness is unwarranted and unprofessional. *For this reason, nonRCT evidence must be allowed when addressing all key questions (specifically #1 and #3).*

In the HTA Process Evaluation, it was stated that "contracted evidence vendors may select one or more clinical experts at the time of scoping the systematic evidence review." The clinical expert for the upcoming review needs to be intimately familiar with the intricacies of proper patient selection and study design, technical 'nuances' of current and proper injection technique, and the utility of various outcome measures. The process for selecting this expert needs to be rational and transparent. It should be a provider highly regarded among their peers in the field of interventional pain management. *A proposal would be for the HTA and its evidence vendor seek guidance from the MPW (multidisciplinary pain workgroup) when deciding on one or more technical experts.*

Thank you for considering my comments. If you have any questions or comments, please feel free to email me at bjmesserli@gmail.com.

Sincerely,

Brandon Messerli DO

September 15, 2015

Dorothy Frost Teeter, Director
Washington State Health Care Authority
626 8th Avenue SE
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Submitted via e-mail: shtap@hca.wa.gov

Dear Ms. Teeter:

Representatives of 15 medical specialty societies, comprising physicians who perform spinal injection procedures and those whose practices rely on them in determining appropriateness of more invasive surgical treatments, have convened to review and comment on the proposed key questions for the Washington State Health Care Authority's (WA HCA) Health Technology Assessment Program's re-review of spinal injections. These medical specialty societies share a common goal with the WA HCA: identifying spinal injections that provide value to the patient and society through measurable improvements in pain and physical functioning with no or minimal adverse events.

We extend to the committee an offer to provide national and international expert input as a resource for this process. We are fully cognizant of the issues of overutilization and inappropriate utilization, and therefore also wish to bring into focus which interventions are effective when treating the various causes of back and neck pain. We have concerns, however, that the questions posed, along with the review's proposed inclusion/exclusion criteria, will not assist in making such determinations, and that the report's conclusions may lead to egregious denial of access to these procedures for many patients suffering from back and neck pain. We trust that due consideration will be given to our comments and that the key questions and inclusion/exclusion criteria will be revised to ensure that the **best available evidence** is addressed scientifically in order to provide an accurate assessment of the procedures reviewed.

Our primary concerns relative to inclusion/exclusion criteria and framing of the key questions fall into four main categories:

- Assertions Regarding the Nonspecific Nature of Back and Neck Pain
- Evidence Base Restriction to Randomized Controlled Trials (RCTs)
- Importance of Subgroup Analyses for Each Question
 - Specific Diagnoses
 - Image Guidance
 - Approach/Access
- Importance of Reliance on Categorical Data, Not Continuous Data

Assertions Regarding the Nonspecific Nature of Back and Neck Pain

The background information provided begins with the assertion that, "Approximately 90% of low back pain is of the nonspecific type, and a similar majority of neck pain is nonspecific." There is no reference cited to support this statement, and this is not substantiated in clinical practice.

Systematic application of controlled anesthetic blocks or provocation procedures can achieve somewhat less sensitive, but far more specific diagnoses than simply relying on symptoms. (1) Radiculopathy has specific observable physical examination and electrophysiologic findings. Radicular pain without radiculopathy can be diagnosed by a combination of history [pain travelling or shooting down the leg in a narrow band (lumbar) or radiating to the distal arm (cervical)], physical exam [e.g. straight leg raising test (lumbar), Spurling's maneuver (cervical)] and controlled selective nerve blocks. Somatic axial pain experienced in the lumbar region can be specifically attributed to the facet joints (dual comparative medial branch blocks), the intervertebral discs (disc stimulation), paraspinal muscles and fasciae (trigger point injections), or the sacroiliac joints (controlled intra-articular blocks and multi-site, multi-depth lateral branch blocks). Cervical axial pain can be attributed to the facet joints by dual comparative medial branch blocks and to the intervertebral discs by disc stimulation. Numerous studies over the past 20 years have established prevalence rates for these specific pain generators and their relationship to age and gender. (2-8) Asserting that 90% of back and neck pain is nonspecific is erroneous and fails to recognize decades of progress in the specific diagnosis of the processes causal of the symptoms of back and neck pain. We feel it is inappropriate to ignore this body of evidence and accept trials whose inclusion criteria are mere symptoms, resulting in heterogeneous patient populations. The review should assess the effectiveness and risks of these procedures in treating patients with specific diagnoses, which have been confirmed by physical examination findings and appropriate diagnostic blocks.

Evidence Base Restriction to Randomized Controlled Trials (RCTs)

With a restriction to randomized controlled trials (RCTs) as the sole evidence to address questions of efficacy, the ensuing report will ignore the **best available** evidence. The exclusion of high quality observational studies of clinical effectiveness removes important information and context from a synthesis of the literature. (9-11) Recent methodology literature suggests that effect estimates from high quality observational trials do not differ significantly from RCTs. (11) Many of the RCTs that will meet the inclusion criteria include patients selected only by symptoms or in whom image guidance has not been utilized. These failings, further discussed below, make such trials irrelevant to current clinical practice and not unexpectedly show poor outcomes. Judging optimal practice of precise needle placement to a 1 - 2mm target zone in three dimensional space with confirmation of medication distribution by real-time observation of contrast flow, by using data from blind injections into an unknown tissue compartment has no validity. There are very few RCTs that utilize current practice standards. Hence examination of current large observational studies adds important information that is more relevant to current standards of practice.

Importance of Subgroup Analyses for Each Question

Specific Diagnosis

It is critical to perform subgroup analyses by specific diagnoses. Many studies fail to adequately specify the process under treatment. For example, there is no physiologic process beyond systemic effect by which steroids delivered to the epidural space would be expected to relieve axial back pain arising from nociception in the intervertebral discs, facet joints, sacroiliac joints, or supporting musculature. There is ample experimental and clinical evidence that radicular pain has an inflammatory basis and is potentially susceptible to targeted delivery of an anti-inflammatory agent to the interface of neural tissue and the compressive lesion. (12) For this reason, it is

imperative that studies included in the assessment have diagnostic specificity, with correlative imaging findings as a requirement for inclusion.

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

Additionally, the identification of the underlying etiologies of pain is essential as different pathologies not only have varying responses to treatment, but also have different natural histories, impacting prognosis. Thus, the time frame of follow-up to determine clinical utility becomes imperative. Some conditions, such as intervertebral disc herniation, can result in debilitating pain, but have an overall favorable natural history. This would be in contrast to neurogenic claudication due to central canal stenosis, which is less likely to resolve spontaneously with time. Thus short-term relief would be very appropriate and expected for pain caused by a disc herniation. To evaluate the long-term effects in this population would be as flawed as evaluating the long-term effectiveness of antibiotics for pneumonia. Again, should we withhold all antibiotics for pneumonia given the largely favorable natural history, or should we state antibiotics are ineffective because all subjects were better at 1 year follow-up? Similarly, should we withhold pain medications from patients with fractures or after orthopedic surgery, as these conditions only result in pain and have favorable natural histories?

Image Guidance

The techniques utilized in the administration of epidural steroids are also critical. Studies have demonstrated that up to 74% of “epidural” steroid injections performed without image guidance either deposit medication external to the epidural space or do not reach the targeted pathology within the ventral epidural space. (13-16). It is critical that studies included in the review are restricted to those that use image guidance to ensure that medications have been delivered to the target.

Image guidance is absolutely essential for the safe and efficacious performance of spinal injection procedures, based on a large body of non-RCT evidence. Failure to do so would place WA HCA in conflict with the Food and Drug Administration’s Safe Use Initiative, which recommends image guidance for epidural steroid injections of all types. (17)

Approach/Access

While image guidance is essential, the technique of delivery is equally important. Many midline interlaminar epidural steroid injection (ILESI) and caudal injection studies suffer from the lack of image guidance; and even when performed with image guidance, these procedures may deliver medication distant from the site of pathology, without certainty that the steroid will reach, or in what concentration it will reach, the target zone in the ventral epidural space. In contrast, transforaminal epidural steroid injection (TFESI) procedures place the needle in direct proximity to the target nerve and verify delivery to that site by observing contrast media flow. (18) Recently described lateral parasagittal ILESI have also been shown to preferentially deliver injectate to the

target ventral epidural space. (19) It is not reasonable to combine these injection techniques in an evaluation of “epidural steroid injections”.

Importance of Reliance on Categorical Data, Not Continuous Data

In addition to image guidance and injection technique, another important study characteristic is the method of reporting outcomes data. Many studies report only continuous data as a comparison between group means in reference to a minimum clinically important difference. However, pain and functional disability data are not normally distributed. Rather, responses are often bimodal, with segregation into responder and non-responder populations that will be concealed by evaluating group means. Categorical outcomes that define the proportion of patients reaching a predefined responder status are critical to meaningful interpretation, as noted in the recent NIH Task Force recommendations on research standards for chronic low back pain. (20)

COMMENTS ON SPECIFIC QUESTIONS

Question 1:

What is the evidence of efficacy and effectiveness of spinal injections?

Suggest that Question 1 is not needed. Question 3 should be the only question relative to efficacy and effectiveness. Assess the evidence by diagnosis, use of image guidance, and approach, relying on the best available literature, not restricting to RCTs of heterogeneous patient populations. Aggregating multiple procedures, or heterogeneous techniques of a class of procedures, is useless.

If retaining Question 1, add considerations of:

- Prevention of spine surgery
- Use of epidurals in conjunction with other modalities (evidence of synergy; e.g. mechanical diagnosis and treatment-based physical therapy)
- Analgesic medication use, separately from opioid use
- Subgroup analysis by diagnoses
- Subgroup analysis by use of image guidance
- Subgroup analysis by approach/access

Question 2: What is the evidence of the safety of spinal injections?

Add considerations of:

- This question must take into consideration comparison of the risks of spine surgery, the typical alternative treatment option in patients properly selected for spine injection.
- This question must also take into consideration comparison of the risks of pharmacologic treatment of persisting spine pain, particularly treatment with opioid analgesics.
- Careful consideration when addressing this question must separate adverse event rates in the context of adherence to society guidelines vs. the rate of adverse events when injections are performed without such rigor. In particular, serious irreversible complications have yet to be reported in most spinal injections performed in accordance with Spine Intervention Society Guidelines. (21-23)
- Subgroup analysis by diagnoses
- Subgroup analysis by use of image guidance
- Subgroup analysis by approach/access
- Case reports provide no insight into the frequency of adverse events.

Question 3: What is the evidence that spinal injections have differential efficacy or safety issues in subpopulations?

- Consideration (d) indicates “diagnosis or time elapsed from fracture” – suggest (d) should be “diagnosis” and another consideration should be “subacute or chronic nature of condition”
- Include all considerations listed in Question 1, along with:
 - Prevention of spine surgery
 - Use of epidurals in conjunction with other modalities (evidence of synergy; e.g. mechanical diagnosis and treatment-based physical therapy)
 - Analgesic medication use, separately from opioid use
 - Subgroup analysis by use of image guidance
 - Subgroup analysis by approach/access

Question 4: What is the evidence of cost implications and cost-effectiveness of spinal injections?

- Cost-comparison of spinal injection treatment paired with other conservative measures (e.g., PT, oral analgesics) to spinal surgery paired with other conservative measures (e.g., PT, oral analgesics) must specifically be addressed given that this is the typically realistic clinical picture.
- Comparisons to individual competing therapies: physical therapy, NSAIDs, opioids, surgery: this inevitably requires an assessment of their clinical effectiveness, where such data exist.
- Subgroup analysis by diagnoses
- Subgroup analysis by use of image guidance
- Subgroup analysis by approach/access

Summary

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

The description of the health technology assessment process on the WA HCA website indicates that clinical experts may be consulted at various points throughout the process. The clinical experts serving in any advisory role for the upcoming review must be intimately familiar with the intricacies of proper patient selection and study design, technical ‘nuances’ of proper injection techniques, and the utility of various outcome measures. The process for selecting these experts needs to be rational and transparent. Experts should be highly regarded among their peers in the field of interventional pain management. We propose that Washington State Health Care Authority and its technology assessment center seek guidance from the Multisociety Pain Workgroup (MPW) in identifying appropriate technical experts.

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

Sincerely,

American Association of Neurological Surgeons

American Academy of Pain Medicine

American Academy of Physical Medicine and Rehabilitation

American College of Radiology

American Pain Society

American Society of Anesthesiologists

American Society of Neuroradiology

American Society of Regional Anesthesia and Pain Medicine

American Society of Spine Radiology

Congress of Neurological Surgeons

North American Neuromodulation Society

North American Spine Society

Society of Interventional Radiology

Spine Intervention Society

Washington State Association of Neurological Surgeons

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From: DRM <DRM@ASIPP.ORG>
Sent: Tuesday, September 15, 2015 1:47 PM
To: HCA ST Health Tech Assessment Prog
Subject: Public Comments on Spinal Injections (Re-review)
Attachments: Manchikanti et al Comments to Annals of Internal Medicine .pdf

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September 15, 2015

Washington State Health Care Authority Technology Assessment
shtap@hca.wa.gov

RE: Public Comments on Spinal Injections (Re-review)

Dear Members of Washington State Health Care Authority:

On behalf of the Board of Directors of the American Society of Interventional Pain Physicians (ASIPP) and 51 state societies, including the Washington State Society of Interventional Pain Physicians, we would like to thank you for this opportunity to provide comments on re-review of spinal injections.

ASIPP is a not-for-profit professional organization founded in 1998 now comprised of over 4,500 interventional pain physicians and other practitioners who are dedicated to ensuring safe, appropriate and equal access to essential pain management services for patients across the country suffering with chronic and acute pain. There are approximately 8,500 appropriately trained and qualified physicians practicing interventional pain management in the United States.

Interventional pain management is defined as the discipline of medicine devoted to the diagnosis and treatment of pain-related disorders principally with the application of interventional techniques in managing subacute, chronic, persistent, and intractable pain, independently or in conjunction with other modalities of treatment.

Interventional pain management techniques are minimally invasive procedures including percutaneous precision needle placement, with placement of drugs in targeted areas or ablation of targeted nerves; and some surgical techniques such as laser or endoscopic discectomy, intrathecal infusion pumps and spinal cord stimulators, for the diagnosis and management of chronic, persistent, or intractable pain.

Over the years, ASIPP has been extensively involved in evidence synthesis and development for appropriate care. ASIPP has published multiple guidelines and multiple systematic reviews on interventional techniques and opioids.

We are hoping that this re-review will look at the evidence appropriately. The previous review was prepared with preconceived opinions rather than scientific basis. If the re-review will be performed by the same individuals and agencies, it is probably not worthwhile to proceed with it. Once again, we are hoping that the goal of the Washington State Healthcare Authority is to provide appropriate care rather than eliminate services based on individual opinions and to enrich a few individuals.

We would like to outline multiple issues with the previous reviews including the recent AHRQ assessment (Chou R, Hashimoto R, Friedly J, et al. Pain Management Injection Therapies for Low Back Pain. Technology Assessment Report

ESIB0813. Prepared by the Pacific Northwest Evidence-based Practice Center under Contract No. HHS 290-2012-00014-I. Rockville, MD: Agency for Healthcare Research and Quality; March 20, 2015.

(<http://www.cms.gov/Medicare/Coverage/DeterminationProcess/Downloads/id98TA.pdf>) and potential publication of multiple manuscripts starting with the *Annals of Internal Medicine* (Chou R, Hashimoto R, Friedly J, et al. Epidural corticosteroid injections for radiculopathy and spinal stenosis: A systematic review and meta-analysis. *Ann Intern Med* 2015; 163:373-381 <http://annals.org/article.aspx?articleid=2430207>) so that such issues can be avoided in the re-review.

1. FINANCIAL CONFLICTS OF INTEREST AND INTELLECTUAL BIAS

The reviewers consisted of commercial agencies with financial conflicts of interest, along with intellectual bias.

- This is in contrast to the IOM guidance where both should be avoided (Eden J, Levit L, Berg A, Morton S [eds]; Committee on Standards for Systematic Reviews of Comparative Effectiveness Research; Institute of Medicine. *Finding What Works in Health Care. Standards for Systematic Reviews*. The National Academies Press, Washington, DC, 2011.)
- The same authors have produced the same erratic reviews without consideration to the facts despite multiple requests to correct their process, obviously yielding the same results: that spinal injections are not effective.

2. INAPPROPRIATE AND ILLOGICAL CONVERSION OF ACTIVE-CONTROLLED TRIALS TO PLACEBO-CONTROLLED TRIALS

The authors of the previous reviews, including the ones from AHRQ, have erroneously considered all active-control trials as placebo control with their own philosophical development. This is not supported by any literature. They did this purely to yield their own opinions without any scientific basis and with intellectual bias, which are quite unscientific.

- The authors omitted extensive literature available on placebos and nocebos, specifically from the National Institutes of Health (NIH) and multiple other agencies.

3. BIASED, PRE-POSSESSED, INTELLECTUALLY BIASED METHODOLOGICAL QUALITY ASSESSMENT

Poor, extremely biased, unscientific, prepossessed methodological quality assessment. The authors in the past, including from Spectrum and AHRQ, utilized pre-possession with a determination to downgrade the studies which were positive in addition to changing active-controlled trials to placebo-controlled trials.

4. UTILIZATION OF INAPPROPRIATE OUTCOME PARAMETERS

The authors utilized inappropriate outcome parameters which attempted to derive the differences between 2 groups in active-controlled trials. These would not yield any results. Outcomes must be monitored from baseline to the follow-up period for each group such as a local anesthetic and steroid group rather than compare the differences between them. There is a large amount of literature on these issues. It would be best if they would follow the literature all of the time, not just when it is convenient.

5. ANALYTIC METHODS

The authors have utilized only quantitative analysis. They lumped together numerous manuscripts with no clinical homogeneity, just based on their own philosophy. They should assess the evidence, both qualitatively as well as quantitatively, rather than only quantitatively.

6. COMPOSITION OF PANEL

We are hoping a biased assessment will not be performed. A proper assessment must include different health technology assessment individuals with at least 50% of the reviewers who are practicing clinicians rather than physician methodologists.

Finally, we have filed a complaint with the AHRQ, of course with no measurable response. In addition, Congress is also inquiring into these issues. Enclosed, please see our comments to *Annals of Internal Medicine*.

If you have any further questions, please feel free to contact us. We will be happy to provide any type of assistance you desire in this matter.

Thank you,

Laxmaiah Manchikanti, MD

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Epidural Corticosteroid Injections for Radiculopathy and Spinal Stenosis: A Systematic Review and Meta-analysis

Roger Chou, MD; Robin Hashimoto, PhD; Janna Friedly, MD; Rongwei Fu, PhD; Christina Bougatsos, MPH; Tracy Dana, MLS; Sean D. Sullivan, BScPharm, PhD; and Jeffrey Jarvik, MD, MPH

[+] Article, Author, and Disclosure Information

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Comments

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Posted on September 3, 2015

Comment

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Conflict of Interest: None Declared

We are concerned that the systematic review by Chou et al (1) will have far reaching consequences on patients who might potentially benefit from epidural corticosteroid injections for radiculopathy and spinal stenosis. This systematic review is similar to an earlier publication by Pinto et al (2). The fundamental flaw of this systematic review and previous one (2) is that the authors have converted all placebo to active-control trials, with unproven hypothesis that all therapeutic effects in the epidural space are secondary to steroids (1). In our opinion, this is a scientifically and clinically incorrect methodology. Noteworthy, the therapeutic effectiveness of local anesthetics on a long-term basis has been illustrated in systematic reviews with an efficacy that was equivalent to steroids except in some circumstances (3). Further, methodologically sound systematic reviews showed efficacy of epidural injections in managing radiculopathy, spinal stenosis, and other ailments (3-5). Chou et al's conversion of active-control trials to placebo control is analogous to studies comparing whole milk to water or skim milk, with water being placebo and skim milk being an active-control. With extensive literature available in reference to placebos and nocebos and their influence on various trials, this approach is unscientific and unjustifiable.

Further, epidural injections have an excellent risk-benefit ratio compared to opioids and NSAIDs, which are themselves responsible for almost 17,000 deaths a year and numerous hospitalizations. Lumbar surgery alone is responsible for over almost 1,300 deaths a year, while deaths over the past two decades related to epidural injections were 131 -- significantly less than any other modality (4,5).

Other deficiencies include inconsistency with standards developed by the Institute of Medicine (IOM) for systematic reviews, perceived intellectual bias and inappropriate methodological quality assessment of the manuscripts. Further, they (1,2) have misinterpreted outcomes assessment data as absolute difference between 2 active control groups, which is not feasible, because active control trials only demonstrate superiority, non-inferiority, or equivalency rather than efficacy. We posit that the absolute effect size can only

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be measured by a true placebo control – not an impure placebo or one converted from an active agent to placebo on paper.

The policy implications of Chou et al's systematic review are such that patients will lose access to epidural injections for radiculopathy and spinal stenosis, and seek alternative treatments including narcotic medications and surgery.

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Epidural Corticosteroid Injections for Radiculopathy and Spinal Stenosis

Posted on September 5, 2015

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Conflict of Interest: None Declared

TO THE EDITOR: Chou and colleagues have tried to address an important area of patient care (1) with all the literature that is available, which unfortunately is not much. This small body of data illustrates more what we do not know than what we do know. The paucity of quality studies in this high profile area of medicine is embarrassing. As the authors describe in the Discussion, much, much more remains to be done.

The authors only briefly mention near the end of the Discussion that, "Research is needed to determine whether injections are more effective when given in the context of a more comprehensive pain management approach." While limited evidence exists for the usefulness of specifically designed physical therapy (PT) programs for both radiculopathy (2, 3) and degenerative lumbar spinal stenosis (2, 4), clinical experience suggests that PT might be effective in improving patient outcomes when put in place as part of an appropriate overall treatment plan.

In practical terms, the immediate-term reduction in pain with epidural corticosteroid injections as was found by the authors might provide a window to begin a productive program of active PT. The combination of epidural corticosteroid use followed by active PT should be studied with longer-term follow-up using the outcome measures of improvements in pain and function and change in risk for requiring surgical intervention.

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