

# **AHRQ on the Draft Technology Assessment “Pain Management Injection Therapies for Low Back Pain”**

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*\*Shared with the International Spine Intervention Society for posting on  
4/10/2015*

## **GENERAL COMMENTS**

The authors are to be congratulated on organizing and reporting a massive quantity of data on controlled trials describing response to spinal injection therapies in patients with “low back pain.” I will offer specific comments regarding areas of concern in each section of the document, but I wish to initially describe my discomfiture with the methodology utilized in this technology assessment. Although AHRQ has defined its methodology with rigor, and adheres to it in this study, this approach obscures important conclusions that emerge when the literature is reviewed more broadly. This takes on societal significance given that public policy will likely flow from this technology assessment. The opportunity for societal harms is not to be ignored.

A primary conclusion of this study is that epidural steroid injections are associated with immediate improvements in pain and possible immediate improvements in function, but that the benefits are small and not sustained. I wish to examine this conclusion in reference to the methodology by which it was obtained. This commentary applies to the several questions posed in the AHRQ technology assessment, but is best illustrated by Question 1, addressing epidural steroid efficacy. The efficacy of injection therapies for radicular pain has been the subject of a great deal of research effort that is unexamined in this assessment. The inclusion criteria select for research methodology: randomized controlled trials of injection therapies versus placebo, randomized comparative effectiveness trials, and large observational trials only with respect to harms. The exclusion of high quality observational studies of clinical effectiveness removes important information and context from a synthesis of the literature. The legacy of Dr. Cochrane is the examination of efficacy, clinical effectiveness and efficiency, not efficacy alone. (1)

The emphasis on research methodology as the primary inclusion criteria may lead to an under-appreciation of other important characteristics of the studies under

examination. Primary among them is specific diagnosis. Many of the studies in the analysis fail to adequately specify the process under treatment. There is no physiologic process beyond systemic effect by which steroids delivered to the epidural space would be expected to affect axial back pain arising from nociception in the intervertebral disc, facet joints, sacroiliac joint 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. (2) Many of the included studies have treated an undefined mix of axial and radicular pain patients; heterogeneity of response is expected, not surprising. The specificity of the diagnosis in the study populations was not included in the assessment of study quality. A randomized controlled trial (RCT) without careful patient selection is of no clinical value and may be misleading, yet its RCT methodology tends to purchase it credence. Examining the 29 studies of “epidural steroid injection” versus placebo, radicular pain alone was specified in 22, a mixture of radicular and back pain in 6 and back pain alone in one. A correlative imaging finding was required for inclusion in only 11 of 29 studies. The nature of the lesions being treated is thus largely unknown, and the degree of neural compression is completely unknown. Two studies have shown that the degree of neural compression is a predictor of success in transforaminal epidural steroid injections (TFESI). (3,4) With minimal neural compression the proportion of responders may be as high as 75%; with high grade compression the response rate may be as low as 25%. The lack of diagnostic specificity in patient selection is unfortunately emphasized by the lack of clarity in the title of this technology assessment. Here “low back pain” is deemed inclusive of axial pain, radicular pain without radiculopathy, and true radiculopathy with a neurologic deficit. The definitions used by the authors are at variance with accepted medical terminology in the fields of neurology and pain management. (5)

The techniques utilized in the administration of epidural steroids are also critical. No randomized studies examined the use of image guidance as a variable. This has, however, been well examined in non-randomized studies, which have shown 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. (6,7,8,9). Examining the 29 studies used to assess efficacy of epidural steroid injections versus a placebo, there were 15 interlaminar or presumed interlaminar epidural steroid injection (ILESIs) studies of which only 1 used fluoroscopic guidance. There were 9 caudal injection studies of which only 1 reported fluoroscopic guidance. Five transforaminal epidural steroid injection (TFESI) studies all utilized fluoroscopic guidance. Hence, with the exception of the 5 TFESI trials, the studies of “epidural steroid injections” deposited an anti-inflammatory agent into an unknown tissue space that was unlikely to reach the site of inflammation.

While image guidance is essential, the technique of delivery is equally important. The ILESIs and caudal injection studies suffer from the lack of image guidance, but also the lack of target specificity inherent in the techniques. Even when performed

with image guidance these procedures 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. TFESI procedures place the needle in direct proximity to the target nerve and can verify delivery to that site by observing contrast media flow. It is not reasonable to combine TFESI procedures with ILESI or caudal injections in an evaluation of “epidural steroid injections.”

As a corollary, many of the included studies are 20-30 years old. Although the studies may be inappropriately aggregated as “epidural steroid injections,” technology and clinical practice have not remained static. Surely the authors would not consider a study on coronary artery bypass grafting from the 1980’s to be reflective of current surgical technique, and useful in evaluating expected outcomes in 2014.

In addition to image guidance and injection technique, another neglected study characteristic is the method of reporting outcomes data. Many studies included in this analysis report only continuous data as a comparison between group means in reference to a minimum clinically important difference. 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. (10) The authors recognize this, and included categorical outcomes when available, but such data often cannot be extracted from the manuscripts, leaving less useful continuous data. In the 5 trials comparing TFESI and ILESI, only continuous data was analyzed.

As ILESI and TFESI techniques are quite different in the likelihood of target specific corticosteroid delivery, it is essential to consider whether there are differences in outcomes. This study makes that assessment based on 5 randomized comparative effectiveness studies, and using pooled continuous data concludes there were no differences in pain relief or functional recovery at immediate or short term, and no difference in pain relief at intermediate term when 2 trials (11,12) “that used lower doses of corticosteroids for interlaminar than transforaminal injections were excluded.” This statement is false; both trials cited used the same dose of steroid for each procedure. Rather, the Rados trial (13), which is incorrectly cited (reference 94, not 142, in the AHRQ assessment), is included in the weighted means despite using twice the steroid dose for interlaminar injections than transforaminal injections. Looking at the studies individually, a study of TFESI versus ILESI versus Caudal injections in patients with radicular pain and correlative imaging (11), using the same steroid doses, showed significantly greater proportions of TFESI patients achieving a categorical outcome for pain relief, with significantly lower levels of pain at 24 weeks, than ILESI or caudal injections. TFESI delivered the medication to the ventral epidural space at the target segment significantly more often, which correlated with pain outcomes. Another study (14) showed significantly greater improvements in pain relief and functional recovery at 6 months for TFESI vs ILESI.

One study (15) showed significantly greater improvements in pain relief with TFESI vs ILESI, but with measurement only at 10-16 days. Another study compared similar steroid doses, but performed periradicular, not epidural injections; it is unknown if this provided distribution to the ventral epidural space, which is necessary for efficacy (16).

Failure to closely evaluate the details of procedural performance in RCTs may result in inappropriate inclusion in pooled data. The utility of pooled group means is itself unclear. The available categorical data suggests the TFESI approach is superior to ILESI. Another method of examination of the efficacy of TFESI versus other epidural injections is comparison of outcomes from explanatory trials. Data from explanatory trials of non-image guided injections yields a number needed to treat > 90. (17, 18, 19, 20, 21) In contrast, a high quality explanatory trial of TFESI yields a number needed to treat of 3. (22) These are distinct procedures that must be evaluated separately. The inclusion of ILESI and caudal injections with TFESI in an artificial category of “epidural steroid injections” is not reasonable.

The methodological flaw of relying only on RCT evidence, and creating an artificial category of “epidural steroid injections”, is brought into focus by examining a broader synthesis of the data supporting TFESI. The most rigorous controlled trial supporting the efficacy of TFESI in patients with radicular pain due to disc herniations compared transforaminal steroids with 4 control arms using categorical outcomes of  $\geq 50\%$  pain relief at one month. (22) Note that this trial required a correlative lesion on imaging; it is incorrectly stated in the AHRQ assessment that it did not do so. Transforaminal injection of steroid produced 54% (95% CI 36, 72) responders, significantly greater than the control arms, which were indistinguishable from one another (15% responders, 95% CI 8, 22). All patients who were relieved of their pain were restored to normal or near normal function, and reduced their need for other health care. All patients previously requiring opioids ceased opioids. These significant outcomes were concealed by continuous data (group means). Another controlled trial used surgical sparing as the primary outcome. Only 29% of patients required surgery after treatment with transforaminal steroids injections compared with 67% treated with transforaminal local anesthetic. (23) The effects were durable in a five-year follow-up study of these patients. (24) A recent supportive observational trial studied patients awaiting surgery for radicular pain; 56% (CI 46, 66) avoiding surgery after a successful TFESI. (25) A randomized, controlled comparative effectiveness trial of TFESI with two steroid formulations showed that 70% of patients with radicular pain due to disc herniation had  $\geq 50\%$  pain relief that was durable at 6 months. (26) Clinical effectiveness was further supported by a large observation study of prospectively collected data on > 2000 consecutive patients receiving a single TFESI for radicular pain due to disc herniation, fixed lateral recess or foraminal stenosis. (27) In this study 46% were responders for pain relief (95% CI 43, 49) and 41% (38, 44) for functional recovery. When patients were segregated by duration of pain syndrome, those with sub-acute pain (< 3 months duration) had 62% (CI 56, 68) responders for pain relief and 59% (CI 53,65) responders for functional recovery, significantly better than patients with chronic pain. This important

information cannot be derived from the small RCTs included in the AHRQ assessment. The important clinical question of the effectiveness of repeat epidural steroid injections is not addressed by a study with methodology qualifying for inclusion in the assessment. However, a recent observational study of prospectively acquired data on over 2000 TFESI in 933 patients demonstrated that repeat TFESI are less effective than an index intervention, although not by a clinically relevant amount. More responsive sub-acute pain patients recovered all prior benefit in pain relief from an index injection that had since waned; early repeat injections for incomplete responders provided cumulative benefit. (28) A systematic review synthesized all the evidence from 6 explanatory trials, 11 pragmatic trials and 20 observational studies of lumbar TFESI and concluded that up to 70% of patients with radicular pain due to disc herniations achieve 50% pain relief at 1-2 months after treatment and 30% achieve complete relief. Between 25% and 40% of patients have relief that lasts 12 months. (29)

The methodology of the AHRQ health technology assessment, with its exclusive reliance on controlled trials, some of them up to 30 years old, which do not carefully consider specific diagnosis (patient selection), standardized technical performance of procedures, or the use of categorical outcomes data, limits the clinical usefulness of this assessment in my judgment. I applaud the heroic effort to assemble this data, but believe it paints an incomplete and misleading view of the totality of the literature. The application of this methodology to Question 1 fails to identify the well-established efficacy and clinical effectiveness of TFESI for radicular pain due to disc herniations from the larger pool of inappropriately aggregated studies of "epidural steroid injections." Formulation of public policy on this basis is flawed.

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## **INTRODUCTION**

The introduction suggests that injection therapies for “low back pain” are directed toward a nonspecific and un-diagnosable process. This is an assertion not based on contemporary evidence. If the authors wish to make this argument, contemporary primary evidence should be cited, if it exists, not their own 12 year-old review article. (ES-1, line 39) The authors should acknowledge that recent literature describes that the systematic application of diagnostic injection procedures can identify specific pain generators (1,2,3) that may then be targeted by specific therapeutic procedures. It is a questionable intellectual leap to conduct a health technology assessment of therapeutic procedures directed toward a symptom, “low back pain,” without a robust discussion of the diagnosis of specific pathophysiologic processes that may be manifest as this symptom.

The definition provided of the symptom, “low back pain” highlights the false premise on which the assessment is based. In the Scope of Review and Key Questions illustration, “Nonspecific, subacute or chronic low back pain” are said to be inclusive of “non-radicular low back pain, low back pain with radiculopathy and low back pain with spinal stenosis.” There is an implicit contradiction here in that there are specific criteria for the diagnosis of axial pain and radiculopathy. Radiculopathy is correctly defined as requiring specific evidence of neural dysfunction on physical exam, to include objective weakness, objective anesthesia, or diminished deep tendon reflexes, or electro-physiologic evidence of neural dysfunction- it is objective, not non-specific. (4) Radicular pain without radiculopathy can be diagnosed by selective nerve blocks. (5) Spinal stenosis is an imaging observation. It is not a disease process. If the authors wish to refer to the recognized disease process of neurogenic intermittent claudication, perhaps best defined in the guidelines of the North American Spine Society, they should do so specifically. (6) Somatic axial pain experienced in the lumbar region can be specifically attributed to the facet joints (dual comparative medial branch blocks), the intervertebral disc (disc stimulation), or the sacroiliac joint (controlled intra-articular blocks and multi-site, multi-depth lateral branch blocks). (5)

It is unfortunate that this health technology assessment does not begin by careful definition of the pathophysiologic processes to be treated by the technology to be assessed. The aggregation of somatic axial lumbar pain, radicular pain with or without radiculopathy, and neurogenic intermittent claudication into the symptom complex “low back pain” sets the stage for confusion and uncertainty. This is analogous to a health technology assessment of therapy for the symptom of chest pain, inclusive of bacterial pneumonia, acute coronary syndrome, and pulmonary embolism. The technology assessment loses credibility at its inception by failing to clearly identify the disease process being treated and the means of its diagnosis.

The authors are inclusive of ablative therapies in the definition of the injection therapies which the topic of this technology assessment, and then exclude them



paragraphs later. Perhaps the definition of the boundaries of the technology assessment could be made from the outset. (ES-1, Line 53)

The authors appropriately point out that the use of spinal therapeutic injections dramatically increased in the late 1990s and the early 2000s. More recent data, presented at the US Food and Drug Association Advisory Panel meeting on epidural steroid injections in Silver Spring, MD (Nov 24, 25, 2014), showed only a modest increase in the absolute number of epidural injections performed from 2009-2013. Annual numbers of epidural steroid injections in Medicare patients (> 65 years of age) increased by 20.5%, while commercially insured epidural steroid injections in the same age group increased by 19.8%. (7) In this time period (2009-2013) the US population > 65 years of age increased by 13.0%. (8) The recent increase in the *rate* of epidural steroid usage in this age group is decidedly modest. Contemporary data would be appropriate in this health technology assessment, as it is available from other agencies of the federal government.

The authors correctly identify many of the reasons for the heterogeneity in the results of studies of the various injection therapies, including definition of terminology, patient selection, varied injection technique, and insufficient duration of follow up. This acknowledgement only makes more puzzling the use of non-standard definitions of terminology, the aggregation of multiple pathophysiologic processes into an ill defined symptom complex, and the aggregation of techniques (interlaminar, caudal, transforaminal, and periradicular injections grouped into a heterogeneous category of epidural steroid injections). The variations in patient selection are acknowledged, but there is insufficient stratification of studies by rigorous patient selection or injection technique.

Note that the definition of transforaminal injections “through the neuroforamen dorsal to the exiting nerve root” is not strictly correct. In the most commonly performed supraneural transforaminal approach the needle is directly superior to the exiting nerve, not dorsal to it. In other variations of the transforaminal approach, the retroneural or infraneural approaches, the needle will lie dorsal to the exiting nerve. Throughout the document, it is apparent that the authors have no specific knowledge of the procedures they critique. This is unfortunate; inclusion of experts in the field to better shape the methodology of inquiry would have likely yielded a more useful assessment. As Dr. Sackett noted in his commentary on evidence based medicine: “Without clinical expertise, practice risks becoming tyrannised by evidence, for even excellent external evidence may be inapplicable to or inappropriate for an individual patient.”(9)

The formulation of the key questions suffers from the attempt to generalize across application of a heterogeneous group of procedures to an inadequately defined symptom complex. Many of the more rational specific questions are subsequently developed in the data presentation.

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## **METHODS**

The problematic selection of studies for inclusion in this assessment based on research methodology, without due consideration for proper patient selection (diagnostic specificity), procedural technique, or use of categorical outcomes measures creates serious doubt as to the validity or utility of this health technology assessment. This is detailed in the general comments section of my review. I will make only more selective comments here.

The definition of “radiculopathy” (ES-4, line 30) is in conflict with that typically used in the fields of neurology or pain medicine. (1)

The inclusion of “therapeutic medial branch blocks” is unexpected. Although addressed in one study, there is no acceptance of this procedure in the field of pain medicine. Dual, comparative medial branch blocks are the only validated, diagnostic procedure for facet mediated pain, but are specifically described as having no therapeutic value in contemporary practice guidelines. (2) There is no physiologic mechanism by which such a procedure could be expected to be effective.

Assessing Quality (ES-6, 7): As noted in the General Comments discussion, the failure to include diagnostic specificity (patient selection) and technical performance of the procedures in the assessment of study quality dooms this process from its inception. It cannot be truthfully stated that this document represents an assessment of efficacy of the procedures said to be under study. It can be argued that it represents an assessment of the heterogeneity of efficacy outcomes of existing clinical practice over a period of 30 years, but those are very different things. Study Quality assessment is addressed in greater detail in the following section.

In the description of categorical outcomes measures (ES-8, line 28) for function, the authors only refer to the Oswestry Disability Index; the Roland Morris Disability Questionnaire (RDQ) is also referenced earlier. The appropriate level for minimally significant improvement in the RDQ is 40%, not the 50% used for the ODI. (3)

### References

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## **RESULTS**

A comprehensive review of the study is found in the general comments section; the problematic inclusion and exclusion of studies is dealt with in that broader discussion of the technology assessment. I will limit my comments here to more selective issues.

### *Study Quality*

Regarding the assessment of study quality, three studies (1,2,3) of epidural injections for “radiculopathy” were rated “good.” Two of those studies used only continuous data in outcomes measurements, and did not require a correlative neural compressive lesion on imaging. (2,3) One study (3) used topographical landmarks augmented by ultrasound to identify the sacral hiatus for caudal epidural injections. There was no use of fluoroscopy, hence it is completely unknown where the medication was delivered- in the epidural space, surrounding musculature, or intravascular. It is absurd to classify this as a “good” study. This underscores the lack of technical awareness of procedural detail by the collective authorship. In contrast, the study widely regarded as the most elegant randomized controlled trial of TFESI (4), which required patients with radicular pain and a correlative lesion (incorrectly stated, page 73), and measured categorical outcomes for pain, as well as functional outcomes, surgical sparing, and other health care use, was rated as “fair.” Another randomized controlled trial compared TFESI to intramuscular saline injections, with a mean follow up of 1.4 years using a composite categorical outcome (> 50% reduction in pain *and* improvement in Roland –Morris score by > 5 points *and* a positive global effect score; all measured > 1 year post treatment). There were 84% responders in the TFESI group versus 48% for the control intervention. (5) This trial was excluded from evaluation for “wrong study design for key question.” (page 245, D-1) The exclusion of this study is not understandable.

The single “good” comparative effectiveness study of epidural injections for “spinal stenosis,” (presumably directed against the disease process of neurogenic intermittent claudication) was well conceived but suffered significant heterogeneity in patient selection, medication dose, and delivery technique. (6)

Among the several studies of facet injections, one study was rated “good.” (7) This study used as its inclusion criteria for facet intervention “positive” MRI findings for facet hypertrophy and a positive response to an intra-articular local anesthetic injection. There is no evidence of any correlation between structural changes of facet hypertrophy and facet joint pain. (8) Intra-articular facet injections of anesthetic have never been validated as a diagnostic procedure and have an unknown placebo response rate. The only validated diagnostic procedure for facet-mediated pain is controlled medial branch block. (9) The criteria used to assess the quality of studies reflect research methodology, but fail to identify other procedural features that affect the validity of those studies. The categorization of studies makes clear that the authors are not familiar with the conduct of these procedures, nor the

technical features that may affect efficacy or effectiveness. The study quality assessment is not credible.

### *Synthesis*

As an example of how the exclusion of all but controlled studies leads to an incomplete and distorted view of the totality of the literature, consider the discussion on page 27 regarding comparative effectiveness studies of different corticosteroids in epidural injections. Only two studies are included (10,11); they constitute but a sample of several important studies examining the effectiveness of particulate versus non-particulate steroid preparations (suspensions versus solutions). All of the 13 case reports of spinal cord infarcts after lumbar TFESI occurred with particulate steroids. These are presumed to act as embolic agents following introduction into a radiculomedullary artery contributing to the anterior spinal artery. No catastrophic outcomes have occurred with the non-particulate steroid dexamethasone. Small comparative effectiveness studies had shown trends toward greater effectiveness of particulate steroids in cervical TFESI (12,13) The Park study (10) showed significantly greater improvement in one pain measure (VAS), but not another (McGill pain questionnaire, not mentioned in the AHRQ assessment) for particulate steroids. There was no difference between particulate and non-particulate steroids in functional improvement. Interventional pain physicians were left in a safety versus efficacy quandary: greater safety with dexamethasone, but possible diminished effectiveness.

The Kennedy comparative effectiveness study (11) was significant. It utilized appropriate pain relief and functional recovery categorical outcomes measured at 6 months, and showed there was no difference in effectiveness of particulate versus non-particulate steroid formulations. This was reinforced by a large observational study of prospectively collected data on > 3,600 consecutive TFESIs with a non-inferiority analysis of the effectiveness of dexamethasone versus particulate steroids. (El-Yahchouchi, 14) Dexamethasone was non-inferior to the particulate steroids in pain and functional recovery categorical outcomes, despite higher glucocorticoid equivalents delivered in particulate steroid patients. Looking over the entirety of the literature, earlier studies (10,12,13) measured outcomes as 2-4 weeks, where there was a trend favoring the particulate steroids. This trend was also seen in the early data points of the Kennedy and El-Yahchouchi studies, but it completely fell away at 2 months post injection and beyond, where particulate and non-particulate steroids were indistinguishable in effectiveness. At intermediate term evaluation, there was no difference in effectiveness of particulate versus non-particulate steroids, and the safer non-particulate was therefore preferred. These latter studies (11, 14) form the basis of the soon to be published FDA Safe Use Initiative on epidural steroid injections. Evaluation of a small fragment of the literature drawn from a much larger clinical practice narrative thus is uninformative, and misleading.

The presentation of the tabular results is exhaustive. The authors are to be congratulated in the successful assemblage of all this information. Although tedious to deal with in PDF format, I have no suggestions for remediation.

Based on the fundamentally flawed methodology, I am in strong disagreement with several of the presented results. Most importantly, it is my assessment that, in contrast to the inappropriately aggregated data regarding epidural steroid injections presented by AHRQ, the totality of the literature demonstrates, in clinical terms:

There is strong evidence for immediate, short and intermediate term categorical improvement in pain and functional deficit due to lumbar radicular pain with or without radiculopathy following technically well performed lumbar transforaminal epidural steroid injections. The evidence is strongest in patients with disc herniations as the cause of the radicular pain. There is evidence of modest quality for a surgical sparing effect for transforaminal epidural steroid injections.

Transforaminal epidural steroid injections are superior to unguided interlaminar and caudal epidural steroid injections in immediate, short and intermediate term relief of radicular pain with or without radiculopathy and in functional recovery.

Particulate and non-particulate steroids are indistinguishable in clinical effectiveness (pain relief and functional recovery) in the immediate, short and intermediate term when delivered by transforaminal epidural injection as a treatment for radicular pain with or without radiculopathy.

Although I disagree with the methodology, I concur with these conclusions of the AHRQ technology assessment, rendered in clinical terms:

There is no evidence that unguided interlaminar or unguided caudal epidural injections provide benefit in pain relief or functional recovery from radicular pain with or without radiculopathy.

There is no evidence that epidural steroid injections by any technique provide benefit in pain relief or functional recovery for non-radicular pain.

There is insufficient evidence at this time to support epidural steroid injections as a therapy for neurogenic intermittent claudication. Better-controlled studies could alter this assessment.

There is insufficient evidence to assess epidural steroid injections versus other interventions. This could be done by comparison of categorical outcomes in placebo controlled trials, if such exist for the other interventions, in the absence of head to head trials. This is of critical

importance, as competing technologies, including non-steroidal anti-inflammatory agents, opioids, and surgical intervention carry a known risk of harms.

There is no current evidence to support the diagnostic or therapeutic use of intra-articular facet injections. No studies have yet been published in which the study cohort has an established diagnosis of facet-mediated pain via controlled medial branch blocks. Until this is reported, the key question of therapeutic efficacy remains unaddressed.

There is no evidence to support the use of corticosteroids for a purported therapeutic medial branch block.

There is insufficient evidence to evaluate the efficacy or effectiveness of intra-articular sacroiliac joint injections.

There is a very low risk of harms associated with epidural steroid injections, or intra-articular facet injections.

I have made no attempt to respond to the hundreds of results statements, but have focused on those I believe most relevant to patient care.

On page 31, line 48, the wrong Cohen trial is cited. It should be reference 64.

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## **DISCUSSION/CONCLUSIONS**

I have outlined my disagreements with AHRQ methodology and the study conclusions in prior segments of this review. The authors compare their efforts to similarly constructed systematic reviews and meta-analyses that examine only data from randomized controlled trials, and unsurprisingly arrive at similar conclusions.

In the paragraph on applicability, the authors note the absence of qualifying controlled studies on epidural injections addressing sub-acute symptomatology, types of corticosteroids used, number and frequency of injections, utilization in the postoperative patient with radicular pain, and integration into comprehensive spine care. A failing of this assessment is that there is evidence available for examination from well-conducted non-controlled trials of transforaminal epidural steroid injections (TFESI) on all of these questions. They inform physicians and patients. They are not perfect evidence, but they provide information of greater clinical value than randomized controlled trials that fail to control for patient selection, standardized and optimized technical performance of procedures or measure categorical outcomes.

To provide examples, the greater responsiveness of patients with sub-acute (versus chronic) radicular pain syndromes to TFESI was examined in a retrospective analysis of prospectively acquired data on 2024 consecutive lumbar TFESI injections. (1) The proportion of responders with sub-acute pain syndromes was 62% for pain reduction (50% improvement) and 59% for functional recovery (40% improvement on Roland-Morris) compared with 38% (pain) and 34% (function) in chronic pain patients (pain > 1 year). (1) The several studies addressing particulate versus non-particulate steroids, a critical topic ignored by this assessment, were detailed in the prior segment. The utility of repeat TFESI injections has been examined in several studies. A systematic review identified nine TFESI studies of disc herniation patients with categorical outcomes data; of patients achieving responder status ( $\geq 50\%$  pain relief), 94% required only a single injection, 4% required two. Multiple injections are usually not necessary (2) A study of 3,645 consecutive lumbar TFESI demonstrated that the response in pain relief and functional recovery at two weeks post TFESI is strongly associated with longer term response, and is thus a rational time to consider repeat injection for incomplete responders, or surgical therapy for non-responders. (3) Another study of 6,582 consecutive lumbar TFESIs for disc herniations *or fixed lesions* demonstrated that within 1 year of an index injection, 22.4 % required an additional injection in hopes of cumulative benefit or recovery of benefit that had waned. 18% used a second injection, only 3.6% a third injection. (4) This study also demonstrated that early repeat TFESI (within 3 months of an index injection) provided statistically significant cumulative benefit to incomplete responders, and that patients with sub-acute pain syndromes undergoing repeat injections could expect complete restoration of relief achieved on an index injection which has since waned. (4) In a study of 156 patients with persistent radicular pain post surgical intervention, 31%

(95% CI  $\pm$  7%) responded to a TFESI and none of these patients required revision surgery. (5) Another study, 69 patients who had failed conservative treatment and were awaiting surgery for chronic radicular pain were offered an integrated program of TFESI and physical therapy. (6) 78% avoided surgery in the subsequent year, with 62% having no pain or negligible pain (VAS < 10/100) and significant functional recovery (Roland–Morris scores < 3/24) at one year follow up. (6) Evidence exists. Although imperfect, it can assist in clinical decision-making.

Regarding limitations of the review process, I would prefer the authors at least acknowledge that the heterogeneity in diagnostic specificity and technical variation in procedural performance present in many of the studies were not considered in grading of the study quality. The inclusion of two to three decade old studies using techniques considered unacceptable in contemporary practice guidelines is a limitation of the process in this reviewer's judgment.

Regarding research gaps, the authors identify many of the important topics yet to be investigated in controlled trials. Evidence from non-controlled trials addresses several of these questions, as noted above, and can inform more rigorous controlled trials. Given the complexity of the issues, the cost involved in controlled trials, and the challenges in recruiting patients with debilitating pain into placebo controlled trials, it is likely that many of these gaps in evidence will never be examined as primary variables in controlled trials. Prioritization is key. In regard to radicular pain, trials of the efficacy, effectiveness and importantly *efficiency* (cost effectiveness) of TFESI when integrated into a comprehensive treatment approach would seem of the highest priority. There is already significant evidence in controlled and uncontrolled trials that TFESI have efficacy and clinical effectiveness in disc herniation patients- its cost effectiveness in the context of comprehensive spine care needs study. There must also be more rigorous comparison of such an integrated treatment against competing technologies to include cognitive behavioral therapy alone, pharmaceuticals, and surgery. Comparators must include clinical effectiveness, efficiency, and harms. Another priority would be assessing the effectiveness and efficiency of TFESI in the treatment of the elderly population with fixed lateral recess or foraminal stenosis causing radicular pain or radiculopathy. In this patient population, comparison with far-lateral, image guided interlaminar injections would be useful.

Any further study of epidural steroid injections in neurogenic claudication patients should focus on documentation of delivery of the pharmaceutical agent to the epidural space. It remains unclear from existing studies where the steroid was delivered.

The authors comment on the need to identify patients with facet joint pain to inform future studies. The mechanism exists: dual comparative medial branch blocks. A rigid diagnostic algorithm should be a predicate to any future study of facet interventions. The same applies for future studies of sacroiliac joint complex interventions. It must first be determined if the pain arises from within the joint

(controlled intra-articular blocks) or the dorsal ligamentous complex (multi-site, multi-depth lateral sacral blocks, with negative intra-articular blocks) or both, before interventions are tested. Diagnosis must precede therapy.

Note: Page 47, lines 13-16. This sentence is incorrectly formulated. I assume it should read ... epidural nonsteroid injections might be more effective than nonepidural injections...

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## **CLARITY/USABILITY**

The most important judgment in this review of the AHRQ Technology Assessment on pain management injection therapies for low back pain is that of its utility in informing clinical practice decisions or public policy. I do not take this matter lightly. Regarding public policy, there can be no doubt that injection therapies for pain of spinal origin have been subject to overutilization, fraud and abuse. Although contemporary data suggest a recent damping of the rise in utilization of epidural steroid injections, the rapid increase in use in the late 1990s and in the decade of 2000-2010 merits concern and assessment. The raw utilization numbers fail to reveal an even more disturbing theme, the wide heterogeneity in practice patterns, suggesting that on a societal basis these procedures are often not being applied with appropriate care in patient selection, or performed with appropriate technical rigor. This is rooted in the lack of a clear and accountable educational and credentialing pathway for physicians who perform interventional procedures for pain of spinal origin. It is for this reason that I have spent countless hours over the past decade teaching and advocating for the use of *only* evidence based interventional pain procedures with initial rigorous diagnosis, followed by careful patient selection, meticulous technical performance, and with ongoing outcomes evaluation as an ethical imperative. I endeavor to conduct my clinical practice in this manner, teach my academic trainees in this manner, and teach and advocate for this within professional societies.

It would appear then that there is an alignment between the concerns that motivated the undertaking of this technology assessment, and the evidence informed beliefs of this reviewer. This might be expected to produce a favorable response. This is sadly not the case. Unfortunately, lack of clarity in diagnosis, restrictive methodology, and lack of attention to patient selection, technical procedural performance, and valid outcomes measures results in several conclusions that I believe are unsupported and erroneous. I do not believe that this technology assessment should be the basis for clinical decision-making or public policy creation.

This is an assessment of therapeutic interventions. Well-founded therapeutic decisions are based on rigorous diagnosis. This assessment begins with the false premise that “low back pain” is overwhelmingly non-specific and not subject to specific diagnosis. This is untrue. Careful application of spinal diagnostic techniques can identify specific pain generators for both somatic axial pain and radicular pain. (1) Only with a specific diagnosis established should therapeutic interventions be applied. Unfortunately, many of the included studies fail to establish a diagnosis prior to intervention; this is not recognized as a study weakness in the assessment of study quality. The authors can, as do I, rightly critique the manner in which spinal injection techniques are applied in the US medical care system. This is, however, quite different from the conclusions reached that the techniques themselves provide no benefit.

The restriction of included studies to randomized controlled trials excludes valuable observational studies that could enrich and expand the evidence base. As Dr. Sackett notes: "Evidence based medicine is not restricted to randomised trials and meta-analyses. It involves tracking down the best external evidence with which to answer our clinical questions. " (2) This is most evident in the failure to evaluate the several recent observational studies which buttress the controlled trial support for the use of transforaminal epidural steroid injections as a useful therapy for radicular pain due to disc herniations. The authors dismiss out of hand all but randomized controlled trials, despite evidence that "well-designed observational studies (with either a cohort or a case-control design) do not systematically overestimate the magnitude of the effects of treatment as compared with those in randomized, controlled trials on the same topic." (3) This is particularly problematic in that many of the included randomized controlled trials fail to establish a diagnosis prior to a therapeutic intervention, or do not rigorously control the technical performance of the procedures, or report only continuous outcomes. If the patient does not have the disease to be treated, or the technique utilized cannot document delivery an anti-inflammatory agent to the site of inflammation, what then is being studied? Continuous outcomes data will conceal segregation of the studied cohort into responders and non-responders. The selected literature is gilded by its randomized controlled methodology, even when it may be of no practical value. The need to maximize the pool of available controlled trials has resulted in the inclusion of irrelevant and archaic controlled studies that bear no relationship to current clinical practice. These factors went unrecognized, as the authorship did not include clinicians active in the field, who could have identified these deficiencies.

When no randomized controlled trials were available for the key questions presented, as was the case for many of the questions addressed to epidural injections, and most of those for the facet and sacroiliac joint interventions, the authors simply noted "insufficient evidence." A better path was suggested by Dr. Sackett: "if no randomised trial has been carried out for our patient's predicament, we must follow the trail to the next best external evidence and work from there." (2) Our patients deserve this. Dr. Concato concurs: "The popular belief that only randomized, controlled trials produce trustworthy results and that all observational studies are misleading does a disservice to patient care, clinical investigation, and the education of healthcare professionals" concluding that "ignoring the evidence from observational studies is not a viable option". (3)

I wish to acknowledge the incredible effort required of the authors and their staffs to assemble, organize and evaluate the controlled studies presented in this technology assessment. I am in agreement with their stated motivation suggesting there is great need to assess, and constrain, the often excessive and improper utilization of interventions directed toward pain of spinal origin. I cannot agree with the methods utilized in this assessment, and hence its conclusions. Were this assessment used to define public policy, it could result in the inappropriate restriction of access to procedural techniques that are effective in relieving pain and

effecting functional recovery in carefully selected patients. Without doubt, such restriction would reduce excessive and inappropriate utilization. Also without doubt, many patients would undeservedly suffer and see their lives diminished. It is unfortunate that the effort and expense involved in creation of this technology assessment could not have been utilized to fund well conceived studies, informed by both knowledgeable clinicians and stringent research expertise, that could have provided answers to the many key questions that remain largely unaddressed.

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