Washington State Health Care Authority

# Extracorporeal shock wave therapy
## for musculoskeletal conditions

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## Draft evidence report:
## Peer review, comment and response

*February 13, 2017*

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# Extracorporeal shock wave therapy

**Provided by:**


**Spectrum Research, Inc.**

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# Draft Evidence Report

**Peer Review, Public Comment & Response**

***February 13, 2017***

## Responses to clinical and peer reviewers

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

Specific responses pertaining to peer reviewer comments are included in Table 1.

- **Alfred C. Gelhorn, MD**
  Weill Cornell Medical College; New York, New York
  Assistant Professor, Department of Rehabilitation Medicine
  Attending Physician
- **Patrick DeHeer, DPM**

  Hoosier Foot and Ankle; Carmel, Indiana
  Attending Physician

Responses to public comment may be found in Table 2.

Full text of peer review and public comments follows the tables.

**Table 1. Responses to Clinical and Peer Reviewers**

| Comment | | Response |
|---|---|---|
| **Alfred C. Gelhorn, MD** | | |
| | **Specific comments** | |
| Introduction | *Overview of topic is adequate?*<br><br>Yes. Though the basic science of ESWT is presented as essentially a series of fortuitous observations, and the mechanism of action of ESWT remains obscure based on the included review. This is potentially important – given the conditions this is used to treat, we want to know if ESWT is effectively anti-inflammatory in effect or if there are true disease modifying properties. The ability of ESWT to fragment calcium is of no real importance in the included pathologic conditions. | Thank you for your comment. Please see background general below. |
| | *Topic of assessment is important to address?*<br><br>Yes. The included conditions are of high importance, causing high levels of clinical disability among patients, lost work hours, and are highly prevalent. Other conservative and surgical treatment options have relatively low success rates, and these conditions therefore remain frustrating and difficult conditions to treat for both clinicians and patients. There would be a high level of enthusiasm for a noninvasive, safe, effective treatment option for tendinopathy, osteoarthritis and plantar fasciitis. | Thank you for your comment |
| | *Public policy and clinical relevance are well defined?*<br><br>No. Section 1.4 appears to be missing, which may include important public policy relevance. | Section 1.4 is now in the report, supplied by the State of Washington. |
| Background, general | *Content of background is sufficient?*<br><br>Yes. However, I would add that it is important to discuss the natural history of the presented conditions, which is to say, what would happen in the absence of any intervention. For plantar fasciitis and uncomplicated lateral epicondylitis, the natural history is generally for disease resolution over a period of approximately 1 year from onset. For adhesive capsulitis, the natural history is for full resolution within 12-24 months in almost all cases. On the other hand, rotator cuff tendinopathy tends to be a progressive disease, with 60% of tears progressing by 2 year follow up. Similarly, Achilles and patellar tendinopathy do not tend to show spontaneous resolution. The importance of considering the natural history is that for conservative treatments, if the natural history is for ultimate resolution but clinical morbidity is high (as is the case for plantar fasciitis and lateral epicondylitis) there is an important role for therapies that decrease pain and improve function in the short term. | Thank you for your comment. We added comments on the natural history to the background section. |

| | Comment | Response |
|---|---|---|
| | For clinical entities that do not tend to resolve over 12-24 months, it becomes more important to find treatments that are effective in the long term when compared with sham or active controls. In other words, short term benefits are an important consideration for the clinician who is trying to help manage patient symptoms when spontaneous resolution can be expected over a period of months. Short term benefits are less helpful when there is no expectation of spontaneous resolution, and in these cases the long term outcomes are most important to evaluate. Therefore, in the context of the present review, I would place more emphasis on the short term results in lateral epicondylitis and plantar fasciitis; and more emphasis on the long term results in rotator cuff, patellar, and Achilles tendinopathies, as well as knee osteoarthritis. | |
| | The mechanism of action of ESWT is presented better in this section than the introduction. However, it still remains biologically questionable. The studies that are cited suggest that there may be intracellular signals that are generated in response to ESWT, and growth factor expression is changed at the cellular level. For biological plausibility, one wants to feel secure in an epistemological rationale for the body to respond to stresses in a certain way. In other words, one might ask: why would cells be sensitive to these waves of supersonic energy? Is the delivered energy a signal of injury to the body? That is, does ESWT in essence produce a focal new injury that the body responds to by initiating a new healing response? Or is ESWT energy simply producing localized heat, not injury at all? Or, in contrast, does ESWT work by modifying conditions outside the cell, perhaps in organizing collagen fibers in the tendons themselves or disrupting calcifications such as in calcific rotator cuff tendinopathy. It is important to try to understand the mechanism in better detail. As pointed out later, it is unclear where ESWT should be focused, whether at the site of pathology in a tendon, or the site of tenderness. The lack of understanding of the true mechanism of action is the reason that clinicians have not standardized issues of ESWT delivery, such as this. It also seems clear that for some organizations such as the Dutch Orthopedic Association, which recommends ESWT for calcific tendinopathy but not non-calcific tendinopathy, the organization's sense is that mechanism of action is clearly in disruption of the calcified region of the tendon. | With respect to mechanism of action, there is none agreed upon. We attempted to amplify this section in the report to clarify different proposed mechanisms and to underscore the lack of consensus around the mechanism. |
| **Report Objectives & Key Questions** | *Aims/objectives clearly address relevant policy and clinical issue?* Yes.<br><br>Key questions clearly defined and adequate for achieving aims? Yes, these key questions are adequate and important. | Thank you for your clinical perspective. |

| | Comment | Response |
|---|---|---|
| **Methods, page 78, Intervention** | *Method for identifying relevant studies is adequate?*<br>Yes<br>*Criteria for the inclusion and exclusion of studies are appropriate?* Yes<br>*Method for Level of Evidence (LoE) rating is appropriate and clearly explained?* Yes<br>*Data abstraction and analysis/review are adequate?* Yes | Thank you for your comment. |
| **Results, page 86, section 4.1.2** | *Amount of detail presented in the results section appropriate?*<br>Yes. The forest plots are excellent and clear.<br>*Key questions are answered?*<br>Plantar fasciitis. There is clearly more evidence for plantar fasciitis than other conditions, and the conclusions are therefore easier to interpret. It is well demonstrated that ESWT (both focused and radial) repeatedly results in decreased pain compared to sham, in multiple methods of describing pain. It is not clear to me that the amount of pain relief is clinically important, however. Mean pain decreases of around 1 to 2 points on a 10-point scale is of questionable clinical importance.<br>I would also highlight the studies that compare ESWT to steroid injection, which is a commonly used procedure for plantar fasciitis in clinical practice. The presented study with lower risk of bias showed a significantly higher decrease in pain when compared with ESWT.<br>Lateral epicondylitis. There is conflicting evidence of effectiveness, depending on how pain is measured. This is concerning to me. In clinical practice, clinical success usually is qualified by pain improvement regardless of how it is measured. I agree that the strength of evidence is highly limited<br>Rotator cuff tendinopathy. Despite study limitations, the best quality evidence shows that functional improvements exist in tandem with pain improvements. The studies that show long term continued benefits are of particular interest and importance as discussed above for this condition, since natural history tends to be of worsening rather than improvement. Similar to my note above regarding comparison with steroid injection, these results should be highlighted, since steroid injection is so commonly used in clinical practice. The results comparing ESWT with needling alone or with steroid injection show a smaller benefit for ESWT. | Thank you for your comments. |

| | Comment | Response |
|---|---|---|
| | Adhesive capsulitis. Radial ESWT appears to be clinically superior to sham while Focused ESWT is not. Why the discrepancy? Neither are compared to the most common clinical interventions, namely physical therapy and glenohumeral joint steroid injection.<br><br>Achilles and patellar tendinopathy: Agree the evidence is too limited to draw any conclusion<br><br>Knee osteoarthritis. Data are too limited to draw conclusions.<br><br>*Figures, tables and appendices clear and easy to read?*<br><br>Yes. The forest plots are excellent and clear. The tables are excellent.<br><br>*Implications of the major findings clearly stated?*<br><br>Not entirely. Partly this is due to the absence of any cost data at all. In evaluating the body of evidence presented, I see a technology that has clear short term benefit in some conditions, though importantly the benefits are small in magnitude. The technology appears safe, and generally well tolerated, though the need to use local anesthesia in some studies suggests that there is significant procedural pain. Given these relatively modest benefits, it is important to know how much this technology costs. This is especially true because studies that compare this with an office based steroid injection (low cost) generally show the benefits seem to favor the steroid injection. So one might ask: if there is an equally or more effective treatment that is commonly performed and cheap, what is the role for ESWT? On the other hand, if costs of ESWT are quite low, this seems a reasonable treatment to offer patients, given the favorable safety profile.<br><br>*Have gaps in the literature been dealt with adequately?*<br><br>Yes.<br><br>*Recommendations address limitations of literature?*<br><br>Yes. The grading of evidence is clearly presented and appropriate. | |
| **Conclusions** | *Are the conclusions reached valid?*<br><br>Yes. Please see my comment above regarding costs, though | Thank you for your comment. |
| **Overall Presentation and Relevancy** | *Is the review well-structured and organized?* Yes<br><br>*Are the main points clearly presented?* Yes<br><br>*Is it relevant to clinical medicine?* Yes. High relevance.<br><br>*Is it important for public policy or public health?* | Thank you for your comments. |

| | Comment | Response |
|---|---|---|
| | Yes, high importance. | |
| **Peer Review: Patrick A. DeHeeter, DPM** | | |
| | **Specific comments** | |
| **Introduction, General** | The overview of the topic was adequate and explained the topic very well. | Thank you. |
| **Introduction** | *Overview of topic is adequate?*<br>The overview of the topic was adequate and explained the topic very well.<br>*Topic of assessment is important to address?*<br>The topic of assessment is important to address because it can provide a less invasive modality of therapy for numerous conditions.<br>*Public policy and clinical relevance are well defined?*<br>Both public policy and clinical relevance were well defined. | Thank you.<br>Thank you.<br>Thank you. |
| **Background, General** | *Content of literature review/background is sufficient?*<br>The content of the literature was very thorough and complete | Thank you. |
| **Objectives & KQs** | *Aims/objectives clearly address relevant policy and clinical issue?* The aims and objectives clearly addressed the relevant policy and clinical issues.<br>*Key questions clearly defined and adequate for achieving aims?*<br>The key questions were clearly defined and adequate for achieving aims. | Thank you.<br>Thank you. |
| **Methods** | *Method for identifying relevant studies is adequate?*<br>The methods used to identify relevant studies were adequate<br>*Criteria for the inclusion and exclusion of studies are appropriate?*<br>The criteria used for inclusion and exclusion of studies were appropriate.<br>*Method for Level of Evidence (LoE) rating is appropriate and clearly explained?*<br>The method for Level of Evidence rating is appropriate and clearly explained in the report.<br>*Data abstraction and analysis/review are adequate?* | Thank you.<br>Thank you.<br>Thank you.<br>Thank you. |

| | Comment | Response |
|---|---|---|
| | The data abstraction and analysis is adequate. | |
| **Results** | *Amount of detail presented in the results section appropriate?*<br>The detail in the results section was appropriate and complete. | Thank you. |
| | *Key questions are answered?*<br>Key questions were answered fully. | Thank you. |
| | *Figures, tables and appendices clear and easy to read?*<br>The figures, tables, and appendices are clear and easy to read. | Thank you. |
| | *Have gaps in the literature been dealt with adequately*? Yes | Thank you. |
| | *Implications of the major findings clearly stated?*<br>This is the one area I was a little unclear on, the results and how those related to any final recommendation. | Thank you. |
| | *Recommendations address limitations of literature?* Yes | Thank you. |
| **Conclusions** | *Are the conclusions reached valid?* Yes | Thank you. |
| **Presentation & Relevancy** | *Is the review well-structured and organized?* The review is very well structured and organized. | Thank you. |
| | *Are the main points clearly presented?*<br>The main points are clearly presented. | Thank you. |
| | *Is it relevant to clinical medicine?*<br>The topic is relevant to clinical medicine. | Thank you. |
| | *Is it important for public policy or public health?*<br>The topic is important and should be considered as an alternative to more invasive procedures. | Thank you. |

## Responses to public comment on draft report

This second section responds to comments received from the following party:

- Gary Franklin, MD, Office of the Medical Director, WA State Department of Labor and Industries

Specific responses pertaining to comments are included in Table 2 below.

Complete comments submitted are attached following the responses below.

**Table 2. Responses to public comment**

| Comment | | Response |
|---|---|---|
| **Gary Franklin, MD<br>Office of the Medical Director, WA State Department of Labor and Industries** | | |
| | **Specific comments** | |
| **Page 7** | " ESWT has gained significant acceptance.." should be deleted. Ref 77 has no reference or documentation for this statement. The Ref itself is an opinion piece, and the author is on the advisory board of one of the manufacturers; it should be deleted. He states that safety is no problem-that's not true. However, the claim in this article that ESWT is used to "induce tissue repair and regeneration" could be used as a benchmark for biological plausibility in the report-what is the evidence that ESWT does that? | The statement and reference was removed from the text. |
| **Page 7** | "The FDA..approved…Ossatron…" May want to put the original FDA study link for plantar fasciitis here: www.accessdata.fda.gov/cdrh_docs/pdf/P990086B.pdf.<br><br>Also, Please compare the FDA study findings with those in the published study. There were no differences in functional outcome or pain drug use. Also, the improvements in treatment group were greater in investigator assessment than in patient self-assessment. The pain outcomes were better but not by much, since both groups improved a lot. There were two plantar fascia tears in the active treatment group.<br><br>Same for the approval for lateral epicondylitis-cit FDA study link: www.accessdata.fda.gov/cdrh_docs/pdf/P010039b.pdf | Thank you for your comment. We added the link as suggested into the text. See the comment with respect to the FDA study findings under outcomes below. |

| | Comment | Response |
|---|---|---|
| **Page 7** | -"breaking calcium deposits" and "causing an inflammatory response"- what is the evidence that these things occur and that if they occur that this "induces tissue repair and regeneration". | Thank you for your comment. There is no consistent agreement on the mechanism by which ESWT may provide a therapeutic benefit. The ones listed are some of the ones proposed. Please see section 2.2.1., Mechanism of Action, in the background of the main report. In addition, we have added a statement that the mechanism of action is not well understood and lacks consensus on page 7. |
| **Page 7** | "synthesis" should be "synthesize" | Thank you; we have made the change. |
| **Page 8** | On PICO, why were high vs low energy excluded Re efficacy and particularly safety? | Thank you for your comment. High versus Low was excluded for efficacy as our concern was not whether a certain attribute of the technology was better than another attribute. Rather, we were interested in whether either high or low was better than another comparator (sham, or other treatment option). However, these studies should be included in the safety section. We edited the PICO and ensured that all high versus low studies that addressed safety concerns were included. |
| **Page 8** | The evidence report states that comparisons of ESWT such as different modalities (e.g., radial vs. focused ESWT, high- vs. low-energy ESWT) are excluded (Page 8). However, at least two studies are included to compare the effect of energy intensity on the treatment outcomes (Page 148-149). The findings are very interesting. Could you please clarify if the statement on Page 11 is an error or if the energy intensity comparison studies are included just for additional information? Are there many RCTs to compare high- vs. low-energy ESWT? As shown on Page 88-93, the effect of high-energy ESWT seems more consistent than low-energy ESWT. Is it possible to modify Key Question #3 to include comparisons of ESWT such as different modalities (e.g., radial vs. focused ESWT, high- vs. low-energy ESWT) at this point? It would be very helpful to know if energy intensity makes difference for other conditions. | Thank you for your comment. Please see above. Our initial desire was to stratify results by high and low energy when there were enough data. However, the data were too sparse to do so. Nevertheless, we labeled the forest plots so the reader could judge for themselves. Note that there is no universal agreed upon cutoff for labeling energy as high, medium or low. We used <1.2 as low, 1.2-2.0 as medium and >2.0 as high energy based on agreement from our clinical experts. We added a section in the methods that explains this further.<br><br>The studies on pages 148-149 were two articles that specifically evaluated high vs. sham, and low vs sham (effect modification) for shoulder/rotator cuff tendinopathy, and are included under KQ3. There were no ESWT energy intensity comparisons versus different treatments or sham in other conditions. |
| **Page 17** | KQ2 summary of results-for the serious events, did you include the 2 plantar fascia tears reported in the FDA study cited above? | Thank you for this question. The published report mentions 1 fascia tear. We added the device related adverse events from the FDA SSED in both |

| | Comment | Response |
|---|---|---|
| | | the detailed tables in the appendix and in the text of the report under KQ2. |
| **Page 18** | The strength of evidence table is a great summary. In the column of "Conclusion", the statement of "statistically and clinically greater improvement" is very clear. However, the statement of "significantly greater improvement" is ambiguous. Does it always mean "significantly greater improvement statistically, but not clinically"? Please clarify. | Yes, it means statistically greater improvement, but not clinically greater improvement. In instances where we could not identify a MCID in the published literature we noted that in the conclusion (in order to differentiate "unknown" from "not clinically meaningful"). We changed all instances of "significantly" to "statistically" for consistency. |
| **Page 19** | The Rompe study-is that a follow-up sub-study with >50% drop out from the original study or a totally different study? | This is a different study from Rompe 1996. This study is Rompe, J. D., et al. (2003). "Shock wave application for chronic plantar fasciitis in running athletes. A prospective, randomized, placebo-controlled trial." Am J Sports Med 31(2): 268-275.<br><br>The 12 month follow-up rates were 72.7% ESWT vs. 82.6% sham |
| **Page 23** | Table on RESWT vs ultrasound for plantar fasciitis. There may be typos in the column of "Conclusion". Should "RESWT vs. sham" be "RESWT vs. ULTRASOUND"? | Yes, thank you for this correction. We made the change in the table. |
| **Page 26** | Rotator cuff tendinopathy for pain. Why the quality ratings of the same two studies (Gerdesmeyer and Hsu) are upgraded from low to moderate overtime? | At long term follow-up, these studies were upgraded 1 – from LOW to MODERATE – for large effect size: the MD between groups on VAS was ≥4.5 points, which is more than 3 times the cut-off for a clinically important difference (of 1.5 points). This amounted to a 71% improvement in the treatment group vs. 8% in the control group. Reasons for downgrading or upgrading are footnoted in the detailed SOE tables at the end of the full report (Section 5) but not in the summary SOE tables included in the Executive Summary. |
| **Page 38** | "commonly utilized"-delete "commonly" | Thank you for your comment. We omitted commonly. |
| **Page 38** | "ESWT has gained significant acceptance.."-again, I would delete this sentence and reference unless you have more direct evidence. | Thank you for your comment. This statement was omitted. |
| **Page 38** | Instead of "goal of promoting healing" I would use "goal of promoting healing by inducing tissue repair and regeneration" | Thank you for your comment. We added this change. |

| | Comment | Response |
|---|---|---|
| **Page 52** | Is plantar fasciitis a tendinopathy? | Thank you for your comment. Plantar fasciitis is not considered a tendinopathy for this report. We corrected the heading and placement. |
| **Page 54-55** | Couldn't these changes just as easily be related to tissue damage caused by the ESWT? | Thank you for this comment. It is our understanding that these changes are seen and thought to be responsible for tissue healing. Whether these changes are mediated as a result of tissue damage caused by ESWT is still unknown to the best of our knowledge. |
| **Page 56** | TENS not covered per prior HTCC coverage decision: www.hca.wa.gov/assets/program/findings_decision_ens_103009[1].pdf | Thank you for your comment. It is included in our report because of the frequency of use. |
| **Page 84** | It would be important to show for each meta-analysis which ones combined higher and lower quality studies. Are there enough studies for any indication to just use high quality studies for the meta-analysis? | We identify the high and low risk of bias studies in all the meta-analyses. Also, we did sensitivity analysis that included only the lowest risk of bias studies when the heterogeneity warranted. |
| **Page 89** | Your clinically important threshold is 1.5-is that a 15% difference out of a 10 point scale, or something else? Our state opioid guideline, and other references, use a 30% improvement in pain and function-how does that compare to the 1.5 threshold you are using. | The % improvement depends on the baseline value. For example, if VAS is 9 at baseline, and 6 at follow-up (a 3 point improvement) that is a 33% improvement. If however, the baseline is 6 and there is a 3 point improvement, this represents a 50% improvement. For pain, 30% change or a 1.5 difference have both been advocated for musculoskeletal pain (Ostelo RW, Deyo RA, Stratford P, et al. Interpreting change scores for pain and functional status in low back pain: towards international consensus regarding minimal important change. Spine (Phila Pa 1976). 2008;33(1):90-4. PMID:<br><br>18165753) and used for prior State HTAs (PRP, spinal injections) and AHRQ HTAs (Noninvasive Treatments for Low Back Pain. Comparative Effectiveness Reviews, No. 169. Investigators: Roger Chou, MD, FACP, Richard Deyo, MD, MPH, Janna Friedly, MD, Andrea Skelly, PhD, MPH, Robin Hashimoto, PhD, Melissa Weimer, DO, MCR, Rochelle Fu, PhD, Tracy Dana, MLS, Paul Kraegel, MSW, Jessica Griffin, MS, Sara Grusing, BA, and Erika Brodt, BS. Pacific Northwest Evidence-based Practice Center Rockville (MD): Agency for Healthcare Research and Quality (US); 2016 Feb.Report No.: 16-EHC004-EF) |

| | Comment | Response |
|---|---|---|
| **Outcomes, Page 90** | On the outcomes, please again look at the original FDA study-it seems that they used more stringent outcomes than I am seeing here in the other reported studies; eg, although most of the composite outcomes for pain are not helpful, the composite of 50% improvement AND VAS </=4 does seem more stringent. The same for two other outcomes: Walking distance without pain, and no/rare use of pain meds (or the opposite, chronic use of pain meds). The Ogden studies may be the only studies (and Were those the studies the FDA relied upon?) using these more stringent outcomes | Thank you for your comment. The outcomes reported in the FDA trial and the Ogden publication were similar. They had 4 criteria: (1) ≥50% improvement of pain (overall) +VAS ≤4, (2) ≥50% improvement of pain on first walking in the morning +VAS ≤4, (3) Self-assessed time one was able to walk with heel pain, (4) no use of prescriptions or over the counter analgesics. In both the FDA report and the journal publication, "composite success" (success on all 4 outcomes) were similarly reported (47% in the ESWT group, and 30% in the sham group, p = .008). In addition, each of the 4 outcomes were reported separately which allowed us to use them in the meta-analysis. It is difficult to interpret composite scores, and in this case, some may question the utility of #4 since over 70% of the patients took medications for pain in another body region other than the heel. |
| | The meta-analyses using proportions rather than mean change don't seem as relevant. What made you decide to focus on that? | Studies assessing continuous variables such as pain report mean differences (differences between changed scores from baseline to follow-up), and/or the proportion of patients who achieve a certain reduction in pain (often 50% or 60% change from baseline.) We report both the proportions and the mean differences in our report. One problem with the mean difference is that it is difficult to interpret even given a MCID cutoff. Additionally, using the MD potentially tempts readers to make inappropriate inferences. For example, if the MCID is 1.5 and the mean difference between treatments is 1.4, clinicians may infer that nobody benefits from the intervention. If the mean difference is 1.6, they may conclude that everyone benefits. Both inferences may be misguided in that they ignore the variation in responses across individuals.<br><br>We chose to focus "responders" who achieve at least a 50% improvement over baseline when the data were available. This is in concert with the Cochrane handbook: "It is also possible for investigators to provide a 'responder' definition to help interpret outcomes (see Chapter 12, Section 12.6.1). It is useful to know the definition that characterizes an individual patient as a "responder" to treatment. Such a responder definition is based upon pre-specified criteria backed by empirically derived evidence supporting the responder definition as a measure of benefit. |

| | Comment | Response |
|---|---|---|
| | | Methods for defining a responder include: (1) a pre-specified change from baseline on one or more scales; (2) a change in score of a certain size or greater (e.g. a 2-point change on an 8-point scale); and (3) a percentage change from baseline."<br><br>Patrick D, Guyatt GH, Acquadro C. Chapter 17: Patient-reported outcomes. In: Higgins JPT, Green S (editors), Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from: www.handbook.cochrane.org. |
| | Can you explain in the results how the proportions could be positive when the change in mean scores are not? | Comparing Figures 5 and 6 where this occurs, there are two explanations: first, though the number of studies in each figure are the same (n=5), they are not all the same studies. Second, one high risk of bias study was a large outlier resulting in a large amount of heterogeneity. Though the point estimate moved in favor of FESWT, the random effects model resulted in a widening of the confidence interval such that the p-value was not statistically significant. When we evaluated the MD in a sensitivity analysis using only the lower risk of bias studies, the difference was statistically significant. |
| **Page 95 and elsewhere** | Unblinded assessment gets you to only moderately low risk of bias? That doesn't make sense-don't you mean moderately high risk of bias? Non-blinded assessment is one of the worst contributors to bias! | This particular study (Radwan 2012) cited on page 95 FESWT was being compared with a surgical procedure (endoscopic partial plantar fascia release); thus it was not possible to blind the patients due to the inherent differences between treatments. Otherwise, this was a well done study and met all but 2 (blind assessment and equal application of co-interventions) of the 8 criteria we use to judge risk of bias. Based on the scheme used by SRI this would make the study only moderately low risk of bias (all RCTs start at low risk of bias thus it was downgraded slightly). Each study is graded independently and criteria are weighted differently. |
| **Pages 97-98** | Figure 14 and Figure 15 are duplicates. Either Figure 14 Figure or 15 is missing. | Thank you for identifying this error. We corrected Fig 14. |
| **Page 98** | The Ibrahim study is an embarrassment-the investigator is unblinded, and the results are too miraculous to be believable-I would delete Fig 16 | The Roles Maudsley outcome score is one frequently used in this literature. It is placed in the "other outcomes measures" category. We agree that a figure is not warranted. We removed the figure but left the narrative. |

| | Comment | Response |
|---|---|---|
| **Page 100** | For lateral epicondylitis-pain with grip would seem to be the most relevant pain outcome, and related to function. Were there any high rate studies with benefit using this outcome? | Thank you for this comment. Grip strength (a measure presumed to be limited by pain) was reported by a few studies, figures 24 and 25. However, the procedure of recording the strength was not always clearly described or there was heterogeneity in the procedure. Nevertheless, we present the data. |
| Page 101 | …again the proportion vs change in mean pain score issue comes up. | See outcomes explanation. |
| Page 141 | "The tendon ruptures occurred in two patients two weeks following FESWT for Achilles tendinopathy", which was 9% in the study (Costa 2005). Table 10. (Page 145) shows that focused ESWT seems to be associated with higher risk of serious adverse events compared to radial ESWT. It would be informative to include ESWT energy level (intensity) information for each study in the table by adding a column. | We have added a column to Table 10 that includes information pertaining to the energy level (intensity) used. |

## Comprehensive Evidence-Based Health Technology Assessment
## Peer Review Form

Thank you for your willingness to read and comment on the Comprehensive Evidence-Based Health Technology Assessment Review for Extracorporeal Shockwave Therapy. Your contribution and time are greatly appreciated.

This form can be filled out electronically on your personal computer. Enter your identification information and comments directly into the shaded areas; use the **TAB** key to move from field to field. Please enter the section, page, and line numbers where relevant. The shaded comment field will expand as you type, allowing for unlimited text. You have been provided comment fields in each section. Should you have more comments than this allows for, please continue with a blank page. Additionally, we are very interested in your evaluation of the ease of use of our Peer Review Form. Please use the last field to enter suggestions for improvement.

When the Peer Review form is complete, save it to your hard drive and return as an e-mail attachment to joe@specri.com

If you have questions or concerns please contact Joe Dettori, PhD at the email above.

**Alfred C. Gellhorn, MD**
Medical Director, Sports Rehabilitation | Rehabilitation Medicine

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**While reviewing these sections please keep the following questions in mind, but please comment on any point:**

## INTRODUCTION

- Overview of topic is adequate?
    - Yes. Though the basic science of ESWT is presented as essentially a series of fortuitous observations, and the mechanism of action of ESWT remains obscure based on the included review. This is potentially important – given the conditions this is used to treat, we want to know if ESWT is effectively anti-inflammatory in effect or if there are true disease modifying properties. The ability of ESWT to fragment calcium is of no real importance in the included pathologic conditions.
- Topic of assessment is important to address?
    - Yes. The included conditions are of high importance, causing high levels of clinical disability among patients, lost work hours, and are highly prevalent. Other conservative and surgical treatment options have relatively low success rates, and these conditions therefore remain frustrating and difficult conditions to treat for both clinicians and patients. There would be a high level of enthusiasm for a noninvasive, safe, effective treatment option for tendinopathy, osteoarthritis and plantar fasciitis.
- Public policy and clinical relevance are well defined?
    - No. Section 1.4 appears to be missing, which may include important public policy relevance

## BACKGROUND

- Content of literature review/background is sufficient?
    - Yes. However, I would add that it is important to discuss the natural history of the presented conditions, which is to say, what would happen in the absence of any intervention. For plantar fasciitis and uncomplicated lateral epicondylitis, the natural history is generally for disease resolution over a period of approximately 1 year from onset. For adhesive capsulitis, the natural history is for full resolution within 12-24 months in almost all cases. On the other hand, rotator cuff tendinopathy tends to be a progressive disease, with 60% of tears progressing by 2 year follow up. Similarly, Achilles and patellar tendinopathy do not tend to show spontaneous resolution. The importance of considering the natural history is that for conservative treatments, if the natural history is for ultimate resolution but clinical morbidity is high (as is the case for plantar fasciitis and lateral epicondylitis) there is an important role for therapies that decrease pain and improve function in the short term. For clinical entities that do not tend to resolve over 12-24 months, it becomes more important to find treatments that are effective in the long term when compared with sham or active controls. In other words, short term benefits are an important consideration for the clinician who is trying to help manage patient symptoms when spontaneous resolution can be expected over a period of months. Short term benefits are less helpful when there is no expectation of spontaneous resolution, and in these cases the long term outcomes are most important to evaluate. Therefore, in the context of the present review, I would place more emphasis on the short term results in lateral epicondylitis and plantar fasciitis; and

more emphasis on the long term results in rotator cuff, patellar, and Achilles tendinopathies, as well as knee osteoarthritis.

The mechanism of action of ESWT is presented better in this section than the introduction. However, it still remains biologically questionable. The studies that are cited suggest that there may be intracellular signals that are generated in response to ESWT, and growth factor expression is changed at the cellular level. For biological plausibility, one wants to feel secure in an epistemological rationale for the body to respond to stresses in a certain way. In other words, one might ask: why would cells be sensitive to these waves of supersonic energy? Is the delivered energy a signal of injury to the body? That is, does ESWT in essence produce a focal new injury that the body responds to by initiating a new healing response? Or is ESWT energy simply producing localized heat, not injury at all? Or, in contrast, does ESWT work by modifying conditions outside the cell, perhaps in organizing collagen fibers in the tendons themselves or disrupting calcifications such as in calcific rotator cuff tendinopathy. It is important to try to understand the mechanism in better detail. As pointed out later, it is unclear where ESWT should be focused, whether at the site of pathology in a tendon, or the site of tenderness. The lack of understanding of the true mechanism of action is the reason that clinicians have not standardized issues of ESWT delivery, such as this. It also seems clear that for some organizations such as the Dutch Orthopedic Association, which recommends ESWT for calcific tendinopathy but not non-calcific tendinopathy, the organization's sense is that mechanism of action is clearly in disruption of the calcified region of the tendon.

## REPORT OBJECTIVES & KEY QUESTIONS

- Aims/objectives clearly address relevant policy and clinical issue?
    - Yes
- Key questions clearly defined and adequate for achieving aims?
    - Yes, these key questions are adequate and important.

## METHODS

- Method for identifying relevant studies is adequate?
    - Yes
- Criteria for the inclusion and exclusion of studies are appropriate?
    - Yes
- Method for Level of Evidence (LoE) rating is appropriate and clearly explained?
    - Yes
- Data abstraction and analysis/review are adequate?
    - Yes

## RESULTS

- Amount of detail presented in the results section appropriate?
    - Yes. The forest plots are excellent and clear.
- Key questions are answered?
    - Plantar fasciitis. There is clearly more evidence for plantar fasciitis than other conditions, and the conclusions are therefore easier to interpret. It is well demonstrated that ESWT (both focused and radial) repeatedly results in decreased pain compared to sham, in multiple methods of describing pain. It is not clear to me that the amount of pain relief is clinically important, however. Mean pain decreases of around 1 to 2 points on a 10-point scale is of questionable clinical importance.
    - I would also highlight the studies that compare ESWT to steroid injection, which is a commonly used procedure for plantar fasciitis in clinical practice. The presented study with

lower risk of bias showed a significantly higher decrease in pain when compared with ESWT.
    - Lateral epicondylitis. There is conflicting evidence of effectiveness, depending on how pain is measured. This is concerning to me. In clinical practice, clinical success usually is qualified by pain improvement regardless of how it is measured. I agree that the strength of evidence is highly limited
    - Rotator cuff tendinopathy. Despite study limitations, the best quality evidence shows that functional improvements exist in tandem with pain improvements. The studies that show long term continued benefits are of particular interest and importance as discussed above for this condition, since natural history tends to be of worsening rather than improvement. Similar to my note above regarding comparison with steroid injection, these results should be highlighted, since steroid injection is so commonly used in clinical practice. The results comparing ESWT with needling alone or with steroid injection show a smaller benefit for ESWT.
    - Adhesive capsulitis. Radial ESWT appears to be clinically superior to sham while Focused ESWT is not. Why the discrepancy? Neither are compared to the most common clinical interventions, namely physical therapy and glenohumeral joint steroid injection.
    - Achilles and patellar tendinopathy: Agree the evidence is too limited to draw any conclusion
    - Knee osteoarthritis. Data are too limited to draw conclusions.
- Figures, tables and appendices clear and easy to read?
    - Yes. The forest plots are excellent and clear. The tables are excellent.
- Implications of the major findings clearly stated?
    - Not entirely. Partly this is due to the absence of any cost data at all. In evaluating the body of evidence presented, I see a technology that has clear short term benefit in some conditions, though importantly the benefits are small in magnitude. The technology appears safe, and generally well tolerated, though the need to use local anesthesia in some studies suggests that there is significant procedural pain. Given these relatively modest benefits, it is important to know how much this technology costs. This is especially true because studies that compare this with an office based steroid injection (low cost) generally show the benefits seem to favor the steroid injection. So one might ask: if there is an equally or more effective treatment that is commonly performed and cheap, what is the role for ESWT? On the other hand, if costs of ESWT are quite low, this seems a reasonable treatment to offer patients, given the favorable safety profile.
- Have gaps in the literature been dealt with adequately?
    - Yes.
- Recommendations address limitations of literature?
    - Yes. The grading of evidence is clearly presented and appropriate.

## CONCLUSIONS

- Are the conclusions reached valid?
    - Yes. Please see my comment above regarding costs, though.

## OVERALL PRESENTATION and RELEVANCY

- Is the review well structured and organized?
    - Yes
- Are the main points clearly presented?
    - Yes
- Is it relevant to clinical medicine?
    - Yes. High relevance.
- Is it important for public policy or public health?
    - Yes, high importance.

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**While reviewing these sections please keep the following questions in mind, but please comment on any point:**

## INTRODUCTION

- Overview of topic is adequate? The overview of the topic was adequate and explained the topic very well.
- Topic of assessment is important to address? The topic of assessment is important to address because it can provide a less invasive modality of therapy for numerous conditions.
- Public policy and clinical relevance are well defined? Both public policy and clinical relevance were well defined.

## BACKGROUND

- Content of literature review/background is sufficient? The content of the literature was very thorough and complete.

## REPORT OBJECTIVES & KEY QUESTIONS

- Aims/objectives clearly address relevant policy and clinical issue? The aims and objectives clearly addressed the relevant policy and clinical issues.
- Key questions clearly defined and adequate for achieving aims? The key questions were clearly defined and adequate for achieving aims.

## METHODS

- Method for identifying relevant studies is adequate? The methods used to identify relevant studies were adequate.
- Criteria for the inclusion and exclusion of studies are appropriate? The criteria used for inclusion and exclusion of studies were appropriate.
- Method for Level of Evidence (LoE) rating is appropriate and clearly explained? The method for Level of Evidence rating is appropriate and clearly explained in the report.
- Data abstraction and analysis/review are adequate? The data abstraction and analysis is adequate.

## RESULTS

- Amount of detail presented in the results section appropriate? The detail in the results section was appropriate and complete.
- Key questions are answered? Key questions were answered fully.
- Figures, tables and appendices clear and easy to read? The figures, tables, and appendices are clear and easy to read.
- Implications of the major findings clearly stated? This is the one area I was a little unclear on, the results and how those related to any final recommendation.
- Have gaps in the literature been dealt with adequately? Yes
- Recommendations address limitations of literature? Yes

## CONCLUSIONS

- Are the conclusions reached valid? Yes

## OVERALL PRESENTATION and RELEVANCY

- Is the review well structured and organized? The review is very well structured and organized.
- Are the main points clearly presented? The main points are clearly presented.
- Is it relevant to clinical medicine? The topic is relevant to clinical medicine.

Is it important for public policy or public health? The topic is important and should be considered as an alternative to more invasive procedures.