Health Technology Assessment

Electrical Neural Stimulation

Public Comments and Responses

October 8, 2009

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SPECTRUM RESEARCH RESPONSE TO PUBLIC COMMENTS

Spectrum is an independent vendor contracted to produce evidence assessment reports for WA HTA program. For transparency, all comments received during the comments process are included. However, comments related to program decisions, process, or other matters not pertaining to the report are acknowledged through inclusion, but are not within the scope of response for report accuracy and completeness.

1. Scott Strassels, PharmD PhD, Assistant Professor, University of Texas at Austin

Comment on decision to examine ENS, SRI response
Information on the methods and rational for selection of technologies for assessment can be found at the program website: http://www.hta.hca.wa.gov/

Comment on including references in Introduction, SRI response
Text expanded and citations added.

Comment on including more about acute pain in Introduction, SRI response

Text changed to encompass pain as a whole. More detail on chronic and acute pain is presented in the Background section.

Comment on including other forms of pain treatment, page 7, SRI response
Suggested therapies added.

Comment on chronic/acute mistypes, page 8, SRI Response

Edited text. Labor pain was not included in the review of acute pain, but evaluated separately in another review; this is why it is not included under the acute pain Cochrane Review.

Comment on definitions of pain acuity and chronicity, page 22, SRI response
The text has been edited to read:

Pain is described by the International Association of the Study of Pain (IASP) as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" [1]. In other words, pain is the symptom felt when inflammation or other changes to the nervous system dues to illness or injury are transmitted to the brain, producing a physical sensation [2]. Typically, the inflammation subsides or the wound heals, the pain

lessens, and eventually goes away. In some cases, however, pain can persist for longer than expected.

Acuity and chronicity of pain are based on how long pain is expected to persist, and whether it lasts longer than expected. Types of acute pain, for example, include pre- and post-operative pain, post-traumatic acute pain, tinnitus, dental procedures and labor pain. Conditions that can lead to chronic pain are arthritis, low back pain, and other musculoskeletal problems.

Comment regarding statement considered an opinion, page 23, SRI response
This sentence was removed from the text.
Comment on basis of LoE and SoE, page 8, SRI response
Yes, SRI's LoE and SoE are based on published approaches to critical appraisal of the literature including those from the Oxford Centre for Evidence-based Medicine, precepts outlined by the Grades of Recommendation Assessment, Development and Evaluation (GRADE) Working Group, and recommendations made by the Agency for Healthcare Research and Quality (AHRQ). SRI's system also takes into account features of methodological quality and important sources of bias and combines epidemiologic principles with characteristics of study design.

There is no universally accepted, standardized approach to critical appraisal of economic evaluation studies. The criteria described in the Quality of Health Economic Studies (QHES) tool[3] provided a basis for the critical appraisal of included economic studies and was augmented with the application of epidemiologic appraisal precepts (see Appendix). The QHES employs widely accepted criteria for appraisal, such as choice and quality of cost and outcomes measures, transparency of model and presentation, use of incremental analysis, uncertainty analysis, and discussion of limitations and funding source and was primarily used to facilitate description of primary strengths and limitations of the studies. In addition to assessment of criteria in the QHES, other factors are important in critical appraisal of studies from an epidemiologic perspective to assist in evaluation of generalizability and potential sources of study bias.

Assessment of the overall strength of evidence for formal economic analyses does not appear to be documented in the literature. For the purposes of this HTA, overall strength was determined by:

- Quality of the individual studies: Where the majority of quality indicators described in the QHES met and were the methods related to patient/claim

selection, patient population considerations and other factors listed above consistent with a high quality design?

- Number of formal analyses (3 or more)
- Consistency of findings and conclusions from analyses across studies.

Comment on VAS, page 42, SRI response
Changed the text to reflect that the VAS was the most common tool used in the included studies/reviews.

Comment on pethidine, page 51, SRI response

It has been noted that pethidine is the British Pharmacopeia name for meperidine (Demerol).

2. Nicole Glazer, PhD MPH, University of Washington

Comment on unclear wording, page 8, SRI response
The text was edited to read "An overall Strength of Evidence (SoE) takes into account the LoE, along with the quantity of studies and consistency of the findings. The SoE can be interpreted to mean how confident one should be that these estimates will remain stable as further research becomes available."

Comment on assessment checklist, page 36, SRI response
Agreed; this has been changed.

Comment on lead-in sentence to safety results, page 80, SRI response
Text has been added.

Comment on reporting of adverse effects, SRI response
It is possible that the low rate of adverse effects could be related to the quality of data collection. One would not expect, however, to have many adverse events given the non-invasiveness of the treatment. Some of the studies explicitly stated whether they collected and/or observed adverse effects, but it was not clear in every instance.

Comment on future research, SRI response

For Key Question 1, the following was added to the lead-in to the summaries on page 85:

> Further research is warranted to evaluate the efficacy and effectiveness of TENS for the treatment of acute and chronic pain in populations that are more similar with respect to the conditions, treatment regimens, study designs, and outcomes assessed.

For Key Question 2, the following was added to the lead-in to the summaries on page 89:

> The limited availability of evidence on the safety of TENS, regardless of how safe it is believed to be, suggests that future studies should collect this information and report on the occurrence of adverse effects.

Comment on conclusions and implications, SRI response
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Comment on prevalence of TENS use, SRI response
There is no good data on utilization of TENS. One estimate now included in text is:

> TENS is a commonly prescribed treatment for both acute and chronic pain. Estimates of use are limited, but there were 275,000 reported TENS prescriptions in 199

3. Technomics Research, LLC, representing Empi, Inc.

Comments on conclusions of the report and the methodology used, SRI response
This comment comes from Technomics Research, LLC, contracted by Empi (a leading manufacturer or TENS devices) to perform research on the effectiveness and cost-effectiveness of ENS for treating chronic musculoskeletal pain. A systematic review (Johnson and Martinson 2007) of ENS for treating chronic musculoskeletal pain forms the basis of their argument; this research was funded by Empi,

Our main reason for excluding the Johnson and Martin meta-analysis was because it included percutaneous electrical nerve stimulation (PENS; 6 of 38), a technology that we

excluded from this assessment. It seems that the positive effect reported in this review was largely influenced by inclusion of the PENS studies. The authors even acknowledge this in their conclusions, stating that "in the meta-regression, PENS was significantly more effective at relieving pain than was TENS."

Second, the authors of the review specifically state that they used broad inclusion criteria. The use of broad criteria allows for heterogeneity between studies in characteristics such as number of applications, duration of each session, total duration of treatment, electrode placement.

Of those comparison for which there were positive effects for TENS (high-frequency, low-frequency, acupuncture-like; n=17 comparisons in 13 study populations), 6 comparisons (6 studies) were given Jadad scores <=3). And these comparisons included TENS given in many different treatment regimens (number of applications, durations, etc.). Six of the positive studies were of osteoarthritis, for which we agree there is some evidence of a positive effect.

For the study receiving the greatest weight of 10.55 (Jarzem et al.), the reviewers do not indicate % change in pain due to each treatment, so it is not clear what was used in the meta-analysis. In addition, there were two papers in the same issue of J. Musculoskeletal Pain by this lead author (Jarzem). Only one of these articles, however, was included – the one reporting positive results when looking at short-term control (single application, frequency not specified) of back pain in a crossover study of 50 patients. The second study, which was not included in the review, looked at low back pain patients who received daily applications and reported no difference in effect between TENS and sham after one month of treatment and three months of follow-up. On the contrary, the latter study is included in the Khadilkar Cochrane Review, but the former was excluded due to insufficient statistical data.

Other methodological issues to consider are: a) for 2 of the positive studies, the reviewers estimated the sample sizes for each comparison group; b) one study included chronic pain <3 mos. and for four studies duration is unknown or not indicated (for 2 of these, they were referrals from a chronic pain center); c) studies varied in whether patients were allowed concurrent therapies or withheld treatments.

Lastly, although statistical methods are available to deal with heterogeneous data when performing meta-analyses, this does not mean that they are always appropriate. The chi-squared test has low power in meta-analysis when studies have small sample size or are few in number, as is the case here. This means that while a statistically significant result may indicate a problem with heterogeneity, a non-significant result must not be taken as evidence of no heterogeneity[4]. In addition, statistical heterogeneity is only one consideration for pooling. Clinical and methodological heterogeneity, which is prevalent across studies of TENS,

must also be considered. In circumstances where clinical and methodological diversity is considerable, combining studies can lead to highly misleading conclusions. In cases like this, it is often more appropriate to present the results in a qualitative manner and to only combine studies for some comparisons or outcomes[4, 5].

With respect to cost-effectiveness, we only included studies from peer- reviewed journals. The manuscript presented by Empi can be considered, once it is published in a peer-reviewed journal, when the HTA is updated at a future date.

4. Agency comments

Comment on addressing exclusion of implantable technologies, page 7, SRI response

Changed wording from ENS to TENS to be more specific. Further description of included/excluded technologies presented in the Methods.

Comment on placebo vs. sham, page 16, SRI response

As described on page 24 under the "Comparator" section, placebo in this report refers to sham treatment.

Comment on inclusion of a sham group, page 16, SRI response

Yes, this study had a sham group. Comparisons involving the sham (placebo) group are described in detail in the Results section (page 61), but are not highlighted in the SoE table.

Comment on noting Medicare/ National Coverage Decision, page 28, SRI response

Text added.

Comment on replacing text in table, page 30, SRI response

Replaced text as suggested.

Comment on inclusion of a low quality review, page 10, SRI response

If the paper meets the *a priori* inclusion criteria (for device, condition, etc.) as well as the general criterion for study design as stated in the methods, it is included and critically appraised. The methodological quality evaluation and critical appraisal provides context for the reader to consider when reviewing the results.

Comment on separating chronic conditions based on SoE, page 16, SRI response

We agree and have broken these out separately.

Comment with respect to "positive effects", page 16, SRI response

Since there was insufficient extractable data to do quantitative analyses, the authors of the review presented the results qualitatively and descriptively.

Studies included used varying outcome measures to assess positive effect: VAS, categorical scales for pain intensity and relief, end of treatment global rating.

Comment on interpretation of SMDs and clinical importance, SRI response
A detailed description of the meaning of the standardized mean difference (SMD) is presented on page 41; it is the difference between the means of the treatment groups divided by the pooled standard deviation of the measurements. This transformation leads to a dimensionless outcome that can be compared across studies where outcome is measured on different scales.

The Methods section was expanded to include the following information about SMDs and clinical importance:

Standardized mean difference
The values reported in either of these scales are used not only to quantify pain intensity and pain relief within patients, but also to compare outcomes between patients. One way to do this is by calculating the absolute benefit, or the improvement in the treatment group less the improvement in the control (comparison) group. The standardized mean difference, referred to as *d*[6] is useful for comparing treatment groups across studies as in meta-analyses. The standardized mean difference is calculated as the difference in means between treatment groups, divided by the pooled standard deviation of the measurements.[7] By this transformation, the outcome becomes dimensionless and the scales become uniform (e.g., for the same degree of pain, values measured on a 100-mm analog scale would be expected to be 20 times larger than values measured on a 5-point ranking scale) but the standard deviation would also be expected to be 20 times larger. The standardized mean difference is useful for comparing studies that measure the same outcomes, but use different methods to do it.

Similar to the standardized mean difference is the weighted mean difference, which is also used in meta-analyses to compare treatment groups across studies. The mean differences in outcome between the groups being studied are weighted to account for different sample sizes and differing precision between studies (large studies with greater precision are assigned higher weights). Unlike the standardized mean difference, the weighted mean difference is an absolute figure that takes on the units of the original outcome measure.

The Cochrane reviews presented in this report most commonly report the standardized mean difference to compare treatment groups. Interpretation is not necessarily intuitive, but the standardized mean difference measures the size of the treatment effect in terms of the standard deviation. For example, an estimate of 0.5 indicates that the treatment changed the mean by half of a standard deviation; similarly, an estimate of 1.0 indicates that the size of the treatment effect is equal to one whole standard deviation.

Clinical importance

> Statistical significance (in differences between treatment groups) is the first criterion that has to be met to consider an outcome clinically important. Although outcomes might be statistically different between two treatment groups, however, this does not necessarily translate to clinically important differences in outcome.
>
> Clinical importance is defined in the literature in many difference ways – it depends not only on the conditions and outcomes being assessed, but also the opinions of individual investigators or clinical panels. The American College of Rheumatology defines clinical improvement in rheumatoid arthritis as ≥20% improvement in tender or swollen joints in combination with ≥20% improvement in 3 of 5 other outcomes (patient pain, patient global assessment, physician global assessment, patient self-assessed disability, acute-phase reactant).[8] A 15% improvement is recommended by the Philadelphia Panel as a minimally important change for back pain.[9]. Other researchers use 50% relief as the outcome to derive relative efficacy of analgesics McQuay et al.[10], and still others recommend a cut-off of 30% relief because this is the level of relief below which it has been observed that patients need to remedicate.[11]
>
> When interpreting standardized mean deviations in terms of clinical importance, there are some rules of thumb. The most widely used is that by Cohen[6], even though it was originally intended for the social sciences. In this interpretation, an SMD value of 0.2 represents a small effect, 0.5 a moderate effect, and 0.8 a large effect. It is important to note, however, that this interpretation reflects only the magnitude of the effect size. Interpretation of both the statistical significance and clinical importance should be taken in context, with consideration for patient and physician beliefs important outcomes.

Using this rationale, we determined clinical importance for statistically significant comparisons in reviews of moderate SoE. The chronic pain and osteoarthritis of the knee reviews met these criteria, however, the chronic pain review did not present quantitative data. For osteoarthritis of the knee, the following text was added:

> Using the criterion of 0.80 to indicate a large effect, differences in pain relief when comparing TENS/ALTENS to placebo and high rate TENS to placebo could be considered clinically important (SMDs -0.79 and -1.12, respectively).

1. International Association for the Study of Pain (IASP) website. Available from:. http://www.iasp-pain.org/AM/Template.cfm?Section=Home&Template=/CM/HTMLDisplay.cfm&ContentID=3058#Pain.

2. *Health, United States, 2006*: Centers for Disease Control, National Center for Health Statistics;2006.

3. Ofman JJ, Sullivan SD, Neumann PJ, al. e. Examining the value and quality of health economic analyses: implications of utilizing the QHES. *J Manag Care Pharm.* Jan-Feb 2003(9):53-61.

4. Higgins JPT, Green S. *Cochrane Handbook for Systematic Reviews of Interventions*. Version 5.0.1 [updated September 2008] ed: The Cochrane Collaboration; 2008.
5. Ades AE, Lu G, Higgins JP. The interpretation of random-effects meta-analysis in decision models. *Med Decis Making.* Nov-Dec 2005;25(6):646-654.
6. Cohen J, ed. *Statistical power analysis for the behavioral sciences, 2nd ed*. Hillside, NJ: Lawrence Erlbaur Associates; 1988.
7. Higgins J, Green S, Cochrane Collaboration. *Cochrane handbook for systematic reviews of interventions*. Chichester, West Sussex ; Hoboken NJ: John Wiley & Sons; 2008.
8. Felson DT, Anderson JJ, Boers M, et al. American College of Rheumatology. Preliminary definition of improvement in rheumatoid arthritis. *Arthritis Rheum.* Jun 1995;38(6):727-735.
9. Philadelphia Panel evidence-based clinical practice guidelines on selected rehabilitation interventions for knee pain. *Phys Ther.* Oct 2001;81(10):1675-1700.
10. McQuay HJ, Barden J, Moore RA. Clinically important changes-what's important and whose change is it anyway? *J Pain Symptom Manage.* May 2003;25(5):395-396.
11. Farrar JT, Berlin JA, Strom BL. Clinically important changes in acute pain outcome measures: a validation study. *J Pain Symptom Manage.* May 2003;25(5):406-411.