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Dear Dr. Uphoff Kato:

The undersigned medical specialty societies, comprising physicians who utilize and/or perform interventional procedures to accurately diagnose and treat patients suffering from pain, would like to take this opportunity to comment on the draft systematic review *Interventional Treatments for Acute and Chronic Pain: Systematic Review.* The medical specialty societies who participated in this review and critique share a common goal with the AHRQ: commitment to identifying pain management therapies that provide value to the patient and society through measurable improvements in pain and physical functioning with no or minimal adverse events.

We are impressed by the quality of the systematic review and wish to commend the authors on this significant undertaking. Our societies support most of the conclusions drawn relative to the evidence regarding included procedures. We do have several suggestions to offer, and trust that these aspects of the report will be revisited to ensure that the best available evidence is addressed scientifically to provide an accurate assessment of the procedures reviewed.

METHODOLOGY

Implementing an evidence base restriction to randomized controlled trials (RCTs) excludes high quality observational studies of clinical effectiveness, which removes important information and context from a synthesis of the literature. When an adequate number of randomized controlled trials with consistent findings are available, it is reasonable to implement this restriction. However, when RCTs are limited either in quantity or consistency, it is important to ascertain whether high quality, prospective, observational studies are available to provide additional evidence about that procedure. For many of the interventional procedures addressed in this review, and in particular for kyphoplasty, we recognize that this is the case and prospective single-arm studies (*e.g.* cohort studies) provide important data regarding the procedures' effectiveness.

VERTEBRAL AUGMENTATION PROCEDURES FOR VERTEBRAL COMPRESSION FRACTURES

In this analysis, vertebroplasty had high applicability to the Medicare population given the age of the patient populations in most of the trials reviewed. But these findings should not be generalized to other vertebral augmentation procedures since there have been statistically significant differences in morbidity and mortality outcomes [1-6] as well as pain relief, restoration of vertebral anatomy, and quality of life [7,8].

While there have been some studies showing an equivocal benefit of vertebroplasty [9-11], there are others, including sham trials, showing statistically significant benefits in pain and function when compared to sham or non-surgical management [12-16]. While sham trials have been performed for vertebroplasty, they have not been performed for kyphoplasty or other vertebral augmentation procedures. One of the reasons contributing to this lack of comparison to sham is the now-known morbidity and mortality benefit that vertebral augmentation provides over non-surgical management. The debate regarding the use of placebo centers on the Declaration of Helsinki, which reinforces the longstanding prohibition against offering placebo instead of effective therapy. This declaration leaves no doubt that if a beneficial treatment for a condition has already been recognized, it is unethical to offer placebo in place of such treatment to anyone in a study of the same condition. Because of this, placebo-controlled trials for osteoporotic medications are, for the most part, not conducted in the United States anymore. The mortality reduction for antiresorptive osteoporosis medications is 11% compared to 24% for vertebroplasty and 55% for kyphoplasty [2].

The multiple types of vertebral augmentation procedures performed on Medicare patients is important to keep in mind considering 'real world' applicability to patient care. The 2018 EVOLVE trial, the largest post-market on-label kyphoplasty trial completed to date, included multiple primary and secondary endpoints to measure many factors in addition to pain and function [17]. This trial used existing Medicare local coverage determination criteria as the inclusion and exclusion criteria and found a statistically significant difference in all primary endpoints and secondary endpoints at all time points through the entire study. Published in 2020, the world's largest vertebral augmentation registry data set included patient-reported outcomes on all aspects of vertebral augmentation for both vertebroplasty and kyphoplasty procedures. A total of 1096 patients were included, with a complete data set on 732 patients. The median pain score decreased from 9 to 0, and the Roland Morris Disability measurement decreased from 21 to 7 [18].

For kyphoplasty and other vertebral augmentation procedures, a review of the best available evidence, provided by large, high-quality observational studies and registries, provides important data on the outcomes of the procedure [7,8,9,12,13,15,17,18]. We strongly suggest that the authors include these data on the effectiveness of these procedures in the treatment of acute pain, improvement of function, and reduction of mortality.

Primary outcomes for the analysis include pain scores and functionality. Mortality is not included as a primary outcome; however, for the Medicare population and estimation of the overall value and benefit of vertebroplasty and vertebral augmentation, this variable should be of utmost importance. In addition to the mortality data referenced above [1 – 6] that consistently show significantly increased mortality in patients who are treated with non-surgical management rather than vertebral augmentation, Hirsch *et al.* calculated the number needed to treat (NNT) to save a life at one and five years. The one-year NNT is 15 patients and the five-year NNT is 12 patients [19]. There are very few procedures or surgeries that save one life for every 12 to 15 patients treated. An earlier meta-analysis found that patients' life expectancy was increased between 2.2 and 7.3 years after vertebral augmentation compared to their counterparts treated with nonsurgical management [3]. Given the importance of these data to the well-being and survival of patients, this should be considered in addition to the data on pain, function, and quality of life improvements.

ALTERNATIVES TO CONVENTIONAL RADIOFREQUENCY ABLATION

Sacroiliac Pain
There appear to be several errors in this section:

- On page 27, crossover numbers for the two studies are juxtaposed.
  - Patel (90): 94% crossover in the sham group
  - Cohen (89): 64% crossover in the sham group
- In Table 4, under diagnostic testing, the description of Patel *et al.* should include "lateral branch block and L5 dorsal ramus block (dual, ≥75% relief)", not "sacroiliac joint and L5 dorsal ramus block (single, ≥75% relief)".
- Cohen (89) did report 6-month data that can be included: dichotomous successful outcome was 57% versus 0%, and mean ODI reduction was 39%.

OCCIPITAL NERVE STIMULATION FOR HEADACHE
Please consider reviewing/including the following references:

1. Dodick DW, Silberstein SD, Reed KL, et al. Safety and efficacy of peripheral nerve stimulation of the occipital nerves for the management of chronic migraine: Long-term results from a randomized, multicenter, double-blinded, controlled study. Cephalalgia 2015;35(4):344–58.
2. Schwedt TJ. Occipital nerve stimulation for chronic migraine--interpreting the ONSTIM feasibility trial. Cephalalgia 2011; 31:262-263.
3. Moisset X, Pereira B, de Andrade DC, Fontaine D, Lantéri-Minet M, Mawet J. Neuromodulation techniques for acute and preventive migraine treatment: a systematic review and meta-analysis of randomized controlled trials. The Journal of Headache and Pain 2020; 21(1): 1-14.

The undersigned societies appreciate the opportunity to provide these comments. If you have any questions or wish to discuss any of our suggestions, please contact Belinda Duszynski, Senior Director of Policy and Practice at the Spine Intervention Society, at bduszynski@SpineIntervention.org.

Sincerely,

American Academy of Pain Medicine
American Academy of Physical Medicine and Rehabilitation
American College of Radiology
American Society of Anesthesiologists
American Society of Neuroradiology
American Society of Regional Anesthesia and Pain Medicine
American Society of Spine Radiology
North American Neuromodulation Society
North American Spine Society
Society of Interventional Radiology
Spine Intervention Society

References

1. Hinde K, Maingard J, Hirsch JA, Phan K, Asadi H, Chandra RV. Mortality outcomes of vertebral augmentation (vertebroplasty and/or balloon kyphoplasty) for osteoporotic vertebral compression fractures: a systematic review and meta-analysis. Radiology 2020;295(1):96-103.
2. Ong KL, Beall DP, Frohbergh M, Lau E, Hirsch JA. Were VCF patients at higher risk of mortality following the 2009 publication of the vertebroplasty "sham" trials? Osteoporosis International 2018;29(2):375-383.
3. Edidin AA, Ong KL, Lau E, Kurtz SM Mortality risk for operated and nonoperated vertebral fracture patients in the medicare population. Journal of bone and mineral research 2011;26 (7):1617-26.
4. Lange A, Kasperk C, Alvares L, Sauermann S, Braun S. Survival and cost comparison of kyphoplasty and percutaneous vertebroplasty using German claims data. Spine 2014;39(4):318-26.
5. Edidin AA, Ong KL, Lau E, Kurtz SM. Morbidity and mortality after vertebral fractures: comparison of vertebral augmentation and nonoperative management in the medicare population. Spine 2015;40(15):1228-41.
6. Chen AT, Cohen DB, Skolasky RL. Impact of nonoperative treatment, vertebroplasty, and kyphoplasty on survival and morbidity after vertebral compression fracture in the Medicare population. J Bone Joint Surg Am 2013;95(19):1729-36.
7. Wardlaw D, Cummings SR, Van Meirhaeghe J, Bastian L, Tillman JB, Ranstam J, Eastell R, Shabe P, Talmadge K, Boonen S. Efficacy and safety of balloon kyphoplasty compared with non-surgical care for vertebral compression fracture (FREE): a randomized controlled trial. Lancet 2009;373(9668):1016-24.
8. Papanastassiou ID, Phillips FM, Meirhaeghe JV, et al. Comparing effects of kyphoplasty, vertebroplasty, and nonsurgical management in a systematic review of randomized and non-randomized controlled studies. Eur Spine J 2012;21(9):1826-43.
9. Beall DP, Lorio MP, Yun M, Runa MJ, Ong KL, Warner CB. Review of vertebral augmentation: an updated meta-analysis of the effectiveness. Int J Spine Surg 2018;12(3):295-321.
10. Kallmes DF, Comstock BA, Heagerty PJ, Turner JA, Wilson DJ, Diamond TH, Edwards R, Gray LA, Stout L, Owen S, Hollingworth W, Ghdoke B, Annesley-Williams DJ, Ralston SH, Jarvik JG. A randomized trial of vertebroplasty for osteoporotic spinal fractures. N Engl J Med 2009; 361:569-579.
11. Buchbinder R, Osborne RH, Ebeling PR, Wark JD, Mitchell P, Wriedt C, Graves S, Staples MP, Murphy B. A randomized trial of vertebroplasty for painful osteoporotic vertebral fractures. N Engl J Med 2009;361:557-568.
12. Clark, W, Bird P, Gonski P, Diamond TH, Smerdely P, McNeil HP, Schlapho G, Bryant C, Barnes E, Gebski. Safety and efficacy of vertebroplasty for acute painful osteoporotic fractures (VAPOUR): a multicentre, randomized, double-blind, placebo-controlled trial. Lancet 2016;388(10052):1408-1416.
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14. Klazen CA, Lohle PN, de Vries J, et al. Vertebroplasty versus conservative treatment in acute osteoporotic vertebral compression fractures (Vertos II): an open-label randomized trial. Lancet 2010;376(9746):1085-1092.
15. Lohle P. The results of Vertos 5: a sham trial comparing vertebroplasty versus sham in the treatment of chronic vertebral compression fractures. European Percutaneous Spine Intervention and Vertebroplasty Workshop. Paris, France. February 1, 2019.

16. Wang H-K, Lu K, Liang C-L, et al. Comparing clinical outcomes following percutaneous vertebroplasty with conservative therapy for acute osteoporotic vertebral compression fractures. Pain Med 2010;11(11):1659-1665.
17. Beall DP, Chambers MF, Thomas SM, Amburgy J, Webb JR, Goodman B, Datta D, Easton R, Linville D, Talati S, Tillman JR. Prospective and multicenter evaluation of outcomes for quality of life and activities of daily living for balloon kyphoplasty in the treatment of vertebral compression fractures: the EVOLVE trial. Neurosurgery 2019 Jan 1;84(1):169-178.
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