Comparative Effectiveness Review
Number 247

Interventional Treatments for Acute and Chronic Pain: Systematic Review

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None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report.

The information in this report is intended to help healthcare decision makers—patients and clinicians, health system leaders, and policymakers, among others—make well-informed decisions and thereby improve the quality of healthcare services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information, i.e., in the context of available resources and circumstances presented by individual patients.

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of healthcare in the United States.

The Centers for Medicare & Medicaid Services requested this report from the EPC Program at AHRQ. AHRQ assigned this report to the following EPC: Pacific Northwest Evidence-based Practice Center (Contract Number: 75Q80120D00006).

The reports and assessments provide organizations with comprehensive, evidence-based information on common medical conditions and new healthcare technologies and strategies. They also identify research gaps in the selected scientific area, identify methodological and scientific weaknesses, suggest research needs, and move the field forward through an unbiased, evidence-based assessment of the available literature. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

To bring the broadest range of experts into the development of evidence reports and health technology assessments, AHRQ encourages the EPCs to form partnerships and enter into collaborations with other medical and research organizations. The EPCs work with these partner organizations to ensure that the evidence reports and technology assessments they produce will become building blocks for healthcare quality improvement projects throughout the Nation. The reports undergo peer review and public comment prior to their release as a final report.

AHRQ expects that the EPC evidence reports and technology assessments, when appropriate, will inform individual health plans, providers, and purchasers as well as the healthcare system as a whole by providing important information to help improve healthcare quality.

If you have comments on this evidence report, they may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 5600 Fishers Lane, Rockville, MD 20857, or by email to epc@ahrq.hhs.gov.

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Technical Expert Panel

In designing the study questions and methodology at the outset of this report, the EPC consulted several technical and content experts. Broad expertise and perspectives were sought. Divergent and conflicted opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore, in the end, study questions, design, methodologic approaches, and/or conclusions do not necessarily represent the views of individual technical and content experts.

Technical Experts must disclose any financial conflicts of interest greater than $5,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

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Prior to publication of the final evidence report, EPCs sought input from independent Peer Reviewers without financial conflicts of interest. However, the conclusions and synthesis of the scientific literature presented in this report do not necessarily represent the views of individual reviewers.

Peer Reviewers must disclose any financial conflicts of interest greater than $5,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential nonfinancial conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential nonfinancial conflicts of interest identified.

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Interventional Treatments for Acute and Chronic Pain: Systematic Review

Structured Abstract

Objective. To evaluate the benefits and harms of selected interventional procedures for acute and chronic pain that are not currently covered by the Centers for Medicare & Medicaid Services (CMS) but are relevant for and have potential utility for use in the Medicare population, or that are covered by CMS but for which there is important uncertainty or controversy regarding use.

Data sources. Electronic databases (Ovid® MEDLINE®, PsycINFO®, the Cochrane Central Register of Controlled Trials, and the Cochrane Database of Systematic Reviews) to April 12, 2021, reference lists, and submissions in response to a Federal Register notice.

Review methods. Using predefined criteria and dual review, we selected randomized controlled trials (RCTs) for 10 interventional procedures and conditions that evaluated pain, function, health status, quality of life, medication use, and harms. Random effects meta-analysis was conducted for vertebral compression fracture; otherwise, outcomes were synthesized qualitatively. Effects were classified as small, moderate, or large using previously defined criteria.

Results. Thirty-seven randomized trials (in 48 publications) were included. Vertebroplasty (13 trials) is probably more effective at reducing pain and improving function in older (>65 years of age) patients, but benefits are small (less than 1 point on a 10-point pain scale). Benefits appear smaller (but still present) in sham-controlled (5 trials) compared with usual care controlled trials (8 trials) and larger in trials of patients with more acute symptoms; however, testing for subgroup effects was limited by imprecision. Vertebroplasty is probably not associated with increased risk of incident vertebral fracture (10 trials). Kyphoplasty (2 trials) is probably more effective than usual care for pain and function in older patients with vertebral compression fracture at up to 1 month (moderate to large benefits) and may be more effective at >1 month to ≥1 year (small to moderate benefits) but has not been compared against sham therapy. Evidence on kyphoplasty and risk of incident fracture was conflicting. In younger (below age for Medicare eligibility) populations, cooled radiofrequency denervation for sacroiliac pain (2 trials) is probably more effective for pain and function versus sham at 1 and 3 months (moderate to large benefits). Cooled radiofrequency for presumed facet joint pain may be similarly effective versus conventional radiofrequency, and piriformis injection with corticosteroid for piriformis syndrome may be more effective than sham injection for pain. For the other interventional procedures and conditions addressed, evidence was too limited to determine benefits and harms.

Conclusions. Vertebroplasty is probably effective at reducing pain and improving function in older patients with vertebral compression fractures; benefits are small but similar to other therapies recommended for pain. Evidence was too limited to separate effects of control type and symptom acuity on effectiveness of vertebroplasty. Kyphoplasty has not been compared against sham but is probably more effective than usual care for vertebral compression fractures in older patients. In younger populations, cooled radiofrequency denervation is probably more effective

than sham for sacroiliac pain. Research is needed to determine the benefits and harms of the other interventional procedures and conditions addressed in this review.

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Evidence Summary

Main Points

- Vertebroplasty is probably more effective than sham or usual care for vertebral compression fractures for reducing pain and improving function in older (Medicare-eligible) populations, but benefits are small. Benefits are smaller in sham compared with usual care controlled trials and larger in trials of patients with more acute symptoms.
- Kyphoplasty is probably more effective than usual care for vertebral compression fractures for reducing pain and improving function in older (Medicare-eligible) populations, but has not been compared against sham.
- Cooled radiofrequency denervation is probably moderately more effective for reducing pain and improving function than sham for sacroiliac pain in younger populations and similarly effective versus conventional radiofrequency for presumed facet joint pain and piriformis corticosteroid injection for piriformis syndrome may be similarly effective versus sham for pain at 1 week, but more effective for reducing pain at 1 month. These interventions were evaluated in younger (non-Medicare-eligible) populations, but findings can probably be applied to older populations.
- Research is needed to determine the benefits and harms of other interventional procedures addressed in this report. Ideally, future trials of interventional procedures should enroll older, Medicare-eligible populations, utilize sham controls, evaluate function as well as pain, include rigorous evaluation of harms, evaluate longer-term outcomes, and evaluate how benefits and harms according to demographic, clinical, and technical factors.

Background and Purpose

The purpose of this systematic review is to evaluate the effectiveness and harms of selected interventional procedures for acute and chronic pain in the Medicare population. The review focuses on procedures which are not currently covered for by the Centers for Medicare & Medicaid Services (CMS) but are relevant for and have potential utility for use in the Medicare population, or procedures that are covered by CMS but for which there is important uncertainty or controversy regarding use.

Methods

Electronic databases (Ovid® MEDLINE®, PsycINFO®, the Cochrane Central Register of Controlled Trials, and the Cochrane Database of Systematic Reviews) were searched through April 12, 2021 for relevant publications. Searches were supplemented by reviewing reference lists and a Federal Register Notice.

Randomized controlled trials (RCTs) of populations undergoing the designated interventional procedures for the specified conditions versus usual care, no treatment, placebo, or sham were selected using predefined criteria and dual review. Observational studies were eligible for assessment of rare, serious adverse events. This review focused on 10 interventional procedures for specific conditions:

1. Vertebral augmentation procedures (**vertebroplasty** and **kyphoplasty**) for pain due to vertebral compression fracture

2. **Cooled radiofrequency denervation** for degenerative back or hip pain and **pulsed radiofrequency denervation** for degenerative back pain
3. **Intradiscal and facet joint platelet-rich plasma** for presumed discogenic back pain
4. **Intradiscal stem cells** for presumed discogenic back pain
5. **Intradiscal methylene blue** for presumed discogenic back pain
6. **Intradiscal ozone** for radicular low back pain or nonradicular, presumed discogenic back pain (protocol modification to include intradiscal ozone plus corticosteroid)
7. **Sphenopalatine block** for trigeminal neuralgia or headache
8. **Occipital stimulation** for headache
9. **Piriformis injection** (local anesthetic, corticosteroid, and/or botulinum toxin) for piriformis syndrome
10. **Peripheral nerve stimulation** for ulnar, median, or radial neuropathy

The main outcomes were pain and function, and additional outcomes were quality of life, emotional function, global improvement, and harms. Outcomes were analyzed at 1 to 2 weeks, 2 to 4 weeks, 1 to 6 months, 6 to 12 months, and 12 months and longer. Meta-analyses were conducted for vertebroplasty versus no vertebroplasty (sham or usual care) and effects on pain, function, quality of life, and harms; analyses were conducted to assess how the control type, duration of symptoms, and other factors impacted findings. Otherwise, meta-analyses were not conducted due to small number of studies, methodological limitations, and study heterogeneity. The magnitude of effects was classified as small, moderate or large using previously defined criteria, and strength of evidence was assessed.

Results

The review included 37 RCTs on the comparative effectiveness of interventional therapies for acute and chronic pain. Evidence was most robust for vertebroplasty, followed by kyphoplasty and radiofrequency denervation, and limited for other interventions. Evidence on vertebroplasty and kyphoplasty was highly relevant to populations eligible for Medicare, based on mean age of over 65 years in the trials. For other interventions, patients were younger and populations eligible for Medicare for reasons other than older age were not addressed. Main findings (focusing on effects on pain and function) are summarized by interventional procedure.

Vertebral Augmentation Procedures

Vertebroplasty

- Vertebroplasty for vertebral compression fracture (13 trials, N=1685) was associated with a small reduction in pain intensity versus sham vertebroplasty or usual care at 1 to 2 weeks (10 trials, N=1093), 1 to 6 months (10 trials, N=1094), 6 to 12 months (8 trials, N=993), and 12 months and longer (9 trials, N=965), and a moderate reduction at 2 to 4 weeks (8 trials, N=918) (strength of evidence [SOE]: low at 1 to 2 weeks, moderate at other time points). Restricting to sham vertebroplasty controls (5 trials, N=536) tended to decrease benefits (no difference at 1 to 2 weeks and small at other time points), but the difference between sham and usual care trials was only statistically significant at 2 to 4 weeks (p for interaction=0.01). Benefits also tended to be larger in trials of patients with more acute compared with less acute pain, but differences were not statistically significant.

- There was insufficient evidence to determine effects of vertebroplasty on function at 1 to 2 weeks (7 trials, N=743), due to marked inconsistency between sham trials (no benefit) and usual care trials (small benefit). Vertebroplasty was associated with a small improvement versus sham or usual care in function at 2 to 4 weeks (6 trials, N=708), 1 to 6 months (7 trials, N=637), 6 to 12 months (6 trials, N=690), and ≥12 months (6 trials, N=612). (SOE: insufficient for 1 to 2 weeks, moderate for 1 to 6 months and 12 months and longer, and high for 2 to 4 weeks and 6 to 12 months).
- Vertebroplasty was not associated with increased risk of incident vertebral fracture at 12 months and longer (7 trials, N=826); evidence on serious adverse events was sparse and imprecise but did not indicate increased risk (SOE: moderate for vertebral fracture, low for serious adverse events).
- Three trials that conducted within-study subgroup analyses found no interaction between duration of symptoms and effects of vertebroplasty and one trial found no interaction between sex or prior vertebral fracture and effects of vertebroplasty.
- A stratified analysis of vertebroplasty trials found no interaction between polymethyl methacrylate (PMMA) volume and effects of vertebroplasty.

Kyphoplasty

- Kyphoplasty for vertebral compression fracture (2 trials, N=434) was associated with large reductions in pain and moderate to large improvement in function versus usual care at 1 week and 1 month in patients with or without cancer. No trial compared kyphoplasty against sham (SOE: low for function at 1 week; moderate for pain and for function at 1 month).
    - In 1 trial (N=300) of patients without cancer, effects on pain and function were small to moderate at 3 months to 2 years (SOE: low).
- Evidence on incident or worsening vertebral fracture was inconsistent and imprecise, based on two trials (N=434) (SOE: insufficient).

Cooled Radiofrequency

- Cooled radiofrequency denervation for sacroiliac pain was associated with a moderate to large reduction in pain and small to large improvement in function versus sham radiofrequency at 1 month (2 trials, N=79); improvements in pain and function at 3 months were moderate (1 trial, N=28) (SOE: moderate for pain and function at 3 months; low for function at 1 month).
- Cooled radiofrequency denervation for presumed facet joint pain was associated with a small, nonstatistically significant reduction in pain versus conventional radiofrequency at 6 months and no difference in function (1 trial, N=43); there were no differences at earlier (1- or 3-month) followup (SOE: low).

Pulsed Radiofrequency

- Evidence was insufficient to assess pulsed radiofrequency denervation for presumed facet joint pain versus sham denervation (1 trial, N=40) or continuous radiofrequency denervation (1 trial, N=40) (SOE: insufficient).

Intradiscal Platelet-Rich Plasma

- Evidence was insufficient to assess intradiscal platelet-rich plasma injection for presumed discogenic back pain (1 trial, N=58) (SOE: insufficient).
- There were no differences between intradiscal platelet-rich plasma injection and saline injection in harms, including no serious adverse events, at up to 3 years following treatment (SOE: low).

Intradiscal Stem Cell Injection

- Evidence was insufficient to assess intradiscal stem cell injection for presumed discogenic back pain (1 trial, N=100) (SOE: insufficient).

Intradiscal Methylene Blue

- Intradiscal methylene blue for presumed discogenic back pain (1 trial, N=81) was associated with no difference versus sham at 6 weeks and 3 months. Evidence was insufficient to determine effects of intradiscal methylene blue at 6 months (2 trials, N=153, with conflicting results) and 12 months or longer (1 trial, N=72) (SOE: low for no difference at 6 weeks and 3 months; insufficient for 6, 12, and 24 months).

Intradiscal Oxygen-Ozone

- Evidence was insufficient to assess intradiscal oxygen-ozone for radicular low back pain (1 trial, N=159) (SOE: insufficient).
- No trial evaluated intradiscal oxygen-ozone injection without corticosteroid or oxygen-ozone injection for presumed (nonradicular) discogenic low back pain.

Sphenopalatine Block

- Evidence was insufficient to assess sphenopalatine block versus sham for headache (1 trial, N=41) (SOE: insufficient).

Occipital Nerve Stimulation

- Evidence was insufficient to assess occipital nerve stimulation versus sham stimulation for headache (1 trial, N=157) (SOE: insufficient).
- For headache, occipital nerve stimulation with adjustable parameters versus usual care at 3 months was associated with a small, nonstatistically significant reduction in pain intensity, moderate decrease in headache related disability, and decrease in headache days (1 trial, N=67) (SOE: low for headache related disability and headache days; insufficient for pain).
- Lead migration occurred in 14 to 24 percent of patients (2 trials, N=224), serious device-related complications requiring hospitalization occurred in 5.9 percent of patients (1 trial, N=67), and persistent pain/numbness at implantation site in 13 percent of patients (1 trial, N=157) (SOE: low).
- One trial (N=67) found occipital nerve stimulation with adjustable parameters associated with superior outcomes compared with stimulation using preset parameters.

Piriformis Injection

- One trial (N=50) found piriformis injection with corticosteroid and local anesthetic for piriformis syndrome associated with no difference versus local anesthetic alone in pain at rest at 1 week; piriformis injection was associated with a moderate reduction in pain at rest versus local anesthetic at 1 month (SOE: low for no difference at 1 week and for benefit at 1 month).
- Evidence was insufficient to assess piriformis injection with botulinum toxin.

Peripheral Nerve Stimulation

- Evidence was insufficient to assess peripheral nerve stimulation for upper extremity peripheral neuropathic pain (SOE: insufficient).

Limitations

We excluded non-English–language articles and did not search for studies published only as abstracts. We did not conduct statistical and graphical methods for assessing for small sample effects (a potential marker for publication bias) due to small numbers of trials and heterogeneity in study design methods, patient populations, and outcomes.

The evidence base had important limitations. For vertebroplasty, trials varied with regard to patient selection criteria (e.g., duration of pain), technical factors (e.g., volume of PMMA), and sham interventions (e.g., sites of local anesthetic infiltration). In addition, the usual care interventions were not well standardized or defined. Pain and function were the most commonly reported outcomes, with limited evidence on quality of life, health status (e.g., Short-Form 36 Health Survey [SF-36]), mood, analgesic (including opioid) use, and other outcomes. Data on harms were relatively sparse and inconsistently reported. The trials were not designed to evaluate how benefits and harms varied in subgroups defined by demographic, clinical, or technical factors. Data on long-term (≥1 year) outcomes was relatively limited.

For the other interventional procedures evaluated in this report, the major limitation was the small numbers of trials, with important methodological shortcomings (e.g., high attrition, lack of intent-to-treat analysis, baseline group differences, small sample sizes, inadequate or unclear randomization or allocation concealment methods, open-label design, and use of unvalidated outcome measures) in almost all eligible studies.

Implications and Conclusions

Vertebroplasty is probably effective at reducing pain and improving function in older patients with vertebral compression fractures, but benefits were small (**Table A**). Effects of vertebroplasty were reduced in sham versus usual care controlled trials and larger in trials of patients with more acute symptoms. However, it is not possible to attribute differences entirely to the control type used, given substantial other differences across trials with regard to duration of pain, PMMA volume, requirement for bone edema on magnetic resonance imaging (MRI), and other factors. Furthermore, there were not statistically significant interactions between control type and effects on pain intensity at other time points, there was heterogeneity among the sham-controlled trials, and there is controversy regarding potential therapeutic effects associated with different sham procedures. To address outstanding questions regarding vertebroplasty, future trials should ideally include sham as well as usual care control groups and include patients with

hyperacute (e.g., <3 weeks) and acute (e.g., 3 to 6 weeks) symptoms. Trials that include sham interventions with and without periosteal local anesthetic could also help clarify whether the sham treatment itself is associated with therapeutic benefits. Kyphoplasty is probably more effective than usual care for vertebral compression fractures in older patients (**Table A**). However, an important limitation of the evidence is the absence of sham-controlled trials of kyphoplasty. Until such evidence becomes available, kyphoplasty may be considered as an alternative to vertebroplasty, particularly in patients with more vertebral body collapse, as the purpose of kyphoplasty is to help restore vertebral body morphology.

Cooled radiofrequency denervation is probably more effective than sham denervation for sacroiliac pain, cooled radiofrequency may be as effective as conventional radiofrequency for presumed facet joint pain, occipital nerve stimulation may be more effective than usual care for headache, and piriformis corticosteroid injection may be more effective than sham for piriformis syndrome (**Table A**). Evidence on harms was limited, but lead migration was common following occipital nerve stimulation placement. Although evidence on these interventions was limited to younger (below the age for Medicare eligibility) populations, there is no obvious reason that findings would not apply to older patients. Evidence on the other interventions and conditions addressed in this review is sparse and insufficient, and additional research is needed to determine benefits of harms (**Table A**). To ideally inform Medicare coverage decisions, future trials of interventional procedures should enroll older, Medicare-eligible populations, utilize sham controls, evaluate function as well as pain, include rigorous evaluation of harms, evaluate longer-term outcomes, and evaluate how benefits and harms according to demographic (age, sex, race/ethnicity), clinical (pain severity, pain duration, use of opioids, psychiatric or medical comorbidities), or technical (dose, intensity, duration, frequency, techniques) factors.

Table A. Interventional pain therapies for acute and chronic pain*

Intervention	Condition	**Pain** 1 to 2 Weeks Effect Size SOE	**Pain** 2 to 4 Weeks Effect Size SOE	**Pain** 1 to 6 Months Effect Size SOE	**Pain** 6 to 12 Months Effect Size SOE	**Pain** ≥12 months Effect Size SOE	**Function** 1 to 2 Weeks Effect Size SOE	**Function** 2 to 4 Weeks Effect Size SOE	**Function** 1 to 6 Months Effect Size SOE	**Function** 6 to 12 Months Effect Size SOE	**Function** ≥12 Months Effect Size SOE
Vertebroplasty vs. sham or usual care	Vertebral compression fractures	Small[†] **+**	Moderate[‡] **++**	Small **++**	Small **++**	Small **++**	Insufficient[§]	Small **+++**	Small **++**	Small **+++**	Small **++**
Kyphoplasty vs. usual care	Vertebral compression fractures	Large **++**	Large **++**	Moderate **+**	Moderate **+**	Small **+**	Moderate **+**	Moderate to large **++**	Moderate **+**	Moderate **+**	Small **+**
Cooled radiofrequency ablation vs. sham	Sacroiliac pain	No evidence	Moderate to large **++**	Moderate **++**	No evidence	No evidence	No evidence	Small to large **+**	Moderate **++**	No evidence	No evidence
Cooled vs. conventional radiofrequency denervation	Presumed facet joint pain	No evidence	None **+**	None **+**	Small **+**	No evidence	No evidence	None **+**	None **+**	None **+**	No evidence
Pulsed radiofrequency denervation vs. sham[‖]	Presumed facet joint pain	No evidence	No evidence	No evidence	Insufficient	Insufficient	No evidence	No evidence	No evidence	Insufficient	Insufficient
Pulsed vs. conventional radiofrequency denervation[‖]	Presumed facet joint pain	No evidence	No evidence	No evidence	Insufficient	Insufficient	No evidence	No evidence	No evidence	Insufficient	Insufficient
Cooled or pulsed radiofrequency denervation vs. sham, usual care, or conventional radiofrequency denervation	Degenerative hip pain	No evidence	No evidence	No evidence	No evidence	No evidence	No evidence	No evidence	No evidence	No evidence	No evidence
Facet joint platelet-rich plasma vs. sham or usual care	Presumed facet joint pain	No evidence	No evidence	No evidence	No evidence	No evidence	No evidence	No evidence	No evidence	No evidence	No evidence

Intervention	Condition	Pain 1 to 2 Weeks Effect Size SOE	Pain 2 to 4 Weeks Effect Size SOE	Pain 1 to 6 Months Effect Size SOE	Pain 6 to 12 Months Effect Size SOE	Pain ≥12 months Effect Size SOE	Function 1 to 2 Weeks Effect Size SOE	Function 2 to 4 Weeks Effect Size SOE	Function 1 to 6 Months Effect Size SOE	Function 6 to 12 Months Effect Size SOE	Function ≥12 Months Effect Size SOE
Intradiscal platelet-rich plasma vs. sham	Discogenic back pain	Insufficient	Insufficient	Insufficient	No evidence	No evidence	Insufficient	Insufficient	Insufficient	No evidence	No evidence
Intradiscal stem cells vs. control*	Discogenic back pain	No evidence	Insufficient	Insufficient	Insufficient	Insufficient	No evidence	Insufficient	Insufficient	Insufficient	Insufficient
Intradiscal methylene blue vs. sham	Discogenic back pain	No evidence	No evidence	None +	None +	Insufficient	No evidence	No evidence	Small +	None +	Insufficient
Intradiscal ozone + corticosteroid vs. corticosteroid	Discogenic back pain	Insufficient	No evidence	Insufficient	Insufficient	No evidence	Insufficient	Insufficient	No evidence	Insufficient	Insufficient
Sphenopalatine block vs. control	Trigeminal neuralgia	No evidence	No evidence	No evidence	No evidence	No evidence	No evidence	No evidence	No evidence	No evidence	No evidence
Sphenopalatine block vs. control‖	Chronic migraine	No evidence	Insufficient	No evidence	Insufficient	No evidence	No evidence	Insufficient	No evidence	Insufficient	No evidence
Occipital nerve stimulation vs. sham‖	Chronic migraine	No evidence	No evidence	Insufficient	No evidence	No evidence	No evidence	No evidence	Insufficient	No evidence	No evidence
Occipital nerve stimulation vs. usual care	Chronic migraine	No evidence	No evidence	Insufficient	No evidence	No evidence	No evidence	No evidence	Insufficient	No evidence	No evidence
Piriformis injection with corticosteroid plus local anesthetic vs. corticosteroid plus local anesthetic, or sham‖	Piriformis syndrome	None +	Moderate +	Insufficient	No evidence	No evidence	No evidence	No evidence	No evidence	No evidence	No evidence
Peripheral nerve stimulation vs. sham	Ulnar, median or radial neuropathy pain	No evidence	No evidence	Insufficient	No evidence	No evidence	No evidence	No evidence	Insufficient	No evidence	No evidence

Abbreviations: SOE = strength of evidence

Effect size: none (i.e., no effect/no statistically significant effect), small, moderate, or large increased risk; SOE: + = low, ++ = moderate, +++ = high.

* Grey shading indicates insufficient or no evidence

†There was no difference in trials with sham control and moderate difference in trials with usual care control, but no statistically significant interaction between control type and effects on pain (p for interaction=0.14)

‡There was a small difference in trials with sham control and large difference in trials with usual care control, with a statistically significant interaction between control type and effect on pain (p for interaction <0.01)

§There was no difference in trials with sham control and small difference in trials with usual care control, but no statistically significant interaction between control type and effects on pain (p for interaction=0.19)

‖Poor-quality trials excluded

Introduction

Background

Pain is nearly universal, contributing substantially to morbidity, mortality, disability, and healthcare system burdens.[1] Acute pain usually lasts for less than 7 days but often extends up to 30 days, and may recur periodically. Although acute pain usually resolves rapidly, in some cases it can persist to become chronic. Chronic pain, defined as pain lasting longer than 3 months[1,2] is a serious public health issue in the United States, affecting approximately 50 million people and resulting in $635 billion in costs.[3,4] Chronic pain substantially impacts physical and mental functioning, reducing productivity and quality of life.

Patients eligible for Medicare due to age or disability are highly impacted by pain. Musculoskeletal conditions such as back pain are the most common Social Security Disability Insurance qualifying diagnosis, accounting for 34 percent of program participants in 2011.[5] In 2016, approximately 13.6 million Americans 65 years of age or older were estimated to have chronic pain and 5.4 million had high-impact chronic pain.[4] The prevalence of chronic pain was 27.6 percent among those 65 to 84 years of age and 33.6 percent among those 85 years of age or older (exceeding any other age group). In older adults, management of pain is often complicated by medical comorbidities, polypharmacy, increased susceptibility to treatment harms, and assessment challenges due to impaired cognition, often resulting in untreated or under treatment of pain.[6,7]

Opioids, traditionally considered the most potent analgesic, are frequently prescribed for acute or chronic pain, including in older adults and those with disabilities.[5,8,9] Therefore, pain management must be considered within the context of the current opioid crisis (related to both illicit and prescription opioids).[10] Opioid prescribing is highest among patients over 65 years of age, and studies indicate recent increases in hospitals admissions and emergency department visits related to opioid use disorder in this age group.[11-14] Therefore, there is a need to identify effective and safe interventions that could augment or replace opioids for pain treatment in this population.

The key decisional dilemma for pain management in Medicare beneficiaries is providing adequate pain relief, in order to improve quality of life and improve function, while minimizing harms. Given concerns regarding opioids, there is great interest in nonopioid pharmacologic and nonpharmacologic therapies and they have become increasingly accepted as first-line therapies. The 2016 Centers for Disease Control and Prevention *Guideline for Prescribing Opioids for Chronic Pain* recommends nonopioid therapy as preferred for treatment of chronic pain,[15-17] though opioids remain an option for appropriately selected and monitored patients. In the aging population, the Pain Management Best Practices Inter-Agency Task Force report recommended consideration of a multidisciplinary approach with nonpharmacologic emphasis.[18] Interventional approaches were also specifically highlighted by the Task Force as an important nonpharmacologic option and data indicate that interventional procedures are frequently used in this population (~5 million procedures annually in Medicare fee-for-service).[19]

The term “interventional procedure” has been applied to a myriad of procedures, ranging from soft tissue injections to minimally invasive surgeries, but in this report it refers to nonsurgical interventional procedures (i.e., excluding minimally invasive surgical procedures). The Inter-Agency Task Force report suggested that a number of interventional procedures be considered for acute or chronic pain,[18] but did not specifically make recommendations for use of these procedures in Medicare populations, in whom optimal management of pain must consider

factors such as medical comorbidities, polypharmacy, presence of disability, falls risk, and cognitive issues.[20]

Purpose of the Review

The purpose of this systematic review is to evaluate the effectiveness and harms of selected interventional procedures in the Medicare population. The review focuses on procedures that are not currently covered by the Centers for Medicare & Medicaid Services (CMS) but are relevant for and have potential utility for use in the Medicare population, or procedures that are covered by CMS but for which there is important uncertainty or controversy regarding use. The intended audiences for this review are CMS and other stakeholders including clinicians, policymakers, patients, and researchers. This review is part of the *Dr. Todd Graham Pain Management Study* and is sponsored by CMS. The Dr. Todd Graham Pain Management Study also includes three complementary topic briefs on pain topics in Medicare populations as well as a separate systematic review[21] on integrated pain management and multidisciplinary multi-modal treatment models.

Scope and Key Question

The draft Key Question and scope were developed by the Evidence-based Practice Center with input from the Agency for Healthcare Research and Quality and CMS, and were revised based on input from a Technical Expert Panel prior to finalization. The interventional therapies were selected based on the following factors: (1) available in the United States but not currently covered by CMS; (2) relevance and potential utility in the Medicare population (i.e., use in Medicare-eligible patients or for pain conditions commonly encountered in this population); and (3) uncertainty or controversy regarding use.

Key Question 1: What are the effectiveness and harms of selected interventional procedures (vertebral augmentation procedures, cooled or pulsed radiofrequency ablation, intradiscal and facet joint platelet-rich plasma, intradiscal methylene blue, intradiscal ozone, sphenopalatine block, occipital nerve stimulation, piriformis injection, and peripheral nerve stimulation) versus placebo, a sham procedure, or no interventional procedure for Medicare beneficiaries with pain?

a. How do the effectiveness and harms vary according to demographic (age, sex, race/ethnicity), clinical (type of pain, severity of pain, prior treatments, medical and psychiatric co-morbidities), and technical factors (variations in techniques, intensity, frequency, dose, and number of treatments)?

The interventional procedures and conditions for this review are:

1. Vertebral augmentation procedures (vertebroplasty and kyphoplasty) for vertebral compression fracture. These procedures are performed for vertebral compression fractures, which are common in the Medicare population and often are due to osteoporosis or metastatic disease. **Vertebroplasty** involves the injection of polymethyl methacrylate (PMMA), commonly known as bone cement, into the collapsed (fractured) vertebral body. In **kyphoplasty**, injection of PMMA is preceded by insertion and inflation of a balloon into the collapsed vertebral body to restore it. Although vertebral augmentation procedures are

covered by CMS, they were selected for inclusion in this review because there is ongoing controversy about their role, due to conflicting trial results.[22,23] The conflicting trial results could be due to use of a sham intervention (mimicking the vertebral augmentation procedure, without injecting PMMA, in order to blind participants to the treatment received) versus a usual care (open-label) control. Other factors that could impact trial results include the fracture age, presence of imaging findings indicating bone marrow edema in the fracture, the volume of PMMA used, and others.

2. Variations on radiofrequency ablation (**cooled radiofrequency ablation** for degenerative low back or hip pain and **pulsed radiofrequency ablation** for degenerative low back pain). Conventional radiofrequency ablation involves the application of continuous high frequency electrical current to ablate nerve tissue thought to be the cause of pain. Evidence indicates that conventional radiofrequency for low back and hip pain may be associated with improved short-term pain and function,[24,25] and it is currently covered by CMS for these conditions as an option for patients with persistent symptoms who do not respond to standard treatments. Cooled and pulsed radiofrequency have been proposed as potential alternatives to conventional radiofrequency. Like conventional radiofrequency ablation, the cooled radiofrequency procedure involves the application of high frequency electrical current. It differs from conventional radiofrequency ablation by using a larger, "cooled" (relative to conventional radiofrequency; heat is still generated) radiofrequency probe, potentially allowing for more targeted, larger and more effective lesions.[26,27] The Coolief™ cooled radiofrequency ablation probe was approved by the U.S. Food and Drug Administration (FDA) for treatment of knee pain. However, it has also been proposed as an alternative to conventional radiofrequency ablation for other indications, including degenerative back and hip pain. Pulsed radiofrequency differs from conventional radiofrequency by delivering a smaller current in brief bursts. Unlike conventional radiofrequency, it is not intended to destroy nerve tissue; rather, it is thought to reduce pain through neuromodulatory effects.[28]
3. **Intradiscal and facet joint platelet-rich plasma** for presumed discogenic back pain or presumed facet joint pain. This procedure involves the injection of autologous platelet-rich plasma, which is rich in growth factors, into the intervertebral disc for low back pain of presumed discogenic origin[29] or into the lumbar facet joint for low back pain of presumed facet joint origin.[30] Platelet-rich plasma is thought to promote endogenous healing processes, though the exact mechanism of action is not well understood.
4. **Intradiscal stem cells** for presumed discogenic back pain. This procedure involves the injection of stem cells, which have potential regenerative potential, into degenerative intervertebral discs for low back pain of presumed discogenic origin.[31] Like platelet-rich plasma, stem cells are thought to promote healing.
5. **Intradiscal methylene blue** for presumed discogenic back pain. This procedure involves the injection of methylene blue, a dye that may prevent fibrosis or ablate sensory endings, into the intervertebral disc for low back pain of presumed discogenic origin.[32] However, the mechanism of action is not well understood.
6. **Intradiscal ozone injection** for radicular or nonradicular back pain. This procedure involves the injection of ozone, a gas with potential anti-inflammatory or other effects, into the intervertebral disc for radicular low back pain due to herniated disk or nonradicular low

back pain of presumed discogenic origin.[32] Ozone may have nucleolytic effects on the intervertebral disc, reducing the size of the herniated disc and relieving pressure on compressed nerve roots, or reduce pain related to discogenic pain through anti-inflammatory effects.[33]

7. **Sphenopalatine block** for trigeminal neuralgia or headache. This procedure is performed for trigeminal neuralgia, migraine headaches, cluster headaches, and other headache syndrome.[34] It involves injection of the sphenopalatine ganglion with a local anesthetic; the FDA has approved three devices for this procedure (SphenoCath® [Dolor Technologies, Scottsdale, AZ], Allevio SPG Nerve Block catheter [Medical Components, Inc., Schwenksville, PA], and Tx360® Nasal Injector [Tian Medical, LLC, Libertyville, IL]). The most common method for approaching the sphenopalatine ganglion is via the transnasal approach.
8. **Occipital nerve stimulator** for headache. This procedure is performed for various headache disorders. Similar to spinal cord stimulation, it involves electrical stimulation of the occipital nerve through use of subcutaneously placed electrodes, which is thought to result in neuromodulation of pain via the gate control pathway.[35] Typically, a successful trial of stimulation is performed before permanent electrodes and a generator are implanted.
9. **Piriformis injection** for piriformis syndrome. Piriformis syndrome results from compression of the sciatic nerve by the piriformis muscle.[36,37] The injection may be performed using corticosteroids (for anti-inflammatory effects), local anesthetics (to decrease muscle spasm), and/or botulinum toxin (also to decrease muscle spasm).
10. **Peripheral nerve stimulation** for ulnar, median, and radial neuropathy. This procedure involves stimulation of peripheral nerves using a mild electrical current, in patients with chronic neuropathic pain such as upper extremity neuropathies.[38] Like occipital nerve stimulation, peripheral nerve stimulation involves the subcutaneous placement of electrodes at the target nerves and is thought to have neuromodulatory effects. Successful trial stimulation is typically required prior to permanent placement.

This review did not address minimally invasive surgical procedures, or orthopedic procedures such as intra-articular or soft tissue corticosteroid, hyaluronic acid, or soft tissue or nonspinal intra-articular platelet-rich plasma injections. The review also did not address soft tissue injections with local anesthetic, corticosteroid, and/or other medications (e.g., botulinum toxin) that are commonly performed in primary care settings and do not require specialized training or expertise. With the exception of vertebral augmentation procedures, it also does not address interventional procedures conducted in the Medicare population that are covered by CMS, are recommended in clinical practice guidelines, and/or have been addressed in other recent and comprehensive systematic reviews (e.g., epidural steroid injection, perioperative peripheral and central regional anesthetic techniques, and spinal cord stimulation).[32,39-44]

Methods

This systematic review follows methods suggested in the *Agency for Healthcare Research and Quality Methods Guide for Effectiveness and Comparative Effectiveness Reviews* (hereafter the "AHRQ Methods Guide") developed for the Evidence-based Practice Centers (EPCs).[45] Methods were determined a priori and a protocol was developed through a process that included public input and was published on the Agency for Healthcare Research and Quality (AHRQ) website (https://effectivehealthcare.ahrq.gov/products/interventional-treatments-pain/protocol) and on the PROSPERO systematic reviews registry (CRD42021226947).

Literature Search Strategy

We conducted electronic searches in Ovid® MEDLINE®, PsycINFO®, Cochrane CENTRAL, and Cochrane Database of Systematic Reviews in April 2021 (see **Appendix A** for full strategies). The search reached back to 1990 for each database. This date corresponds to publication of the earliest clinical studies on the interventional procedures addressed in this review. Reference lists of relevant systematic reviews were screened for additional studies.

Inclusion and Exclusion Criteria and Study Selection

The criteria for inclusion and exclusion of studies for this review were based on the Key Question. The population was adults (≥18 years of age) undergoing one of the specified interventional procedures for pain. Details regarding the populations, interventions, comparators, outcomes, timing, and setting (PICOTS) are summarized in **Table 1**. Briefly, we included studies of populations undergoing the designated interventional procedures for the specified conditions. Pain could be of any duration, though for all of the conditions other than vertebral compression fracture, symptoms are typically subacute or chronic before interventional procedures are performed. Although the population of interest was patients eligible for Medicare, we did not restrict inclusion to studies of patients meeting Medicare eligibility criteria (e.g., based on age, presence of disability, or end-stage renal disease), in order to provide a more comprehensive synthesis of the available literature, and because findings in younger populations may be applicable to older populations. However, studies of patients eligible for Medicare were highlighted, when available.

We restricted inclusion to studies of the selected interventions administered as single therapy, in order to isolate the effects of the intervention. The exception was ozone therapy, for which we included trials of intradiscal ozone administered with an epidural corticosteroid, because there were no trials of ozone without corticosteroid. Comparisons were against a sham control, usual care, or no treatment. Sham controlled trials utilize a procedure that mimic the intervention of interest, without purported therapeutic benefit. Use of sham controls enables blinding of patients to the treatment received, avoiding placebo effects that could inflate estimates due to expectations of benefits. In usual care or no treatment trials, there is no attempt to blind patients to the treatment received. Although usual care or no treatment trials can overestimate benefits due to placebo effects, they are also more pragmatic, reflecting how treatments are administered in clinical practice.[46] In addition to placebo effects, other reasons that sham and usual care trials may conflict include any therapeutic effects of the sham interventions or differences between sham and usual care trials with regard to the populations evaluated, intervention methods, or other factors. For cooled and pulsed radiofrequency denervation, we also included comparisons against conventional radiofrequency denervation, since these interventions are considered

modifications of conventional radiofrequency denervation. For ozone plus corticosteroid therapy, we modified the protocol to also include trials with a corticosteroid control arm (with or without local anesthetic), in order to assess the incremental effects of ozone therapy in addition to a corticosteroid.

Outcomes were pain, function, quality of life, health status, mood, medication use (including opioids), and harms. The review focused on randomized controlled trials (RCTs), given the susceptibility of observational and other non-randomized studies to bias and confounding, particularly for more subjective outcomes such as pain and function.[47,48] In the specific case of interventional pain treatments, there are a number of examples of non-randomized studies[49-56] that overestimated benefits compared with RCTs.[43,57] However, cohort studies were eligible for evaluation of benefits if no RCTs were available; large (n>500) observational studies were eligible for evaluation of rare, serious harms.[58]

We excluded studies published only as conference abstracts, restricted inclusion to English-language articles, and excluded studies of nonhuman subjects. Studies had to report original data to be included.

All citations were reviewed by one investigator for potential inclusion and full text review. Excluded abstracts were reviewed by a second investigator to confirm the exclusion decision. Each full-text article was independently reviewed for eligibility by two team members. Disagreements were resolved by consensus.

Searches were updated for new publications while the draft report was posted for public comment. Literature identified during the update search was assessed using the process described above for the original search. Any new eligible literature identified in the update search was incorporated into the report prior to finalization.

Table 1. PICOTS (population, intervention, comparator, outcome, timing, setting)

PICOTS	Inclusion	Exclusion
Population	Adults with pain of any duration (pain conditions for each interventional procedure specified below); will highlight studies of populations applicable to Medicare, defined as patients enrolled in Medicare, age ≥65 years, or patients with disability (including end-stage renal disease), if available Population subgroups of interest include those based on demographics (age, sex, race/ethnicity) and clinical factors (type of pain, severity of pain, prior treatments, medical and psychiatric comorbidities, including presence of disability [including end-stage renal disease], prior substance use disorder, and psychological comorbidities)	• Patients undergoing end-of-life care, terminally ill (e.g., hospice) patients; those under supervised palliative care; those with pain due to metastatic or advanced cancer • Children

PICOTS	Inclusion	Exclusion
Intervention	1) Vertebral augmentation procedures (vertebroplasty and kyphoplasty) for pain due to vertebral compression fracture 2) Cooled radiofrequency denervation for degenerative back or hip pain and pulsed radiofrequency denervation for degenerative back pain 3) Intradiscal and facet joint platelet-rich plasma for presumed discogenic back pain 4) Intradiscal stem cells for presumed discogenic back pain 5) Intradiscal methylene blue for presumed discogenic back pain 6) Intradiscal ozone for radicular low back pain or nonradicular, presumed discogenic back pain • Protocol modification to include intradiscal ozone plus corticosteroid 7) Sphenopalatine block for trigeminal neuralgia or headache 8) Occipital stimulation for headache 9) Piriformis injection (local anesthetic, corticosteroid, and/or botulinum toxin) for piriformis syndrome 10) Peripheral nerve stimulation for ulnar, median, or radial neuropathy Technical factors of interest as potential modifiers of treatment effect include variations in techniques, intensity, frequency, dose, or number of treatments.	• Minimally invasive surgical procedures • Orthopedic intra-articular and soft tissue injections • Local soft tissue injections • Other interventional procedures and conditions not listed as included
Comparator	Placebo, sham interventional procedure, or no interventional procedure For cooled and pulsed radiofrequency denervation: conventional (thermal, continuous) radiofrequency denervation • For intradiscal ozone, protocol modification to include corticosteroid without ozone	Active treatments, other than conventional radiofrequency denervation as a comparison for cooled radiofrequency denervation
Outcome	• ***Primary:*** Pain, function • ***Secondary***: Health-related quality of life, emotional function (e.g., depression, anxiety), opioid use, surgery rates • Global improvement • Harms (e.g., bleeding, infection, other complications), adverse events, unintended consequences	**Patient-oriented outcomes** • Non-validated instruments for outcomes (e.g., pain, function, health-related quality of life, depression, etc.) • Intermediate outcomes (e.g., range of motion, physical strength, etc.)
Timing	Duration of followup: ≥1 week; categorized as 1 to 2 weeks, 2 to 4 weeks, 1 to 6 months, 6 to 12 months, and 12 months and longer	<1 week
Setting	Any	None
Study design, publication type	Randomized clinical trials and cohort studies if randomized clinical trials are not available Large (n>500) case series for serious, rare harms	• Case reports • Case series (other than large case series for serious, rare harms) • Case-control studies, cross-sectional studies • Conference proceedings, editorials, letters, white papers, citations that have not been peer-reviewed

Data Abstraction and Data Management

For studies meeting inclusion criteria, evidence tables were created to show data on study characteristics, outcomes, and applicability. If necessary, data were estimated from graphs provided in the studies. We also calculated standard deviations for baseline and followup data from standard errors or 95 percent confidence intervals (CIs) if necessary using standard formulas,[59] and calculated mean differences or relative risks with 95 percent CIs using online calculators.[60,61] Abstracted and calculated data were verified for accuracy and completeness by a second team member.

Effects on pain were abstracted as mean difference in pain intensity (continuous) and likelihood of experiencing improvement in pain (dichotomous) based on meeting a certain threshold ("pain response"). For pain and other outcomes evaluated as continuous outcomes, we abstracted adjusted mean differences at followup if available, as well as unadjusted differences in followup scores or change from baseline, and unadjusted differences in change from baseline. Pain intensity using a 0 to 100 scale was transformed to a 0 to 10 scale for ease of interpretation. For pain evaluated as a dichotomous outcomes (pain response), we abstracted (in descending order of prioritization) the proportion of patients experiencing improvement in pain intensity of at least 30 percent, at least 50 percent, or improvement in pain at an alternative threshold (e.g., ≥25%, or >2 point improvement on a 0 to 10 scale), or pain relief rated as moderate, good, or similar using a categorical scale.

Effects on function were based on the mean improvement in a functional scale (dichotomous) or the proportion of patients meeting a defined threshold of functional improvement (dichotomous, e.g. improvement in function of at least 30 percent or at least "moderate" improvement on a categorical scale). The most common functional outcomes were the Roland-Morris Disability Questionnaire (RDQ, 0 to 24 scale) or Oswestry Disability Index (ODI, 0 to 100 scale) for low back pain and the Migraine Disability Test (MIDAS) for migraine (based on number of disability days in the last 3 months for various activities; score >20 indicates severe disability); on each of these scales higher values indicate greater functional disability. Effects on health status (most commonly, the Short-form-36 Physical or Mental Component Summary Scales [0 to 100 scale, higher score indicate better health status]), generic quality of life (e.g., the EuroQOL 5-Dimension Questionnaire [EQ-5D, 0 to 1 scale, higher score indicates better quality of life]), condition-specific quality of life (e.g., the Quality of Life Questionnaire of the European Foundation for Osteoporosis [QUALEFFO, 0 to 100 scale, higher score indicates worse quality of life]), and mood (e.g., Beck Depression Inventory [BDI, 0 to 63 scale, higher value indicates more severe depression symptoms], Profile of Mood States [POMS, 0 to 200 scale, higher values indicates worse mood state], or others) were based on mean improvements in scales designed to assess these domains.

For pain, function, mood, and disease-specific quality of life (QUALEFFO), negative values for mean improvement indicate a better outcome; for health status and generic quality of life (EQ-5D), positive values indicate a better outcome. Effects on harms were based on the proportion of patients experiencing harms (mortality, serious adverse events, any adverse event, and incident vertebral fracture). The duration of pain symptoms at the time of study enrollment was classified as acute (<4 weeks), subacute (4 to 12 weeks), or chronic (>12 weeks). Outcomes were evaluated at predefined followup periods: ≥1 to ≤2 weeks (hereafter written as "1 to 2 weeks"), >2 weeks to ≥1 month ("2 to 4 weeks"), >1 to <6 months ("1 to 6 months"), ≥6 to <12 months ("6 to 12 months"), and ≥12 months ("12 months and longer").

Study data was abstracted by one team member and all data were verified for accuracy and completeness by a second team member. A record of studies excluded at the full-text level with reasons for exclusion was maintained (**Appendix B**).

Quality (Risk of Bias) Assessment of Individual Studies

Methods from the AHRQ Methods Guide were used in concordance with the approach recommended in the chapter, Assessing the Risk of Bias of Individual Studies When Comparing Medical Interventions.[45,62] RCTs were assessed based on criteria established in the *Cochrane Handbook for Systematic Reviews of Interventions (Chapter 8.5 Risk of Bias Tool)*,[63] and instruments tailored to observational studies were used for nonrandomized studies[64] (**Appendix C**). Each study was independently reviewed for risk of bias by two team members. Any disagreements were resolved by consensus. Based on the risk of bias assessment, individual included studies were rated as "good," "fair," or "poor" quality as described below:

Poor quality studies were not excluded a priori. When meta-analysis was conducted subgroup analysis was performed based on study quality. When meta-analysis was not conducted, results from poor quality studies were described but conclusions were based on higher (fair and good) quality studies when available.

Data Analysis and Synthesis

We constructed evidence tables showing study characteristics, results, and quality ratings for all included studies, and summary tables to highlight the main findings, organized by Key Question (intervention and condition).

Meta-analysis were limited to vertebroplasty, due to the small number of studies for other interventions, methodological limitations in the studies, and variability in the studies, including outcome measures assessed, timing of assessment, and patient characteristics.[65] For interventions other than vertebroplasty, evidence was synthesized qualitatively.

Subgroup analyses were conducted to evaluate how pain duration, volume, presence of bone marrow edema, and study quality impacted estimates. Details regarding meta-analysis methods are provided in **Appendix D**.

A sub-Key Question addressed how benefits and harms varied according to demographic (age, sex, race/ethnicity), clinical (type of pain, severity of pain, prior treatments, medical and psychiatric comorbidities), and technical factors (variations in techniques, intensity, frequency, dose, and number of treatments). Although planned techniques to assess these factors included sensitivity and stratified analyses, other than polymethyl methacrylate (PMMA) volume, evidence was too limited to apply these techniques. However, we evaluated findings from within-study subgroup analyses on these factors when available.

The magnitude of effects for pain and function were classified using used in other recent AHRQ reviews on pain conducted at our EPC.[66-70] A small effect was defined for pain as a mean between-group difference following treatment of 0.5 to 1.0 points on a 0- to 10-point numeric rating scale (NRS) or visual analogue scale (VAS) and for function as a standard mean deviation (SMD) of 0.2 to 0.5 or a mean difference of 5 to 10 points on the 0 to 100-point ODI, 1 to 2 points on the 0 to 24-point RDQ, or equivalent. A moderate effect was defined for pain as a mean difference of 1 to 2 points on a 0- to 10-point NRS or VAS and for function as an SMD of 0.5 to 0.8, or a mean difference of 10 to 20 points on the ODI, 2 to 5 points on the RDQ, or equivalent. Large/substantial effects were defined as greater than moderate. We applied similar thresholds to other outcomes measures.[71] Small effects using this system may not meet proposed

thresholds for clinically meaningful effects.[72] However, there is variability in estimated minimum clinically important differences across studies, therapies for pain (included those recommended in guidelines) are often associated with effects below minimum clinically important difference thresholds,[44,73-76] and the clinical relevance of effects classified as small might vary for individual patients depending on preferences, baseline symptom severity, harms, cost, and other factors.[77,78] For some individuals, a small improvement in pain, function, or other outcomes using a treatment with low cost or no serious harms may be important.

Grading the Strength of Evidence

Regardless of whether evidence was synthesized quantitatively or qualitatively, the strength of evidence (SOE) was assessed as high, moderate, low, or insufficient, using the approach described in the AHRQ Methods Guide, based on study limitations, consistency, directness, precision, and reporting bias (**Appendix E**).[45] Based on input from the Technical Expert Panel, pain and function were classified as primary outcomes and the other outcomes were classified as secondary. When higher (fair- or good-quality) studies were available, poor-quality studies were not used to determine SOE. To ensure consistency and validity of the SOE evaluation, the initial assessment was made by one investigator and independently reviewed by at least one other investigator using the following criteria, with disagreements resolved by consensus.

Plain-language statements were used in the Abstract and Main Points to indicate the SOE. High SOE was described as "is associated with" or simply "reduces/increases;" moderate SOE was described as "probably;" and low SOE was described as "may".

Assessing Applicability

Applicability to U.S. practice settings and the Medicare population (i.e., patients eligible for Medicare due to age 65 or greater or disability [including end-stage renal failure (ESRD)]) were assessed based on the AHRQ Methods Guide, using the PICOTS framework.[45] Applicability refers to the degree to which outcomes associated with the intervention are likely to be similar across patients and settings relevant to the care of the Medicare population based on the populations, interventions, comparisons, and outcomes synthesized across included studies. Factors that may affect applicability, which we identified a priori, include: (1) patient factors (e.g., age and disability status, medical and psychiatric comorbidities, symptom severity, duration and underlying pain condition); (2) technical factors (e.g., medications used [for procedures that involve medications], intensity or dose, number of treatments, frequency of treatments, duration of treatment, use of imaging guidance, technique utilized, and clinical background of person performing the procedure [e.g., anesthesia pain medicine, interventional radiology, or other]); (3) comparators (e.g., sham procedure, no treatment, or usual care); (4) outcomes (e.g., use of nonstandardized or unvalidated outcomes); and (5) settings (e.g., country). We used information regarding these factors to assess the extent to which interventions and results are likely most relevant to real-world clinical practice in typical U.S. settings that include the Medicare population and provided a qualitative summary of our assessment.

Peer Review and Public Commentary

Experts were invited to provide external peer review of this systematic review; AHRQ and an associate editor also provided comments. In addition, the draft report was posted on the AHRQ website for 4 weeks for public comment. Comments were reviewed, considered, and addressed

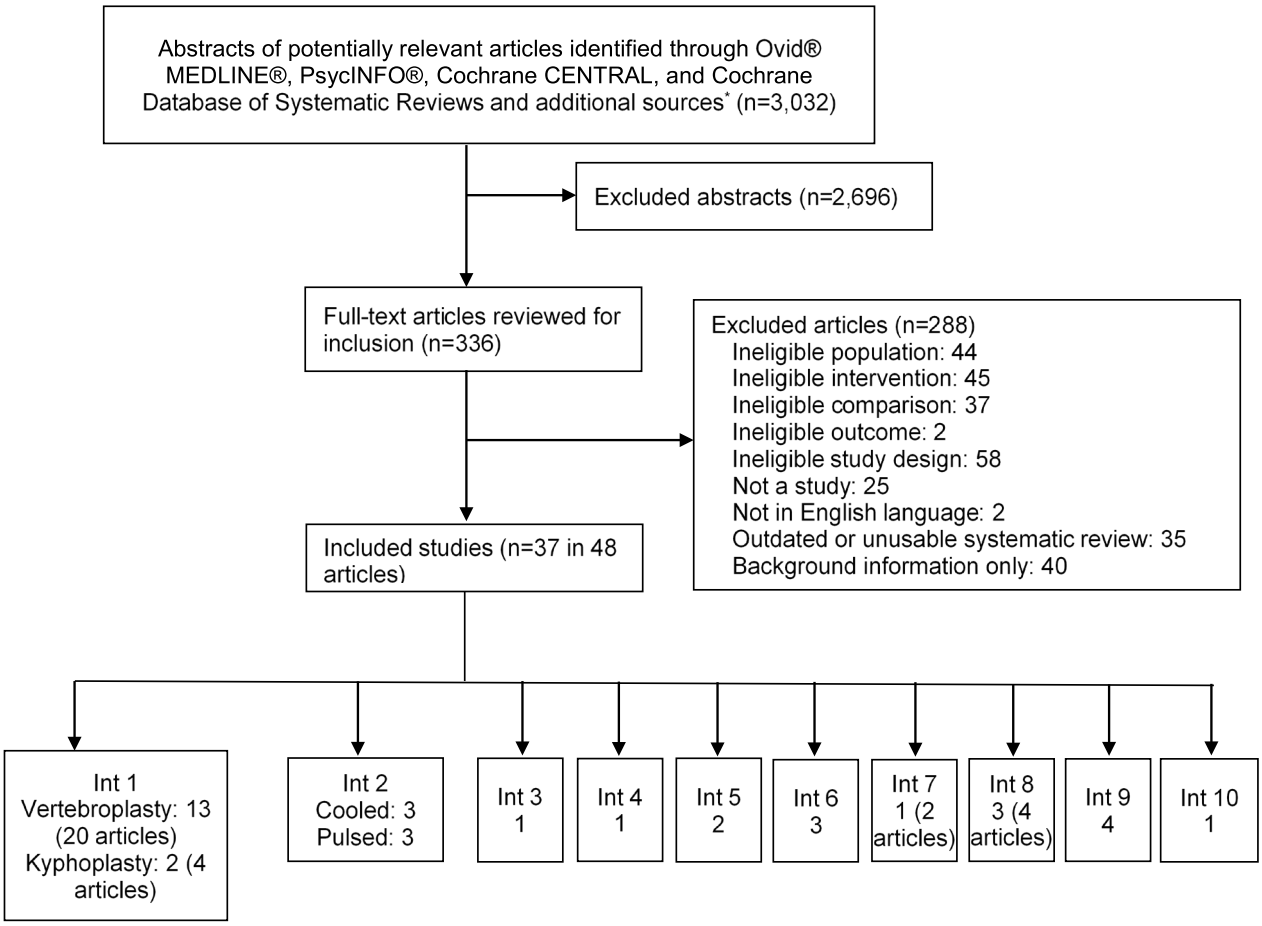
as appropriate. Edits were made for clarity and accuracy; however, no changes were made to the evidence or to our conclusions.

Results

Results of Literature Search

A total of 3,032 references from electronic database searches and reference lists were reviewed. From these, 336 full-text papers were evaluated for inclusion. After review of full-text papers, 288 articles were excluded. Across all interventions, 37 randomized controlled trials (RCTs) (in 48 publications) were included (**Figure 1 and Appendix F**). Thirteen trials addressed vertebroplasty, two kyphoplasty, four piriformis injections, three occipital nerve stimulation, three cooled radiofrequency, three pulsed radiofrequency, two methylene blue, three ozone, and one each sphenopalatine block, platelet-rich plasma, stem cells, and peripheral nerve stimulation. See **Appendix G** for data abstraction tables, **Appendix H** for quality tables, and **Appendix I** for additional meta-analysis results.

Figure 1. Literature flow diagram



Abbreviations: Int = interventional procedures and conditions†

*Additional sources include suggested references, reference lists, etc.

† Int 1=vertebral augmentation procedures (vertebroplasty and kyphoplasty) for pain due to vertebral compression fracture, Int 2=cooled radiofrequency denervation for degenerative back or hip pain and pulsed radiofrequency denervation for degenerative back pain, Int 3=intradiscal and facet joint platelet-rich plasma for presumed discogenic back pain, Int 4=intradiscal stem cells for presumed discogenic back pain, Int 5=intradiscal methylene blue for presumed discogenic back pain, Int 6=intradiscal ozone for

radicular low back pain or nonradicular, presumed discogenic back pain (protocol modification to include intradiscal ozone plus corticosteroid), Int 7=sphenopalatine block for trigeminal neuralgia or headache, Int 8=occipital stimulation for headache, Int 9=piriformis injection (local anesthetic, corticosteroid, and/or botulinum toxin) for piriformis syndrome, Int 10=peripheral nerve stimulation for ulnar, median, or radial neuropathy

Vertebral Augmentation Procedures for Vertebral Compression Fractures

Vertebroplasty

Key Points

- Vertebroplasty for vertebral compression fracture (13 trials, N=1685, mean age 66 to 80 years) was associated with a small reduction in pain intensity versus sham vertebroplasty or usual care at 1 to 2 weeks (10 trials, N=1093), 1 to 6 months (10 trials, N=1094), 6 to 12 months (8 trials, N=993), and 12 months and longer (9 trials, N=965); and a moderate reduction at 2 to 4 weeks (8 trials, N=918) (strength of evidence [SOE]: low at 1 to 2 weeks, moderate at other time points). Restricting to sham vertebroplasty controls (5 trials, N=536) tended to decrease benefits (no difference at 1 to 2 weeks and small at other time points), but the difference between sham and usual care trials was only statistically significant at 2 to 4 weeks (p for interaction=0.01). Benefits also tended to be larger in trials of patients with more acute compared with less acute pain, but differences were not statistically significant.
- There was insufficient evidence to determine effects of vertebroplasty on function at 1 to 2 weeks (7 trials, N=743), due to marked inconsistency between sham trials (no benefit) and usual care trials (small benefit) Vertebroplasty was associated with a small improvement versus sham or usual care in function at 2 to 4 weeks (6 trials, N=708), 1 to 6 months (7 trials, N=637), 6 to 12 months (6 trials, N=690), and ≥12 months (6 trials, N=612). (SOE: insufficient for 1 to 2 weeks, moderate for 1 to 6 months and 12 months and longer, and high for 2 to 4 weeks and 6 to 12 months).
- Vertebroplasty was not associated with increased risk of incident vertebral fracture at 12 months and longer (7 trials, N=826); evidence on serious adverse events was sparse and imprecise but did not indicate increased risk (SOE: moderate for vertebral fracture, low for serious adverse events).
- Three trials that conducted within-study subgroup analyses found no interaction between duration of symptoms and effects of vertebroplasty and one trial found no interaction between sex or prior vertebral fracture and effects of vertebroplasty.
- A stratified analysis of vertebroplasty trials found no interaction between polymethyl methacrylate (PMMA) volume and effects of vertebroplasty.

Description of Included Studies

Thirteen trials (reported in 20 publications) compared vertebroplasty versus a sham procedure (5 trials)[79-83] or usual care (8 trials)[84-91] (**Appendix Table G-1 to G-3 and Table 2**). Sample sizes ranged from 34 to 400 (N=1685). Seven trials were conducted in Europe,[81,82,84,87-90] two trials in Australia,[79,80] two trials in China,[85,91] and one trial in Iran;[86] one trial[83] was conducted in the United Kingdom, Australia, and the United States. The mean age of enrollees

ranged from 66 to 80 years; in one trial[88] that did not report the mean age the range was 56 to 82 years. One trial[88] was restricted to females and in the others, the proportion female ranged from 64 to 87 percent. The trials focused on patients with osteoporotic compression fractures and excluded patients with fracture due to cancer. Two trials restricted inclusion to patients with acute pain (up to 4 to 6 weeks),[88,91] five trials restricted inclusion to patients with acute or subacute pain (up to 6 to 10 weeks),[80-82,87,89] three trials enrolled patients with acute, subacute, or chronic pain (up to 12 months),[79,83,84] and three trials restricted inclusion to patients with subacute or chronic pain (≥3 months,[85] 4 weeks to 1 year,[86] or 6 weeks to 5 months[90]). Mean or median pain duration was <4 weeks in four trials,[80,88,89,91] 4 to 8 weeks in three trials (including one trial that did not report average pain duration but was restricted to patients with pain for ≤8 weeks),[81,82,87] and ≥8 weeks in six trials.[79,83-86,90] Ten trials[80-82,84-88,90,91] required participants to have magnetic resonance imaging (MRI) findings consistent with bone marrow edema at the vertebral fracture site, a marker of greater acuity. The average volume of PMMA used in vertebroplasty ranged from 2.6 to 7.5 ml; two trials[80,81] reported use of greater than 5 ml and the others reported less than 5 ml or did not report the PMMA volume. The duration of followup ranged from 6 to 24 months.

Four trials were rated good quality,[79-81,83] five trials were rated fair quality,[82,84,85,87,90] and four trials poor quality[86,88,89,91] (**Appendix Table H-1**). The good-quality trials utilized sham vertebroplasty for blinding; sham procedures consisted of needle insertion or pressure on the back to simulate needle insertion, tapping to simulate entry of the needle into bone, and preparation of PMMA to mimic the sounds and smells of vertebroplasty. In three of the five sham-controlled trials, patients randomized to sham received the same periosteal infiltration of local anesthetic as patients randomized to vertebroplasty.[79,81,83] In one sham-controlled trial,[82] local anesthetic was injected into the vertebral body and in the fifth trial,[80] patients randomized to sham received subcutaneous but not periosteal local anesthetic. In the open-label trials, usual care consisted of various nonsurgical therapies (analgesics, physical therapy, graded activity, and braces or walking aids), but only one trial[86] described specific medications and doses. In addition to open-label design, other limitations in the fair-quality trials (including one sham-controlled trial)[82] included failure to report randomization or allocation concealment methods, baseline group differences, high attrition, or lack of intent-to-treat analysis. One poor-quality trial[88] did not report efficacy outcomes in the usual care arm and another poor-quality trial[86] had serious data discrepancies—implausible values for standard deviations or results (mean differences, 95% confidence intervals [CIs], and p values) inconsistent with reported data. Therefore, neither of these trials was utilized in efficacy meta-analyses, but contributed data on harms.

Table 2. Study characteristics of vertebroplasty trials

Study, Year Country Quality	Mean Age (Years)	Percent Female	Number Randomized	Pain Duration Inclusion Criteria	Mean/Median Pain Duration (Weeks)	PMMA Volume (ml)	Bone Marrow Edema on MRI Required	Control Type	Duration of Followup (Months)
Buchbinder, 2009[79,92,93] Australia Good	77	79	78	Up to 12 months	9.0 to 9.5	2.8	No	Sham (including periosteal local anesthetic)	24
Clark, 2016[80,94] Australia Good	80	73	120	<6 weeks	2.6	7.5	Yes	Sham (subcutaneous but not periosteal local anesthetic)	6
Firanescu, 2018[81,95] the Netherlands Good	75.8	75	180	≤9 weeks	5 to 8	5.1	Yes	Sham (including periosteal local anesthetic)	12
Hansen, 2019[82] Denmark Fair	69.9	87	52	≤8 weeks	NR	2 to 4	Yes	Sham (including local anesthetic into vertebral body)	12
Kallmes, 2009[83,96] U.K., Australia, U.S. Good	73.8	76	131	Up to 12 months	17.8	2.6	No	Sham (including periosteal local anesthetic)	12
Blasco, 2012[84] Spain Fair	73.2	78	125	Up to 12 months	20.4	NR	Yes	Usual care	12
Chen, 2014[85] China Fair	65.5	70	96	≥3 months	30.4	3.6	Yes	Usual care	12
Farrokhi, 2011[86] Iran Poor	72 to 74	73	82	4 weeks to 1 year, mean 27 to 30 weeks	27 to 30	3.5	Yes	Usual care	36
Klazen, 2010[87,97] the Netherlands and Belgium Fair	75.3	69	202	≤6 weeks	4	4.1	Yes	Usual care	12
Leali, 2016[88] Italy, France, Switzerland Poor	NR (range 56 to 82)	100	400	Acute (not defined)	NR	4	Yes	Usual care	6

Study, Year Country Quality	Mean Age (Years)	Percent Female	Number Randomized	Pain Duration Inclusion Criteria	Mean/Median Pain Duration (Weeks)	PMMA Volume (ml)	Bone Marrow Edema on MRI Required	Control Type	Duration of Followup (Months)
Rousing, 2009[89,98] Denmark Poor	80	82	50	≤8 weeks	1.1	NR	No	Usual care	12
Voormolen, 2007[90] the Netherlands Fair	73	82	34	6 weeks to 5 months	11.7	3.2	Yes	Usual care	12
Yang, 2016[91] China Poor	76.7	64	135	Acute (not defined)	0.8	4.5	Yes	Usual care	12

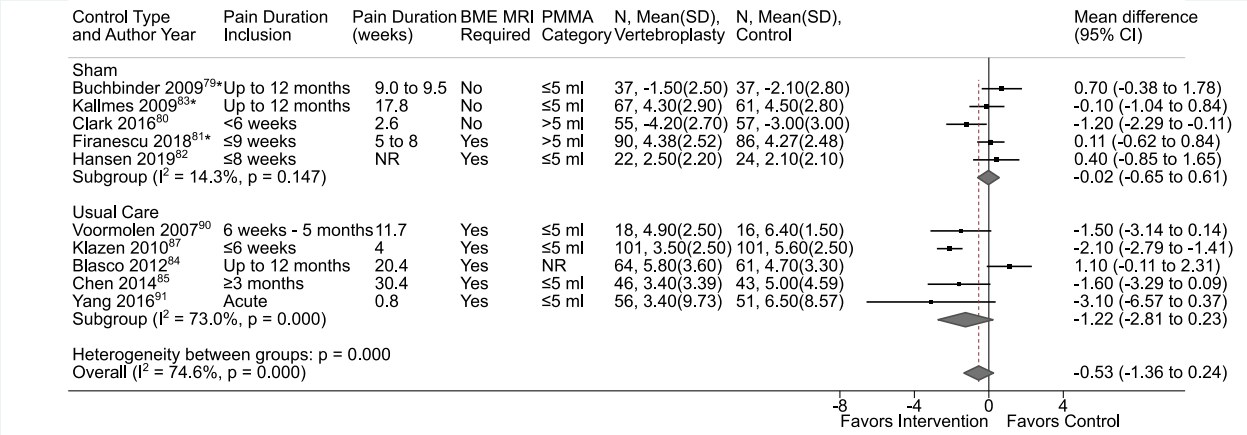
Abbreviations: MRI = magnetic resonance imaging; NR = not reported; PMMA = polymethyl methacrylate

Detailed Synthesis

Pain

At 1 to 2 weeks, the difference between vertebroplasty versus sham or usual care was small and not statistically significant (10 trials, mean difference -0.53 on a 0 to 10 scale, 95% CI, -1.36 to 0.24, I^2=75%, **Figure 2**).[79-85,87,90,91] Vertebroplasty was associated with a moderate reduction in pain intensity versus sham vertebroplasty or usual care at 2 to 4 weeks to 1 month (8 trials, mean difference -1.05 on a 0 to 10 scale, 95% CI, -1.80 to -0.32, I^2=64%, **Figure 3**),[79-83,85,87,91] with a small reduction in pain intensity at 1 to 6 months (10 trials, mean difference -0.76, 95% CI, -1.17 to -0.38, I^2=5.5%, **Figure 4**),[79-85,87,89,91] 6 to 12 months (8 trials, mean difference -0.73, 95% CI, -1.33 to -0.15, I^2=43%, **Figure 5**),[79-81,83-85,87,91] and 12 months and longer (9 trials, mean difference -0.87, 95% CI, -1.43 to -0.31, I^2=42%, **Figure 6**).[79,81-85,87,89,91] At 2 to 4 weeks, the pain reduction between trials using sham control versus usual care was significantly different (p for interaction=0.01). Pain reduction in sham controlled trials was significantly lower (5 trials, mean difference -0.57, 95% CI, -1.09 to -0.05, I^2=0%) than in trials of usual care (3 trials, mean difference -2.27, 95% CI, -3.20 to -0.94, I^2=0%). Among the sham controlled trials, the largest effect (mean difference -1.40, 95% CI -2.44 to -0.36) was observed in the trial that enrolled patients with the most acute symptoms (<6 weeks, mean 2.6 weeks).[80] At other time points, there were no statistically significant differences in pain reduction between trials using sham or usual care controls, though across time points estimates were smaller with sham than usual care and stratified estimates were imprecise (**Appendix Tables I-1 and I-2**). Benefits also tended to be larger in trials that enrolled patients with more acute pain. However, differences were not statistically significant, only one trial[91] restricted enrollment to patients with acute pain, and only one sham-controlled trial[80] reported mean pain duration of <4 weeks. Reductions in pain intensity also did not differ according to presence of bone marrow edema on MRI (required to be enrolled in trial versus not required), PMMA volume (>5 or ≤5 ml), or study quality (good, fair, or poor). However, subgroup estimates were based on small numbers of trials and were imprecise. For analyses with at least 10 trials, graphical and statistical tests did not indicate small study effects (p for Egger's test=0.59 at 1 to 2 weeks [**Appendix Figure I-1**] and p=0.62 at 1 to 6 months [**Appendix Figure I-2**]).

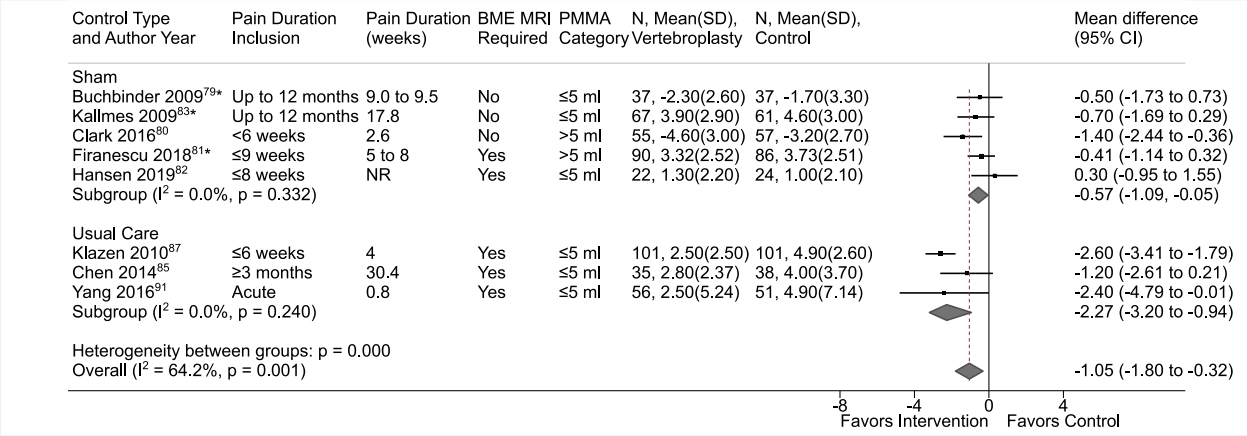
Figure 2. Vertebroplasty versus sham or usual care, pain (continuous) at 1 to 2 weeks



Abbreviations: BME = bone marrow edema; CI = confidence interval; MRI = magnetic resonance imaging; PMMA = polymethyl methacrylate; SD = standard deviation

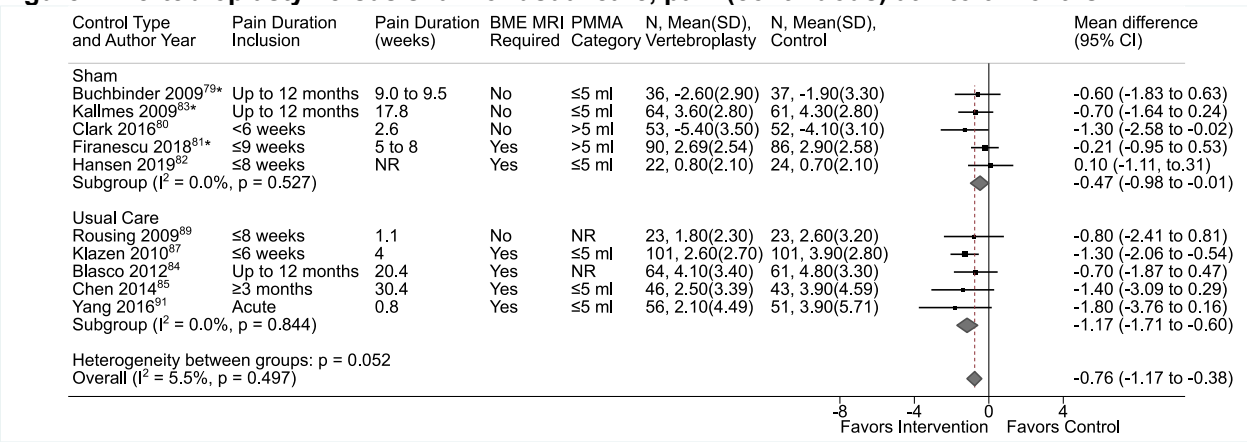
*Adjusted mean difference from a regression model was used

Figure 3. Vertebroplasty versus sham or usual care, pain (continuous) at 2 to 4 weeks



Abbreviations: BME = bone marrow edema; CI = confidence interval; MRI = magnetic resonance imaging; PMMA = polymethyl methacrylate; SD = standard deviation

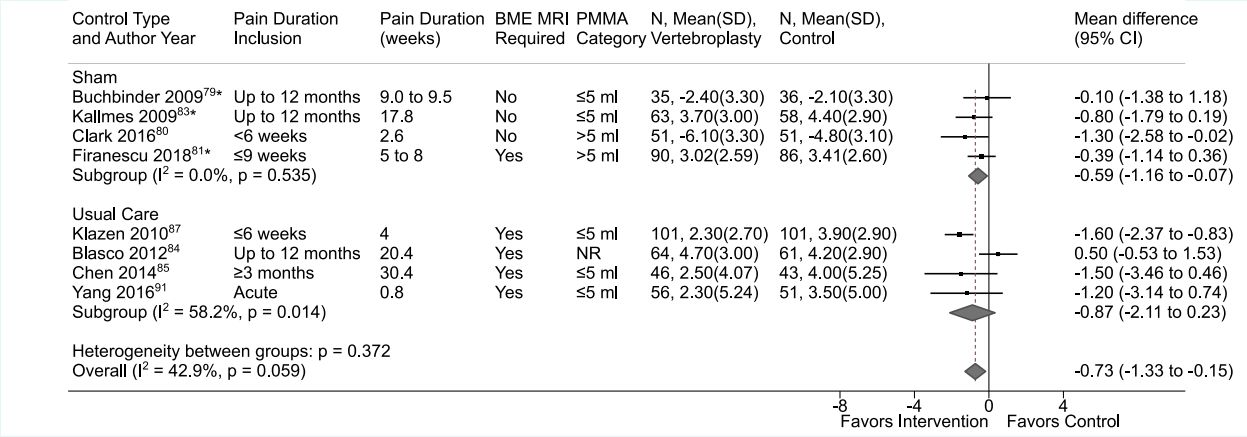
Figure 4. Vertebroplasty versus sham or usual care, pain (continuous) at 1 to 6 months



Abbreviations: BME = bone marrow edema; CI = confidence interval; MRI = magnetic resonance imaging; PMMA = polymethyl methacrylate; SD = standard deviation

*Adjusted mean difference from a regression model was used

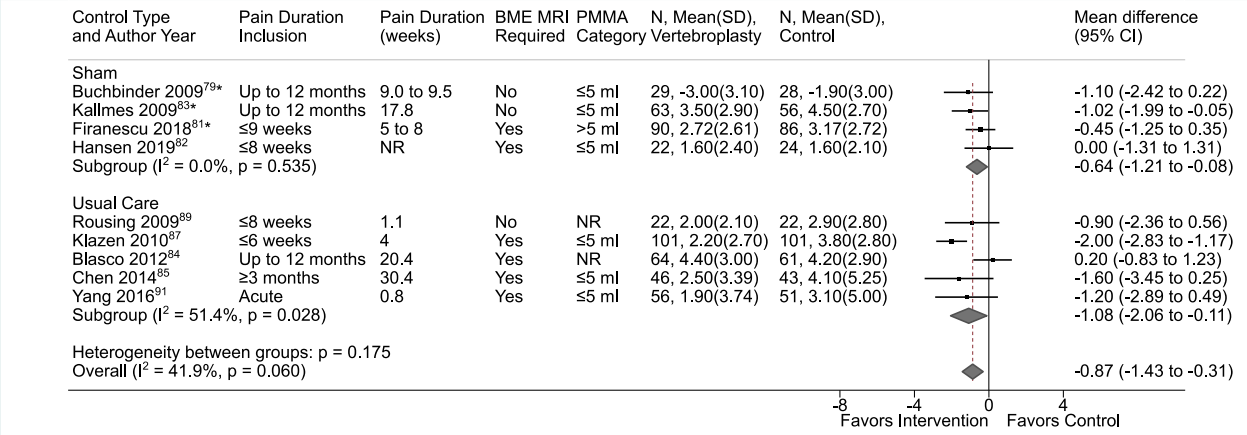
Figure 5. Vertebroplasty versus sham or usual care, pain (continuous) at 6 to 12 months



Abbreviations: BME = bone marrow edema; CI = confidence interval; MRI = magnetic resonance imaging; PMMA = polymethyl methacrylate; SD = standard deviation

*Adjusted mean difference from a regression model was used

Figure 6. Vertebroplasty versus sham or usual care, pain (continuous) at 12 months and longer

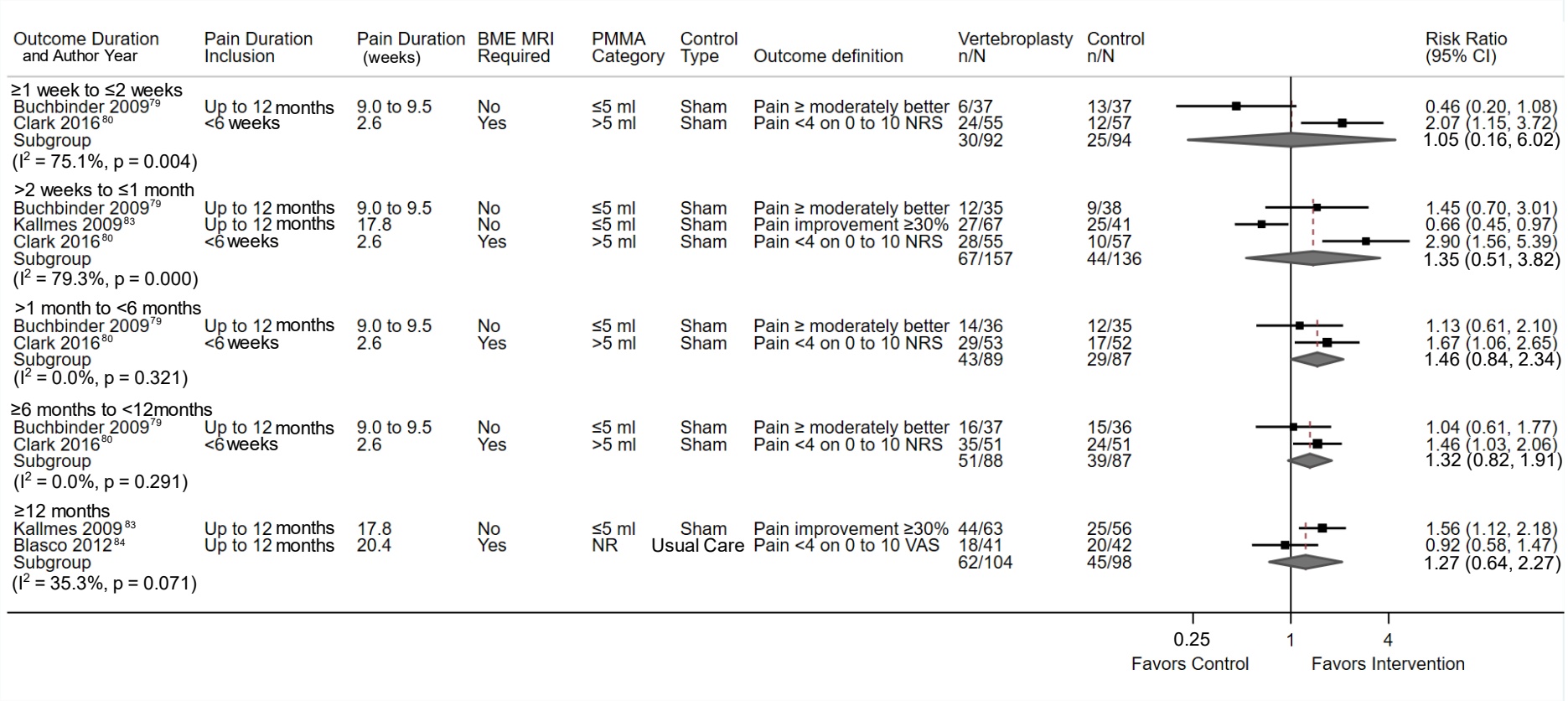


Abbreviations: BME = bone marrow edema; CI = confidence interval; MRI = magnetic resonance imaging; PMMA = polymethyl methacrylate; SD = standard deviation

*Adjusted mean difference from a regression model was used

Few trials evaluated the association between vertebroplasty versus sham or usual care and likelihood of experiencing a pain response (defined as pain at least moderately better,[79] pain <4 on a 0 to 10 numeric rating scale (NRS),[80,83,84] or pain improvement ≥30%[83]). Results favored vertebroplasty at 2 to 4 weeks (3 trials),[79,80,83] 1 to 6 months (2 trials),[79,80] 6 to 12 months (2 trials),[79,80] and 12 months and longer (2 trials),[83,84] with relative risk (RR) estimates that ranged from 1.27 to 1.46 (**Figure 7 and Appendix Table I-3**). However, estimates were imprecise and nonstatistically significant. At 1 to 2 weeks, the estimate was very imprecise (2 trials, RR 1.05, 95% CI, 0.16 to 6.02, I^2=75%).[79,80]

Figure 7. Vertebroplasty versus sham or usual care and likelihood of a pain response

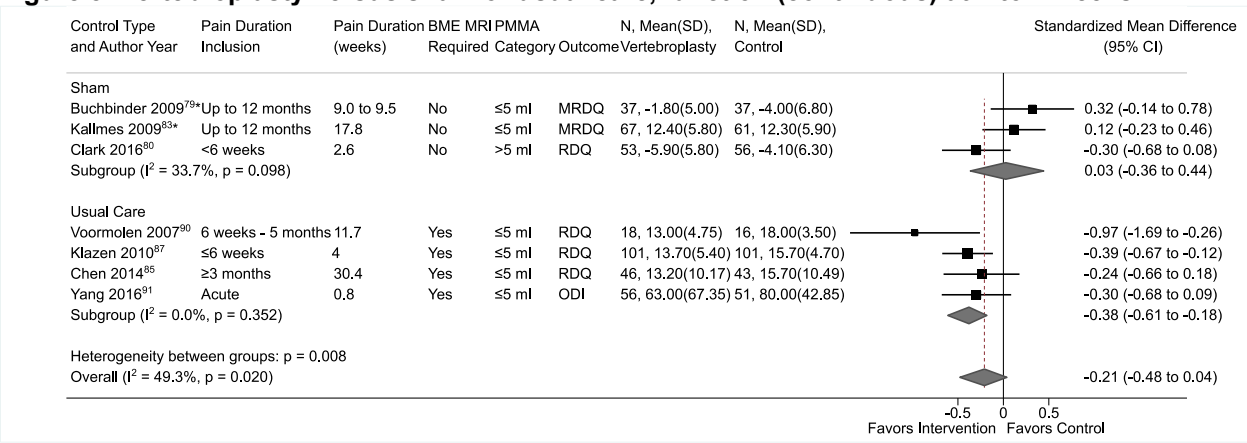


Abbreviations: BME = bone marrow edema; CI = confidence interval; MRI = magnetic resonance imaging; PMMA = polymethyl methacrylate; SD = standard deviation

Function

Vertebroplasty was also associated with a small improvement in back-related function versus sham or usual care at 1 to 2 weeks (standard mean deviation [SMD] -0.21, 95% CI, -0.48 to 0.04, I^2=49%, **Figure 8**).[79,80,83,85,87,90,91] However, the estimate was imprecise and statistical heterogeneity was present. Vertebroplasty was associated with a small improvement in back-related function versus sham or usual care at 2 to 4 weeks (6 trials, SMD -0.27, 95% CI, -0.42 to -0.12, I^2=0%, **Figure 9**),[79,80,83,85,87,91] 1 to 6 months (7 trials, SMD -0.28, 95% CI, -0.43 to -0.11, I^2=0%, **Figure 10**),[79,80,83,85,87,89,91] 6 to 12 months (6 trials, SMD -0.29, 95% CI, -0.45 to -0.14, I^2=0%, **Figure 11**),[79,80,83,85,87,91] and at 12 months and longer (6 trials, SMD -0.23, 95% CI, -0.39 to -0.06, I^2=0%, **Figure 12**).[79,83,85,87,89,91] All trials except for two assessed function using the Roland-Morris Disability Questionnaire (RDQ) (scale 0 to 24) or modified RDQ (scale 0 to 23); differences on the RDQ or modified RDQ at these times points ranged from -1.64 to -1.90 points. At 1 to 2 weeks, there was marked inconsistency between the estimate from trials of sham (3 trials, SMD 0.03, 95% CI, -0.36 to 0.44, I^2=34%) and usual care (3 trials, SMD -0.38, 95% CI, -0.61 to -0.18, I^2=0%), though the difference was not statistically significant (p for interaction=0.10). At other time points, estimates from sham and usual care trials were similar. Effects of vertebroplasty on function did not differ based on average pain duration at enrollment or study quality (**Appendix Tables I-4 and I-5**). However, subgroup analyses were limited by small numbers of trials, with imprecise estimates.

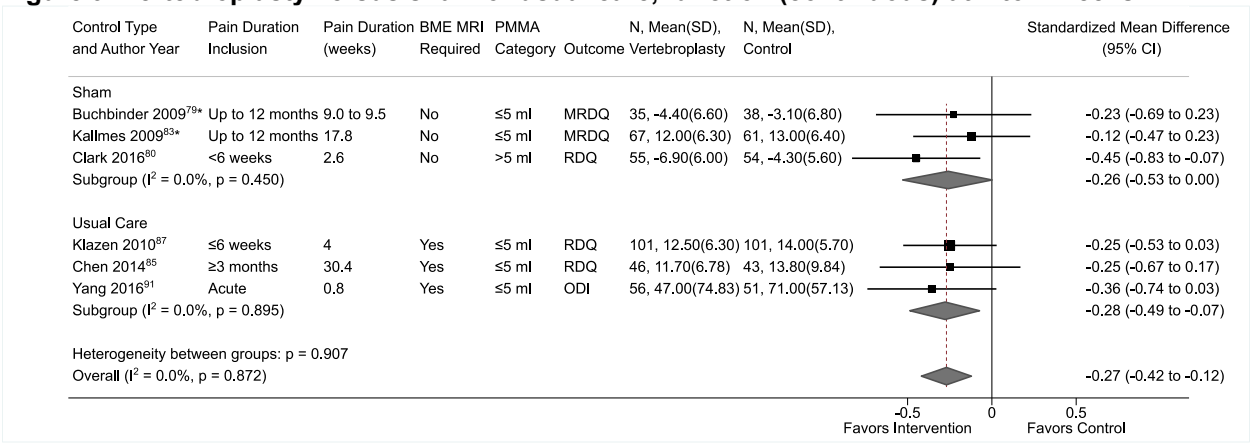
Figure 8. Vertebroplasty versus sham or usual care, function (continuous) at 1 to 2 weeks



Abbreviations: BME = bone marrow edema; CI = confidence interval; MRI = magnetic resonance imaging; PMMA = polymethyl methacrylate; SD = standard deviation

*Adjusted mean difference from a regression model was used

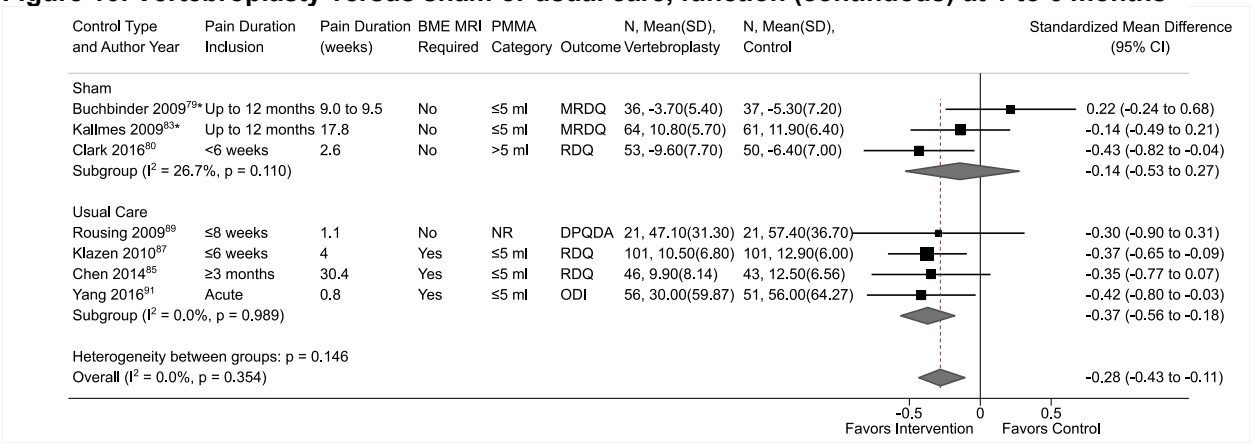
Figure 9. Vertebroplasty versus sham or usual care, function (continuous) at 2 to 4 weeks



Abbreviations: BME = bone marrow edema; CI = confidence interval; MRI = magnetic resonance imaging; PMMA = polymethyl methacrylate; SD = standard deviation

*Adjusted mean difference from a regression model was used

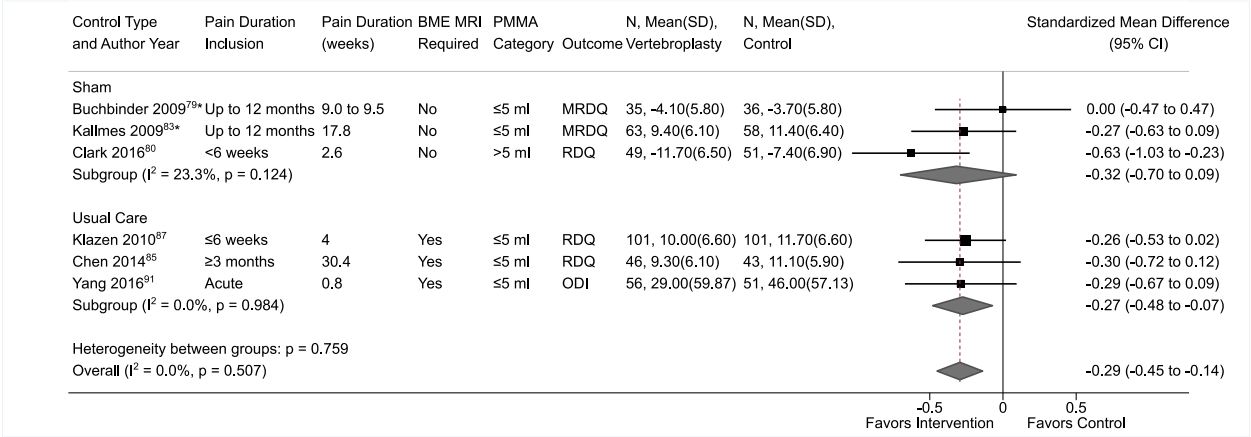
Figure 10. Vertebroplasty versus sham or usual care, function (continuous) at 1 to 6 months



Abbreviations: BME = bone marrow edema; CI = confidence interval; MRI = magnetic resonance imaging; PMMA = polymethyl methacrylate; SD = standard deviation

*Adjusted mean difference from a regression model was used

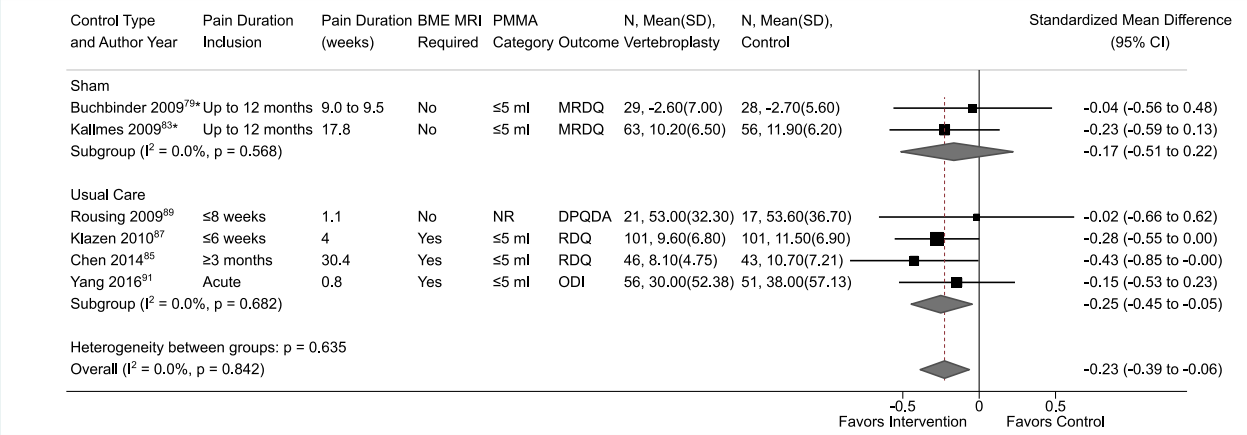
Figure 11. Vertebroplasty versus sham or usual care, function (continuous) at 6 to 12 months



Abbreviations: BME = bone marrow edema; CI = confidence interval; MRI = magnetic resonance imaging; PMMA = polymethyl methacrylate; SD = standard deviation

*Adjusted mean difference from a regression model was used

Figure 12. Vertebroplasty versus sham or usual care, function (continuous) at 12 months and longer



Abbreviations: BME = bone marrow edema; CI = confidence interval; MRI = magnetic resonance imaging; PMMA = polymethyl methacrylate; SD = standard deviation

*Adjusted mean difference from a regression model was used

Only one trial (mean pain duration at enrollment 17.8 weeks) evaluated the association between vertebroplasty versus sham or usual care and likelihood of experiencing functional improvement (defined as RDQ improved ≥30%).[83] Vertebroplasty was associated with reduced likelihood of functional improvement versus sham at 2 to 4 weeks (relative risk [RR] 0.66, 95% CI, 0.45 to 0.97), but increased likelihood at 12 months and longer (RR 1.56, 95% CI, 1.12 to 2.18).

Other Outcomes

Vertebroplasty was associated with a small improvement versus sham or usual care in general quality of life as measured by the EuroQOL 5-Dimension Questionnaire (EQ-5D) at 2 to 4 weeks (4 trials, mean difference 0.05, 95% CI, 0.02 to 0.09, I^2=0%, **Appendix Figure I-3**)[79,80,83,87] and at 6 to 12 months (3 trials, mean difference 0.06, 95% CI, 0.02 to 0.11, I^2=0%, **Appendix Figure I-4**).[79,80,87] At other time points there were no differences or the difference was not statistically significant (**Appendix Figures I-5 to I-7**). Effects of vertebroplasty on the EQ-5D did not significantly differ according to study quality, but subgroup analyses were limited by small numbers of trials and estimates were imprecise (**Appendix Tables I-6 and I-7**).

Vertebroplasty was associated with no difference in Quality of Life Questionnaire of the European Foundation for Osteoporosis (QUALEFFO) scores (a vertebral fracture-specific measure of quality of life) at all time points (**Appendix Figures I-8 to I-12**).[79,80,84,87,90,91] Differences on the QUALEFFO were very small (below the threshold for small), ranging from -1.45 to -2.98 points on a 0 to 100 scale. There was no statistically significant difference in effects of vertebroplasty on the QUALEFFO score based on control type or study quality, but subgroup analyses were limited by small numbers of trials and estimates were imprecise (**Appendix Tables I-6 and I-7**).

Vertebroplasty was associated with no difference versus sham or usual care in Short-Form 36 Health Survey Physical Component Score (SF-36 PCS) or Short-Form 36 Health Survey Mental Component Score (SF-36 MCS) at any time point (mean differences 1.16 points on a 0 to 100 scale favoring vertebroplasty to -3.08 points favoring controls), but findings were based on one or two trials and most estimates were imprecise (**Appendix Figures I-13 and I-14, and Appendix Table I-8**).[82,83,89]

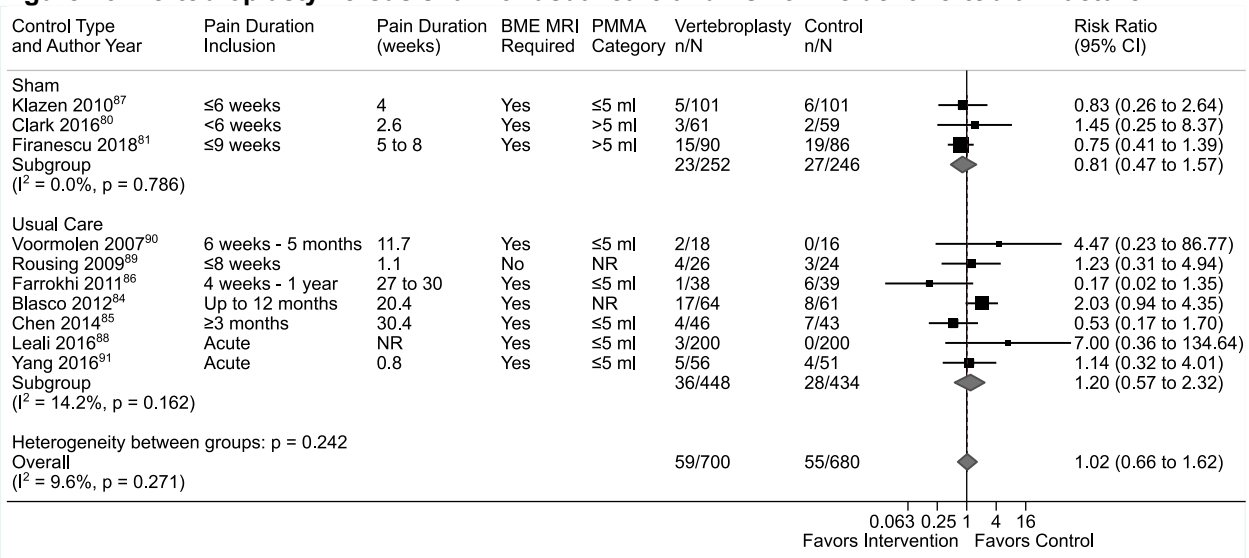
Estimates for effects of vertebroplasty versus sham or usual care on likelihood of opioid use (defined as continued opioid use[79,81,83,84] or major opioid use) were imprecise, based on one to three trials at each time point (**Appendix Figure I-15 and Appendix Table I-3**). One other trial found similar rates of opioid use with vertebroplasty versus sham at 12 weeks and 12 months, but data were not provided.[82] Three trials found vertebroplasty associated with decreased likelihood of pain medication use (not restricted to opioids). In one trial, RR estimates ranged from 0.23 to 0.37 at 1 week to 12 months. In the other two trials, results were reported as statistically significant but risk estimates were not provided.[87,88]

Harms

Vertebroplasty was not associated with increased risk of incident vertebral fracture versus sham or usual care, though some imprecision was present (10 trials, RR 1.02, 95% CI, 0.66 to 1.62, I^2=9.6%, **Figure 13**).[80,81,84-91] Results were similar when the analysis was restricted to trials with ≥12 months followup (7 trials, RR 0.94, 95% CI, 0.55 to 1.49, I^2=15%).[81,84-87,89,91] There was no interaction between control type, pain duration, requirement for bone marrow edema on MRI for inclusion, PMMA volume, or study quality and risk of incident fracture, but stratified analyses were limited by small numbers of trials and imprecision. Estimates at 1 to 2 weeks and at 6 to 12 months were very imprecise (**Appendix Table I-9**).

Vertebroplasty was not associated with increased risk of mortality versus sham or usual care (7 trials, RR 0.88, 95% CI, 0.50 to 1.53, I^2=0%, **Appendix Figure I-16**).[80,81,84,86-89] Findings were similar at 6 to 12 months (3 trials, RR 0.76, 95% CI, 0.23 to 2.65, I^2=0%)[80,84,88] or 12 months and longer (5 trials, RR 0.98, 95% CI, 0.51 to 1.87, I^2=0%),[81,84,86,87,89] but estimates were more imprecise **(Appendix Table I-9**). Estimates for risk of serious adverse events were also imprecise at 6 to 12 months (subgroup analysis of patients with pain ≤3 weeks in the VAPOUR, vertebroplasty for acute painful osteoporotic fractures, trial,[80] RR 0.67, 95% CI, 0.12 to 3.79)[94] and 12 months and longer (1 trial, RR 0.95, 95% CI, 0.06 to 14.90),[83] based on few events (5 and 2, respectively). One poor-quality trial found vertebroplasty associated with decreased risk of any adverse event versus usual care (16.1% vs. 35.3%, RR 0.46, 95% CI, 0.23 to 0.92).[91]

Figure 13. Vertebroplasty versus sham or usual care and risk of incident vertebral fracture



Abbreviations: BME = bone marrow edema; CI = confidence interval; MRI = magnetic resonance imaging; PMMA = polymethyl methacrylate; SD = standard deviation

Effects of Demographic, Clinical, and Technical Factors

Results of study-level stratified analyses based on pain duration are described above. Three trials of vertebroplasty also reported within-study subgroup analyses based on clinical or demographic factors. One trial found no interactions between duration of symptoms (<6 vs. ≥6 weeks, or as a continuous measure), sex, or prior vertebral fractures and effects of vertebroplasty on outcomes (p for interaction >0.10 for all of these factors).[79] Another study found that vertebroplasty was associated with decreased pain intensity in patients with <13 weeks (mean difference -0.8 on a 0 to 10 scale, 95% CI, -2.5 to 0.8) or 14 to 26 weeks of pain (mean difference -1.3, 95% CI, -3.4 to 0.8) but not in patients with 27 to 52 weeks of pain (mean difference 0.0, 95% CI, -1.6 to 1.7).[83] However, stratified estimates were imprecise, with overlapping CIs. The third trial also found no statistically significant difference between fracture duration (1 to 3 weeks vs. 4 to 6 weeks) and benefits of vertebroplasty, though benefits were larger in the more acute group (p for interaction 0.12).[94]

Evidence on how benefits and harms of vertebroplasty varied according to technical factors was very limited. As described above, a stratified analysis found no interaction between PMMA volume and effects on pain related to vertebral fracture.

Kyphoplasty

Key Points

- Kyphoplasty for vertebral compression fracture (2 trials, N=434, mean age 64 and 73 years) was associated with large reductions in pain and moderate to large improvement in function versus usual care at 1 week and 1 month in patients with or without cancer. No trial compared kyphoplasty against sham (SOE: low for function at 1 week; moderate for pain and for function at 1 month).
- In one trial (N=300) of patients without cancer, effects on pain and function were small to moderate at 3 months to 2 years (SOE: low).

- Evidence on incident or worsening vertebral fracture was inconsistent and imprecise, based on two trials (N=434) (SOE: insufficient).

Description of Included Studies

Two trials (n=134 and 300) compared kyphoplasty versus usual care for vertebral compression fracture (**Appendix Table G-1 to G-3 and Table 3**).[99-102] The population differed in the trials: one trial[102] (FREE, Fracture Reduction Evaluation trial) excluded patients with vertebral fractures related to cancer (mean age 73 years, 77% female); the other trial (CAFE [Cancer Patient Fracture Evaluation]) restricted inclusion to patients with cancer (mean age 64 years, 58% female).[99] Both trials were multinational; neither trial reported what type of provider performed kyphoplasty. In FREE, enrollment was restricted to patients with fracture duration of 3 months or more (mean 6 weeks) with bone marrow edema on MRI; CAFE did not specify fracture duration (median 3.5 months) or require presence of bone marrow edema on imaging (67% had edema). Baseline pain intensity was similar in both trials (~7 on a 0 to 10 scale). Neither trial reported the PMMA volume utilized and both trials described usual care as involving various nonsurgical treatments, but did not otherwise specify usual care. FREE reported followup through 2 years.[100,102] Although CAFE evaluated outcomes through 6 months, crossover from usual care to kyphoplasty was high (59%) after 1 month (compared with 8% in FREE at 1 year); therefore, we focused on 1-month outcomes from CAFE. Both trials were rated fair quality, mainly due to open-label design and differential loss to followup (**Appendix Table H-1**).

Table 3. Study characteristics of kyphoplasty trials

Study, Year Country Quality	Mean Age (Years)	Percent Female	Number Randomized	Pain Duration Inclusion Criteria	Mean/Median Pain Duration (Weeks)	PMMA Volume (ml)	Bone Marrow Edema on MRI Required	Control Type	Duration of Followup (Months)
Berenson, 2011[99] Australia, Canada, Europe, U.S. Fair	63.9	58	134	Not specified	15.2	NR	No	Usual care	1
Wardlaw, 2009[100-102] Europe and U.S. Fair	73.2	77	300	≤3 months	6	NR	Yes	Usual care	24

Abbreviations: MRI = magnetic resonance imaging; NR = not reported; PMMA = polymethyl methacrylate

Detailed Synthesis

Pain

Both trials found kyphoplasty associated with reduced pain versus usual care. In FREE, effects were large at 1 week (analysis of variance [ANOVA] mean difference -2.2 on a 0 to 10 scale, 95% CI, -2.8 to -1.6), decreasing to small at 1 to 2 years (ANOVA mean difference -0.8 to -0.9).[100,102] In CAFE, the effects on pain were large at 1 week and 1 month (mean difference in change from baseline -3.5 to -3.3 on a 0 to 10 scale).[99] Neither trial evaluated pain as a dichotomous outcome.

Function

Both trials also found kyphoplasty associated with improved function versus usual care. Similar to effects on pain, FREE found that differences between kyphoplasty versus usual care on function were moderate at 1 month (ANOVA mean difference -4.0 on the 0 to 24 RDQ, 95% CI, -5.5 to -2.6) but the benefit was attenuated at 1 year (ANOVA mean difference -2.6, 95% CI, -4.1 to -2.0 at 1 year); at 2 years the effect was small (ANOVA mean difference -1.4, 95% CI, -1.4, p=0.05 [CI not reported]).[100,102] In CAFE, kyphoplasty was associated with a large improvement in RDQ versus usual care at 1 month (mean difference -8.4, 95% CI, -7.6 to -9.2).[99]

Other Outcomes

FREE found kyphoplasty associated with a small improvement in SF-36 PCS score versus placebo at 1 month (ANOVA mean difference 5.2 on a 0 to 100 scale, 95% CI, 2.9 to 7.4); differences were attenuated and below the threshold for small at longer followup and no longer statistically significant at 1 or 2 years.[100,102] Effects on the EQ-5D also favored kyphoplasty at 1 month (ANOVA mean difference 0.18 on a 0 to 1 scale, 95% CI, 0.08 to 0.28) but were attenuated at 1 or 2 years (ANOVA mean difference 0.12). Kyphoplasty was associated with decreased likelihood of any opioid use at 6 months (29.8% vs. 42.9%, p=0.4), with no difference by 1 year (28.0% vs. 33.7%, p=1.0); there was no difference in the likelihood of strong opioid use at 1 month or 1 year.

CAFE found kyphoplasty associated with moderate improvement versus usual care in SF-36 PCS score (mean difference in change from baseline 11.1, 95% CI, 10.7 to 11.5) and small improvement versus usual care in SF-36 MCS score (mean difference in change from baseline 8.4, 95% CI, 7.7 to 9.1) at 1 month.[99] Kyphoplasty was also associated with reduced likelihood of analgesic use at 1 month (52.3% vs. 82.0%, RR 0.64, 95% CI, 0.49 to 0.83).

Harms

FREE found no difference between kyphoplasty versus usual care in mortality, serious adverse events, or any adverse event, though estimates were imprecise.[101,102] The estimate for new of worsening fracture also was imprecise, but the proportion with this outcome was higher in the kyphoplasty arm (33.0% vs. 25.3%, absolute risk difference 7.7%, 95% CI, -4.5 to 20.0).

In CAFE, kyphoplasty was associated with increased likelihood of mortality (32.9%, vs. 18.8%, 95% CI, 0.95 to 3.23) and any adverse event (37.1% vs. 29.7%, RR 1.27, 95% CI, 0.78 to 2.06) that were not statistically significant.[99] However, there were few adverse events resulting in death (2.9% [2/70] vs. 1.6% [1/64]). There were also few incident symptomatic fractures (2.9% [2/70] vs. 7.8% [5/64]). Injury or procedural complications occurred in 5.7% (4/70) of patients in the kyphoplasty arm.

Alternatives to Conventional Radiofrequency Ablation

Cooled Radiofrequency Denervation

Key Points

Versus Sham Radiofrequency Denervation for Sacroiliac Pain

- Cooled radiofrequency denervation for sacroiliac pain was associated with a moderate to large reduction in pain and small to large improvement in function versus sham radiofrequency at 1 month (2 trials, N=79); improvements in pain and function at 3 months were moderate (1 trial, N=28) (SOE: moderate for pain and function at 3 months; low for function at 1 month).

Versus Conventional Radiofrequency Denervation for Presumed Facet Joint Pain

- Cooled radiofrequency denervation for presumed facet joint pain was associated with a small, nonstatistically significant reduction in pain versus conventional radiofrequency at 6 months and no difference in function (1 trial, N=43); there were no differences at earlier (1 or 3 month) followup (SOE: low).

Across Trials of Cooled and Pulsed Radiofrequency Denervation

- Harms were not well-reported, but when recorded were usually related to temporary increase in pain. No serious complications were reported (SOE: low).
- The mean age of participants ranged from 52 to 59 years.

Cooled Radiofrequency Denervation Versus Sham Radiofrequency Denervation for Sacroiliac Pain

Description of Included Studies

Two trials (n=28 and 51) evaluated cooled radiofrequency denervation versus sham radiofrequency for sacroiliac pain. (**Appendix Table G-4 to G-6 and Table 4**).[103,104] Both trials were conducted in the United States. Mean age was 52 and 59 years and the proportion female 61 to 72 percent. Both trials required patients to have pain in the sacroiliac area for at least 6 months and persistent pain despite standard nonoperative therapies. Patients had to have at least 75 percent pain relief with a single[103] or repeat[104]diagnostic sacroiliac block. Baseline pain intensity was ~6 on a 0 to 10 scale in both trials. In both trials, cooled radiofrequency denervation was performed with imaging guidance; details regarding the radiofrequency techniques are shown in **Table 4**. Sham radiofrequency involved needle placement as for active treatment, without radiofrequency lesioning; in one trial,[103] lidocaine was administered. Both trials were rated fair quality; methodological shortcomings included unclear randomization methods and high crossover without intent-to-treat analysis (**Appendix Table H-1**). Crossover was high: in one trial,[104] 94 percent (16/17) of patients randomized to sham treatment crossed over to cooled radiofrequency denervation after 3 months and in the other,[103] 64 percent (9/14) crossed over after 1 month. Therefore, results focus on outcomes prior to high crossover (3 and 1 months, respectively).

Table 4. Study characteristics and results for cooled radiofrequency ablation trials

Study, Year Country Quality	Mean Age (Years)	Percent Female	Number Randomized	Duration of Symptoms (Months)	Diagnostic Testing	Cooled or Pulsed Radiofrequency Parameters	Control Type	Duration of Followup (Months)	Pain	Function
Cohen, 2008[103] U.S. Fair	51.8	61	28	≥6	Sacroiliac joint block (single, ≥75% relief)	2 minutes at 60° C, target tissue heated to 75° C (L4 and L5 dorsal rami treated with conventional RF for 90 seconds at 80° C)	Sham RF	3	Dichotomous Successful outcome* 1 month: 79% vs. 14.3%, RR 5.50 (95% CI, 1.48 to 20.42) 3 months: 64% vs. 0%, RR 0.36 (95% CI, 0.18 to 0.72) Continuous NRS 0 to 10, mean (SD) 1 month: 2.4 (2.0) vs. 6.3 (2.4), p<0.05 3 months: 2.4 (2.3) vs. 6 (0), p>0.05	ODI 0 to 100, mean (SD) 1 month: 20.9 (10.9) vs. 43.6 (14), p<0.05 3 months: 18.5 (11.6) vs. 24 (8.5), p>0.05
Patel, 2012[104] U.S. Fair	58.7	72	51	>6	S1-S3 lateral branch and L5 dorsal ramus block (dual, ≥75% relief)	150 seconds at 60° C	Sham RF	3	Dichotomous ≥50% pain intensity improvement 3 months: 53% vs. 29%, RR 1.80 (95% CI, 0.80 to 4.01) Continuous NRS 0 to 10, mean change (SD) 1 month: -2.7 (2.6) vs. -1.7 (2.0), p=0.16 3 months: -2.4 (2.7) vs. -0.8 (2.4), p=0.04	Dichotomous ≥10% ODI improved 3 months: 41.2% vs. 5.9%, RR 7.00 (95% CI, 1.00 to 48.88) Continuous ODI 0 to 100, mean change (SD) 1 month: -12 (14) vs. -4 (11), p=0.046 3 months: -11 (17) vs. 2 (6), p=0.01

Study, Year Country Quality	Mean Age (Years)	Percent Female	Number Randomized	Duration of Symptoms (Months)	Diagnostic Testing	Cooled or Pulsed Radiofrequency Parameters	Control Type	Duration of Followup (Months)	Pain	Function
McCormick, 2019[105] U.S. Good	55.8	59	43	≥6	Medial branch block (single, >75% relief)	165 seconds at 60° C, target tissue heated to >80° C	Conventional RF (90 seconds at 80° C)	6	Dichotomous ≥50% NRS improved 6 months: 52.3% vs. 44.4%, RR 1.18 (95% CI, 0.61 to 2.28) Continuous NRS 0 to 10, mean change (SD) 6 months: -3.8 (2.5) vs. -3.0 (3.2), p=0.41	Dichotomous ≥30% ODI improved 6 months: 61.9% vs. 44.4%, RR 1.39 (95% CI, 0.75 to 2.58) Continuous ODI 0 to 100, mean change (SD) 6 months: -11.3 (11.2) vs. -8.1 (12.3), p=0.40

Abbreviations: CI = confidence interval; NR = not reported; NRS = numeric rating scale; ODI = Oswestry Disability Index; PRF = pulsed radiofrequency ablation; RF = radiofrequency ablation; RR = relative risk; SD = standard deviation; VAS = visual analogue scale

*Successful outcome was defined as ≥50% improvement in pain, positive Global Perceived Effect, and ≥10-point improvement in ODI or ≥4 point improvement in ODI and >20% reduction in opioid use or complete cessation of nonopioid analgesic

Detailed Synthesis

Pain

Both trials found cooled radiofrequency associated with reduced pain versus sham at 1 month; effects were moderate to large (mean difference 1.0 to 2.9 points on a 0 to 10 scale).[103,104] At 3 months, one trial found cooled radiofrequency associated with a persistent moderate reduction in pain (mean change from baseline -2.4 vs. -0.8, p=0.04).[103] In this trial, cooled radiofrequency was also associated with increased likelihood of pain intensity improvement of at least 50 percent at 3 months, though the difference was not statistically significant (53% vs. 29%, RR 0.81, 95% CI, 0.81 to 4.01).[103]

Function

Both trials found cooled radiofrequency associated with improved function versus sham at 1 month; effects were small in one trial (mean change from baseline -12 vs. -4 on the 0 to 100 Oswestry Disability Index [ODI], p=0.046)[103] and large in the other trial (mean 20.9 vs. 43.6 on the ODI, p<0.05).[104] One trial found cooled radiofrequency associated with a moderate improvement versus sham in ODI at 3 months (mean change from baseline -11 vs. 2, p=001).[103] In this trial, patients randomized to cooled radiofrequency were also more likely to experience an ODI improvement of at least 10 points (41% vs. 5.9%, RR 7.00, 95% CI, 1.00 to 48.88).

Other Outcomes

One trial found cooled radiofrequency associated with improved SF-36 PCS versus sham at 3 months (mean change from baseline 14 vs. 3 on 0 to 100 scale, p=0.04); the difference at 1 month was small and not statistically significant.[103] Cooled radiofrequency was also associated with improvement in Assessment of Quality of Life score at 3 months (mean 0.69 vs. 0.56 on 0 to 1 scale, p=0.048). The other trial found cooled radiofrequency associated with increased likelihood of a more than 20 percent reduction in opioid use or complete cessation of nonopioid analgesics at 1 month (77% vs. 8%, p<0.05).[104] Both trials found cooled radiofrequency associated with increased likelihood of experiencing a composite outcome of treatment success. In one trial,[104] treatment success was defined as at least a 50 percent improvement in pain, positive Global Perceived Effect, and at least a 10 point improvement in ODI or at least a 4 point improvement in ODI and reduction in medication use and assessed at 1 month (79% vs. 14.3%, RR 5.50, 95% CI, 1.48 to 20.42); in the other,[103] it was defined as pain intensity improved at least 50 percent and either 10 point increase in SF-36 bodily pain or 10 point decrease in ODI and assessed at 3 months (47% vs. 12%, RR 4.00, 95% CI, 1.04 to 15.43).

Harms

One trial reported no serious complications, though some patients reported temporary worsening pain typically lasting 5 to 10 days after the procedure; one patient in the cooled radiofrequency arm reported transient nonpainful buttock paresthesias.[103] Harms were not reported in the other trial.[104]

Cooled Versus Conventional Radiofrequency Denervation for Presumed Lumbar Facet Joint Pain

Description of Included Studies

One good-quality trial (n=43) conducted in the United States compared cooled radiofrequency versus conventional radiofrequency for presumed lumbar facet joint pain (**Appendix Table G-4 to G-6, Appendix Table H-1, and Table 4**).[105] Patients had to have a positive response (≥75% pain relief) to one set of diagnostic medial branch nerve blocks. Mean age was 56 years and 59 percent of participants were female; the mean duration of pain was 86 months. Baseline pain intensity was approximately 7 on a 0 to 10 NRS. Cooled radiofrequency to medial branch nerve targets was performed for 165 seconds at 60 degrees C (intraregional temperature >80 degrees C). Conventional radiofrequency was performed for 90 seconds at 80 degrees C.

Detailed Synthesis

Pain

Cooled radiofrequency denervation was associated with a small, nonstatistically significant greater reduction in pain versus conventional radiofrequency at 6 months (mean change from baseline -3.8 vs. -3.0 on a 0 to 10 scale, p=0.41); there were also no statistically significant differences at 1 or 3 months.[105] There was no difference in likelihood of experiencing at least a 50 percent improvement in pain at 6 months (52.3% vs. 44.4%, RR 1.18, 95% CI, 0.61 to 2.28).

Function

There was no difference between cooled versus conventional radiofrequency in improvement in ODI at 1, 3, or 6 months.[105] Cooled radiofrequency was associated with increased likelihood of experiencing at least a 30 percent improvement in ODI that was not statistically significant (61.9% vs. 44.4%, RR 1.39, 95% CI, 0.75 to 2.58).

Other Outcomes

There was no difference between cooled versus conventional radiofrequency in Global Impression of Change at 6 months (mean 2 vs. 2 on a 1 to 7 scale, p=0.51).[105]

Harms

No serious adverse events were reported with either cooled or conventional radiofrequency.[105] Self-limited post-procedural pain was reported in two patients.

Pulsed Radiofrequency Denervation

Key Points

- Evidence was insufficient to assess pulsed radiofrequency denervation for presumed facet joint pain versus sham denervation (1 trial, N=40) or continuous radiofrequency denervation (1 trial, N=40) (SOE: insufficient).

Across Trials of Cooled and Pulsed Radiofrequency Denervation

- Harms were not well-reported, but when recorded were usually related to temporary increase in pain. No serious complications were reported (SOE: low).

- The mean age of participants ranged from 52 to 59 years.

Pulsed Versus Sham Radiofrequency Denervation for Presumed Lumbar Facet Joint Pain

Description of Included Studies

One fair-quality trial[106] and one poor-quality trial[107] compared pulsed versus conventional radiofrequency denervation for presumed lumbar facet joint pain (**Appendix Table G-4 to G-6 and Table 5**). In both trials, patients had to have a positive response (>50% or complete/near complete pain relief) to one or two diagnostic medial branch blocks. The fair-quality trial (n=40) evaluated pulsed (2 Hz waves for 4 minutes [45 V] to 42 degrees C) versus electrode placement without radiofrequency current and administration of a local anesthetic.[106] Mean age was 49 years, 57 percent of participants were female, and the mean duration of pain was 35 months. In the poor-quality trial (n=50),[107] mean age was 57 years and the proportion female 65 percent. It compared pulsed radiofrequency (2 Hz waves for 2 minutes at 42 degrees C) of the dorsal root ganglia versus electrode placement without radiofrequency current (no local anesthetic).[107] Methodological limitations in both trials included failure to report allocation concealment methods, unclear masking of care providers, and high or unclear attrition (**Appendix Table H-1**). In addition, the poor quality trial did not report randomization methods or baseline characteristics, did not conduct intent-to-treat analysis, and had discrepancies in reported results.

Table 5. Study characteristics and results of pulsed radiofrequency ablation trials

Study, Year Country Quality	Mean Age (Years)	Percent Female	Number Randomized	Duration of Symptoms (Months)	Diagnostic Testing	Cooled or Pulsed Radiofrequency Parameters	Control Type	Duration of Followup (Months)	Pain	Function
Kroll, 2008[108] U.S. Poor	58.2	54	50	> 1	Medial branch block (dual, >50% relief)	120 seconds at 42° C, pulse duration 20 ms, pulse rate 2 Hz	Conventional RF (75 seconds at 80° C)	3	VAS 0 to 10, mean (SD) 3 months: 5.1 (2.1) vs. 5.2 (2.7)	ODI 0 to 100, mean (SD) 3 months: 42.2 (19.0) vs. 41.7 (16.9)
Moussa, 2020[107] Egypt Poor	57	65	150	≥12	Medial dorsal branch block (single, complete or near complete relief)	Four 2-minute cycles at ≤42° C, pulse rate 2 Hz, 45 V unilaterally or bilaterally	A: Conventional RF (90 seconds at 85° C) B: Sham RF	36	<u>Dichotomous</u> >50% back pain reduction 3 months: 84% vs. 64% vs. 56%, RR 0.44 (95% CI, 0.21 to 0.93) PRF vs. RF, RR 0.36 (95% CI, 0.18 to 0.74) PRF vs. sham 6 months: 78% vs. 48% vs. 16%, RR 0.42 995% CI, 0.23 to 0.76) PRF vs. RF, RR 0.26 (95% CI, 0.15 to 0.45) PRF vs. sham 1 year: 74% vs. 36% vs. 6%, RR 0.41 (95% CI, 0.24 to 0.68) PRF vs. RF, RR 0.28 (95% CI, 0.17 to 0.44) PRF vs. sham 2 years: 70% vs. 12% vs. 2%, RR 0.34 (95% CI, 0.22 to 0.52) PRF vs. RF, RR 0.31 (95% CI, 0.20 to 0.47) PRF vs. sham 3 years: 68% vs. 6% vs. 2%, RR 0.34 (95% CI, 0.23 to 0.51) PRF vs. RF, RR 0.33 (95% CI, 0.22 to 0.49) PRF vs. sham <u>Continuous</u> VAS 0 to 10, mean change (SD) 3 months: -8.5 vs. -5.4 vs. -5.2, p=0.01 6 months: -8.3 vs. -5.2 vs. -2.3, p=0.01 1 year: -8.1 vs. -5 vs. -0.7, p=0.01 2 years: -7.9 vs. -2.3 vs. -0.5, p=0.01 3 years: -7.7 vs. -2.2 vs.- 0.4, p=0.003	ODI 0 to 100, mean change (SD) 3 months: -50.5 vs. -34. 9 vs. -33.6, p=0.05 6 months: -48.1 vs. -30.3 vs. -10.8, p=0.03 1 year: -43.9 vs.-26.4 vs. -5.5, p=0.01 2 years: -39.3 vs. -15.3 vs. -3.7, p=0.01 3 years: -39.2 vs. -6.3 vs. -2, p=0.004

Study, Year Country Quality	Mean Age (Years)	Percent Female	Number Randomized	Duration of Symptoms (Months)	Diagnostic Testing	Cooled or Pulsed Radiofrequency Parameters	Control Type	Duration of Followup (Months)	Pain	Function
Tekin, 2007[106] Turkey Fair	59.3	57	60	>6	Medial branch block (single, >50% relief)	4 minutes at 42° C, pulse rate 2 Hz, 45 V	A: Conventional RF (90 seconds at 80° C) B: Sham RF	12	VAS 0 to 10, mean (SD) 6 months: 2.9 (1.6) vs. 2.3 (1.3) vs. 3.1 (0.8), p=0.19 PRF vs. RF and p=0.62 PRF vs. sham 1 year: 3.5 (1.3) vs. 2.4 (1.1) vs. 3.9 (1.2), p=0.004 for PRF vs. RF and p=0.31 PRF vs. sham	ODI 0 to 100, mean (SD) 6 months: 25.3 (6.9) vs. 25.1 (6.4) vs. 28.9 (5.7), p=0.92 PRF vs. RF, p=0.07 PRF vs. sham -1 year: 28.5 (6.1) vs. 28.0 (7.1) vs. 33.6 (5.7), p=0.81 PRF vs. RF and p=0.006 PRF vs. sham

Abbreviations: CI = confidence interval; ODI = Oswestry Disability Index; PRF = pulsed radiofrequency ablation; RF = radiofrequency ablation; RR = relative risk; SD = standard deviation; VAS = visual analogue scale

Detailed Synthesis

Pain

The fair-quality trial found no difference between pulsed versus radiofrequency denervation versus sham (with local anesthetic) at 6 months (2.9 vs. 3.1 on a 0 to 10 visual analogue scale [VAS], p=0.62) or 1 year (3.5 vs. 3.9, p=0.31).[106]

The poor-quality trial found pulsed radiofrequency of the dorsal root ganglia associated with a large reduction in pain versus sham (without local anesthetic) at 3 months to 3 years (differences ranged from 3.3 to 7.3 points on a 0 to 10 VAS).[107] Pulsed radiofrequency was also associated with an increased likelihood of experiencing greater than a 50 percent reduction in back pain (absolute differences ranged from 28% to 68%).

Function

The fair-quality trial found pulsed radiofrequency of the medial branches and sham (with local anesthetic) associated with similar function at 6 months (mean 25.4 vs. 28.9 on the 0 to 100 ODI, p=0.07), though the difference was slightly larger and favored sham at 1 year (mean 28.5 vs. 33.6, p=0.006).[106]

The poor-quality trial found pulsed radiofrequency of the dorsal root ganglia associated with moderate to large improvement in function versus sham (without local anesthetic) at 3 months to 3 years (differences ranged from 16.9 to 38.4 points on the 0 to 100 ODI).[107]

Other Outcomes

The fair-quality trial found both pulsed radiofrequency of the medial branches and sham (with local anesthetic) associated with high likelihood of analgesic use at 1 year (75% vs. 95%) and patient satisfaction reported as good or excellent (85% vs. 70%); differences were not statistically significant.[106]

The poor-quality trial found pulsed radiofrequency of the dorsal root ganglia associated with an increased likelihood of a composite outcome of success versus conventional radiofrequency denervation (absolute difference 30% to 72%), and greater decrease in World Health Organization (WHO) analgesic intake score (mean difference in change from baseline on a 0 to 3 scale ranged from 0.4 to 1.9 points) at 3 months to 3 years.[107]

Harms

Neither trial reported harms.[106,107]

Pulsed Versus Conventional Radiofrequency Denervation for Presumed Lumbar Facet Joint Pain

Description of Included Studies

One fair-quality trial[106] and two poor-quality trials[107,108] compared pulsed versus conventional radiofrequency denervation for presumed lumbar facet joint pain (**Appendix Table G-4 to G-6 and Table 5**). In all of the trials, patients had to have a positive response to one or two diagnostic medial branch blocks. The fair-quality trial (n=40) was conducted in Turkey and evaluated pulsed (2 Hz waves for 4 minutes [45 V] to 42 degrees C) versus conventional (90 seconds to 80 degrees C) radiofrequency denervation of the medial branches.[106] Mean age was 49 years, 57 percent of participants were female, and the mean duration of pain was 35 months.

The two poor-quality trials (n=50 and 100) were conducted in Egypt and the United States.[107,108] Mean ages were 57 and 59 years and the proportion female 54 percent and 65 percent. Patients had to have chronic pain in both trials, but mean pain duration was not reported. One poor-quality trial compared pulsed radiofrequency (2 Hz waves for 2 minutes at 42 degrees C) of the dorsal root ganglia versus conventional radiofrequency (85 degrees C for 90 seconds) of the medial branches, potentially complicating interpretation because of different denervation targets.[107] The other trial compared pulsed radiofrequency (2 Hz waves for 2 minutes at 42 degrees C) versus conventional radiofrequency (80 degrees C for 75 seconds) of the medial branches.[108] Across trials, methodological limitations included failure to report allocation concealment methods, unclear masking of care providers, and high or unclear attrition (**Appendix Table H-1**). In addition, the poor-quality trials did not report randomization methods, baseline characteristics, did not conduct intent-to-treat analysis, and had discrepancies in reported results.

Detailed Synthesis

Pain

The fair-quality trial found a small, nonstatistically significant difference between pulsed versus radiofrequency denervation at 6 months (mean 2.9 vs. 2.3 on a 0 to 10 VAS, p=0.19), but pulsed radiofrequency denervation was associated with moderate increased pain at 1 year (mean 3.5 vs. 2.4, p=0.004).[106]

The two poor-quality trials reported inconsistent effects on pain intensity.[107,108] The trial of pulsed versus conventional radiofrequency denervation of the medial branches found no difference in pain intensity at 3 months,[108] but the trial of pulsed radiofrequency of the dorsal root ganglia versus conventional radiofrequency denervation of the medial branches found a large reduction in pain with pulsed radiofrequency at 3 months through 3 year (mean differences 3.1 to 5.6 points on a 0 to 10 scale).[107] In this trial, pulsed radiofrequency was also associated with an increased likelihood of experiencing a greater than 50 percent reduction in back pain (absolute difference ranged from 20% to 60%).

Function

The fair-quality trial found no difference between pulsed versus radiofrequency denervation of the medial branches at 6 months (25.4 vs. 25.1 on the 0 to 100 ODI, p=0.92) or 1 year (28.5 vs. 28.0 on the ODI, p=0.81).[106]

The two poor-quality trials reported inconsistent effects on pain intensity.[107,108] The trial of pulsed versus conventional radiofrequency denervation of the medial branches found no difference in function (ODI) at 3 months,[108] but the trial of pulsed radiofrequency of the dorsal root ganglia versus conventional radiofrequency denervation of the medial branches found a moderate to large reduction in pain with pulsed radiofrequency at 3 months through 3 years (differences on the 0 to 100 ODI ranged from 15.6 to 32.9 point).[107]

Other Outcomes

The fair-quality trial found pulsed radiofrequency of the medial branches associated with increased likelihood of analgesic use versus conventional radiofrequency of the medial branches at 1 year (75% vs. 40%, RR 1.88, 95% CI, 1.04 to 3.39).[106] There was no difference in likelihood of patient satisfaction rating of good or excellent (85% vs. 95%).

One poor-quality trial found pulsed radiofrequency of the dorsal root ganglia associated with increased likelihood of a composite outcome of success versus conventional radiofrequency denervation (absolute difference 22% to 58%), and greater decrease in WHO analgesic intake score (mean difference in change from baseline on a 0 to 3 scale ranged from 0.3 to 1.4 points) at 3 months to 3 years.[107]

Harms

One poor-quality trial reported no adverse events.[108] Harms were not reported in the other two trials.[106,107]

Intradiscal and Facet Joint Platelet-Rich Plasma for Low Back Pain of Presumed Discogenic Origin or Into the Lumbar Facet Joint for Low Back Pain of Presumed Facet Joint Origin

Key Points

- Evidence was insufficient to assess intradiscal platelet-rich plasma injection for presumed discogenic back pain (1 trial, N=58) (SOE: insufficient).
- There were no differences between stem cell and saline injection in harms, including no serious adverse events, at up to 3 years following treatment (SOE: low).
- The mean age of participants was 42 years.

Description of Included Studies

One small (n=47) trial conducted in the United States compared intradiscal platelet-rich plasma (PRP) versus sham (contrast agent) injection for presumed discogenic low back pain (**Appendix Table G-7 to G-9 and Table 6**).[109] Pain had to be chronic (>6 months; mean duration not reported) and patients had to have a concordant response on single provocative discography prior to undergoing the injection. The mean age of participants was 42 years; 66 percent were female. At baseline, current pain averaged 4.7 on a 0 to 10 NRS; baseline mean best pain was 2.5 and mean worst pain 7.9. Under fluoroscopic guidance, patients received 1 to 2 ml platelet-rich plasma (3 to 4 ml divided for multiple discs) or 1 to 2 ml contrast agent in the affected disc(s) and outcomes compared through 8 weeks, at which point the trial was unblinded and crossover permitted (88% [15/17] of those randomized to sham crossed over to PRP). The trial was rated fair quality, due to baseline imbalance in sex, unclear randomization method, and lack of intent-to-treat analysis (**Appendix Table H-1**)

No trial evaluated facet joint PRP injection versus sham or usual care.

Table 6. Study characteristics and results of platelet-rich plasma trial

Study, Year Country Quality	Mean Age (Years)	Percent Female	Number Randomized	Duration of Symptoms (Months)	Diagnostic Testing	Platelet-Rich Plasma Intervention	Control Type	Duration of Followup (Months)	Pain	Function
Tuakli-Wosornu, 2016[109] U.S. Fair	42.32	66	57	≥6	Disc protrusion <5 mm on MRI or CT	1-2 ml injected into target discs	Sham (contrast agent) injection	2	NRS 0 to 10 worst pain, mean difference (95% CI) 1 week: -0.53 (-1.67 to 0.61) 1 month: -0.70 (-1.82 to 0.42) 2 months: -1.01 (-2.38 to 0.36)	FRI 0 to 100, mean difference (95% CI) 1 week: 3.84 (-5.41 to 13.09) 1 month: -0.92 (-10.90 to 9.06) 2 months: -6.46 (-17.99 to 5.07)

Abbreviations: CI = confidence interval; CT = computed tomography; FRI = Functional Rating Index; MRI = magnetic resonance imaging; NRS = numeric rating scale

Detailed Synthesis

Pain

Intradiscal PRP was associated with small to moderate decreases in current pain versus sham at 1, 4, and 8 weeks, but differences were not statistically significant (mean differences -0.57 to -1.30 points on a 0 to 10 NRS). Results were similar for best and worst pain. There was also no difference on the SF-36 bodily pain subscale.

Function

There were no differences between intradiscal PRP versus sham in function (based on the Functional Rating Index) at 1, 4, or 8 weeks; mean differences ranged from -0.93 to 3.84 points on a 0 to 100 scale.[109] There were also no difference on the SF-36 physical function subscale.

Other Outcomes

Intradiscal PRP was associated with increased likelihood versus sham of patient reporting of "satisfied" or "would undergo procedure again" versus sham (55.6% vs. 17.6%, RR 3.15, 95% CI, 1.07 to 9.28).[109] However, it was unclear if assessment occurred prior to or after unblinding.

Harms

No cases of disc space infection, neurologic injury, or progressive herniation were reported.[109]

Intradiscal Stem Cells for Low Back Pain of Presumed Discogenic Origin

Key Points

- Evidence was insufficient to assess intradiscal stem cell injection for presumed discogenic back pain (1 trial, N=100) (SOE: insufficient).
- Mean age was 42 years.

Description of Included Studies

One trial (n=100) compared intradiscal injection of allogenic mesenchymal stem cells in hyaluronic acid delivery versus intradiscal hyaluronic acid alone or saline for chronic low back pain of presumed discogenic origin (**Appendix Table G-10 and G-11, and Table 7**).[110] The study was conducted at 13 sites in the United States and Australia. Study participants had chronic low back pain for at least 6 months that was refractory to at least 3 months of conservative treatment. Patients were not required to undergo provocative discography, but among those who did, only those with a concordant pain response at one level were enrolled. Mean age of participants was 42 years and 47 percent were female. The mean duration of discogenic disease was 5.8 years and mean pain score was 7 on a 0 to 10 VAS. Patients were randomized to 6 million (1.0 ml at 30 million/5 ml) or 18 million (1.0 ml at 90 million/5 ml) allogenic mesenchymal stem cells (each mixed with 1% hyaluronic acid) versus 2 ml of 1 percent hyaluronic acid alone, or 2 ml saline. Although saline and hyaluronic acid injections were both considered inactive controls, hyaluronic acid could have potential therapeutic effects; therefore, results described here primarily focus on findings against saline injection. Outcomes were

assessed from 1 month to 3 years after treatment. The study was rated fair quality due to presence of baseline differences (**Appendix Table H-1**). Specifically, the 18 million stem cell group included a higher proportion of male participants (70% versus 50%), was younger (38 years versus 44 years) and had a shorter duration of disease (3.7 years versus 5.9 years) than the saline control group.

Table 7. Study characteristics and results of intradiscal stem cell trial

Study, Year Country Quality	Mean Age (Years)	Percent Female	Number Randomized	Duration of Symptoms (Months)	Diagnostic Testing	Control Type	Duration of Followup (Months)	Pain	Function
Amirdelfan 2020[110] Australia and U.S. Fair	41.9	47	100	Mean 69.7	Degenerative disc disease at one level from L1 to S1	Saline	36	Dichotomous ≥50% reduction in VAS from baseline 6 months: 67% vs. 50% 12 months: 60% vs. 20%, p<0.05 24 months: 50% vs. 15%, p<0.05 36 months: 50% vs. 20%, p<0.05 Continuous VAS LSM (95% CI) 1 month: -28.05 (-37.52 to -18.57) vs. -23.21 (-34.63 to -11.80) 3 months: -38.70 (-48.18 to -29.23) vs. -28.86 (-40.28 to -17.45) 6 months: -42.70 (-52.35 to -33.06) vs. -32.22 (-44.26 to -20.19) 12 months: -36.65 (-46.47 to -26.82) vs. -17.29 (-30.05 to -4.53) 24 months: -19.44 (-25.46 to -13.43) vs. -9.06 (-16.74 to -1.38), p<0.05 36 months: -18.44 (-24.46 to -12.43) vs. -7.69 (-15.36 to -0.01), p<0.05	Dichotomous ≥15 point reduction on ODI from baseline 6 months: 63% vs. 25% 12 months: 50% vs. 20%, p<0.05 24 months: 47% vs. 15%, p<0.05 36 months: 47% vs. 15%, p<0.05 Continuous ODI LSM (95% CI) 1 month: -13.07 (-18.77 to -7.37) vs. -10.80 (-17.67 to -3.93) 3 months: -17.31 (-23.01 to -11.61) vs. -14.00 (-20.87 to -7.13) 6 months: -18.02 (-23.63 to -12.42) vs. -12.64 (-19.88 to -5.39) 12 months: -17.54 (-23.44 to -11.64) vs. -9.31 (-16.99 to -1.63) 24 months: -19.44 (-25.46 to -13.43) vs. -9.06 (-16.74 to -1.38), p<0.05 36 months: -18.44 (-24.46 to -12.43) vs. -7.69 (-15.36 to -0.01), p<0.05

Abbreviations: CI = confidence interval; LSM = least square mean; ODI = Oswestry Disability Index; VAS = visual analogue scale

Detailed Synthesis

Pain

Intradiscal injection of 6 or 18 million stem cells was associated with a small improvement in pain versus saline injection that was not statistically significant at 1, 3, and 6 months (least squares mean differences adjusted for posttreatment interventions ranged from 0.38 to 1.05 points on a 0 to 10 VAS).[110] At 1 to 3 years, stem cell injections were associated with moderate to large, statistically significant reduction in pain (differences ranged from 1.61 to 2.62 points). Both stem cell doses were associated with increased likelihood of at least a 50 percent reduction in pain at 1 year (60.0% vs. 20.0% for 6 million stem cell dose, RR 3.00, 95% CI, 1.19 to 7.56 and 53.3% vs. 20.0%, for 18 million stem cell dose, RR 2.67, 95% CI, 1.04 to 6.81) and the 6 million stem cell dose was associated with increased likelihood of at least 50 percent pain reduction at 2 years (50.0% vs. 20.0%, RR 3.33, 95% CI, 1.11 to 10.04). Although results also favored stem cell injections at 6 months and 3 years, the differences were smaller and not statistically significant. Results for stem cell injections versus hyaluronic acid alone injection also favored stem cells, but at most time points differences were smaller relative to comparisons against usual care, and few differences were statistically significant. There was no pattern to indicate that the higher stem cell dose was associated with greater effects on pain than the lower dose.

Function

Intradiscal injection of 6 or 18 million stem cells was associated with no differences in ODI versus saline injection at 1, 3, and 6 months.[110] At 1, 2, and 3 years, stem cell injections were associated with small to moderate reductions in function that were statistically significant (differences ranged from 8.23 to 18.15 points on the 0 to 100 ODI). Stem cell injections were also associated with increased likelihood of at least a 15-point improvement in the ODI at 2 or 3 years (at 3 years, 46.7% vs. 25.0% for 6 million stem cell dose, RR 3.11, 95% CI, 1.02 to 9.45 and 50.0% vs. 15.0% for 18 million stem cell injection, RR 3.33, 95% CI, 1.11 to 10.04). The 6 million stem cell dose was also associated at increased likelihood of ODI response at 6 months (63.3% vs. 25.0%, RR 2.53, 95% CI, 1.13 to 5.67); although the point estimate was similar at 1 year the difference was not statistically significant. Results for stem cell injections versus hyaluronic acid alone were similar to results versus saline at 1 to 6 months and indicated slightly reduced differences at 1 to 3 years. There was no pattern to indicate that the higher stem cell dose was associated with greater effects on function than the lower dose.

Other Outcomes

Stem cell injections were associated with increased likelihood of experiencing a composite measure of treatment response (≥30% pain reduction and ≥10-point ODI improvement) versus saline injection at 6 months to 3 years, but the differences were only statistically significant for the 18 million stem cell dose at 1 year (56.7% vs. 20.0%) and the 6 million stem cell injection at 2 years (46.7% vs. 15.0%).[110]

The 18 million stem cell injection was associated with greater improvement in SF-36 PCS versus saline ($p=0.025$) or hyaluronic acid ($p=0.04$) at 3 years (mean differences not reported). There were no statistically significant differences between injections versus controls in SF-36 MCS and PCS at earlier time points.

Harms

There were no deaths reported in the study, and no statistically significant differences between groups in the risk of serious adverse events, any adverse event, or withdrawals due to adverse events.[110]

Effects of Dose

As described above, there was no pattern to indicate that a higher dose (18 million) of intradiscal stem cells was associated with superior outcomes compared with a lower dose (6 million).[109]

Intradiscal Methylene Blue for Low Back Pain of Presumed Discogenic Origin

Key Points

- Intradiscal methylene blue for presumed discogenic back pain (1 trial, N=81) was associated with no difference versus sham at 6 weeks and 3 months. Evidence was insufficient to determine effects of intradiscal methylene blue at 6 months (2 trials, N=153, with conflicting results) and 12 months or longer (1 trial, N=72) (SOE: low for no difference at 6 weeks and 3 months; insufficient for 6, 12 and 24 months).
- Both trials of intradiscal methylene blue excluded patients older than 66 years of age (mean 41 years).

Description of Included Studies

Two trials (n=84 and 72) compared intradiscal methylene blue versus sham intradiscal therapy in patients with presumed discogenic back pain (**Appendix Table G-12 to G-14 and Table 8**).[111,112] The trials were conducted in the Netherlands (the IMBI Study[111]) and China.[112] Methods of the Dutch trial were intentionally similar to the earlier Chinese trial, in an effort to determine whether its results could be duplicated. The mean age was 41 years in both trials, and both trials excluded patients older than 66 years. The proportion of female patients was 72 percent in one trial[111] and 43 percent in the other.[112] Baseline pain intensity was similar (mean 6.6 and 7.0, on a 0 to 10 scale). Although both trials enrolled patients with chronic pain, the duration of pain symptoms was longer in the Dutch trial (9 years)[111] than the Chinese trial.[112] In both trials, the diagnosis of discogenic back pain was based on a positive response to provocative discography, with negative control discs. In addition, the Dutch trial excluded patients with multilevel discogenic pain or facet pain based on confirmatory facet block.[111] Both trials compared an intradiscal injection of methylene blue (1 ml; 10 mg/ml) or saline (1 ml); both groups received 2 percent lidocaine (0.5 ml) injection. Duration of followup was 6 months in the Dutch trial[111] and 2 years in the Chinese trial.[112] The Dutch trial was rated good quality[111] and the Chinese trial fair quality,[112] mainly for unclear allocation concealment (**Appendix Table H-1**).

Table 8. Study characteristics and results of intradiscal methylene blue trials

Study, Year Country Quality	Mean Age (Years)	Percent Female	Number Randomized	Duration of Symptoms (Months)	Diagnostic Testing	Methylene Blue Intervention	Control Type	Duration of Followup (Months)	Pain	Function
Kallewaard, 2019[111] the Netherlands Good	41.1	72	81	≥6	Positive provocative discography at pressure <50 PSI above opening pressure	Intradiscal 1 ml (10 mg/ml) methylene blue + 0.5 ml lidocaine hydrochloride 2% + 0.5 ml contrast dye	Sham injection(lidocaine, saline, and contrast)	6	Dichotomous ≥30% improvement 6 weeks: 15% vs. 17%, RR 1.02 (95% CI, 0.85 to 1.24) 3 months: 25% vs. 24%, RR 0.99 (95% CI, 0.77 to 1.27) 6 months: 35% vs. 27%, RR 0.89 (95% CI, 0.66 to 1.19) Continuous NRS 0 to 10, mean difference in mean change (95% CI) 6 weeks: -0.4 (-1.2 to 0.3) 3 months: -0.5 (-1.3 to 0.4) 6 months: -0.2 (-1.2 to 0.80)	ODI 0 to 100, mean change (SD) 6 weeks: -8.0 (17.1) vs. -1.7 (9.8), p=0.046 -3 months: -8.8 (18.4) vs. -3.6 (9.9), p=0.12 -6 months: -7.8 (16.9) vs. -5.5 (10.5), p=0.46
Peng, 2010[112] China Fair	41.7	43	72	Mean of 40.8	Positive discography, pressure and volume parameters NR, with at least one negative adjacent control disc	Intradiscal 1 (10 mg/ml) methylene blue + 1 ml lidocaine hydrochloride 2%	Sham injection (lidocaine and saline)	24	NRS 0 to 10, mean difference (95% CI) 6 months: 3.86 (3.15 to 4.56) 12 months: 4.08 (3.36 to 4.81) 24 months: 4.05 (3.34 to 4.77)	ODI 0 to 100, mean difference (95% CI) 6 months: 32.40 (27.62 to 37.18) 12 months: 34.70 (29.19 to 40.20) 24 months: 34.80 (29.37 to 40.22)

Abbreviations: CI = confidence interval; NR = not reported; NRS = numeric rating scale; ODI = Oswestry Disability Index; PSI = pound-force per square inch; RR = relative risk; SD = standard deviation

Detailed Synthesis

Pain

The two trials reported discordant effects of intradiscal methylene blue on pain. In the Chinese trial, intradiscal methylene blue was associated with large reduction in pain versus sham at 6, 12, and 24 months (mean differences 3.86 to 4.08 points on a 0 to 11 NRS).[112] However, the Dutch trial found no differences between intradiscal methylene blue versus sham in pain at 6 weeks, 3 months, or 6 months (mean differences 0.4 to 0.5 points on a 0 to 11 NRS).[111] The Dutch trial also found methylene blue and sham associated with similar likelihood of at least a 30 percent reduction in NRS (at 6 months, 35.0% [14/40] vs. 26.8% [11/41], p=0.43). The Chinese trial did not evaluate the likelihood of experiencing a pain response.

Function

Results of the two trials were also discordant regarding function. In the Chinese trial, intradiscal methylene blue was associated with large improvement in function versus sham (mean differences 32.4 to 34.8 points on the 0 to 100 ODI at 6, 12, and 24 months).[112] In the Dutch trial, methylene blue was associated with a small improvement in function at 6 weeks (mean difference -6.3, 95% CI, -12.4 to -0.17 on the ODI), but differences were reduced and no longer statistically significant at 3 or 6 months (mean differences -5.2 to -2.3 points).[111]

Other Outcomes

As with pain and function, effects of methylene blue on medication use was also discordant. At 6 months, the Chinese trial[112] found methylene blue associated with marked reduction in likelihood of regular nonsteroidal anti-inflammatory drug (NSAID) or opioid use (8.3% vs. 42.9%, p=0.002) but the Dutch trial[111] found no difference in likelihood of strong opioid use (7.5% vs. 9.8%, p=1.0). The Dutch trial also found no differences between methylene blue versus sham in EQ-5D, SF-36 PCS, SF-36 MCS, or patient global impression of change "much improved" or "improved" at 6 weeks, 3 months, or 6 months; these outcomes were not evaluated in the Chinese trial.

Harms

Reporting of harms was limited. The Chinese trial reported no cases of nerve injury or disc space infection with methylene blue or sham, and no cases of back pain aggravation with methylene blue.[112] The Dutch trial found no difference in risk of any adverse event (data not reported); two serious adverse events that did not appear due to the methylene blue procedure were reported (unrelated elective surgery and hospitalization for laryngitis).[111]

Intradiscal Ozone Injection for Radicular Low Back Pain or Nonradicular Low Back Pain of Presumed Discogenic Origin

Key Points

- Evidence was insufficient to assess intradiscal oxygen-ozone for radicular low back pain (1 trial, N=159) (SOE: insufficient).
- No trial evaluated intradiscal oxygen-ozone injection without corticosteroid or oxygen-ozone injection for presumed (nonradicular) discogenic low back pain.

- Mean age ranged from 40 to 51 years.

Description of Included Studies

No trial evaluated intradiscal ozone injection alone for radicular or nonradicular low back pain. Three trials (n=80 to 159, total N=339) evaluated intradiscal ozone (mixed with oxygen) plus corticosteroid injection for radicular back pain (**Appendix Table G-15 to G-17 and Table 9**).[113-115] The studies were conducted in Italy,[113] Egypt,[114] and India.[115] Mean age of study participants ranged from 40 to 51 years and 45 to 62 percent were female. The mean duration of pain was 8 and 15 weeks in two trials[113,114] and 9 months in one trial.[115] Baseline ODI ranged from 31 to 72; only one trial[115] reported baseline pain (mean 7.1 on a 0 to 10 VAS). In all trials, patients had radicular pain with concordant herniated disc on MRI and injections were performed with CT or fluoroscopic guidance. The amount of intradiscal oxygen-ozone (concentration 28 or 40 µg/ml) administered ranged from 5 to 10 ml; in one trial, patients also received transforaminal epidural oxygen-ozone (volume 5 to 7 ml). Oxygen-ozone was administered with a corticosteroid (triamcinolone or methylprednisolone) in all trials, two[113,114] of which also administered ropivacaine. The corticosteroid was intradiscal and epidural in two trials[113,114] and epidural only in one trial.[115] All three trials compared oxygen-ozone plus corticosteroid versus corticosteroid without oxygen-ozone; one trial[114] also evaluated a local anesthetic only (without corticosteroid) control injection (site not specified). The duration of followup was 6 months.

One trial[113] was rated fair quality and two trials[114,115] poor quality, including the trial that compared an oxygen-ozone versus local anesthetic alone injection (**Appendix Table H-1**). Methodological limitations in all trials included unclear randomization and allocation methods and failure to report attrition. The poor-quality trials also did not clearly blind patients, had poor reporting of outcomes, data discrepancies, and potential selective outcomes reporting.

No trial evaluated intradiscal ozone injection for presumed (nonradicular) discogenic back pain.

Table 9. Study characteristics and results of intradiscal ozone trials

Study, Year Country Quality	Mean Age (Years)	Percent Female	Number Randomized	Duration of Symptoms (Months)	Diagnostic Testing	Ozone Intervention	Control Type	Duration of Followup (Months)	Pain	Function
Gallucci, 2007[113] Italy Fair	40.48	45	159	Mean 3.75	MRI- or CT-confirmed disc herniation	Oxygen-ozone intradiscal 5-7 ml (concentration 28 µg/ml) Triamcinolone acetonide 2 ml (1 ml intradiscal and 1 ml epidural) Ropivacaine 2% 2-4 ml (1 ml intradiscal and ~2 ml epidural)	Steroid	6	NR	ODI <20% 2 weeks: 88% vs. 90%, p=0.72 3 months: 78% vs. 67%, p=0.14 6 months: 745 vs. 47%, p<0.001
Haseeb, 2019[114] Egypt Poor	42.44	58	80	Mean 2	MRI-confirmed disc herniation	Oxygen-ozone intradiscal 5-7 ml and intraforaminal mean 6.5 ml (concentration 28 µg/ml) Triamcinolone acetonide 2 ml 40 mg/ml (1 ml intradiscal and 1 ml intraforaminal) Ropivacaine 2% 2-4 ml intradiscal and intraforaminal	Steroid	6	NR	ODI 0 to 100, mean change (SD) 2 weeks: -20.40 (9.66) vs. -16.60 (7.33), mean difference -3.80 (-7.56 to -0.04) 3 months: -18.95 (8.55) vs. -13.30 (5.66), mean difference -5.65 (-8.83 to -2.47) 6 months: -14.73 (9.60) vs. -9.88 (5.79), mean difference -4.85 (-8.32 to -1.38)
Haseeb, 2019[114] Egypt Poor	42.44	58	60	Mean 2	MRI-confirmed disc herniation	Oxygen-ozone intradiscal 5-7 ml and intraforaminal mean 6.5 ml (concentration 28 µg/ml) Triamcinolone acetonide 2 ml 40 mg/ml (1 ml intradiscal and 1 ml intraforaminal) Ropivacaine 2% 2-4 ml intradiscal and intraforaminal	Sham	6	NR	ODI 0 to 100, mean change (SD) 2 weeks: --20.40 (9.66) vs. -3.10 (3.72), mean difference -17.30 (95% CI, -20.71 to -13.89) 3 months: -18.95 (8.55) vs. -2.10 (3.81), mean difference -16.85 (95% CI, -19.98 to -13.72)

Study, Year Country Quality	Mean Age (Years)	Percent Female	Number Randomized	Duration of Symptoms (Months)	Diagnostic Testing	Ozone Intervention	Control Type	Duration of Followup (Months)	Pain	Function
Nilachandra, 2016[115] India Poor	51.3	62	80	Mean: 9.45	MRI-confirmed disc herniation	Oxygen-ozone 10 ml intradiscal (concentration 40 µg/ml)	Steroid	6	VAS 0 to 10, mean (SD) 1 week: 3.50 (1.16) vs. 3.25 (1.03), mean difference 0.25 (95% CI, -0.23 to 0.73) 2 weeks: 2.54 (0.89) vs. 2.75 (0.74), mean difference -0.21 (95% CI, -0.57 to 0.15) 3 months: 1.54 (1.15) vs. 2.84 (0.64), mean difference -1.30 (95% CI, -1.72 to -0.88) 6 months: 0.86 (0.69 vs. 2.24 (0.93), mean difference -1.38 (95% CI, -1.75 to -1.01)	ODI 0 to 100, mean (SD) 1 week: 38.98 (7.61) vs. 42.45 (9.97), mean difference -3.47 (95% CI, -7.36 to 0.42) 2 weeks: 34.13 (7.94) vs. 36.20 (4.27), mean difference -2.07 (95% CI, -4.89 to 0.75) 3 months: 25.14 (7.92) vs. 36.21 (4.67), mean difference -12.06 (95% CI, -15.01 to -9.11) 6 months: 18.28 (8.77) vs. 29.00 (6.78), mean difference -10.72 95% CI, (-14.32 to -7.12)

Abbreviations: CI = confidence interval; CT = computed tomography; MRI = magnetic resonance imaging; ODI = Oswestry Disability Index; SD = standard deviation

Detailed Synthesis

Pain

Only one poor-quality trial reported effects on pain.[115] It found no difference between intradiscal oxygen-ozone plus epidural methylprednisolone injection versus methylprednisolone alone at 1 (mean difference 0.25 on a 0 to 10 scale, 95% CI, -0.23 to 0.73) or 2 weeks (mean differences -0.21, 95% CI, -0.57 to 0.15). However, oxygen-ozone was associated with a moderate decrease in pain versus corticosteroid alone at 3 (mean difference -1.30, 95% CI, -1.72 to -0.88) and 6 months (mean difference -1.38, 95% CI, -1.75 to -1.01).

Function

The fair-quality trial found no differences between oxygen-ozone, corticosteroid, and local anesthetic versus corticosteroid plus local anesthetic without oxygen-ozone in likelihood of ODI score less than 20 (0 to 100 scale) at 2 or 3 weeks.[113] Oxygen-ozone was associated with an increased likelihood of achieving an ODI score less than 20 at 6 months (74% vs. 47%, RR 1.59, 95% CI, 1.21 to 2.08)

The two poor-quality trials found little difference between oxygen-ozone and corticosteroid (with or without local anesthetic) versus corticosteroid without oxygen-ozone in the ODI at 1 or 2 weeks.[114,115] Differences on the ODI were larger and statistically significant at 3 and 6 months (mean differences -10.7 to -4.8 points). One poor-quality trial found oxygen-ozone, corticosteroid and local anesthetic injection associated with moderate improvement in the ODI versus local anesthetic alone (without steroid) at 2 weeks and 3 months (mean differences 17 points).[114]

Other Outcomes

The trials did not evaluate outcomes other than pain or function.

Harms

No serious adverse events were reported in any trial. The risk of any adverse event was higher in the oxygen-ozone group when compared with lidocaine alone (RR 3.17, 95% CI, 1.06 to 9.45) in one poor-quality trial.[114]

Sphenopalatine Block for Trigeminal Neuralgia and Headache

Key Points

- Evidence was insufficient to assess sphenopalatine block versus sham for headache (1 trial, N=41) (SOE: insufficient).
- The mean age of patients in the trial of sphenopalatine block was 41 years.

Description of Included Studies

One trial (n=41) reported in two publications compared 0.5 percent intranasal bupivacaine versus saline sphenopalatine block via the intranasal approach using a flexible device (Tx360, Tian Medical Inc., Lombard, IL) in patients with chronic migraine headache (**Appendix Table G-18 and G-19, and Table 10**).[116,117] Blocks were administered 12 times over a 6-week period (12 total treatments). Study participants had a mean age of 41 years and were predominately

female (76%). Study inclusion criteria required at least a 3-month history of migraine; mean duration since migraine diagnosis was 8.6 years duration. Patients using schedule II opioids for migraine were excluded. On average, patients reported 15 days of migraine days per month, 22 headache days per month, and had a baseline mean pain score (0 to 10 NRS) of 3.37. The study was rated poor quality; limitations included high overall (27%) and differential attrition (43% in sham arm) at 1 month post-treatment followup, as well as lack of intent-to-treat analysis (**Appendix Table H-1**). In addition, the trial did not report the scales used to assess a number of outcomes (quality of life [general activity, work, and mood], analgesic use, and global impression of change).

No trial or controlled observational study evaluated sphenopalatine block for trigeminal neuralgia.

Table 10. Study characteristics and results of sphenopalatine block trial

Study, Year Country Quality	Mean Age (Years)	Percent Female	Number Randomized	Duration of Symptoms (Months)	Headache Type	Approach	Control Type	Duration of Followup (Months)	Pain	Function
Cady, 2015[116,117] U.S. Poor	41.3	76	41	Mean 103.2	Chronic migraine (IHS criteria)	Transnasal, using Tx360 device	Placebo	1	NRS 0 to 10, mean difference (95% CI) 1 day: -1.35 (-3.17 to 0.47) 1 month: -0.55 (-2.54 to 1.44) 6 months: -1.14 (-3.06 to 0.78)	HIT-6 36 to 78 (higher score=greater impact), mean difference (95% CI) 1 month: -2.69 (-7.32 to 1.94) 6 months: -2.84 (-7.71 to 2.03)

Abbreviations: CI = confidence interval; HIT-6 = Headache Impact TestIHS = International Headache Society; NRS = numerical rating scale

Detailed Synthesis

Pain

At 24 hours following treatments (data pooled for all 12 treatment sessions), sphenopalatine block was associated with moderate decrease in pain intensity versus sham (mean 2.85 vs. 4.20 on a 0 to 10 NRS, ANOVA $p<0.001$).[116,117] However, differences were small and not statistically significant 1 and 6 months after completing the course of treatments (3.36 vs. 3.91 at 1 month and 2.86 vs. 4.00 at 6 months), though sphenopalatine block was associated with fewer number of headaches days per month at 1 month (17.44 vs. 22.82, ANOVA $p>0.05$).

Function

Effects of sphenopalatine block versus sham on the Headache Impact Test (HIT-6) were small and not statistically significant at 24 hours following treatments or at 1 to 6 months after completing the course of treatment (differences ~3 points on a 36 to 78 scale). There were also no differences in general activity or normal work at 1 or 6 months, but the scales used to measure these outcomes were not reported.

Other Outcomes

There were no differences between sphenopalatine block versus sham in acute medication use at 6 weeks, mood at 1 or 6 months, or patient global impression of change at 24 hours following treatments.[116,117] However, the scales used to report these outcomes were not reported.

Harms

There was no difference in any adverse events (mean 7.52 vs. 5.00, $p=0.30$); only one serious adverse event following sphenopalatine block that was probably not related to the intervention was reported (pulmonary embolus resulting in death 81 days after treatment).[116,117]

Occipital Nerve Stimulation for Headache

Key Points

- Evidence was insufficient to assess occipital nerve stimulation versus sham stimulation for headache (1 trial, N=157) (SOE: insufficient).
- For headache, occipital nerve stimulation with adjustable parameters versus usual care at 3 months was associated with a small, nonstatistically significant reduction in pain intensity, moderate decrease in headache related disability, and decrease in headache days (1 trial, N=67) (SOE: low for headache related disability and headache days; insufficient for pain).
- Lead migration occurred in 14 to 24 percent of patients (2 trials, N=224), serious device-related complications requiring hospitalization occurred in 5.9 percent of patients (1 trial, N=67), and persistent pain/numbness at implantation site in 13 percent of patients (1 trial, N=157) (SOE: low).
- One trial (N=67) found occipital nerve stimulation with adjustable parameters associated with superior outcomes compared with stimulation using preset parameters.
- The mean age of patients ranged from 43 to 46 years.

Description of Included Studies

Three trials (number randomized 30, 67, and 157, total=254) evaluated occipital nerve stimulation for chronic headache (**Appendix Table G-20 to G-22 and Table 11**).[118-120] Two trials[118,120] were multicenter studies; one additional publication[121] reported results from a single participating center (n=20) in one[120] of the trials. The trials were conducted in the United States, Italy, and Europe. The mean age ranged from 43 to 46 years and the proportion female ranged from 76 to 80 percent. Two trials[118,120] restricted inclusion to patients who met criteria for chronic migraine headaches and one trial[119] included patients with chronic migraine or medication overuse headache; all trials required patients to have unsuccessfully tried at least two prior treatments. Two trials[119,120] required patients to experience at least 50 percent pain relief with trial stimulation and one trial[118] required at least 50 percent response to a diagnostic occipital nerve block. Electrodes were placed subcutaneously and occipital nerve stimulation was compared against sham stimulation (electrodes placed but no current applied) (two trials)[119,120] or usual care (one trial).[118] One trial permitted some adjustment of stimulation parameters,[119] one trial randomized patients to adjustable or preset stimulation parameters,[118] and one trial[120] did not report stimulation parameters (**Table 11**). One crossover trial was rated poor quality due to failure to report randomization or allocation concealment methods, unclear blinding, and potential selective outcomes reporting; in addition, the analysis did not account for use of crossover design (**Appendix Table H-1**).[119] The other two trials were rated fair quality.

Table 11. Study characteristics and results of occipital nerve stimulation trials

Study, Year Country Quality	Mean Age (Years)	Percent Female	Number Randomized	Duration of Symptoms (Months)	Diagnosis Eligibility	Stimulation Intervention	Control Type	Duration of Followup (Months)	Pain	Function
Serra, 2012[119] Italy Poor	46	76	30	Mean NR	Unsuccessfully tried ≥2 prior treatments and ≥50% response to temporary ONS	Pulse frequency 50 Hz, pulse width 330 to 450 µs, maximum stimulation amplitude 10.5 V	Sham	1	Scale 0 to 10, median (IQR), first crossover period: 5 (5 to 6) vs. 7.5 (7.8), p<0.001 Headache days/week, median (IQR), first crossover period: 2.1 (1.2 to 3.3) vs. 6.3 (3.6 to 7), p<0.001	NR
Silberstein, 2012[120] U.S. Fair	44.9	79	157	Mean 23.3	Unsuccessfully tried ≥2 prior treatments and ≥50% response to temporary ONS	Stimulation parameters not reported ("programmed for appropriate stimulation")	Sham	3	Dichotomous ≥50% reduction in headache pain intensity: 17.1% vs. 13.5%, RR 1.27 (95% CI, 0.57 to 2.86) "Good" or "excellent" headache relief: 50% vs. 18%, RR 2.86 (95% CI, 1.53 to 5.34) Continuous Headache days, mean change (SD NR): -27.2% vs. -14.9%, p<0.05	MIDAS score (>20=severe disability), mean (SD NR) at 12 weeks: -64.6 vs. -20.4 mean difference (95% CI): -44.2 (-65.3 to -22.8)
Mekhail, 2017[121] (single center from Silberstein 2012) U.S. Fair	44.6	75	20	Mean NR	Unsuccessfully tried ≥2 prior treatments and ≥50% response to temporary ONS	Stimulation parameters not reported ("programmed for appropriate stimulation")	Sham	3	Dichotomous ≥50% reduction in headache pain intensity: 17.1% vs. 0%, RR 0.71 (95% CI, 0.51 to 0.99) Continuous VAS 0 to 10, average daily pain intensity, mean change (SD) -4 weeks: -2.16 (1.02) vs. 0.34 (0.99), p<0.001 -12 weeks: -2.30 (1.15) vs. 0.79 (1.06), p<0.001	MIDAS score (>20=severe disability), mean change (SD) at 12 weeks: -85.21 (40.63) vs. -12.17 (60.43), p=0.008

Study, Year Country Quality	Mean Age (Years)	Percent Female	Number Randomized	Duration of Symptoms (Months)	Diagnosis Eligibility	Stimulation Intervention	Control Type	Duration of Followup (Months)	Pain	Function
Saper, 2011[118] Canada, U.S., and U.K. Fair	43	80	67	Mean 22	Unsuccessfully tried ≥2 prior treatments and ≥50% response to diagnostic ONS	A: Adjustable: Pulse frequency 3 to 130 Hz, pulse width 60 to 450 µs, pulse amplitude 0 to 10.5 V; adjustable by patient for pain B: Preset: 1 minute per day; other parameters not described	Usual care	3	Dichotomous Response*: 39.3% vs. 0%, RR 14.3 (95% CI, 0.9 to 227.8) Continuous Scale 0 to 10, mean change (SD): -1.5 (1.6) vs. -0.6 (1.0); p>0.05 for all comparison	Functional disability (scale NR), mean change (SD): 0.3 (0.5) vs. 0.0 (0.3)

Abbreviations: CI = confidence interval; IQR = interquartile range; NR = not reported; ONS = occipital nerve stimulation; RR = relative risk; SD = standard deviation; VAS = visual analogue scale

* ≥50% reduction in headache days per month or ≥3-point reduction in overall pain intensity from baseline

Detailed Synthesis

Pain

One fair-quality trial found occipital nerve stimulation associated with similar likelihood of the primary study outcome of at least a 50 percent reduction in headache pain intensity versus sham stimulation at 12 weeks (17.1% vs. 13.5%, RR 1.27, 95% CI, 0.57 to 2.86).[120] However, occipital nerve stimulation was associated with increased likelihood of at least a 30 percent reduction in headache pain intensity that just met the threshold for statistical significance (33.3% vs. 17.3%, RR 1.93, 95% CI, 1.00 to 3.70). Average effects on pain intensity were not reported in the main publication reporting full multicenter results, but a report from a single center (n=20) participating in the trial found occipital nerve stimulation associated with a large decrease in pain intensity at 4 weeks (mean change from baseline -2.16 vs. 0.34 on a 0 to 10 scale, $p<0.001$) and 12 weeks (mean change from baseline -2.30 vs. 0.79, $p<0.001$). The poor-quality crossover trial also found occipital nerve stimulation associated with a large decrease in pain intensity versus sham stimulation at the end of the initial 1-month (prior to crossover) period (median 5 vs. 7.5, $p<0.001$).[119]

The other fair-quality trial found occipital nerve stimulation with adjustable parameters associated with greater reduction in pain versus usual care at 3 months, but the difference was small and not statistically significant (mean change from baseline -1.5 vs. -0.6 on a 0 to 10 scale).[118] There was no difference between stimulation using preset parameters versus usual care in pain.

Function

One fair-quality trial found occipital nerve stimulation associated with greater improvement in headache related disability versus sham stimulation at 12 weeks (mean change from baseline -64.6 vs. -20.4 on the Migraine Disability Test (MIDAS) score [>20=severe disability], mean difference -44.2, 95% CI, -65.3 to -22.8).[120] The poor-quality crossover trial of occipital nerve stimulation versus sham did not report effects on headache related disability by treatment group.[119]

The other fair-quality trial found occipital nerve stimulation with adjustable parameters associated with larger decrease in headache disability category versus usual care at 3 months (mean change in MIDAS severity category -1.3, 95% CI, -2.25 to -0.35); one category level refers to the MIDAS score decreasing from the "severe" to "moderate" or "moderate" to "mild" category.[118] There was no difference between stimulation using preset parameters versus usual care in headache related disability.

Other Outcomes

One fair-quality trial found occipital nerve stimulation associated with greater percent decrease in headache days (mean change from baseline -27.2% vs. -14.9%, $p<0.05$) and increased likelihood of reporting "good" or "excellent" headache relief versus sham stimulation (50% vs. 18%, RR 2.86, 95% CI, 1.53 to 5.34) at 12 weeks.[120] The other fair-quality trial found occipital nerve stimulation with adjustable parameters associated with greater decrease in headaches days/month versus usual care at 3 months (mean difference -5.7 days, 95% CI, -10.9 to -0.54). Stimulation was also associated with greater improvement from baseline in Profile of Mood States score (mean difference -8.3 on a 0 to 168 scale, 95% CI, -15.2 to -1.4) and SF-36

MCS (mean difference 7.0 on a 0 to 100 scale, 95% CI, 1.7 to 12.3).[118] There were no differences between occipital nerve stimulation with present parameters versus usual care in headache days or measures of psychological well-being.

Harms

The most common device-related adverse event was lead migration, which occurred in 14 to 24 percent of patients in two trials. One trial reported three cases of serious device-related adverse events requiring hospitalization (5.9% [3/51]).[118] The events were implant site infection, lead migration, and postoperative nausea. In the other trial, persistent pain or numbness at the implant or lead site was reported in 13.1 percent of patients, skin erosion in 3.7 percent, and wound site complications in 2.8 percent.[120]

Effects of Technical Factors

As described above, one trial found occipital nerve stimulation with patient-adjustable parameters associated with superior outcomes compared with stimulation using preset (nonadjusted) parameters.[118]

Piriformis Injection for Piriformis Syndrome

Key Points

- One trial (N=50) found piriformis injection with corticosteroid and local anesthetic for piriformis syndrome associated with no difference versus local anesthetic alone in pain at rest at 1 week; piriformis injection was associated with a moderate reduction in pain at rest versus local anesthetic at 1 month (SOE: low for no difference at 1 week and for benefit at 1 month).
- Evidence was insufficient to assess piriformis injection with botulinum toxin.
- The mean age of participants ranged from 42 to 57 years.

Description of Included Studies

Four RCTs assessed the effectiveness of piriformis injection for piriformis syndrome (**Appendix Table G-23 to G-25 and Table 12**).[122-125] Ten participants were randomized in one small pilot trial[122] and the sample sizes in the other trials ranged from 50 to 87. In three trials, diagnosis of piriformis syndrome required a positive flexion, adduction and internal rotation (FAIR) test. The fourth trial[122] based diagnosis of piriformis syndrome on history and physical examination. In three trials, mean age ranged from 42 to 57 and symptom duration ranged from 2 to 3 years.[122,123,125] One trial did not report demographic or clinical characteristics.[124] The comparisons varied: three trials compared botulinum toxin A (dose 100 to 300 units) versus placebo (saline) injection,[122-124] one of which also evaluated a corticosteroid (triamcinolone acetonide 20 mg) plus local anesthetic (lidocaine) control injection.[123] The fourth trial compared a corticosteroid (betamethasone) plus lidocaine injection versus lidocaine alone.[125] Imaging or electromyographic guidance was used in all trials (**Table 12**).

Table 12. Study characteristics and results of piriformis injection trials

Study, Year Country Quality	Mean Age (Years)	Percent Female	Number Randomized	Duration of Symptoms (Months)	Diagnostic Criteria	Piriformis Injection	Control Type	Duration of Followup (Months)	Pain	Function
Childers, 2002[122] U.S Poor	42.1	100	10	≥3	H-reflex testing not used for inclusion	Botulinum toxin type A 100 units (fluoroscopic guidance)	Placebo	2.5	Mean difference (95% CI), VAS 0 to 10 1 week: -2.2 (-4.4 to 0.02) 4 weeks: -1.5 (-4.6 to 1.6) 9 weeks: -1.0 (-3.4 to 1.4)	Mean difference (95% CI) in interference with activities, VAS 0 to 10 1 week: -2.1 (-4.9 to 0.7) 4 weeks: -2.4 (-5.2 to 0.4) 9 weeks: -3.2 (-6.0 to -0.4)
Fishman, 2002[123] U.S Poor	57.4	67	87	Mean 38.4	Positive FAIR test (posterior tibial nerve H-reflex >1.86 ms)	A. Botulinum toxin type A 200 units (electromyographic guidance) B. Triamcinolone acetonide 20 mg + 1.5 ml 2% lidocaine (electromyographic guidance)	Placebo	3	RR (95% CI) of ≥50% improvement: 9.29 (1.36 to 63.53)	NR
Fishman, 2017[124] U.S Poor	NR	NR	56	NR	Positive FAIR test (posterior tibial or fibular nerve H-reflex >1.86 ms)	Botulinum toxin type A 300 units (electromyographic guidance)	Placebo	3	Mean (SD) change from baseline, scale unclear 4 weeks: -0.39 (0.31) vs. -0.05 (0.12), p<0.0001 12 weeks: -0.65 (0.24) vs. -0.008 (0.02), p<0.0001	NR

Study, Year Country Quality	Mean Age (Years)	Percent Female	Number Randomized	Duration of Symptoms (Months)	Diagnostic Criteria	Piriformis Injection	Control Type	Duration of Followup (Months)	Pain	Function
Misirlioglu, 2015[125] Turkey Fair	46.3	84	50	Mean 20.3	Positive FAIR test (threshold not reported)	Betamethasone 1 ml + 4 ml 2% lidocaine (ultrasound guidance)	Sham	3	Mean difference (95% CI) at rest, VAS 0 to 10 1 week: 0.40 (-0.97 to 1.77) 1 month: 1.20 (-0.03 to 2.43) 3 months: 1.20 (0.26 to 2.14) Mean difference (95% CI) with activity, VAS 0 to 10 1 week: 1.10 (-0.50 to 2.70) 1 month: 2.00 (0.70 to 3.30) 3 months: 1.30 (-0.13 to 2.73) Mean difference (95% CI) during sleep, VAS 0 to 10 1 week: 0.80 (-0.68 to 2.28) 1 month: 0.40 (-0.57 to 1.37) 3 months: 0.60 (-0.29 to 1.49)	NR

Abbreviations: CI = confidence interval; FAIR = flexion, adduction, and internal rotation; NR = not reported; RR = relative risk; SD = standard deviation; VAS = visual analogue scale

The trial of a corticosteroid plus lidocaine versus lidocaine was rated fair quality and the other three trials were rated poor quality (**Appendix Table H-1**). Methodological limitations in the poor-quality trials included unclear randomization and allocation concealment, unreported baseline characteristics, unclear blinding of outcome assessors and care providers, high attrition, lack of intent-to-treat analysis, and use of unreported (potentially unvalidated) scales to measure outcomes, including pain. In addition to a very small sample size, the pilot trial did not account for crossover design in the analysis.[122]

Detailed Synthesis

Pain

The fair-quality trial (n=50) found no difference between piriformis injection with corticosteroid plus lidocaine versus lidocaine alone in pain at rest at 1 week (mean difference 0.40 on 0 to 10 VAS, 95% CI, -0.97 to 1.77).[125] Differences were larger (mean difference 1.20) at 1 and 3 months, but only statistically significant at 1 month. A corticosteroid plus lidocaine was associated with a large reduction in pain with activity at 1 month (mean difference -2.00, 95% CI, -3.30 to -0.70); differences were smaller at 1 week and 3 months (mean differences -1.10 and -1.30 points) and not statistically significant. For pain at sleep, mean differences were less than 1 point and not statistically significant.

Three poor-quality trials (n=10, 50, and 56)[122-124] found piriformis injection with botulinum toxin A associated with reduced pain versus placebo (saline) injection at 2 to 12 week followup and one poor-quality trial (n=61)[123] found piriformis injection with corticosteroid plus lidocaine associated with reduced pain versus placebo, but results are difficult to interpret due to serious methodological limitations.

Function

One poor-quality trial found piriformis injection with botulinum toxin A associated with improvement in interference with daily activities versus placebo (saline) at 1 and 4 weeks, but enrolled a small sample (n=10) and did not report the instrument used to measure this outcome.[122] The other trials did not report function.

Other Outcomes

One small (n=10) poor-quality trial found piriformis injection with botulinum toxin A associated with decreased distress versus placebo (saline) injection at 1 week, using an unreported instrument.[122]

Harms

The fair-quality trial reported similar rates of transient sciatic nerve block with piriformis injections with corticosteroid plus lidocaine and lidocaine alone (24.0% vs. 27.3%).[125] Reporting of harms in the poor-quality trials was limited. The small crossover trial reported no serious adverse events[122] and one trial reported similar rates of any adverse event between piriformis injection with botulinum toxin versus saline (RR 0.96, 95% CI, 0.32 to 2.94).[124]

Peripheral Nerve Stimulation for Ulnar, Median, and Radial Neuropathy

Key Points

- Evidence was insufficient to assess peripheral nerve stimulation for upper extremity peripheral neuropathic pain (SOE: insufficient).

Description of Included Studies

No RCT or controlled observational study compared peripheral nerve stimulation versus usual care, no stimulation, or sham for upper extremity (ulnar, median, or radial nerve) neuropathy. One RCT (n=94) compared peripheral nerve stimulation versus sham (current not applied) for patients with chronic (>3 months) upper extremity, lower extremity, or trunk peripheral neuropathic pain; some results were reported in the subgroup of patients with upper extremity pain (n=26) (**Appendix Table G-26 and G-27, and Table 13**).[126] Specific causes of upper extremity pain were not reported, though pain had to be posttraumatic or postsurgical. The mean age of patients was 53 years and 42 percent were female. The mean duration of pain was not reported. Lead placement was performed with imaging (ultrasound or fluoroscopic guidance) and test stimulation for verification. Parameters varied with phase duration 70 to 500 μ/sec, pulse rate 1 to 200 Hz, time on ranging from 10 minutes to 12 hours (mean 6 hours per day). Typical settings were 200 μ/sec and 100 Hz, with amplitude set for paresthesia. Outcomes were assessed at 3 months. The trial was rated fair quality due to failure to report allocation concealment methods, unclear blinding of outcome assessors and care providers, and failure to report attrition (**Appendix Table H-1**).

Table 13. Study characteristics and results of peripheral nerve stimulation trial

Study, Year Country Quality	Mean Age (Years)	Percent Female	Number Randomized	Duration of Symptoms (Months)	Diagnosis Criteria	Control Type	Duration of Followup (Months)	Pain	Function
Deer, 2016[126] U.S. Fair	53	41.5	94	≥3	Severe intractable chronic pain of peripheral nerve origin associated with posttraumatic/postsurgical neuralgia for ≥3 months, worst pain level in the last 24 hours ≥5 (NRS 0 to 10), pain is attributable to a lesion or disease of the somatosensory nervous system	Sham	12	Dichotomous Responders at 3 months -Overall (n=94): 38% vs. 10%, RR 3.70 (95% CI, 1.49 to 9.21) -Upper extremity pain (n=26): 33% vs. 0%, RR 10.4 (95% CI, 0.6 to 175.2) Continuous % reduction, mean (SD) -Overall (n=94): -27.2% vs. -2.3%, mean difference -24.9%, p<0.0001 -Upper extremity pain (n=26): -29.2% (33.3) vs. -6.5% (20.0), mean difference -19.8% (95% CI, -44.6 to 5.0)	SF-12 0 to 100, mean change (SD) at 3 months -Overall: 1.4 (5.9) vs. -0.2 (3.4), p=0.04

Abbreviations: CI = confidence interval; NRS = numeric rating scale; RR = relative risk; SD = standard deviation; SF-12 = Short Form 12-item
*Responders were defined as those with ≥30% reduction in pain and no increase in pain medication

Detailed Synthesis

Pain

Among the subgroup of patients with upper extremity pain, peripheral nerve stimulation was associated with greater percent change from baseline in pain intensity at 3 months, but the estimate was imprecise and not statistically significant (mean difference -19.8%, 95% CI, -44.6 to 5.0).[126] The estimate for treatment response (defined as ≥30% reduction in pain with no increase in pain medication use) also favored peripheral nerve stimulation, but was very imprecise (33% vs. 0%, RR 10.4, 95% CI, 0.6 to 175.2).

Function and Other Outcomes

The trial did not report function and other outcomes separately for the subgroup of patients with upper extremity pain.[126] For all participants, peripheral nerve stimulation was associated with greater improvement in Brief Pain Inventory general activity score (mean change from baseline -2.3 vs. -0.4 on a 0 to 10 scale, p=0.001). Peripheral nerve stimulation was also associated with greater improvement in Short-Form 12 (SF-12), but the difference was very small (mean change from baseline 1.4 vs. -0.2 on a 0 to 100 scale, p=0.04).

Harms

Harms were not reported separately for the subgroup of patients with upper extremity pain. Among all participants, there was no difference between peripheral nerve stimulation versus sham in likelihood of any adverse events, device related adverse events, or nondevice related adverse events.[126] There were no serious device-related serious adverse events.

Discussion

Key Findings and Strength of Evidence

The key findings of this review are summarized in **Table 14** and the summary of evidence table (**Appendix J**). **Table 14** shows effects of the interventional procedures and comparisons evaluated in this report on pain and function at five predefined followup intervals, including the magnitude of benefit and strength of evidence assessment. The summary of evidence table provides additional details about the domains used to determine strength of evidence for pain, function, and additional outcomes.

Table 14. Interventional pain therapies for acute and chronic pain*

Intervention	Condition	**Pain** 1 to 2 weeks Effect Size SOE	**Pain** 2 to 4 weeks Effect Size SOE	**Pain** 1 to 6 months Effect Size SOE	**Pain** 6 to 12 months Effect Size SOE	**Pain** ≥12 months Effect Size SOE	**Function** 1 to 2 weeks Effect Size SOE	**Function** 2 to 4 weeks Effect Size SOE	**Function** 1 to 6 months Effect Size SOE	**Function** 6 to 12 months Effect Size SOE	**Function** ≥12 months Effect Size SOE
Vertebroplasty vs. sham or usual care	Vertebral compression fractures	Small[†] **+**	Moderate[‡] **++**	Small **++**	Small **++**	Small **++**	Insufficient[§]	Small **+++**	Small **++**	Small **+++**	Small **++**
Kyphoplasty vs. usual care	Vertebral compression fractures	Large **++**	Large **++**	Moderate **+**	Moderate **+**	Small **+**	Moderate **+**	Moderate to large **++**	Moderate **+**	Moderate **+**	Small **+**
Cooled radiofrequency ablation vs. sham	Sacroiliac pain	No evidence	Moderate to large **++**	Moderate **++**	No evidence	No evidence	No evidence	Small to large **+**	Moderate **++**	No evidence	No evidence
Cooled vs. conventional radiofrequency denervation	Presumed facet joint pain	No evidence	None **+**	None **+**	Small **+**	No evidence	No evidence	None **+**	None **+**	None **+**	No evidence
Pulsed radiofrequency denervation vs. sham[‖]	Presumed facet joint pain	No evidence	No evidence	No evidence	Insufficient	Insufficient	No evidence	No evidence	No evidence	Insufficient	Insufficient
Pulsed vs. conventional radiofrequency denervation[‖]	Presumed facet joint pain	No evidence	No evidence	No evidence	Insufficient	Insufficient	No evidence	No evidence	No evidence	Insufficient	Insufficient
Cooled or pulsed radiofrequency denervation vs. sham, usual care, or conventional radiofrequency denervation	Degenerative hip pain	No evidence	No evidence	No evidence	No evidence	No evidence	No evidence	No evidence	No evidence	No evidence	No evidence
Facet joint platelet-rich plasma vs. sham or usual care	Presumed facet joint pain	No evidence	No evidence	No evidence	No evidence	No evidence	No evidence	No evidence	No evidence	No evidence	No evidence

Intervention	Condition	Pain 1 to 2 weeks Effect Size SOE	Pain 2 to 4 weeks Effect Size SOE	Pain 1 to 6 months Effect Size SOE	Pain 6 to 12 months Effect Size SOE	Pain ≥12 months Effect Size SOE	Function 1 to 2 weeks Effect Size SOE	Function 2 to 4 weeks Effect Size SOE	Function 1 to 6 months Effect Size SOE	Function 6 to 12 months Effect Size SOE	Function ≥12 months Effect Size SOE
Intradiscal platelet-rich plasma vs. sham	Discogenic back pain	Insufficient	Insufficient	Insufficient	No evidence	No evidence	Insufficient	Insufficient	Insufficient	No evidence	No evidence
Intradiscal stem cells vs. control*	Discogenic back pain	No evidence	Insufficient	Insufficient	Insufficient	Insufficient	No evidence	Insufficient	Insufficient	Insufficient	Insufficient
Intradiscal methylene blue vs. sham	Discogenic back pain	No evidence	No evidence	None +	None +	Insufficient	No evidence	No evidence	Small +	None +	Insufficient
Intradiscal ozone + corticosteroid vs. corticosteroid	Discogenic back pain	Insufficient	No evidence	Insufficient	Insufficient	No evidence	Insufficient	Insufficient	No evidence	Insufficient	Insufficient
Sphenopalatine block vs. control	Trigeminal neuralgia	No evidence	No evidence	No evidence	No evidence	No evidence	No evidence	No evidence	No evidence	No evidence	No evidence
Sphenopalatine block vs. control‖	Chronic migraine	No evidence	Insufficient	No evidence	Insufficient	No evidence	No evidence	Insufficient	No evidence	Insufficient	No evidence
Occipital nerve stimulation vs. sham‖	Chronic migraine	No evidence	No evidence	Insufficient	No evidence	No evidence	No evidence	No evidence	Insufficient	No evidence	No evidence
Occipital nerve stimulation vs. usual care	Chronic migraine	No evidence	No evidence	Insufficient	No evidence	No evidence	No evidence	No evidence	Insufficient	No evidence	No evidence
Piriformis injection with corticosteroid plus local anesthetic vs. corticosteroid plus local anesthetic, or sham‖	Piriformis syndrome	None +	Moderate +	Insufficient	No evidence	No evidence	No evidence	No evidence	No evidence	No evidence	No evidence
Peripheral nerve stimulation vs. sham	Ulnar, median or radial neuropathy pain	No evidence	No evidence	Insufficient	No evidence	No evidence	No evidence	No evidence	Insufficient	No evidence	No evidence

Abbreviations: SOE = strength of evidence

Effect size: none (i.e., no effect/no statistically significant effect), small, moderate, or large increased risk; SOE: + = low, ++ = moderate, +++ = high.

*Grey shading indicates insufficient or no evidence

†There was no difference in trials with sham control and moderate difference in trials with usual care control, but no statistically significant interaction between control type and effects on pain (p for interaction=0.14)

‡There was a small difference in trials with sham control and large difference in trials with usual care control, with a statistically significant interaction between control type and effect on pain (p for interaction <0.01)

§There was no difference in trials with sham control and small difference in trials with usual care control, but no statistically significant interaction between control type and effects on pain (p for interaction=0.19)

‖Poor-quality trials excluded

Vertebroplasty was the only intervention evaluated in a sufficient number of trials to permit meta-analysis. The evidence on vertebroplasty was of high applicability to Medicare populations due to enrollment of older (>65 years of age) patients in all of the trials, consistent with the epidemiology of osteoporotic compression fractures, which predominantly impacts older patients. Based on pooled estimates, vertebroplasty was associated with small improvements in pain and function versus controls (sham or usual care) at most time points evaluated (ranging from 1 to 2 weeks to 12 months and longer). Mean differences for pain ranged from 0.53 to 1.05 points on a 0 to 10 scale and were less than 2 points on the 0 to 24 Roland–Morris Disability Questionnaire (RDQ). Although these differences were below proposed minimally important differences (1.5 points for pain[72,127,128] and 2 to 3 points or higher for the RDQ),[72,129,130] they are comparable to the benefits observed for other treatments used for pain, including nonsteroidal anti-inflammatory drugs[75] or antidepressants[74] for low back pain, epidural corticosteroid injection for lumbar radiculopathy,[44] and opioids for chronic pain,[76] which are also below proposed minimum clinically important differences. Because average differences may obscure larger benefits that occur in some patients, evaluating effects on pain or function based on the likelihood of achieving a clinical response (e.g., ≥30% or at least moderate improvement) can provide complementary information. However, few trials reported the likelihood of achieving a pain or function response. Results were imprecise with nonstatistically significant differences, though the likelihood of achieving a pain response favored vertebroplasty at 2 to 4 weeks, 1 to 6 months, and 6 to 12 months.

Although statistical heterogeneity was present in some pooled estimates on effects of vertebroplasty, the overall findings were consistent with a small benefit. Sources of heterogeneity could include the type of control (sham versus usual care), the type of sham (with or without periosteal local anesthetic), or the duration of pain. Benefits of vertebroplasty were generally larger in trials with usual care rather than sham controls. This is consistent with increased susceptibility of usual care trials to placebo effects, due to their open-label design, leading to overestimation of effectiveness due to expectations regarding benefits. However, differences between control type and effects on pain or function were only statistically significant for pain at 2 to 4 weeks (at this time point, the effect was small in sham-controlled trials and large in trials with usual care control). However, our ability to identify statistically significant interactions was limited by the relatively small number of trials in subgroup analyses, resulting in imprecise estimates.

Other potential sources of heterogeneity include fracture duration (more acute fractures potentially more responsive to treatment),[94] whether the trials restricted enrollment to patients with imaging findings indicating bone marrow edema at fracture sites (a marker of fracture acuity),[131] or the volume of cement used in the vertebroplasty procedure (polymethyl methacrylate [PMMA] volume).[132] Although trials of acute fractures (based on either inclusion criterion of <4 weeks or average pain duration at enrollment of <4 weeks) generally reported larger estimates of benefit that trials of patients with longer duration of fracture, few trials evaluated patients with acute fractures (only 1 trial[91] was restricted to patients with acute fractures and the average duration <4 weeks in only 3 trials),[80,89,91] subgroup estimates were imprecise, and analyses indicated no statistically significant subgroup effects. In addition, only one sham-controlled trial[80] focused on patients with acute pain (mean duration <3 weeks), potentially confounding analyses on control type and pain duration. Further, among the sham-controlled trials, this trial reported the largest (moderate) benefits of vertebroplasty on pain intensity at 2 to 4 weeks.[80] Although three trials that performed within-study subgroup analyses

found no statistically significant interaction between fracture duration and effects of vertebroplasty, acute fractures were defined differently in each trial (<3, <6, or <13 weeks)[79,80,83] and two of the trials[80,83] reported larger benefit were in patients with more acute fractures. Requiring bone marrow imaging on magnetic resonance imaging (MRI) (a marker of fracture acuity) for trial enrollment was not associated with differential effects on pain and results did not indicate a difference in effects of vertebroplasty based on larger average PMMA volume used.

Another factor that could partially explain decreased effects of vertebroplasty in sham-controlled trials is related to use of local anesthetic infiltration in patients randomized to sham.[81] In four sham-controlled trials that found no benefit of vertebroplasty, patients underwent periosteal or vertebral body local anesthetic infiltration.[79,81-83] In the fifth trial, which found vertebroplasty associated with moderate benefits, patients randomized to sham underwent subcutaneous but not periosteal local anesthetic infiltration.[80] If infiltration of local anesthetic into periosteum or bone is associated with therapeutic benefits for fracture beyond subcutaneous infiltration, it is possible that its use in sham could attenuate benefits of vertebroplasty. However, this would require that infiltration of cement not have a therapeutic effect beyond local anesthetic—even though stabilization of the fracture with cement is the proposed mechanism of action of vertebroplasty. Furthermore, effects of local anesthetic would need to persist long beyond their expected duration (generally 1 to 8 hours), as differences between sham and usual care controlled trials are observed at long term (months to beyond a year) followup (**Table 4**). It was not possible to isolate the effects of local anesthetic bone infiltration from the sham-controlled trials, because the trial[80] that only utilized subcutaneous local anesthetic infiltration differed from the others in several other ways that might impact effectiveness, including use of the largest PMMA volume (7.5 ml vs. 2 to 5.1 ml) and enrolment of the most acute patients (<6 weeks, with mean duration of 2.6 weeks vs. mean of up to 17.8 weeks in the other sham trials).

Evidence on other outcomes of vertebroplasty was more limited, but indicated small effects on general quality of life (EuroQOL 5-Dimension Questionnaire [EQ-5D]) at some time points, no differences in condition-specific quality of life (Quality of Life Questionnaire of the European Foundation for Osteoporosis [QUALEFFO]), and no difference in Short-Form 36 Health Survey Physical Component Score (SF-36 PCS) or Short-Form 36 Health Survey Mental Component Score (SF-36 MCS) status. There was no increased risk of incident vertebral fractures or mortality, though some imprecision in estimates was present; evidence on serious harms was very imprecise but also did not indicate increased risk.

Like vertebroplasty, kyphoplasty is a vertebral augmentation procedure, but involves restoration of vertebral body height before injecting cement. Evidence was limited to two open-label trials, one of which focused on patients with fracture and cancer.[99,102] Kyphoplasty was associated with large improvement in pain and moderate improvement in function at 1 week and 1 month, moderate benefits through 1 year, and small improvements at 2 years. These findings may be an overestimate, due to potential placebo effects in open-label, usual care trials. There was no increased risk of serious adverse events, but evidence on incident vertebral fracture and mortality was inconsistent and imprecise.

Cooled and pulsed radiofrequency denervation are alternatives to conventional radiofrequency involving use of a cooler probe or decreased current in shorter bursts. Based on two trials, cooled radiofrequency was associated with moderate to large improvement in pain at 1 month and moderate improvement at 3 month compared with sham in patients with sacroiliac pain.[103,104] For function, benefits were small to large at 1 month and moderate at 3 months. However, there were no statistically significant differences between cooled versus conventional

radiofrequency denervation for presumed facet joint pain in pain or function.[105] Evidence on pulsed radiofrequency versus sham or conventional radiofrequency denervation for presumed facet joint pain was insufficient, based on a single fair-quality trial with imprecise estimates.[106] Based on limited evidence, occipital nerve stimulation for headache may be more effective than usual care for improving headache-related disability and reducing headache days (lead migration was common and other device-related complications have been reported) and piriformis corticosteroid injection for piriformis syndrome may be similarly effective versus sham for pain at 1 week, but more effective for reducing pain at 1 month.

Interpretation of the results of two trials of intradiscal methylene blue trials for presumed discogenic back pain is challenging. Intradiscal methylene blue was associated with large benefits versus sham at 6 months in pain and function in an initial trial.[112] However, a subsequent trial[111] found no differences between methylene blue versus sham in pain or function at 6 months, despite mimicking the study design of the earlier trial. The earlier trial also found large benefits at 12 and 24 months; the subsequent trial did not evaluate outcomes beyond 6 months, but found no differences in pain and small improvements in function at 6 weeks and 3 months. It is unclear why 6 month results of the trials were discordant, though the earlier trial[112] was assessed as lower (fair) quality, reported a higher participation rate (58% of screened participants enrolled compared with 6% in the subsequent trial), did not exclude patients with multilevel disease, and did not exclude patients with positive response to a facet joint block, it is not clear why these differences would result in greater benefits of intradiscal methylene blue.

For the other interventions addressed in this report, evidence was generally insufficient to determine benefits and harms, based on single fair-quality trials with methodological limitations, often with imprecise estimates. No study evaluated cooled radiofrequency denervation versus sham or usual care for degenerative hip conditions, intradiscal ozone for nonradicular, presumed discogenic back pain, piriformis injection with botulinum toxin for piriformis syndrome, or sphenopalatine block for trigeminal neuralgia.

Findings in Relation to What Is Already Known

Our findings regarding vertebroplasty are generally consistent with a recent systematic review of randomized controlled trials (RCTs) that also found vertebroplasty associated with small effects on pain and function versus sham treatments that were below prespecified minimum clinically important thresholds, with larger effects in trials of vertebroplasty versus usual care.[22] Our review differs from this prior review by performing analyses on additional potential modifiers of treatment effect (PMMA volume, presence of bone marrow edema on MRI), including overall as well as stratified estimates from sham- and usual care-controlled trials, evaluating pain duration based on inclusion criteria as well as mean duration of symptoms, and incorporating additional recently studies and publications[81,82,94,95] from a more recent literature search. We showed that PMMA volume and requiring presence of bone marrow edema on MRI had little impact on estimates. We also showed that sham and usual care trials reported similar effects on pain and function at some time points and that pain duration appeared to affect treatment estimates, suggesting that differences are multifactorial and not solely related to the type of control used. Unlike another recent review of vertebroplasty in older adults that included RCTs and non-RCTs, we restricted inclusion to RCTs, strengthening the certainty in findings, though overall conclusions were similar.[133] We also identified additional data on mortality, serious adverse events, and incident fractures to provide more robust estimates and confidence that vertebroplasty does not increase risk of these outcomes (though some imprecision persists).

Two recent meta-analyses[134,135] that included observational studies, which may be a useful supplement to RCTs for evaluating harms, were consistent with our review in finding no association between vertebroplasty versus nonsurgical management and increased risk of subsequent incident fractures or mortality. In one of the reviews, vertebroplasty was associated with a protective effect on mortality (hazard ratio 0.78, 95% confidence interval, 0.69 to 0.71).[134] We found no indication of a protective effect of vertebroplasty on mortality, suggesting that the findings based on observational studies should be interpreted with caution and could be related to confounding by indication, if patients are selected for vertebroplasty based in part on being healthier and at lower risk of mortality.

Our findings regarding kyphoplasty are consistent with a recent systematic review that also found no sham-controlled trials and greater reduction in pain and improvement in function versus usual care.[136] Our findings are also consistent with a recent systematic review[137] of cooled radiofrequency denervation and association with benefit for sacroiliac pain that included RCTs as well as observational studies. Although a recent systematic review evaluated radiofrequency denervation for chronic back pain, it did not focus on effects of pulsed or cooled radiofrequency specifically.[24] Regarding the other interventional procedures addressed in this report, we found systematic reviews to be lacking, likely reflecting the paucity of evidence. Therefore, our review adds to what is known by providing a systematic synthesis of the available evidence. Our review of reference lists from nonsystematic reviews verified the absence of additional RCTs.

Applicability

As previously noted, evidence on vertebroplasty and kyphoplasty is highly relevant for Medicare-eligible patients. These procedures are performed for vertebral compression fractures, most commonly due to osteoporosis, a condition which increases in prevalence with age. All trials of vertebroplasty and kyphoplasty enrolled patients with a mean age of 65 years of older, with the exception of one trial[99] of kyphoplasty for vertebral compression fractures related to cancer in which the mean age was 64 years. Trials of vertebroplasty and kyphoplasty generally appeared to use techniques consistent with current practice and most were conducted in very high human development index countries, likely increasing applicability to clinical practice in the United States. The majority of participants in the trials were women, consistent with the sex distribution of this condition, but one trial found no association between sex and effects of vertebroplasty.[79]

The evidence on the other interventional procedures evaluated in this report may be less directly applicable to Medicare-eligible patients. The mean age of trial participants for these procedures ranged from 40 to 59 years and some trials (e.g., the trials of intradiscal methylene blue for presumed discogenic back pain)[111,112] specifically excluded older (>66 years) patients. No trial reported results stratified by older age or other factors relevant for determining Medicare eligibility, such as disability status or presence of end-stage renal disease. The lack of direct evidence in Medicare-eligible patients is unsurprising, given the overall lack of evidence on these procedures.

Implications for Clinical and Policy Decision Making

Our review has implications for clinical and policy decision making. Findings of this review may inform use of vertebroplasty in Medicare-eligible patients. Although benefits of vertebroplasty were classified as small, they are comparable with the benefits observed with other therapies for pain, including nonsteroidal anti-inflammatory drugs[75] and antidepressants[74]

for chronic low back pain, opioids for chronic pain,[76] epidural corticosteroid injections for lumbar radiculopathy,[44] and psychological therapies for chronic pain.[138] For all of these therapies, pain reduction averaged 0.5 to less than 1.0 point on a 0 to 10 scale. For vertebroplasty, interpretation of small benefits is complicated by inability to completely disentangle effects of study design (sham vs. usual care) from other factors (pain duration, potential therapeutic effects of sham, and others) that may impact estimates of benefit.

Use of vertebroplasty for treatment of vertebral compression fractures remains controversial. Decisions regarding use of vertebroplasty should take into consideration the severity of pain and response to analgesics and other medical management. In patients with more severe pain who are not responding to medical management, factors that may inform decisions to use vertebroplasty include the relatively small benefit, uncertainty regarding potential benefits (including magnitude of placebo effects) and harms (including risk of incident vertebral fracture), costs, and variability in patient preferences or how they value small average benefits. This approach is consistent with a proposed (not finalized) Medicare Local Coverage Determination document.[139] In the proposed Local Coverage Determination, presence of bone marrow edema on imaging is required. Based on the evidence reviewed in this report, there is insufficient evidence to identify subgroups more likely to benefit from vertebroplasty based on pain duration or presence of bone marrow edema, or technical factors associated with greater benefit, such as optimal PMMA volume.

Although our report found that kyphoplasty was associated with larger benefits than vertebroplasty, these estimates are likely an overestimate, given that results are derived from open-label, usual care-controlled trials. Systematic reviews that included trials that directly compared kyphoplasty versus vertebroplasty (not eligible for our report) found no differences between the procedures, supporting similarity in benefits.[22] Therefore, considerations like those described for vertebroplasty are also likely to be relevant for decisions regarding kyphoplasty. Of note, kyphoplasty is considered a more technically complex procedure and more costly, but is usually preferred when there is more compression of the vertebral body, and there is more uncertainty with regard to benefits as well as harms.

Cooled radiofrequency denervation appears to have potential for treatment of sacroiliac pain. Selection of patients for this procedure should take into account that in both trials in which cooled radiofrequency denervation was found to be effective, patients were selected on the basis of a positive response to a sacroiliac diagnostic block and lack of response to conventional (medical) therapy. A factor complicating use of cooled radiofrequency was that the trials utilized different techniques, with insufficient evidence to determine the optimal method: in one trial,[103] cooled radiofrequency denervation was performed to the S1 to S3 lateral branches and conventional radiofrequency denervation to the L4 and L5 dorsal rami, whereas in the other trial[104] cooled radiofrequency was performed at the L5 dorsal ramus and the S1 to S3 sites. The trials required patients to have at least a 75 percent reduction in pain with diagnostic block, which should inform considerations regarding patient selection for this procedure.

For the other interventional procedures and conditions evaluated in this report, current evidence was too limited to guide clinical and policy decision making. For some interventions and comparisons, current evidence suggested no benefit, though the strength of evidence was low (methylene blue vs. sham for presumed discogenic back pain and cooled vs. conventional radiofrequency denervation for presumed facet joint pain).

Limitations of the Systematic Review Process

We focused on randomized trials, because observational and other non-randomized studies are more susceptible to bias and confounding, especially when assessing more subjective outcomes such as pain and function.[48] Furthermore, non-randomized studies have been shown to overestimate benefits of interventional pain treatments. For example, non-randomized studies of vertebroplasty reported complete and sustained pain relief in 78 percent to 90 percent of patients and non-randomized studies of intradiscal electrothermal therapy[55] and transforaminal epidural steroid injection[53] reported reductions in pain intensity of 2 to 4.5 points on a 10 point pain scale versus usual care or sham, compared with less than 1 point in RCTs of these therapies..[43,57] Although cohort studies assessing benefits would have been included if no RCTs were available, there was at least 1 RCT for all interventions addressed in this report. We also planned to include large (n>500) case series on rare and serious harms, but did not identify such eligible studies.

We excluded non-English language articles and did not search for or include non-peer reviewed studies or studies published only as abstracts. This resulted in the exclusion of one completed sham-controlled trial (n=80) of patients with chronic (>3 months) vertebral compression fractures published as a non-peer-reviewed preprint;[140] results were consistent with our analyses in finding vertebroplasty associated with small to moderate benefits in pain intensity and quality of life. Meta-analyses were not possible for interventions other than vertebroplasty, due to small numbers of studies and methodological limitations. In the meta-analyses of vertebroplasty, assessment for small sample effects (a potential marker of publication bias) using statistical and graphical methods was limited to analyses on pain intensity at two time points with 10 trials (neither indicated small sample effects); the other analyses included fewer than 10 trials, a proposed threshold for informative analyses of small sample effects.[141] Analyses of subgroup effects in the vertebroplasty meta-analyses were limited by small numbers of trials in subgroups, with imprecise estimates. In addition, subgroup analyses were based on study level data, which are limited in their ability to evaluate factors that vary on an individual level (e.g., pain duration or severity). We did not have access to individual patient data, which would have enabled more robust evaluations of demographic, clinical, and technical characteristics and impacts on vertebroplasty outcomes. Some pooled estimates were associated with high statistical heterogeneity; because of anticipated heterogeneity, a random effects model was used to perform meta-analysis. We excluded active-controlled trials, focusing on outcomes compared with sham or usual care controls, with the exception of trials of cooled or pulsed radiofrequency denervation versus conventional radiofrequency denervation, which were included because these techniques have been proposed as alternatives to conventional radiofrequency denervation. We excluded trials that combined multiple therapies in order to focus on the effects of the specific interventional procedures of interest, with the exception of intradiscal ozone plus epidural corticosteroid versus epidural corticosteroid for lumbar radiculopathy with herniated disc, which was included because no trial evaluated intradiscal ozone therapy alone and epidural corticosteroids are considered a standard treatment for this condition. We did not address outcomes prior to 1 week; therefore, our review does not address immediate and very early outcomes of interventional procedures. Such very early outcomes are likely more relevant for patients with acute pain than for the chronic pain conditions addressed by most of the interventions in this report. For parallel group trials in which high crossover rates occurred (usually from sham or usual care to the intervention), we focused on results reported prior to high crossover, to preserve randomization and the intent-to-treat approach.

Limitations of Evidence Base

The evidence base had important limitations. For vertebroplasty, trials varied with regard to patient selection criteria (e.g., duration of pain), technical factors (e.g., volume of PMMA), and sham interventions (e.g., sites of local anesthetic infiltration); in addition, the usual care interventions were not well standardized or defined. Some factors were correlated (e.g., only 1 sham-controlled trial enrolled patients with pain <4 weeks and did not utilize periosteal local anesthetic injection like the other trials) and evidence was insufficient to fully disentangle the effects of these factors. Pain and function were the most commonly reported outcomes, with limited evidence on quality of life, health status (e.g., SF-36), mood, analgesic (including opioid) use, and other outcomes. Most results were based on mean differences in outcomes, with few trials reporting the likelihood of achieving a clinically relevant response. Data on harms were relatively sparse and inconsistently reported. The trials were not designed to evaluate how benefits and harms varied in populations defined by demographic, clinical, or technical factors. Data on long-term (≥1 year) outcomes was relatively limited.

For the other interventional procedures evaluated in this report, the major limitation was the small numbers of trials, with important methodological shortcomings in almost all available trials. There was also variability with regard to use of sham or usual care comparators, as well as among sham and usual care treatments, representing a potential source of heterogeneity. Usual care was often not well described, making it difficult to determine applicability to clinical practice. For kyphoplasty, a major limitation is the absence of sham-controlled trials.

Research Recommendations

For vertebroplasty, the need for additional RCTs has been questioned, given moderate to high certainty that benefits are likely to be no greater than small.[142] However, a number of outstanding questions regarding vertebroplasty remain, including whether some sham interventions have therapeutic effects and whether benefits are greater in patients with hyperacute (e.g., <3 weeks pain). If conducted, future RCTs should be sham-controlled to reduce potential placebo effects and be designed to address effects of pain duration on effects of vertebroplasty (e.g., via sufficiently powered subgroup analyses of patients with <3 weeks and of patients with <3 weeks and 3 to 6 weeks pain), whether periosteal infiltration with local anesthetic without administration of PMMA is associated with an independent, persistent therapeutic effect (e.g., via inclusion of control arms using different sham with and without periosteal local anesthetic), and long-term outcomes, including harms. Alternatively, an individual patient data meta-analysis of existing trials could more robustly evaluate how factors such as pain duration, baseline pain severity, PMMA volume, MRI findings, and other factors impact outcomes of vertebroplasty. Comparator treatments, including the components of usual care, should be described with sufficient detail to determine applicability to practice.

For the other procedures addressed in this report, there is a need for rigorous RCTs to clarify benefits and harms. As illustrated by the example of intradiscal methylene blue, promising results of future RCTs will require confirmatory trials. Ideally, future RCTs should attempt to minimize placebo effects by utilizing appropriate sham interventions and include rigorous assessment of harms and longer-term outcomes. For cooled radiofrequency for sacroiliac pain, additional research would be helpful to clarify optimal techniques, given the variability in methods between the two available trials.[103,104] Prospective clinical registries designed to

evaluate uncommon and serious harms would be a useful supplement to RCTs, given likely sample size limitations.

Conclusions

Vertebroplasty is probably effective at reducing pain and improving function in older patients with vertebral compression fractures; benefits are small but similar to other therapies recommended for pain. Evidence was too limited to separate effects of control type and symptom acuity on effectiveness of vertebroplasty. Kyphoplasty has not been compared against sham, but is probably more effective than usual care for vertebral compression fractures in older patients. In younger populations, cooled radiofrequency denervation is probably more effective than sham for sacroiliac pain. Research is needed to determine the benefits and harms of the other interventional procedures and conditions addressed in this review.

References

1. Institute of Medicine. Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research. Washington, DC: The National Academies Press; 2011.
2. Treede RD, Rief W, Barke A, et al. Chronic pain as a symptom or a disease: the IASP Classification of Chronic Pain for the International Classification of Diseases (ICD-11). Pain. 2019 Jan;160(1):19-27. doi: 10.1097/j.pain.0000000000001384. PMID: 30586067.
3. Gaskin DJ, Richard P. The Economic Costs of Pain in the United States. J. Pain. 2012;13(8):715-24. doi: 10.1016/j.jpain.2012.03.009. PMID: 22607834.
4. Dahlhamer J, Lucas J, Zelaya C, et al. Prevalence of Chronic Pain and High-Impact Chronic Pain Among Adults - United States, 2016. 0149-2195 (Print) 0149-2195. Sep 14 2018. doi: 10.15585/mmwr.mm6736a2. PMID: 30212442.
5. Morden NE, Munson JC, Colla CH, et al. Prescription opioid use among disabled Medicare beneficiaries: intensity, trends, and regional variation. Med Care. 2014 Sep;52(9):852-9. doi: 10.1097/mlr.0000000000000183. PMID: 25119955.
6. Makris UE, Abrams RC, Gurland B, et al. Management of persistent pain in the older patient: a clinical review. JAMA. 2014;312(8):825-36. doi: 10.1001/jama.2014.9405. PMID: 25157726.
7. Cavalieri TA. Managing pain in geriatric patients. J Am Osteopath Assoc. 2007;107(suppl_4):ES10-ES6.
8. Kuo YF, Raji MA, Chen NW, et al. Trends in opioid prescriptions among Part D medicare recipients from 2007 to 2012. Am J Med. 2016 Feb;129(2):221.e21-30. doi: 10.1016/j.amjmed.2015.10.002. PMID: 26522794.
9. Olfson M, Wang S, Wall MM, et al. Trends in opioid prescribing and self-reported pain among US adults. Health Aff (Millwood). 2020 Jan;39(1):146-54. doi: 10.1377/hlthaff.2019.00783. PMID: 31905067.
10. Hargan ED, Department of Health and Human Services. Determination that a public health emergency exists (https://www.cms.gov/About-CMS/Agency-Information/Emergency/Downloads/October_26_2017_Public_Health_Declaration_for_Opioids_Crisis.pdf). 2017 Oct.
11. Weiss AJ, Heslin KC, Barrett ML, et al. Opioid-related Inpatient Stays and Emergency Department Visits Among Patients aged 65 Years and Older, 2010 and 2015: Statistical brief #244 Agency for Healthcare Research and Quality (US). Rockville (MD): 2006. PMID: 30475561.
12. Huhn AS, Strain EC, Tompkins DA, et al. A hidden aspect of the U.S. opioid crisis: Rise in first-time treatment admissions for older adults with opioid use disorder. Drug Alcohol Depend. 2018 Dec 1;193:142-7. doi: 10.1016/j.drugalcdep.2018.10.002. PMID: 30384321.
13. Centers for Disease Control and Prevention. 2018 Annual Surveillance Report of Drug-Related Risks and Outcomes — United States. Surveillance Special Report. U.S. Department of Health and Human Services; August 31, 2018. https://www.cdc.gov/drugoverdose/pdf/pubs/2018-cdc-drug-surveillance-report.pdf. Accessed July 7, 2020.
14. Schieber LZ, Guy GP, Jr., Seth P, et al. Variation in Adult Outpatient Opioid Prescription Dispensing by Age and Sex - United States, 2008-2018. MMWR Morb Mortal Wkly Rep. 2020 Mar 20;69(11):298-302. doi: 10.15585/mmwr.mm6911a5. PMID: 32191686.
15. Dowell D, Haegerich TM, Chou R. CDC Guideline for Prescribing Opioids for Chronic Pain--United States, 2016. Jama. 2016 Apr 19;315(15):1624-45. doi: 10.1001/jama.2016.1464. PMID: 26977696.

16. Dowell D, Haegerich TM, Chou R. CDC Guideline for Prescribing Opioids for Chronic Pain - United States, 2016. 1057-5987. Mar 18 2016. doi: 10.15585/mmwr.rr6501e1. PMID: 26987082.

17. Reisner L. Pharmacological management of persistent pain in older persons. J Pain. 2011 Mar;12(3 Suppl 1):S21-9. doi: 10.1016/j.jpain.2011.01.001. PMID: 21396598.

18. Pain Management Best Practices Inter-Agency Task Force Report: Updates, Apps, Inconsistencies, and Recommendations. Final Report. U.S. Department of Health and Human Services; May 9, 2019. Available at: https://www.hhs.gov/ash/advisory-committees/pain/reports/index.html. Accessed July 2, 2020.

19. Manchikanti L, Singh V, Hirsch JA. Facility payments for interventional pain management procedures: Impact of proposed rules. Pain physician. 2016 Sep-Oct;19(7):E957-84. PMID: 27676688.

20. Gazelka HM, Leal JC, Lapid MI, et al. Opioids in older adults: indications, prescribing, complications, and alternative therapies for primary care. Mayo Clin Proc. 2020 Apr;95(4):793-800. doi: 10.1016/j.mayocp.2020.02.002. PMID: 32247352.

21. Skelly A. Integrated Pain Management Programs. 2020.

22. Buchbinder R, Johnston RV, Rischin KJ, et al. Percutaneous vertebroplasty for osteoporotic vertebral compression fracture. Cochrane Database Syst Rev. 2018 Nov 06;11:CD006349. doi: 10.1002/14651858.CD006349.pub4. PMID: 30399208.

23. Davies E. No more vetebroplasty for acute vertebral compression fractures? Bmj. 2018 May 9;361:k1756. doi: 10.1136/bmj.k1756. PMID: 29743282.

24. Chappell ME, Lakshman R, Trotter P, et al. Radiofrequency denervation for chronic back pain: a systematic review and meta-analysis. BMJ Open. 2020 Jul 21;10(7):e035540. doi: 10.1136/bmjopen-2019-035540. PMID: 32699129.

25. Bhatia A, Hoydonckx Y, Peng P, et al. Radiofrequency procedures to relieve chronic hip pain: an evidence-based narrative review. Reg Anesth Pain Med. 2018 Jan;43(1):72-83. doi: 10.1097/aap.0000000000000694. PMID: 29140960.

26. Kapural L, Jolly S, Mantoan J, et al. Cooled Radiofrequency Neurotomy of the Articular Sensory Branches of the Obturator and Femoral Nerves - Combined Approach Using Fluoroscopy and Ultrasound Guidance: Technical Report, and Observational Study on Safety and Efficacy. Pain physician. 2018 May;21(3):279-84. PMID: 29871372.

27. Hintz A. Non-inferiority of Cooled vs Traditional Radiofrequency Ablation of the Lumbar Medial Branch Nerves in the Treatment of Axial Low Back Pain. The Spine Journal. 2017;17(10):S120. doi: 10.1016/j.spinee.2017.07.105.

28. Contreras Lopez WO, Navarro PA, Vargas MD, et al. Pulsed radiofrequency versus continuous radiofrequency for facet joint low back pain: a systematic review. World Neurosurg. 2019 Feb;122:390-6. doi: 10.1016/j.wneu.2018.10.191. PMID: 30404055.

29. Levi D, Horn S, Tyszko S, et al. Intradiscal Platelet-Rich Plasma Injection for Chronic Discogenic Low Back Pain: Preliminary Results from a Prospective Trial. Pain Med. 2016 Jun;17(6):1010-22. doi: 10.1093/pm/pnv053. PMID: 26814283.

30. Wu J, Du Z, Lv Y, et al. A new technique for the treatment of lumbar facet joint syndrome using intra-articular injection with autologous platelet rich plasma. Pain physician. 2016 Nov-Dec;19(8):617-25. PMID: 27906940.

31. Meisel HJ, Agarwal N, Hsieh PC, et al. Cell therapy for treatment of intervertebral disc degeneration: a systematic review. Global spine j. 2019 May;9(1 Suppl):39s-52s. doi: 10.1177/2192568219829024. PMID: 31157145.

32. Kim SH, Ahn SH, Cho YW, et al. Effect of Intradiscal Methylene Blue Injection for the Chronic Discogenic Low Back Pain: One Year Prospective Follow-up Study. Ann Rehabil Med. 2012 Oct;36(5):657-64. doi: 10.5535/arm.2012.36.5.657. PMID: 23185730.

33. Ezeldin M, Leonardi M, Princiotta C, et al. Percutaneous ozone nucleolysis for lumbar disc herniation. Neuroradiology. 2018;60(11):1231-41. doi: 10.1007/s00234-018-2083-4. PMID: 132699262. Language: English. Entry Date: 20181102. Revision Date: 20191101. Publication Type: Article.

34. Ho KWD, Przkora R, Kumar S. Sphenopalatine ganglion: block, radiofrequency ablation and neurostimulation - a systematic review. J Headache Pain. 2017 Dec 28;18(1):118. doi: 10.1186/s10194-017-0826-y. PMID: 29285576.

35. Lambru G, Matharu MS. Occipital nerve stimulation in primary headache syndromes. Ther Adv Neurol Disord. 2012 Jan;5(1):57-67. doi: 10.1177/1756285611420903. PMID: 22276076.

36. Boyajian-O'Neill LA, McClain RL, Coleman MK, et al. Diagnosis and management of piriformis syndrome: an osteopathic approach. J Am Osteopath Assoc. 2008 Nov;108(11):657-64. doi: 10.7556/jaoa.2008.108.11.657. PMID: 19011229.

37. Hopayian K, Song F, Riera R, et al. The clinical features of the piriformis syndrome: a systematic review. Eur Spine J. 2010 Dec;19(12):2095-109. doi: 10.1007/s00586-010-1504-9. PMID: 20596735.

38. Kozak J, Kobesova A, Vrba I, et al. Peripheral nerve stimulation in intractable neuropathic pain. Neuro Endocrinol Lett. 2011;32(3):226-33. PMID: 21712779.

39. Duarte RV, Nevitt S, McNicol E, et al. Systematic review and meta-analysis of placebo/sham controlled randomised trials of spinal cord stimulation for neuropathic pain. Pain. 2020 Jan;161(1):24-35. doi: 10.1097/j.pain.0000000000001689. PMID: 31453983.

40. Weinstein EJ, Levene JL, Cohen MS, et al. Local anaesthetics and regional anaesthesia versus conventional analgesia for preventing persistent postoperative pain in adults and children. Cochrane Database Syst Rev. 2018 Apr 25;4(4):Cd007105. doi: 10.1002/14651858.CD007105.pub3. PMID: 29694674.

41. Practice guidelines for acute pain management in the perioperative setting: an updated report by the American Society of Anesthesiologists Task Force on Acute Pain Management. Anesthesiology. 2012 Feb;116(2):248-73. doi: 10.1097/ALN.0b013e31823c1030. PMID: 22227789.

42. Chou R, Gordon DB, de Leon-Casasola OA, et al. Management of Postoperative Pain: A Clinical Practice Guideline From the American Pain Society, the American Society of Regional Anesthesia and Pain Medicine, and the American Society of Anesthesiologists' Committee on Regional Anesthesia, Executive Committee, and Administrative Council. J Pain. 2016 Feb;17(2):131-57. doi: 10.1016/j.jpain.2015.12.008. PMID: 26827847.

43. Oliveira CB, Maher CG, Ferreira ML, et al. Epidural corticosteroid injections for lumbosacral radicular pain. Cochrane Database Syst Rev. 2020 Apr 9;4(4):Cd013577. doi: 10.1002/14651858.Cd013577. PMID: 32271952.

44. Chou R, Hashimoto R, Friedly J, et al. Epidural Corticosteroid Injections for Radiculopathy and Spinal Stenosis: A Systematic Review and Meta-analysis. Ann Intern Med. 2015 Sep 1;163(5):373-81. doi: 10.7326/m15-0934. PMID: 26302454.

45. Methods Guide for Effectiveness and Comparative Effectiveness Reviews. Rockville, MD: Agency for Healthcare Research and Quality. https://effectivehealthcare.ahrq.gov/topics/cer-methods-guide/overview. Accessed September 21, 2020.

46. Gamerman V, Cai T, Elsäßer A. Pragmatic randomized clinical trials: best practices and statistical guidance. Health Serv Outcomes Res Methodol. 2019;19(1):23-35. doi: 10.1007/s10742-018-0192-5.

47. Guyatt GH, Oxman AD, Kunz R, et al. What is "quality of evidence" and why is it important to clinicians? Bmj. 2008 May 3;336(7651):995-8. doi: 10.1136/bmj.39490.551019.BE. PMID: 18456631.

48. Cohen SP, Wallace M, Rauck RL, et al. Unique aspects of clinical trials of invasive therapies for chronic pain. Pain Rep. 2019 May-Jun;4(3):e687. doi: 10.1097/pr9.0000000000000687. PMID: 31583336.

49. Carragee EJ. The vertebroplasty affair: the mysterious case of the disappearing effect size. Spine J. 2010 Mar;10(3):191-2. doi: 10.1016/j.spinee.2010.01.002. PMID: 20207329.

50. Cyteval C, Fescquet N, Thomas E, et al. Predictive factors of efficacy of periradicular corticosteroid injections for lumbar radiculopathy. AJNR Am J Neuroradiol. 2006 May;27(5):978-82. PMID: 16687527.

51. Weiner BK, Fraser RD. Foraminal injection for lateral lumbar disc herniation. J Bone Joint Surg Br. 1997 Sep;79(5):804-7. doi: 10.1302/0301-620x.79b5.7636. PMID: 9331040.

52. Wang JC, Lin E, Brodke DS, et al. Epidural injections for the treatment of symptomatic lumbar herniated discs. J Spinal Disord Tech. 2002 Aug;15(4):269-72. doi: 10.1097/00024720-200208000-00001. PMID: 12177540.

53. Vad VB, Bhat AL, Lutz GE, et al. Transforaminal epidural steroid injections in lumbosacral radiculopathy: a prospective randomized study. Spine (Phila Pa 1976). 2002 Jan 1;27(1):11-6. doi: 10.1097/00007632-200201010-00005. PMID: 11805628.

54. Karasek M, Bogduk N. Twelve-month follow-up of a controlled trial of intradiscal thermal anuloplasty for back pain due to internal disc disruption. Spine (Phila Pa 1976). 2000 Oct 15;25(20):2601-7. doi: 10.1097/00007632-200010150-00010. PMID: 11034644.

55. Bogduk N, Karasek M. Two-year follow-up of a controlled trial of intradiscal electrothermal anuloplasty for chronic low back pain resulting from internal disc disruption. Spine J. 2002 Sep-Oct;2(5):343-50. doi: 10.1016/s1529-9430(02)00409-6. PMID: 14589465.

56. Saal JA, Saal JS. Intradiscal electrothermal treatment for chronic discogenic low back pain: a prospective outcome study with minimum 1-year follow-up. Spine (Phila Pa 1976). 2000 Oct 15;25(20):2622-7. doi: 10.1097/00007632-200010150-00013. PMID: 11034647.

57. Henschke N, Kuijpers T, Rubinstein SM, et al. Injection therapy and denervation procedures for chronic low-back pain: a systematic review. Eur Spine J. 2010 Sep;19(9):1425-49. doi: 10.1007/s00586-010-1411-0. PMID: 20424870.

58. Chou R, Aronson N, Atkins D, et al. AHRQ series paper 4: assessing harms when comparing medical interventions: AHRQ and the effective health-care program. Journal of clinical epidemiology. 2010 May;63(5):502-12. doi: 10.1016/j.jclinepi.2008.06.007. PMID: 18823754.

59. 7.7.3.2 Obtaining standard deviations from standard errors and confidence intervals for group means. https://handbook-5-1.cochrane.org/chapter_7/7_7_3_2_obtaining_standard_deviations_from_standard_errors_and.htm. Accessed February 26, 2021.

60. MedCalc. Relative risk calculator. https://www.medcalc.org/calc/relative_risk.php. Accessed February 26, 2021.

61. MedCalc. Comparison means calculator. https://www.medcalc.org/calc/comparison_of_means.php. Accessed February 26, 2021.

62. Viswanathan M, Patnode CD, Berkman ND, et al. Chapter 9: Assessing the Risk of Bias of Individual Studies in Systematic Reviews of Health Care Interventions. In: Methods Guide for Effectiveness and Comparative Effectiveness Reviews. AHRQ Publication No. 10(14)-EHC063-EF. Rockville, MD: Agency for Healthcare Research and Quality; Jan 2014. Chapters available at: www.effectivehealthcare.ahrq.gov.

63. Higgins J, Green S. Cochrane Handbook for Systematic Reviews of Interventions. Version 5.1. 0. The Cochrane Collaboration; March 2011. http://handbook-5-1.cochrane.org/. Accessed September 21, 2020.

64. U.S. Preventive Services Task Force Procedure Manual. https://www.uspreventiveservicestaskforce.org/uspstf/procedure-manual. Accessed September 21, 2020.

65. Morton SC, Murad MH, O'Connor E, et al. Quantitative Synthesis—An Update. Methods Guide for Comparative Effectiveness Reviews. (Prepared by the Scientific Resource Center under Contract No. 290-2012-0004-C). AHRQ Publication No. 18-EHC007-EF. Rockville, MD: Agency for Healthcare Research and Quality; February 2018. Posted final reports are located on the Effective Health Care Program search page (https://effectivehealthcare.ahrq.gov/). https://doi.org/10.23970/AHRQEPCMETHGUIDE3.

66. Systematic Review Update: Noninvasive Nonpharmacologic Treatments for Chronic Pain. Agency for Healthcare Research and Quality. https://effectivehealthcare.ahrq.gov/topics/noninvasive-nonpharm-pain-update/protocol. Accessed August 8, 2019.

67. Nonopioid Pharmacologic Treatments for Chronic Pain. Agency for Healthcare Research and Quality. https://effectivehealthcare.ahrq.gov/topics/nonopioid-chronic-pain/protocol. Accessed August 8, 2019.

68. Opioid Treatments for Chronic Pain. Agency for Healthcare Research and Quality. https://effectivehealthcare.ahrq.gov/topics/opioids-chronic-pain/protocol. Accessed August 8, 2019.

69. Chou R, Deyo R, Friedly J, et al. Noninvasive Treatments for Low Back Pain. Comparative Effectiveness Review No. 169. (Prepared by the Pacific Northwest Evidence-based Practice Center under Contract No. 290-2012-00014-I.) AHRQ Publication No. 16-EHC004-EF. Rockville, MD: Agency for Healthcare Research and Quality; February 2016.

70. Skelly AC, Chou R, Dettori JR, et al. Noninvasive Nonpharmacological Treatment for Chronic Pain: A Systematic Review. Comparative Effectiveness Review No. 209. (Prepared by the Pacific Northwest Evidence-based Practice Center under Contract No. 290-2015-00009-I.) AHRQ Publication No 18-EHC013-EF. : . Rockville, MD: Agency for Healthcare Research and Quality; June 2018. https://effectivehealthcare.ahrq.gov/topics/nonpharma-treatment-pain/research-2018 PMID: 30179389.

71. Escobar A, Quintana JM, Bilbao A, et al. Responsiveness and clinically important differences for the WOMAC and SF-36 after total knee replacement. Osteoarthritis Cartilage. 2007 Mar;15(3):273-80. doi: 10.1016/j.joca.2006.09.001. PMID: 17052924.

72. 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 Jan 1;33(1):90-4. doi: 10.1097/BRS.0b013e31815e3a10. PMID: 18165753.

73. Skelly AC, Chou R, Dettori JR, et al. AHRQ Comparative Effectiveness Reviews. Noninvasive Nonpharmacological Treatment for Chronic Pain: A Systematic Review Update. Rockville (MD): Agency for Healthcare Research and Quality (US); 2020.

74. Ferreira GE, McLachlan AJ, Lin CC, et al. Efficacy and safety of antidepressants for the treatment of back pain and osteoarthritis: systematic review and meta-analysis. Bmj. 2021 Jan 20;372:m4825. doi: 10.1136/bmj.m4825. PMID: 33472813.

75. Machado GC, Maher CG, Ferreira PH, et al. Non-steroidal anti-inflammatory drugs for spinal pain: a systematic review and meta-analysis. Ann Rheum Dis. 2017 Jul;76(7):1269-78. doi: 10.1136/annrheumdis-2016-210597. PMID: 28153830.

76. Busse JW, Wang L, Kamaleldin M, et al. Opioids for Chronic Noncancer Pain: A Systematic Review and Meta-analysis. Jama. 2018 Dec 18;320(23):2448-60. doi: 10.1001/jama.2018.18472. PMID: 30561481.

77. Jayadevappa R, Cook R, Chhatre S. Minimal important difference to infer changes in health-related quality of life-a systematic review. Journal of clinical epidemiology. 2017 Sep;89:188-98. doi: 10.1016/j.jclinepi.2017.06.009. PMID: 28676426.

78. Keurentjes JC, Van Tol FR, Fiocco M, et al. Minimal clinically important differences in health-related quality of life after total hip or knee replacement: A systematic review. Bone Joint Res. 2012 May;1(5):71-7. doi: 10.1302/2046-3758.15.2000065. PMID: 23610674.

79. Buchbinder R, Osborne RH, Ebeling PR, et al. A randomized trial of vertebroplasty for painful osteoporotic vertebral fractures. N Engl J Med. 2009 Aug 06;361(6):557-68. doi: 10.1056/NEJMoa0900429. PMID: 19657121.

80. Clark W, Bird P, Gonski P, et al. Safety and efficacy of vertebroplasty for acute painful osteoporotic fractures (VAPOUR): a multicentre, randomised, double-blind, placebo-controlled trial. Lancet. 2016 Oct 01;388(10052):1408-16. doi: 10.1016/S0140-6736(16)31341-1. PMID: 27544377.

81. Firanescu CE, de Vries J, Lodder P, et al. Vertebroplasty versus sham procedure for painful acute osteoporotic vertebral compression fractures (VERTOS IV): randomised sham controlled clinical trial. Bmj. 2018 May 09;361:k1551. doi: 10.1136/bmj.k1551. PMID: 29743284.

82. Hansen E, Simony A, Carreon L, et al. Vertebroplasty vs. SHAM for Treating Osteoporotic Vertebral Compression Fractures: A Double Blind RCT. Integr J Orthop Traumatol. 2019;2(4):1-6. doi: 10.31038/IJOT.2019244.

83. Kallmes DF, Comstock BA, Heagerty PJ, et al. A randomized trial of vertebroplasty for osteoporotic spinal fractures. N Engl J Med. 2009 Aug 06;361(6):569-79. doi: 10.1056/NEJMoa0900563. PMID: 19657122.

84. Blasco J, Martinez-Ferrer A, Macho J, et al. Effect of vertebroplasty on pain relief, quality of life, and the incidence of new vertebral fractures: a 12-month randomized follow-up, controlled trial. J Bone Miner Res. 2012 May;27(5):1159-66. doi: 10.1002/jbmr.1564. PMID: 22513649.

85. Chen D, An ZQ, Song S, et al. Percutaneous vertebroplasty compared with conservative treatment in patients with chronic painful osteoporotic spinal fractures. J Clin Neurosci. 2014 Mar;21(3):473-7. doi: 10.1016/j.jocn.2013.05.017. PMID: 24315046.

86. Farrokhi MR, Alibai E, Maghami Z. Randomized controlled trial of percutaneous vertebroplasty versus optimal medical management for the relief of pain and disability in acute osteoporotic vertebral compression fractures. J Neurosurg Spine. 2011 May;14(5):561-9. doi: 10.3171/2010.12.SPINE10286. PMID: 21375382.

87. Klazen CA, Lohle PN, de Vries J, et al. Vertebroplasty versus conservative treatment in acute osteoporotic vertebral compression fractures (Vertos II): an open-label randomised trial. Lancet. 2010 Sep 25;376(9746):1085-92. doi: 10.1016/S0140-6736(10)60954-3. PMID: 20701962.

88. Leali PT, Solla F, Maestretti G, et al. Safety and efficacy of vertebroplasty in the treatment of osteoporotic vertebral compression fractures: A prospective multicenter international randomized controlled study. Clin. 2016 Sep-Dec;13(3):234-6. doi: 10.11138/ccmbm/2016.13.3.234. PMID: 28228788.

89. Rousing R, Andersen MO, Jespersen SM, et al. Percutaneous vertebroplasty compared to conservative treatment in patients with painful acute or subacute osteoporotic vertebral fractures: three-months follow-up in a clinical randomized study. Spine. 2009 Jun 01;34(13):1349-54. doi: 10.1097/BRS.0b013e3181a4e628. PMID: 19478654.

90. Voormolen MH, Mali WP, Lohle PN, et al. Percutaneous vertebroplasty compared with optimal pain medication treatment: short-term clinical outcome of patients with subacute or chronic painful osteoporotic vertebral compression fractures. The VERTOS study. AJNR Am J Neuroradiol. 2007 Mar;28(3):555-60. PMID: 17353335.

91. Yang EZ, Xu JG, Huang GZ, et al. Percutaneous vertebroplasty versus conservative treatment in aged patients with acute osteoporotic vertebral compression fractures: a prospective randomized controlled clinical study. Spine. 2016 Apr;41(8):653-60. doi: 10.1097/BRS.0000000000001298. PMID: 26630417.

92. Kroon F, Staples M, Ebeling PR, et al. Two-year results of a randomized placebo-controlled trial of vertebroplasty for acute osteoporotic vertebral fractures. J Bone Miner Res. 2014 Jun;29(6):1346-55. doi: 10.1002/jbmr.2157. PMID: 24967454.

93. Staples MP, Howe BM, Ringler MD, et al. New vertebral fractures after vertebroplasty: 2-year results from a randomised controlled trial. Arch Osteoporos. 2015;10:229. doi: 10.1007/s11657-015-0229-0. PMID: 26272712.

94. Diamond T, Clark W, Bird P, et al. Early vertebroplasty within 3 weeks of fracture for acute painful vertebral osteoporotic fractures: subgroup analysis of the VAPOUR trial and review of the literature. Eur Spine J. 2020 Jul;29(7):1606-13. doi: 10.1007/s00586-020-06362-2. PMID: 32170438.

95. Firanescu CE, de Vries J, Lodder P, et al. Percutaneous vertebroplasty is no risk factor for new vertebral fractures and protects against further height loss(VERTOS IV). Cardiovasc Intervent Radiol. 2019 Jul;42(7):991-1000. doi: 10.1007/s00270-019-02205-w. PMID: 30941490.

96. Comstock BA, Sitlani CM, Jarvik JG, et al. Investigational vertebroplasty safety and efficacy trial (INVEST): patient-reported outcomes through 1 year. Radiology. 2013 Oct;269(1):224-31. doi: 10.1148/radiol.13120821. PMID: 23696683.

97. Venmans A, Klazen CA, van Rooij WJ, et al. Postprocedural CT for perivertebral cement leakage in percutaneous vertebroplasty is not necessary--results from VERTOS II. Neuroradiology. 2011 Jan;53(1):19-22. doi: 10.1007/s00234-010-0705-6. PMID: 20442991.

98. Rousing R, Hansen KL, Andersen MO, et al. Twelve-months follow-up in forty-nine patients with acute/semiacute osteoporotic vertebral fractures treated conservatively or with percutaneous vertebroplasty: a clinical randomized study. Spine. 2010 Mar 01;35(5):478-82. doi: 10.1097/BRS.0b013e3181b71bd1. PMID: 20190623.

99. Berenson J, Pflugmacher R, Jarzem P, et al. Balloon kyphoplasty versus non-surgical fracture management for treatment of painful vertebral body compression fractures in patients with cancer: a multicentre, randomised controlled trial. The lancet. 2011;Oncology. 12(3):225-35. PMID: CN-00787315.

100. Boonen S, Van Meirhaeghe J, Bastian L, et al. Balloon kyphoplasty for the treatment of acute vertebral compression fractures: 2-year results from a randomized trial. J Bone Miner Res. 2011 Jul;26(7):1627-37. doi: 10.1002/jbmr.364. PMID: 21337428.

101. Van Meirhaeghe J, Bastian L, Boonen S, et al. A randomized trial of balloon kyphoplasty and nonsurgical management for treating acute vertebral compression fractures: vertebral body kyphosis correction and surgical parameters. Spine. 2013 May 20;38(12):971-83. doi: 10.1097/BRS.0b013e31828e8e22. PMID: 23446769.

102. Wardlaw D, Cummings SR, Van Meirhaeghe J, et al. Efficacy and safety of balloon kyphoplasty compared with non-surgical care for vertebral compression fracture (FREE): a randomised controlled trial. Lancet. 2009 Mar 21;373(9668):1016-24. doi: 10.1016/S0140-6736(09)60010-6. PMID: 19246088.

103. Cohen SP, Hurley RW, Buckenmaier CC, 3rd, et al. Randomized placebo-controlled study evaluating lateral branch radiofrequency denervation for sacroiliac joint pain. Anesthesiology. 2008 Aug;109(2):279-88. doi: 10.1097/ALN.0b013e31817f4c7c. PMID: 18648237.

104. Patel N, Gross A, Brown L, et al. A randomized, placebo-controlled study to assess the efficacy of lateral branch neurotomy for chronic sacroiliac joint pain. Pain Med. 2012 Mar;13(3):383-98. doi: 10.1111/j.1526-4637.2012.01328.x. PMID: 22299761.

105. McCormick ZL, Choi H, Reddy R, et al. Randomized prospective trial of cooled versus traditional radiofrequency ablation of the medial branch nerves for the treatment of lumbar facet joint pain. Reg Anesth Pain Med. 2019 Mar;44(3):389-97. doi: 10.1136/rapm-2018-000035. PMID: 30777903.

106. Tekin I, Mirzai H, Ok G, et al. A comparison of conventional and pulsed radiofrequency denervation in the treatment of chronic facet joint pain. Clin J Pain. 2007 Jul-Aug;23(6):524-9. PMID: 17575493.

107. Moussa WM, Khedr W, Elsawy M. Percutaneous pulsed radiofrequency treatment of dorsal root ganglion for treatment of lumbar facet syndrome. Clin Neurol Neurosurg. 2020 Dec;199:106253. doi: 10.1016/j.clineuro.2020.106253. PMID: 33045627.

108. Kroll HR, Kim D, Danic MJ, et al. A randomized, double-blind, prospective study comparing the efficacy of continuous versus pulsed radiofrequency in the treatment of lumbar facet syndrome. J Clin Anesth. 2008 Nov;20(7):534-7. doi: 10.1016/j.jclinane.2008.05.021. PMID: 19041042.

109. Tuakli-Wosornu YA, Terry A, Boachie-Adjei K, et al. Lumbar intradiskal platelet-rich plasma (PRP) injections: A prospective, double-blind, randomized controlled study. Pm R. 2016 Jan;8(1):1-10; quiz doi: 10.1016/j.pmrj.2015.08.010. PMID: 26314234.

110. Amirdelfan K, Bae H, McJunkin T, et al. Allogeneic mesenchymal precursor cells treatment for chronic low back pain associated with degenerative disc disease: a prospective randomized, placebo-controlled 36-month study of safety and efficacy. Spine J. 2020 Oct 09;09:212-30. doi: 10.1016/j.spinee.2020.10.004. PMID: 33045417.

111. Kallewaard JW, Wintraecken VM, Geurts JW, et al. A multicenter randomized controlled trial on the efficacy of intradiscal methylene blue injection for chronic discogenic low back pain: the IMBI study. Pain. 2019 Apr;160(4):945-53. doi: 10.1097/j.pain.0000000000001475. PMID: 30730862.

112. Peng B, Pang X, Wu Y, et al. A randomized placebo-controlled trial of intradiscal methylene blue injection for the treatment of chronic discogenic low back pain. Pain. 2010 Apr;149(1):124-9. doi: 10.1016/j.pain.2010.01.021. PMID: 20167430.

113. Gallucci M, Limbucci N, Zugaro L, et al. Sciatica: treatment with intradiscal and intraforaminal injections of steroid and oxygen-ozone versus steroid only. Radiology. 2007 Mar;242(3):907-13. PMID: 17209164.

114. Haseeb AESA, Abd El Hares AEH, Abd El Moez KM, et al. Comparative Study between Treatment of Lumbar Disc Herniation with Intra Discal Ozone and Transforaminal Steroid Injection versus Steroid Injection only. The Egyptian Journal of Hospital Medicine. 2019;74(4):705-20. doi: 10.12816/ejhm.2019.24068.

115. Nilachandra L, Darendrajit L, Joy Singh A, et al. Ozone nucleolysis in the management of prolapsed lumbar intervertebral disc in reducing pain and disability: a randomized controlled study. PARIPEX-Indian Journal of Research. 2016 Nov;5(11):51-4.

116. Cady RK, Saper J, Dexter K, et al. Long-term efficacy of a double-blind, placebo-controlled, randomized study for repetitive sphenopalatine blockade with bupivacaine vs. saline with the Tx360 device for treatment of chronic migraine. Headache. 2015 Apr;55(4):529-42. doi: 10.1111/head.12546. PMID: 25828648.

117. Cady R, Saper J, Dexter K, et al. A double-blind, placebo-controlled study of repetitive transnasal sphenopalatine ganglion blockade with tx360(R) as acute treatment for chronic migraine. Headache. 2015 Jan;55(1):101-16. doi: 10.1111/head.12458. PMID: 25338927.

118. Saper JR, Dodick DW, Silberstein SD, et al. Occipital nerve stimulation for the treatment of intractable chronic migraine headache: ONSTIM feasibility study. Cephalalgia. 2011 Feb;31(3):271-85. doi: 10.1177/0333102410381142. PMID: 20861241.

119. Serra G, Marchioretto F. Occipital nerve stimulation for chronic migraine: a randomized trial. Pain physician. 2012 May-Jun;15(3):245-53. PMID: 22622909.

120. Silberstein SD, Dodick DW, Saper J, et al. Safety and efficacy of peripheral nerve stimulation of the occipital nerves for the management of chronic migraine: results from a randomized, multicenter, double-blinded, controlled study. Cephalalgia. 2012 Dec;32(16):1165-79. doi: 10.1177/0333102412462642. PMID: 23034698.

121. Mekhail NA, Estemalik E, Azer G, et al. Safety and efficacy of occipital nerves stimulation for the treatment of chronic migraines: randomized, double-blind, controlled single-center experience. Pain pract. 2017 Jun;17(5):669-77. doi: 10.1111/papr.12504. PMID: 27779368.

122. Childers MK, Wilson DJ, Gnatz SM, et al. Botulinum toxin type A use in piriformis muscle syndrome: a pilot study. Am J Phys Med Rehabil. 2002 Oct;81(10):751-9. PMID: 12362115.

123. Fishman LM, Anderson C, Rosner B. BOTOX and physical therapy in the treatment of piriformis syndrome. Am J Phys Med Rehabil. 2002 Dec;81(12):936-42. doi: 10.1097/00002060-200212000-00009. PMID: 12447093.

124. Fishman LM, Wilkins AN, Rosner B. Electrophysiologically identified piriformis syndrome is successfully treated with incobotulinum toxin a and physical therapy. Muscle Nerve. 2017 Aug;56(2):258-63. doi: 10.1002/mus.25504. PMID: 27935076.

125. Misirlioglu TO, Akgun K, Palamar D, et al. Piriformis syndrome: comparison of the effectiveness of local anesthetic and corticosteroid injections: a double-blinded, randomized controlled study. Pain physician. 2015 Mar-Apr;18(2):163-71. PMID: 25794202.

126. Deer T, Pope J, Benyamin R, et al. Prospective, multicenter, randomized, double-blinded, partial crossover study to assess the safety and efficacy of the novel neuromodulation system in the treatment of patients with chronic pain of peripheral nerve origin. Neuromodulation. 2016 Jan;19(1):91-100. doi: 10.1111/ner.12381. PMID: 26799373.

127. Huskisson EC. Measurement of pain. J Rheumatol. 1982 Sep-Oct;9(5):768-9. PMID: 6184474.

128. Grotle M, Brox JI, Vøllestad NK. Concurrent comparison of responsiveness in pain and functional status measurements used for patients with low back pain. Spine (Phila Pa 1976). 2004 Nov 1;29(21):E492-501. doi: 10.1097/01.brs.0000143664.02702.0b. PMID: 15507789.

129. Trout AT, Kallmes DF, Gray LA, et al. Evaluation of vertebroplasty with a validated outcome measure: the Roland-Morris Disability Questionnaire. AJNR Am J Neuroradiol. 2005 Nov-Dec;26(10):2652-7. PMID: 16286418.

130. Bombardier C, Hayden J, Beaton DE. Minimal clinically important difference. Low back pain: outcome measures. J Rheumatol. 2001 Feb;28(2):431-8. PMID: 11246692.

131. Elnoamany HA. Influence of Vertebral Bone Marrow Edema on Outcome in Non-Acute Osteoporotic Patients Treated with Percutaneous Vertebroplasty. Asian spine j. 2016 Jun;10(3):436-42. doi: 10.4184/asj.2016.10.3.436. PMID: 27340521.

132. Boszczyk B. Volume matters: a review of procedural details of two randomised controlled vertebroplasty trials of 2009. Eur Spine J. 2010 Nov;19(11):1837-40. doi: 10.1007/s00586-010-1525-4. PMID: 20686793.

133. Sanli I, van Kuijk SMJ, de Bie RA, et al. Percutaneous cement augmentation in the treatment of osteoporotic vertebral fractures (OVFs) in the elderly: a systematic review. Eur Spine J. 2020 Jul;29(7):1553-72. doi: 10.1007/s00586-020-06391-x. PMID: 32240375.

134. Hinde K, Maingard J, Hirsch JA, et al. Mortality outcomes of vertebral augmentation (vertebroplasty and/or balloon kyphoplasty) for osteoporotic vertebral compression fractures: a systematic review and meta-analysis. Radiology. 2020 Apr;295(1):96-103. doi: 10.1148/radiol.2020191294. PMID: 32068503.

135. Zhang H, Xu C, Zhang T, et al. Does percutaneous vertebroplasty or balloon kyphoplasty for osteoporotic vertebral compression fractures increase the incidence of new vertebral fractures? A meta-analysis. Pain physician. 2017 Jan-Feb;20(1):13-28. PMID: 28072794.

136. Rodriguez AJ, Fink HA, Mirigian L, et al. Pain, quality of life, and safety outcomes of kyphoplasty for vertebral compression fractures: report of a task force of the American society for bone and mineral research. J Bone Miner Res. 2017 Sep;32(9):1935-44. doi: 10.1002/jbmr.3170. PMID: 28513888.

137. Sun HH, Zhuang SY, Hong X, et al. The efficacy and safety of using cooled radiofrequency in treating chronic sacroiliac joint pain: A PRISMA-compliant meta-analysis. Medicine (Baltimore). 2018 Feb;97(6):9809. doi: 10.1097/MD.0000000000009809. PMID: 29419679.

138. Williams ACC, Fisher E, Hearn L, et al. Psychological therapies for the management of chronic pain (excluding headache) in adults. Cochrane Database Syst Rev. 2020 Aug 12;8(8):Cd007407. doi: 10.1002/14651858.CD007407.pub4. PMID: 32794606.

139. Proposed Local Coverage Determination (LCD): Percutaneous Vertebral Augmentation (PVA) for Vertebral Compression Fracture (VCF) (DL35130). https://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=38876&ver=&NCAId=143&MCDId=5&SearchType=Advanced&CoverageSelection=Both&NCSelection=NCA%257CCAL%257CNCD%257CMEDCAC%257CTA%257CMCD&ArticleType=Ed%257CKey%257CSAD%257CFAQ&PolicyType=Final&s=5%257C6%257C66%257C67%257C9%257C38%257C63%257C41%257C64%257C65%257C44&KeyWord=wheelchairs&KeyWordLookUp=Doc&KeyWordSearchType=Exact&kq=true&bc=IAAAACgAIAAA&. Accessed February 26, 2021.

140. Carli D, Venmans A, Lodder P, et al. Vertebroplasty Versus Sham Intervention for Painful Chronic Osteoporotic Vertebral Compression Fractures (VERTOS 5): Randomised Sham Controlled Clinical Trial. SSRN Electronic Journal. 2020 Oct 27 doi: 10.2139/ssrn.3712918.

141. Sterne JA, Sutton AJ, Ioannidis JP, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. Bmj. 2011 Jul 22;343:d4002. doi: 10.1136/bmj.d4002. PMID: 21784880.

142. Ebeling PR, Akesson K, Bauer DC, et al. The efficacy and safety of vertebral augmentation: a second ASBMR task force report. J Bone Miner Res. 2019 Jan;34(1):3-21. doi: 10.1002/jbmr.3653. PMID: 30677181.

Abbreviations and Acronyms

ANOVA	analysis of variance
ARD	absolute risk difference
BMD	bone mineral density
BME	bone marrow edema
BMI	body mass index
BPI	Brief Pain Inventory
BTX-A	botulinum toxin type-A
CAFE	Cancer Patient Fracture Evaluation
CI	confidence interval
CT	computed tomography
EMG	electromyographic
EQ-5D	EuroQOL 5-Dimension Questionnaire
FAIR	flexion, adduction, internal rotation
FREE	Fracture Reduction Evaluation
HIT-6	Headache Impact Test-6
HR	hazard ratio
ICHD-II	International Classification of Headache Disorders, second edition
IHS	International Headache Society
IMBI	intradiscal methylene blue injection
INVEST	Investigational Vertebroplasty Safety and Efficacy Trial
IPG	implantable pulse generator
IQR	interquartile range
IU	International Unit
LBP	low-back pain
LSM	least squares mean
MCS	Mental Component Summary
MIDAS	migraine disability assessment
MMSE	Mini-Mental State Exam
MPC	mesenchymal precursor cell
MR	magnetic resonance
MRI	magnetic resonance imaging
MRI-STIR	magnetic resonance imaging short tau inversion recovery
NR	not reported
NRS	numerical rating scale
NS	not significant
NSAID	nonsteroidal anti-inflammatory drug
ODI	Oswestry Disability Index
ONSTIM	occipital nerve stimulation for the treatment of intractable chronic migraine headache
OR	odds ratio
PCS	Physical Component Summary
PE	pulmonary embolism
PGIC	Patient's Global Impression of Change
PMMA	polymethyl methacrylate

PSI	pounds per square inch
PVP	percutaneous vertebroplasty
QALY	quality-adjusted life-year
QUALEFFO	Quality of Life Questionnaire of the European Foundation for Osteoporosis
RCT	randomized controlled trial
RDQ	Roland–Morris Disability Questionnaire
RFA	Radio frequency denervation/ablation
RR	relative risk
SAE	serious adverse event
SD	standard deviation
SF-12	Short-Form 12
SF-36	Short-Form 36 Health Survey
SF-36 MCS	Short-Form 36 Health Survey Mental Component Score
SF-36 PCS	Short-Form 36 Health Survey Physical Component Score
SMD	standard mean deviation
SOF–ADL	Study of Osteoporotic Fractures–Activities of Daily Living
TL	thoracolumbar junction
VAPOUR	vertebroplasty for acute painful osteoporotic fractures
VAS	visual analogue scale
VB	vertebral body
VCF	vertebral compression fracture
VERTOS	percutaneous vertebroplasty compared with optimal pain medication treatment: short-term clinical outcome of patients with subacute or chronic painful osteoporotic vertebral compression fractures
VERTOS II	vertebroplasty versus conservative treatments in acute osteoporotic vertebral compression fractures
VERTOS IV	vertebroplasty versus sham procedure for painful acute osteoporotic vertebral compression fractures
VOPE	vertebroplasty vs. sham for treating osteoporotic vertebral compression fractures: a double blind RCT
WHO	World Health Organization
WPAI	Work Productivity and Activity Index

Appendix A. Search Strategies

Database: Ovid MEDLINE(R) ALL 1946 to December 08, 2020

1 Chronic Pain/
2 exp arthralgia/ or exp back pain/ or exp headache/ or exp musculoskeletal pain/ or neck pain/ or exp neuralgia/ or exp nociceptive pain/ or pain, intractable/ or fibromyalgia/ or myalgia/
3 Pain/
4 (acute or chronic).ti,ab,kw.
5 3 and 4
6 ((acute or chronic or persistent or intractable or refractory) adj3 pain).ti,ab,kw.
7 (((back or spine or spinal or discogenic or leg or hip or musculoskeletal or neuropathic or nociceptive or radicular or "non-radicular") adj1 pain) or headache or arthritis or fibromyalgia or osteoarthritis or neuralgia or neuropathy).ti,ab,kw.
8 1 or 2 or 5 or 6 or 7
9 Medicare/
10 medicare.ti,ab,kf.
11 9 or 10
12 exp Vertebroplasty/
13 (vertebroplasty or kyphoplasty).ti,ab,kf.
14 Piriformis Muscle Syndrome/
15 inject*.ti,ab,kf.
16 14 and 15
17 (piriformis adj3 inject*).ti,ab,kf.
18 Sphenopalatine Ganglion Block/
19 (sphenopalatine adj3 block*).ti,ab,kf.
20 Electric Stimulation Therapy/
21 Occipital Lobe/
22 20 and 21
23 (occipital adj3 stimulation).ti,ab,kf.
24 ((cool* or puls*) adj3 radiofrequency).ti,ab,kf.
25 Platelet-Rich Plasma/
26 ("platelet rich plasma" or "stem cell*").ti,ab,kf.
27 Stem Cells/
28 (intradisc* or "intra disc*" or facet or joint).ti,ab,kf,sh.
29 (25 or 26 or 27) and 28
30 Methylene Blue/
31 "methylene blue".ti,ab,kf.
32 (30 or 31) and 28
33 Ozone/
34 ozone.ti,ab,kf.
35 (33 or 34) and 28
36 (peripheral nerve adj2 stimulat*).ti,ab,kf.
37 18 or 19 or 22 or 23 or 24 or 29 or 32 or 35 or 36
38 Fractures, Compression/
39 ((vertebra* or compression) adj2 fracture*).ti,ab,kf.
40 8 and 37
41 11 and (12 or 13 or 16 or 17 or 37)

42 (12 or 13) and (38 or 39)
43 16 or 17
44 40 or 41 or 42 or 43
45 44 not (cancer or malignan* or child* or adolescen*).ti.
46 (Animals/ or Models, Animal/ or Disease Models, Animal/) not Humans/
47 ((animal or animals or avian or bird or birds or bovine or canine or cow* or dog or dogs or cat or cats or feline or hamster* or horse* or lamb or lamb* or mouse or mice or monkey or monkeys or murine or pig or piglet* or pigs or porcine or primate* or rabbit* or rat or rats or rodent* or songbird* or veterinar*) not (human* or patient*)).ti,kf,jw.
48 or/46-47
49 45 not 48
50 (random* or control* or trial or systematic or "meta analysis" or metaanalysis or cohort or prospective or retrospective or observational or "case series").ti,ab,kf,sh,pt.
51 49 and 50
52 limit 51 to english language
53 limit 52 to yr = "1990 -Current"

Database: EBM Reviews - Cochrane Central Register of Controlled Trials November 2020
1 Chronic Pain/
2 exp arthralgia/ or exp back pain/ or exp headache/ or exp musculoskeletal pain/ or neck pain/ or exp neuralgia/ or exp nociceptive pain/ or pain, intractable/ or fibromyalgia/ or myalgia/
3 Pain/
4 (acute or chronic).ti,ab,kw.
5 3 and 4
6 ((acute or chronic or persistent or intractable or refractory) adj3 pain).ti,ab,kw.
7 (((back or spine or spinal or discogenic or leg or hip or musculoskeletal or neuropathic or nociceptive or radicular or "non-radicular") adj1 pain) or headache or arthritis or fibromyalgia or osteoarthritis or neuralgia or neuropathy).ti,ab,kw.
8 1 or 2 or 5 or 6 or 7
9 Medicare/
10 medicare.ti,ab,kw.
11 9 or 10
12 exp Vertebroplasty/
13 (vertebroplasty or kyphoplasty).ti,ab,kw.
14 Piriformis Muscle Syndrome/
15 inject*.ti,ab,kw.
16 14 and 15
17 (piriformis adj3 inject*).ti,ab,kw.
18 Sphenopalatine Ganglion Block/
19 (sphenopalatine adj3 block*).ti,ab,kw.
20 Electric Stimulation Therapy/
21 Occipital Lobe/
22 20 and 21
23 (occipital adj3 stimulation).ti,ab,kw.
24 ((cool* or puls*) adj3 radiofrequency).ti,ab,kw.
25 Platelet-Rich Plasma/

26 ("platelet rich plasma" or "stem cell*").ti,ab,kw.
27 Stem Cells/
28 (intradisc* or "intra disc*" or facet or joint).ti,ab,kw.
29 (25 or 26 or 27) and 28
30 Methylene Blue/
31 "methylene blue".ti,ab,kw.
32 (30 or 31) and 28
33 Ozone/
34 ozone.ti,ab,kw.
35 (33 or 34) and 28
36 (peripheral nerve adj2 stimulat*).ti,ab,kw.
37 18 or 19 or 22 or 23 or 24 or 29 or 32 or 35 or 36
38 Fractures, Compression/
39 ((vertebra* or compression) adj2 fracture*).ti,ab,kw.
40 8 and 37
41 11 and (12 or 13 or 16 or 17 or 37)
42 (12 or 13) and (38 or 39)
43 16 or 17
44 40 or 41 or 42 or 43
45 conference abstract.pt.
46 "journal: conference abstract".pt.
47 "journal: conference review".pt.
48 "http://.www.who.int/trialsearch*".so.
49 "https://clinicaltrials.gov*".so.
50 45 or 46 or 47 or 48 or 49
51 44 not 50
52 limit 51 to english language
53 limit 52 to yr = "1990 -Current"

Database: EBM Reviews - Cochrane Database of Systematic Reviews 2005 to December 03, 2020
1 (vertebroplasty or kyphoplasty).ti,ab.
2 (piriformis and inject*).ti,ab.
3 (sphenopalatine and block*).ti,ab.
4 (occipital and stimulation).ti,ab.
5 ((cool* or puls*) and radiofrequency).ti,ab.
6 "platelet rich plasma".ti,ab.
7 stem cell*.ti,ab.
8 (intradisc* or "intra disc*" or facet or joint).ti,ab.
9 "methylene blue".ti,ab.
10 ozone.ti,ab.
11 (peripheral nerve and stimulat*).ti,ab.
12 6 or 7 or 9 or 10
13 8 and 12
14 1 or 2 or 3 or 4 or 5 or 11 or 13

Database: APA PsycInfo 1806 to November Week 5 2020

1 Chronic Pain/

2 exp arthralgia/ or exp back pain/ or exp headache/ or exp musculoskeletal pain/ or neck pain/ or exp neuralgia/ or exp nociceptive pain/ or pain, intractable/ or fibromyalgia/ or myalgia/

3 Pain/

4 (acute or chronic).ti,ab.

5 3 and 4

6 ((acute or chronic or persistent or intractable or refractory) adj3 pain).ti,ab.

7 (((back or spine or spinal or discogenic or leg or hip or musculoskeletal or neuropathic or nociceptive or radicular or "non-radicular") adj1 pain) or headache or arthritis or fibromyalgia or osteoarthritis or neuralgia or neuropathy).ti,ab.

8 1 or 2 or 5 or 6 or 7

9 Medicare/

10 medicare.ti,ab.

11 9 or 10

12 (vertebroplasty or kyphoplasty).ti,ab.

13 (piriformis and inject*).ti,ab.

14 (sphenopalatine adj3 block*).ti,ab.

15 (occipital adj3 stimulation).ti,ab.

16 ((cool* or puls*) adj3 radiofrequency).ti,ab.

17 "platelet rich plasma".ti,ab.

18 stem cell*.ti,ab.

19 (intradisc* or "intra disc*" or facet or joint).ti,ab.

20 "methylene blue".ti,ab.

21 ozone.ti,ab. (267)

22 (peripheral nerve adj2 stimulat*).ti,ab.

23 ((vertebra* or compression) adj2 fracture*).ti,ab.

24 17 or 18 or 20 or 21

25 19 and 24

26 12 and 23

27 13 or 14 or 15 or 16 or 22 or 25 or 26

28 8 and 27

29 11 and 27

30 26 or 28 or 29

31 ((animal or animals or avian or bird or birds or bovine or canine or cow* or dog or dogs or cat or cats or feline or hamster* or horse* or lamb or lamb* or mouse or mice or monkey or monkeys or murine or pig or piglet* or pigs or porcine or primate* or rabbit* or rat or rats or rodent* or songbird* or veterinar*) not (human* or patient*)).ti,jw.

32 30 not 31

33 limit 32 to english language

34 limit 33 to yr = "1990 -Current"

Database: EBSCOHost CINAHL Plus through December 9, 2020

S1 vertebroplasty OR kyphoplasty

S2 compression fracture

S3 vertebral fracture

S4 S2 OR S3
S5 S1 AND S4
S6 piriformis AND injection
S7 sphenopalatine AND (neuralgia OR headache)
S8 occipital AND stimulation AND headache
S9 (cooled OR pulsed) AND radiofrequency
S10 pain
S11 S9 AND S10
S12 platelet rich plasma AND (intradiscal OR facet) AND pain
S13 methylene blue AND pain
S14 ozone AND pain
S15 peripheral nerve stimulation AND (pain OR neuropathic OR neuropathy)
S16 S5 OR S6 OR S7 OR S8 OR S11 OR S12 OR S13 OR S14 OR S15
S17 S5 OR S6 OR S7 OR S8 OR S11 OR S12 OR S13 OR S14 OR S15; Limiters - Published Date: 19900101-20201231; English Language; Exclude MEDLINE records

Appendix B. List of Excluded Studies

2 = Ineligible population
3 = Ineligible intervention
4 = Ineligible comparison
5 = Ineligible outcome
6 = Ineligible study design
7 = Not a study
8 = Not in English language
9 = Outdated or unusable systematic review
10 = Background paper

1. Erratum...Erdine S, Bilir A, Cosman ER, Cosman ER Jr. Ultrastructural changes in axons following exposure to pulsed radiofrequency fields. Pain Pract. 2009;9:407-417. Pain pract. 2010;10(3):264-. doi: 10.1111/j.1533-2500.2010.00379.x. PMID: 105196084. Language: English. Entry Date: 20100702. Revision Date: 20200708. Publication Type: Journal Article. Exclusion: 7.

2. Erratum...Van Boxem K, Van Eerd M, Brinkhuize T, Patijn J, Van Kleef M, Van Zundert J. Radiofrequency and pulsed radiofrequency treatment of chronic pain syndromes: the available evidence. Pain Pract 2008;5:385-393. Pain pract. 2010;10(2):164-. doi: 10.1111/j.1533-2500.2010.00368.x. PMID: 105131187. Language: English. Entry Date: 20100409. Revision Date: 20200708. Publication Type: Journal Article. Exclusion: 7.

3. Sun Peng-Fei, Jia Yu-Hua, and Sibel Eyigor Pulsed radiofrequency versus conventional transcutaneous electrical nerve stimulation in painful shoulder: a prospective, randomized study – can you really have the conclusion?...Pulsed radiofrequency versus conventional transcutaneous electrical nerve stimulation in painful shoulder: a prospective, randomized study. Thousand Oaks, California: Sage Publications Inc.; 2011. p. 856-7. Exclusion: 7.

4. Pulmonary embolism caused by cement leakage during percutaneous vertebroplasty: a case report of successful conservative management. 2012;25:481-5. doi: 10.1177/197140091202500411. Exclusion: 6.

5. Increased Nuclear T2 Signal Intensity and Improved Function and Pain in a Patient One Year After an Intradiscal Platelet-Rich Plasma Injection. 2017;18:1197-9. doi: 10.1093/pm/pnw299. Exclusion: 7.

6. Sphenopalatine Ganglion Block for Postdural Puncture Headache. 2020;21:2615-6. doi: 10.1093/pm/pnz351. Exclusion: 7.

7. Abejon D, Garcia-del-Valle S, Fuentes ML, et al. Pulsed radiofrequency in lumbar radicular pain: clinical effects in various etiological groups. Pain pract. 2007 Mar;7(1):21-6. PMID: 17305674. Exclusion: 6.

8. Abhinav K, Park ND, Prakash SK, et al. Novel use of narrow paddle electrodes for occipital nerve stimulation--technical note. Neuromodulation. 2013 Nov-Dec;16(6):607-9. doi: 10.1111/j.1525-1403.2012.00524.x. PMID: 23106950. Exclusion: 6.

9. Aebi M. Vertebroplasty: about sense and nonsense of uncontrolled "controlled randomized prospective trials". Eur Spine J. 2009 Sep;18(9):1247-8. doi: 10.1007/s00586-009-1164-9. PMID: 19756780. Exclusion: 7.

10. Aebi M. Editorial: vertebroplasty: about sense and nonsense of uncontrolled "controlled randomized prospective trials". Eur Spine J. 2009;18(9):1247-8. PMID: CN-01783404 NEW. Exclusion: 7.

11. Ahn DK, Lee S, Kim DG, et al. Percutaneous vertebroplasty using fresh frozen allogeneic bone chips as filler. Clin. 2014 Mar;6(1):49-55. doi: 10.4055/cios.2014.6.1.49. PMID: 24605189. Exclusion: 6.

12. Ahn Y, Lee JH, Lee HY, et al. Predictive factors for subsequent vertebral fracture after percutaneous vertebroplasty. J Neurosurg Spine. 2008 Aug;9(2):129-36. doi: 10.3171/SPI/2008/9/8/129. PMID: 18764744. Exclusion: 6.

13. Ahn Y, Lee SH. Vertebroplasty for adjacent vertebral fracture following lumbar interbody fusion. Br J Neurosurg. 2011 Feb;25(1):104-8. doi: 10.3109/02688697.2010.508848. PMID: 20825286. Exclusion: 6.

14. Aibar-Duran JA, Alvarez Holzapfel MJ, Rodriguez Rodriguez R, et al. Occipital nerve stimulation and deep brain stimulation for refractory cluster headache: a prospective analysis of efficacy over time. J Neurosurg. 2020 Jan 17:1-8. doi: 10.3171/2019.11.JNS192042. PMID: 31952039. Exclusion: 4.

15. Aiyer R, Noori S, Schirripa F, et al. Treatment of knee osteoarthritic pain with platelet-rich plasma: a systematic review of clinical studies. Pain manag. 2021 Apr;11(4):419-31. doi: https://dx.doi.org/10.2217/pmt-2020-0052. PMID: 33764185. Exclusion: 2.

16. Akeda K, Ohishi K, Masuda K, et al. Intradiscal Injection of Autologous Platelet-Rich Plasma Releasate to Treat Discogenic Low Back Pain: A Preliminary Clinical Trial. Asian spine j. 2017 Jun;11(3):380-9. doi: 10.4184/asj.2017.11.3.380. PMID: 28670405. Exclusion: 4.

17. Akeda K, Yamada J, Linn ET, et al. Platelet-rich plasma in the management of chronic low back pain: A critical review. J Pain Res. 2019;12:753-67. doi: 10.2147/JPR.S153085. PMID: 30881089. Exclusion: 9.

18. Al-Ali F, Barrow T, Luke K. Vertebroplasty: what is important and what is not. AJNR Am J Neuroradiol. 2009 Nov;30(10):1835-9. doi: 10.3174/ajnr.A1732. PMID: 19713320. Exclusion: 6.

19. Albayrak A, Ozcafer R, Balioglu MB, et al. Piriformis syndrome: treatment of a rare cause of posterior hip pain with fluoroscopic-guided injection. Hip int. 2015 Mar-Apr;25(2):172-5. doi: 10.5301/hipint.5000219. PMID: 25837782. Exclusion: 4.

20. Albers CE, Schott PM, Ahmad SS, et al. Vertebral body lavage Reduces hemodynamic response to vertebral body wugmentation with PMMA. Global spine j. 2019 Aug;9(5):499-504. doi: 10.1177/2192568218803106. PMID: 31431872. Exclusion: 3.

21. Alhashash M, Shousha M, Barakat AS, et al. Effects of polymethylmethacrylate cement viscosity and bone porosity on cement leakage and new vertebral fractures after percutaneous vertebroplasty: A prospective study. Global spine j. 2019 Oct;9(7):754-60. doi: 10.1177/2192568219830327. PMID: 31552157. Exclusion: 3.

22. Alsalmi S, Capel C, Chenin L, et al. Robot-assisted intravertebral augmentation corrects local kyphosis more effectively than a conventional fluoroscopy-guided technique. J Neurosurg Spine. 2018 Nov 30;30(2):289-95. doi: 10.3171/2018.8.SPINE18197. PMID: 30544363. Exclusion: 3.

23. Alvarez L, Alcaraz M, Perez-Higueras A, et al. Percutaneous vertebroplasty: functional improvement in patients with osteoporotic compression fractures. Spine. 2006 May 01;31(10):1113-8. PMID: 16648745. Exclusion: 6.

24. Amar AP, Larsen DW, Teitelbaum GP. Use of a screw-syringe injector for cement delivery during kyphoplasty: technical report. Neurosurgery. 2003 Aug;53(2):380-2; discussion 3. PMID: 12925255. Exclusion: 3.

25. Amoretti N, Guinebert S, Kastler A, et al. Symptomatic Schmorl's nodes: role of percutaneous vertebroplasty. Open study on 52 patients. Neuroradiology. 2019 Apr;61(4):405-10. doi: 10.1007/s00234-019-02171-7. PMID: 30778620. Exclusion: 6.

26. Anderson PA, Froyshteter AB, Tontz WL, Jr. Meta-analysis of vertebral augmentation compared with conservative treatment for osteoporotic spinal fractures. J Bone Miner Res. 2013 Feb;28(2):372-82. doi: 10.1002/jbmr.1762. PMID: 22991246. Exclusion: 9.

27. Anjana Reddy VS, Sharma C, Chang KY, et al. 'Simplicity' radiofrequency neurotomy of sacroiliac joint: a real life 1-year follow-up UK data. Br J Pain. 2016 May;10(2):90-9. doi: 10.1177/2049463715627287. PMID: 27551419. Exclusion: 6.

28. Anonymous. Vertebroplasty versus sham procedure for painful acute osteoporotic vertebral compression fractures (VERTOS IV): randomised sham controlled clinical trial. Bmj. 2018 Jul 04;362:k2937. doi: 10.1136/bmj.k2937. PMID: 29973351. Exclusion: 7.

29. Anselmetti GC, Manca A, Montemurro F, et al. Percutaneous vertebroplasty in multiple myeloma: prospective long-term follow-up in 106 consecutive patients. Cardiovasc Intervent Radiol. 2012 Feb;35(1):139-45. doi: 10.1007/s00270-011-0111-4. PMID: 21305282. Exclusion: 6.

30. Anselmetti GC, Manca A, Tutton S, et al. Percutaneous vertebral augmentation assisted by PEEK implant in painful osteolytic vertebral metastasis involving the vertebral wall: experience on 40 patients. Pain physician. 2013 Jul-Aug;16(4):397-404. PMID: 23877463. Exclusion: 6.

31. Anselmetti GC, Zoarski G, Manca A, et al. Percutaneous vertebroplasty and bone cement leakage: clinical experience with a new high-viscosity bone cement and delivery system for vertebral augmentation in benign and malignant compression fractures. Cardiovasc Intervent Radiol. 2008 Sep-Oct;31(5):937-47. doi: 10.1007/s00270-008-9324-6. PMID: 18389186. Exclusion: 4.

32. Aquino-Jose VM, Blinder V, Johnson J, et al. Ultrasound-guided trigger point injection for piriformis syndrome in the emergency department. J Am Coll Emerg Physicians Open. 2020 Oct;1(5):876-9. doi: 10.1002/emp2.12153. PMID: 33145535. Exclusion: 6.

33. Arabmotlagh M, Rickert M, Lukas A, et al. Small cavity creation in the vertebral body reduces the rate of cement leakage during vertebroplasty. J Orthop Res. 2017 Jan;35(1):154-9. doi: 10.1002/jor.23215. PMID: 26919407. Exclusion: 6.

34. Astur N, Avanzi O. Balloon kyphoplasty in the treatment of neoplastic spine lesions: A systematic review. Global spine j. 2019 May;9(3):348-56. doi: 10.1177/2192568218768774. PMID: 31192104. Exclusion: 9.

35. Aurora SK, Dodick DW, Turkel CC, et al. OnabotulinumtoxinA for treatment of chronic migraine: results from the double-blind, randomized, placebo-controlled phase of the PREEMPT 1 trial. Cephalalgia. 2010 Jul;30(7):793-803. doi: 10.1177/0333102410364676. PMID: 20647170. Exclusion: 2.

36. Bae H, Shen M, Maurer P, et al. Clinical experience using Cortoss for treating vertebral compression fractures with vertebroplasty and kyphoplasty: twenty four-month follow-up. Spine (Phila Pa 1976). 2010 Sep 15;35(20):E1030-6. doi: 10.1097/BRS.0b013e3181dcda75. PMID: 20844420. Exclusion: 4.

37. Bastian L, Schils F, Tillman JB, et al. A randomized trial comparing 2 techniques of balloon kyphoplasty and curette use for obtaining vertebral body height restoration and angular-deformity correction in vertebral compression fractures due to osteoporosis. AJNR Am J Neuroradiol. 2013 Mar;34(3):666-75. doi: 10.3174/ajnr.A3363. PMID: 23179647. Exclusion: 4.

38. Bonetti M, Fontana A, Cotticelli B, et al. Intraforaminal O(2)-O(3) versus periradicular steroidal infiltrations in lower back pain: randomized controlled study. AJNR Am J Neuroradiol. 2005 May;26(5):996-1000. PMID: 15891150. Exclusion: 4.

39. Bono F, Salvino D, Mazza MR, et al. The influence of ictal cutaneous allodynia on the response to occipital transcutaneous electrical stimulation in chronic migraine and chronic tension-type headache: a randomized, sham-controlled study. Cephalalgia. 2015 Apr;35(5):389-98. doi: 10.1177/0333102414544909. PMID: 25078717. Exclusion: 3.

40. Buchbinder R, Osborne RH, Ebeling PR, et al. Vertebroplasty was not effective for painful osteoporotic vertebral fractures. Journal of bone and joint surgery. 2010;American volume. 92(5):1263-. doi: 10.2106/JBJS.9205.ebo443. PMID: 20439677. Exclusion: 7.

41. Buchbinder R, Osborne RH, Ebeling PR, et al. Efficacy and safety of vertebroplasty for treatment of painful osteoporotic vertebral fractures: a randomised controlled trial [ACTRN012605000079640]. BMC Musculoskelet Disord. 2008 Nov 25;9:156. doi: 10.1186/1471-2474-9-156. PMID: 19025665. Exclusion: 7.

42. Cadalso RT, Jr., Daugherty J, Holmes C, et al. Efficacy of electrical stimulation of the occipital nerve in intractable primary headache disorders: a systematic review with meta-analyses. J Oral Facial Pain Headache. 2018 2018;32(1):40-52. doi: 10.11607/ofph.1784. PMID: 29161336. Exclusion: 10.

43. Cánovas Martínez L, Orduña Valls J, Paramés Mosquera E, et al. Sacroiliac joint pain: Prospective, randomised, experimental and comparative study of thermal radiofrequency with sacroiliac joint block. Rev Esp Anestesiol Reanim. 2016 May;63(5):267-72. doi: 10.1016/j.redar.2015.08.003. PMID: 26642949. Exclusion: 3.

44. Cao Z, Li Y, Gao F, et al. Mesenchymal Stem Cells: A New Choice for Nonsurgical Treatment of OA? Results from a Bayesian Network Meta-Analysis. Biomed Res Int. 2021;2021:6663003. doi: https://dx.doi.org/10.1155/2021/6663003. PMID: 33614784. Exclusion: 2.

45. Carrondo Cottin S, Gallani N, Cantin L, et al. Occipital nerve stimulation for non-migrainous chronic headaches: a systematic review protocol. Syst. 2019 July 22;8(1):181. doi: 10.1186/s13643-019-1101-x. PMID: 31331392. Exclusion: 10.

46. Cetin A, Yektas A. Evaluation of the short- and long-term effectiveness of pulsed radiofrequency and conventional radiofrequency performed for medial branch block in patients with lumbar facet joint pain. Pain Research & Management Vol 2018 2018, ArtID 7492753. 2018 Nov;2018 doi: http://dx.doi.org/10.1155/2018/7492753. PMID: 2018-64001-001. Exclusion: 6.

47. Chang MC, Cho YW, Ahn SH. Comparison between bipolar pulsed radiofrequency and monopolar pulsed radiofrequency in chronic lumbosacral radicular pain: A randomized controlled trial. Medicine (Baltimore). 2017 Mar;96(9):e6236. doi: 10.1097/MD.0000000000006236. PMID: 28248888. Exclusion: 4.

48. Chang MC, Park D. The Effect of Intradiscal Platelet-Rich Plasma Injection for Management of Discogenic Lower Back Pain: A Meta-Analysis. J Pain Res. 2021;14:505-12. doi: https://dx.doi.org/10.2147/JPR.S292335. PMID: 33642874. Exclusion: 9.

49. Chen W, Xie W, Xiao Z, et al. Incidence of cement leakage between unilateral and bilateral percutaneous vertebral augmentation for osteoporotic vertebral compression fractures: a meta-analysis of randomized controlled trials. World Neurosurg. 2019 Feb;122:342-8. doi: 10.1016/j.wneu.2018.10.143. PMID: 30391616. Exclusion: 10.

50. Chen WC, Tsai SHL, Goyal A, et al. Comparison between vertebroplasty with high or low viscosity cement augmentation or kyphoplasty in cement leakage rate for patients with vertebral compression fracture: a systematic review and network meta-analysis. Eur Spine J. 2020 Nov 13;13 doi: 10.1007/s00586-020-06636-9. PMID: 33185740. Exclusion: 10.

51. Chen X, Guo W, Li Q, et al. Is unilateral percutaneous kyphoplasty superior to bilateral percutaneous kyphoplasty for osteoporotic vertebral compression fractures? evidence from a systematic review of discordant meta-analyses. Pain physician. 2018 Jul;21(4):327-36. PMID: 30045590. Exclusion: 10.

52. Chen X, Ren J, Zhang J, et al. Impact of cement placement and leakage in osteoporotic vertebral compression fractures followed by percutaneous vertebroplasty. Clin Spine Surg. 2016 Aug;29(7):365-70. doi: 10.1097/BSD.0b013e3182aa28d6. PMID: 24005031. Exclusion: 6.

53. Chen YC, Zhang L, Li EN, et al. Unilateral versus bilateral percutaneous vertebroplasty for osteoporotic vertebral compression fractures in elderly patients: A meta-analysis. Medicine (Baltimore). 2019 Feb;98(8):e14317. doi: 10.1097/MD.0000000000014317. PMID: 30813133. Exclusion: 10.

54. Chen YF, Bramley G, Unwin G, et al. Occipital nerve stimulation for chronic migraine--a systematic review and meta-analysis. PLoS ONE. 2015 Mar 20;10(3):e0116786. doi: 10.1371/journal.pone.0116786. PMID: 25793740. Exclusion: 10.

55. Cheng X, Long HQ, Xu JH, et al. Comparison of unilateral versus bilateral percutaneous kyphoplasty for the treatment of patients with osteoporosis vertebral compression fracture (OVCF): a systematic review and meta-analysis. Eur Spine J. 2016 Nov;25(11):3439-49. doi: 10.1007/s00586-016-4395-6. PMID: 26814475. Exclusion: 10.

56. Cheng Y, Liu Y. Percutaneous curved vertebroplasty in the treatment of thoracolumbar osteoporotic vertebral compression fractures. J Int Med Res. 2019 Jun;47(6):2424-33. doi: 10.1177/0300060519836917. PMID: 31007103. Exclusion: 4.

57. Cheung G, Chow E, Holden L, et al. Percutaneous vertebroplasty in patients with intractable pain from osteoporotic or metastatic fractures: A prospective study using quality-of-life assessment. Can Assoc Radiol J. 2006 Feb;57(1):13-21. PMID: 16719207. Exclusion: 4.

58. Chitale A, Prasad S. An evidence-based analysis of vertebroplasty and kyphoplasty. J Neurosurg Sci. 2013 Jun;57(2):129-37. PMID: 23676862. Exclusion: 10.

59. Chua NH, Vissers KC, Sluijter ME. Pulsed radiofrequency treatment in interventional pain management: mechanisms and potential indications-a review. Acta Neurochir (Wien). 2011 Apr;153(4):763-71. doi: 10.1007/s00701-010-0881-5. PMID: 21116663. Exclusion: 10.

60. Cohen S, Levin D, Mellender S, et al. Topical sphenopalatine ganglion block compared with epidural blood patch for postdural puncture headache management in postpartum patients: a retrospective review. Reg Anesth Pain Med. 2018 Nov;43(8):880-4. doi: 10.1097/AAP.0000000000000840. PMID: 30063655. Exclusion: 6.

61. Cohen SP, Peterlin BL, Fulton L, et al. Randomized, double-blind, comparative-effectiveness study comparing pulsed radiofrequency to steroid injections for occipital neuralgia or migraine with occipital nerve tenderness. Pain. 2015 Dec;156(12):2585-94. doi: 10.1097/j.pain.0000000000000373. PMID: 26447705. Exclusion: 2.

62. Contreras Lopez WO, Navarro PA, Vargas MD, et al. Pulsed radiofrequency versus continuous radiofrequency for facet joint low back pain: a systematic review. World Neurosurg. 2019 Feb;122:390-6. doi: 10.1016/j.wneu.2018.10.191. PMID: 30404055. Exclusion: 10.

63. Cornelis FH, Joly Q, Nouri-Neuville M, et al. Innovative spine implants for improved augmentation and stability in neoplastic vertebral compression fracture. Medicina (Kaunas). 2019 Jul 31;55(8):31. doi: 10.3390/medicina55080426. PMID: 31370309. Exclusion: 10.

64. Crockett MT, Moynagh M, Long N, et al. Ozone-augmented percutaneous discectomy: a novel treatment option for refractory discogenic sciatica. Clin Radiol. 2014 Dec;69(12):1280-6. doi: 10.1016/j.crad.2014.08.008. PMID: 25240564. Exclusion: 6.

65. De Leacy R, Chandra RV, Barr JD, et al. The evidentiary basis of vertebral augmentation: a 2019 update. J Neurointerv Surg. 2020 May;12(5):442-7. doi: 10.1136/neurintsurg-2019-015026. PMID: 31974279. Exclusion: 10.

66. De M, Mohan VK, Bhoi D, et al. Transforaminal epidural injection of local anesthetic and dorsal root ganglion pulsed radiofrequency treatment in lumbar radicular pain: a randomized, triple-blind, active-control trial. Pain pract. 2020 Feb;20(2):154-67. doi: 10.1111/papr.12840. PMID: 31538405. Exclusion: 2.

67. Deer TR, Gilmore CA, Desai MJ, et al. Percutaneous Peripheral Nerve Stimulation of the Medial Branch Nerves for the Treatment of Chronic Axial Back Pain in Patients After Radiofrequency Ablation. Pain Med. 2021 Mar 18;22(3):548-60. doi: https://dx.doi.org/10.1093/pm/pnaa432. PMID: 33616178. Exclusion: 4.

68. Dere K, Akbas M, Sen H, et al. Comparing the effectiveness of thiocolchicoside and triamcinolone in piriformis syndrome treatment. Turkiye Klinikleri Journal of Medical Sciences. 2009;29(5):1267-72. PMID: 105265429. Language: English. Entry Date: 20100122. Revision Date: 20150711. Publication Type: Journal Article. Exclusion: 3.

69. Desai MJ, Mansfield JT, Robinson DM, et al. Regenerative Medicine for Axial and Radicular Spine-Related Pain: A Narrative Review. Pain pract. 2020;20(4):437-53. doi: 10.1111/papr.12868. PMID: 142690387. Language: English. Entry Date: 20200415. Revision Date: 20200504. Publication Type: Article. Exclusion: 10.

70. Diamond T, Clark W, Bird P, et al. Percutaneous vertebroplasty for acute painful osteoporotic vertebral fractures-benefits shown in VAPOUR trial masked when pooled with other clinical trials. J Bone Miner Res. 2019 Jun;34(6):1182-4. doi: 10.1002/jbmr.3725. PMID: 31136012. Exclusion: 7.

71. Diamond TH, Bryant C, Browne L, et al. Clinical outcomes after acute osteoporotic vertebral fractures: a 2-year non-randomised trial comparing percutaneous vertebroplasty with conservative therapy. Med J Aust. 2006 Feb 06;184(3):113-7. PMID: 16460295. Exclusion: 6.

72. Diamond TH, Champion B, Clark WA. Management of acute osteoporotic vertebral fractures: a nonrandomized trial comparing percutaneous vertebroplasty with conservative therapy. Am J Med. 2003 Mar;114(4):257-65. PMID: 12681451. Exclusion: 6.

73. Diener HC, Dodick DW, Aurora SK, et al. OnabotulinumtoxinA for treatment of chronic migraine: results from the double-blind, randomized, placebo-controlled phase of the PREEMPT 2 trial. Cephalalgia. 2010 Jul;30(7):804-14. doi: 10.1177/0333102410364677. PMID: 20647171. Exclusion: 2.

74. Ding W, Yang S, Guo X, et al. Intradiscal Methylene Blue Injection for Discogenic Low Back Pain: A Meta-Analysis. Pain pract. 2019;19(1):118-29. doi: 10.1111/papr.12725. PMID: 134021908. Language: English. Entry Date: 20190111. Revision Date: 20200101. Publication Type: Article. Exclusion: 10.

75. Ding Y, Li H, Yao P, et al. Clinical observation of CT-guided intra-articular conventional radiofrequency and pulsed radiofrequency in the treatment of chronic sacroiliac joint pain. J Pain Res. 2018;11:2359-66. doi: 10.2147/JPR.S179712. PMID: 30410388. Exclusion: 6.

76. Do KH, Ahn SH, Cho YW, et al. Comparison of intra-articular lumbar facet joint pulsed radiofrequency and intra-articular lumbar facet joint corticosteroid injection for management of lumbar facet joint pain: A randomized controlled trial. Medicine (Baltimore). 2017 Mar;96(13):e6524. doi: 10.1097/MD.0000000000006524. PMID: 28353611. Exclusion: 4.

77. Dobrogowski J, Wrzosek A, Wordliczek J. Radiofrequency denervation with or without addition of pentoxifylline or methylprednisolone for chronic lumbar zygapophysial joint pain. Pharmacol Rep. 2005 Jul-Aug;57(4):475-80. PMID: 16129914. Exclusion: 3.

78. 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 Apr;35(4):344-58. doi: 10.1177/0333102414543331. PMID: 25078718. Exclusion: 6.

79. Dohm M, Black CM, Dacre A, et al. A randomized trial comparing balloon kyphoplasty and vertebroplasty for vertebral compression fractures due to osteoporosis. AJNR Am J Neuroradiol. 2014 Dec;35(12):2227-36. doi: 10.3174/ajnr.A4127. PMID: 25300981. Exclusion: 4.

80. Dondas A, Luca A, Alexa T, et al. Repeated methylene blue administration produces analgesia in experimental pain. J Headache Pain. 2013;14:1-. doi: 10.1186/1129-2377-14-S1-P86. PMID: 104100557. Language: English. Entry Date: 20140718. Revision Date: 20200708. Publication Type: Journal Article. Exclusion: 2.

81. Du J, Li X, Lin X. Kyphoplasty versus vertebroplasty in the treatment of painful osteoporotic vertebral compression fractures: two-year follow-up in a prospective controlled study. Acta Orthop Belg. 2014 Dec;80(4):477-86. PMID: 26280719. Exclusion: 4.

82. Du JP, Fan Y, Liu JJ, et al. The analysis of MSTMOVCF (Multi-segment thoracolumbar mild osteoporotic fractures surgery or conservative treatment) based on ASTLOF (the assessment system of thoracolumbar osteoporotic fracture). Sci. 2018 May 29;8(1):8185. doi: 10.1038/s41598-018-26562-7. PMID: 29844542. Exclusion: 6.

83. Ducic I, Felder JM, 3rd, Fantus SA. A systematic review of peripheral nerve interventional treatments for chronic headaches. Ann Plast Surg. 2014 Apr;72(4):439-45. doi: 10.1097/SAP.0000000000000063. PMID: 24374395. Exclusion: 10.

84. Duger C, Kol IO, Kaygusuz K, et al. Effects of facet joint nerve block addition to radiofrequency in the treatment of low back pain. Healthmed. 2012;6(6):2052-6. PMID: CN-00902974. Exclusion: 3.

85. Dutta K, Dey S, Bhattacharyya P, et al. Comparison of efficacy of lateral branch pulsed radiofrequency denervation and intraarticular depot methylprednisolone injection for sacroiliac joint pain. Pain physician. 2018 Sep;21(5):489-96. PMID: 30282393. Exclusion: 4.

86. Dworkin RH, Turk DC, Wyrwich KW, et al. Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. J Pain. 2008 Feb;9(2):105-21. doi: 10.1016/j.jpain.2007.09.005. PMID: 18055266. Exclusion: 7.

87. Eck JC, Nachtigall D, Humphreys SC, et al. Comparison of vertebroplasty and balloon kyphoplasty for treatment of vertebral compression fractures: a meta-analysis of the literature. Spine J. 2008 May-Jun;8(3):488-97. PMID: 17588820. Exclusion: 10.

88. Eisenberg E, Waisbrod H, Gerbershagen HU. Long-term peripheral nerve stimulation for painful nerve injuries. Clin J Pain. 2004 May-Jun;20(3):143-6. PMID: 15100589. Exclusion: 6.

89. Elawamy A, Kamel EZ, Hassanien M, et al. Implication of two different doses of intradiscal ozone-oxygen injection upon the pain alleviation in patients with low back pain: a randomized, single-blind study. Pain physician. 2018 Jan;21(1):25-31. PMID: 29357333. Exclusion: 4.

90. Eldabe SS, Taylor RS, Goossens S, et al. A randomized controlled trial of subcutaneous nerve stimulation for back pain due to failed back surgery syndrome: The subQStim study. Neuromodulation. 2019 Jul;22(5):519-28. doi: 10.1111/ner.12784. PMID: 29704437. Exclusion: 2.

91. En X, Hao DJ. Percutaneous kyphoplasty versus conservative treatment in acute and subacute osteoporotic vertebral compression fractures (OVCF): a double-blinded, randomized controlled clinical trial (RCT) in the population of Western China. Spine journal. 2013;13(9):90S-1S. doi: 10.1016/j.spinee.2013.07.247. PMID: CN-01006814. Exclusion: 7.

92. Ercalik T, Kilic M. Efficacy of intradiscal ozone therapy with or without periforaminal steroid injection on lumbar disc herniation: A double-blinded controlled study. Pain physician. 2020 09;23(5):477-84. PMID: 32967390. Exclusion: 3.

93. Evans AJ, Kip KE, Brinjikji W, et al. Randomized controlled trial of vertebroplasty versus kyphoplasty in the treatment of vertebral compression fractures. J Neurointerv Surg. 2016 Jul;8(7):756-63. doi: 10.1136/neurintsurg-2015-011811. PMID: 26109687. Exclusion: 4.

94. Facchini G, Spinnato P, Guglielmi G, et al. A comprehensive review of pulsed radiofrequency in the treatment of pain associated with different spinal conditions. Br J Radiol. 2017 May;90(1073):20150406. doi: 10.1259/bjr.20150406. PMID: 28186832. Exclusion: 10.

95. Fanous SN, Saleh EG, Abd Elghafar EM, et al. Randomized controlled trials between dorsal root ganglion thermal radiofrequency, pulsed radiofrequency and steroids for the management of intractable metastatic back pain in thoracic vertebral body. British journal of pain. 2020 PMID: CN-02161430 NEW. Exclusion: 2.

96. Farrokhi MR, Lotfi M, Masoudi MS, et al. Effects of methylene blue on postoperative low-back pain and functional outcomes after lumbar open discectomy: a triple-blind, randomized placebo-controlled trial. J Neurosurg Spine. 2016 Jan;24(1):7-15. doi: 10.3171/2015.3.SPINE141172. PMID: 26360148. Exclusion: 2.

97. Feng H, Huang P, Zhang X, et al. Unilateral versus bilateral percutaneous kyphoplasty for osteoporotic vertebral compression fractures: A systematic review and meta-analysis of RCTs. J Orthop Res. 2015 Nov;33(11):1713-23. doi: 10.1002/jor.22957. PMID: 26123667. Exclusion: 10.

98. Feng L, Shen JM, Feng C, et al. Comparison of radiofrequency kyphoplasty (RFK) and balloon kyphoplasty (BKP) in the treatment of vertebral compression fractures: A meta-analysis. Medicine (Baltimore). 2017 Jun;96(25):e7150. doi: 10.1097/MD.0000000000007150. PMID: 28640091. Exclusion: 10.

99. Fernández Sanromán J, Fernández Ferro M, Costas López A, et al. Does injection of plasma rich in growth factors after temporomandibular joint arthroscopy improve outcomes in patients with Wilkes stage IV internal derangement? A randomized prospective clinical study. Int J Oral Maxillofac Surg. 2016 Jul;45(7):828-35. doi: 10.1016/j.ijom.2016.01.018. PMID: 26922496. Exclusion: 2.

100. Fernández-Ferro M, Fernández-Sanromán J, Blanco-Carrión A, et al. Comparison of intra-articular injection of plasma rich in growth factors versus hyaluronic acid following arthroscopy in the treatment of temporomandibular dysfunction: A randomised prospective study. J Craniomaxillofac Surg. 2017 Apr;45(4):449-54. doi: 10.1016/j.jcms.2017.01.010. PMID: 28237253. Exclusion: 2.

101. Filardo G, Kon E, Roffi A, et al. Platelet-rich plasma: why intra-articular? A systematic review of preclinical studies and clinical evidence on PRP for joint degeneration. Knee Surg Sports Traumatol Arthrosc. 2015 Sep;23(9):2459-74. doi: 10.1007/s00167-013-2743-1. PMID: 24275957. Exclusion: 10.

102. Firanescu C, Lohle PN, de Vries J, et al. A randomised sham controlled trial of vertebroplasty for painful acute osteoporotic vertebral fractures (VERTOS IV). Trials. 2011 Apr 05;12:93. doi: 10.1186/1745-6215-12-93. PMID: 21466679. Exclusion: 7.

103. Foster L, Clapp L, Erickson M, et al. Botulinum toxin A and chronic low back pain: a randomized, double-blind study. Neurology. 2001 May 22;56(10):1290-3. doi: 10.1212/wnl.56.10.1290. PMID: 11376175. Exclusion: 2.

104. Fowler IM, Tucker AA, Weimerskirch BP, et al. A randomized comparison of the efficacy of 2 techniques for piriformis muscle injection: ultrasound-guided versus nerve stimulator with fluoroscopic guidance. Reg Anesth Pain Med. 2014 Mar-Apr;39(2):126-32. doi: 10.1097/AAP.0000000000000056. PMID: 24509422. Exclusion: 3.

105. Frankel BM, Krishna V. Meta-analysis: vertebroplasty for vertebral compression fracture ineffective in improving pain and function. Evid Based Med. 2012 Oct;17(5):142-3. doi: 10.1136/ebmed-2011-100215. PMID: 22044795. Exclusion: 10.

106. Freitas TDS, Fonoff ET, Marquez Neto OR, et al. Peripheral nerve stimulation for painful mononeuropathy secondary to leprosy: a 12-month follow-up study. Neuromodulation. 2018 Apr;21(3):310-6. doi: 10.1111/ner.12714. PMID: 29082637. Exclusion: 6.

107. Freund B, Kotchetkov IS, Rao A. The Efficacy of Botulinum Toxin in Cluster Headache: A Systematic Review. Journal of Oral & Facial Pain & Headache. 2020 Spring2020;34(2):129-34. doi: 10.11607/ofph.2444. PMID: 143591374. Language: English. Entry Date: 20200608. Revision Date: 20200613. Publication Type: Article. Exclusion: 9.

108. Fritzell P, Ohlin A, Borgstrom F. Cost-effectiveness of balloon kyphoplasty versus standard medical treatment in patients with osteoporotic vertebral compression fracture: a Swedish multicenter randomized controlled trial with 2-year follow-up. Spine. 2011 Dec 15;36(26):2243-51. doi: 10.1097/BRS.0b013e3182322d0f. PMID: 21912321. Exclusion: 5.

109. Fukui S, Nitta K, Iwashita N, et al. Intradiscal pulsed radiofrequency for chronic lumbar discogenic low back pain: a one year prospective outcome study using discoblock for diagnosis. Pain physician. 2013 Jul-Aug;16(4):435-42. PMID: 23877468. Exclusion: 6.

110. Gabrhelik T, Michalek P, Adamus M. Pulsed radiofrequency therapy versus greater occipital nerve block in the management of refractory cervicogenic headache - a pilot study. Prague Med Rep. 2011;112(4):279-87. PMID: 22142523. Exclusion: 2.

111. Gao Y, Huo M, Fan X, et al. Effect of PVP with a mesh-hold bone-filling mesh bag and different viscosities of bone cement in the treatment of osteoporotic vertebral compression fractures. Int J Clin Exp Med. 2020;13(7):5006-12. PMID: CN-02161078 NEW. Exclusion: 4.

112. Gautam S, Rastogi V, Jain A, et al. Comparative evaluation of oxygen-ozone therapy and combined use of oxygen-ozone therapy with percutaneous intradiscal radiofrequency thermocoagulation for the treatment of lumbar disc herniation. Pain pract. 2011 Mar-Apr;11(2):160-6. doi: 10.1111/j.1533-2500.2010.00409.x. PMID: 20642485. Exclusion: 4.

113. Genev IK, Tobin MK, Zaidi SP, et al. Spinal compression fracture management: A review of current treatment strategies and possible future avenues. Global spine j. 2017 Feb;7(1):71-82. doi: 10.1055/s-0036-1583288. PMID: 28451512. Exclusion: 10.

114. Gill JB, Kuper M, Chin PC, et al. Comparing pain reduction following kyphoplasty and vertebroplasty for osteoporotic vertebral compression fractures. Pain physician. 2007 Jul;10(4):583-90. PMID: 17660858. Exclusion: 10.

115. Gilula L, Persenaire M. Subsequent fractures post-vertebral augmentation: analysis of a prospective randomized trial in osteoporotic vertebral compression fractures. AJNR Am J Neuroradiol. 2013 Jan;34(1):221-7. doi: 10.3174/ajnr.A3156. PMID: 22743641. Exclusion: 3.

116. Goadsby PJ, Sahai-Srivastava S, Kezirian EJ, et al. Safety and efficacy of sphenopalatine ganglion stimulation for chronic cluster headache: a double-blind, randomised controlled trial. The lancet. 2019;Neurology. 18(12):1081-90. PMID: CN-02006591. Exclusion: 3.

117. Grafe IA, Da Fonseca K, Hillmeier J, et al. Reduction of pain and fracture incidence after kyphoplasty: 1-year outcomes of a prospective controlled trial of patients with primary osteoporosis. Osteoporos Int. 2005 Dec;16(12):2005-12. PMID: 16078092. Exclusion: 6.

118. Gray LA, Jarvik JG, Heagerty PJ, et al. INvestigational Vertebroplasty Efficacy and Safety Trial (INVEST): a randomized controlled trial of percutaneous vertebroplasty. BMC Musculoskelet Disord. 2007 Dec 20;8:126. PMID: 18096050. Exclusion: 7.

119. Griffoni C, Lukassen JNM, Babbi L, et al. Percutaneous vertebroplasty and balloon kyphoplasty in the treatment of osteoporotic vertebral fractures: a prospective randomized comparison. Eur Spine J. 2020 Jul;29(7):1614-20. doi: 10.1007/s00586-020-06434-3. PMID: 32361843. Exclusion: 4.

120. Gu CN, Brinjikji W, Evans AJ, et al. Outcomes of vertebroplasty compared with kyphoplasty: a systematic review and meta-analysis. J Neurointerv Surg. 2016 Jun;8(6):636-42. doi: 10.1136/neurintsurg-2015-011714. PMID: 25964376. Exclusion: 9.

121. Guo X, Ding W, Liu L, et al. Intradiscal methylene blue injection for discogenic low back pain: a meta-analysis. Pain pract. 2019 Jan;19(1):118-29. doi: 10.1111/papr.12725. PMID: 30039642. Exclusion: 10.

122. Guo Z, Wang W, Gao WS, et al. Comparison the clinical outcomes and complications of high-viscosity versus low-viscosity in osteoporotic vertebral compression fractures. Medicine (Baltimore). 2017 Dec;96(48):e8936. doi: 10.1097/MD.0000000000008936. PMID: 29310386. Exclusion: 4.

123. Haigler MC, Abdulrehman E, Siddappa S, et al. Use of platelet-rich plasma, platelet-rich growth factor with arthrocentesis or arthroscopy to treat temporomandibular joint osteoarthritis: Systematic review with meta-analyses. J Am Dent Assoc. 2018 Nov;149(11):940-52. doi: 10.1016/j.adaj.2018.07.025. PMID: 30724168. Exclusion: 9.

124. Han S, Wan S, Ning L, et al. Percutaneous vertebroplasty versus balloon kyphoplasty for treatment of osteoporotic vertebral compression fracture: a meta-analysis of randomised and non-randomised controlled trials. Int Orthop. 2011 Sep;35(9):1349-58. doi: 10.1007/s00264-011-1283-x. PMID: 21637959. Exclusion: 10.

125. Han SL, Wan SL, Li QT, et al. Is vertebroplasty a risk factor for subsequent vertebral fracture, meta-analysis of published evidence? Osteoporos Int. 2015 Jan;26(1):113-22. doi: 10.1007/s00198-014-2848-5. PMID: 25149856. Exclusion: 10.

126. Hansen EJ, Simony A, Rousing R, et al. Double Blind Placebo-controlled Trial of Percutaneous Vertebroplasty (VOPE). Global spine j. 2016;6(1_suppl):s-0036-1582763-s-0036-. doi: 10.1055/s-0036-1582763. Exclusion: 7.

127. Hashemi M, Hashemian M, Mohajerani SA, et al. Effect of pulsed radiofrequency in treatment of facet-joint origin back pain in patients with degenerative spondylolisthesis. Eur Spine J. 2014 Sep;23(9):1927-32. doi: 10.1007/s00586-014-3412-x. PMID: 24997616. Exclusion: 2.

128. Hazzard MA, Huang KT, Toche UN, et al. Comparison of vertebroplasty, kyphoplasty, and nonsurgical management of vertebral compression fractures and impact on US healthcare resource utilization. Asian spine j. 2014 Oct;8(5):605-14. doi: 10.4184/asj.2014.8.5.605. PMID: 25346813. Exclusion: 6.

129. Hegab AF, Ali HE, Elmasry M, et al. Platelet-rich plasma injection as an effective treatment for temporomandibular joint osteoarthritis. J Oral Maxillofac Surg. 2015 Sep;73(9):1706-13. doi: 10.1016/j.joms.2015.03.045. PMID: 25882438. Exclusion: 2.

130. Hernigou P, Dubory A, Homma Y, et al. Cell therapy versus simultaneous contralateral decompression in symptomatic corticosteroid osteonecrosis: a thirty year follow-up prospective randomized study of one hundred and twenty five adult patients. Int Orthop. 2018 Jul;42(7):1639-49. doi: 10.1007/s00264-018-3941-8. PMID: 29744647. Exclusion: 3.

131. Hinde K, Maingard J, Hirsch JA, et al. Mortality outcomes of vertebral augmentation (vertebroplasty and/or balloon kyphoplasty) for osteoporotic vertebral compression fractures: a systematic review and meta-analysis. Radiology. 2020 Apr;295(1):96-103. doi: 10.1148/radiol.2020191294. PMID: 32068503. Exclusion: 9.

132. Hintz A. 84 - Non-inferiority of Cooled vs Traditional Radiofrequency Ablation of the Lumbar Medial Branch Nerves in the Treatment of Axial Low Back Pain. Spine Journal. 2017;17:S120-S. doi: 10.1016/j.spinee.2017.07.105. PMID: 125611602. Language: English. Entry Date: In Process. Revision Date: 20171017. Publication Type: Article. Supplement Title: Oct2017 Supplement. Journal Subset: Biomedical. Exclusion: 7.

133. Ho KY, Hadi MA, Pasutharnchat K, et al. Cooled radiofrequency denervation for treatment of sacroiliac joint pain: two-year results from 20 cases. J Pain Res. 2013;6:505-11. doi: 10.2147/jpr.S46827. PMID: 23869175. Exclusion: 6.

134. Hoffmeister E. Researchers find vertebroplasty not superior to placebo for recent-onset fracture or severe back pain. Lippincott's Bone & Joint Newsletter. 2011;17(10):109-13. PMID: 108213033. Language: English. Entry Date: 20120106. Revision Date: 20150712. Publication Type: Journal Article. Exclusion: 10.

135. Hofmeister M, Memedovich A, Brown S, et al. Effectiveness of neurostimulation technologies for the management of chronic pain: a systematic review. Neuromodulation. 2020 Feb;23(2):150-7. doi: 10.1111/ner.13020. PMID: 31310417. Exclusion: 10.

136. Hong T, Wang H, Li G, et al. Systematic review and meta-analysis of 12 randomized controlled trials evaluating the efficacy of invasive radiofrequency treatment for knee pain and function. Biomed Res Int. 2019 Jun 26;2019:9037510. doi: 10.1155/2019/9037510. PMID: 31346525. Exclusion: 10.

137. Hoshino M, Takahashi S, Yasuda H, et al. Balloon kyphoplasty versus conservative treatment for acute osteoporotic vertebral fractures with poor prognostic factors: propensity score matched analysis using data from two prospective multicenter studies. Spine. 2019 Jan 15;44(2):110-7. doi: 10.1097/BRS.0000000000002769. PMID: 29958202. Exclusion: 6.

138. Huang CH, Wang WH, Kor CT, et al. Risk of venous thromboembolism in elderly patients with vertebral compression fracture: A population-based case-control study. Medicine (Baltimore). 2020 May;99(18):e20072. doi: 10.1097/MD.0000000000020072. PMID: 32358388. Exclusion: 6.

139. Huang Z, Zhang L. Treatment of osteoporotic vertebral compressive fractures with percutaneous kyphoplasty and oral Zishengukang. J Tradit Chin Med. 2012 Dec;32(4):561-4. doi: 10.1016/s0254-6272(13)60071-0. PMID: 23427389. Exclusion: 3.

140. Hulme PA, Krebs J, Ferguson SJ, et al. Vertebroplasty and kyphoplasty: a systematic review of 69 clinical studies. Spine. 2006 Aug 01;31(17):1983-2001. PMID: 16924218. Exclusion: 10.

141. Hung KC, Chen JY, Ho CN, et al. Use of sphenopalatine ganglion block in patients with postdural puncture headache: a pilot meta-analysis. Br J Anaesth. 2020 Oct 29;29:25-7. doi: 10.1016/j.bja.2020.10.005. PMID: 33131755. Exclusion: 10.

142. Iida K, Harimaya K, Tarukado K, et al. Kyphosis progression after balloon kyphoplasty compared with conservative treatment. Asian spine j. 2019 Jul 09:928-35. doi: 10.31616/asj.2018.0329. PMID: 31281176. Exclusion: 6.

143. Ishiguro S, Kasai Y, Sudo A, et al. Percutaneous vertebroplasty for osteoporotic compression fractures using calcium phosphate cement. J. 2010 Dec;18(3):346-51. doi: 10.1177/230949901001800318. PMID: 21187549. Exclusion: 6.

144. Jain D, Goyal T, Verma N, et al. Intradiscal platelet-rich plasma injection for discogenic low back pain and correlation with platelet concentration: a prospective clinical trial. Pain Med. 2020 Aug 31;31:2719-25. doi: 10.1093/pm/pnaa254. PMID: 32869064. Exclusion: 6.

145. Janzen VD, Scudds R. Sphenopalatine blocks in the treatment of pain in fibromyalgia and myofascial pain syndrome. Laryngoscope. 1997 Oct;107(10):1420-2. PMID: 9331324. Exclusion: 2.

146. Jena BR, Paswan A, Singh Y, et al. A comparative study of continuous versus pulsed radiofrequency discectomy for management of low backache: Prospective randomized, double-blind study. Anesthesia Essays and Researches. 2016 Sep-Dec;10(3):602-6. doi: 10.4103/0259-1162.186616. PMID: 27746559. Exclusion: 2.

147. Jiang P, Mao L, Qiao L, et al. Efficacy and safety of mesenchymal stem cell injections for patients with osteoarthritis: a meta-analysis and review of RCTs. Arch Orthop Trauma Surg. 2021 Jan 28;28:28. doi: https://dx.doi.org/10.1007/s00402-020-03703-0. PMID: 33507375. Exclusion: 9.

148. Jones JC, Miller JA, Sudarshana DM, et al. Predictors of favorable quality of life outcome following kyphoplasty and vertebroplasty. J Neurosurg Spine. 2019 May 24;31(3):389-96. doi: 10.3171/2019.3.SPINE18419. PMID: 31125962. Exclusion: 6.

149. Ju DG, Kanim LE, Bae HW. Is there clinical improvement associated with intradiscal therapies? a comparison across randomized controlled studies. Global spine j. 2020 Oct 13:2192568220963058. doi: 10.1177/2192568220963058. PMID: 33047622. Exclusion: 10.

150. Juch JNS, Maas ET, Ostelo R, et al. Effect of Radiofrequency Denervation on Pain Intensity Among Patients With Chronic Low Back Pain: The Mint Randomized Clinical Trials. Jama. 2017 Jul 4;318(1):68-81. doi: 10.1001/jama.2017.7918. PMID: 28672319. Exclusion: 3.

151. Jürgens T, Jensen R, Kaube H, et al. EHMTI-0227. Therapeutic effectiveness of sphenopalatine ganglion (SPG) stimulation for cluster headache - pathway registry study interim results at 6 months. J Headache Pain. 2014;15:1-. doi: 10.1186/1129-2377-15-S1-C26. PMID: 103899322. Language: English. Entry Date: 20141001. Revision Date: 20150710. Publication Type: Journal Article. Supplement Title: Sep2014 Supplement. Journal Subset: Biomedical. Exclusion: 3.

152. Kallewaard JW, Geurts JW, Kessels A, et al. Efficacy, safety, and predictors of intradiscal methylene blue injection for discogenic low back pain: results of a multicenter prospective clinical series. Pain pract. 2016 Apr;16(4):405-12. doi: 10.1111/papr.12283. PMID: 25753429. Exclusion: 4.

153. Kapural L, Nageeb F, Kapural M, et al. Cooled radiofrequency system for the treatment of chronic pain from sacroiliitis: the first case-series. Pain pract. 2008 Sep-Oct;8(5):348-54. doi: 10.1111/j.1533-2500.2008.00231.x. PMID: 18844853. Exclusion: 6.

154. Kasperk C, Grafe IA, Schmitt S, et al. Three-year outcomes after kyphoplasty in patients with osteoporosis with painful vertebral fractures. J Vasc Interv Radiol. 2010 May;21(5):701-9. doi: 10.1016/j.jvir.2010.01.003. PMID: 20304677. Exclusion: 6.

155. Kasperk C, Hillmeier J, Noldge G, et al. Treatment of painful vertebral fractures by kyphoplasty in patients with primary osteoporosis: a prospective nonrandomized controlled study. J Bone Miner Res. 2005 Apr;20(4):604-12. PMID: 15765179. Exclusion: 6.

156. Ke M, Yinghui F, Yi J, et al. Efficacy of pulsed radiofrequency in the treatment of thoracic postherpetic neuralgia from the angulus costae: a randomized, double-blinded, controlled trial. Pain physician. 2013 Jan;16(1):15-25. PMID: 23340530. Exclusion: 2.

157. Klazen CA, Verhaar HJ, Lampmann LE, et al. VERTOS II: percutaneous vertebroplasty versus conservative therapy in patients with painful osteoporotic vertebral compression fractures; rationale, objectives and design of a multicenter randomized controlled trial. Trials. 2007 Oct 31;8:33. doi: 10.1186/1745-6215-8-33. PMID: 17973983. Exclusion: 7.

158. Kloimstein H, Likar R, Kern M, et al. Peripheral nerve field stimulation (PNFS) in chronic low back pain: a prospective multicenter study. Neuromodulation. 2014 Feb;17(2):180-7. doi: 10.1111/ner.12139. PMID: 24320718. Exclusion: 4.

159. Koh W, Choi SS, Karm MH, et al. Treatment of chronic lumbosacral radicular pain using adjuvant pulsed radiofrequency: a randomized controlled study. Pain Med. 2015 Mar;16(3):432-41. doi: 10.1111/pme.12624. PMID: 25530347. Exclusion: 3.

160. Komp M, Ruetten S, Godolias G. Minimally invasive therapy for functionally unstable osteoporotic vertebral fracture by means of kyphoplasty: prospective comparative study of 19 surgically and 17 conservatively treated patients. J Miner Stoffwechs. 2004;11(Suppl 1):13-5. Exclusion: 8.

161. Korovessis P, Vardakastanis K, Repantis T, et al. Balloon kyphoplasty versus KIVA vertebral augmentation--comparison of 2 techniques for osteoporotic vertebral body fractures: a prospective randomized study. Spine. 2013 Feb 15;38(4):292-9. doi: 10.1097/BRS.0b013e31826b3aef. PMID: 23407406. Exclusion: 4.

162. Korovessis P, Vardakastanis K, Vitsas V, et al. Is Kiva implant advantageous to balloon kyphoplasty in treating osteolytic metastasis to the spine? Comparison of 2 percutaneous minimal invasive spine techniques: a prospective randomized controlled short-term study. Spine. 2014 Feb 15;39(4):231-9. doi: 10.1097/BRS.0000000000000112. PMID: 24253785. Exclusion: 4.

163. Ku B, Jun M, Lee JH, et al. Short-term efficacy of pulsed radiofrequency thermal stimulation on acupoints for chronic low back pain: A preliminary study of a randomized, single-blinded, placebo-controlled trial. Evid Based Complement Alternat Med. 2018;2018:4510909. doi: 10.1155/2018/4510909. PMID: 30158995. Exclusion: 3.

164. Kwak SG, Lee DG, Chang MC. Effectiveness of pulsed radiofrequency treatment on cervical radicular pain: A meta-analysis. Medicine (Baltimore). 2018 Aug;97(31):e11761. doi: 10.1097/MD.0000000000011761. PMID: 30075599. Exclusion: 10.

165. Lee DG, Ahn SH, Lee J. Comparative effectivenesses of pulsed radiofrequency and transforaminal steroid injection for radicular pain due to disc herniation: a prospective randomized trial. J Korean Med Sci. 2016 Aug;31(8):1324-30. doi: 10.3346/jkms.2016.31.8.1324. PMID: 27478346. Exclusion: 4.

166. Lee HM, Park SY, Lee SH, et al. Comparative analysis of clinical outcomes in patients with osteoporotic vertebral compression fractures (OVCFs): conservative treatment versus balloon kyphoplasty. Spine J. 2012 Nov;12(11):998-1005. doi: 10.1016/j.spinee.2012.08.024. PMID: 23026068. Exclusion: 6.

167. Levi D, Horn S, Tyszko S, et al. Intradiscal platelet-rich plasma injection for chronic discogenic low back pain: preliminary results from a prospective trial. Pain Med. 2016 Jun;17(6):1010-22. doi: 10.1093/pm/pnv053. PMID: 26814283. Exclusion: 6.

168. Levy H, Seydafkan S, Rice JD, et al. Comparative efficacy of vertebroplasty, kyphoplasty, and medical therapy for vertebral fractures on survival and prevention of recurrent fractures. Endocr Pract. 2012 Jul-Aug;18(4):499-507. doi: 10.4158/EP11349.OR. PMID: 22440996. Exclusion: 6.

169. Li D, Sun G, Sun H, et al. Combined therapy of pulsed radiofrequency and nerve block in postherpetic neuralgia patients: a randomized clinical trial. Peerj. 2018;6:e4852. doi: 10.7717/peerj.4852. PMID: 29888123. Exclusion: 2.

170. Li HM, Zhang RJ, Gao H, et al. New vertebral fractures after osteoporotic vertebral compression fracture between balloon kyphoplasty and nonsurgical treatment PRISMA. Medicine (Baltimore). 2018 Oct;97(40):e12666. doi: 10.1097/MD.0000000000012666. PMID: 30290650. Exclusion: 10.

171. Li WS, Cai YF, Cong L. The Effect of Vertebral Augmentation Procedure on Painful OVCFs: A Meta-Analysis of Randomized Controlled Trials. Global spine j. 2021 Mar 11:2192568221999369. doi: https://dx.doi.org/10.1177/2192568221999369. PMID: 33706568. Exclusion: 9.

172. Li Y, Hai Y, Li L, et al. Early effects of vertebroplasty or kyphoplasty versus conservative treatment of vertebral compression fractures in elderly polytrauma patients. Arch Orthop Trauma Surg. 2015 Dec;135(12):1633-6. doi: 10.1007/s00402-015-2311-x. PMID: 26559063. Exclusion: 6.

173. Lin J, Hsieh Y-C, Chien L-N, et al. P27 - Vertebroplasty Associated with a Lower Risk of Mortality and Morbidity of Aged Patients with Painful Vertebral Compression Fractures: A Population-Based Propensity Score Matching Cohort Study in Taiwan. Spine Journal. 2016;16:S262-S. doi: 10.1016/j.spinee.2016.07.352. PMID: 118698909. Language: English. Entry Date: In Process. Revision Date: 20161014. Publication Type: Article. Supplement Title: Oct2016 Supplement. Journal Subset: Biomedical. Exclusion: 7.

174. Lipton RB. PRISM study: occipital nerve stimulation for treatment-refractory migraine. Abstract PO47. 2009 doi: 10.1111/J.1468-2982.2009.01960.X. Exclusion: 7.

175. Liu J, Li X, Tang D, et al. Comparing pain reduction following vertebroplasty and conservative treatment for osteoporotic vertebral compression fractures: a meta-analysis of randomized controlled trials. Pain physician. 2013 Sep-Oct;16(5):455-64. PMID: 24077192. Exclusion: 10.

176. Liu JT, Liao WJ, Tan WC, et al. Balloon kyphoplasty versus vertebroplasty for treatment of osteoporotic vertebral compression fracture: a prospective, comparative, and randomized clinical study. Osteoporos Int. 2010 Feb;21(2):359-64. doi: 10.1007/s00198-009-0952-8. PMID: 19513578. Exclusion: 4.

177. Liu Q, Cao J, Kong JJ. Clinical effect of balloon kyphoplasty in elderly patients with multiple osteoporotic vertebral fracture. Niger J Clin Pract. 2019 Mar;22(3):289-92. doi: 10.4103/njcp.njcp_8_18. PMID: 30837413. Exclusion: 6.

178. Ma K, Yiqun M, Wu T, et al. Efficacy of diclofenac sodium in pain relief after conventional radiofrequency denervation for chronic facet joint pain: a double-blind randomized controlled trial. Pain Med. 2011 Jan;12(1):27-35. doi: 10.1111/j.1526-4637.2010.00978.x. PMID: 21040436. Exclusion: 3.

179. Ma Y, Wang T, Liao J, et al. Efficacy of autologous bone marrow buffy coat grafting combined with core decompression in patients with avascular necrosis of femoral head: a prospective, double-blinded, randomized, controlled study. Stem Cell Res Ther. 2014 Oct 14;5(5):115. doi: 10.1186/scrt505. PMID: 25315149. Exclusion: 3.

180. Macias-Hernandez SI, Chavez-Arias DD, Miranda-Duarte A, et al. Percutaneous vertebroplasty versus conservative treatment and rehabilitation in women with vertebral fractures due to osteoporosis: a prospective comparative study. Rev Invest Clin. 2015 Mar-Apr;67(2):98-103. PMID: 25938842. Exclusion: 6.

181. Magalhaes FN, Dotta L, Sasse A, et al. Ozone therapy as a treatment for low back pain secondary to herniated disc: a systematic review and meta-analysis of randomized controlled trials. Pain physician. 2012 Mar-Apr;15(2):115-29. PMID: 22430658. Exclusion: 10.

182. Mahapatra AK. Peer review report 1 on "Percutaneous Vertebroplasty Versus Conservative Treatment for Osteoporotic Vertebral Compression Fractures: An Updated Meta-analysis of Prospective Randomized Controlled Trials". Int J Surg. 2017;37:593-. doi: 10.1016/j.ijsu.2017.10.009. PMID: 127136384. Language: English. Entry Date: In Process. Revision Date: 20180108. Publication Type: Article. Supplement Title: Jan2017 Supplement 1. Journal Subset: Biomedical. Exclusion: 10.

183. Makharita MY, El Bendary HM, Sonbul ZM, et al. Ultrasound-guided pulsed radiofrequency in the management of thoracic postherpetic neuralgia: a randomized, double-blinded, controlled trial. Clin J Pain. 2018 Nov;34(11):1017-24. doi: 10.1097/AJP.0000000000000629. PMID: 29757758. Exclusion: 2.

184. Mao Q, Wang W, Xu T, et al. Combination treatment of biomechanical support and targeted intra-arterial infusion of peripheral blood stem cells mobilized by granulocyte-colony stimulating factor for the osteonecrosis of the femoral head: a randomized controlled clinical trial. J Bone Miner Res. 2015 Apr;30(4):647-56. doi: 10.1002/jbmr.2390. PMID: 25349059. Exclusion: 3.

185. Martinez-Ferrer A, Blasco J, Carrasco JL, et al. Risk factors for the development of vertebral fractures after percutaneous vertebroplasty. J Bone Miner Res. 2013 Aug;28(8):1821-9. doi: 10.1002/jbmr.1899. PMID: 23427068. Exclusion: 3.

186. Masala S, Crusco S, Meschini A, et al. Piriformis syndrome: long-term follow-up in patients treated with percutaneous injection of anesthetic and corticosteroid under CT guidance. Cardiovasc Intervent Radiol. 2012 Apr;35(2):375-82. doi: 10.1007/s00270-011-0185-z. PMID: 21607823. Exclusion: 6.

187. Mazzantini M, Carpeggiani P, d'Ascanio A, et al. Long-term prospective study of osteoporotic patients treated with percutaneous vertebroplasty after fragility fractures. Osteoporos Int. 2011 May;22(5):1599-607. doi: 10.1007/s00198-010-1341-z. PMID: 20661546. Exclusion: 6.

188. Mehta V, Poply K, Husband M, et al. The Effects of Radiofrequency Neurotomy Using a Strip-Lesioning Device on Patients with Sacroiliac Joint Pain: Results from a Single-Center, Randomized, Sham-Controlled Trial. Pain physician. 2018 Nov;21(6):607-18. PMID: 30508988. Exclusion: 3.

189. Monfett M, Harrison J, Boachie-Adjei K, et al. Intradiscal platelet-rich plasma (PRP) injections for discogenic low back pain: an update. Int Orthop. 2016 Jun;40(6):1321-8. doi: 10.1007/s00264-016-3178-3. PMID: 27073034. Exclusion: 7.

190. Muzumdar D. Peer review report 3 on "Percutaneous Vertebroplasty Versus Conservative Treatment for Osteoporotic Vertebral Compression Fractures: An Updated Meta-analysis of Prospective Randomized Controlled Trials". Int J Surg. 2017;37:565-. doi: 10.1016/j.ijsu.2017.10.011. PMID: 127136348. Language: English. Entry Date: In Process. Revision Date: 20180108. Publication Type: Article. Supplement Title: Jan2017 Supplement 1. Journal Subset: Biomedical. Exclusion: 10.

191. Nebreda C, Vallejo R, Salvador E, et al. Comparative study of the thermal or conventional radiofrequency and pulsed radiofrequency in the treatment of pain in the lumbar facet origin arthropathy. Revista de la sociedad espanola del dolor. 2016;23(4):170-4. PMID: CN-01176960. Exclusion: 8.

192. Omar AS, Ibrahim ME, Ahmed AS, et al. Local injection of autologous platelet rich plasma and corticosteroid in treatment of lateral epicondylitis and plantar fasciitis: randomized clinical trial. Egyptian rheumatologist. 2012;34(2):43-9. PMID: CN-00896010. Exclusion: 2.

193. Orhurhu V, Khan F, Quispe RC, et al. Use of radiofrequency ablation for the management of facial pain: A systematic review. Pain physician. 2020 11;23(6):E559-E80. PMID: 33185371. Exclusion: 2.

194. Oswald J, Shahi V, Chakravarthy KV. Prospective case series on the use of peripheral nerve stimulation for focal mononeuropathy treatment. Pain manag. 2019 Nov;9(6):551-8. doi: 10.2217/pmt-2019-0028. PMID: 31686589. Exclusion: 6.

195. Ozcan S, Muz A, Yildiz Altun A, et al. Intradiscal ozone therapy for lumbar disc herniation. Cell Mol Biol (Noisy-le-grand). 2018 Apr 30;64(5):52-5. PMID: 29729693. Exclusion: 6.

196. Paoloni M, Di Sante L, Cacchio A, et al. Intramuscular oxygen-ozone therapy in the treatment of acute back pain with lumbar disc herniation: a multicenter, randomized, double-blind, clinical trial of active and simulated lumbar paravertebral injection. Spine. 2009 Jun 01;34(13):1337-44. doi: 10.1097/BRS.0b013e3181a3c18d. PMID: 19478653. Exclusion: 3.

197. Papanastassiou ID, Phillips FM, Van Meirhaeghe J, et al. Comparing effects of kyphoplasty, vertebroplasty, and non-surgical management in a systematic review of randomized and non-randomized controlled studies. Eur Spine J. 2012 Sep;21(9):1826-43. doi: 10.1007/s00586-012-2314-z. PMID: 22543412. Exclusion: 9.

198. Patel N. Twelve-month follow-up of a randomized trial assessing cooled radiofrequency denervation as a treatment for sacroiliac region pain. Pain pract. 2016 Feb;16(2):154-67. doi: 10.1111/papr.12269. PMID: 25565322. Exclusion: 6.

199. Paterson KL, Nicholls M, Bennell KL, et al. Intra-articular injection of photo-activated platelet-rich plasma in patients with knee osteoarthritis: a double-blind, randomized controlled pilot study. BMC Musculoskelet Disord. 2016;17(67) PMID: CN-01260047. Exclusion: 3.

200. Peeters CM, Leijs MJ, Reijman M, et al. Safety of intra-articular cell-therapy with culture-expanded stem cells in humans: a systematic literature review. Osteoarthritis Cartilage. 2013 Oct;21(10):1465-73. doi: 10.1016/j.joca.2013.06.025. PMID: 23831631. Exclusion: 9.

201. Peng B, Zhang Y, Hou S, et al. Intradiscal methylene blue injection for the treatment of chronic discogenic low back pain. Eur Spine J. 2007 Jan;16(1):33-8. PMID: 16496191. Exclusion: 4.

202. peng-fei S, yu-hua J. Pulsed radiofrequency versus conventional transcutaneous electrical nerve stimulation in painful shoulder: a prospective, randomized study - can you really have the conclusion? Clin Rehabil. 2011 Sep;25(9):856-7. doi: 10.1177/0269215511400270. PMID: 21865447. Exclusion: 7.

203. Pepke W, Kasten P, Beckmann NA, et al. Core Decompression and Autologous Bone Marrow Concentrate for Treatment of Femoral Head Osteonecrosis: A Randomized Prospective Study. Orthop Rev (Pavia). 2016 Mar 21;8(1):6162. doi: 10.4081/or.2016.6162. PMID: 27114808. Exclusion: 3.

204. Pernientakis SS, Masouros PT, Margiannis CP, et al. Radiofrequency kyphoplasty for the treatment of osteoporotic vertebral fractures: A review of the literature. Journal of Research & Practice on the Musculoskeletal System (JRPMS). 2018;2(3):85-8. doi: 10.22540/JRPMS-02-085. Exclusion: 9.

205. Piazzolla A, Bizzoca D, Solarino G, et al. Vertebral fragility fractures: clinical and radiological results of augmentation and fixation-a systematic review of randomized controlled clinical trials. Aging Clin Exp Res. 2020 Jul;32(7):1219-32. doi: 10.1007/s40520-019-01289-1. PMID: 31471888. Exclusion: 9.

206. Plazier M, Dekelver I, Vanneste S, et al. Occipital nerve stimulation in fibromyalgia: a double-blind placebo-controlled pilot study with a six-month follow-up. Neuromodulation. 2014 Apr;17(3):256-63. doi: 10.1111/ner.12121. PMID: 24118206. Exclusion: 2.

207. Plazier M, Ost J, Stassijns G, et al. C2 nerve field stimulation for the treatment of fibromyalgia: a prospective, double-blind, randomized, controlled cross-over study. Brain Stimul. 2015 Jul-Aug;8(4):751-7. doi: 10.1016/j.brs.2015.03.002. PMID: 25910427. Exclusion: 2.

208. Popeney CA, Alo KM. Peripheral neurostimulation for the treatment of chronic, disabling transformed migraine. Headache. 2003 Apr;43(4):369-75. PMID: 12656708. Exclusion: 6.

209. Pourtaheri S, Luo W, Cui C, et al. Vertebral augmentation is superior to nonoperative care at reducing lower back pain for symptomatic osteoporotic compression fractures: A meta-analysis. Clin Spine Surg. 2018 Oct;31(8):339-44. doi: 10.1097/BSD.0000000000000670. PMID: 29901504. Exclusion: 9.

210. Rayegani SM, Raeissadat SA, Taheri MS, et al. Does intra articular platelet rich plasma injection improve function, pain and quality of life in patients with osteoarthritis of the knee? A randomized clinical trial. Orthopedic reviews. 2014;6(3):112-7. PMID: CN-01013946. Exclusion: 2.

211. Rodrigo D, Acin P, Bermejo P. Occipital nerve stimulation for refractory chronic migraine: results of a long-term prospective study. Pain physician. 2017 Jan-Feb;20(1):151-9. PMID: 28072807. Exclusion: 4.

212. RodrÍGuez-PiÑEro M, Vargas VV, Sarmiento ASJ. Long-Term Efficacy of Ultrasound-Guided Injection of IncobotulinumtoxinA in Piriformis Syndrome. Oxford University Press / USA; 2018. p. 408-11. Exclusion: 7.

213. Romero FR, Vital RB, Zanini MA, et al. Long-term follow-up in sacroiliac joint pain patients treated with radiofrequency ablative therapy. Arq Neuropsiquiatr. 2015 Jun;73(6):476-9. doi: 10.1590/0004-282x20150049. PMID: 26083881. Exclusion: 3.

214. Sanapati J, Manchikanti L, Atluri S, et al. Do regenerative medicine therapies provide long-term relief in chronic low back pain: A systematic review and metaanalysis. Pain physician. 2018 Nov;21(6):515-40. PMID: 30508983. Exclusion: 9.

215. Santana-Pineda MM, Vanlinthout LE, Santana-Ramirez S, et al. A randomized controlled trial to compare analgesia and functional improvement after continuous neuroablative and pulsed neuromodulative radiofrequency treatment of the genicular nerves in patients with knee osteoarthritis up to one year after the intervention. Pain Med. 2021 Mar 18;12:637-52. doi: 10.1093/pm/pnaa309. PMID: 33179073. Exclusion: 2.

216. Saxena AK, Lakshman K, Sharma T, et al. Modulation of serum BDNF levels in postherpetic neuralgia following pulsed radiofrequency of intercostal nerve and pregabalin. Pain manag. 2016;6(3):217-27. doi: 10.2217/pmt.16.3. PMID: 27094801. Exclusion: 2.

217. Schoenen J, Jensen RH, Lantéri-Minet M, et al. Stimulation of the sphenopalatine ganglion (SPG) for cluster headache treatment. Pathway CH-1: a randomized, sham-controlled study. Cephalalgia. 2013 Jul;33(10):816-30. doi: 10.1177/0333102412473667. PMID: 23314784. Exclusion: 3.

218. Sen RK, Tripathy SK, Aggarwal S, et al. Early results of core decompression and autologous bone marrow mononuclear cells instillation in femoral head osteonecrosis: a randomized control study. J Arthroplasty. 2012 May;27(5):679-86. doi: 10.1016/j.arth.2011.08.008. PMID: 22000577. Exclusion: 3.

219. Shanthanna H, Chan P, McChesney J, et al. Pulsed radiofrequency treatment of the lumbar dorsal root ganglion in patients with chronic lumbar radicular pain: a randomized, placebo-controlled pilot study. J Pain Res. 2014 Jan 10;7:47-55. doi: 10.2147/JPR.S55749. PMID: 24453500. Exclusion: 2.

220. Sharan A, Huh B, Narouze S, et al. Analysis of adverse events in the management of chronic migraine by peripheral nerve stimulation. Neuromodulation. 2015 Jun;18(4):305-12. doi: 10.1111/ner.12243. PMID: 25313847. Exclusion: 6.

221. Shi MM, Cai XZ, Lin T, et al. Is there really no benefit of vertebroplasty for osteoporotic vertebral fractures? A meta-analysis. Clin Orthop. 2012 Oct;470(10):2785-99. doi: 10.1007/s11999-012-2404-6. PMID: 22729693. Exclusion: 9.

222. Shi-Ming G, Wen-Juan L, Yun-Mei H, et al. Percutaneous vertebroplasty and percutaneous balloon kyphoplasty for osteoporotic vertebral compression fracture: A metaanalysis. Indian j. 2015 Jul-Aug;49(4):377-87. doi: 10.4103/0019-5413.154892. PMID: 26229156. Exclusion: 9.

223. Shih CL, Shen PC, Lu CC, et al. A comparison of efficacy among different radiofrequency ablation techniques for the treatment of lumbar facet joint and sacroiliac joint pain: A systematic review and meta-analysis. Clin Neurol Neurosurg. 2020 Aug;195:105854. doi: 10.1016/j.clineuro.2020.105854. Exclusion: 10.

224. Shin SM, Kwak SG, Lee DG, et al. Clinical effectiveness of intra-articular pulsed radiofrequency compared to intra-articular corticosteroid injection for management of atlanto-occipital joint pain: A prospective randomized controlled pilot study. Spine. 2018 Jun 01;43(11):741-6. doi: 10.1097/BRS.0000000000002414. PMID: 28902105. Exclusion: 2.

225. Silberstein S. Efficacy of Occipital Stimulation for the Management of Intractable, Chronic Migraine: Results from a Prospective, Multicenter, Double-Blinded, Controlled Study. 2012 doi: 10.1111/j.1526-4610.2012.02174.x. Exclusion: 7.

226. Silberstein SD, Dodick DW, Saper J, et al. "Safety and efficacy of peripheral nerve stimulation of the occipital nerves for the management of chronic migraine: Results from a randomized, multicenter, double-blinded, controlled study": Corrigendum. Cephalalgia. 2014 Oct;34(11):944. doi: http://dx.doi.org/10.1177/0333102414544419. PMID: 2014-42746-015. Exclusion: 7.

227. Simopoulos TT, Kraemer J, Nagda JV, et al. Response to pulsed and continuous radiofrequency lesioning of the dorsal root ganglion and segmental nerves in patients with chronic lumbar radicular pain. Pain physician. 2008 Mar-Apr;11(2):137-44. PMID: 18354708. Exclusion: 3.

228. Singla V, Batra YK, Bharti N, et al. Steroid vs. platelet-rich plasma in ultrasound-guided sacroiliac joint injection for chronic low back pain. Pain pract. 2017 Jul;17(6):782-91. doi: 10.1111/papr.12526. PMID: 27677100. Exclusion: 4.

229. Slavin KV. Peripheral nerve stimulation for neuropathic pain. Neurother. 2008 Jan;5(1):100-6. doi: http://dx.doi.org/10.1016/j.nurt.2007.11.005. PMID: 2008-09761-011. Exclusion: 6.

230. Slotty P, Bara G, Kowatz L, et al. Occipital nerve stimulation for chronic migraine: A randomized trial on subthreshold stimulation. Cephalalgia. 2015 Jan;35(1):73-8. doi: http://dx.doi.org/10.1177/0333102414534082. PMID: 2014-55163-008. Exclusion: 2.

231. Spakova T, Rosocha J, Lacko M, et al. Treatment of knee joint osteoarthritis with autologous platelet-rich plasma in comparison with hyaluronic acid. Am J Phys Med Rehabil. 2012 May;91(5):411-7. doi: 10.1097/PHM.0b013e3182aab72. PMID: 22513879. Exclusion: 2.

232. Staples MP, Kallmes DF, Comstock BA, et al. Effectiveness of vertebroplasty using individual patient data from two randomised placebo controlled trials: meta-analysis. Bmj. 2011 Jul 12;343:3952. doi: 10.1136/bmj.d3952. PMID: 21750078. Exclusion: 9.

233. Stelzer W, Aiglesberger M, Stelzer D, et al. Use of cooled radiofrequency lateral branch neurotomy for the treatment of sacroiliac joint-mediated low back pain: a large case series. Pain Med. 2013 Jan;14(1):29-35. doi: 10.1111/pme.12014. PMID: 23279364. Exclusion: 6.

234. Stelzer W, Stelzer V, Stelzer D, et al. Influence of BMI, gender, and sports on pain decrease and medication usage after facet-medial branch neurotomy or SI joint lateral branch cooled RF-neurotomy in case of low back pain: original research in the Austrian population. J Pain Res. 2017;10:183-90. doi: 10.2147/jpr.S121897. PMID: 28144161. Exclusion: 6.

235. Stevenson M, Gomersall T, Lloyd Jones M, et al. Percutaneous vertebroplasty and percutaneous balloon kyphoplasty for the treatment of osteoporotic vertebral fractures: a systematic review and cost-effectiveness analysis. Health Technol Assess. 2014 Mar;18(17):1-290. doi: 10.3310/hta18170. PMID: 24650687. Exclusion: 9.

236. Sun H, Li C. Comparison of unilateral and bilateral percutaneous vertebroplasty for osteoporotic vertebral compression fractures: a systematic review and meta-analysis. J. 2016 Dec 01;11(1):156. doi: 10.1186/s13018-016-0479-6. PMID: 27908277. Exclusion: 3.

237. Sun H, Lu PP, Liu YJ, et al. Can unilateral kyphoplasty replace bilateral kyphoplasty in treatment of osteoporotic vertebral compression fractures? A systematic review and meta-analysis. Pain physician. 2016 Nov-Dec;19(8):551-63. PMID: 27906934. Exclusion: 3.

238. Sun HH, Zhuang SY, Hong X, et al. The efficacy and safety of using cooled radiofrequency in treating chronic sacroiliac joint pain: A PRISMA-compliant meta-analysis. Medicine (Baltimore). 2018 Feb;97(6):9809. doi: 10.1097/MD.0000000000009809. PMID: 29419679. Exclusion: 9.

239. Tabatabaee RM, Saberi S, Parvizi J, et al. Combining Concentrated Autologous Bone Marrow Stem Cells Injection With Core Decompression Improves Outcome for Patients with Early-Stage Osteonecrosis of the Femoral Head: A Comparative Study. J Arthroplasty. 2015 Sep;30(9 Suppl):11-5. doi: 10.1016/j.arth.2015.06.022. PMID: 26143238. Exclusion: 2.

240. Taylor RS, Fritzell P, Taylor RJ. Balloon kyphoplasty in the management of vertebral compression fractures: an updated systematic review and meta-analysis. Eur Spine J. 2007 Aug;16(8):1085-100. PMID: 17277923. Exclusion: 9.

241. Taylor RS, Taylor RJ, Fritzell P. Balloon kyphoplasty and vertebroplasty for vertebral compression fractures: a comparative systematic review of efficacy and safety. Spine. 2006 Nov 01;31(23):2747-55. PMID: 17077747. Exclusion: 3.

242. Tian J, Xiang L, Zhou D, et al. The clinical efficacy of vertebroplasty on osteoporotic vertebral compression fracture: a meta-analysis. Int J Surg. 2014 Dec;12(12):1249-53. doi: 10.1016/j.ijsu.2014.10.027. PMID: 25448642. Exclusion: 9.

243. Tietze DC, Geissler K, Borchers J. The effects of platelet-rich plasma in the treatment of large-joint osteoarthritis: a systematic review. Phys Sportsmed. 2014 May;42(2):27-37. doi: 10.3810/psm.2014.05.2055. PMID: 24875970. Exclusion: 9.

244. Trams E, Kulinski K, Kozar-Kaminska K, et al. The clinical use of platelet-rich plasma in knee disorders and surgery-A systematic review and meta-analysis. Life (Basel). 2020 Jun 25;10(6):25. doi: 10.3390/life10060094. PMID: 32630404. Exclusion: 2.

245. Urits I, Viswanath O, Galasso AC, et al. Platelet-rich plasma for the treatment of low back pain: a comprehensive review. Curr Pain Headache Rep. 2019 Jul 03;23(7):52. doi: 10.1007/s11916-019-0797-6. PMID: 31270622. Exclusion: 9.

246. van Tilburg CW, Schuurmans FA, Stronks DL, et al. Randomized Sham-controlled Double-Blind Multicenter Clinical Trial to Ascertain the Effect of Percutaneous Radiofrequency Treatment for Sacroiliac Joint Pain: Three-month Results. Clin J Pain. 2016 Nov;32(11):921-6. doi: 10.1097/ajp.0000000000000351. PMID: 26889616. Exclusion: 3.

247. Van Zundert J, Patijn J, Kessels A, et al. Pulsed radiofrequency adjacent to the cervical dorsal root ganglion in chronic cervical radicular pain: a double blind sham controlled randomized clinical trial. Pain. 2007 Jan;127(1-2):173-82. PMID: 17055165. Exclusion: 2.

248. Vangsness CT, Farr J, Boyd J, et al. Adult human mesenchymal stem cells delivered via intra-articular injection to the knee following partial medial meniscectomy: a randomized, double-blind, controlled study. Journal of bone and joint surgery. 2014;American volume. 96(2):90-8. PMID: CN-00985400. Exclusion: 2.

249. Vanni D, Pantalone A, Bigossi F, et al. New perspective for third generation percutaneous vertebral augmentation procedures: Preliminary results at 12 months. J Craniovertebr Junction Spine. 2012 Jul;3(2):47-51. doi: 10.4103/0974-8237.116537. PMID: 24082683. Exclusion: 4.

250. Vigneri S, Sindaco G, La Grua M, et al. Electrocatheter-mediated high-voltage pulsed radiofrequency of the dorsal root ganglion in the treatment of chronic lumbosacral neuropathic pain: a randomized controlled study. Clin J Pain. 2020 Jan;36(1):25-33. doi: 10.1097/AJP.0000000000000766. PMID: 31577546. Exclusion: 2.

251. Vuka I, Dosenovic S, Marcius T, et al. Efficacy and safety of pulsed radiofrequency as a method of dorsal root ganglia stimulation for treatment of non-neuropathic pain: a systematic review. BMC anesthesiol. 2020 May 04;20(1):105. doi: 10.1186/s12871-020-01023-9. PMID: 32366286. Exclusion: 2.

252. Vuka I, Marcius T, Dosenovic S, et al. Efficacy and safety of pulsed radiofrequency as a method of dorsal root ganglia stimulation in patients with neuropathic pain: A systematic review. Pain Med. 2020 Jun 03;03:3320-43. doi: 10.1093/pm/pnaa141. PMID: 32488240. Exclusion: 9.

253. Wan C, Dong DS, Song T. High-voltage, long-duration pulsed radiofrequency on Gasserian ganglion improves acute/subacute zoster-related trigeminal neuralgia: A randomized, double-blinded, controlled trial. Pain physician. 2019 Jul;22(4):361-8. PMID: 31337167. Exclusion: 2.

254. Wang B, Guo H, Yuan L, et al. A prospective randomized controlled study comparing the pain relief in patients with osteoporotic vertebral compression fractures with the use of vertebroplasty or facet blocking. Eur Spine J. 2016 Nov;25(11):3486-94. doi: 10.1007/s00586-016-4425-4. PMID: 26850264. Exclusion: 4.

255. Wang D, Zhang K, Han S, et al. PainVision R apparatus for assessment of efficacy of pulsed radiofrequency combined with pharmacological therapy in the treatment of postherpetic neuralgia and correlations with measurements. Biomed Res Int. 2017 Mar 5;2017:5670219. doi: 10.1155/2017/5670219. PMID: 28357404. Exclusion: 2.

256. Wang F, Zhou Q, Xiao L, et al. A randomized comparative study of pulsed radiofrequency treatment with or without selective nerve root block for chronic cervical radicular pain. Pain pract. 2017 Jun;17(5):589-95. doi: 10.1111/papr.12493. PMID: 27739217. Exclusion: 2.

257. Wang H, Sribastav SS, Ye F, et al. Comparison of percutaneous vertebroplasty and balloon kyphoplasty for the treatment of single level vertebral compression fractures: a meta-analysis of the literature. Pain physician. 2015 May-Jun;18(3):209-22. PMID: 26000665. Exclusion: 3.

258. Wang HK, Lu K, Liang CL, et al. Comparing clinical outcomes following percutaneous vertebroplasty with conservative therapy for acute osteoporotic vertebral compression fractures. Pain Med. 2010 Nov;11(11):1659-65. doi: 10.1111/j.1526-4637.2010.00959.x. PMID: 21044255. Exclusion: 6.

259. Wang L, Huang S, Li S, et al. Efficacy and safety of umbilical cord mesenchymal stem cell therapy for Rheumatoid Arthritis patients: a prospective phase I/II study. Drug Des Devel Ther. 2019;13:4331-40. doi: 10.2147/DDDT.S225613. PMID: 31908418. Exclusion: 2.

260. Waseem Z, Boulias C, Gordon A, et al. Botulinum toxin injections for low-back pain and sciatica. Cochrane Database Syst Rev. 2011 Jan 19(1):CD008257. doi: 10.1002/14651858.CD008257.pub2. PMID: 21249702. Exclusion: 9.

261. Werner CM, Osterhoff G, Schlickeiser J, et al. Vertebral body stenting versus kyphoplasty for the treatment of osteoporotic vertebral compression fractures: a randomized trial. J Bone Joint Surg Am. 2013 Apr 03;95(7):577-84. doi: 10.2106/JBJS.L.00024. PMID: 23553291. Exclusion: 4.

262. Wu CY, Lin HC, Chen SF, et al. Efficacy of pulsed radiofrequency in herpetic neuralgia: A meta-analysis of randomized controlled trials. Clin J Pain. 2020 Nov;36(11):887-95. doi: 10.1097/AJP.0000000000000867. PMID: 32701526. Exclusion: 9.

263. Wu H, Zhou J, Chen J, et al. Therapeutic efficacy and safety of radiofrequency ablation for the treatment of trigeminal neuralgia: a systematic review and meta-analysis. J Pain Res. 2019;12:423-41. doi: 10.2147/JPR.S176960. PMID: 30697063. Exclusion: 2.

264. Wu J, Zhou J, Liu C, et al. A prospective study comparing platelet-rich plasma and local anesthetic (LA)/corticosteroid in intra-articular injection for the treatment of lumbar facet joint syndrome. Pain pract. 2017 Sep;17(7):914-24. doi: 10.1111/papr.12544. PMID: 27989008. Exclusion: 3.

265. Xiang GH, Tong MJ, Lou C, et al. The role of unilateral balloon kyphoplasty for the treatment of patients with OVCFS: A systematic review and meta-analysis. Pain physician. 2018 May;21(3):209-18. PMID: 29871365. Exclusion: 3.

266. Xu J, Sun Z, Wu J, et al. Peripheral Nerve Stimulation in Pain Management: A Systematic Review. Pain physician. 2021 Mar;24(2):E131-E52. PMID: 33740342. Exclusion: 9.

267. Yang H, Liu T, Zhou J, et al. Kyphoplasty versus vertebroplasty for painful osteoporotic vertebral compression fractures-which one is better? A systematic review and meta-analysis. Int J Spine Surg. 2013;7:e45-57. doi: 10.1016/j.ijsp.2013.03.001. PMID: 25694904. Exclusion: 3.

268. Yang LY, Wang XL, Zhou L, et al. A systematic review and meta-analysis of randomized controlled trials of unilateral versus bilateral kyphoplasty for osteoporotic vertebral compression fractures. Pain physician. 2013 Jul-Aug;16(4):277-90. PMID: 23877445. Exclusion: 3.

269. Yang S, Chen C, Wang H, et al. A systematic review of unilateral versus bilateral percutaneous vertebroplasty/percutaneous kyphoplasty for osteoporotic vertebral compression fractures. Acta Orthop Traumatol Turc. 2017 Jul;51(4):290-7. doi: 10.1016/j.aott.2017.05.006. PMID: 28647158. Exclusion: 3.

270. Yang Y, Song M, Fan Y, et al. Occipital nerve stimulation for migraine: A systematic review. Pain pract. 2016 Apr;16(4):509-17. doi: 10.1111/papr.12303. PMID: 25865962. Exclusion: 9.

271. Yi X, Lu H, Tian F, et al. Recompression in new levels after percutaneous vertebroplasty and kyphoplasty compared with conservative treatment. Arch Orthop Trauma Surg. 2014 Jan;134(1):21-30. doi: 10.1007/s00402-013-1886-3. PMID: 24287674. Exclusion: 3.

272. Yin P, Li Z, Zhu S, et al. The treatment of osteoporotic thoraco-lumbar burst fractures by unilateral percutaneous kyphoplasty: A prospective observation study. Eur J Pain. 2020 March;24(3):659-64. doi: 10.1002/ejp.1516. PMID: 31782863. Exclusion: 6.

273. Yokoyama K, Kawanishi M, Yamada M, et al. Comparative study of percutaneous vertebral body perforation and vertebroplasty for the treatment of painful vertebral compression fractures. AJNR Am J Neuroradiol. 2012 Apr;33(4):685-9. doi: 10.3174/ajnr.A2847. PMID: 22194379. Exclusion: 6.

274. Yoon YM, Han SR, Lee SJ, et al. The efficacy of pulsed radiofrequency treatment of cervical radicular pain patients. Korean J. 2014 Sep;11(3):109-12. doi: 10.14245/kjs.2014.11.3.109. PMID: 25346754. Exclusion: 4.

275. Yu W, Xu W, Jiang X, et al. Risk factors for recollapse of the augmented vertebrae after percutaneous vertebral augmentation: a systematic review and meta-analysis. World Neurosurg. 2018 Mar;111:119-29. doi: 10.1016/j.wneu.2017.12.019. PMID: 29253703. Exclusion: 9.

276. Zambello A, Fara B, Tabaracci G, et al. Epidural steroid injection vs paravertebral O2O3 infiltration for symptomatic herniated disc refractory to conventional treatment: A prospective randomized study. Rivista Italiana di Ossigeno-Ozonoterapia. 2006 10/01;5:123-7. Exclusion: 4.

277. Zhan Y, Jiang J, Liao H, et al. Risk factors for cement leakage after vertebroplasty or kyphoplasty: a meta-analysis of published evidence. World Neurosurg. 2017 May;101:633-42. doi: 10.1016/j.wneu.2017.01.124. PMID: 28192270. Exclusion: 9.

278. Zhang C, Fang X, Huang Z, et al. Addition of bone marrow stem cells therapy achieves better clinical outcomes and lower rates of disease progression compared with core decompression alone for early stage osteonecrosis of the femoral head: a systematic review and meta-analysis. J Am Acad Orthop Surg. 2020 Dec 1;28:973-9. doi: 10.5435/JAAOS-D-19-00816. PMID: 32118614. Exclusion: 9.

279. Zhang L, Wang J, Feng X, et al. A comparison of high viscosity bone cement and low viscosity bone cement vertebroplasty for severe osteoporotic vertebral compression fractures. Clin Neurol Neurosurg. 2015 Feb;129:10-6. doi: 10.1016/j.clineuro.2014.11.018. PMID: 25524481. Exclusion: 4.

280. Zhang L, Zhai P. A comparison of percutaneous vertebroplasty versus conservative treatment in terms of treatment effect for osteoporotic vertebral compression fractures: a meta-analysis. Surg Innov. 2020 Feb;27(1):19-25. doi: 10.1177/1553350619869535. PMID: 31423902. Exclusion: 9.

281. Zhang T, Wang Y, Zhang P, et al. What are the risk factors for adjacent vertebral fracture after vertebral augmentation? A meta-analysis of published studies. Global spine j. 2020 Dec 04:2192568220978223. doi: 10.1177/2192568220978223. PMID: 33272041. Exclusion: 9.

282. Zhang Y, Ma Y, Jiang J, et al. Treatment of the lumbar disc herniation with intradiscal and intraforaminal injection of oxygen-ozone. J Back Musculoskeletal Rehabil. 2013;26(3):317-22. doi: 10.3233/BMR-130386. PMID: 23893147. Exclusion: 6.

283. Zhang Y, Song J, Hou Y, et al. Clinical research about the improved PVP method in treatment of acute osteoporotic vertebral compression fractures. J. 2019 Sep-Dec;27(3):2309499019864667. doi: 10.1177/2309499019864667. PMID: 31382815. Exclusion: 5.

284. Zhao D, Cui D, Wang B, et al. Treatment of early stage osteonecrosis of the femoral head with autologous implantation of bone marrow-derived and cultured mesenchymal stem cells. Bone. 2012 Jan;50(1):325-30. doi: 10.1016/j.bone.2011.11.002. PMID: 22094904. Exclusion: 2.

285. Zhao G, Liu X, Li F. Balloon kyphoplasty versus percutaneous vertebroplasty for treatment of osteoporotic vertebral compression fractures (OVCFs). Osteoporos Int. 2016 Sep;27(9):2823-34. doi: 10.1007/s00198-016-3610-y. PMID: 27121344. Exclusion: 4.

286. Zheng Y, Gu M, Shi D, et al. Tomography-guided palisade sacroiliac joint radiofrequency neurotomy versus celecoxib for ankylosing spondylitis: a open-label, randomized, and controlled trial. Rheumatol Int. 2014 Sep;34(9):1195-202. doi: 10.1007/s00296-014-2959-5. PMID: 24518967. Exclusion: 3.

287. Zhiyong C, Yun T, Hui F, et al. Unilateral versus bilateral balloon kyphoplasty for osteoporotic vertebral compression fractures: a systematic review of overlapping meta-analyses. Pain physician. 2019 Jan;22(1):15-28. PMID: 30700065. Exclusion: 3.

288. Zhu Y, Cheng J, Yin J, et al. Therapeutic effect of kyphoplasty and balloon vertebroplasty on osteoporotic vertebral compression fracture: A systematic review and meta-analysis of randomized controlled trials. Medicine (Baltimore). 2019 Nov;98(45):e17810. doi: 10.1097/MD.0000000000017810. PMID: 31702634. Exclusion: 3.

Appendix C. Quality Rating Criteria

Randomized Controlled Trials

Selection Bias

- Randomization Sequence Generation: Is the method used to generate the allocation sequence described in sufficient detail to allow an assessment of whether it should produce comparable groups?
- Allocation Concealment: Is the method used to conceal the allocation sequence described in sufficient detail to determine whether intervention allocations could have been foreseen in advance of, or during, enrollment?

Performance Bias

- Blinding of Participants and Personnel: Are the measures used to blind study participants and personnel from knowledge of which intervention a participant received adequate to ensure blinding was effective?

Detection Bias

- Blinding of Outcome Assessments: Are measures used to blind outcome assessors from knowledge of which intervention a participant received adequate to ensure the intended blinding was effective.

Attrition Bias

- Incomplete Outcome Data: To what degree do missing data and attrition likely affect outcomes (20% overall or differential between groups is considered high risk)?

Reporting Bias

- Selective Reporting: Do authors pre-specify outcomes and report findings for all outcomes?

Other Sources of Bias

- State any important concerns about bias not addressed in other domains. Primarily assessed on concerns of contamination, confounding, and baseline differences.

Selections for each criteria included: **Yes, No,** and **Unclear**.

Definition of Ratings Based on Above Criteria

Good

- Least risk of bias, results generally considered valid
- Employ valid methods for selection, inclusion, and allocation of patients to treatment; report similar baseline characteristics in different treatment groups; clearly describe attrition and have low attrition; use appropriate means for preventing bias (e.g., blinding

of patients, care providers, and outcomes assessors); and use appropriate analytic methods (e.g., intention-to-treat analysis)

Fair

- Susceptible to some bias but not enough to necessarily invalidate results
- May not meet all criteria for good quality, but no flaw is likely to cause major bias; the study may be missing information making it difficult to assess limitations and potential problems
- Category is broad; studies with this rating will vary in strengths and weaknesses; some fair-quality studies are likely to be valid, while others may be only possibly valid

Poor

- Significant flaws that imply biases of various kinds that may invalidate results; "fatal flaws" in design, analysis or reporting; large amounts of missing information; discrepancies in reporting; or serious problems with intervention delivery
- Studies are at least as likely to reflect flaws in the study design or execution as the true difference between the compared interventions
- Considered to be less reliable than higher quality studies when synthesizing the evidence, particularly if discrepancies between studies are present

Source: Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 6.2. The Cochrane Collaboration, 2021. http://handbook.cochrane.org. Used with permission.

Appendix D. Detailed Statistical Methods

Random effects meta-analysis using the profile likelihood method was performed to combine randomized trials of vertebroplasty versus sham vertebroplasty or usual care. Because of the potential impact of the type of control group on treatment effects, the primary analysis was stratified according to whether the control group received a sham intervention or usual care. Separate analyses were performed for the prespecified followup duration categories (1 to 2 weeks, 2 to 4 weeks, 1 to 6 months, 6 to 12 months, and 12 months and longer). For studies that reported outcomes at more than one time point within a duration category, we used data for the longest duration within the category.

For continuous outcomes, mean differences was the effect measure for pain, health status, quality of life, and mental health outcomes, and pain scales were converted to a common 0 to 10 scale. For function, standard mean difference (SMD) was the effect measure due to differences in the scales used (most commonly, RDQ and ODI). We also pooled data separately for RDQ and ODI, using the original scales, to aid in interpretation of results. For health status, we pooled SF-36 Physical Component Summary (PCS) and Mental Component Summary (MCS) scores. For quality of life, we pooled the EQ-5D (a generic measure of quality of life) separately from the QUALEFFO score (an osteoporosis-specific measure of quality of life). For both mean difference and SMD, adjusted or unadjusted mean difference from the analysis of covariance or other appropriate regression models was used if available, followed by difference in followup score and change score. There were no missing SDs for followup or change scores that needed imputation. When reported SDs were implausibly small, we re-calculated SDs based on the assumption that they were actually standard errors and misreported as SDs (a conservative [i.e., resulting in less precise estimates] assumption); sensitivity analysis was conducted using SDs as reported. Estimates were slightly larger in the sensitivity analysis but did not change overall conclusions and are not described further.

Pooled relative risks (RR) were estimated for binary outcomes including pain response, function improvement, mortality, medication use, and incident vertebral fracture. When a study reported dichotomized pain or function response using multiple thresholds, data were selected for inclusion in the meta-analysis in the following descending order: 30 percent or more improvement, an alternative numerical threshold closest to 30 percent or more improvement, and "moderate" or "good" (or similar categories, for pain relief) on a categorical scale.

Statistical heterogeneity was assessed using the I^2 statistic[51] and the Cochran's χ^2 test. All meta-analyses were conducted using Stata/SE 16.1 (StataCorp, College Station, TX). For pain intensity, which was the most commonly evaluated outcome, a stratified analysis was performed based on the trials' pain duration inclusion criteria (acute [<4 weeks], acute or subacute [up to 6 to 10 weeks], acute through chronic [up to 12 months], or subacute or chronic only [acute excluded]); because pain inclusion criteria were overlapping and studies using the same inclusion criterion (e.g. up to 12 months) could enroll populations with substantially different average pain duration, we also analyzed pain duration according to the mean/median at enrollment (<4 weeks, 4 to 8 weeks, or ≥8 weeks). Stratified analyses were also performed on PMMA volume (<5 ml or ≥5 ml), MRI findings of bone marrow edema required for inclusion (yes or no), and quality (good, fair, or poor). For function, which was evaluated in four to seven trials (depending on time point), stratified analysis was limited to mean/median pain duration and study quality. For other outcomes, due to small numbers of trials, analyses were only stratified by control type. Differences in treatment effects among subgroups were evaluated using meta-regression. For analyses with at least 10 trials, small sample effects were evaluated using funnel plots and the Egger test.

Appendix E. Grading the Strength of Evidence

Criteria:

- Study limitations (low, medium, or high level of study limitations)
  - Rated according to the degree to which studies for a given outcome are likely to reduce bias based on study design and conduct across individual studies. Evidence was rated down for study limitations when higher-quality studies were not available or if there were few higher-quality trials and estimates differed in analyses stratified by study quality.
- Consistency (consistent, inconsistent, or unknown/not applicable)
  - Rated by degree to which studies find similar magnitude of effect (i.e., range sizes are similar) or same direction of effect (i.e., effect sizes have the same sign). When pooled estimates were available, evidence was rated inconsistent if the I^2 was greater than 40 percent, unless findings were consistent in subgroup analyses and there were sufficient trials (>20) for subgroup analyses to be informative.
- Directness (direct or indirect)
  - Rated by degree to which the outcome is directly or indirectly related to health outcomes of interest. Patient centered outcomes are considered direct
- Precision (precise or imprecise)
  - Describes the level of certainty of the estimate of effect for a particular outcome with a precise estimate being on that allows a clinically useful conclusion. This may be based on sufficiency of sample size and number of events, and if these are adequate, the interpretation of the confidence interval. Evidence was rated imprecise if the pooled estimate confidence interval (CI) crossed the null and the threshold for small magnitude of effect.
- Reporting bias (suspected or undetected)
  - Publication bias, selective outcome reporting, and selective analysis reporting are types of reporting bias. Reporting bias is difficult to assess as systematic identification of unpublished evidence is challenging. If sufficient numbers of RCTs (>10) are available, quantitative funnel plot analysis may be done.

An overall SOE grade of high, moderate, low, or insufficient was assigned, based on a four-level scale by evaluating and weighing the combined results of the above domains. Bodies of evidence consisting of RCTs are initially considered as high strength. The strength of the evidence may be downgraded based on limitations identified in the domains described above. The SOE levels were defined as:

- High—High confidence that the estimate of effect lies close to the true effect for this outcome. The body of evidence has few or no deficiencies. We believe that the findings are stable, i.e., another study would not change the conclusions.
- Moderate—Moderate confidence that the estimate of effect lies close to the true effect for this outcome. The body of evidence has some deficiencies. We believe that the findings are likely to be stable, but some doubt remains.
- Low—Limited confidence that the estimate of effect lies close to the true effect for this outcome. The body of evidence has major or numerous deficiencies (or both). We believe that additional evidence is needed before concluding either that the findings are stable or that the estimate of effect is close to the true effect.

- Insufficient—No evidence, unable to estimate an effect, ore no confidence in the estimate of effect for this outcome. No evidence is available or the body of evidence has unacceptable deficiencies, precluding reaching a conclusion.

Appendix F. List of Included Studies

1. Amirdelfan K, Bae H, McJunkin T, et al. Allogeneic Mesenchymal Precursor Cells Treatment for Chronic Low Back Pain Associated with Degenerative Disc Disease: A Prospective Randomized, Placebo-Controlled 36-Month Study of Safety and Efficacy. Spine J. 2020 Oct 09;09:09. doi: https://dx.doi.org/10.1016/j.spinee.2020.10.004. PMID: 33045417.
2. Berenson J, Pflugmacher R, Jarzem P, et al. Balloon kyphoplasty versus non-surgical fracture management for treatment of painful vertebral body compression fractures in patients with cancer: a multicentre, randomised controlled trial. The lancet. 2011;Oncology. 12(3):225-35. PMID: CN-00787315.
3. Blasco J, Martinez-Ferrer A, Macho J, et al. Effect of vertebroplasty on pain relief, quality of life, and the incidence of new vertebral fractures: a 12-month randomized follow-up, controlled trial. J Bone Miner Res. 2012 May;27(5):1159-66. doi: https://dx.doi.org/10.1002/jbmr.1564. PMID: 22513649.
4. Boonen S, Van Meirhaeghe J, Bastian L, et al. Balloon kyphoplasty for the treatment of acute vertebral compression fractures: 2-year results from a randomized trial. J Bone Miner Res. 2011 Jul;26(7):1627-37. doi: https://dx.doi.org/10.1002/jbmr.364. PMID: 21337428.
5. Buchbinder R, Osborne RH, Ebeling PR, et al. A randomized trial of vertebroplasty for painful osteoporotic vertebral fractures. N Engl J Med. 2009 Aug 06;361(6):557-68. doi: https://dx.doi.org/10.1056/NEJMoa0900429. PMID: 19657121.
6. Cady R, Saper J, Dexter K, et al. A double-blind, placebo-controlled study of repetitive transnasal sphenopalatine ganglion blockade with tx360(R) as acute treatment for chronic migraine. Headache. 2015 Jan;55(1):101-16. doi: https://dx.doi.org/10.1111/head.12458. PMID: 25338927.
7. Cady RK, Saper J, Dexter K, et al. Long-term efficacy of a double-blind, placebo-controlled, randomized study for repetitive sphenopalatine blockade with bupivacaine vs. saline with the Tx360 device for treatment of chronic migraine. Headache. 2015 Apr;55(4):529-42. doi: https://dx.doi.org/10.1111/head.12546. PMID: 25828648.
8. Chen D, An ZQ, Song S, et al. Percutaneous vertebroplasty compared with conservative treatment in patients with chronic painful osteoporotic spinal fractures. J Clin Neurosci. 2014 Mar;21(3):473-7. doi: https://dx.doi.org/10.1016/j.jocn.2013.05.017. PMID: 24315046.
9. Childers MK, Wilson DJ, Gnatz SM, et al. Botulinum toxin type A use in piriformis muscle syndrome: a pilot study. Am J Phys Med Rehabil. 2002 Oct;81(10):751-9. PMID: 12362115.
10. Clark W, Bird P, Gonski P, et al. Safety and efficacy of vertebroplasty for acute painful osteoporotic fractures (VAPOUR): a multicentre, randomised, double-blind, placebo-controlled trial. Lancet. 2016 Oct 01;388(10052):1408-16. doi: https://dx.doi.org/10.1016/S0140-6736(16)31341-1. PMID: 27544377.
11. Cohen SP, Hurley RW, Buckenmaier CC, 3rd, et al. Randomized placebo-controlled study evaluating lateral branch radiofrequency denervation for sacroiliac joint pain. Anesthesiology. 2008 Aug;109(2):279-88. doi: https://dx.doi.org/10.1097/ALN.0b013e31817f4c7c. PMID: 18648237.
12. Comstock BA, Sitlani CM, Jarvik JG, et al. Investigational vertebroplasty safety and efficacy trial (INVEST): patient-reported outcomes through 1 year. Radiology. 2013 Oct;269(1):224-31. doi: https://dx.doi.org/10.1148/radiol.13120821. PMID: 23696683.

13. Deer T, Pope J, Benyamin R, et al. Prospective, Multicenter, Randomized, Double-Blinded, Partial Crossover Study to Assess the Safety and Efficacy of the Novel Neuromodulation System in the Treatment of Patients With Chronic Pain of Peripheral Nerve Origin. Neuromodulation. 2016 Jan;19(1):91-100. doi: https://dx.doi.org/10.1111/ner.12381. PMID: 26799373.

14. Diamond T, Clark W, Bird P, et al. Early vertebroplasty within 3 weeks of fracture for acute painful vertebral osteoporotic fractures: subgroup analysis of the VAPOUR trial and review of the literature. Eur Spine J. 2020 Jul;29(7):1606-13. doi: https://dx.doi.org/10.1007/s00586-020-06362-2. PMID: 32170438.

15. Farrokhi MR, Alibai E, Maghami Z. Randomized controlled trial of percutaneous vertebroplasty versus optimal medical management for the relief of pain and disability in acute osteoporotic vertebral compression fractures. J Neurosurg Spine. 2011 May;14(5):561-9. doi: https://dx.doi.org/10.3171/2010.12.SPINE10286. PMID: 21375382.

16. Firanescu CE, de Vries J, Lodder P, et al. Percutaneous Vertebroplasty is no Risk Factor for New Vertebral Fractures and Protects Against Further Height Loss (VERTOS IV). Cardiovasc Intervent Radiol. 2019 Jul;42(7):991-1000. doi: https://dx.doi.org/10.1007/s00270-019-02205-w. PMID: 30941490.

17. Firanescu CE, de Vries J, Lodder P, et al. Vertebroplasty versus sham procedure for painful acute osteoporotic vertebral compression fractures (VERTOS IV): randomised sham controlled clinical trial. Bmj. 2018 05 09;361:k1551. doi: https://dx.doi.org/10.1136/bmj.k1551. PMID: 29743284.

18. Fishman LM, Anderson C, Rosner B. BOTOX and physical therapy in the treatment of piriformis syndrome. Am J Phys Med Rehabil. 2002 Dec;81(12):936-42. doi: 10.1097/00002060-200212000-00009. PMID: 12447093.

19. Fishman LM, Wilkins AN, Rosner B. Electrophysiologically identified piriformis syndrome is successfully treated with incobotulinum toxin a and physical therapy. Muscle Nerve. 2017 08;56(2):258-63. doi: https://dx.doi.org/10.1002/mus.25504. PMID: 27935076.

20. Gallucci M, Limbucci N, Zugaro L, et al. Sciatica: treatment with intradiscal and intraforaminal injections of steroid and oxygen-ozone versus steroid only. Radiology. 2007 Mar;242(3):907-13. PMID: 17209164.

21. Hansen E, Simony A, Carreon L, et al. Vertebroplasty vs. SHAM for Treating Osteoporotic Vertebral Compression Fractures: A Double Blind RCT. Integr J Orthop Traumatol. 2019;2(4):1-6. doi: 10.31038/IJOT.2019244.

22. Haseeb AESA, Abd El Hares AEH, Abd El Moez KM, et al. Comparative Study between Treatment of Lumbar Disc Herniation with Intra Discal Ozone and Transforaminal Steroid Injection versus Steroid Injection only. The Egyptian Journal of Hospital Medicine. 2019;74(4):705-20. doi: 10.12816/ejhm.2019.24068.

23. Kallewaard JW, Wintraecken VM, Geurts JW, et al. A multicenter randomized controlled trial on the efficacy of intradiscal methylene blue injection for chronic discogenic low back pain: the IMBI study. Pain. 2019 Apr;160(4):945-53. doi: https://dx.doi.org/10.1097/j.pain.0000000000001475. PMID: 30730862.

24. Kallmes DF, Comstock BA, Heagerty PJ, et al. A randomized trial of vertebroplasty for osteoporotic spinal fractures. N Engl J Med. 2009 Aug 06;361(6):569-79. doi: https://dx.doi.org/10.1056/NEJMoa0900563. PMID: 19657122.

25. Klazen CA, Lohle PN, de Vries J, et al. Vertebroplasty versus conservative treatment in acute osteoporotic vertebral compression fractures (Vertos II): an open-label randomised trial. Lancet. 2010 Sep 25;376(9746):1085-92. doi: https://dx.doi.org/10.1016/S0140-6736(10)60954-3. PMID: 20701962.

26. Kroll HR, Kim D, Danic MJ, et al. A randomized, double-blind, prospective study comparing the efficacy of continuous versus pulsed radiofrequency in the treatment of lumbar facet syndrome. J Clin Anesth. 2008 Nov;20(7):534-7. doi: https://dx.doi.org/10.1016/j.jclinane.2008.05.021. PMID: 19041042.

27. Kroon F, Staples M, Ebeling PR, et al. Two-year results of a randomized placebo-controlled trial of vertebroplasty for acute osteoporotic vertebral fractures. J Bone Miner Res. 2014 Jun;29(6):1346-55. PMID: 24967454.

28. Leali PT, Solla F, Maestretti G, et al. Safety and efficacy of vertebroplasty in the treatment of osteoporotic vertebral compression fractures: a prospective multicenter international randomized controlled study. Clin. 2016 Sep-Dec;13(3):234-6. doi: https://dx.doi.org/10.11138/ccmbm/2016.13.3.234. PMID: 28228788.

29. McCormick ZL, Choi H, Reddy R, et al. Randomized prospective trial of cooled versus traditional radiofrequency ablation of the medial branch nerves for the treatment of lumbar facet joint pain. Reg Anesth Pain Med. 2019 03;44(3):389-97. doi: https://dx.doi.org/10.1136/rapm-2018-000035. PMID: 30777903.

30. Mekhail NA, Estemalik E, Azer G, et al. Safety and Efficacy of Occipital Nerves Stimulation for the Treatment of Chronic Migraines: Randomized, Double-blind, Controlled Single-center Experience. Pain pract. 2017 06;17(5):669-77. doi: https://dx.doi.org/10.1111/papr.12504. PMID: 27779368.

31. Misirlioglu TO, Akgun K, Palamar D, et al. Piriformis syndrome: comparison of the effectiveness of local anesthetic and corticosteroid injections: a double-blinded, randomized controlled study. Pain physician. 2015 Mar-Apr;18(2):163-71. PMID: 25794202.

32. Moussa WM, Khedr W, Elsawy M. Percutaneous pulsed radiofrequency treatment of dorsal root ganglion for treatment of lumbar facet syndrome. Clin Neurol Neurosurg. 2020 Dec;199:106253. doi: https://dx.doi.org/10.1016/j.clineuro.2020.106253. PMID: 33045627.

33. Nilachandra L, Darendrajit L, Joy Singh A, et al. Ozone nucleolysis in the management of prolapsed lumbar intervertebral disc in reducing pain and disability: a randomized controlled study. PARIPEX-Indian Journal of Research. 2016 Nov;5(11):51-4.

34. Patel N, Gross A, Brown L, et al. A randomized, placebo-controlled study to assess the efficacy of lateral branch neurotomy for chronic sacroiliac joint pain. Pain Med. 2012 Mar;13(3):383-98. doi: https://dx.doi.org/10.1111/j.1526-4637.2012.01328.x. PMID: 22299761.

35. Peng B, Pang X, Wu Y, et al. A randomized placebo-controlled trial of intradiscal methylene blue injection for the treatment of chronic discogenic low back pain. Pain. 2010 Apr;149(1):124-9. doi: https://dx.doi.org/10.1016/j.pain.2010.01.021. PMID: 20167430.

36. Rousing R, Andersen MO, Jespersen SM, et al. Percutaneous vertebroplasty compared to conservative treatment in patients with painful acute or subacute osteoporotic vertebral fractures: three-months follow-up in a clinical randomized study. Spine. 2009 Jun 01;34(13):1349-54. doi: https://dx.doi.org/10.1097/BRS.0b013e3181a4e628. PMID: 19478654.

37. Rousing R, Hansen KL, Andersen MO, et al. Twelve-months follow-up in forty-nine patients with acute/semiacute osteoporotic vertebral fractures treated conservatively or with percutaneous vertebroplasty: a clinical randomized study. Spine. 2010 Mar 01;35(5):478-82. doi: https://dx.doi.org/10.1097/BRS.0b013e3181b71bd1. PMID: 20190623.

38. Saper JR, Dodick DW, Silberstein SD, et al. Occipital nerve stimulation for the treatment of intractable chronic migraine headache: ONSTIM feasibility study. Cephalalgia. 2011 Feb;31(3):271-85. doi: https://dx.doi.org/10.1177/0333102410381142. PMID: 20861241.

39. Serra G, Marchioretto F. Occipital nerve stimulation for chronic migraine: a randomized trial. Pain physician. 2012 May-Jun;15(3):245-53. PMID: 22622909.

40. Silberstein SD, Dodick DW, Saper J, et al. Safety and efficacy of peripheral nerve stimulation of the occipital nerves for the management of chronic migraine: results from a randomized, multicenter, double-blinded, controlled study. Cephalalgia. 2012 Dec;32(16):1165-79. doi: https://dx.doi.org/10.1177/0333102412462642. PMID: 23034698.

41. Staples MP, Howe BM, Ringler MD, et al. New vertebral fractures after vertebroplasty: 2-year results from a randomised controlled trial. Arch Osteoporos. 2015;10:229. doi: https://dx.doi.org/10.1007/s11657-015-0229-0. PMID: 26272712.

42. Tekin I, Mirzai H, Ok G, et al. A comparison of conventional and pulsed radiofrequency denervation in the treatment of chronic facet joint pain. Clin J Pain. 2007 Jul-Aug;23(6):524-9. PMID: 17575493.

43. Tuakli-Wosornu YA, Terry A, Boachie-Adjei K, et al. Lumbar Intradiskal Platelet-Rich Plasma (PRP) Injections: A Prospective, Double-Blind, Randomized Controlled Study. Pm R. 2016 Jan;8(1):1-10; quiz doi: https://dx.doi.org/10.1016/j.pmrj.2015.08.010. PMID: 26314234.

44. Van Meirhaeghe J, Bastian L, Boonen S, et al. A randomized trial of balloon kyphoplasty and nonsurgical management for treating acute vertebral compression fractures: vertebral body kyphosis correction and surgical parameters. Spine. 2013 May 20;38(12):971-83. doi: https://dx.doi.org/10.1097/BRS.0b013e31828e8e22. PMID: 23446769.

45. Venmans A, Klazen CA, van Rooij WJ, et al. Postprocedural CT for perivertebral cement leakage in percutaneous vertebroplasty is not necessary--results from VERTOS II. Neuroradiology. 2011 Jan;53(1):19-22. doi: https://dx.doi.org/10.1007/s00234-010-0705-6. PMID: 20442991.

46. Voormolen MH, Mali WP, Lohle PN, et al. Percutaneous vertebroplasty compared with optimal pain medication treatment: short-term clinical outcome of patients with subacute or chronic painful osteoporotic vertebral compression fractures. The VERTOS study. AJNR Am J Neuroradiol. 2007 Mar;28(3):555-60. PMID: 17353335.

47. Wardlaw D, Cummings SR, Van Meirhaeghe J, et al. Efficacy and safety of balloon kyphoplasty compared with non-surgical care for vertebral compression fracture (FREE): a randomised controlled trial. Lancet. 2009 Mar 21;373(9668):1016-24. doi: https://dx.doi.org/10.1016/S0140-6736(09)60010-6. PMID: 19246088.

48. Yang EZ, Xu JG, Huang GZ, et al. Percutaneous Vertebroplasty Versus Conservative Treatment in Aged Patients With Acute Osteoporotic Vertebral Compression Fractures: A Prospective Randomized Controlled Clinical Study. Spine. 2016 Apr;41(8):653-60. doi: https://dx.doi.org/10.1097/BRS.0000000000001298. PMID: 26630417.

Appendix G. Data Abstraction Tables

Table G-1. Trials of vertebral augmentation procedures to treat vertebral compression fractures – study characteristics

Vertebral Augmentation Procedure	Author, Year Trial	Study Design Duration	Setting/Provider Type Country	Eligibility Criteria	Interventions
Vertebroplasty	Blasco, 2012	RCT 12 months	1 center, interventional radiology Spain	Osteoporotic VCF from T4 to L5 with clinical onset <12 months, confirmed by spine radiograph and by the presence of edema on MRI or activity on bone scan, and pain VAS (0 to 10) ≥4 Excluded: untreatable coagulopathy, active local or systemic infection, current malignancy, vertebral canal occupation by a fragment of the vertebral body or nonosteoporotic VCF, active associated disorders (i.e., fibromyalgia or spondyloarthropathies) or other disorders (i.e., dementia) potentially interfering with assessment of quality of life and pain	A: Vertebroplasty: Most procedure performed with bilateral transpedicular 10-gauge or 13-gauge needle injection of PMMA cement (Exolent Spine, Elmdown, London, UK, mean volume not reported). CT immediately or 24 hours after the procedure B: Usual care: Analgesics and nasal calcitonin (doses not reported); intrathecal infusion (25 μg fentanyl and 1.5 mg bupivacaine) for breakthrough pain or if medications ineffective
Vertebroplasty	Buchbinder, 2009 Additional publications: Kroon, 2014 and Staples 2015	RCT 24 months (see Kroon 2014 for 12 and 24 month results)	4 centers, interventional radiology Australia	Back pain ≤12 months duration, 1 or 2 recent vertebral fractures (defined as vertebral collapse of grade 1 or higher [scale 0 to 3, higher numbers indicating greater vertebral collapse], and edema, a fracture line, or both within the vertebral body on MRI Excluded: >2 recent vertebral fractures, spinal cancer, neurologic complications, osteoporotic vertebral collapse >90%, fracture through or destruction of the posterior wall, retro pulsed bony fragment or bony fragments impinging on the spinal cord, medical conditions that would make the patient ineligible for emergency decompressive surgery if needed, previous vertebroplasty	A: Vertebroplasty: Periosteum of the posterior lamina infiltrated with local anesthetic, 13-gauge needle was placed posterolaterally relative to the eye of the pedicle and guided into the anterior two-thirds of the fractured vertebral body and approximately 3 ml prepared PMMA slowly injected into the vertebral body (mean 2.8 ml [SD 1.2]); satisfactory infiltration of the vertebral body confirmed radiographically B: Sham vertebroplasty: Periosteum of the posterior lamina infiltrated with local anesthetic, 13-gauge needle inserted as for vertebroplasty, then the central sharp stylet was replaced with a blunt stylet; to simulate vertebroplasty, the vertebral body was gently tapped; PMMA was prepared so that its smell permeated the room
Vertebroplasty	Staples, 2015 Secondary publication of Buchbinder 2009	RCT additional followup 2 years	see Buchbinder, 2009	see Buchbinder, 2009	see Buchbinder, 2009
Vertebroplasty	Kroon, 2014 Secondary publication of Buchbinder, 2009	RCT 2 years	see Buchbinder, 2009	see Buchbinder, 2009	see Buchbinder, 2009

Vertebral Augmentation Procedure	Author, Year Trial	Study Design Duration	Setting/Provider Type Country	Eligibility Criteria	Interventions
Vertebroplasty	Chen, 2014	RCT 12 months	1 center, orthopedic surgery China	Chronic osteoporotic compression spinal fractures on MRI (low signal on T1-weighted and high signal on T2-weighted scans) and persistent back pain for ≥3 months Excluded: NR	A: Vertebroplasty: Bone puncture needle (13 G, Cook Medical, Bloomington, IN, USA) was placed transpedicularly in the fractured vertebra. After removal of the inner needle, commercially available PMMA (Osteo-Firm, Cook Medical) was injected into the fractured vertebra under continuous fluoroscopic monitoring (mean 3.6 ml [range 3 to 6 mL]). B: Usual care: Offered brace treatment, analgesia, general mobilizing physiotherapy, and osteoporotic medication treatment, including vitamin D and bisphosphonate
Vertebroplasty	Clark, 2016 VAPOUR	RCT 6 months	4 centers, interventional radiology Australia	≥60 years with back pain of <6 weeks, NRS score ≥7, MRI confirming 1 or 2 recent fractures. Excluded: chronic back pain requiring opiate use, substantial fracture retropulsion, acute infection, spinal malignancy, neurological complications, and >2 vertebral fractures.	A: Vertebroplasty: 11-guage or 13-gauge vertebroplasty needle introduced into the vertebral body with unipedicular or bipedicular technique with fluoroscopic guidance, using an AVAMAX kit (CareFusion Corporation). Aimed to fill vertebral body with PMMA from superior to inferior endplate, mid-pedicle to mid-pedicle in frontal projection, and from anterior cortex to posterior third of vertebral body (mean 7.5 ml [SD 2.8]) B: Sham vertebroplasty: Subcutaneous lidocaine but not periosteal numbing. Manual skin pressure and regular tapping on the needle was done, mimicking vertebroplasty needle advanced, with conversation about PMMA mixing and injection to suggest vertebroplasty was being done.
Vertebroplasty	Diamond, 2020 VAPOUR	RCT 6 months	4 centers, interventional radiology Australia	Patients included in the VAPOUR (Clark, 2016) trial with fractures ≤3 weeks in duration.	See Clark, 2016
Vertebroplasty	Farrokhi, 2011	RCT 36 months	1 center, neurosurgery Iran	VCF with 10 to 70% loss of vertebral body height; severe back pain related to VCF refractory to medications for ≥4 weeks and ≤1 year; focal tenderness on examination related to level of fracture; T-score <-2.5 on bone densitometry; vacuum phenomenon or bone marrow edema of vertebral fracture on MR imaging; unresponsive to medical therapy Excluded: uncorrected coagulopathy; local or systemic infection; secondary osteoporosis; impaired cardiopulmonary function; dementia; posterior wall defect of the VB on CT studies; painless VCF; spinal cancer; traumatic fracture; and neurological complications	A: Vertebroplasty: 11-gauge needle inserted into the vertebral body via a unilateral parapedicular approach in 35 patients (87.5%) and via a bilateral transpedicular approach in 5 patients (12.5%). A bilateral transpedicular approach was used only if there was inadequate instillation of cement with the unilateral approach under fluoroscopy. A PMMA mixture was injected into the vertebral body (mean 3.5 ml for 1 level fracture and 5 ml for multilevel fractures) B: Usual care: Acetaminophen 250 mg with codeine twice daily, ibuprofen 400 mg twice daily, calcium 1000 mg daily, vitamin D 400 IU daily, alendronate 70 mg orally once weekly, and calcitonin 200 IU daily

Vertebral Augmentation Procedure	Author, Year Trial	Study Design Duration	Setting/Provider Type Country	Eligibility Criteria	Interventions
Vertebroplasty	Firanescu, 2018 & 2019 VERTOS IV	RCT 12 months	4 centers, interventional radiology the Netherlands	≥50 years, T5 to L5 focal back pain of ≤9 weeks duration, bone density T score ≤-1, ≥15% loss vertebral height, bone edema on MRI Excluded: severe cardiopulmonary morbidity, untreatable coagulopathy, systemic or local spine infection, suspected malignancy, neurological symptoms, or inability to undergo MRI	A: Vertebroplasty: Bone biopsy needles at vertebral body positioned bilaterally, using standard transpedicular placements with local anesthetic (1% lidocaine into each pedicle followed by 0.25% ropivacaine) unless conscious sedation required (50 µg fentanyl in 22% of patients), PMMA injection stopped when cement leakage was noticed via CT (mean PMMA volume 5.1 ml [SD 1.8]). In participants with multiple fractures, all were treated. B: Sham vertebroplasty: Stab incisions at level of the vertebral body, local anesthetic as above, PMMA prepared in close proximity to the participants to duplicate mixing sound and smell; simulated procedure using verbal and physical cues.
Vertebroplasty	Hansen, 2019 VOPE	RCT 12 months	1 center, surgery Denmark	Osteoporotic VCF from T5 to L5, VAS >7.0 (0 to 10 scale), ≤8 weeks of back pain and a MRI-STIR sequence showing edema. Excluded: history of malignancy, age <50 years, known allergy towards vertebroplasty components, dementia (based on MMSE), long bone osteoporotic fracture	A: Vertebroplasty: 11-gauge needles inserted into the fractured vertebral body via the pedicles under fluoroscopic guidance and a biopsy specimen was taken, then 2 to 4 ml of bone cement was injected into fracture vertebral body. B: Sham vertebroplasty: Same procedure, with bone cement mixed to create the odor similar to a PVP-procedure; lidocaine 2 ml (10 mg/ml) injected into fractured vertebral body.
Vertebroplasty	Kallmes, 2009 and Comstock, 2013 INVEST	RCT 12 months	11 centers, provider type not described U.K., Australia, and U.S.	≥50 years, 1 to 3 painful osteoporotic VCFs between T4 and L5, duration <1 year, inadequate relief with standard medical therapy, pain ≥3 (0 to 10 scale) Excluded: evidence or suspicion of neoplasm in the target vertebral body, substantial retropulsion of bony fragments, concomitant hip fracture, active infection, uncorrectable bleeding diatheses, surgery within the previous 60 days, lack of access to a telephone, inability to communicate in English, and dementia.	A: Vertebroplasty: Subcutaneous tissues overlying pedicle infiltrated with 1% lidocaine and periosteum of pedicles infiltrated with 0.25% bupivacaine. 11- or 13-gauge needles passed into the central aspect of the target vertebra or vertebrae. Barium opacified PMMA was prepared on the bench and infused under constant lateral fluoroscopy into the vertebral body. Infusion stopped when the PMMA reached to the posterior aspect of the vertebral body or entered an extra osseous space (mean PMMA volume 2.6 ml). B: Sham vertebroplasty: Subcutaneous tissues overlying pedicle infiltrated with 1% lidocaine and periosteum of pedicles infiltrated with 0.25% bupivacaine. Verbal and physical cues, such as pressure on the patient's back, then methacrylate monomer opened to simulate the odor associated with mixing of PMMA, but needle not placed and PMMA not infused

Vertebral Augmentation Procedure	Author, Year Trial	Study Design Duration	Setting/Provider Type Country	Eligibility Criteria	Interventions
Vertebroplasty	Klazen, 2010 and Venmans, 2011 VERTOS II	RCT 12 months	6 centers, interventional radiology the Netherlands and Belgium	≥50 years, ≥15% height loss, fracture at thoracic 5 or lower (meaning toward lumbar region), bone edema on MRI, back pain ≤6 weeks, ≥5 VAS (0 to 10 scale) Excluded: severe cardiopulmonary comorbidity; untreatable coagulopathy; systemic or local spine infection; suspected underlying malignant disease; radicular syndrome; spinal-cord compression syndrome; and contraindication for MRI	A: Vertebroplasty: Two 11- or 13- gauge bone-biopsy needles placed transpedicularly in the fractured vertebral body. PMMA bone cement (Osteo-Firm, COOK Medical, Bloomington, IN, USA) injected through bone-biopsy needles under continuous fluoroscopic monitoring (mean PMMA volume 4.1 ml [SD 1.5]). B: Usual care: Not defined
Vertebroplasty	Leali, 2016	RCT 6 months	Multicenter (number of centers not reported), provider type not described Italy, France, Switzerland	Postmenopausal women with 1 thoracic or lumbar VCF caused by primary or secondary osteoporosis with severe acute (not defined) pain, VCF height of the visible loss of vertebral body in radiography and standard evidence of osteoporosis on bone densitometry, bone marrow edema of the affected VCF on spine MRI, and the presence of evidence of an acute fracture. Excluded: pathological fracture due to myeloma/metastasis, retropulsion mass of bone fragments in the spinal canal, unstable cardiopulmonary conditions, coagulopathy incurable, systemic infection in progress, or local infection spine, radicular syndrome or spinal cord compression.	A: Vertebroplasty: Transpedicular approach under local anesthesia with (mepivacaine 2% and ropivacaine 10%). PMMA (mean 4 ml) was injected into each fractured vertebral body under fluoroscopy B: Usual care: Pain medication, osteoporosis medication, physiotherapy or bracing
Vertebroplasty	Rousing, 2009 & 2010	RCT 12 months	1 center, orthopedic surgery Denmark	Intractable pain due to acute (<2 weeks, 40 patients) or subacute (between 2 and 8 weeks, 10 patients) osteoporotic fractures preventing the patient in taking care of oneself, and sufficient cognitive function to complete the study Excluded: <65 years, uncorrected therapeutic anticoagulation, senile dementia, impaired cognitive function or other cerebral disease, infection in the spine or the overlying skin, malignant disease, bone metabolic disease, fracture of tubular bone, or allergy to radiopaque agents.	A: Vertebroplasty: 11- to 13-gauge needles were placed using a uni or bilateral transpedicular approach. Bone cement (PMMA) injected under continuous fluoroscopy (PMMA volume not reported). B: Usual care: Not described

Vertebral Augmentation Procedure	Author, Year Trial	Study Design Duration	Setting/Provider Type Country	Eligibility Criteria	Interventions
Vertebroplasty	Voormolen, 2007 VERTOS	RCT 12 months	3 centers, orthopedic surgery and radiology the Netherlands	≥50 years with VCF with ≥15% height loss of the vertebral body on x-ray of the spine, invalidating back pain related to the VCF refractive to medical therapy for 6 weeks to 6 months, focal tenderness on physical examination related to the level of the VCF, bone mineral density T-score <-2.0, bone marrow edema of the affected VCF on MR imaging scan of the spine. Excluded: poor cardiopulmonary condition, untreatable coagulopathy, ongoing systemic infection or local infection of the spine (osteomyelitis, spondylodiscitis), radiculopathy or myelopathy, indication of other underlying disease than osteoporosis	A: Vertebroplasty: Performed under local anesthesia, bilateral transpedicular approach used with continuous fluoroscopy. PMMA injected using 11- or 13-gauge needle (mean PMMA volume 3.2 ml). B: Usual care: Stepped analgesics with acetaminophen, NSAIDs, or opiate derivatives.
Vertebroplasty	Yang, 2016	RCT 1 year	1 center, surgery China	>70 years with acute (not defined) osteoporotic vertebral compression fracture, back pain VAS ≥5 (0 to 10 scale), BMD T-score -1 or worse, low signal on T1-weighted and high signal on T2-weighted MRI, fracture at T5 level or lower, no wheelchair use prior to trauma Excluded: chronic back pain; suspected underlying malignant disease; spine infection retropulsion of bony fragments; spinal cord compression syndrome; concomitant hip fracture; severe cardiopulmonary comorbidity; major coagulopathy	A. Vertebroplasty: Bone puncture needle placed transpedicularly in the fractured vertebral body under fluoroscopic monitoring; PMMA injected into the fractured vertebra with the fluoroscopic control (mean 4.5 [SD 1.2] ml per vertebral body); CT scan performed to identity cement distribution and leakage. B. Usual care: Bed rest for 2 weeks, then patients encouraged to stand and walk with brace and assistance. NSAIDs with additional analgesics (e.g. tramadol and morphine) added if needed. Physical therapy initiated 2 weeks after diagnosis. Both groups received bisphosphonates, calcium supplementation, and vitamin D.
Kyphoplasty	Berenson, 2011 CAFE Trial	RCT 1 month (prior to allowed crossover)	22 centers, provider type not described Australia, Canada, Europe, and U.S.	≥21 years with cancer and 1 to 3 painful VCFs (T5 to L5) clinically diagnosed in conjunction with either plain radiographs or MRI; NRS ≥4 and RDQ ≥10 Excluded: presence of osteoblastic tumors, primary bone tumors, plasmacytoma at the index VCF, substantial clinical morbidities, VCF morphology deemed unsuitable for kyphoplasty, needed additional surgical treatment for the index fracture, needed treatment with high dose steroids, IV pain medication, nerve blocks.	A: Kyphoplasty: Balloon kyphoplasty performed with introducer tools, inflatable bone tamps, and PMMA bone cement and delivery devices (Medtronic Spine, Sunnyvale, CA, USA), by a percutaneous bilateral, transpedicular, or extrapedicular method (PMMA volume not reported). B: Usual care: Continued on non-surgical management, including analgesics, bed rest, bracing, physiotherapy, rehabilitation programs, walking aids, radiation treatment, other antitumor therapy; medications were calcium, vitamin D supplements, and antiresorptive or anabolic agents as necessary

Vertebral Augmentation Procedure	Author, Year Trial	Study Design Duration	Setting/Provider Type Country	Eligibility Criteria	Interventions
Kyphoplasty	Wardlaw, 2009 FREE Trial Additional publications: Boonen, 2013 and Van Meirhaege, 2013	RCT 1 year	21 sites, provider type not described Europe and U.S.	≥21 years with 1 to 3 vertebral fractures from T5 through L5; duration ≤3 months, ≥1 fracture with edema by MRI and ≥1 with ≥15% height loss (single fractures met both criteria). Excluded: chronic fracture; pedicle fracture; previous vertebroplasty; neurological deficit; radicular pain; spinal cord compression or canal narrowing; taking uninterruptible anticoagulation therapy; allergies to kyphoplasty materials or contraindications to MRI; dementia or unable to walk before fracture; vertebral fractures from primary bone tumors, osteoblastic metastases, or high energy trauma.	A. Kyphoplasty: Use of introducer instruments, inflatable bone tamps, and PMMA by a percutaneous, bilateral, transpedicular, or extrapedicular approach (mean PMMA volume not reported). B. Usual care: Analgesics, bed rest, back braces, physiotherapy, rehabilitation programs, and walking aids according to standard practices of participating hospitals.
Kyphoplasty	Boonen, 2011 FREE Trial Secondary publication of Wardlaw 2009	RCT additional followup 2 years	see Wardlaw 2009	see Wardlaw, 2009	see Wardlaw, 2009
Kyphoplasty	Van Meirhaeghe, 2013 FREE Trial Secondary publication of Wardlaw, 2009	RCT 2 years	see Wardlaw 2009	see Wardlaw, 2009	see Wardlaw, 2009

Abbreviations: ANCOVA = analysis of covariance; ANOVA = analysis of variance; ARD = absolute risk difference; BMD = bone mineral density; CAFE = Cancer Patient Fracture Evaluation; CI = confidence interval; CT = computed tomography; EQ-5D = EuroQOL 5-Dimension Questionnaire; FREE = Fracture Reduction Evaluation; HR = hazard ratio; INVEST = Investigational Vertebroplasty Safety and Efficacy Trial; IQR = interquartile range; IU = International Unit; LBP = low-back pain; MCS = Mental Component Summary; MMSE = Mini-Mental State Exam; MR = magnetic resonance; MRI = magnetic resonance imaging; MRI-STIR = magnetic resonance imaging short tau inversion recovery; NR = not reported; NRS = numeric rating scale; NS = not significant; ODI = Oswestry Disability Index; OR = odds ratio; PCS = Physical Component Summary; PMMA = polymethylmethacrylate; PVP = percutaneous vertebroplasty; QALY = quality-adjusted life-year; QUALEFFO = Quality of Life Questionnaire of the European Foundation for Osteoporosis; RCT = randomized controlled trial; RDQ = Roland–Morris Disability Questionnaire; RR = risk ratio; SAE = serious adverse event; SD = standard deviation; SF-36 = Short-Form 36; SOF–ADL = Study of Osteoporotic Fractures–Activities of Daily Living; TL = thoracolumbar junction; VAPOUR = vertebroplasty for acute painful osteoporotic fractures; VAS = visual analogue scale; VB = vertebral body; VCF = vertebral compression fracture; VERTOS = percutaneous vertebroplasty compared with optimal pain medication treatment: short-term clinical outcome of patients with subacute or chronic painful osteoporotic vertebral compression fractures; VERTOS II = vertebroplasty vs. conservative treatments in acute osteoporotic vertebral compression fractures; VERTOS IV = vertebroplasty vs. sham procedure for painful acute osteoporotic vertebral compression fractures; VOPE = vertebroplasty vs. sham for treating osteoporotic vertebral compression fractures: a double blind RCT

See Appendix F, List of Included Studies, for full citations

Table G-2. Trials of vertebral augmentation procedures to treat vertebral compression fractures – additional study characteristics

Vertebral Augmentation Procedure	Author, Year Trial	Sample Characteristics	Screened Eligible Randomized Analyzed Crossover	Sponsor	Quality
Vertebroplasty	Blasco, 2012	Mean (SD) age, years: 73.2 (9.3) Female: 78% Race: NR Symptom duration (mean [SD], months): 4.7 (3.8) Symptom onset <6 weeks: 4.8% Symptom onset <4 months: 51% Number of vertebral fractures at baseline (mean [SD]: 3.29 (2.51) 2 initial fractures: 25% >2 initial fractures: 49% A vs. B Baseline pain (mean [SD], 0 to 10 VAS): 7.21 (2.8) vs. 6.31 (2.7) Baseline QUALEFFO-41 (mean [SD], 0 to 100 scale): 65.2 (16) vs. 59.2 (16)	Screened: 219 Eligible: 139 Randomized: 125 (64 vs. 61) Completed followup: 110 (54 vs. 56) at 2 months, 104 (50 vs. 54) at 6 months, 95 (47 vs. 48) at 12 months Analyzed: Appears to be 125 (64 vs. 61) for continuous variables	Fundació La Marató de TV3, the Spanish Society of Medical Radiology, Catalan Society of Rheumatology	Fair
Vertebroplasty	Buchbinder, 2009 Additional publications: Kroon, 2014 and Staples, 2015	Mean (SD) age, years: 77 (11.91) Female: 79% Race: NR Duration of back pain (median [IQR], weeks): 9.0 (3.7 to 13.0) vs. 9.5 (3.0 to 17.0) Number of vertebral bodies treated: -1: 82% -2: 18% Previous vertebral fracture: 50% Opioid use for pain: 82% Medication use for osteoporosis: 92% A vs. B Baseline overall pain (mean [SD], 0 to 10 VAS): 7.4 (2.1) vs. 7.1 (2.3) Baseline QUALEFFO total score: 56.9 (13.4) vs. 59.6 (17.1) Baseline Assessment of Quality of Life (AQoL) score (mean [SD], -0.04 to 1.0 scale): 0.33 (0.25) vs. 0.27 (0.26) Baseline modified RDQ (mean [SD], 0 to 23 scale): 17.3 (2.8) vs. 17.3 (2.9) Baseline EQ-5D (mean [SD], 0 to 1 scale): 0.30 (0.32) vs. 0.28 (0.33)	Screened: 468 Eligible: 220 Randomized: 78 (38 vs. 40) Completed followup: 73 (36 vs. 37) at 3 months, 71 (35 vs. 36) at 6 months Analyzed: 73 (36 vs. 37) at 3 months, 71 (35 vs. 36) at 6 months	National Health and Medical Research Council of Australia, Arthritis Australia, the Cabrini Education and Research Institute, Cook Australia.	Good

Vertebral Augmentation Procedure	Author, Year Trial	Sample Characteristics	Screened Eligible Randomized Analyzed Crossover	Sponsor	Quality
Vertebroplasty	Staples, 2015 Secondary publication of Buchbinder, 2009	see Buchbinder, 2009	Screened: 468 Eligible: 220 Randomized: 78 (38 vs. 40) Analyzed: 70 (34 vs. 36) at 1 year, 64 (32 vs. 32) at 2 years	see Buchbinder, 2009	see Buchbinder, 2009
Vertebroplasty	Kroon, 2014 Secondary publication of Buchbinder, 2009	see Buchbinder, 2009	Screened: 468 Eligible: 220 Randomized: 78 (38 vs. 40) Analyzed: 57 (29 vs. 28) at 24 months	see Buchbinder, 2009	see Buchbinder, 2009
Vertebroplasty	Chen, 2014	Mean (SD) age, years: 65.5 (9.1) Female: 70% Race: NR Duration of pain (mean [SD], months): 6.98 (2.77) Number of VCF (mean [SD]): 2.14 (0.72) Use of osteoporosis drugs: 34% A vs. B Baseline pain (mean [SD], 0 to 10 VAS): 6.5 (0.9) vs. 6.4 (0.9) Baseline ODI (mean [SD], 0 to 100 scale): 59.9 (2.2) vs. 57.9 (1.9) Baseline RDQ (mean [SD], 0 to 24 scale): 18.6 (1.8) vs. 16.7 (1.3)	Screened: NR Eligible: NR Randomized: 96 (46 vs. 50) Completed followup: 89 (46 vs. 43) Analyzed: 89 (46 vs. 43)	None	Fair

Vertebral Augmentation Procedure	Author, Year Trial	Sample Characteristics	Screened Eligible Randomized Analyzed Crossover	Sponsor	Quality
Vertebroplasty	Clark, 2016 VAPOUR	Mean (SD) age, years: 80 (7) Female: 73% Race: NR Fracture duration (mean [SD], weeks): 2.6 (1.5) Fracture duration 1 to 3 weeks: 79% Fracture duration 4 to 6 weeks: 21% Location of fracture - Lumbar: 14% - Thoracic: 29% - Thoracolumbar: 61% Taking opioids for pain: 88% Inpatient: 57% Previous osteoporotic fractures: 57% A vs. B Baseline pain intensity, last 24 hours (mean [SD], 0 to 100 VAS converted to 0 to 10 scale): 8.1 (1.8) vs. 8.2 (1.5) Baseline pain intensity, last 24 hours (mean [SD], 0 to 10 NRS): 8.6 (1.3) vs. 8.6 (1.2) Baseline RDQ (mean [SD], 0 to 24): 19.5 (3.5) vs. 19.8 (3.7) Baseline EQ-5D (mean [SD, 0 to 1): 0.60 (0.07) vs. 0.59 (0.06) Baseline QUALEFFO score (mean [SD, 0 to 100): 65.4 (11.4) vs. 67.7 (11.2)	Screened: 302 Eligible: 154 Randomized: 120 (61 vs. 59) Complete followup: 105 (53 vs. 52) at 3 months, 102 (51 vs. 51) at 6 months Analyzed: 112 (55 vs. 57) at 14 days, 105 (53 vs. 52) at 3 months, 102 (51 vs. 51) at 6 months	CareFusion Corporation	Good
Vertebroplasty	Diamond, 2020 VAPOUR	Mean (SD) age, years: 81 (NR) Female: 73% Race: NR Mean lumbar spine T-score: -4.3 Receiving anti-osteoporotic therapies: 75% Genant grade 3 vertebral deformities: 71% Inpatient: 63% Mean (SD) duration of fracture, weeks: 2.6 (1.5) A vs. B Pain intensity (mean [SD], 0 to 10 NRS): 8.7 (1.3) vs. 8.6 (1.2) RDQ (mean [SD], 0 to 24 scale): 19.7 (2.8) vs. 19.9 (4.1) QUALEFFO score (mean [SD], 0 to 100 scale): 67.0 (11.0) vs. 68.8 (11.7) EQ-5D score (mean [SD], 0 to 1 scale): 0.59 (0.06) vs. 0.59 (0.06)	Screened: 120 Eligible: NR Randomized: 93 (46 vs. 47) Analyzed for primary outcome: 86 (43 vs. 43)	CareFusion Corporation	Good

Vertebral Augmentation Procedure	Author, Year Trial	Sample Characteristics	Screened Eligible Randomized Analyzed Crossover	Sponsor	Quality
Vertebroplasty	Farrokhi, 2011	Mean age: 72 vs. 74 (range 55-90) Female: 73% Race: NR Mean duration of LBP, weeks: 27 vs. 30 (range 4 to 54) Total number of VCFs: 190 Grade of treated VCF - Mild: 61% - Moderate: 29% - Severe: 6% Shape of treated VCF - Wedge: 84% - Biconcave: 16% Taking acetaminophen with codeine: 73% Taking NSAIDs: 63% A vs. B Baseline pain intensity (mean [SD], 0 to 10 VAS): 8.4 (1.6) vs. 7.2 (1.7) Baseline ODI (mean [SD, 0 to 100 scale): 51.2 (2.2) vs. 47.1 (2.8)	Screened: 105 Eligible: 84 Randomized: 82 (40 vs. 42) Completed followup: 77 (38 vs. 39) at 12 months, 76 (37 vs. 39) at 36 months Analyzed: 82 (40 vs. 42) at 2 and 6 months, 76 (37 vs. 39) at 3 years Crossover: 0 vs. 10 (3 at <6 months, 7 from 1 to 3 years)	Vice chancellor for research affairs Shiraz University of Medical Sciences and Apadana Tajhizgostar Co. provided grant support.	Poor
Vertebroplasty	Firanescu, 2018 & 2019 VERTOS IV	Mean (SD) age, years:75.8 (9.5) Female: 75% Race: NR Duration of back pain (median [IQR], days): 43 (29 to 52) vs. 36 (24 to 51) Duration from radiographic diagnosis (median [IQR], days): 13 (7 to 18) vs. 11 (7 to 17) Type of fracture (Genant classification) - Mild: 38% - Moderate: 57% - Severe: 32% - Wedge: 69% - Biconcave: 58% Number of VCF: 223 Mean (SD) RDQ: 17.9 (4.6) On drugs for osteoporosis: 52% Weak opioids: 17% Strong opioids: 38% A vs. B Baseline pain intensity (mean [SD], 0 to 10 VAS): 7.7 (1.4) vs. 7.9 (1.6) Baseline RDQ (mean [SD], 0 to 24): 18.0 (4.5) vs. 17.8 (4.7) Baseline QUALEFFO score (mean [SD], 0 to 100): 68.4 (17.1) vs. 69.7 (17.9)	Screened: 1280 Eligible: 336 Randomized: 180 (91 vs. 89) Completed followup: 171 (87 vs. 84) at 3 months, 152 (76 vs. 76 at 1 year Analyzed: 176 (90 vs. 86) at 1 year	Stryker (grant No S-1-013)	Good

Vertebral Augmentation Procedure	Author, Year Trial	Sample Characteristics	Screened Eligible Randomized Analyzed Crossover	Sponsor	Quality
Vertebroplasty	Hansen, 2019 VOPE	Mean (SD NR) age, years: 69.9 Female: 87% Race: NR BMD T-score: -2.44 A vs. B Baseline pain intensity at rest (mean [SD, 0 to 100 VAS converted to 0 to 10 scale): 4.1 (2.1) vs. 5.3 (2.1) Baseline SF-36 Physical Component Summary (mean [SD, 0 to 100 scale): 25.1 (6.9) vs. 25.5 (4.6) Baseline SF-36 Mental Component Summary (mean [SD], 0 to 100 scale): 42.0 (9.8) vs. 44.3 (13.1) Baseline EQ-5D (mean [SD NR], 0 to 1 scale): 0.44 vs. 0.49	Screened: 342 Eligible: NR Randomized: 52 (26 vs. 26) Completed followup: 46 (22 vs. 24) Analyzed: 46 (22 vs. 24)	Danish Rheumatism Association	Fair
Vertebroplasty	Kallmes, 2009 and Comstock, 2013 INVEST	Mean (SD) age, years: 73.8 (9.5) Female: 76% White: 97% Mean (SD) pain duration, weeks: 17.9 (57.7) Reported use of opioids: 59% A vs. B Baseline modified RDQ (mean [SD], 0 to 23 scale): 16.6 (3.8) vs. 17.5 (4.1) Baseline average pain intensity in last 24 hours (mean [SD], 0 to 10 VAS): 6.9 (2.0) vs. 7.2 (1.8) Baseline SF-36 PCS (mean [SD], 0 to 100 scale): 25.3 (7.8) vs. 25.3 (7.3) Baseline SF-36 MCS (mean [SD], 0 to 100 scale): 44.8 (11.8) vs. 41.5 (14.1) Baseline EQ-5D (mean [SD], 0 to 1 scale): 0.57 (0.18) vs. 0.54 (0.23) Baseline Study of Osteoporotic Fractures-Activities of Daily Living (SOF-ADL) scale (mean [SD], 0 to 18 scale): 10.0 (3.6) vs. 10.3 (2.8)	Screened: 1813 Eligible: 431 Randomized: 131 (68 vs. 63) Completed followup: 125 (64 vs. 61) at 3 months, 119 (63 vs. 56 at 1 year) Analyzed: 125 (64 vs. 61) at 3 months; 119 (63 vs. 56) at 1 year Crossover: 35 (8 vs. 27) at 3 months; 49 (38 vs. 11) at 1 year	National Institute of Arthritis and Muscular-Skeletal and Skin Diseases	Good

Vertebral Augmentation Procedure	Author, Year Trial	Sample Characteristics	Screened Eligible Randomized Analyzed Crossover	Sponsor	Quality
Vertebroplasty	Klazen, 2010 and Venmans, 2011 VERTOS II	Mean (SD) age, years: 75.3 (9.1) Female: 69% Race: NR Mean (SD) duration of pain, days: 28.0 (16.6) Use of osteoporosis drugs: 25% Mean (SD) number of vertebral compression fractures: 2.3 (1.7) A vs. B Baseline pain intensity (mean [SD], 0 to 10 VAS): 7.8 (1.5) vs. 7.5 (1.6) Baseline RDQ (mean [SD], 0 to 24 scale): 18.6 (3.6) vs. 17.2 (4.2) Baseline QUALEFFO score (mean [SD], 0 to 100 scale): 58.7 (13.5) vs. 54.7 (14.4) Baseline EQ-5D (mean [SD], 0 to 1 scale): 0.27 (0.03) vs. 0.38 (0.03)	Screened: 934 Eligible: 434 Randomized: 202 (101 vs. 101) Completed followup: 178 (92 vs. 86) at 3 months, 163 (86 vs. 77) at 1 year Analyzed: 202 (101 vs. 101) Crossover: 16 (6 vs. 10) at 1 year	ZonMw (Dutch organization for health care research and innovation of care); Unrestricted grant COOK Medical	Fair
Vertebroplasty	Leali, 2016	Mean age: NR (range 56 to 82 years) Female: 100% Race: NR Fracture duration: NR Fracture site (among vertebroplasty patients) - Lumbar: 47.5% - Thoracic vertebrae: 52.5% Opioid analgesic use: Not reported A vs. B Baseline pain (mean [SD NR], 0 to 10 VAS): 4.8 vs. NR Baseline ODI (mean [SD NR], 0 to 100 scale): 53.6	Screened: NR Eligible: NR Randomized: 400 (200 vs. 200) Completed followup: Not reported Analyzed: Not reported	NR	Poor

Vertebral Augmentation Procedure	Author, Year Trial	Sample Characteristics	Screened Eligible Randomized Analyzed Crossover	Sponsor	Quality
Vertebroplasty	Rousing, 2009 & 2010	Mean age, years: 80 (range 65 to 96) Female: 82% Race: NR Mean (SD) duration of fracture, days: 7.6 (11.7) A vs. B Baseline pain (mean [SD], 0 to 10 VAS: 7.5 (1.9) vs. 8.8 (1.1) Baseline SF-36 PCS (mean [SD], 0 to 100 scale): 36.7 (13.0) vs. 33.4 (14.1) Baseline SF-36 MCS (mean [SD], 0 to 100 scale): 49.7 (11.9) vs. 49.6 (15.0) Baseline Dallas Pain Questionnaire, daily activities (mean [SD], 0 to 100 scale): 47.8 (47.5) vs. 68.5 (44.7) Baseline Dallas Pain Questionnaire, anxiety and depression (mean [SD], 0 to 100 scale): 31.5 (26.4) vs. 43.0 (46.2) EQ-5D (mean [SD], 0 to 100 scale): 0.36 (0.31) vs. 0.08 (0.44)	Screened: NR Eligible: NR Randomized: 50 (26 vs. 24) Completed followup: 46 (23 vs. 23) at 3 months, 45 (23 vs. 22) at 12 months Analyzed: 47 (24 vs. 23) at 3 months, 45 (23 vs. 22) at 12 months	Foundation and Danish government funds	Poor
Vertebroplasty	Voormolen, 2007 VERTOS	Mean age, years: 73 (range 55 to 88) Female: 82% Race: NR Mean duration of back pain, days: 81 (range 46 to 141) Total number of VCFs: 108 Grade of VCF - Mild: 12% - Moderate: 22% - Severe: 65% Shape of VCF - Wedge: 78% - Bio concave: 22% On opiate derivative: 32% On NSAIDs: 27% On paracetamol: 32% A vs. B Baseline pain (mean [range], 0 to 10 VAS): 7.1 (5 to 9) vs. 7.6 (5 to 10) Baseline RDQ (mean [range], 0 to 24 scale): 15.7 (8 to 22) vs. 17.8 (9 to 24) Baseline QUALEFFO (mean [range], 0 to 100 scale): 60 (37 to 86) vs. 67 (38 to 86) Baseline analgesic use (mean [range], 0 to 3 scale): 1.9 (0 to 3) vs. 1.7 (0 to 3)	Screened: NR Eligible: NR Randomized: 34 Completed followup: 34 (18 vs. 16) at 2 weeks Analyzed: 34 (18 vs. 16) Crossover: None prior to 2 weeks (14 patients in usual care arm crossed over after 2 week assessment)	NR	Fair

Vertebral Augmentation Procedure	Author, Year Trial	Sample Characteristics	Screened Eligible Randomized Analyzed Crossover	Sponsor	Quality
Vertebroplasty	Yang, 2016	Mean (SD) age, years: 76.7 (5.81) Female: 64% Race: NR Mean (SD) time since onset of pain, days: 5.55 (3.85) Fracture location (based on 123 total fractures) -Thoracic spine (~T10): 4.9% (6/123) -TL junction (T11 to L2): 71.5% (88/123) -Lumbar spine (L3 to L5): 23.6% (29/123) A vs. B Baseline pain (mean [SD], 0 to 10 VAS): 7.5 (1.1) vs. 7.7 (1.1) Baseline ODI (mean [SD], 0 to 100 scale): 80.2 (9.9) vs. 81.5 (9.7) Baseline QUALEFFO score (mean [SD], 0 to 100 scale): 78.1 (8.1) vs. 77.5 (8.6)	Screened: NR Eligible: 158 Randomized: 135 (66 vs. 69) Completed followup: 107 (56 vs. 51) at 1 year Analyzed: 107 (56 vs. 51) at 1 year Crossover: 8 (0 vs. 8; 2 additional patients in usual care group underwent open surgery) at 1 year	No external funding	Poor
Kyphoplasty	Berenson, 2011 CAFE Trial	Mean (SD) age, years: 63.9 (11.1) Female: 58% Race: 88% White, 7.0% Black, 1.6% Asian, 0.8% Hispanic, 2.3% other Symptomatic fracture duration (median [IQR], months): 3.5 (1.2 to 6.8) Edema on MRI: 67% Prior radiation treatment: 49% - Spinal irradiation: 21% Prior chemotherapy or hormonal treatments: 83% A vs. B Baseline pain (mean [SD], 0 to 10 NRS): 7.3 (1.4) vs. 7.3 (1.4) Baseline RDQ (mean [SD NR], 0 to 24): 17.6 vs. 18.2	Screened: 477 Eligible: 223 Randomized: 134 (70 vs. 64) Completed followup: 117 (65 vs. 52) at 1 month Analyzed: 117 (65 vs. 52) at 1 month Crossover in usual care arm after 1 month: 59% (38/64)	Medtronic Spine LLC.	Fair

Vertebral Augmentation Procedure	Author, Year Trial	Sample Characteristics	Screened Eligible Randomized Analyzed Crossover	Sponsor	Quality
Kyphoplasty	Wardlaw, 2009 FREE Trial Additional publications: Boonen, 2013 and Van Meirhaege, 2013	Mean (SD) age, years: 73.16 (9.35) Female: 77% Race: NR Mean (SD) duration of fracture, weeks: 6.0 (4.82) Number of fractures -One: 72% -Two: 21% -Three: 7.7% Fracture location -Thoracic (T5-T9): 22.0% -Thoracolumbar junction (T10-L2): 62.8% -Lumbar (L3-L5): 15.2% Glucocorticoid use: 17% Strong opioid use: 14% Opioid + nonopioid: 57% A vs. B Baseline pain (mean [SD], 0 to 10 VAS): 6.9 (2.2) vs. 7.0 (2.2) Baseline RDQ (mean [SD], 0 to 24 scale): 17 (6.2) vs. 17 (6.2) SF-36 PCS (mean [SD], 0 to 100 scale): 26 (12.2) vs. 26 (12.5) Baseline EQ-5D (mean [SD], 0 to 24 scale): 1.7 (0.31) vs. 1.7 (0.31)	Screened: 1279 Eligible: 624 Randomized: 300 (149 vs. 151) Completed followup: 251 (134 vs. 117) at 3 months, 235 (124 vs. 111 at 1 year) Analyzed: 300 (149 vs. 151) Crossover: 24 (10 vs.14)	Medtronic Spine LLC	Fair
Kyphoplasty	Boonen, 2011 FREE Trial Secondary publication of Wardlaw 2009	see Wardlaw, 2009	Screened: 1279 Eligible: 624 Randomized: 300 (149 vs. 151) Completed followup: 232 (120 vs. 112) at 2 years Analyzed: 300 (149 vs. 151) at 2 years	see Wardlaw, 2009	see Wardlaw, 2009
Kyphoplasty	Van Meirhaeghe, 2013 FREE Trial Secondary publication of Wardlaw 2009	see Wardlaw, 2009	see Wardlaw 2009	see Wardlaw, 2009	see Wardlaw, 2009

Abbreviations: ANCOVA = analysis of covariance; ANOVA = analysis of variance; ARD = absolute risk difference; BMD = bone mineral density; CAFE = Cancer Patient Fracture Evaluation; CI = confidence interval; CT = computed tomography; EQ-5D = EuroQOL 5-Dimension Questionnaire; FREE = Fracture Reduction Evaluation; HR = hazard ratio; INVEST = Investigational Vertebroplasty Safety and Efficacy Trial; IQR = interquartile range; IU = International Unit; LBP = low-back pain; MCS = Mental Component Summary; MMSE = Mini-Mental State Exam; MR = magnetic resonance; MRI = magnetic resonance imaging; MRI-STIR = magnetic resonance imaging short tau inversion recovery; NR = not reported; NRS = numeric rating scale; NS = not significant; ODI = Oswestry Disability Index; OR = odds ratio; PCS = Physical Component Summary; PMMA = polymethylmethacrylate; PVP =

percutaneous vertebroplasty; QALY = quality-adjusted life-year; QUALEFFO = Quality of Life Questionnaire of the European Foundation for Osteoporosis; RCT = randomized controlled trial; RDQ = Roland–Morris Disability Questionnaire; RR = risk ratio; SAE = serious adverse event; SD = standard deviation; SF-36 = Short-Form 36; SOF–ADL = Study of Osteoporotic Fractures–Activities of Daily Living; TL = thoracolumbar junction; VAPOUR = vertebroplasty for acute painful osteoporotic fractures; VAS = visual analogue scale; VB = vertebral body; VCF = vertebral compression fracture; VERTOS = percutaneous vertebroplasty compared with optimal pain medication treatment: short-term clinical outcome of patients with subacute or chronic painful osteoporotic vertebral compression fractures; VERTOS II = vertebroplasty vs. conservative treatments in acute osteoporotic vertebral compression fractures; VERTOS IV = vertebroplasty vs. sham procedure for painful acute osteoporotic vertebral compression fractures; VOPE = vertebroplasty vs. sham for treating osteoporotic vertebral compression fractures: a double blind RCT

See Appendix F, List of Included Studies, for full citations

Table G-3. Trials of vertebral augmentation procedures to treat vertebral compression fractures – results

Vertebral Augmentation Procedure	Author, Year Trial	Results	Adverse Events and Withdrawals Due to Adverse Events
Vertebroplasty	Blasco, 2012	A vs. B Pain (mean [SD] improvement from baseline, 0 to 10 VAS): 3.07 (0.45) vs. 1.59 (0.42) at 2 months, p = 0.0172; Pain (mean [SD], 0 to 10 VAS) -2 weeks: 5.8 (3.6) vs. 4.7(3.3) -2 months: 4.1 (3.4) vs. 4.8 (3.3) -6 months: 4.7 (3.0) vs. 4.2 (2.9) -12 months: 4.4 (3.0) vs. 4.2 (2.9) QUALEFFO-41, total score (mean [SD]. 0 to 100 scale) -2 weeks: 62 (18) vs. 57 (18) -2 months: 57 (18) vs. 55 (18) -6 months: 54 (18) vs. 52 (18) -12 months: 54 (18) vs. 52 (18) Vertebral pain <4 on 0 to 10 VAS: 56.1% (23/41) vs. 52.4% (22/42) at 12 months, RR 1.07 (95% CI, 072 to 1.59)* Minor opioid use -2 weeks: 23.2% (13/56) vs. 32.8% (19/58), RR 0.71 (95% CI, 0.39 to 1.29)* -2 months: 26.9% (14/52) vs. 28.6% (16/56), RR 0.94 (95% CI, 0.51 to 1.73)* -6 months: 16.3% (8/49) vs. 26.9% (14/52), RR 0.61 (95% CI, 0.28 to 1.32)* -12 months: 17.1% (7/41) vs. 23.8% (10/42) , RR 0.72 (95% CI, 0.30 to 1.70)* Major opioid use -2 weeks: 35.7% (20/56) vs. 29.3% (17/58), RR 1.22 (95% CI, 0.72 to 2.07)* -2 months: 30.1% (16/52) vs. 30.4% (17/56), RR 1.01 (95% CI, 0.57 to 1.79)* -6 months: 36.7% (18/49) vs. 32.7% (17/52), RR 1.12 (95% CI, 0.66 to 1.92)* -12 months: 36.6% (15/41) vs. 16.7% (7/42), RR 2.19 (95% CI, 0.99 to 4.82)*	A vs. B Mortality: 4.7% (3/64) vs. 9.8% (6/61) at 12 months, RR 0.48 (95% CI, 0.12 to 1.82)* New radiological vertebral fracture: 26% (17/64) vs. 13% (8/61) at 12 months; OR 2.78 (95% CI, 1.02 to 7.62)

Vertebral Augmentation Procedure	Author, Year Trial	Results	Adverse Events and Withdrawals Due to Adverse Events
Vertebroplasty	Buchbinder, 2009 Additional publications: Kroon, 2014 and Staples, 2015	A vs. B Overall pain (mean change from baseline [SD], 0 to 10 VAS) -1 week: -1.5 (2.5) vs. -2.1 (2.8), adjusted mean difference 0.7 (95% CI, -0.4 to 1.8) -1 month: -2.3 (2.6) vs. -1.7 (3.3), adjusted mean difference -0.5 (95% CI, -1.7 to 0.8) -3 months: -2.6 (2.9) vs. -1.9 (3.3), adjusted mean difference -0.6 (95% CI, -1.8 to 0.7) -6 months: -2.4 (3.3) vs. -2.1 (3.3); adjusted mean difference -0.1 (95% CI, -1.4 to 1.2) Modified RDQ (mean change from baseline [SD], 0 to 23 scale) -1 week: -1.8 (5.0) vs. -4.0 (6.8), adjusted mean difference 2.1 (95% CI, -0.9 to 5.2) -1 month: -4.4 (6.6) vs. -3.1 (6.8), adjusted mean difference -1.7 (95% CI, -5.2 to 1.8) -3 months: -3.7 (5.4) vs. -5.3 (7.2), adjusted mean difference 1.5 (95% CI, -1.7 to 4.8) -6 months: -4.1 (5.8) vs. -3.7 (5.8), adjusted mean difference 0.0 (95% CI, -2.9 to 3.0) QUALEFFO total score (mean change from baseline [SD], 0 to 100 scale) -1 week: 0.5 (7.4) vs. -3.6 (9.2), adjusted mean difference 4.0 (95% CI, 0.2 to 7.8) -1 month: -2.8 (9.3) vs. -2.4 (12.3), adjusted mean difference -0.9 (95% CI, -6.0 to 4.2) -3 months: -6.0 (9.6) vs. -6.1 (13.7), adjusted mean difference -0.7 (95% CI, -5.7 to 4.4) -6 months: -6.4 (13.4) vs. -6.1 (13.4), adjusted mean difference -0.6 (95% CI, -6.2 to 5.1) AQoL score (mean change from baseline [SD], -0.04 to 1.0 scale) -1 week: 0.0 (0.2) vs. 0.0 (0.2), adjusted mean difference 0.0 (95% CI, -0.1 to 0.1) -1 month: 0.0 (0.2) vs. 0.1 (0.3), adjusted mean difference 0.0 (95% CI, -0.1 to 0.1) -3 months: 0.0 (0.2) vs. 0.1 (0.3), adjusted mean difference 0.0 (95% CI, -0.1 to 0.1) -6 months: 0.0 (0.3) vs. 0.1 (0.3), adjusted mean difference 0.1 (95% CI, -0.1 to 0.2) EQ-5D score (mean change from baseline [SD], 0 to 1 scale) -1 week: 0.1 (0.3) vs. 0.1 (0.3), adjusted mean difference 0.0 (95% CI, -0.1 to 0.2) -1 month: 0.1 (0.3) vs. 0.1 (0.3), adjusted mean difference 0.0 (95% CI, -0.1 to 0.1) -3 months: 0.2 (0.3) vs. 0.2 (0.4), adjusted mean difference 0.0 (95% CI, -0.1 to 0.2) -6 months: 0.2 (0.4) vs. 0.2 (0.4), adjusted mean difference 0.0 (95% CI, -0.1 to 0.2) Perceived pain moderately or a great deal better: 16.2% (6/37) vs. 35.1% (13/37) at 1 week, adjusted RR 0.5 (95% CI, 0.2 to 1.1); 34.3% (12/35) vs. 23.7% (9/38) at 1 month, adjusted RR 1.5 (95% CI, 0.7 to 3.0); 38.9% (14/36) vs. 34.3% (12/35) at 3 months, adjusted RR 1.2 (95% CI, 0.6 to 2.2); 43.2% (16/37) vs. 41.7% (15/36) at 6 months, adjusted RR 1.1 (95% CI, 0.6 to 1.9) Opioids discontinued (denominator those taking opioids at baseline): 10.0% (3/30) vs. 20.6% (7/34) at 1 week, RR 0.48 (95% CI, 0.14 to 1.71);* 13.3% (4/30) vs. 26.5% (9/34) at 1 month, RR 0.50 (95% CI, 0.17 to 1.47);* 36.7% (11/30) vs. 32.4% (11/34) at 3 months, RR 1.13 (95% CI, 0.58 to 2.23)*; 56.7% (17/30) vs. 52.9% (18/34) at 6 months, RR 1.07 (95% CI, 0.68 to 1.67)*	A vs. B Mortality: 5.3% (2/38) vs. 2.5% (1/40) at 6 months, RR 2.11 (95% CI, 0.20 to 22.28) Incident clinical vertebral fracture: 7.9% (3/38) vs. 5.0% (2/40) at 6 months, RR 1.58 (95% CI, 0.28 to 8.94) Osteomyelitis: 2.6% (1/38) vs. 0% (0/40), RR 3.15 (95% CI, 0.13 to 75.12)*

Vertebral Augmentation Procedure	Author, Year Trial	Results	Adverse Events and Withdrawals Due to Adverse Events
Vertebroplasty	Staples, 2015 Secondary publication of Buchbinder, 2009	Not reported	A vs. B New fracture, any level, HR (95% CI): 1.80 (0.83 to 3.94) -Adjacent level: 2.30 (0.57 to 9.29) -Non-adjacent level: 1.45 (0.55 to 3.81) -Treated level: Not calculable (no fracture in placebo group) -Untreated level: 1.69 (0.77 to 3.74) New or progressed fracture, any level, HR (95% CI): 1.29 (0.80 to 2.08) -Adjacent level: 2.18 (0.74 to 6.42) -Non-adjacent level: 1.18 (0.58 to 2.43) -Treated level: 1.05 (0.47 to 2.34) -Untreated level: 1.69 (0.77 to 3.74)
Vertebroplasty	Kroon, 2014 Secondary publication of Buchbinder, 2009	A vs. B Pain (mean change from baseline [SD], 0 to 10 pain scale) -12 months: -2.4 (2.7) vs. -1.9 (2.8), adjusted mean difference -0.3 (95% CI, -1.5 to 0.9) -24 months: -3.0 (3.1) vs. -1.9 (3.0), adjusted mean difference -1.1 (95% CI, -2.4 to 0.3) QUALEFFO total (mean change from baseline [SD], 0 to 100 scale) -12 months: -6.7 (12.2) vs. -8.8 (13.3), adjusted mean difference 1.3 (95% CI, -4.3 to 7.0) -24 months: -5.9 (10.7) vs. -4.6 (15.0), adjusted mean difference -2.1 (95% CI, -8.5 to 4.4) RDQ (mean change from baseline [SD], 0 to 24 scale) -12 months: -2.0 (5.7) vs. -2.6 (6.9), adjusted mean difference 0.5 (95% CI, -3.2 to 4.3) -24 months: -2.6 (7.0) vs. -2.7 (5.6), adjusted mean difference -0.3 (95% CI, -4.1 to 3.5) EQ-5D (mean change from baseline [SD], 0 to 1 scale) -12 months: 0.2 (0.4) vs. 0.2 (0.4), adjusted mean difference 0.0 (95% CI, -0.2 to 0.2) -24 months: 0.2 (0.4) vs. 0.2 (0.4), adjusted mean difference 0.0 (95% CI, -0.2 to 0.2) Perceived pain better -12 months: 45% (15/33) vs. 44% (15/34), RR 1.0 (95% CI, 0.7 to 1.9) -24 months: 41% (12/29) vs. 36% (10/28), RR 1.2 (95% CI, 0.6 to 2.2)	A vs. B Mortality: 13% (5/37) vs. 19% (7/37) at 24 months, all deaths unrelated to trial, RR 0.71 (95% CI, 0.25 to 2.05)* New fractures at 2 years: 14 vs. 13

Vertebral Augmentation Procedure	Author, Year Trial	Results	Adverse Events and Withdrawals Due to Adverse Events
Vertebroplasty	Chen, 2014	A vs. B Pain (mean [SD], 0 to 10 VAS), all p<0.001 - 1 week: 3.4 (0.5) vs. 5.0 (0.7) - 1 month: 2.8 (0.4) vs. 4.0 (0.6) - 3 months: 2.5 (0.5) vs. 3.9 (0.7) - 6 months: 2.5 (0.6) vs. 4.0 (0.8) - 12 months: 2.5 (0.5) vs. 4.1 (0.8) RDQ (mean [SD], 0 to 24 scale), all p<0.001 - 1 week: 13.2 (1.5) vs. 15.7 (1.6) - 1 month: 11.7 (1.0) vs. 13.8 (1.5) - 3 months: 9.9 (1.2) vs. 12.5 (1.0) - 6 months: 9.3 (0.9) vs. 11.1 (0.9) - 12 months: 8.1 (0.7) vs. 10.7 (1.1) ODI (mean [SD], 0 to 100 scale), all p<0.001 - 1 week: 30.3 (3.2) vs. 44.5 (3.9) - 1 month: 20.4 (3.1) vs. 35.4 (2.9) - 3 months: 16.6 (1.6) vs. 30.0 (2.4) - 6 months: 15.5 (1.1) vs. 31.3 (3.5) - 12 months: 15.0 (1.3) vs. 32.1 (4.5) Pain medication use, all p<0.001 - 1 week: 37% (17/46) vs. 100% (43/43), RR 0.37 (95% CI, 0.25 to 0.54)* - 1 month: 28% (13/46) vs. 77% (33/34), RR 0.29 (95% CI, 0.18 to 0.46)* - 3 months: 15% (7/46) vs. 60% (26/43), RR 0.25 (95% CI, 0.12 to 0.52)* - 6 months: 13% (6/46) vs. 56% (24/43), RR 0.23 (95% CI, 0.10 to 0.52)* - 12 months: 15% (7/46) vs. 65% (23/43), RR 0.28 (95% CI, 0.14 to 0.59)*	A vs. B Mortality: No cases reported Incident vertebral compression fractures: 8.7% (4/46) vs. 16.3% (7/43) at 12 months, RR 0.60 (95% CI, 0.19 to 1.90)

Vertebral Augmentation Procedure	Author, Year Trial	Results	Adverse Events and Withdrawals Due to Adverse Events
Vertebroplasty	Clark, 2016 VAPOUR	A vs. B Pain intensity (mean change from baseline [SD], 0 to 10 NRS) - 3 days: -3.5 (2.6) vs. -1.8 (2.3), mean difference -1.8 (95% CI, -2.7 to -0.8) - 14 days: -4.2 (2.7) vs. -3.0 (3.0), mean difference -1.2 (95% CI, -2.3 to -0.1) - 1 month: -4.6 (3.0) vs. -3.2 (2.7), mean difference -1.4 (95% CI, -2.5 to -0.4) - 3 months: -5.4 (3.5) vs. -4.1 (3.1), mean difference -1.3 (95% CI, -2.60 to 2.6) - 6 months: -6.1 (3.3) vs. -4.8 (3.1), mean difference -1.3 (95% CI, -2.6 to 0) Pain intensity (mean [SD], 0 to 100 VAS converted to 0 to 10 scale) - 14 days: 3.9 (2.8) vs. 4.9 (2.8), mean difference -1.0 (95% CI, -3.6 to 0.4) - 6 months: 2.3 (2.6) vs. 3.4 (2.7), mean difference -1.1 (95% CI, -2.3 to 0) NRS <4 (0 to 10 scale) - 3 days: 31% (18/58) vs. 9% (5/55), ARD 22% (95% CI, 8 to 36) - 14 days: 44% (24/55) vs. 21% (12/57), ARD 23% (95% CI, 6 to 39) - Thoracolumbar fractures: 61% (20/33) vs. 13% (4/31), ARD 48% (95% CI, 27 to 68) - Non-thoracolumbar fractures: 15% (3/20) vs. 30% (7/23), ARD -15% (95% CI, -40 to 9) - Fracture duration >3 to 6 weeks (n = 24): NR vs. NR, ARD -4% (95% CI, -39 to 31) - Fracture duration ≤3 weeks (n = 86): NR vs. NR, difference 31% (95% CI, 12 to 50) - 1 month: 51% (28/55) vs. 18% (10/57), ARD 33% (95% CI, 17 to 50) - 3 months: 55% (29/53) vs. 33% (17/52), ARD 22% (95% CI, 4 to 41) - 6 months: 69% (35/51) vs. 47% (24/51), ARD 22% (95% CI, 3 to 40) RDQ (mean change from baseline [SD], 0 to 24 scale) - 3 days: -4.5 (6.2) vs. -2.9 (4.4), mean difference -1.6 (95% CI, -3.6 to 0.4) - 14 days: -5.9 (5.8) vs. -4.1 (6.3), mean difference -1.8 (95% CI, -4.1 to 0.5) - 1 month: -6.9 (6.0) vs. -4.3 (5.6), mean difference -2.6 (95% CI, -4.8 to -0.4) - 3 months: -9.6 (7.7) vs. -6.4 (7.0), mean difference -3.2 (95% CI, -6.1 to -0.3) - 6 months: -11.7 (6.5) vs. -7.4 (6.9), mean difference -4.2 (95% CI, -6.9 to -1.6) EQ-5D (mean [SD], 0 to 1 scale) - 3 days: 0.69 (0.11) vs. 0.65 (0.09), mean difference 0.03 (95% CI, -0.05 to 0.07) - 14 days: 0.69 (0.10) vs. 0.68 (0.11), mean difference 0.01 (95% CI, -0.03 to 0.06) - 1 month: 0.75 (0.11) vs. 0.70 (0.11), mean difference 0.05 (95% CI, 0 to 0.09) - 3 months: 0.75 (0.12) vs. 0.71 (0.11), mean difference 0.03 (95% CI, -0.01 to 0.08) - 6 months: 0.80 (0.11) vs. 0.74 (0.12), mean difference 0.06 (95% CI, 0.01 to 0.10) QUALEFFO score (0 to 100 scale) - 14 days: 49 (13) vs. 55 (14), mean difference -6 (95% CI, -11 to -1) - 1 month: 49 (17) vs. 52 (15) , mean difference -4 (95% CI, -10 to 3) - 6 months: 38 (15) vs. 45 (16), mean difference -7 (95% CI, -13 to -1)	A vs. B Mortality: 4.9% (3/61) vs. 6.8% (4/59) at 6 months, RR 0.72 (95% CI, 0.17 to 3.10)* SAEs related to procedure: 3.3% (2/61; respiratory arrest or humerus fracture during transfer) vs. NR SAEs related to fracture: NR vs. 3.4% (2/59; spinal cord compression with resolution [n = 1] or paraplegia [n = 1]) Incident vertebral compression fracture: 4.9% (3/61) vs. 3.4% (2/59) at 6 months, RR 1.45 (95% CI, 0.25 to 8.37)*
Vertebroplasty	Clark, 2016 VAPOUR (Cont.)	Analgesic use - 3 days: 97% (57/59) vs. 98% (56/57), ARD -2% (95% CI, -7 to 4) - 14 days: 88% (49/56) vs. 91% (52/57), ARD -4% (95% CI, -15 to 8) - 1 month: 75% (41/55) vs. 88% (50/57), ARD -13% (95% CI, -28 to 1) - 3 months: 64% (34/53) vs. 83% (44/53), ARD -19% (95% CI, -35 to -2) - 6 months: 58% (29/50) vs. 76% (39/51), ARD -18% (95% CI, -36 to 1) Opiate use: no difference between groups, data not provided	

Vertebral Augmentation Procedure	Author, Year Trial	Results	Adverse Events and Withdrawals Due to Adverse Events
Vertebroplasty	Diamond, 2020 VAPOUR	A vs. B NRS score <4 (0 to 10 scale) - 3 days: 33% (14/43) vs. 7% (3/43), ARD 26% (95% CI, 10 to 42) - 14 days: 51% (21/41) vs. 20% (9/45) , ARD 31% (95% CI, 12 to 50) - 1 month: 55% (22/40) vs. 16% (7/45), ARD 29% (95% CI, 21 to 58) - 3 months: 54% (21/39) vs. 29% (12/41), ARD 25% (95% CI, 4 to 46) - 6 months: 74% (28/38) vs. 48% (19/40), ARD 26% (95% CI, 5 to 47) Pain intensity (mean [SD], 0 to 10 NRS) - 3 days: 4.8 (2.4) vs. 7.2 (2.0), mean difference -2.4 (95% CI, -3.5 to -1.5) - 14 days: 3.8 (2.6) vs. 5.6 (2.8), mean difference -1.9 (95% CI, -3.0 to -0.7) - 1 month: 3.7 (2.7) vs. 5.5 (2.5), mean difference -1.9 (95% CI, -3.0 to -0.7) - 3 months: 3.1 (3.1) vs. 4.5 (3.0), mean difference -1.4 (95% CI, -2.8 to -0.1) - 6 months: 2.1 (2.6) vs. 3.5 (2.6), mean difference -1.4 (95% CI, -2.6 to -0.3) RDQ (mean [SD], 0 to 24 scale) - 3 days: 14.0 (6.5) vs. 17.1 (4.2), mean difference -3.1 (95% CI, -5.4 to -0.7) - 14 days: 13.1 (6.2) vs. 16.0 (6.3), mean difference -2.9 (95% CI, -5.6 to -0.2) - 1 month: 12.9 (5.9) vs. 15.4 (5.9), mean difference -2.5 (95% CI, -5.1 to 0.1) - 3 months: 10.2 (7.5) vs. 13.6 (6.2), mean difference -3.4 (95% CI, -6.5 to -0.3) - 6 months: 9.0 (6.4) vs. 12.5 (6.5), mean difference -3.4 (95% CI, -6.4 to -0.5)	A vs. B SAEs: 4.6% (2/43; hypoventilation and humeral fracture) vs. 4.6% (2/43; spinal cord compression, 1 with paraplegia), RR 1.00 (95% CI, 0.15 to 6.78)*
Vertebroplasty	Farrokhi, 2011	A vs. B Pain intensity (mean [SD], 0 to 10 VAS) - 1 week: 3.3 (1.5) vs. 6.4 (2.1), mean difference -3.1 (95% CI, -3.72 to -2.28) - 2 months: 3.2 (2.2) vs. 6.1 (2.1), mean difference -2.9 (95% CI, -4.9 to -0.81) - 6 months: 2.2 (2.1) vs. 4.1 (1.5), mean difference -1.9 (95% CI, -3.25 to -0.55) - 12 months: 2.2 (2.1) vs. 4.1 (1.8), mean difference -1.9 (95% CI, -2.9 to 0.90) - 24 months: 2.8 (2.0) vs. 3.7 (2.0), mean difference -0.5 (-95% CI, 1.39 to 0.5) - 36 months: 1.8 (1.7) vs. 3.7 (2.5), mean difference -1.5 (95% CI, -9.85 to 6.85) ODI (mean [SD], 0 to 100 scale) - 1 week: 30.1 (3.0) vs. 44.0 (2.5), mean difference -14 (95% CI, -15 to -12.82) - 2 months: 15.0 (2.2) vs. 30.0 (3.1), mean difference -15 (95% CI, -16.76 to -13.24) - 6 months: 10.0 (2.0) vs. 21.0 (2.5), mean difference -11 (95% CI, -12.17 to -7.83) - 12 months: 8.0 (3.2) vs. 20.0 (1.7), mean difference -12 (95% CI, -13.5 to -11.5) - 24 months: 8.0 (2.2) vs. 20.0 (2.0), mean difference -12 (95% CI, -13.32 to -10.68) - 36 months: 8.0 (1.7) vs. 22.0 (1.2), mean difference -14 (95% CI, -14.91 to -13.09)	A vs. B Mortality: 5% (2/40) vs. 2.4% (1/42) at 12 months (no deaths reported from 12 to 36 months), RR 2.10 (95% CI, 0.20 to 22.26)* New fracture: 2.6% (1/38) vs. 15.4% (6/39) at 2 years, RR 0.17 (95% CI, 0.02 to 1.35)* Epidural cement leakage with lower extremity pain and weakness: 2.5% (1/40) vs. NR Venous emboli or infection: No cases

Vertebral Augmentation Procedure	Author, Year Trial	Results	Adverse Events and Withdrawals Due to Adverse Events
Vertebroplasty	Firanescu, 2018 & 2019 VERTOS IV	A vs. B Pain intensity (mean [SD], 0 to 10 VAS) - 1 day: 5.24 (2.49) vs. 4.82 (2.48), adjusted mean difference 0.43 (95% CI, -0.31 to 1.17) - 1 week: 4.38 (2.52) vs. 4.27 (2.48), adjusted mean difference 0.11 (95% CI, -0.63 to 0.85) - 1 month: 3.32 (2.52) vs. 3.73 (2.51), adjusted mean difference -0.41 (95% CI, -1.15 to 0.33) - 3 months: 2.69 (2.54) vs. 2.90 (2.58), adjusted mean difference -0.21 (95% CI, -0.96 to 0.54) - 6 months: 3.02 (2.59) vs. 3.41 (2.60), adjusted mean difference -0.39 (95% CI, -1.15 to 0.37) - 12 months: 2.72 (2.61) vs. 3.17 (2.72), adjusted mean difference -0.45 (95% CI, -1.24 to 0.37) On weak opioids at 1 month: 6.7% (6/90) vs. 4.7% (4/86), RR 1.43 (95% CI, 0.42 to 4.90)* On strong opioids at 1 month: 20.0% (18/90) vs. 22.1% (19/86), RR 0.90 (95% CI, 0.51 to 1.60)*	A vs. B Mortality: 8.8% (8/91) vs. 5.6% (5/89) at 1 year, RR 1.56 (95% CI, 0.53 to 4.60)* Incident vertebral compression fracture: 16.7% (15/90) vs. 22.1% (19/86) at 1 year; number of fractures 31 vs. 28 OR 0.71 (95% CI, 0.33 to 1.50) Underwent re-treatment for new fracture: 7% (6/90) vs. 7% (6/86), RR 0.95 (95% CI, 0.32 to 2.85)* Location of new fractures, all p = NS - Adjacent above: 52% (16/31) vs. 50% (14/28), OR 1.07 (95% CI, 0.38 to 2.96) - Between (sandwich): 3% (1/31) vs. 4% (1/28), OR 0.90 (955 CI, 0.05 to 15.10) - Distant: 45% (14/31) vs. 46% (13/28), OR 0.95 (95% CI, 0.34 to 2.65) Procedure related adverse reactions: 2.2% (2/90, 1 respiratory insufficiency and 1 vasovagal reaction) vs. NR
Vertebroplasty	Hansen, 2019 VOPE	A vs. B Pain at rest (mean [SD], 0 to 10 VAS) - 1 week: 2.5 (2.2) vs. 2.1 (2.1), mean difference 0.4 (95% CI, -0.9 to 1.7) - 4 weeks: 1.3 (2.2) vs. 1.0 (2.1). mean difference 0.3 (95% CI, -1.0 to 1.6) - 12 weeks: 0.8 (2.1) vs. 0.7 (2.1), mean difference 0.1 (95% CI, -1.1 to 1.3) - 52 weeks: 1.6 (2.4) vs. 1.6 (2.1), mean difference 0.0 (95% CI, -1.3 to 1.3) SF-36 PCS (mean [SD], 0 to 100 scale) - 3 months: 31.4 (10.0) vs. 33.9 (10.6), mean difference -2.5 (95% CI, -8.6 to 3.6) - 12 months: 31.9 (9.2) vs. 35.2 (11.9), mean difference -3.3 (95% CI, -9.7 to 3.1) SF-36 MCS (mean [SD], 0 to 100 scale) - 3 months: 49.7 (12.0) vs. 51.4 (11.0), mean difference -1.7 (95% CI, -8.5 to 5.1) - 12 months: 48.6 (10.8) vs. 53.6 (10.3), mean difference -5.0 (95% CI, -11.3 to 1.3) EQ-5D (mean [SD] 0 to 100 scale) - 3 months: 0.68 (0.23) vs. 0.71 (0.23), mean difference -0.03 (95% CI, -0.17 to 0.11) - 12 months: 0.67 (0.27) vs. 0.74 (0.22), mean difference -0.07 (95% CI, -0.22 to 0.08) Opioid use: Similar in two groups at 0 to 12 weeks and 12 months, data not provided	NR

Vertebral Augmentation Procedure	Author, Year Trial	Results	Adverse Events and Withdrawals Due to Adverse Events
Vertebroplasty	Kallmes, 2009 and Comstock, 2013 INVEST	A vs. B Pain intensity (mean [SD], 0 to 10 VAS) - 3 days: 4.2 (2.8) vs. 3.9 (2.9), ANCOVA mean difference 0.4 (95% CI, -0.5 to 1.5) - 14 days: 4.3 (2.9) vs. 4.5 (2.8), ANCOVA mean difference -0.1 (95% CI, -1.1 to 0.8) - 1 month: 3.9 (2.9) vs. 4.6 (3.0), ANCOVA mean difference -0.7 (95% CI, -1.7 to 0.3) - 3 months: 3.6 (2.8) vs. 4.3 (2.8), ANCOVA mean difference -0.7 (95% CI, -1.7 to 0.2) - 6 months: 3.7 (3.0) vs. 4.4 (2.9), ANCOVA mean difference -0.8 (95% CI, -1.8 to 0.2) - 12 months: 3.5 (2.9) vs. 4.5 (2.7), ANCOVA mean difference -1.0 (95% CI, -2.0 to -0.04) Pain improvement ≥30%: 64% (43/67) vs. 48% (29/61) at 1 month, RR 0.68 (95% CI, 0.46 to 1.02); 70% (44/63)* vs. 45% (25/56) at 1 year, RR 0.54 (95% CI, 0.35 to 0.85)* ANCOVA mean difference in pain intensity (95% CI) at 1 month - Patients with <13 weeks of pain: -0.8 (-2.5 to 0.8) - Patients with 14 to 26 weeks of pain: -1.3 (-3.4 to 0.8) - Patients with 27 to 52 weeks of pain: 0.0 (-1.6 to 1.7) Modified RDQ (mean [SD], 0 to 23 scale) - 3 days: 13.0 (5.2) vs. 12.5 (5.5), ANCOVA mean difference 0.9 (95% CI, -0.8 to 2.7) - 14 days: 12.4 (5.8) vs. 12.3 (5.9), ANCOVA mean difference 0.6 (95% CI, -1.2 to 2.4) - 1 month: 12.0 (6.3) vs. 13.0 (6.4), ANCOVA mean difference -0.7 (95% CI, -2.8 to 1.3) - 3 months: 10.8 (5.7) vs. 11.9 (6.4), ANCOVA mean difference -0.8 (95% CI, -2.6 to 1.2) - 6 months: 9.4 (6.1) vs. 11.4 (6.4), ANCOVA mean difference -1.6 (95% CI, -3.8 to 0.5) - 12 months: 10.2 (6.5) vs. 11.9 (6.2), ANCOVA mean difference -1.4 (95% CI, -3.6 to 0.9) RDQ improvement ≥30%: 40% (27/67) vs. 41% (25/41) at 1 month, RR 1.53 (95% CI, 0.99 to 2.35);* 70% (44/63) vs. 45% (25/56) at 1 year, RR 0.54 (95% CI, 0.35 to 0.85)* SF-36 PCS (mean [SD], 0 to 100 scale): 29.7 (9.6) vs. 28.7 (8.0) at 1 month, ANCOVA mean difference 1.0 (95% CI, -1.7 to 3.7) SF-36 MCS (mean [SD], 0 to 100 scale): 46.9 (12.0) vs. 45.6 (14.8) at 1 month, ANCOVA mean difference 1.0 (95% CI, -3.7 to 4.6) EQ-5D (mean [SD], 0 to 1 scale): 0.70 (0.18) vs. 0.64 (0.20) at 1 month, ANCOVA mean difference 0.05 (95% CI, -0.01 to 0.11) SOF-ADL (mean [SD], 0 to 18 scale): 7.7 (3.7) vs. 8.2 (3.6) at 1 month, ANCOVA mean difference -0.4 (95% CI, -1.6 to 0.8) Opioid use: 54% (36/67) vs. 43% (26/61) at 1 month, adjusted OR 1.15 (95% CI, 0.98 to 1.35)	A vs. B Mortality: None reported SAEs: 1.6% (1/64), injury to thecal sac) vs. 1.6% (1/61), tachycardia and rigors), RR 0.95 (95% CI, 0.06 to 14.90)*

Vertebral Augmentation Procedure	Author, Year Trial	Results	Adverse Events and Withdrawals Due to Adverse Events
Vertebroplasty	Klazen, 2010 and Venmans, 2011 VERTOS II	A vs. B Pain intensity (mean [SD], 0 to 10 VAS) - 1 day: 3.7 (2.4) vs. 6.7 (2.1), p<0.0001 - 1 week: 3.5 (2.5) vs. 5.6 (2.5), p<0.0001 - 1 month: 2.5 (2.5) vs. 4.9 (2.6), ANOVA mean difference -2.60 (95% CI, -3.37 to -1.74) - 3 months: 2.5 (2.7) vs. 3.9 (2.8), p = 0.025 - 6 months: 2.3 (2.7) vs. 3.9 (2.9), p = 0.014 - 1 year: 2.2 (2.7) vs. 3.8 (2.8), ANOVA mean difference -2.0 (95% CI, -2.80 to -1.13) RDQ (mean [SD], 0 to 24 scale) - 1 week: 13.7 (5.4) vs. 15.7 (4.7) - 1 month: 12.5 (6.3) vs. 14 (5.7) - 3 months: 10.5 (6.8) vs. 12.9 (6.0) - 6 months: 10.0 (6.6) vs. 11.7 (6.6) - 1 year: 9.6 (6.8) vs. 11.5 (6.9) QUALEFFO score (mean [SD], 0 to 100 scale) - 1 week: 45.6 (14.5) vs. 49.5 (15.5) - 1 month: 42.9 (15.8) vs. 47.1 (16.1) - 3 months: 39.6 (17.1) vs. 44.2 (16.6) - 6 months: 38.9 (17.8) vs. 42.3 (18.3) - 1 year: 39.7 (18.3) vs. 42.2 (17.9) EQ-5D (mean [SD], 0 to 1 scale) -1 week: 0.6 (0.3) vs. 0.5 (0.3) -1 month: 0.6 (0.2) vs. 0.5 (0.3) -3 months: 0.6 (0.3) vs. 0.6 (0.3) -6 months: 0.7 (0.3) vs. 0.6 (0.3) -1 year: 0.7 (0.3) vs. 0.6 (0.3) QALY (mean differences adjusted for baseline): 0.10 (95% CI, 0.006 to 0.014) at 1 month and 0.11 (95% CI, 0.04 to 0.18) at 1 year Use of drugs: Favored vertebroplasty at 1 day (p<0.0001), 1 week (p = 0.001), and 1 month (p = 0.03); data otherwise not reported Total costs (€ [SD]): 2612 (148) vs. 3838 (746) at 1 month (p<0.0001); 9183 (10779) vs. 6327 (11873) at 1 year (p = 0.09)	A vs. B Mortality: 5.0% (5/101) vs. 5.9% (6/101) at 1 year, RR 0.83 (95% CI, 0.26 to 2.64)* Incident vertebral facture: 16.5% (15/91) vs. 24.7% (21/85) at 1 year, RR 0.67 (95% CI, 0.37 to 1.21)*
Vertebroplasty	Leali, 2016	A vs. B Pain intensity (mean [SD NR], 0 to 10 VAS): 2.3 vs. NR at 1 day ODI (mean [SD NR], 0 to 100 scale): 31.7 vs. NR at 1 day Discontinued analgesics: 65% (120/200) vs. NR at 2 days - Reports patients in usual care group had no change in pain or disability, but data not provided - Reports results at 6 weeks, 3 months, and 6 months similar in both groups, but data not provided	A vs. B Mortality: 0.5% (1/200) vs. 1.5% (3/200) at 6 months, RR 0.33 (95% CI, 0.03 to 3.18)* Minor complications: 1.0% (2/200) vs. NR New vertebral fracture above treated fracture: 1.5% (3/200) vs. 0% (0/200) at 6 weeks, RR 7.00 (95% CI, 0.36 to 134.65)*

Vertebral Augmentation Procedure	Author, Year Trial	Results	Adverse Events and Withdrawals Due to Adverse Events
Vertebroplasty	Rousing, 2009 & 2010	A vs. B Pain intensity (mean [SD], 0 to 10 VAS) - 3 months: 1.8 (2.3) vs. 2.6 (3.2), p = 0.32 - 1 year: 2.0 (2.1) vs. 2.9 (2.8), p = 0.29 SF-36 PCS (mean [SD], 0 to 100 scale) - 3 months: 34.0 (9.0) vs. 29.3 (10.3), p = 0.12 - 1 year: 32.1 (9.1) vs. 30.5 (11.5), p = 0.63 SF-36 MCS (mean [SD], 0 to 100 scale) - 3 months: 48.9 (11.8) vs. 46.2 (15.0), p = 0.51 - 12 months: 48.7 (12.7) vs. 49.0 (11.2), p = 0.93 EQ-5D (mean [SD], 0 to 1 scale) - 3 months: 0.73 (0.14) vs. 0.54 (0.30), p = 0.04 - 12 months: 0.68 (0.17) vs. 0.57 (0.25), p = 0.19 Dallas Pain Questionnaire, daily activities (mean [SD], 0 to 100 scale) - 3 months: 47.1 (31.3) vs. 57.4 (36.7), p = 0.33 - 12 months: 53.0 (32.3) vs. 53.6 (36.7), p = 0.95 Dallas Pain Questionnaire, anxiety and depression (mean [SD], 0 to 100 scale) - 3 months: 28.7 (28.2) vs. 40.0 (38.4), p = 0.30 - 12 months: 31.3 (26.8) vs. 35.3 (30.0), p = 0.70	A vs. B Mortality: 3.8% (1/26) vs. 4.2% (1/26) at 3 months, RR 1.00 (95% CI, 0.07 to 15.15);* 7.7% (2/26) vs. 8.3% (2/24) at 1 year, RR 0.92 (95% CI, 0.14 to 6.05)* Any incident vertebral fracture: 11.5% (3/26) vs. 4.2% (1/24) at 3 months, RR 2.77 (95% CI, 0.31 to 24.85);* 15.4% (4/26) vs. 12.5% (3/24) at 12 months, RR 1.23 (95% CI, 0.31 to 4.94)* Adjacent incident vertebral fracture: 3.8% (1/26) vs. 0% (0/24) at 3 months, RR 2.78 (95% CI, 0.12 to 65.09)* 3.8% (1/26) vs. 0% (0/24) at 12 months, RR 2.78 (95% CI, 0.12 to 65.09) Symptomatic incident vertebral fracture: 0% (0/26) vs. 12.5% (3/24) at 12 months, RR 0.13 (95% CI, 0.01 to 2.43)*
Vertebroplasty	Voormolen, 2007 VERTOS	A vs. B Pain intensity (mean [range], 0 to 10 VAS) -1 day: 4.7 (1 to 8) vs. 7.1 (5 to 10), mean difference -2.4 (95% CI, -3.7 to -1.0) -2 weeks: 4.9 (0 to 10) vs. 6.4 (3 to 9), mean difference -1.5 (95% CI, -3.2 to 0.2) Analgesic use (mean [range], 0 to 3 scale) -1 day: 1.1 (0 to 3) vs. 2.5 (1 to 3), mean difference -1.4 (95% CI, -2.1 to -0.8) -2 weeks: 1.2 (0 to 3) vs. 2.6 (2 to 3), mean difference -1.4 (95% CI, -2.0 to -0.8) RDQ (mean [range], 0 to 24 scale) -2 weeks: 13 (3 to 22) vs. 18 (9 to 23), mean difference -5 (95% CI, -8.4 to -1.2) QUALEFFO (mean [range, 0 to 100 scale) -2 weeks: 53 (28 to 79) vs. 67 (40 to 88), mean difference -14 (95% CI, -24.7 to -3.4)	A vs. B Mortality: None reported Incident vertebral compression fracture: 11.1% (2/18) vs. 0% (0/16) at 2 weeks, RR 4.47 (95% CI, 0.23 to 86.77)*

Vertebral Augmentation Procedure	Author, Year Trial	Results	Adverse Events and Withdrawals Due to Adverse Events
Vertebroplasty	Yang, 2016	A vs. B Pain intensity (mean [SD], 0 to 10 VAS) -1 day: 4.2 (1.1) vs. 7.3 (1.1), mean difference -3.1 (95% CI, -3.5 to -2.7) -1 week: 3.4 (1.3) vs. 6.5 (1.2), mean difference -3.1 (95% CI, -3.6 to -2.6) -1 month: 2.5 (0.7) vs. 4.9 (1.0), mean difference -2.4 (95% CI, -2.7 to -2.1) -3 months: 2.1 (0.6) vs. 3.9 (0.8), mean difference -1.8 (95% CI, -2.1 to -1.5) -6 months: 2.3 (0.7) vs. 3.5 (0.7), mean difference -1.2 (95% CI, -1.5 to -0.9) -1 year: 1.9 (0.5) vs. 3.1 (0.7), mean difference -1.2 (95% CI, -1.4 to -1.0) ODI (mean [SD], 0 to 100 scale) -1 week: 63 (9) vs. 80 (6), mean difference -17 (95% CI, -20 to -14) -1 month: 47 (10) vs. 71 (8), mean difference -24 (95% CI, -27 to -21) -3 months: 30 (8) vs. 56 (9), mean difference -26 (95% CI, -29 to -23) -6 months: 29 (8) vs. 46 (8), mean difference -17 (95% CI, -20 to -14) -1 year: 30 (7) vs. 38 (8), mean difference -8 (95% CI, -11 to -5) QUALEFFO (mean [SD], 0 to 100 scale) -1 week: 65 (7) vs. 75 (7), mean difference -10 (95% CI, -13 to -7) -1 month: 50 (7) vs. 66 (5), mean difference -16 (95% CI, -18 to -14) -3 months: 42 (6) vs. 56 (5), mean difference -14 (95% CI, -16 to -12) -6 months: 39 (5) vs. 52 (4), mean difference -13 (95% CI, -15 to -11) -1 year: 41 (6) vs. 49 (5), mean difference -8 (95% CI, -10 to -6) Able to walk one day after procedure (A) vs. able to walk after two weeks bed rest (B): 100% (56/56) vs. 23.5% (12/51), RR 4.12 (95% CI, 2.54 to 6.69) Very satisfied or satisfied: 73.2% (41/56) vs. 58.8% (30/51), RR 0.65 (95% CI, 0.38 to 1.12)*	A vs. B Mortality: None reported Any adverse event: 16.1% (9/56) vs. 35.3% (18/51), RR 0.46 (95% CI, 0.23 to 0.92) Incident vertebral fracture: 8.9% (5/56) vs. 7.8% (4/51) at 1 year, RR 1.14 (95% CI, 0.32 to 4.01)
Kyphoplasty	Berenson, 2011 CAFE Trial	A vs. B Pain (mean, 0 to 10 NRS): 3.5 (2.2) vs. 7.0 (1.5) at 7 days, mean difference in change from baseline -3.5 (95% CI -3.8 to -3.2); 3.3 (2.6) vs. 6.9 (1.1) at 1 month, mean difference in change from baseline -3.3 (95% CI, -3.6 to -3.0) RDQ (mean, 0 to 24): 9.1 vs. 18.0 at 1 month, mean difference -8.4 (95% CI -7.6 to -9.2) SF-36 Mental Component Summary (mean difference in change from baseline, 0 to 100): 8.4 (95% CI, 7.7 to 9.1) at 1 month SF-36 Physical Component Summary (mean difference in change from baseline, 0 to 100): 11.1 (95% CI, 10.7 to 11.5) at 1 month Karnofsky Performance Status (mean difference in change from baseline, 0 to 100) 15.3 (95% CI, 13.5 to 17.1) at 1 month Karnofsky Performance Status score improved >10 points: 65.1% (41/63) vs. 26.5% (13/49) at 1 month, RR 2.45 (95% CI, 1.49 to 4.04)* Karnofsky Performance Status score ≥70: 74.6% (47/63) vs. 38.8% (19/49) at 1 month, RR 1.92 (95% CI, 1.32 to 2.81)* Analgesic use: 52.3% (34/65) vs. 82.0% (41/50) at 1 month, RR 0.64 (95% CI, 0.49 to 0.83)*	A vs. B vs. C Mortality: 32.9% (23/70) vs. 18.8% (12/64), RR 1.75 (95% CI, 0.95 to 3.22)* Any adverse event: 37.1% (26/70) vs. 29.7% (19/64), RR 1.25 (95% CI, 0.77 to 2.03)* Adverse events resulting in death: 2.9% (2/70) vs. 1.6% (1/64), RR 1.83 (95% CI, 0.17 to 19.69)* Back pain: 5.7% (4/70) vs. 7.8% (5/64), RR 0.73 (95% CI, 0.20 to 2.60)* Incident symptomatic fracture: 2.9% (2/70) vs. 7.8% (5/64), RR 0.36 (95% CI, 0.07 to 1.82)* Injury or procedural complications: 5.7% (4/70) vs. 0% (0/64), RR 8.24 (95% CI, 0.45 to 150.10)*

Vertebral Augmentation Procedure	Author, Year Trial	Results	Adverse Events and Withdrawals Due to Adverse Events
Kyphoplasty	Wardlaw, 2009 FREE Trial Additional publications: Boonen, 2013 and Van Meirhaege, 2013	A vs B Pain intensity (mean [SD], 0 to 10 VAS) -1 week: 3.5 (2.4) vs. 6.0 (2.4), ANOVA mean difference -2.2 (95% CI, -2.8 to -1.6) -1 month: 3.4 (2.4) vs. 5.5 (2.3) -3 months: 2.9 (2.3) vs. 4.5 (2.2) -6 months: 2.7 (2.3) vs. 4.3 (2.2) -1 year: 2.8 (2.2) vs. 3.8 (2.1), ANOVA mean difference -0.9 (95% CI, -1.5 to -0.3) RDQ (mean [SD], 0 to 24 scale) -1 month: 11 (5.8) vs. 15 (5.7), ANOVA mean difference -4.0 (95% CI, -5.5 to -2.6) -3 months: 9 (5.5) vs. 13 (5.3) -6 months: 8 (5.4) vs. 12 (5.3) -1 year: 9 (5.2) vs. 11 (5.1), ANOVA mean difference -2.6 (95% CI, -4.1 to -2.0) SF-36 PCS (mean [SD], 0 to 100 scale) -1 month: 33 (8.9) vs. 27 (8.6), ANOVA mean difference 5.2 (95% CI, 2.9 to 7.4) -3 months: 35 (8.8) vs. 31 (8.0), ANOVA mean difference 4.0 (95% CI, 1.6 to 6.3) -6 months: 37 (8.6) vs. 33 (8.0), ANOVA mean difference 3.2 (95% CI, 0.9 to 5.6) -1 year: 36 (8.3) vs. 34 (7.9), ANOVA mean difference 1.5 (95% CI, -0.8 to 3.9) EQ-5D (mean [SD, 0 to 1 scale) -1 month: 0.54 (0.36) vs. 0.37 (0.34), ANOVA mean difference 0.18 (95% CI, 0.08 to 0.28) -3 months: 0.58 (0.35) vs. 0.49 (0.32) -6 months: 0.62 (0.34) vs. 0.51 (0.32) -1 year: 0.60 (0.34) vs. 0.51 (0.32), ANOVA mean difference 12 (95% CI, 0.01 to 0.22) Strong opioid use -1 month: 5% (6/114) vs. 8% (9/115), RR 0.67 (95% CI, 0.25 to 1.83)* -1 year: 4% (5/117) vs. 5% (5/101), RR 0.86 (95% CI, 0.26 to 2.90)* Opioid + nonopioid use -1 month: 41% (47/114) vs. 57% (65/115), RR 0.73 (95% CI, 0.56 to 0.96)* -1 year: 24% (28/117) vs. 29% (29/101), RR 0.83 (95% CI, 0.53 to 1.30)*	A vs B Mortality: 6.0% (9/149) vs. 4.6% (7/151) at 12 months, RR 1.30 (95% CI, 0.50 to 3.41) Serious adverse events (death, life-threatening injury, or permanent impairment; or required extended hospital stay or intervention to prevent impairment): 38.9% (58/149) vs. 35.8% (54/151), RR 1.09 (95% CI, 0.81 to 1.46) Any adverse event: 87.2% (130/149) vs. 80.1% (122/151), RR 1.08 (95% CI, 0.98 to 1.19) Withdrawal due to adverse events: 0.7% (1/149) vs. 0.7% (1/151), RR 1.01 (95% CI, 0.06 to 16.05) New or worsening fracture: 33.0% (38/115) vs. 25.3% (24/95) at 1 year; ARD 7.7% (95% CI, -4.5% to 20.0%)

Vertebral Augmentation Procedure	Author, Year Trial	Results	Adverse Events and Withdrawals Due to Adverse Events
Kyphoplasty	Boonen, 2011 FREE Trial Secondary publication of Wardlaw, 2009	A vs. B Pain (mean [SD], 0 to 10 VAS) -2 years: 2.8 (2.8) vs. 3.7 (2.8), ANOVA mean difference -0.80 (95% CI, -1.39 to -0.20) RDQ (mean [SD], 0 to 24 scale) -2 years: 9 (6.2) vs. 10 (6.3), ANOVA mean difference -1.43 (95% CI NR); p = 0.051 SF-36 PCS (mean [SD], 0 to 100 scale) -2 years: 36 (12.5) vs. 34 (12.5), ANOVA mean difference 1.68 (95% CI, -0.63 to 3.99) EQ-5D (mean [SD], 0 to 1 scale) 2 years: 0.61 (0.37) vs. 0.53 (0.38), ANOVA mean difference 0.12 (95% CI, 0.06 to 0.18) Satisfaction (mean difference [95% CI] on 0 to 20 scale): 2.31 (1.19 to 3.43) at 24 months Opioid use -6 months: 29.8% (37/124) vs. 42.9% (48/112), RR 0.69 (95% CI, 0.49 to 0.98)* -1 year: 28.0% (33/118) vs. 33.7% (34/101), RR 0.83 (95% CI, 0.56 to 1.24)* -2 years: 8.8% (10/114) vs. 9.5% (10/105), RR 0.92 (95% CI, 0.40 to 2.12)*	A vs B Mortality: 8.0% (12/149) vs. 7.3% (11/151) at 24 months, RR1.11 (95% CI, 0.50 to 2.43) SAEs: 49.7% (74/149) vs. 48.3% (73/151), RR 1.03 (95% CI, 0.82 to 1.29) Any adverse event: 89.9% (134/149) vs. 88.7% (134/151), RR 1.01 (95% CI, 0.94 to 1.10) Withdrawal due to adverse events: 0.7% (1/149) vs. 0.7% (1/151), RR 1.01 (95% CI, 0.06 to 16.05) Incident vertebral fracture (any): 47.5% (56/118) vs. 44.1% (45/102), RR 1.08 (95% CI, 0.81 to 1.44) Incident adjacent vertebral fracture: 23.7% (28/118) vs. 16.7% (17/102), RR 1.42 (95% CI, 0.83 to 2.45)* Clinically recognized incident vertebral fracture: 22.0% (26/118) vs. 16.7% (17/102), RR 1.32 (95% CI, 0.76 to 2.29)*
Kyphoplasty	Van Meirhaeghe, 2013 FREE Trial Secondary publication of Wardlaw, 2009	see Wardlaw 2009 and Boonen 2011	A vs B Serious adverse events: 16.1% (24/149) vs. 11.2% (17/151) at 30 days, RR 1.43 (95% CI, 0.80 to 2.55) Any adverse event: 63.1% (94/149) vs. 36.4% (55/151) at 30 days, RR 1.73 (95% CI, 1.36 to 2.21) Infection: 11.4% (17/149) vs. 5.3% (8/151), RR 2.15 (95% CI, 0.96 to 4.84)

*Calculated

Abbreviations: ANCOVA = analysis of covariance; ANOVA = analysis of variance; ARD = absolute risk difference; BMD = bone mineral density; CAFE = Cancer Patient Fracture Evaluation; CI = confidence interval; CT = computed tomography; EQ-5D = EuroQOL 5-Dimension Questionnaire; FREE = Fracture Reduction Evaluation; HR = hazard ratio; INVEST = Investigational Vertebroplasty Safety and Efficacy Trial; IQR = interquartile range; IU = International Unit; LBP = low-back pain; MCS = Mental Component Summary; MMSE = Mini-Mental State Exam; MR = magnetic resonance; MRI = magnetic resonance imaging; MRI-STIR = magnetic resonance imaging short tau inversion recovery; NR = not reported; NRS = numeric rating scale; NS = not significant; ODI = Oswestry Disability Index; OR = odds ratio; PCS = Physical Component Summary; PMMA = polymethylmethacrylate; PVP = percutaneous vertebroplasty; QALY = quality-adjusted life-year; QUALEFFO = Quality of Life Questionnaire of the European Foundation for Osteoporosis; RCT = randomized controlled trial; RDQ = Roland–Morris Disability Questionnaire; RR = risk ratio; SAE = serious adverse event; SD = standard deviation; SF-36 = Short-Form 36; SOF–ADL = Study of Osteoporotic Fractures–Activities of Daily Living; TL = thoracolumbar junction; VAPOUR = vertebroplasty for acute painful osteoporotic fractures; VAS = visual analogue scale; VB = vertebral body; VCF = vertebral compression fracture; VERTOS = percutaneous vertebroplasty compared with optimal pain medication treatment: short-term clinical outcome of patients with subacute or chronic painful osteoporotic vertebral compression fractures; VERTOS II = vertebroplasty vs. conservative treatments in acute osteoporotic vertebral compression fractures; VERTOS IV = vertebroplasty vs. sham procedure for painful acute osteoporotic vertebral compression fractures; VOPE = vertebroplasty vs. sham for treating osteoporotic vertebral compression fractures: a double blind RCT

See Appendix F, List of Included Studies, for full citations

Table G-4. Trials of cooled and pulsed radiofrequency denervation – study characteristics

Type of Denervation	Author, Year Trial	Study Design Duration	Number of Centers/Provider Type Country	Eligibility Criteria	Interventions
Cooled radiofrequency	Cohen, 2008	RCT 3 months (prior to crossover)	1 center, anesthesia pain medicine U.S.	≥18 years with sacroiliac pain (axial low back or buttock pain ≥6 months, tenderness overlying the sacroiliac joint[s]), failure to respond to conservative therapy (including >2 months pain relief with sacroiliac joint corticosteroid injection), pain relief ≥75% following single diagnostic sacroiliac joint injection Excluded: focal neurologic signs or symptoms, radiologic evidence of a symptomatic herniated disc, spondyloarthropathy, untreated coagulopathy, and unstable medical or psychiatric illness	A: Cooled radiofrequency denervation: For S1 to S3 lateral branches, 17-gauge, 75-mm cooled electrodes with 4 mm active tips (Baylis Medical, Montreal, Quebec, Canada) placed between 3 and 5 mm from the lateral border of the sacral foramina at predesignated positions. Placement confirmed with electrostimulation (concordant sensation at 0.5 V or less). Administered 0.5 ml 2% lidocaine, followed by water-cooled radiofrequency heating system (Pain Management SInergy System; Baylis Medical) and generator (PMG-115-TD, V2.0A; Baylis Medical) applied for 2 minutes at 60°C, with target tissue heated to 75°C (resulting lesion diameter 8 to 10 mm). -For L4 and L5 dorsal rami, conventional radiofrequency with 22-gauge SMK-C10 cannula with 5-mm active tips inserted parallel to the course of the nerve until bone contacted. Placement confirmed with electrostimulation at 50 Hz, with concordant sensation achieved at ≤0.5 V; absence of leg contractions verified with stimulation at 2 Hz up to ≤2 V. Administered 0.5 ml 2% lidocaine followed by 90 second, 80°C radiofrequency lesion B: Sham radiofrequency: Electrodes positioned similarly and electrostimulation performed in identical manner. Administered 0.5 2% lidocaine but no current administered (procedure time similar to active treatment). Offered crossover to conventional (non-cooled) radiofrequency denervation as described above.
Cooled radiofrequency	McCormick, 2019	RCT 6 months	1 center, anesthesia pain medicine U.S.	Low back pain ≥6 months, NRS ≥4 on 0 to 10 scale, no response to conventional therapy, pain diagram suggesting possibility of facet-mediated pain, referred pain not beyond the knee (if present), positive response to one set of diagnostic medial branch nerve blocks defined as >75% reduction in pain following diagnostic blocks with local anesthetic (0.5 mL of 0.5% bupivacaine or 2% lidocaine) Excluded: focal neurologic signs or symptoms, radiologic evidence of symptomatic herniated disc or nerve root impingement related to spinal stenosis, previous radiofrequency ablation for similar symptoms, active systemic or local infection, coagulopathy or other bleeding disorder, current anticoagulants or antiplatelet medications	A: Cooled radiofrequency denervation: 17-gauge cooled radiofrequency ablation introducer needle placed at medial branch nerve targets, 18-gauge cooled radiofrequency ablation probe with a 4 mm active tip (Coolief Cooled Radiofrequency Kit, Halyard Health, Alpharetta, Georgia) with 2 mm gap between the electrode tip and the base of the superior articular process. Motor testing (2.0 V, 2 Hz) performed at each target site. Administered 1 ml of 2% lidocaine through the introducer needle, followed by cooled radiofrequency ablation lesioning for 165 seconds at each site, generator temperature set to 60°C (intralesional temperature >80°C). Administered 0.5 ml 0.5% bupivacaine following procedure B: Conventional radiofrequency denervation: 20-gauge traditional radiofrequency ablation probes with 10 mm active tips (Baylis Medical, Montreal, Canada) placed at medial branch nerve targets using parallel technique. Motor testing and local anesthetic as described for cooled radiofrequency. Radiofrequency lesioning performed for 90 seconds at 80°C at each target site.

Type of Denervation	Author, Year Trial	Study Design Duration	Number of Centers/Provider Type Country	Eligibility Criteria	Interventions
Cooled radiofrequency	Patel, 2012	RCT 3 months (prior to crossover)	1 center, anesthesia pain medicine. U.S.	>18 years, predominantly axial pain below the L5 vertebrae >6 months; 3-day average NRS between 4 and 8 (0 to 10 scale); failure to achieve adequate improvement with comprehensive non-operative treatment, other sources of LBP excluded; ≥75% dual relief between 4 hours and 7 days following S1-S3 lateral branch and L5 dorsal ramus diagnostic block Excluded: history of potentially confounding intervertebral disc disease or facet joint pain; Beck Depression Inventory score >20; irreversible psychological barriers to recovery; spinal pathology that may impede recovery such as spondylolisthesis at L5/S1, or scoliosis; symptomatic moderate or severe foraminal or central canal stenosis; systemic infection or localized infection at anticipated introducer entry site; concomitant cervical or thoracic pain; uncontrolled or acute illness; chronic severe conditions; active radicular pain; immunosuppression; worker's compensation, injury litigation, or disability remuneration; >30 mg morphine daily or equivalent use; active smokers	A: Cooled radiofrequency denervation: For L5 dorsal ramus, introducer needle placed under fluoroscopy to junction of S1 superior articular process and sacral ala; stylet replaced with SInergy Probe (Kimberly Clark Health Care). Accurate electrode placement confirmed and 0.5 cc 2% lidocaine and 0.75% bupivacaine injected, then radiofrequency energy delivered for 150 seconds at 60°C. For S1 to S3 lateral branch sites, 27-gauge needle placed under fluoroscopy 7 mm lateral to S1 posterior sacral foramen for localization. Introducer advanced and 17-gauge, 75-mm cooled electrode with 4 mm active tip (Kimberly Clark Health Care) inserted 2 mm from surface of the sacrum. Impedance confirmed at 100 to 500 W. Radiofrequency lesioning performed as described for L5 dorsal ramus. To form an arc-shaped treated area lateral to the S1 posterior sacral foramen, 2 additional lesions were created at that level. Similar technique used for S2 and S3 sites (2 lesions at S3). Post-lesioning, 1 cc of a 1:1 mixture of 2% lidocaine and 0.75% bupivacaine administered. B: Sham radiofrequency: Needle placement as described for A, but no cooled radiofrequency lesioning performed

Type of Denervation	Author, Year Trial	Study Design Duration	Number of Centers/Provider Type Country	Eligibility Criteria	Interventions
Pulsed radiofrequency	Kroll, 2008	RCT 3 months	1 center, anesthesia pain medicine U.S.	≥18 years, unilateral or bilateral lumbar back pain >1 month, ASA physical status I to III with no radiating symptoms below the knee, radiographically ruled out disc herniation and spinal stenosis, symptoms reproduced by extension-rotation of the lumbar spine and palpation of the paraspinal region, >50% pain reduction based on subjects' mean VAS pain assessment for ≥3 hours after two separate diagnostic medial branch blocks Excluded: history of previous back surgery, neurological deficits, claudication, active psychiatric disorder, bleeding disorder, active infection, involved in current litigation	A: Pulsed radiofrequency denervation: Radiofrequency cannula was either 21-gauge, 100-mm (Model PMC21-100-5; Baylis Medical Co., Montreal, QC, Canada) or 20-gauge, 145-mm length (Model PMC20-145-5, Baylis Medical Co) with 5 mm active tip. Under fluoroscopy, positioned cannula for the L1 to L4 medial branches at the superior, medial edges of the posterior surfaces of the transverse processes at the junction with the articular pillars and for the L5 medial branch at the junction of the medial end of the ala of the sacrum with the articular pillar. Baylis Pain Management Generator (Model PMG-115) with 100-mm (Model PMP21-100) or 145-mm (Model PMP-20- 145) radiofrequency probe used. Placed radiofrequency probes through the cannulae and confirmed placement by provocative sensory testing at a frequency of 50 Hz at <1 volt and absence of motor stimulation in the lower extremity at a frequency of 2 Hz and up to 2.5 volts. Pulsed radiofrequency lesioning was delivered at 42° C with a pulse duration of 20 ms and pulse rate of two Hz for 120 seconds. B: Continuous radiofrequency denervation: As above, with radiofrequency lesioning was at 80°C for 75 seconds.

Type of Denervation	Author, Year Trial	Study Design Duration	Number of Centers/Provider Type Country	Eligibility Criteria	Interventions
Pulsed radiofrequency	Moussa, 2020	RCT 3 years	1 center, neurosurgery Egypt	≥18 years with continuous chronic LBP with or without pain radiating into the upper leg for ≥1 year with unsatisfactory improvement in response to ≥3 months of conservative treatment, clinical manifestations suggesting facet joint pain (e.g., paraspinal tenderness and increasing pain on spinal extension), pain VAS ≥7 (0 to 10 scale) on 2 different occasions separated by at least 2 weeks, complete or near complete reduction of VAS score 30 minutes after fluoroscopically-guided 0.5% bupivacaine diagnostic block of medial dorsal branch of segmental L3, L4, and L5 nerve roots Excluded: surgical causes of low back pain (e.g., spondylolisthesis and fracture spine, prior lumbar surgery, major comorbidities (e.g., uncontrolled diabetes mellitus, uncontrolled hypertension, cardiac diseases, malignancy and bleeding diathesis), prior radiofrequency treatment for LBP, presence of radicular syndromes, infection at the injection site, pregnancy, possible work compensation litigation, score ≥50 on the Zung Self Rating Depression Scale	A: Pulsed radiofrequency denervation of dorsal root ganglia: Thermocouple electrode (CSK, 20 cm length with 10 mm active tip) placed perpendicular to the dorsal root ganglion under fluoroscopy. Motor and sensory stimulation at 2 and 50 Hz to confirmed electrode tip proximity to dorsal root ganglia with presence of ipsilateral lower limb muscle contractions and paraesthesia at <0.5 V. Pulsed radiofrequency (NeuroTherm NT1100, St. Jude Medical, Inc., Saint Paul, MN, United States) of the dorsal root ganglia L4, L5, and S1 administered with 4 2 minute cycles using 2 Hz stimulation at 45 V unilaterally or bilaterally, with the cannulae tip temperature not exceeding 42°C. B: Continuous radiofrequency denervation of medial branch: As for pulsed radiofrequency, except electrode was placed parallel to the medial dorsal branch (junction of the superior articular process and the transverse process where the medial dorsal branch is, without the electrode tip projecting past the ventral border of the facet column); absence of ipsilateral lower limb muscle contractions and paresthesia on stimulation; and continuous radiofrequency performed at L3 to 4, L4 to 5 and L5-S1 levels at 85°C for 90 seconds with 3 lesions at each level (2 mm intervals between lesions) C: Sham radiofrequency denervation: As above, except radiofrequency generator switched on but did not delivering current to the thermocouple electrode. All patients received 1 ml of a mixture of equal volume of bupivacaine 0.5 % and methylprednisolone acetate 40 mg/mL at the conclusion of the procedure through the electrode needle.

Type of Denervation	Author, Year Trial	Study Design Duration	Number of Centers/Provider Type Country	Eligibility Criteria	Interventions
Pulsed radiofrequency	Tekin, 2007	RCT 1 years	1 center, anesthesia pain medicine Turkey	>17 years with >6 months of continuous LBP with or without radiation into the upper leg, focal tenderness over the facet joints, pain on hyperextension, no finding of obvious neurologic defect, no indication for low back surgery, no radicular syndrome, unresponsiveness to traditional conservative treatments, positive (>50% improvement in pain, duration consistent with expected duration of local anesthetic used) response to single diagnostic medial branch block using 0.3 ml 2% lidocaine Excluded: prior radiofrequency treatment, coagulation disturbances, allergies to radiopaque contrast media or local anesthetics, malignancy	A. Pulsed radiofrequency denervation: 22-gauge 10 cm SMK-C10 electrode, 2-mm active tip placed at angle between the superior articular process and transverse process for the segmental medial branches of lumbar nerve roots. Impedance verified at 300 to 700 Ohms and sensory stimulation (50 Hz) reproduced pain at <0.5 V and did not result in leg contractions at 1 V; contractions of the multifidus muscle observed between 0.3 and 0.5 V L1 to L3 or L3 to L5 treated; 0.5 ml 2% prilocaine followed with 2 Hz pulsed radiofrequency waves for 4 minutes (45 V) to a temperature of 42 degrees C. B. Continuous radiofrequency denervation: As above, except used an electrode with 10-mm active tip and treated continuously for 90 seconds to 80 degrees C C. Sham radiofrequency denervation: Electrodes and thermocouple probes positioned similarly without switching on radiofrequency current, only 0.3 ml 0.5% bupivacaine injected

Abbreviations: ASA American Society of Anesthesiologists; LBP = low-back pain; NR = not reported; NRS = numeric rating scale; ODI = Oswestry Disability Index; RCT = randomized controlled trial; VAS = visual analogue scale; WHO World Health Organization

See Appendix F, List of Included Studies, for full citations

Table G-5. Trials of cooled and pulsed radiofrequency denervation – additional study characteristics

Type of Denervation	Author, Year Trial	Sample Characteristics	Screened Eligible Randomized Analyzed	Sponsor	Quality
Cooled radiofrequency	Cohen, 2008	Mean (SD) age, years: 51.85 (13.35) Female: 61% Race: NR Mean duration of back pain: NR Failed back surgery syndrome: 21% Opioid use: 46% Mean (SD) opioid dosage, morphine equivalents per day: 52.68 (46.41) A vs. B Baseline pain intensity (mean [SD], 0 to 10 NRS): 6.1 (1.8) vs. 6.5 (1.9) Baseline ODI (mean [SD], 0 to 100 scale): 37.1 (10.6) vs. 47.9 (9.3)	Screened: 90 Eligible: NR Lost to followup: 0 Randomized: 28 (14 vs. 14) Lost to followup: None reported Analyzed: 28 (14 vs. 14) Crossover: 9 (0 vs. 9) at 1 month and 11 (0 vs. 11) at 3 months	John P. Murtha Neuroscience and Pain Institute, Army Regional Anesthesia and Pain Medicine Initiative, National Institutes of Health	Fair
Cooled radiofrequency	McCormick, 2019	Mean (SD) age, years: 55.82 (13.61) Female: 59% Race: NR Mean (SD) duration of pain, months: 86.15 (90.39) % (SD) relief from diagnostic block: 85.38% (15.44) Mean (SD) morphine equivalents: 11.02 (21.46) A vs. B Baseline pain intensity (mean [SD], 0 to 10 NRS): 7.4 vs. 6.9 (1.5) Baseline ODI (mean [SD, 0 to 100 scale): 29.1 (7.0) vs. 26.7 (8.7)	Screened: 48 Eligible and enrolled: 48 Randomized: 43 (22 vs. 21) Completed followup: 40 (21 vs. 19) Analyzed: 39 (21 vs. 19)	Midwest Pain Society	Good
Cooled radiofrequency	Patel, 2012	Mean (SD) age, years: 58.7 (14.7) Female: 72% Race: NR Duration of pain 6 to 12 months: 13.7% Duration of pain 12 to 24 months: 15.7% Duration of pain >24 months: 68.6% Prior treatment with opioids: 45.1% Prior treatment with antiinflammatory drugs: 66.7% Prior treatment with injections: 41.2% A vs. B Baseline pain intensity (mean [SD], 0 to 10 NRS): 6.1 (1.3) vs. 5.8 (1.3) Baseline SF-36 physical functioning (mean [SD], 0 to 100 scale): 50 (20) vs. 47 (24) Baseline ODI (mean [SD], 0 to 100 scale): 37 (14) vs. 35 (10) Baseline Assessment of Quality of Life (AQoL) score (mean [SD], 0 to 1 scale): 0.60 (0.19) vs. 0.54 (0.16)	Screened: 304 Eligible: 151 Randomized: 51 (34 vs. 17) Completed followup: 51 (34 vs. 17) at 3 months, 44 (27 vs. 17) at 6 months Analyzed: 51 (34 vs. 17) at 3 months Crossover: 16 (0 vs. 16)	Baylis Medical	Fair

Type of Denervation	Author, Year Trial	Sample Characteristics	Screened Eligible Randomized Analyzed	Sponsor	Quality
Pulsed radiofrequency	Kroll, 2008	Mean (SD) age, years: 58.25 (10.13) Female: 54% Race: NR Pain duration: NR A vs. B Baseline pain intensity (mean [SD], 0 to 100 VAS transformed to 0 to 10 scale): 6.4 (1.8) vs. 7.6 (1.6) ODI (mean [SD], 0 to 100 scale): 44.9 (10.4) vs. 52.0 (17.3)	Screened: NR Eligible: NR Randomized: 50 (25 vs. 25) Completed followup: 26 (13 vs. 13) Analyzed: 26 (13 vs. 13)	Anesthesia Research Fund, Henry Ford Hospital	Poor
Pulsed radiofrequency	Moussa, 2020	Mean, (SD) age, years: 56.97 (NR) Female: 65.3% Race: NR Duration of low back pain: NR Baseline pain medication use: NR Baseline pain intensity: NR Baseline ODI: NR	Screened: NR Eligible: 241 Randomized: 150 (50 vs. 50 vs. 50) Completed followup: 0 at 6 months; 8 at 12 months; 27 at 3 years (not reported by group) Analyzed: 150 (50 vs. 50 vs. 50)	No funding	Poor
Pulsed radiofrequency	Tekin, 2007	Mean (SD) age, years: 59.33 (8.33) Female: 57% Race: NR Mean (SD) duration of pain, months: 35.13 (11.88) A vs. B vs. C Baseline pain intensity (mean [SD, 0 to 10 VAS): 6.6 (1.6) vs. 6.5 (1.5) vs. 6.8 (1.6) Baseline ODI (mean [SD, 0 to 100 scale): 39.4 (5.0) vs. 39.2 (3.5) vs. 40.1 (2.8)	Screened: NR Eligible: 60 Randomized: 60 (20 vs. 20 vs. 20) Completed followup: NR Analyzed: 60	NR	Fair

Abbreviations: IQR = interquartile range; LBP = low-back pain; NR = not reported; NRS = numeric rating scale; ODI = Oswestry Disability Index; SD = standard deviation; VAS = visual analogue scale; WHO World Health Organization

See Appendix F, List of Included Studies, for full citations

Table G-6. Trials of cooled and pulsed radiofrequency denervation – results

Type of Denervation	Author, Year Trial	Results	Adverse Events and Withdrawals Due to Adverse Events
Cooled radiofrequency	Cohen, 2008	A vs. B. vs. C Pain intensity (mean [SD], 0 to 10 NRS) - 1 month: 2.4 (2.0) vs. 6.3 (2.4), p<0.05 - 3 months: 2.4 (2.3) vs. 6 (0), p>0.05 - 6 months: 2.6 (2.2) vs. no data ODI (mean [SD]. 0 to 100 scale) - 1 month: 20.9 (10.9) vs. 43.6 (14), p<0.05 - 3 months: 18.5 (11.6) vs. 24 (8.5), p>0.05 - 6 months: 22.6 (10.6) vs. no data Positive Global Perceived Effect (pain improved, treatment improved ability to perform daily activities, and satisfied with treatment and would recommend to others) - 1 month: 93% (13/14) vs. 21% (3/14), p<0.05 - 3 months: 83% (10/12) vs. 0% (0/2), p>0.05 - 6 months: 89% (8/9) vs. no data >20% reduction in opioid use or complete cessation of nonopioid analgesic - 1 month: 77% (10/13) vs. 8% (1/13), p<0.05 - 3 months: 82% (9/11) vs. 0% (0/2), p>0.05 - 6 months: 67% (8/12)) vs. no data Successful outcome (≥50% improvement in pain, positive Global Perceived Effect, and ≥10 point improvement in ODI or ≥4 point improvement in ODI and reduction in medication use [as defined above]) - 1 month: 79% (11/14) vs. 14.3% (2/14), RR 5.50 (95% CI, 1.48 to 20.42) - 3 months: 64% (9/14) vs. 0% (0/2), RR 0.36 (95% CI, 0.18 to 0.72)* - 6 months: 57% (8/14) vs. no data Duration of pain relief (mean [SD], months): 5.8 (4.2) vs. 0.7 (1.6	Serious complications: None reported Temporary worsening pain typically lasting between 5 and 10 days after the procedure reported; 1 patient reported transient nonpainful buttock paresthesias that resolved without therapy in the radiofrequency treatment group
Cooled radiofrequency	McCormick, 2019	A vs. B Pain intensity (mean change from baseline [SD], 0 to 10 NRS) -6 months: -3.8 (2.5) vs. -3.0 (3.2), p = 0.41 (no differences at 1 or 3 months) NRS improved ≥50% -6 months: 52.3% (11/21) vs. 44.4% (8/18), RR 1.18 (95% CI, 0.61 to 2.28) ODI (mean change from baseline [SD], 0 to 100 scale) -6 months: -11.3 (11.2) vs. -8.1 (12.3), p = 0.40 (no difference at 1 or 3 months) ODI improved ≥30% -6 months: 61.9% (13/21) vs. 44.4% (8/18), RR 1.39 (95% CI, 0.75 to 2.58) Global Impression of Change (median [IQR], 1 to 7 scale) -6 months: 2 (3) vs. 2 (3), p = 0.51	Serious adverse events: None reported Self-limited post-procedure pain reported in 2 patients

Type of Denervation	Author, Year Trial	Results	Adverse Events and Withdrawals Due to Adverse Events
Cooled radiofrequency	Patel, 2012	A vs. B Pain intensity (mean change from baseline [SD], 0 to 10 NRS) -1 month: -2.7 (2.6) vs. -1.7 (2.0), p = 0.16 -3 months: -2.4 (2.7) vs. -0.8 (2.4), p = 0.04 SF-36 physical functioning (mean change from baseline [SD], 0 to 100 scale) -1 month: 10 (17) vs. 5 (12), p = 0.24 -3 months: 14 (19) vs. 3 (12), p = 0.04 ODI (mean change from baseline [SD], 0 to 100 scale) -1 month: -12 (14) vs. -4 (11), p = 0.046 -3 months: -11 (17) vs. 2 (6), p = 0.01 AQoL (mean [SD], 0 to 1 scale) -3 months: 0.69 (0.21) vs. 0.56 (0.21), p = 0.048 Pain intensity improved ≥50%: 53% (18/34) vs. 29% (5/17) at 3 months, RR 1.80 (95% CI, 0.80 to 4.01) Treatment success (pain intensity improved ≥50% and either 10 point increase in SF-36 bodily pain or 10 point decrease in ODI): 47% (16/34) vs. 12% (2/17) at 3 months, RR 4.00 (95% CI, 1.04 to 15.43) Global Perceived Effect pain "decreased a lot" or "completely gone") -3 months: 47% (6/34) vs. 8% (n/N unclear) at 3 months, p<0.05 ODI improved ≥10 points: 41.2% (14/34) vs. 5.9% (1/17) at 3 months, RR 7.00 (95% CI, 1.00 to 48.88)	NR
Pulsed radiofrequency	Kroll, 2008	A vs. B Pain intensity (mean [SD], 0 to 100 VAS transformed to 0 to 10 scale) - 3 months: 5.1 (2.1) vs. 5.2 (2.7); mean improvement (SD) -1.1% (4.5) vs. -2.5% (5.0), p = 0.46 ODI (mean [SD], 0 to 100 scale): - 3 months: 42.2 (19.0) vs. 41.7 (16.9); mean improvement (SD) -4.1% (44.3) vs. -18.3% (30.7), p = 0.35	No adverse events during procedure and no complications at 3 months

Type of Denervation	Author, Year Trial	Results	Adverse Events and Withdrawals Due to Adverse Events
Cooled radiofrequency	Moussa, 2020	A vs. B vs. C Success (defined as ≥50% reduction in median back pain intensity without a drop in daily activities or raise in analgesic intake or ≥25% in median back pain intensity with ≥25% increase in daily activities and ≥25% drop in analgesic intake) -3 months: 90% (45/50) vs. 68% (34/50) vs. 60% (30/50), RR 0.31 (95% CI, 0.12 to 0.79)* A vs. B, RR 0.25 (95% CI, 0.10 to 0.61)* A vs. C -6 months: 84% (42/50) vs. 34% (27/50) vs. 20% (10/50), RR 0.35 (95% CI, 0.17 to 0.70)* A vs. B, RR 0.20 (95% CI, 0.10 to 0.38)* A vs. C -1 year: 78% (39/50) vs. 40% (20/50) vs. 8% (4/50), RR 0.29 (95% CI, 0.17 to 0.50)* A vs. B, RR 0.24 (95% CI, 0.14 to 0.41)* A vs. C - 2 years: 70% (35/50) vs. 24% (12/50) vs. 2% (1/50), RR 0.39 (95% CI, 0.25 to 0.62)* A vs. B, RR 0.31 (95% CI, 0.20 to 0.47)* A vs. C - 3 years: 68% (34/50) vs. 10% (5/50) vs. 2% (1/50), RR 0.35 (95% CI, 0.23 to 0.54)* A vs. B, RR 0.33 (95% CI 0.22 to 0.49)* A vs. C Back pain intensity (mean change [SD NR], 0 to 10 VAS) -3 months: -8.5 vs. -5.4 vs. -5.2, p = 0.01 -6 months: -8.3 vs. -5.2 vs. -2.3, p = 0.01 -1 year: -8.1 vs. -5 vs. -0.7, p = 0.01 -2 years: -7.9 vs. -2.3 vs. -0.5, p = 0.01 -3 years: -7.7 vs. -2.2 vs.- 0.4, p = 0.003 >50% reduction in back pain -3 months: 84% (42/50) vs. 64% (32/50) vs. 56% (28/50), RR 0.44 (95% CI, 0.21 to 0.93)* A vs. B, RR 0.36 (95% CI, 0.18 to 0.74)* A vs. C -6 months: 78% (39/50) vs. 48% (24/50) vs. 16% (8/50), RR 0.42 995% CI, 0.23 to 0.76)* A vs. B, RR 0.26 (95% CI, 0.15 to 0.45)* A vs. C -1 year: 74% (37/50) vs. 36% (18/50) vs. 6% (3/50), RR 0.41 (95% CI, 0.24 to 0.68)* A vs. B, RR 0.28 (95% CI, 0.17 to 0.44)* A vs. C -2 years: 70% (35/50) vs. 12% (6/50) vs. 2% (1/50), RR 0.34 (95% CI, 0.22 to 0.52)* A vs. B, RR 0.31 (95% CI, 0.20 to 0.47)* A vs. C -3 years: 68% (34/50) vs. 6% (3/50) vs. 2% (1/50), RR 0.34 (95% CI, 0.23 to 0.51)* A vs. B, RR 0.33 (95% CI, 0.22 to 0.49)* A vs. C ODI (mean change [SD NR], 0 to 100 scale) -3 months: -50.5 vs. -34. 9 vs. -33.6, p = 0.05 -6 months: -48.1 vs. -30.3 vs. -10.8, p = 0.03 -1 year: -43.9 vs.- 26.4 vs. -5.5, p = 0.01 -2 years: -39.3 vs. -15.3 vs. -3.7, p = 0.01 -3 years: -39.2 vs. -6.3 vs. -2, p = 0.004 WHO analgesic intake score (mean change [SD NR], 0 to 3 scale) -3 months: 2.4 vs. 2 vs. 2, p = 0.04 -6 months: 2.3 vs. 1.9 vs. 0.8, p = 0.04 -1 year: 2.1 vs. 1.8 vs. 0.2, p = 0.03 -2 years: 2 vs. 0.6 vs. 0.1, p = 0.01 -3 years: 1.9 vs. 0.5 vs. 0.1, p = 0.003	NR

Type of Denervation	Author, Year Trial	Results	Adverse Events and Withdrawals Due to Adverse Events
Cooled radiofrequency	Tekin, 2007	A vs. B vs. C Pain (mean [SD], 0 to 10 VAS) -6 months: 2.9 (1.6) vs. 2.3 (1.3) vs. 3.1 (0.8), p = 0.19 for A vs. B and p = 0.62 for A vs. C -1 year: 3.5 (1.3) vs. 2.4 (1.1) vs. 3.9 (1.2), p = 0.004 for A vs. B and p = 0.31 for A vs. C ODI (mean [SD], 0 to 100 scale) -6 months: 25.3 (6.9) vs. 25.1 (6.4) vs. 28.9 (5.7), p = 0.92 for A vs. B and p = 0.07 for A vs. C -1 year: 28.5 (6.1) vs. 28.0 (7.1) vs. 33.6 (5.7), p = 0.81 for A vs. B and p = 0.006 for A vs. C Analgesic use: 75% (15/20) vs. 40% (8/20) vs. 95% (19/20) at 1 year, RR 1.88 (95% CI, 1.04 to 3.39) for A vs. B Patient satisfaction good or excellent: 85% (17/20) vs. 95% (19/20) vs. 70% (14/20) at 1 year	NR

Abbreviations: CI = confidence interval; IQR = interquartile range; LBP = low-back pain; NR = not reported; NRS = numeric rating scale; ODI = Oswestry Disability Index; RR = risk ratio; SD = standard deviation; VAS = visual analogue scale; WHO World Health Organization

See Appendix F, List of Included Studies, for full citations

Table G-7. Trials of intradiscal and facet joint platelet rich plasma for presumed discogenic back pain – study characteristics

Author, Year Trial	Study Design Duration	Setting/Provider Type Country	Eligibility Criteria	Interventions
Tuakli-Wosornu, 2016	RCT 8 weeks	1 center, physical medical and rehabilitation U.S.	Refractory LBP ≥6 months, failure of conservative treatment measures (oral medications, rehabilitation therapy, and/or injection therapy), maintained intervertebral disc height ≥50%, disc protrusion <5 mm on MRI or CT, concordant pain on provocative discography (1 to 2 ml) with presence of a grade 3 or 4 annular fissure Excluded: presence of a known bleeding disorder, current anticoagulation therapy, pregnancy, systemic infection or skin infection over the puncture site, allergy to contrast agent, presence of a psychiatric condition (e.g., posttraumatic stress disorder, schizophrenia), solid bone fusion preventing access to the disc, severe spinal canal compromise at the levels to be investigated, extrusions or sequestered disc fragments, previous spinal surgery, spondylolysis, spondylolisthesis, discordant pain on discography, presence of a grade 5 annular fissure with demonstrated extravasation of contrast	A: Platelet-rich plasma injection: 1 to 2 ml of platelet-rich plasma injected mid-portion of discs that elicited concordant pain on discography with fluoroscopic guidance (for multiple discs, a total of 3 to 4 ml was split among the discs) B: Sham: 1 to 2 ml contrast agent, as above

Abbreviations: CT = computed tomography; LBP = low-back pain; MRI = magnetic resonance imaging; RCT = randomized controlled trial; U.S. = United States

See Appendix F, List of Included Studies, for full citations

Table G-8. Trials of intradiscal and facet joint platelet rich plasma for presumed discogenic back pain – additional study characteristics

Author, Year Trial	Sample Characteristics	Screened Eligible Randomized Complete Followup Analyzed	Sponsor	Quality
Tuakli-Wosornu, 2016	Mean (SD) age, years: 42.32 (8.41) Female: 66% Race: NR Pain duration: NR A vs. B Baseline current pain (mean [SD], 0 to 10 NRS): 4.74 (2.21) vs. 4.61 (2.21) Baseline best pain (mean [SD] 0 to 10 NRS): 2.81 (1.78) vs. 2.08 (1.74) Baseline worst pain (mean [SD], 0 to 10 NRS): 7.98 (1.56) vs. 7.72 (1.53) Baseline Functional Rating Index (mean [SD], 0 to 100): 51.47 (15.62) vs. 45.37 (15.61) Baseline SF-36 bodily pain (mean [SD], 0 to 100): 43.28 (21.11) vs. 47.92 (21.13) Baseline SF-36 physical function (mean [SD], 0 to 100): 56.40 (18.52) vs. 56.11 (18.54)	Screened: 109 Eligible: 84 Randomized: 58 (36 vs. 22) Completed followup: 57 (35 vs. 22) at 8 weeks Analyzed: 47 (29 vs. 18) at 8 weeks	Hospital for Special Surgery Physiatry Research & Education Fund, Harvest Technologies Corporation	Fair

Abbreviations: NR = not reported; NRS = numeric rating scale; SD = standard deviation

See Appendix F, List of Included Studies, for full citations

Table G-9. Trials of intradiscal and facet joint platelet rich plasma for presumed discogenic back pain – results

Author, Year Trial	Results	Adverse Events and Withdrawals Due to Adverse Events
Tuakli-Wosornu, 2016	A vs. B Current pain (mean [SD], 0 to 10 NRS) -1 week: 4.21 (1.99) vs. 4.78 (1.99), mean difference -0.57 (95% CI, -1.74 to 0.60) -4 weeks: 4.00 (2.21) vs. 4.61 (2.21), mean difference -0.61 (95% CI, -1.91 to 0.69) -8 weeks: 3.09 (2.59) vs. 4.39 (2.59), mean difference -1.30 (95% CI, -2.82 to 0.22) Best pain (mean [SD], 0 to 10 NRS) -1 week: 2.88 (1.83) vs. 2.44 (1.82), mean difference 0.44 (95% CI, -0.63 to 1.51) -4 weeks: 2.53 (1.83) vs. 2.28 (1.82), mean difference 0.25 (95% CI, -0.82 to 1.32) -8 weeks: 2.00 (2.06) vs. 2.72 (2.12), mean difference -0.72 (95% CI, -1.95 to 0.51) Worst pain (mean [SD], 0 to 10 NRS) -1 week: 6.86 (1.94) vs. 7.39 (1.95), mean difference -0.53 (95% CI, -1.67 to 0.61) -4 weeks: 6.41 (1.88) vs. 7.11 (1.91), mean difference -0.70 (95% CI, -1.82 to 0.42) -8 weeks: 5.82 (2.33) vs. 6.83 (2.33), mean difference -1.01 (95% CI, -2.38 to 0.36) Functional Rating Index (mean [SD], 0 to 100 scale) -1 week: 49.83 (15.72) vs. 45.99 (15.74), mean difference 3.84 (95% CI, -5.41 to 13.09) -4 weeks: 43.25 (16.68) vs. 44.17 (17.14), mean difference -0.92 (95% CI, -10.90 to 9.06) - 8 weeks: 37.99 (19.60) vs. 44.45 (19.60); mean difference -6.46 (95% CI, -17.99 to 5.07) SF-36 Bodily Pain (mean [SD], 0 to 100 scale) -1 week: 40.52 (21.76) vs. 47.22 (21.76), mean difference -6.70 (95% CI, -19.50 to 6.10) -4 weeks: 55.17 (19.98) vs. 47.22 (19.98), mean difference 7.95 (95% CI, -3.80 to 19.70) -8 weeks: 61.29 (22.19) vs. 52.78 (22.19), mean difference 8.51 (95% CI, -4.54 to 21.56) SF-36 Physical Function (mean [SD], 0 to 100 scale) - 1 week: 51.63 (20.46) vs. 51.28 (20.04), mean difference 0.35 (95% CI, -11.53 to 12.23) - 4 weeks: 58.43 (21.17) vs. 60.97 (21.43), mean difference -2.54 (95% CI, -15.08 to 10.00) - 8 weeks: 61.70 (22.89) vs. 57.08 (22.91), mean difference 4.62 (95% CI, -8.85 to 18.09) "Satisfied" or "would undergo procedure again": 55.6% (15/27) vs. 17.6% (3/17), RR 3.15 (95% CI, 1.07 to 9.28)	No adverse events of disk space infection, neurologic injury, or progressive herniation

Abbreviations: CI = confidence interval; NR = not reported; NRS = numeric rating scale; RR = risk ratio; SD = standard deviation; SF-36 = Short-Form 36

See Appendix F, List of Included Studies, for full citations

Table G-10. Trial of stem cells for presumed discogenic back pain –study characteristics

Author, Year	Study Design Duration	Setting/Provider Type Country	Eligibility Criteria	Interventions	Sample Characteristics	Screened Eligible Randomized Analyzed	Sponsor	Quality
Amirdelfan, 2020	RCT 3 years	13 centers; provider type not reported Australia and U.S.	≥18 years with documented diagnosis of degenerative disc disease at one level from L1 to S1, chronic LBP for ≥6 months, prior failed 3 months conservative treatment; provocative discography optional but if performed, only patients with concordant pain at 1 level eligible Excluded: comorbidities that could confound the safety or efficacy of mesenchymal precursor cells	A. Intradiscal allogenic mesenchymal precursor cells: 6 million cells (1.0 mL of the 30 million/5 mL MPC product) mixed with 1.0 mL of 1% hyaluronic acid B. Intradiscal allogenic mesenchymal precursor cells: 18 million cells (1.0 mL of the 90 million/5 mL MPC product) mixed with 1.0 mL of 1% hyaluronic acid C. Intradiscal hyaluronic acid: 2 ml of 1% hyaluronic acid D. Intradiscal saline: 2 ml sterile saline Use of imaging guidance not reported	Mean age, years: 41.9 Female: 47% Race/ethnicity: 86% white, 4% Black, 2% Asian, 1% other, 7% Hispanic Mean duration of degenerative disc disease, years: 5.81 Mean VAS (scale 0 to 100): 70.12 Mean ODI: 49.06 A vs. B vs. C vs. D Male sex: 40% vs. 70% vs. 50% vs. 50%; B vs. C or D: p≤0.50 Mean age, years: 45.1 vs. 37.9 vs. 40.3 vs. 44.5; B vs. D: p≤0.50 Mean duration of degenerative disc disease, years: 8.4 vs. 3.7 vs. 5.0 vs. 5.9; B vs. D: ≤0.50 Baseline pain (mean [SD], 0 to 100 VAS transformed to 0 to 10 scale): 6.97 (2.46) vs. 7.15 (2.46) vs. 7.18 (2.40) vs. 6.69 (2.40) Baseline ODI (mean [SD NR]): 52.07 (16.34) vs. 50.67 (16.34) vs. 46.80 (15.96) vs. 44.40 (15.96)	Screened: 148 Eligible: 100 Enrolled: 100 Analyzed: 100 (data imputed)	Mesoblast	Fair

Abbreviations: LBP = low-back pain; MPC = mesenchymal precursor cell; NR = not reported; ODI = Oswestry Disability Index; RCT = randomized controlled trial; SD = standard deviation; U.S. = United States; VAS = visual analogue scale

See Appendix F, List of Included Studies, for full citations

Table G-11. Trial of stem cells for presumed discogenic back pain – results

Author, Year Trial	Results	Adverse Events and Withdrawals Due to Adverse Events
Amirdelfan, 2020	A vs. B vs. C vs. D (p>0.05 unless indicated) Pain, LSM change from baseline (SD), 0 to 10 VAS, adjusted for post-treatment interventions) -30 days: -2.80 (2.29) vs. -2.97 (2.50) vs. -2.05 (2.44) vs. -2.32 (2.44) -3 months: -3.87 (2.49) vs. -3.53 (2.48) vs. -1.91 (2.43) vs. -2.89 (2.44); **A or B vs. C: p≤0.05** -6 months: -4.27 (2.49) vs. -3.60 (2.50) vs. -2.85 (2.43) vs. -3.22 (2.42) -1 year: -3.66 (2.48) vs. -3.82 (2.48) vs. -2.42 (2.42) vs. -1.73 (2.39); **A or B vs. D: p≤0.05** -2 years: -3.48 (2.37) vs. -3.27 (2.47) vs. -2.40 (2.38) vs. -1.20 (2.39); **A or B vs. D: p≤0.05** -3 years: -3.21 (2.48) vs. -4.22 (2.45) vs. -3.01 (2.36) vs. -1.60 (2.39); **B vs. D: p≤0.05** Pain, proportion with ≥30% reduction in pain VAS from baseline; RR (95% CI) -6 months: 76.7% (23/30) vs. 66.7% (20/30) vs. 50.0% (10/20) vs. 60.0% (12/20) A vs. C: 1.53 (0.95 to 2.48) A vs. D: 1.28 (0.85 to 1.92) B vs. C: 1.33 (0.80 to 2.21) B vs. D: 1.11 (0.72 to 1.72) -1 year: 63.3% (19/30) vs. 66.7% (20/30) vs. 40.0% (8/20) vs. 35.0% (7/20) A vs. C: 1.58 (0.87 to 2.89) A vs. D: 1.81 (0.94 to 3.49) B vs. C: 1.67 (0.92 to 3.02) B vs. D: 1.90 (1.00 to 3.64) -2 years: 53.3% (16/30) vs. 53.3% (16/30) vs. 35.0% (7/20) vs. 15.0% (3/20) A vs. C: 1.52 (0.77 to 3.02) A vs. D: 3.56 (1.19 to 10.64) B vs. C: 1.52 (0.77 to 3.02) B vs. D: 3.56 (1.19 to 10.64) -3 years: 53.3.0% (16/30) vs. 56.7% (17/30) vs. 45.0% (9/20) vs. 20.0% (4/20) A vs. C: 1.19 (0.66 to 2.14) A vs. D: 2.67 (1.04 to 6.81) B vs. C: 1.26 (0.71 to 2.24) B vs. D: 2.83 (1.12 to 7.19)	A vs. B vs. C vs. D Mortality: no deaths in any group Serious adverse events: 16.7% (5/30) vs. 10.0% (3/30) vs. 5.0% (1/20) vs. 15.0% (3/20) A vs. C: RR 3.33 (95% CI, 0.42 to 26.45) A vs. D: RR 1.11 (95% CI, 0.30 to 4.14) B vs. C: RR 2.00 (95% CI, 0.22 to 17.89) B vs. D: RR 0.67 (95% CI, 0.15 to 2.98) Any adverse event: 16.7% (5/30) vs. 10.0% (3/30) vs. 5.0% (1/20) vs. 15.0% (3/20) A vs. C: RR 3.33 (95% CI, 0.42 to 26.45) A vs. D: RR 1.11 (95% CI, 0.30 to 4.14) B vs. C: RR 2.00 (95% CI, 0.22 to 17.89) B vs. D: RR 0.67 (95% CI, 0.15 to 2.98) Withdrawal due to adverse events: 6.7% (2/30) vs. 6.7% (2/30) vs. 0% vs. 0% A vs. C: RR 3.39 (95% CI, 0.17 to 67.05) A vs. D: RR 3.39 (95% CI, 0.17 to 67.05) B vs. C: RR 3.39 (95% CI, 0.17 to 67.05) B vs. D: RR 3.39 (95% CI, 0.17 to 67.05)

Author, Year Trial	Results	Adverse Events and Withdrawals Due to Adverse Events
Amirdelfan, 2020, continued	Pain, proportion with ≥50% reduction in pain VAS from baseline; RR (95% CI) -6 months: 66.7% (20/30) vs. 60.0% (18/30) vs. 40.0% (8/20) vs. 50.0% (10/20) A vs. C: 1.67 (0.92 to 3.02) A vs. D: 1.33 (0.80 to 2.21) B vs. C: 1.50 (0.81 to 2.76) B vs. D: 1.20 (0.71 to 2.03) -1 year: 60.0% (18/30) vs. 53.3% (16/30) vs. 30.0% (6/20) vs. 20.0% (4/20) A vs. C: 2.00 (0.96 to 4.15) A vs. D: 3.00 (1.19 to 7.56) B vs. C: 1.78 (0.84 to 3.76) B vs. D: 2.67 (1.04 to 6.81) -2 years: 50.0% (15/30) vs. 36.7% (11/30) vs. 30.0% (6/20) vs. 15.0% (3/20) A vs. C: 1.67 (0.78 to 3.56) A vs. D: 3.33 (1.11 to 10.04) B vs. C: 1.22 (0.54 to 2.77) B vs. D: 2.44 (0.78 to 7.68) -3 years: 43.3% (13/30) vs. 50.0% (15/30) vs. 35.0% (7/20) vs. 20.0% (4/20) A vs. C: 1.24 (0.60 to 2.55) A vs. D: 2.17 (0.82 to 5.70) B vs. C: 1.43 (0.71 to 2.87) B vs. D: 2.50 (0.97 to 6.44) Function, ODI LSM change from baseline (SD) 0 to 100 scale; adjusted for post-treatment interventions -30 days: -13.07 (14.98) vs. -12.39 (15.00) vs. -10.25 (14.66) vs. -10.80 (14.68) -3 months: -17.31 (14.99) vs. -16.82 (14.66) vs. -12.14 (14.61) vs. -14.00 (14.68) -6 months: -18.02 (14.45) vs. -21.66 (15.53) vs. -14.67 (12.26) vs. -12.64 (14.57) -1 year: -17.54 (14.91) vs. -20.38 (14.94) vs. -14.44 (14.55) vs. -9.31 (14.41); B vs. D: p≤0.05 -2 years: -19.44 (14.89) vs. -21.40 (14.84) vs. -11.65 (14.30) vs. -9.06 (14.41); A or B vs. D: p≤0.05 -3 years: -18.44 (14.89) vs. -25.84 (14.73) vs. -14.12 (14.20) vs. -7.69 (14.40); A or B vs. D: p≤0.05	

Author, Year Trial	Results	Adverse Events and Withdrawals Due to Adverse Events
Amirdelfan, 2020, continued	Function, proportion with ≥10 point reduction ODI from baseline; RR (95% CI) -6 months: 70.0% (21/30) vs. 66.7% (20/30) vs. 50.0% (10/20) vs. 40.0% (8/20) A vs. C: 1.40 (0.85 to 2.30) A vs. D: 1.75 (0.97 to 3.14) B vs. C: 1.33 (0.80 to 2.21) B vs. D: 1.67 (0.92 to 3.02) -1 years: 50.0% (15/30) vs. 66.7% (20/30) vs. 50.0% (10/20) vs. 25.0% (5/20) A vs. C: 1.00 (0.57 to 1.76) A vs. D: 2.00 (0.86 to 4.63) B vs. C: 1.33 (0.80 to 2.21) B vs. D: 2.67 (1.20 to 5.94) -2 years: 56.7% (17/30) vs. 50.0% (15/30) vs. 35.0% (7/20) vs. 25.0% (5/20) A vs. C: 1.62 (0.82 to 3.18) A vs. D: 2.27 (1.00 to 5.15) B vs. C: 1.43 (0.71 to 2.87) B vs. D: 2.00 (0.86 to 4.63) -3 years: 53.3% (16/30) vs. 53.3% (16/30) vs. 35.0% (7/20) vs. 20.0% (4/20) A vs. C: 1.52 (0.77 to 3.02) A vs. D: 2.67 (1.04 to 6.81) B vs. C: 1.52 (0.77 to 3.02) B vs. D: 2.67 (1.04 to 6.81) Function, proportion with ≥15 point reduction ODI from baseline; RR (95% CI) -6 months: 63.3% (19/30) vs. 50.0% (15/30) vs. 45.0% (9/20) vs. 25.0% (5/20) A vs. C: 1.41 (0.81 to 2.45) A vs. D: 2.53 (1.13 to 5.67) B vs. C: 1.11 (0.61 to 2.03) B vs. D: 2.00 (0.86 to 4.63) -1 years: 50.0% (15/30) vs. 50.0% (15/30) vs. 35.0% (7/20) vs. 20.0% (4/20) A vs. C: 1.43 (0.71 to 2.87) A vs. D: 2.50 (0.97 to 6.44) B vs. C: 1.43 (0.71 to 2.87) B vs. D: 2.50 (0.97 to 6.44) -2 years: 46.7% (14/30) vs. 46.7% (14/30) vs. 30.0% (6/20) vs. 15.0% (3/20) A vs. C: 1.56 (0.72 to 3.36) A vs. D: 3.11 (1.02 to 9.45) B vs. C: 1.56 (0.72 to 3.36) B vs. D: 3.11 (1.02 to 9.45) -3 years: 46.7% (14/30) vs. 50.0% (15/30) vs. 25.0% (5/20) vs. 15.0% (3/20) A vs. C: 1.87 (0.80 to 4.37) A vs. D: 3.11 (1.02 to 9.45) B vs. C: 2.00 (0.86 to 4.63) B vs. D: 3.33 (1.11 to 10.04)	

Author, Year Trial	Results	Adverse Events and Withdrawals Due to Adverse Events
Amirdelfan, 2020, continued	Function, WPAI score, change from baseline -3 years: B vs. D: p = 0.05 Pain and function composite outcome, proportion with ≥30% reduction in pain VAS and ≥10 point reduction ODI from baseline; RR (95% CI) -6 months: 63.3% (19/30) vs. 50.0% (15/30) vs. 35.0% (7/20) vs. 40.0% (8/20) A vs. C: 1.81 (0.94 to 3.49) A vs. D: 1.58 (0.87 to 2.89) B vs. C: 1.43 (0.71 to 2.87) B vs. D: 1.25 (0.66 to 2.38) -1 years: 46.7% (14/30) vs. 56.7% (17/30) vs. 40.0% (8/20) vs. 20.0% (4/20) A vs. C: 1.17 (0.60 to 2.26) A vs. D: 2.33 (0.90 to 6.07) B vs. C: 1.42 (0.76 to 2.64) B vs. D: 2.83 (1.12 to 7.19) -2 years: 46.7% (14/30) vs. 43.3% (13/30) vs. 25.0% (5/20) vs. 15.0% (3/20) A vs. C: 1.87 (0.80 to 4.37) A vs. D: 3.11 (1.02 to 9.45) B vs. C: 1.73 (0.73 to 4.11) B vs. D: 2.89 (0.94 to 8.86) -3 years: 46.7% (14/30) vs. 46.7% (14/30) vs. 35.0% (7/20) vs. 20.0% (4/20) A vs. C: 1.33 (0.66 to 2.71) A vs. D: 2.33 (0.90 to 6.07) B vs. C: 1.33 (0.66 to 2.71) B vs. D: 2.33 (0.90 to 6.07) Quality of life, SF-36, physical component score, change from baseline -3 years: B vs. C: p = 0.04; B vs. D: p = 0.025	

Abbreviations: CI = confidence interval; LBP = low-back pain; MPC = mesenchymal precursor cell; LSM = least squares mean; NR = not reported; ODI = Oswestry Disability Index; RCT = randomized controlled trial; RR = risk ratio; SD = standard deviation; SF-36 = Short-Form 36; VAS = visual analogue scale; WPAI = Work Productivity and Activity Index

See Appendix F, List of Included Studies, for full citations

Table G-12. Trials of methylene blue for presumed discogenic back pain – study characteristics

Author, Year Trial	Study Design Duration	Setting/Provider Type Country	Eligibility Criteria	Interventions
Kallewaard, 2019 IMBI Study	RCT 6 months	4 centers, anesthesia pain medicine the Netherlands	18 to 66 years with a history consistent with lumbar discogenic pain, LBP duration ≥6 months, poor response to ≥6 weeks conservative treatment, no motor deficit on neurological examination, pain intensity ≥5 (0 to 10 NRS) in seated position, MRI in the past 12 months to rule out severe disk degeneration (>50% height loss), negative facet joint blockade, positive provocative discography (at pressure <50 PSI above opening pressure), pain severity ≥7 (0 to 10 NRS) or ≥70% reproduction of worst spontaneous pain; ≥1 adjacent control level tested) Excluded: discogenic pain confirmed on more than 2 levels, extruded or sequestered herniated nucleus pulposus, previous lumbar surgery or invasive intradiscal procedures on suspected levels, had grade 1 to 5 spondylolisthesis, had a BMI of 35 or more, pregnant, received coagulopathy or oral anticoagulant therapy, infection.	A. Intradiscal methylene blue: 1 ml (10 mg/ml) methylene blue + 0.5 ml lidocaine hydrochloride 2%, and 0.5 ml contrast dye injected at 0.02 ml/sec in symptomatic disc(s) and ≥1 adjacent control disc B. Sham intradiscal therapy: 1 ml saline + 0.5 ml lidocaine hydrochloride 2%, and 0.5 ml contrast dye injected as above
Peng, 2010	RCT 2 years	1 center, provider type not reported China	20 to 65 years, chronic LBP without radiculopathy but with evidence of lumbar disc degeneration on MRI, preliminary diagnosis of discogenic low back pain, positive discography (pressure and volume parameters not reported; exact reproduction of usual pain response pattern, and posterior annular disruption extending into the outer annulus or beyond the confines of the outer annulus by the contrast medium; at least one negative adjacent control disc) Excluded: lumbar disc herniation, spinal instability, lumbar canal stenosis, spondylolysis, spondylolisthesis, disc degeneration with endplate Modic changes, neurologic disease, inflammatory arthritis, tumor, infection	A. Intradiscal methylene blue: 1 mL (1%; 10 mg/mL) methylene blue + 1 ml lidocaine hydrochloride 2% B. Sham intradiscal injection: 1 ml saline + 1 ml lidocaine hydrochloride 2%

Abbreviations: BMI = body mass index; IMBI = intradiscal methylene blue injection; LBP = low-back pain; MRI = magnetic resonance imaging; NR = not reported; NRS = numeric rating scale; NSAID = nonsteroidal anti-inflammatory drug; ODI = Oswestry Disability Index; PSI = pounds per square inch; RCT = randomized controlled trial; VAS = visual analogue scale

See Appendix F, List of Included Studies, for full citations

Table G-13. Trials of methylene blue for presumed discogenic back pain – additional study characteristics

Author, Year Trial	Sample Characteristics	Screened Eligible Randomized Completed Followup Analyzed	Sponsor	Quality
Kallewaard, 2019 IMBI Study	Mean (SD) age, years: 41.1 (9.91) Female: 72% Race: NR Mean (SD) duration of pain, years: 9.34 (7.98) Strong opioid use: 11% Weak opioid or antineuropathic medication use: 25% A vs. B Baseline pain intensity (mean [SD], 0 to 10 NRS): 6.6 (1.4) vs. 6.6 (1.6) Baseline SF-36 PCS (mean [SD], 0 to 100 scale): 49.8 (17.3) vs. 46.9 (19.0) Baseline SF-36 MCS (mean [SD], 0 to 100 scale): 66.1 (16.5) vs. 63.9 (23.0) Baseline ODI (mean [SD], 0 to 100 scale): 44.5 (14.1) vs. 42.8 (15.9) Baseline EQ-5D health status (mean [SD], 0 to 100 VAS): 52.9 (16.5) vs. 51.8 (18.8)	Screened: 1364 Eligible: 432 Randomized: 81 (40 vs. 41, excluding 3 post-randomization exclusions) Complete followup: 81 (40 vs. 41) Analyzed: 81 (40 vs. 41)	The Netherlands Organization for Health Research and Development	Good
Peng, 2010	Mean (SD) age, years: 41.7 (13.3) Female: 43% Race: NR Mean (SD) duration of low back pain, years: 3.4 (1.7) A vs. B Baseline pain (mean [SD], 0 to 100 NRS converted to 0 to 10 scale): 7.2 (12.4) vs. 6.7 (11.6) Baseline ODI (mean [SD], 0 to 100 scale): 48.5 (5.1) vs. 49.5 (6.7)	Screened: 136 Eligible: 72 Randomized: 72 (36 vs. 36) Completed followup: 71 (36 vs. 35) Analyzed: 71 (36 vs. 35)	Foundation of Capital Medical Development, Beijing, China; 304th Hospital grant	Fair

Abbreviations: EQ-5D = EuroQOL 5-Dimension Questionnaire; MCS = Mental Component SummaryNR = not reported; NRS = numeric rating scale; ODI = Oswestry Disability Index; PCS = Physical Component Summary; SD = standard deviation; SF-36 = Short-Form 36; VAS = visual analogue scale

See Appendix F, List of Included Studies, for full citations

Table G-14. Trials of methylene blue for presumed discogenic back pain – results

Author, Year Trial	Results	Adverse Events and Withdrawals Due to Adverse Events
Kallewaard, 2019 IMBI Study	A vs. B Pain (mean change from baseline [SD], 0 to 10 NRS) -6 weeks: -0.9 (1.8) vs. -0.5 (1.4), mean difference -0.4 (95% CI, -1.2 to 0.3) -3 months: -1.2 (2.3) vs. -0.7 (1.7), mean difference -0.5 (95% CI, -1.3 to 0.4) -6 months: -1.4 (2.3) vs. -1.2 (2.4), mean difference -0.2 (95% CI, -1.2 to 0.80) Pain improved ≥30% -6 weeks: 15.0% (6/40) vs. 17.1% (7/41), RR 1.02 (95% CI, 0.85 to 1.24)* -3 months: 25.0% (10/40) vs. 24.4% (10/41), RR 0.99 (95% CI, 0.77 to 1.27)* -6 months: 35.0% (14/40) vs. 26.8% (11/41), RR 0.89 (95% CI, 0.66 to 1.19)* Patients' Global Impression of Change "much improved" or "improved" -6 weeks: 12.5% (5/40) vs. 14.6% (6/41), RR 1.02 (95% CI, 0.86 to 1.22)* -3 months: 20.0% (8/40) vs. 26.8% (11/41), RR 1.09 (95% CI, 0.86 to 1.39)* -6 months: 25.0% (10/40) vs. 24.4% (10/41), RR 1.00 (95% CI, 0.78 to 1.29)* ODI (mean change from baseline [SD], 0 to 100 scale) -6 weeks: -8.0 (17.1) vs. -1.7 (9.8), p = 0.046 -3 months: -8.8 (18.4) vs. -3.6 (9.9), p = 0.12 -6 months: -7.8 (16.9) vs. -5.5 (10.5), p = 0.46	A vs. B SAEs: 5.0% (2/40, unrelated elective surgery and hospitalization due to laryngitis) vs. 0% (0/41), RR 5.12 (95% CI, 0.25 to 103.47)* Any adverse event (n/N NR) -6 weeks: p = 0.20 -3 months: p = 0.46 -6 months: p = 0.36
Kallewaard, 2019 IMBI Study (continued)	EQ-5D health status (mean change from baseline [SD], 0 to100 VAS) -6 weeks: 3.1 (21.4) vs. 4.2 (20.7), p = 0.73 -3 months: 6.7 (21.3) vs. 3.8 (22.3), p = 0.48 -6 months: 7.7 (23.9) vs. 5.6 (23.2), p = 0.74 SF-36 PCS (mean change from baseline [SD], 0 to 100 scale) -6 weeks: 5.9 (19.6) vs. 8.7 (20.5), p = 0.54 -3 months: 9.3 (21.9) vs. 9.2 (15.4), p = 0.98 -6 months: 11.1 (22.4) vs.10.9 (18.7), p = 0.97 SF-36 MCS (mean change from baseline [SD], 0 to100 scale) -6 weeks: 3.3 (15.5) vs. 4.0 (12.1), p = 0.81 -3 months: 6.5 (17.3) vs. 4.3 (13.5), p = 0.52 -6 months: 21.9 (10.3) vs. 21.5 (7.8), p = 0.93 Strong opioid use -6 weeks: 2.5% (1/40) vs. 12.2% (5/41), RR 0.20 (95% CI, 0.02 to 1.68)* -3 months: 5.0% (2/40) vs. 14.6% (6/41), RR 0.34 (95% CI, 0.07 to 1.59)* -6 months: 7.5% (3/40) vs. 9.8% (4/41), RR 0.77 (95% CI, 0.18 to 3.22)* Weak opioid or antineuropathic medication use -6 weeks: 32.5% (13/40) vs. 22.0% (9/41), RR 1.48 (95% CI, 0.71 to 3.07)* -3 months: 42.5% (17/40) vs. 19.5% (8/41), RR 2.18 (95% CI, 1.06 to 4.47)* -6 months: 30.0% (12/40) vs. 24.3% (10/41), RR 1.23 (95% CI, 0.60 to 2.52)*	

Author, Year Trial	Results	Adverse Events and Withdrawals Due to Adverse Events
Peng, 2010	A vs. B Pain (mean [SD], 0 to 100 NRS converted to 0 to 10 scale) -6 months: 2.49 (1.74) vs. 6.35 (1.17), mean difference 3.86 (95% CI, 3.15 to 4.56) -12 months: 2.16 (1.79) vs. 6.24 (1.20), mean difference 4.08 (95% CI, 3.36 to 4.81) -24 months: 1.98 (1.60) vs. 6.04 (1.41), mean difference 4.05 (95% CI, 3.34 to 4.77) ODI (mean [SD], 0 to 100 scale) -6 months: 16.00 (11.91) vs. 48.40 (7.77), mean difference 32.40 (95% CI, 27.62 to 37.18) -12 months: 14.39 (12.87) vs. 49.09 (10.20), mean difference 34.70 (95% CI, 29.19 to 40.20) -24 months: 12.89 (11.95) vs. 47.69 (10.92), mean difference 34.80 (95% CI, 29.37 to 40.22) Regular NSAID or opioid use: 8.3% (3/36) vs. 42.9% (15/35), RR 0.19 (95% CI, 0.06 to 0.61)* Completely satisfied or satisfied: 91.6% (33/36) vs. 14.3% (5/35), RR 0.10 (95% CI, 0.03 to 0.29)*	Narrative report of no disc space infection or nerve root stab injury in either group; no nerve root injury or back pain aggravation in methylene blue group

*Calculated

Abbreviations: CI = confidence interval; EQ-5D = EuroQOL 5-Dimension Questionnaire; IMBI = intradiscal methylene blue injection; LBP = low-back pain; MCS = Mental Component Summary; MRI = magnetic resonance imaging; NR = not reported; NRS = numeric rating scale; NSAID = nonsteroidal anti-inflammatory drug; ODI = Oswestry Disability Index; PCS = Physical Component Summary; PSI = pounds per square inch; RCT = randomized controlled trial; RR = risk ratio; SD = standard deviation; SF-36 = Short-Form 36; VAS = visual analogue scale

See Appendix F, List of Included Studies, for full citations

Table G-15. Trials of intradiscal ozone injection for radicular low back pain or nonradicular low back pain of presumed discogenic origin – study characteristics

Author, Year Trial	Study Design Duration	Setting/Provider Type Country	Eligibility Criteria	Interventions
Gallucci, 2007	RCT 6 months	1 center, neuroradiology Italy	Unilateral radicular pain, herniation site concordant with the neurologic level, ODI >30 (0 to 100 scale), duration of pain ≥8 weeks, conservative therapy for 2 to 4 weeks with no or poor clinical improvement; discography performed in a few patients initially but discontinued Excluded: facet pain syndrome, sacroileitis, bone lesions, or previous spine surgery	A. Oxygen-ozone, corticosteroid, and local anesthetic injection: Under CT guidance via paravertebral (92.4%) or interlaminar (7.6%) approach, intradiscal injection of 5 to 7 ml O_2 to O_3 (ozone concentration 28 µg/ml), 2 ml triamcinolone acetonide (1 ml in epidural space and 1 ml intradiscal) and 2 to 4 ml 2% ropivacaine (~2 ml in epidural space and 1 ml intradiscal); mean total volume 6.8 ml intradiscal and 9.5 ml intraforaminal (12.3 ml oxygen-ozone) B. Corticosteroid and local anesthetic injection: Corticosteroid and local anesthetic as above, without oxygen-ozone; mean total volume 3 ml intradiscal and 2 ml intraforaminal
Haseeb, 2019	RCT 6 months	1 center, physical medicine and rehabilitation Egypt	Unilateral radicular pain for ≥8 weeks with MRI-confirmed disc herniation, ODI>30 (0 to 100 scale), conservative therapy for 2 to 4 weeks with no or poor clinical improvement. Excluded: facet syndrome, sacroileitis, previous spine surgery, absence of disc herniation, major neurologica deficits, radiculitis secondary to spinal stenosis, radiculitis without disc herniation, sequestrated disc contents, multiple discs involved, suspected spondylodiscitis	A. Oxygen-ozone, corticosteroid, and local anesthetic injection: Under fluoroscopic guidance via posterolateral extrapedicular approach, 5 to 7 ml O_2 to O_3 (ozone concentration 28 µg/ml) intradiscal (mean 5.8 ml) and 5 to 7 ml O2 to O3 intraforaminal (mean 6.5 ml) + 2 ml 40 mg/ml triamcinolone acetonide (1 ml intradiscal and 1 ml intraforaminal) + 2 to 4 ml 2% ropivacaine intraforaminal and intradiscal injection B. Corticosteroid and local anesthetic injection: As above, without O_2 to O_3 C. Sham injection: 1.5 ml 1% lidocaine alone
Nilachandra, 2016	RCT 6 months	1 center, physical medicine and rehabilitation India	20 to 55 years with radicular back pain and prolapsed intervertebral disc confirmed with MRI, VAS ≥5, ODI >40 (0 to 100 scale) Excluded: cauda equina syndrome, prior lumbar surgery, multilevel disc prolapse	A. Oxygen-ozone and corticosteroid injection: Under fluoroscopic guidance, intradiscal 10 ml O_2 to O_3 (ozone concentration 40 µg/ml) (target just lateral to the superior articular process) + methylprednisolone 80 mg via transforaminal approach B. Corticosteroid injection: Methylprednisolone 80 mg, epidural via transforaminal approach

Abbreviations: CI = confidence interval; CT computed tomography; MRI = magnetic resonance imaging; NR = not reported; ODI = Oswestry Disability Index; RCT = randomized controlled trial; RR = risk ratio; SD = standard deviation; VAS = visual analogue scale

See Appendix F, List of Included Studies, for full citations

Table G-16. Trials of intradiscal ozone injection for radicular low back pain or nonradicular low back pain of presumed discogenic origin – additional study characteristics

Author, Year	Sample Characteristics	Screened Eligible Randomized Completed Followup Analyzed	Sponsor	Quality
Gallucci, 2007	Mean age, years: 40.48 Female: 45% Race: NR Mean duration radicular pain, weeks: 15 L3 to L4 disc herniation: 14.5% L4 to L5 disc herniation: 38.4% L5 to S1 disc herniation: 47.2% A vs. B Baseline ODI (mean [SD NR], 0 to 100 scale): 58.4 vs. 57.5	Screened: NR Eligible: NR Randomized: 159 (82 vs. 77) Complete followup: NR Analyzed: 159 (82 vs. 77)	NR	Fair
Haseeb, 2019	Mean (SD) age, years: 42.44 (7.7) Female: 58% Race: NR Mean duration of radicular pain, weeks: 8 A vs. B vs. C Baseline ODI (mean [SD], 0 to 100 scale): 34.38 (12.24) vs. 29.38 (7.18) vs. 29.20 (9.54)	Screened: NR Eligible: NR Randomized: 100 (40 vs. 40 vs. 20) Completed followup: NR Analyzed: NR	NR	Poor
Nilachandra, 2016	Mean (SD) age, years: 51.3 (8.64) Female: 62% Race: NR Mean (SD) duration of radicular pain, months: 9.45 (3.02) L3 to L4 prolapse: 22.5% L4 to L5 prolapse: 66.2% L5 to S1 prolapse: 22.5% A vs. B Baseline pain (mean [SD], 0 to 10 VAS): 7.13 (1.04) vs. 7.25 (1.10) Baseline ODI (mean [SD], 0 to 100 scale): 70.90 (7.55) vs. 73.05 (7.51)	Screened: NR Eligible: NR Randomized: 80 (40 vs. 40) Completed followup: NR Analyzed: 75 (37 vs. 38) at 3 months, 73 (36 vs. 37) at 6 months	NR	Poor

Abbreviations: CI = confidence interval; CT computed tomography; MRI = magnetic resonance imaging; NR = not reported; ODI = Oswestry Disability Index; RCT = randomized controlled trial; RR = risk ratio; SD = standard deviation; VAS = visual analogue scale

See Appendix F, List of Included Studies, for full citations

Table G-17. Trials of intradiscal ozone injection for radicular low back pain or nonradicular low back pain of presumed discogenic origin – results

Author, Year	Results	Adverse Events and Withdrawals Due to Adverse Events
Gallucci, 2007	A vs. B ODI <20 on 0 to 100 scale -2 weeks: 88% (72/82) vs. 90% (69/77), RR 0.98 (95% CI, 0.88 to 1.09) -3 months: 78% (64/82) vs. 67% (52/77), RR 1.16 (95% CI, 0.95 to 1.40) -6 months: 74% (61/82) vs. 47% (36/77), RR 1.59 (95% CI, 1.21 to 2.08)	A vs. B Narrative report of no major or minor complications in either group
Haseeb, 2019	A vs. B ODI (mean change from baseline [SD], 0 to 100 scale) -2 weeks: -20.40 (9.66) vs. -16.60 (7.33), mean difference -3.80 (95% CI, -7.56 to -0.04) -3 months: -18.95 (8.55) vs. -13.30 (5.66), mean difference -5.65 (95% CI, -8.83 to -2.47) -6 months: -14.73 (9.60) vs. -9.88 (5.79), mean difference -4.85 (95% CI, -8.32 to -1.38) A vs. C ODI (mean change from baseline [SD], 0 to 100 scale) -2 weeks: -20.40 (9.66) vs. -3.10 (3.72), mean difference -17.30 (95% CI, -20.71 to -13.89) -3 months: -18.95 (8.55) vs. -2.10 (3.81), mean difference -16.85 (95% CI, -19.98 to -13.72) -6 months: Data not reported for group C at 6 months	A vs. B Any adverse event: 47.5% (19/40) vs. 27.5% (11/40), RR 1.73 (95% CI, 0.95 to 3.15) A vs. C Any adverse event: 47.5% (19/40) vs. 15.0% (3/20), RR 3.17 (95% CI, 1.06 to 9.45)
Nilachandra, 2016	A vs. B Pain (mean [SD], 0 to 10 VAS) -1 week: 3.50 (1.16) vs. 3.25 (1.03), mean difference 0.25 (95% CI, -0.23 to 0.73) -2 weeks: 2.54 (0.89) vs. 2.75 (0.74), mean difference -0.21 (95% CI, -0.57 to 0.15) -3 months: 1.54 (1.15) vs. 2.84 (0.64), mean difference -1.30 (95% CI, -1.72 to -0.88) -6 months: 0.86 (0.69 vs. 2.24 (0.93), mean difference -1.38 (95% CI, -1.75 to -1.01) ODI (mean [SD], 0 to 100 scale) -1 week: 38.98 (7.61) vs. 42.45 (9.97), mean difference -3.47 (95% CI, -7.36 to 0.42) -2 weeks: 34.13 (7.94) vs. 36.20 (4.27), mean difference -2.07 (95% CI, -4.89 to 0.75) -3 months: 25.14 (7.92) vs. 36.21 (4.67), mean difference -12.06 (95% CI, -15.01 to -9.11) -6 months: 18.28 (8.77) vs. 29.00 (6.78), mean difference -10.72 (95% CI, -14.32 to -7.12)	No serious adverse events in either group

Abbreviations: CI = confidence interval; CT computed tomography; MRI = magnetic resonance imaging; NR = not reported; ODI = Oswestry Disability Index; RCT = randomized controlled trial; RR = risk ratio; SD = standard deviation; VAS = visual analogue scale

See Appendix F, List of Included Studies, for full citations

Table G-18. Trial of sphenopalatine block for trigeminal neuralgia or headaches – study characteristics

Author, Year	Study Design Duration	Setting/Interventionist Country	Eligibility Criteria	Interventions	Sample Characteristics	Screened Eligible Randomized Analyzed	Sponsor	Quality
Cady, 2015a & b	RCT 1 month	Headache specialty clinics U.S.	18 to 80 years with history of chronic migraines defined by the Headache Classification Committee of the International Headache Society ICHD-II appendix definition 2006 and by history for ≥3 months, if on migraine medications (preventive or abortive) must be stable for 30 days prior to enrollment. Excluded: nasal problems that would interfere with the procedure, neoplasm, nasal medications that would confound results, current cocaine user, treating migraines with Schedule II narcotics, allergy to bupivacaine, pregnant or breastfeeding, concurrent cervicogenic headache or occipital neuralgia, severe clinical depression or anxiety.	A: Sphenopalatine block: 0.5% bupivacaine B: Placebo: saline sphenopalatine block	Mean (SD) age, years: 41.3 (12.6) Female: 76% White: 83% Black: 10% Other race/ethnicity: 7% Mean duration of chronic migraine diagnosis, years: 8.58 Mean number of migraine days in a month: 15.2 Mean number of headache days in a month: 23.6 Mean (SD) NRS score (scale 0 to 10 scale): 3.37 (2.7)	Screened: 55 Eligible: 43 Randomized: 41 (27 vs. 14) Analyzed for primary outcome: 38 (26 vs. 12)	Tian Medical Inc.	Poor

Abbreviations: ICHD-II = International Classification of Headache Disorders, second edition; NR = not reported; NRS = numeric rating scale; RCT = randomized controlled trial; SD = standard deviation

See Appendix F, List of Included Studies, for full citations

Table G-19. Trial of sphenopalatine block for trigeminal neuralgia or headaches – results

Author, Year Trial	Results	Adverse Events and Withdrawals Due to Adverse Events
Cady, 2015a & b	A vs. B Pain, mean (SD) NRS score (scale 0 to 10); mean difference (95% CI) - 1 day: 2.85 (2.74) vs. 4.20 (2.62); -1.35 (-3.17 to 0.47) - 1 month: 3.36 (2.87) vs. 3.91 (2.30); -0.55 (-2.54 to 1.44) - 6 months: 2.86 (2.62) vs. 4.00 (2.27); -1.14 (-3.06 to 0.78) Pain, mean (SD) NRS percent change from baseline -1 day: -15.5% (69.9) vs. 13.5% (78.8); p = 0.94 Pain, mean (SD) number of headache days; mean difference (95% CI) -1 month: 17.44 (9.08) vs. 22.82 (5.36); -5.38 (-10.14 to -0.62) Function, mean HIT-6 score (scale 36-78; higher score = greater impact); mean difference (95% CI) - 1 month: 59.23 (8.97) vs. 61.92 (5.45); -2.69 (-7.32 to 1.94) - 6 months: 59.58 (9.14) vs. 62.42 (5.96); -2.84 (-7.71 to 2.03) Quality of life, mean (SD) PGIC scores - 1 day: 3.08 (1.26) vs. 3.88 (1.02), p = 0.04 Quality of life, mean (SD) general activity score; mean difference (95% CI) -1 month: 2.64 (2.91) vs. 3.91 (2.81); -1.27 (-3.68 to 1.14) -6 months: 2.68 (2.87) vs. 4.00 (3.32); -1.32 (-4.06 to 1.42) Quality of life, mean (SD) mood score; mean difference (95% CI) -1 month: 2.96 (3.43) vs. 3.82 (3.40); -0.86 (-3.76 to 2.04) -6 months: 3.18 (3.26) vs. 5.71 (3.68); -2.53 (-5.58 to 0.52) Quality of life, mean (SD) work score; mean difference (95% CI) -1 month: 2.52 (3.14) vs. 3.45 (2.94); -0.93 (-3.47 to 1.61) -6 months: 2.59 (2.77) vs. 3.71 (3.50); -1.12 (-3.96 to 1.72)	A vs. B Any adverse event, mean (SD): 7.52 (8.16) vs. 5.00 (7.06); p = 0.30 Serious adverse events: 0% (0/27) vs. 7% (1/14; PE resulting in death 81 days posttreatment); RR 0.18 (95% CI, 0.01 to 4.12)

Abbreviations: CI = confidence interval; HIT-6 Headache Impact Test-6; NR = not reported; NRS = numeric rating scale; PE = pulmonary embolism; PGIC = Patient's Global Impression of Change; RR = risk ratio; SD = standard deviation

See Appendix F, List of Included Studies, for full citations

Table G-20. Trials of occipital nerve stimulator for various headache disorders – study characteristics

Author, Year Trial	Study Design Duration	Setting/Provider Type Country	Eligibility Criteria	Interventions
Saper, 2011 ONSTIM	RCT 3 months	9 centers, usually anesthesiologist Canada, U.K., and U.S.	≥18 year olds with diagnosis of chronic migraine (≥15 days/month for >3 months) refractory to prophylactic treatment from ≥2 drug classes with response to a temporary, short-acting local anesthetic occipital nerve block (≥50% reduction in migraine pain within 24 hours) Excluded: previous destructive ganglionectomy, rhizotomy section or neurectomy procedure affecting C2/C3/occipital distribution, recent (within last 3 years) clinical trial participation, neurostimulation (implanted or external) for headache or other head or neck pain within last year	A. Occipital nerve stimulation, adjustable: 1 or 2 leads implanted subcutaneously superficial to the fascia and muscle layer at C1 level; pulse frequency 3 to 130 Hz, pulse width 60 to 450 µs, pulse amplitude 0 to 10.5 V; parameters adjustable by patient to minimize pain B. Occipital nerve stimulation, preset: As above, but stimulator preset to 1 minute per day stimulation C. Usual care
Serra, 2012	RCT (crossover) 1 month (per crossover period)	1 center, surgeon Italy	≥18 year old outpatients with chronic migraine or medication overuse headache refractory to ≥2 prophylactic treatments or with intolerable side effects to treatment, >50% reduction in number or severity of attacks within 15 to 30 days of temporary occipital nerve stimulation implantation Excluded: previous occipital surgery, destructive ganglionectomy, local drug injection, or nerve-blocks in the last 90 days	A. Occipital nerve stimulation: Percutaneous quadripolar lead implanted under local anesthetic and mild sedation. Permanent neurostimulator implanted; stimulation at frequency of 50 Hz, pulse width 330 to 450 µs, maximum stimulation amplitude 10.5 V. B. Sham occipital nerve stimulation: As above, but internal neurostimulator was inactive (turned off)
Silberstein, 2012	RCT 12 weeks	15 centers, surgery U.S.	Diagnosed with chronic migraine headache with the following criteria: headaches on ≥15 days per month for >3 months, average headache duration of >4 hours/day, met IHS criteria for migraine without aura (1.1), migraine with aura (1.2) or probable migraine (1.6) on >50% of headache days, headache not attributable to another disorder; previously tried ≥2 migraine specific acute medications; refractory to ≥2 different classes of prophylactic medications; pain ≥6 on 0 to 10 VAS; headache location posterior head or cervical region; ≥50% reduction in pain or adequate paresthesia coverage in painful areas with trial stimulation Excluded: medication overuse headaches; prior destructive procedure affecting C2/C3/occipital distribution; started new medications or therapy to treat headaches within 8 weeks; received neurotoxin therapy within 6 months; met IHS criteria for chronic tension-type headache, hypnic headache, hemicrania continua, or new daily persistent headache	A: Occipital nerve stimulation: Leads placed on either side of midline caudally along the nerve or, more commonly, perpendicular to the course of the occipital nerves at the level of the craniocervical junction. Stimulation parameters not reported ("programmed for appropriate stimulation"). B: Sham occipital nerve stimulation: Leads placed as above, but no stimulation administered.
Mekhail, 2017 (single center from Silberstein 2012)	RCT 12 weeks	Single center from the Silberstein, 2012 study	See Silberstein, 2012	See Silberstein, 2012

Abbreviations: IHS = International Headache Society; ONSTIM = occipital nerve stimulation for the treatment of intractable chronic migraine headache; RCT = randomized controlled trial; U.K. = United Kingdom; U.S. = United States; VAS = visual analogue scale

See Appendix F, List of Included Studies, for full citations

Table G-21. Trials of occipital nerve stimulator for various headache disorders – additional study characteristics

Author, Year Trial	Sample Characteristics	Screened Eligible Randomized Complete Followup Analyzed	Sponsor	Quality
Saper, 2011 ONSTIM	Mean (SD) age, years: 43 (10.6) Female: 80% Race: NR Mean (SD) duration of migraine, years: 22 (12.3) Mean (SD) number of headache days/month: 23.2 (5.4) A vs. B vs. C Baseline pain: NR Baseline disability score (mean [SD], scale NR): 4.0 (0.2) vs. 3.9 (0.3) vs. 4.0 (0.0)	Screened: 110 Eligible: NR Randomized: 67 (33 vs. 17 vs. 17) Completed followup: 61 (28 vs. 16 vs. 17) Analyzed: 61 (28 vs. 16 vs. 17) at 3 months	Medtronic Neuromodulation	Fair
Serra, 2012	Mean (SD) age, years: 46 (11) Female: 76% Race: NR Duration of migraine diagnosis: NR Baseline headache severity (median [IQR], 0 to 10 NRS): 8 (7-8) Baseline headache days/week (mean [SD]): 5.8 (1.6) Baseline MIDAS score (median [IQR], >20 = severe disability): 79 (30-135)	Screened: NR Eligible: 34 Randomized: 30 Completed followup: 29 Analyzed: 29	No external funding	Poor
Silberstein, 2012	Mean (SD) age, years: 44. 9 (11.0) Female: 79% Duration of headaches, mean (SD) years: 23.3 (14.4) Mean (SD) number of headache days: 21.3 (7.0) Unilateral headaches: 31.8% Bilateral headaches: 68.2% A vs. B Baseline pain (mean [SD], 0 to 100 VAS transformed to 0 to 10 scale): 5.99 (1.68) vs. 5.60 (1.70) Baseline MIDAS score (mean [SD], >20 = severe disability): 158.4 (76.8) vs. 152.7 (77.1)	Screened: 268 Eligible: 187 Randomized: 157 (105 vs. 52) Completed followup 157 (105 vs. 52) Analyzed: 157 (105 vs. 52)	St. Jude Medical Neuromodulation Division	Fair
Mekhail, 2017 (single center from Silberstein 2012)	Mean (SD) age, years: 44.6 (12.6) Female: 75% Mean (SD) headache duration, hours: 18.5 (15.1) Cause of headaches - Unknown: 70% - Trauma: 15% - Other: 15% Bilateral headaches: 65% Unilateral headaches: 35% A vs. B Baseline pain (mean [SD], 0 to 100 VAS transformed to 0 to 10 scale): 5.09 (1.80) vs. 5.99 (2.34) Baseline MIDAS score (mean [SD], >20 = severe disability): 168.00 (55.36) vs. 183.33 (60.43)	Screened: NR Eligible: NR Randomized: 20 (14 vs. 6) Analyzed: 20 (14 vs. 6)	See Silberstein, 2012	Fair

Abbreviations: IQR = interquartile range; MIDAS = migraine disability assessment; NR = not reported; ONSTIM = occipital nerve stimulation for the treatment of intractable chronic migraine headache; SD = standard deviation; VAS = visual analogue scale

See Appendix F, List of Included Studies, for full citations

Table G-22. Trials of occipital nerve stimulator for various headache disorders – results

Author, Year Trial	Results	Adverse Events and Withdrawals Due to Adverse Events
Saper, 2011 ONSTIM	A vs. B vs. C Pain (mean change from baseline [SD], 0 to 10 scale): -1.5 (1.6) vs. -0.5 (1.3) vs. -0.6 (1.0); p>0.05 for all comparisons Headache days/month (mean change from baseline [SD]): -6.7 (10.0) vs. -1.5 (4.6) vs. -1.0 (4.2), mean difference -5.7 (95% CI, -10.9 to -0.54) for A vs. C Severe headache days/month (mean change from baseline [SD]): -5.1 (8.7) vs. -2.2 (6.4) vs. -0.8 (5.6), mean difference -4.3 (95% CI, -9.1 to 0.47) for A vs. C ≥50% reduction in headache days per month or ≥3-point reduction in overall pain intensity from baseline: 39.3% (11/28) vs. 6.2% (1/16) vs. 0% (0/17), RR 14.3 (95% CI, 0.9 to 227.8) for A vs. C Profile of Mood States (mean change from baseline [SD], 0 to 168 scale): -8.7 (12.0) vs. -1.6 (10.1) vs. -0.4 (9.4), mean difference -8.3 (95% CI, -15.2 to -1.4) for A vs. C Functional disability (mean change from baseline [SD], scale not reported): 0.3 (0.5) vs. NR vs. 0.0 (0.3) Acute medication use (mean change from baseline [SD], scale not reported): 1.6 (7.6) vs. NR vs. -0.6 (5.0) MIDAS category score (mean change from baseline [SD], 0 to 3 scale): -1.3 (1.8) vs. NR vs. 0.0 (0.9), mean difference -1.3 (95% CI, -2.2 to -0.4) for A vs. C SF-36 Mental Health (mean change from baseline [SD], 0 to 100 scale): 5.5 (9.7) vs. NR vs. -1.5 (6.3), mean difference 7.0 (95% CI, 1.7 to 12.3) for A vs. C	A vs. B vs. C vs. D Any non-device-related adverse event: 52% (17/33) vs. 76% (13/17) vs. 53% (9/17) vs. 75% (6/8); p>0.05 for all comparisons Overall Intraoperative failure: 3.8% (2/53) Serious device-related adverse event requiring hospitalization: 5.9% (3/51) (implant site infection, lead migration, postoperative nausea) Lead migration: 24% (12/51) Long-term complications or nerve damage: None
Serra, 2012	A vs. B Pain (median [IQR], 0 to 10 scale), first crossover period: 5 (5 to 6) vs. 7.5 (7.8), p<0.001 Headache days/week (median [IQR]), first crossover period: 2.1 (1.2 to 3.3) vs. 6.3 (3.6 to 7), p<0.001	Overall: 5 adverse events (2 severe infections, 3 lead migration)
Silberstein, 2012	A vs. B ≥50% reduction in headache pain intensity: 17.1% (18/105) vs. 13.5% (7/52), RR 1.27 (95% CI, 0.57 to 2.86) ≥30% reduction in headache pain intensity: 33.3% (35/105) vs. 17.3% (9/52), RR 1.93 (95% CI, 1.00 to 3.70) Headache days (mean change from baseline [SD NR]): -27.2% vs. -14.9%, p<0.05 "Good" or "excellent" headache relief: 50% (52/105) vs. 18% (9/52), RR 2.86 (95% CI, 1.53 to 5.34) MIDAS score (mean [SD NR], >20 = severe disability) at 12 weeks: -64.6 vs. -20.4, mean difference -44.2 (95% CI, -65.3 to -22.8)	A vs. B Total adverse events: 73 vs. 34 Lead migration: 14.0% vs. 4.7%, p = 0.41 Lead breakage/fracture: 1.9% vs. 0%, p>0.05 Persistent pain and/or numbness at IPG/lead site: 13.1% vs. 8.4%, p = 0.63 Skin erosion: 3.7% vs. 2.8%, p = 1.0 Wound site complications: 2.8% vs. 0.9%, p = 1.0 Non-device/procedure-related adverse events: 7.5% vs. 1.9%, p = 0.50

Author, Year Trial	Results	Adverse Events and Withdrawals Due to Adverse Events
Mekhail, 2017 (single center from Silberstein, 2012)	A vs. B ≥50% reduction in headache pain intensity: 17.1% (4/14) vs. 0% (0/6), RR 0.71 (95% CI, 0.51 to 0.99)* ≥30% reduction in headache pain intensity: 85.7% (12/14) vs. 66.7% (4/6), RR 0.43 (95% CI, 0.08 to 2.37)* Patients who achieved % average daily VAS reduction and no increase in headache duration or frequency - 30% at 12 weeks: 86% (12/14) vs.66% (4/6), p = 0.373 - 50% at 12 weeks: 29% (4/14) vs. 0%, p = 0.018 Average daily pain intensity (mean change from baseline [SD], 0 to 100 VAS transformed to 0 to 10 scale) -4 weeks: -2.16 (1.02) vs. 0.34 (0.99), p<0.001 -12 weeks: -2.30 (1.15) vs. 0.79 (1.06), p<0.001 Headache days (mean change from baseline [SD]) -4 weeks: -11.50 (6.29) vs. -0.95 (5.93), p<0.05 -12 weeks: -12.32 (8.88) vs. -0.15 (5.27), p = 0.02 MIDAS score (mean change from baseline [SD], >20 = severe disability) -12 weeks: -85.21 (40.63) vs. -12.17 (60.43), p = 0.008	A vs. B Any adverse events: 35.7% (5/14) vs. 50% (3/6) Stimulation related: 0% vs. 17% (1/6) - Nausea/vomiting: 0% vs. 17% (1/6) Hardware related: 14% (2/14) vs. 33% (2/6) - Lead migration: 14% (2/14) vs. 17% (1/6) Persistent pain or numbness: 7% (1/14) vs. 0% Wound site complication: 7% (1/14) vs. 0%

Abbreviations: CI = confidence interval; IQR = interquartile range; IPG = implantable pulse generator; MIDAS = migraine disability assessment; NR = not reported; NRS = numeric rating scale; ONSTIM = occipital nerve stimulation for the treatment of intractable chronic migraine headache; RR = risk ratio; SD = standard deviation; SF-36 = Short-Form 36; VAS = visual analogue scale

See Appendix F, List of Included Studies, for full citations

Table G-23. Trials of piriformis injection for piriformis syndrome – study characteristics

Author, Year Trial	Study Design Duration	Setting/Provider Type Country	Eligibility Criteria	Interventions
Childers, 2002	RCT (crossover) 10 weeks	1 center, physical medicine and rehabilitation clinic U.S.	>18 years; buttock, hip, and lower limb intermittent positional pain for ≥3 months reproduced by 2 of 3 maneuvers: palpation over point midway between the sacrum and greater trochanter of the femur, active hip abduction in the lateral recumbent position, and rectal palpation of the ipsilateral side of the involved limb; pain aggravated by sitting, stair climbing, and leg crossing; pain >5 on 0 to 10 VAS Excluded: imaging studies demonstrated evidence of a herniated lumbar disk or nerve root impingement, or electromyographic examination demonstrated spontaneous discharges in the lumbar paraspinal muscles suggestive of pathology proximal to the sciatic notch.	A: Botulinum toxin type A piriformis injection :100 units intramuscular injection under fluoroscopic guidance to piriformis muscle; placement verified with electromyography and pattern of radiotracer spread B: Placebo injection : Intramuscular preservative-free normal saline injection as above Crossover occurred after 10 weeks
Fishman, 2002	RCT 3 months	1 center, physical medicine and rehabilitation U.S.	Buttock tenderness and sciatica, with positive FAIR test (defined as prolongation of posterior tibial H-reflex >1.86 ms) Excluded: NR	A: Botulinum toxin type A piriformis injection: 200 units 2 ml intramuscular injection under electromyographic guidance (based on location of points at which 2 to 6 mA at 0.05 ms stimulus duration stimulated significant motility along the course of the piriformis muscle) B: Corticosteroid piriformis injection: Triamcinolone acetonide: 20 mg in 0.5 ml solution + 1.5 ml of 2% lidocaine (2 ml total injection volume) intramuscular injection, as above C: Placebo injection: 2 ml saline intramuscular injection as above All groups received physical therapy twice weekly (ultrasound, hot packs or cold spray, stretching, myofascial release, McKenzie exercise, lumbosacral corset when in the flexion, adduction, and internal rotation position)
Fishman, 2017	RCT 3 months	1 center, physical medicine and rehabilitation U.S.	≥18 years; ≥2 of the following conditions: buttock pain, sciatica, tenderness at the intersection of the piriformis muscle and sciatic nerve; or positive straight-leg raise of ≤60°, or 15° deficit on the affected side; functional prolongation of the posterior tibial or fibular nerve H-reflex (>1.86 ms, positive FAIR test) Excluded: positive sharp waves or fibrillation potentials in the lumbar paraspinal muscles on EMG assessment; thrombocytopenia; anticoagulation; autoimmune disease; previous exposure to BTX-A; previous buttock surgery; neuromuscular disease; weight <90 pounds; vascular anomalies.	A: Botulinum toxin type A piriformis injection: 300 units 3 ml intramuscular injection to 4 piriformis muscle sites (the most medial injection was made just lateral to the greater sciatic foramen along the line linking its midpoint to the greater trochanter) including the myoneural junctions of the S1 to S2 nerve fibers that innervate the piriformis muscle; placement with electromyographic guidance B: Placebo injection: 3 ml saline injection as above Both groups received physical therapy weekly (piriformis muscle stretch and ultrasound)

Author, Year Trial	Study Design Duration	Setting/Provider Type Country	Eligibility Criteria	Interventions
Misirlioglu, 2015	RCT 3 months	1 center, physical medicine and rehabilitation Turkey	18 to 70 years; unilateral hip and/or leg pain with positive FAIR test and tenderness and/or trigger point at the piriformis muscle. Excluded: neurological deficit; limited lumbar and/or hip range of motion; prior surgery at the lumbar and/or hip region; BMI >35 kg/m^2; history of inflammatory or infectious disease; active psychiatric disease; uncontrolled hypertension; uncontrolled diabetes mellitus; uncompensated chronic heart/liver/renal deficiency; vascular/tumoral disease.	A: Corticosteroid piriformis injection: 1 ml betametazone + 4 ml 2% lidocaine intramuscular injection to piriformis muscle with ultrasound guidance B: Sham injection: 5 ml 2% lidocaine intramuscular injection to piriformis muscle with ultrasound guidance

Abbreviations: BMI = body mass index; BTX-A = botulinum toxin type-A; FAIR = flexion, adduction, internal rotation; NR = not reported; RCT = randomized controlled trial; VAS = visual analogue scale

See Appendix F, List of Included Studies, for full citations

Table G-24. Trials of piriformis injection for piriformis syndrome – additional study characteristics

Author, Year	Sample Characteristics	Screened Eligible Randomized Analyzed	Sponsor	Quality
Childers, 2002	Mean (SD) age: 42.1 (5.7) Female: 100% Race: NR Mean (SD) duration of symptoms: 38.7 (21) months A vs. B Baseline pain (mean [SD], 0 to 10 VAS): 7.6 (1.9) vs. 7.4 (1.6) Baseline interference with activities (mean [SD], 0 to 10 VAS): 7.8 (2.1) vs. 7.7 (1.7) Baseline distress (mean [SD], 0 to 10 VAS): 6.8 (2.6) vs. 7.5 (1.7)	Screened: NR Eligible: NR Randomized: 10 Completed followup: 9 Analyzed: 9	NR	Poor
Fishman, 2002	Mean (SD) age, years: 57.4 (13.4) Female: 67% Race: NR Mean (SD) duration of sciatica, years: 3.2 (3.6) Baseline pain, function: NR	Screened: NR Eligible: NR Randomized: 87 (26 vs. 37 vs. 24) Completed followup: 67 (31 vs. 21 vs. 15) Analyzed: 67 (31 vs. 21 vs. 15)	NR	Poor
Fishman, 2017	Mean age: NR Female: NR Race: NR A vs. B Baseline pain (mean [SD], unclear scale): 0.71	Screened: NR Eligible: NR Randomized: 56 (26 vs. 28) Analyzed: 29 (25 vs. 24) at 4 weeks, 38 (19 vs. 19) at 8 weeks, 15 (9 vs. 6) at 12 weeks	NR	Poor
Misirlioglu, 2015	Mean (SD) age, years: 46.3 (13.8) Female: 84% Race: NR Mean (SD) symptom duration, months: 20.3 (29.5) Left side pain: 60% Right side pain: 40% Local pain: 17% Radiating pain: 83% History of trauma: 42% A vs. B Baseline pain at rest (mean [SD], 0 to 10 VAS): 3.6 (3.1) vs. 2.8. (3.1) Baseline pain with activity (mean [SD], 0 to 10 VAS): 7.4 (2.4) vs. 7.2 (2.0) Baseline pain during sleep (mean [SD], 0 to 10 VAS): 3.8 (3.9) vs. 3.3 (3.2)	Screened: 57 Eligible: 50 Randomized: 50 (25 vs. 25) Completed followup: 47 (25 vs. 22) Analyzed: 47 (25 vs. 22)	None	Fair

Abbreviations: NR = not reported; SD = standard deviation; VAS = visual analogue scale

See Appendix F, List of Included Studies, for full citations

Table G-25. Trials of piriformis injection for piriformis syndrome – results

Author, Year	Results	Adverse Events and Withdrawals Due to Adverse Events
Childers, 2002	A vs. B Pain (mean [SD], 0 to 10 VAS) -1 week: 5.4 (2.5) vs. 7.6 (1.9), mean difference -2.2 (95% CI, -4.4 to 0.02) -4 weeks: 5.5 (3.5) vs. 7.0 (2.7), mean difference -1.5 (95% CI, -4.6 to 1.6) -9 weeks: 6.0 (2.5) vs. 7.0 (2.3), mean difference -1.0 (95% CI, -3.4 to 1.4) Interference with activities (mean [SD], 0 to 10 VAS) -1 week: 5.7 (3.1) vs. 7.8 (2.4), mean difference -2.1 (95% CI, -4.9 to 0.7) -4 weeks: 5.6 (3.6) vs. 8.0 (1.7), mean difference -2.4 (95% CI, -5.2 to 0.4) -9 weeks: 4.9 (3.8) vs. 8.1 (1.1), mean difference -3.2 (95% CI, -6.0 to -0.4) Distress (mean [SD], 0 to 10 VAS) -1 week: 4.6 (2.7) vs. 7.7 (2.0), mean difference -3.1 (95% CI, -5.5 to -0.7) -4 weeks: 4.9 (3.3) vs. 7.2 (2.9), mean difference -2.3 (95% CI, -5.4 to 0.8) -9 weeks: 6.1 (3.1) vs. 7.2 (2.5), mean difference -1.1 (95% CI, -3.9 to 1.7)	No serious adverse events
Fishman, 2002	A vs. B vs. C ≥50% improvement in pain VAS at last 2 visits (through week 12): 65% (13/21) vs. 32% (10/31) vs. 6% (1/15); RR 9.29 (95% CI, 1.36 to 63.53) for A vs. C, RR 4.84 (95% CI, 0.68 to 34.39) for B vs. C, RR 1.92 (95% CI, 1.04 to 3.53) for A vs. B	NR
Fishman, 2017	A vs. B Pain intensity (mean change from baseline [SD], unclear scale) -2 weeks: -0.36 (0.23) vs. -0.04 (0.19), p<0.0001 -4 weeks: -0.39 (0.31) vs. -0.05 (0.12), p<0.0001 -6 weeks: -0.55 (0.29) vs. -0.04 (0.10), p<0.001 -8 weeks: -0.65 (0.16); 0.00 (0.13), p<0.001 -10 weeks: -0.55 (0.31) vs. -0.04 (0.10), p<0.0001 -12 weeks: -0.65 (0.24) vs. -0.008 (0.02), p<0.0001	A vs. B Any adverse event: 18.5% (5/27) vs. 19.2% (5/26), RR 0.96 (95% CI, 0.32 to 2.94)
Misirlioglu, 2015	A vs. B Pain at rest (mean [SD], 0 to 10 VAS) - 1 week: 1.4 (2.7) vs. 1.0 (2.1), mean difference 0.40 (95% CI, -0.97 to 1.77) - 1 month: 1.7 (2.9) vs. 0.5 (1.1), mean difference 1.20 (95% CI, -0.03 to 2.43) - 3 months: 1.6 (2.1) vs. 0.4 (1.1), mean difference 1.20 (95% CI, 0.26 to 2.14) Pain with activity (mean [SD], 0 to 10 VAS) - 1 week: 4.6 (3.0) vs. 3.5 (2.6), mean difference 1.10 (95% CI, -0.50 to 2.70) - 1 month: 3.9 (2.9) vs. 1.9 (1.5), mean difference 2.00 (95% CI, 0.70 to 3.30) - 3 months: 3.0 (2.7) vs. 1.7 (2.3), mean difference 1.30 (95% CI, -0.13 to 2.73) Pain during sleep (mean [SD], 0 to 10 VAS) - 1 week: 2.1 (3.2) vs. 1.3 (1.9), mean difference 0.80 (95% CI, -0.68 to 2.28) - 1 month: 1.0 (1.9) vs. 0.6 (1.5), mean difference 0.40 (95% CI, -0.57 to 1.37) - 3 months: 1.0 (2.0) vs. 0.4 (1.0), mean difference 0.60 (95% CI, -0.29 to 1.49)	A vs. B Sciatic nerve block: 24.0% (6/25) vs. 27.3% (6/22), RR 0.88 (95% CI, 0.33 to 2.33);* all resolved in hours after the procedure No other complications reported

Abbreviations: CI = confidence interval; NR = not reported; RR = risk ratio; SD = standard deviation; VAS = visual analogue scale

See Appendix F, List of Included Studies, for full citations

Table G-26. Trial of peripheral nerve stimulation for chronic pain – study characteristics

Author, Year Trial	Study Design Duration	Setting/Provider Type Country	Eligibility Criteria	Interventions	Sample Characteristics	Screened Eligible Randomized Completed Followup Analyzed	Sponsor	Quality
Deer, 2016	RCT 12 months	13 centers, provider type not reported U.S.	≥22 years with severe intractable chronic pain of peripheral nerve origin associated with posttraumatic/postsurgical neuralgia for ≥3 months, worst pain level in the last 24 hours ≥5 (NRS 0 to 10), pain is attributable to a lesion or disease of the somatosensory nervous system; stable regimen of pain medications for ≥4 weeks and able to maintain an equivalent dosage during followup Excluded: active systemic infection; immunocompromised; may need diathermy or therapeutic ultrasound at the implant site; implanted medical device within 15 cm of the intended placement site for peripheral nerve stimulator; bleeding disorders or active anticoagulation that cannot be discontinued for implantation.	A: Peripheral nerve stimulation: Lead placement under fluoroscopic or ultrasound guidance, placement confirmed with test stimulation; stimulation parameters phase duration 70 to 500 m/sec, pulse rate 1 to 200 Hz, time on ranged from 10 minutes to 12 hours (mean 6 hours per day at 3-month study visit). Typical settings were 200 m/sec; 100 Hz; amplitude set for paresthesia. B: Sham stimulation: Stimulator placed but no therapeutic stimulation provided	Mean (SD) age, years: 53.0 (11.1) Female: 41.5% White: 91.5% Black/African American: 3.2% Native American: 1.1% Hispanic: 3.2% Other race/ethnicity: 1.1% Pain in lower extremity: 28.7% Pain in upper extremity: 27.7% Pain in trunk: 43.6% A vs. B Baseline BPI worst pain (mean [SD], 0 to 10 scale): 8.1 (1.1) vs. 8.0 (1.1) Baseline BPI, general activity (mean [SD], 0 to 10 scale): 6.6 (2.2) vs. 6.5 (1.8) SF-12 (mean, 0 to 100 scale): 35.5 (4.9) vs. 36.0 (4.3)	Screened: 147 Eligible: NR Randomized: 94 (45 vs. 49) Complete followup: Unclear Analyzed: 94 (45 vs. 49)	Bioness, Inc	Fair

Abbreviations: BPI = Brief Pain Inventory; CI = confidence interval; NR = not reported; NRS = numeric rating scale; NS = not significant; RCT = randomized controlled trial; RR = risk ratio; SD = standard deviation; SF-12 = Short-Form 12

See Appendix F, List of Included Studies, for full citations

Table G-27. Trial of peripheral nerve stimulation for chronic pain – results

Author, Year Trial	Results	Adverse Events and Withdrawals Due to Adverse Events
Deer, 2016	A vs. B Pain (mean % reduction [SD]), overall (n = 94): -27.2% vs. -2.3%, mean difference -24.9% (p<0.0001) - Upper extremity pain (n = 26): -29.2% (33.3) vs. -6.5% (20.0), mean difference -19.8% (95% CI, -44.6 to 5.0) Responders (at least 30% reduction in pain and no increase in pain medication), overall: 38% (17/45) vs. 10% (5/49) at 3 months, RR 3.70 (95% CI, 1.49 to 9.21) - Upper extremity pain: 33% (4/12) vs. 0% (0/14) at 3 months, RR 10.4 (95% CI 0.6 to 175.2) BPI general activity (mean change from baseline [SD], 0 to 10 scale), overall: -2.3 (2.7) vs. -0.4 (2.0) at 3 months, p = 0.001 SF-12 (mean change from baseline [SD], 0 to 100 scale), overall: 1.4 (5.9) vs. -0.2 (3.4) at 3 months, p = 0.04 Pain medication increased at 3 months, overall: 2.2% (1/45) vs. 4.1% (2/49) at 3 months, p = NS Clinical Global Impression (mean [SD], 0 to 7 scale), overall: 4.8 (1.5) vs. 2.5 (1.9) at 3 months, p<0.0001	A vs. B (overall sample) Any adverse events: 42.2% (19/45) vs. 32.6% (16/49) Device related adverse events: 31.1% (14/45) vs. 26.5% (13/49) Nondevice-related adverse events: 11.1% (5/45) vs. 6.1% (3/49) Serious adverse events: 20% (9/45) vs. 22.4% (11/49) Device related serious adverse events: 0% vs. 0% Nondevice related serious adverse events: 20% (9/45) vs. 22.4% (11/49)

Abbreviations: BPI = Brief Pain Inventory; CI = confidence interval; NR = not reported; NRS = numeric rating scale; NS = not significant; RCT = randomized controlled trial; RR = risk ratio; SD = standard deviation; SF-12 = Short-Form 12

See Appendix F, List of Included Studies, for full citations

Appendix H. Quality Table

Table H-1. Quality assessments of randomized controlled trials

Author, Year Country	Randomization Adequate?	Allocation Concealment Adequate?	Groups Similar at Baseline?	Outcome Assessors Masked?	Care Provider Masked?	Patient Masked?	Acceptable Levels of Overall Attrition and Between-Group Differences in Attrition?	Intention-to-Treat (ITT) Analysis	Avoidance of Selective Outcomes Reporting	Quality Rating	Comments
Amirdelfan 2020 Australia and U.S.	Unclear	Yes	No	Yes	No	Yes	Yes/Yes	Yes	Yes	Fair	
Berenson, 2011 Australia, Canada, Europe, U.S.	Yes	Yes	Yes	No (except for safety)	No	No	Yes/No	No	Yes	Fair	Outcomes after 1 month not relevant (high crossover); focusing on 1 month results there was differential but not high attrition; loss to followup was 10% and no imputation for missing data
Blasco, 2012 Spain	Yes	Unclear	No (pain)	Unclear	No	No	No (24%)/Yes	Unclear	Yes	Fair	
Buchbinder, 2009 Australia	Yes	Yes	Yes	Yes	No	Yes	Yes/Yes	Yes	Yes	Good	
Cady, 2015 U.S.	Yes	Yes	Yes	Yes	Unclear	Yes	No/No (at 1 month post-treatment)	No	Yes	Poor	At 1 month attrition was 27% and loss in the sham group was 43%.
Chen, 2014 China	Unclear	Unclear	Yes	Unclear	No	No	Yes/Yes	Yes	Yes	Fair	Attrition was low so ITT is OK

Author, Year Country	Randomization Adequate?	Allocation Concealment Adequate?	Groups Similar at Baseline?	Outcome Assessors Masked?	Care Provider Masked?	Patient Masked?	Acceptable Levels of Overall Attrition and Between-Group Differences in Attrition?	Intention-to-Treat (ITT) Analysis	Avoidance of Selective Outcomes Reporting	Quality Rating	Comments
Childers, 2002 U.S	Unclear	Unclear	Yes	Unclear	Unclear	Yes	Yes/Yes	Yes	Yes	Poor	Analysis did not account for crossover design; scales not reported and may be unvalidated
Clark, 2016 Australia	Yes	Yes	Yes	Yes	Yes	Yes	Yes/Yes	Yes	Yes	Good	
Cohen, 2008 U.S.	Unclear	Yes	No (ODI)	Yes	No	Yes	Yes/Yes	No (at 3 months and beyond, due to high crossover)	Yes	Fair	High crossover at 3 months; crossover patients excluded from analysis
Deer, 2016 U.S.	Yes	Unclear	Yes	Unclear	Unclear	Yes	Unclear	Yes	Yes	Fair	
Farrokhi, 2011 Iran	Yes	Yes	No (pain)	Yes	No	No	Yes/Yes	Yes	Yes	Poor	Serious data discrepancies (implausible values for standard deviations and results inconsistent with reported data)
Firanescu, 2018 the Netherlands	Yes	Unclear	Yes	Yes	Unclear	Yes	Yes/Yes	Yes	Yes	Good	
Fishman, 2002 U.S	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	No/Yes	No	Unclear	Poor	
Fishman, 2017 U.S	Unclear	Unclear	UNclear	Unclear	Unclear	Yes	No/No	No	Unclear	Poor	Scale used to measure pain not reported
Gallucci, 2007 Italy	Unclear	Unclear	Yes	Yes	Unclear	Yes	Unclear	Yes	Yes	Fair	

Author, Year Country	Randomization Adequate?	Allocation Concealment Adequate?	Groups Similar at Baseline?	Outcome Assessors Masked?	Care Provider Masked?	Patient Masked?	Acceptable Levels of Overall Attrition and Between-Group Differences in Attrition?	Intention-to-Treat (ITT) Analysis	Avoidance of Selective Outcomes Reporting	Quality Rating	Comments
Hansen, 2019 Denmark	Unclear	Yes	No (pain)	Yes	Unclear	Yes	Yes/Yes	No	Yes	Fair	Attrition was >10% and did not do imputation or other method for handling missing data. Envelop probably ok for allocation concealment
Haseeb, 2019 Egypt	Unclear	Unclear	Unclear	Yes	Unclear	Unclear	Unclear	Unclear	No	Poor	
Kallewaard, 2019 the Netherlands	Yes	Yes	Yes	Yes	Unclear	Yes	Yes/Yes	Yes	Yes	Good	
Kallmes, 2009 U.K., Austraia, U.S.	Yes	Yes	Yes	Yes	Yes	Yes	Yes/Yes	Yes	Yes	Good	
Klazen, 2010 the Netherlands and Belgium	Yes	Yes	Yes	No	No	No	Yes/Yes	Yes	Yes	Fair	Open-label is one of the major issues with these trials
Kroll, 2008 U.S.	Yes	Unclear	No (pain)	Unclear	No	Yes	No/Unclear	No	Yes	Poor	
Leali, 2016 Italy, France, Switzerland	Unclear	Unclear	Unclear	Unclear	No	No	Unclear	Unclear	Unclear	Poor	
McCormick, 2019 U.S.	Yes	Yes	Yes	Yes	No	Yes	Yes/Yes	Yes	Yes	Good	

Author, Year Country	Randomization Adequate?	Allocation Concealment Adequate?	Groups Similar at Baseline?	Outcome Assessors Masked?	Care Provider Masked?	Patient Masked?	Acceptable Levels of Overall Attrition and Between-Group Differences in Attrition?	Intention-to-Treat (ITT) Analysis	Avoidance of Selective Outcomes Reporting	Quality Rating	Comments
Mekhail, 2017 (single center from Silberstein 2012) U.S.	Yes	Yes	Unclear	Unclear	Yes	Yes	Yes/Yes	Yes	Yes	Fair	Single center from Silberstein 2012 multicenter trial
Misirlioglu, 2015 Turkey	Unclear	Yes	Yes	Yes	Yes	Yes	Yes/Yes	Yes	Yes	Fair	
Moussa, 2020 Egypt	Unclear	Unclear	Unclear	Yes	No	Yes	Unclear	Unclear	Yes	Poor	Data discrepancies present
Nilachandra, 2016 India	Unclear	Unclear	Yes	No	No	Unclear	Unclear	Yes	Unclear	Poor	
Patel, 2012 U.S.	Unclear	Unclear	Yes	Yes	No	Yes	Yes/Yes	No (at 3 months and beyond, due to high crossover)	Yes	Fair	High crossover, appear to have been excluded from analysis at 3 months
Peng, 2010 China	Yes	Unclear	Yes	Yes	No	Yes	Yes/Yes	Yes	Yes	Fair	
Rousing, 2009 Denmark	Unclear	Yes	No (pain, EQ-5D)	Unclear	No	No	Yes/Yes	Yes	Yes	Poor	Missing baseline data
Saper, 2011 Canada, U.S., and U.K.	Unclear	Yes	Yes	Yes	Yes	No	Yes/Yes	Yes	Unclear	Fair	
Serra, 2012 Italy	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Yes/Yes	Yes	Unclear	Poor	Analyses did not account for crossover design
Silberstein, 2012 U.S.	Yes	Yes	Yes	Unclear	Yes	Yes	Yes/Yes	Yes	Yes	Fair	Stimulation parameters not reported
Tekin, 2007 Turkey	Yes	Unclear	Yes	Yes	No	Yes	Unclear	Unclear	Yes	Fair	

Author, Year Country	Randomization Adequate?	Allocation Concealment Adequate?	Groups Similar at Baseline?	Outcome Assessors Masked?	Care Provider Masked?	Patient Masked?	Acceptable Levels of Overall Attrition and Between-Group Differences in Attrition?	Intention-to-Treat (ITT) Analysis	Avoidance of Selective Outcomes Reporting	Quality Rating	Comments
Tuakli-Wosornu, 2016 U.S.	Unclear	Yes	No (% female)	Yes	Yes	Yes	Yes/Yes	No	Yes	Fair	Doesn't meet criteria for ITT since they didn't do any imputation etc.
Voormolen, 2007 the Netherlands	Unclear	Yes	Yes	Unclear	No	No	Yes/Yes	Yes	Yes	Fair	
Wardlaw, 2009 Europe and U.S.	Yes	Unclear	Yes	Unclear	No	No	Yes/No	Yes	Yes	Fair	At 3 months there was >10% different in loss to followup between groups
Yang, 2016 China	Year	Unclear	Yes	No	No	No	No/No	No	Yes	Poor	

Abbreviations: ODI = Oswestry Disability Index; U.S = United States

See Appendix F, List of Included Studies, for full citations

Appendix I. Meta-Analysis Results

Table I-1. Stratified analyses, vertebroplasty versus sham or usual care, pain (continuous) at 1 to 2 weeks and at 2 to 4 weeks*

Analysis	Subgroup	Mean Difference (95% CI), 1 to 2 Weeks	I^2	Number of Trials (N)	p†	Mean Difference (95% CI), 2 to 4 Weeks	I^2	Number of Trials (N)	p†
All trials	--	-0.53 (-1.36 to 0.24)	75%	10 (1093)	--	-1.05 (-1.80 to -0.32)	64%	8 (918)	--
Control type	• Sham	-0.02 (-0.65 to 0.61)	14%	5 (536)	0.14	-0.57 (-1.09 to -0.05)	0%	5 (536)	0.01
	• Usual care	-1.22 (-2.81 to 0.23)	73%	5 (557)	--	-2.27 (-3.20 to -0.94)	0%	3 (382)	--
Pain duration (inclusion criteria)	• <4 weeks	-3.10 (-6.57 to 0.37)	--	1 (107)	0.18	-2.40 (-4.79 to -0.01)	--	1 (107)	0.79
	• <6 to 10 weeks	-0.75 (-2.02 to 0.59)	80%	4 (536)	--	-1.08 (-2.43 to 0.33)	81%	4 (536)	--
	• <12 months	0.46 (-0.30 to 1.37)	0%	3 (327)	--	-0.62 (-1.51 to 0.29)	0%	2 (199)	--
	• ≥4 to 6 weeks	-1.55 (-2.89 to -0.21)	0%	2 (123)	--	-1.20 (-2.61 to 0.21)	--	1 (73)	--
Pain duration (mean or median)	• <4 weeks	-1.37 (-0.37 to -0.05)	0%	2 (219)	0.49	-1.56 (-3.14 to -0.40)	0%	2 (219)	0.70
	• 4 to 8 weeks	-0.60 (-2.38 to 1.28)	86%	3 (424)	--	-0.96 (-2.90 to 1.07)	86%	3 (211)	--
	• >8 weeks	-0.11 (-1.32 to 0.92)	58%	5 (450)	--	-0.75 (-1.48 to -0.05)	0%	3 (275)	--
Bone marrow edema on MRI	• Required	-0.72 (-1.91 to 0.35)	78%	7 (779)	0.56	-1.17 (-2.44 to 0.04)	75%	5 (604)	0.72
	• Not required	-0.19 (-1.42 to 1.02)	49%	3 (314)	--	-0.90 (-1.59 to -0.17)	0%	3 (314)	--
PMMA volume	• >5 ml	-0.41 (-2.09 to 1.04)	45%	2 (288)	0.39	-0.75 (-2.05 to 0.28)	4.3%	2 (288)	0.77
	• ≤5 ml	-0.80 (-1.90 to 0.19)	72%	7 (680)	--	-1.13 (-2.14 to -0.13)	66%	6 (630)	--
Study quality	• Good	-0.09 (-0.89 to 0.67)	28%	4 (490)	0.38	-0.70 (-1.27 to -0.19)	0%	4 (490)	0.54
	• Fair	-0.74 (-2.14 to 0.67)	78%	5 (496)	--	-1.25 (-3.16 to 0.78)	78%	3 (321)	--
	• Poor	-3.10 (-6.57 to 0.37)	--	1 (107)	--	-2.40 (-4.79 to -0.01)	--	1 (107)	--

Abbreviations: CI = confidence interval; ml = milliliter; MRI = magnetic resonance imaging; N = number of subjects; PMMA = polymethyl methacrylate

*Pain is on a 0 to 10 scale (higher values indicate more severe pain) and that negative mean difference values indicate less pain with vertebroplasty

†For interaction

Table I-2. Stratified analyses, vertebroplasty versus sham or usual care, pain (continuous) at 1 to 6 months, 6 to 12 months, and 12 months and longer*

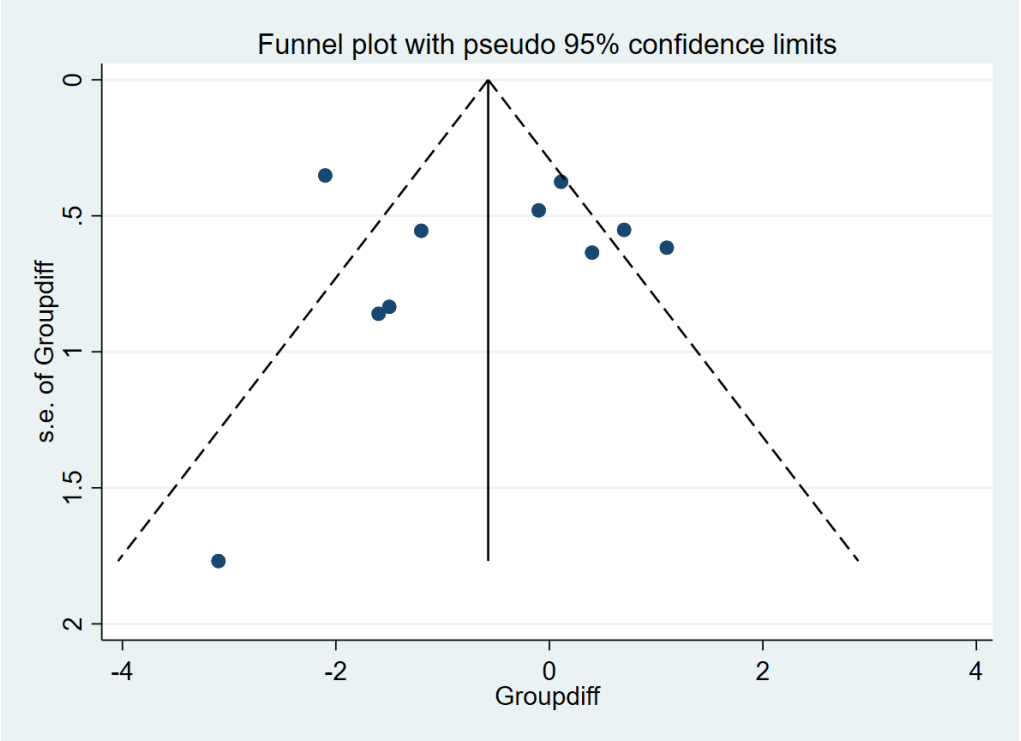
Analysis	Subgroup	Mean Difference (95% CI), 1 to 6 Months	I^2	No. of Trials (N)	p†	Mean Difference (95% CI), 6 to 12 Months	I^2	No. of Trials (N)	p†	Mean Difference (95% CI), 12 Months and Longer	I^2	N T (N
All trials	--	-0.76 (-1.17 to -0.38)	5.5%	10 (1094)	--	-0.73 (-1.33 to -0.15)	43%	8 (993)	--	-0.87 (-1.43 to -0.31)	42%	9
Control type	• Sham	-0.47 (-0.98 to -0.01)	0%	5 (525)	0.09	-0.59 (-1.16 to -0.07)	0%	4 (470)	0.71	-0.64 (-1.21 to -0.08)	0%	4
	• Usual care	-1.17 (-1.71 to -0.60)	0%	5 (569)	--	-0.87 (-2.81 to 0.23)	58%	4 (523)	--	-1.08 (-2.06 to -0.11)	51%	5
Pain duration (inclusion criteria)	• <4 weeks	-1.80 (-3.76 to 0.16)	--	1 (107)	0.68	-1.20 (-3.14 to 0.74)	--	1 (107)	0.46	-1.20 (-2.89 to 0.49)	--	1
	• <6 to 10 weeks	-0.70 (-1.36 to -0.03)	29%	5 (575)	--	-1.05 (-2.02 to -0.14)	42%	3 (480)	--	-0.91 (-1.88 to 0.15)	57%	4
	• <12 months	-0.67 (-1.32 to -0.03)	0%	3 (323)	--	-0.16 (-1.07 to 0.80)	14%	3 (317)	--	-0.60 (-1.61 to 0.36)	18%	3
	• ≥4 to 6 weeks	-1.40 (-3.09 to 0.29)	--	1 (89)	--	-1.50 (-3.46 to 0.46)	--	1 (89)	--	-1.60 (-3.45 to 0.25)	--	1
Pain duration (mean or median)	• <4 weeks	-1.25 (-2.22 to -0.31)	0%	3 (258)	0.54	-1.27 (-2.52 to 0.01)	0%	2 (209)	0.46	-1.03 (-2.34 to 0.24)	0%	2
	• 4 to 8 weeks	-0.56 (-1.48 to 0.48)	46%	3 (424)	--	-0.99 (-2.45 to 0.47)	58%	2 (378)	--	-0.90 (-2.23 to 0.54)	68%	3
	• >8 weeks	-0.76 (-1.37 to -0.17)	0%	4 (412)	--	-0.30 (-1.26 to 0.51)	16%	4 (406)	--	-0.72 (-1.67 to 0.07)	17%	4
Bone marrow edema on MRI	• Required	-0.74 (-1.40 to -0.16)	24%	6 (745)	0.84	-0.73 (-1.71 to 0.17)	57%	5 (699)	0.995	-0.80 (-1.65 to 0.03)	57%	6
	• Not required	-0.82 (-1.44 to -0.22)	0%	4 (349)	--	-0.74 (-1.52 to 0.05)	0%	3 (294)	--	-1.02 (-1.73 to -0.30)	0%	3
PMMA volume	• >5 ml	-0.48 (-1.92 to 0.50)	0%	2 (281)	0.73	-0.62 (-1.84 to 0.25)	0%	2 (278)	0.19	-0.45 (-1.25 to 0.35)	--	1
	• ≤5 ml	-0.90 (-1.41 to -0.34)	0%	6 (642)	--	-1.09 (-1.72 to -0.34)	8.9%	5 (590)	--	-1.22 (-1.85 to -0.50)	24%	6
Study quality	• Good	-0.56 (-1.17 to -0.07)	0%	4 (479)	0.59	-0.59 (-1.16 to -0.07)	0%	4 (470)	0.89	-0.75 (-1.45 to -0.16)	0%	3
	• Fair	-0.90 (-1.58 to -0.06)	5.9%	4 (462)	--	-0.81 (-2.50 to 0.82)	68%	3 (416)	--	-0.84 (-2.14 to 0.46)	66%	4
	• Poor	-1.20 (-2.86 to 0.32)	--	2 (153)	--	-1.20 (-3.14 to 0.74)	--	1 (107)	--	-1.03 (-2.32 to 0.24)	0%	2

Abbreviations: CI = confidence interval; ml = millimeter; MRI = magnetic resonance imaging; N = number of subjects; PMMA = polymethyl methacrylate

*Pain is on a 0 to 10 scale (higher values indicate more severe pain) and that negative mean difference values indicate less pain with vertebroplasty

†For interaction

Figure I-1. Funnel plot of vertebroplasty versus sham or usual care, pain (continuous), 1 to 2 weeks



Abbreviations: SE = standard error

Figure I-2. Funnel plot of vertebroplasty versus sham or usual care, pain (continuous), 1 to 6 months

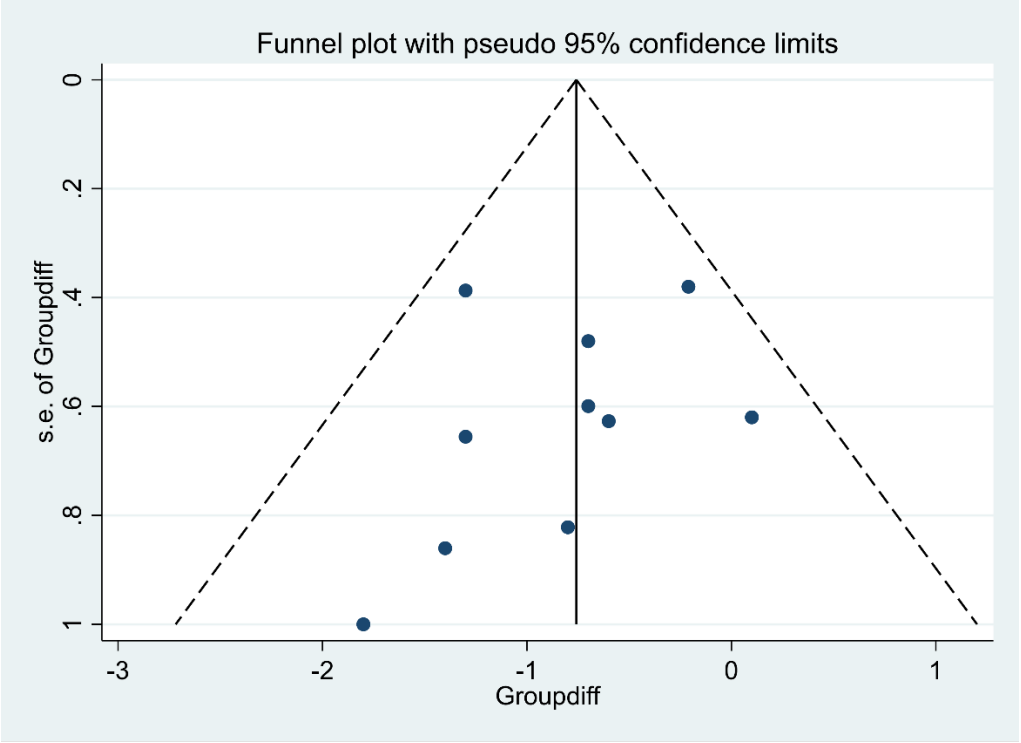


Table I-3. Vertebroplasty versus sham or usual care, pain, function, and opioid use (dichotomous)

Followup Duration	Pain, RR (95% CI)	Function, RR (95% CI)	Opioid Use, RR (95% CI)
1 to 2 weeks	1.05 (0.16 to 6.02)	--	0.66 (0.30 to 1.27)
I^2	75%	--	0%
No. of trials (N)	2 (186)	--	2 (178)
2 to 4 weeks	1.35 (0.51 to 3.82)	0.66 (0.45 to 0.97)	1.08 (0.58 to 1.48)
I^2	79%	--	0%
No. of trials (N)	3 (293)	1 (108)	3 (368)
1 to 6 months	1.46 (0.84 to 2.34)	--	1.02 (0.60 to 1.75)
I^2	0%	--	0%
No. of trials (N)	2 (176)	--	2 (172)
6 to 12 months	1.32 (0.82 to 1.91)	--	0.93 (0.44 to 1.57)
I^2	0%	--	0%
No. of trials (N)	2 (175)	--	2 (165)
12 months and longer	1.27 (0.64 to 2.27)	1.56 (1.12 to 2.18)	0.72 (0.30 to 1.70)
I^2	35%	--	--
No. of trials (N)	2 (202)	1 (119)	1 (83)

Abbreviations: CI = confidence interval; N = number of subjects; RR = relative risk

Table I-4. Stratified analyses, vertebroplasty versus sham or usual care, function (continuous) at 1 to 2 weeks and at 2 to 4 weeks*

Analysis	Subgroup	SMD (95% CI), 1 to 2 Weeks	I^2	Number of Trials (N)	p†	SMD (95% CI), 2 to 4 Weeks	I^2	Number of Trials (N)	p†
All trials	--	-0.21 (-0.48 to 0.04)	49%	7 (743)	--	-0.27 (-0.42 to -0.12)	0%	6 (708)	--
Control type	• Sham	0.03 (-0.36 to 0.44)	34%	3 (311)	0.10	-0.26 (-0.53 to 0.00)	0%	3 (310)	0.91
	• Usual care	-0.38 (-0.61 to -0.18)	0%	4 (432)	--	-0.28 (-0.49 to -0.07)	0%	3 (398)	--
Pain duration (mean or median)	• <4 weeks	-0.30 (-0.60 to 0.01)	0%	2 (216)	0.85	-0.40 (-0.72 to -0.09)	0%	2 (107)	0.55
	• 4 to 8 weeks	-0.39 (-0.67 to -0.12)	--	1 (202)	--	-0.25 (-0.53 to 0.03)	--	1 (202)	--
	• >8 weeks	-0.11 (-0.71 to 0.39)	65%	4 (325)	--	-0.19 (-0.43 to 0.05)	--	3 (290)	--
Study quality	• Good	0.03 (-0.36 to 0.44)	34%	3 (311)	0.28	-0.26 (-0.53 to 0.00)	0%	3 (310)	0.89
	• Fair	-0.41 (-0.78 to -0.15)	0%	3 (325)	--	-0.25 (-0.52 to 0.02)	0%	2 (291)	--
	• Poor	-0.30 (-0.68 to 0.09)	--	1 (107)	--	-0.36 (-0.74 to 0.03)	--	1 (107)	--
Scale	On original scale RDQ or modified RDQ‡	-1.24 (-3.30 to 0.68)	61%	6 (636)	--	-1.64 (-2.71 to -0.60)	0%	5 (601)	--

Abbreviations: ODI = Oswestry Disability Index; RDQ = Roland-Morris Disability Questionnaire; SMD = standardized mean difference

*Negative values for SMDs or mean differences indicate less functional impairment with vertebroplasty

†For interaction

‡RDQ is measured on 0 to 24 scale and modified RDQ on 0 to 23 scale, with higher values indicating greater functional impairment (and will need to define RDQ)

Table I-5. Stratified analyses, vertebroplasty versus sham or usual care, function (continuous) at 1 to 6 months, 6 to 12 months, and 12 months and longer*

Analysis	Subgroup	SMD (95% CI), 1 to 6 Months	I^2	No. of Trials (N)	p†	SMD (95% CI), 6 to 12 Months	I^2	No. of Trials (N)	p†	SMD (95% CI), 12 Months and Longer	I^2	No. of Trials (N)	p
All trials	--	-0.28 (-0.43 to -0.11)	0%	7 (637)	--	-0.29 (-0.45 to -0.14)	0%	6 (690)	--	-0.23 (-0.39 to -0.06)	0%	6 (612)	--
Control type	• Sham	-0.14 (-0.53 to 0.27)	27%	3 (301)	0.21	-0.32 (-0.70 to 0.09)	23%	3 (292)	0.78	-0.17 (-0.51 to 0.22)	0%	2 (176)	0
	• Usual care	-0.37 (-0.56 to -0.18)	0%	4 (440)	--	-0.27 (-0.48 to -0.07)	0%	3 (398)	--	-0.25 (-0.45 to -0.05)	0%	4 (436)	--
Pain duration (mean or median)	• <4 weeks	-0.40 (-0.66 to -0.14)	0%	3 (252)	0.30	-0.45 (-0.88 to -0.03)	0%	2 (207)	0.27	-0.11 (-0.50 to 0.31)	0%	2 (145)	0
	• 4 to 8 weeks	-0.37 (-0.65 to -0.09)	NA	1 (202)	--	-0.26 (-0.53 to 0.02)	NA	1 (202)	--	-0.28 (-0.55 to 0.00)	NA	1 (202)	--
	• >8 weeks	-0.11 (-0.43 to 0.24)	0%	3 (287)	--	-0.21 (-0.46 to 0.06)	0%	3 (281)	--	-0.25 (-0.52 to 0.03)	0%	3 (265)	--
Study quality	• Good	-0.14 (-0.53 to 0.27)	27%	3 (301)	0.46	-0.32 (-0.70 to 0.09)	23%	3 (292)	0.54	-0.17 (-0.51 to 0.22)	0%	2 (176)	0
	• Fair	-0.37 (-0.64 to -0.09)	0%	2 (291)	--	-0.27 (-0.55 to 0.00)	0%	2 (291)	--	-0.32 (-0.63 to -0.05)	0%	2 (291)	--
	• Poor	-0.38 (-0.76 to 0.03)	0%	2 (149)	--	-0.29 (-0.67 to 0.09)	--	1 (107)	--	-0.11 (-0.50 to 0.31)	0%	2 (145)	--
Scale	On original scale RDQ or modified RDQ	-1.66 (-3.05 to -0.09)	2%	4 (592)	--	-1.90 (-3.09 to -0.73)	0%	5 (543)	--	-1.78 (-3.00 to -0.52)	0%	4 (427)	--

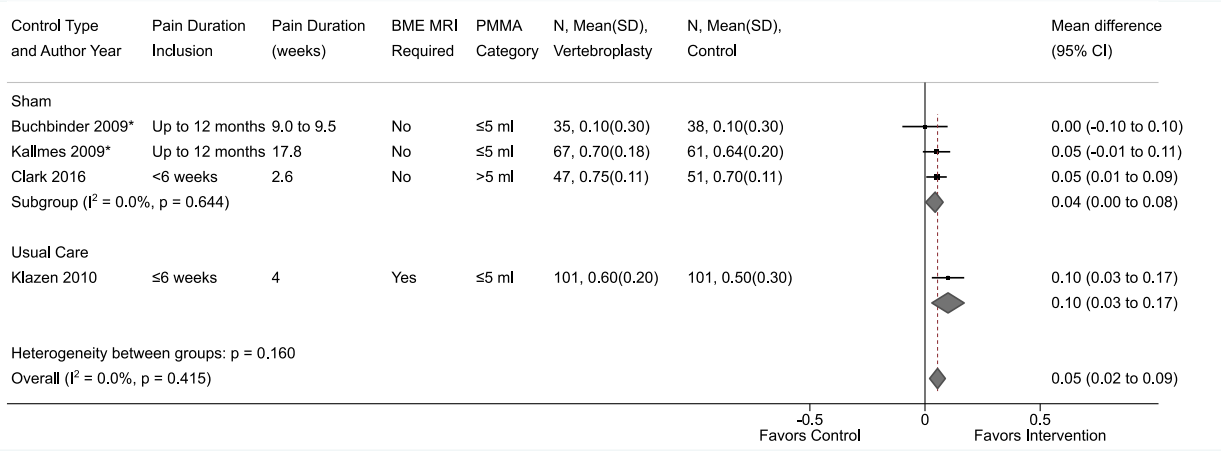
Abbreviations: CI = confidence interval; N = number of subjects; RDQ = Roland-Morris Disability Questionnaire; SMD = standardized mean difference

*Negative values for standardized mean differences or mean differences indicate less functional impairment with vertebroplasty

†For interaction

‡RDQ is measured on 0 to 24 scale and modified RDQ on 0 to 23 scale, with higher values indicating greater functional impairment

Figure I-3. Vertebroplasty versus sham or usual care, EQ-5D (continuous) at 2 to 4 weeks

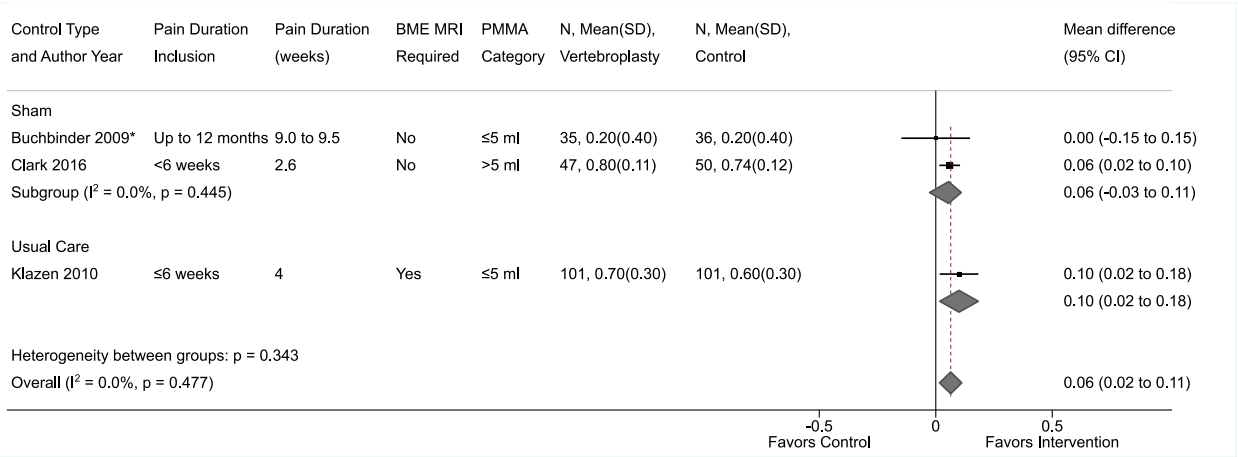


Abbreviations: BME = bone marrow edema; CI = confidence interval; MRI = magnetic resonance imaging; PMMA = polymethyl methacrylate; SD = standard deviation

*Adjusted mean difference from a regression model was used

See Appendix F, List of Included Studies, for full citations

Figure I-4. Vertebroplasty versus sham or usual care, EQ-5D (continuous) at 6 to 12 months

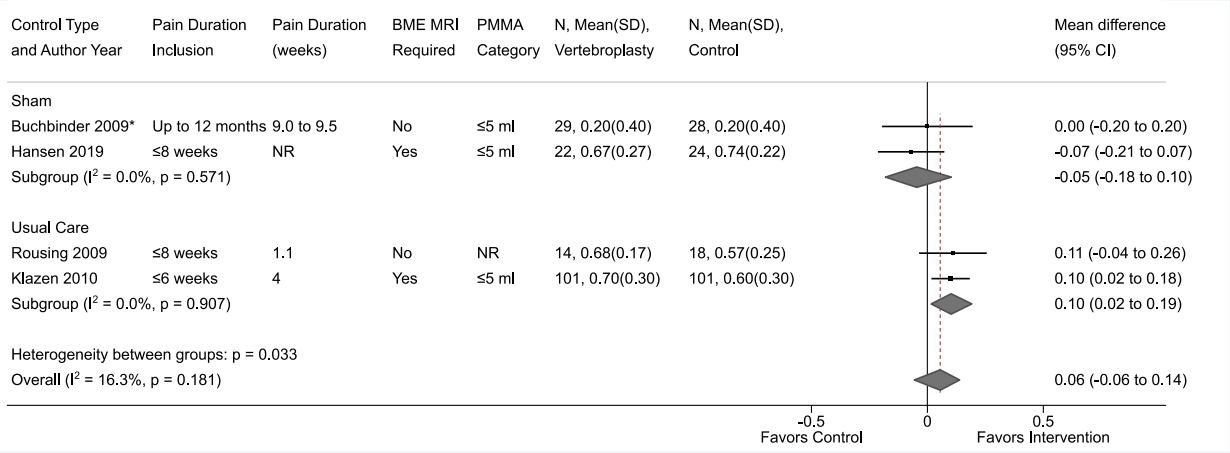


Abbreviations: BME = bone marrow edema; CI = confidence interval; MRI = magnetic resonance imaging; PMMA = polymethyl methacrylate; SD = standard deviation

*Adjusted mean difference from a regression model was used

See Appendix F, List of Included Studies, for full citations

Figure I-5. Vertebroplasty versus sham or usual care, EQ-5D (continuous) at 12 months and longer

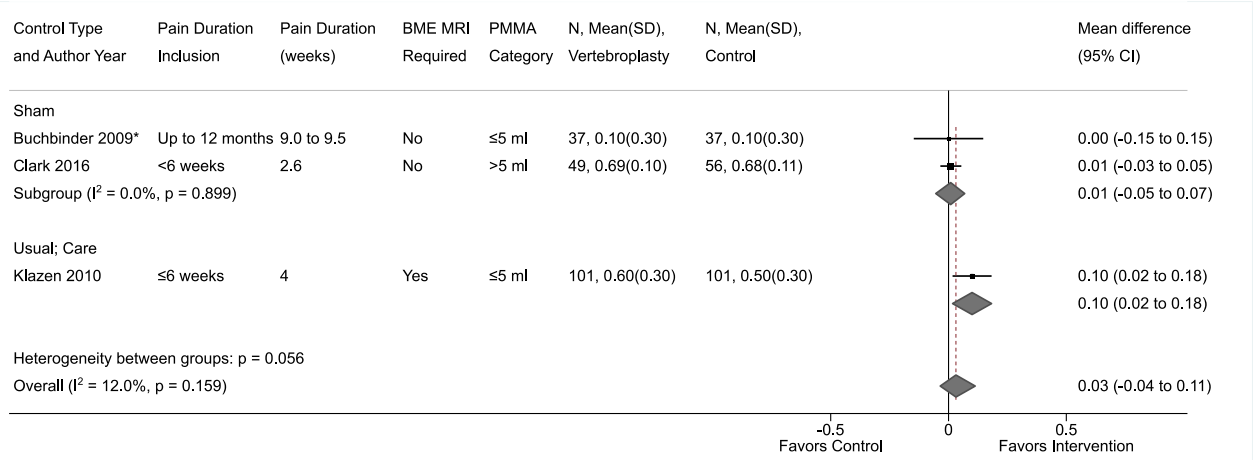


Abbreviations: BME = bone marrow edema; CI = confidence interval; MRI = magnetic resonance imaging; PMMA = polymethyl methacrylate; SD = standard deviation

*Adjusted mean difference from a regression model was used

See Appendix F, List of Included Studies, for full citations

Figure I-6. Vertebroplasty versus sham or usual care, EQ-5D (continuous) at 1 to 2 weeks

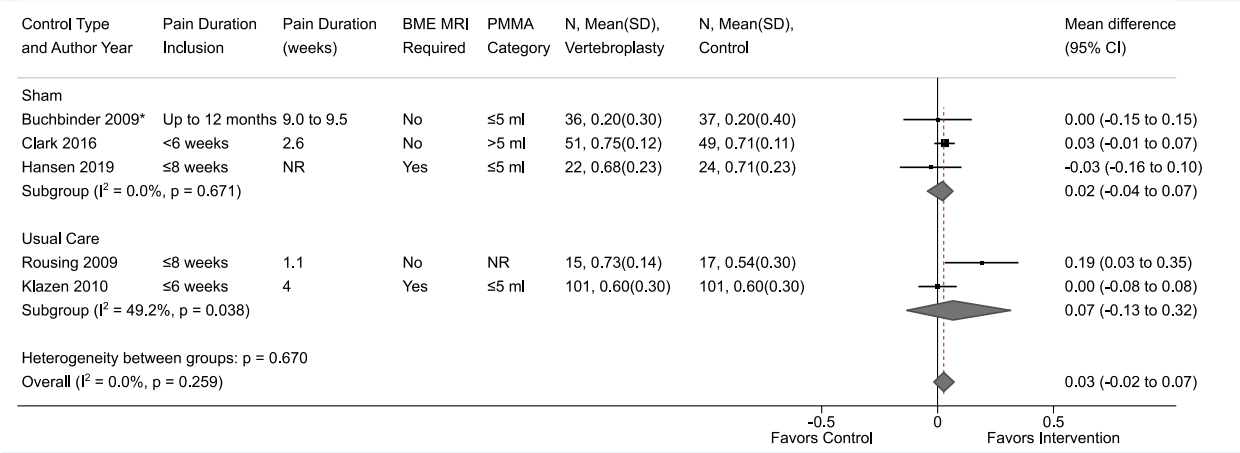


Abbreviations: BME = bone marrow edema; CI = confidence interval; MRI = magnetic resonance imaging; PMMA = polymethyl methacrylate; SD = standard deviation

*Adjusted mean difference from a regression model was used

See Appendix F, List of Included Studies, for full citations

Figure I-7. Vertebroplasty versus sham or usual care, EQ-5D (continuous) at 1 to 6 months



Abbreviations: BME = bone marrow edema; CI = confidence interval; MRI = magnetic resonance imaging; PMMA = polymethyl methacrylate; SD = standard deviation

*Adjusted mean difference from a regression model was used

See Appendix F, List of Included Studies, for full citations

Table I-6. Vertebroplasty versus sham or usual care, quality of life (continuous) at 1 to 2 weeks and at 2 to 4 weeks

Analysis	Subgroup	Mean Difference (95% CI), 1 to 2 Weeks	I^2	Number of Trials (N)	p*	Mean Difference (95% CI), 2 to 4 Weeks	I^2	Number of Trials (N)	p*
EQ-5D, all trials†	--	0.03 (-0.04 to 0.11)	12%	3 (381)	--	0.05 (0.02 to 0.09)	0%	4 (501)	--
EQ-5D, control type	• Sham	0.01 (-0.05 to 0.07)	0%	2 (179)	0.31	0.04 (0.00 to 0.08)	0%	3 (299)	0.29
	• Usual care	0.10 (0.02 to 0.18)	--	1 (202)	--	0.10 (0.03 to 0.17)	0%	1 (202)	--
EQ-5D, study quality	• Good	0.01 (-0.05 to 0.07)	0%	2 (179)	0.31	0.04 (0.00 to 0.08)	0%	3 (299)	0.29
	• Fair	0.10 (0.02 to 0.18)	--	1 (202)	--	0.10 (0.03 to 0.17)	0%	1 (202)	--
	• Poor	--	--	--	--	--	--	--	--
QUALEFFO, all trials‡	--	-2.55 (-9.46 to 3.16)	76%	6 (644)	--	-2.11 (-10.44 to 3.54)	63%	4 (482)	--
QUALEFFO, control type	• Sham	-0.73 (-13.01 to 11.09)	80%	2 (176)	0.64	0.94 (-9.37 to 9.63)	52%	2 (173)	0.36
	• Usual care	-4.00 (-14.59 to 4.67)	68%	4 (468)	--	-4.95 (-17.56 to 0.72)	0%	2 (309)	
QUALEFFO, study quality	• Good	-0.73 (-13.01 to 11.09)	80%	2 (176)	0.81	0.94 (-9.37 to 9.63)	52%	2 (173)	0.53
	• Fair	-3.36 (-15.72 to 7.67)	76%	3 (361)	--	-4.20 (-8.60 to 0.20)	--	1 (202)	--
	• Poor	-10.00 (-29.40 to 9.40)	--	1 (107)	--	-16.00 (-32.86 to 0.86)	--	1 (107)	--

Abbreviations: CI = confidence interval; EQ-5D = EuroQol-5 Dimension; QUALEFFO = Quality of Life for Osteoporosis

*For interaction

†EQ-5D is on a 0 to 1 scale (higher score indicates better quality of life) and that positive mean difference values indicated better quality of life with vertebroplasty

‡QUALEFFO is on a 0 to 100 scale (higher score indicates worse quality of life) and that negative mean difference values indicate better quality of life with vertebroplasty.

Table I-7. Vertebroplasty versus sham or usual care, quality of life (continuous) at 1 to 6 months, 6 to 12 months, and 12 months and longer

Analysis	Subgroup	Mean Difference (95% CI), 1 to 6 Months	I^2	No. of Trials (N)	p*	Mean Difference (95% CI), 6 to 12 Months	I^2	No. of Trials (N)	p*	Mean Difference (95% CI), 12 Months and Longer	I^2	No. of Trials (N)	p*
EQ-5D, all trials†	--	0.03 (-0.02 to 0.07)	0%	5 (433)	--	0.06 (0.02 to 0.11)	0%	3 (370)	--	0.06 (-0.06 to 0.14)	16%	4 (337)	--
EQ-5D, control type	• Sham	0.02 (-0.04 to 0.07)	0%	3 (199)	0.52	0.06 (-0.03 to 0.11)	0%	2 (168)	0.52	-0.05 (-0.18 to 0.10)	0%	2 (103)	0.
	• Usual care	0.07 (-0.13 to 0.32)	49%	2 (234)	--	0.10 (0.02 to 0.18)	--	1 (202)	--	0.10 (0.02 to 0.19)	0%	2 (234)	--
EQ-5D, study quality	• Good	0.03 (-0.04 to 0.08)	0%	2 (173)	0.29	0.06 (-0.03 to 0.11)	0%	2 (168)	0.52	0.00 (-0.20 to 0.20)	--	1 (57)	0.
	• Fair	-0.01 (-0.10 to 0.07)	0%	2 (228)	--	0.10 (0.02 to 0.18)	--	1 (202)	--	0.04 (-0.18 to 0.22)	47%	2 (228)	--
	• Poor	0.19 (0.03 to 0.35)	--	1 (32)	--	--	--	--	--	0.11 (-0.04 to 0.26)	--	1 (32)	--
QUALEFFO, all trials‡	--	-2.16 (-7.08 to 1.81)	0%	4 (507)	--	-2.98 (-7.62 to 0.69)	15%	5 (599)	--	-1.45 (-5.12 to 2.06)	0%	4 (491)	--
QUALEFFO, control type	• Sham	-0.70 (-5.66 to 4.26)	--	1 (73)	0.73	-3.63 (-11.49 to 3.94)	16%	2 (165)	0.90	-2.10 (-8.41 to 4.21)	--	1 (57)	0.
	• Usual care	-2.92 (-12.16 to 3.51)	17%	3 (434)	--	-2.36 (-11.42 to 3.52)	0%	3 (434)	--	-1.21 (-6.68 to 3.54)	0%	3 (434)	--
QUALEFFO, study quality	• Good	-0.70 (-5.66 to 4.26)	--	1 (73)	0.58	-3.63 (-11.49 to 3.94)	16%	2 (165)	0.44	-2.10 (-8.41 to 4.21)	--	1 (57)	0.
	• Fair	-2.06 (-9.25 to 6.43)	22%	2 (327)	--	-1.33 (-7.25 to 5.64)	0%	2 (327)	--	-0.77 (-6.06 to 5.33)	0%	2 (327)	--
	• Poor	-14.00 (-29.31 to 1.31)	--	1 (107)	--	-13.00 (-25.55 to -0.45)	--	1 (107)	--	-8.00 (-23.31 to 7.31)	--	1 (107)	--

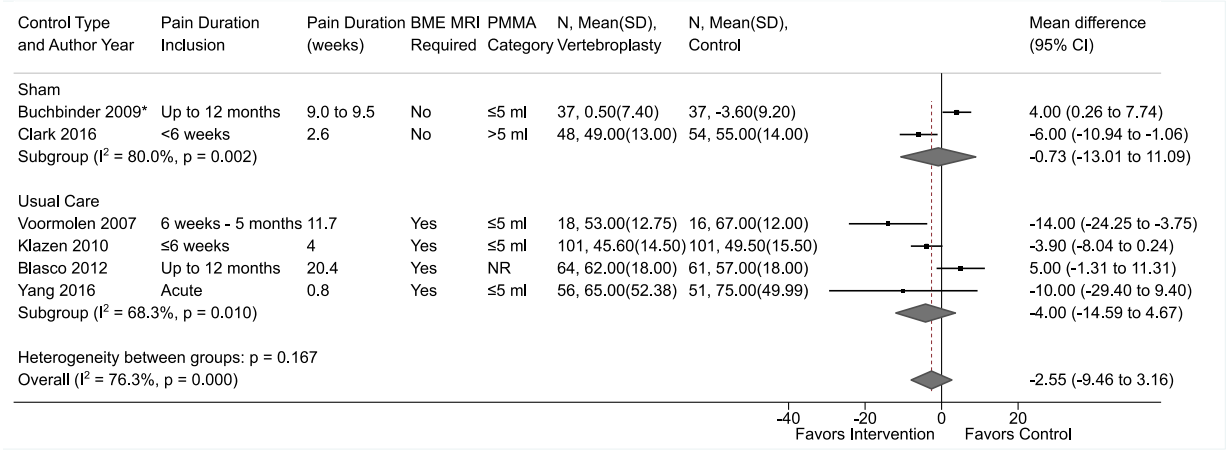
Abbreviations: CI = confidence interval; EQ-5D = EuroQol-5 Dimension; N = number of subjects; QUALEFFO = Quality of Life for Osteoporosis

*For interaction

†EQ-5D is on a 0 to 1 scale (higher score indicates better quality of life) and that positive mean difference values indicated better quality of life with vertebroplasty

‡QUALEFFO is on a 0 to 100 scale (higher score indicates worse quality of life) and that negative mean difference values indicate better quality of life with vertebroplasty.

Figure I-8. Vertebroplasty versus sham or usual care on the QUALEFFO at 1 to 2 weeks

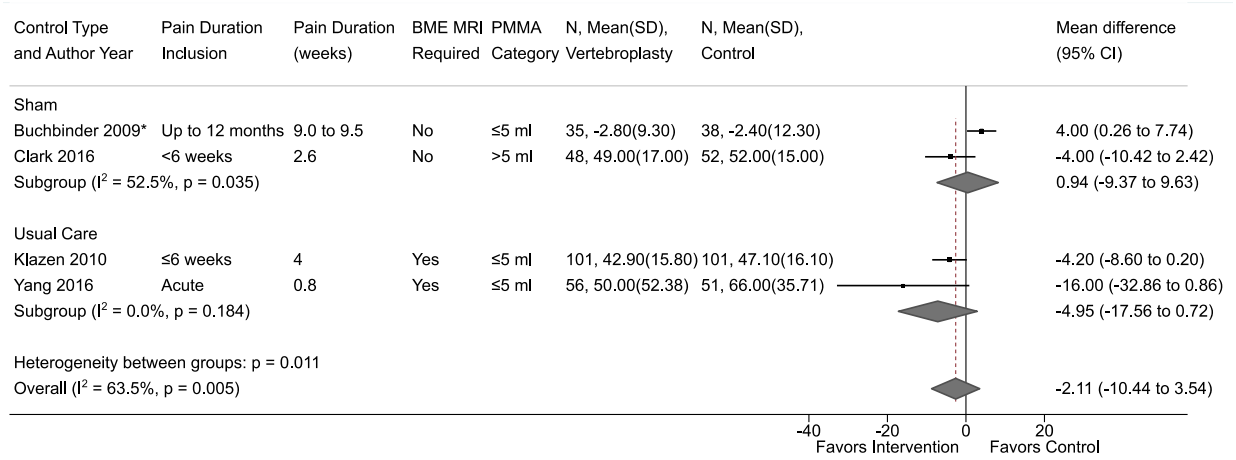


Abbreviations: BME = bone marrow edema; CI = confidence interval; MRI = magnetic resonance imaging; PMMA = polymethyl methacrylate; SD = standard deviation

*Adjusted mean difference from a regression model was used

See Appendix F, List of Included Studies, for full citations

Figure I-9. Vertebroplasty versus sham or usual care on the QUALEFFO at 2 to 4 weeks

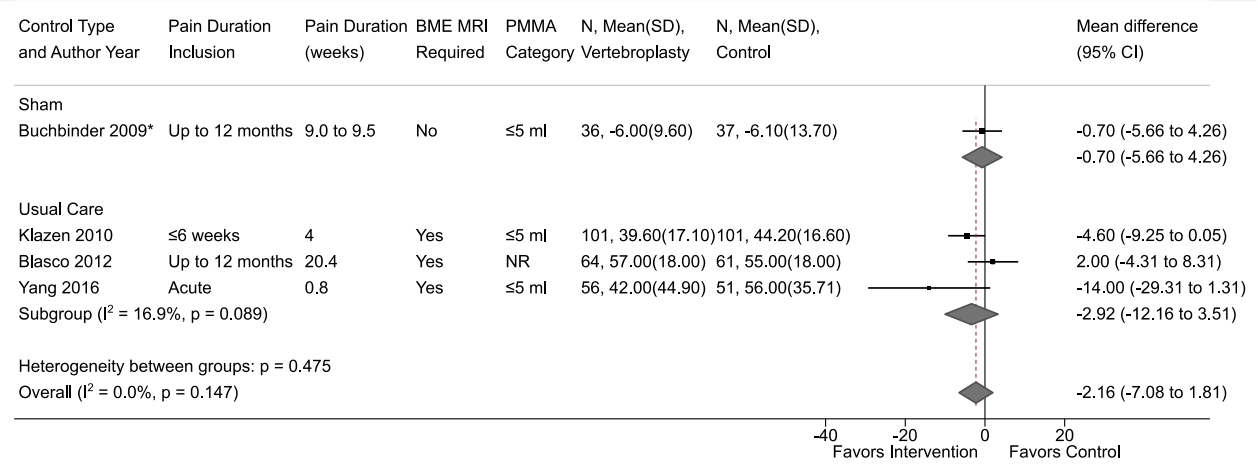


Abbreviations: BME = bone marrow edema; CI = confidence interval; MRI = magnetic resonance imaging; PMMA = polymethyl methacrylate; SD = standard deviation

*Adjusted mean difference from a regression model was used

See Appendix F, List of Included Studies, for full citations

Figure I-10. Vertebroplasty versus sham or usual care on the QUALEFFO at 1 to 6 months

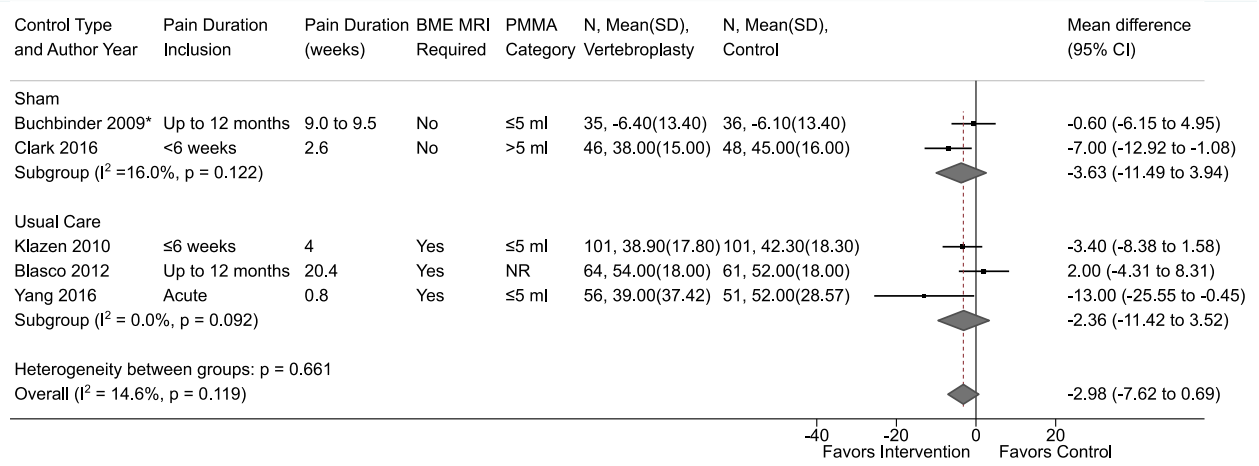


Abbreviations: BME = bone marrow edema; CI = confidence interval; MRI = magnetic resonance imaging; PMMA = polymethyl methacrylate; SD = standard deviation

*Adjusted mean difference from a regression model was used

See Appendix F, List of Included Studies, for full citations

Figure I-11. Vertebroplasty versus sham or usual care on the QUALEFFO at 6 to 12 months

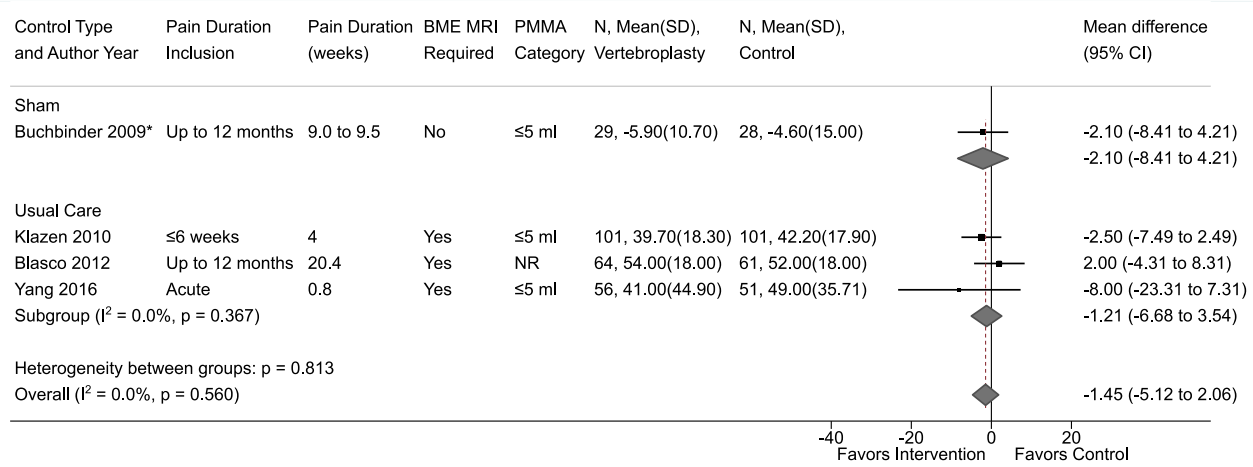


Abbreviations: BME = bone marrow edema; CI = confidence interval; MRI = magnetic resonance imaging; PMMA = polymethyl methacrylate; SD = standard deviation

*Adjusted mean difference from a regression model was used

See Appendix F, List of Included Studies, for full citations

Figure I-12. Vertebroplasty versus sham or usual care on the QUALEFFO at 12 months and longer

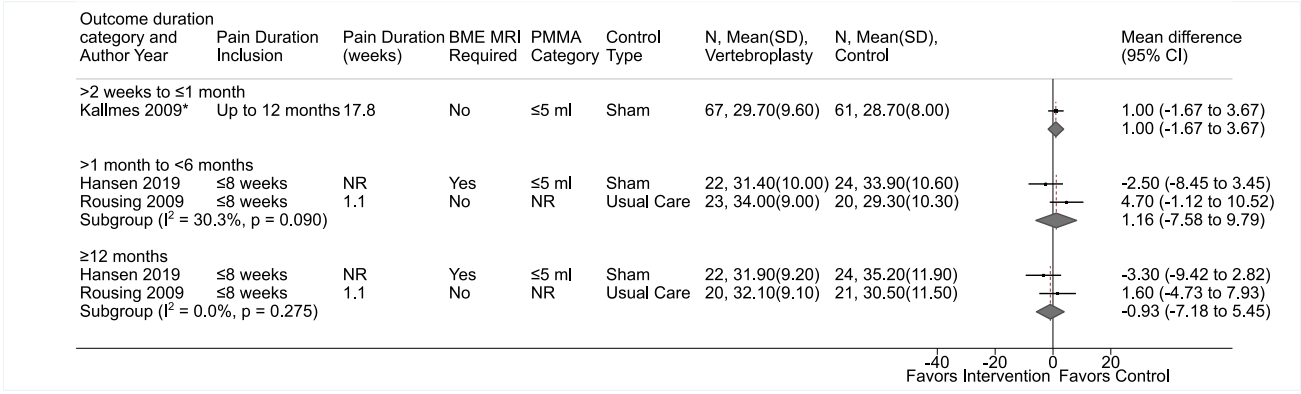


Abbreviations: BME = bone marrow edema; CI = confidence interval; MRI = magnetic resonance imaging; PMMA = polymethyl methacrylate; SD = standard deviation

*Adjusted mean difference from a regression model was used

See Appendix F, List of Included Studies, for full citations

Figure I-13. Vertebroplasty versus sham or usual care on the Short-Form 36 Physical Component Summary Scores

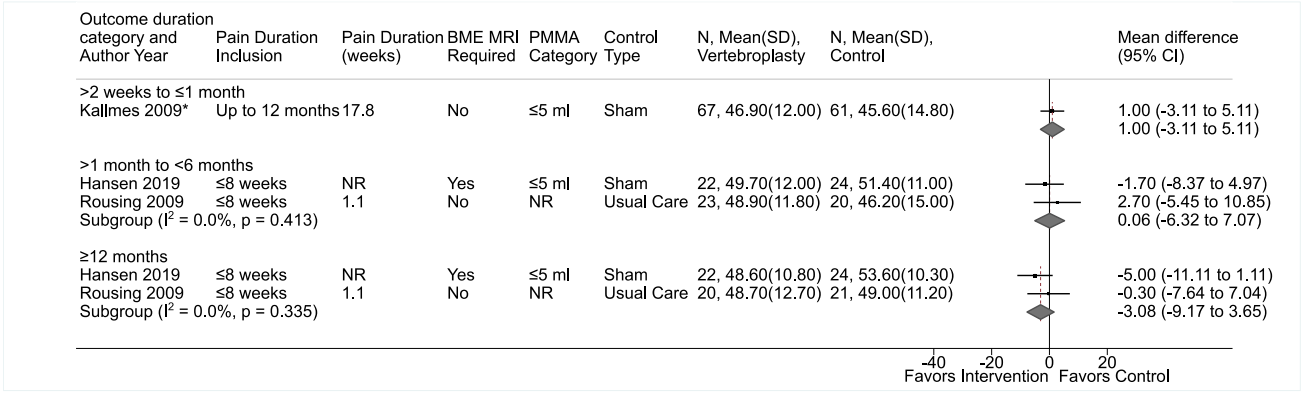


Abbreviations: BME = bone marrow edema; CI = confidence interval; MRI = magnetic resonance imaging; PMMA = polymethyl methacrylate; SD = standard deviation

*Adjusted mean difference from a regression model was used

See Appendix F, List of Included Studies, for full citations

Figure I-14. Vertebroplasty versus sham or usual care on the Short-Form 36 Mental Component Summary Scores



Abbreviations: BME = bone marrow edema; CI = confidence interval; MRI = magnetic resonance imaging; PMMA = polymethyl methacrylate; SD = standard deviation

*Adjusted mean difference from a regression model was used

See Appendix F, List of Included Studies, for full citations

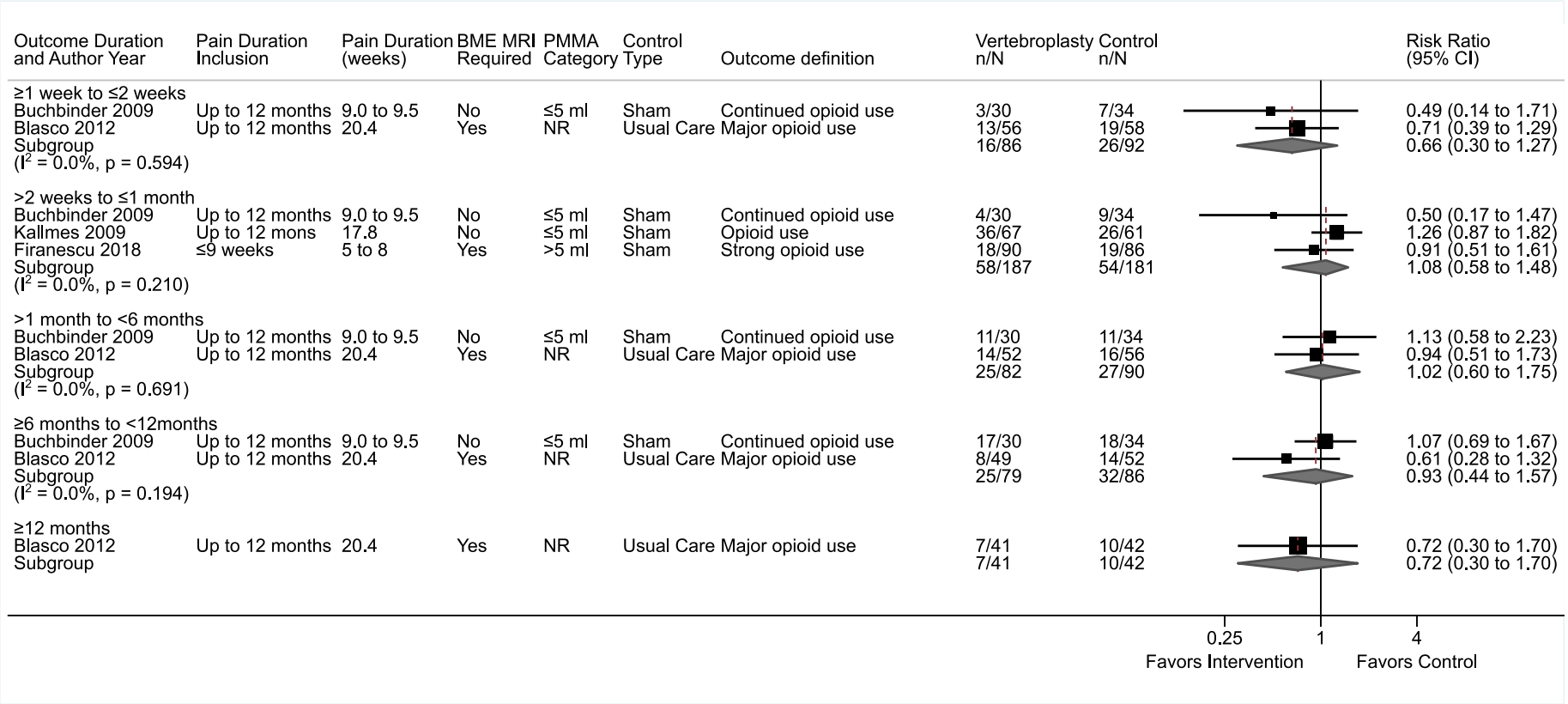
Table I-8. Vertebroplasty versus sham or usual care, Short-Form 36 Physical and Mental Component Summary Scores (continuous)

Followup Duration	SF-36 Physical Component Summary Score (0 to 100 Scale)*	SF-Mental Component Summary Score (0 to 100 Scale)*
2 to 4 weeks	Mean difference 1.00 (95% CI, -1.67 to 3.67)	Mean difference 1.00 (95% CI, -3.11 to 5.11)
I^2	--	--
No. of trials (N)	1 (128)	1 (128)
1 to 6 months	Mean difference 1.16 (95% CI, -7.58 to 9.79)	Mean difference 0.06 (95% CI, -6.32 to 7.07)
I^2	30%	0%
No. of trials (N)	2 (89)	2 (89)
12 months and longer	Mean difference -0.93 (95% CI, -7.18 to 5.45)	Mean difference -3.08 (95% CI, -9.17 to 3.65)
I^2	0%	0%
No. of trials (N)	2 (87)	2 (87)

Abbreviations: CI = confidence interval; N = number of subjects; SF-36 = Short-Form 36

*Positive values indicate that health status is better in the vertebroplasty arm

Figure I-15. Vertebroplasty versus sham or usual care and risk of opioid use



Abbreviations: BME = bone marrow edema; CI = confidence interval; MRI = magnetic resonance imaging; PMMA = polymethyl methacrylate; SD = standard deviation

See Appendix F, List of Included Studies, for full citations

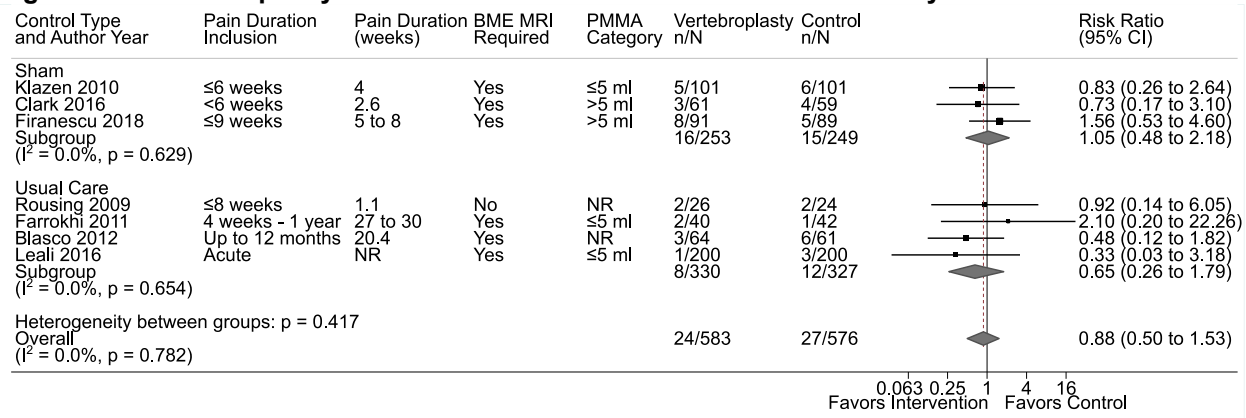
Table I-9. Vertebroplasty versus sham or usual care and risk of mortality, incident vertebral fracture, and serious adverse events

Followup Duration	Mortality RR (95% CI)	Vertebral Fracture RR (95% CI)	Serious Adverse Events RR (95% CI)
All trials	0.88 (0.50 to 1.53)	1.02 (0.66 to 1.62)	--
I^2	0%	9.6%	--
No. of trials (N)	7 (1159)	10 (1380)	--
1 to 2 weeks	--	4.47 (0.23 to 86.77)	--
I^2	--	--	--
No. of trials (N)	--	1 (34)	--
2 to 4 weeks	--	1.90 (0.59 to 7.22)	--
I^2	--	0%	--
No. of trials (N)	--	3 (598)	--
6 to 12 months	0.76 (0.23 to 2.65)	--	0.67 (0.12 to 3.79)
I^2	0%	--	0%
No. of trials (N)	3 (598)	--	1 (86)
12 months and longer*	0.98 (0.51 to 1.87)	0.94 (0.55 to 1.49)	0.95 (0.06 to 14.90)
I^2	0%	15%	--
No. of trials (N)	5 (639)	7 (826)	1 (125)

Abbreviations: CI = confidence interval; N = number of subjects; RR = relative risk

*1 trial reported vertebral fractures through 24 months

Figure I-16. Vertebroplasty versus sham or usual care and risk of mortality



Abbreviations: BME = bone marrow edema; CI = confidence interval; MRI = magnetic resonance imaging; PMMA = polymethyl methacrylate; SD = standard deviation

See Appendix F, List of Included Studies, for full citations

Appendix J. Strength of Evidence

Table J-1. Strength of evidence

Intervention	Outcomes	Number of Studies	Number of Subjects	Directness	Precision	Study Limitations	Consistency	Findings (95% CI)	SOE
Vertebroplasty vs. sham or usual care for vertebral compression fractures	Pain (≥1 to ≤2 w)	10 RCTs	1093	Direct	Imprecise	Low	Inconsistent	Overall: MD -0.53 (-1.36 to 0.24) Vs. sham: MD -0.02 (-0.65 to 0.61) Vs. usual care: MD -1.22 (-2.81 to 0.23)	Low for benefit
	Pain (>2 w to ≤1 m)	8 RCTs	918	Direct	Precise	Low	Inconsistent	Overall: MD -1.05 (-1.80 to -0.32) Vs. sham: MD -0.57 (-1.09 to -0.05) Vs. usual care: MD -2.27 (-3.20 to -0.94)	Moderate for benefit
	Pain (>1 to <6 m)	10 RCTs	1094	Direct	Precise	Low	Inconsistent*	Overall: MD -0.76 (-1.17 to -0.38) Vs. sham: MD -0.47 (-0.98 to -0.01) Vs. usual care: MD -1.17 (-1.71 to -0.60)	Moderate for benefit
	Pain (≥6 to <12 m)	8 RCTs	993	Direct	Precise	Low	Inconsistent	Overall: MD -0.73 (-1.33 to -0.15) Vs. sham: MD -0.59 (-1.16 to -0.07) Vs. usual care: MD -0.87 (-2.81 to 0.23)	Moderate for benefit
	Pain (≥12 m)	9 RCTs	965	Direct	Precise	Low	Inconsistent	Overall: MD -0.87 (-1.43 to -0.31) Vs. sham: MD -0.64 (-1.21 to -0.08) Vs. usual care: -1.08 (-2.06 to -0.11)	Moderate for benefit
	Function (≥1 to ≤2 w)	7 RCTs	743	Direct	Imprecise	Low	Inconsistent	Overall: SMD -0.21 (-0.48 to 0.04) Vs. sham: SMD 0.03 (-0.36 to 0.44) Vs. usual care: SMD -0.38 (-0.61 to -0.18)	Insufficient
	Function (>2 w to ≤1 m)	6 RCTs	708	Direct	Precise	Low	Consistent	Overall: SMD -0.27 (-0.42 to -0.12) Vs. sham: SMD -0.26 (-0.53 to 0.00) Vs. usual care: SMD -0.28 (-0.49 to -0.07)	High for benefit
	Function (>1 to <6 m)	7 RCTs	741	Direct	Precise	Low	Inconsistent*	Overall: SMD -0.28 (-0.43 to -0.11) Vs. sham: SMD -0.14 (-0.53 to 0.27) Vs. usual care: SMD -0.37 (-0.56 to -0.18)	Moderate for benefit
	Function (≥6 to <12 m)	6 RCTs	690	Direct	Precise	Low	Consistent	Overall: SMD -0.29 (-0.45 to -0.14) Vs. sham: SMD -0.32 (-0.70 to 0.09) Vs. usual care: SMD -0.27 (-0.48 to -0.07)	High for benefit

Intervention	Outcomes	Number of Studies	Number of Subjects	Directness	Precision	Study Limitations	Consistency	Findings (95% CI)	SOE
Vertebroplasty vs. sham or usual care for vertebral compression fractures, continued	Function (≥12 m)	6 RCTs	612	Direct	Precise	Low	Inconsistent*	Overall: SMD -0.23 (-0.39 to -0.06) Vs. sham: SMD -0.17 (-0.51 to 0.22) Vs. usual care SMD -0.25 (-0.45 to -0.05)	Moderate for benefit
	Quality of life (general) (≥1 to ≤2 w)	3 RCTs	381	Direct	Imprecise	Low	Inconsistent*	Overall: MD 0.03 (-0.04 to 0.11) Vs. sham: 0.01 (-0.05 to 0.07) Vs. usual care: 0.10 (0.02 to 0.18)	Low for no benefit
	Quality of life (general) (>2 w to ≤1 m)	4 RCTs	501	Direct	Imprecise	Low	Inconsistent*	Overall: MD 0.05 (0.02 to 0.09) Vs. sham: MD 0.04 (0.00 to 0.08) Vs. usual care: MD 0.10 (0.03 to 0.17)	Low for benefit
	Quality of life (general) (>1 to <6 m)	5 RCTs	453	Direct	Imprecise	Low	Inconsistent	Overall: MD 0.03 (-0.02 to 0.07) Vs. sham: MD 0.02 (-0.04 to 0.07) Vs. usual care: 0.07 (-0.13 to 0.32)	Low for no benefit
	Quality of life (general) (≥6 to <12 m)	3 RCTs	370	Direct	Precise	Low	Consistent	Overall: MD 0.06 (0.02 to 0.11) Vs. sham: MD 0.06 (-0.03 to 0.11) Vs. usual care: MD 0.10 (0.02 to 0.18)	High for benefit
	Quality of life (general) (≥12 m)	4 RCTs	337	Direct	Imprecise	Low	Inconsistent*	Overall: MD 0.06 (-0.06 to 0.14) Vs. sham: MD -0.05 (-0.18 to 0.10) Vs. usual care: MD 0.10 (0.02 to 0.19)	Insufficien†
	Quality of life (condition-specific) (≥1 to ≤2 w)	6 RCTs	644	Direct	Imprecise	Low	Inconsistent	Overall: MD -2.55 (-9.46 to 3.15) Vs. sham: -0.73 (-13.01 to 11.09) Vs. usual care: -4.00 (-14.59 to 4.67)	Low for no benefit
	Quality of life (condition-specific) (>2 w to ≤1 m)	4 RCTs	482	Direct	Imprecise	Low	Inconsistent	Overall: MD -2.11 (-10.44 to 3.54) Vs. sham: 0.94 (-9.37 to 9.63) Vs. usual care: -4.95 (-17.56 to 0.72)	Low for no benefit
	Quality of life (condition-specific) (>1 to <6 m)	4 RCTs	507	Direct	Imprecise	Low	Consistent	Overall: MD -2.16 (-7.08 to 1.81) Vs. sham: MD -0.70 (-5.66 to 4.26) Vs. usual care: MD -2.92 (-12.16 to 3.51)	Moderate for no benefit
	Quality of life (condition-specific) (≥6 to <12 m)	5 RCTs	599	Direct	Imprecise	Low	Consistent	MD -2.98 (-7.62 to 0.69) Vs. sham: -3.63 (-11.49 to 3.94) Vs. usual care: -2.36 (-11.42 to 3.52)	Moderate for no benefit
	Quality of life (condition-specific) (≥12 m)	4 RCTs	491	Direct	Imprecise	Low	Consistent	Overall: -1.45 (-5.12 to 2.06) Vs. sham: MD -2.10 (-8.41 to 4.21) Vs. usual care: MD -1.21 (-6.68 to 3.54)	Moderate for no benefit

Intervention	Outcomes	Number of Studies	Number of Subjects	Directness	Precision	Study Limitations	Consistency	Findings (95% CI)	SOE
Vertebroplasty vs. sham or usual care for vertebral compression fractures, continued	Health status (SF-36 PCS and MCS) (>2 w to ≤1 m, >1 to 6 m, and ≥12 m)	1 to 2 RCTs	87 to 128	Direct	Imprecise	Low	Consistent	Mean differences ranged from -0.93 to 1.16 points on the SF-36 PCS and from -3.08 to 1.00 points on the SF-36 MCS	Low for no benefit
	Mortality	7 RCTs	1159	Direct	Imprecise	Low	Consistent	RR 0.88 (0.50 to 1.53)	Moderate for no increased risk
	Incident vertebral fractures	10 RCTs	1380	Direct	Imprecise	Low	Consistent	RR 1.02 (0.66 to 1.62)	Moderate for no increased risk
	Serious adverse events	2 RCTs	211	Direct	Imprecise	Low	Unable to assess	≥6 to <12 m (1 trial): RR 0.67 (0.12 to 3.79) ≥12 m (1 trial): RR 0.95 (0.06 to 14.90)	Low for no increased risk
Kyphoplasty vs. usual care for vertebral compression fractures	Pain (1 w and 1 m)	2 RCTs	434	Direct	Precise	Moderate	Consistent	Large reductions	Moderate for benefit
	Pain (3 m, 6 m, 1 y, 2 y)	1 RCT	300	Direct	Precise	Moderate	Unable to assess	3 m, 6 m, 1 y: Moderate reduction 2 y: Small reduction	Low for benefit
	Function (1 w and 1 m)	2 RCTs	434	Direct	Precise	Moderate	Unable to assess at 1 w; consistent at 1 m	1 w: Moderate improvement (1 trial) 1 m: Moderate to large improvement (2 trials)	Low for benefit at 1 w, moderate for benefit at 1 m
	Function (3 m, 6 m, 1 y, 2 y)	1 RCT	300	Direct	Precise	Moderate	Unable to assess	3 m, 6 m, 1 y: Moderate improvement 2 y: Small improvement	Low for benefit
	SF-36 Health status (≥1 m)	2 RCTs	434	Direct	Precise	Moderate	Consistent	Small to moderate improvement at up to 1 m, no difference at 1 y	Moderate for benefit at up to 1 m, low for no benefit at ≥1 y
	Quality of life (≥1 m)	1 RCT	300	Direct	Precise	Moderate	Unable to assess	Moderate improvement at 1 m, no difference at 1 to 2 y	Low for benefit at 1 m, low for no difference at ≥1 y

Intervention	Outcomes	Number of Studies	Number of Subjects	Directness	Precision	Study Limitations	Consistency	Findings (95% CI)	SOE
Kyphoplasty vs. usual care for vertebral compression fractures, continued	Mortality	2 RCTs	434	Direct	Imprecise	Moderate	Inconsistent	No difference in one trial and increased risk in one trial	Insufficient
	Incident or worsening vertebral fracture	2 RCTs	434	Direct	Imprecise	Moderate	Inconsistent	Increased risk in one trial and few events with imprecise estimate in one trial	Insufficient
	Serious adverse events	2 RCTs	434	Direct	Imprecise	Moderate	Unable to assess	No difference in risk	Low for no increased risk
Cooled radiofrequency denervation vs. sham for sacroiliac pain	Pain (1 and 3 m)	2 RCTs	79	Direct	Precise	Moderate	Consistent	1 m: Moderate to large improvement 3 m: Moderate improvement	Moderate for benefit
	Function (1 and 3 m)	2 RCTs	79	Direct	Precise	Moderate	Inconsistency§	1 m: Small to large improvement 3 m: Moderate improvement	Low for benefit at 1 m; moderate for benefit at 3 m
	Health status, quality of life (3 m)	1 RCT	28	Direct	Precise	Moderate	Unable to assess	3 m: Moderate improvement	Low for benefit at 3 m
	Opioid use (1 m)	1 RCT	51	Direct	Precise	Moderate	Unable to assess	1 m: Large reduction	Low for benefit at 1 m
	Treatment success (composite outcome) (1 and 3 m)	2 RCTs	79	Direct	Precise	Moderate	Unable to assess (1 study at each time point)	1 m: Large benefit 3 m: Large benefit	Low for benefit
	Harms	1 RCT	28	Direct	Imprecise	Moderate	Unable to assess	No serious complications and temporary worsening of pain reported	Insufficient
Cooled vs. continuous radiofrequency denervation for presumed lumbar facet joint pain	Pain (1, 3, and 6 m)	1 RCT	43	Direct	Imprecise	Low	Unable to assess	1 and 3 m: No difference 6 m: Small reduction	Low for benefit at 6 m and for no benefit at 1 and 3 m
	Function (1, 3, and 6 m)	1 RCT	43	Direct	Imprecise	Low	Unable to assess	No differences	Low for no benefit

Intervention	Outcomes	Number of Studies	Number of Subjects	Directness	Precision	Study Limitations	Consistency	Findings (95% CI)	SOE
Cooled vs. continuous radiofrequency denervation for presumed lumbar facet joint pain, continued	Harms	1 RCT	43	Direct	Imprecise	Low	Unable to assess	No serious adverse events; self-limited post-procedural pain in two patients	Low for no increased risk
Pulsed radiofrequency‡ denervation vs. sham for presumed lumbar facet joint pain	Pain (6 m, 1 y)	1 RCT	40	Direct	Imprecise	Moderate	Unable to assess	No differences	Insufficient
	Function (6 m, 1 y)	1 RCT	40	Direct	Imprecise	Moderate	Unable to assess	No differences	Insufficient
	Analgesic use (1 year)	1 RCT	40	Direct	Imprecise	Moderate	Unable to assess	No difference	Insufficient
	Harms	No evidence	--	--	--	--	--	--	No evidence
Pulsed vs. continuous radiofrequency denervation for presumed lumbar facet joint pain‡	Pain (6 m, 1 y)	1 RCT	40	Direct	Imprecise	Moderate	Unable to assess	6 m: No difference 1 y: Moderate increase	Insufficient
	Function (6 m, 1 y)	1 RCT	40	Direct	Imprecise	Moderate	Unable to assess	No differences	Insufficient
	Analgesic use (1 y)	1 RCT	40	Direct	Imprecise	Moderate	Unable to assess	Increased analgesic use	Insufficient
	Harms	No evidence	--	--	--	--	--	--	No evidence
Platelet rich plasma vs. sham for presumed discogenic back pain	Pain (1, 4, and 8 weeks)	1 RCT	58	Direct	Imprecise	Moderate	Unable to assess	1 and 4 w: Small reductions 8 w: Moderate reduction	Insufficient
	Function (1, 4, and 8 weeks)	1 RCT	58	Direct	Imprecise	Moderate	Unable to assess	No differences	Insufficient
	Harms	1 RCT	58	Direct	Imprecise	Moderate	Unable to assess	No cases of disc space infection, neurologic injury, or progressive herniation	Insufficient
Intradiscal stem cells vs. sham for presumed discogenic back pain	Pain (1, 3, and 6 m)	1 RCT	100	Direct	Imprecise	Moderate	Unable to assess	Small reductions	Insufficient

Intervention	Outcomes	Number of Studies	Number of Subjects	Directness	Precision	Study Limitations	Consistency	Findings (95% CI)	SOE
Intradiscal stem cells vs. sham for presumed discogenic back pain, continued	Pain (1, 2, and 3 y)	1 RCT	100	Direct	Precise	Moderate	Unable to assess	Moderate to large reductions	Insufficient
	Function (1, 3, and 6 m)	1 RCT	100	Direct	Imprecise	Moderate	Unable to assess	No differences	Insufficient
	Function (1, 2, and 3 y)	1 RCT	100	Direct	Precise	Moderate	Unable to assess	Small to moderate improvements	Insufficient
	Treatment success (6 m to 3 y)	1 RCT	100	Direct	Imprecise	Moderate	Unable to assess	Moderate benefit	Insufficient
	Harms	1 RCT	100	Direct	Imprecise	Moderate	Unable to assess	No differences in risk of serious adverse events or any adverse event	Insufficient
Intradiscal methylene blue vs. sham for presumed discogenic back pain	Pain (6 m)	2 RCTs	153	Direct	Precise	Moderate	Inconsistent	Large benefit in initial trial but no benefit in subsequent trial	Low for no benefit
	Pain (6 w and 3 m)	1 RCT	81	Direct	Imprecise	Low	Unable to assess	No differences	Low for no benefit
	Pain (12 and 24 m)	1 RCT	72	Direct	Precise	Moderate	Unable to assess	Large benefit	Insufficient
	Function (6 m)	2 RCTs	153	Direct	Precise	Moderate	Inconsistent	Large benefit in initial trial but no benefit in subsequent trial	Low for no benefit
	Function (6 w and 3 m)	1 RCT	81	Direct	Imprecise	Low	Unable to assess	6 w and 3 m: Small improvement	Low for benefit
	Function (12 and 24 m)	1 RCT	72	Direct	Precise	Moderate	Unable to assess	Large benefit	Insufficient
	Opioid use	2 RCTs	153	Direct	Precise	Moderate	Inconsistent	Large reduction in initial trial but no difference in subsequent trial	Insufficient
	Harms	2 RCTs	153	Direct	Imprecise	Moderate	Consistent	No serious adverse events related to procedure and no difference in risk of any adverse event	Low for no increased risk
Intradiscal ozone + corticosteroid vs. corticosteroid for radiculopathy due to herniated disc	Pain (1 w, 2 w, 3 m, 6 m)‡	1 RCT	159	Direct	Imprecise	High	Unable to assess	1 and 2 w: No differences 3 and 6 m: Moderate reduction	Insufficient

Intervention	Outcomes	Number of Studies	Number of Subjects	Directness	Precision	Study Limitations	Consistency	Findings (95% CI)	SOE
Intradiscal ozone + corticosteroid vs. corticosteroid for radiculopathy due to herniated disc, continued	Function (2 or 3 w, 6 m) ‡	1 RCT	159	Direct	Imprecise	Moderate	Unable to assess	2 or 3 w: No difference 6 m: Moderate improvement	Insufficient
	Harms	3 RCT	339	Direct	Imprecise	High	Unable to assess	No serious adverse events in any trial; increased risk of any adverse event in one trial	Insufficient
Sphenopalatine block vs. sham for chronic migraine	Pain (1 and 6 m)	1 RCT	41	Direct	Imprecise	Moderate	Unable to assess	1 m: Small benefit (p>0.05) 6 m: Moderate benefit (p>0.05)	Insufficient
	Function (1 and 6 m)	1 RCT	41	Direct	Imprecise	Moderate	Unable to assess	1 and 6 m: Small benefit (p>0.05)	Insufficient
	Any adverse event	1 RCT	41	Direct	Imprecise	Moderate	Unable to assess	No difference	Insufficient
Occipital nerve stimulation vs. sham for chronic migraine‡	Pain (12 w)	1 RCT	157	Direct	Imprecise	Moderate	Unable to assess	Similar likelihood of ≥50% reduction in pain intensity, increased likelihood of ≥30% reduction in pain intensity	Insufficient
	Function (12 w)	1 RCT	157	Direct	Imprecise	Moderate	Unable to assess	Large improvement	Insufficient
	Headache days (12 w)	1 RCT	157	Direct	Imprecise	Moderate	Unable to assess	Small improvement	Insufficient
Occipital nerve stimulation vs. usual care for chronic migraine	Pain (3 m)	1 RCT	67	Direct	Imprecise	Moderate	Unable to assess	Small improvement for stimulation with adjustable parameters; no difference for stimulation using parameter parameters	Insufficient
	Function (3 m)	1 RCT	67	Direct	Imprecise	Moderate	Unable to assess	Large improvement for stimulation with adjustable parameters; no difference for stimulation using preset parameters	Insufficient
	Headache days, mood	1 RCT	67	Direct	Precise	Moderate	Unable to assess	Small improvement for stimulation with adjustable parameters for headache days and mood; no differences for stimulation using present parameters	Low for benefit for stimulation with adjustable parameters

Intervention	Outcomes	Number of Studies	Number of Subjects	Directness	Precision	Study Limitations	Consistency	Findings (95% CI)	SOE
Occipital nerve stimulation vs. usual care for chronic migraine, continued	Harms	2 RCTs	224	Direct	Imprecise	Moderate	Consistent	Lead migration occurred in 14 to 24 percent of patients in two trials. Few serious device-related adverse events	Low for risk of lead migration and no increased risk of serious harms
Piriformis injection with corticosteroid and local anesthetic vs. local anesthetic for piriformis syndrome	Pain at rest‡ (1 w to 3 m)	1 RCT	50	Direct	Imprecise	Moderate	Unable to assess	No difference at 1 week, moderate improvement at 1 and 3 months, but only statistically significant at 1 month	Low for no benefit at 1 w and benefit at 1 m, insufficient at 3 m
	Function	1 RCT	50	Direct	Imprecise	High	Unable to assess	Insufficient	Insufficient
	Transient sciatic nerve block	1 RCT	50	Direct	Imprecise	Moderate	Unable to assess	No difference	Low for no difference
	Serious adverse events	1 RCT	50	Direct	Imprecise	High	Unable to assess	Insufficient	Insufficient
Peripheral nerve stimulation vs. sham or control for ulnar, radial, or median neuropathy	Pain, function, harms (3 m)	1 subgroup analysis from RCT	94	Indirect	Imprecise	Moderate	Unable to assess	Insufficient	Insufficient

Abbreviations: AE = adverse events; CI = confidence interval; m = month(s); MD = mean difference; RCT = randomized controlled trial; RR = risk ratio; SMD = standard mean difference; SOE = strength of evidence; w = week(s); y = year(s)

*Statistical heterogeneity low, but inconsistency in magnitude of benefit between trials of sham and usual care

†SOE graded as insufficient due to marked inconsistency (different directions of effect) between estimates from trials of sham and trials of usual care

‡SOE assessment excludes poor-quality trials

§inconsistency in magnitude of benefit at 1 month