Washington State Health Care Authority

Peripheral nerve ablation for the treatment of limb pain

Final evidence report

December 10, 2018

Health Technology Assessment Program (HTA)

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The authors would like to acknowledge the contributions of the following:
Galen Gamble, BA, Andrew Hamilton, MLS, MS, Heather Katcher, PhD, RD, and the independent peer reviewers of this report

This health technology assessment report is based on research conducted by the Center for Evidence-based Policy (Center) under contract to the Washington State Health Care Authority (HCA). This report is an independent assessment of the technology question(s) described based on accepted methodological principles. The findings and conclusions contained herein are those of the authors, who are responsible for the content. These findings and conclusions do not necessarily represent the views of the Washington HCA and thus, no statement in this report shall be construed as an official position or policy of the HCA.

The information in this assessment is intended to assist health care decision makers, clinicians, patients, and policy makers in making evidence-based decisions that may improve the quality and cost-effectiveness of health care services. Information in this report is not a substitute for sound clinical judgment. Those making decisions regarding the provision of health care services should consider this report in a manner similar to any other medical reference, integrating the information with all other pertinent information to make decisions within the context of individual patient circumstances and resource availability.

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Conflict of Interest Disclosures: No authors have conflicts of interest to disclose. All authors have completed and submitted the Oregon Health & Science University form for Disclosure of Potential Conflicts of Interest, and none were reported.

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List of Abbreviations

AOFAS	American Orthopedic Foot and Ankle Society
BMI	body mass index
CI	confidence interval
cRFA	cooled radiofrequency ablation
FDA	U.S. Food and Drug Administration
GPE	Global Perceived Effect
IAS	intra-articular corticosteroid
KSS	Knee Society Score
MCID	minimal clinically important differences
NHP	Nottingham Health Profile
NR	not reported
NRS	numerical rating scale
OKS	Oxford Knee Score
PGI-I	Patient Global Impression of Improvement
PGIC	Patient Global Impression of Change
pRF	pulsed radiofrequency
RCT	randomized controlled trial
RF	radiofrequency
RFA	radiofrequency ablation
SF-36	Short Form 36
SPADI	Shoulder Pain and Disability Index
TENS	transcutaneous electrical nerve stimulation
TKA	total knee arthroplasty
VAS	Visual Analog Scale
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index

Executive Summary

Structured Abstract

Purpose

The purpose of this evidence report is to review the effectiveness, safety, and cost-effectiveness of peripheral nerve ablation for the treatment of limb pain.

Data Sources

We searched Ovid MEDLINE and In-Process & Other Non-Indexed Citations from inception through October 15, 2018; the Cochrane Database of Systematic Reviews and the Cochrane Central Register of Controlled Trials through September 6, 2018; the National Library of Medicine clinical trials registry; relevant professional society and organization clinical practice guidelines; and public and private payer coverage policies.

Study Selection

Using *a priori* criteria, we conducted dual independent title and abstract screening and full-text article review for English language randomized controlled trials (RCTs) of adults and children who had peripheral nerve ablation for limb pain. A third reviewer settled discrepancies.

Data Extraction and Risk of Bias Assessment

One researcher used standardized procedures to extract relevant data from each of the included studies, and a second researcher checked all data entry for accuracy. We performed dual, independent methodological risk-of-bias assessment on each included study and guideline. A third reviewer settled discrepancies.

Data Synthesis and Analysis

We applied the Grading of Recommendations, Assessment, Development, and Evaluation Working Group (GRADE) system to rate the overall quality of evidence on selected measures of function and pain. No meta-analyses were possible because of noncomparability in interventions, comparators, and outcome measures.

Results

Our searches returned a total of 1,890 unduplicated records. Of these, 13 RCTs met inclusion criteria: 7 for osteoarthritic knee pain, 4 for shoulder pain, and 2 for pain from plantar fasciitis. In addition, 8 nonrandomized studies on the harms associated with nerve ablation procedures met inclusion criteria. No studies were identified on economic outcomes. Results for intervention effectiveness are summarized below by anatomical location (knee, shoulder, and plantar foot).

Knee

Four included RCTs of conventional radiofrequency ablation (RFA) for knee pain found some improvement in knee function and pain measures, but none followed participants for more than 6 months. One RCT followed participants who had persistent pain at least 6 months after total knee arthroplasty (TKA) and were randomized to RFA vs. genicular nerve corticosteroid injections. The RCT authors found no statistically significant differences at any time point during

that year. One RCT using the OKS and 2 others using the total WOMAC score found statistically significant improvements at 3 months for the conventional RFA group. There was continued improvement in WOMAC scores in the 1 RCT that reported it at 6 months. Similarly, these 3 RCTs found statistically significant improvements for the conventional RFA group at 3 months using a VAS pain scale. All 5 studies that evaluated RFA had significant limitations and were rated as having a high risk of bias.

There was 1 RCT of cooled RFA (cRFA) and 1 RCT of cryoablation for knee pain. Cooled RFA improved OKS function measures and NRS pain measures at 6 months compared to an intra-articular steroid injection (IAS). Cryoablation of the genicular nerves improved WOMAC total scores at 1 to 3 months compared to a sham procedure, but not at 4 months of follow-up. Both of these RCTs were also assessed as having a high risk of bias.

Shoulder

Four RCTs of peripheral nerve ablation for shoulder pain compared pulsed radiofrequency (pRF) to different control interventions. One RCT found that the IAS control group demonstrated superior improvement for functional and pain outcomes at up to 3 months of follow-up. There were no statistically significant differences in measures of pain or function in an RCT of pRF compared to a photobiomodulation (laser) comparison group at up to 6 months of follow-up. Neither of the 2 other RCTs demonstrated statistically significant improvements in pain or function outcomes when compared to a sham procedure or TENS therapy at 1 to 3 months of follow-up. Each of these 4 RCTs had significant limitations and were assessed as having a high risk of bias.

Plantar Foot

One RCT, assessed to be at high risk of bias, found some improved pain outcomes, including the overall VAS score, at 4 weeks in the pRF group compared to a sham control group. Another RCT, assessed as having a moderate risk of bias, compared conventional RFA to a sham procedure and found that function and pain measures demonstrated statistically significant improvements at 12 weeks.

Harms

We found little evidence of serious harms in randomized and nonrandomized studies. There were few reports of serious adverse events and device malfunctions in U.S. government databases.

Limitations

Common limitations across this evidence base were small study sample sizes, inadequate length of follow-up to assess either the durability of benefits or the development of harms, and use of suboptimal or inadequate comparators. It is not clear that any study included a population that had optimal noninterventive treatment prior to trial entry or was composed of people for whom definitive management was appropriate, limiting comparability to current U.S. guidelines and practice. Some studies demonstrated a substantial placebo effect in the control group (i.e.,

participants who received a placebo or sham showed improvement in outcomes from baseline to follow-up measures). Many studies had large or differential losses to follow-up, and in some cases used a last observation carried forward analysis. No RCT had an adequate description of allocation concealment. In some RCTs, there was insufficient detail about co-interventions such as medications or adjunctive physical therapies. In addition, there was substantial uncertainty regarding many statistical analyses because of multiple testing without appropriate partitioning of *P* values and lack of consideration or controlling for known confounders such as smoking, age, sex, and body weight. Most RCTs were funded by device manufacturers or had authors with declared financial relationships with those companies, and many of the other studies did not report either study funding or author disclosures.

Guidelines and Payer Policies

No identified clinical practice guideline made a recommendation for the use of these nerve ablation procedures. We found no Medicare National Coverage Determination or relevant private payer policy for coverage of these ablation procedures for any indication. One relevant Medicare Local Coverage Determination on nerve blockades for treatment of chronic pain and neuropathy states that thermal (not pulsed) RF is covered for a variety of pain diagnoses, including knee, hip, and shoulder pain.

Conclusions

Using the GRADE system, we found very low quality of evidence in favor of peripheral nerve ablation to improve some short-term functional and pain measures for moderate to severe chronic pain from knee osteoarthritis, shoulder pain resulting from various conditions, and plantar fasciitis. No identified clinical practice guidelines recommend use of these procedures, and payers consider them as investigational. There are numerous ongoing clinical trials that may increase the amount of data available to evaluate the benefits and harms of some of these procedures in the future.

Background

Chronic limb pain can occur in a joint, such as the hip, shoulder, or knee, and most often results from osteoarthritis.[1] Other causes of chronic limb pain include traumatic injury, rheumatoid arthritis, postoperative pain syndromes, and soft tissue-related conditions.[2] Treatments for chronic limb pain aim to reduce symptoms and improve function,[2] and include physical activity, weight loss, medications, physical therapy, complementary and alternative therapies, and surgery.[3]

Technology of Interest

Peripheral nerve ablation, using chemical, surgical, or thermal ablation techniques, destroys sensory nerve tissues that transmit pain signals from the affected area back to the brain. Three types of RFA have been developed. Conventional thermal RFA is a minimally invasive procedure that uses heat and coagulation necrosis to damage or destroy nerve tissue.[2] Pulsed RF treatment uses short bursts of RF current and generate lower tissue temperatures compared to continuous

current conventional RFA.[2] Cooled RF devices apply more energy at the desired location, but use water cooling to prevent as much heat from diffusing beyond the target area.[4] Cryoablation uses a cryogen within a probe casing to deliver very cold temperatures that damage the nerves.[5]

The devices used in nerve ablation are regulated by the U.S. Food and Drug Administration (FDA), and the manufacturers (or previous manufacturer if the device has been acquired by another company) of the devices used in the studies included in this evidence review have all received Section 501(k) premarket approval from the FDA.

Policy Context

Peripheral nerve ablation is one of many available treatments for patients with limb pain. This topic was selected for a health technology assessment because of high concerns for the safety and efficacy of the procedure and medium/high concern for cost.

Methods

This evidence review is based on the final key questions published on September 6, 2018.[6] The draft key questions were open for public comment from July 27 to August 9, 2018, and appropriate revisions were made to the key questions based on the comments and responses.[7]

Key Questions

1. What is the evidence of efficacy and effectiveness for peripheral nerve ablation for limb pain compared to other active interventions, placebos, sham procedures, or no treatment?
2. What direct harms are associated with peripheral nerve ablation for limb pain compared to other active interventions, placebos, sham procedures, or no treatment?
3. Do important patient efficacy/effectiveness outcomes or direct harms from peripheral nerve ablation for limb pain vary by:
    a. Indication
    b. Patient characteristics
4. What are the cost-effectiveness and other economic outcomes of peripheral nerve ablation for limb pain compared to other active interventions, placebos, sham procedures, or no treatment?

Data Sources and Searches

We conducted searches of Ovid MEDLINE and In-Process & Other Non-Indexed Citations databases from inception through October 15, 2018, and the Cochrane Database of Systematic Reviews and Central Register of Controlled Trials from inception through September 6, 2018. Additional sources for health technology assessments and evidence reviews and studies from reference lists, public comment submissions, and the National Clinical Trials database were examined. The FDA's Manufacturer and User Facility Device Experience (MAUDE) database and Medical Device Recall database were queried. Evidence sources and the Agency for Healthcare Research and Quality (AHRQ) National Guideline Clearinghouse were searched for clinical practice guidelines. We searched the Centers for Medicare & Medicaid Services website for the

Medicare Coverage Database for National and Local Coverage Determinations and private payers' websites for relevant coverage policies.

Study Selection

Two Center researchers independently screened titles and abstracts for potential inclusion and independently evaluated all studies selected for full-text review. A third reviewer settled discrepancies.

Data Abstraction and Quality Assessment

Using standardized and piloted processes and forms, one Center researcher extracted data and a second researcher checked the data abstraction for accuracy. Two researchers independently evaluated each included study and clinical practice guideline for methodological risk of bias.

Data Analysis and Synthesis

When authors did not report mean differences or there were discrepancies in reporting, we used GraphPad for t-tests to estimate mean differences, 95% confidence intervals, and two-tailed *P* values. We planned to conduct a meta-analysis of key outcomes if a sufficient number of studies reported equivalent outcomes at similar timeframes. However, a meta-analysis was not possible because of the wide variation in interventions, comparators, and outcomes measurement. We assigned selected outcomes a summary judgment for the overall quality of evidence using the system developed by the GRADE Working Group.[8,9]

Results

Our searches returned a total of 1,890 unduplicated records. Of these, 13 RCTs met inclusion criteria: 7 RCTs for knee pain,[10-15] 4 for shoulder pain,[16-19] and 2 for pain from plantar fasciitis.[20,21] In addition, 8 nonrandomized studies[22-29] on the harms associated with nerve ablation procedures met inclusion criteria for key question 2. No studies were identified for key question 4 on economic outcomes. Results for intervention effectiveness are summarized below by anatomical location (knee, shoulder, and plantar foot).

For purposes of GRADE ratings, the function measures selected were the WOMAC and OKS total score for knee procedures, the SPADI total score for shoulder procedures, and the AOFAS ankle-hindfoot scale for foot procedures. We selected overall VAS pain scales as the pain measure for GRADE reporting. The most commonly reported time point for function and pain measures was at 3 months postprocedure, and so we assessed GRADE outcomes at this time point, recognizing that it is not likely that the durability of either functional or pain benefits can be assessed at this time.

Key Question 1: Effectiveness

Knee

Four RCTs[10,12,13,15,30] of conventional RFA for knee pain found some improvement in knee function and pain measures, but only 1[13] followed participants for more than 6 months posttreatment. This small RCT[13] was conducted among participants who had a prior TKA and

found statistically significant improvement with RFA for pain only at 6 months, but not at 1, 3, or 12 months. The authors[13] also reported functional measure improvements for the RFA group at months 1, 3, and 6 using the KSS instrument, and at months 1 and 3 with use of the OKS. One RCT[10] using the OKS and 2 others[12,30] using the total WOMAC score found statistically significant improvements at 3 months for the conventional RFA group. One of these RCTs[12] followed patients to 6 months and found a continued improvement in WOMAC scores. Using a VAS pain scale, 3 RCTs[10,12,30] found statistically significant improvements for the conventional RFA group at 3 months. All 5[10,12,13,15,30] studies that evaluated conventional RFA had significant limitations, with high risk-of-bias assessments for all 5 studies.

There was 1 RCT[11] of cooled RFA[11] and 1 RCT[14] of cryoablation for knee pain. Cooled RFA[11] improved OKS function measures and NRS pain measures at 6 months compared to IAS. Cryoablation of the genicular nerves improved WOMAC total scores at 1 to 3 months compared to a sham procedure, but not at 4 months of follow-up.[14] Each of these RCTs[11,14] had significant limitations, with the RCT[11] of cooled RFA[11] assessed as having a moderate risk of bias and the RCT[14] of cryoneurolysis assessed as having high risk of bias.

Shoulder

Each of the 4 RCTs[16-19] of peripheral nerve ablation for shoulder pain compared pRF to a different control intervention. One RCT[16] found that the IAS group demonstrated superior improvement for functional and pain outcomes at up to 3 months. Another RCT[19] reported no statistically significant differences in measures of function or pain compared to a photobiomodulation (laser) comparison group at up to 6 months of follow-up. Neither of the other 2 RCTs[17,18] demonstrated statistically significant improvements in pain or function outcomes when compared to a sham procedure[17] or TENS[18] therapy at 1 to 3 months of follow-up. All 4 RCTs[16-19] had significant limitations and were assessed as having a high risk of bias.

Plantar Foot

One RCT[20] assessed to be at high risk of bias, found some improved pain outcomes, including the overall VAS score, at 4 weeks in the pRF group compared to a sham control group. Another RCT,[21] assessed as having a moderate risk of bias, found that function and pain measures showed statistically significant improvements at 12 weeks.

Key Question 2: Harms

We found little evidence of serious harms in randomized and nonrandomized studies, although most studies did not describe a robust method for assessing and capturing harms as part of the outcome measurement process. Most harms described in RCTs involved immediate procedure-related side effects such as bruising or procedural pain and did not involve long-term follow-up. Only the RCT[13] of conventional RFA for knee pain collected outcomes at 12 months postprocedure. We identified 8 additional eligible nonrandomized studies of harms.[22-29] Nonrandomized studies also generally reported limited harms related to immediate and expected procedural effects, similar to those reported in the RCTs. There were few reports of serious adverse events and device malfunctions in U.S. government databases. However, harms

such as patient burns were described, raising the question of whether a higher incidence of serious harms might be noted if use of these interventions became more widespread.

Key Question 3: Special Populations

No RCT reported procedural outcomes stratified by age, sex, race, or other demographic factors. One RCT[13] was conducted in a clinically distinct subpopulation of participants who had at least 6 months of persistent pain after a TKA. The study is described in detail under key question 1. This RCT[13] found statistically significant effects of conventional RFA compared to a corticosteroid injection control group for some measures of function, pain, and quality of life, for some time points up to 6 months.

Key Question 4: Cost-Effectiveness and Other Economic Outcomes

Our searches did not retrieve any studies that reported economic outcomes, including cost-effectiveness.

Summary

Although our searches identified multiple RCTs for nerve ablation procedures for 3 anatomical areas (knee, shoulder, and foot), the identified studies have a high risk of bias and other limitations. The certainty with which we can make any conclusions about the effectiveness or harms of these interventions is very low. This means that we expect that any effects, of either benefits or harms, are likely to be different than found in this review as additional studies are added to the evidence base. In summarizing outcomes using the GRADE approach, we were only able to compare study outcomes at 3 months postprocedure for most procedures. For knee function, we included both the OKS and total WOMAC scales. For shoulder function, we included the SPADI score, and for plantar foot function, we included the AOFAS ankle-hindfoot score. For knee, shoulder, and foot pain outcomes, we included the VAS pain and NRS scales. For each scale, we assessed whether there was a statistically significant and clinically meaningful difference based on common thresholds for minimal clinically important differences[31,32] (MCID). Table 3 summarizes these findings, other strengths and limitations of this body of evidence, and the GRADE ratings for selected pain and function outcomes.

Five RCTs[10,12,13,15,30] of conventional RFA for knee pain found some improvement in knee function and pain measures, but only 1[13] followed participants for more than 6 months. Two RCTs[10,13] using the OKS and 2 other RCTs[12,30] using the total WOMAC found statistically significant improvements at 3 months for the conventional RFA group, which likely meet the MCID threshold.[31] Similarly, 3 RCTs[10,12,30] using a VAS pain scale found statistically significant improvements for the conventional RFA group at 3 months that likely meet the MCID threshold.[33]

There was 1 RCT[11] of cooled RFA assessed as having a moderate risk of bias and another[14] of cryoablation for knee pain assessed as having a high risk of bias. Both[11,14] RCTs found some benefits of the ablation intervention in terms of functional and pain outcomes. For purposes of the GRADE table, we found very low quality of evidence that cooled RFA[11] improved OKS

function measures and NRS pain measures at 3 months compared to IAS and likely met the MCID for that scale.[32,33] We also found very low quality of evidence that cryoablation of the genicular nerves improved WOMAC total scores at 3 months compared to a sham procedure and that the difference likely met the MCID threshold.[31] The studies had significant methodological limitations and were single, unreplicated RCTs.

The 4 RCTs on the use of pRF of the suprascapular nerve each used a different comparator.[16-19] The IAS comparison group in 1 RCT[16] generally found that the IAS group had superior improvements for functional and pain outcomes. The photobiomodulation control group in another RCT[19] reported generally better SPADI scores at 1, 3, and 6 months and better VAS pain scores at 1 and 3 months compared to the pRF group, but these differences were not statistically significant. The other 2 RCTs did not demonstrate statistically or clinically meaningful improvements[33] for pain or function when compared to a sham procedure[17] or TENS[18] therapy. For GRADE outcomes, we found very low quality of evidence from 1 RCT[16] that IAS was superior to pRF in terms of the SPADI total score at 3 months and VAS night pain (but not other VAS pain measures), but that these differences were not likely to meet MCID thresholds.[33,34] All of these studies[16-19] had significant limitations, including small sample sizes, short length of follow-up, and inconsistent direction of effect, and were assessed as having a high risk of bias.

There were only 2 RCTs that met inclusion criteria for interventions to treat the pain of plantar fasciitis: 1 used conventional RFA[20] and 1 used pRF[21]; both used a sham comparator. In the pRF RCT,[21] function assessed with the AOFAS score and pain assessed with the overall VAS measure demonstrated improvements at 12 weeks. For purposes of the GRADE table, we found that these improvements were likely to meet MCID thresholds.[35-37] However, our confidence in these findings is very low, given that there is a single small study with multiple methodological limitations. The RFA RCT[20] found some improved pain outcomes, including the overall VAS score, at 4 weeks in the intervention group. This difference would also be likely to meet MCID for VAS,[35] but did not meet our minimal GRADE standard of 3 months' follow-up for the outcome. We are therefore unable to rate confidence in any outcome for RFA treatment for plantar foot pain based on this single study.

Common study limitations across this body of evidence were small sample sizes, inadequate length of follow-up to assess either the durability of benefits or the development of harms, use of inappropriate or suboptimal comparators, and lack of demonstrated clinical significance for some outcome measures even when there was demonstrated statistical significance. It is not clear that any study included a population that had optimal noninterventive treatment prior to trial entry or was composed of people for whom definitive management was appropriate, limiting comparability to current U.S. guidelines and practice. Some studies demonstrated a substantial placebo effect in the control group (i.e., participants who received a placebo or sham showed improvement in outcomes from baseline to follow-up measures). Many studies had large or differential losses to follow-up and some replaced missing data with a last observation carried forward approach. No RCT had an adequate description of allocation concealment. In

some RCTs, there was no detail about co-interventions such as medications or adjunctive physical therapy. In addition, there was substantial uncertainty regarding many statistical analyses because of multiple testing without appropriate partitioning of *P* values and lack of consideration or controlling for known confounders such as smoking, age, sex, and weight. Several RCTs were funded by device manufacturers or had authors with declared financial relationships with those companies. Other RCTs did not report either study funding or author disclosures. Although we do not know the precise effect of these relationships in the area we investigated, a 2017 Cochrane systematic review found that industry sponsorship of drug and device studies is associated with more favorable study conclusions when compared to studies with other sources of funding.[38]

We found little evidence of serious harms in randomized and nonrandomized studies, although no identified study described a robust method for assessing and capturing harms as part of the outcome measurement process. There were few reports of patient harms and device malfunctions in U.S. government databases, but serious adverse events have been reported, which raises the question of whether a higher incidence of serious harms would occur if use of these interventions became more widespread.

There are few studies and a low number of participants enrolled for these types of interventions, particularly when subdivided by the anatomical location, type of ablation procedure, and comparator group. No meta-analysis was feasible for any outcome because of noncomparability of intervention, comparator, and outcomes among included RCTs. We found only very low quality of evidence for all selected outcomes.

Clinical Practice Guidelines

We included any clinical practice guideline that met basic eligibility criteria and discussed management of limb pain, whether or not it specifically mentioned peripheral nerve ablation. Our searches identified 8 eligible guidelines. One was rated as having good methodological quality,[39] 5 had fair methodological quality,[40-44] and 2 were rated as having poor methodological quality.[45-47]

The 2014 clinical practice guideline from the Association of Extremity Nerve Surgeons does not recommend ablation, including cryoablation and RFA, in the primary treatment of Morton's neuroma.[45] A 2013 guideline on elbow disorders from the American College of Occupational and Environmental Medicine states that there is no recommendation for or against the use of diathermy for the treatment of acute, subacute, or chronic lateral epicondylalgia.[41] The 2018 guideline from the American College of Foot and Ankle Surgeons (ACFAS) does not make a recommendation on bipolar RF treatment for chronic, refractory plantar fasciitis, concluding that the evidence on this treatment is uncertain—neither appropriate nor inappropriate.[47]

Three guidelines on osteoarthritis pain management, from the American Academy of Orthopaedic Surgeons (2013),[40] the National Institute for Health and Care Excellence (2014),[39] and the Veterans Administration/Department of Defense (2014),[42] do not include

recommendations or discussion of peripheral nerve ablation. The American Physical Therapy Association's[43] clinical practice guideline on the treatment of plantar fasciitis does not mention peripheral nerve ablation.

Selected Payer Coverage Determinations

No Medicare National Coverage Determination was identified related to peripheral nerve ablation for limb pain. One relevant Medicare Local Coverage Determination on nerve blockades for treatment of chronic pain and neuropathy[48] stated that thermal (not pulsed) RF is covered for a variety of pain diagnoses, including knee, hip, and shoulder pain. Of the 3 private payers we reviewed, no payer covers any peripheral nerve ablation treatment for limb pain.

Aetna has 4 policies that address nerve ablation, which consider these nerve ablation treatments to be experimental and investigational.[49-52] The Aetna policies do not cover pulsed RF for any indication;[49] cryotherapy or patellar denervation for knee osteoarthritis;[50] pulsed or thermal RF lesioning for plantar fasciitis;[51] or cryoablation to treat lower extremity peripheral nerve damage, Morton's neuroma, or other types of neuroma.[52]

The Cigna policy on peripheral nerve ablation does not cover cryoablation; RFA; or electrical, chemical, or laser ablation for peripheral nerve pain indications.[53] Cigna also does not cover RF lesioning for plantar fasciitis pain treatment.[54]

The Regence policy on emerging medical technologies does not cover nerve ablation (including cryoablation) of the upper or lower extremity peripheral nerves, nerve plexus, or other truncal nerves and considers these procedures investigational.[55] Regence's policy does not cover ablation using magnetic resonance-guided focused ultrasound and high-intensity focused ultrasound procedures.[56]

Conclusions

The strengths of this systematic review are that we comprehensively searched multiple databases for eligible studies of peripheral nerve ablation to treat limb pain and conducted independent, dual study screening, selection, and risk-of-bias assessment. Limitations of this report were inclusion of only English language literature and that we did not include unpublished studies or contact authors to resolve any questions about published studies. Our methodological quality assessment relied on the clarity and completeness of reporting of included published studies. Many of the RCTs we reviewed either did not adhere to CONSORT[57] publishing standards for RCTs or conducted trials that did not adhere to the best methodological standards. We were unable to conduct any meta-analyses because of lack of comparability among 2 or more individual RCTs.

We found very low quality of evidence in favor of peripheral nerve ablation to improve some short-term functional and pain measures. Overall, 7 RCTs[10-14,21,30] found some improvements in short-term functional status and level of pain that were both statistically significant and likely to be clinically meaningful. However, these improvements were generally small in magnitude and

not consistent. Positive outcomes were often reported in only 1 RCT, on 1 scale or subscale, or at 1 time period. One RCT found small, statistically significant improvements in shoulder function and pain with the control intervention of IAS injections compared to pRF treatments.[16] Potential harms of these procedures appear to be uncommon, but have been poorly reported in published studies. We found no studies that reported RCTs for peripheral nerve ablation to treat pain at other anatomical sites, including the wrist, elbow, hip, ankle, or the digits.

There are 12 ongoing RCTs of various modalities for peripheral nerve ablation to treat pain in the knee (9 studies), foot (1 study), hip (1 study), and postamputation phantom lower limb pain (1 study) that are expected to be completed between 2018 and 2021. Although the data on these procedures are sparse, studies have been registered and could contribute increasing amounts of data to this field with time. The current paucity of evidence to support these procedures is reflected in the lack of clinical endorsement in clinical practice guidelines and payer coverage policies.

Technical Report

Background

Chronic limb pain can markedly limit quality of life if it is not effectively managed. Chronic limb pain can occur in a joint, such as the hip, shoulder, or knee and most often results from osteoarthritis.[1] Osteoarthritis involves the breakdown of joint cartilage and ultimately the synovial tissues and bone. Symptoms include joint pain, swelling, and stiffness, which can affect the patient's ability to function.[3] Other causes of chronic limb pain include traumatic injury, rheumatoid arthritis, postoperative pain syndromes, or soft tissue-related (e.g., muscles, tendons, ligaments, fascia) conditions.[2] Treatments for most conditions that cause limb pain, including osteoarthritis, aim to reduce symptoms and improve function, although most treatments do not modify the natural history or progression of the disease.[2]

The initial management of osteoarthritic joint pain is generally conservative. Commonly recommended treatments include muscle strengthening, stretching, physical activity, assistive devices, and weight loss, if applicable.[39,40,44,47] When conservative nonpharmacological measures are not sufficient in achieving adequate comfort and function, then guidelines commonly recommend the use of pain medications, including oral or topical NSAIDs and oral acetaminophen; opioids are reserved for patients who cannot use other types of pain medications or who have pain that cannot be adequately treated with other medications.[39,40]

Intra-articular corticosteroid injections are sometimes a treatment option when NSAIDs or other medications are not sufficient, but are not effective for long-term use because of short duration of action and acceleration of osteoarthritis.[39,58,59] Clinical practice guidelines generally do not recommend the use of other types of intra-articular injections, including viscosupplementation products that contain hyaluronic acid, because they have not been found to be effective.[39,40,44,60]

A 2018 network meta-analysis[61] compared and ranked the effectiveness of nonsurgical treatments for knee osteoarthritis pain and joint function. Treatments were ranked 1 to 10 based on effectiveness for reducing pain and improving function. The authors reported that naproxen, an NSAID, was most likely to improve pain and function. Several other NSAIDs also made the top 10[61]:

1. Naproxen
2. Corticosteroids
3. Intra-articular platelet-rich plasma injections
4. Ibuprofen
5. Celecoxib
6. Diclofenac
7. Hyaluronic acid
8. Intra-articular placebo
9. Acetaminophen
10. Oral placebo

For intractable joint pain with advanced osteoarthritis, joint replacement, also known as arthroplasty, is the standard of care.[39,40,44,60] However, there are patients for whom medical and surgical treatment, including arthroplasty, is contraindicated or not desired. This report was undertaken to assess whether nerve ablation procedures were effective and safe to treat pain and diminished functions from osteoarthritis or other types of musculoskeletal pain syndromes.

Technology of Interest

Peripheral nerve ablation has been used in an attempt to reduce symptoms in patients with limb pain by destroying sensory nerve tissues that transmit pain signals from the affected area back to the brain. Peripheral nerve ablation can be accomplished in several ways, including chemical ablation, surgical ablation, and RFA. Three types of RFA have been developed: conventional, pulsed, and cooled.[62]

Conventional thermal RFA is a minimally invasive procedure that uses heat and coagulation necrosis to damage or destroy nerve tissue.[2] A high frequency electrical current is applied to the target tissue using a needle electrode that is inserted through the skin.[2] The electrode generates heat (80°C to 90°C), which coagulates a small volume of tissue at and around the nerve target.[2] The goal is to destroy peripheral sensory nerve endings, resulting in alleviation of pain.[2] However, the affected nerves do regenerate with time, often causing the pain to return.[2,62]

Pulsed RF uses short bursts of RF current, rather than the continuous current of conventional RFA.[2] The heat from pRF (not exceeding 45°C) causes less damage than conventional thermal RFA.[2,62] Some researchers think that the electromagnetic field generated with pRF is responsible for the neuromodulatory effect, rather than the heat generated by the procedure.[62] Pulsed RF has been proposed as a possibly safer alternative to continuous RFA in the treatment of a variety of pain syndromes, including those where the involved nerve has both sensory and motor function, such as the suprascapular nerve for the shoulder.[2] Although nerve regeneration occurs with all forms of RF treatment, the duration of effect of pRF is usually shorter than with conventional thermal RF.[62] However, the effect of any type of neural RF treatment can diminish over time, requiring retreatment or alternative interventions.[62]

Cooled RF is a newer technology that uses a water-cooled RF probe to create a larger lesion size, and therefore treat a larger area than other forms of thermal RFA.[4] Cooled RF devices apply more energy at the desired location, but use water cooling to prevent as much heat from diffusing beyond the target area.[4] Cryoablation uses a cryogen within the probe casing to deliver very cold temperatures that damage the nerves.[5]

Devices Used in Peripheral Nerve Ablation

Peripheral nerve ablation, as a medical procedure, is not regulated by U.S. Food and Drug Administration (FDA). The devices used in nerve ablation are regulated by the FDA. The manufacturers (or previous manufacturer if the device has been acquired by another company) of the devices used in the studies included in this evidence review have all received Section 501(k) premarket approval from the FDA. The 501(k) premarket approval for these devices is

based on the device being substantially equivalent to legally marketed predicate devices marketed in interstate commerce prior to May 1976, when the Medical Device Amendments were enacted.[63] The studies included in this evidence review used ablation devices (RF generators or cryogen delivery devices and probe tips) produced by NeuroTherm, Boston Scientific (formerly Cosman and Radionics), Avanos (formerly Halyard Health and Baylis), and Myoscience. These devices are described below.

NeuroTherm

NeuroTherm produces RF devices that can be used for both continuous and pulsed RFA. The most recent model of NeuroTherm's RF generators is NT2000IX.[64] The NeuroTherm NT-1000 received FDA premarket approval in 2006 with indications for creating lesions in neural tissue.[65] The NT-2000 device received approval in 2011 for use in creating lesions in neural tissue.[66]

Boston Scientific/Cosman/Radionics

Boston Scientific produces devices that can be used for both continuous and pulsed RFA, and the most recent model is the G4 Generator.[67] This generator was previously produced by Cosman, which received FDA premarket approval in 2008, and it is indicated for producing nerve lesions to treat pain.[68] The company that produced the device prior to Cosman, Radionics, received initial FDA premarket approval for the RFG-3C Plus device in 1998 for lesioning neural tissue.[69]

Avanos/Halyard Health/Baylis

Halyard Health (rebranded as Avanos in June 2018) manufactures the Coolief Cooled RF device,[4] which was previously manufactured by Baylis. Halyard Health received FDA premarket approval for the Coolief Cooled RF Kit in 2016[70] and the Coolief Cooled RF Probe in 2017.[71] The approval includes indications for producing lesions in nerve tissue, and specifically for producing genicular nerve lesions for treating radiologically confirmed knee osteoarthritis pain that has not improved with at least 6 months of conservative therapy and that had a ≥ 50% reduction in pain after a diagnostic genicular nerve block.[71] A search of the FDA premarket approval database found multiple premarket approvals for Baylis RF lesion devices starting in 1998.[72] For cooled RF, the first Baylis Duocool pain management probe was approved in 2010,[73] and the first approval of the Baylis Osteocool RFA system was in 2012.[74]

Myoscience

Myoscience produces the iovera° cryoablation system. Nitrous oxide is used as the cryogen to create temperatures as cold as -88°C at the distal end of the Smart Tip.[5] Myoscience received FDA premarket approval for iovera°; with the most recent approval in 2018.[75] This approval includes iovera° indications for producing lesions in peripheral nerve tissue and relief of pain from knee osteoarthritis for up to 90 days.[75] A search of the FDA premarket approval database found 4 premarket approvals for iovera° starting in 2014 and 5 approvals for Mysoscience's Cryo-Touch starting in 2009.[72]

Policy Context

Peripheral nerve ablation is one of many available treatments for patients with limb pain. This topic was selected for a health technology assessment because of high concerns for the safety and efficacy of the procedure and medium/high concern for cost.

This evidence review will help to inform Washington's independent Health Technology Clinical Committee as the committee determines coverage regarding peripheral nerve ablation for patients with limb pain.

Washington State Utilization and Cost Data

Populations

The Peripheral Nerve Ablation for Limb Pain analysis examined member utilization and cost data from the following agencies:

- PEBB/UMP (Public Employees Benefit Board Uniform Medical Plan)
- PEBB Medicare
- Department of Labor and Industries (LNI) workers' compensation plan
- Managed Care Medicaid (MCO)
- Medicaid Fee-for-Service (FFS)

The analysis assessed 3 calendar years (2015 to 2017) of paid claims. Data inclusion criteria required that:

1. Patients were greater than 18 years old.
2. Claim include the targeted CPT/HCPCS code from Table A.
3. Same claim include a primary diagnosis code from Table B.

Table A

Targeted CPT Codes and Descriptions

Destruction by neurolytic agent may include chemical (e.g., alcohol, glycerol, phenol), cold, or radiofrequency techniques.

CPT	Description
64640	Destruction by neurolytic agent; other peripheral nerve or branch

Table B
Specified Diagnosis Descriptions for Nerve Ablation for Limb Pain

Categorized Description	
Regional Pain Syndrome	Neuralgia, Neuritis, And Radiculitis
Dev Dis Jt-Pelvic/Thigh	Neuropathy
Enthesopathy	Organic Writers' Cramp
Lesion Femoral Nerve	Osteoarthritis Extremity/Joint
Lesion Plantar Nerve	Osteophyte Joint
Central Pain Syndrome	Shoulder Lesions
Meralgia Paresthetica	Pain In Extremity/Joint
Metatarsalgia	Peroneal Tendinitis
Mononeuritis	Plantar Fascial Fibromatosis
Mononeuropathies	Myalgia And Myositis
Monoplegia Limb	Sprain Other Ligament
Chronic Pain	Tarsal Tunnel Syndrome
Synovitis And Tenosynovitis	Ulnar Nerve Lesion

Methods

Paid claims for the targeted CPT procedure code (Table A) were identified. Next, claims were evaluated for existing diagnosis codes. Those diagnosis codes were evaluated to exclude chronic neurologic conditions such as cerebral palsy, Parkinson's disease, and multiple sclerosis. Additionally, diagnoses unrelated to extremity pain (i.e., migraines) were excluded. Data evaluation examined utilization trends, individual and aggregate CPT coding, costs, and distribution by diagnosis codes.

Table C
2015 to 2017 Utilization and Costs
Peripheral Nerve Ablation for Limb Pain with Specified Diagnoses
Members > 18 years old,
PEBB/UMP/ PEBB Medicare, LNI, Medicaid Fee-for-Service, and Medicaid Managed Care

PEBB/UMP
72 unique patients over three years

Year	Unique Patients	Procedures	Average Procedures/ Patient	Average Paid/ Ablation	Total Paid All Services Ablations
2015	23	39	1.7	$292	$30,801
2016	21	32	1.5	$288	$24,582
2017	27	29	1.0	$361	$29,769

PEBB Medicare
83 unique patients over 3 years
PEBB pays secondary to Medicare

Year	Unique Patients	Procedures	Average Procedures/ Patient	Average Paid/ Ablation	Total Paid All Services Ablations
2015	21	26	1.2	$107	$3,778
2016	39	50	1.3	$105	$7,654
2017	34	48	1.4	$80	$6,293

LNI
16 unique patients over 3 years
Utilization displayed in aggregate due to small numbers
*Allowed dollars = Paid Dollars

Year	Unique Patients	Procedures	Average Procedures/ Patient	Average Allowed*/ Ablation	Total Allowed* All Services Ablation
2015 - 2017	19	74	3.9	$743	$98,255

Medicaid: MCO and FFS
MCO and FFS patients are not mutually exclusive over the three year period
Dual eligibility claims were excluded
103 unique patients over 3 years

Year	Unique Patients	Procedures	Average Procedures/ Patient	Median Paid/ Ablation	Total Paid All Services Ablation
2015	30	43	1.4	$81	$20,659
2016	27	42	1.5	$155	$32,569
2017	28	40	1.4	$120	$22,515

Table D
2015 to 2017
Distribution of Specified Diagnosis for Nerve Ablation for Limb Pain
All Agencies

Categorized Description	Count
Pain in Extremity/Joint	146
Plantar Nerve Lesion - Extremity	129
Mononeuropathies Lower Limb	57
Osteoarthritis Extremity/Joint	50
Mononeuritis Leg	14
Other Nerve Lesion	11
Organic Writers' Cramp	7
Meralgia Paresthetica	7
Tarsal Tunnel Syndrome	7
Monoplegia Limb	6

Definitions for Utilization Tables

Unique members	Unique, non-duplicated member, reported by agency
Count of Procedures (CPT)	Count of unduplicated nerve ablation CPT codes on a single date
Total Paid All Services Ablation	Total paid dollars for all services on date of nerve ablation

Methods

This evidence review is based on the final key questions published on September 6, 2018.[6] The draft key questions were open for public comment from July 27 to August 9, 2018, and appropriate revisions were made to the key questions based on the comments and responses.[7] The PICO (population, intervention, comparator, outcome) statement that guided development of key questions is listed below.

Population: Adults and children with chronic limb pain caused by osteoarthritis or other conditions

Interventions: Peripheral nerve ablation using any technique

Comparators: Other treatments for limb pain including:

- Medication
- Surgery
- Behavioral or psychological interventions
- Physical therapy or other noninvasive nonmedication therapies
- Placebo
- Sham procedures
- Usual care or no specific treatment
- No comparator (for harms only)

Outcomes:

- Primary outcomes: short-term and long-term function measured by a validated method
- Secondary outcomes: short-term and long-term pain measured by a validated method
- Safety: harms directly related to the intervention
- Indirect outcomes: use of subsequent interventions to control the pain that was the original indication for the initial peripheral nerve ablation procedure
- Economic: cost-effectiveness outcomes (e.g., cost per improved outcome) or cost-utility outcomes (e.g., cost per quality-adjusted life year [QALY], incremental cost-effectiveness ratio [ICER])

Key Questions

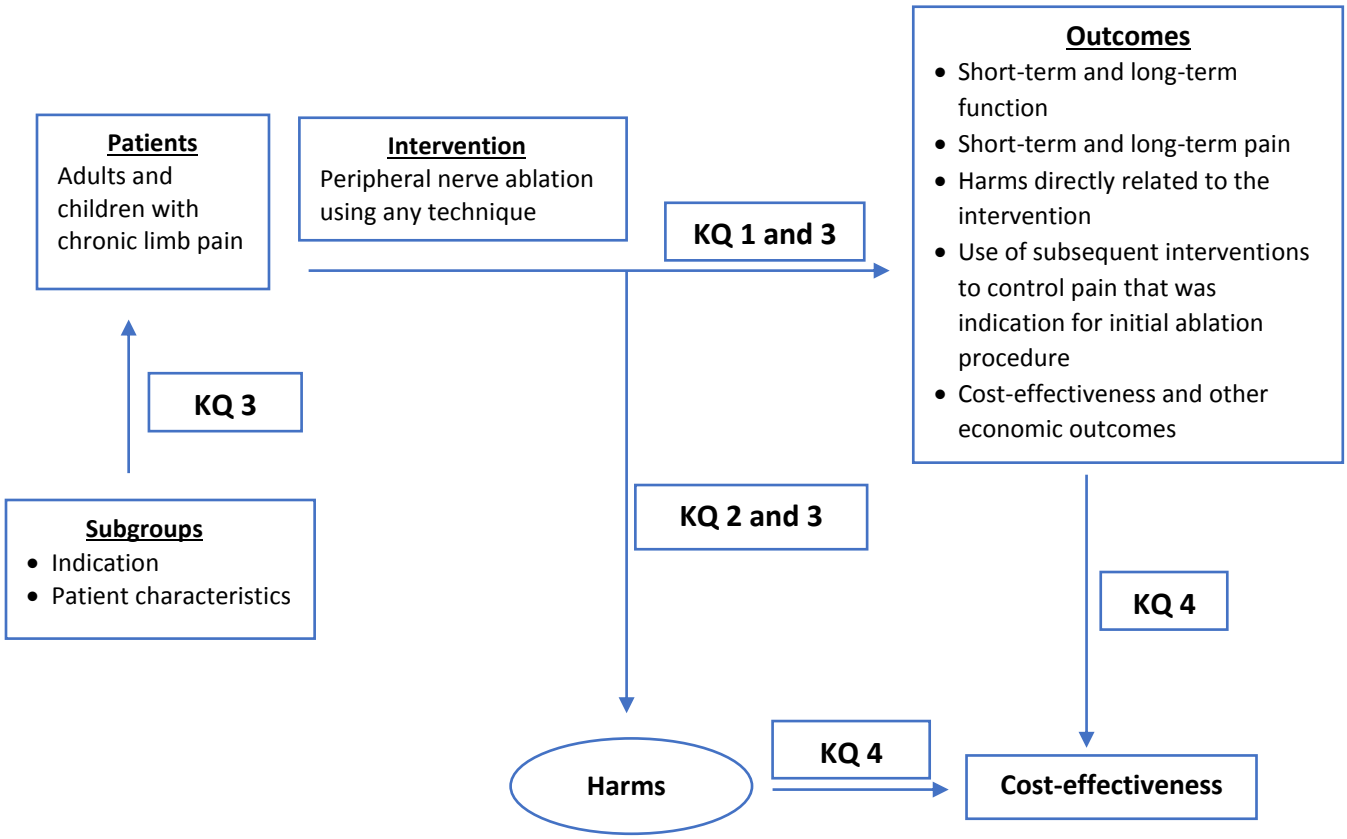
1. What is the evidence of efficacy and effectiveness for peripheral nerve ablation for limb pain compared to other active interventions, placebos, sham procedures, or no treatment?
2. What direct harms are associated with peripheral nerve ablation for limb pain compared to other active interventions, placebos, sham procedures, or no treatment?
3. Do important patient efficacy/effectiveness outcomes or direct harms from peripheral nerve ablation for limb pain vary by:
    a. Indication
    b. Patient characteristics

4. What are the cost-effectiveness and other economic outcomes of peripheral nerve ablation for limb pain compared to other active interventions, placebos, sham procedures, or no treatment?

Analytic Framework

The analytic framework shown in Figure 1 guided the selection, synthesis, and interpretation of available evidence.

Figure 1. Analytic Framework



Eligible Studies

Table 1 summarizes the study inclusion and exclusion criteria.

Table 1. Study Inclusion and Exclusion Criteria

Study component	Inclusion	Exclusion
Populations	Adults and children with chronic limb pain attributable to osteoarthritis or other conditions	Pain that does not arise from an extremity joint or soft tissue
Interventions	Peripheral nerve ablation using any technique (i.e.., heat, cold, or chemical or physical interruption of a nerve)	Ablation as part of another surgical intervention Procedures involving the central nervous system, or procedures involving the sympathetic nervous system or nerve roots in close proximity to the spine Procedures that did not identify specific nerve targets for treatment
Comparators	Other treatments for limb pain including: • Medication • Surgery • Behavioral or psychological interventions • Physical therapy or other noninvasive nonmedication therapies • Placebo • Sham procedures • Usual care or no specific treatment • No comparator (for harms only)	Studies without a comparator intervention Studies with indirect comparisons Studies with an outdated comparator or a comparator intervention that is not available in the U.S.
Outcomes	• Primary outcomes: short-term and long-term function measured by a validated method • Secondary outcomes: short-term and long-term pain measured by a validated method • Safety: harms directly related to the intervention • Indirect outcomes: use of subsequent interventions to control the pain that was the original indication for the initial peripheral nerve ablation procedure • Economic: cost-effectiveness outcomes (e.g., cost per improved outcome) or cost-utility outcomes (e.g., QALY, ICER)	Other outcomes

Study component	Inclusion	Exclusion
Study design	• KQ 1–4 ○ Randomized controlled trials ○ Systematic reviews that include randomized controlled trials • Additional studies/data for KQ 2–3 (harms) ○ Nonrandomized comparative studies, if evidence for the intervention or device is included in KQ1 ○ Nonrandomized studies without a comparator will be assessed for harms only, if evidence for the intervention is included in KQ1 ○ Governmental or other registries and databases containing reports of procedure-related harms or device recalls (e.g., FDA MAUDE database, FDA Medical Device Recall database) • Additional studies/data for KQ 4 ○ Cost-effectiveness studies and other formal comparative economic evaluations ○ Systematic reviews of cost-effectiveness studies and other formal comparative economic evaluations	Abstracts, conference proceedings, posters, editorials, letters, case reports and case series with fewer than 10 participants (for harms only), studies with harms outcomes for an intervention that is not included in KQ1
Publication	• Studies in peer-reviewed journals, technology assessments or publicly available FDA or other federal government reports • Published in English • Published from database inception through October 15, 2018	Studies whose abstracts do not allow study characteristics to be determined Studies that cannot be located Duplicate publications of the same study that do not report different outcomes or follow-up times, or single site reports from multicenter studies Studies in languages other than English

Abbreviations. FDA: U.S. Food and Drug Administration; KQ: key question.

Data Sources and Searches

We conducted a search of the peer-reviewed published literature using multiple online databases. The time period for MEDLINE and Cochrane Library searches was from database inception to October 15, 2018 for MEDLINE and database inception to September 6, 2018 for the Cochrane Library databases.

RCTs and systematic reviews (with and without meta-analysis) and health technology assessments that included RCTs were considered for key questions 1 to 4. Nonrandomized comparative studies and nonrandomized studies without a comparator, were also considered for the harm-related aspects of key questions 2 and 3 if evidence for the intervention was included in key question 1. Registries and databases containing reports of procedure-related harms or device recalls, such as the FDA's Manufacturer and User Facility Device Experience (MAUDE) database and Medical Device Recall database were queried. Cost-effectiveness studies and other comparative economic evaluations, along with systematic reviews (with and without meta-analysis) reporting economic outcomes, were also considered for Key Question 4.

The following electronic databases were searched to identify relevant peer-reviewed studies:

- Ovid MEDLINE and In-Process & Other Non-Indexed Citations
- Cochrane Database of Systematic Reviews
- Cochrane Central Register of Controlled Trials

The Ovid MEDLINE search strategy is in Appendix A. We also screened reference lists of relevant studies and used lateral search functions such as *related articles* and *cited by*. These additional sources were searched:

- Agency for Healthcare Research and Quality (AHRQ)
- National Institute for Health and Care Excellence (NICE)—Evidence
- Veterans Administration Evidence-based Synthesis Program

We searched these sources for systematic reviews and clinical practice guidelines using the same search terms outlined for the evidence search. In addition, a search of the AHRQ's National Guideline Clearinghouse (guidelines.gov) was conducted in June 2018, and websites of relevant professional organizations for guidelines were also searched. These searches used terms related to peripheral nerve ablation. Guidelines published in the past 5 years (January 2013 to current) were considered for inclusion.

Using the Google search engine, we conducted a general internet search for appropriate published studies and relevant gray literature. In addition, we searched the Centers for Medicare & Medicaid Services website for the Medicare Coverage Database for National Coverage Determinations and Local Coverage Determinations applying to the state of Washington. The Aetna, Cigna, and Regence websites were searched for coverage policies for these private payers.

To identify relevant ongoing clinical trials, we searched the online database of clinical trials (ClinicalTrials.gov) maintained by the National Library of Medicine at the National Institutes of Health. This search included terms related to ablation, cryoneurolysis, and the brand names of nerve ablation devices. Information in this database is provided by the sponsor or principal investigator of clinical studies. Studies are generally registered in the database when they begin, and information is updated as the study progresses. We also considered studies submitted as part of the public comment process for possible inclusion for this review.

Screening

Two Center researchers independently screened titles and abstracts and had discussions to reach agreement on exclusion. For studies that the two researchers could not agree on whether to exclude by title and abstract screening, a full-text review for inclusion criteria was performed. The two researchers had discussions to reach agreement on inclusion after the full-text review, and any remaining disagreement among these assessments was settled by a third researcher.

Data Abstraction and Quality Assessment

One Center researcher used standardized procedures to extract relevant data from each of the included trials, and another investigator cross-checked all data entered for accuracy.

Two independent Center researchers evaluated each eligible study for methodological risk of bias. The two researchers had discussions to reach agreement on the risk-of-bias assessments, and any remaining disagreement among these assessments was settled by a third independent researcher. Each trial was assessed using Center instruments adapted from national and international standards and assessments for methodological quality.[76-81] A rating of high, moderate, or low risk of bias was assigned to each included study based on adherence to recommended methods and potential for internal and external biases. The risk-of-bias criteria for all of the study types are in Appendix B.

Two independent Center researchers evaluated the methodological quality of eligible clinical practice guidelines. The two researchers had discussions to reach agreement on the quality assessments, and any remaining disagreement among these assessments was settled by a third independent researcher. The methodological quality of clinical practice guidelines was rated as good, fair, or poor. The assessment criteria for the methodological quality of clinical practice guidelines are in Appendix B.

Data Analysis and Synthesis

When authors did not report mean differences or there were discrepancies in reporting, we used GraphPad for t-tests to estimate mean differences, 95% confidence intervals, and two-tailed p-values. We planned to conduct a meta-analysis of key outcomes if a sufficient number of studies reported equivalent outcomes at similar timeframes. However, a meta-analysis was not possible because of the wide variation in interventions, comparators, and outcomes measurement.

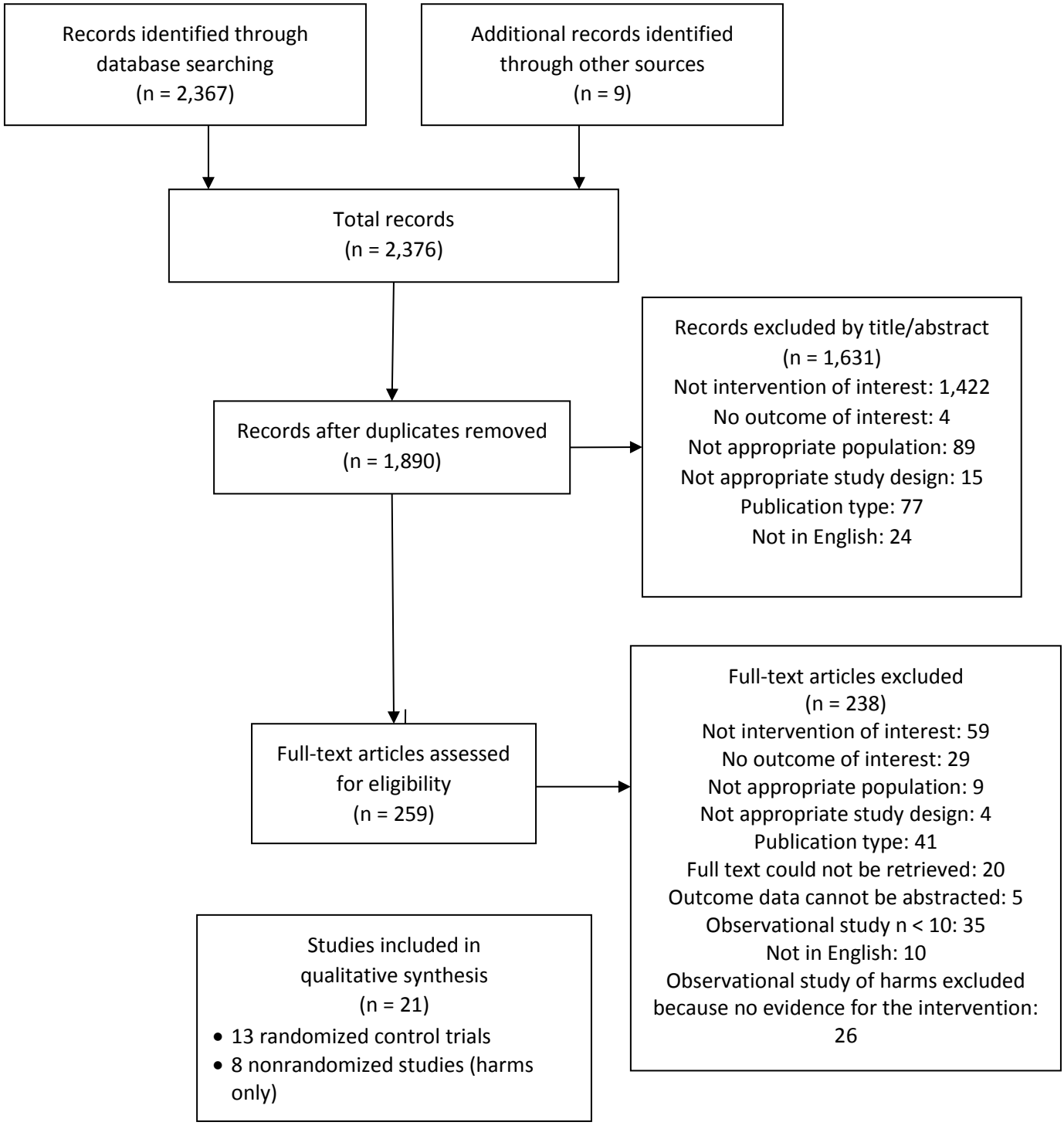
Center researchers assigned selected outcomes a summary judgment for the overall quality of evidence using the system developed by the GRADE Working Group.[8,9] The outcomes were selected from measures of function and pain and based on the availability of common measures

at equivalent time points. Specific measures were selected in a post hoc manner based on the outcomes that were available among included studies.

The GRADE system[9] defines the overall quality of a body of evidence for an outcome in the following manner:

- **High**: Raters are very confident that the estimate of the effect of the intervention on the outcome lies close to the true effect. Typical sets of studies are RCTs with few or no limitations, and the estimate of effect is likely stable.
- **Moderate**: Raters are moderately confident in the estimate of the effect of the intervention on the outcome. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is different. Typical sets of studies are RCTs with some limitations or well-performed nonrandomized studies with additional strengths that guard against potential bias and have large estimates of effects.
- **Low**: Raters have little confidence in the estimate of the effect of the intervention on the outcome. The true effect may be substantially different from the estimate of the effect. Typical sets of studies are RCTs with serious limitations or nonrandomized studies without special strengths.
- **Very low**: Raters have no confidence in the estimate of the effect of the intervention on the outcome. The true effect is likely to be substantially different from the estimate of effect. Typical sets of studies are nonrandomized studies with serious limitations or inconsistent results across studies.
- **Not applicable**: Researchers did not identify any eligible articles.

Figure 2. PRISMA Study Flow Diagram



Evidence Summary

Our searches returned a total of 2,367 records, and an additional 9 records were added from other sources: 7 from reviewing reference lists, 1 study registered at ClinicalTrials.gov, and 1 identified via public comment. No additional studies, beyond those identified in electronic databases, were found through Google and gray literature searches. After duplicates were removed, there were 1,890 records. Of the 1,890 records, 259 required full-text review to determine eligibility. Of these, 13 RCTs met inclusion criteria for key questions 1, 2, and 3. Seven RCTs involved procedures for knee pain,[10-15] 4 met inclusion criteria for shoulder pain,[16-19] and 2 met inclusion criteria for pain from plantar fasciitis.[20,21] In addition, 8 nonrandomized studies on the harms associated with nerve ablation procedures identified in included RCTs to treat knee pain,[24-26,28,29] shoulder pain,[23] or pain from plantar fasciitis[22,27] met inclusion criteria for key question 2.

Measures of Limb Pain Symptoms

Multiple types of measures are used to assess the symptoms of limb pain, including measures that assess patient function, pain, and improvement after treatment. Measures that were used in the assessment of outcomes in the studies included in this evidence review are described in Appendix H. The measures, ranges of scores, and directionality are summarized in Table 2.

Table 2. Outcome Scales and Measures Used in Included Studies

Scale or Measure	Data Source	What Is Measured	Score Range Directionality
Measures That Include Function Outcomes			
WOMAC function[82]	Patient questionnaire	Physical function	2 versions of scoring: 0 to 68 or 0 to 170 Lower score is better function
WOMAC stiffness[82]	Patient questionnaire	Physical function	2 versions of scoring: 0 to 8 or 0 to 20 Lower score is less stiffness
WOMAC pain[82]	Patient questionnaire	Pain	2 versions of scoring: 0 to 20 or 0 to 50 Lower score is less pain
WOMAC total[82]	Patient questionnaire	Physical function, pain	Total of subscores–2 versions: 0 to 96 or 0 to 240 Lower score is better well-being
Oxford knee scores (OKS)[83]	Patient questionnaire	Knee physical function, pain	12 to 60 12 is best outcome

Scale or Measure	Data Source	What Is Measured	Score Range Directionality
Knee Society Score (KSS)[84,85]	Doctor evaluation of patient	Knee physical function, pain	0 to 100 Higher number is better function
SPADI disability[86]	Patient questionnaire	Shoulder disability	0 to 80 Lower number is less disability
SPADI pain[86]	Patient questionnaire	Shoulder pain	0 to 50 Lower number is less pain
SPADI total[86]	Patient questionnaire	Shoulder disability, pain	0 to 130 Lower number is less disability/pain
Range of motion[87]	Goniometer measure of patient mobility	Shoulder: flexion, extension, abduction, external rotation, and internal rotation assessed as active and passive	Varies for each joint and motion Higher score is greater range of motion
Constant-Murley score[88]	Physical measure of patient abilities	Shoulder function	0 to 65 points Higher score is better function
American Orthopedic Foot and Ankle Society (AOFAS) ankle-hindfoot score[89]	Patient questionnaire	Plantar fasciitis function and pain	0 to 100 Higher score is better outcome
Short Form 36 (SF-36)[90]	Patient questionnaire	Physical functioning, physical role, bodily pain, general health, vitality, social functioning, emotional role, and mental health	0 to 100 for the subscales and the total Higher number is better well-being
Nottingham Health Profile (NHP)[91]	Patient questionnaire	Pain, physical activity, energy, sleep, social isolation, emotional reaction	0 to 600 Higher number is better health status
Measures of Pain Only			
Visual Analog Scale (VAS)[92]	Patient questionnaire	Pain	0 to 10 or 0 to 100 0 is no pain
Numerical rating scale (NRS)[93,94]	Patient questionnaire	Pain	11-point scale, 0 to 10 0 is no pain

Scale or Measure	Data Source	What Is Measured	Score Range Directionality
Other Measures			
Beck Depression Inventory[95]	Patient questionnaire	Depression	0 to 63 Lower number is less depression
Patient Global Impression of Improvement (PGI-I)[96]	Patient or provider questionnaire	Improvement after treatment	1 to 7 Higher number is better outcome
Patient Global Impression of Change (PGIC)[14]	Patient or provider questionnaire	Improvement after treatment	1 to 7 Lower number is better outcome
Global perceived effect (GPE)[97]	Patient or provider questionnaire	Improvement after treatment	1 to 7 Lower number is better outcome

Key Question 1: Effectiveness

This section describes the RCTs and the outcomes associated with nerve ablation procedures for each of the 3 anatomical areas (knee, shoulder, and plantar foot) for which there were RCTs providing evidence of efficacy/effectiveness for patient function, pain, or other related outcomes. If more than one nerve ablation mode for a particular anatomic area was used, we have presented study characteristics and outcomes, by the ablation mode, in each section. Detailed evidence tables for each study are in Appendix C.

For purposes of GRADE reporting, the function measures selected were the WOMAC and OKS total score for knee procedures, the SPADI total score for shoulder procedures, and the AOFAS ankle-hindfoot scale for foot procedures. Although these scales combine subscale measures of both function and pain, they are widely used as representations of overall joint function. In addition, not all included studies reported the subscales independently. For the outcome category of pain, we selected overall VAS pain scales at 3 months postprocedure. The most commonly reported time point for these scales was at 3 months postprocedure, and so we limited GRADE outcomes to this time point, recognizing that it is unlikely that the durability of either functional or pain benefits can be assessed at 3 months and that studies reporting similar outcomes at longer-term time points are needed. Only 5[11-13,16,17] of the 13 included RCTs reported outcomes at 6 or 12 months after the intervention. For each scale used for a GRADE outcome, we assessed whether there was a statistically significant difference, and if there was then we next assessed whether that difference was likely to be clinically meaningful based on common thresholds for MCID.[31-37] GRADE ratings for these selected function and pain outcomes are presented so that readers can make some assessment of the general direction and reliability of treatment effects. These ratings must be interpreted with the knowledge that there were limited data with which to assess these domains.

Knee

Study characteristics

Three ablation technologies were studied across 7 RCTs. In the findings sections below, we have grouped studies by the technology used in the intervention group. Five RCTs used conventional RFA,[10,12,13,15,30] 1 used cRFA,[11] and 1 used cryoneurolysis.[14] Both conventional and cRFA use heat to damage the nerve; cryoneurolysis uses very cold temperatures to damage the tissue. Detailed study and population characteristics are in Appendix C, Table 4. The full study outcome details are in Appendix C, Table 9.

Conventional RFA

The genicular nerve targets used in all 5 RCTs of conventional RFA were the superior lateral, superior medial, and inferior medial nerves.[10,12,13,15,30] No study performed ablation of the inferior lateral genicular nerve because of its proximity to the common peroneal nerve and the danger of resulting motor nerve damage.[10,12,13,15,30] The intent in each study was to use the heat generated by the RF device at the inserted probe tip to destroy sensory nerves that carry pain signals from the osteoarthritic knee while avoiding damage to the motor nerves that control knee function.[10,12,13,15,30]

There were some differences in the time and temperature of the ablative protocol itself: the RCT conducted by El-Hakeim et al.[12] used a probe temperature of 80°C for 3 rounds of 90 seconds each at each nerve target. Choi et al.,[10] Qudsi-Sinclair et al.,[13] and Sari et al.[15] each conducted a single round of 90 seconds at each nerve target site, but Choi et al.[10] used a probe temperature of 70°C, whereas Sari et al.[15] and Qudsi-Sinclair et al.[13] used a temperature of 80°C. Ray et al.[30] used 2 90 second rounds at 80°C.[30] The RCT by El-Hakeim et al.[12] used a Cosman TCD RF generator,[13] and the other 3 used the NeuroTherm device to generate the RF signal.[10,12,15] Ray et al.[30] did not specify the device used.[30] Fluoroscopy was used for procedural imaging in all 5 of these RCTs, and similar procedural techniques were employed.[10,12,13,15,30]

The study by Qudsi-Sinclair et al.[13] enrolled only participants with persistent pain for at least 6 months after total knee arthroplasty, and the other studies enrolled participants with moderate to severe knee osteoarthritis.[10,12,15] Two[13,15] studies compared the RFA procedure to corticosteroid injections, and 2 studies[10,12] compared the RFA intervention to sham procedures. Triamcinolone acetate, 20 mg, was introduced via each of the 3 sham RFA cannulas at the nerve target site in the control group of the study by Qudsi-Sinclair et al.[13] Sari et al.[15] described a single injection of intra-articular corticosteroids solution containing bupivacaine, morphine, and 1 mL of the corticosteroid betamethasone. However, Sari et al.[15] did not report the actual milligram dose of betamethasone instilled. Ray et al.[30] compared RFA to an intra-articular viscosupplementation injection with hylan A and B polymers.[30] Choi et al.[10] did not describe whether participants were allowed to maintain or start adjunctive pain medications. The control group in the RCT by El-Hakeim et al.[12] was given oral analgesics, including acetaminophen; the nonsteroidal anti-inflammatory diclofenac; and physical therapy as needed. Participants enrolled in the study by Qudsi-Sinclair et al.[13] remained on their baseline medications as needed. Sari et

al.[15] used a protocol allowing only acetaminophen and did not permit any physical therapy for participants. Ray et al.[30] stated that patients who were on any kind of corticosteroid in the 4 weeks before the study or any NSAID in the 2 weeks before the study were excluded. However, Ray et al.[30] also stated that patients in the viscosupplementation group were advised to resume their oral medications and made no mention of resumption or use of other medications in the RFA group.

All 5 RCTs that used conventional RFA provided outcome measures related to function and pain, and were relatively small: study samples ranged from 24 to 73 participants.[10,12,13,15,30] Across studies, the participants generally had a mean age in the 50s to 60s and were predominately female. In the 5 RCTs, participants in 1 study[12] were, on average, obese, with a body mass index [BMI] $\geq$ 30; participants in 2 studies had, on average, normal BMIs[10,15], and 2 studies[13,30] did not report average BMI. The 5 conventional RFA studies were done in South Korea,[10] Egypt,[12] India,[30] Spain,[13] and Turkey.[15]

Although all 5 studies were described as RCTs, none provided details about allocation concealment.[10,12,13,15,30] No conventional RFA study, with the exception of the RCT by Choi et al.,[10] masked investigators and participants, and none masked outcome assessors. However, the control group procedure used by Choi et al.[10] was not clearly described, raising questions about whether clinicians or participants might have been able to determine group allocation. The RCTs by Choi et al.[10] and Qudsi-Sinclair et al.[13] did not contain a statement declaring the research funder. The authors of all the RCTs conducted many assessments, using several measures across multiple time points, but there were few individual points at which there were statistically significant differences. Although the authors of all 5 studies performed these types of multiple statistical comparisons, none partitioned the *P* value in their statistical tests. In addition, although baseline differences between groups were often present, no study adjusted analyses for confounders such as age, sex, obesity, underlying disease severity, or length of symptoms. All 5 RCTs were assessed to be at high risk of bias.[10,12,13,15 30]

Functional outcomes

Functional outcomes generally improved from baseline for both study groups and across all 5 RCTs[10,12,13,15,30] that used conventional RFA. However, comparisons of functional outcomes between the intervention and control groups had few statistically significant differences at the various time periods assessed, which had a wide range from 1 day to 12 months.[10,12,13,15,30] Function, as measured by the OKS, improved at 1 and 3 months after genicular RFA in 2 studies.[10,13] We calculated the mean difference in OKS score for the Qudsi-Sinclair et al. [13] study and found that those statistically significantly differences did not persist at 6 and 12 months of follow-up. Qudsi-Sinclair et al.[13] also found statistically significant differences in function as measured by the KSS instrument at 1, 3, and 6 months, but not at 12 months. The WOMAC function subscale showed improvement at 6 months in the RCT by El-Hakeim et al.[12] (but not at 2 weeks and 3 months) and at 1 month (but not at 3 months) in the RCT by Sari et al.[15] in the RFA groups. Ray et al.[30] reported statistically significant improvement in the total WOMAC score

at each period of follow-up (1, 4, and 12 weeks) for the RFA group compared to the viscosupplementation group, but no function subscores were reported.

Pain outcomes

Pain outcomes also generally improved from baseline for both study groups across all 5 RCTs[10,12,13,15,30] evaluating conventional RFA, but there were few statistically significant differences between study groups. Comparisons of changes in pain ratings between groups from baseline measurements, as measured with a VAS scale, improved at 4 and 12 weeks in the RCT by Choi et al.[10] at 2 weeks, 3 months, and 6 months in the RCT by El-Hakeim et al.,[12] at 1, 4, and 12 weeks by Ray et al.,[30] and at 1 and 2 months in the RCT by Sari et al.[15] Qudsi-Sinclair et al.[13] reported pain using the NRS instrument, which is similar to the VAS. When we calculated the mean NRS differences we found statistically significant differences at 6 months, but not at 1, 3, and 12 months. Two RCTs reported pain using the WOMAC pain subscale, and the RCT by El-Hakeim et al.[12] found improvement in the RFA group at 3 and 6 months compared to the comparison group, but there were no statistically significant differences at 1 and 2 months in the Sari et al. study.[15] Choi et al. reported an improvement on the Global Perceived Effect scale at 4 and 12 weeks after genicular nerve RFA compared to the sham control group.[10]

Other outcomes

Change in oral pain medication use was reported in the RCT by Qudsi-Sinclair et al.[13] of conventional RFA for osteoarthritic knee pain. The study was small, with only 14 participants in each group at 6- and 12-month follow-ups.[13] There were small differences in the number of participants using opioid pain medications at both time periods: 50% of the cRFA group used opioids compared to 64% of the control group, at baseline. Opioid medications were used by 14% of the cRFA group and 21% of the control group at 1 year of follow-up. No formal statistical testing to assess a difference was reported.[13]

The Patient Global Impression Scale of Improvement was used to report patient satisfaction in the RCT by Qudsi-Sinclair et al. of conventional RFA.[13] Enrollment was small, and no formal statistical testing was performed. Although 3 of 14 participants in the RF group said they were "much better" at 12 months than they had been at baseline, 4 of 14 in the control group said they were "a little better" compared to baseline, and 2 in each group reported they were "very much better."[13]

Quality of life was measured using the SF-36 instrument at 3- and 12- months postprocedure in the RCT by Qudsi-Sinclair et al. that involved conventional RFA.[13] Our calculated mean differences showed a statistically significant difference between groups at months 3 and 12, but was not reported at 1 and 6 months.[13]

Cooled RFA

One RCT compared cRFA to a single intra-articular corticosteroid (IAS) injection.[11] Davis et al. screened 233 participants with moderate to severe knee pain and randomized 151 participants who had a positive response to a diagnostic block in this multicenter trial.[11] Genicular nerve

ablation involving the superomedial and inferomedial branches of the saphenous nerve and the superolateral branch of the femoral nerve was conducted (n = 67, after 9 participants did not complete the intervention) using the Coolief cRFA system.[11] Each of the 3 nerve sites was identified with fluoroscopy, anesthetized with local anesthetic (although about a quarter required conscious sedation as well) and subjected to cRFA at 60°C for 150 seconds to an average tissue temperature of 80°C.[11] Control group participants (n = 71, after 4 withdrew from the study or had exclusion criteria) received IAS injections using 40 mg of methylprednisolone acetate or the equivalent of triamcinolone acetate or betamethasone.[11] Although the study used an intention-to-treat analysis, 76% of the cRFA group completed the study compared to 91% of the IAS participants.[11] The primary outcome was the proportion of participants who had a 50% or greater reduction from baseline knee pain at 6 months, as measured by the NRS scale.[11]

The RCT by Davis et al. had several methodological limitations, including no details regarding randomization.[11] In the public comment document, the manufacturer and study sponsor (Avanos) stated that, "It was an error to not discuss the randomization process in more detail." The comments submitted by Avanos added information that randomization was conducted using sealed, sequentially numbered envelopes and that no deviations from the randomization process were noted by auditors.

Individuals in the IAS comparison group received 1 of 3 allowed corticosteroids, depending on the preferences of the clinical site.[11] The study specified a dose of 40 mg of methylprednisolone acetate, and that "dose equivalents" of other corticosteroids could be used per the usual protocol of the site. The actual doses of the other steroid medications were not reported. Furthermore, the expected duration of effect for IAS is shorter than the 6-month follow-up period of the study, potentially biasing the later outcome assessments toward the intervention group.[58,98] The substantially different proportions of participant follow-up in the intervention and comparator group (76% vs. 91%) at 6 months raises the question of whether people in the intervention group withdrew from the study because of adverse events or complications.[11] If so, this would bias the results in favor of the intervention group. Public comments submitted by the manufacturer and study sponsor, Avanos, stated that "no patient withdrew as a result of an adverse event." The analysis plan for this study did partition the *P* value to correct for multiple comparisons.[11]

Funding for the study was provided by the manufacturer to the investigator's institutions to cover study costs.[11] The authors stated that data management, study site monitoring, and statistical services were provided by an independent third party.[11] The study publication did not state whether the manufacturer was involved in the decision to publish or had access to data prior to analysis and publication.[11] Public comments submitted by the manufacturer and study sponsor, Avanos, stated that as an industry-sponsored study, "the sponsor owns the data as well as the ultimate decision to publish. However, the sponsor maintained an administrative role in creation and submission of the manuscript at the guidance of a steering committee, specifically created to manage the process for this research. The steering committee was created by utilizing

several of the investigators in the trial (as consultants) to make decisions about content, publication target, timing, language, etc." At the time of publication, 5 of the 12 authors were on the manufacturer's clinical advisory board, and the other 7 reported no financial conflicts of interest.[11] This RCT was initially assessed as having a high risk of bias because there was no information about randomization method or allocation concealment, lack of outcome assessment masking, differential loss to follow-up, and funding by the manufacturer. After receipt of public comments regarding randomization methods, we changed this assessment to a moderate risk of bias.

Functional outcomes

Davis et al. used the OKS instrument to rate knee function at baseline, 1, 3, and 6 months post-cRFA procedure or IAS injection.[11] There were no statistically significant differences between the groups at baseline.[11] The difference in mean OKS scores between the groups was statistically significant in favor of the cRFA group at 1 month (mean difference = 4; [95% CI, 0.98 to 7; P = .004]), 3 months (mean difference = 10; [95% CI, 7.28 to 12.7; P < .0001]), and 6 months (mean difference = 13.3; [95% CI, 10.28 to 16.4; P < .0001]) postprocedure.[11] The difference between means increased across all follow-up periods, indicating widening differences across time.[11] The distribution of participants across OKS classification groups (ranging from severe to satisfactory function) shifted as well.[11] Although no participant had satisfactory function at baseline, 20 of 65 in the cRFA group compared to 2 of 68 in the IAS group at 3 months, and 23 of 58 in the cRFA group compared to 2 of 67 in the IAS group at 6 months, had satisfactory function (P < .0001 at both time points for difference across 4 severity categories).

Pain outcomes

The study's primary outcome, the comparative proportion of participants who had a 50% or greater reduction in usual pain level from baseline to 6 months postintervention, using the 11-point NRS scale (0 to 10), was statistically different in favor of the cRFA intervention (74% [95% CI, 62.9 to 85.4] vs. 16% [95% CI, 7.4 to 24.9]; P < .0001).[11] Mean reductions in the NRS score in favor of the cRFA group were reported at 1 month postintervention (-4.2 ± 2.5 vs. -3.3 ± 2.3; P = .02) and 3 months postintervention (-4.4 ± 2.3 vs. -1.9 ± 2.1; P < .0001), although the proportion of participants that reported ≥ 50% reductions was not given.[11]

Other outcomes

Up to a third of participants enrolled in the RCT by Davis et al. (25% of cRFA participants and 35% of IAS participants) used opioid medications at baseline, although the morphine equivalent daily dose was not different between groups.[11] The mean proportion of participants using an opioid drug did not differ at any study follow-up interval.[11]

Non-opioid pain medications were used by 43% of the cRFA group and 45% of the IAS group at baseline, without a difference in the mean dose of non-opioid medications.[11] There was a statistically significant difference in the mean dose of non-opioid medications used between the groups at 3 and 6 months (3 months: −16.1 ± 89.8 mg vs. 64.7 ± 201.4 mg; P = .03 and 6 months: −34.5 ± 128.9 mg vs. 135.5 ± 391 mg; P = .02).[11]

The RCT by Davis et al. also used the Global Perceived Effect scale to measure participants' perceived improvement after treatment compared to baseline. There was no statistically significant difference at 1 month, but there were statistically significant differences at 3 and 6 months (3 months: 80% [95% CI, 70 to 90] vs. 31% [95% CI, 19.6 to 42.1]; *P* < .0001) and 6 months: 91% [95% CI, 83.9 to 98.8] vs. 24% [95% CI, 13.4 to 34.4); *P* < .0001]).[11]

Cryoneurolysis

One RCT, by Radnovich et al., compared cryoneurolysis of the infrapatellar branch of the saphenous nerve to a sham procedure for osteoarthritic knee pain.[14] Cryoneurolysis was performed using the iovera° device.[14] This device uses a cryogen (nitrous oxide) to cool a probe tip to -88°C to damage the nerve and thus interrupt sensory signals arising distal to the area of ablation.[14] The RCT screened 345 participants with moderate to severe knee pain, of which 165 were excluded, largely for not meeting full inclusion criteria; 180 participants were randomized in a 2:1 ratio to cryoneurolysis (n = 121) or the sham procedure (n = 59).[14] The procedures were performed by clinical examination only, without ultrasound or fluoroscopic imaging guidance.[14] The average age of participants was 61, and they predominantly identified as white with an average BMI of 30.[14]

The primary outcome was the mean difference from baseline to 30 days for the WOMAC pain subscale with subsequent testing of secondary outcomes in a prespecified order if there was a difference in the primary outcome.[14] The trial was conducted using an adaptive design that allowed interim examination of the data after 80 participants were enrolled and at every 20 participants after that point up to a maximum of 180 participants.[14] The authors stated that this design feature was used to allow early stopping for success or futility.[14] Participants were prohibited from taking pain medications of any kind other than acetaminophen for rescue use (up to 4 grams/day) and using any other adjunctive treatments.[14] Use of all other "prohibited" pain medications or treatments were recorded as protocol violations and participants were asked to discontinue all of them prior to assessment visits, including at least 24 hours without acetaminophen rescue.[14] The RCT continued assessments after 120 days of follow-up only if participants continued to report decreased pain compared to baseline.[14]

Missing data were replaced with the participant's baseline value for that measure, but the total number of missing values and the time points at which they were imputed with baseline values were not described in the publication.[14] Although the trial flow diagram is unclear, it appears that 31 of 121 participants in the treatment group (26%) and 7 of 59 (12%) in the control group were lost to follow-up (unreachable, withdrew consent, missed visit, had a prohibited treatment, or died) and might have had imputed outcome measures used in analyses.[14]

Limitations of the RCT by Radnovich et al. were unclear allocation concealment, high loss to follow-up in both groups at 180 days, and lack of follow-up from 120 to 180 days among participants who were not intervention responders. The authors reported that while patients did not initially often know to which group they were assigned, they began to guess their group

assignment with time.[14] This may have biased patients in the intervention group to report their outcomes more favorably at later time points in the study.

The adaptive study design allowed the manufacturer, which funded the study, to make decisions about continuing the trial. The publication stated that the manufacturer had a role in study design, data analysis, and the decision to publish, but did not have roles in interpreting study data or writing the paper. Two of 16 authors had declared financial relationships with the manufacturer. This study was assessed as having a high risk of bias.

Functional outcomes

Function was assessed using the WOMAC physical function subscale. Each group had improvement in the mean total WOMAC score, as well as each component subscale, at each assessment time from 30 to 120 days, compared to the baseline for that group (intervention or sham).[14] There were statistically significant differences in the LS mean differences from the baseline score between groups at day 30 (-21.30; 95% CI, -34.02 to -8.57; *P* = .0012); day 60 (-13.14; 95% CI, -26.43 to -0.39; *P* = .044); and day 90 (-15.89; 95% CI, -28.93 to -2.86; *P* = .017), but not at day 120 (-9.16; 95% CI, -22.04 to 3.72; *P* = .16).[14]

Pain outcomes

There were statistically significant differences in the mean change in the WOMAC pain subscale from baseline to days 30, 60, and 90: day 30, -7.12; 95% CI, -11.01 to -3.22; *P* = .0004; day 60, -4.65; 95% CI, -8.48 to -01.82; *P* = .02; and day 90, -5.67; 95% CI, -9.69 to -1.64; *P* = .006.[14] There was not a statistically significant difference in the mean change at day 120 (-2.82; 95% CI, -6.77 to 1.13; *P* = .16).[14]

Radnovich et al. also measured pain using a 100-point VAS scale. Using this instrument, there was a statistically significant difference between groups in the mean change from baseline at day 30, but not at days 60 and 120.[14]

Other outcomes

There was no statistically significant difference between the cryoneurolysis and sham treatment groups in quality of life at any time point using the SF-36 instrument.[14] The authors stated that the cryoneurolysis group experienced statistically significant changes in the knee pain and function measure using the disease-specific version of the SF-36, but that this improvement did not translate into an overall improvement in the SF-36 quality of life measure.[14]

Similarly, there were no statistically significant differences between groups in the proportion of participants who had a positive response on the 7-category (from *very much worse* to *very much improved*) PGIC scale.[14]

Shoulder

Four RCTs studied pulsed RF (pRF) of the suprascapular nerve for chronic shoulder pain.[16-19] Each RCT used a similar treatment protocol with fluoroscopic guidance and a treatment time of 4 minutes at 42°C. Strictly speaking, pRF may not be neuroablative in nature, but

neuromodulatory.[62] Pulsed RF is generally used instead of conventional RFA or other ablative interventions on the suprascapular nerve because of its mixed sensory and motor function.[99] Three[16,18,19] of the 4 studies used the NeuroTherm RF device and 1 study[17] used the RFG-2b device manufactured by Baylis Medical. Detailed study and population characteristics are in Appendix C, Table 7. The full study outcome details are in Appendix C, Table 12.

Each of the 4 studies used a different comparator. Eyigor et al. compared pRF to IAS injections with 20 mg of triamcinolone acetate and bupivacaine local anesthetic at the glenohumeral and acromioclavicular joints and in the subacromial space.[16] Gofeld et al.[17] compared pRF to a sham procedure that included procedural anesthesia of 2 mL of 1% lidocaine local anesthetic at the suprascapular nerve for both groups. The control group in the RCT by Korkmaz et al.[18] received transcutaneous electrical nerve stimulation (TENS) treatment for 20 minutes per session each of 5 days per week for a month. Each TENS treatment, with electrodes placed on the anterior and posterior aspects of the affected shoulder, was delivered at a frequency of 100 Hz with a 15 mA amplitude.[18] Both groups in the RCT by Korkmaz et al. received a physiotherapist-supervised one-on-one exercise intervention 5 days per week for a month, with sessions that lasted at least 30 minutes.[18] Exercises included range of motion, stretching, and strengthening components.[18] Ökmen et al. had a similar exercise regimen as part of the intervention in both groups.[19] Exercise sessions were performed twice per day at home during the 2-week intervention period.[19] The control group in the RCT by Ökmen et al. received photobiomodulation (laser) therapy using a BTL-6000 high intensity laser device, with 2 initial "analgesia" treatments at 48-hour intervals, followed by 5 "biostimulation" sessions every 48 hours for 10 days.[19]

Three[16,18,19] of the 4 RCTs enrolled fairly similar populations: most had an average age of participants in their mid-50s with the exception of the Gofeld et al.[17] RCT, which enrolled an older population whose average age was 68 years in the intervention group and 70 years in the control group. The Gofeld et al.[17] RCT was conducted in Canada; the other 3[16,18,19] were conducted in Turkey. These RCTs were small, with sample sizes ranging from 22[17] to 70[19] participants.

There were several common limitations across these 4 studies,[16-19] including no mention of or lack of specificity on allocation concealment, and no or inadequate masking of outcome assessors. Masking of clinicians and participants was either not mentioned or not performed in 3 studies.[16,18,19] No study conducted analyses adjusted for confounders, and multiple comparisons were made without partitioning of *P* values. Two studies[16,17] did not mention funding source or provide any interest declaration for authors, and a third[18] had unclear statements of funding and interests. All 4 studies were assessed to be at a high risk of bias.[16-19]

Functional outcomes

Function was assessed in all 4 studies[16-19] with the SPADI instrument. [86] Eyigor et al.[16] reported that disability and pain scores at 1, 4, and 12 weeks improved for both the pRF and IAS groups compared to baseline values. However, when the groups were compared, there were statistically significant differences in favor of the IAS group for the total and pain subscale scores at 1, 4, and

12 weeks of follow-up.[16] The authors did not perform statistical testing of the difference between groups for the SPADI disability subscale.[16] Eyigor et al.[16] did not find statistically significant differences between groups at any time point for several range of motion measures (active and passive flexion, external and internal rotation). However, Eyigor et al.[16] did report a statistically significant improvement at weeks 1 and 4 in favor of the IAS group for active and passive abduction of the shoulder.

Gofeld et al.[17] had high participant loss to follow-up at 6 months, with only 67% of the pRF group and 50% of the sham group continuing in the study at that point. The authors' per-protocol analysis found no statistically significant differences in SPADI scores between the groups.[17] The main study narrative contains analyses using a last observation carried forward approach, which would effectively turn this study from an RCT into an observational study.[17] No formal statistical tests comparing treatment groups were performed.[17]

Korkmaz et al.[18] compared pRF to the suprascapular nerve versus shoulder TENS for a month; both groups received the same physical therapy protocol for a month. Although the SPADI disability and pain subscores improved for each group at 1, 4, and 12 weeks compared to baseline, there were few differences when the groups were compared.[18] The SPADI total score was statistically significantly better in the pRF group at week 1; the total score was not different at 4 and 12 weeks.[18] The SPADI disability subscale was not statistically different between groups at any time period.[18]

Ökmen et al.[19] compared pRF and photobiomodulation (laser) treatment for chronic shoulder pain and did not find statistically significant differences in either the total SPADI or the SPADI disability subscale at 1, 3, and 6 months.

Pain outcomes

In addition to the improvement in the SPADI pain subscale for the IAS group at 1, 3, and 12 weeks, Eyigor et al.[16] reported statistically significant improvements for the IAS group for VAS pain scores at night in weeks 1, 4, and 12; VAS at rest scores in weeks 1 and 4; and VAS during movement score at week 1. However, Eyigor et al.[16] did not find a statistically significant difference between the groups on any of the more pain-related SF-36 subscales, including the bodily pain subscale. Patient- and physician-rated satisfaction with the results of the procedure were improved for the IAS group at 1, 4, and 12 weeks compared to the pRF group.[16]

Gofeld et al.[17] measured pain using the NRS-11 and did not find a statistically significant difference when a per-protocol analysis was performed. No formal statistical tests comparing treatment groups were performed.[17]

Korkmaz et al.[18] did not find significant differences in the SPADI pain subscale between groups at 1 week, 4 weeks, or 12 weeks. There was also no significant difference in the VAS pain scale at any point.[18] However, each group did have statistically significant improvements on these measures at all time points compared to that group's baseline score.[18]

Ökmen et al.[19] did not find significant differences on the SPADI pain subscale between the photobiomodulation and pRF groups at 1, 3, and 6 months, and there were no significant differences between groups using the VAS pain scale at 1, 3, and 12 months.

Other outcomes

There were no statistically significant differences between the groups in the RCT by Eyigor et al.[16] at 12 weeks in the SF-36 total score or in any of the SF-36 subscales, including physical functioning, physical role, and social functioning. Eyigor et al.[16] reported that paracetamol (acetaminophen) use was statistically significantly lower in the IAS group compared to the pRF group and decreased compared to baseline at all time periods (1, 4, and 12 weeks) only in the IAS group. Eyigor et al.[16] found no statistically significant differences between groups with regard to depression, as measured by the Beck Depression Inventory.[95]

Gofeld et al.[17] used the Constant and Murley scale recommended by the European Society for Shoulder and Elbow Surgery to assess shoulder range of motion and strength and did not find a difference when a per-protocol analysis was used.[17] No formal statistical tests comparing treatment groups were performed.[17] Gofeld et al. reported that patient satisfaction was statistically significantly higher in the pRF groups at 1 and 3 months, but not at 6 months of follow-up.[17] It is not clear whether the authors used a last observation carried forward or a per-protocol analysis for this outcome.[17]

Korkmaz et al.[18] used the SF-36[90] to measure quality of life and did not find any significant differences between the pRF and TENS groups at 1, 4, and 12 weeks. There was also no significant difference between groups for use of paracetamol and patient or physician satisfaction.[18]

Ökmen et al.[19] reported general health using the NHP,[91] which gathers information on physical, emotional, and social impacts of disease. Participants reported pain, physical activity, energy, sleep, social isolation, and emotional reactions. Although both the pRF and photobiomodulation groups improved at 1, 3, and 6 months, there were no statistically significant differences between groups at any time period.[19]

Plantar Fasciitis

Two RCTs examined RF treatment for pain from plantar fasciitis.[20,21] Landsman et al.[20] conducted a U.S. based crossover RCT using conventional RFA without any imaging guidance for 8 participants and compared them to 9 participants who received a sham procedure. Study participant demographic characteristics were not provided.[20] The specific nerve target was not named, but the cRFA was applied at 2 adjacent sites at the medial heel area inferior to the medial malleolus using 90°C for 60 seconds at both sites, with the photos in the article providing us sufficient information to classify the nerve target as the posterior tibial nerve.[20] Seven participants from the sham group crossed over to the active treatment group at 4 weeks; no participants from the cRFA group crossed over.[20] Results in this section are only presented for the randomized portion of the study at 4 weeks of follow-up.

Wu et al.[21] conducted an RCT in Taiwan of ultrasound-guided pRF for 120 seconds at 42°C at the posterior tibial nerve (PTN) and compared this to a sham procedure. The mean age of participants was 47 years.[21] Wu et al.[21] randomized 18 participants per group and reported outcomes at 1, 4, 8, and 12 weeks.

Neither study discussed a procedure for allocation concealment.[20,21] Landsman et al. did not use a paired or conditional analysis for this crossover RCT, and we therefore restricted data abstraction to the first 4 weeks of the study before crossover occurred. Although participants could have one or both feet treated, the number with bilateral procedures was not provided by Landsman et al.[20] Wu et al. also allowed one or both feet to be treated among randomized subjects and the analysis was by feet, rather than by participant.[21] The RCT by Landsman et al. was funded by the manufacturer, but the role of the funder was not detailed.[20] In addition, the first author was a paid consultant for the manufacturer, and there were no declarations for the other 4 authors.[20] Landsman et al.[20] was assessed as having high risk of bias and Wu et al.[21] was assessed as having a moderate risk of bias. Detailed study and population characteristics are in Appendix C, Table 8. The full study outcome details are in Appendix C, Table 12.

In the sections below, we discuss the findings of these studies in separate sections by the mode of nerve ablation used.

Conventional RFA

Functional outcomes

Landsman et al.[20] did not report any functional outcomes.

Pain outcomes

Landsman et al.[20] reported that the cRFA group had statistically significantly improved first step, peak, and average pain scores on a 10-point VAS scale compared to the sham treatment group at 4 weeks.

Other outcomes

No other outcomes of interest were reported in the RCT by Landsman et al.[20]

Pulsed RFA

Functional outcomes

Wu et al.[21] used the AOFAS ankle-hindfoot score, which is a 100-point scale with 3 subscales measuring foot pain (40 points), alignment (10 points), and function (50 points). Wu et al.[21] did not report subscale scores, but did find a statistically significant improvement in the total AOFAS score in the pRF group compared to the control group at 1, 4, 8, and 12 weeks.

Pain outcomes

Wu et al.[21] reported that first step and overall pain were statistically significantly improved in the pRF group compared to the control group at 1, 4, 8, and 12 weeks, using a 10-point VAS scale.

Other outcomes

No other outcomes of interest were reported in the RCT by Wu et al.[21]

Key Question 2: Harms

Included RCTs had small sample sizes and were likely not adequately powered to detect harms related to procedures and most either reported that there were no serious harms or did not mention harms. No RCT described a detailed plan for assessing side effects and adverse events related to procedures. The RCTs primarily reported short-term outcomes; only the RCT by Quadi-Sinclair[13] of conventional RFA for knee pain collected outcomes at 12 months postprocedure. Although most procedure-related complications will be apparent close to the time of the intervention, other side effects and harms could take time to develop. We therefore also included nonrandomized studies for harms outcomes associated with the procedures for which we found RCTs for inclusion for key question 1. We located 8 additional eligible nonrandomized studies of harms.[22-29] Nonrandomized studies generally reported limited harms related to immediate and expected procedural effects, similar to the reports described in the RCTs. All nonrandomized studies were assessed as having a high risk of bias. Common limitations across nonrandomized studies included unclear or unreported harms assessment procedures, lack of outcome assessment masking, lack of control for confounding factors, inadequate sample size, and inadequate length of follow-up.[22-29] Several nonrandomized studies did not report funding sources or provide disclosures for authors, or had potential conflicts of interest from these factors.[23-27,29]

The sections below are organized by anatomic area; the knee and foot procedures sections are organized by the mode of ablation used. Within each of those subsections, the results are then described by harms reported in the RCTs and then the harms reported in the nonrandomized studies.

Knee Procedures

Conventional RFA

Among the 4 RCTs[10,12,13,15] that used conventional RFA, the RCTs by El-Hakeim et al.[12] and Sari et al.[15] reported no adverse events or complications. An unspecified number of participants in the RCTs by Choi et al.[10] and Qudsi-Sinclair[13] reported periosteal pain during the procedure when the probe tip touched a bony surface.

Four nonrandomized studies[24-26,29] of conventional RFA for genicular nerve ablation generally reported few complications. Iannaccone et al.[24] studied 26 participants (31 knees) and reported 1 case of transient knee numbness at 6 months of follow-up. Ikeuchi et al.[25] conducted a prospective cohort study of 18 participants and found 2 common but minor complications; 67% of participants had bleeding without hematoma formation at the procedure site, and 78% experienced transient hypoesthesia in the region of the procedure for 2 to 6 weeks. Kirdemir et al.[26] published a case series of 49 participants with no reported complications at 3 months of follow-up. Sari et al.[29] conducted an RCT of fluoroscopy versus ultrasound imaging during conventional RFA for knee pain. We combined the study arms for purposes of harms assessment because the intervention randomized was not related to the type of ablation or knee treatment

received. No complications were reported for any of the 50 participants at 6 months of follow-up.[29]

Cooled RFA

The RCT by Davis et al.[11] reported 61 adverse events in the cRFA treatment group and 65 in the control group. Three participants in the cRFA group had a total of 4 serious adverse events: acute respiratory failure, severe acute asthma or exacerbation of asthma, and pyelonephritis.[11] Seven participants in the control group had a total of 8 serious adverse events: abdominal pain related to a small bowel obstruction, nausea and vomiting, gastric volvulus, worsening of a hiatal hernia, opioid overdose, 2 heart attacks, and 1 death.[11] The authors reported that none of the serious adverse events were related to the intervention or control treatments.[11] The proportion of all adverse events that were unrelated or unlikely related to the study interventions was 77% in the cooled RF group and 97% in the control group, but no formal statistical testing was performed on this difference.[11]

McCormick et al.[28] conducted a retrospective chart review of 33 participants (52 knees) who underwent cRFA with the Coolief device and reported no serious adverse events related to the procedure at 6 months or greater of follow-up.

Cryoablation

The RCT by Radnovich et al.[14] of genicular nerve ablation using the iovera° device reported 243 adverse events among 113 participants. There were a total of 4 serious adverse events: 1 pulmonary embolism in a control group participant, 1 participant in the intervention group who had 2 myocardial infarctions, and another who was diagnosed with lung cancer.[14] The authors stated that all of these events were unrelated to the device or procedure.[14] The authors identified 84 adverse events that were possibly or probably related to the device or procedure.[14] The number of device- or procedure-related adverse events was reported as being similar in the 2 groups, but formal statistical testing was not performed.[14] Adverse events included bruising; numbness, tingling or altered sensation, local pain or swelling tenderness; itching; crusting; erythema; hyperpigmentation; knee pain; and vasovagal reaction.[14] One of the device- or procedure-related events was rated as severe by the authors, involving a sham procedure participant who had altered sensation at the device entry site.[14]

No nonrandomized studies were located in our search that reported harms related to use of the iovera° device.

Shoulder Procedures

All 4 included RCTs described procedures using pulsed RF.[16-19] Among the 4 RCTs, Ökmen et al.[19] reported no complications, Gofeld et al.[17] did not mention complications or adverse events, and Korkmaz et al.[18] reported that there were no serious side effects or complications. Eyigor et al.[16] reported that 2 participants in the pRF group and 1 in the IAS control group had bruising at the probe or injection entry site.

Only 1 nonrandomized study, a case series of 28 participants, was found in our search.[23] Gabrhelik et al.[23] reported 2 adverse events during 6 months of follow-up. One participant experienced postprocedure hypotension and 1 had a small hematoma at the procedure site.[23]

Foot Procedures

Conventional RFA

Landsman et al.[20] used conventional RFA for treatment of plantar foot pain. The authors[20] did not give details about the number of participants who experienced adverse events, but did report that adverse events occurred that were related to injections, including bruising, dizziness, vasovagal reactions, and pain related to nerve localization.

Two nonrandomized studies contributed information related to harms from conventional RFA for plantar foot pain.[22,27] Erken[22] followed 29 participants (35 feet) for 2 years in a prospective case series and reported 6 complications. One participant had a hematoma that resolved at 1 month; 2 participants experienced neuropathic pain that was treated with pregabalin and resolved within 3 months; and 2 participants (3 feet) had transient foot discomfort that was resolved within 4 weeks after the procedure.[22] Linden et al.[27] conducted a retrospective case series of 22 participants (31 feet) that reported individual cases of bruising, peroneal tendonitis, lateral calf pain, persistent poststatis dyskinesia (pain occurring after rest, including first step pain), and the feeling of walking on a "wad of tissue" under the foot. In addition, 2 participants who had procedures on both feet reported that there was greater improvement in 1 foot compared to the other.[27]

Pulsed RFA

Wu et al.[21] stated that participants were observed for only 30 minutes after the procedure and that no participant had significant complications, such as pain, bleeding, or weakness, during that period. An indeterminate number of participants had plantar numbness in the control group, likely related to administration of local anesthetic near the PTN.[21] Although Wu et al.[21] followed participants for 12 weeks postprocedure, no adverse events were described.

Reports from MAUDE and Recalls Databases

Because of the limited reporting of harms in published studies, we also conducted a search of the MAUDE database for each of the devices used in the randomized and nonrandomized studies included for key questions 1 and 2. The search was conducted on reports posted through September 2018, and the searchable database contains reports from the past 10 years. A search was also conducted of the FDA database of Medical Device Recalls, from its inception in 2002 through October 13, 2018. Findings from these searches are described below, and a detailed table of database reports is in Appendix G.

Avanos (Halyard Health) Coolief Multi-Cooled RF Kit, formerly Baylis Medical

The Baylis cooled RFA devices are now manufactured by Halyard Health, which was rebranded as Avanos in 2018. No MAUDE database reports were identified for Avanos Coolief devices, and 2 MAUDE reports were identified for Halyard Health's Coolief Multi-Cooled RF Kit related to

treatments for limb pain. The reports, from 2016 and 2017, were related to the use of cooled RFA of the genicular nerve and of the femoral nerve. A patient (age and sex not reported) receiving a genicular nerve ablation treatment received a burn of unknown degree. A female patient, approximately 78 years old, undergoing femoral nerve treatment (indication not specified) began bleeding heavily when the needle was inserted near the femoral nerve. She was admitted to intensive care for 7 days before being discharged. It was determined that the patient was on blood thinner medication (specific medication not specified) until 24 hours prior to the procedure. Baylis had 1 report related to nerve ablation treatments for limb pain. In this 2015 report, the patient receiving a standard RF procedure for knee pain received minor burns when the RF generator, set for 90°C, raised to 99°C before shutting off.

No recalls were identified for Halyard Health Coolief devices. Two recalls were identified for Baylis RFA devices, both for minor reasons that did not result in patient harm. Baylis Medical LumbarCool Pain Management System was recalled in 2010 because the device name on the product packing sleeve was incorrect. Baylis RF cannulas were recalled in 2013 because a pouch of individually wrapped cannulas was not sealed.

Boston Scientific, formerly Cosman and Radionics

A search of the MAUDE database for the Boston Scientific brand name Cosman and the manufacturer Cosman did not identify any reports related to ablative treatments for limb pain. One recall was identified: Cosman Nitinol TC Reusable Electrodes were recalled in 2018 because the epoxy resin that holds the electrode in the hub exhibited signs of damage after multiple reprocessing cycles, which can inhibit complete resterilizing of the device. No MAUDE reports or product recalls were identified for RFA devices manufactured by Radionics.

Myoscience iovera°

A MAUDE database search for the manufacturer Myoscience and the brand iovera° identified 1 report for the iovera° device. This report, from July 2018, involved a broken iovera° Smart Tip needle. No other details were provided. Two product recalls were identified for the iovera° Smart Tip, from 2013 and 2015, both related to product labeling requirements without mention of any patient harm.

NeuroTherm

A MAUDE database search for the manufacturer NeuroTherm identified 4 reports related to treatments for limb pain reported between 2015 and 2017. Three reports were for leg burns during treatments for knee pain. Two of the participants had minor burns, and the third was referred to a wound care clinic for treatment. No further details were available for this case. The fourth report was for a patient with shoulder pain who was not able to receive treatment on the scheduled day because of a minor device malfunction.

Three recalls were identified for NeuroTherm devices. In 2016, NT2000IX software was shipped with the international setting turned on, which allowed access to modes not cleared for use in the U.S., and no harms were reported. A 2016 recall occurred because a straight needle was

label as a curved needle. There was a 2009 recall because a distal tip was found to have a flaw that might cause it to detach from the probe.

Key Question 3: Subpopulations

No RCT reported procedural outcomes stratified by age, sex, race, or other demographic factors. The only RCT that was conducted in a clinically distinct subpopulation was the RCT by Qudsi-Sinclair et al.,[13] which involved a study sample of 28 participants who had at least 6 months of persistent pain after total knee arthroplasty. The study is described in detail under key question 1. Briefly, this RCT found some statistically significant effects of conventional RFA compared to corticosteroid injections for measures of function and pain at 1, 3, and 6 months and for quality of life at 3 and 12 months.[13]

Key Question 4: Cost and Cost-Effectiveness

Our search did not retrieve any studies that reported economic outcomes, including cost-effectiveness.

Summary

Although our searches identified multiple RCTs for nerve ablation procedures for 3 anatomical areas—knee, shoulder, and foot—the available studies have a high risk of bias along with other limitations, and therefore the certainty with which we can make any conclusions about the effectiveness or harms of these interventions is very low. In attempting to summarize outcomes for the GRADE table, we were only able to compare study outcomes at 3 months postprocedure for most procedures. For knee function we included both the OKS and total WOMAC scales. For shoulder function, we included the SPADI score, and for foot function we included the AOFAS ankle-hindfoot score. For knee, shoulder, and foot pain outcomes, we included both VAS pain and NRS scales. For each scale, we assessed whether there was a statistically significant and clinically meaningful difference based on common thresholds for MCID.[31,32] Table 3 summarizes these findings, other strengths and limitations of this body of evidence, and the GRADE ratings for selected pain and function outcomes.

For RCTs, GRADE ratings of quality of evidence begin as high and then are downgraded for limitations in the domains of risk of bias, indirectness, imprecision, inconsistency, and publication bias. If risk of bias was moderate we downgraded by one level and if it was high we downgraded by 2 levels as recommended by both Cochrane[78] and GRADE[9]. Because limb pain caused by osteoarthritis or other types of damage is usually chronic in nature, we assessed a lack of longer term outcomes is a limitation in the domain of indirectness for GRADE ratings.[9] Other factors considered in the domain of indirectness included study location outside the U.S., and whether the comparator used was a standard and adequate treatment.[9] When there was one study for a particular anatomic area or method of nerve ablation we downgraded the quality of evidence for imprecision.[9] We downgraded for the domain of inconsistency if the group of studies in a particular anatomic area using the same method of nerve ablation had opposite findings.[9] We were unable to rate the GRADE domain for potential publication bias due to insufficient numbers of studies. However, we did note several studies in our review of studies

registered with the National Library of Medicine database that are listed as completed and which have not been published. The methodology manual for Cochrane systematic reviews also notes that industry funded studies are less likely to be published or to be delayed in publication compared to those funded by government agencies.[78] These features both raise the question of possible publication bias in this area of this review, but without definitive evidence of that we chose not to downgrade any outcome for publication bias.

Four[10,12,15,30] RCTs of conventional RFA for knee pain found some improvement in knee function and pain measures, but none followed participants for more than 6 months. The only RCT[13] that tracked outcomes for a year was conducted in participants that were post-total knee arthroplasty (TKA) and did find some differences in pain and function at some time points. One RCT[10] using the OKS and 2 others[12,30] using the total WOMAC found statistically significant improvements at 3 months for the conventional RFA group, which likely meet the threshold for an MCID.[31] Similarly, 2 RCTs[10,12] using a VAS pain scale found statistically significant improvements for the conventional RFA group at 3 months that likely meet the MCID threshold.[33]

There was 1 RCT each of cooled RFA[11] and cryoablation[14] for knee pain. These 2 studies enrolled somewhat larger groups of participants (151[11] and 180,[14] respectively) than did the conventional RFA studies. Both[11,14] RCTs found some benefits at some time periods for the intervention in terms of functional and pain outcomes. For purposes of the GRADE table, we found very low quality of evidence that cooled RFA[11] improved OKS function measures and NRS pain measures at 3 months compared to IAS, and that the difference likely met the MCID for that scale.[32,33] We also found very low quality of evidence that cryoneurolysis of the genicular nerves improved WOMAC total scores at 3 months compared to a sham procedure and that the difference likely meets the MCID threshold.[31] However, the RCT by Davis et al.[11] was assessed as having a moderate risk of bias and the RCT by Radnovich et al.[14] was assessed as having high risk of bias. The studies had significant methodological limitations and were single RCTs of particular modes of ablation without replication RCTs. Neither RCT had a large sample size or follow-up duration to either demonstrate definitive benefit or exclude important harms.[11,14] Given the risk of bias, imprecision from having only one study each, and indirectness because of lack of long-term outcomes, we are very uncertain about the reliability of any outcome from these studies.

It should be noted that there are limitations to nearly all of the comparators used in the RCTs of PNA for knee osteoarthritis. A recent network meta-analysis by Jevsevar et al.[61] ranked the short-term efficacy of nonsurgical interventions for knee osteoarthritis pain for reducing pain and improving function. Naproxen was at the top of the combined pain and function improvement ranking, followed by intra-articular corticosteroids, intra-articular platelet-rich plasma and 3 NSAIDs. The intervention with the lowest ranking was oral placebo, followed by acetaminophen, intra-articular placebo, and hyaluronic acid.[61] However, this analysis did not account for differences in the dose, frequency, or coadministration of various medications.[61] The group of RCTs included in our review used various control interventions, including no treatment.

Although various corticosteroid preparations and doses were used in the studies, there is little agreement about the optimal regimen.[100,101] The 2013 AAOS[40] guideline included a systematic review and meta-analysis of pharmacological treatments and made a strong recommendation for oral or topical NSAIDs or tramadol and were unable to make a recommendation for or against acetaminophen, opioids, or intra-articular corticosteroids because of inconclusive evidence. The AAOS review did not make recommendations regarding optimal dose or frequency of these medications. The AAOS[40] guideline also strongly recommended against the use of hyaluronic acid viscosupplementation because of lack of efficacy.

The 4 RCTs on the use of pRF of the suprascapular nerve each used a different comparator.[16-19] Eyigor et al.[16] compared the intervention to IAS injection and generally found that the IAS group demonstrated superior improvement for functional and pain outcomes. Ökmen et al.[19] also found that the photobiomodulation control group had better SPADI scores at 1, 3, and 6 months and better VAS pain scores at 1 and 3 months compared to the pRF group, but these differences were not statistically significant. The other 2 RCTs did not demonstrate clinically meaningful improvements[33] for pain, function, or other outcomes when compared to a sham procedure[17] or TENS[18] therapy. For GRADE outcomes, we found very low quality of evidence from 1 RCT[16] that IAS was superior to pRF in terms of the SPADI total score at 3 months and VAS night pain (but not other VAS pain measures), but that these differences did not likely meet MCID thresholds.[33,34] No other GRADE outcomes for the shoulder RCTs were statistically significant. All of these studies[16-19] had significant limitations, including small sample sizes, short length of follow-up, and inconsistent direction of effect, and were assessed as having a high risk of bias. This means that we are very uncertain about the reliability of any of these outcomes.

There were only 2 RCTs that met inclusion criteria for interventions to treat the pain of plantar fasciitis: 1[20] used conventional RFA and 1[21] used pRF; both used a sham comparator. In the Wu et al.[21] study, function assessed with the AOFAS score and pain assessed with the overall VAS measure demonstrated improvements at 12 weeks. For purposes of the GRADE table, we found that these improvements likely also meet MCID thresholds.[35-37] However, our confidence in these findings is very low, given that there is a single small study with multiple methodological and application limitations.

Landsman et al.[20] found some improved pain outcomes, including the overall VAS score, at 4 weeks in the pRF group. This difference would also likely meet MCID for VAS,[35] but did not meet our minimal GRADE standard of 3 months for the outcome. We are therefore unable to rate confidence in any outcome for this modality based on this single study.

Common study limitations across this evidence base were small sample sizes, inadequate length of follow-up to assess either the durability of benefits or the development of harms, use of inappropriate comparators, and lack of demonstrated clinical significance for some outcome measures even when there was demonstrated statistical significance. Some studies demonstrated a substantial placebo effect in the control group (i.e., participants who received a placebo or sham showed improvement in outcomes from baseline to follow-up measures).

Many studies had large or differential losses to follow-up. No RCT had an adequate description of allocation concealment. In some RCTs, there was no detail about co-interventions such as medications or adjunctive physical therapy. Most studies had limitations regarding the adequacy of the comparator intervention, contributing to indirectness of the evidence. In addition, there was substantial uncertainty regarding many statistical analyses because of multiple testing without appropriate partitioning of *P* values and lack of consideration or controlling for known confounders such as smoking, age, sex, and weight.

Although we found little evidence of serious harms in randomized and nonrandomized studies, no study described a robust method for assessing and capturing harms as part of the outcome measurement process. There were a few reports of patient harms and device malfunctions in U.S. government databases, raising the question of whether a higher incidence of serious harms would be demonstrated if these interventions became more widespread or were used in patient populations and for indications that have not been studied.

There are few studies and a low number of participants enrolled for these types of interventions, particularly when subdivided by the anatomical location, type of ablation procedure, and comparator group. No meta-analysis was feasible for any outcome because of noncomparability of intervention, comparator, and outcomes among included RCTs. We found only very low quality of evidence for all selected outcomes. This means that we expect that any effects, of either benefits or harms, are likely to be different than found in this review as additional studies are added to the evidence base.

Table 3. GRADE Summary of Evidence

Outcome	Number of Participants (N) Studies (k)	Findings	Quality of Evidence	Rationale
Knee (conventional RFA)[33]				
Function—WOMAC total or OKS at 3 months	N = 223 k = 5	1 RCT[10] used the OKS and found both a statistically significant and clinically meaningful improvement; 2 RCTs[12,30] used the WOMAC total score and found both a statistically significant and clinically meaningful improvement; 1 RCT limited to a post-TKA population found statistically significant and clinically meaningful improvements in function as rated by the OKS. All were favoring RFA. The other RCT[15] found no statistically significant difference between groups.	Very low ●○○○	QoE downgraded 2 levels for serious ROB and 1 level for indirectness (study locations, suboptimal comparator intervention, lack of longer-term outcomes)
Pain—VAS or NRS at 3 months	N = 150 k = 4	3 RCTs[10,12,30] used the VAS and found both a statistically significant and clinically meaningful improvement favoring RFA, and another[13] used the NRS and did not find statistically significant difference.	Very low ●○○○	QoE downgraded 2 levels for serious ROB; and 1 level for indirectness (study location, suboptimal comparator intervention, lack of longer-term outcomes)
Knee (cRFA)				
Function—OKS at 3 months	N = 151 k = 1	1 RCT[11] found both a statistically significant and clinically meaningful improvement favoring cRFA.	Very low ●○○○	QoE downgraded 1 level for moderate ROB, 1 level for imprecision (single study), and 1 level for indirectness (lack of longer-term outcomes, suboptimal comparator intervention)
Pain—NRS at 3 months	N = 151 k = 1	1 RCT[11] found both a statistically significant and clinically meaningful	Very low ●○○○	QoE downgraded 1 level for moderate ROB, 1 level for imprecision (single study), and 1 level for indirectness (lack of

Outcome	Number of Participants (N) Studies (k)	Findings	Quality of Evidence	Rationale
		improvement favoring cRFA.		longer-term outcomes, suboptimal comparator intervention)
Knee (cryoablation)				
Function—WOMAC total at 3 months	N = 180 k = 1	1 RCT[14] found both a statistically significant and clinically meaningful improvement favoring cryoablation.	Very low ●○○○	QoE downgraded 2 levels for serious ROB, 1 level for imprecision (single study), and 1 level for indirectness (lack of longer-term outcomes, suboptimal comparator intervention)
Pain—WOMAC pain at 3 months	N = 180 k = 1	1 RCT[14] found both a statistically significant and clinically meaningful improvement favoring cryoablation.	Very low ●○○○	QoE downgraded 2 levels for serious ROB, 1 level for imprecision (single study), and 1 level for indirectness (lack of longer-term outcomes, suboptimal comparator intervention)
Shoulder (pulsed RF)				
Function—SPADI total at 3 months	N = 171 k = 4	1 RCT[16] had a statistically significant difference in favor of IAS comparator. 1 RCT[19] had improvement with photobiomodulation comparator and 2[17,18] with pRF, but none of the differences were statistically significant. Differences were all small and likely below a clinically important threshold.	Very low ●○○○	QoE downgraded 2 levels for serious ROB; 1 level for inconsistency (better scores with control group in 2 studies and with intervention group in 2 studies); and 1 level for indirectness (study location, suboptimal or uncommonly used comparator, lack of longer-term outcomes, composite outcome)
Pain—VAS pain at 3 moths	N = 149 k = 3	2 RCTs[16,18] measured VAS at night, rest, and with motion; 1 RCT[19] presented a total VAS. 1 RCT[16] found a statistically significant, but small and likely not clinically meaningful, difference in VAS night pain favoring the IAS group. No other study found a statistically significant difference.	Very low ●○○○	QoE downgraded 2 levels for serious ROB; and 1 level for indirectness (study location, suboptimal or uncommonly used comparator, lack of long-term outcomes)

Outcome	Number of Participants (N) Studies (k)	Findings	Quality of Evidence	Rationale
Plantar Foot (pRF)				
Function—AOFAS ankle-hindfoot score at 3 months	N = 36 k = 1	1 RCT[21] found statistically significant and clinically meaningful improvement after pRF compared to sham treatment.	Very low ●○○○	QoE downgraded 1 level for moderate ROB; 1 level for imprecision (single study); and 1 level for indirectness (study location, lack of longer-term functional outcomes, composite outcome, suboptimal comparator intervention)
Pain—VAS overall at 3 months	N = 36 k = 1	1 RCT[21] found statistically significant and clinically meaningful improvements in overall VAS pain score.	Very low ●○○○	QoE downgraded 1 level for moderate ROB; 1 level for imprecision (single study); and 1 level for indirectness (study location, lack of longer-term outcomes, suboptimal comparator intervention)
Plantar Foot (conventional RFA)				
Function—no measure identified	N = 0 k = 0	NA	NA	NA
Pain—VAS overall at 3 months	N = 0 k = 0	Reported VAS only at 1 month	NA	NA

Abbreviations. AOFAS: American Orthopedic Foot and Ankle Society; cRFA: cooled radiofrequency ablation; IAS: intra-articular corticosteroid; NA: not applicable; NRS: numerical rating scale; OKS: Oxford Knee Score; pRF: pulsed radiofrequency; QoE; quality of evidence; RCT: randomized controlled trial; RFA: radiofrequency ablation; ROB: risk of bias; SF-36: Short Form 36; SPADI: Shoulder Pain and Disability Index; VAS: visual analog scale; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index.

Clinical Practice Guidelines

A search for clinical practice guidelines related to the treatment of limb pain identified 8 eligible guidelines, although the majority of these guidelines do not include discussion of or recommendations regarding peripheral nerve ablation. We included any guideline that met basic eligibility criteria and discussed management of limb pain, whether or not it specifically mentioned peripheral nerve ablation.

The 2013 clinical practice guideline on elbow disorders from the American College of Occupational and Environmental Medicine states that there is no recommendation for or against the use of diathermy for the treatment of acute, subacute, or chronic lateral epicondylalgia.[41] We rated this guideline as having fair methodological quality because of limitations in the rigor of

development of the evidence and recommendations, as well as lack of detail about the role of the funder and how panelist conflicts were managed.

The 2014 guideline from the Association of Extremity Nerve Surgeons does not recommend ablation, including cryoablation and RFA, in the primary treatment of Morton's Neuroma.[45] We rated this guideline as having poor methodological quality because there were no explanations of how evidence was synthesized for the review, how recommendations were determined, and how editorial independence was assured.

The 2018 American College of Foot and Ankle Surgeons (ACFAS) guideline on adult-acquired infracalcaneal heel pain does not make a recommendation on bipolar RF treatment for chronic, refractory plantar fasciitis, concluding that the evidence on this treatment is uncertain—neither appropriate nor inappropriate.[47] We rated this guideline as having poor methodological quality because there were no explanations of how evidence was synthesized for the review or how recommendations were determined, and there was a lack of detail about how conflicts of interest among panelists were managed.

Four guidelines on osteoarthritis pain management do not include recommendations or discussion of peripheral nerve ablation. Two of these are fair methodological quality guidelines from the American Academy of Orthopaedic Surgeons, including guidelines for osteoarthritis of the hip,[44] and knee.[40] The good methodological quality 2014 guideline from National Institute for Health and Care Excellence[39] and the fair methodological quality 2014 guideline on hip and knee osteoarthritis from the Veterans Administration/Department of Defense[42] do not mention peripheral nerve ablation as a treatment for persistent pain attributable to osteoarthritis. The American Physical Therapy Association has a fair methodological quality guideline on the treatment of plantar fasciitis[43] that does not mention peripheral nerve ablation. Details about methodological assessments of all guidelines are located in Appendix D, Table 19.

Selected Payer Coverage Determinations

A search was conducted for Medicare coverage policies and 3 private payers: Aetna, Cigna, and Regence. No Medicare National Coverage Determination was found that mentioned peripheral nerve ablation for limb pain. One Medicare Local Coverage Determination that covers Washington noted that local anesthetic nerve blocks are covered for several indications, including knee, hip, and shoulder pain.[48] The determination then states, "Longer-lasting or permanent blockage may be induced with the injection of neurolytic agents and/or application of thermal (not pulsed) radiofrequency."[48] Among the 3 private payers, no payer provides coverage for any peripheral nerve ablation treatment for limb pain, as outlined below. Some of the indications and procedures listed by private payers are not directly applicable to the evidence included in this report, but have been included here for completeness.

Aetna has 4 policies that address nerve ablation, and these policies consider these treatments to be experimental and investigational.[49-52] The Aetna policies do not cover pulsed RF for any indication.[49] Aetna's policy on osteoarthritis of the knee does not provide coverage for

cryotherapy or patellar denervation.[50] Aetna does not cover pulsed or thermal RF lesioning for plantar fasciitis.[51] Aetna does not cover cryoablation to treat lower extremity peripheral nerve damage, Morton's neuroma, or other types of neuroma.[52]

The Cigna policy on peripheral nerve ablation does not cover peripheral nerve destruction using cryoablation; radiofrequency ablation; or electrical, chemical, or laser ablation.[53] This policy specifically considers these procedures experimental; investigational; or unproven for treatment of knee pain, foot/heel pain, and lower extremity pain resulting from complex regional pain syndrome, peripheral nerve entrapment/compression, or peripheral neuropathy.[53] Cigna does not cover RF lesioning for pain resulting from plantar fasciitis and considers it experimental and investigational.[54]

The Regence policy on emerging medical technologies does not cover nerve ablation (including cryoablation) of the upper or lower extremity peripheral nerves, nerve plexus, or other truncal nerves because nerve ablation is investigational.[55] Regence's policy does not cover ablation using magnetic resonance-guided focused ultrasound and high-intensity focused ultrasound procedures for pain, and considers these treatments to be investigational.[56]

Ongoing Trials

A search of the National Clinical Trials database was conducted for studies related to nerve ablation. Of the studies included in this evidence review, 5 were found in the National Clinical Trials database.[10-12,14,21] Twelve other ongoing trials would likely be included in this evidence review, but have not been published yet. These studies, to be completed between 2018 and 2021, consist of 9 knee studies, 1 hip study, 1 foot study, 1 postamputation lower limb pain study. There were no registered studies of procedures for shoulder pain or plantar fasciitis. The modalities involved in the studies of knee pain procedures consist of 4 of RFA (1 of these in post-TKA patients), 2 pRF, 2 cooled RF, and 1 using magnetic resonance-guided focused ultrasound.

Conclusions

The strengths of this systematic review are that we comprehensively searched multiple databases for eligible studies of peripheral nerve ablation to treat limb pain and conducted independent, dual study screening, selection, and risk-of-bias assessment. Limitations of this report were inclusion of only English language literature and inability to include any unpublished literature (with the exception of the FDA MAUDE and recalls databases) or to contact authors to resolve any questions about published studies. Our methodological quality assessment relied on the clarity and completeness of reporting of included published studies. Over the past 22 years, the Consolidated Standards of Reporting Trials (CONSORT) Statement has provided an evidence-based, minimum set of recommendations for authors and journals to encourage the transparent and complete reporting of RCTs.[57] Use of CONSORT in developing and publishing RCTs improves their reporting and can facilitate their critical appraisal and interpretation.[57] Unfortunately, many of the RCTs we reviewed either did not adhere to these standards or

conducted trials that did not adhere to the best methodological standards of conduct. We were unable to conduct any meta-analyses because of lack of comparability among 2 or more individual RCTs.

We found very low quality of evidence in favor of peripheral nerve ablation to improve some short-term functional and pain measures. Overall, 7 RCTs[10-14,21,30] found some improvements in short-term functional status and level of pain that were both statistically significant and likely clinically meaningful. However, these improvements were small in magnitude and not consistent. Positive outcomes were often reported in only 1 RCT, on 1 scale or subscale, or at 1 time period, and not in others. One RCT found small, statistically significant improvements in shoulder function and pain with IAS injections compared to pRF treatments.[16]

The populations included in RCTs that evaluated anatomical areas of the knee and shoulder generally were aged 60 to 70 years, predominantly female, and with moderate to severe chronic joint pain due to osteoarthritis. It is not clear that any study included a population that had optimal noninterventive treatment prior to trial entry or was composed of people for whom definitive management was appropriate, limiting comparability to current U.S. guidelines and practice. The evidence is nearly exclusively limited to outcomes that occurred within 3 to 6 months of the intervention. Most RCTs lacked sufficient sample size for evaluation of efficacy outcomes and several were limited by high losses to follow-up. Several RCTs were funded by device manufacturers or had authors with declared financial relationships with those companies. Other RCTs did not report either study funding or author disclosures. Although we do not know the precise effect of these relationships in the area we investigated, a 2017 Cochrane systematic review found that industry sponsorship of drug and device studies is associated with more favorable study conclusions when compared to studies with other sources of funding.[38]

Our conclusions can only apply to evaluated ablation procedures used to treat knee, shoulder, or plantar foot pain compared to a variety of active and sham comparator treatments. No studies involved head-to-head comparisons of nerve ablation techniques. We found no studies that reported RCTs for peripheral nerve ablation to treat pain at other anatomic sites, including the wrist, elbow, hip, ankle, or the digits. With the exception of 1 RCT[13] of conventional RFA for persistent knee pain at least 6 months after TKA, we did not find evidence related to any selected subgroup. Potential harms of these procedures appear to be uncommon, but have been poorly reported in published studies. There are, however, a few cases of serious harms for all types of nerve ablation identified in published and unpublished sources. Our search found no studies that reported economic outcomes related to any of these procedures.

No identified clinical practice guideline makes a recommendation for the use of these ablation techniques. No private payers cover these ablation procedures for any indication, although thermal (not pulsed) RF is covered for a variety of pain diagnoses, including knee, hip, and shoulder pain in 1 Medicare Local Coverage Determination on nerve blockades for treatment of chronic pain and neuropathy. There are 12 ongoing RCTs of various modalities for peripheral nerve ablation to treat pain in the knee (9 studies), foot (1 study), hip (1 study), and

postamputation phantom lower limb pain (1 study) that are expected to be completed between 2018 and 2021. We found no registrations of additional ongoing studies related to treatment of shoulder pain or plantar fasciitis. Although the data on these procedures are sparse, studies have been registered and could contribute increasing amounts of data to this field with time. The current paucity of evidence to support these procedures is reflected in the lack of clinical endorsement in clinical practice guidelines and payer coverage policies.

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Appendix A. Search Strategy

Databases:

- Ovid MEDLINE
- Ovid MEDLINE In-Process & Other Non-Indexed Citations
- EBM Reviews—Cochrane Central Register of Controlled Trials
- EBM Reviews—Cochrane Database of Systematic Reviews

1 Catheter Ablation/

2 exp Pulsed Radiofrequency Treatment/

3 exp radio waves/tu

4 exp Cryosurgery/

5 exp DENERVATION/

6 ((rf or radiofreq* or radio freq* or radiowav* or radio wav* or microwav*) adj5 ((ablat* or denervat* or neurotom* or (cut or cuts or cutting or sever or severs or severing or destroy*)) adj3 (nerv* or neuro*))).mp. [mp=ti, ab, ot, nm, hw, fx, kf, px, rx, ui, sy, sh, kw, tx, ct]

7 ((rf or radiofreq* or radio freq* or radiowav* or radio wav* or microwav*) adj5 (surger* or surgic* or therap* or treat*)).mp. [mp=ti, ab, ot, nm, hw, fx, kf, px, rx, ui, sy, sh, kw, tx, ct]

8 (cryoablat* or cryosurg*).mp. [mp=ti, ab, ot, nm, hw, fx, kf, px, rx, ui, sy, sh, kw, tx, ct]

9 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8

10 exp PAIN/

11 exp Pain Management/

12 exp Pain Measurement/

13 exp Pain Threshold/

14 exp Hyperalgesia/

15 exp Pain Perception/

16 exp complex regional pain syndromes/

17 exp osteoarthritis/

18 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17

19 exp Lower Extremity/

20 exp Knee Joint/

21 exp hip joint/

22 exp foot joint/

23 19 or 20 or 21 or 22

24 exp Upper Extremity/

25 exp Bones of Upper Extremity/

26 exp Arm Injuries/ or exp Hand Injuries/ or exp Wrist Injuries/ or exp Shoulder Injuries/ or exp Ulnar Nerve Compression Syndromes/

27 exp Elbow Joint/ or exp Shoulder Joint/ or exp Wrist Joint/ or exp Hand Joints/ (46042)

28 24 or 25 or 26 or 27

29 23 or 28

30 exp Fasciitis, Plantar/

31 exp Sciatica/

32 exp OSTEOARTHRITIS, HIP/

33 exp OSTEOARTHRITIS, KNEE/

34 ((arthrit* or osteoarthrit*) adj5 (knee* or patella* or hip or hips or ankle* or tarsal* or metatarsal* or lower extremit* or leg or legs)).mp.

35 (fasciit* adj3 (plantar or foot or feet)).mp. [mp=ti, ab, ot, nm, hw, fx, kf, px, rx, ui, sy, sh, kw, tx, ct]

36 (sciatica or (sciatic* adj3 pain*)).mp. [mp=ti, ab, ot, nm, hw, fx, kf, px, rx, ui, sy, sh, kw, tx, ct]

37 ((arthrit* or osteoarthrit*) adj5 (arm or arms or hand or hands or finger* or wrist* or carpal* or elbow* or shoulder* or upper extremit*)).mp.

38 genicular.mp.

39 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38

40 9 and ((18 and 29) or 39)

41 limit 40 to english language [Limit not valid in CDSR; records were retained]

42 limit 40 to abstracts [Limit not valid in CDSR; records were retained]

43 41 or 42

44 remove duplicates from 43

45 limit 44 to (comparative study or controlled clinical trial or evaluation studies or meta analysis or randomized controlled trial or systematic reviews) [Limit not valid in CCTR,CDSR; records were retained]

46 limit 45 to (meta analysis or systematic reviews) [Limit not valid in CCTR,CDSR; records were retained]

47 limit 45 to randomized controlled trial [Limit not valid in CDSR; records were retained]

48 limit 45 to controlled clinical trial [Limit not valid in CDSR; records were retained]

49 exp Epidemiologic Studies/

50 44 and 49

51 limit 45 to (comparative study or evaluation studies) [Limit not valid in CCTR,CDSR; records were retained]

52 47 not 46

53 48 not (46 or 47)

54 50 not (46 or 47 or 53)

55 51 not (46 or 47 or 48 or 54)

56 44 not (46 or 47 or 48 or 54)

Appendix B. Additional Methods

Risk of Bias Assessment: Randomized Controlled Trials

Domain	Domain Elements The elements included in each domain are assessed and rated as *Yes*, *No*, *Unclear*, or *Not Applicable* based on performance and documentation of the individual elements in each domain. The overall risk of bias for the study is assessed as *High*, *Moderate,* or *Low* based on assessment of how well the overall study methods and processes were performed to limit bias and ensure validity.
Randomization	• An appropriate method of randomization is used to allocate participants or clusters to groups, such as a computer random number generator • Baseline characteristics between groups or clusters are similar
Allocation Concealment	• An adequate concealment method is used to prevent investigators and participants from influencing enrollment or intervention allocation
Intervention	• Intervention and comparator intervention applied equally to groups • Co-interventions appropriate and applied equally to groups • Control selected is an appropriate intervention
Outcomes	• Outcomes are measured using valid and reliable measures • Investigators use single outcome measures and do not rely on composite outcomes, or the outcome of interest can be calculated from the composite outcome • The trial has an appropriate length of follow-up and groups are assessed at the same time points • Outcome reporting of entire group or subgroups is not selective
Masking (Blinding) of Investigators and Participants	• Investigators and participants are unaware (masked or blinded) of intervention status
Masking (Blinding) of Outcome Assessors	• Outcome assessors are unaware (masked or blinded) of intervention status
Intention to Treat Analysis	• Participants are analyzed based on random assignment (intention-to-treat analysis)
Statistical Analysis	• Participants lost to follow-up unlikely to significantly bias the results (i.e., complete follow-up of ≥ 80% of the participants overall and nondifferential, ≤ 10% difference between groups) • The most appropriate summary estimate (e.g., risk ratio, hazard ratio) is used • Paired or conditional analysis used for crossover RCT • Clustering appropriately accounted for in a cluster-randomized trial (e.g., use of an intraclass correlation coefficient)
Other Biases (as appropriate)	List others in table footnote and describe, such as: • Sample size adequacy • Interim analysis or early stopping • Recruitment bias, including run-in period used inappropriately • Use of unsuitable crossover intervention in a crossover RCT

Domain	Domain Elements The elements included in each domain are assessed and rated as *Yes*, *No*, *Unclear*, or *Not Applicable* based on performance and documentation of the individual elements in each domain. The overall risk of bias for the study is assessed as *High*, *Moderate,* or *Low* based on assessment of how well the overall study methods and processes were performed to limit bias and ensure validity.
Interest Disclosure	• Disclosures of interest are provided for authors/funders/commissioners of the study • Interests are unlikely to significantly affect study validity
Funding	• There is a description of source(s) of funding • Funding source is unlikely to have a significant impact on study validity

Risk of Bias Assessment: Observational Trials

Domain	Domain Elements **The elements included in each domain are assessed and rated as *Yes*, *No*, *Unclear*, or *Not Applicable* based on performance and documentation of the individual elements in each domain. The overall risk of bias for the study is assessed as *High*, *Moderate* or *Low*, based on assessment of how well the overall study methods and processes were performed to limit bias and ensure validity.**
Participant Selection	For cohort studies: • The two groups being studied are selected from source populations that are comparable in all respects other than the factor under investigation, or statistical adjustment is used appropriately to achieve this • The study indicates how many of the people asked to take part did so, in each of the groups being studied • The likelihood that some eligible participants might have the outcome at the time of enrolment is assessed and taken into account in the analysis • Fewer than 20% of individuals or clusters in each arm of the study dropped out before the study was completed For case-control studies: • Cases and controls are clearly specified and defined, with the inclusion and exclusion criteria applied appropriately • Cases may be selected by meeting inclusion criteria, controls may be selected by meeting inclusion criteria and then being matched to cases • Sampling selection (ratio of cases to control) is justified • Cases and controls selected from the same population and same timeframe. When not all cases and controls are selected from the same population, they are randomly selected • Among cases, investigators confirm that the exposure occurred before the development of the disease being studied and/or the likelihood that some eligible participants might have the outcome at the time of enrolment is assessed and taken into account in the analysis
Intervention	• The assessment of exposure to the intervention is reliable • Exposure level or prognostic factors are assessed at multiple times across the length of the study, if appropriate • For case-control studies assessors of (intervention) exposure status are unaware (masked or blinded) to the case or control status of participants there is a method to limit the effects of recall bias on the assessment of exposure to the intervention
Control	• Control condition represents an appropriate comparator
Outcome	• There is a precise definition of the outcomes used • Outcomes are measured using valid and reliable measures, evidence from other sources is used to demonstrate that the method of outcome assessment is valid and reliable • Investigators use single outcome measures and do not rely on composite outcomes, or the outcome of interest can be calculated from the composite outcome

Domain	Domain Elements The elements included in each domain are assessed and rated as *Yes*, *No*, *Unclear*, or *Not Applicable* based on performance and documentation of the individual elements in each domain. The overall risk of bias for the study is assessed as *High*, *Moderate* or *Low*, based on assessment of how well the overall study methods and processes were performed to limit bias and ensure validity.
	• The study has an appropriate length of follow-up for the outcome reported and groups are assessed at the same time points • Outcome reporting of entire group or subgroups is not selective • When patient-reported outcomes are used there is a method for validating the measure
Masked Outcome Assessment	• The assessment of outcome(s) is made blind to exposure status. Where outcome assessment blinding was not possible, there is recognition that knowledge of exposure status could have influenced the assessment of outcome • For case-control study: assessors of exposure status are unaware (masked or blinded) of the case or control status of participant)
Confounding	• The main potential confounders are identified and taken into account in the design and analysis of the study
Statistical Analysis	• Comparison is made between full participants and those who dropped out or were lost to follow-up, by exposure status • If the groups were not followed for an equal length of time, the analysis was adjusted for differences in the length of follow-up • All major confounders are adjusted for using multiple variable logistic regression or other appropriate statistical methods • Confidence intervals (or information with which to calculate them) are provided • For case-control studies that use matching, conditional analysis is conducted or matching factors are adjusted for in the analysis
Other Biases (as appropriate)	List others in table footnote and describe, e.g., • Sample size adequacy
Interest Disclosure	• Disclosures of interest are provided for authors/funders/commissioners of the study • Interests are unlikely to significantly affect study validity
Funding Source	• There is a description of source(s) of funding • Funding source is unlikely to have a significant impact on study validity

Risk of Bias Assessment: Clinical Practice Guidelines

Domain	Domain Elements Assessment indicates how well the guideline methodology and development process were performed to limit bias and ensure validity for elements in domain (each domain rated as *Good*, *Fair*, or *Poor* overall based on performance and documentation of elements)
Rigor of Development: Evidence	• Systematic literature search that meets quality standards for a systematic review (i.e., comprehensive search strategy with, at a minimum, 2 or more electronic databases) • The criteria used to select evidence for inclusion is clear and appropriate • The strengths and limitations of individual evidence sources is assessed and overall quality of the body of evidence assessed
Rigor of Development: Recommendations	• Methods for developing recommendations clearly described and appropriate • There is an explicit link between recommendations and supporting evidence • The balance of benefits and harms is considered in formulating recommendations • The guideline has been reviewed by external expert peer reviewers • The updating procedure for the guideline is specified in the guideline or related materials (e.g., specialty society website)
Editorial Independence	• There is a description of source(s) of funding and the views of the funder(s) are unlikely to have influenced the content or validity of the guideline • Disclosures of interests for guideline panel members are provided and are unlikely to have a significant impact on the overall validity of the guideline (e.g., a process for members to recuse themselves from participating on recommendations for which they have a significant conflict is provided)
Scope And Purpose	• Objectives specifically described • Health question(s) specifically described • Target population(s) for guideline recommendations is specified (e.g., patients in primary care) and target users for the guideline (e.g., primary care clinicians)
Stakeholder Involvement	• Relevant professional groups represented • Views and preferences of target population(s) sought (e.g. clinicians and patients)
Clarity And Presentation	• Recommendations are specific and unambiguous • Different management options are clearly presented • Key recommendations are easily identifiable
Applicability	• Provides advice and/or tools on how the recommendation(s) can be put into practice • Description of facilitators and barriers to its application • Potential resource implications considered • Criteria for implementation monitoring, audit, and/or performance measures based on the guideline are presented

Appendix C. Evidence Tables

Abbreviations Used in Evidence Tables

AOFAS: American Orthopedic Foot and Ankle Society

CI: confidence interval

cRFA: cooled radiofrequency ablation

GPE: Global Perceived Effect

HA: hyaluronic acid

h/o: history of

IA: intra-articular

IAS: intra-articular corticosteroid

IPBSN: infrapatellar branch of saphenous nerve

KSS: Knee Society Score

MD: mean difference

NHP: Nottingham Health Profile

NR: not reported

NRS: Numerical Rating Scale

NSAIDs: nonsteroidal anti-inflammatory drugs

OKS: Oxford Knee Score

PGI-I: Patient Global Impression of Improvement

PGIC : Patient Global Impression of Change

PT: physical therapy

pRF: pulsed radiofrequency

RCT: randomized controlled trial

RF: radiofrequency

RFA: radiofrequency ablation

ROM: range of motion

s: seconds

SD: standard deviation

SF-36: Short Form 36

SPADI: Shoulder Pain and Disability Index

VAS: Visual Analog Scale

WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index

Table 4. Study Characteristics for Randomized Controlled Trials: Conventional RFA for Knee Pain

Citation Setting NCT# (if available)	Population Description	Inclusion and Exclusion Criteria	Intervention Description	Comparator Description	Outcomes measured
Choi et al., 2011[10] South Korea NCT00924677	Total N = 35 treatment n = 18, control n = 17 Mean age: 67 years Gender: 5 (14%) male, 30 (86%) female Mean BMI: 26.4 Mean duration of symptoms: 6.9 years Mean VAS: 77.7 Mean OKS: 39.5 Kellgren–Lawrence classification: 7 (20%) Grade 2, 15 (43%) Grade 3, 13 (37%) Grade 4	Inclusion criteria (must meet all): Knee pain of at least moderate intensity on most or all days for ≥ 3 months; Kellgren-Lawrence grade 2 to 4 (evaluated by a radiologist); no response to prior treatments, including physiotherapy, oral analgesics, and IAS or HA injection; age 50 to 80 years Exclusion criteria (excluded if met any criterion): h/o of knee surgery or electroacupuncture treatments; IAS or HA injection in past 3 months; acute knee pain; other connective tissue diseases affecting the knee; sciatic pain; serious neurologic or psychiatric disorders; pacemakers; anticoagulant medications	RFA using unspecified NeuroTherm device Participants in both groups advised to continue medications; no medication changes allowed Anesthesia: 1 mL 1% lidocaine to skin and soft tissues and 2 mL of 2% lidocaine at ablation site Device placement: Genicular nerves (superior lateral, middle superior medial, inferior medial) confirmed with sensory stimulation and absence of motor response Ablation:	Sham procedure (anesthesia at ablation site and insertion of probe cannula without activation of RF generator) Participants in both groups advised to continue medications previously prescribed for knee osteoarthritis and other degenerative diseases, and prohibited from making alterations to their medications	Time points for all outcome measures: Baseline, postprocedure, and weeks 1, 4, and 12 Function: None Function and Pain: OKS Pain: VAS (100 mm) Proportion of participants achieving at least 50% knee pain relief at 12 weeks. Safety: Adverse effects reported to physician at each visit; could report by telephone Other outcomes: GPE for patient satisfaction

Citation Setting NCT# (if available)	Population Description	Inclusion and Exclusion Criteria	Intervention Description	Comparator Description	Outcomes measured
			70°C, 90 seconds; 1 RF lesion for each genicular nerve Procedural imaging: Fluoroscopy		
El-Hakeim et al., 2018[12] Egypt NCT03224637	Total N = 60 treatment n = 30, control n = 30 Mean age: 59 years Gender: 21 (35%) male, 39 (65%) female Mean BMI: 31.1 Mean disease duration: 6.6 months X-ray grading: 35 (58%) Grade 3, 25 (42%) Grade 4 IAS injection >3 months ago: 22 (36.7%) once, 34 (56.7%) twice	Inclusion criteria (must meet all): Knee osteoarthritis diagnosed with American College of Rheumatology criteria; Kellgren-Lawrence grade 3 or 4 Exclusion criteria (excluded if met any criterion): h/o knee surgery; received IAS or HA in past 3 months; associated radicular pain; connective tissue disease affecting the knee; other causes of pain (e.g., radiculopathy); contraindication for invasive interventions, systemic, or local infection; psychiatric disorders	RFA with unspecified NeuroTherm device Paracetamol supplementation allowed if pain experienced in treated region Anesthesia: 2 mL lidocaine 1% to skin and soft tissues and 2 mL lidocaine 2% at ablation site Device placement: Genicular nerves (upper medial, upper lateral, and lower medial), confirmed with sensory stimulation and	Oral paracetamol (maximum dose 1 g/6 hours), nonsteroidal anti-inflammatory Diclofenac sodium 75 mg 2 times a day, and physiotherapy if needed	Time points for all outcome measures: Baseline, week 2, month 3, and month 6 Function: WOMAC disability Pain: VAS (10 point) Safety: Complications related to RFA were recorded Other outcomes: Patient satisfaction using Likert scale

Citation Setting NCT# (if available)	Population Description	Inclusion and Exclusion Criteria	Intervention Description	Comparator Description	Outcomes measured
			absence of motor response Ablation: 80 °C, 270 seconds (3 cycles of 90 sec.) Procedural imaging: Fluoroscopy		
Qudsi-Sinclair et al., 2016[13] Spain	Total N = 28 treatment n = 14, control n = 14 Mean age: 69 years Gender: 7 (27%) male, 19 (73%) female Mean pain duration after TKA: 37 months Mean VAS: 6.7 Mean KSS: 42.8 Mean SF-36: 62.6	Inclusion criteria (must meet all): > 6 months of persistent pain after TKA and conservative treatment; age > 18 years Exclusion criteria (excluded if met any criterion): Possible cause for the pain identified (e.g., signs of infection or loosening of the prosthetic material); h/o RF treatment; known radiculopathy; connective tissue diseases (e.g., rheumatoid arthritis); current anticoagulant treatment; allergy to metals, broken material, or periprosthetic fractures; skin infection in the area to be treated; severe psychiatric or neurological disease; pregnancy; local tumor-related disease	RFA using Cosman TCD RF electrode and Cosman G4 RF generator In both groups, medication treatment adapted based on the patient's symptoms during each evaluation Anesthesia: 1 mL of 2% lidocaine to the skin and soft tissues at 3 injections points and 2 mL of 2% lidocaine at the 3 ablation sites Device placement:	2 mL of 0.25% levobupivacaine hydrochloride and 0.5 mL of triamcinolone acetonide injected at the 3 genicular nerves In both groups, medication treatment adapted based on the patient's symptoms during each evaluation	Time points for all outcome measures: Baseline, day 1, week 1, and months 3, 6, and 12 Function: SF-36 Function and Pain: OKS KSS Pain: NRS Safety: Side effects and incidents documented

Citation Setting NCT# (if available)	Population Description	Inclusion and Exclusion Criteria	Intervention Description	Comparator Description	Outcomes measured
			Genicular nerves (superolateral, superomedial, and inferomedial), confirmed with sensory stimulation and absence of motor response Ablation: 80°C, 90 seconds at each of 3 genicular nerves Procedural imaging: Fluoroscopy		Other outcomes: PGI-I Medication use classified using the World Health Organization pain ladder
Ray et al., 2018[30] India	Total N = 24 treatment n = 12, control n = 12 Mean age: 53 years Gender: 8 (34%) male, 16 (66%) female	Inclusion criteria (must meet all): Knee osteoarthritis of the medial femorotibial joint as defined by the American College of Rheumatology; Kellgren–Lawrence grade 1 to 3 evaluated by the weight-bearing anteroposterior X-rays of the tibiofemoral joint using the bilateral standing extended view; able to walk; VAS > 4 on 10-point scale; age above 40	RFA using unspecified device Anesthesia: 1 mL 1% preservative free lignocaine to skin and soft tissues and 2 mL of 1% lignocaine at each ablation site Device placement: Genicular nerves (superolateral,	Hyaluronic acid injection (hylan A + hylan B, 48 mg), with injection site confirmed by fluoroscopy Patients advised to take oral medication as before	Time points for all outcome measures: Baseline and weeks 1, 4, and 12 Function: None Function and Pain: WOMAC Pain:

Citation Setting NCT# (if available)	Population Description	Inclusion and Exclusion Criteria	Intervention Description	Comparator Description	Outcomes measured
		Exclusion criteria (excluded if met any criterion): Secondary knee osteoarthritis; severe osteoarthritis (K/L grade >3) in a location other than the knee joint; rheumatoid arthritis; joint replacement surgery in either knee or a hip; oral, topical, or intra-articular steroid during the 4 weeks before the study; oral, topical, or suppository NSAID within 2 weeks before the study; hematological, cardiac, hepatic, or renal disorders; meniscal tear, ligament injury, bursitis, or popliteal cyst; blood investigations suggestive of infection	superomedial, and inferomedial), confirmed with sensory stimulation and absence of motor response Ablation: 2 lesions for each genicular nerve at 80°C for 90 s Procedural imaging: Fluoroscopy		VAS (10 cm) Safety: Adverse effects reported Other outcomes: None
Sari et al., 2016[15] Turkey	Total N = 73 treatment n = 37, control n = 36 Mean age: 64 years Gender: 16 (23%) male, 55 (77%) female Mean BMI: 23.2 Mean disease duration: 5 years	Inclusion criteria (must meet all): Osteoarthritis diagnosis using criteria recommended by the American College of Rheumatology; stage 2 or higher radiological changes based on the Kellgren-Lawrence scale; pain of at least moderate severity or pain on a daily basis > 3 months; clinically unresponsive to conservative treatment modalities (i.e.., PT and rehabilitation practices, orally administered analgesics, anti-	RFA using unspecified NeuroTherm device Participants in both groups asked not to take medications for pain relief Anesthesia: 2% lidocaine subcutaneous injections	IA injection of 2.5 mL bupivacaine, 2.5 mg morphine and 1 mL betamethasone into patellofemoral joint space by a superolateral approach Participants in both groups asked not to take medications for pain relief	Time points for all outcome measures: Baseline and months 1 and 3 Function: WOMAC function WOMAC stiffness Pain: VAS (10 cm) WOMAC pain

Citation Setting NCT# (if available)	Population Description	Inclusion and Exclusion Criteria	Intervention Description	Comparator Description	Outcomes measured
		inflammatory agents; unable to have arthroplasty; age 50 to 80 years Exclusion criteria (excluded if met any criterion): h/o knee surgery; acute knee pain; connective tissue disorder that affects the knee joint; anticoagulant medication; serious neurological or psychiatric conditions	Device placement: Genicular nerves on the lateral and medial aspects of lower end of femoral bone, on the medial aspect of the tibia, confirmed with sensory testing and absence of motor response Ablation: 80°C for 90 s for each nerve Procedural imaging: Fluoroscopy		Safety: Postprocedure complications and adverse effects were recorded Other outcomes: None

Table 5. Study Characteristics for Randomized Controlled Trials: Cooled RFA for Knee Pain

Citation Setting NCT# (if available)	Population Description	Inclusion and Exclusion Criteria	Intervention Description	Comparator Description	Outcomes measured
Davis et al., 2018[11] U.S. NCT02343003	Total N = 151 treatment n = 76, control n = 75 Mean age: 64 years Gender: 52 (34%) male, 99 (66%) female Race: 119 (79%) White, 27 (18%) Black, 1 (1%) Asian/Pacific Islander, 0 (0%) American Indian/AK Native, 4 (3%) Other Mean BMI: 30.5 Mean duration of knee pain: 115 months Radiographic evaluation: 53 (35%) Grade 2, 67 (44%) Grade 3, 31 (21%) Grade 4 Mean NRS: 7.1	Inclusion criteria (must meet all): Radiological confirmation of osteoarthritis grades 2 to 4 in past 12 months; knee pain ≥ 6 months that was unresponsive to conservative treatments (i.e., PT, oral analgesics, IAS injections, viscosupplementation); NRS ≥ 6; OKS ≤ 35; positive diagnostic genicular nerve block (decrease ≥50% in NRS); if participant was taking an opioid or morphine-equivalent medication, dosage must be clinically stable (<10% change in dosage for ≥2 months) Exclusion criteria (excluded if met any criterion): h/o total knee arthroplasty, h/o knee RF block or ablation; coagulopathy; h/o systemic inflammatory conditions (e.g., rheumatoid arthritis); uncontrolled diabetes; cancer; BMI > 40	Cooled RFA with Coolief System Medication use was monitored in both groups, with no restrictions described Anesthesia: Unspecified local anesthetic to skin and soft tissue and ablation sites were anesthetized with 1% lidocaine Device placement: Genicular nerves (superior lateral, superior medial, and inferior medial) confirmed with sensory stimulation and lack of motor response Ablation:	Corticosteroid injection into the suprapatellar pouch equivalent to 40 mg Depo-Medrol (methylprednisolone acetate) Medication use was monitored in both groups, with no restrictions described	Time points for all outcome measures: Baseline and months 1, 3, and 6 Function: None Function and Pain: OKS Pain: NRS Proportion of participants whose knee pain was reduced by 50% or greater from baseline at 6 months Safety: Participants evaluated for adverse events at each visit Other outcomes: GPE Opioid and nonopioid (NSAIDs) analgesic use, as measured by participant

Citation Setting NCT# (if available)	Population Description	Inclusion and Exclusion Criteria	Intervention Description	Comparator Description	Outcomes measured
			Cooled RFA, 60°C, 150 seconds, heat generated average maximum tissue temperatures > 80°C Procedural imaging: Fluoroscopy		self-reported average daily dosage

Table 6. Study Characteristics for Randomized Controlled Trials: Cryoneurolysis for Knee Pain

Citation Setting NCT# (if available)	Population Description	Inclusion and Exclusion Criteria	Intervention Description	Comparator Description	Outcomes measured
Radnovich et al., 2017[14] U.S. NCT02260921	Total N = 180 treatment n = 121, control n = 59 Median age: 61 years (range 36-75) Gender: 61 (34%) male, 119 (66%) female Race: 160 (89%) White, 16 (9%) Black, 3 (2%) Asian/Pacific Islander, 2 (1%) American Indian/AK Native, 1 (1%) Other Mean BMI: 29 Mean time since diagnosis: 73 months Kellgren-Lawrence classification: 94 (52%) Grade 2, 86 (48%) Grade 3 Mean WOMAC pain score: 30.8 Mean VAS: 67.8	Inclusion criteria (must meet all): Self-reported knee pain in the anterior or inferior medial aspect of knee; WOMAC pain score ≥ 20 at baseline; knee pain ≥ 40 mm on a 100 mm VAS when performing one of these activities - standing from a seated position or walking up/down stairs; when performing the activity that elicited the worst pain, ≥ 50% reduction in VAS pain following a diagnostic lidocaine block of the IPBSN; maintenance of a stable schedule of prescription and OTC pain medications for ≥ 2 weeks prior to screening; able to tolerate a washout of prescription and OTC pain medication for >5 times the half-life of the medication; able to tolerate a washout of adjunctive therapies for knee pain for 72 hours prior to the baseline visit; able to discontinue all pain medication or adjunctive therapy for knee pain throughout the duration of the study, other than maximum of acetaminophen 4 mg/day as rescue medication during the 24 hours prior to each follow-up visit Exclusion criteria (excluded if met any criterion): h/o or planned (< 12 months) partial or full knee replacement; h/o cryoneurolysis treatment; received IAS injection in past 3 months or IA injection of HA in past 6 months; PT or acupuncture in past 3 months; h/o surgery in the	Cryoneurolysis using iovera° device with Smart Tip Participants in both groups prohibited from taking prescription or OTC pain medications other than acetaminophen Anesthesia: Unspecified amount of lidocaine administered cutaneously and subcutaneously Device placement: Infrapatellar branch of the saphenous nerve, guided by visualization and palpation of anatomical landmarks Ablation: Cryogen (NO2) to the Smart Tip comprised of	Sham procedure (local anesthesia and insertion of sham Smart Tip that displayed same lights and activation features as active Smart Tip) Participants in both groups prohibited from taking prescription or OTC pain medications other than acetaminophen	Time points for all outcome measures: Baseline and days 1, 7, 30, 60, 90, and 120 Function: SF-36 WOMAC function WOMAC stiffness Function and Pain: WOMAC total WOMAC total responders, participants who experienced > 30% reduction from baseline Pain: WOMAC pain WOMAC pain responders, participants who experienced > 30% reduction from baseline

Citation Setting NCT# (if available)	Population Description	Inclusion and Exclusion Criteria	Intervention Description	Comparator Description	Outcomes measured
		treatment area that may alter the anatomy of the IPBSN or result in scar tissue; majority of primary knee pain located outside the anterior/inferior medial aspect of the knee; diagnosis that in the opinion of the Investigator directly contributes to knee pain; gross deformity of the knee including varus or valgus (<15 degrees); BMI ≥ 35; any concomitant inflammatory disease or other condition that affects the joints (e.g., rheumatoid arthritis, metabolic bone disease, gout, active infection); h/o cryoglobulinemia, paroxysmal cold hemoglobinuria, cold urticaria, Raynaud's disease, or pes anserinus bursitis; disease of the spine, hip, contralateral knee, or other lower extremity joint that would affect the assessment of the knee; use of long-acting opioids in the past 3 months; use of immediate-release opioids > 3 days per week in past month; current enrollment in investigational drug or device study or participation in past 30 days; open or infected wound in the treatment area; acetaminophen intolerance or allergy; lidocaine allergy; clotting disorder or use of an anticoagulant in past 7 days; pregnant or planning to become pregnant; local skin condition at the treatment site that in investigator's opinion would adversely affect treatment or outcomes; chronic medical condition or medication that in the investigator's opinion would affect participation or patient safety	three 27-gauge closed-end needles Procedural imaging: None		VAS (100 point) VAS responders, participants who experienced > 30% reduction from baseline Safety: Adverse device effects that the investigator considered related to study treatment, device, or procedure, assessed at each follow-up visit Other outcomes: Patient Global Impression of Change (PGIC) 7-point scale (1 = very much improved, 7 = very much worse); PGIC responders defined as participants who indicated that they were "very much improved" or "much improved" at each follow-up assessment

Table 7. Study Characteristics for Randomized Controlled Trials: Shoulder Pain

Citation Setting NCT# (if available)	Population Description	Inclusion and Exclusion Criteria	Intervention Description	Comparator Description	Outcomes measured
Eyigor et al., 2010[16] Turkey	Total N = 50 treatment n = 25, control n = 25 Mean age: 61 years Gender: 14 (28%) male, 36 (72%) female Mean symptom duration: 10.1 months Diagnosis: 21 (42%) supraspinatus tendinopathy, 24 (48%) partial tears of the supraspinatus tendon, 1 (2%) biceps tendinopathy, 4 (8%) acromioclavicular joint osteoarthritis	Inclusion criteria (must meet all): Shoulder pain ≥ 3 months or rotator cuff lesion pathology detected by ultrasonography; age 18 to 80 years Exclusion criteria (excluded if met any criterion): h/o of shoulder surgery or nerve blocks; IA injection in the past 3 months, trauma or PT in past 6 months; severe musculoskeletal impairment, Inflammatory arthritis (e.g., rheumatoid arthritis, ankylosing spondylitis); active synovitis in the joints; advanced osteoarthritis; referred pain in shoulder; neurologic impairment (e.g., stroke, Parkinson disease, paresis); severe cardiovascular disease (e.g., acute myocardial infarction, congestive heart failure, uncontrolled hypertension); unstable chronic or terminal illness (e.g., diabetes mellitus, malignancies); bleeding problems; major depression; severe cognitive impairment	Pulsed RF using NeuroTherm JK25T Medication use was monitored in both groups, with no restrictions described In both groups, exercises for increasing the ROM, strengthening exercises, Codman exercises, pulley exercises, and finger ladder exercises were recommended. Anesthesia: 0.5mL prilocaine to the skin and 3.5mL bupivacaine at ablation site Device placement: Suprascapular notch confirmed by imaging, sensorial stimulation,	Using fluoroscopy, a mixture of 0.5mL triamcinolone, 3.5mL bupivacaine, and 3mL serum physiologic injected with 3.5mL to glenohumeral joint, 2.5mL to subacromial space, and 1mL to acromioclavicular joint Medication use was monitored in both groups, with no restrictions described In both groups, exercises for increasing the ROM, strengthening exercises, Codman exercises, pulley exercises, and finger ladder exercises were recommended.	Time points for all outcome measures: Baseline and weeks 1, 4, and 12 Function: SF-36 and subscales ROM measure with universal goniometer at flexion, extension, abduction, external rotation, and internal rotation, assessed as active and passive Function and Pain: SPADI Pain: Maximum and mean VAS (10 cm) pain during movement, at night, and at rest in the last 2 weeks Safety: Participants evaluated for complications

Citation Setting NCT# (if available)	Population Description	Inclusion and Exclusion Criteria	Intervention Description	Comparator Description	Outcomes measured
			and absence of motor response Ablation: Pulsed RF, 45 V, 200 ms, 42 degree Procedural imaging: Fluoroscopy		Other outcomes: Beck Depression Inventory Medication requirements Patient and physician assessment of effectiveness of treatment: 0=ineffective, 1=minor effects, 2=moderately effective, 3=good results, and 4=very good results
Gofeld et al., 2012[17] Canada	Total N = 22 treatment n = 12, control n = 10 Mean age: 69 years Gender: 5 (23%) male, 17 (77%) female Mean pain duration: 34 months Mean NRS: 6.3 Previous treatment includes opioids: 4 (18%)	Inclusion criteria (must meet all): Shoulder pain > 3 months duration; clinical and imaging confirmation of adhesive capsulitis, tendinosis, arthritis, rotator cuff or capsular tears Exclusion criteria (excluded if met any criterion): Extrinsic source of shoulder pain (e.g., cervical radiculopathy); pain related to bony fracture; postsurgical pain; anticoagulation therapy; major psychopathology; psychiatric illness; ongoing litigation and secondary gain, including those on the workers compensation benefits	Pulsed RF using Baylis Medical RFG-2b No medication restrictions described Anesthesia: 2 mL 1% lidocaine at ablation site Device placement: Suprascapular notch, confirmed with sensory and absence of motor response Ablation:	Sham procedure (anesthesia at ablation site and insertion of probe, but probe connected to a dummy box that made similar sounds as RF generator) No medication restrictions described	Time points for all outcome measures: Baseline and months 1, 3, and 6 Function: None Pain and Function: SPADI Constant–Murley Score Pain: NRS (11-point) Safety : None

Citation Setting NCT# (if available)	Population Description	Inclusion and Exclusion Criteria	Intervention Description	Comparator Description	Outcomes measured
			Pulsed RF, 42°C, 120 second Procedural imaging: Fluoroscopy		Other outcomes: Satisfaction Likert scale index
Korkmaz et al., 2010[18] Turkey	Total N = 40 treatment n = 20, control n = 20 Mean age: 55 years Gender: 12 (30%) male, 28 (70%) female Mean symptom duration:: 9.7 months Diagnosis: 21 (52%) supraspinatus tendinopathy, 18 (45%) partial tears of the supraspinatus tendon, 1 (3%) acromioclavicular joint osteoarthritis	Inclusion criteria (must meet all): Shoulder pain ≥ 3 months; diagnosed with ultrasonography and anterior-posterior X-rays; age 18 to 80 years Exclusion criteria (excluded if met any criterion): h/o shoulder surgery or nerve blocks; IA injection in past 3 months; trauma or PT in past 6 months; inflammatory arthritis (e.g., rheumatoid arthritis, ankylosing spondylitis); active synovitis in the joints; advanced osteoarthritis; referred pain in the shoulder; severe musculoskeletal impairment; neurological impairment (e.g., stroke, Parkinson's disease, paresis); severe cardiovascular disease (i.e., acute myocardial infarction, congestive heart failure, uncontrolled hypertension); unstable chronic or terminal illness	Pulsed RF with NeuroTherm JK25T In both groups, patients allowed to use paracetamol and asked to stop NSAIDs before the study and reminded to avoid using NSAIDs during the study Both groups had one-to-one exercise program, with exercises performed 5 days/week for 4 weeks, lasting at least 30 minutes Anesthesia: Unspecified local anesthesia applied to skin	Transcutaneous electrical nerve stimulation applied with Enraf Nonius Sonoplus 492 on the anterior and posterior aspects of the joint for 20 minutes, 5 times/week for 20 sessions, mean frequency 100 Hz, 15 mA amplitude, 150 µsn In both groups, patients allowed to use paracetamol and asked to stop NSAIDs before the study and reminded to avoid using NSAIDs during the study	Time points for all outcome measures: Baseline and weeks 1, 4 and 12 Function: SF-36 ROM measured by goniometer SPADI disability Function and Pain: SPADI total Pain: VAS (10 cm) SPADI pain Safety: Participants evaluated for complications and side-effects Other outcomes:

Citation Setting NCT# (if available)	Population Description	Inclusion and Exclusion Criteria	Intervention Description	Comparator Description	Outcomes measured
		(e.g., diabetes mellitus, malignancies); bleeding problems; major depression; severe cognitive impairment	Device placement: Suprascapular nerve, confirmed by sensorial stimulation and absence of motor response Ablation: Pulsed RF, 45 V, 200 msn, 42°C Procedural imaging: Fluoroscopy .	Both groups had one-to-one exercise program, with exercises performed 5 days/week for 4 weeks, lasting at least 30 minutes	Amount of paracetamol used
Ökmen et al., 2017[19] Turkey	Total N = 59 treatment n = 30, control n = 29 Mean age: 52 years Gender: 25 (42%) male, 34 (58%) female	Inclusion criteria (must meet all): Chronic shoulder pain due to impingement syndrome; shoulder pain >3 months; age 30 to 75 years Exclusion criteria (excluded if met any criterion): h/o PT and injection therapy in past 6 months; previous surgical procedure and metal implant placement; h/o trauma or fracture; limited shoulder movements > 20%; cervical radicular pain; inflammatory rheumatic disease; malignancy	Pulsed RF using unspecified NeuroTherm device No medication restrictions described Both groups taught ROM, Codman's, stretching, and strengthening exercises, and instructed to perform exercises twice each day with 5 repeats for each exercise	Photobiomodulation therapy using BTL-6000 High Intensity Laser Phase I: pulsed mode, 1064 nm wavelength, 8 Watts, 250 s, 25 Hz, pulse duration time < 150 ms, applied in 2 sessions at 48-h intervals Phase II: 1064 nm wavelength, 7 Watts, 357 s, continuous mode, applied in 5	Time points for all outcome measures: Pretreatment, posttreatment, and months 1, 3, and 6 Function: SPADI disability Function and Pain: SPADI total Pain: VAS (100 point)

Citation Setting NCT# (if available)	Population Description	Inclusion and Exclusion Criteria	Intervention Description	Comparator Description	Outcomes measured
			Anesthesia: 3 ml prilocaine to the cutaneous and subcutaneous tissue Device placement: Suprascapular notch, confirmed with sensorial stimulus and appropriate muscular response Ablation: Pulsed RF, 45V, 200 ms, 42 °C for 240 s Procedural imaging: Fluoroscopy	sessions at 48-h intervals No medication restrictions described Both groups taught ROM, Codman's, stretching, and strengthening exercises, and instructed to perform exercises twice each day with 5 repeats for each exercise	Safety: Observed complications Other outcomes: NHP

Table 8. Study Characteristics for Randomized Controlled Trials: Plantar Fasciitis

Citation Setting NCT# (if available)	Population Description	Inclusion and Exclusion Criteria	Intervention Description	Comparator Description	Outcomes measured
Landsman et al., 2013[20] U.S.	Total N = 17 treatment n = 8, control n = 9 Mean VAS first-step pain: 8.5 Mean VAS initial average pain: 7.3 Mean VAS initial peak pain: 9.2	Inclusion criteria (must meet all): Heel pain at plantar medial aspect of the heel; pain for ≥3 months, rated ≥36/10 at peak intensity, and ≥5/10 average at screening; inadequate relief from ≥3 of prior treatments, including PT, arch supports, shoe modifications, corticosteroid injection, night splint, strapping, stretching exercises, oral NSAIDs or corticosteroid; ability to consent and comply with study regimen; age ≥ 18 years Exclusion criteria (excluded if met any criterion): Previous heel pain surgery; h/o nerve ablation treatment; current or prior calcaneal fracture; fat pad atrophy, calcaneal bursitis, or other heel anomaly; h/o more proximal nerve injury; peripheral nerve neuropathy requiring medication; nonpalpable dorsalis pedis or posterior tibial pulses; heel insensitivity to Semmes-Weinstein monofilament; fibromyalgia; current drug or alcohol treatment; h/o RSD; pregnancy; acetaminophen or other pain	RFA using NeuroTherm NT250 No medication restrictions described Anesthesia: 1 ml 2% lidocaine, antero-medial heel and 1ml 0.5% bupivacaine at ablation site Device placement: Confirmed with sensory stimulation and absence of motor response (specific nerve target not named) Ablation: 90°C, 60s., at 2 adjacent sites, antero-medial heel inferior to medical calcaneus Procedural imaging: None	Sham comparator (anesthesia at ablation site and probe cannula without insertion of electrode, device timer turned on to replicate sounds) No medication restrictions described	Time points for all outcome measures: Baseline and weekly for 4 weeks Function: None Pain: VAS (10 point), first morning step VAS, overall peak pain VAS, average pain Safety: Reported events Other outcomes: None

Citation Setting NCT# (if available)	Population Description	Inclusion and Exclusion Criteria	Intervention Description	Comparator Description	Outcomes measured
		medication intolerance; local anesthesia allergy; long-term oral corticosteroid treatment			
Wu et al., 2017[21] Taiwan	Total N = 36 patients, 40 feet treatment n = 18 patients, n = 20 feet control n = 18 patients, n = 20 feet Mean age: 47 years Gender: 19 (47%) male, 21 (53%) female Mean body weight: 68 kG Duration of symptoms: 9.8 months Mean VAS first-step: 6.3 Mean VAS overall pain: 6.0 Mean AOFAS ankle-hindfoot score: 58.0 Mean plantar fascia thickness: 55.9 mm	Inclusion criteria (must meet all): Active plantar fasciitis for >6 months; tenderness at the origin of the plantar fascia on the calcaneal tuberosity; plantar fascia thickness >4 mm as measured by ultrasonography; lack of relief with conservative therapy (i.e., rest, orthoses, stretching, strengthening exercises, analgesic agents, steroid injections, or extracorporal shockwave therapy) Exclusion Criteria (excluded if met any criterion): h/o surgery on the plantar fascia or heel or platelet-rich plasma injection; extracorporal shockwave therapy or local steroid injections in past 3 months; inflammatory arthritis; neurologic defects of the foot; peripheral vascular disease; leg length discrepancies; coagulopathy; infection; cancer; pregnancy	Pulsed RF using unspecified device No patients in either group reported using medications during the study Anesthesia: None indicated for treatment group Device placement: Posterior tibial nerve (not confirmed by sensory or motor testing) Ablation: Pulsed RF stimulation, 120 seconds at 2Hz, with a 30-ms pulse width at 42°C Procedural imaging: Ultrasound	Sham procedure and 0.5mL of 2% lidocaine injected to the posterior tibial nerve and (ensuring blinding by turning off sound of RF generator, covering participant's head, and increasing the volume of music in room) No patients in either group reported using medications during the study	Time points for all outcome measures: Baseline and weeks 1, 4, 8, and 12 Function: None Function and Pain: AOFAS ankle-hindfoot score Pain: VAS (10 point) first-step pain VAS heel pain over the course of the day during the previous week Safety: Participants observed for 30 minutes after treatment Other outcomes: Plantar fascia thickness (measured by

Citation Setting NCT# (if available)	Population Description	Inclusion and Exclusion Criteria	Intervention Description	Comparator Description	Outcomes measured
					ultrasonography - mean of 3 thickness measurements of the proximal origin of the plantar fascia into the calcaneal tubercle

Table 9. Evidence Table for Randomized Controlled Trials: Conventional RFA for Knee Pain

Part 1

Citation N	VAS-pain (treatment vs. control)	WOMAC Total (treatment vs. control)	WOMAC Pain (treatment vs. control)	WOMAC Stiffness (treatment vs. control)	WOMAC Difficulties or Function (treatment vs. control)	NRS (treatment vs. control)
Choi et al., 2011[10] N = 35	Change in VAS from baseline to week 1 (MD ± SD): 41.2 ± 18.3 vs. 33.7 ± 13.8; *P* = .19 Change in VAS from baseline to week 4 (MD ± SD): 44.7 ± 17.7 vs. 4.2 ± 16.1; *P* < .001 Change in VAS from baseline to week 12 (MD ± SD): 35.9 ± 23.2 vs. -1.1 ± 6.5; *P* < .001 At least 50% knee pain relief at 12 weeks: 10 (59%) vs. 0 (0%); *P* < .001	NR	NR	NR	NR	NR
El-Hakeim, et al. 2018[12] N = 60	VAS (mean ± SD) Baseline: 7.1 ± 0.2 vs. 6.9 ± 0.2 (*P* = .62) Week 2: 2.5 ± 0.3 vs. 3.6 ± 0.3 (*P* = .004)	WOMAC total (mean ± SD) Baseline: 93.5 ± 1.9 vs. 54.1 ± 3.0 (*P* = .09)	WOMAC pain (mean ± SD) Baseline: 19.7 ± 0.4 vs. 11.3 ± 0.6 (*P* = .78)	WOMAC stiffness (mean ± SD) Baseline: 7.9 ± 0.3 vs. 4.6 ± 0.3 (*P* = .07)	WOMAC difficulties (mean ± SD) Baseline: 66.0 ± 1.4 vs. 37.5 ± 2.2 (*P* = .15)	NR

Citation N	VAS-pain (treatment vs. control)	WOMAC Total (treatment vs. control)	WOMAC Pain (treatment vs. control)	WOMAC Stiffness (treatment vs. control)	WOMAC Difficulties or Function (treatment vs. control)	NRS (treatment vs. control)
	Month 3: 2.8 ± 0.5 vs. 4.9 ± 0.2 (*P* < .001) Month 6: 3.1 ± 0.3 vs. 5.7 ± 0.3 (*P* < .001)	Week 2: 21.7 ± 4.4 vs. 30.9 ± 2.5 (*P* = .17) Month 3: 24.2 ± 4.3 vs. 37.1 ± 1.9 (*P* = .1) Month 6: 33.1 ± 4.1 vs. 43.5 ± 2.0 (*P* < .001)	Week 2: 3.7 ± 0.9 vs. 3.8 ± 0.4 (*P* = .1) Month 3: 4.6 ± 0.9 vs. 4.5 ± 0.3 (*P* = .01) Month 6: 6.6 ± 0.9 vs. 7.9 ± 0.5 (*P* < .001)	Week 2: 3.6 ± 0.3 vs. 3.0 ± 0.3 (*P* = .5) Month 3: 3.7 ± 0.4 vs. 3.1 ± 0.2 (*P* = .004) Month 6: 3.6 ± 0.4 vs. 3.2 ± 0.2 (*P* < .001)	Week 2: 14.4 ± 3.2 vs. 24.1 ± 1.8 (*P* = .36) Month 3: 15.9 ± 3.2 vs. 29.4 ± 1.6 (*P* = .16) Month 6: 23.0 ± 3 vs. 32.4 ± 1.9 (*P* = .007)	
Qudsi-Sinclair et al., 2016[13] N = 28	NR	NR	NR	NR	NR	We calculated these mean differences, 95% confidence intervals, and two-tailed p-values Change in NRS score from baseline to month 1: MD, 0.73; 95% CI, -0.59 to 2.00; *P* = .27 Change in NRS score from baseline to month 3:

Citation N	VAS-pain (treatment vs. control)	WOMAC Total (treatment vs. control)	WOMAC Pain (treatment vs. control)	WOMAC Stiffness (treatment vs. control)	WOMAC Difficulties or Function (treatment vs. control)	NRS (treatment vs. control)
						MD, -0.90; 95% CI, -2.19 to 0.39; *P* = .16 Change in NRS score from baseline to month 6: MD, -1.03; 95% CI, -1.98 to -0.08; *P* = .03 Change in NRS score from baseline to month 12: MD, -1.32; 95% CI, -2.68 to 0.04; *P* = .06
Ray et al., 2018[30] N = 24	VAS (mean ± SD) Baseline: 8.25 ± 0.62 vs. 8.16 ± 0.72 (*P* = .75) Week 1: 1.91 ± 1.64 vs. 4.66 ± 1.55 (*P* < .001) Week 4: 1.75 ± 1.28 vs. 5.16 ± 1.80 (*P* < .001) Week 12: 1.83 ± 1.52 vs. 6.33 ± 1.82 (*P* < .001)	WOMAC Total (mean ± SD) Baseline: 81.15 ± 4.40 vs. 80.46 ± 3.56 (*P* = .68) Week 1: 11.45 ± 4.68 vs. 44.35 ± 11.83 (*P* < .0001) Week 4: 12.24 ± 4.31 vs. 52.17 ± 17.85 (*P* < .0001) Week 12: 12.06 ± 4.03 vs. 59.93 ± 15.99 (*P* < .0001)	NR	NR	NR	NR

Citation N	VAS-pain (treatment vs. control)	WOMAC Total (treatment vs. control)	WOMAC Pain (treatment vs. control)	WOMAC Stiffness (treatment vs. control)	WOMAC Difficulties or Function (treatment vs. control)	NRS (treatment vs. control)
Sari et al., 2016[15] N = 73	VAS pain at baseline (unclear if mean or median): 8 vs. 8 (*P* = NR) VAS pain at month 1 (unclear if mean or median): 2 vs. 5 (*P* < .001) VAS pain at month 3 (unclear if mean or median): 4 vs. 5.5 (*P* < .001)	WOMAC Total at baseline (mean ± SD): 56.32 ± 9.13 vs. 47.19 ± 11.98 (*P* = .001) WOMAC Total at month 1 (mean ± SD): 29.16 ± 8.66 vs. 37.53 ± 11.46 (*P* = .001) WOMAC Total at month 3 (mean ± SD): 39.70 ± 8.89 vs. 42.33 ± 10.95 (*P* = .26) Note: data are for specified time points, and not changes from baseline; there were substantial baseline differences that are not accounted for by the analysis	WOMAC Pain at baseline (median [25 to 75 percentiles]): 12 (10.75 to 14.25) vs. 10 (8 to 12.5); *P* = .001 WOMAC Pain at month 1 (median [25 to 75 percentiles]): 6 (5 to 8) vs. 7 (5 to 9); *P* = .27 WOMAC Pain at month 3 (median [25 to 75 percentiles]): 8 (7.75 to 9) vs. 9 (6.5 to 10); *P* = .639 Note: data are for specified time points, and not changes from baseline; there were substantial baseline differences that	WOMAC Stiffness at baseline (median [25 to 75 percentiles]): 2 (1.5 to 4) vs. 4 (1 to 5); *P* = .25 WOMAC Stiffness at month 1 (median [25 to 75 percentiles]): 1 (0 to 2) vs. 2 (0 to 3,5); *P* = .06 WOMAC Stiffness at month 3 (median [25 to 75 percentiles]): 2 (0 to 3) vs. 3 (1.5 to 5); *P* = .007 Note: data are for specified time points, and not changes from baseline; there were substantial baseline differences that are not accounted for by the analysis	WOMAC Function at baseline (median [25 to 75 percentiles]): 41 (36.75 to 46) vs. 36 (26 to 39); *P* < .001 WOMAC Function at month 1 (median [25 to 75 percentiles]): 24 (17 to 27) vs. 29.5 (22 to 35); *P* = .003 WOMAC Function at month 3 (median [25 to 75 percentiles]): 31 (25.75 to 34.25) vs. 30 (26 to 34.5); *P* = .51 Note: data are for specified time points, and not changes from baseline; there were substantial baseline differences that are not accounted for by the analysis	NR

Citation N	VAS-pain (treatment vs. control)	WOMAC Total (treatment vs. control)	WOMAC Pain (treatment vs. control)	WOMAC Stiffness (treatment vs. control)	WOMAC Difficulties or Function (treatment vs. control)	NRS (treatment vs. control)
			are not accounted for by the analysis			

Table 9. Evidence Table for Randomized Controlled Trials: Conventional RFA for Knee Pain

Part 2

Citation N	OKS (treatment vs. control)	KSS (treatment vs. control)	GPE or PGIC (treatment vs. control)	SF-36 (treatment vs. control)	Satisfaction (treatment vs. control)	Pain Med Use (treatment vs. control)	Adverse Events
Choi et al., 2011[10] N = 38	Change in OKS from baseline to week 1 (MD ± SD): 16.2 ± 9.5 vs. 12.4 ± 4.3; *P* = .296 Change in OKS from baseline to week 4 (MD ± SD): 14.1 ± 9.7 vs. 2.3 ± 4.8; *P* < .001 Change in OKS from baseline to week 12 (MD ± SD): 12.4 ± 10.7 vs. 0.3 ± 1.3; *P* < .001	NR	NR	NR	Patient satisfaction with GPE Week 1: 5.5 ± 0.7 vs. 5.3 ± 0.8; *P* = .46 Week 4: 5.9 ± 0.9 vs. 4.3 ± 0.8; *P* < .001 Week 12: 5.5 ± 1.1 vs. 3.7 ± 0.5; *P* < .001	NR	Periosteal pain during intervention procedure reported by several participants, but authors did not provide more detail. 2 RF and 1 control participants left study (authors reported these losses were not related to intervention status)
El-Hakeim, 2018[12] N = 60	NR	NR	NR	NR	Patient satisfaction was equivalent for the 2 groups at baseline and week 2	No participants in treatment group needed supplementary analgesia during the follow-up period; not	No adverse events reported

Citation N	OKS (treatment vs. control)	KSS (treatment vs. control)	GPE or PGIC (treatment vs. control)	SF-36 (treatment vs. control)	Satisfaction (treatment vs. control)	Pain Med Use (treatment vs. control)	Adverse Events
					Patient satisfaction at month 3 (mean): 3.6 vs. 2.5 (*P* < .05) Patient satisfaction at month 6 (mean): 3.4 vs. 1.6 (*P* < .05)	reported for control group	
Qudsi-Sinclair et al., 2016[13] N = 28	*We calculated these mean differences, 95% confidence intervals, and two-tailed p-values* Change in OKS score from baseline to month 1: MD, -6.01; 95% CI, -9.48 to -2.54; *P* = .001 Change in OKS score from baseline to month 3: MD, -5.51; 95% CI, -9.54 to -1.48; *P* = .009	*We calculated these mean differences, 95% confidence intervals, and two-tailed p-values* Change in KSS score from baseline to month 1: MD, -8.40; 95% CI, -11.81 to -4.99; *P* < .0001 Change in KSS score from baseline to month 3: MD, -10.20; 95% CI, -14.47 to -5.93; *P* < .0001	PGI-I at month 6 - very much or much better: 9 (65%) vs. 5 (35%) (*P* = NR) PGI-I at year 1- very much or much better: 6 (43%) vs. 3 (21%) (*P* = NR)	*We calculated these mean differences, 95% confidence intervals, and two-tailed p-values* Change in SF-36 score from baseline to month 3: MD, 10.49; 95% CI, 2.14 to 18.84; *P* = .02 Change in SF-36 score from baseline to month 12: MD, 15.38; 95% CI, 9.39 to 21.37; *P* <.0001	NR	Opioid use Baseline: 7 (50%) vs. 9 (64%) (*P* = NR) Month 6: 3 (21%) vs. 5 (36%) (*P* = NR) Month 12: 2 (14%) vs. 3 (21%) (*P* = NR)	Pain when RF cannula touched the periosteum in some participants

Citation N	OKS (treatment vs. control)	KSS (treatment vs. control)	GPE or PGIC (treatment vs. control)	SF-36 (treatment vs. control)	Satisfaction (treatment vs. control)	Pain Med Use (treatment vs. control)	Adverse Events
	Change in OKS score from baseline to month 6: MD, -2.93; 95% CI, -6.60 to 0.74; *P* = .11 Change in OKS score from baseline to month 12: MD, 1.99; 95% CI, -2.08 to 6.06; *P* = .32	Change in KSS score from baseline to month 6: MD, -6.44; 95% CI, -10.77 to -2.11; *P* = .005 Change in KSS score from baseline to month 12: MD, -1.63; 95% CI, -6.03 to 2.77; *P* = .45					
Ray et al., 2018[30] N = 24	NR	NR	NR	NR	NR	NR	No adverse effects reported
Sari et al., 2016[15] N = 73	NR	NR	NR	NR	NR	NR	No adverse events or complications reported

Table 10. Evidence Table for Randomized Controlled Trials: Cooled RFA for Knee Pain

Part 1

Citation N	VAS Pain (treatment vs. control)	WOMAC Total (treatment vs. control)	WOMAC Pain (treatment vs. control)	WOMAC Stiffness (treatment vs. control)	WOMAC Difficulties or Function (treatment vs. control)	NRS (treatment vs. control)
Davis et al., 2018[11] N = 151	NR	NR	NR	NR	NR	Change in difference in group means for NRS from baseline to month 1 (n = 136) (MD ± SD): -4.2 ± 2.5 vs. -3.3 ± 2.3; *P* = .02 Change in difference in group means, for NRS from baseline to month 3 (n = 133) (MD ± SD): -4.4 ± 2.3 vs. -1.9 ± 2.1; *P* < .0001 Change in difference in group means for NRS from baseline to month 6 (n = 126) (MD ± SD): -4.9 ± 2.4 vs. -1.3 ± 2.2; *P* < .0001 Participants with ≥50% reduction in NRS score at month 6 (n = 126): 74% (95% CI, 62.9–85.4) vs. 16% (95% CI, 7.4–24.9); *P* < .0001

Table 10. Evidence Table for Randomized Controlled Trials: Cooled RFA for Knee Pain

Part 2

Citation N	OKS (treatment vs. control)	KSS (treatment vs. control)	GPE or PGIC (treatment vs. control)	SF-36 (treatment vs. control)	Satisfaction (treatment vs. control)	Pain Med Use (treatment vs. control)	Adverse Events
Davis et al., 2018[11] N = 151	OKS at baseline (n = 138) (Mean ± SD): 16.7 ± 4 vs. 16.9 ± 5 Difference in group means at baseline: −0.2 (95% CI, −1.8 to 1.3; *P* = .83 OKS at month 1 (n = 136) (Mean ± SD): 33.3 ± 9.2 vs. 29.4 ± 8.5 Difference in group means at month 1: 4 (95% CI, 0.98 to 7.0; *P* = .004)	NR	Proportion of participants reporting GPE improvement at month 1 (n = 136): 79% (95% CI, 69.1 to 89.1) vs. 67% (95% CI, 55.3 to 78.1); *P* = .1 Proportion of participants reporting GPE improvement at month 3 (n = 133): 80% (95% CI, 70.0 to 90.0) vs. 31% (95% CI, 19.6 to 42.1); *P* < .0001) Proportion of participants reporting GPE improvement at month 6 (n = 126):	NR	NR	Opioid use at baseline: 25% (95% CI, 15.0 to 35.0) vs. 35% (95% CI, 23.6 to 45.7) Average total daily dose (morphine equivalence) at baseline (n = 138) (MD ± SD): 28 ± 28.9 mg vs. 27.2 ± 22.1 mg; *P* = .75 No statistically significant differences between groups in change in opioid dosage at months 1, 3, and 6 (*P* = NR) Use of NSAIDs at baseline (n = 138): 43% (95% CI, 32.0 to 54.8 vs. 45% (95% CI, 33.8 to 56.9); *P* = NR	61 adverse events reported in treatment group and 65 reported in control group Percentage of adverse events that were unrelated or unlikely related to study intervention 77% vs. 97% (*P* = NR) 3 participants in the treatment group experienced 4 serious adverse events: *Acute respiratory failure *Severe acute asthma *Exacerbation of asthma *Pyelonephritis 7 participants in the control group experienced 8 serious adverse events: *Death *Heart attack (2) *Opioid overdose *Worsening of hiatal hernia *Gastric volvulus *Nausea and vomiting

Citation N	OKS (treatment vs. control)	KSS (treatment vs. control)	GPE or PGIC (treatment vs. control)	SF-36 (treatment vs. control)	Satisfaction (treatment vs. control)	Pain Med Use (treatment vs. control)	Adverse Events
	OKS at month 3 (n = 133) (Mean ± SD): 34.6 ± 8.3 vs. 24.6 ± 7.6 Difference in group means at month 3: 10 (95% CI, 7.28 to 12.7; *P* < .0001) OKS at month 6 (n = 126) (Mean ± SD): 35.7 ± 8.8 vs. 22.4 ± 8.5 Difference in group means at month 6 (n = 126): 13.3 (95% CI, 10.28 to 16.4; *P* < .0001)		91% (95% CI, 83.9 to 98.8) vs. 24% (95% CI, 13.4 to 34.4); *P* < .0001)			Mean change in NSAIDs dosage from baseline to month 1 (n = 136) (MD ± SD): 0 ± 0 mg vs. 94.8 ± 354.5 mg; *P* = .08 Mean change in NSAIDs dosage from baseline to month 3 (n = 133) (MD ± SD): −16.1 ± 89.8 mg vs. 64.7 ± 201.4 mg; *P* = .03 Mean change in NSAIDs dosage from baseline to month 6 (n = 126) (MD ± SD): −34.5 ± 128.9 mg vs. 135.5 ± 391 mg; *P* = .02	*Abdominal pain secondary to small bowel obstruction None of the serious adverse events were related to the study treatments

Table 11. Evidence Table for Randomized Controlled Trials: Cryoneurolysis for Knee Pain

Part 1

Citation	VAS-pain (treatment vs. control)	WOMAC Total (treatment vs. control)	WOMAC Pain (treatment vs. control)	WOMAC Stiffness (treatment vs. control)	WOMAC Difficulties or Function (treatment vs. control)	NRS (treatment vs. control)
Radnovich et al., 2017[14] N = 180 (2:1 randomization, treatment: control)	Difference in least squares mean change in VAS pain from baseline to Day 30 (n = 176): -12.25 (95% CI, -21.16 to -3.35; *P* = .007) Difference in least squares mean change in VAS pain from baseline to Day 60 (n = 170): -6.09 (95% CI, -15.11 to 2.94; *P* = .19) Difference in least squares mean change in VAS pain from baseline to Day 90 (n = 169: -6.32 (95% CI, -15.66 to 3.01; *P* = .18) Difference in least squares mean change in VAS pain from baseline	Difference in least squares mean change in WOMAC total from baseline to Day 30 (n = 176): -30.52 (95% CI, -48.52 to -12.53; *P* = .001) Difference in least squares mean change in WOMAC total from baseline to Day 60 (n = 170): -19.47 (95% CI, -37.64 to -1.30; *P* = .036) Difference in least squares mean change in WOMAC total from baseline to Day 90 (n = 169): -23.80 (95% CI, -42.02 to -5.57; *P* = .011) Difference in least squares mean change in WOMAC total from	Difference in least squares mean change in WOMAC pain from baseline to Day 30 (n = 176): -7.12 (95% CI, -11.01 to -3.22; *P* = .0004) Difference in least squares mean change in WOMAC pain from baseline to Day 60 (n = 170): -4.65 (95% CI, -8.48 to -01.82; *P* = .018) Difference in least squares mean change in WOMAC pain from baseline to Day 90 (n = 169): -5.67 (95% CI, -9.69 to -1.64; *P* = .006) Difference in least squares mean change in	Difference in least squares mean change in WOMAC stiffness from baseline to Day 30 (n = 176): -2.32 (95% CI, -3.97 to -0.68; *P* = .006) Difference in least squares mean change in WOMAC stiffness from baseline to Day 60 (n = 170): -1.64 (95% CI, -3.36 to 0.08; *P* = .062) Difference in least squares mean change in WOMAC stiffness from baseline to Day 90 (n = 169): -1.83 (95% CI, -3.50 to -0.15; *P* = .033) Difference in least squares mean change in WOMAC stiffness from	Difference in least squares mean change in WOMAC difficulties from baseline to Day 30 (n = 176): -21.30 (95% CI, -34.02 to -8.57; *P* = .001) Difference in least squares mean change in WOMAC difficulties from baseline to Day 60 (n = 170): -13.14 (95% CI, -26.43 to -0.39; *P* = .044) Difference in least squares mean change in WOMAC difficulties from baseline to Day 90 (n = 169): -15.89 (95% CI, -28.93 to -2.86; *P* = .017) Difference in least squares mean change in WOMAC difficulties from	NR

Citation	VAS-pain (treatment vs. control)	WOMAC Total (treatment vs. control)	WOMAC Pain (treatment vs. control)	WOMAC Stiffness (treatment vs. control)	WOMAC Difficulties or Function (treatment vs. control)	NRS (treatment vs. control)
	to Day 120 (n = 167): -4.90 (95% CI, -13.99 to 4.20; *P* = .29) VAS pain responders (participants who experienced > 30% reduction from baseline) Day 30 (n = 176): 71.1% vs. 50.9%; *P* = .012 Day 60 (n = 170): 71.1% vs. 61.0%; *P* = .18 Day 90 (n = 169): 69.4% vs. 62.7%; *P* = .40 Day 120 (n = 167): 87.5% vs. 61.2%; *P* = .51	baseline to Day 120 (n = 167): -13.01 (95% CI, -31.32 to 5.31; *P* = .163) WOMAC total responders (participants who experienced > 30% reduction from baseline) Day 30 (n = 176): 72.7% vs. 44.1%; *P* = .0003 Day 60 (n = 170): 71.1% vs. 55.9%; *P* = .03 Day 90 (n = 169): 52.5% vs. 52.5%; *P* = .007 Day 120 (n = 167): 69.4% vs. 62.7%; *P* = .40	WOMAC pain from baseline to Day 120 (n = 167): -2.82; 95% CI, -6.77 to 1.13; *P* = .161 WOMAC pain responders (participants who experienced > 30% reduction from baseline) Day 30 (n = 176): 72.7% vs. 47.5%; *P* = .0015 Day 60 (n = 170): 71.9% vs. 55.9%; *P* = .043 Day 90 (n = 169): 72.7% vs. 55.9%; *P* = .028 Day 120 (n = 167): 69.4% vs. 62.7%; *P* = .40	baseline to Day 120 (n = 167): -1.27 (95% CI, -3.00 to 0.47; *P* = .15)	baseline to Day 120 (n = 167): -9.16 (95% CI, -22.04 to 3.72; *P* = .16)	

Table 11. Evidence Table for Randomized Controlled Trials: Cryoneurolysis for Knee Pain

Part 2

Citation	OKS (treatment vs. control)	KSS (treatment vs. control)	GPE or PGIC (treatment vs. control)	SF-36 (treatment vs. control)	Satisfaction (treatment vs. control)	Pain Med Use (treatment vs. control)	Adverse Events
Radnovich et al., 2017[14] N = 180	NR	NR	No statistically significant differences between groups in the proportion of PGIC responders at 30, 60, 90, or 120 days PGIC for treatment group at day 120 (n = 167): Very much improved 25 (22.5)% Much improved 34 (30.6%) Minimally improved 21 (18.9%) No change 16 (14.4%) Minimally worse 9 (8.1%)	No statistically significant differences in change in SF-36 total There were no statistically significant differences between groups on the SF-36 at baseline or at 30, 60, 90, or 120 days SF-36 scores at Day 120 (n = 167) (mean ± SD) Physical Component: 42.6 ± 10.24 vs. 39.7 ± 9.37 (*P* = NR) Mental Component: 52.5 ± 9.77 vs. 53.9 ± 7.69 (*P* = NR)	NR	NR	243 adverse events in 113 participants: 4 were serious adverse events, all unrelated to the device or procedure: 1 control group participant had a pulmonary embolism 1 treatment group participant had 2 myocardial infarctions, resulting in death 1 treatment group participant diagnosed with malignant lung neoplasm 84 adverse events were possibly or probably related to the device or procedure Number of device- or procedure-related adverse events was similar in the two groups 1 device- or procedure-related AE was rated as severe: sham treatment participant experienced administration site altered sensation

Citation	OKS (treatment vs. control)	KSS (treatment vs. control)	GPE or PGIC (treatment vs. control)	SF-36 (treatment vs. control)	Satisfaction (treatment vs. control)	Pain Med Use (treatment vs. control)	Adverse Events
			Much worse 5 (5.4%) Very much worse 0 (0%) PGIC for control group at day 120 (n = 167): Very much improved 9 (16.1%) Much improved 18 (32.1%) Minimally improved 11 (19.6%) No change 13 (23.2%) Minimally worse 3 (5.4%) Much worse 2 (3.6%) Very much worse 0 (0%) Data for all time points presented in the study's supplemental appendix	Physical Function: 56.5 ± 27.15 vs. 47.9 ± 26.62 (*P* = NR) Role-Physical: 57.0 ± 41.99 vs. 51.8 ± 41.52 (*P* = NR) Bodily Pain: 56.2 ± 22.89 vs. 53.4 ± 20.04 (*P* = NR) General Health: 73.9 ± 16.03 vs. 71.4 ± 15.23 (*P* = NR) Vitality: 60.0 ± 17.04 vs. 61.0 ± 16.55 (*P* = NR) Social Functioning: 83.7 ± 21.04 vs. 82.6 ± 18.41 (*P* = NR) Role-Emotional: 76.3 ± 38.77 vs. 74.4 ± 38.13 (*P* = NR) Mental Health: 72.4 ± 15.14 vs. 74.6 ± 10.58 (*P* = NR) Health Transition: 2.4 ± 0.88 vs. 2.6 ± 0.81 (*P* = NR)			Adverse events related to study device or procedure Any adverse event: 47 (47%) vs. 27 (46%) (*P* = NR) Bruising: 4 (3%) vs. 2 (3%) (*P* = NR) Altered sensation: (3) 2% vs. 2 (3%) (*P* = NR) Local pain: 9 (7%) vs. 4 (6%) (*P* = NR) Tingling: 3 (2%) vs. 1 (2%) (*P* = NR) Swelling: 3 (2%) vs. 3 (5%) (*P* = NR) Numbness: 18 (15%) vs. 1 (1%) (*P* = NR) Tenderness upon palpation: 14 (12%) vs. 8 (14%) (*P* = NR) Itching: 2 (2%) vs. 0 (0%) (*P* = NR) Redness: 0 (0%) vs. 2 (3%) (*P* = NR) Knee pain: 0 (0%) vs. 3 (5%) (*P* = NR) Pain aggravated: 0 (0%) vs. 1 (2%) (*P* = NR) Vasovagal reaction: 1 (1%) vs. 0 (0%) (*P* = NR) Side-effects Altered sensation: 25 (21%) vs. 11 (19%) (*P* = NR) Bruising: 93 (77%) vs. 31 (52%) (*P* = NR)

Citation	OKS (treatment vs. control)	KSS (treatment vs. control)	GPE or PGIC (treatment vs. control)	SF-36 (treatment vs. control)	Satisfaction (treatment vs. control)	Pain Med Use (treatment vs. control)	Adverse Events
				Data for all time points presented in the study's supplemental appendix			Crusting: 6 (5%) vs. 3 (5%) (*P* = NR) Hyperpigmentation: 1 (1%) vs. 0 (0%) (*P* = NR) Itching: 7 (6%) vs. 2 (3%) (*P* = NR) Local pain: 26 (22%) vs. 1 (19%) (*P* = NR) Numbness: 63 (52%) vs. 32 (54%) (*P* = NR) Redness: 50 (41%) vs. 24 (41%) (*P* = NR) Swelling: 49 (40%) vs. 16 (27%) (*P* = NR) Tenderness on palpation: 46 (38%) vs. 23 (39%) (*P* = NR) Tingling: 17 (14%) vs. 2 (3%) (*P* = NR)

Table 12. Evidence Table for Randomized Controlled Trials: Shoulder Pain

Part 1

Citation N	VAS-pain (treatment vs. control)	NRS (treatment vs. control)	ROM (treatment vs. control)	SPADI (treatment vs. control)	NHP (treatment vs. control)	SF-36 (treatment vs. control)
Eyigor et al., 2010[16] N = 50	VAS pain at night (mean ± SD) Baseline: 6.5 ± 1.5 vs. 6.3 ± 1.7 (*P* ≥ .05) Week 1: 4.6 ± 2.0 vs. 2.4 ± 2.0 (*P* < .05) Week 4: 2.7 ± 1.4 vs. 1.6 ± 1.1 (*P* < .05) Week 12: 1.65 ± 0.7 vs. 1.2 ± 0.9 (*P* < .05) VAS pain at rest (mean ± SD) Baseline: 3.8 ± 1.5 vs. 3.75 ± 1.4 (*P* ≥ .05) Week 1: 2.4 ± 1.9 vs. 1.4 ± 1.3 (*P* < .05) Week 4: 1.2 ± 1.2 vs. 0.6 ± 0.5 (*P* < .05) Week 12: 0.5 ± 0.5 vs. 0.2 ± 0.4 (*P* ≥ 0) VAS pain during movement (mean ± SD) Baseline: 6.3 ± 1.4 vs. 6.3 ± 1.4 (*P* ≥ .05)	NR	No significant difference between groups on improvement of ROM measured with universal goniometer (active and passive flexion, active and passive abduction, active and passive external rotation, and active and passive internal rotation) from baseline to weeks 1, 4, and 12 (*P* ≥ .05); statistical significance of baseline differences not reported Active abduction ROM (mean ± SD) Baseline: 116.0 ± 21.1vs. 110.5 ± 28.2 (*P* ≥ .05) Week 1: 131.0 ± 23.9 vs. 138.5 ± 26.9 (*P* < .05) Week 4: 149.0 ± 19.7 vs. 157.7 ± 18.1(*P* < .05) Passive abduction ROM Baseline: 139.7 ± 19.7 vs. 132.5 ± 24.0 (*P* ≥ .05)	SPADI Disability (mean ± SD) Baseline: 55.2 ± 19.4 vs. 53.4 ± 17.1 (*P* = NR) Week 1: 35.9 ± 18.7 vs. 31.3 ± 22.6 (*P* = NR) Week 4: 19.6 ± 13.8 vs. 16.5 ± 12.7 (*P* = NR) Week 12: 9.9 ± 7.9 vs. 10.8 ± 9.3 (*P* = NR) SPADI pain (mean ± SD) Baseline: 59.1 ± 17.6 vs. 62.4 ± 14.6 (*P* ≥ .05) Week 1: 41.1 ± 19.3 vs. 28.0 ± 17.6 (*P* < .05) Week 4: 25.1 ± 15.4 vs. 18.1 ± 12.7 (*P* < .05) Week 12: 15.2 ± 8.7 vs. 10.1 ± 10.2 (*P* < .05) SPADI Total (mean ± SD) Baseline: 120.3 ± 25.7 vs. 115.6 ± 25.5 (*P* ≥ .05) Week 1: 81.2 ± 31.4 vs. 58.5 ± 36.8 (*P* < .05)	NR	SF-36 scores at week 12 (mean ± SD) Physical functioning: 67.5 ± 17.1 vs. 68.5 ± 17.4 (*P* ≥ .05) Physical role: 53.7 ± 24.7 vs. 51.2 ± 36.7 (*P* ≥ .05) Bodily pain: 62.7 ± 15.1 vs. 67.4 ± 17.5 (*P* ≥ .05) General health: 56.3 ± 16.8 vs. 51.0 ± 19.3 (*P* ≥ .05) Vitality: 54.7 ± 9.5 vs. 51.5 ± 12.1 (*P* ≥ .05) Social functioning: 72.5 ± 17.9 vs. 69.2 ± 24.6 (*P* ≥ .05) Emotional role: 28.2 ± 18.3 vs. 59.2 ± 23.4 (*P* ≥ .05) Mental health: 53.6 ± 14.4 vs. 58.4 ± 12.8 (*P* ≥ .05)

Citation N	VAS-pain (treatment vs. control)	NRS (treatment vs. control)	ROM (treatment vs. control)	SPADI (treatment vs. control)	NHP (treatment vs. control)	SF-36 (treatment vs. control)
	Week 1: 4.3 ± 2.1 vs. 3.0 ± 1.8 (*P* < .05) Week 4: 2.7 ± 1.4 vs. 1.9 ± 1.0 (*P* ≥ .05) Week 12: 1.6 ± 0.7 vs. 1.3 ± 0.8 (*P* ≥ .05)		Week 1: 149.5 ± 18.9 vs. 157.2 ± 20.6 (*P* = < .05) Week 4: 162.7 ± 14.5 vs. 170.2 ± 11.2 (*P* = < .05)	Week 4: 46.9 ± 24.8 vs. 37.1 ± 24.9 (*P* < .05) Week 12: 26.7 ± 14.5 vs. 22.9 ± 19.8 (*P* < .05)		
Gofeld et al., 2012[17] N = 22	NR	NRS Baseline: 6.3 vs. 6.4 (*P* = NR) Month 1 (n = 22): 3.1 vs. 5.1 (*P* = NR) Month 3 (n = 16): 2.7 vs. 4.3 (*P* = NR) Month 6 (n = 13): 2.9 vs. 5.5 (*P* = NR) No statistically significant differences between groups found over time in NRS, using repeated measures ANOVA	NR	SPADI Baseline: 56.2 vs. 50.8 (*P* = NR) Month 1 (n = 22): 41.2 vs. 47.1 (*P* = NR) Month 3 (n = 16): 35.2 vs. 45.5 (*P* = NR) Month 6 (n = 13): 36.4 vs. 44.5 (*P* = NR) No statistically significant differences between groups found over time in SPADI, using repeated measures ANOVA	NR	NR
Korkmaz et al., 2010[18] N = 40	VAS at night (mean ± SD) Baseline: 6.3 ± 1.7 vs. 6.2 ± 1.4 (*P* ≥ .05) Week 1: 4.4 ± 2.0 vs. 4.6 ± 1.8 (*P* ≥ .05) Week 4: 2.7 ± 1.2 vs. 3.0 ± 1.41 (*P* ≥ .05) Week 12: 1.8 ± 0.9 vs. 2.10 ± 0.96 (*P* ≥ .05)	NR	No significant differences between groups at any time point (*P* ≥ .05) for active and passive flexion, active and passive abduction, active and passive external rotation, and active and passive internal rotation	SPADI disability (mean ± SD) Baseline: 55.3 ± 19.4 vs. 51.3 ± 16.1 (*P* ≥ .05) Week 1: 35.9 ± 18.7 vs. 40.8 ± 18.2 (*P* ≥ .05) Week 4: 19.7 ± 13.8 vs. 23.4 ± 14.7 (*P* ≥ .05) Week 12: 9.9 ± 7.9 vs. 12.4 ± 10.3 (*P* ≥ .05)	NR	SF-36 scores at baseline (mean ± SD) Physical functioning: 56.20 ± 16.05 vs. 61.75 ± 12.01 (*P* ≥ .05) Physical role: 8.12 ± 10.75 vs. 12.95 ± 22.00 (*P* ≥ .05)

Citation N	VAS-pain (treatment vs. control)	NRS (treatment vs. control)	ROM (treatment vs. control)	SPADI (treatment vs. control)	NHP (treatment vs. control)	SF-36 (treatment vs. control)
	VAS at rest (mean ± SD) Baseline: 3.8 ± 1.5 vs. 3.5 ± 1.8 (*P* ≥ .05) Week 1: 2.4 ± 1.4 vs. 2.2 ± 1.3 (*P* ≥ .05) Week 4: 1.3 ± 0.9 vs. 1.8 ± 1.43 (*P* ≥ .05) Week 12: 0.8 ± 0.7 vs. 0.95 ± 0.68 (*P* ≥ .05) VAS during movement (mean ± SD) Baseline: 7.0 ± 1.6 vs. 6.0 ± 1.5 (*P* ≥ .05) Week 1: 5.2 ± 1.8 vs. 4.8 ± 2.0 (*P* ≥ .05) Week 4: 2.9 ± 1.0 vs. 2.7 ± 1.55 (*P* ≥ .05) Week 12: 2.3 ± 0.8 vs. 2.10 ± 1.29 (*P* ≥ .05)			SPADI Pain (mean ± SD) Baseline: 59.1 ± 17.6 vs. 60.3 ± 17.0 (*P* ≥ .05) Week 1: 41.1 ± 19.3 vs. 50.9 ± 16.6 (*P* ≥ .05) Week 4: 25.1 ± 15.5 vs. 37.7 ± 41.0 (*P* ≥ .05) Week 12: 15.2 ± 8.7 vs. 18.0 ± 11.4 (*P* ≥ .05) SPADI Total (mean ± SD) Baseline: 120.3 ± 19.4 vs. 117.4 ± 21.1 (*P* ≥ .05) Week 1: 81.4 ± 21.0 vs. 93.9 ± 31.3 (*P* ≥ .05) Week 4: 45.9 ± 14.5 vs. 54.7 ± 26.7 (*P* ≥ .05) Week 12: 25.5 ± 10.1 vs. 32.4 ± 20.5 (*P* ≥ .05)		Bodily pain: 27.40 ± 11.27 vs. 28.55 ± 13.12 (*P* ≥ .05) General health: 49.95 21.94 vs. 51.60 ± 18.42 (*P* ≥ .05) Vitality: 50.73 ± 6.95 vs. 53.50 ± 14.24 (*P* ≥ .05) Social functioning: 57.21 ± 21.94 vs. 49.37 ± 22.75 (*P* ≥ .05) Emotional role: 55.70 ± 18.33 59 vs. 51.62 ± 22.86 (*P* ≥ .05) Mental health: 50.12 ± 16.44 vs. 52.90 ± 16.87 (*P* ≥ .05) SF-36 scores at week 12 (mean ± SD) Physical functioning: 69.5 ± 16.09 vs. 74.25 ± 10.03 (*P* ≥ .05)

Citation N	VAS-pain (treatment vs. control)	NRS (treatment vs. control)	ROM (treatment vs. control)	SPADI (treatment vs. control)	NHP (treatment vs. control)	SF-36 (treatment vs. control)
						Physical role: 55.35 ± 14.90 vs. 60.00 ± 23.50 (*P* ≥ .05) Bodily pain: 67.37 ± 14.83 vs. 61.25 ± 17.07 (*P* ≥ .05) General health: 55.85 ± 18.67 vs. 56.73 ± 13.95 (*P* ≥ .05) Vitality: 55.95 ± 10.02 vs. 56.25 ± 12.65 (*P* ≥ .05) Social functioning: 81.24 ± 16.09 vs. 74.37 ± 16.95 (*P* ≥ .05) Emotional role: 59.15 ± 20.48 vs. 54.93 ± 19.54 (*P* ≥ .05) Mental health: 54.74 ± 16.67 vs. 56.20 ± 16.02 (*P* ≥ .05)
Ökmen et al., 2017[19] N = 59	VAS (median [min to max]) Pretreatment: 64 (19 to 85) vs 63 (19 to 85); *P* = .97	NR	NR	SPADI Disability (median [min to max]) Pretreatment: 45.5 (26 to 73) vs. 47 (26 to 73); *P* = .85 Immediate posttreatment: 11 (1 to 47) vs. 12 (1 to 47); *P* = .99	NHP (median [min to max]) Pretreatment: 289.3 (41.4 to 502.3) vs. 308.9 (97.0 to 502.3); *P* = .81	NR

Citation N	VAS-pain (treatment vs. control)	NRS (treatment vs. control)	ROM (treatment vs. control)	SPADI (treatment vs. control)	NHP (treatment vs. control)	SF-36 (treatment vs. control)
	Immediate posttreatment: 20 (8 to 40) 20 (8 to 40); *P* = .95 Month 1: 15.5 (0 to 61) vs. 13 (0 to 61); *P* = .50 Month 3: 21.5 (8 to 40) vs. 20 (8 to 40); *P* = .54 Month 12: 20 (8 to 40) vs. 20 (8 to 40); *P* = .84			Month 1: 11 (0 to 53) vs. 7 (0 to 53); *P* = .51 Month 3: 14 (2 to 47) vs. 13 (2 to 47); *P* = .49 Month 6: 13.5 (1 to 47) vs. 12 (1 to 47); *P* = .58 SPADI Pain (median [min to max]) Pretreatment: 37.5 (19 to 48) vs. 39 (19 to 48); *P* = .80 Immediate posttreatment: 11.5 (0 to 39) vs. 11 (0 to 39); *P* = .7 Month 1: 10 (0 to 41) vs. 8 (0 to 41); *P* = .52 Month 3: 13.5 (2 to 39) vs. 12 (0 to 39); *P* = .21 Month 6: 12 (3 to 39) vs. 12 (0 to 39); *P* = .386 SPADI Total (median [min to max]) Pretreatment: 88 (47 to 121) vs. 88 (47 to 121); *P* = .843 Immediate posttreatment: 20.5 (5 to 86) vs. 19 (5 to 86); *P* = .933 Month 1: 24 (0 to 94) vs. 16 (0 to 94); *P* = .523	Immediate posttreatment: 147.6 (0.0 to 468.2) vs. 202.8 (10.0 to 502.3); *P* = .10 Month 1: 78.4 (0.0 to 468.2) vs. 79.3 (0.0 to 391.9); *P* = .85 Month 3: 76.5 (0.0 to 254.2) vs. 75.4 (0.0 to 330.4); *P* = .80 Month 6: 80.4 (0.0 to 330.4) vs. 77.6 (0.0 to 330.4); *P* = .64	

Citation N	VAS-pain (treatment vs. control)	NRS (treatment vs. control)	ROM (treatment vs. control)	SPADI (treatment vs. control)	NHP (treatment vs. control)	SF-36 (treatment vs. control)
				Month 3: 26.5 (6 to 86) vs. 20 (5 to 86); *P* = .347 Month 6: 26.5 (7 to 86) vs. 20 (5 to 86); *P* = .395		

Table 12. Evidence Table for Randomized Controlled Trials: Shoulder Pain

Part 2

Citation N	Constant-Murley (treatment vs. control)	BDI (treatment vs. control)	Patient or doctor satisfaction (treatment vs. control)	Oral pain medication use (treatment vs. control)	Adverse Events
Eyigor et al., 2010[16] N = 50	NR	BDI at baseline (mean ± SD): 6.20 ± 4.36 vs. 4.25 ± 3.35 (*P* = NR) BDI at week 12 (mean ± SD): 4.85 ± 2.45 vs. 3.95 ± 3.76 (*P* = NR) No statistically significant difference between groups in BDI subscores at week 12 (*P* ≥ .05)	Patient satisfaction (good or very good results) Week 1: 7 (14%) vs. 16 (32%) (*P* < .05) Week 4: 10 (20%) vs. 18 (36%) (*P* < .05) Week 12: 15 (30%) vs. 20 (40%) (*P* < .05) Doctor satisfaction (good or very good results) Week 1: 6 (12%) vs. 19 (38%) (*P* < .05) Week 4: 12 (24%) vs. 20 (40%) (*P* < .05) Week 12: 20 (40%) vs. 21 (42%) (*P* < .05)	In weeks 1, 4, and 12, paracetamol consumption was significantly lower in corticosteroid group (*P* < .05)	Ecchymosis at entry point in 2 participants in treatment group and 1 patient in control group
Gofeld et al., 2012[17] N = 22	Constant-Murley (mean ± SD) Baseline: 32.3 vs. 38.1 (*P* = NR) Month 1 (n = 22): 45.2 vs. 41.3 (*P* = NR) Month 3 (n = 16): 51.8 vs. 41.4 (*P* = NR)	NR	Patient satisfaction Month 1 (n = 22): 5.7 vs. 3.7 (*P* = .04) Month 3 (n = 16): 6.0 vs. 3.9 (*P* = .03) Month 6 (n = 13): 5.6 vs. 4.2 (*P* = NR)	NR	NR

Citation N	Constant-Murley (treatment vs. control)	BDI (treatment vs. control)	Patient or doctor satisfaction (treatment vs. control)	Oral pain medication use (treatment vs. control)	Adverse Events
	Month 6 (n = 13): 47.6 vs. 41.2 (*P* = NR) No statistically significant differences between groups found over time in Constant-Murley, using repeated measures ANOVA				
Korkmaz et al., 2010[18] N = 40	NR	NR	No statistically significant differences between groups in patient satisfaction at week 1, 4, or 12 ($P \geq .05$) No statistically significant differences between groups in physician satisfaction at weeks 1, 4, or 12 ($P \geq .05$)	No statistically significant differences between groups in the use of paracetamol at week 1, 4, or 12 ($P \geq .05$)	No serious side-effects or complications reported
Ökmen et al., 2017[19] N = 59	NR	NR	NR	NR	No complications reported

Table 13. Evidence Table for Randomized Controlled Trials: Plantar Fasciitis

Citation N	VAS overall pain (treatment vs. control)	VAS first step pain (treatment vs. control)	VAS peak pain (treatment vs. control)	Other outcomes (treatment vs. control)	Adverse Events
Landsman et al., 2013[20] N = 17	Change in VAS average pain from baseline to week 4 (MD ± SD): 4.06 ± 2.10 vs. 0.8 ± 1.81; *P* = .047	Change in VAS first-step pain from baseline to week 4 (MD ± SD): 5.00 ± 3.90 vs. 1.33 ± 2.30; *P* = .30	Change in VAS peak pain baseline to week 4 (MD ± SD): 5.33 ± 4.31 vs. 1.80 ± 2.08; *P* = .048	NR	Adverse events were not reported with specificity; authors stated that adverse effects were all related to injections: ecchymosis at injection site, dizziness, vasovagal response, and pain with nerve localization
Wu et al., 2017[21] N = 36 patients, 40 feet	Change in VAS overall pain from baseline to week 1 (MD ± SD): -2.73 ± 1.46 vs. -0.52 ± 0.30 (*P* < .001) Change in VAS overall pain from baseline to week 4 (MD ± SD): -3.65 ± 1.66 vs. -0.20 ± 0.20 (*P* < .001) Change in VAS overall pain from baseline to week 8 (MD ± SD): -3.91 ± 1.85 vs. -0.13 ± 0.21 (*P* < .001)	Change in VAS first step pain from baseline to week 1 (MD ± SD): -3.08 ± 1.49 vs. -0.61 ± 0.43 (*P* < .001) Change in VAS first step pain from baseline to week 4 (MD ± SD): -3.64 ± 1.46 vs. -0.17 ± 0.19 (*P* < .001) Change in VAS first step pain from baseline to week 8 (MD ± SD): -3.99 ± 2.03 vs. -0.16 ± 0.55 (*P* < .001)	NR	Change in AOFAS ankle-hindfoot from baseline to week 1 (MD ± SD): 19.65 ± 13.93 vs. 3.60 ± 5.56 (*P* < .001) Change in AOFAS ankle-hindfoot from baseline to week 4 (MD ± SD): 27.10 ± 16.67 vs. 3.05 ± 6.53 (*P* < .001) Change in AOFAS ankle-hindfoot from baseline to week 8 (MD ± SD): 27.85 ± 17.55 vs. 1.00 ± 8.93 (*P* < .001) Change in AOFAS ankle-hindfoot from baseline to week 12 (MD ± SD): 32.10 ± 16.84 vs. -0.50 ± 8.59 (*P* < .001)	"All patients were observed for 30 minutes after the injection and were discharged with no significant complications (e.g., pain, bleeding, weakness) except for some numbness of the plantar area in the control group."[21(p.965)]

Citation N	VAS overall pain (treatment vs. control)	VAS first step pain (treatment vs. control)	VAS peak pain (treatment vs. control)	Other outcomes (treatment vs. control)	Adverse Events
	Change in VAS overall pain from baseline to week 12 (MD ± SD): -4.49 ± 2.10 vs. 0.02 ± 0.31 (*P* < .001)	Change in VAS first step pain from baseline to week 12 (MD ± SD): -4.59 ± 2.04 vs. -0.11 ± 0.30 (*P* < .001)		Change in plantar thickness (mm) from baseline to week 1 (MD ± SD): -0.68 ± 0.58 vs. -0.31 ± 0.30 (*P* = .015) Change in plantar thickness (mm) from baseline to week 4 (MD ± SD): -0.89 ± 0.69 vs. -0.30 ± 0.81 (*P* = .017) Change in plantar thickness (mm) from baseline to week 8 (MD ± SD): -1.02 ± 0.71 vs. -0.30 ± 0.65 (*P* = .002) Change in plantar thickness (mm) from baseline to week 12 (MD ± SD): -1.12 ± 0.82 vs. -0.08 ± 0.34 (*P* < .001)	

Table 14. Evidence Table for Observational Studies: Knee Pain

Citation Setting Study Design	Population Description	Inclusion and Exclusion Criteria	Intervention Description	Adverse Events
Iannaccone, et al., 2017[24] U.S. Retrospective/ prospective case series with 6 month follow-up	N = 26 participants, 31 knees Mean age (range): 72 years (41 to 96) Gender: 10 (32%) male, 16 (68%) female Mean BMI (range): 28.5 (24 to 37) H/o knee surgery: 10 (32%) H/o PT: 13 (42%) H/o steroid or HA injection: 14 (45%)	Inclusion criteria (must meet all): Knee osteoarthritis, where diagnostic blocks (1 mL bupivicaine at each genicular nerve) provided ≥ 80% pain relief; Exclusion criteria (excluded if met any criterion): Knee had a mechanical injury (e.g., meniscal tear, tendon damage); advanced systemic disease (e.g., decompensated heart failure, pneumonia, or dementia leaving them too debilitated to participate in follow-up); chronic rheumatologic disorder	RFA using unspecified device Anesthesia: None reported Device placement: Genicular nerves (superior lateral, superior medial, and inferior medial periosteal areas) confirmed with sensory stimulation and absence of motor response Ablation: 60°C, 120 s Procedural imaging: Fluoroscopy	1 participant described transient numbness of the knee post procedure
Ikeuchi et al., 2011[25] Japan Prospective cohort study of RFA and nerve block with 6 month follow-up: data presented here for RFA arm only	N = 18 (RFA arm only) Mean age: 77 years Gender: 2 (6%) male, 33 (94%) female Mean disease duration: 10 years Mean WOMAC total: 41 Mean VAS pain: 57 Hydrarthrosis: 9 (26%)	Inclusion criteria (must meet all): Refractory anteromedial knee pain associated with radiological knee osteoarthritis; Kellgren–Lawrence classification grade 3 or 4; h/o conservative treatments > 3 months; VAS > 30 mm; age > 65 years Exclusion criteria (excluded if met any criterion):	RFA using unspecified NeuroTherm device Anesthesia: 0.5 mL lidocaine applied to the skin and 1 mL lidocaine at ablation site Device placement:	Subcutaneous bleeding at the site of needle insertion in 67% of participants, with no hematoma formation Hypoesthesia at the IPBSN region in 78% of participants, which lasted for 2–6 weeks

Citation Setting Study Design	Population Description	Inclusion and Exclusion Criteria	Intervention Description	Adverse Events
		h/o septic arthritis; coagulation disturbances; allergies to local anesthetics; steroid use; cardiac pacemaker; mental handicap or psychiatric conditions precluding adequate communication	Medial retinacular nerve and infrapatellar branch of the saphenous nerve, confirmed with sensory stimulation Ablation: RFA, 70°C, 90 s Procedural imaging: None	
Kirdemir et al., 2017[26] Turkey Prospective case series with 12 week follow-up	N = 49 Mean age: 64 years Gender: 8 (16%) male, 41 (84%) female ASA: 12 (25%) I, 26 (53%) II, 11 (22%) III Kellgren-Lawrence classification: 17 (35%) 2, 22 (45%) 3, 10 (20%) 4 Medication use: 43 (88%) Mean VAS: 8.9 Mean WOMAC pain: 15.8 Mean WOMAC stiffness: 6.48 Mean WOMAC function: 42.46 Mean WOMAC total: 64.26	Inclusion criteria (must meet all): Kellgren–Lawrence classification stage 2 to 4; not responded to 6-month period of conservative treatment (e.g., physiotherapy, analgesics, IAS or HA injection); age 55 to 75 years Exclusion criteria (excluded if met any criterion): h/o knee surgery; IA injection within the last 6 months; acute knee pain; connective tissue disease affecting the knee; sciatic pain; use of anticoagulants,; systemic infection or localized infection in the procedure area; cardiac pacemaker; severe neurological or psychiatric disease	RFA using unspecified device Anesthesia: 1% lidocaine applied to skin Device placement: Each genicular nerve, confirmed with sensory stimulation and absence of motor response Ablation: RFA, 80°C, 90 s Procedural imaging: Fluoroscopy	No complications developed in any participant

Citation Setting Study Design	Population Description	Inclusion and Exclusion Criteria	Intervention Description	Adverse Events
McCormick et al., 2017[28] U.S. Cross-sectional survey and retrospective chart review ≥6 months after ablation	N = 33 participants, 52 knees Mean age (range): 66 years (62 to 77) Gender: 10 (30%) male, 23 (70%) female Mean BMI: 31 Duration of pain: 10 (19%) ≤2 years, 24 (46%) >2 to 5 years, 18 (35%) > 5 years Mean NRS: 8	Inclusion criteria (must meet all): 50% or greater concordant pain relief of typical knee pain during walking and weight bearing following a set of diagnostic superomedial, superolateral, and inferomedial genicular nerve blocks with 1mL of 2% lidocaine at each location; C-RFA of the superomedial, superolateral, and inferomedial genicular nerves ≥ 6 months ago; native symptomatic knee(s); age 18 to 89 years Exclusion criteria (excluded if met any criterion): None	Cooled RFA using Coolief device Anesthesia: Skin wheal of 1 to 2 mL 1% lidocaine and 1.0 mL 2% lidocaine at ablation site Device placement: Genicular nerves (superior lateral, superior medial, inferior medial) Ablation: Cooled RFA, 150 s, 60°C which imparts a tissue temperature of 77°C to 80°C Procedural imaging: Fluoroscopy	No serious reported adverse events related to the procedure
Sari et al., 2017[29] Turkey RCT comparing fluoroscopy vs. ultrasound imaging during RFA with 3 month follow-up; data for both study arms combined are presented here	N = 50 Mean age: 66 years Gender: 6 (12%) male, 44 (88%) female Mean BMI: 30.2 Disease duration: 2.5 years Mean VAS: 7.5 Mean WOMAC total: 49.2 Mean WOMAC pain: 11.69 Mean WOMAC stiffness: 2.90	Inclusion criteria (must meet all): Kellgren-Lawrence classification grades 2 to 4 or participants suffering from moderate to severe pain and those suffering from pain every day for > 3 months who were clinically non-responsive to conservative treatments (i.e. physical therapy and rehabilitation, oral analgesics, anti-inflammatory drugs); age 50 to 80 years Exclusion criteria (excluded if met any criterion):	RFA using unspecified NeuroTherm device Anesthesia: Intradermal and subcutaneous administration of 2 % lidocaine and 2 ml 0.05% bupivacaine + 1/3 (betamethasone dipropionate 6.43 + betamethasone sodium phosphate 2.63 mg at ablation site Device placement:	No complications in any participants

Citation Setting Study Design	Population Description	Inclusion and Exclusion Criteria	Intervention Description	Adverse Events
	Mean WOMAC function: 34.82	h/o knee surgery; acute knee pain; other tissue diseases affecting the knee; IA steroid or HA injection in past 3 months; anticoagulant therapy; serious neurological or psychiatric disorder	Genicular nerves (superior-lateral, superior-medial, inferomedial), confirmed with sensory stimulation and absence of motor response Ablation: RFA, 80°C, 90 s Procedural imaging: Fluoroscopy or ultrasound	

Table 15. Evidence Table for Observational Studies: Shoulder Pain

Citation Setting Study Design	Population Description	Inclusion and Exclusion Criteria	Intervention Description	Adverse Events
Gabrhelik et al., 2010[23] Czech Republic Retrospective case series with 6 month follow-up	N = 28 Mean age: 55 years Gender: 11 (39%) male, 17 (61%) female Mean pain duration: 17 weeks Mean VAS pain at rest: 4.9 Mean VAS pain during activity: 7.0 Mean VAS pain at night: 3.1 Medication use: 5 (18%) none, 16 (57%) nonopioids only, 7 (25%) opioids	Inclusion criteria (must meet all): sub-acute or chronic shoulder pain unresponsive to conservative treatment for a period of at least 4 weeks, including pharmacotherapy (opioid analgesics, NSAIDs, paracetamol, adjuvant medication) and physiotherapy Exclusion criteria (excluded if met any criterion): Pain of visceral origin, cervicobrachial syndrome or other vertebrogenic syndromes	Group A (n = 14) Pulsed RF with Radionics 3 RF generator Anesthesia: 6 mL of 0.25% of levobupivacaine local anesthetic, 3 ml of 1% of lidocaine at puncture site, and 6 mL 0.25% levobupivacaine at end of therapy Device placement: Suprascapular nerve, confirmed with sensorial stimulation and absence of motor response Ablation: Pulsed RF, 2 cycles, 120 s, 40 V, < 42°C Procedural imaging: Fluoroscopy Group B (n = 14) Same procedures as group A with steroid (20 mg of methylprednisolone) added to the levobupivacaine injection after ablation	1 participant who took regular morning antihypertensive tablets suffered brief hypotension after the procedure. 1 participant developed a small hematoma at the site of the procedure

Table 16. Evidence Table for Observational Studies: Plantar Fasciitis

Citation Setting Study Design	Population Description	Inclusion and Exclusion Criteria	Intervention Description	Adverse Events
Erken et al., 2014[22] Turkey Prospective case series with 2 year follow-up	N = 29 participants, 35 feet Mean age (range): 47.4 years (30 to 88) Gender: 14 (48%) male, 15 (52%) female Mean VAS: 9.2 Mean AOFAS: 66.9	Inclusion criteria (must meet all): Calcaneal spur on x-ray or plantar fasciitis on MRI; heel pain at plantar medial aspect ≥6 months; ≥2 conservative treatments >3 months ago (stretching exercises and ice treatment, oral anti-inflammatory and heel pad, PT, steroid injections, night splints, extracorporal shockwave therapy); benefited from trial local anesthetic injection Exclusion criteria (excluded if met any criterion): h/o surgery in the heel region; h/o trauma or fracture of calcaneus; peripheral neuropathies and radiculopathy proven by electromyography studies or physical examination; abnormalities around the heel; severe arthritic changes; peripheral vascular ischemia; open wound or infection in heel region; calcaneal lesions including benign tumors; severe fat pad atrophy, calcaneal bursitis, and skin; pregnancy	RFA with Baylis Medical Pain Management Optima Anesthesia: 0.5 cc of lidocaine HCl 20 mg/mL with epinephrine HCl 0.0125 mg/mL applied to skin, 1 cc lidocaine HCl 20 mg/mL with epinephrine HCl 0.0125 mg/mL at the ablation site, and 1 mL of plain 0.5% bupivacaine after ablation Device placement: Calcaneal branches of the inferior calcaneal nerve, confirmed with sensorial stimulation and absence of motor response Ablation: 90°C, 75 s after 15 s warm-up time Procedural imaging: Ultrasound	No major complications during the study 1 participant developed hematoma, which resolved by itself in 1 month 2 participants had neuropathic pain, which was resolved with pregabalin medication within 3 months 3 feet had transient discomfort, which resolved in 4 weeks

Citation Setting Study Design	Population Description	Inclusion and Exclusion Criteria	Intervention Description	Adverse Events
Liden et al., 2009[27] U.S. Retrospective case series with 1 year follow-up	N = 22 participants, 31 feet Heel pain ≥ 1 year: 15 (68%) Mean VAS 8.12	Inclusion criteria (must meet all): Heel pain present ≥6 months; previously attempted ≥ 2 of these conservative measures: arch supports (custom or noncustom), home stretching, PT, steroid injection, oral anti-inflammatories, icing, night splint, taping/strapping; ≥18 years old Exclusion criteria (excluded if met any criterion): h/o surgery on affected heel; h/o trauma or fracture of the heel; pain related to peripheral neuropathy or ischemia; inability to tolerate injections to the heel region; allergy to local anesthetics or steroids; open wounds on the study foot; local or systemic infection when the procedure was to be performed	RFA using NeuroTherm NT250 Anesthesia: 1 mL of 2% plain lidocaine applied to skin and 1 mL of 0.5% plain bupivacaine at ablation site Device placement: Medial calcaneal nerve, confirmed with sensory stimulation and absence of motor response Ablation: RFA, 90°C, 90 s Procedural imaging: None	Complications associated with the intervention: 1 bruising at injection site, resolved without additional treatment 1 peroneal tendonitis, resolved with anti-inflammatory medications after 2 weeks 1 lateral calf pain, resolved after 2 wks. with oral NSAIDs 1 sensation of walking on a ''wad of tissue,'' that resolved after 1 mo. 1 persistent poststatic dyskinesia, at 6 months 2 with more improvement in one foot than the other (bilateral cases only), at 6 months

Appendix D. Risk of Bias Assessments

Table 17. Risk of Bias: Randomized Controlled Trials

Study	Randomization	Allocation Concealment	Intervention	Outcomes	Investigator & Participant Masking	Outcome Assessor Masking	Intention to Treat Analysis	Statistical Analysis	Other Biases	Interest Disclosure	Funding	Overall Assessment	Comments
Choi et al., 2011[10]	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Unclear	No	Yes	No	High	Outcome assessors not specified and unclear if masked to treatment allocation; multiple comparisons without *P* value partitioning; small sample size; no funding source stated
Davis et al., 2018[11]	Unclear (changed to Yes after receipt of public comments)	No (changed to unclear after receipt of public comments)	Yes	Yes	No	No	Yes	No	No	No	No	Moderate	Lack of detail about randomization was clarified in public comment; information about allocation concealment method was unclear after public comment; actual dosage of 2 of 3 steroids used in comparator group not specified; differential loss to follow-up; 5 of 12 authors are on the manufacturer's clinical advisory board; funding was provided to each investigators institution by the manufacturer to

Study	Randomization	Allocation Concealment	Intervention	Outcomes	Investigator & Participant Masking	Outcome Assessor Masking	Intention to Treat Analysis	Statistical Analysis	Other Biases	Interest Disclosure	Funding	Overall Assessment	Comments
													cover costs of study without a role for the company in data management, site monitoring, or statistical services, but no declaration of involvement in decision to publish or content of publication.
El-Hakeim et al., 2018[12]	Yes	No	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	High	No information on allocation concealment; no masking of participants or clinicians; lack of control for baseline differences or other confounders; multiple comparisons without *P* value partitioning
Eyigor et al., 2010[16]	Unclear	No	Unclear	Yes	No	No	Yes	Yes	Yes	No	No	High	No mention of allocation concealment; dose of TAC into shoulder spaces may not be optimal; no mention of masking or blinding of participants and clinicians, no financial disclosure or funding stated

Study	Randomization	Allocation Concealment	Intervention	Outcomes	Investigator & Participant Masking	Outcome Assessor Masking	Intention to Treat Analysis	Statistical Analysis	Other Biases	Interest Disclosure	Funding	Overall Assessment	Comments
Gofeld et al., 2013[17]	No	Unclear	Yes	Yes	Yes	No	Unclear	No	No	No	Unclear	High	No randomization method described; unclear allocation procedure; outcome assessors not masked; small sample size; high dropout rate; no financial disclosure or role of funder stated
Korkmaz et al., 2010[18]	Unclear	No	No	Yes	No	Unclear	Yes	Yes	No	Yes	No	High	Allocation concealment not discussed; clinician and patient aware of assignment; some outcome assessors masked and others were not; small sample size and only 12 weeks follow-up
Landsman et al., 2013[20]	Yes	No	Yes	Unclear	Unclear	Yes	Unclear	No	No	No	No	High	No allocation concealment procedure discussed; no validated outcome measures used; Investigator/clinician not masked; small sample size; short follow-up of 4 weeks (patients could cross over after that point); funded by manufacturer; lead author is a paid

Study	Randomization	Allocation Concealment	Intervention	Outcomes	Investigator & Participant Masking	Outcome Assessor Masking	Intention to Treat Analysis	Statistical Analysis	Other Biases	Interest Disclosure	Funding	Overall Assessment	Comments
													consultant for manufacturer
Ökmen et al., 2017[19]	Yes	No	Unclear	Yes	No	No	Yes	Yes	Yes	Yes	Yes	High	No specific discussion of allocation concealment method. unclear if application of laser therapy is considered adequate treatment; no descriptions of masking for any parties
Qudsi-Sinclair et al., 2017[13]	Yes	Unclear	No	Yes	No	Yes	Yes	Unclear	No	Yes	No	High	No detailed description of allocation concealment; comparator dose of TAC likely suboptimal at 20mg x 1 dose; no masking of participants or clinicians; multiple comparisons without *P* value partitioning; small sample size; no funding statement.
Radnovich et al., 2017[14]	Yes	Unclear	Unclear	Yes	Yes	Yes	Yes	No	No	No	No	High	Not adequate description of allocation concealment; unclear trial flow diagram to assess loss to follow-up; manufacturer funded study and assisted study design, analysis of data

Study	Randomization	Allocation Concealment	Intervention	Outcomes	Investigator & Participant Masking	Outcome Assessor Masking	Intention to Treat Analysis	Statistical Analysis	Other Biases	Interest Disclosure	Funding	Overall Assessment	Comments
													and decision to publish; 2 of 16 authors had financial relationships with manufacturer
Ray et al., 2018[30]	Yes	No	Yes	Yes	No	No	No	No	No	Yes	Yes	High	No description of allocation concealment; no discussion of masking; very small sample size; limited description of demographic characteristics; limited description of statistical methods
Sari et al., 2016[15]	Yes	No	Unclear	Unclear	No	No	Yes	Unclear	Yes	Yes	Yes	High	No allocation concealment mentioned; dose of betamethasone comparator is not given; no mention of masking; multiple comparisons without *P* value partitioning
Wu et al., 2017[21]	Yes	No	Yes	Yes	No	Yes	Yes	Unclear	No	Yes	Yes	Moderate	Allocation concealment not discussed; 18 patients, but 20 feet enrolled in each group with feet as the unit of analysis; short follow-up of 12 weeks

Table 18. Risk of Bias: Observational Studies

Study	Participant Selection	Intervention	Control	Outcome	Masked Outcome Assessment	Confounding	Statistical Analysis	Other Biases	Interest Disclosure	Funding Source	Overall Assessment
Erken et al., 2014[22]	Not Applicable	Yes	Not Applicable	No	No	No	No	No	Yes	Yes	High
Gabrhelik et al., 2010[23]	Not Applicable	Yes	Not Applicable	No	No	No	No	No	Yes	No	High
Iannaccone et al., 2017[24]	Not Applicable	Yes	Not Applicable	Unclear	No	No	No	No	Yes	No	High
Ikeuchi et al., 2011[25]	Not Applicable	Yes	Not Applicable	No	No	No	No	No	Yes	No	High
Kirdemir et al., 2017[26]	Not Applicable	Yes	Not Applicable	No	No	No	No	No	No	No	High
Liden et al., 2009[27]	Not Applicable	Yes	Not Applicable	No	No	No	No	No	No	Unclear	High
McCormick et al., 2017[28]	Not Applicable	Yes	Not Applicable	No	No	No	No	No	Yes	Yes	High
Sari et al., 2017[29]	Not Applicable	Yes	Not Applicable	No	No	No	No	No	Yes	No	High

Table 19. Risk of Bias: Guidelines

Guideline Developer, Topic, Year	Rigor of Development—Evidence	Rigor of Development—Recommendations	Editorial Independence	Scope & Purpose	Stakeholder Involvement	Clarity & Presentation	Applicability	Overall Assessment
American Academy of Orthopaedic Surgeons, knee osteoarthritis, 2013[40]	Fair	Fair	Fair	Fair	Fair	Fair	Poor	Fair
American Academy of Orthopaedic Surgeons, hip osteoarthritis, 2017[44]	Fair	Fair	Fair	Fair	Fair	Fair	Poor	Fair
American College of Foot and Ankle Surgeons, infracalcaneal heel pain, 2018[47]	Poor	Poor	Fair	Fair	Poor	Fair	Poor	Poor
American College of Occupational and Environmental Medicine, elbow disorders, 2013[41]	Fair	Fair	Fair	Good	Fair	Fair	Fair	Fair
American Physical Therapy Association, plantar fasciitis, 2014[43]	Fair	Fair	Fair	Good	Fair	Fair	Fair	Fair
Association of Extremity Nerve Surgeons, clinical practice guideline--denervation, 2014[45]	Poor	Poor	Poor	Poor	Poor	Poor	Fair	Poor
Department of Veterans Affairs/Department of Defense, hip and knee osteoarthritis, 2014[42]	Good	Fair	Good	Good	Fair	Good	Good	Fair
National Institute for Health and Care Excellence, osteoarthritis, 2014[39]	Good	Good	Good	Good	Good	Good	Good	Good

Appendix E. GRADE Quality of Evidence

Number of Participants and Studies	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Comments	Overall Quality of Evidence Rating
Knee (conventional RFA)							
Outcome: Function—WOMAC total or OKS at 3 months							
n = 223 k = 5	Very serious (-2)	No serious limitations identified	Serious (-1)	No serious limitations identified	NA	ROB (high all studies) Indirectness (study locations, suboptimal comparator, lack of longer term outcomes)	Very low ●○○○
Outcome: Pain—VAS or NRS at 3 months							
n = 150 k = 4	Very serious (-2)	No serious limitations identified	Serious (-1)	No serious limitations identified	NA	ROB (high in all studies) Indirectness (study locations, suboptimal comparator, lack of longer term outcomes)	Very low ●○○○
Knee (cooled RFA)							
Outcome: Function—OKS at 3 months							
n = 151 k = 1	Serious (-1)	No serious limitations identified	Serious (-1)	Serious (-1)	NA	ROB (moderate) Imprecision (single study) Indirectness (lack of longer term outcomes, suboptimal comparator)	Very low ●○○○
Outcome: Pain—NRS at 3 months							
n = 151 k = 1	Very serious (-2)	No serious limitations identified	Serious (-1)	Serious (-1)	NA	ROB (high) Imprecision (single study) Indirectness (lack of longer term outcomes, suboptimal comparator)	Very low ●○○○

Number of Participants and Studies	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Comments	Overall Quality of Evidence Rating
Knee (cryoablation)							
Outcome: Function—WOMAC total at 3 months							
n = 180 k = 1	Very serious (-2)	No serious limitations identified	Serious (-1)	Serious (-1)	NA	ROB (high) Imprecision (single study) Indirectness (lack of longer term outcomes, suboptimal comparator)	Very low ●○○○
Outcome: Pain—VAS at 3 months							
n = 180 k = 1	Very serious (-2)	No serious limitations identified	Serious (-1)	Serious (-1)	NA	ROB (high) Imprecision (single study) Indirectness (lack of longer term outcomes, suboptimal comparator)	Very low ●○○○
Shoulder (pulsed RF)							
Outcome: Function—SPADI at 3 months							
n = 171 k = 4	Very serious (-2)	Serious (-1)	Serious (-1)	Serious (-1)	NA	ROB (high in 3 of 4 studies) Inconsistency (results favoring pRF or control in different studies) Indirectness (study location, suboptimal or uncommonly used comparator, lack of longer term outcomes, composite outcome)	Very low ●○○○
Outcome: Pain—VAS at 3 months							
n = 149 k = 3	Very serious (-2)	No serious limitations identified	Serious (-1)	No serious limitations identified	NA	ROB (high in 2 of 3 studies) Indirectness (study location, suboptimal or uncommonly used comparator, lack of	Very low ●○○○

Number of Participants and Studies	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Comments	Overall Quality of Evidence Rating
						longer term outcomes, composite outcome)	
Plantar Fasciitis (pulsed RFA)							
Outcome: Function—AOFAS at 3 months							
n = 36 k = 1	Serious (-1)	No serious limitations identified	Serious (-1)	Serious (-1)	NA	ROB (high) Imprecision (single study) Indirectness (study location, lack of longer term outcomes, suboptimal comparator)	Very low ●○○○
Outcome: Pain—VAS at 3 months							
n = 36 k = 1	Serious (-1)	No serious limitations identified	Serious (-1)	Serious (-1)	NA	ROB (high) Imprecision (single study) Indirectness (study location, lack of longer term outcomes, suboptimal comparator)	Very low ●○○○
Plantar Fasciitis (conventional RFA)							
Outcome: Function (no measures identified)							
n = 0 k = 0	NA	NA	NA	NA	NA	NA	NA
Outcome: Pain—VAS at 3 months							
n = 0 k = 0	NA	NA	NA	NA	NA	NA	NA

Appendix F. Studies Registered at ClinicalTrials.gov

Registered clinical trial number	Title of study	Study completion date (from https://clinicaltrials.gov/	Status of publications and whether study eligible for possible inclusion in systematic review
NCT00924677 (South Korea)	The Effect of Therapeutic Methods for Chronic Knee Osteoarthritis Pain	June 2009	Published study included in review[10]
NCT03224637 (Egypt)	Radiofrequency Neurotomy In Relieving Chronic Knee Pain	February 2016	Published study included in review[12]
NCT02260921 (U.S)	Study to Evaluate the Iovera° Device for Temporary Relief From Knee Pain	June 2016	Published study included in review[14]
NCT02242513 (Taiwan)	Ultrasound-guided Pulsed Radiofrequency for Plantar Fasciitis	July 2016	Published study included in review[21]
NCT02343003 (U.S.)	Nerve Ablation by Cooled Radiofrequency Compared to Corticosteroid Injection for Management of Knee Pain	March 2017	Published study included in review[11]
NCT02826850 (Brazil)	Saphenous Nerve Radiofrequency for Knee Osteoarthritis Trial	March 2018	No published study; RCT would likely be included in review
NCT03628482 (Belgium)	Pulsed Radiofrequency to Relieve Knee Pain	November 2018	No published study; study would likely be included for harms outcome
NCT02931435 (U.S.)	Radiofrequency For Chronic Knee Pain Post-Arthroplasty	November 2018	No published study; RCT would likely be included in review
NCT03613610 (Egypt)	Radio-frequency Ablation in Knee Osteoarthritis by Three Needles Technique	November 2018	No published study; RCT would likely be included in review
NCT02915120 (Spain)	Ultrasound-Guided Pulsed Radiofrequency In The Treatment Of Patients With Osteoarthritis Knee (USPRFGENOAK)	December 2018	No published study; RCT would likely be included in review
NCT02260869 (U.S.)	Efficacy of Cooled and Monopolar Radiofrequency Ablation of the Geniculate Nerves for the Treatment of Chronic Osteoarthritic Knee Pain	July 2019	No published study; RCT would likely be included in review

Registered clinical trial number	Title of study	Study completion date (from https://clinicaltrials.gov/	Status of publications and whether study eligible for possible inclusion in systematic review
NCT03381248 (U.S.)	Cooled Radiofrequency vs. Hyaluronic Acid to Manage Knee Pain	October 2019	No published study; RCT would likely be included in review
NCT03647332 (U.S.)	Use of Cooled Radiofrequency for the Treatment of Hip Pain Associated With OA of the Hip Compared to Intra-articular Steroid Injections	December 2019	No published study; RCT would likely be included in review
NCT02947321 (U.S.)	Genicular Radiofrequency Ablation Efficacy in Achieving Total Knee Pain Reduction Trial	December 2019	No published study; RCT would likely be included in review
NCT03453372 (Italy)	MRgFUS in the Treatment of Osteoarthritic Knee Pain	January 2020	No published study; RCT would likely be included in review
NCT02838758 (U.S.)	Compare Ultrasound Assisted Cold Therapy and Lidocaine Injection to Treat Morton's Neuroma	December 2020	No published study; RCT would likely be included in review
NCT03449667 (U.S.)	Cryoanalgesia to Treat Post-Amputation Phantom Limb Pain: A Department of Defense Funded Multicenter Study	September 2021	No published study; RCT would likely be included in review
NCT00165997 (U.S.)	Quality of Life in Patients Post Radiofrequency Ablation	October 2007 Terminated	No published study, study terminated
NCT01140659 (Brazil)	Objective Evaluation of Patients With Palmar Hyperhidrosis Submitted to Two Levels of Sympathectomy: T3 and T4.	February 2010	No published study; not intervention of interest
NCT02688543 (Spain)	Radiofrequency Ablation of Genicular Nerves for Advanced Osteoarthrosis of the Knee Joint 1 Year Follow-up.	January 2016	Published study excluded from review (no outcome of interest)
NCT02284113 (U.S.)	A Randomized, Study to Evaluate the Iovera° Device in Treating Pain Associated With Total Knee Arthroplasty	June 2016	No published study; not intervention of interest
NCT02680392 (Canada)	Functional Outcome and Analgesia in TKA: Radiofrequency vs Continuous Adductor Canal Block	October 2016	No published study; not intervention of interest

Registered clinical trial number	Title of study	Study completion date (from https://clinicaltrials.gov/	Status of publications and whether study eligible for possible inclusion in systematic review
NCT02546336 (Canada)	Ultrasound-Guided Hip Joint Cooled Radiofrequency Denervation	December 2016	No published study; no outcome of interest
NCT03343808 (Spain)	Retrospective Study of the Results of Cooled Radiofrequency for Genicular Nerves Neurotomy in 40 Consecutive Patients With Osteoarthritis of the Knee and Painful Knee Arthroplasty	May 2017	No published study; no outcome of interest
NCT02873611 (Israel)	Estimation of the Localization Accuracy of the Genicular Ablation Procedure Applied for Chronic Pain Suppression	August 2017	No published study; no outcome of interest
NCT02578108 (U.S.)	Diagnostic Genicular Nerve Block Prior to Radiofrequency Ablation for Knee Osteoarthritis Pain	January 2018	Published study excluded from review (no outcome of interest)
NCT02746874 (U.S.)	Does Radiofrequency Ablation of the Articular Nerves of the Knee Prior to Total Knee Replacement Improve Pain Outcomes	November 2018	No published study; not intervention of interest
NCT02925442 (U.S.)	Genicular Radiofrequency Ablation for Unilateral Knee Arthroplasty Pain Management	December 2018	No published study; not intervention of interest
NCT03631030 (U.S.)	Cooled RF Lesion MRI Characteristics	January 2019	No published study; not intervention of interest
NCT03379883 (Egypt)	Genicular Nerve and Intra-articular Radiofrequency Versus Platelet Rich Plasma Injection for Knee Osteoarthritis	February 2019	No published study; not an appropriate comparator
NCT03676179 (Thailand)	The Comparison of Anterior Knee Pain in Patella With or Without Denervation in Medial Unicompartmental Knee Arthroplasty: Prospective Cohort Study	March 2019	No published study; not intervention of interest
NCT03567187 (U.S.)	Cryoneurolysis for Improvements in Pain, ADL and QOL in Patients With Ankle Osteoarthritis	June 2019	No published study; no outcome of interest

Registered clinical trial number	Title of study	Study completion date (from https://clinicaltrials.gov/	Status of publications and whether study eligible for possible inclusion in systematic review
NCT03389880 (Thailand)	Comparative Study Between Patellar Denervation and Non-patellar Denervation in Total Knee Arthroplasty With Patellar Resurfacing	December 2019	No published study; not intervention of interest
NCT03378362 (Sweden)	Pain Relief and Functional Outcome After Partial Denervation of the Wrist	January 2020	No published study; no outcome of interest
NCT03506828 (Egypt)	Phenol With Fluoroscopy Guided Radiofrequency Ablation of T2-T3in Palmar Hyperhidrosis	January 2020	No published study; not intervention of interest
NCT03615976 (Egypt)	Arthroscopic Treatment of Resistant Cases of Patellofemoral Pain	March 2021	No published study; not intervention of interest

Appendix G. MAUDE and Recall Reports

Table 20. Reports on RFA Devices Used to Treat Limb Pain from MAUDE Database

Manufacturer Date	Brand Name	Device Problem
Baylis Medical Company Inc 8/17/2015	RF Nitinol Probe (Now produced by Halyard Health)	During standard RF procedure of the left knee, temperature was set at 90°C, but began to climb to 99°C, when the generator shut off. There were 3 different RF needles used on different nerves of the knee, and a skin burn occurred. The device was replaced and the procedure was completed without incident. The patient is currently stable and doing fine.
Halyard Health 9/26/2017	Coolief Cooled RF Kit	Physician stated that patient had a subcutaneous wound where he performed cooled RF of the knee, lesioning the inferior genicular nerve. The physician was unable to quantify if the burn was a 1st, 2nd, or 3rd degree burn and stated that he is no longer following the patient. The patient is currently using silvadene on the wound and has not reported receiving further treatment for the wound.
Halyard Health 8/16/2016	Coolief Cooled RF Kit	During a cooled RF procedure on a female patient in her late70s, the patient began bleeding heavily when the needle was placed for the articular branch of the femoral nerve. It was discovered that the patient was on blood thinner medication up to 24 hours prior to the procedure. The patient was admitted to the intensive care unit for treatment and remained there for 7 days before being discharged.
Myoscience 7/17/2018	iovera° Smart Tip (3X6.9Mm)	Broken needle tip.
NeuroTherm, Inc 10/16/2017	4 Lesion NT2000IX Pain Management RF Generator	Prior to a procedure to treat shoulder pain, there was a communications error on the screen indicating that the controller was not responding or was incompatible. The generator emitted a beep during the self-test. The generator was powered off and reset, but there was no resolution. There were no patient consequences and the procedure was cancelled due to the generator issue.
NeuroTherm, Inc 2/3/2015	Disposable Grounding Pad w/Cable	During a RFA procedure, a patient burn occurred where the grounding pad was applied to the right posterior thigh. It was noted the pad was not applied to an area with hair or lotion present. Two small blisters were

Manufacturer Date	Brand Name	Device Problem
		observed at the site of the pad after the procedure, and the patient was treated with silvadene cream and discharged.
NeuroTherm, Inc 12/16/2015	Disposable Grounding Pad w/Cable	During a genicular RF procedure, a patient burn occurred after the grounding pad was placed on the right thigh. When the grounding pad was removed after the procedure, a 2nd degree burn was noted on the skin. No treatment was necessary.
NeuroTherm, Inc	Disposable Grounding Pad w/Cable	During a genicular nerve ablation procedure, a patient burn occurred after a disposable grounding pad was placed on the right calf of a diaphoretic patient. The procedure was completed and the patient discharged to home, at which time the patient noticed a burn at the site of the grounding pad. The patient then went to the emergency room was referred to a wound care clinic for treatment.

Table 21. Reports on RFA Devices from the Medical Device Recall Database

Company	Brand Name	Date Termination Date	Recall Reason
Baylis Medical Company Inc.	BMC RF Cannula (Now produced by Halyard Health)	2/26/2013 5/23/2013	Report received that upon opening a box containing 10 sterile cannula, the pouch package of 5 of the 10 individually packaged cannula had not been sealed along one edge. Thus the pouch was open and the device could fall out of the pouch when retrieved from the shelf box. The cannulas were not used on any patients.
Baylis Medical Company Inc.	Baylis Medical LumbarCool Pain Management System (Now produced by Halyard Health)	6/3/2010 10/4/2010	Name of the device reflected on the product packing sleeve is incorrect.
Cosman Medical, LLC	Nitinol TC Reusable Electrodes (TCN)	2/22/2018 9/14/2018	After multiple reprocessing cycles, the epoxy resin which holds the TCN Electrode in the hub can exhibit signs of damage. In some cases, this damage may result in the inability to fully remove blood or tissue residuals prior to cleaning and re-sterilizing the device.
Myoscience Inc	iovera° 155 Smart Tip	7/22/2015 9/8/2015	The expiration date on the outer box label and the pouch label is incorrect. Instead of indicating the correct expiration of 12/2015, the labels were incorrectly labeled 5/2016.
Myoscience Inc	iovera° Smart Tip	7/19/2013 7/15/2014	The outer box of the product had a down revision label which did not include the US labeling requirements, specifically the symbol descriptors and also the "Caution: Federal Law (USA) restricts this device to sale by or on the order of a physician." This product was previously labeled for EU distribution only.
NeuroTherm, Inc	NT200iX RF Generator	4/9/2016 4/14/2016	NT2000iX software was shipped with the international setting turned on. The international settings include access to Corodotomy, Bi-Polar, and No Temperature modes were not cleared for use in the U.S.
NeuroTherm, Inc	NeuroTherm Curved RF cannula	3/24/2016 3/25/2016	Straight needle was labeled as a curved needle.
NeuroTherm, Inc	NeuroTherm Simplicity III RF Electrode	1/13/2009 9/24/2009	Distal tip may detach from the probe.

Appendix H. Measures of Limb Pain Symptoms

Measures That Include Function Outcomes

The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) is a validated measure of osteoarthritis disability.[82] Individual questions are scored on a zero to 4 Likert scale or zero to 10 VAS scale.[82] There are validated WOMAC subscales for function (17 questions), stiffness (2 questions), and pain (5 questions).[82] Total scores range from zero to 96 or zero to 240, depending on whether the Likert or VAS scale is used.[82]

The Oxford Knee Score (OKS) is a validated, joint-specific, self-administered questionnaire with 12 questions.[83] Each question is scored from 1 to 5, with 1 representing the best outcome or least symptoms.[83] The scores from each question are added together, and the total score ranges from 12 to 60; lower numbers represent better outcomes.[83]

The Knee Society Score (KSS) involves a validated questionnaire completed by the evaluating clinician that assesses pain, joint balance, knee alignment, and knee stability.[85,102] The KSS scores range from zero to 100; higher numbers represent better function.[85,102]

The Shoulder Pain and Disability Index (SPADI) is a validated patient questionnaire that measures disability and pain related to shoulder pathology.[86,103] There are 8 questions on the disability subscale, which measure the degree of difficulty in the movements of the patient, and 5 questions for the pain subscale.[86] Each question ranges from zero to 10, and the total score ranges from zero to 130; lower numbers represent less disability or pain.[86]

Range of motion of the shoulder can be assessed using a goniometer (a tool that measures the angle at a joint) is a validated measure of shoulder mobility.[87] Components of range of motion include flexion, extension, abduction, external rotation, and internal rotation, assessed in both active and passive ranges.[87]

The validated scoring system developed by Constant and Murley consists of 4 measurements to assess shoulder function.[17] Each shoulder is assessed separately for range of motion and strength, and the total scores range from zero to 65 points.[17]

American Orthopedic Foot and Ankle Society (AOFAS) ankle-hindfoot score is a common, validated measurement of plantar fasciitis severity.[89,104] Scoring is done in 3 components: pain (zero to 40 points), functional aspects (zero to 50 points), and alignment (zero to 10 points).[89] Total AOFAS scores range from zero to 100, and higher scores indicate better outcomes or functional status.[89]

The Short Form 36 (SF-36) is a common, validated measure of quality of life, and is used for a variety of patient populations.[105] The SF-36 consists of 36 questions, either Likert scales or binary responses, across the subscales for physical functioning, physical role, bodily pain, general health, vitality, social functioning, emotional role, and mental health.[90] The subscales and total

score are weighted so that the range of scores is from zero to 100; higher numbers represent better health or well-being.[105]

The Nottingham Health Profile (NHP) has 38 questions in a validated measure of 6 components: pain, physical activity, energy, sleep, social isolation, and emotional reaction.[91] The scores range from zero to 100 for each component; 100 represents the best health status.[91]

Measures of Pain Only

The visual analog scale (VAS) is a validated way to measure pain, usually by indicating a position along a continuous line between 2 endpoints, either on a zero to 10 or zero to 100 scale.[92] The endpoints are anchored with the extremes (e.g., zero is no pain at all, and 10 or 100 is unbearable pain or pain as bad as it could be).[92]

The 11-point numerical rating scale (NRS) is a validated scale of pain intensity ranging from zero to 10 with whole number responses.[93,94] On the NRS, zero represents no pain and 10 represents unbearable pain.[93,94]

Other Measures

The Beck Depression Inventory (BDI) is a validated measure of the presence and degree of depression, consisting of 21 questions scored zero to 3.[95] Total scores range from zero to 63, with higher numbers representing more severe depression.[95]

The Patient Global Impression of Improvement (PGI-I), Patient Global Impression of Change (PGIC), and Global Perceived Effect (GPE) measure a patient's impression of changes after treatment a 7-point scales. The PGI-I is a validated measure, where lower numbers mean better outcomes: 1-Very much better, 2-Much better, 3-A little better, 4-No change, 5-A little worse, 6-Much worse, 7-Very much worse.[96] On the PGIC, lower numbers also mean better outcomes, although the answer categories are different: 1-Very much improved, 2-Much improved, 3-Minimally improved, 4-No change, 5-Minimally worse, 6-Much worse, 7-Very much worse.[14] Global Perceived Effect (GPE) is a validated scale with the following answer categories: 1-Worst ever, 2-Much worse, 3-Worse, 4-Not improved but not worse, 5-Improved, 6-Much improved, 7-Best ever.[97]

Appendix I. See Attachment for Excluded Studies