Evidence based interventional pain practice: according to clinical diagnoses

NEDERLANDSE VERENIGING VOOR ANESTHESIOLOGIE

Vlaamse Anesthesiologische Vereniging voor Pijnbestrijding
VAVP
vzw

Introduction

In 2012, the Nederlandse Vereniging voor Anesthesiologie Sectie Pijn- en Palliatieve geneeskunde (NVA) and the Vlaamse Anesthesiologische Vereniging voor Pijnbestrijding (VAVP) published a guideline on Interventional Pain Medicine. [1] As part of the original publication the authors highlighted that this guideline on interventional pain management can be considered an ongoing project. The searches that informed the original guidelines were at the start of this project in 2015 between 5.5 and 7.5 years out of date and so it is important that updates to this guidance include recently published literature. The methodology for literature retrieval; and selection of the publications to be withheld, as well as the method for evidence scoring, should evolve with each update". The guideline committee decided to use the GRADE methodology, the current golden standard for the preparation of clinical guidelines.

Background

Clinical guidelines are systematically developed statements to assist practitioners and patients to make decisions about appropriate health care for specific clinical circumstances. NICE defines clinical guidelines as "recommendations based on the best available evidence, for the care of people by healthcare and other professionals."[2] A more detailed definition was provided by the Institute of Medicine (IOM) study entitled "Practice Guidelines That We Can Trust":
"Clinical practice guidelines are statements that include recommendations intended to optimize patient care that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options."[3]
As reflected in this definition, in order for guidelines to reflect the best available evidence it is important that they are based on a comprehensive systematic review of all available evidence. Systematic reviews provide an explicit approach to reviewing and summarizing evidence from studies. They follow a defined structure to identify, evaluate and summarize all available evidence addressing a particular research question. Key steps in a systematic review include specification of explicit inclusion criteria, an extensive literature search to identify all relevant studies, extraction of key data, assessment of the validity of included studies, and a structured statistical and/or qualitative synthesis of results.[4]
GRADE presents a systematic and transparent framework for clarifying questions, determining the outcomes of interest, summarizing the evidence that addresses a question, and moving from the evidence to a recommendation or decision. [5-8]GRADE is currently the most widely accepted and used framework for developing guidelines. More than 50 organizations worldwide, many highly influential, have endorsed the framework (http://www.gradeworkinggroup.org/). It rates the quality of a complete body of evidence for a specific outcome in a specific population.

Aim guideline

The aim of the guideline is to update the evidence on efficacy of interventional pain management procedures.

Content of the guideline

In the original 2012 guideline we described for each diagnosis the definition of the diagnosis, the epidemiology, if known the etiology and pathophysiology, the signs and symptoms, if applicable the additional lab tests including X ray examination etc., the differential diagnosis, the evidence of conservative and interventional treatments, the technical aspects of the application of the invasive

pain management procedure and the place of the invasive procedures in the treatment algorithm. On this moment the updated guideline just limits to the quality of evidence, the considerations about risk and benefits, the cost effectiveness if available etc. and the recommendations. This updated guideline does not guide in the place of the interventional pain management procedure in the treatment algorithm. In general, interventional procedure will be offered to the patient if more conventional procedures have failed. Although in individual cases or procedures a deviation is imaginable.
A next step in the process of making this guideline is creating more clarity about the place of these procedures in the treatment algorithm. This is especially important for referral doctors.

Target audience

The guideline is primarily intended for the anesthesiologist pain specialists applying these interventional pain managements procedures in their clinical practice. Other stakeholders are referring doctors, other workers in healthcare involved in these procedures and reimbursement policy makers.

Patient perspective

The patient associations were involved in the sticking point analysis before the start of the guideline development and will be involved in the authorization phase. In the implementation phase, individual hospitals will translate the content of the guideline in patient information leaflets and websites.

Authorisation

The guideline is authorized by the Nederlandse Vereniging voor Anesthesiologie, the Nederlandse Vereniging voor Neurologie and the Nederlandse Vereniging van Revalidatieartsen.

Funding

Project Guideline 'Evidence based interventional pain practice' development was funded by the Quality Fund for Medical Specialists (SKMS).

Summary

A summary of the guideline can be found here.

Guideline committee

Members guideline committee

- Prof.dr. F.J.P.M. Huygen (chairman); ErasmusMC, Rotterdam
- Drs. J.W. Kallewaard, Rijnstate Ziekenhuis, Arnhem
- Prof.dr. M. van Kleef, MUMC, Maastricht
- Prof.dr. M. van Tulder, VU, Amsterdam
- Dr. K. Van Boxem, World Institute of Pain Benelux Ziekenhuis Zuid Oost Limburg, Genk
- Dr. J. Van Zundert, Vlaamse Anesthesiologische Vereniging voor Pijnbestrijding, Ziekenhuis Zuid Oost Limburg, Genk
- Prof.dr. K. Vissers, World Institute of Pain USA ,Radboud UMC, Nijmegen

Executive members guideline committee

Mrs. N. Van Hecke

Drs. M. van Grotel, executive director Nederlandse Vereniging voor Anesthesiologie

Independent epidemiologist

Prof. dr. J. Kleijnen, MUMC Maastricht/York

Methods

Research question

What is the effectiveness of interventional pain management techniques that can be administered by anesthesiologists for the following conditions:

1 Trigeminal neuralgia
2 Cluster headache
3 Persistent idiopathic facial pain
4 Cervical radicular pain
5 Cervical facet joint pain
6 Cervicogenic headache
7 Whiplash Associated Disorders
8 Occipital neuralgia
9 Thoracic radicular pain
10 Thoracic facet joint pain
11 Lumbosacral radicular pain
11a Failed Back Surgery Syndrome
12 Lumbar facet joint pain
13 Spinal canal stenosis
14 Sacroiliac joint pain
15 Discogenic pain
16 Complex regional pain syndrome
17 Herpes zoster and postherpetic neuralgia
18 Painful diabetic polyneuropathy
19 Meralgia paresthetica
20 Carpal tunnel syndrome
21 Phantom pain
23 Traumatic plexus lesion
25 Chronic refractory angina pectoris
26a Raynaud's syndrome
26 Chronic ischemic pain of the extremities
27 Chronic pancreatitis
28 Pain in patients with cancer

Sticking point analysis

After determining the research question, we did a sticking point analysis. We performed an inventory of sticking points in health care and possible impeding factors for the introduction of the future directive. We questioned the following stakeholders:

Nederlandse Vereniging voor Neurochirurgie,
Nederlandse Vereniging voor Orthopedie,
Nederlandse Vereniging voor Neurologie,
Koninklijk Genootschap van Fysiotherapeuten,
Nederlands Huisartsen Genootschap
Vereniging van Revalidatieartsen.

V&VN pijnverpleegkundigen/verpleegkundig specialisten pijn,
Nederlands Instituut van Psychologen
Pijnpatienten naar één stem
Nederlandse Vereniging voor Rugpatiënten

We received answers from Pijnpatienten naar één stem and the NHG.

Pijnpatienten naar één stem asked attention for 2 topics, namely: 1. Communication (treatment, not being taken seriously, not listening well, joint decision making, talking about sexuality, little consultation between practitioners, unclear head treatment, adherence) and 2. Satisfaction (obtained advice and the result of the treatment are disappointing, waiting list). The NHG asked for a connection of the updated guideline to NHG Standards (NHG-Standard Pain)

Review of the literature

An independent epidemiologist, Prof.dr. J. Kleijnen, MUMC, Maastricht/York, was asked to review the literature. This review aimed to identify and summarize relevant evidence using GRADE methodology to inform guidelines on interventional pain management produced by the NVA and VAVP. This objective was achieved by: conducting a review of existing systematic reviews, randomized controlled trials (RCTs) and, where appropriate, observational studies of pain management for Trigeminal Neuralgia; Cluster Headache; Persistent Idiopathic Facial Pain; Cervical Radicular Pain; Cervical Facet Pain; Cervicogenic Headache; Whiplash-Associated Disorders; Occipital Neuralgia; Thoracic Pain; Lumbosacral Radicular Pain; Failed back surgery syndrome; Pain due to Spinal Canal Stenosis; Pain Originating from the Lumbar Facet Joints; Sacroiliac Joint Pain; Discogenic Low Back Pain; Complex Regional Pain Syndrome; Herpes Zoster and Post-Herpetic Neuralgia; Painful Diabetic Polyneuropathy; Carpal Tunnel Syndrome; Meralgia Parasthetica; Phantom Pain; Traumatic Plexus Lesion; Pain in Patients with Cancer; Chronic Refractory Angina Pectoris; Ischemic Pain in the Extremities and Raynaud's Phenomenon and Pain in Chronic Pancreatitis.

Inclusion criteria

Studies that meet the following criteria were eligible for inclusion:

Participants

Patients (adults or children) with any of the following conditions: Trigeminal Neuralgia; Cluster Headache; Persistent Idiopathic Facial Pain; Cervical Radicular Pain; Cervical Facet Pain; Cervicogenic Headache; Whiplash-Associated Disorders; Occipital Neuralgia; Painful shoulder complaints; Thoracic Pain; Lumbosacral Radicular Pain; Failed Back Surgery Syndrome; Pain due to Spinal Canal Stenosis; Pain Originating from the Lumbar Facet Joints; Sacroiliac Joint Pain; Discogenic Low Back Pain; Complex Regional Pain Syndrome; Herpes Zoster and Post-Herpetic Neuralgia; Painful Diabetic Polyneuropathy; Carpal Tunnel Syndrome; Meralgia Parasthetica; Phantom Pain; Acnes; Traumatic Plexus Lesion; Pain in Patients with Cancer; Chronic Refractory Angina Pectoris; Ischemic Pain in the Extremities and Raynaud's Phenomenon; or Pain in Chronic Pancreatitis.

Interventions

Interventional treatments were understood to be those involving a procedure to target the source of the patient's pain such as occipital nerve stimulation for cluster headache. A list of interventions based on the previous guidelines were eligible; these are summarized by population in Appendix 1. Any identified RCT of possible interventional treatments which are not listed in the protocol were referred to the clinicians for decisions on inclusion in the review.

Outcome

Inclusion was not restricted based on outcome.

- Study design

For interventional management, systematic reviews (SRs) and randomized controlled trials (RCTs) were eligible. If no relevant RCTs were identified for any pre-specified interventional technique of interest, then case-control or cohort studies were eligible.

Literature search

Literature searches were conducted for each of the conditions of interest. The searches were carried out using a stepwise approach to identify relevant studies according to study design:

- Systematic reviews and guidelines, for all interventions of interest, including conservative management
- Randomized controlled trials
- Observational studies (case-control or cohort studies), for interventional treatments only

Only in the event of no relevant systematic reviews or RCTs of interventional studies being identified further searches were conducted to identify observational studies.

Systematic reviews were identified by screening the in-house KSR Pain database of systematic reviews. This consists of systematic reviews identified by regular literature searches of a range of bibliographic databases. Additionally, a search for recent guidelines was undertaken.
The search strategies used to identify RCTs combined relevant search terms comprising of indexed keywords (e.g. Medical Subject Headings, MeSH) and text terms appearing in the titles and/or abstracts of database records for each of the target conditions.

Search methods met best practice standards in systematic reviews[9, 10]. The search strategies were developed specifically for each database and the keywords adapted according to the configuration of each database. Searches were limited by date range for the RCTs and observational studies to 1990-2014. Where appropriate, searches were limited to remove animal studies. Searches were not limited by language or publication status.

The Embase search strategy used to search for the KSR Pain database, and examples of draft Embase search strategies for the RCT searches are presented in Appendix 3. An example of the observational studies search filter to be used if evidence is not identified from the systematic review and RCT searches is also provided in Appendix 3.

1) Systematic reviews and guidelines

The following databases are searched for the KSR Pain database of systematic reviews:

- Cochrane Database of Systematic Reviews (CDSR) (Wiley Online Library)
- Database of Abstracts of Reviews of Effects (Wiley Online Library)
- Medline In-Process Citations, Medline Daily Update (OvidSP)
- Embase (OvidSP)
- CINAHL (Cumulative Index to Nursing and Allied Health Literature) (EBSCO)
- PsycINFO (OvidSP)

- Allied and Complementary Medicine Database (AMED) (ProQuest) For recent guidelines, the National Guideline Clearinghouse (www.guideline.gov/) were searched for the period 2010-2015.

2) RCTs

The following databases were searched from 1994 to the present for RCTs and, where appropriate, including a search filter designed to identify RCTs.[11]

Medline (OvidSP)

Medline In-Process Citations, Medline Daily Update (OvidSP)

PubMed (NLM)

Embase (OvidSP)

Cochrane Central Register of Controlled Trials (CENTRAL) (Wiley Online Library)

3) Observational studies

If no evidence from systematic reviews and RCTS were identified the following databases were searched from 1994 to the present and included a search filter designed to identify observational studies.[12]

- Medline (OvidSP)
- Medline In-Process Citations, Medline Daily Update (OvidSP)
- PubMed (NLM)
- Embase (OvidSP)

Reference checking

The bibliographies of identified research and review articles were checked for relevant studies. Handling of citations.

Quality assurance within the search process
The main Embase strategy for each search was independently peer reviewed by a second Information Specialist, using the CADTH Peer Review checklist.[13]

Study selection

Two reviewers independently screened the titles and abstracts of all reports identified by the searches; any discrepancies were discussed and resolved by consensus. Full copies of all studies deemed potentially relevant were obtained. One reviewer assessed full text papers for inclusion, a second reviewer checked the decision; any disagreements were resolved by consensus.

Data extraction

For interventional studies, we extracted details on the following: participant characteristics; study design; brief inclusion and exclusion criteria; brief intervention details; details of outcomes assessed and results. Data were only extracted for outcomes rated as critical or important for each topic area (see section on GRADE below). Data were extracted by one reviewer and checked by a second; any disagreements was resolved by consensus.

Quality assessment

Systematic reviews were assessed for methodological quality using the ROBIS tool.[14] This tool aims

to assess the risk of bias in systematic reviews and includes domains covering study eligibility criteria, identification and selection of studies, data collection and study appraisal, synthesis and findings, and interpretation (Appendix 4a). Trials were assessed for methodological quality using the Cochrane Risk of Bias tool (Appendix 4b).[15] This includes items covering selection bias (random sequence generation and allocation concealment), performance bias (participant blinding), detection bias (blinding of outcome assessors) attrition bias (incomplete outcome data), and reporting bias (selective reporting). There was also an additional field for other sources of bias. We believe that all important concerns about bias were included in the other domains in the tool and so no further domains were added. We used the new Cochrane risk of bias tool for non-randomized studies to assess the risk of bias in observational studies.[16] Domains included cover bias due to confounding, bias in the selection of participants into the study, bias due to departures from intended interventions, bias due to missing data, bias in taking measurements, and bias in selection of the reported result.

For all tools, if at least one of the domains is rated as "high" the study will be considered at high risk of bias, if all domains are judged as "low" the trial will be considered at low risk of bias, otherwise the trial will be considered at "unclear" risk of bias. The risk of bias assessment was conducted as part of the data extraction process.

Synthesis

The synthesis was based around GRADE methodology. If sufficient studies assessing similar populations and outcomes were found, then a formal meta-analysis was used to estimate summary measures of effect.
For dichotomous data, we calculated the relative risk (RR) for each trial with the associated 95% confidence intervals (CIs). Continuous data were analyzed as the mean difference between groups and associated 95% CIs. For multi-arm studies, we analyzed each intervention arm compared to the control group separately. For cross-over trials, data for the first period of the trial only were extracted and included in the meta-analysis.
Because systematic differences between studies (heterogeneity) were found, the random-effects model was used to calculate summary estimates. Heterogeneity was investigated visually using forest plots and statistically using the I2 and Q statistics.
Following GRADE methodology, the quality of evidence was assessed for risk of bias, publication bias, imprecision, inconsistency, indirectness, magnitude of effect, dose- response gradient and the effects of any confounding.

- Risk of bias describes any limitations in the design and execution of a collection of studies, for example failure to properly randomize the participants, failure to blind participants and investigators or selective reporting of outcomes (see section on Quality assessment).
- Publication bias is a measure of the degree to which the available published data are skewed by selective publication of trials dependent on their results, e.g. positive trials are more likely to be published than those with negative results (see section on Analysis).
- Imprecision assesses the degree to which random error influences the interpretation of the results.
- Inconsistency captures the degree of heterogeneity between studies in terms of their PICO elements, i.e. how comparable are the studies to each other (see section on Analysis).
- Indirectness refers to evidence that may be considered relevant, but not directly studied in the appropriate population, or with the appropriate comparator(s).

- The remaining GRADE criteria can be used to rate up the quality of evidence if there is a very large effect of intervention, if there is evidence of a dose response or if the effects of any confounding would reduce rather than increase any observed effects. Each of the GRADE criteria was described in detail in a series of papers published by the GRADE working group. Appendix 5a presents GRADE definitions, categories, and factors affecting the quality of evidence. For each intervention for each population of interest, we will develop GRADE evidence profiles and summary of findings tables to summarize the evidence and rate the quality of evidence (See Appendix 5b for an example of an evidence profile). We selected a maximum of three critical or important outcomes for each topic area for which to produce GRADE evidence summaries. A list of critical or important outcomes was agreed with the NVA and the VAVP. The three most critical outcomes for each topic were used to create GRADE summaries. See Appendix 2.

Reports

For each of the studied interventions a scientific conclusion was formulated by the independent epidemiologist. The guideline committee carefully checked all the scientific conclusions and the underlying literature and reports. In case of doubt, the outcome was discussed with the epidemiologist.

For each of the studied interventions we made further considerations in addition to (the quality of) the scientific evidence. Other aspects are important and are considered, such as the expertise of the working group members, the patient values and preferences, costs, availability of facilities and organizational matters. In addition, the literature published after the search is also included in the recitals. These aspects are, insofar as not part of the literature summary, mentioned and assessed (weighed) under the heading Considerations. A last check on newer literature was made in March 2018.

The scientific conclusion and the further considerations result in a recommendation. The recommendations provide answers to the initial research question and are based on the available scientific evidence and the most important considerations. The strength of the scientific evidence and the weight assigned to the considerations by the working group together determine the strength of the recommendation. In accordance with the GRADE method, a low evidential value of conclusions in the systematic literature analysis does not exclude a strong recommendation a priori, and weak recommendations are also possible if there is a high level of evidence. The strength of the recommendation is always determined by weighing all relevant arguments together.

Originally, we planned to study 28 conditions. During the process it became clear that painful shoulder pain is a too heterogeneous topic and that for ACNES the literature was too limited to make any conclusion, consideration and or recommendation at all. The guideline committee decided that on this moment they will not be part of the guideline.

Authorization process

Following the guideline for guidelines (adviescommissie Richtlijnen Medisch specialistische richtlijnen 2.0) the draft guideline is submitted to the relevant (scientific) associations and (patient) organizations for comment. The comments are collected and discussed with the working group. Following the comments, the draft guideline is adapted and definitively determined by the working group. The final guideline is presented to the participating (scientific) associations and (patient) organizations for authorization and authorized or approved by them. The reports will be available

via: https://richtlijnendatabase.nl. This process should be finished in December 2018.

Implementation, e.g. in the various phases of the guideline development, account was taken of the implementation of the guideline and the practical feasibility of the recommendations. In doing so, explicit attention was paid to factors that could promote or impede the introduction of the guideline in practice. The guideline is distributed digitally among all relevant professional groups. The guideline can also be downloaded from the website of the Guidelines Database.
In a next step, scientific articles of each diagnosis will be developed and submitted, for peer review, to the Journal of Pain Practice. For consideration, is to collect the different articles and publish in a textbook. This process must be finished in December 2019.

Indicators and analysis knowledge gaps

Indicators will be developed and knowledge gaps analysis will be performed.

Disclosures

Prof.dr. FJPM Huygen (chairman), Erasmusmc, Rotterdam –advisory board Abbott
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Appendixes

APPENDIX 1: ELIGIBLE POPULATIONS AND INTERVENTIONS

Population	Interventional treatments
Trigeminal Neuralgia	Surgical microvascular decompression (MVD). Stereotactic radiation therapy, Gamma knife. Percutaneous balloon microcompression. Radiofrequency (RF) treatment of the Gasserian ganglion Pulsed RF treatment of the Gasserian ganglion Percutaneous glycerol rhizolysis
Cluster Headache	RF treatment of the pterygopalatine ganglion (sphenopalatinum) Occipital nerve stimulation
Persistent Idiopathic Facial Pain	Pulsed RF treatment of the ganglion pterygopalatinum (sphenopalatinum)
Cervical Radicular Pain	Interlaminar epidural corticosteroid administration Transforaminal epidural corticosteroid administration RF treatment adjacent to the cervical ganglion spinale (DRG) Pulsed RF treatment adjacent to the cervical ganglion spinale (DRG) Spinal cord stimulation
Cervical Facet Pain	Intra-articular injections Therapeutic (repetitive) cervical ramus medialis (medial branch) of the ramus dorsalis block (local anaesthetic with or without corticosteroid) RF treatment of the cervical ramus medialis (medial branch) of the ramus dorsalis
Cervicogenic Headache	Injection of nervus occipitalis major with corticosteroid + local anesthetic Injection of atlanto - axial joint with corticosteroid + local anesthetic RF treatment of the cervical ramus medialis (medial branch) of the ramus dorsalis Pulsed RF treatment of the cervical ganglion spinale (DRG) (C2 – C3)
Whiplash-Associated Disorders	Botulinum toxin type A Intra-articular corticosteroid injection RF treatment of the cervical ramus medialis (medial branch) of the ramus dorsalis
Occipital Neuralgia	Single infiltration of the nervi occipitales with local anaesthetic and corticosteroids Pulsed RF treatment of the nervi occipitales Pulsed RF treatment of the cervical ganglion spinale (DRG) Subcutaneous stimulation of the nervi occipitales Botulinum toxin A injection
Painful Shoulder Complaints	Corticosteroid injections Continuous cervical epidural infusion Continuous cervical epidural infusion
Thoracic Pain	Intercostal block RF treatment of thoracic ganglion spinale (DRG) Pulsed RF treatment of thoracic ganglion spinale (DRG)
Lumbosacral Radicular Pain	Interlaminar epidural corticosteroid administration Transforaminal epidural corticosteroid administration in “ contained herniation ” Transforaminal epidural corticosteroid administration in “ extruded herniation ” RF lesioning adjacent to the lumbar ganglion spinale (DRG) Pulsed RF treatment adjacent to the lumbar ganglion spinale (DRG) Spinal cord stimulation (FBSS only)

Population	Interventional treatments
	Adhesiolysis — epiduroscopy
Pain Originating from the Lumbar Facet Joints	Intra - articular corticosteroid injections RF treatment of the lumbar rami mediales (medial branches) of the dorsal ramus
Sacroiliac Joint Pain	Therapeutic intra - articular injections with corticosteroids and local anesthetic RF treatment of rami dorsales and rami laterals Pulsed RF treatment of rami dorsales and rami laterals Cooled / RF treatment of the rami laterales
Coccygodynia	Local injections corticosteroids/local anesthetic Intradiscal corticosteroid injections, ganglion impar block, RF ganglion impar, caudal block Neurostimulation
Discogenic Low Back Pain	Intradiscal corticosteroid administration RF treatment of the discus intervertebralis Intradiscal electrothermal therapy Biacuplasty Disctrode RF of the ramus communicans
Complex Regional Pain Syndrome	Intravenous regional block guanethidine Ganglion stellatum (stellate ganglion) block Lumbar sympathetic block Plexus brachialis block Epidural infusion analgesia Spinal cord stimulation Peripheral nerve stimulation
Herpes Zoster and Post-Herpatic Neuralgia	Interventional pain treatment of acute herpes zoster Epidural corticosteroid injections Sympathetic nerve block One - time epidural corticosteroid injection Repeated paravertebral injections Sympathetic nerve block Epidural corticosteroid injections Sympathetic nerve block Intrathecal injection Spinal cord stimulation
Painful Diabetic Polyneuropathy	Spinal cord stimulation
Carpal Tunnel Syndrome	Local injections with corticosteroids Pulsed RF treatment median nerve
Meralgia Parasthetica	Lateral femoral cutaneous nerve (LFCN) infiltration with local anesthetic ± corticosteroid Pulsed RF treatment of LFCN Spinal cord stimulation
Phantom Pain	Pulsed RF treatment of the stump neuroma Pulsed RF treatment adjacent to the spinal ganglion (DRG) Spinal cord stimulation
Traumatic Plexus Lesion	Spinal cord stimulation
Pain in Patients with Cancer	Intrathecal medication delivery Epidural medication delivery Cervical cordotomy

Population	Interventional treatments
	Neurolytic plexus coeliacus block Neurolytic nervus splanchnicus block Neurolytic plexus hypogastricus block Intrathecal phenolization of lower sacral roots of cauda equine Vertebroplasty Kyphoplasty
Chronic Refractory Angina Pectoris	Spinal cord stimulation
Ischemic Pain in the Extremities and Raynaud's Phenomenon	Sympathectomy Spinal cord stimulation
Pain in Chronic Pancreatitis	RF nervus splanchnicus block Spinal cord stimulation

APPENDIX 2: PROPOSED OUTCOMES PER CONDITION

Population	Critical / Important Outcomes to extract	Three most Important Outcomes to be used for GRADE
Trigeminal Neuralgia	Immediate pain relief Complete pain relief without medication at one / two / three years Quality of life at one year Patient satisfaction at one year Adverse events at any time including mortality	
Cluster Headache	Reduction in pain intensity at 15 or 30 minutes Pain-free at 15 or 30 minutes without use of rescue medication Time to pain-free response Recurrence of headache Use of rescue medication Adverse events at any time	
Persistent Idiopathic Facial Pain	Reduction in pain intensity Use of analgesics Pain quality Sleep quality Psychological symptoms Quality of life Adverse events	
Cervical Radicular Pain	Reduction in mean neck and arm pain scores at 1 day Reduction in mean neck and arm pain scores at 12 months Patient satisfaction Adverse events	
Cervical Facet Pain	Pain relief (short-term relief = up to 6 months and long-term > 6 months). Improvement in functional status Psychological status Return to work Reduction in opioid intake Adverse events	
Cervicogenic Headache	Headache frequency (% days per week) Headache intensity (VAS) Headache duration (average no of hours per week) Disability (Von Korff disability scale) Flexion rotation test Neck pain and disability Analgesic use (mean no of pain killers per day, % of days needed) Adverse events	

Population	Critical / Important Outcomes to extract	Three most Important Outcomes to be used for GRADE
Whiplash-Associated Disorders	Pain intensity at six months post-treatment Disability at six months Functional ability at six months Quality of life Adverse events	
Occipital Neuralgia	Total pain index at 6 months Pain intensity on VAS scale at 6 months Adverse events	
Painful Shoulder Complaints	Range of movement Pain Functional status Adverse events	
Thoracic Pain	Pain relief (short-term relief = up to 6 months and long-term > 6 months). Improvement in functional status Psychological status Return to work Reduction in opioid intake Adverse events	
Lumbosacral Radicular Pain	Pain relief (short-term relief = up to 6 months and long-term > 6 months). Improvement in functional status Psychological status Return to work Reduction in opioid intake Adverse events	
Pain Originating from the Lumbar Facet Joints	Pain relief (short-term relief = up to 6 months and long-term > 6 months). Improvement in functional status Psychological status Return to work Reduction in opioid intake Adverse events	
Sacroiliac Joint Pain	Pain relief (short-term relief = up to 6 months and long-term > 6 months). Improvement in functional status Psychological status Return to work Reduction in opioid intake Adverse events	
Coccygodynia	Pain relief (short-term relief = up to 6 months and long-term > 6 months) Disability	

Population	Critical / Important Outcomes to extract	Three most Important Outcomes to be used for GRADE
	Adverse events	
Discogenic Low Back Pain	Pain relief (short-term relief = up to 6 months and long-term > 6 months). Improvement in functional status Psychological status Return to work Reduction in opioid intake Adverse events	
Complex Regional Pain Syndrome	Pain relief (short-term relief = up to 6 months and long-term > 6 months). Pain intensity level Adverse events	
Herpes Zoster and Post-Herpatic Neuralgia	Presence of PHN 6 months after onset of acute herpetic rash Pain severity at 12 months Quality of life at six months Adverse events	
Painful Diabetic Polyneuropathy	Patient-reported pain relief of 30% or greater. Patient-reported pain relief of 50% or greater. Adverse events	
Carpal Tunnel Syndrome	Overall improvement of CTS symptoms as measured on Symptom Severity Score (short term and long-term) Disability measured with DASH questionnaire Function measured on functional Status questionnaire Grip strength Time to work or usual activities Adverse events	
Meralgia Parasthetica	Resolution of symptoms at least three months after intervention Improvement in symptoms at least three months after intervention Adverse events	
Phantom Pain	Patient reported pain using standard validated scales Patient-reported non-painful phantom sensations using validated scales Patient satisfaction Activities of daily living and ambulation Range of movement Quality of life	

Population	Critical / Important Outcomes to extract	Three most Important Outcomes to be used for GRADE
	Anxiety / depression Use of pain coping strategies Sleep Analgesic consumption Hospital attendance Need for other health care interventions Adverse events	
Traumatic Plexus Lesion	Range of movement Pain Functional status Adverse events	
Pain in Patients with Cancer	Reduction of pain (VAS) Health-related quality of life Physical and functional abilities pain-related anxiety and depression Adverse events	
Chronic Refractory Angina Pectoris	Myocardial ischaema Exercise capacity Pain control Quality of life Adverse events	
Ischemic Pain in the Extremities and Raynaud's Phenomenon	Attack rates of Raynaud's phenomenon Duration of attacks Severity scores Treatment preference scores Quality of life Physiological measures Adverse events	
Pain in Chronic Pancreatitis	Pain on VAS scale Proportion of pain-free participants Need for pain medication Quality of life Number of admissions to hospital Duration of hospital stay Number of pancreatitis events Adverse events	

APPENDIX 3: EXAMPLE SEARCH STRATEGIES

SYSTEMATIC REVIEWS: KSR PAIN DATABASE SEARCH

Embase (OvidSP): 1974-2015/02/06
Searched 9.2.15

1 systematic review/ (80011)
2 "systematic review (topic)"/ (8472)
3 meta analysis/ (82999)
4 "meta analysis (topic)"/ (15464)
5 (meta anal$ or metaanal$ or metanal$).ti,ab,ot. (86876)
6 (systematic$ adj2 (review$ or overview$)).ti,ab,ot. (77642)
7 (systematic literature adj (search$ or synthesis or syntheses)).ti,ab,ot. (3457)
8 evidence based review$.ti,ab,ot. (1731)
9 integrative review$.ti,ab,ot. (879)
10 structured analysis.ti,ab,ot. (158)
11 (evidence synthesis or evidence syntheses).ti,ab,ot. (1612)
12 (meta synthes$ or metasynthes$).ti,ab,ot. (369)
13 (medline or pubmed or cochrane or embase or cinahl or psyc?lit or psyc?info or science citation index or electronic databases or online databases or literature databases or bibliographic databases).ab. (118355)
14 (systematic$ adj2 search$).ab. (13877)
15 search strategy.ti,ab. (11488)
16 data extraction.ab. (12197)
17 selection criteria.ab. (19800)
18 (pooled adj2 (data or analysis)).ab. (14566)
19 (inclusion criteria or exclusion criteria).ab. (75116)
20 or/13-19 (206938)
21 review$.ti,pt. (2158513)
22 20 and 21 (90718)
23 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 22 (234404)
24 animal/ (1579484)
25 animal experiment/ (1801696)
26 (rat or rats or mouse or mice or murine or rodent or rodents or hamster or hamsters or pig or pigs or porcine or rabbit or rabbits or animal or animals or dogs or dog or cats or cow or bovine or sheep or ovine or monkey or monkeys).ti,ab,ot,hw. (5716476)
27 or/24-26 (5716476)
28 exp human/ (15139951)
29 human experiment/ (329303)
30 or/28-29 (15141380)
31 27 not (27 and 30) (4566470)
32 23 not 31 (231957)
33 (letter or editorial).pt. (1313434)
34 conference.so. (1628341)
35 32 not (33 or 34) (198562)
36 limit 35 to yr="2010 -Current" (95461)
37 exp *Pain/ (313902)

38 (pain or pains or painful$ or pained).ti,ab,ot. (604153)
39 (hurt or hurting or hurts).ti,ab,ot. (3212)
40 (sore or soreness or tender$ or discomfort or ache$ or aching or agony).ti,ab,ot. (95420)
41 (nociception or nociperception or algiatry).ti,ab,ot. (8730)
42 (allodynia or alveolalgia or backache or causalgia or cephalalgia or cheiragra or chiragra or coxalgia or coxodynia or cystalgia or dorsalgia or dysmenorrh?ea or dyspareunia or dysuria or erythromelalgia or failed back surgery syndrome or fibromyalgia or gastralgia or headache$ or hepatalgia or intermittent claudication or ischialgia or lumbago or lumbalgia or lumbodynia or mastalgia or mastodynia or meralgia paresthetica or metatarsalgia or migraine$ or myalgia or neuralgia or odontalgia or odynophagia or orchalgia or otalgia or paroxysmal hemicrania or piriformis syndrome or piriformis muscle syndrome or pleuralgia or polymyalgia or prostatalgia or prostatodynia or psychalgia or rachialgia or radiculalgia or sciatica or SUNCT syndrome or toothache or vulvodynia).ti,ab,ot. (170372)
43 exp *Analgesia/ (45635)
44 (analgesia or analgesic$ or audioanalgesia or Diffuse Noxious Inhibitory Control or electroanalgesia or hyperalgesia or hypoalgesia or neuroleptanalgesia or Transcutaneous Electric Nerve Stimulation).ti,ab,ot. (131041)
45 (pain or analgesia).jx. (76327)
46 (1399-6576 or 0001-5172 or 1365-2044 or 0003-2999 or 1528-1175 or 0003-3022 or 1471-6771 or 0007-0912 or 1496-8975 or 0832-610X or 1468-2982 or 0333-1024 or 1951-6398 or 1011-288X or 0743-345X or 1743-291X or 0969-9260).is. (91694)
47 or/37-46 (994783)
48 36 and 47 (7976)

RCT SEARCH STRATEGY DRAFTS

1 TRIGEMINAL NEURALGIA, 3 PERSISTENT IDIOPATHIC FACIAL PAIN

Embase (OvidSP): 1974-2015/week 12
Searched 25.3.15

1 trigeminus neuralgia/ (8955)
2 ((trigeminus or trigeminal or epileptiform or trifacial) adj3 (neuralgia$ or neuropathy)).ti,ab,ot,hw. (9822)
3 (Prosopalgia or prosoponeuralgia or "tic douloureux" or "Fothergill$ disease").ti,ab,ot,hw. (313)
4 or/1-3 (9861)
5 (cranial adj3 (nerve$ or nervus) adj3 ("5" or "v" or fifth or five)).ti,ab,ot,hw. (887)
6 (trigemin$ adj3 (nerve$ or nervus or Ganglion)).ti,ab,ot,hw. (18004)
7 trigeminal nerve/ or "CN V".ti,ab,ot. (10265)
8 ((Mandibular or Maxillary or ophthalmic) adj3 (nerve$ or nervous)).ti,ab,ot,hw. (4786)
9 or/5-8 (22478)
10 exp Pain/ or (pain or pains or painful$ or sore$ or tender$ or discomfort or ache$ or aching).ti,ab,ot. (1152767)
11 9 and 10 (7634)
12 4 or 11 [Trigeminal Neuralgia] (14499)
13 face pain/ (8086)

14 ((persistent or idiopathic or chronic or psychogenic or atypical or daily or continuous) adj2 (facial pain or face pain or facial neuralgia$ or face neuralgia$)).ti,ab,ot,hw. (754)
15 (persistent adj3 idiopathic adj3 neuralgia$).ti,ab,ot,hw. (9)
16 PIFP.ti,ab,ot,hw. (23)
17 ((persistent or idiopathic or chronic or psychogenic or atypical or daily or continuous) adj2 (craniofacial pain or craniofacial neuralgia$)).ti,ab,ot,hw. (30)
18 ((persistent or idiopathic or chronic or psychogenic or atypical or daily or continuous) adj2 (orofacial pain or orofacial neuralgia$)).ti,ab,ot,hw. (309)
19 or/13-18 [Persistent Idiopathic Facial Pain] (8351)
20 Random$.tw. or placebo$.mp. or double-blind$.tw. (1176226)
21 animal/ (1618122)
22 animal experiment/ (1834449)
23 (rat or rats or mouse or mice or murine or rodent or rodents or hamster or hamsters or pig or pigs or porcine or rabbit or rabbits or animal or animals or dogs or dog or cats or cow or bovine or sheep or ovine or monkey or monkeys).ti,ab,ot,hw. (5841228)
24 or/21-23 (5841228)
25 exp human/ (15623819)
26 human experiment/ (334698)
27 or/25-26 (15625250)
28 24 not (24 and 27) (4644382)
29 20 not 28 (1051306)
30 (editorial or letter).pt. (1340861)
31 29 not 30 (1034366)
32 (1994$ or 1995$ or 1996$ or 1997$ or 1998$ or 1999$ or 2000$ or 2001$ or 2002$ or 2003$ or 2004$ or 2005$ or 2006$ or 2007$ or 2008$ or 2009$ or 2010$ or 2011$ or 2012$ or 2013$ or 2014$ or 2015$).dd,em. or (1994$ or 1995$ or 1996$ or 1997$ or 1998$ or 1999$ or 2000$ or 2001$ or 2002$ or 2003$ or 2004$ or 2005$ or 2006$ or 2007$ or 2008$ or 2009$ or 2010$ or 2011$ or 2012$ or 2013$ or 2014$ or 2015$).yr. (18867012)
33 12 and 31 and 32 [Trigeminal Neuralgia + RCT] (700)
34 19 and 31 and 32 [Persistent Idiopathic Facial Pain + RCT] (641)
35 33 or 34 (1275)

Trials filter:
Wong SS, Wilczynski NL, Haynes RB. Developing optimal search strategies for detecting clinically sound treatment studies in EMBASE. Journal of the Medical Library Association 2006;94(1):41-7. Best optimization of sensitivity and specificity

2 CLUSTER HEADACHE

Embase (OvidSP): 1974-2015/week 12
Searched 25.3.15

1 exp cluster headache/ (4373)
2 ((cluster$ adj2 headache$) or (cluster$ adj2 head ache$)).ti,ab,ot,hw. (4829)
3 (alarm clock headache$ or alarm clock head ache$).ti,ab,ot,hw. (7)
4 migrainous neuralgia.ti,ab,ot,hw. (43)
5 cluster migraine$.ti,ab,ot,hw. (16)
6 Horton$ cephalalgia.ti,ab,ot,hw. (3)

7 ((erythroprosopalgia adj1 Bing) or ciliary neuralgia or (erythromelalgia adj2 head) or Horton$ headache$ or histaminic cephalalgia or petrosal neuralgia or sphenopalatine neuralgia or vidian neuralgia or Sluder$ neuralgia or hemicrania angioparalyticia).ti,ab,ot,hw. (93)
8 or/1-7 (4912)
9 Random$.tw. or placebo$.mp. or double-blind$.tw. (1176226)
10 animal/ (1618122)
11 animal experiment/ (1834449)
12 (rat or rats or mouse or mice or murine or rodent or rodents or hamster or hamsters or pig or pigs or porcine or rabbit or rabbits or animal or animals or dogs or dog or cats or cow or bovine or sheep or ovine or monkey or monkeys).ti,ab,ot,hw. (5841228)
13 or/10-12 (5841228)
14 exp human/ (15623819)
15 human experiment/ (334698)
16 or/14-15 (15625250)
17 13 not (13 and 16) (4644382)
18 9 not 17 (1051306)
19 (editorial or letter).pt. (1340861)
20 18 not 19 (1034366)
21 (1994$ or 1995$ or 1996$ or 1997$ or 1998$ or 1999$ or 2000$ or 2001$ or 2002$ or 2003$ or 2004$ or 2005$ or 2006$ or 2007$ or 2008$ or 2009$ or 2010$ or 2011$ or 2012$ or 2013$ or 2014$ or 2015$).dd,em. or (1994$ or 1995$ or 1996$ or 1997$ or 1998$ or 1999$ or 2000$ or 2001$ or 2002$ or 2003$ or 2004$ or 2005$ or 2006$ or 2007$ or 2008$ or 2009$ or 2010$ or 2011$ or 2012$ or 2013$ or 2014$ or 2015$).yr. (18867012)
22 8 and 20 and 21 (415)

Trials filter:
Wong SS, Wilczynski NL, Haynes RB. Developing optimal search strategies for detecting clinically sound treatment studies in EMBASE. Journal of the Medical Library Association 2006;94(1):41-7. Best optimization of sensitivity and specificity

4 CERVICAL RADICULAR PAIN, 5 CERVICAL FACET PAIN, 6 CERVICOGENIC HEADACHE, 7 WHIPLASH, 8 OCCIPITAL NEURALGIA

Embase (OvidSP): 1974-2015/week 12
Searched 25.3.15

1 radicular pain/ (2471)
2 (radicular adj3 (pain$ or neuralgia$ or symptom$ or sign or signs or finding$)).ti,ab,hw,ot. (4580)
3 radiculalgia.ti,ab,hw,ot. (94)
4 or/1-3 (4635)
5 radiculopathy/ (7281)
6 (radiculitis or radiculitides or radiculopath$ or polyradiculopath$).ti,ab,hw,ot. (10932)
7 (nerve root adj3 (pain$ or neuralgia$ or inflammation$ or disorder$ or compression$ or avulsion$)).ti,ab,hw,ot. (3522)
8 or/5-7 (13725)

9 cervical spine/ (28958)
10 neck/ or neck muscle/ (41383)
11 (cervical or cervicodorsal or neck).ti,ab,hw,ot. (440900)
12 or/9-11 (440900)
13 8 and 12 (3552)
14 4 or 13 [Cervical Radicular Pain] (7811)
15 Neck Pain/ (13961)
16 ((cervical or cervicodorsal or neck) adj3 (pain$ or syndrom$ or inflam$ or neuralgia$ or symptom$ or discomfort or ache or aching)).ti,ab,hw,ot. (23737)
17 (cervicalgia$ or cervicodynia$ or neckache$).ti,ab,ot,hw. (190)
18 or/15-17 [Cervical facet pain] (23830)
19 secondary headache/ (554)
20 ((cervicogenic or cervical or secondary or analges$ or rebound or post dural or postdural or puncture$ or post trauma$ or posttrauma$ or vascular) adj3 (headache$ or head ache$ or cephalgia$)).ti,ab,ot,hw. (6520)
21 19 or 20 [Cervicogenic headache] (6520)
22 whiplash injury/ (3771)
23 whiplash.ti,ab,ot,hw. (4254)
24 ((Hyperexten$ or hyperflexion) adj3 neck).ti,ab,ot,hw. (254)
25 "Cervical acceleration-deceleration".ti,ab,ot,hw. (5)
26 or/22-25 [Whiplash] (4454)
27 occipital lobe/ and (pain/ or headache/ or neuralgia/) (687)
28 ((occipital or C2 or arnold$) adj3 (neuralgia or headache$ or head ache$ or pain$)).ti,ab,ot,hw. (1396)
29 27 or 28 [Occipital neuralgia] (2033)
30 Random$.tw. or placebo$.mp. or double-blind$.tw. (1176226)
31 animal/ (1618122)
32 animal experiment/ (1834449)
33 (rat or rats or mouse or mice or murine or rodent or rodents or hamster or hamsters or pig or pigs or porcine or rabbit or rabbits or animal or animals or dogs or dog or cats or cow or bovine or sheep or ovine or monkey or monkeys).ti,ab,ot,hw. (5841228)
34 or/31-33 (5841228)
35 exp human/ (15623819)
36 human experiment/ (334698)
37 35 or 36 (15625250)
38 34 not (34 and 37) (4644382)
39 30 not 38 (1051306)
40 (editorial or letter).pt. (1340861)
41 39 not 40 (1034366)
42 (1994$ or 1995$ or 1996$ or 1997$ or 1998$ or 1999$ or 2000$ or 2001$ or 2002$ or 2003$ or 2004$ or 2005$ or 2006$ or 2007$ or 2008$ or 2009$ or 2010$ or 2011$ or 2012$ or 2013$ or 2014$ or 2015$).dd,em. or (1994$ or 1995$ or 1996$ or 1997$ or 1998$ or 1999$ or 2000$ or 2001$ or 2002$ or 2003$ or 2004$ or 2005$ or 2006$ or 2007$ or 2008$ or 2009$ or 2010$ or 2011$ or 2012$ or 2013$ or 2014$ or 2015$).yr. (18867012)
43 14 and 41 and 42 [Cervical Radicular Pain + RCT] (754)
44 18 and 41 and 42 [Cervical facet pain + RCT] (2484)
45 21 and 41 and 42 [Cervicogenic headache + RCT] (682)

46 26 and 41 and 42 [Whiplash + RCT] (291)
47 29 and 41 and 42 [Occipital neuralgia + RCT] (68)
48 or/43-47 (3779)

Trials filter:
Wong SS, Wilczynski NL, Haynes RB. Developing optimal search strategies for detecting clinically sound treatment studies in EMBASE. Journal of the Medical Library Association 2006;94(1):41-7. Best optimization of sensitivity and specificity

9 PAINFUL SHOULDER COMPLAINTS, 22 TRAUMATIC PLEXUS LESION

Embase (OvidSP): 1974-2015/week 12
Searched 26.3.15

1 shoulder pain/ (10184)
2 humeroscapular periarthritis/ (1314)
3 Shoulder Impingement Syndrome/ (1756)
4 (shoulder$ adj3 (pain$ or complaint$ or neuralgia or irritat$ or inflam$ or impinge$ or traum$ or discomfort or dysfunct$)).ti,ab,ot,hw. (15924)
5 ((glenohumeral or acromioclavicular or Rotator Cuff) adj3 (pain$ or complaint$ or neuralgia or irritat$ or inflam$ or traum$ or discomfort or dysfunct$ or arthritis or osteoarthritis)).ti,ab,ot,hw. (1205)
6 ((shoulder$ or adhesive or humeroscapular or scapularis or scapulo or humeroscapularis or scapulohumeralis or scapulohumeral) adj3 (capsulitis or Capsulitides or bursitis or frozen or periarthritis or periarthropathia or peri-arthritis or arthritis or osteoarthritis or tenosynovitus)).ti,ab,ot,hw. (4299)
7 ((swimmer$ or thrower$) adj3 shoulder$).ti,ab,ot,hw. (107)
8 or/1-7 [Painful shoulder] (19550)
9 brachial plexus injury/ (3733)
10 ((brachial$ or plexus) adj3 (lesion$ or injur$ or trauma$ or damag$ or paralys$ or palsy or palsies or neuropath$ or dysfunc$)).ti,ab,ot,hw. (8246)
11 (brachial adj2 plexopath$).ti,ab,ot,hw. (719)
12 ((Klumpke$ or dejerine$ or erb$ or duchenne) adj2 (paralys$ or palsy or palsies)).ti,ab,ot,hw. (386)
13 or/9-12 [Traumatic plexus lesion] (8767)
14 Random$.tw. or placebo$.mp. or double-blind$.tw. (1176226)
15 animal/ (1618122)
16 animal experiment/ (1834449)
17 (rat or rats or mouse or mice or murine or rodent or rodents or hamster or hamsters or pig or pigs or porcine or rabbit or rabbits or animal or animals or dogs or dog or cats or cow or bovine or sheep or ovine or monkey or monkeys).ti,ab,ot,hw. (5841228)
18 or/15-17 (5841228)
19 exp human/ (15623819)
20 human experiment/ (334698)
21 19 or 20 (15625250)
22 18 not (18 and 21) (4644382)
23 14 not 22 (1051306)

24 (editorial or letter).pt. (1340861)
25 23 not 24 (1034366)
26 (1994$ or 1995$ or 1996$ or 1997$ or 1998$ or 1999$ or 2000$ or 2001$ or 2002$ or 2003$ or 2004$ or 2005$ or 2006$ or 2007$ or 2008$ or 2009$ or 2010$ or 2011$ or 2012$ or 2013$ or 2014$ or 2015$).dd,em. or (1994$ or 1995$ or 1996$ or 1997$ or 1998$ or 1999$ or 2000$ or 2001$ or 2002$ or 2003$ or 2004$ or 2005$ or 2006$ or 2007$ or 2008$ or 2009$ or 2010$ or 2011$ or 2012$ or 2013$ or 2014$ or 2015$).yr. (18867012)
27 8 and 25 and 26 [Painful shoulder + RCT] (2004)
28 13 and 25 and 26 [Traumatic plexus lesion + RCT] (196)
29 27 or 28 (2189)

Trials filter:
Wong SS, Wilczynski NL, Haynes RB. Developing optimal search strategies for detecting clinically sound treatment studies in EMBASE. Journal of the Medical Library Association 2006;94(1):41-7. Best optimization of sensitivity and specificity

10 THORACIC PAIN - INTERVENTIONS: INTERCOSTAL BLOCK, RADIOFREQUENCY, VERTEBROPLASTY

Embase (OvidSP): 1974-2015/week 12
Searched 27.3.15

1 Thorax pain/ (53081)
2 (Chest or thorax or thoracic).ti,ab,ot,hw. (482148)
3 exp pain/ (879389)
4 (pain or pains or painful$ or pained).ti,ab,ot. (628565)
5 (hurt or hurting or hurts).ti,ab,ot. (3313)
6 (sore or soreness or tender$ or discomfort or ache$ or aching or agony).ti,ab,ot. (99543)
7 (nociception or nociperception or algiatry).ti,ab,ot. (9042)
8 or/3-7 (1150988)
9 2 and 8 (104134)
10 1 or 9 (104134)
11 Random$.tw. or placebo$.mp. or double-blind$.tw. (1176226)
12 animal/ (1618122)
13 animal experiment/ (1834449)
14 (rat or rats or mouse or mice or murine or rodent or rodents or hamster or hamsters or pig or pigs or porcine or rabbit or rabbits or animal or animals or dogs or dog or cats or cow or bovine or sheep or ovine or monkey or monkeys).ti,ab,ot,hw. (5841228)
15 or/12-14 (5841228)
16 exp human/ (15623819)
17 human experiment/ (334698)
18 16 or 17 (15625250)
19 15 not (15 and 18) (4644382)
20 11 not 19 (1051306)
21 (editorial or letter).pt. (1340861)
22 20 not 21 (1034366)

23 (1994$ or 1995$ or 1996$ or 1997$ or 1998$ or 1999$ or 2000$ or 2001$ or 2002$ or 2003$ or 2004$ or 2005$ or 2006$ or 2007$ or 2008$ or 2009$ or 2010$ or 2011$ or 2012$ or 2013$ or 2014$ or 2015$).dd,em. or (1994$ or 1995$ or 1996$ or 1997$ or 1998$ or 1999$ or 2000$ or 2001$ or 2002$ or 2003$ or 2004$ or 2005$ or 2006$ or 2007$ or 2008$ or 2009$ or 2010$ or 2011$ or 2012$ or 2013$ or 2014$ or 2015$).yr. (18867012)
24 10 and 22 and 23 [Thoracic + RCT] (7776)
25 intercostal nerve block/ (458)
26 ((intercostal or thoracic) adj3 block$).ti,ab,ot,hw. (1590)
27 ICNB.ti,ab,ot. (11)
28 or/25-27 (1592)
29 24 and 28 [Thoracic + Intercostal + RCT] (153)
30 10 and 23 and 28 [Thoracic + Intercostal] (575)
31 exp electrostimulation therapy/ (183386)
32 radiofrequency/ (13006)
33 (radiofreq$ or radio freq$).ti,ab,ot,hw. (50718)
34 (RF or PRF).ti,ab,ot. (35733)
35 or/31-34 (256080)
36 24 and 35 [Thoracic + Radiofrequency + RCT] (243)
37 10 and 23 and 35 [Thoracic + Radiofrequency] (2516)
38 exp Vertebroplasty/ (4558)
39 (vertebroplast$ or kyphoplast$).ti,ab,hw,ot. (5083)
40 38 or 39 (5083)
41 24 and 40 [Thoracic + vertebroplasty + RCT] (28)
42 10 and 23 and 40 [Thoracic + vertebroplasty] (468)
43 29 or 36 or 41 [RCT] (408)
44 30 or 37 or 42 [no RCT filter] (3463)

11 LUMBOSACRAL RADICULAR PAIN, 12 LUMBAR FACET JOINTS, 13 SACROILIAC JOINT PAIN, 14 COCCYGODYNIA, 15 DISCOGENIC LOW BACK PAIN

Embase (OvidSP): 1974-2015/week 12
Searched 25.3.15

1 sciatica/ or Ischialgia/ (6349)
2 radicular pain/ and exp back/ (879)
3 (radicul$ adj3 (lumba$ or lumbo$ or sacra$ or spin$ or back)).ti,ab,ot,hw. (3581)
4 (sciatica or ischias or lumboischialgia).ti,ab,ot,hw. (4481)
5 (sciatic adj3 (pain or neuritis or neuralgia or irritat$ or inflammat$ or traum$ or discomfort or dysfunct$)).ti,ab,ot,hw. (1271)
6 ischiatic.ti,ab,ot,hw. (243)
7 or/1-6 [Lumbrosacral radicular pain] (12191)
8 lumbar spine/ or lumbar vertebra/ or zygapophyseal joint/ (48593)
9 ((lumba$ or lumbo$) adj2 (facet$ or joint$ or verteb$ or spin$ or zygapophys$ or apophyseal or z-joint$)).ti,ab,ot. (47965)
10 (facetogenic or faceto-genic).ti,ab,ot. (24)
11 or/8-10 (68183)
12 exp pain/ (879389)

13 (pain or pains or painful$ or pained).ti,ab,ot. (628565)
14 (hurt or hurting or hurts).ti,ab,ot. (3313)
15 (sore or soreness or tender$ or discomfort or ache$ or aching or agony).ti,ab,ot. (99543)
16 (nociception or nociperception or algiatry).ti,ab,ot. (9042)
17 or/12-16 (1150988)
18 11 and 17 [Lumbar Facet Pain] (20096)
19 Sacroiliitis/ or (Sacroiliiti$ or sacroiliti$ or sacroileiti$).ti,ab,ot,hw. (3557)
20 sacroiliac joint/ or articulatio sacroiliaca.ti,ab,ot,hw. (4657)
21 ((ileosacral or iliosacral or sacroiliac$ or sacro iliac$ or SI) adj3 joint$).ti,ab,ot,hw. (6172)
22 ((ileosacral or iliosacral or sacroiliac$ or sacro iliac$) adj3 (arthritis or osteoarthritis or syndrome$)).ti,ab,ot,hw. (252)
23 (SIJ or SIJD).ti,ab,ot. (536)
24 ((ileo or ilio or iliac$) adj2 sacral).ti,ab,ot,hw. (172)
25 or/19-24 (8637)
26 25 and 17 [Sacroiliac joint pain] (3851)
27 (coccydynia or coccygodynia or coccalgia or coccyxdynia or coccyodynia or coccidynia or coccigodynia or coccyxgodynia or coccydinia or coccidinia or coccyalgia or coccygalgia or coccydnia).af. (388)
28 coccygeal bone/ or (coccygeal or coccyx or os coccyges or tail bone or tailbone or tail-bone).ti,ab,ot,hw. (2315)
29 exp Pain/ or (pain or pains or painful$ or sore$ or tender$ or discomfort or ache$ or aching or strains or strained or sprain or sprains or sprained or injur$ or damag$ or fractur$ or dislocat$).ti,ab,ot,hw. (3188062)
30 ((posterior or anterior) adj3 luxation).ti,ab,ot,hw. (171)
31 (hypermobility or hyper mobility or spicule or "bon$ spur").ti,ab,ot,hw. (4235)
32 or/29-31 (3190651)
33 28 and 32 (774)
34 27 or 33 [Coccygodynia] (948)
35 Low Back Pain/ (37933)
36 Discogenic pain/ (391)
37 ((lumbal or lumbosacral or lumbo-sacral or lumbar$ or low or lower) adj3 (backache$ or back-ache$ or backpain$)).ti,ab,ot. (429)
38 ((lumbal or lumbar or lumbosacral or lumbo-sacral or spine or spinal) adj3 (pain or pains or painful$ or pained or hurt or hurts or hurting or sore or soreness or tender$ or discomfort or aching or agony or ache$ or backache$ or backpain$)).ti,ab,ot. (10896)
39 ((lowback or loin) adj3 (pain or pains or ache$ or painful$ or pained or hurt or hurts or hurting or sore or soreness or tender$ or discomfort or aching or agony)).ti,ab,ot. (833)
40 ((lumbar or lumbal or lumbosacral or lumbo-sacral) adj2 syndrome$).ti,ab,ot. (885)
41 (lumbalgesia or lumbalgia or lumbodynia or lumbago).ti,ab,ot. (1855)
42 ((lumbosacroiliac or lumbo-sacroiliac) adj3 (pain or pains or ache$ or strain or strains or painful$ or pained or hurt or hurts or hurting or sore or soreness or tender$ or discomfort or aching or agony)).ti,ab,ot. (0)
43 ((discogenic$ or disco-genic$) adj3 (back or backpain$ or pain or pains or ache$ or strain or strains or backache$ or syndrome$ or painful$ or pained or hurt or hurts or hurting or sore or soreness or tender$ or discomfort or aching or agony)).ti,ab,ot. (978)

44 (LBP or DLBP or D-LBP).ti,ab,ot. (5552)
45 or/35-44 (49955)
46 exp Intervertebral disk/ (11281)
47 intervertebral disk hernia/ (14812)
48 Lumbar Disk/ (2520)
49 ((intervertebra$ or inter-vertebra$ or vertebra$ or spine or spinal$ or lumbar) adj2 (disc$ or disk$)).ti,ab,ot. (22954)
50 discus intervertebralis.ti,ab,ot. (12)
51 (annulus fibrosis or annulus fibrosus or nucleus pulposus disci intervertebralis or pulpy nucleus or nucleus pulposus).ti,ab,ot. (4302)
52 ((Lower or low) adj1 back).ti,ab,ot. (30417)
53 (discus lumbalis or ((intra-disc$ or intra-disk$ or intradisk$ or intradisc$) adj2 pressure)).ti,ab,ot. (427)
54 or/46-53 (62669)
55 Backache/ (36059)
56 Pain/ (221122)
57 Chronic Pain/ (36593)
58 Inflammatory Pain/ (1102)
59 Nociceptive pain/ (583)
60 or/55-59 (279636)
61 54 and 60 (11810)
62 45 or 61 [Discogenic Lower Back Pain] (55092)
63 Random$.tw. or placebo$.mp. or double-blind$.tw. (1176226)
64 animal/ (1618122)
65 animal experiment/ (1834449)
66 (rat or rats or mouse or mice or murine or rodent or rodents or hamster or hamsters or pig or pigs or porcine or rabbit or rabbits or animal or animals or dogs or dog or cats or cow or bovine or sheep or ovine or monkey or monkeys).ti,ab,ot,hw. (5841228)
67 or/64-66 (5841228)
68 exp human/ (15623819)
69 human experiment/ (334698)
70 or/68-69 (15625250)
71 67 not (67 and 70) (4644382)
72 63 not 71 (1051306)
73 (editorial or letter).pt. (1340861)
74 72 not 73 (1034366)
75 (1994$ or 1995$ or 1996$ or 1997$ or 1998$ or 1999$ or 2000$ or 2001$ or 2002$ or 2003$ or 2004$ or 2005$ or 2006$ or 2007$ or 2008$ or 2009$ or 2010$ or 2011$ or 2012$ or 2013$ or 2014$ or 2015$).dd,em. or (1994$ or 1995$ or 1996$ or 1997$ or 1998$ or 1999$ or 2000$ or 2001$ or 2002$ or 2003$ or 2004$ or 2005$ or 2006$ or 2007$ or 2008$ or 2009$ or 2010$ or 2011$ or 2012$ or 2013$ or 2014$ or 2015$).yr. (18867012)
76 7 and 74 and 75 [Lumbrosacral radicular pain + RCT] (945)
77 18 and 74 and 75 [Lumbar Facet Pain + RCT] (1975)
78 26 and 74 and 75 [Sacroiliac joint pain + RCT] (257)
79 34 and 74 and 75 [Coccygodynia + RCT] (33)
80 62 and 74 and 75 [Discogenic Lower Back Pain + RCT] (6024)
81 or/76-80 (7667)

Trials filter:
Wong SS, Wilczynski NL, Haynes RB. Developing optimal search strategies for detecting clinically sound treatment studies in EMBASE. Journal of the Medical Library Association 2006;94(1):41-7. Best optimization of sensitivity and specificity

16 COMPLEX REGIONAL PAIN

Embase (OvidSP): 1974-2015/week 12
Searched 25.3.15

1 exp complex regional pain syndrome/ (7608)
2 (CRPS or CRPS$2 or complex regional pain syndrome$).ti,ab,hw,ot. (5861)
3 (posttrauma$ dystroph$ or post trauma$ dystroph$ or reflex$ neurovascular dystroph$).ti,ab,hw,ot. (61)
4 (reflex$ sympathetic dystroph$ or (sudeck$ adj2 atroph$) or algodystroph$ or algoneurodystroph$).ti,ab,hw,ot. (3120)
5 (algo dystroph$ or algo neurodystroph$).ti,ab,hw,ot. (33)
6 (shoulder hand adj2 (syndrom$ or dystroph$)).ti,ab,hw,ot. (551)
7 (cervical adj2 sympathetic dystroph$).ti,ab,hw,ot. (2)
8 (causalgia or (pain adj2 deafferentation)).ti,ab,hw,ot. (1349)
9 or/1-8 (9846)
10 Random$.tw. or placebo$.mp. or double-blind$.tw. (1176226)
11 animal/ (1618122)
12 animal experiment/ (1834449)
13 (rat or rats or mouse or mice or murine or rodent or rodents or hamster or hamsters or pig or pigs or porcine or rabbit or rabbits or animal or animals or dogs or dog or cats or cow or bovine or sheep or ovine or monkey or monkeys).ti,ab,ot,hw. (5841228)
14 or/11-13 (5841228)
15 exp human/ (15623819)
16 human experiment/ (334698)
17 15 or 16 (15625250)
18 14 not (14 and 17) (4644382)
19 10 not 18 (1051306)
20 (editorial or letter).pt. (1340861)
21 19 not 20 (1034366)
22 (1994$ or 1995$ or 1996$ or 1997$ or 1998$ or 1999$ or 2000$ or 2001$ or 2002$ or 2003$ or 2004$ or 2005$ or 2006$ or 2007$ or 2008$ or 2009$ or 2010$ or 2011$ or 2012$ or 2013$ or 2014$ or 2015$).dd,em. or (1994$ or 1995$ or 1996$ or 1997$ or 1998$ or 1999$ or 2000$ or 2001$ or 2002$ or 2003$ or 2004$ or 2005$ or 2006$ or 2007$ or 2008$ or 2009$ or 2010$ or 2011$ or 2012$ or 2013$ or 2014$ or 2015$).yr. (18867012)
23 9 and 21 and 22 (631)

Trials filter:
Wong SS, Wilczynski NL, Haynes RB. Developing optimal search strategies for detecting clinically sound treatment studies in EMBASE. Journal of the Medical Library Association 2006;94(1):41-7. Best optimization of sensitivity and specificity

17 HERPES ZOSTER & POST-HERPATIC NEURALGIA

Embase (OvidSP): 1974-2015/week 12
Searched 26.3.15

1 exp herpes zoster/ (18835)
2 (shingles or varicellovirus or (herpes adj2 zoster) or (varicella adj2 zoster) or chicken pox or chickenpox).ti,ab,ot,hw. (36358)
3 (postherpetic or post herpetic).ti,ab,ot,hw. (5157)
4 (VZV or PHN).ti,ab. (6434)
5 or/1-4 (40049)
6 exp pain/ (880464)
7 (pain or pains or painful$ or pained or neuralgia$).ti,ab,ot. (635170)
8 (hurt or hurting or hurts).ti,ab,ot. (3315)
9 (sore or soreness or tender$ or discomfort or ache$ or aching or agony).ti,ab,ot. (99640)
10 (nociception or nociperception or algiatry).ti,ab,ot. (9053)
11 or/6-10 (1153045)
12 5 and 11 (10577)
13 Random$.tw. or placebo$.mp. or double-blind$.tw. (1177510)
14 animal/ (1618126)
15 animal experiment/ (1836227)
16 (rat or rats or mouse or mice or murine or rodent or rodents or hamster or hamsters or pig or pigs or porcine or rabbit or rabbits or animal or animals or dogs or dog or cats or cow or bovine or sheep or ovine or monkey or monkeys).ti,ab,ot,hw. (5844647)
17 or/14-16 (5844647)
18 exp human/ (15636444)
19 human experiment/ (334937)
20 18 or 19 (15637875)
21 17 not (17 and 20) (4646807)
22 13 not 21 (1052443)
23 (editorial or letter).pt. (1342065)
24 22 not 23 (1035480)
25 (1994$ or 1995$ or 1996$ or 1997$ or 1998$ or 1999$ or 2000$ or 2001$ or 2002$ or 2003$ or 2004$ or 2005$ or 2006$ or 2007$ or 2008$ or 2009$ or 2010$ or 2011$ or 2012$ or 2013$ or 2014$ or 2015$).dd,em. or (1994$ or 1995$ or 1996$ or 1997$ or 1998$ or 1999$ or 2000$ or 2001$ or 2002$ or 2003$ or 2004$ or 2005$ or 2006$ or 2007$ or 2008$ or 2009$ or 2010$ or 2011$ or 2012$ or 2013$ or 2014$ or 2015$).yr. (18885853)
26 12 and 24 and 25 (1885)

Trials filter:
Wong SS, Wilczynski NL, Haynes RB. Developing optimal search strategies for detecting clinically sound treatment studies in EMBASE. Journal of the Medical Library Association 2006;94(1):41-7. Best optimization of sensitivity and specificity

18 PAINFUL DIABETIC POLYNEUROPATHY

Embase (OvidSP): 1974-2015/week 12
Searched 26.3.15

1 diabetic neuropathy/ (18344)
2 (diabet$ adj3 (polyneuropath$ or neuropath$ or neuritis or polyneuritis)).ti,ab,ot,hw. (23263)
3 or/1-2 (23263)
4 Random$.tw. or placebo$.mp. or double-blind$.tw. (1176226)
5 animal/ (1618122)
6 animal experiment/ (1834449)
7 (rat or rats or mouse or mice or murine or rodent or rodents or hamster or hamsters or pig or pigs or porcine or rabbit or rabbits or animal or animals or dogs or dog or cats or cow or bovine or sheep or ovine or monkey or monkeys).ti,ab,ot,hw. (5841228)
8 or/5-7 (5841228)
9 exp human/ (15623819)
10 human experiment/ (334698)
11 9 or 10 (15625250)
12 8 not (8 and 11) (4644382)
13 4 not 12 (1051306)
14 (editorial or letter).pt. (1340861)
15 13 not 14 (1034366)
16 (1994$ or 1995$ or 1996$ or 1997$ or 1998$ or 1999$ or 2000$ or 2001$ or 2002$ or 2003$ or 2004$ or 2005$ or 2006$ or 2007$ or 2008$ or 2009$ or 2010$ or 2011$ or 2012$ or 2013$ or 2014$ or 2015$).dd,em. or (1994$ or 1995$ or 1996$ or 1997$ or 1998$ or 1999$ or 2000$ or 2001$ or 2002$ or 2003$ or 2004$ or 2005$ or 2006$ or 2007$ or 2008$ or 2009$ or 2010$ or 2011$ or 2012$ or 2013$ or 2014$ or 2015$).yr. (18867012)
17 3 and 15 and 16 (2223)

Trials filter:
Wong SS, Wilczynski NL, Haynes RB. Developing optimal search strategies for detecting clinically sound treatment studies in EMBASE. Journal of the Medical Library Association 2006;94(1):41-7. Best optimization of sensitivity and specificity

19 CARPAL TUNNEL SYNDROME, 25 ISCHEMIC PAIN IN THE EXTREMITIES AND REYNAUD'S PHENOMENON

Embase (OvidSP): 1974-2015/week 12
Searched 26.3.15

1 Carpal Tunnel Syndrome/ (11498)
2 (carpal adj3 (canal or tunnel or nerve$) adj3 (syndrome$ or compres$ or neuropath$ or entrap$)).ti,ab,ot,hw. (12360)
3 (entrapment adj3 neuropath$ adj3 carpal).ti,ab,ot,hw. (31)
4 ("amyotrophy thenar" adj3 carpal).ti,ab,ot,hw. (0)
5 (median adj3 neuropathy).ti,ab,ot,hw. (449)
6 or/1-5 [Carpal tunnel syndrome] (12564)
7 critical limb ischemia/ (1556)
8 ((isch?emic or isch?emia) adj3 (extremit$ or peripheral or periphery)).ti,ab,ot,hw. (4443)
9 ((critical or isch?emic or isch?emia) adj3 vascular disease$).ti,ab,ot,hw. (979)

10 ((critical or severe) adj3 (limb$ or leg or legs or feet or foot or toe or toes or hand or hands or finger$) adj3 (isch?emic or isch?emia or pain$)).ti,ab,ot,hw. (5487)
11 Raynaud phenomenon/ (11049)
12 (Raynaud$ adj3 (disease$ or phenomenon$ or gangrene or syndrome$)).ti,ab,ot,hw. (12532)
13 (white adj3 (finger$ or toes or toe)).ti,ab,ot,hw. (532)
14 (hereditary adj3 cold).ti,ab,ot,hw. (7)
15 Buerger disease/ (3500)
16 (buerger$ adj3 (disease$ or syndrome$)).ti,ab,ot,hw. (3617)
17 ((thromboangiitis or thrombangeitis or arteritis or endangiitis or endarteritis) adj3 (obliterans or obliterating or obliterative or stenosing)).ti,ab,ot,hw. (1772)
18 (blood suppl$ adj3 extrem$).ti,ab,ot,hw. (266)
19 or/7-18 [Ischaemic pain extremities & Raynaud's] (27030)
20 Random$.tw. or placebo$.mp. or double-blind$.tw. (1176226)
21 animal/ (1618122)
22 animal experiment/ (1834449)
23 (rat or rats or mouse or mice or murine or rodent or rodents or hamster or hamsters or pig or pigs or porcine or rabbit or rabbits or animal or animals or dogs or dog or cats or cow or bovine or sheep or ovine or monkey or monkeys).ti,ab,ot,hw. (5841228)
24 or/21-23 (5841228)
25 exp human/ (15623819)
26 human experiment/ (334698)
27 25 or 26 (15625250)
28 24 not (24 and 27) (4644382)
29 20 not 28 (1051306)
30 (editorial or letter).pt. (1340861)
31 29 not 30 (1034366)
32 (1994$ or 1995$ or 1996$ or 1997$ or 1998$ or 1999$ or 2000$ or 2001$ or 2002$ or 2003$ or 2004$ or 2005$ or 2006$ or 2007$ or 2008$ or 2009$ or 2010$ or 2011$ or 2012$ or 2013$ or 2014$ or 2015$).dd,em. or (1994$ or 1995$ or 1996$ or 1997$ or 1998$ or 1999$ or 2000$ or 2001$ or 2002$ or 2003$ or 2004$ or 2005$ or 2006$ or 2007$ or 2008$ or 2009$ or 2010$ or 2011$ or 2012$ or 2013$ or 2014$ or 2015$).yr. (18867012)
33 6 and 31 and 32 [Carpal tunnel syndrome + RCT] (860)
34 19 and 31 and 32 [Ischaemic pain extremities & Raynaud's + RCT] (1582)
35 33 or 34 (2437)

Trials filter:
Wong SS, Wilczynski NL, Haynes RB. Developing optimal search strategies for detecting clinically sound treatment studies in EMBASE. Journal of the Medical Library Association 2006;94(1):41-7. Best optimization of sensitivity and specificity

20 MERALGIA PARESTHETICA

Embase (OvidSP): 1974-2015/week 12
Searched 26.3.15

1 meralgia paresthetica/ (497)

2 (Meralgia adj2 par?esthetic$).af. (682)
3 ((bernhardt or Bernhardt-Roth) adj3 (disease$ or syndrome$ or sensation disturbance)).ti,ab,ot,hw. (5)
4 thigh/ or Thigh$.ti,ab,ot,hw. (31539)
5 Paresthesia/ or (Paresthesia$ or paraesthesia$ or paresthetic or formication$ or dysesthesia$).ti,ab,ot,hw. (40756)
6 exp pain/ (880464)
7 (pain or pains or painful$ or pained).ti,ab,ot. (629195)
8 (hurt or hurting or hurts).ti,ab,ot. (3315)
9 (sore or soreness or tender$ or discomfort or ache$ or aching or agony).ti,ab,ot. (99640)
10 (nociception or nociperception or algiatry).ti,ab,ot. (9053)
11 or/5-10 (1168129)
12 4 and 11 (6717)
13 or/1-3,12 (7154)
14 Random$.tw. or placebo$.mp. or double-blind$.tw. (1177510)
15 animal/ (1618126)
16 animal experiment/ (1836227)
17 (rat or rats or mouse or mice or murine or rodent or rodents or hamster or hamsters or pig or pigs or porcine or rabbit or rabbits or animal or animals or dogs or dog or cats or cow or bovine or sheep or ovine or monkey or monkeys).ti,ab,ot,hw. (5844647)
18 or/15-17 (5844647)
19 exp human/ (15636444)
20 human experiment/ (334937)
21 or/19-20 (15637875)
22 18 not (18 and 21) (4646807)
23 14 not 22 (1052443)
24 (editorial or letter).pt. (1342065)
25 23 not 24 (1035480)
26 (1994$ or 1995$ or 1996$ or 1997$ or 1998$ or 1999$ or 2000$ or 2001$ or 2002$ or 2003$ or 2004$ or 2005$ or 2006$ or 2007$ or 2008$ or 2009$ or 2010$ or 2011$ or 2012$ or 2013$ or 2014$ or 2015$).dd,em. or (1994$ or 1995$ or 1996$ or 1997$ or 1998$ or 1999$ or 2000$ or 2001$ or 2002$ or 2003$ or 2004$ or 2005$ or 2006$ or 2007$ or 2008$ or 2009$ or 2010$ or 2011$ or 2012$ or 2013$ or 2014$ or 2015$).yr. (18885853)
27 13 and 25 and 26 (499)

Trials filter:
Wong SS, Wilczynski NL, Haynes RB. Developing optimal search strategies for detecting clinically sound treatment studies in EMBASE. Journal of the Medical Library Association 2006;94(1):41-7. Best optimization of sensitivity and specificity

21 PHANTOM PAIN

Embase (OvidSP): 1974-2015/week 12
Searched 26.3.15

1 phantom pain/ or pseudomelia$.ti,ab,ot,hw. (1652)
2 ((phantom or fantom) adj3 pain$).af. (2380)

3 or/1-2 (2380)
4 ((phantom or fantom or amputat$ or missing or lost or remov$ or absent) adj3 (limb$ or extremit$ or leg$ or arm$ or foot or feet or hand$ or organ$ or breast$ or sensation$)).ti,ab,ot,hw. (33966)
5 (phantom-limb$ or PLP).ti,ab,ot,hw. (5905)
6 or/4-5 (38362)
7 exp pain/ (879389)
8 (pain or pains or painful$ or pained).ti,ab,ot. (628565)
9 (hurt or hurting or hurts).ti,ab,ot. (3313)
10 (sore or soreness or tender$ or discomfort or ache$ or aching or agony).ti,ab,ot. (99543)
11 (nociception or nociperception or algiatry).ti,ab,ot. (9042)
12 or/7-11 (1150988)
13 6 and 12 (4726)
14 3 or 13 (5603)
15 Random$.tw. or placebo$.mp. or double-blind$.tw. (1176226)
16 animal/ (1618122)
17 animal experiment/ (1834449)
18 (rat or rats or mouse or mice or murine or rodent or rodents or hamster or hamsters or pig or pigs or porcine or rabbit or rabbits or animal or animals or dogs or dog or cats or cow or bovine or sheep or ovine or monkey or monkeys).ti,ab,ot,hw. (5841228)
19 or/16-18 (5841228)
20 exp human/ (15623819)
21 human experiment/ (334698)
22 or/20-21 (15625250)
23 19 not (19 and 22) (4644382)
24 15 not 23 (1051306)
25 (editorial or letter).pt. (1340861)
26 24 not 25 (1034366)
27 (1994$ or 1995$ or 1996$ or 1997$ or 1998$ or 1999$ or 2000$ or 2001$ or 2002$ or 2003$ or 2004$ or 2005$ or 2006$ or 2007$ or 2008$ or 2009$ or 2010$ or 2011$ or 2012$ or 2013$ or 2014$ or 2015$).dd,em. or (1994$ or 1995$ or 1996$ or 1997$ or 1998$ or 1999$ or 2000$ or 2001$ or 2002$ or 2003$ or 2004$ or 2005$ or 2006$ or 2007$ or 2008$ or 2009$ or 2010$ or 2011$ or 2012$ or 2013$ or 2014$ or 2015$).yr. (18867012)
28 14 and 26 and 27 (492)

Trials filter:
Wong SS, Wilczynski NL, Haynes RB. Developing optimal search strategies for detecting clinically sound treatment studies in EMBASE. Journal of the Medical Library Association 2006;94(1):41-7. Best optimization of sensitivity and specificity

23 CANCER PAIN - INTERVENTIONS: INTRATHECAL BLOCK, CORDOTOMY, NEUROLYTIC BLOCK, PHENOLIZATION, VERTEBROPLASTY

Embase (OvidSP): 1974-2015/week 12
Searched 27.3.15

1 exp neoplasm/ (3436451)
2 (cancer$ or neoplasm$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or metasta$ or meta-sta$ or sarcoma$ or adenoma$ or lesion$).ti,ab. (3641520)
3 1 or 2 (4560279)
4 exp pain/ (879389)
5 (pain or pains or painful$ or pained or neuralgia$).ti,ab,ot. (634537)
6 (hurt or hurting or hurts).ti,ab,ot. (3313)
7 (sore or soreness or tender$ or discomfort or ache$ or aching or agony).ti,ab,ot. (99543)
8 (nociception or nociperception or algiatry).ti,ab,ot. (9042)
9 or/4-8 (1151733)
10 3 and 9 (267587)
11 Random$.tw. or placebo$.mp. or double-blind$.tw. (1176226)
12 animal/ (1618122)
13 animal experiment/ (1834449)
14 (rat or rats or mouse or mice or murine or rodent or rodents or hamster or hamsters or pig or pigs or porcine or rabbit or rabbits or animal or animals or dogs or dog or cats or cow or bovine or sheep or ovine or monkey or monkeys).ti,ab,ot,hw. (5841228)
15 or/12-14 (5841228)
16 exp human/ (15623819)
17 human experiment/ (334698)
18 16 or 17 (15625250)
19 15 not (15 and 18) (4644382)
20 11 not 19 (1051306)
21 (editorial or letter).pt. (1340861)
22 20 not 21 (1034366)
23 (1994$ or 1995$ or 1996$ or 1997$ or 1998$ or 1999$ or 2000$ or 2001$ or 2002$ or 2003$ or 2004$ or 2005$ or 2006$ or 2007$ or 2008$ or 2009$ or 2010$ or 2011$ or 2012$ or 2013$ or 2014$ or 2015$).dd,em. or (1994$ or 1995$ or 1996$ or 1997$ or 1998$ or 1999$ or 2000$ or 2001$ or 2002$ or 2003$ or 2004$ or 2005$ or 2006$ or 2007$ or 2008$ or 2009$ or 2010$ or 2011$ or 2012$ or 2013$ or 2014$ or 2015$).yr. (18867012)
24 10 and 22 and 23 [Cancer pain + RCT] (24749)
25 exp intraspinal drug administration/ (25935)
26 epidural anesthesia/ (26457)
27 (intrathecal or intra thecal or intraspinal or intra spinal).ti,ab,ot. (26888)
28 (epidural or extradural or peridural).ti,ab,hw,ot. (61754)
29 or/25-28 (93581)
30 24 and 29 [Cancer + Intrathecal + RCT] (464)
31 10 and 23 and 29 [Cancer + Intrathecal] (5991)
32 Cordotomy/ (1593)
33 (cordotom$ or chordotom$ or myelotom$).ti,ab,hw,ot. (2075)
34 32 or 33 (2075)
35 24 and 34 [Cancer + Cordotomy + RCT] (8)
36 10 and 23 and 34 [Cancer + Cordotomy] (313)
37 exp Nerve Block/ (27121)
38 ((nerve or nervus or autonomic$ or conduction or neurogenic) adj3 block$).ti,ab,hw,ot. (31892)

39 (neurolys?s or chemodenervation$).ti,ab,hw,ot. (3543)
40 (neurolytic adj3 (plexus or block$)).ti,ab,hw,ot. (347)
41 ((suprascapularis or splanchnicus) adj3 block$).ti,ab,ot,hw. (9)
42 Celiac Plexus/ (1249)
43 ((celiac$ or coeliac$) adj3 (plexus or block$)).ti,ab,hw,ot. (1673)
44 NCPB.ti,ab,ot. (52)
45 hypogastric plexus/ (641)
46 ((hypogastric$ or presacral) adj3 (block$ or plexus)).ti,ab,hw,ot. (909)
47 ((phenol$ or plexus or block$) adj3 (sacral or lumbosacral or sacrum or (cauda adj2 equina) or (filum adj2 terminal))).ti,ab,ot,hw. (2448)
48 or/37-47 (43272)
49 24 and 48 [Cancer + Neurolytic block/phenolization + RCT] (314)
50 10 and 23 and 48 [Cancer + Neurolytic block/phenolization] (2580)
51 exp Vertebroplasty/ (4558)
52 (vertebroplast$ or kyphoplast$).ti,ab,hw,ot. (5083)
53 51 or 52 (5083)
54 24 and 53 [Cancer + vertebroplasty + RCT] (100)
55 10 and 23 and 53 [Cancer + vertebroplasty] (1309)
56 30 or 35 or 49 or 54 [RCT] (819)
57 31 or 36 or 50 or 55 [no RCT filter] (9520)
58 30 or 36 or 50 or 55 [Intrathecal RCT + other sets no RCT] (4507)

Trials filter:
Wong SS, Wilczynski NL, Haynes RB. Developing optimal search strategies for detecting clinically sound treatment studies in EMBASE. Journal of the Medical Library Association 2006;94(1):41-7. Best optimization of sensitivity and specificity

24 CHRONIC REFRACTORY ANGINA PECTORIS-INTERVENTION: SPINAL CORD STIMULATION

Embase (OvidSP): 1974-2015/week 12
Searched 26.3.15

1 exp angina pectoris/ (80743)
2 angina$.ti,ab,hw,ot. (93825)
3 (stenocardia$ or angor pectoris).ti,ab,ot,hw. (944)
4 (acute adj2 coronary adj2 syndrome$).ti,ab,ot. (31921)
5 or/1-4 (121823)
6 spinal cord stimulation/ (4023)
7 (electrostimulation therapy/ or electrostimulation/) and exp spinal cord/ (3757)
8 ((spinal or spine$ or dorsal) adj3 stimulat$).ti,ab,hw,ot. (8935)
9 scs.ti,ab,hw,ot. (6257)
10 or/6-9 (16559)
11 5 and 10 (504)
12 animal/ (1618122)
13 animal experiment/ (1834449)

14 (rat or rats or mouse or mice or murine or rodent or rodents or hamster or hamsters or pig or pigs or porcine or rabbit or rabbits or animal or animals or dogs or dog or cats or cow or bovine or sheep or ovine or monkey or monkeys).ti,ab,ot,hw. (5841228)
15 or/12-14 (5841228)
16 exp human/ (15623819)
17 human experiment/ (334698)
18 16 or 17 (15625250)
19 15 not (15 and 18) (4644382)
20 (editorial or letter).pt. (1340861)
21 11 not (19 or 20) (457)
22 (1994$ or 1995$ or 1996$ or 1997$ or 1998$ or 1999$ or 2000$ or 2001$ or 2002$ or 2003$ or 2004$ or 2005$ or 2006$ or 2007$ or 2008$ or 2009$ or 2010$ or 2011$ or 2012$ or 2013$ or 2014$ or 2015$).dd,em. or (1994$ or 1995$ or 1996$ or 1997$ or 1998$ or 1999$ or 2000$ or 2001$ or 2002$ or 2003$ or 2004$ or 2005$ or 2006$ or 2007$ or 2008$ or 2009$ or 2010$ or 2011$ or 2012$ or 2013$ or 2014$ or 2015$).yr. (18867012)
23 21 and 22 (436)

No study design filter

26 PAIN IN CHRONIC PANCREATITIS

Embase (OvidSP): 1974-2015/week 12
Searched 26.3.15

1 chronic pancreatitis/ (14149)
2 (chronic adj3 pancrea$).ti,ab,ot,hw. (21695)
3 (pancrea$ adj3 (inflam$ or damag$ or injur$)).ti,ab,ot. (7707)
4 or/1-3 (28093)
5 exp Pain/ (879389)
6 (pain or pains or painful$ or pained).ti,ab,ot. (628565)
7 (hurt or hurting or hurts).ti,ab,ot. (3313)
8 (sore or soreness or tender$ or discomfort or ache$ or aching or agony).ti,ab,ot. (99543)
9 (nociception or nociperception or algiatry).ti,ab,ot. (9042)
10 or/5-9 (1150988)
11 4 and 10 (5302)
12 Random$.tw. or placebo$.mp. or double-blind$.tw. (1176226)
13 animal/ (1618122)
14 animal experiment/ (1834449)
15 (rat or rats or mouse or mice or murine or rodent or rodents or hamster or hamsters or pig or pigs or porcine or rabbit or rabbits or animal or animals or dogs or dog or cats or cow or bovine or sheep or ovine or monkey or monkeys).ti,ab,ot,hw. (5841228)
16 or/13-15 (5841228)
17 exp human/ (15623819)
18 human experiment/ (334698)
19 17 or 18 (15625250)
20 16 not (16 and 19) (4644382)
21 12 not 20 (1051306)

22 (editorial or letter).pt. (1340861)
23 21 not 22 (1034366)
24 (1994$ or 1995$ or 1996$ or 1997$ or 1998$ or 1999$ or 2000$ or 2001$ or 2002$ or 2003$ or 2004$ or 2005$ or 2006$ or 2007$ or 2008$ or 2009$ or 2010$ or 2011$ or 2012$ or 2013$ or 2014$ or 2015$).dd,em. or (1994$ or 1995$ or 1996$ or 1997$ or 1998$ or 1999$ or 2000$ or 2001$ or 2002$ or 2003$ or 2004$ or 2005$ or 2006$ or 2007$ or 2008$ or 2009$ or 2010$ or 2011$ or 2012$ or 2013$ or 2014$ or 2015$).yr. (18867012)
25 11 and 23 and 24 (326)

OBSERVATIONAL STUDIES SEARCH FILTER

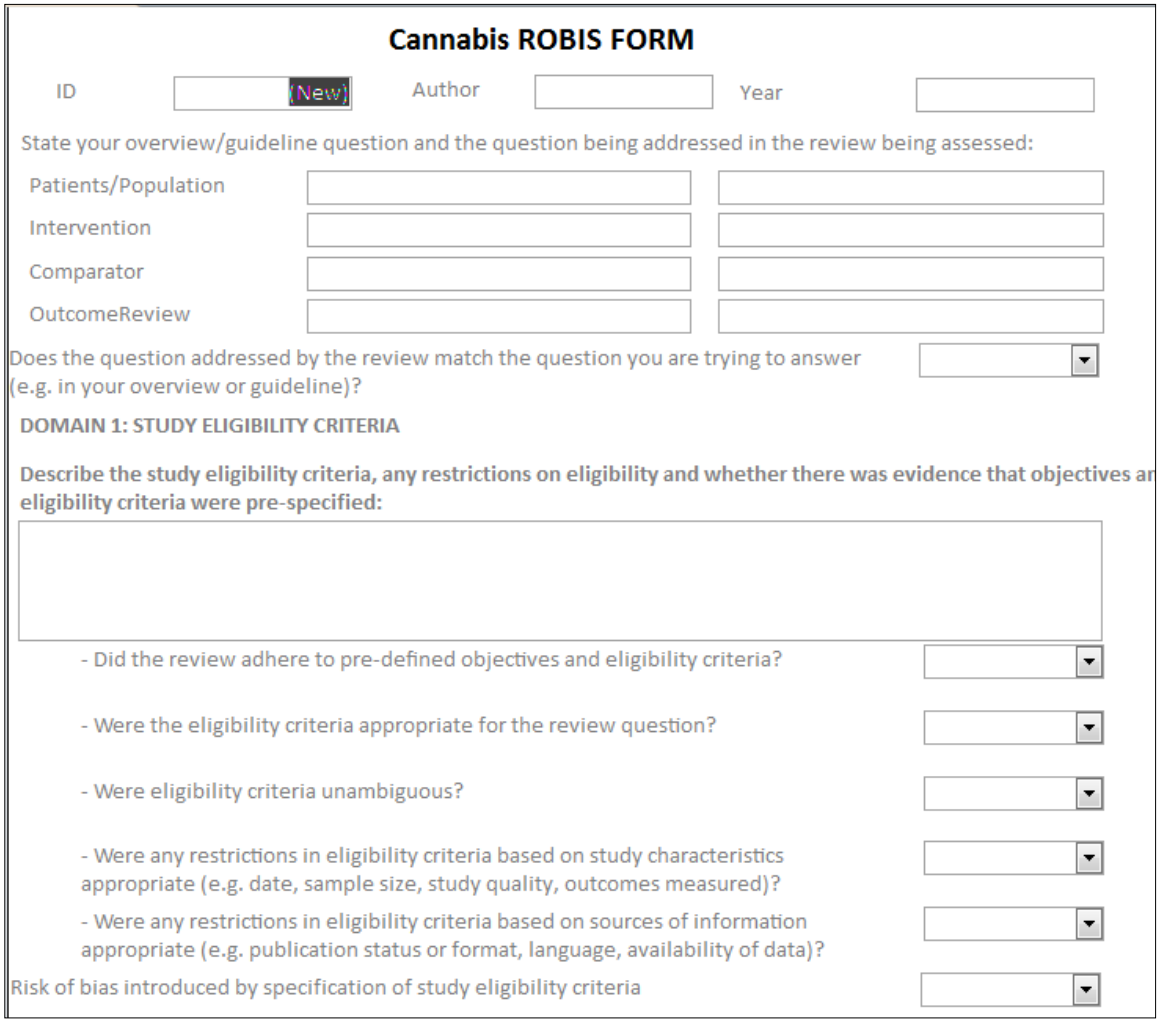
Embase (OvidSP)

1 Clinical study/
2 Case control study/
3 Family study/
4 Longitudinal study/
5 Retrospective study/
6 Prospective study/
7 Randomized controlled trials/
8 6 not 7
9 Cohort analysis/
10 (Cohort adj (study or studies)).mp.
11 (Case control adj (study or studies)).tw.
12 (follow up adj (study or studies)).tw.
13 (observational adj (study or studies)).tw.
14 (epidemiologic$ adj (study or studies)).tw.
15 (cross sectional adj (study or studies)).tw.
16 or/1-5,8-15

Scottish Intercollegiate Guidelines Network (SIGN). Search filters: observational studies [Embase (OvidSP)]. Edinburgh: SIGN, Last modified 16/05/14 Available from: http://www.sign.ac.uk/methodology/filters.html#obs

APPENDIX 4: EXAMPLE RISK OF BIAS ASSESSMENT FORMS

4A ROBIS TOOL FOR SYSTEMATIC REVIEWS[14]



Cannabis ROBIS FORM

ID (New) Author Year

State your overview/guideline question and the question being addressed in the review being assessed:

Patients/Population		
Intervention		
Comparator		
OutcomeReview		

Does the question addressed by the review match the question you are trying to answer (e.g. in your overview or guideline)?

DOMAIN 1: STUDY ELIGIBILITY CRITERIA

Describe the study eligibility criteria, any restrictions on eligibility and whether there was evidence that objectives ar eligibility criteria were pre-specified:

- Did the review adhere to pre-defined objectives and eligibility criteria?
- Were the eligibility criteria appropriate for the review question?
- Were eligibility criteria unambiguous?
- Were any restrictions in eligibility criteria based on study characteristics appropriate (e.g. date, sample size, study quality, outcomes measured)?
- Were any restrictions in eligibility criteria based on sources of information appropriate (e.g. publication status or format, language, availability of data)?

Risk of bias introduced by specification of study eligibility criteria

DOMAIN 2: IDENTIFICATION AND SELECTION OF STUDIES

Describe methods of study identification and selection (e.g. number of reviewers involved):

- Did the review search an appropriate range of databases/electronic sources for published and unpublished reports?
- Were methods additional to database searching used to identify relevant reports?
- Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible?
- Did the search methods avoid restrictions based on date, publication format, or languages
- Were efforts made to minimise error in selection of studies?

Risk of bias introduced by methods used to identify and/or select studies

DOMAIN 3: DATA COLLECTION AND STUDY APPRAISAL

Describe methods of data collection, what data were extracted from studies or collected through other means, how risk of bias was assessed (e.g. number of reviewers involved) and the tool used to assess risk of bias:

- Were efforts made to minimise error in data collection?
- Were sufficient study characteristics considered for both review authors and readers to be able to interpret the results?
- Were all relevant study results collected for use in the synthesis?
- Was risk of bias (or methodological quality) formally assessed using an appropriate tool?

Risk of bias introduced by methods used to collect data and appraise studies

DOMAIN 4: SYNTHESIS AND FINDINGS

Describe synthesis methods:

- Did the synthesis include all studies that it should, or use techniques to account for missing studies?
- Were all pre-defined analyses reported or their absence explained?
- Was the synthesis appropriate given the degree of similarity in the research questions, study designs and outcomes across included studies?
- Was heterogeneity in results minimal, or addressed in the synthesis?
- Was robustness of the finding(s) assessed e.g. through sensitivity analysis?
- Were biases in primary studies minimal or addressed in the synthesis?
- Was a complete account provided of results including variation and uncertainty?

Risk of bias introduced by the synthesis

DOMAIN 5: INTERPRETATION

Describe whether conclusions were supported by the evidence:

- Was the quality of the evidence considered when interpreting the results and drawing conclusions?
- Was the relevance of identified studies to the review's research question appropriately considered?
- Did the reviewers avoid selecting or emphasising results on the basis of their statistical significance?

Risk of bias introduced by the interpretation of results

4B COCHRANE RISK OF BIAS TOOL FOR RCTS[16]

Risk of bias assessment

Author		StudyID
	Support for judgement	**Risk of bias**
Random Sequence Generation		
Allocation Concealment		
Participant/Personnel blinding		
Outcome assessor blinding		
Incomplete Outcome Data		
Selective outcome reporting		
Comments		

APPENDIX 5: GRADE FRAMEWORK AND PROFILES

5A DEFINITION, CATEGORIES, AND FACTORS AFFECTING THE QUALITY OF EVIDENCE

Definition: The extent of our confidence that the estimate of an effect is adequate to support a particular decision or recommendation

Categories:

- **High**: we are very confident in the effect estimate: the true effect lies close to that of the estimate of the effect.
- **Moderate**: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- **Low**: we have limited confidence in the effect estimate: the true effect may be substantially different from the estimate of the effect.
- **Very low**: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Factors affecting quality of evidence

<table>
<tr><th>Study design</th><th>Initial grade</th><th>Grade lowered if</th><th>Grade raised if</th><th>Final grade</th></tr>
<tr><td>Randomized trial →</td><td>High</td><td rowspan="4">Limitations of design
Inconsistency
Indirectness
Imprecision
Publication bias</td><td rowspan="4">Large effect
Dose response
All plausible confounding would reduce a demonstrated effect</td><td>High</td></tr>
<tr><td></td><td>Moderate</td><td>Moderate</td></tr>
<tr><td>Observational study →</td><td>Low</td><td>Low</td></tr>
<tr><td></td><td>Very low</td><td>Very low</td></tr>
</table>

5B EXAMPLE OF AN EVIDENCE PROFILE

Evidence Profile – Community-based care for chronic wound management

Quality Assessment							Summary of Findings				
							No of Patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Wound Care Team	Usual Care	Relative (95% CI)	Absolute	Quality
Proportion of Wounds Healed (follow-up 6 months; Proportion of wounds healed)											
1[1]	randomised trials	serious[2]	no serious inconsistency	serious[3]	serious[4]	none	112/180 (62.2%)	85/162 (52.5%)	RR 1.19 (0.99 to 1.43)	100 fewer per 1000 (from 5 fewer to 226 more)	⊕OOO VERY LOW
Proportion of Persons with wounds healed (follow-up mean 3 months)											
1	observational studies[5]	serious[6]	no serious inconsistency	no serious indirectness	serious[7]	strong association[8]	100/180 (55.6%)	18/78 (23.1%)	OR 4.17 (2.28 to 7.62)	325 more per 1000 (from 175 more to 465 more)	⊕OOO VERY LOW
Persons with BPI score=0 (follow-up mean 6 months; Brief Pain Inventory9)											
1	randomised trials[1]	serious[2]	no serious inconsistency	serious[3]	serious[4]	none	49/127 (38.6%)	29/119 (24.4%)	RR 1.58 (1.08 to 2.33)	141 more per 1000 (from 19 more to 324 more)	⊕OOO VERY LOW
Proportion of Persons needing daily treatments (follow-up mean 3 months)											
1	randomised trials[1]	serious[2]	no serious inconsistency	serious[3]	serious[4]	none	49/127 (38.6%)	29/119 (24.4%)	RR 1.58 (1.08 to 2.33)	141 more per 1000 (from 19 more to 324 more)	⊕OOO VERY LOW

[1] One Study by Vu et al. 2007
[2] Alternating randomization, lack of allocation concealment
[3] Nursing Home setting not a community-based study
[4] Sparse data, one small study
[5] One study by Harrison et al. 2005
[6] Outcome measure not assessed independent of the exposure status
[7] One study contributing to body of evidence therefore considered sparse data
[8] Relative odds reduction of 76%
[9] 11-point scale (0-10) to assess wound-associated pain

From: Medical Advisory Secretariat. Community-based care for chronic wound management: an evidence-based analysis. Ontario Health Technology Assessment Series 2009; 9(18).

Appendix 6 Evidence tables with analysis

1. Trigeminal Neuralgia

SYSTEMATIC REVIEWS IDENTIFIED

We identified the following relevant reviews published between 2010 and 2015. See table. A Cochrane review covered all the included interventions but was somewhat out of date and restricted to RCTs and quasi-RCTs. The remaining reviews covered one intervention each. For each intervention we have placed most emphasis on the most up to date review.

Systematic Review	**Zakrzewska (2011)**	**Tuleasca (2014)**	**Varela-Lema (2015)**	**Xia (2014)**
Search end date	May 2010	NR	Oct 2013	June 2013
Surgical microvascular decompression	Y			Y
Stereotactic radiation therapy, Gamma knife	Y	Y	Y	
Percutaneous balloon microcompression	Y			
Radiofrequency treatment of the Gasserian ganglion	Y			
Pulsed radiofrequency treatment of the Gasserian ganglion	Y			
Percutaneous glycerol rhizolysis	Y			

ASSESSMENT OF THE REVIEW EVIDENCE

All Interventions

Study Reference	**Participants**	**Interventions**	**Comparators**	**Outcomes**	**Study Designs**
Zakrzewska (2011)	Patients with classical trigeminal neuralgia	Any neurosurgical procedure	Any	Primary: complete pain relief after one year. Secondary: surgical morbidity, QoL, patient satisfaction, adverse events	RCTs and quasi-RCTs

Results

Only three studies reported on the pre-specified outcomes and had acceptable methodological quality. As these studies concerned different interventions, no meta-analysis was done.

One trial, which involved 40 participants, compared two techniques of radiofrequency of the Gasserian ganglion at six months. Pulsed RF resulted in return of pain in all participants by three months. When this group were converted to conventional (continuous) treatment, these participants achieved pain control comparable to the group that had received conventional treatment from the outset. Sensory changes were common in the continuous treatment group. In

another trial, of 87 participants, investigators compared radiation treatment to the trigeminal nerve at one or two isocentres in the posterior fossa. There were insufficient data to determine if one technique was superior to another. A third study compared two techniques for RF in 54 participants for 10 to 54 months. Both techniques produced pain relief, but relief was more sustained and side effects fewer if a neuronavigation system was used.

Last Search date	Studies identified in review	Bottom Line
May 2010	11	The authors stated that there was little evidence to provide the patient with guidance as to the most effective surgical procedure for the management of trigeminal neuralgia. There is an urgent need to gain high-quality evidence. This was a Cochrane review and results are likely to be reliable.

Surgical microvascular decompression

Study Reference	Participants	Interventions	Comparators	Outcomes	Study Designs
Xia (2014) [6]	Not pre-specified. Patients with trigeminal neuralgia	Surgical microvascular decompression	Not pre-specified	Not pre-specified. Success rate and complications considered.	Not pre-specified. Observational studies included

Results Based on the 26 observational studies identified by this review (6847 patients), over an average follow-up of 35.8 months, postoperative success rates ranged from 60% to 96.7%. Overall success rate was 83.5% (95% Confidence interval (CI) 79.6 to 89.1). Where reported, the need for repeat MVD ranged from 0 to 33.3%. Transient complications were reported that included incisional infection in 1.3% (95% CI: 0.1 to 2.5), facial palsy in 2.9% (95% CI: 0.5 to 6.2), facial numbness in 9.1% (95% CI: 1.3 to 19.6), hearing change 1.9% (95% CI: 0.2 to 3.9) and cerebrospinal fluid leak in 1.6% (95% CI: 0.7 to 2.5). Mortality was 0.1% (95% CI: 0.02 to 0.2).

Last Search date	Studies identified in review	Bottom Line
June 2013	26 observational studies	The authors of this review stated that microvascular decompression is effective and safe but that to avoid complications, attention should be paid to every step of the process. This review was at high risk of bias and findings should be approached with caution.

Stereotactic radiation therapy, Gamma knife

Study Reference	Participants	Interventions	Comparators	Outcomes	Study Designs
Varela-Lema (2015)[5]	Drug-resistant trigeminal neuralgia or patients who did not tolerate medical treatment	Stereotactic RadioSurgery (SRS) with a linear accelerator (LINAC)	Not pre-specified (in practice: none, other types of SRS, different LINAC protocols/machines	Effectiveness (pain control), safety, costs	Any except narrative reviews and single case studies

Results
Satisfactory pain relief was achieved in 75 % – 96 % of patients treated, 5 % - 29 % had a recurrence within a year. Facial numbness was observed in 7.5 % - 50 % (average 26.4 %), serious complications were rare. Costs were not reported.

Last Search date	Studies identified in review	Bottom Line
Oct 2013	11	The authors concluded that the effectiveness of LINAC-based SRS could be equal to or even superior to that of the gamma knife. However, no RCTs were identified, so the true efficacy and safety of this technique was not possible to estimate.

Study Reference	Participants	Interventions	Comparators	Outcomes	Study Designs
Tuleasca (2014)[4]	Patients undergoing repeat radiosurgery for recurrent trigeminal neuralgia	Repeat radiosurgery	NR	Initial pain cessation, hypaesthesia recurrence	NR

Results
All twenty included studies (626 patients) were retrospective. Only four studies had > 40 patients, four were long-term studies. Studies were heterogeneous in patient selection criteria, outcome assessment and techniques used.

Effective (> 50 %) initial pain relief was reported in median 88% (range 60% to 100 %) of patients. Median rate of (new) hypaesthesia was 33 % (range 11 % to 80 %). Pain recurrence ranged from 5.3 % to 32 % in the short term (median 24 months).

Last Search date	Studies identified in review	Bottom Line
NR	20 observational studies	The authors stated that the current literature is sparse and that there is a need for longer follow up and uniformity to establish the safety and efficacy of GKS retreatment. Efficacy seems to be comparable to first GKS, toxicity (as evident in new hypaesthesia) is much higher. Although the review had a number of methodological limitations and was rated at high risk of bias, this overall conclusion appears to be fair.

RELEVANT TRIALS PUBLISHED SUBSEQUENT TO THE SYSTEMATIC REVIEW

We identified the following RCTs published subsequent to the reviews.

Intervention	Study
Surgical microvascular decompression	No further RCTs
Stereotactic radiation therapy, Gamma knife	No further RCTs
Percutaneous balloon microcompression	No further RCTs
Radiofrequency treatment of the Gasserian ganglion	Li (2012)
Pulsed Radiofrequency treatment of the Gasserian ganglion	Li (2012)
Percutaneous glycerol rhizolysis	No further RCTs

Radiofrequency treatment of the Gasserian ganglion (RCT)

Study	**Li (2012)**
Country	China
Study Design	RCT
Single/Multiple centre	Single centre
Recruitment dates	May 2006 to September 2007
Condition	Classic Trigeminal neuralgia in the maxillary and/or mandibular nerve distribution
Patient inclusion criteria	TN of more than six months' duration; a pain rating (during the attack) of ≥ 6 on NRS; no satisfactory pain relief with medical treatment for > 3 months; and/or intolerable side effects using oral medications.
Patient exclusion criteria	TN involving the ophthalmic nerve distribution; secondary TN (multiple sclerosis, tumour, or herpes zoster infection); past invasive treatment (radiofrequency, ethanol or glycerinum injection, gamma-knife, or microvascular decompression); serious cardiopulmonary dysfunction; coagulation dysfunction; and patients unable to cooperate.
Mean age (SD)	57.0 (10.9)
Total no (% male)	62.1
Mean duration of symptoms	75.6 (SD 60.2) months
No randomized	60

Li (2012) Treatment Details

No in interventions	20 per group (Short duration continuous (SCRF), long duration continuous (LCRF), pulsed combined continuous (PCRF))
Treatment details	Patients fasted prior to the procedure and received an i.m. injection of 0.5 mg atropine 30 min before treatment. Patients were placed in a supine position with their head overhanging. Route was determined by CT scan. Patients received 0.5% lidocaine. A 22-gauge insulated needle was inserted in the marked point. The insertion point was adjusted according to a laser. When the insertion depth of the needle was equal to that measured in the pre-determined route, a repeat CT was performed to confirm the location of the needle tip. Motor stimulation was performed (2 Hz, ≥ 2V) to contract masseter muscle and sensory stimulation (50 Hz, ≤ 0.5V) was applied to elicit paraesthesia in the affected area. If paraesthesia was not induced, or occurred in the unaffected branch, the needle position was readjusted. A test dose of 0.5% lidocaine (0.2ml) was injected to confirm loss of sensation. Patients administered i.v. anaesthesia fentanyl (1-1.5 µg/kg) and propofil (1.0 mg/kg); no tracheal intubation. Short duration continuous (SCRF): 75^0C CRF for 120s to 180s long duration continuous (LCRF): 75^0C CRF for 240s to 300s pulsed combined continuous (PCRF): 42^0C PRF for 10 minutes (2 bursts per second of 20ms), then 75^0C CRF for 120s to 180s
Conservative treatments allowed	If recurrent or residual pain was intolerable, patients were asked to return to the hospital and carbamazepine was prescribed.

Li (2012) Outcome Details

Primary Efficacy outcome	Pain intensity (NRS score) 0 = no pain, 10 = worst pain.
Safety assessed?	Yes
Length of follow up	1 day, 3 days, 7 days, 3 months, 6 months, 12 months.

Li (2012) Results (Pain)

	SCRF group	**LCRF group**	**PCRF group**	**Mean difference***
Baseline	8.3 (1.0)	8.2 (1.8)	8.7 (1.0)	$p = 0.468$
3 months	0.4 (0.2)	0.2 (0.5)	0.1 (0.3)	$p = 0.587$
6 months	0.4 (1.0)	0.3 (0.7)	0.2 (0.4)	$p = 0.593$
12 months	0.4 (0.8)	0.3 (0.7)	0.2 (0.4)	$p = 0.511$

Li (2012) Cochrane Risk of Bias

Study		**Li (2012)**[8]
Randomisation	Low	Using a table of random numbers
Allocation Concealment	Unclear	Sealed envelope was opened immediately prior to application of the procedure; unclear if envelopes were opaque
Blinding of participants	Low	Patients were blinded
Blinding of caregivers	High	Unblinded
Blinding of assessors	Low	Specialists who evaluated patients were blinded
Incomplete outcome data	Low	2 patients did not complete follow-up (1 died from metastatic carcinoma 8 months after treatment; the other was lost to follow-up because of incorrect contact information)
Selective reporting	Low	None identified
Other Biases	Low	None identified

Author(s): Jos Kleijnen
Date: 2016-10-30
Question: Should surgical microvascular decompression be used for trigeminal neuralgia?
Settings: Treatment by anaesthetists
Bibliography: Xia L, Zhong J, Zhu J, Wang YN, Dou NN, Liu MX, et al. Effectiveness and safety of microvascular decompression surgery for treatment of trigeminal neuralgia: a systematic review. J Craniofac Surg 2014;25(4):1413-7.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Surgical microvascular decompression	Control	Relative (95% CI)	Absolute		
Pain free[1] (follow-up mean 35.8 months; assessed with: Various measures)												
26	Observational studies[2]	Serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias[4]	5717/6847 (83.5%)[5]	-	-	-	⊕OOO VERY LOW	CRITICAL
Mortality (follow-up mean 35.8 months)												
26	observational studies[2]	serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias[4]	7/6847 (0.1%)[5]	-	-	-	⊕OOO VERY LOW	CRITICAL

[1] Average effect across 26 studies
[2] case series
[3] Systematic review had limitations and was judged at high risk of bias
[4] Small case series may only be published if positive results can be reported
[5] Number of patients calculated from percentages reported in paper

Author(s): Jos Kleijnen
Date: 2016-10-30
Question: Should stereotactic radiation therapy be used for trigeminal neuralgia?
Settings: Treatment by anaesthetists
Bibliography: Varela-Lema L, Lopez-Garcia M, Maceira-Rozas M, Munoz-Garzon V. Linear accelerator stereotactic radiosurgery for trigeminal neuralgia. Pain Physician 2015;18(1):15-27.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Stereotactic radiation therapy	Control	Relative (95% CI)	Absolute		
Satisfactory pain relief (follow-up 6-56.5 months)												
11	observational studies[1]	no serious risk of bias	serious[2]	no serious indirectness	no serious imprecision	reporting bias[3]	476/559 (85.2%)[4]	-	-	-	⊕OOO VERY LOW	CRITICAL
Facial numbness (follow-up 6-56.5 months)												
11	observational studies[1]	no serious risk of bias	serious[2]	no serious indirectness	no serious imprecision	reporting bias[3]	148/559 (26.5%)[4]	-	-	-	⊕OOO VERY LOW	IMPORTANT

[1] case series
[2] Studies were heterogeneous in terms of equipment, treatment guidelines and selection of patients
[3] Small case series may only be published if positive results can be reported, here we have multiple small studies
[4] Number of patients calculated from percentages reported in paper

Author(s): Jos Kleijnen
Date: 2016-10-30
Question: Should gamma knife be used for trigeminal neuralgia?
Settings: Treatment by anaesthetists
Bibliography: Tuleasca C, Carron R, Resseguier N, Donnet A, Roussel P, Gaudart J, et al. Repeat gamma knife surgery for recurrent trigeminal neuralgia: long-term outcomes and systematic review. J Neurosurg 2014;121 Suppl:210-21.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Gamma knife**	**Control**	**Relative (95% CI)**	**Absolute**		
Pain relief (follow-up 8-72 months)												
20	observational studies[1]	no serious risk of bias	serious[2]	no serious indirectness	no serious imprecision	reporting bias[3]	551/626 (88%)[4]	-	-	-	⊕OOO VERY LOW	CRITICAL
Hypesthesia (follow-up 8=72 months)												
20	observational studies[1]	no serious risk of bias	serious[2]	no serious indirectness	no serious imprecision	reporting bias[3]	207/626 (33.1%)[4]	-	-	-	⊕OOO VERY LOW	

[1] case series
[2] The populations of patients were heterogeneous at baseline and there was no uniformity of patient selection criteria for retreatment; outcomes were assessed differently; techniques employed were also highly variable
[3] Small case series may only be published if positive results can be reported, here we have multiple small studies
[4] Number of patients calculated from percentages reported in paper

Author(s): Jos Kleijnen
Date: 2016-10-30
Question: Should (pulsed) radiofrequency treatment of the Gasserian ganglion be used for trigeminal neuralgia?
Settings: Treatment by anaesthetists
Bibliography: Zakrzewska JM, Akram H. Neurosurgical interventions for the treatment of classical trigeminal neuralgia. Cochrane Database of Systematic Reviews 2011, Issue 9. Art. No.: CD007312. DOI: 10.1002/14651858.CD007312.pub2. Li X, Ni J, Yang L, Wu B, He M, Zhang X, et al. A prospective study of Gasserian ganglion pulsed radiofrequency combined with continuous radiofrequency for the treatment of trigeminal neuralgia. Journal of Clinical Neuroscience 2012;19(6):824-8. Erdine S, Ozyalcin NS, Cimen A, Celik M, Talu GK, Disci R. Comparison of pulsed radiofrequency with conventional radiofrequency in the treatment of idiopathic trigeminal neuralgia. Eur J Pain 2007;11(3):309-13

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**(pulsed) radiofrequency treatment of the Gasserian ganglion**	**Control**	**Relative (95% CI)**	**Absolute**		
Overall improvement (follow-up mean 6 months)												
1	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	reporting bias[2]	20/20 (100%)	2/20 (10%)	-	100 fewer per 1000 (from 100 fewer to 100 fewer)	⊕⊕OO LOW	
								0%		-		
Pain intensity (follow-up mean 12 months; Better indicated by lower values)												
1	randomized trials	serious[3]	no serious inconsistency	no serious indirectness	serious[4]	reporting bias[2]	20	20	-	MD 0.2 higher (0 to 0 higher)	⊕OOO VERY LOW	

[1] Small study with 20 patients per group comparing conventional with pulsed radiofrequency treatment
[2] Only 2 randomised trials were identified
[3] Unblinded caregivers in trial
[4] Small trial comparing short duration continuous (SCRF) with long duration continuous (LCRF) and with pulsed combined continuous (PCRF) radiofrequency treatment

2. Cluster Headache

SYSTEMATIC REVIEWS IDENTIFIED

We did not identify any systematic reviews published between 2010 and 2015 of Radiofrequency treatment of the pterygopalatine ganglion (sphenopalatinum), Peripheral nerve stimulation of ganglion pterygopalatinum or Occipital nerve stimulation.

RELEVANT TRIALS PUBLISHED SUBSEQUENT TO THE SYSTEMATIC REVIEW

We searched for RCTs and identified the following published subsequent to the previous guidance.

Intervention	**Study**
Radiofrequency treatment of the pterygopalatine ganglion (sphenopalatinum)	No RCTs identified
Peripheral nerve stimulation of ganglion pterygopalatinum	Schoenen (2013)
Occipital nerve stimulation	Wilbrink (2013) *

* Protocol only. Trial is due to be completed in December 2016. Details can be found below:

Peripheral nerve stimulation of ganglion pterygopalatinum (RCT)

Study	**Schoenen (2013)**
Country	Multinational (6 European sites)
Study Design	RCT (unit of randomisation is cluster headache attack)
Single/Multiple centre	6 centres
Recruitment status	Completed
Patient inclusion criteria	18 to 65 years old, diagnosed with Chronic Cluster Headache according to 2004 International Headache Society (HIS) criteria, ≥ 4 CHs/week, patient dissatisfaction with current headache treatments, patient able to distinguish cluster headaches from other headaches
Patient mean age	45 (Range 20 to 63)
No of CH attacks per week	19.2 Range 4 to 70)
No randomised	32 (27 m, 5f) Randomisation per attack, 1:1:1 (full stimulation: sub-perception stimulation: sham stimulation)
No in intervention	32
No in control	32 (patients acted as their own controls)
Intervention details	Autonomic Technologies Inc. (ATI) SPG Neurostimulator was implanted under general anaesthesia using the trans-oral, gingival buccal technique. Electrodes positioned within pterygopalatine fossa (PPF) proximate to SPG verified by X-ray. Stimulation parameters were adjusted bi-weekly as necessary. Maximum amplitude programmed to be slightly higher than patient discomfort amplitude. Using remote controller patient could apply stimulation

	and control amplitude up to highest level programmed by clinician. Patients applied stimulation for 15 mins when they had a headache attack of at least moderate intensity.
Control details	Random insertion of either sub-perception stimulation or sham stimulation when remote control activated during cluster headache attack.
Conservative treatments allowed	Patients required to maintain type and dosage of preventative headache medications from one month prior to study enrolment to completion of the experimental period.
Primary Efficacy outcome	Pain relief at 15 mins following start of stimulation. (Categorical pain scale 0-4 (0: no pain, 4: very severe pain), relief if pain decreased from 2-4 to 0 or 1).
Primary Safety outcome	Device or procedure-related serious adverse events from implantation to end of the experimental period
Method of Outcome Assessment	Electronic headache diary
Results	Pain relief was achieved in 67.1% of full stimulation-treated attacks at 15 mins compared to 7.4% of sham stimulation ($p < 0.0001$). Pain relief after sub-perception stimulation (and 7.3% relief) was not significantly different from sham stimulation. 19 of 28 (68%) of patients experienced a clinically significant improvement (randomisation per attack: observational data). Full details of all secondary outcomes are provided in the article. Five device or procedure-related serious adverse events occurred. Three SPG neurostimulator lead revisions and two SPG neurostimulator explant procedures were classified as SAEs. One explant procedure left the patient with partially resolved dysesthesia in the maxillary nerve. Sensory disturbance occurred in 81% of patients with localised loss of sensation in maxillary nerve being most common. Full details of all adverse events are provided in the article.

Cochrane Risk of Bias

Study		**Schoenen (2013)**
Randomisation	Unclear	Unsure how randomisation sequence generated
Allocation Concealment	Low	Patients could not predict the sequence
Blinding of participants	High	The patient was aware of which treatment was given
Blinding of caregivers	Low	Caregivers unaware of sequence
Blinding of assessors	High	Patient-assessed outcomes
Incomplete outcome data	High	All attacks included (but not all patients)
Selective reporting	Low	All outcomes appear to be reported
Other Biases	Low	No evidence of other biases

Occipital Nerve Stimulation (protocol for RCT)

Study	Wilbrink (2013) (ICON trial)
Country	International (The Netherlands and other European countries)
Study Design	Randomised controlled triple blinded trial
Single/Multiple centre	Multicentre
Recruitment status	Recruiting
Patient inclusion criteria	Patients ≥ 18 years with medically intractable chronic cluster headache with ≥ 4 attacks per week and no abnormalities on MRI related to cluster headache. Recruited from tertiary headache clinics
No to be randomised	144
Treatment details	High amplitude occipital nerve stimulation (60 Hz, 450 microsec.) (100%) 100 % amplitude is defined here as 90 % of the perception – uncomfortable stimulation threshold range. Bilateral stimulation for 6 months, stepwise increase (month1 40 %, month 2 70 %, thereafter 100 %.
Control details	Low amplitude stimulation: same, but stimulation amplitude 10%, 20% and 30% (two months each)
Conservative treatments allowed	Patients to agree to maintain existing cluster headache medication from four weeks prior to baseline and throughout the double blind phase of the study. New medication not allowed.
Primary Efficacy outcome	Reduction in attack frequency from baseline at 6 months (4-week periods, baseline and 6^{th} month).
Method of Outcome Assessment	Patients to complete electronic diaries 3 months during the whole study period (3 months baseline, 6 months triple blind, 6 months open stimulation) to assess frequency and intensity of attacks and QoL using SF-36. During three periods of 6 weeks (end of baseline, end of blinded part of study, end of study) time and day, intensity and use of attack medications for each attack is documented.
Safety assessed?	Yes, all and treatment-related adverse events recorded at every clinic visit

OBSERVATIONAL STUDIES

As no fully published RCTs were identified for two of the three interventions, we searched for observational studies published since the previous guidance.[1] We identified the following studies. Observational studies without a control group (case series, case reports) were excluded from our original protocol. However, they are mentioned here for information purposes as no better evidence is available.

Intervention	**Study**
Radiofrequency treatment of the pterygopalatine ganglion (sphenopalatinum)	Chua (2011) *
Occipital nerve stimulation	De Quintana (2010)
	Fontaine (2011)
	Magis (2011)
	Mueller (2011)
	Muller (2010)

*Pulsed radiofrequency

Pulsed radiofrequency treatment of the pterygopalatine ganglion (sphenopalatinum) Case Series

Study	**Chua (2011)**
Patients	Three patients (1m, 2F) with cluster headaches > 10 years' duration with minimal relief from conservative treatment.
Follow up	4 months
Results	Two of the three patients experienced almost complete pain relief and cessation of attacks up to 4 months after the procedure. One patient experienced no change in pain scores but rated her overall improvement as 30 to 40%. No neurological adverse effects or complications were reported during or after the procedure.

Occipital nerve stimulation Case Series

Study	De Quintana (2010)	Fontaine (2011)	Magis (2011)	Mueller (2011), Muller (2010)
Patients	4 patients (3m, 1F) with drug-resistant cluster headache lasting 1 to 16 years.	13 patients with drug-resistant chronic cluster headache (CCH) acc. to the International Headache Society, lasting > 2 years, ≥ 1 daily attack	15 patients with drug-resistant CCH	10 patients with CCH
Follow up	6 months	Mean follow-up 14.6 months	Mean follow-up 36.82 months (range 11-64 months)	Mean follow-up 12 months (range 3-18 months)
Results	At 6 months, there was a 56% (range: 25-95%) reduction in the frequency, a 48.8% (range: 20-60%) decrease in the intensity and a 63.8% (range: 0-88.8%) reduction in the duration of the attacks. All patients showed a 15.4% (range: 6-31.5%) improvement in their quality of life based on SF-36. In all cases but one there was a significant reduction in the amount and dosage of medication required. Postoperative complications were not observed. All patients would recommend the procedure.	The mean attack frequency and intensity decreased by 68% and 49%, respectively. At last follow-up, 10/13 patients were considered as responders (improvement >50%). Prophylactic treatment could be stopped or reduced in 8/13 cases. Local infection occurred in one patient, leading to hardware removal.	One patient had an immediate post-operative infection. Among the 14 remaining patients, 11 (80%) had ≥ 90% improvement. Two patients did not respond or described mild improvement. Four patients (29%) were able to reduce their prophylaxis. Five of 14 (36%) patients had side shift with infrequent contralateral attacks and/or isolated ipsilateral autonomic attacks without pain. Two patients found ONS-related paraesthesia unbearable: one had his stimulator removed, and the other switched it off.	Frequency, duration, and severity of the cluster attacks were reduced in 90% of the patients. 70% of the patients needed less medication during the attacks. One generator had to be exchanged due to a local infection. Another patient had to be re-operated due to a scar tissue formation around the thoracic connector.

Author(s): Jos Kleijnen
Date: 2016-10-27
Question: Should Radiofrequency treatment of the pterygopalatine ganglion be used for cluster headache?
Settings: Treatment by anaesthetists
Bibliography: Chua NH, Vissers KC, Wilder-Smith OH. Quantitative sensory testing may predict response to sphenopalatine ganglion pulsed radiofrequency treatment in cluster headaches: a case series. Pain Pract 2011;11 (5):439-45 Sanders M, Zuurmond WW. Efficacy of sphenopalatine ganglion blockade in 66 patients suffering from cluster headache: a 12- to 70-month follow-up evaluation. J Neurosurg. 1997;87:876-880. Filippini-de Moor G, Barendse G, Van Kleef M, et al. Retrospective analysis of radiofrequency lesions of the sphenopalatine ganglion in the treatment of 19 cluster headache patients. The Pain Clinic. 1999;11:285-292. Narouze S, Kapural L, Casanova J, Mekhail N. Sphenopalatine ganglion radiofrequency ablation for the management of chronic cluster headache. Headache. 2009;49:571-577.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Radiofrequency treatment of the pterygopalatine ganglion**	**Control**	**Relative (95% CI)**	**Absolute**		
Pain relief (follow-up 4-70 months)												
4	observational studies[1,2]	very serious[1]	no serious inconsistency	no serious indirectness	serious[1]	none	-	-	-	-	⊕OOO VERY LOW	CRITICAL
Neurological adverse effects or complications (follow-up mean 4 months)												
1	observational studies[1,2]	very serious[1]	no serious inconsistency	no serious indirectness	very serious[1]	reporting bias	0/3 (0%)	-	-	-	⊕OOO VERY LOW	CRITICAL

[1] 4 small case series, the largest with 19 patients
[2] case series

Author(s): Jos Kleijnen
Date: 2016-10-27
Question: Should Peripheral nerve stimulation of ganglion pterygopalatinum be used for cluster headache?
Settings: Treatment by anaesthetists
Bibliography: Schoenen J, Jensen RH, Lantéri-Minet M, Láinez MJ, Gaul C, Goodman AM, et al. Stimulation of the sphenopalatine ganglion (SPG) for cluster headache treatment. Pathway CH-1: a randomized, sham-controlled study. Cephalalgia 2013;33(10):816-30.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Peripheral nerve stimulation of ganglion pterygopalatinum	Control	Relative (95% CI)	Absolute		
Pain relief[1] (follow-up mean 15 minutes; measured with: Categorical pain scale 0-4; Better indicated by higher values)												
1	randomized trials	very serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	28	28	-	MD 59.7 higher (0 to 0 higher)	⊕⊕OO LOW	CRITICAL
Device or procedure-related serious adverse events												
1	observational studies[3]	serious[4]	no serious inconsistency	no serious indirectness	serious[4]	none	6/32 (18.8%)	-	-	-		CRITICAL

[1] 127/190 (67.1%) attacks successfully treated by active intervention, compared with 15/192 (7.4%) attacks successfully treated by sham intervention
[2] No successful blinding of participants and assessors; all attacks included but not all patients; analyses based on attacks not patients
[3] For the outcome of serious adverse events this study is effectively a case series
[4] Study in only 32 patients

Author(s): Jos Kleijnen
Date: 2016-10-27
Question: Should Occipital Nerve Stimulation be used for cluster headache?
Settings: Treatment by anaesthetists
Bibliography: de Quintana-Schmidt C, Casajuana-Garreta E, Molet-Teixido J, Garcia-Bach M, Roig C, Clavel-Laria P, et al. [Stimulation of the occipital nerve in the treatment of drug-resistant cluster headache]. Rev Neurol 2010;51(1):19-26 Fontaine D, Christophe Sol J, Raoul S, Fabre N, Geraud G, Magne C, et al. Treatment of refractory chronic cluster headache by chronic occipital nerve stimulation. Cephalalgia 2011;31(10):1101-5 Magis D, Gerardy PY, Remacle JM, Schoenen J. Sustained effectiveness of occipital nerve stimulation in drug-resistant chronic cluster headache. Headache 2011;51(8):1191-201 Mueller OM, Gaul C, Katsarava Z, Diener HC, Sure U, Gasser T. Occipital nerve stimulation for the treatment of chronic cluster headache - lessons learned from 18 months experience. Cen Eur Neurosurg 2011;72(2):84-9 Muller OM, Gaul C, Katsarava Z, Sure U, Diener HC, Gasser T. [Bilateral occipital nerve stimulation for the treatment of chronic cluster headache: case series and initiation of a prospective study]. Fortschr Neurol Psychiatr 2010;78(12):709-14

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Occipital Nerve Stimulation	Control	Relative (95% CI)	Absolute		
Various outcomes (follow-up 6-64 months)												
4	observational studies[1]	very serious[2]	no serious inconsistency	no serious indirectness	very serious[2]	reporting bias[3]	-	-	-	-	⊕OOO VERY LOW	CRITICAL
Serious adverse events												
4	observational studies[1]	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	reporting bias[3]	5/42 (11.9%)	-	-	-	⊕OOO VERY LOW	CRITICAL

[1] case series
[2] The studies included only 4, 10, 13 and 15 patients
[3] Small case series may only be published if positive results can be reported, here we have multiple small studies

3. Persistent Idiopathic Facial Pain

SYSTEMATIC REVIEWS IDENTIFIED

No relevant systematic reviews were identified.

POTENTIALLY RELEVANT TRIALS

No relevant trials were identified for any of the interventions.

OBSERVATIONAL STUDIES

The following relevant observational studies were identified since the previous guidance.

Intervention	Study
Pulsed RF of the ganglion pterygopalatinum (sphenopalatinum)	Brunete (2014) *
RF of the ganglion pterygopalatinum (sphenopalatinum)	Oomen (2012) **

*Conference abstract only, **Paper not available, data taken from abstract

Pulsed RF of the ganglion pterygopalatinum (sphenopalatinum)

Brunete (2014)

Aims	Methods	Results	Authors' Conclusions
To evaluate the results achieved after the implementation of clinical guidelines on pulsed RF of the ganglion pterygopalatinum (sphenopalatinum)procedure	All patients who had PRF-SPG were followed up for 6 months. Data were derived from phone conversations and clinical follow-up visits.	Eight patients were included. Three had atypical facial pain, three had trigeminal neuralgia and two had chronic headache. Three patients reported no pain relief from the procedure, three complete pain relief for six months and two mild-moderate pain relief for three-four months. Unclear from abstract which results relate to atypical facial pain	PRF-SPG seems to be a rewarding and safe intervention in the treatment of these pain disorders. Further trials are needed to confirm our results in bigger populations.

RF of the ganglion pterygopalatinum (sphenopalatinum)

Oomen (2012)

Aims	Methods	Results	Authors' Conclusions
To study the effect of radiofrequency thermocoagulation (RFT) of the sphenopalatine ganglion (SPG) on headache and facial pain conditions following critical re-evaluation of the original diagnosis.	This was a retrospective study of clinical records gathered over 4 consecutive years of all 15 facial pain or headache patients who underwent RFT of the SPG at a tertiary pain clinic; diagnoses were re-evaluated, after which the effect of RFT on facial pain was assessed.	After application of new criteria for Sluder's neuralgia (SN) and strict criteria for cluster headache (CH), seven patients out of the 15 turned out to have been diagnosed correctly. Nine of the 15 patients showed considerable pain relief after RFT of the SPG. Positive results were most frequent among patients with Sluder's neuropathy, atypical facial pain, and CH. However, repeated RFT procedures were needed in most patients. Unclear from abstract which results relate to atypical facial pain.	Correct headache and facial pain diagnosis is vital to assess the outcome of different treatment strategies. Even in a tertiary centre, headache and facial pain can be misdiagnosed. RFT of the SPG may be effective in patients with facial pain, but repeated procedures are often needed.

ONGOING TRIALS

We searched two trial registers (ClinicalTrials.gov and WHO ICTRP) but could not identify any ongoing trials related to RF or pulsed RF of the ganglion pterygopalatinum (sphenopalatinum).

Author(s): Jos Kleijnen
Date: 2017-04-25
Question: Should pulsed RF of the ganglion pterygopalatinum be used for persistent idiopathic facial pain?
Settings: Treatment by anaesthetists
Bibliography: Brunete T, Nieto C, Garcia Del Valle S, Molina R, Martienz P. Pulsed radiofrequency of sphenopalatine ganglion: clinical evaluation. Reg Anesth Pain Med. 2014;39(5 SUPPL. 1):E303. Bayer E, Racz GB, Miles D, Heavner J. Sphenopalatine Ganglion Pulsed Radiofrequency Treatment in 30 Patients Suffering from Chronic Face and Head Pain. Pain Practice. 2005;5(3):223-7.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Pulsed RF of the ganglion pterygopalatinum**	**Control**	**Relative (95% CI)**	**Absolute**		
Pain relief												
2	observational studies[1]	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	-	-	-	-	⊕OOO VERY LOW	CRITICAL

Author(s): Jos Kleijnen
Date: 2017-04-25
Question: Should RF of the ganglion pterygopalatinum be used for persistent idiopathic facial pain?
Settings: Treatment by anaesthetists
Bibliography: Oomen KP, van Wijck AJ, Hordijk GJ, de Ru JA. Effects of radiofrequency thermocoagulation of the sphenopalatine ganglion on headache and facial pain: correlation with diagnosis. J Orofac Pain. 2012;26(1):59-64.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RF of the ganglion pterygopalatinum	Control	Relative (95% CI)	Absolute		
Pain relief												
1	observational studies	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	-	-	-	-	⊕OOO VERY LOW	CRITICAL
								0%		-		

[1] Case series
[2] Not all patients had idiopathic facial pain
[3] Small study in 15 patients

4. Cervical Radicular Pain

SYSTEMATIC REVIEWS IDENTIFIED

We identified the following reviews published between 2010 and 2015 for cervical radicular pain. See table.

Intervention	Relevant Review(s)	Search date	Studies Identified in review	Meta-analysis
Interlaminar epidural corticosteroid administration	No reviews identified*			
Transforaminal epidural corticosteroid administration	Engel (2014)	June (2013)	16 (3 RCTs, 13 observational studies)	N
RF treatment adjacent to the cervical ganglion spinale (DRG)	No reviews identified*			
Pulsed RF treatment adjacent to the cervical ganglion spinale (DRG)	Chua (2011)	May 2010	1 RCT**	N
Spinal cord stimulation	No reviews identified*			

*specific to cervical radicular pain

** The only relevant trial was included in the previous guidance, so this has not been assessed.

ASSESSMENT OF THE REVIEW EVIDENCE

Transforaminal epidural corticosteroid administration

Study Reference	Participants	Interventions	Comparators	Outcomes	Study Designs
Engel (2014)	Patients receiving a fluoroscopically guided cervical transforaminal injection of steroids (CTFIS)	(CTFIS)	Any or none	Any.	Any except case reports and conference abstracts for effectiveness. Any including case reports for safety

Results
Thirteen observational studies were identified along with three RCTs of transforaminal injections. Not all results were able to be included in the review. Of the RCTs, one was excluded from the results due to study design limitations and the other two were treated as observational studies as two types of transforaminal injection were compared. Six primary studies (all observational data) reported some patients gaining at least 50% relief of radicular pain for at least four weeks after treatment. Percentages gaining such relief varied from 24% to 63% across the studies. Complete relief of radicular pain for at least four weeks ranged from 10% to 28% based on five studies. Only two studies reported on avoidance of surgery, with conflicting results: in 23 % and 63 % surgery was avoided. Evidence was rated very low on GRADE. Twenty-four studies describing complications were included in the review. This evidence was mainly case reports and rated very low. Serious complications were identified; there is evidence that complications are underreported.

Last Search date	Studies identified in review	Bottom Line
June 2013	16	This review concluded that fluoroscopically guided cervical transforaminal injection of steroids may be effective in easing pain and reducing need for surgery but the evidence is of very low quality. The authors stated that the benefits of the procedures are compromised by the risks of serious complications. Whilst the review had a number of limitations, including restriction to English-language publications only, these overall conclusions appear to be reasonable.

RELEVANT RANDOMISED CONTROLLED TRIALS

In addition to the reviews identified, we located the following randomised controlled trials. See Table.

Intervention	Study
Interlaminar epidural corticosteroid administration	Cohen (2014)[6]
Transforaminal epidural corticosteroid administration	Bureau (2014)[7]
	Woo (2015)[8]
RF treatment adjacent to the cervical ganglion spinale (DRG)	None identified
Pulsed RF treatment adjacent to the cervical ganglion spinale (DRG)	None identified
Spinal cord stimulation	None identified

EVIDENCE FROM RCTS

Interlaminar epidural corticosteroid administration

Study	**Cohen (2014)**[6]
Setting	United States
Study Design	RCT (multicentre)
Study population	Patients with cervical radicular pain extending into the arm(s) based on history and physical; NRS arm pain score ≥ 4/10 or equivalent in intensity to neck pain; MRI correlation of symptoms with pathology; and age ≥ 18 yr. No previous ESI.
Patient details	49.1% M Age 47.8 (median, 47.0; 95% interquartile range, 40.0 to 55.0)
Intervention 1	Cervical ESI: (n= 55). 3-ml solution of 60 mg of depo-methylprednisolone and normal saline administered via interlaminar route under fluoroscopic guidance. Repeat injections could be performed after the 1- and 3 month follow-ups at the discretion of the physician for patients who experienced either a recurrence of pain after resolution or only partial benefit.
Intervention 2	Combination of Cervical ESI and Conservative care (n= 55). Both ESI and pharmacotherapy with gabapentin and/or nortriptyline plus PT. PT was initiated within 1 week of enrolment. Treatments could include education, electrical simulation, ultrasound, massage, and exercise. Individuals who already failed PT could opt out, pursue alternative treatments, or choose only parts of the PT regimen they had not tried.
Control	Conservative care consisting of pharmacotherapy and PT (n= 59)
Outcomes	Average arm pain score over the past week at 1-month follow up, Neck disability index (NDI), Global perceived effect, Adverse effects and complications
Follow up duration	6 months

Results between groups at 1 month

	Cervical ESI group	Combination group	Conservative group	Mean difference*
Pain Scores	4.2 (95%CI, 3.5 to 4.9)	3.5 (95% CI, 2.8 to 4.2)	4.3 (95% CI, 3.6 to 5.0)	P = 0.26
Neck pain	4.6 (95%CI, 3.9 to 5.3)	3.5 (95%CI, 2.8 to 4.3)	4.7 (95%CI, 3.9 to 5)	P = 0.047
Mean reduction in arm pain (average decrease)	-2.0 (95%CI, -2.7 to -1.3)	-3.1 (95%CI,-3.8 to -2.3)	-1.8 (95%CI, - 2.5 to -1.2)	P = 0.035
Mean reduction in NDI	-6.8 (95%CI,-10.3 to -3.4)	-11.8 (95%CI,-15.5 to -8.2)	-8.2 (95%CI,-11.6 to -4.9)	P = 0.15

*In pairwise comparisons between the ESI and conservative groups, no significant differences were observed on any outcome measured.

Results at 3 and 6 months (Last-observation-carried-forward analysis including treatment dropouts but not study dropouts)

Successful treatment outcome	Cervical ESI group	Combination group	Conservative group	P value
1 month (n, %)	29/54 (53.7)	33/51 (64.7)	30/58 (51.7)	0.35
3 months (n, %)	18/49 (36.7)	29/51 (56.9)	15/56 (26.8)	0.006
6 months (n, %)	12/47 (25.5)	22/50 (44.0)	13/55 (23.6)	0.06

Using last-observation-carried-forward analysis, continuous parameters did not reach statistical significance (P <0.017) when adjustments were made for multiple comparisons.

Risk of bias

Cochrane Risk of Bias

Cohen (2014)		
Randomisation	Low	Computer-generated randomisation tables
Allocation Concealment	Unclear	No information
Blinding of participants	High	Not blinded
Blinding of caregivers	High	Not blinded
Blinding of assessors	Low	Investigator unaware of treatment allocation
Incomplete outcome data	Unclear	Last observation carried forward used for those exiting the study because of lack of effect after 1 and 3 months may have underestimated spontaneous recovery.
Selective reporting	Low	
Other Biases	High	Dropout reasons not fully explained per group

Transforaminal epidural corticosteroid administration

Study	**Bureau (2014)**	**Woo (2015)**
Setting	Canada	South Korea
Study Design	RCT (single centre)	RCT (single centre)
Study population	56 patients with evidence of a cervical radiculopathy involving 1 spinal nerve of ≥1 month's duration refractory to medical treatment; symptoms of cervical pain radiating to the upper limb; and signs of altered sensations, abnormal reflexes, or motor weakness caused by degenerative spondylosis and/or disk herniation (documented at CT or MRI imaging) and a current mean pain score of ≥6 on VAS 0 to 10.	30 patients with cervical radicular pain that was unresponsive to conservative management, which was also concordant with the impinged nerve root caused by foraminal stenosis and/or pathology as seen on MRI.
Patient details	TFSI: M 15/28, mean age 52 (SD 11.1) IFSI: M: 8/28, mean age 44 (SD 8.3)	76.7 % M, Mean Age 55.0 years (SD 10.5)
Intervention details	Transforaminal Steroid Injection (TFSI): 1 ml of dexamethasone sodium phosphate, 10 mg/ml injected in the posterolateral aspect of the foramen under intermittent CT fluoroscopy.	1 ml of 1 % lidocaine mixed with 2.5 mg dexamethasone was injected via the transforaminal route under fluoroscopic guidance. Correct needle placement was checked with injection of 0.2-0.3 ml of contrast. The procedure was repeated after 2 and 4 weeks if pain was > 3 (NRS 0-10).
Comparator details	Intra-articular Facet Steroid Injection (IFSI): 1 ml of dexamethasone sodium phosphate, 10 mg/ml injected in the facet joint space under intermittent CT fluoroscopy.	Same procedure, but 0.125 % lidocaine.
Outcomes	Pain severity (VAS 0 to 100), Neck Disability Index (NDI): (10 items from	Pain (NRS 0 to 10), Odom's criteria: 1) excellent – all preoperative symptoms relieved, 2) good –

	0 (no disability) to 5 (total disability), use of pain medication (MQS).	minimal persistence of preoperative symptoms; abnormal findings unchanged or improved, 3) fair – definite relief of some preoperative symptoms and 4) poor – symptoms and signs unchanged or exacerbated.
Follow up duration	4 weeks	2 weeks, 4 weeks, 6 weeks (and 3 months for those having repeated injections)
Results	IFSI VAS reduction from baseline 45.3% (95% CI: 21.4 to 69.2), TFSI VAS reduction from baseline 9.8% (+11.5 to -31.2) IFSI NDI improvement 24.3% (+2.9 to -51.5), TFSI NDI improvement 9.6% (+15.2 to -34.4) No adverse events occurred following the interventions.	Intervention (1%): Pain (NRS) decreased from 6.07 ± 1.83 to 2.87 ± 2.30 at 4 weeks. Comparator (0.125 %): from 6.87 ± 1.60 to 3.07 ± 2.73 Pain (NRS≤3/10) at 3 months 11 (73.33%) in intervention vs. 12 (80%) in comparator group. At least 50 % reduction of pain at 3 months 10 (66.67%) (intervention) vs. 11 (73.33%) (comparator). Outcome according to Odom's criteria was similar.

Risk of bias

Bureau (2014))		
Randomisation	Low	Computer generated and administered by person not involved with the patients
Allocation Concealment	Low	Sealed envelopes sequentially numbered from 1 to 56.
Blinding of participants	Low	
Blinding of caregivers	Low	
Blinding of assessors	Low	
Incomplete outcome data	Low	
Selective reporting	Low	
Other Biases	Low	

Woo (2015)		
Randomisation	Low	Computer-generated randomisation table
Allocation Concealment	Unclear	No information
Blinding of participants	Low	Patients and physicians participating in the study were unaware of the group assignments
Blinding of caregivers	Low	
Blinding of assessors	Low	
Incomplete outcome data	Unclear	No information on number of patients followed up to 3 months (because of repeated injections)
Selective reporting	Low	
Other Biases	Low	

OBSERVATIONAL STUDIES

We searched for observational studies for the two interventions where no systematic reviews or RCTs were identified and found the following relevant studies:

Intervention	Study
RF treatment adjacent to the cervical ganglion spinale (DRG)	None identified
Pulsed RF treatment adjacent to the cervical ganglion spinale (DRG)	Chao (2008)
	Choi (2012)
	Yoon (2014)
Spinal cord stimulation	Smits (2013) *
	Zhou (2013) *

*Conference abstract

EVIDENCE FROM OBSERVATIONAL STUDIES

Pulsed RF treatment adjacent to the cervical ganglion spinale (DRG)

Study	Chao (2008)	Choi (2012) Ahn (2011)	Yoon (2014)
Setting	Taiwan?	Dept of Rehabilitation Medicine, Yeungnam University, Daegu, Korea	Dept of Neurosurgery, Ilsan Paik Hospital, Goyang, Korea
Study Design	Case series	Case series	Case series
Study population	49 patients with cervical radicular pain due to a herniated intervertebral disk (44) or previous failed surgery (5), > 3 months failure with conservative treatment. Diagnosis was based on clinical features, physical examination, dynamic X-ray and MRI/CT. Patients with symptoms due to mild or moderate bulging disk were included. The study was part of a larger one that also included patient with lumbar radicular pain.	21 patients with persistent cervical radicular pain despite repeated (mean: 3) TFESIs. Sustained pain (radiating into the arm) score > 4 (0-10 NRS). Positive response to segmental nerve blockade, MRI/CT and electrophysiological findings corresponding to clinical findings.	22 patients with sustained segmental pain of > 4 on NRS after conservative management. Patients had clinical findings corresponding with MRICT findings. They also had a positive reaction (twice!) to diagnostic blocks with ropivacaine.
Patient details	17M, 32F, Mean age 53.2 (10.99)	16M, 5F, Mean Age 60	12M, 10F, Mean age 54 (10)
Intervention details	Pulsed RF in 2 to 4 (mean: 2.5) spinal levels unilaterally. With fluoroscopic guidance using C-arm, a 10-cm 22-gauge curved-tip cannula	PRF on the symptomatic cervical DRG. With fluoroscopy using C-arm and a 22-gauge curved-tip cannula with a 4 mm active tip, placed near	A 10-cm 22-gauge SMKC10 electrode with 10-mm active tip was placed adjacent to the cervical DRG. Correct needle position was

	with a 1-cm active tip electrode was placed adjacent to the DRG within the intervertebral foramen. 2-Hz pulsed RF waves were applied for 120s at 45 V with max. temp 42 °C. Three patients had a second PRF at the contralateral side, >= months later applied for 120s at 45 V.	the DRG. Needle position was checked with sensory stimulation (< 0.3 V). 2-Hz pulsed RF waves were applied for 120s at 45V, temperature <= 42 °C.	checked with sensory stimulation (< 0.8 V). PRF was applied twice for 120 seconds at a setting of 2Hz and 45V, with the end point being an electrode tip temperature not exceeding 42°C.
Outcomes	Percentage pain relief using VAS 0 to 100.	NRS for arm pain. Successful pain relief defined as ≥ 50% reduction in NRS score from baseline. Patient treatment satisfaction also assessed	NRS (0-10). A successful outcome was defined as >= 50 % pain relief at 6 months.
Follow up duration	Up to 12 months	Up to 12 months	Up to 6 months
Results	27 of 49 patients (55.1%) had ≥ 50% pain relief at 3 months, 22 of 40 at 6 months, 12 of 21 at 9 months, and 4 of & at 1 year (no information on number of dropouts)	Fourteen (66.7%) of 21 patients reported pain relief of ≥ 50% at 3, 6 and 12-month follow-up. Fifteen patients (71.4%) were satisfied with their current status at 12 months. No serious adverse effects.	The success rate was 68% (15/22) after six months of follow-up. PRF induced complications were not observed. No prognostic factors for treatment success were identified.

Spinal cord stimulation

Study	**Smits (2013)**
Setting	NR
Study Design	Retrospective chart review
Study population	14 patients with Failed Neck Surgery Syndrome and intractable chronic cervical radicular pain
Patient details	7M, 7F. Mean age 55 (SD 2.5) years
Intervention details	Spinal cord stimulation (details NR)
Outcomes	Pain measured on VAS (0 to 10), Re-interventions
Follow up duration	98.3 (SD 17.6) months
Results	VAS scores at final follow up decreased compared to baseline (4.0+/-0.4 vs. 8.6+/-0.18, P=0.029). The global perceived effect at final follow up was an improvement of 66% +/- 2.4 %. At the end of follow-up, 13 patients were prepared to undergo the same procedure if necessary. Six re-interventions were needed: 3 due to lead fractures and 3 due to lead dislocations.

Author(s): Jos Kleijnen
Date: 2016-12-07
Question: Should interlaminar epidural corticosteroid administration be used for cervical radicular pain?
Settings: Treatment by anaesthetists
Bibliography: Cohen SP, Hayek S, Semenov Y, Pasquina PF, White RL, Veizi E, et al. Epidural steroid injections, conservative treatment, or combination treatment for cervical radicular pain: a multicenter, randomized, comparative-effectiveness study. Anesthesiology 2014;121(5):1045-55.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Interlaminar epidural corticosteroid administration**	**Control**	**Relative (95% CI)**	**Absolute**		
Global perceived effect (follow-up mean 6 months; assessed with: Successful treatment outcome)												
1	randomized trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision[2]	none	22/50 (44%)	13/55 (23.6%)	RR 1.86 (1.05 to 3.29)	203 more per 1000 (from 12 more to 541 more)	⊕⊕⊕O MODERATE	CRITICAL
								23.6%		203 more per 1000 (from 12 more to 540 more)		

[1] Dropout reasons not fully explained per group, no blinding
[2] Wide 95% confidence interval; but fairly clear effect

Author(s): Jos Kleijnen
Date: 2016-12-07
Question: Should transforaminal epidural corticosteroid administration be used for cervical radicular pain?
Settings: Treatment by anaesthetists
Bibliography: Engel A, King W, Macvicar J. The effectiveness and risks of fluoroscopically guided cervical transforaminal injections of steroids: a systematic review with comprehensive analysis of the published data. Pain Med 2014;15(3):386-402. Bureau NJ, Moser T, Dagher JH, Shedid D, Li M, Brassard P, et al. Transforaminal versus intra-articular facet corticosteroid injections for the treatment of cervical radiculopathy: a randomized, double-blind, controlled study. AJNR Am J Neuroradiol 2014;35(8):1467-74.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Transforaminal epidural corticosteroid administration	Control	Relative (95% CI)	Absolute		
Adverse effects												
21	observational studies[1,2]	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	-	-	-	⊕OOO VERY LOW	CRITICAL

[1] case reports
[2] Serious complications reported in 21 studies including 13 deaths and 31 brain and spinal cord infarctions. Also numerous other serious and persistent CNS injuries

Author(s): Jos Kleijnen
Date: 2016-12-07
Question: Should RF treatment adjacent to the cervical ganglion spinale be used for cervical radicular pain?
Settings: Treatment by anaesthetists
Bibliography: van Kleef M, Liem L, Lousberg R, Barendse G, Kessels F, Sluijter M. Radiofrequency lesion adjacent to the dorsal root ganglion for cervicobrachial pain: a prospective double blind randomized study. Neurosurgery. 1996;38:1127-1131

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RF treatment adjacent to the cervical ganglion spinale	Control	Relative (95% CI)	Absolute		
Pain (follow-up mean 8 weeks; measured with: VAS; Better indicated by lower values)												
1	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	9	11	-	MD 3.20 lower (5.52 to 0.88 lower)	⊕⊕⊕O MODERATE	CRITICAL

[1] Small trial with 9 and 11 patients in the groups

Author(s): Jos Kleijnen
Date: 2016-12-07
Question: Should pulsed RF treatment adjacent to the cervical ganglion spinale be used for cervical radicular pain?
Settings: Treatment by anaesthetists
Bibliography: Van Zundert J, Patijn J, Kessels A, Lame I, van Suijlekom H, van Kleef M. Pulsed radiofrequency adjacent to the cervical dorsal root ganglion in chronic cervical radicular pain: a double blind sham controlled randomized clinical trial. Pain. 2007;127:173-182.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Pulsed RF treatment adjacent to the cervical ganglion spinale**	**Control**	**Relative (95% CI)**	**Absolute**		
Pain (follow-up mean 3 months; assessed with: >50% pain improvement)												
1	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	9/11 (81.8%)	4/12 (33.3%)	RR 2.45 (1.05 to 5.73)	483 more per 1000 (from 17 more to 1000 more)	⊕⊕⊕O MODERATE	CRITICAL
								33.3%		483 more per 1000 (from 17 more to 1000 more)		

[1] Small trial with 11 and 12 patients in the groups

5. Cervical Facet Pain

SYSTEMATIC REVIEWS IDENTIFIED

We identified a number of reviews published between 2010 and 2015. Some were of poor quality, for example with very limited searching. Others appeared to be earlier versions of later reviews. We compared the studies included in these reviews and noted a number of differences. Some of the discrepancies can be explained by differing inclusion criteria between the reviews. For example the review by Manchikanti requires trials to have a minimum follow up of three months. Reasons for omission of some studies is less clear. However after evaluation of the three most relevant reviews we believe that the majority of the most up to date reliable evidence can be found in the review by Manchikanti. See table below. A ROBIS assessment of the quality of the three reviews can be found in the appendices.

Intervention	Relevant Review(s)	Search date	Studies Identified in review	Meta-analysis
Intra-articular injections	Manchikanti (2015)	March 2015	2 RCTs	N
Therapeutic (repetitive) cervical ramus medialis (medial branch) of the ramus dorsalis block (local anaesthetic with or without corticosteroid)	Manchikanti (2015)	March 2015	1 RCT, 1 observational study	N
RF treatment of the cervical ramus medialis (medial branch) of the ramus dorsalis	Manchikanti (2015)	March 2015	1 RCT, 4 observational studies	N

The Review Evidence

Study Reference	Participants	Interventions	Comparators	Outcomes	Study Designs
Manchikanti (2015)	Patients with chronic neck pain, mid back pain, upper back pain or low back pain of at least 3 months duration.	Cervical, thoracic, and lumbar facet joint interventions appropriately performed with proper technique under image	NR	The primary outcome measure was pain relief (short-term relief ≤ 6 months and long-term > 6 months). Secondary outcome measures were	Randomised controlled trials, Observational studies

	Patients with acute trauma, fractures, malignancies, and inflammatory diseases were excluded.	guidance (fluoroscopy, computed tomography [CT], or magnetic resonance imaging [MRI]) were included. Blind and ultrasound-guided interventions were excluded		improvement in functional status, psychological status, return to work, and reduction in opioid intake consumption	

Results

A total of 21 randomised trials and five observational studies met the inclusion criteria of the review. Four RCTs and four observational studies were relevant to cervical facet pain.

Intra-articular injections: 2 RCTs.

One trial showed no statistically significant differences between local anaesthetic and steroid injections in pain relief in a sample of 41 patients with a short-follow-up.[6] One trial had numerous methodological problems and a high withdrawal rate although some positive results were noted.[7] Evidence was rated 'Level 4' (evidence obtained from multiple moderate or low quality relevant observational studies) by the review.

Therapeutic (repetitive) cervical ramus medialis (medial branch) of the ramus dorsalis block (local anaesthetic with or without corticosteroid):
1 RCT, 1 Observational study.

The RCT found 85% of the local anaesthetic group and 93% of the local anaesthetic plus steroid group reported pain relief at the end of two years.[8] The observational study found improvements compared to baseline in pain relief, disability status, psychological status and return to work. Evidence was rated 'Level 2' (evidence obtained from at least one relevant high quality randomised controlled trial or multiple relevant moderate or low quality randomised controlled trials) by the review.

RF treatment of the cervical ramus medialis (medial branch) of the ramus dorsalis: 1 RCT, 3 Observational studies

The RCT was small (24 patients) and statistical analysis had some limitations. However it showed that the median time of return of pain in the treatment group was 263 days and eight days in the control group.[9] The three observational studies were also supportive of radiofrequency. Evidence was rated 'Level 2' (evidence obtained from at least one relevant high quality randomised controlled trial or multiple relevant moderate or low quality randomised controlled trials) by the review.

Last Search date	Studies identified in review	Bottom Line
March 2015	29	The evidence for radiofrequency neurotomy in the lumbar, cervical, and thoracic spines is variable. Overall there was a lack of high quality studies.

RELEVANT TRIALS PUBLISHED SUBSEQUENT TO THE SYSTEMATIC REVIEW

We did not identify any RCTs published subsequent to the review by Manchikanti (2015). [2] However the following trials appear to be ongoing / unpublished and should provide valuable information when published.

ONGOING / UNPUBLISHED STUDIES

ClinicalTrials.gov Identifier	NCT00476684 trial completed
Study Title	The Effect of Radiofrequency-treatment on Patients with Facet-joint Pain in Cervical- and Lumbar-columna
Sponsor:	Norwegian University of Science and Technology
Study Design	Allocation: Randomized Endpoint Classification: Efficacy Study Intervention Model: Factorial Assignment Masking: Double Blind (Subject, Outcomes Assessor) Primary Purpose: Treatment
Condition	Neck Pain Low Back Pain
Intervention	Procedure: radiofrequency treatment of the medial branch Procedure: sham neurotomy
Study Start Date	August 2004
Study Completion Date	May 2011
Ages Eligible for Study	20 Years to 75 Years

ClinicalTrials.gov Identifier	NCT01882959
Sponsor:	Turku University Hospital-Finland
Official Title	Radiofrequency Denervation for Reducing Chronic Pain: a Meta-analysis
Condition	Chronic Neck Pain Chronic Low Back Pain
Intervention	Radiofrequency Denervation
Ages Eligible for Study:	Study Start Date18 Years and older
Study Start Date	January 2013
Study Completion Date	February 2013
Enrollment	374

ClinicalTrials.gov Identifier	NCT01808586
Sponsor	Lawson Health Research Institute, Canada
Study Start Date	May 2013
Estimated Primary Completion Date	December 2015
Ages Eligible for Study	18 Years to 65 Years
Condition	Chronic Mechanical (Myofascial) Neck Pain
Intervention	Procedure: Betamethasone Procedure: Dexamethasone Procedure: Intramuscular Lidocaine Behavioral: Home Exercise
Study Design	Allocation: Randomized Endpoint Classification: Efficacy Study Intervention Model: Parallel Assignment Masking: Double Blind (Subject, Outcomes Assessor) Primary Purpose: Treatment Phase 2
Official Title	Facet Versus Trigger Point Injection for Management of Chronic Muscular Neck Pain: A Randomized Clinical Trial and Creation of a Clinical Prediction Algorithm

ClinicalTrials.gov Identifier	NCT01743326
Sponsor	Maastricht University Medical Center
Study Start Date	November 2012
Estimated Study Completion Date	June 2015
Ages Eligible for Study	25 Years to 90 Years
Percutaneous Radiofrequency Denervation of the Cervical Facet Joints Compared With Cervical Medial Branch Block of the Facet Joints for Patients With Chronic Degenerative Neck Pain : A Prospective Randomized Clinical Study	
Study Design	Allocation: Randomized Endpoint Classification: Efficacy Study Intervention Model: Parallel Assignment Masking: Double Blind (Subject, Outcomes Assessor) Primary Purpose: Treatment
Procedure	Radio Frequency Denervation Local Anesthesia
Outcomes	Numeric Rating Scale (NRS), Patient global Impression of Change on a 7 point Likert Scale (PGIC), consumption of pain medication (MQS), Patient Specific Functional Scale, Quality of life scale (RAND 36), Hospital Anxiety and Depression scale (HADS), and Neck Disability Index (NDI, Dutch version).

Having identified a systematic review including RCTs, we did not search for observational studies. Observational studies are at greater risk of bias and would not be sufficiently robust to make recommendations for practice.

Author(s): Jos Kleijnen
Date: 2016-10-30
Question: Should intra-articular injections be used for cervical facet joint pain?
Settings: Treatment by anaesthetists
Bibliography: Manchikanti L, Kaye AD, Boswell MV, Bakshi S, Gharibo CG, Grami V, et al. A systematic review and best evidence synthesis of the effectiveness of therapeutic facet joint interventions in managing chronic spinal pain. Pain Physician 2015;18(4):E535-82.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intra-articular injections	Control	Relative (95% CI)	Absolute		
Pain relief (follow-up mean 3.5 days; Better indicated by lower values)												
1	randomized trials	serious[1]	no serious inconsistency	no serious indirectness	serious[1]	none	21	20	-	MD 0.5 higher (0 to 0 higher)	⊕⊕OO LOW	CRITICAL

[1] Small trial comparing steroid with local anaesthetic; principle outcome (return of pain to 50% of preinjection level) was reached between 3-3.5 days follow-up

Author(s): Jos Kleijnen
Date: 2016-10-30
Question: Should therapeutic injections at the cervical ramus medialis be used for cervical facet joint pain?
Settings: Treatment by anaesthetists
Bibliography: Manchikanti L, Kaye AD, Boswell MV, Bakshi S, Gharibo CG, Grami V, et al. A systematic review and best evidence synthesis of the effectiveness of therapeutic facet joint interventions in managing chronic spinal pain. Pain Physician 2015;18(4):E535-82.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Therapeutic injections at the cervical ramus medialis**	**Control**	**Relative (95% CI)**	**Absolute**		
Pain relief (follow-up mean 2 patient-years)												
1	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias[1]	56/60 (93.3%)[2]	51/60 (85%)	-	850 fewer per 1000 (from 850 fewer to 850 fewer)	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		

[1] Only one RCT was found comparing bupivacaine plus steroid with bupivacaine alone which does not appear to have been replicated
[2] Number of events calculated from reported percentages in paper

Author(s): Jos Kleijnen
Date: 2016-10-30
Question: Should radiofrequency treatment of the cervical ramus medialis be used for cervical facet joint pain?
Settings: Treatment by anaesthetists
Bibliography: Manchikanti L, Kaye AD, Boswell MV, Bakshi S, Gharibo CG, Grami V, et al. A systematic review and best evidence synthesis of the effectiveness of therapeutic facet joint interventions in managing chronic spinal pain. Pain Physician 2015;18(4):E535-82.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Radiofrequency treatment of the cervical ramus medialis**	**Control**	**Relative (95% CI)**	**Absolute**		
Time to return of pain to 50% of preoperative level (follow-up mean 263 days; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	reporting bias[2]	12	12	-	MD 255 higher (0 to 0 higher)	⊕⊕OO LOW	CRITICAL
Numbness (follow-up mean 263 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	reporting bias[2]	5/12 (41.7%)	0/12 (0%)	-	-	⊕⊕OO LOW	IMPORTANT
								0%		-		

[1] Data are based on only 24 patients
[2] Only one RCT comparing radiofrequency neurotomy with placebo was found which does not appear to have been replicated

6. Cervicogenic Headache

SYSTEMATIC REVIEWS IDENTIFIED

We identified the following relevant reviews published between 2010 and 2015.

Intervention	Relevant Review(s)	Search date	Studies Identified in review	Meta-analysis
Injection of nervus occipitalis major / atlanto-axial joint with corticosteroid and local anaesthetic	Ashkenazi (2010)	Not stated	1 RCT and 5 observational studies	N
RF treatment of the cervical ramus medialis (medial branch) of the ramus dorsalis	Nagar (2015)	March 2014	4 RCTs, 5 non-randomised studies	N
Pulsed RF treatment of the nervi occipitales				
Pulsed RF of the DRG (c2 – C3)				

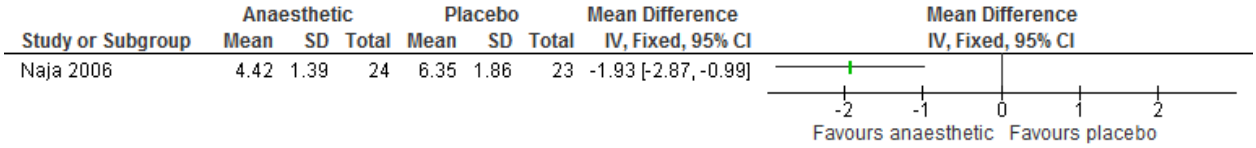
ASSESSMENT OF THE REVIEW EVIDENCE

Injection of nervus occipitalis major / atlanto-axial joint with corticosteroid and local anaesthetic

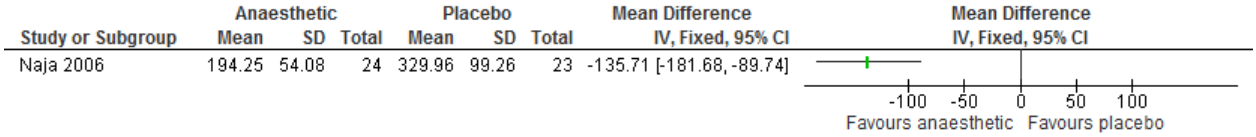
Study Reference	Participants	Interventions	Comparators	Outcomes	Study Designs
Ashkenazi (2010)	Patients with migraine, cluster headache, chronic daily headache, cervicogenic headache, trigeminal neuralgia and post-dural puncture headache	Peripheral nerve blocks and trigger point injections	Not reported	Not pre-specified.	NR

Results
Results were generally positive across the review but based on methodologically limited studies. Four observational studies (157 participants) found some improvements in headache at varying time points when peripheral blocks were used for migraine. When peripheral nerve blocks were used for cluster headache one controlled trial and four observational studies showed decreases in attacks or minor headache improvement. For chronic daily headache a RCT found no significant between group differences for headache severity, an open label trial found no change in headache severity and two observational studies had positive outcomes for partial response or headache relief. For cervicogenic headache a placebo-controlled trial (Naja 2006) found significant head pain improvement at 2 weeks. Five further non-randomised studies showed positive results in terms of pain relief although one study noted that 87% of participants required repeated injection.

Naja 2006 VAS scores after 2 weeks



Naja 2006 Total Pain Index scores after 2 weeks



Last Search date	Studies identified in review	Bottom Line
Not reported	Not reported	The authors of this review concluded that there was a lack of controlled data on the efficacy of peripheral nerve blocks and trigger point injections in headache management and that further studies are required. The reliability of the findings of this review is limited due to a number of methodological problems.

RF treatment of the cervical ramus medialis (medial branch) of the ramus dorsalis and Pulsed RF treatment of the nervi occipitales and of the DRG

Study Reference	Participants	Interventions	Comparators	Outcomes	Study Designs
Nagar (2015)[4]	Adult (18+ years to 80 years) patients with cervicogenic pain	Radiofrequency ablation, pulsed radiofrequency ablation	Not pre-specified. Not all studies had a control group.	Reduction in pain scores and improvement in quality of life	Randomised controlled trials and prospective non-randomised trials, case control, cohort, and cross-sectional studies

Results
Overall nine studies investigated the clinical utility of RFA or PRF for the management of cervicogenic headache. Three randomised trials and four observational studies assessed the effectiveness of RFA. Of these, one small RCT presented positive findings for pain relief but two RCTs did not show significant benefits with RFA. Both studies investigating PRF (one randomised trial and one observational study) presented positive findings. Overall the review did not find strong evidence of effectiveness for RFA or pulsed RFA.

Last Search date	Studies identified in review	Bottom Line
January 2014	6	The review concluded that there is limited evidence for RF and pulsed RF treatments for the management of cervicogenic headache and that high quality RCTs are needed. It was unclear if some studies might have been missed from the review but the overall recommendation for high quality trials to strengthen the evidence appears valid.

RELEVANT TRIALS PUBLISHED SUBSEQUENT TO THE SYSTEMATIC REVIEW

We did not identify any RCTs published subsequent to the reviews

Author(s): Jos Kleijnen
Date: 2016-11-03
Question: Should Injection with local anaesthetics and/or corticosteroids be used for cervicogenic headache?
Settings: Treatment by anaesthetists
Bibliography: Ashkenazi A, Blumenfeld A, Napchan U, Narouze S, Grosberg B, Nett R, et al. Peripheral nerve blocks and trigger point injections in headache management - a systematic review and suggestions for future research. Headache 2010;50(6):943-52

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Injection with local anaesthetics and/or corticosteroids	Control	Relative (95% CI)	Absolute		
Pain on VAS (follow-up mean 2 weeks; measured with: VAS; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	24	23	-	MD 1.93 lower (2.87 to 0.99 lower)	⊕⊕⊕O MODERATE	CRITICAL
Total Pain Index (follow-up mean 2 weeks; measured with: TPI; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	24	23	-	MD 135.71 lower (181.68 to 89.74 lower)	⊕⊕⊕O MODERATE	CRITICAL

[1] Small trial in 50 patients

Author(s): Jos Kleijnen
Date: 2016-11-03
Question: Should RF treatment of the cervical ramus medialis (medial branch) of the ramus dorsalis be used for cervicogenic headache?
Settings: Treatment by anaesthetists
Bibliography: Nagar VR, Birthi P, Grider JS, Asopa A. Systematic review of radiofrequency ablation and pulsed radiofrequency for management of cervicogenic headache. Pain Physician 2015;18(2):109-30

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**RF treatment of the cervical ramus medialis (medial branch) of the ramus dorsalis**	**Control**	**Relative (95% CI)**	**Absolute**		
Pain												
3	randomised trials	serious[1]	serious[2]	no serious indirectness	serious[1]	none	-	-	-	-	⊕OOO VERY LOW	CRITICAL
								0%		-		

[1] Three small trials of 12, 24 and 30 patients.
[2] One study reported positive findings, the other two did not.

Author(s): Jos Kleijnen
Date: 2016-11-03
Question: Should Pulsed RF treatment of the nervi occipitales be used for cervicogenic headache?
Settings: Treatment by anaesthetists
Bibliography: Nagar VR, Birthi P, Grider JS, Asopa A. Systematic review of radiofrequency ablation and pulsed radiofrequency for management of cervicogenic headache. Pain Physician 2015;18(2):109-30

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pulsed RF treatment of the nervi occipitales	Control	Relative (95% CI)	Absolute		
Pain (follow-up mean 9 months; assessed with: VAS)												
1	randomised trials	serious	no serious inconsistency	no serious indirectness	serious[1]	none	-	-	-	-	⊕⊕OO LOW	CRITICAL
								0%		-		

[1] Small trial in 30 patients

7. Whiplash-Associated Disorders

SYSTEMATIC REVIEWS IDENTIFIED

The following table lists the relevant reviews and any gaps in the review evidence.

Intervention	Relevant Review(s)	Search date	Studies identified in review	Meta-analysis
Botulinum toxin	Zhang (2011)	To August 2009	3 RCTs	Y
	Teasell (2010)	To March 2009	3 RCTs 1 Case series	N
Radiofrequency treatment of the cervical ramus medialis (medial branch) of the ramus dorsalis	Teasell (2010)	To March 2009	1 RCT 7 observational studies	N
Intra-articular corticosteroid injection	Teasell (2010)	To March 2009	1 RCT 2 Case series	N

The review by Teasell was part of a series of reviews considering interventions for whiplash associated disorder. Part 5 focuses on surgical and injection-based interventions for chronic WAD which covers the topics in this report. Following the previous guidance which stated that intervention treatments are only considered after a minimum of six months of symptoms, we did not include the review of interventions for subacute WAD which covered WAD of two to 12 weeks only. We also identified a review by Linde which included one published RCT of chronic headache attributed to whiplash injury. This RCT was included in the review by Teasell. A further review of mechanical neck disorders did not include any WAD studies.[11]

ASSESSMENT OF THE REVIEW EVIDENCE

Review 1

Study Reference	Participants	Interventions	Comparators	Outcomes	Study Designs
Zhang (2011)	Patients with chronic musculoskeletal pain	Intramuscular or subcutaneous botulinum toxin type A (BoNTA) injections	Placebos or other non-active therapies including exercise	Reduction in pain severity (self-assessment)	Randomised controlled trials

Results

- Pooled results from the review showed small to moderate pain reduction with the treatment of botulinum toxin type A (BoNTA) patients when compared to control (standard mean difference [SMD] = -0.27, 95% confidence interval [CI], -0.44 to -0.11).
- Based on 3 studies (96 patients) BoNTA did not lead to greater pain relief in WAD (SMD = 0.00, 95% CI, -0.41 to 0.40)

Last search date	**Studies identified in review**	**Bottom Line**
August 2009	21 of which 3 were relevant	The evidence indicated that botulinum toxin type A treatments can result in a small to moderate pain relief in patients with musculoskeletal pain. However no effect was observed for whiplash associated disorders. This review was overall reasonable but more clarity on eligible studies and a full account of the search strategy would have helped ascertain reliability.

Review 2

Study Reference	**Participants**	**Interventions**	**Comparators**	**Outcomes**	**Study Designs**
Teasell (2010)	Adults ≥18 years) with ≥ 60% of participants having a whiplash-injury	Surgical and injection-based interventions initiated during the chronic phase of WAD therapy (> 3 months post-injury)	Not pre-specified. Placebo and active interventions included	Not pre-specified.	Not pre-specified. RCTs and observational studies included

Results

- Radiofrequency neurotomy was found to be moderately effective in treatment for whiplash-related pain, although relief is not permanent in patients with chronic WAD based on one RCT of good methodological quality and 7 observational studies.

- Intra-articular corticosteroid injections did not appear to be effective for WAD based on one RCT and 2 case series.
- Botulinum toxin injections showed contradictory evidence during the chronic stage of WAD based on 3 RCTs and one observational study.

Last Search date	Studies identified in review	Bottom Line
March 2009	23 of which 15 relevant	The authors noted that the conclusions in this review are mainly based on one RCT per intervention and as such should be approached with caution. Radiofrequency neurotomy has overall positive results whereas botulinum toxin injections are mixed and intra-articular injections are unlikely to be of benefit. However, the evidence is not yet strong enough to definitely establish of any of the invasive treatments for whiplash-associated disorder. Further research was recommended to ascertain the role of these interventions in the treatment of chronic whiplash-associated disorder. Although the review had a number of methodological limitations these overall conclusions and recommendations appear to be appropriate.

RELEVANT TRIALS PUBLISHED SUBSEQUENT TO THE SYSTEMATIC REVIEWS

As the evidence in the identified systematic reviews lacked currency, a search was made for relevant randomised controlled trials published since 2009. However no trials were identified.

Author(s): Jos Kleijnen
Date: 2016-11-03
Question: Should botulinum toxin be used for whiplash associated disorder ?
Settings: Treatment by anaesthetists
Bibliography: Zhang T, Adatia A, Zarin W, Moitri M, Vijenthira A, Chu R, et al. The efficacy of botulinum toxin type A in managing chronic musculoskeletal pain: a systematic review and meta analysis. Inflammopharmacology 2011;19(1):21-34 Teasell RW, McClure JA, Walton D, Pretty J, Salter K, Meyer M, et al. A research synthesis of therapeutic interventions for whiplash-associated disorder (WAD): part 5 - surgical and injection-based interventions for chronic WAD. Pain Res Manag 2010;15(5):323-34

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Botulinum toxin	Control	Relative (95% CI)	Absolute		
Pain reduction (follow-up median 16 weeks; measured with: VAS 0-10; Better indicated by lower values)												
3	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	50	46	-	MD 0.0 higher (0.41 lower to 0.40 higher)	⊕⊕⊕O MODERATE	

[1] Three small studies in 20, 37 and 40 patients

Author(s): Jos Kleijnen
Date: 2016-11-03
Question: Should radiofrequency treatment of the cervical ramus medialis (medial branch) of the ramus dorsalis be used for whiplash associated disorder ?
Settings: Treatment by anaesthetists
Bibliography: Teasell RW, McClure JA, Walton D, Pretty J, Salter K, Meyer M, et al. A research synthesis of therapeutic interventions for whiplash-associated disorder (WAD): part 5 - surgical and injection-based interventions for chronic WAD. Pain Res Manag 2010;15(5):323-34.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Radiofrequency treatment of the cervical ramus medialis (medial branch) of the ramus dorsalis**	**Control**	**Relative (95% CI)**	**Absolute**		
Time to return to 50% of preoperative pain (follow-up median 263 days; measured with: VAS; Better indicated by higher values)												
1	randomized trials	serious[1]	no serious inconsistency	no serious indirectness	serious[1]	none	12	12	-	MD 255 higher (0 to 0 higher)	⊕⊕OO LOW	CRITICAL

[1] Small trial of 24 patients.

Author(s): Jos Kleijnen
Date: 2016-11-03
Question: Should intra-articular corticosteroid injection be used for whiplash associated disorder ?
Settings: Treatment by anaesthetists
Bibliography:

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intra-articular corticosteroid injection	Control	Relative (95% CI)	Absolute		
Median time in days to return of 50% preinjection pain (follow-up mean 12 weeks; measured with: Telephone and clinic visits; Better indicated by higher values)												
1	randomized trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	21	20	-	MD 0.5 higher (0 to 0 higher)	⊕OOO VERY LOW	CRITICAL

[1] PEDRO score 7 out of 10
[2] One trial comparing steroid with anaesthetic injections. No untreated control group.
[3] Small study in 41 patients

8. Occipital Neuralgia

SYSTEMATIC REVIEWS IDENTIFIED

We identified the following reviews published between 2010 and 2015. See table.

Intervention	Relevant Review(s)	Search date	Studies Identified in review	Meta-analysis
Single infiltration of the nervi occipitales with local anaesthetic and corticosteroids	No reviews identified			
Pulsed Radiofrequency treatment of the nervi occipitales	No reviews identified			
Pulsed Radiofrequency treatment of DRG	No reviews identified			
Subcutaneous stimulation of the nervi occipitales	No reviews identified			
Botulinum toxin A injection	Linde (2011)	Up to Dec 2010	3 obs studies (13 patients)	N

Only one review of relevance was identified. Of 37 studies in the review of Botulinum toxin A injection by Linde only three were relevant to occipital neuralgia**.**

ASSESSMENT OF THE REVIEW EVIDENCE

Botulinum toxin A injection

Study Reference	Participants	Interventions	Comparators	Outcomes	Study Designs
Linde (2011)	Participants with secondary headache and cranial neuralgias	Botulinum toxin	Placebo	Pain intensity and headache frequency	Randomised controlled trials, open-label studies, case reports

Results

- Two case studies and one case report were identified of occipital neuralgia. The authors did not report these results in detail but improvements in some pain measurements were reported across the 13 patients in these studies.

Last Search date	Studies identified in review	Bottom Line
December 2010	37 (3 relevant)	This review found limited evidence to suggest the use of botulinum toxin treatment in secondary headaches and cranial neuralgias. The review had a number of limitations including the potential for missing studies, lack of information on the review process and a lack of quality assessment of the included primary studies.

RELEVANT TRIALS PUBLISHED SUBSEQUENT TO THE PREVIOUS GUIDANCE

We identified one RCT conducted since the previous guidance.[4] The RCT was presented as a conference abstract but we were unable to identify a full publication. Therefore it is impossible to assess the quality of the trial.[4] Brief study details and results taken from the abstract are presented below.

Study	Seo (2010)
Setting	Unclear
Study Design	Randomised Controlled Trial
Study population	Thirty-six patients with greater occipital neuralgia (GON)
Patient details	20 F, 16 M all satisfying the International Classification Headache Disorders Criteria for GON.
Intervention details	Lidocaine injection (n = 12), BTX-A injection(n = 12), or saline injection(n =12). Greater occipital nerve was identified at its point of entry to the scalp, along the superior nuchal line midway between the mastoid process and occipital protuberance. The point at which maximal tenderness was elicited was used as the injection site. Approximately 1.5 ml of 2% lidocaine, 30 units of BTX-A, or 1.5 ml of saline were injected.
Follow up duration	One month
Results	Pain measured by VAS was significantly decreased in groups receiving the lidocaine or BTX-A injections (time of measurement not reported); however, it did not significantly change in the physiological saline injection group. At one month post treatment, the BTX-A group exhibited better VAS scores than those for both the lidocaine and saline groups ($p<0.016$).

OBSERVATIONAL STUDIES PUBLISHED SUBSEQUENT TO THE PREVIOUS GUIDANCE

We searched for observational studies and identified the following.

Intervention	**Study**
Single infiltration of the nervi occipitales with local anaesthetic and corticosteroids	Kastler (2015) Allen (2015) *
Pulsed radiofrequency treatment of the nervi occipitales	Choi (2012) Huang (2012)
Pulsed radiofrequency treatment of the of the DRG	No studies
Subcutaneous stimulation of the nervi occipitales	Palmisani (2013) Magown (2009) de la Cruz (2014) *
Botulinum toxin A injection	Pierric (2013) *

*abstract only

Data from observational studies

Single infiltration of the nervi occipitales with local anaesthetic and corticosteroids

Study	Kastler (2015)	Allen (2015)
Setting	Neuroradiology and MRI Unit, CLUNI, Grenoble University Hospital, France	Unclear
Study Design	Case series	Retrospective chart review
Study population	33 patients (37 procedures) with suspected ON with refractory pain for ≥ 3 months (Criteria A and B of IHS's definition of ON)	562 patients who had received ≥ 1 ONB and attended ≥ 1 follow up appointment.
Patient details	23F, 10M. Mean age 51.8 years Patients had left GON neuralgia in 13 cases, right GON neuralgia in 16 cases and bilateral GON neuralgia in 4 cases. A history of cervical trauma was noted in 20 patients, and a history of cervical surgery in one. Mean symptom duration 3.16 years (range 0.5 to 20).	423F, 139M. Mean age 58.6 (SD 16.7) years
Intervention details	CT guided GON infiltration at the first bend of the GON, in the fatty space between the inferior obliquus capitis and semispinalis capitis muscles. Local subcutaneous injections of lidocaine hydrochloride (1 %) at defined skin entry point. Under CT guidance needle guided to defined target. Diluted	Unclear, included steroid

	iodinated contrast material injected (1 ml). Mixture of fast- and slow acting anaesthetic (1.5 ml lidocaine hydrochloride 1 %, and 3 ml ropivacaïne chlorhydrate 2 mg/mL) injected followed by 1.5 mL cortivazol (3.75 mg). Patient supervised 30 mins at CT unit.	
Follow up duration	12 to 24 months	Unclear
Results	Pain evaluated with VAS scores 0 to 10 Clinical success defined by pain relief ≥ 50% lasting ≥3 months. Seventy five percent pain reduction and above considered excellent, 50% to 74 % considered good. The clinical success rate was 32 of 37 procedures (86 %). In case of clinical success, mean pain relief duration following the procedure was 9.16 months (range 3 to 24). Pain medication could be discontinued in 15 patients, decreased in 6. No major complications occurred during or after the procedure.	10-point numeric scale used to assess patient response: poor (0 to 3), good (4 to 6) and very good (7 to 10) point improvement. 458 patients rated their response to ONB as good or very good (82%). Of 323 patients previously treated with medical management alone, 261 (81 %) had a good or very good response. ONB was equally effective irrespective of age and gender.

Pulsed radiofrequency treatment of the nervi occipitales

Study	Choi (2012)	Huang (2012)
Setting	School of Medicine, Kyung Hee University, South Korea	Johns Hopkins Medical Institutions and Walter Reed Army Medical Center, US
Study Design	Case series	Retrospective chart review
Study population	10 patients with occipital neuralgia according to International Classification of Headaches Disorders criteria unresponsive to conservative management. A positive response (>= 50 % pain relief) to GON (and/) or LON block was one of the most important criteria.	102 patients with primary diagnosis of ON according to HIS (including ≥ 50 % pain reduction after a diagnostic block).
Patient details	7F, 3M, Median age 52 (range 34 to 70 years), 6 bilateral, 4 unilateral ON	75 F, 27M, Mean age 51.2 years (S.D. 14.5 years, range 22 to 83 years), 55 bilateral, 47 unilateral ON Average duration of pain 6.9 years (range: 1 to 44). 36% reported a traumatic inciting event, 59% had a co-existing chronic pain condition, 38% were receiving opioid therapy and 33%

		were either receiving or seeking disability or pursuing a worker's compensation complaint.
Intervention details	Fluoroscopically guided GON and LON PRF. Skin was anaesthetised with 5% lidocaine gel. A disposable 22-gauge, 5 cm radiofrequency cannula with a 5 mm active tip was inserted at the levels of both the GON and LON. After stimulation, PRF was performed at 42°C for a total of 240 pulses at each site.	Superficial anaesthesia and, if necessary, iv sedation. For each nerve, a 20-gauge radiofrequency needle with a 10-mm active tip was inserted at a slightly oblique (i.e., 20°–45°) angle toward the anticipated area(s) of neural tissue. Whenever possible, attempts were made to align the electrode more parallel than perpendicular (i.e., <45°) to the target nerve to maximize the surrounding electromagnetic field. After satisfactory needle position was confirmed with electrical stimulation, PRF given with 40-60 V, 2 Hz frequency, 20 ms pulses in a 1-second cycle, 120-second duration per cycle and 42°C plateau temperature. 62.8% of patients had both GON and LON treated. 59.8 % had two or more cycles of PRF (within the treatment session).
Follow up duration	Mean 7.5 months (range 6 to 10 months)	NR (>= 3 months)
Results	Mean VAS score before the pre-diagnostic block period was 6.9 and declined to 1.2 and 0.8 at post PRF and last follow-up period, respectively ($p<0.001$, and $p<0.001$). The mean Total Pain Index (TPI) score before the pre-di-agnostic block period was 232.7 and declined to 53.7 and 40.6. at post PRF and last follow-up period, respectively ($p<0.001$, and $p<0.001$) 8 of 10 (80%) completely stopped using analgesics following PRF treatment. One patient (10%) reported a substantial reduction in analgesic requirements and pharmacotherapy was maintained in one patient who had partial recurrence of headaches. There were no complications or adverse effects of treatment.	Fifty-two (51%) patients had ≥ 50% pain relief and satisfaction with treatment lasting at least 3 months. Variables associated with a positive outcome included a traumatic inciting event (65.7% success rate; P = 0.03), lower diagnostic block volumes (odds ratio [OR]: 0.72; 95% confidence interval [CI]: 0.62 to 0.82), and multiple cycles of PRF (OR: 2.95; 95% CI: 1.77 to 4.92). Lower diagnostic block volume (increasing specificity) and two or more cycles were associated with better outcome in multivariable analyses, disability/workers compensation or litigation with worse outcome. Six "complications" were noted, five of which consisted of temporary worsening pain.

Subcutaneous stimulation of the nervi occipitales

Study	Palmisani (2013)	Magown (2009)	de la Cruz (2014)
Setting	Guy's &St Thomas NHS Trust, London, and Sapienza University at Sant'Andrea Hospital, Rome	Pain Management Unit within Queen Elizabeth hospital, Capital Health District (Nova Scotia, Canada)	'Albany, NY'
Study Design	Chart review supplemented with telephone interview (to confirm data accuracy, system efficacy, and check patients' diagnosis according to ICHD-II classification	Description of new, open surgical technique to place neurostimulation electrode over the greater occipital nerve, illustrated with results in 7 patients	Prospective study
Study population	25 patients of whom 3 had occipital neuralgia and had ON stimulator implantation within previous 6 years	Patients fulfilling diagnostic criteria (presumably ICHD) for ON, with tenderness over the affected nerve and positive result of double-blind test of local anaesthetic/saline at C2 nerve root.	Nine patients with a PNS device implanted after having ≥ 50 % pain improvement in trial stimulation. Two of them had occipital neuralgia.
Patient details	2F, 1M with bilateral occipital neuralgia. One attended a multi-disciplinary two week pre-implant programme (PIP)	5 F, 2 M, mean age 44 (SD 9 years) with ON (traumatic in 5, idiopathic in 1, after cervical surgery in 1)	NR
Follow up duration	28 months (2 patients), 31 months (1 patient)	Mean 17.7 months (SD 11.3 months)	Mean 4.3 months
Results	All three had successful trial stimulation and all reported > 50% reduction in severity and frequency of pain at follow up. One patient required revision surgery for a tilted implanted pulse generator.	Mean VAS pain score decreased from 88.2 to 3.6 postoperative (pain at last follow-up not reported). A seroma developed in one patient, with infection leading to explantation. Five patients stopped medication, one reduced, and one had unchanged medication.	Beck Depression Index improved from 16.6 to 9.8 ($p = 0.01$), Pain Catastrophizing Scale from 32.8 to 18.5 ($p = 0.006$). In the four patients with 6 months follow-up Oswestry Disability Scale improved from 43.2 to 28.0 ($p = 0.035$). Pain results were not reported, nor were results for specific diagnostic categories.

Botulinum toxin A injection

Study	Pierric (2013
Setting	Unclear

Study Design	Case series
Study population	4 cases of greater occipital neuralgia uncontrolled by usual therapy
Patient details	100% female. Mean age 61 years with symptom > 14 months. All unilateral greater occipital neuralgia.
Intervention details	Injection was unilateral with a minimum of 30 UI in the trapezius at the same site of the pain preceded by electromyographic detection and completed if needed by injection in the splenius capitis.
Follow up duration	Reduction of pain evaluated by percentage of improvement at 10 days and 3 months. Toxicity was also evaluated systematically.
Results	All cases had abnormalities in electromyography evaluation before injection. 'Improvement of pain was of 60% compared with the pain before and maintain at one month. No side effect was declared. No significant reduction of rescue therapy was observed in one case.' (extracted verbatim from abstract)

Author(s): Jos Kleijnen
Date: 2017-04-25
Question: Should single infiltration of the nervi occipitales with local anesthetic and corticosteroids be used for occipital neuralgia?
Settings: Treatment by anaesthetists
Bibliography: Seo MW, Kim KJ. Comparison of the analgesic effects of injections with botulinum toxin A, lidocain, or saline in the treatment of greater occipital neuralgia. In: Journal of Neurology. Conference: 20th Meeting of the European Neurological Society Berlin Germany. Conference Start: 20100619 Conference End: 20100623. Conference Publication: (var.pagings). 257 (pp S98-S99), 2010. Date of Publication: June 2010., 2010. Kastler A, Onana Y, Comte A, Attye A, Lajoie JL, Kastler B. A simplified CT-guided approach for greater occipital nerve infiltration in the management of occipital neuralgia. Eur Radiol 2015;25(8):2512-8. Allen S, Mookadam F, Grover M, Starling A, Cha S, Mookadam M. Efficacy of occipital nerve block in patients suffering from occipital neuralgia. Paper presented at 17th Congress of the International Headache Society; 14-17 May 2015; Valencia: Spain. Cephalalgia 2015;35(6 Suppl 1):21-22.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Single infiltration of the nervi occipitales with local anesthetic and corticosteroids**	**Control**	**Relative (95% CI)**	**Absolute**		
Pain relief												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	-	-	-	-	⊕OOO VERY LOW	CRITICAL
								0%		-		

[1] The RCT was only reported as an abstract with limited information. Two further observational studies were identified.
[2] Three groups of only 12 patients
[3] Unable to find full publication

Author(s): Jos Kleijnen
Date: 2017-04-25
Question: Should pulsed Radiofrequency PRF treatment of the nervi occipitales be used for occipital neuralgia?
Settings: Treatment by anaesthetists
Bibliography: Vanelderen P, Lataster A, Levy R, Mekhail N, van Kleef M, Van Zundert J. 8. Occipital neuralgia. Pain Pract.10:137-144. Choi HJ, Oh IH, Choi SK, Lim YJ. Clinical outcomes of pulsed radiofrequency neuromodulation for the treatment of occipital neuralgia. J Korean Neurosurg Soc 2012;51(5):281-5. Huang JH, Galvagno SM, Jr., Hameed M, Wilkinson I, Erdek MA, Patel A, et al. Occipital nerve pulsed radiofrequency treatment: a multi-center study evaluating predictors of outcome. Pain Med 2012;13(4):489-97.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Pulsed Radiofrequency PRF treatment of the nervi occipitales**	**Control**	**Relative (95% CI)**	**Absolute**		
Pain relief												
3	observational studies[1]	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	-	-	-	⊕OOO VERY LOW	CRITICAL
								0%		-		

[1] case series

Author(s): Jos Kleijnen
Date: 2017-04-25
Question: Should PRF treatment of the cervical ganglion spinale (DRG) be used for Occipital neuralgia?
Settings: Treatment by anaesthetists
Bibliography: Van Zundert J, Lamé IE, de Louw A, Jansen J, Kessels F, Patijn J, et al. Percutaneous Pulsed Radiofrequency Treatment of the Cervical Dorsal Root Ganglion in the Treatment of Chronic Cervical Pain Syndromes: A Clinical Audit. Neuromodulation. 2003;6:6-14.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PRF treatment of the cervical ganglion spinale (DRG)	Control	Relative (95% CI)	Absolute		
Pain												
1	observational studies[1]	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	-	-	-	-	⊕OOO VERY LOW	CRITICAL
								0%		-		

[1] case reports
[2] Very few patients

Author(s): Jos Kleijnen
Date: 2017-04-25
Question: Should subcutaneous stimulation of the nervi occipitales be used for occipital neuralgia?
Settings: Treatment by anaesthetists
Bibliography: Palmisani S, Al-Kaisy A, Arcioni R, Smith T, Negro A, Lambru G, et al. A six year retrospective review of occipital nerve stimulation practice--controversies and challenges of an emerging technique for treating refractory headache syndromes. J Headache Pain 2013;14:67. Magown P, Garcia R, Beauprie I, Mendez IM. Occipital nerve stimulation for intractable occipital neuralgia: an open surgical technique. Clin Neurosurg 2009;56:119-24. De La Cruz P, Campbell JC, Wilock M, Haller J, Oth SGR, Pullano E, et al. Prospective investigation of peripheral nerve stimulation functional outcomes in chronic pain patients. Paper presented at Biennial Meeting of the American Society for Stereotactic and Functional Neurosurgery; 31 May-3 Jun 2014; Washington, DC: United States. Stereotact Funct Neurosurg 2014;92(Suppl 1):30.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Subcutaneous stimulation of the nervi occipitales	Control	Relative (95% CI)	Absolute		
Pain relief												
3	observational studies[1]	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	-	-	-	-	⊕OOO VERY LOW	CRITICAL
								0%		-		

[1] case series
[2] Very small studies including less than 10 patients each

Author(s): Jos Kleijnen
Date: 2017-04-25
Question: Should botulinum toxin A injection be used for occipital neuralgia?
Settings: Treatment by anaesthetists
Bibliography: Linde M, Hagen K, Stovner LJ. Botulinum toxin treatment of secondary headaches and cranial neuralgias: a review of evidence. Acta Neurol Scand Suppl 2011(191):50-5. Seo MW, Kim KJ. Comparison of the analgesic effects of injections with botulinum toxin A, lidocain, or saline in the treatment of greater occipital neuralgia. In: Journal of Neurology. Conference: 20th Meeting of the European Neurological Society Berlin Germany. Conference Start: 20100619 Conference End: 20100623. Conference Publication: (var.pagings). 257 (pp S98-S99), 2010. Date of Publication: June 2010., 2010. Pierric G, Sylvie C, Henr RJ. Botulinum toxin a for the treatment of greater occipital neuralgia: Pathophysiological considerations for efficacy. Cephalalgia. Conference: 2013 International Headache Congress of the International Headache Society and American Headache Society Boston, MA United States. Conference Start: 20130627 Conference End: 20130630. Conference Publication: (var.pagings). 33 (pp 92), 2013. Date of Publication: June 2013. 2013.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Botulinum toxin A injection	Control	Relative (95% CI)	Absolute		
Pain relief												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	-	-	-	-	⊕OOO VERY LOW	CRITICAL
								0%		-		

[1] Only published as abstract; also 4 very small observational studies
[2] Small trial with 12 patients per group
[3] We could not find a full publication of the trial reported as an abstract

9. Thoracic Radicular Pain

SYSTEMATIC REVIEWS IDENTIFIED

We identified the following reviews published between 2010 and 2015 for the management of thoracic pain. See table.

Intervention	Relevant Review(s)	Search date	Studies Identified in review	Meta-analysis
Intercostal block	No relevant reviews			
RF treatment of the dorsal root ganglion (DRG)	Pope (2013)	Dec 2012	14 (2 relevant)	N
Pulsed RF treatment of the DRG	Pope (2013)	Dec 2012	16 (1 relevant)	N

ASSESSMENT OF THE REVIEW EVIDENCE

RF and pulsed RF treatment of the dorsal root ganglion (DRG)

Study Reference	Participants	Interventions	Comparators	Outcomes	Study Designs
Pope (2013)	Patients with chronic pain	Ganglionectomy, conventional and pulsed radiofrequency of the DRG	NA	Pain relief	Randomised controlled trials and cohort studies were included.

Results
Studies of three dorsal root ganglion treatment strategies i.e. ganglionectomy, conventional radiofrequency, and pulsed radiofrequency treatment were identified. Seven studies described ganglionectomy; 14 described conventional radiofrequency and 16 studies were of pulsed radiofrequency. Overall evidence was relatively poor on which to draw conclusions. Two studies relating specifically to thoracic pain provided support for radiofrequency. One study found pulsed RF of the DRG was superior to medical management or intercostal nerve PRF at three months.

Last Search date	Studies identified in review	Bottom Line
Dec 1, 2012	37 (of which 3 relevant)	This review highlighted the poor evidence on current therapeutic strategies based on the dorsal root ganglion and showed the need for further prospective studies. Although there were a number of limitations in the conduct of the review, this conclusion appears to be appropriate.

RELEVANT RANDOMISED CONTROLLED TRIALS

We did not identify any relevant randomised controlled trials for the three named interventions for thoracic pain.

OBSERVATIONAL STUDIES

Intercostal Blockade

We did not identify any relevant observational studies other than a case report published as a conference abstract[4] and a case series describing intercostal neuralgia as a complication of thoracic disk surgery.[5] Neither provided numerical data in results.

The case report described a 41-year-old male patient with intractable intercostal neuralgia due to a history of rib fractures [4] The patient was refractory to physical therapy, transforaminal epidural steroid injection and trigger point injections. Ultrasound-guided injections of T7 and T8 intercostal nerves were done 7 cm lateral to the spinous processes of the corresponding levels. At each of the two locations, a 3-mL mixture of 0.5 mL dexamethasone and 2.5 mL 1% lidocaine was injected. The patient experienced pain relief which lasted 'many months', with decreased use of oral pain medications and improvement in daily living activities.

The case series report described strategies to reduce morbidity in thoracic disc surgery.[5] Three of 55 patients had intercostal neuralgia persisting beyond three months. It was stated that these three patients had intercostal nerve blocks and radiofrequency lesioning, and symptoms were resolved by six months. However no details were provided.

RF and pulsed RF treatment of the dorsal root ganglion (DRG)

We did not identify any observational studies of RF or pulsed RF of the DRG published since the previous guidance2 and the systematic review.

Author(s): Jos Kleijnen
Date: 2016-12-06
Question: Should intercostal nerve block be used for thoracic radicular pain?
Settings: Treatment by anaesthetists
Bibliography: Strom RG, Mathur V, Givans H, Kondziolka DS, Perin NI. Technical modifications and decision-making to reduce morbidity in thoracic disc surgery: An institutional experience and treatment algorithm. Clin Neurol Neurosurg 2015;133:75-82.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intercostal nerve block	Control	Relative (95% CI)	Absolute		
Persisting neuralgia (follow-up median 6 months)												
1	observational studies[1]	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/55 (0%)	-	-	-	⊕OOO VERY LOW	CRITICAL

[1] case series
[2] Little information provided

Author(s): Jos Kleijnen
Date: 2016-12-06
Question: Should (Pulsed) Radiofrequency treatments be used for thoracic radicular pain?
Settings: Treatment by anaesthetists
Bibliography: Pope JE, Deer TR, Kramer J. A systematic review: current and future directions of dorsal root ganglion therapeutics to treat chronic pain. Pain Med 2013;14(10):1477-96.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	(Pulsed) Radiofrequency treatments	Control	Relative (95% CI)	Absolute		
Pain (follow-up median 24 months; assessed with: Excellent or good long term result)												
1	observational studies[1]	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	35/45 (77.8%)	-	-	-	⊕⊕OO LOW	CRITICAL

[1] case series

10. Thoracic Facet Pain

SYSTEMATIC REVIEWS IDENTIFIED

We identified one up to date review published between 2010 and 2015 of radiofrequency for thoracic facet pain. See table.

Intervention	Relevant Review(s)	Search end date	Studies Identified in review	Meta-analysis
Radiofrequency	Manchikanti (2015)	March 2015	Overall review: 21 RCTs, 5 Observational studies Relevant to condition and intervention: 1 RCT	N

ASSESSMENT OF THE REVIEW EVIDENCE

Radiofrequency of the Thoracic Facet

Study Reference	Participants	Interventions	Comparators	Outcomes	Study Designs
Manchikanti (2015)[1]	Patients with chronic neck pain, mid back, upper back or low back pain ≥ 3 months were included. Patients with acute trauma, fractures, malignancies, and inflammatory diseases were excluded.	Cervical, thoracic, and lumbar facet joint interventions performed with proper technique under image guidance (fluoroscopy, computed tomography [CT], or magnetic resonance imaging [MRI]) were included.	NR	The primary outcome was pain relief (short-term ≤ 6 months and long-term > 6 months). Secondary outcomes were improvement in functional status, psychological status, return to work, and reduction in opioid intake.	RCTs, Observational studies

Results

A total of 21 randomised trials met the inclusion criteria of the review. However only one trial Joo (2013)[5] evaluated thoracic radiofrequency neurotomy. It compared radiofrequency ablation (RFA) to alcohol ablation (AA). Results of this trial are outlined. Further details of the patient characteristics can be found in Appendix B.

The main outcome of the included trial[5] was recurrence, which was defined as ≥7 on the NRS scale and ≥22% on the ODI scale. Results showed that after RFA and AA, one and 17 patients, respectively, were without recurring thoracolumbar facet joint pain. The median effective periods in the RFA and AA groups were 10.7 (range 5.4 to 24) and 24 (range 16.8 to 24) months, respectively (P = 0.000). No significant complications were identified other than pain in the injection site in five RF patients and seven AA patients that passed within 24 hours in both groups.

Last Search date	Studies identified in review	Bottom Line
March 2015	21	The evidence for radiofrequency neurotomy in the lumbar, cervical, and thoracic spines is variable. Overall there was a lack of high quality studies.

RELEVANT TRIALS PUBLISHED SUBSEQUENT TO THE SYSTEMATIC REVIEW

We did not identify any RCTs published subsequent to the review by Manchikanti (2015). However the following trial is ongoing and should provide valuable information when published.

Study Type	Interventional
ClinicalTrials.gov Identifier:	NCT02073292
Official Title:	A Randomized Controlled Trial Comparing Thermal and Cooled Radiofrequency Ablation Techniques of Thoracic Facets' Medial Branches to Manage Thoracic Pain
Primary Outcome Measures	Pain Score on the visual analogue scale
Study Start Date:	March 2014
Estimated Study Completion Date	February 2017
Ages Eligible for Study	18 Years to 90 Years
In this study, the investigators will compare the differences between standard RFA (90°C) and "cooled" RFA (60°C) ablation techniques and determine if one is better for pain relief.	
Sponsor	The Cleveland Clinic

Having identified a systematic review including a RCT, we did not search for observational studies. Observational studies are at greater risk of bias and would not be sufficiently robust to make recommendations for practice.

Author(s): Jos Kleijnen
Date: 2016-12-06
Question: Should (Pulsed) Radiofrequency treatments be used for pain originating from the thoracic facet joints?
Settings: Treatment by anaesthetists
Bibliography: Manchikanti L, Kaye AD, Boswell MV, Bakshi S, Gharibo CG, Grami V, et al. A Systematic Review and Best Evidence Synthesis of the Effectiveness of Therapeutic Facet Joint Interventions in Managing Chronic Spinal Pain. Pain Physician. 2015;18:E535-582. Joo YC, Park JY, Kim KH. Comparison of alcohol ablation with repeated thermal radiofrequency ablation in medial branch neurotomy for the treatment of recurrent thoracolumbar facet joint pain. J Anesth 2013;27(3):390-5.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	(Pulsed) Radiofrequency treatments	Control	Relative (95% CI)	Absolute		
Recurrence (follow-up mean 24 months; assessed with: NRS >= 7 or Oswestry Disability Index >= 22%)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	strong association[3]	19/20 (95%)	3/20 (15%)	-	150 fewer per 1000 (from 150 fewer to 150 fewer)	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		

[1] No blinding
[2] Comparison with alcohol ablation
[3] 17 patients without recurrence after alcohol ablation, and only one patient without recurrence after radiofrequency treatment

Author(s): Jos Kleijnen
Date: 2016-12-06
Question: Should intra articular corticosteroid injections be used for pain originating from the thoracic facet joints?
Settings: Treatment by anaesthetists
Bibliography: Manchikanti L, Kaye AD, Boswell MV, Bakshi S, Gharibo CG, Grami V, et al. A Systematic Review and Best Evidence Synthesis of the Effectiveness of Therapeutic Facet Joint Interventions in Managing Chronic Spinal Pain. Pain Physician. 2015;18:E535-582. Manchikanti L, Singh V, Falco FJ, Cash KA, Pampati V, Fellows B. The role of thoracic medial branch blocks in managing chronic mid and upper back pain: a randomized, double-blind, active-control trial with a 2-year followup. Anesthesiol Res Pract. 2012;2012:585806.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intra articular corticosteroid injections	Control	Relative (95% CI)	Absolute		
Pain (follow-up mean 2 months; measured with: NRS; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	50	50	-	MD 0 higher (0.43 lower to 0.43 higher)	⊕⊕⊕⊕ HIGH	CRITICAL
Disability (follow-up mean 24 months; measured with: Oswestry disability index; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	50	50	-	MD 0.7 lower (1.09 lower to 2.49 higher)	⊕⊕⊕⊕ HIGH	CRITICAL

11. Lumbosacral Radicular Pain

SYSTEMATIC REVIEWS IDENTIFIED

We identified the following reviews published between 2010 and 2015 on which we based the analysis for painful lumbosacral radicular pain.

Intervention	Relevant Review (s)	Search end date	Studies included	Meta-analysis
Interlaminar epidural corticosteroid administration	Shamliyan (2014) *	Jan 2014	79 'references'	N
Transforaminal epidural corticosteroid administration in "contained herniation" or in "extruded herniation"	Shamliyan (2014) *	Jan 2014	79 'references'	N
Transforaminal epidural anti TNF administration	Wang (2014)	July 2013	9 RCTs, 2 Obs	Y
RF lesioning adjacent to the lumbar ganglion spinale (DRG)	Pope (2013)	Dec 2012	14 studies (not all lumbosacral radicular pain)	N
Pulsed RF treatment adjacent to the lumbar ganglion spinale (DRG)	Pope (2013)	Dec 2012	16 studies (not all lumbosacral radicular pain)	N
Adhesiolysis — epiduroscopy	No relevant systematic reviews identified			

*****A review of reviews. See next section for other review evidence identified.

ASSESSMENT OF THE REVIEW EVIDENCE

Interlaminar epidural corticosteroid administration and Transforaminal epidural corticosteroid administration in "contained herniation" or in "extruded herniation"

Since the previous guidance, a number of systematic reviews have been published in relation to epidural injections for lumbosacral radicular pain.[6-21] These are listed in the references. The reviews have evaluated epidural injections without distinction between types of injection or have investigated either transforaminal or interlaminar administration of corticosteroids or have compared the two methods. Lumbosacral radicular pain has been considered separately or within reviews of other types of back pain. None of the reviews appear to have set out to investigate the role of transforaminal epidural corticosteroid administration in 'contained herniation' or in 'extruded herniation' as requested by the commissioners. Given the size and scope of this project it was decided to base the results for these two interventions on the review of evidence conducted by Shamliyan (2014).

Study Reference	Participants	Interventions	Comparators	Outcomes	Study Designs
Shamliyan (2014)	Adults aged ≥ 18 with benign lumbosacral radicular pain > 12 weeks Excluded: Pregnant women Patients with recent trauma, tumours or cauda equine syndrome Nursing home residents	Epidural steroid injections with or without fluoroscopic guidance	Placebo, epidural anaesthetics, nonpharmacological treatments Inc. physical therapy or acupuncture / acupressure	Short and long-term (> 12 weeks) Pain Global symptom relief Functional improvement Reduction in disability Patient perception of improvement Return to work Use of opioid and non-opioid analgesia Need for surgery Quality of life Adverse effects	Guidelines Systematic reviews RCTs Large observational cohorts for safety

Shamliyan (2014) Results

Epidural steroid injections provide short term but not long-term (> 12 weeks) relief of leg pain and improvement in function when compared with placebo (high quality GRADE evidence). The clinical benefit is small (< 10 points improvement on a 100 point scale).

Transforaminal corticosteroids are better than placebo in reducing leg pain at long-term follow-up with no improvement in disability (very low GRADE evidence).

Injection of steroids is no more effective than injection of local anaesthetics alone (moderate GRADE evidence).

Pain at 12 months for any injections is cited from Choi et al. Epidural steroid injection therapy for low back pain: a meta-analysis International Journal of Technology Assessment in Health Care, 29:3 (2013), 244–253. WMD -0.08 (-0.26 to 0.10)

Post procedural complications are uncommon, but risk of contamination and serious injections is very high (high quality evidence).

There is insufficient evidence to link short-term effectiveness of steroid injections and differing patient characteristics.

Last Search date	Studies identified in review	Bottom Line
January 2014	79 references	Evidence does not support routine use of epidural steroid injections for chronic lumbosacral radicular pain.

Transforaminal epidural anti TNF administration

Study Reference	Participants	Interventions	Comparators	Outcomes	Study Designs
Wang (2014)	Patients (> 18 years) diagnosed with sciatica caused by lumbar disc herniation and/or lumbar spinal stenosis confirmed with CT/MRI, regardless of the duration of symptoms.	Tumour necrosis factor -alpha inhibitors	Placebo or steroid	Lower back pain (VAS), leg pain assessment (VAS), Oswestry Disability Index, overall satisfaction or return to work, discectomy or radicular block	Randomised and cross-over controlled trials, non-randomised concurrent trials, before-after controlled trials, and case-control studies

Wang (2014) Results
Tumour necrosis factor alpha (TNF-α) inhibitors did not relieve lower back and leg pain significantly, at short term, medium-term and long-term follow-ups ($p > 0.05$), in comparison to the control condition (placebo or steroid).

TNF-α inhibitors did not increase the proportion of patients who felt overall satisfaction (global perceived effect) or were able to return to work at short term, medium-term and long-term follow-ups ($p > 0.05$).

TNF- α inhibitors were found to reduce the risk of discectomy or radicular block (combined endpoint; Risk Ratio (RR) = 0.51, 95% CI 0.26 to 1.00, 3 studies) at medium-term follow-up, but no effect was seen at short-term (RR = 0.64, 95% CI 0.17 to 2.40, 4 studies) and long-term follow-ups (RR = 0.64, 95% CI 0.40 to 1.03,4 studies).

Last Search date	Studies identified in review	Bottom Line
July 1 2013	11	The review demonstrated that tumour necrosis factor-alpha inhibitors showed limited clinical value in the treatment of sciatica. Conclusions are based on small numbers of patients and diverse studies so should be treated with some caution.

Radiofrequency and Pulsed Radiofrequency

Study Reference	Participants	Interventions	Comparators	Outcomes	Study Designs
Pope (2013)	Patients with chronic pain	Ganglionectomy, conventional and pulsed radiofrequency of the DRG	NA	Pain relief	Randomised controlled trials and cohort studies were included.

Pope (2013) Results
Studies of three dorsal root ganglion treatment strategies i.e. ganglionectomy, conventional radiofrequency, and pulsed radiofrequency treatment were identified. Seven studies described ganglionectomy; 14 described conventional radiofrequency and 16 studies were of pulsed radiofrequency. Overall evidence was relatively poor on which to draw conclusions.

Last Search date	Studies identified in review	Bottom Line
Dec 1, 2012	37	This review highlighted the poor evidence on current therapeutic strategies based on the dorsal root ganglion and showed the need for further prospective studies. Although there were a number of limitations in the conduct of the review, this conclusion appears to be appropriate.

RELEVANT TRIALS PUBLISHED SUBSEQUENT TO THE SYSTEMATIC REVIEWS

We identified the following trials published subsequent to the reviews. See Table.

Intervention	Study
Pulsed RF treatment adjacent to the lumbar ganglion spinale (DRG)	Shanthanna (2014) Fujii (2012) *
Adhesiolysis — epiduroscopy	Gerdesmeyer (2013)

*Japanese language paper, not available in full, conference abstract only

Pulsed Radiofrequency

Study 1 details

Study	**Shanthanna (2014)**
Country	Canada
Study Design	Triple-blind placebo-controlled RCT
Single/Multiple centre	Single
Recruitment dates	Unclear
Condition	Chronic lumbar radicular pain
Patient inclusion criteria	Age 18 years or older; a history of chronic lumbar radicular pain of at least 4 months' duration; an average pain score of ≥5 on a VAS of 0 to 10; and failure of conservative therapy (e.g., physiotherapy, medication trial). Clinical features of lumbosacral radicular pain (segmental pain of a radicular nature originating from the lumbar or sacral segments and radiating below the knee joint, and with a shooting or lancinating quality corresponding to a dermatome suggestive of the involved nerve root). CT/MRI imaging findings of pathology concordant with the side and level of their clinical features.
Patient exclusion criteria	Any contraindication to neuraxial injections, history of predominant back pain over leg pain, significant anatomic deformity (either congenital or acquired) making it difficult to access the foramen (CT/MRI imaging), severe psychiatric illness, presence of cancer accounting for back pain, inability to communicate in English, allergy to local anaesthetics or contrast medium, and a history of motor findings in the affected leg.
Mean age (Range)	Median age 62 PRF, 57 placebo (range 35-85)
Total no (% male)	31 (58 % male)
Duration of symptoms	Not reported (≥ 4 months, inclusion criterion)
Aetiology of pain	Disc related: 7 PRF, 8 placebo; Spinal foraminal stenosis: 5 PRF, 5 placebo; Previous back surgery with fibrosis: 4 PRF, 2 placebo
No randomised	31 (32 included, one patient declined after inclusion but before randomization)
No in intervention	PRF 16
No in control	Placebo 15
Treatment details	A 10 cm, 22-gauge radiofrequency needle with a 5 mm curved active tip was used. Target identification and needle positioning were performed similar to the technique described by Simopoulos et al.[25] A radiculogram was done to confirm appropriate placement and all patients had their respective DRG stimulated for confirmation of the appropriate nerve root involved. Proximity of the needle to the DRG was determined by appropriate sensory stimulation with 50 Hz (0.4–0.6 V), and motor stimulation at 2 Hz was used to determine a threshold 1.5–2.0 times greater than the sensory threshold to avoid placement near the anterior nerve root. PRF treatment at 42°C for 120 seconds to the DRG. Levels of DRG treated: L3: 1 PRF, 0 placebo; L4: 4 PRF, 3 placebo; L5: 10 PRF, 10 placebo; S1: 2 PRF, 2 placebo (1 abandoned)

Control details	Sham PRF treatment: low intensity (0.2 V) sensory stimulation (50 Hz), without any active treatment for 120 seconds.		
Conservative treatments allowed	Patients could request rescue analgesia in the form of appropriate analgesics and/or a transforaminal epidural steroid injection.		
Primary Efficacy outcome	Primary aim was to assess the feasibility of a larger efficacy study.		
Safety assessed?	Yes		
Length of follow up	3 months (1 day, 1 week, 4 weeks, 2 and 3 months)		
	PRF	**Placebo**	
Effective pain relief (≤ 50 % decrease) 4 weeks	5 / 16 (31 %)	3 / 15 (20 %)	OR = 1.81 (95% CI: 0.36 to 9.09, p = 0.467)
Mean VAS pain score 3 months	5.40	6.15	n.s.
Adverse effects	No major adverse effects	No major adverse effects	

Cochrane Risk of Bias assessment

	Shanthanna (2014)	
Randomisation	low	Randomization with allocation block sizes of 2, 4, and 6 by research person not involved in any other part of the study
Allocation Concealment	low	Allocation given to the assistant in a sealed opaque envelope to be handed over to the nurse operating the radiofrequency machine.
Blinding of participants	low	Credible sham procedure, noise of the RF machine masked by playing music
Blinding of caregivers	low	Physician could not see RF machine, music
Blinding of assessors	low	Assessor blinded
Incomplete outcome data	low	2 PRF patients lost to follow-up, 1 placebo patient did not receive intervention (inability to place needle). Missing outcomes imputed using 'multiple imputation'.
Selective reporting	low	No evidence of this
Other Biases	low	None identified

Pulsed RF Study 2 Details (taken from abstract)

Study	**Fujii (2012)**
Country	Japan
Study Design	RCT (PRF vs. nerve root block)
Condition	Lumbosacral radicular pain
Total no (% male)	27
Intervention	PRF current was applied for 120 seconds after root block.
Control	Root block only (no details)
Outcomes assessed	Pain on Visual analogue scale (VAS) was assessed immediately, 2 hours, 1 day, 1 week, 1 month, 3 months, 6 months, and 1 year after the procedure.
Results	In both groups, the VAS at 6 months and 1 year after procedure significantly decreased compared with before treatment (P<0.05) (no data provided). There were no significant differences in VAS between the two groups at the same time points.

Adhesiolysis — epiduroscopy

Study Details

Study	**Gerdesmeyer (2013)**
Country	Germany
Study Design	Double-blind placebo-controlled RCT
Single/Multiple centre	Multiple centres (N = 4)
Recruitment dates	Not reported
Condition	Lumbosacral radicular pain
Patient inclusion criteria	Chronic lumbar radicular pain without neurological motor deficits after disc protrusion or after failed disc surgery • Age > 18 years • 4 months of unsuccessful conservative treatment i.e., must have undergone at least 1 unsuccessful non-pharmacological treatment and at least 2 unsuccessful pharmacological treatments • Time gap of at least 4 / 6 weeks since last interventional procedure (corticosteroid injection, anesthetic injection; iontophoresis, epidural injections) • Score of > 4 on the VAS scale • Score of > 45 on Oswestry Score
Patient exclusion criteria	Neurological motor deficits accompanying the radicular pain • Various diseases: cancer, rheumatoid disease, collagenosis, diabetes mellitus, liver disorders, urogenital or sexual dysfunction Inflammation with significant pathological laboratory findings • Immunosuppressive or long- time cortisone therapy • Disturbance of coagulation • Vertebral body fracture, spinal stenosis, Polysegmental disc disease • Previous epidural catheter interventions

	• Hypersensitivity to local anaesthesics, Hyaluronidase, contrast • Peripheral nerve entrapment • Workers compensation
Mean age (SD)	48 (13)
Total no (% male)	90 (50 % male)
Duration of symptoms Months. Mean (SD)	6.9 (2.7)
No randomised	90
No in intervention	46
No in control	44
Treatment details	A 16 gauge RK needle was placed onto the sacral canal via the sacral hiatus under fluoroscopic guidance, 10 mL of contrast was injected to confirm epidural placement and identify any filling defects suggestive of epidural adhesions. Next a Tun- L-Kath® was inserted and advanced to the antero-lateral area of the filling defect. Then injection of: - local anaesthetic (10 mL 0.25% bupivacaine) - 10 mL of preservative-free saline containing 150 U/mL of hyaluronidase. - Saline (10 mL, 10%) containing 40 mg triamcinolone along with 2 mL of 0.25% bupivacaine. The catheter was left in place. The next 2 days injection of - 10 mL of 0.25% bupivacaine followed by - 10 mL 10% saline and 2 mL 0.25% bupivacaine (slow injection)
Control details	A needle and catheter were inserted as for the lysis group except the needle was intentionally inserted so it did not enter the spinal canal and the catheter was inserted into the subcutaneous tissue overlying the afflicted level. Injection of 10 ml of preservative-free saline, again the next two days.
Conservative treatments allowed	All participants were prescribed physical therapy with no activity restrictions. Patients were provided with rescue medication of 14g paracetamol maximum/week (not to exceed 2 g/day) or 14g metamizol maximum/week if requested
Primary Efficacy outcome	Difference in percent change of Oswestry Disability Index scores 3 months after intervention.
Safety assessed?	Yes (reported, not mentioned in methods)
Length of follow up	12 months (3, 6, 12 months)

	Intervention	**Placebo**	
ODI after 3 months	26.4 (10.8)	41.8 (14.6)	P < 0.01
Baseline ODI	55.3 (11.6)	55.4 (11.5)	0.97
(ODI after 6 months)	11.9 (8.7)	37.3 (13.1)	P < 0.01
Improvements were sustained and still significantly different between groups at 6 and 12 months.			
Two procedural complications were observed in the intervention group (1 dura puncture and 1 catheter displacement). (Transient neurological deficiencies occurred more frequently in the lysis group (42 vs. 6 patients). All resolved spontaneously within the hospitalisation period. No adverse events were found at 3, 6 or 12 months follow up.			

Cochrane Risk of Bias assessment

	Gerdesmeyer (2013)	
Randomisation	low	Computer-generated random list, permuted blocks of 4 to 8, stratified by treatment centre (n=4)
Allocation Concealment	low	Non-transparent envelopes
Blinding of participants	low	Patients were described as blinded.
Blinding of caregivers	low	Only the physician placing the catheter was aware of randomisation status. It is stated that the orthopaedic surgeon giving the 'repetitive injections' was blinded too.
Blinding of assessors	low	Blinded
Incomplete outcome data	low	Follow-up almost complete (1 in intervention and 1 in placebo group lost to follow-up, LOCF). 2 intervention patients did not receive intervention but sensitivity analysis was conducted to account for this.
Selective reporting	low	No evidence of this
Other Biases	low	None detected

Author(s): Jos Kleijnen
Date: 2016-11-03
Question: Should epidural corticosteroid in “contained herniation” or in “extruded herniation” be used for lumbosacral radicular pain?
Settings: Treatment by anaesthetists
Bibliography: Shamliyan TA, Staal JB, Goldmann D, Sands-Lincoln M. Epidural steroid injections for radicular lumbosacral pain: A systematic review. Phys Med Rehabil Clin N Am 2014;25(2):471-489.e49. Pinto RZ, Maher CG, Ferreira ML, Hancock M, Oliveira VC, McLachlan AJ, et al. Epidural corticosteroid injections in the management of sciatica: a systematic review and meta-analysis. Ann Intern Med 2012;157(12):865-77.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Epidural corticosteroid in “contained herniation” or in “extruded herniation”	Control	Relative (95% CI)	Absolute		
Any pain at 12 months (follow-up mean 12 months; measured with: Various instruments; Better indicated by lower values)												
9	randomized trials	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision	none	321	362	-	MD 0.08 lower (0.26 lower to 0.1 higher)	⊕⊕⊕O MODERATE	CRITICAL
Disability at 12 months (follow-up mean 12 months; measured with: Oswestry disability index; Better indicated by lower values)												
9	randomized trials	no serious risk of bias	serious[2]	serious[1]	no serious imprecision	none	402	441	-	MD 0.10 higher (0.35 lower to 0.54 higher)	⊕⊕OO LOW	CRITICAL
Leg pain up to 3 months (follow-up 2-13 weeks; measured with: Scale 0-100; Better indicated by lower values)												
14	randomized trials	serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	664	652	-	MD 6.2 lower (9.4 to 3.0 lower)	⊕⊕⊕O MODERATE	CRITICAL

[1] All techniques combined
[2] Considerable heterogeneity I-squared 89.6%
[3] Issues with concealment of treatment allocation, therapist blinding and intention-to-treat analyses

Author(s): Jos Kleijnen
Date: 2016-11-03
Question: Should epidural transforaminal anti TNF alpha administration be used for lumbosacral radicular pain?
Settings: Treatment by anaesthetists
Bibliography: Wang YF, Chen PY, Chang W, Zhu FQ, Xu LL, Wang SL, et al. Clinical significance of tumor necrosis factor-a inhibitors in the treatment of sciatica: a systematic review and meta-analysis. PLoS One 2014;9(7).

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Epidural transforaminal anti TNF alpha administration	Control	Relative (95% CI)	Absolute		
Lower back pain (follow-up 0-3 months; measured with: VAS; Better indicated by lower values)												
3	randomized trials	serious[1]	serious[2]	no serious indirectness	no serious imprecision	none	0	-	-	SMD 0.34 lower (0.89 lower to 0.22 higher)	⊕⊕OO LOW	CRITICAL
Leg pain (follow-up mean 0-3 months; measured with: VAS; Better indicated by lower values)												
7	randomized trials	serious[1]	serious[3]	no serious indirectness	no serious imprecision	none	0	-	-	SMD 0.41 lower (0.85 lower to 0.02 higher)	⊕⊕OO LOW	CRITICAL
Disability (follow-up mean 0-3 months; measured with: Oswestry Disability Index; Better indicated by lower values)												
7	randomized trials	serious[1]	serious[4]	no serious indirectness	no serious imprecision	none	0	-	-	MD 5.34 lower (14.5 lower to 3.82 higher)	⊕⊕OO LOW	CRITICAL

[1] Trials had multiple shortcomings in risk of bias assessments
[2] I-squared 65.5%; trials of anti TNF versus placebo
[3] I-squared 60%; trials of anti TNF versus placebo
[4] I-squared 74.5%; trials of anti TNF versus placebo

Author(s): Jos Kleijnen
Date: 2016-11-03
Question: Should radiofrequency and pulsed radiofrequency treatment be used for lumbosacral radicular pain?
Settings: Treatment by anaesthetists
Bibliography: Pope JE, Deer TR, Kramer J. A systematic review: current and future directions of dorsal root ganglion therapeutics to treat chronic pain. Pain Med 2013;14(10):1477-96.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Radiofrequency and pulsed radiofrequency treatment	Control	Relative (95% CI)	Absolute		
Pain												
30	observational studies	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	-	-	-	⊕OOO VERY LOW	CRITICAL
								0%		-		

[1] 14 studies described conventional radiofrequency and 16 studies were of pulsed radiofrequency. Overall evidence was poor.

12. Failed back Surgery Syndrome

SYSTEMATIC REVIEWS IDENTIFIED

We identified the following relevant systematic reviews and guidelines published between 2010 and 2015 of interventions for failed back surgery syndrome. For each intervention we have used the one with the most up to date search.

Intervention	Relevant Review (s) / Guidelines	Search end date	Relevant studies included	Meta-analysis
Spinal cord stimulation, DRG stimulation	Itz (2015)	June 2011	0 (but 2 are discussed)	N
Epiduroscopy/adhesiolysis	Helm (2013)	Sept 2012	6 studies	N

ASSESSMENT OF THE REVIEW EVIDENCE

Epiduroscopy/adhesiolysis

Study Reference	Participants	Interventions	Comparators	Outcomes	Study Designs
Helm (2013)	Patients with chronic low back pain due to post-lumbar laminectomy syndrome with or without radicular findings of ≥ 6 months' duration.	Spinal endoscopic procedures	Not pre-specified	Pain relief, functional improvement, change in psychological status, return to work, reduction in opioid use or interventions, Complications	All study designs with outcome evaluation > 6 months except non-systematic reviews, book chapters and case reports

Results
One RCT of high quality with 80% of patients having post-lumbar laminectomy syndrome was included in the review. Based on this RCT of adhesiolysis, together with one observational study rated as high quality and two rated as moderate quality, evidence was rated fair for short term (< 12 months) and long term (≥ 12 months) in the treatment of chronic low back pain and / or leg pain due to post lumbar surgery syndrome. Incidence and severity of complications were reported to be low.*

*In the trial, effects of a single procedure were assessed. Number of procedures in the high-quality observational study were 1.3 / year. Number of procedures was not mentioned for the other studies.

Last Search date	Studies identified in review	Bottom Line
Sept 2012	6	The authors concluded that there is fair evidence for spinal endoscopy for the treatment of persistent low back and / or leg pain in post-lumbar surgery. Although the review had some methodological limitations, this conclusion appears to be reasonable. However complications did not appear to have been gathered systematically.

RELEVANT TRIALS PUBLISHED SUBSEQUENT TO THE SYSTEMATIC REVIEWS

We identified a number of trials published or in progress subsequent to the systematic reviews. See Table.

Intervention	Study
Spinal cord stimulation, DRG stimulation	PROCESS (Eldabe (2010) *) EVIDENCE (North (2011) **) PROMISE (Rigoard (2013) **) ESTIMET (Roulaud (2015) **)
Epiduroscopy/adhesiolysis	No relevant trials

*Further reporting of a previously published trial

**Protocol only

EVIDENCE FROM RCTS

Spinal Cord Stimulation

The Process trial[12] has been cited in the previous guidance.[1] It compared SCS to conventional medical management in a group of patients with failed back surgery syndrome. The study found improved pain relief, function and health-related quality of life with SCS at six months. Improved outcomes with SCS were sustained at 24 months although crossovers between treatments were permitted. We identified a further paper by Eldabe[8] relating to this trial. The authors examined components of outcome measures related to function and quality of life. They found that 36 to 40% of patients experienced marked disability in standing and lifting and quality of life problems (pain and discomfort) at 24 months.

Trial identifier	NCT01036529	NCT01697358	NCT01628237
Study name	EVIDENCE	PROMISE	ESTIMET
Paper referenced	North (2011)	Rigoard (2013)	Roulaud (2015)
Sponsor	Boston Scientific Corporation	MedtronicNeuro	Poitiers University Hospital
Condition	Failed Back Surgery Syndrome	Predominant low back pain due to failed back surgery syndrome	Failed Back Surgery Syndrome
Intervention	Precision® Spinal Cord Stimulation	Multicolumn Spinal Cord Stimulation	Multicolumn spinal cord stimulation
Control	Reoperation	Optimal Medical Management	Monocolumn spinal cord stimulation
Primary outcome	Proportion of patients ≥50% self-reported leg pain relief from baseline without crossover to other treatment at 3, 6, 12 months	Proportion of patients with ≥50% reduction in low back pain intensity at 6 months	Visual Analogue Scale Low Back pain at Month 6
Study start date	Feb (2010)	Jan (2013)	May (2012)
Study completion date	May (2013)	April (2016)	January (2015)
Study status	Terminated due to slow enrolment	Ongoing (not recruiting)	Completed
Results available	28 of 200 planned subjects enrolled. Based on the small numbers and early termination, primary outcome measures were not analysed.	No study results available	No study results available

Author(s): Jos Kleijnen
Date: 2016-11-14
Question: Should spinal cord stimulation, DRG stimulation be used for failed back surgery syndrome?
Settings: Treatment by anaesthetists
Bibliography: Eldabe S, Kumar K, Buchser E, Taylor RS. An analysis of the components of pain, function, and health-related quality of life in patients with failed back surgery syndrome treated with spinal cord stimulation or conventional medical management. Neuromodulation 2010;13(3):201-9. Kumar K, Taylor RS, Jacques L, Eldabe S, Meglio M, Molet J, et al. Spinal cord stimulation versus conventional medical management for neuropathic pain: a multicentre randomised controlled trial in patients with failed back surgery syndrome. Pain 2007;132(1-2):179-88.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Spinal cord stimulation, DRG stimulation	Control	Relative (95% CI)	Absolute		
50% or more leg pain relief (follow-up mean 6 months)												
1	randomized trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	24/50 (48%)	4/44 (9.1%)	-	91 fewer per 1000 (from 91 fewer to 91 fewer)	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
Disabilty (follow-up mean 6 months; measured with: Oswestry disability index; Better indicated by lower values)												
1	randomized trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	50	44	-	MD 11.2 lower (21.2 to 1.3 lower)	⊕⊕⊕O MODERATE	CRITICAL
Patient satisfaction (follow-up mean 6 months; assessed with: Satisfied with pain relief)												
1	randomized trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	33/50 (66%)	8/44 (18.2%)	-	182 fewer per 1000 (from 182 fewer to 182 fewer)	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		

[1] Blinding not possible

Author(s): Jos Kleijnen
Date: 2017-04-06
Question: Should adhesiolysis be used for failed back surgery syndrome?
Settings: Treatment by anaesthetists
Bibliography: Helm S, Hayek SM, Colson J, Chopra P, Deer TR, Justiz R, et al. Spinal endoscopic adhesiolysis in post lumbar surgery syndrome: an update of assessment of the evidence. Pain Physician 2013;16(2 Suppl):SE125-50. Manchikanti L, Boswell MV, Rivera JJ, Pampati VS, Damron KS, McManus CD, et al. A randomized, controlled trial of spinal endoscopic adhesiolysis in chronic refractory low back and lower extremity pain [ISRCTN 16558617]. BMC Anesthesiol 2005;5:10.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Adhesiolysis**	**Control**	**Relative (95% CI)**	**Absolute**		
Pain relief (follow-up mean 12 months; assessed with: >50% pain relief)												
1	randomized trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	strong association[2]	24/50 (48%)	0/33 (0%)	-	-	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		
Disability (follow-up mean 12 months; measured with: Oswestry disability index; Better indicated by lower values)												
1	randomized trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	50	33	-	MD 8 lower (12.14 to 3.86 lower)	⊕⊕⊕O MODERATE	CRITICAL

[1] Only partial blinding
[2] 0 out of 33 patients in control group, 24/50 in intervention group

Author(s): Jos Kleijnen
Date: 2017-04-06
Question: Should epiduroscopy be used for failed back surgery syndrome?
Settings: Treatment by anaesthetists
Bibliography: Helm S, Hayek SM, Colson J, Chopra P, Deer TR, Justiz R, et al. Spinal endoscopic adhesiolysis in post lumbar surgery syndrome: an update of assessment of the evidence. Pain Physician 2013;16(2 Suppl):SE125-50.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Epiduroscopy	Control	Relative (95% CI)	Absolute		
Pain relief (follow-up 3-60 months; assessed with: VAS)												
5	observational studies[1]	serious[1,2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	-		-	-	⊕OOO VERY LOW	
								-		-		
								0%		-		

[1] case-control and other study designs together
[2] Based on five observational studies of which only one was considered of good quality, the authors concluded that there is fair evidence for spinal endoscopy for the treatment of persistent low back and / or leg pain in post-lumbar surgery. Although the review had some methodological limitations, this conclusion appears to be reasonable. However complications did not appear to have been gathered systematically.

13. Pain due to spinal canal stenosis

SYSTEMATIC REVIEWS IDENTIFIED

We identified a number of systematic reviews and guidelines published between 2010 and 2015 of the requested interventions for spinal stenosis. See table.

Intervention	Relevant Review(s) / guidelines	Search end date	Studies included	Meta-analysis
Spinal cord stimulation	Deer (2014)	Unclear	0	NA
Pulsed RF treatment adj to the lumbar ganglion spinale	Pope (2013)	Dec 2012	0	NA
RF lesioning adj to the lumbar ganglion spinale	Pope (2013)	Dec 2012	0	NA
Interlaminar epidural corticosteroid administration	Meng (2015)	Feb 2015	13 RCTs	Yes
Transforaminal epidural corticosteroid administration				
Epiduroscopy	No reviews identified			

We could not identify any systematic reviews of spinal cord stimulation for spinal cord stenosis. A consensus guideline relating to spinal cord stimulation was published in 2014 but did not identify any studies. This guideline is not discussed further in the report. In a systematic review of radiofrequency and pulsed radiofrequency for chronic pain, no studies relating to spinal stenosis were identified. This review is not discussed further although an assessment of its quality is included in the appendix. We identified a systematic review of epidural corticosteroid administration by Liu and colleagues which we considered to have been superseded the review by Meng and colleagues. A systematic review by Chou (2015) was also identified but had fewer trials of spinal stenosis than the review by Meng so was not used. The review by Meng is discussed in this report.

ASSESSMENT OF THE REVIEW EVIDENCE

Interlaminar epidural corticosteroid administration and Transforaminal epidural corticosteroid administration

Study Reference	Participants	Interventions	Comparators	Outcomes	Study Designs
Meng (2015)	Patients diagnosed with spinal stenosis with radicular pain who had a history of chronic function-limiting low back pain and lower extremity pain	Epidural injections of local anesthetic with steroids	Epidural injections of local anesthetic alone	Pain relief (NRS), functional improvement Oswestry Disability Index (ODI), opioid intake, average number of injections per year, total relief per year, and weight changes.	Randomized controlled trials

Results

13 Studies were included, with 1465 patients overall (sample sizes 19 – 400). Routes of administration were interlaminar (3 studies), transforaminal (2 studies), caudal (5 studies) and unspecified (3 studies).
Significant pain relief (≥ 50%) was demonstrated in 52 % at three months, 57 % at 6 months and 55 at 12 months. Functions improved too, and opioid intake decreases. No (significant) differences between the groups were found at all, except that patients who had received steroids with local anesthetics had average 29.3 (SD 19.7) weeks of pain relief per year, against 33.8 (SD 19.3) weeks for those on local anesthetics alone. They had a (non-significant) lower number on injections per year too: 3.2 (SD 1.3) versus 3.4 (SD 1.2). Due to limited reporting across the trials the authors could not analyze effects of the route of administration (interlaminar, transforaminal or caudal).

Last Search date	Studies identified in review	Bottom Line
Feb 5, 2015	13 RCTs	Addition of steroids to local anesthetics for epidural injection does not appear to increase effectiveness. Except for the – observational – finding that about half of the patients benefit with about 3 injections per year, the question of effectiveness of epidural injections as such was not addressed, nor was the route of administration. The reliability of the review was unclear due to a lack of reporting on the review process.

RELEVANT RANDOMISED CONTROLLED TRIALS

We identified the following trials published subsequent to the existing systematic review[5] or to the previous guidance where no up to date reviews exist.

Intervention	Study
Pulsed RF treatment adj to the lumbar ganglion spinale (DRG)	Koh (2015)
Interlaminar epidural corticosteroid administration	Manchikanti (2015)

EVIDENCE FROM RCTS

Pulsed RF treatment adj to the lumbar ganglion spinale (DRG)

Study	Koh (2015)
Country	South Korea
Study Design	RCT (Single Centre)
Study population	Patients aged ≥ 20 years with chronic refractory lumbar radicular pain caused by lumbar spinal stenosis (LRP lasting ≥ 12 weeks, dominant leg pain with less intense back pain, failure of conservative management). Exclusion criteria: unbearable (> 9) or trivial (< 4) pain, motor weakness or neurological deficits, S1 radicular symptoms. Only patients who had had >= 2 points or 30 % pain reduction for <= 6 weeks after transforaminal epidural injection of steroids and local anesthetics were included. Spinal stenosis was confirmed with MRI.
Patient details	%Male: 34, Mean age: 65.5 (SD 8.1) years.
Intervention	31 patients received PRF. The RF probe was positioned near the DRG under fluoroscopic control. Position was checked with sensory (< 0.5 V) and motor (> 1.5 x sensory stimulation threshold) stimulation. Three cycles of PRF at 42 °C for 120 seconds, with slight adjustment of probe position in between. Then transforaminal injection of local anesthetic with steroid was given (2-3 ml of 1% preservative-free lidocaine with 20 mg of triamcinolone acetonide), after confirmation of epidural spread. Treatment level: L5 29 patients, L4 + L5 2 patients, unilateral 28, bilateral 3 patients.
Control	31 patients had sham PRF (with the transforaminal injection): identical procedure, but PRF generator not activated by the operating room nurse (display concealed from patients and procedure-performing physician). Treatment level L4 1 patient, L5 28 patients, L4 + L5 2 patients, all unilateral.
Outcomes	Primary outcome: number of successful responders to treatment in each group. Successful response was defined as: 1) ≥ 50% or 4 point reduction in the NRS pain intensity without a corresponding increase in ODI or MQS or <4 points on the GPE scale, or 2) > 30% or 2-point reduction in the NRS with a simultaneous ≥ 30% or 10-point decrease in ODI at 1, 2 and 3 months), >= 25 % drop in MQS, or mean score >= on the GPE scale.
Follow up duration	Up to 3 months
Brief results	The percentage of patients who demonstrated successful treatment results was higher in the PRF group compared with the control group at 2 months (p = 0.032) and 3 months (p = 0.018). Two months: 48.4% [95% CI; 32.0 to 65.2] vs 19.4% [95% CI; 8.8 to 36.7], three months: 38.7% [95% CI; 23.7 to 56.2] vs 9.7% [95% CI; 2.6 to 25.7].

Risk of Bias

Randomization	Low	Computer-generated
Allocation Concealment	Low	Concealment until the end of the study from patients and outcome assessor
Blinding of participants	Low	Injection procedure and type of drug used were not revealed to the patients until study completion
Blinding of caregivers	Low	The nurse in the operation room concealed the patient and the procedure-performing physician
Blinding of assessors	Low	Outcome assessors were blinded
Incomplete outcome data	Low	ITT was applied, and the data of every randomised subject were analysed each month, regardless of lost to follow-up or withdraw (considered treatment failure)
Selective reporting	Low	
Other Biases	Low	

Interlaminar epidural corticosteroid administration

Study	**Manchikanti (2015)**
Country	US
Study Design	RCT (single center)
Study population	Patients with central spinal stenosis with radicular pain of at least 6 months' duration. Patients must have chronic function-limiting low back and lower extremity pain, and must have undergone conservative management with insufficient improvement but not had surgery. Opioid use was an exclusion criterion.
Patient details	43 % male, mean age 52.3 years (SD 14.4)
Intervention	60 patients received lumbar interlaminar epidural injections of 5 ml of 0.5 % preservative-free lidocaine, mixed with 1ml (6 mg) of betamethasone, with a total volume of 6ml. The needle was placed under intermittent fluoroscopic control, and confirmed by injection of non-ionic contrast medium. Injections were given at L5/S1, or one space below the stenosis level. Repeat procedures were performed in patients with deterioration of pain relief and/or functional status below 50%.
Control	60 patients received identical injections, but with 6 ml of 0.5 % preservative-free lidocaine only. 0.5%, 6ml. Repeat procedures were performed in patients with deterioration of pain relief and/or functional status < 50%.
Outcomes	The primary outcome measure was significant improvement of at least 50% based on NRS and ODI scores. Patients experiencing at least 3 weeks of consistent improvement with 2 initial injections were considered as successful and categorized as such.
Follow up duration	24 months
Brief results	At least 50% improvement on NRS and ODI: Steroid Injection: 73%, Local Anaesthetic alone 72%. Overall significant improvement after 2 years was

	achieved for 68.9 ± 37.7 weeks in the steroid group and 65.7 ± 37.3 weeks in the local anesthetic group. The mean number of procedures per patient was 5.6 (SD 2.7) in the steroid group and 5.1 (SD 2.5) in the local anesthetic group.

Risk of bias

Randomization	Low	Computer-generated simple random allocation
Allocation Concealment	Low	Allocation kept by one of the 3 study coordinators.
Blinding of participants	Low	Patients were blinded
Blinding of caregivers	Low	Physician was blinded (study coordinators prepared the drugs)
Blinding of assessors	Low	All other personnel were blinded
Incomplete outcome data	Low	ITT was performed after sensitivity analysis (using last follow up score, best case scenario, and worst case scenario). Last follow up or initial data was used for unavailable data
Selective reporting	Low	
Other Biases	High	One author is a consultant for St. Jude Medical Inc. and Joimax Inc.

OBSERVATIONAL STUDIES

As we identified no reviews or trials on spinal cord stimulation for patients with spinal canal stenosis we conducted an observational study search. The observational studies identified are listed in the table.

Study	**Kamihara (2014)**	**Pahapill (2011) ***
Setting	Japan	Not stated
Study Design	Case series	Case series
Study population	91 patients with lumbar spinal stenosis-associated leg pain resistant to drug or nerve block therapies. Diagnosis was confirmed by MRI and, where necessary, tests such as electromyography.	Six patients with refractory SLS deemed poor surgical candidates who had had 5-day percutaneous trial stimulation
Patient details	35M, 56F, Mean age 73.2 (SD 8.9)	Aged 50 to 88 years
Intervention details	91 patients had 7 days of trial stimulation (Pisces Quad or Pisces Quad compact lead, puncture at the T12/L1 or L1/2 level). If they had a positive response (>= 50 % pain reduction) SCS with an implanted pulse generator was offered (Itrel 3® or Synergy V® Medtronic)).	All were implanted with dual percutaneous lead systems as outpatients under conscious sedation.
Outcomes	Good response defined as SCS continued for ≥ 1 year after implantation	

Follow up duration	Mean 34.5 (SD 22.5) months	Average 18 months
Results	59 of 91 (65%) of patients showed ≥ 50% pain relief in trial stimulation. SCS implantation was performed on 41 patients of whom 39 (95%) showed a good response. Pain levels not reported.	All procedures were well tolerated with no revisions. At last follow-up 5 of the 6 patients continued to have > 50% pain relief with increased function.

*****Conference abstract only, so limited reporting

Author(s): Jos Kleijnen
Date: 2016-11-03
Question: Should spinal cord stimulation be used for pain originating from degenerative spinal stenosis ?
Settings: Treatment by anaesthetists
Bibliography: Kamihara M, Nakano S, Fukunaga T, Ikeda K, Tsunetoh T, Tanada D, et al. Spinal cord stimulation for treatment of leg pain associated with lumbar spinal stenosis. Neuromodulation 2014;17(4):340-4; discussion 345.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Spinal cord stimulation	Control	Relative (95% CI)	Absolute		
Good response to SCS (follow-up mean 34.5 months)												
1	observational studies	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	39/41 (95.1%)	-	-	-	⊕OOO VERY LOW	IMPORTANT
								0%		-		

[1] Case series in 91 patients of whom 41 received SCS of whom 39 showed "good response". No pain measurement.
[2] No pain measurement. No control group.

Author(s): Jos Kleijnen
Date: 2016-11-03
Question: Should pulsed radio frequency treatment adjacent to the dorsal root ganglion be used for pain originating from degenerative spinal stenosis ?
Settings: Treatment by anaesthetists
Bibliography: Koh W, Choi SS, Karm MH, Suh JH, Leem JG, Lee JD, et al. Treatment of chronic lumbosacral radicular pain using adjuvant pulsed radiofrequency: a randomized controlled study. Pain Med 2015;16(3):432-41.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Pulsed radio frequency treatment adjacent to the dorsal root ganglion**	**Control**	**Relative (95% CI)**	**Absolute**		
Successful response (follow-up mean 3 months; assessed with: Composite)												
1	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	12/31 (38.7%)	3/31 (9.7%)	-	290 fewer per 1000 (from 0 more to 0 more)	⊕⊕⊕O MODERATE	CRITICAL

[1] Small trial with 31 patients in each group

Author(s): Jos Kleijnen
Date: 2016-11-03
Question: Should RF lesioning adjacent to the dorsal root ganglion be used for pain originating from degenerative spinal stenosis?
Settings: Treatment by anaesthetists
Bibliography: No evidence found

Author(s): Jos Kleijnen
Date: 2016-11-03
Question: Should epidural steroid and or local anaesthetic administration be used for pain originating from degenerative spinal stenosis?
Settings: Treatment by anaesthetists
Bibliography: Meng H, Fei Q, Wang B, Yang Y, Li D, Li J, et al. Epidural injections with or without steroids in managing chronic low back pain secondary to lumbar spinal stenosis: a meta-analysis of 13 randomized controlled trials. Drug Des Devel Ther 2015;9(4657-67). Manchikanti L, Cash KA, McManus CD, Damron KS, Pampati V, Falco FJ. A randomized, double-blind controlled trial of lumbar interlaminar epidural injections in central spinal stenosis: 2-year follow-up. Pain Physician 2015;18(1):79-92.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Epidural steroid and or local anaesthetic administration**	**Control**	**Relative (95% CI)**	**Absolute**		
Pain relief improvement (follow-up mean 12 months; assessed with: Various)												
13	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	-	RR 1 (0.85 to 1.18)	-	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		
Pain scores (follow-up mean 12 months; measured with: NRS; Better indicated by lower values)												
13	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	0	-	-	MD 0.34 lower (1.29 lower to 0.62 higher)	⊕⊕⊕⊕ HIGH	CRITICAL
Functional improvements (follow-up mean 12 months; assessed with: Various)												
13	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	-	RR 0.98 (0.83 to 1.14)	-	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		
Disability (follow-up mean 12 months; measured with: Oswestry Disability Index; Better indicated by lower values)												
13	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	0	-	-	MD 0.27 lower (0.96 lower to 0.42 higher)	⊕⊕⊕⊕ HIGH	CRITICAL

Author(s): Jos Kleijnen
Date: 2016-11-03
Question: Should epiduroscopy be used for pain originating from degenerative spinal stenosis?
Settings: Treatment by anaesthetists
Bibliography: No evidence found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14. Pain Originating from the Lumbar Facet Joints

OVERVIEW OF TRIALS

Twenty-two RCTs met the inclusion criteria for pain originating from the lumbar facet. Table below gives an overview of the trials.

Study	Participants					Intervention		
	Total Nos	Mean Age (SD)	% male	Mean duration of pain (SD)	Psyc problems excluded?	Intervention	Comparator	Cons treatments allowed?
Ackerman (2008)	46	39.7 (2.9)	57	7.4 (2) weeks	No	IAC injection (intraarticular)	IAC injection (medial branch nerve blocks)	No
Civelek (2012)	100	54 (17)	29	18.7 (12.3) months	No	IAC injection	RF	Unclear
Dobrogowski (2005)	45	66.4 (8.94)	51	4.18 (2.44) years	Yes	RF with steroid	RF without steroid	Unclear
Duger (2012)	120	50.68 (12.10)	Unclear	11 (5.08) months	Yes	IAC injection	RF	Unclear
Fuchs (2005)	60	65.4 (9.1)	30	Nr	No	Hyaluronic acid	IAC injection	Unclear
Galiano (2007)	40	49 (10)	53	Nr	No	IAC injection (ultrasound guided)	IAC injection (CT guided)	Unclear
Gallagher (1994)	41	Unclear	nr	Nr	Yes	RF	Placebo	Unclear
Hashemi (2014)	80	64.1 (12.06)	71	3.6 years	Yes	Pulsed RF	Extra-articular injection	Unclear
Joo (2013)	40	68.25 (15.9)	43	Nr	Unclear	RF	Alcohol ablation	Unclear
Kawu (2011)	18	44.3 (11.4)	61	Nr	No	IAC injection	Physiotherapy	Unclear
Kroll (2008)	50	58 (10)	46	nr	Yes	Pulsed RF	Continuous RF	Unclear
Lakemeier(2013)	56	57 (9.9)	63	Nr (Inc criteria: over 24 months	Yes	RF	IAC injection	Yes

Leclaire (2001)	70	46.55 (9.55)	35.7	nr	No	RF	Placebo	Yes
Marchikanti (2010)	120	47(16)	40	108 (98) months	Yes	LFJ nerve blocks	IAC injection	Yes

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Study	Participants					Intervention		
	Total Nos	Mean Age (SD)	% male	Mean duration of pain (SD)	Psyc problems excluded?	Intervention	Comparator	Cons treatments allowed?
Moon (2013)	68	65.6 (14.1)	34	40.8 (40.6) months	Yes	RF (distal approach)	RF (tunnel approach)	Unclear
Nath (2008)	40	55	38	12 years	Yes	RF	Placebo	Unclear
Ribeiro (2013)	60	64	18	4.3 years	No	IAC injection	Triamcinolone acetonide injections	Yes
Sanders (1999)	34	61.8 (16.6)	74	Nr	Yes	Percutaneous-articularfacet denervation (PIFD)	RF	Unclear
Tekin (2007)	60	59.3 (8.5)	43	35.1 (11.9) months	Yes	Pulsed RF	Continuous RF	Yes
van Kleef (1999)	31	43.9 (6.4)	36	Median 48 months	No	RF	Placebo	Unclear
Van Wijk (2005)	81	47.5 (12.1)	28.4	Nr (inc criteria> 6 months)	Yes	RF	Placebo	Yes
Yun (2012)	57	56.4 (9.13)	47.4	3 (2.2) months	No	IAC injection (fluoroscopy guidance)	IAC injection (US guidance)	Unclear

Study ID	Randomisation	Allocation Concealment	Are participants Blinded?	Are caregivers blinded?	Blinding of assessors	Incomplete outcome data	Selective reporting	Other biases
Hashemi (2014)	Low	Unclear	High	High	Low	Unclear	High	Unclear
Ribeiro (2013)	Low	Unclear	Low	High	Low	Low	Low	High
Duger (2012)	High	High	High	High	Unclear	Unclear	Unclear	High
Lakemeier(2013)	Low	Low	Low	High	Low	High	Low	Unclear
van Kleef (1999)	Low	Low	Low	Low	Low	Unclear	Unclear	Unclear
Joo (2013)	Unclear	Unclear	High	High	Unclear	Unclear	Low	Low
Moon (2013)	Unclear	Unclear	Unclear	High	Unclear	High	Low	High
Fuchs	Low	Unclear	High	High	Low	Low	Low	Unclear
Yun	Unclear	High	High	High	High	Low	Low	Unclear
Leclaire	Low	Low	Low	High	Low	Low	Low	Low
van Wijk	Low	Low	Low	Low	Low	Low	Low	Low
Gallagher (1994)	High	Unclear	Low	Unclear	Low	High	High	Low
Civelek (2012)	Low	Unclear	Unclear	Unclear	Low	Low	Low	Low
Kawu (2011)	Unclear	Unclear	High	High	Unclear	Unclear	Low	High
Manchikanti (2010)	Low	Unclear	Low	Low	Unclear	Low	Low	Low
Kroll (2008)	Low	Unclear	Low	High	Unclear	High	Low	High
Ackerman (2008)	Low	Unclear	Low	Unclear	Low	High	Unclear	High
Nath (2008)	Low	Low	Low	Low	Low	Low	Low	Low
Galiano (2007)	Low	Unclear	High	High	Unclear	Low	Low	Low
Tekin (2007)	Low	Unclear	Low	Unclear	Low	Unclear	Low	Unclear

Sanders (1999)	Unclear	Unclear	High	High	Low	Low	Low	Unclear
Dobrogowski (2005)	Unclear	Unclear	High	High	High	Low	unclear	Low

1 'Low' indicates low risk of bias. The more domains rated 'low' the higher the study quality.

Question: Should Intra-articular injection of corticosteroid vs Physiotherapy be used for Pain originating from the Lumbar Facet Joint?

Bibliography: Kaw u (2011)

Quality assessment							Summary of Findings				
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study eventrates (%)**		**Relative effect** (95% CI)	**Anticipatedabsolute effects**	
							With Physiotherapy	**With Intra-articular injection of corticosteroid**		**Risk with Physiotherapy**	**Risk difference withIntra-articular injection of corticosteroid** (95% CI)
Pain at 6 months (CRITICAL OUTCOME; measured w ith: VAS 0 - 10; range of scores: 0-10; Better indicated by low er values)											
18 (1 study) 6 months	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	undetected	⊕⊕⊖⊖ **LOW**[1,2] due to risk of bias, imprecision	8	10	-		Not pooled[3]
Disability at 6 months (CRITICAL OUTCOME; measured w ith: ODI 0 - 100; range of scores: 0-100; Better indicated by low er values)											
18 (1 study)	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	undetected	⊕⊕⊖⊖ **LOW**[1,2] due to risk of bias, imprecision	8	10	-		Not pooled[4]

[1] Risk of bias: Randomization and allocation concealment is not clear. Participants and caregivers not blinded. No information on whether outcome assessors were blinded.

[2] Imprecision: One small study (18 participants)

[3] Pain scores Mean (SD) Baseline· IAC injection: 7.6 (1.8) · Physiotherapy: 7.2 (2.2) 6 month pain outcomes · IAC injection: 4 .0 (1.5) · Physiotherapy. 5.1 (1.5) · P<0.032

[4] Disability scores: Mean (SD) Bas eline. Intervention: 56.1 (7.8), Physiotherapy: 58.0 (8.7). 6 month outcome scores. Intervention: 38.6 (5.0), Physiotherapy: 46.3 (5.8). p=0.013.

Question: Should Intra-articular injection with corticosteroid vs Injection without steroids be used for Pain originating from the Lumbar Facet Joint?

Bibliography: Manchikanti (2010)

Quality assessment							Summary of Findings			
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study eventrates (%)**		**Relative effect** (95% CI)	**Anticipatedabsolute effects**	
							With Injection without steroids	**With Intra-articular injection with corticosteroid**		**Risk with Injection without steroids**	**Risk difference with Intra-articular injection with corticosteroid** (95% CI)
Pain at 12 months (CRITICAL OUTCOME; measured w ith: NRS 0 - 10; range of scores: 0-10; Better indicated by low er values)											
120 (1 study) 12 months	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	undetected	⊕⊕⊕⊖ **MODERATE**[1] due to imprecision	60	60	-		Not pooled[2]
Disability at 12 months (CRITICAL OUTCOME; measured w ith: ODI 0 - 100[3]; Better indicated by low er values)											
0 (1 study) 12 months	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	undetected	See comment	-	0	-		Not pooled[3]

[1] Imprecision: Single relatively small study (120 participants)

[2] Pain scores Mean (SD) Baseline. IAC injection without steroids: 8.22 (0.78). IAC injection with steroids: 7.93 (0.99), 12 mon ths outcomes. IAC Injection without steroids 3.57 (1.45), IAC injection with steroids 3.40(1.08)

[3] Disability outcomes Mean (SD) Baseline• IAC injection without steroids: 26.6 (4.6) • IAC injection with steroids: 25.9 (5.0) 12 months • IAC injection without steroids: 12.3 (4.8) • IAC injection with steroids: 12.0 (5.4) No difference in effect between intervention and comparator

Question: Should Steroid intraarticular injection vs Intramuscular injection be used for Pain originating from the Lumbar Facet Joint?

Bibliography: Ribeiro (2013)

Quality assessment							Summary of Findings			
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect** (95% CI)	**Anticipated absolute effects**
							With Intramuscular injection	**With Steroid intraarticular injection**		**Risk with Intramuscular injection**	**Risk difference with Steroid intraarticular injection** (95% CI)
Pain at 6 months (CRITICAL OUTCOME; measured w ith: VAS 0-10; Better indicated by low er values)											
60 (1 study) 6 months	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	undetected	⊕⊕⊕⊖ **MODERATE**[1] due to imprecision	29	31	-		Not pooled[2]

[1] Imprecision: One small study (60 patients).

[2] At 6 months mean improvement in the intervention group w as 55.2% (95% CI: 43.2 to 67) and in the control group w as 45.2% (95% CI:50.3 to 62.2). p<0.54.

Question: Should Intra-articular injection with (hyaluronic acid) vs Intra-articular injection with glucorticoids be used for Pain originating from the Lumbar Facet Joint?

Bibliography: Fuchs (2005)

Quality assessment							Summary of Findings			
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**	**Relative effect** (95% CI)	**Anticipated absolute effects**	
							With Intra-articular injection with glucorticoids / **With Intra-articular injection with (hyaluronic acid)**		**Risk with Intra-articular injection with glucorticoids** / **Risk difference with Intra-articular injection with (hyaluronic acid)** (95% CI)	
Pain at 6 months (CRITICAL OUTCOME; measured w ith: VAS 0-100; range of scores: 0-100; Better indicated by low er values)										
59 (1 study) 6 months	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	undetected	⨁⨁⨀⨀ **LOW**[1,2] due to risk of bias, imprecision	30	29	-	Not pooled)[3]
Disability at 6 months (CRITICAL OUTCOME; measured w ith: ODI 0-100; range of scores: 0-100; Better indicated by low er values)										
59 (1 study) 6 months	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	undetected	⨁⨁⨀⨀ **LOW**[1,2] due to risk of bias, imprecision	30	29	-	Not pooled[4]

[1] Risk of bias: Patients and caregivers not blinded

[2] Imprecision: One small study (59 participants)

[3] Pain intensity scores. Mean (SD): Baseline- Hyaluronic acid 69.2 (14.2), Glucocorticoids. 68.7 (11.5), 6 month outcome scores. Hyaluronic acid 38.0 (26.5), Glucocorticoids
33.4 (20.7). Change in pain Hyaluronic acid:- 45%, Glucocorticoids: -51.7%

[4] Disability outcomes Mean (SD) Baseline· Hyaluronic acid: 20.7 (8.5) · Glucocorticoids: 12.6 (9.7) 6 months · Hyaluronic acid -18.4 (6.2) · Glucocorticoids-13.0 (7.1) Mean change in disability · Hyaluronic acid-39.1 % · Glucocorticoids-29.5 %

Question: Should Intra-articular injection with corticosteroid vs Medial branch block be used for Pain originating from the Lumbar Facet Joint?

Bibliography: Ackerman (2008)

Quality assessment							Summary of Findings			
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect** (95% CI)	**Anticipated absolute effects**
							With Medial branch block	**With Intra-articular injection with corticosteroid**		**Risk with Medial branch block**	**Risk difference with Intra-articular injection with corticosteroid** (95% CI)
Pain at 3 months (measured w ith: numeric pain intensity score NPIS (0-10); range of scores: 0-10; Better indicated by low er values)											
46 (1 study) 3 months	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	undetected	⨁⨁⨀⨀ **LOW**[1,2] due to risk of bias, imprecision	23	23	-		Not pooled[3]
Disability at 3 months (measured w ith: ODI (0-50); range of scores: 0-50; Better indicated by low er values)											
46 (1 study) 3 months	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	undetected	⨁⨁⨀⨀ **LOW**[1,2] due to risk of bias, imprecision	23	23	-		Not pooled[4]

[1] Risk of bias: No information on allocation concealment, caregivers not blinded, no information on patients who withdrew from the study

[2] Imprecision: One small study (46 participants)

[3] Pain scores: Mean (SD) Baseline IAC injection (intraarticular) 7.8 (1.3) Medial branch block. 8.1 (1.9), 3 month outcomes IAC injection (intraarticular) 3.2 (0.7), medial branch block 5.4 (1.8)

[4] Disability scores: Mean (SD), Baseline: Intraarticular injection 31(7), Medial branch block: 34 (3). 3 month outcome scores. Intraarticular injection. 12(4), Medial branch blocks: 23 (5). p<=0.05

Question: Should Intra-articular injection of corticosteroid vs Radiofrequency be used for Pain originating from the Lumbar Facet Joint?

Bibliography: Civelek (2012)

Quality assessment							Summary of Findings				
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect** (95% CI)	**Anticipated absolute effects**	
							With Radiofrequency	**With Intra-articular injection of corticosteroid**		**Risk with Radiofrequency**	**Risk difference with Intra-articular injection of corticosteroid** (95% CI)
Pain at 12 months (CRITICAL OUTCOME; measured w ith: Visual Numeric Pain Scale ; range of scores: 0-10; Better indicated by low er values)											
100 (1 study) 12 months	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	undetected	⊕⊕⊕⊖ **MODERATE**[1] due to imprecision	50	50	-		Not pooled)[2]

[1] Imprecision: One small study (100 patients)

[2] Pain scores: Mean (SD). Baseline.Facet Joint Injection 8.5, Radiofrequency 8.2 p=0.06, 12 month outcome scores. Facet Joint I njection 4.9, Radiofrequency 2.6, p<0.001

Question: Should RF of lumbar medial branches of dorsal ramus vs Sham radiofrequency be used for Pain originating from the Lumbar facet joints?

Bibliography: Van Wijk (2005), van Kleef (1999), Leclaire (2001), Gallagher (1994), Nath (2008)

Quality assessment							Summary of Findings			
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%) With Sham radiofrequency	Study event rates (%) With RF of lumbar medial branches of dorsal ramus	Relative effect (95% CI)	Anticipated absolute effects Risk with Sham radiofrequency	Anticipated absolute effects Risk difference with RF of lumbar medial branches of dorsal ramus (95% CI)
Pain (CRITICAL OUTCOME; measured w ith: VAS ; range of scores: 0-10; Better indicated by low er values)											
182 (3 studies) 3 months	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	undetected	⊕⊕⊖⊖ **LOW**[1] due to imprecision	91[1]	91	-		Not pooled[2,3]
Disability and Change in Disability (CRITICAL OUTCOME; measured w ith: ODI; range of scores: 0-100; Better indicated by low er values)											
101 (2 studies[4]) 3 months	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[4]	undetected	⊕⊕⊖⊖ **LOW**[4] due to imprecision	50	51	-		Not pooled[5]
Change in pain (CRITICAL OUTCOME; measured w ith: VAS ; range of scores: 0-10; Better indicated by low er values)											
40 (1 study[6]) 6 months	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[6]	undetected	⊕⊕⊖⊖ **LOW**[6] due to imprecision	20[6]	20	-		Not pooled[3]
Change in pain (CRITICAL OUTCOME[1]; measured w ith: VAS ; range of scores: 0-10; Better indicated by low er values)											
182 (3 studies) 3 months	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	undetected	⊕⊕⊖⊖ **LOW**[1] due to	91	91	-		Not pooled[2]

						imprecision				
Pain (measured w ith: VAS[7]; Better indicated by low er values)										
63 (2 studies[8,9]) 6 months[3]	serious[10]	no serious inconsistency	no serious indirectness	serious[8]	undetected	⊕⊕⊖⊖ **LOW**[8,10] due to risk of bias, imprecision	25 38	-		Not pooled

[1] Three studies (van Kleef, Van Wijk, LeClaire) but still small samplesize

[2] Pain scores. Leclaire Mean: 3 months RF lumbar 52.3/Placebo 44.4) Mean difference between treatments: -7.6 (95 % CI -20.3-5.1) not significant van Wijk Mean change in pain baselineto 3 months RF lumbar -2.1, Placebo-1.6 Non-significant difference in pain between treatments van Kleef Mean (SD) 3 months RF lumbar 2.8 (2.4)/Placebo 4.8 (2.5) Mean difference between treatments Unadj:1.94 (90% CI: 0.24 -3.64)/Adj:2.46 (90% CI: 0.72-4.2)

[3] Pain scores Nath. 6 month back pain scores- RF lumbar 3.88, placebo 3.68 · Mean change in pain RF lumbar -2.1, placebo. -0.7 · Mean differences between treatments:-1.4 (95%CI -3.0 to 0.17) Gallegher Baseline Pain scores · RF lumbar 58 (4.2)/ 68 (5.4) · Placebo 72 (5.6)/60 (7.3) 6 months Pain scores · RF lumbar 44 (7.2)/ 70 (8.1) · Placebo 70 (8.5)/ 38 (10.2)

[4] Disability outcomes: 2 studies (Le Claire, van Kleef)

[5] Leclaire Disability outcomes Mean (SD) Baseline· RF sacroiliac:-38.3 (14.7) · Placebo:- 36.4 (14.6) 3 months · RF sacroiliac:- 33.6 (nr) · Placebo:- 33.7 (nr) Mean change in disability · RF sacroiliac:- 4.7 (12.0) · Placebo:- 2.7 (9.1) Differences in mean changes: 1.9 (95%CI -3.2-7.0) van Kleef Disability outcomes Mean (SD) Baseline· RF lumbar: 31.0 (14.2) · Placebo: 38.0(13.1) 3 month outcome data not provided Mea n change in disability · RF lumbar: -11.07 · Placebo: 1.69 Differences in mean changes baselineto 3 months · Unadj: 15.751 (90% CI: 4.16 to 21.35) · Adj: 10.90 (90% CI: 1.76 to 20.0)

[6] One small study (Nath)

[7] One study VAS 0-10 (Nath), one study VAS 0-100 (Gallagher).

[8] Two small studies (Nath, Gallagher)

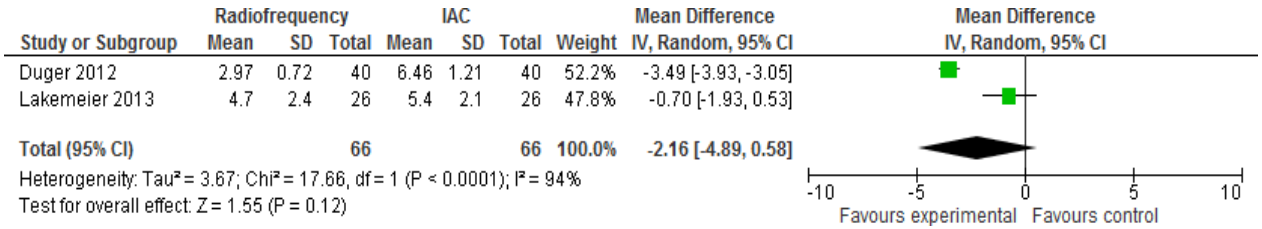
[9] Gallagher is a three arm trial. The table presents two arms RF lumbar good response versus Placebo

[10] Gallagher - patients self-selected into groups based on their response to diagnostic block.

RF versus intra-articular corticosteroid

The evidence for this comparison is based on a meta-analysis of two trials for the outcome of pain at six months. (Dugar and Lakemeier[25, 26]) which is shown in Figure 2.

Pain at six months RF vs intra-articular corticosteroid



Question: Should RF of lumbar rami mediales of the dorsal ramus vs Steroid be used for Pain originating from the Lumbar Facet Joints?

Bibliography: Meta-analysis of Dugar (2012) and Lakemeier (2013)

Quality assessment							Summary of Findings			
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**	**Relative effect** (95% CI)	**Anticipated absolute effects**	
							With Steroid	**With RF of lumbar rami mediales of the dorsal ramus**	**Risk with Steroid**	**Risk difference with RF of lumbar rami mediales of the dorsal ramus** (95% CI)
Pain reduction (CRITICAL OUTCOME; measured w ith: VAS 0 - 10; Better indicated by low er values)										
132 (2 studies) 6 months	serious[1]	serious[2]	no serious indirectness	serious[3]	undetected	⊕⊖⊖⊖ **VERY LOW**[1,2,3] due to risk of bias, inconsistency, imprecision	66	66	**-**		The mean pain reduction in the intervention groups w as **2.16 lower** (4.89 low er to 0.58 higher)[4]
Disability (CRITICAL OUTCOME; measured w ith: ODI 0 - 100; Better indicated by low er values)										
0 (1 study) 6 months	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[5]	undetected	See comment	-	0	**-**		Not pooled)[6]

[1] Risk of Bias: Caregivers not blinded (Duger, Lakemeier), not strictly ITT analysis (Lakemeier), Participants - blinding is unlikely (Duger)

[2] Inconsistency: Duger found a significant difference in favour of the intervention where Lakemeier found no difference.

[3] Imprecision: Two small studies

[4] meta-analysis using randomeffect model (see report for explanation).

[5] Imprecision: One small study

[6] Lakemeier Disability outcomes Mean (SD) Baseline· RF lumbar: 0.8 (16.4) · IAC injection: 38.7 (18.4) 6 months · RF lumbar: 2 8.0 (20.0) · IAC injection: 33.0 (17.4) Mean change in disability · RF lumbar: 12.8 (24.8) · IAC injection: 5.7 (20.9) Differences in mean changes: 0.46 (0.29 to 0.62)

Question: Should Pulsed RF of lumbar rami medialis of the dorsal ramus vs Extra-articular corticosteroid injection be used for Pain originating from the Lumbar Facet Joints?

Bibliography: Hashemi (2014)

Quality assessment							Summary of Findings				
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect** (95% CI)	**Anticipated absolute effects**	
							With Extra-articular corticosteroid injection	**With Pulsed RF of lumbar rami medialis of the dorsal ramus**		**Risk with Extra-articular corticosteroid injection**	**Risk difference with Pulsed RF of lumbar rami medialis of the dorsal ramus** (95% CI)
Pain relief 6 months (CRITICAL OUTCOME; measured w ith: Numerical rating scale 0-10; Better indicated by low er values)											
80 (1 study) 6 months	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	undetected	⊕⊖⊖⊖ **VERY LOW**[1,2] due to risk of bias, imprecision	40	40	-		Not pooled[2,3,4]
Change in disability at 6 months (CRITICAL OUTCOME; measured w ith: ODI 0 - 100; range of scores: 0-100; Better indicated by low er values)											
80 (1 study) 6 months	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	undetected	⊕⊖⊖⊖ **VERY LOW**[1,2] due to risk of bias, imprecision	40	40	-		Not pooled[5]

[1] Risk of bias: Allocation concealment unclear, blinding of caregivers and patients unlikely as interventions very different, s electivereporting, ambigious reporting of NRS pain results.

[2] Imprecision: One small study (80 participants)

[3] Mean difference between baselineand 6 months in intervention group was 5. Mean difference between baselineand 6 months in control group 0.7 (estimated from graph). 'PRF significantly reduced NRS at 6 months follow up compared to comparator' according to text but no data p rovided.

[4] The mean NRS for low back pain reduced significantly from 7.4 ± 1.1 at pre-treatment to 2.4 ± 1.9 at 6 months (p = 0.035) in PRF group. Pulsed radiofrequency (PRF) significantly reduced NRS at 12 weeks (p = 0.012) and 6 months (p = 0.02) follow-up compared to steroid ? bupivacaine, but it was not significantly different at 6 weeks (p = 0.75). Overall findings areunclear as results presented in abstract on pain use a different scale

[5] Disability outcomes Mean (SD) PRF lumbar · Baseline. 75.6 (14 .3) · 6 months. 19.3 (9.5) Data for comparator is unclear. Text states that ODI% was significantly lower in PRF

group at 12 weeks and 6 months compared to steroid plus bupivacaine group (p = 0.022 and 0.03, respectively)

Question: Should Pulsed RF vs Continuous RF be used for Pain originating from the lumbar facet joint?

Bibliography: Tekin (2007), Kroll (2008)

Quality assessment							Summary of Findings				
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%) With Continuous RF	With Pulsed RF	Relative effect (95% CI)		Anticipated absolute effects Risk with Continuous RF (95% CI)	Risk difference with Pulsed RF
Pain reduction at 12 months (CRITICAL OUTCOME; measured w ith: VAS 0 - 10; range of scores: 0-10; Better indicated by low er values)												
40 (1 study[3]) 12 months[3]	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	undetected	⊕⊕⊖⊖ **LOW**[1,2] due to risk of bias, imprecision	20	20	-		The mean pain reduction at 12 months in the intervention groups was **1.50 low er** (2.21 to 0.79 low er)[4]	
Pain at 3 months (CRITICAL OUTCOME; measured w ith: VAS 0 - 100; range of scores: 0-100; Better indicated by low er values)												
26 (1 study[6]) 3 months[6]	serious[5]	no serious inconsistency	no serious indirectness	serious[2]	undetected	⊕⊕⊖⊖ **LOW**[2,5] due to risk of bias, imprecision	13	13	-		Not pooled	
Disability at 12 months (CRITICAL OUTCOME; measured w ith: ODI 0 - 100; range of scores: 0-100; Better indicated by low er values)												
40 (1 study[3]) 12 months[3]	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	undetected	⊕⊕⊖⊖ **LOW**[1,2] due to risk of bias, imprecision	20[7]	20	-		Not pooled[8,9]	
Disability at 3 months (CRITICAL OUTCOME; measured w ith: ODI 0 - 100; range of scores: 0-100; Better indicated by low er values)												
26 (1 study[6]) 3 months[6]	serious[5]	no serious inconsistency	no serious indirectness	serious[2]	undetected	⊕⊕⊖⊖ **LOW**[2,5] due to risk of bias, imprecision	13	13	-		Not pooled	

[1] Risk of bias: At potential risk for selection bias and unclear blinding procedures and poor reporting of study methodology.

[2] Imprecision: One small study

[3] Tekin

Tekin. Mean (SD): baseline PRF lumbar 6.6 (1.6) RF lumbar 6.5 (1.5), pain outcomes at 12 months PRF lumbar, 3.5 (1.3), RF lumbar. 2.4(1.1)

[5] Allocation concealment unclear, caregivers not blinded, outcome assessors unclearif blinded, high dropout.

[6] Kroll

[7] 3 arm trial

[8] Tekin Disability outcomes Mean (SD) Baseline· PRF lumbar 39.4 (5.0) · RF lumbar 39.2 (3.5) 12 months · PRF lumbar: 28.5 (6.1) · RF lumbar: 28.0 (7.1) Kroll) Disability outcomes Mean (SD) Baseline· PRF lumbar - 44.9 (10.4) · RF lumbar- 52.0 (17.3) 3 Months · PRF lumbar - 42.2 (19.0) · RF lumbar- 41.7 (16.9)

[9] Similar effect seen for disability outcomes for Tekin (2007) and Kroll (2008). No difference in effect between PRF and RF-Continuous

Intervention	Outcome(s)	Relevant Trials	GRADE
Steroid intra-articular injection compared to Intramuscular injection	Pain at 6 months	Ribeiro	Moderate
Intra-articular injection of corticosteroid compared to Radiofrequency	Pain at 12 months	Civelek	Moderate
Intra-articular injection of corticosteroid compared to Physiotherapy	Pain at 6 months Disability at 6 months	Kawu	Low
Intra-articular injection with corticosteroid compared to Injection without steroids	Pain at 12 months Disability at 12 months	Manchikanti	Moderate
Intra-articular injection with corticosteroid compared to Medial branch block	Pain at 3 months Disability at 3 months	Ackerman	Low
Intra-articular injection with (hyaluronic acid) compared to Intra-articular injection with glucorticoids	Pain at 6 months Disability at 6 months	Fuchs	Low
RF of lumbar rami mediales of the dorsal ramus compared to Steroid	Pain at 6 months	Dugar Lakemeier	Very Low
	Disability at 6 months	Lakemeier	Moderate
Pulsed RF of lumbarrami medialis of the dorsal ramus compared to Extra-articular corticosteroid injection	Pain at 6 months Change in disability at 6months	Hashemi	Low
Pulsed RF compared to Continuous RF	Pain reduction at 12 months Disability reduction at 12 months	Tekin	Low
	Pain at 3 months Disability at 3 months	Kroll	Low

RF of lumbar medial branches of dorsal ramus compared to Sham radiofrequency	Pain at 3 months	Van Wijk, van Kleef and Leclaire, Gallagher, Nath	Low
	Change in pain at 3 months	Van Wijk, van Kleef and Leclaire	Low
	Change in pain at 6 months	Nath	Low
	Change in disability at 3 months	van Kleef and Leclaire	Low

15. Sacroiliac Joint Pain

Overview of trials

Six RCTs met the inclusion criteria for sacroiliac joint pain. Table below gives an overview of the trials

Study	Participants					Intervention		
	Total Nos	Mean Age (SD)	% male	Mean duration of pain (SD)	Psyc problems excluded?	Intervention	Comparator	Cons treatments allowed?
Cohen (2012)	28	51.9 (13.4)	39.2	nr	Yes	Cooled RF	Sham procedure	No
Jee	120	60.8 (8.3)	28	6.26 (2.34) months	Yes	IAC injection (ultrasound guided)	IAC injection (Fluoroscopy guided)	No
Kim	50	60.2 (14.1	29	42.1 (nr)	Yes	IAC injection	Prolotherapy	No
Patel	51	58.7 (14.7)	27	Nr	Yes	Cooled RF	Sham procedure	Unclear
Visser	51	46.2 (13.9)	27	25 (18.5) weeks	No	IAC injection	Physiotherapy	No
Zheng	155	42.2 (14.0)	73	8.2 (7.0) years	Yes	RF	Oral celecoxib	No

Study ID	Randomization	Allocation Concealment	Are participants Blinded?	Are caregivers blinded?	Blinding of assessors	Incomplete outcome data	Selective reporting	Other biases
Visser	Low	Low	High	High	Low	High	High	Unclear
Jee	Low	Unclear	High	High	Low	Unclear	Low	Unclear
Patel	Unclear	Low	Low	High	Low	Low	Low	Low
Kim	Low	Unclear	Low	High	Unclear	Low	Unclear	Low

Cohen	Low	Low	Low	High	Low	Low	Low	Low
Zheng	Low	Unclear	High	High	Unclear	Low	Low	Low

1 'Low' indicates low risk of bias. The more domains rated 'low' the higher the study quality.

Question: Should Intra-articular corticosteroid vs Manual therapy or physiotherapy be used for Sacroiliac joint pain?

Bibliography: Visser (2013)

Quality assessment							Summary of Findings			
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect** (95% CI)	**Anticipated absolute effects**	
							With therapy	**Manual or physiotherapy**		**Risk with Manual therapy**	**Risk difference with Intra-articular corticosteroid** (95% CI)
Pain at 3 months (CRITICAL OUTCOME; measured w ith: VAS 0 - 10; Better indicated by low er values)											
0 (1 study)	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	undetected	See comment	-	0	-		Not Pooled[3,4]

[1] Risk of bias: Caregivers not blinded, largeloss to follow-up.

[2] Small samplesize

[3] Baseline Pain scores Mean (SD): Intra-articularcorticosteroid 5.7 (1.7), Manual therapy 5.2 (1.4), Physiotherapy 4.3 (1.2). 3 month pain scores Mean (SD). Intra -articular corticosteroid 5.0 (1.9), Manual therapy 3.3 (2.3), Physiotherapy 3.9 (1.4).

[4] Success rates for patients treated: Intra-articularinjection - 50% 9/18 patients, Manual therapy 72% 13/18 patients, Physiotherapy 20% 3/15 patients.

Three arm study.

Question: Should Intra-articular steroid therapy vs Prolotherapy be used for Sacroiliac joint pain?[1,2]

Bibliography: Kim (2010)

Quality assessment							Summary of Findings			
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects
							With Prolotherapy	With Intra-articular steroid therapy		Risk with Prolotherapy	Risk difference with Intra-articular steroid therapy (95% CI)
Disability at 6 months (CRITICAL OUTCOME; measured w ith: ODI 0 - 100; Better indicated by higher values)											
48 (1 study)	serious[3]	no serious inconsistency[4]	no serious indirectness	serious[5]	undetected	⨁⨁⨀⨀ **LOW**[3,4,5] due to risk of bias, imprecision	25	23	-	Not pooled [7]	Not pooled)[6]
Pain relief at 6 months (CRITICAL OUTCOME; measured w ith: NRS 0 - 10; Better indicated by low er values)											
50 (1 study)	serious[3]	no serious inconsistency[4]	no serious indirectness	serious[5]	undetected	⨁⨁⨀⨀ **LOW**[3,4,5] due to risk of bias, imprecision	26	24	-	Not pooled [7]	Not pooled[7]

[1] The steroid group received 2.5 mL of 0.125% levobupivacainewith 40 mg of triamcinolone.

[2] Prolotherapy group received 2.5 mL of 25% dextrose solution prepared by diluting 50% dextrose water with 0.25% levobupivacain e.

[3] Risk of bias: Caregiver not blinded but outcome patient-assessed (patient was blinded). Unclear allocation concealment. Not I TT.

[4] Single study

[5] Imprecision: One small study

[6] Disability scores: Baseline Mean (SD) Prolotherapy 33.9 (15.5), Steroid 35.7 (20.4).

[7] The cumulativeincidenceof greater than 50% pain relief at 6 months was 63.6% in the prolotherapy group and 27.2% in the steroid group. Baseline Pain scores (SD) were similar: prolotherapy: 6.3; intra-articular steroid therapy: 6.7.

Question: Should Palisade Radiofrequency vs Oral celecoxib be used for Sacroiliac Joint Pain?

Bibliography: Zheng (2014)

Quality assessment							Summary of Findings			
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect** (95% CI)	**Anticipated absolute effects**
							With Oral celecoxib	**With Palisade Radiofrequency**		**Risk with Oral celecoxib**	**Risk difference with Palisade Radiofrequency** (95% CI)
Global pain intensity at 3 months (CRITICAL OUTCOME; measured w ith: VAS 0 - 10[1]; Better indicated by low er values)											
155 (1 study) 24 w eeks	serious[2]	no serious inconsistency	serious[3]	serious	undetected	⊕⊖⊖⊖ **VERY LOW**[2,3] due to risk of bias, indirectness, imprecision	73	82	-		The mean global pain intensity at 3 months in the intervention groups w as **1.9 lower** (2.4 to 1.4 low er)[1,4]
Global pain intensity at 6 months (CRITICAL OUTCOME; measured w ith: VAS 0 - 10; Better indicated by low er values)											
155 (1 study)	serious[2]	no serious inconsistency	serious[3]	serious[5]	undetected	⊕⊖⊖⊖ **VERY LOW**[2,3,5] due to risk of bias, indirectness, imprecision	73	82	-		The mean global pain intensity at 6 months in the intervention groups w as **2.2 lower** (2.6 to 1.6 low er)[1,6]

[1] Results presented as comparison of outcomes from baselineto week 12 and week 24.

[2] Risk of bias: Participants, caregivers not blinded and outcome assessors unclear if blinded. Open label study.

[3] Population is patients with ankylosing spondylitis. Findings may not be applicableto whole population with sacroiliacpain.

[4] Baselinepain intensity Mean (SD): Palisade Radiofrequency: 7.2 (3.0), Oral Celecoxib 6.9 (3.3); 3 months global pain intensi ty: Palisade Radiofrequency: 2.5 (1.8), Oral Celecoxib 4.4 (1.9). Mean change in pain: Palisade Radiofrequency: -65.3%, Oral Celecoxib: -36.2%. Differences in mean change 1.9.

[5] Imprecision: A singlestudy, relatively small samplesize(155 patients)

[6] 6 months global pain intensity Mean (SD): Palisaderadiofrequency 2.8 (1.6), Oral celecoxib 5.0 (1.5). Mean change in pain at 6 months: Palisaderadiofrequency: -61.1%, Oral celecoxib: -27.5%, Difference in mean changes 2.2

Question: Should Continuous cooled RFA vs Sham procedure with no current be used for Sacroiliac joint pain?

Bibliography: Cohen (2008) and Patel (2012)

Quality assessment							Summary of Findings			
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With Sham procedure with no current	With Continuous cooled RFA		Risk with Sham procedure with no current	Risk difference with Continuous cooled RFA (95% CI)
Pain relief (CRITICAL OUTCOME; measured w ith: NRS 0 - 10; Better indicated by low er values)											
76 (2 studies[2]) 3 months	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	undetected	⊕⊕⊕⊖ **MODERATE**[1] due to imprecision	28	48	-		Not pooled[3]
Change in pain at 3 months (CRITICAL OUTCOME; measured w ith: NRS 0 - 10; Better indicated by low er values)											
51 (1 study[5]) 3 months	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	undetected	⊕⊕⊖⊖ **LOW**[1] due to imprecision	17[4]	34	-		Not pooled[4]
Change in disability at 3 months (CRITICAL OUTCOME; measured w ith: ODI 0 - 100; range of scores: 0-100; Better indicated by low er values)											
47 (1 study[5]) 3 months	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	undetected	⊕⊕⊖⊖ **LOW**[1] due to imprecision	15[5]	32	-		Not pooled[6]
Disability (CRITICAL OUTCOME; measured w ith: ODI ; range of scores: 0-100; Better indicated by low er values)											
72 (2 studies[8]) 3 months	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2,7]	undetected	⊕⊕⊕⊖ **MODERATE**[2,7] due to imprecision	26[2]	46	-		Not pooled[6,9]

[1] Imprecision: One small study (25 participants)

[2] Cohen, Patel

[3] Cohen: Mean (SD): Baselinepain score: Intervention - 6.1 (1.8), Placebo - 6.5 (1.9); 3 month outcome pain score: Intervention - 2.4 (2.3), Placebo - 6.0 (0). Significant pain relief at 3 months relativeto baseline.

[4] Patel: Intervention - 2.4 (SD 2.7), Sham - 0.8 (SD 2.4), difference in means -1.6(SD 0,3). Pain Outcome at 3 months.

[5] Patel

[6] Patel: Baseline Mean (SD) Disability Score, Intervention 37 (14), Placebo 35 (10). difference in means at 3 months post inter vention -11(17)

[7] Imprecision: 2 small studies. 72 participants

[8] Cohen

[9] Cohen: Disability score: Mean (SD) Baseline Intervention 37.1(10.6), Placebo 47.9 (9.3). 3 months Intervention 18.5 (11.6), P lacebo 24 (8.5). Reduction in Disability for both the intervention and placebo group

Interventions	Outcomes	Relevant Trials	GRADE
Intra-articular injections			
Prolotherapy compared to Steroid therapy	Pain at 6 months	Kim	Low
	Disability at 6 months		Low
Intra-articular corticosteroid compared to Manual therapy or physiotherapy	Pain at 3 months	Visser	Very low
Pulsed RF treatment of rami dorsales and rami laterals		None	Insufficient
RF: Palisade Radiofrequency compared to Oral celecoxib	Pain intensity at 3 months	Zheng	Very low
	Pain intensity at 6 months	Zheng	Very Low
Cooled RF treatment of rami laterals			
Continuous cooled RFA compared to Sham procedure with no current	Pain relief at 3months	Cohen and Patel	Moderate
	Change in pain at 3 months	Patel	Low
	Disability at 3 months	Cohen and Patel	Moderate
	Change in disability at 3 months	Patel	Low

16. Discogenic Low Back Pain

Ten RCTs met the inclusion criteria for discogenic pain.

Study		Participants				Intervention		
	Total Nos	Mean Age (SD)	% male	Mean duration of pain (SD)	Psyc problems excluded?	Intervention	Comparator	Cons treatments allowed?
Barendse (2001)	28	43.5 (8.0)	35.7	nr Median: 48 months	No	RF discus	Placebo	Yes[1]
Cao	120	42.3 (8.7)	62.5	nr	Unclear	IDC injection	Placebo	Unclear
Ercelen (2003)	39	38.78 (6.80)	40.5	nr	No	RF discus (360 s)	RF discus (120s)	Unclear
Freeman (2005)	57	38.85 (8.1)	73.6	58.81 (57.73) months	Yes	IDET	Placebo	Yes
Kapural	64	39.3 (10.4)	47	Nr (most patients > 24 months)	Yes	Biacuplasty	Placebo	Yes
Khot (2004)	120	43.8 (9.1)	45.8	Nr	Unclear	IDC injection	Placebo	Unclear
Kvarstein (2009)	20	42.2 (9.5)	30	nr (most patients > 24 months)	Yes	Disctrode	Placebo	Yes
Oh (2004)	49	42.8 (6.9)	42.9	47.1 (14.0) months	Yes	RF ramus communicans	Placebo	Yes
Pauza (2004)	54	41.2 (9.2)	46.9	nr (most over 24 months)	Yes	IDET	Placebo	Yes
Peng (2010)	72	41.67 (13.29	56.9	3.35 (1.65) years	Yes	MB	Placebo	Yes

1 Analgesics allowed. Conservative treatments only if patient classed as failure and left study

Study ID	Randomisation	Allocation Concealment	Are participants Blinded?	Are caregivers blinded?	Blinding of assessors	Incomplete outcome data	Selective reporting	Other biases
Kapural	Low	Low	Low	Low	Low	Unclear	Low	Low
Cao	Unclear	Low	Low	Low	Low	Low	Low	Low
Peng (2010)	Low	Low	Low	Low	Low	Low	Low	Low
Kvarstein (2009)	Low	Unclear	Low	Low	Low	Low	Low	Low
Freeman (2005)	Low	Low	Low	Low	Low	High	Low	Low
Khot (2004)	Unclear	Unclear	Low	High	Low	High	Unclear	Unclear
Pauza(2004)	Low	Low	Low	Low	Low	Low	Low	Low
Ercelen (2003)	Unclear	Unclear	High	High	Unclear	Low	Low	Low
Barendse (2001)	Low	Low	Low	Low	Low	Low	Low	Unclear
Oh (2004)	Unclear	Unclear	High	High	High	Unclear	Low	Unclear

Question: Should Methylene Blue Injection vs Sham procedure be used for discogenic low back pain?

Bibliography: Peng (2010)

Quality assessment							Summary of Findings			
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With procedure	Sham With Methylene Blue Injection		Risk with Sham procedure	Risk difference with Methylene Blue Injection (95% CI)
Pain at 12 months (CRITICAL OUTCOME; measured w ith: NRS 0 - 100; range of scores: 0-100; Better indicated by low er values)											
71 (1 study) 12 months	no serious risk of bias[1]	no serious inconsistency	no serious indirectness	serious[2]	undetected	⊕⊕⊕⊖ **MODERATE**[1,2] due to imprecision	35	36	-		Not pooled[3,4]
Disability at 12 months (measured w ith: ODI 0 - 100; range of scores: 0-100; Better indicated by low er values)											
71 (1 study) 12 months	no serious risk of bias[1]	no serious inconsistency	no serious indirectness	serious[2]	undetected	⊕⊕⊕⊖ **MODERATE**[1,2] due to imprecision	35	36	-		Not pooled[5]

[1] Risk of bias: Not ITT. However only one person lost to follow up.

[2] Imprecision: One small study (71 participants)

[3] Mean reduction in pain as measured by NRS of 52.5 in the intervention group. Outcomes measured at 6, 12 and 24 months. There was a significant difference n pain scores at all time points.

[4] Pain scores: Mean (SD) Baseline: Intervention: 72.33 (12.35), Pl acebo: 67.28 (11.45), 12 month outcomes: Intervention: 21.58 (17.93), Placebo 62.40 (12.05). Mean difference 40.82 95% CI 33.56-48.07.

[5] Disability scores: Mean (SD) Baseline: Intervention 48.47 (5.12), Placebo 49.37 (6.79), 12 month outcome scores: Inter vention 14.39 (12.87), Placebo 49.09 (10.20). Mean difference: 34.70 95% CI 29.19-40.20. Difference in mean changes not reported

Question: Should Intradiscal corticosteroid administration vs Placebo be used for discogenic low back pain?

Bibliography: Cao (2011) and Khot (2004)

Quality assessment							Summary of Findings			
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect** (95% CI)	**Anticipated absolute effects**
							With Placebo	**With Intradiscal corticosteroid administration**		**Risk with Placebo** / **Risk difference with Intradiscal corticosteroid administration** (95% CI)
Intensity of Low Back Pain at 6 months (CRITICAL OUTCOME; measured w ith: VAS (0 to 10); Better indicated by low er values)										
40 (1 study[3])	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	undetected	⊕⊕⊖⊖ **LOW**[1] due to imprecision	20[1,2]	20	-	Not pooled[4,5]
Disability at 6 months (CRITICAL OUTCOME; measured w ith: ODI 0 - 100[4]; Better indicated by low er values)										
120 (1 study[3])	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	undetected	⊕⊕⊖⊖ **LOW**[1] due to imprecision	60[6]	60	-	Not pooled[7]
Pain at 12 months (CRITICAL OUTCOME; measured w ith: NRS 0 - 10; Better indicated by low er values)										
120 (1 study[6])	serious[8]	no serious inconsistency	no serious indirectness	very serious[1]	undetected	⊕⊖⊖⊖ **VERY LOW**[1,8] due to risk of bias, imprecision	60	60	-	Not pooled
Disability at 12 months (CRITICAL OUTCOME; measured w ith: Osw estry Low back pain questionnaire[4]; Better indicated by low er values)										
120 (1 study[6])	serious[8]	no serious inconsistency	no serious indirectness	serious[1]	undetected	⊕⊕⊖⊖ **LOW**[1,8] due to risk of	60[6]	60	-	Not pooled[7]

						bias, imprecision				

[1] Imprecision: One small study (120 participants)

[2] Cao is a 6 arm study comparing two Modic types and two interventions. The participant numbers presented is for the interventi on of interest to this study versus saline placebo

[3] Cao

[4] According to the Oswestry Low Back Pain Disability Questionnaire

[5] Pain scores: Cao (2011), Mean (SD) Modic type 1, Baseline Steroid Injection 6.5 (1.18), Saline 7.1 (1.61), Steroid plus herb. 6 month pain scores: Steroid injection 2.3 (0.95), Saline 7.5 (1.08), Steroid plus herb. Modic type 11. Baseline. Steroid injection 6 .8 (1.30), Saline 6.5 (1.20), Steroid plus herb. 6 mont pain scores: Steroid injection 2.1(0.99), Saline 6.4 (1.07). Steroid plus herb

[6] Khot

[7] Disability scores. Khot (2004) Mean (SD). Baseline Intervention: 50.8 (14.4), Placebo 49.8 (16.6). Mean change i n disability as measured at 12 months. Intervention: 2.3 (16.87), Placebo 3.4 (12.93).

[8] Lack of information on randomisation, not ITT, greater than 20% dropout.

Question: Should RF treatment of the discus invertebralis vs Sham procedure be used for discogenic low back pain?

Bibliography: Barendse (2001)

Quality assessment							Summary of Findings			
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect** (95% CI)	**Anticipated absolute effects**
							With Sham procedure	**With RF treatment of the discus invertebralis**		**Risk with Sham procedure**	**Risk difference with RF treatment of the discus invertebralis** (95% CI)
Pain at 3 months (CRITICAL OUTCOME; measured w ith: VAS 0 - 10; Better indicated by low er values)											
28 (1 study[2])	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	undetected	⊕⊕⊖⊖ **LOW**[1] due to imprecision	15[2]	13	-		Not pooled[3]

Disability at 3 months (CRITICAL OUTCOME; measured w ith: ODI 0 - 100; Better indicated by low er values)										
28 (1 study[2])	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	undetected	⊕⊕⊖⊖ **LOW**[1] due to imprecision	15	13	-	Not pooled[4]
Change in pain at 3 months (measured w ith: VAS 0 - 10; Better indicated by low er values)										
28 (1 study[2])	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	undetected	⊕⊕⊖⊖ **LOW**[1] due to imprecision	15	13	-	Not pooled[5]
Change in disability at 3 months (CRITICAL OUTCOME; measured w ith: ODI 0 - 100; Better indicated by low er values)										
28 (1 study[2])	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	undetected	⊕⊕⊖⊖ **LOW**[1] Due to imprecision	15	13	-	No t pooled[6]

[1] Imprecision: One small study

[2] Barendse

[3] Pain scores. Mean (SD) Baseline: Intervention 6.5 (1.3), Placebo 5.5 (1.1), 3 month pain scores not reported. Mean change in pain at 3 months. Intervention -0.61, Placebo

-1.14.

[4] Disability scores. Mean (SD) Baseline: Intervention- 43.7 (11.6), Placebo- 40.7 (9.5), 3 month disability scores not reported. Mean change in disability at 3 months: Intervention -2.62, Placebo -4.93

[5] Pain scores: Differences in mean changes Intervention - Placebo. -0.53 (90% CI: -1.95-0.89)

[6] Disability scores: Differences in mean changes. Intervention - Placebo: -2.31 (90% CI -10.08, -5.45).

Question: Should Biacuplasty vs Sham procedure be used for discogenic low back pain?

Bibliography: Kapural (2013)

Quality assessment							Summary of Findings			
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With procedure	Sham With Biacuplasty		Risk with Sham procedure	Risk difference with Biacuplasty (95% CI)
Pain relief at 6 months (CRITICAL OUTCOME; measured w ith: NRS 0 - 10; range of scores: 0-10; Better indicated by low er values)											
56 (1 study) 6 months	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	undetected	⊕⊕⊕⊖ **MODERATE**[1] due to imprecision	29	27	-		Not pooled[2]
Disability at 6 months (CRITICAL OUTCOME; measured w ith: ODI 0 - 100; range of scores: 0-100; Better indicated by low er values)											
56 (1 study) 6 months	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	undetected	⊕⊕⊕⊖ **MODERATE**[1] due to imprecision	29	27	-		Not pooled[3]

[1] Imprecision, One small study (56 participants)

[2] Mean (SD) Pain scores: Baseline:- Intervention 7.13 (1.61), Placebo 7.1 (1.98). Pain scores at 6 months: Intervention 4.94 (2.15), Placebo 6.58 (2.11). Mean ch angein pain Intervention -2.19 (2.43), Placebo -0.64 (2.10). Difference in mean changes not reported.

[3] Disability scores. Mean (SD): Baseline:- Intervention 40.37 (12.30), Placebo 40.93 (13.56). 6 months disability scores:- Intervention 32.94 (16.14), Placebo 41.17 (13.94). Change in disability scores: Intervention -7.43 (10.11), Placebo 0.53 (10.57). Difference in mean changes not reported.

Question: Should Intradiscal Electrothermal Therapy vs Sham procedure be used for discogenic low back pain?

Bibliography: Pauza (2004) and Freeman (2005)

Quality assessment							Summary of Findings			
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects
							With Sham procedure	With Intradiscal Electrothermal Therapy		Risk with Sham procedure	Risk difference with Intradiscal Electrothermal Therapy (95% CI)
Pain (CRITICAL OUTCOME; measured w ith: VAS 0-10; Better indicated by low er values)											
56 (1 study[2]) 6 months	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	undetected	⊕⊕⊕⊖ **MODERATE**[1] due to imprecision	24	32	-		Not pooled[3,4,5]
Change in pain at 6 months (CRITICAL OUTCOME; measured w ith: VAS 0 - 10; Better indicated by low er values)											
56 (1 study[2])	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	undetected	⊕⊕⊕⊖ **MODERATE**[1] due to imprecision	24[2]	32	-		Not pooled)[3,5,6]
Disability (measured w ith: ODI 0 - 100; Better indicated by low er values)											
113 (2 studies[2,7]) 6 months	no serious risk of bias	serious[3]	no serious indirectness	serious[8]	undetected	⊕⊕⊖⊖ **LOW**[3,8] due to inconsistency, imprecision	43	70	-		Not pooled[9]

[1] Imprecision: One small study

[2] Pauza

[3] Inconsistency: The benefits found in Pauza were not identified in Freeman.

[4] Pain at 6 months (Pauza) : Mean (SD) Baseline IDET: 6.5 (1.6), Placebo: 6.5 (1.8). 6 month outcome scores. IDET 4.2 (2.6), Pl acebo: 5.4 (2.7)

[5] VAS scale(Pain) reported in paper by Freeman but no results presented

[6] Change in pain (Pauza): Mean (SD). Intervention - Mean change in pain 2.4 (2.3), Placebo 1.1 (2.6). Differences in mean change - not reported.

[7] Freeman

[8] Imprecision: Two small studies

[9] Disability scores (Freeman). Mean (SD). Baseline IDET: 41.42 (14.80), Placebo 40.74 (11.84). 6 month outc ome scores IDET: 39.77 (16.28), Placebo 41.58 (11.29).

Question: Should RF treatment of the ramus communicans vs Sham procedure be used for discogenic low back pain?

Bibliography: Oh (2004)

Quality assessment							Summary of Findings			
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect** (95% CI)	**Anticipated absolute effects**
							With Sham procedure	**With RF treatment of the ramus communicans**		**Risk with Sham procedure**	**Risk difference with RF treatment of the ramus communicans** (95% CI)
Pain at 3 months (CRITICAL OUTCOME; measured w ith: VAS 0-10; range of scores: 0-10; Better indicated by low er values)											
49 (1 study)	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	undetected	⊕⊖⊖⊖ **VERY LOW**[1,2] due to risk of bias, imprecision	23	26	-		The mean pain at 3 months in the intervention groups w as **0 higher** (0 to 0 higher)[3]
Disability [4] (CRITICAL OUTCOME; measured w ith: SF-36 Physical function subscale; range of scores: 0-100; Better indicated by low er values)											
49 (1 study) 3 months	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	undetected	⊕⊖⊖⊖ **VERY LOW**[1,2] due to risk of bias, imprecision	23	26	-		The mean disability in the intervention groups w as **0 higher** (0 to 0 higher)[5]

[1] Risk of bias: No information on randomisation, allocation concealment, blinding or outcome assessment. Discrepancy between ta ble 1 and 3 re baselineradiofrequency SD/

[2] Imprecision: One small study. (49 participants)

[3] Pain scores: Mean (SD). Baseline Intervention: 7.14 (1.3), Placebo: 7.0 (1.6); 3 month pain scores Intervention: 3.82 (1.5), Placebo 6.3 (1.1).

[4] Disability as measured by the SF36 phyisical function score

[5] Disability Scores: Mean (SD). Baseline Intervention: 43.7 (3.9), Placebo: 44.1 (4.3); 3 month disability scores Intervention: 58.9 (4.8), Placebo: 46.5 (3.4)

Question: Should Disctrode vs Sham procedure be used for discogenic low back pain?

Bibliography: Kvarstein (2009)

Quality assessment							Summary of Findings			
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect** (95% CI)	**Anticipated absolute effects**
							With procedure	**Sham With Disctrode**		**Risk with Sham procedure** **Risk difference with Disctrode** (95% CI)
Pain at 12 months (CRITICAL OUTCOME; measured w ith: NRS 0 - 10; range of scores: 0-10; Better indicated by low er values)										
20 (1 study) 12 months	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	undetected	⊕⊕⊖⊖ **LOW**[1] due to imprecision	10	10	-	Not pooled[2]
Disability at 12 months (CRITICAL OUTCOME; measured w ith: ODI 0 - 100; range of scores: 0-100; Better indicated by low er values)										
20 (1 study) 12 months	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	undetected	⊕⊕⊖⊖ **LOW**[1] due to imprecision	10	10	-	Not pooled[3]

[1] Imprecision: One small study (20 participants)

[2] Pain scores. Mean (SD). Baseline: Intervention 4.6 (1.8), Placebo 5.5 (2.0), 12 month outcome: Intervention: 3.2 (2.3), Placebo 4.9 (2.1).

[3] Disability scores: Mean (SD). Baseline: Intervention 31.6 (10.2), Placebo 30.4 (15.3), 12 month outcome: Intervention 20.0 (16.2), Placebo 30.0 (17.1)

Intervention	Outcome	Relevant trial	GRADE
Biacuplasty			
Biacuplasty compared to Sham procedure	Pain relief at 6 months Disability at 6 months	Kapural	Moderate
Disctrode			
Disctrode compared to Sham procedure	Pain relief at 12 months Disability at 12 months	Kvarstein	Low
Methylene Blue injection			
Methylene Blue Injection compared to Sham procedure	Pain at 12 months Disability at 12 months	Peng	Moderate
Intradiscal electrothermal therapy			
Intradiscal Electrothermal Therapy compared to Sham procedure	Pain at 6 months	Pauza	Moderate
	Change in pain at 6 months	Pauza	Moderate
	Disability at 6 months	Pauza Freeman	Low
Intradiscal corticosteroid administration			
Intradiscal corticosteroid administration compared to Placebo	Pain at 12 months	Cao	Very low
	Pain intensity at 12 months	Khot	Low
	Disability at 6 months	Cao	Low
	Disability at 12 months	Khot	Low
RF treatment of the discus invertebralis			
RF treatment of discus invertebralis compared to Sham procedure	Pain at 3 months	Barendse	Low
	Disability at 3 months	Barendse	Low
	Change in pain at 3 months	Barendse	Low
	Change in disability at 3months	Barendse	Low
RF treatment of ramus communicans			
RF treatment of the ramus communicans compared to Sham procedure	Pain at 3 months	Oh	Very low
	Disability at 3 months	Oh	Very low

16. Complex Regional Pain Syndrome

SYSTEMATIC REVIEWS IDENTIFIED

We identified a number of potentially relevant reviews published between 2010 and 2015 for complex regional pain syndrome.

One review by Straube and colleagues of cervico-thoracic or lumbar sympathectomy[3] was assessed. However this Cochrane review included just one trial [4] which was identified in the previous guidance.[1]

Two reviews, one of ketamine conducted by Azari[5] and one conducted by Tran[6] covering a range of treatments appeared to have been superseded by later reviews.

We identified a review by Xu and colleagues of intravenous therapies for complex regional pain syndrome but this was only reported as a conference abstract and could not therefore be included.[7]

Finally we identified an overview of reviews of treatment for CRPS by O'Connell[8] and an overview of reviews and trials on ketamine for CRPS[9] which did not appear to add to the data already presented.

The review evidence in this report is based on the two most up to date, relevant reviews by Cossins[10] which covers a range of interventions and a systematic review by Stanton focusing on local anesthetic sympathetic blockade.[11]

ASSESSMENT OF THE REVIEW EVIDENCE

Study Reference	Participants	Interventions	Comparators	Outcomes	Study Designs
Cossins (2013)	Adult patients with either complex regional pain syndrome I or II (without/with associated injury to a major nerve)	Any treatment or preventative measure	Placebo / control group. Studies without placebo/control group (that is: active interventions only) were included only if significant differences were found.	Pain intensity measured by numerical rating scale (NRS), visual analogue scale (VAS), verbal rating scale (VRS), or a neuropathic pain scale (NPS) or prevention of CRPS as an outcome measure	Randomized controlled trials (parallel group or crossover), where the randomization method was considered appropriate

Results

- The review found moderate evidence for the efficacy of low-dose IV ketamine infusion in long-standing CRPS (two studies).
- There was limited evidence for the efficacy of spinal cord stimulation (SCS) based on one positive high-quality trial.
- The SCS trial was the only trial in this review period with more than 50 patients per treatment arm and a follow-up period of over 1 year.
- Most published trials in CRPS were small with a short follow-up period, although several novel interventions investigated in the last decade appeared promising.

Last search date	Studies identified in review	Bottom Line
February 2012 (from June 2000 following an earlier review)	29	The interventions this review found strong evidence of effectiveness for are outside the scope of this report. Some evidence was found for effectiveness of low-dose intravenous ketamine, and quite limited evidence for spinal cord stimulation in long-standing upper limb CRPS. Most trials were small, with a short follow-up period. The review was open to bias and results should be interpreted with caution.

Study Reference	Participants	Interventions	Comparators	Outcomes	Study Designs
Stanton (2013)	Children or adults with CRPS	Selective sympathetic blockade with local anaesthetics	Any: Placebo / no treatment or usual care / other active interventions	Pain intensity levels, the proportion who achieved moderate (30 %) or substantial (50 %) pain relief, the duration of pain relief, and adverse effects	Randomised controlled trials

Results

Twelve studies were included in the review (n = 386), all of which were found to be at high or unclear risk of bias. Three small studies compared local anaesthetic sympathetic blockade (LASB) to placebo or sham procedure. Two small studies (23 participants in intervention arms) did not demonstrate significant short-term benefit for LASB in reducing pain by 50% when compared to placebo, Risk Ratio 1.18 (95% CI: 0.76 to 1.84). Five out of 8 eight trials compared LASB to another active intervention and found no difference in pain outcomes between sympathetic block and other active treatments. In two others differences were small and/or short-lived. Five studies reported adverse effects, all with minor effects reported.

Last search date	Studies identified in review	Bottom Line
November 2012	12	This reliable review could not draw firm conclusions on the efficacy and safety of local anaesthetic sympathetic blockade in complex regional pain syndrome due to the paucity of evidence. Existing evidence suggested a lack of efficacy.

RELEVANT TRIALS PUBLISHED SUBSEQUENT TO THE SYSTEMATIC REVIEWS

We identified the following trial published subsequent to this review. See Table.

Intervention	Study
Thoracic sympathetic block	De Oliveira Rocha (2014)[12]

Study	De Oliveira Rocha (2014)[12]
Study Design	Double-blind sham-controlled RCT
Study population	37 patients with CRPS type I of the upper extremity ≥ 6 months, without pain relief (NRS >4) after 4 weeks of standardised rehabilitation and pharmacological treatment.
Patient details	17 M, 19 F, mean age 44.7, N = 36, 1 patient excluded after randomisation because of seizure)
Intervention details	17 patients received an injection of 5 ml of 0.75 % ropivacaine with 5 ml of 2 % triamcinolone in the T2 sympathetic thoracic ganglion, lateral to the T2 vertebra. Needle position was checked with fluoroscopy.
Comparator details	19 patients received an identical injection, but in the subcutaneous space at the T2 level. Again fluoroscopy was used.
Outcomes	Primary outcome was average pain score of the BPI at 1 and 12 months. Other outcomes: Other BPI scores, NPSI, MPQ, quality of life (WHOQOL-bref) and mood (HADS). Intervention check: temperature difference between hands.
Follow up duration	12 months
Results	At 1 month, BPI average pain intensity was not significantly different between groups: TSB 3.59 (sd 3.2), control 4.84 (sd 2.7), p = 0.249. At 12 months, the TSB group had lower scores: TSB 3.47 (sd 3.5) vs control 5.86 (sd 2.9), p = 0.046. Baseline values were 5.35 (sd 2.1) and 6.37 (sd 1.9), respectively, pain had decreased significantly in the TSB group (p < 0.05). The TSB group scored better on other BPI variables, MPQ and on the NPSI evoked pain subscores too. All TSB patients had had > 2 °C temperature difference after the block. There were no major adverse events, number of minor adverse events was similar between the groups. Blinding appeared to have been effective.

Risk of Bias	De Oliveira Rocha (2014)	
Randomisation	Low	Patients chose manila (quite opaque, made from manila hemp) envelope from an urn.
Allocation Concealment	Low	
Blinding of participants	Low	
Blinding of caregivers	High	Not possible
Blinding of assessors	Low	Researchers who had no role in the blocking procedure or patient screening performed all clinical assessments.
Incomplete outcome data	Low	Follow-up complete at 1 month, 7 patients (TSB 2, control 5) lost to follow-up at 12 months. ITT analysis
Selective reporting	Low	
Other Biases	Low	Seems to be a carefully conducted, well-designed study

Author(s): Jos Kleijnen
Date: 2017-04-06
Question: Should sympathetic blocks with local anesthetics be used for Complex Regional Pain Syndrome?
Settings: Treatment by anaesthetists
Bibliography: Stanton TR, Wand BM, Carr DB, Birklein F, Wasner GL, O'Connell NE. Local anaesthetic sympathetic blockade for complex regional pain syndrome. Cochrane Database of Systematic Reviews 2013, Issue 8. Art. No.: CD004598. DOI: 10.1002/14651858.CD004598.pub3, 2013.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sympathetic blocks with local anesthetics	Control	Relative (95% CI)	Absolute		
Pain relief (follow-up 1-12 months)												
12	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	-	-	-	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		

[1] Twelve studies were included in the review (n = 386), all of which were found to be at high or unclear risk of bias. Three small studies compared local anaesthetic sympathetic blockade (LASB) to placebo or sham procedure. Two small studies (23 participants in intervention arms) did not demonstrate significant short-term benefit for LASB in reducing pain by 50% when compared to placebo, Risk Ratio 1.18 (95% CI: 0.76 to 1.84). Five out of 8 eight trials compared LASB to another active intervention and found no difference in pain outcomes between sympathetic block and other active treatments. In two others differences were small and/or short-lived. Five studies reported adverse effects, all with minor effects reported.

Author(s): Jos Kleijnen
Date: 2017-04-07
Question: Should thoracic sympathetic block be used for Complex Regional Pain Syndrome?
Settings: Treatment by anaesthetists
Bibliography: de Oliveira Rocha R, Teixeira MJ, Yeng LT, Cantara MG, Faria VG, Liggieri V, et al. Thoracic sympathetic block for the treatment of complex regional pain syndrome type I: a double-blind randomized controlled study. Pain. 2014;155(11):2274-81

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Thoracic sympathetic block	Control	Relative (95% CI)	Absolute		
Average pain score (follow-up mean 12 months; assessed with: BPI)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2,3]	none	-	-	-	-	⊕⊕OO LOW	CRITICAL
								0%		-		

[1] Problems with blinding and 7 out of 36 patients lost to follow up at 12 months.
[2] Small study, 17 patients in the TSB group and 19 in the control group
[3] At 1 month, BPI average pain intensity was not significantly different between groups: TSB 3.59 (sd 3.2), control 4.84 (sd 2.7), p = 0.249. At 12 months, the TSB group had lower scores: TSB 3.47 (sd 3.5) vs control 5.86 (sd 2.9), p = 0.046. Baseline values were 5.35 (sd 2.1) and 6.37 (sd 1.9), respectively, pain had decreased significantly in the TSB group (p < 0.05). The TSB group scored better on other BPI variables, MPQ and on the NPSI evoked pain subscores too. All TSB patients had had > 2 °C temperature difference after the block. There were no major adverse events, number of minor adverse events was similar between the groups.

Author(s): Jos Kleijnen
Date: 2017-04-07
Question: Should intravenous regional blocks with guanethidine be used for Complex Regional Pain Syndrome?
Settings: Treatment by anaesthetists
Bibliography: Jadad AR, Carroll D, Glynn CJ, McQuay HJ. Intravenous regional sympathetic blockade for pain relief in reflex sympathetic dystrophy: a systematic review and a randomized, double-blind crossover study. J Pain Symptom Manage. 1995;10(1):13-20. Ramamurthy S, Hoffman J. Intravenous regional guanethidine in the treatment of reflex sympathetic dystrophy/causalgia: a randomized, double-blind study. Guanethidine Study Group. Anesth Analg. 1995;81(4):718-23. Livingstone JA, Atkins RM. Intravenous regional guanethidine blockade in the treatment of post-traumatic complex regional pain syndrome type 1 (algodystrophy) of the hand. The Journal of bone and joint surgery British volume. 2002;84(3):380-6.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intravenous regional blocks with guanethidine	Control	Relative (95% CI)	Absolute		
Pain reduction (follow-up 1-6 months)												
3	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	-	-	-	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		

[1] The recommendations in the previous guideline were based on a double-blind crossover study with saline, high-dose and low-dose guanethidine, no significant differences between groups was found. All groups reported less than 30% pain reduction; there was no evidence of a dose-response for guanethidine. The trial was stopped prematurely after serious adverse events in 2 patients with the high dose of guanethidine. A double-blind controlled multicenter RCT comparing IVRB with guanethidine or placebo in a group of 60 CRPS patients found no differences in long-term outcome. In another RCT, in a group of 57 CRPS patients, comparing IVRB with guanethidine to saline, again, no significant long-term differences were found.

Author(s): Jos Kleijnen
Date: 2017-04-07
Question: Should spinal cord stimulation be used for Complex Regional Pain Syndrome?
Settings: Treatment by anaesthetists
Bibliography: Cossins L, Okell RW, Cameron H, Simpson B, Poole HM, Goebel A. Treatment of complex regional pain syndrome in adults: a systematic review of randomized controlled trials published from June 2000 to February 2012. Eur J Pain 2013;17(2):158-73.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Spinal cord stimulation	Control	Relative (95% CI)	Absolute		
Reduction in pain intensity (follow-up 1-5 years)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	-	-	-	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		

[1] In this small study, 54 patients with CRPS were included and randomized 2:1 to receive SCS and physical therapy or a standard regimen of physical therapy alone. Thirty-six patients were assigned to and treated with a test SCS. Twenty-four of those reported a reduction in pain and in these patients a definitive system was implanted. Eighteen patients only received physical therapy. Six months posttreatment, the intention to treat (ITT) analysis showed a clear reduction in pain intensity in the group with stimulated patients despite the fact that only 24 of the 36 patients were actually treated with SCS. The positive effects on pain and global perceived effect remained in an ITT analysis 2 years after implantation.

Author(s): Jos Kleijnen
Date: 2017-04-07
Question: Should peripheral nerve stimulation be used for Complex Regional Pain Syndrome?
Settings: Treatment by anaesthetists
Bibliography: Hassenbusch SJ, Stanton-Hicks M, Schoppa D, Walsh JG, Covington EC. Long-term results of peripheral nerve stimulation for reflex sympathetic dystrophy. J Neurosurg. 1996;84(3):415-23. Buschmann D, Oppel F. [Peripheral nerve stimulation for pain relief in CRPS II and phantom-limb pain]. Schmerz. 1999;13(2):113-20.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Peripheral nerve stimulation	Control	Relative (95% CI)	Absolute		
Pain reduction (follow-up 2-4 years)												
2	observational studies[1]	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	-	-	-	⊕OOO VERY LOW	CRITICAL
								0%		-		

[1] case series
[2] In a prospective case series, peripheral nerve stimulation (PNS) with surgically placed plate type electrodes connected with an implantable pulse generator reduced allodynic and spontaneous pain in 19 (63%) out of 30 implanted patients with CRPS and symptoms in the distribution of 1 major peripheral nerve. In a retrospective study with 52 patients (48 CRPS-2 patients and 4 phantom limb patients), 47 patients were implanted after a positive trial stimulation. Of these patients, 43 (91%) had lasting excellent to good success with marked pain reduction and reduction of pain related disability.

Author(s): Jos Kleijnen
Date: 2017-04-07
Question: Should IV ketamine infusion be used for Complex Regional Pain Syndrome?
Settings: Treatment by anaesthetists
Bibliography: Cossins L, Okell RW, Cameron H, Simpson B, Poole HM, Goebel A. Treatment of complex regional pain syndrome in adults: a systematic review of randomized controlled trials published from June 2000 to February 2012. Eur J Pain 2013;17(2):158-73.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IV ketamine infusion	Control	Relative (95% CI)	Absolute		
Pain reduction (follow-up mean 3 months)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	-	-	-	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		

[1] The review found moderate evidence for the efficacy of low-dose IV ketamine infusion in longstanding CRPS (two RCTs). IV infusion of low-dose ketamine (4.5 days of continuous treatment or 10 consecutive working days of outpatient treatment) significantly reduced pain compared with placebo in one high-quality and one low-quality trial in long-standing CRPS.

17. Herpes Zoster and Post-Herpetic Neuralgia

SYSTEMATIC REVIEWS / GUIDELINES IDENTIFIED

We did not identify any reviews published between 2010 and 2015 for herpes zoster / post-herpetic neuralgia.

We identified recent guidelines of relevance[3] conducted by the International Association for the Study of Pain (IASP) Neuropathic Pain Special Interest Group (NeuPSIG). A brief outline of the research methods underpinning these guidelines and the recommendations made is given below.

NeuPSIG Guidelines[3]

Methods

Searching of the evidence was up to 2013 (exact date not specified). Systematic reviews, trials and observational studies were eligible provided five or more patients were included. Strength of evidence was summarized according to GRADE and recommendations made based on this evidence. Recommendations were not intended to be used as a basis for reimbursement decisions.

Recommendations

Indication / Intervention	Quality of evidence	Strength of recommendation	Comments
Herpes zoster Epidural or paravertebral nerve blocks (local anesthetics and steroids) for treatment of pain	Moderate	Weak	Provides relief of pain but has not been compared against less invasive treatments. The authors remark that (repeated) blocks may help prevent PHN, but do not translate this into a recommendation.
PHN: Intrathecal steroid and local anesthetic injections	Low	Inconclusive	Unreplicated positive RCT but concerns about the RCT and about safety. Recommendation: 'Any use of this treatment approach limited to formal clinical trials and not routine care'.
PHN: Sympathetic nerve block	Moderate	Against	Non-randomised studies have not shown benefit
PHN: Spinal cord stimulation	Low	Inconclusive	Weak evidence but positive case series results in refractory PHN
PHN: Pulsed radiofrequency	Low	Inconclusive	Single RCT showing efficacy up to 6 months

Other interventions were either not mentioned, or no evidence specific for herpes zoster /PHN was found.

Key to table

Moderate quality: at least one high quality RCT or two or more high quality observational studies with consistent results or reasonable extrapolation of two or more high quality RCTs

Low quality: some evidence of effect but conclusions limited by study design limitations, inconsistent results or extrapolation of questionable reliability

Weak recommendation: the balance of desirable effects vs. harmful effects seems to favor the desirable effects. Most patients would want the intervention but many would not; shared decision making that explicitly incorporates the risks and potential benefits of the procedure and the patient's preferences is recommended.

Inconclusive recommendation: there is insufficient evidence to recommend for or against the intervention.

Recommendation against using the intervention: at least fair evidence that the intervention is ineffective or that anticipated harmful effects outweigh potential for desirable effects.

RELEVANT TRIALS

We identified a number of randomised controlled trials postdating the NeuPSIG guidelines or not covered by the NeuPSIG guidelines.[3]

Intervention	**Study**
Interventional pain treatment of acute herpes zoster	Makharita (2015)
	Makharita (2012)
PHN: Intrathecal administration	Dureja (2010)
PHN: Epidural corticosteroid injections	Dureja (2010)
PHN: Transcutaneous nerve stimulation	Barbarisi (2010)

EVIDENCE FROM RANDOMISED TRIALS

Interventional pain treatment of acute herpes zoster

Study	**Makharita (2015)**
Setting	University hospital Egypt
Study Design	Double-blind placebo-controlled RCT
Study population	Patients aged > 50 years with chest wall herpes zoster eruptions for < 1 week, at least moderate (> 3 on 10-cm VAS) pain who were receiving appropriate antiviral therapy (5 dd 800 mg of acyclovir for 7 days starting < 72 hours after eruption)
Patient details	138 patients, mean age 56.5 years (sd 3.4) 47.1 % male
Intervention details	70 patients received a paravertebral block with 8 mg of dexamethasone in 10 ml of 0.25 % bupivacaine. The injections was given by a combination of the 'walking off the transverse process' and 'loss of resistance techniques', under fluoroscopic control. Needle location and paravertebral spread were confirmed with contrast injection. All patients

	received pregabalin 150 mg twice daily, as long as pain > 3 (tapered off thereafter).
Comparator details	68 patients received a sham block with 10 ml of saline, identical procedure, with pregabalin.
Outcomes	Pain (10 cm VAS). Results not reported, though. Time to complete resolution of pain. Prevalence of PHN (= pain > 0 (?)) at 3 and 6 months, time to healing of eruption.
Follow up duration	24 weeks
Results	Intervention patients had shorter duration of pain: 24.6 (sd 23.7) days vs 35.9 (sd 29.1) days, p 0.013. Prevalence of PHN tended to be lower at 3 months (11.4 % vs 22.1 %, p 0.094), was lower at 6 months: 5.7 % vs 16.2 %, p 0.048. The eruptions healed faster too: 23.3 (sd 7.0) days vs 31.2 (sd 6.7) days, p < 0.001.

Study	**Makharita (2012)**
Setting	University hospital Egypt
Study Design	Double-blind placebo-controlled RCT
Study population	Patients aged > 50 years with herpes zoster of the face for < 2 weeks, who were receiving or had received appropriate antiviral therapy.
Patient details	61 patients, mean age 60.1 years (sd 2.7) years (64 randomised)
Intervention details	31 patients received 2 stellate ganglion blocks with 6 ml of 0.125 % bupivacaine with 8 mg of dexamethasone (total volume 8 ml) a week apart. The needle was advanced to the junction of the C6 transverse process with the vertebral body under fluoroscopic control. Correct placement was confirmed with contrast injection. All patients received pregabalin 150 mg twice daily, as long as pain > 3 (tapered off thereafter).
Comparator details	30 patients received sham blocks with 8 ml of saline, identical procedure, with pregabalin.
Outcomes	Pain (10 cm VAS). Time to complete resolution of pain. Prevalence of PHN (= pain > 0 (?)) at 3 and 6 months, patient satisfaction.
Follow up duration	6 months
Results	Intervention patients had shorter duration of pain: vs 43.6 (sd 28.7) days vs 23.8 (sd 18) days, p 0.002. Prevalence of PHN was lower at 3 months (6.5 % vs 26.7 %, p 0.043) and 6 months: 0 % vs 13.3 %, p 0.035. Pain scores were lower at all follow-up points (1 week to 6 months). Patient satisfaction was higher too at both 3 and 6 months.

Cochrane Risk of Bias

	Makharita (2015)		**Makharita (2012)**	
Randomisation	low	Computer-generated	low	Computer-generated
Allocation Concealment	low		low	
Blinding of participants	low	Sham block	unclear	Patients might be able to sense left/right differences in vasodilatation/warmth.
Blinding of caregivers	low		low	
Blinding of assessors	low		low	
Incomplete outcome data	low		low	
Selective reporting	unclear	Pain levels not reported	low	
Other Biases	low		low	

Post-herpetic Neuralgia

Study	**Dureja (2010)**
Setting	2 pain centers in India
Study Design	Double-blind RCT
Study population	Patients aged 35-70 with pain and allodynia due to herpes zoster of 3-6 months' duration involving only the lumbosacral dermatomes
Patient details	145 patients (randomized: 150), mean age 57.4 years (sd 8.0), 54.5% male
Int1 (methylprednisolone) details	49 Patients: Epidural injection of 60 mg methylprednisolone suspended in 10 ml of saline. Injection in the L1-L2 or L2-L3 intervertebral space by loss of resistance technique under fluoroscopic control, confirmation of correct needle placement with non-ionized contrast. Placebo intrathecal injection (2 ml of preservative-free saline, see below).
Int2 (midazolam) details	48 Patients: Intrathecal injection of 2 ml (2 mg) midazolam, preservative-free in the intrathecal space. Injection one segment lower than the epidural injection (L2-L3 or L3-L4), intrathecal placement confirmed by free flow of cerebrospinal fluid through the needle. Placebo epidural injection (10 ml of saline).
Int3 (combination) details	48 Patients: Both epidural injection of 60 mg methylprednisolone and 2 mg midazolam.
Outcomes	Pain and allodynia (10-cm VAS), area of allodynia, use of pain medication (paracetamol or tramadol) (up to 4 weeks)
Follow up duration	12 weeks
Results	Patients in the combination group had significantly lower pain and allodynia scores than the patients in either the midazolam or de methylprednisolone groups at 4, 8 and 12 weeks. At all time points, more patients in the combination group had effective (> 50%) pain relief than those in the two other groups. At 12 weeks, 19 % of the combination group, 3 % of the midazolam group and 5 % of the

	prednisolone group had effective pain relief. At 4 weeks, the combination group used less pain medication too.

Study	**Barbarisi (2010)**
Setting	University hospital, Italy
Study Design	Placebo-controlled double-blind RCT
Study population	30 patients aged 50-80 years with postherpetic spontaneous pain and allodynia > 3 months after disappearance of the rash. Primary location cervical, thoracic lumbar or sacral, pain > 60 mm (100 mm VAS), SF-MPQ > 20
Patient details	30 patients, mean age 64.5 years (sd 8.4) 50 % male
Intervention details	16 patients received TENS, 30 minutes per day for 4 weeks. 8 Pairs of single-use 3-cm electrodes applied around the neuralgic pain area. Stimulation intensity was adjusted 3 to 5 times during the session to produce a sustained paresthetic sensation for the whole session. Patients also received Pregabalin, 150 mg per day, up titrated (before randomization) to 300 or 600 mg if necessary to obtain VAS < 60 mm.
Comparator details	14 Patients received placebo-TENS, same protocol but 0 V intensity. They also received Pregabalin, see above.
Outcomes	Primary outcome: 100 mm VAS (pain previous week). Secondary: other SF-MPQ sections (VAS is second section), sleep interference.
Follow up duration	4 weeks
Results	The titration phase resulted in 17 patients taking 300 mg pregabalin and 13 taking 600 mg (150 mg: 0). Results were presented separately for the 300 mg and 600 mg groups. In the 300 mg group, TENS resulted in 13.88 mm lower VAS score at 4 weeks than placebo TENS (95 % CI: -15.22 mm to -12.55). In the 600 mg group, the difference was 9.09 mm (95 % CI -10.61 to -7.57). Patients with TENS had less interference with sleep and higher quality of life too.

Cochrane Risk of Bias

	Dureja (2010)		**Barbarisi (2010)**	
Randomization	low		low	Computer-generated
Allocation Concealment	unclear	No information	unclear	No information
Blinding of participants	low		high	TENS patients were told that they should feel electrical stimulation, not pain. Placebo patients were told that they should not feel anything.
Blinding of caregivers	high	No mention that blinded	High	Not blinded
Blinding of assessors	low		low	
Incomplete outcome data	low		low	
Selective reporting	low		low	

Other Biases	low		low	

OBSERVATIONAL STUDIES

We searched for observational studies for the two interventions not covered in the NeuPSIG guidelines and where we had identified no RCTs (conventional radiofrequency and drezotomy). We identified the following relevant studies:

Intervention	**Study**
Conventional radiofrequency	No studies
Drezotomy	Chivukula (2015)[8]

EVIDENCE FROM OBSERVATIONAL STUDIES

Drezotomy

Study	**Chivukula (2015)**
Setting	University hospital USA
Study Design	Retrospective case series
Study population	All patients who had nucleus caudatus or spinal dorsal root entry zone lesioning and by a single surgeon between Jan 1991 and 2014
Patient details	Of the 83 patients identified, 22 had postherpetic neuralgia: 3 in the head/face, 5 patients cervical and 14 thoracic level.
Intervention details	Head/face (nucleus caudatus): a C1 hemilaminectomy was performed with suboccipital craniectomy. A single line of caudalis DREZ lesions was made at 75 °C for 20 seconds at 1-mm intervals. Lesions were made with a specially designed electrode consisting of 2 dedicated electrodes at right angles to each other: 1.2 mm tip for lesions below the dorsal C1 sensory rootles, 20-mm above. Spinal: hemi-laminectomy, identification of the intact dorsal nerve roots above and below the region of avulsion. DREZ radiofrequency lesions were made at 75 °C for 15 seconds at 1-mm intervals along the intermediolateral sulcus in a caudal to rostral fashion. A Nashold thermocouple DREZ electrode (NTCD-TC) was used, with a 2-mm active tip and 0.25 mm diameter. The electrode was penetrated sharply into the DREZ at a depth of 2.0 mm and held at a 25 ° angle to the dorsal nerve rootlet.
Comparator details	n.a.
Outcomes	Pain reduction (NRS) and satisfaction with the operation, collected by telephone interview at end of follow-up (so pre-operative pain levels had to be recollected years later).
Follow up duration	Mean 11.9 years (range 1.6-20.6)
Results	Of the 22 patients with PHN, the authors stated that “3 of 5 patients with cervical PHN and 11 of 14 patients thoracic PHN reported excellent pain relief (although less than complete) that lasted an average of 4.2 years (range, 9 months to 6.2 years) before relapse. However, 3 patients (2 with thoracic PHN and 1 with cervical PHN) developed postoperative

	paresis in the ipsilateral limbs along the supply of the involved nerved roots." Pain relief lasted < 1 year in 2 of the 22 patients, 1 to 5 years in 13 patients and > 5 years in 7 patients. Seven patients were satisfied with the procedures, 15 were very or extremely satisfied. Quality of life had improved in nine patients.

Study	**Liu (2015)**
Setting	University hospital, China
Study Design	Retrospective case series
Study population	Patients with refractory postherpetic neuralgia
Patient details	6 patients (4 men, 2 women), mean age 64.5 years (range 54- 75) with postherpetic pain between T6 and T12 level, symptoms for 12 to 60 months. All patients had previously been treated with neural blocks as well as medications, but without success.
Intervention details	Temporary spinal cord stimulation for 5 to 7 days was used to define where the drezotomy should be done. For the SCS under local anesthesia a quadripolar lead was inserted in the epidural space. The position of the electrode and the stimulation parameters were adjusted until the patient felt satisfactory pain relief. Then the lead was secured surgically. If the patient had satisfactory pain relief with SCS, DREZotomy was performed under general anaesthesia via a semi-laminectomy. The location of the electrode was used to confirm the target level. Dotted microcoagulations at low intensity (about 10 mA) were performed through a 3-mm deep incision with an angle of 45 ° ventromedially in the dorsolateral sulcus.
Comparator details	None
Outcomes	VAS 0 to 10 pain (median previous week)
Follow up duration	4 to 24 months
Results	During SCS, 4 patients had satisfactory pain relief, in two patients the affected area of the spinal cord was longer than the electrode could cover. In one the pain could nevertheless be controlled by adjustment of the stimulation parameters. The other patient still felt pain and declined drezotomy. So 5 patients had drezotomy: mean pain decreased from 8.4 (range 7 to 10) at baseline to 2.6 (range 1 to 5) at last follow-up.

Author(s): Jos Kleijnen
Date: 2017-05-04
Question: Should paravertebral injections be used for acute herpes zoster?
Settings: Treatment by anaesthetists
Bibliography: Dworkin RH, O'Connor AB, Kent J, Mackey SC, Raja SN, Stacey BR, et al. Interventional management of neuropathic pain: NeuPSIG recommendations. Pain 2013;154(11):2249-61. Makharita MY, Amr YM, El-Bayoumy Y. Single Paravertebral Injection for Acute Thoracic Herpes Zoster: A Randomized Controlled Trial. Pain Pract 2015;15(3):229-235. Makharita MY, Amr YM, El-Bayoumy Y. Effect of early stellate ganglion blockade for facial pain from acute herpes zoster and incidence of postherpetic neuralgia. Pain Physician 2012;15(6):467-74.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Paravertebral injections	Control	Relative (95% CI)	Absolute		
Pain												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	-	-	-	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		

Author(s): Jos Kleijnen
Date: 2017-05-04
Question: Should epidural injection of local anesthetics and/or glucocorticoids be used for acute herpes zoster?
Settings: Treatment by anaesthetists
Bibliography: van Wijck AJ, Opstelten W, Moons KG, van Essen GA, Stolker RJ, Kalkman CJ, et al. The PINE study of epidural steroids and local anaesthetics to prevent postherpetic neuralgia: a randomised controlled trial. Lancet. 2006;367(9506):219-24. Pasqualucci A, Pasqualucci V, Galla F, De Angelis V, Marzocchi V, Colussi R, et al. Prevention of post-herpetic neuralgia: acyclovir and prednisolone versus epidural local anesthetic and methylprednisolone. Acta Anaesthesiol Scand. 2000;44(8):910-8.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Epidural injection of local anesthetics and/or glucocorticoids**	**Control**	**Relative (95% CI)**	**Absolute**		
Pain												
2	randomized trials	no serious risk of bias	serious[1]	no serious indirectness	no serious imprecision	none	-	-	-	-	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		

[1] Different comparison in only 2 randomized trials available

Author(s): Jos Kleijnen
Date: 2017-05-04
Question: Should sympathetic nerve block be used for acute herpes zoster?
Settings: Treatment by anaesthetists
Bibliography: van Zundert J, Patijn J, Hartrick CT, Lataster A, Huygen FJPM, Mekhail N, et al., eds. Evidence-based interventional pain medicine: according to clinical diagnoses Chichester: Wiley-Blackwell, 2012. Dworkin RH, O'Connor AB, Kent J, Mackey SC, Raja SN, Stacey BR, et al. Interventional management of neuropathic pain: NeuPSIG recommendations. Pain 2013;154(11):2249-61.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sympathetic nerve block	Control	Relative (95% CI)	Absolute		
Pain												
1	randomized trials	serious[1]	no serious inconsistency	no serious indirectness	serious[1]	none	-	-	-	-	⊕⊕OO LOW	CRITICAL
								0%		-		

[1] Small randomized trial and observational studies

Author(s): Jos Kleijnen
Date: 2017-05-04
Question: Should intrathecal corticosteroid injections be used for post herpetic neuralgia?
Settings: Treatment by anaesthetists
Bibliography: Dureja GP, Usmani H, Khan M, Tahseen M, Jamal A. Efficacy of intrathecal midazolam with or without epidural methylprednisolone for management of post-herpetic neuralgia involving lumbosacral dermatomes. Pain Physician 2010;13(3):213-221. Rijsdijk M, van Wijck AJ, Meulenhoff PC, Kavelaars A, van der Tweel I, Kalkman CJ. No beneficial effect of intrathecal methylprednisolone acetate in postherpetic neuralgia patients. Eur J Pain 2013;17(5):714-23. Dworkin RH, O'Connor AB, Kent J, Mackey SC, Raja SN, Stacey BR, et al. Interventional management of neuropathic pain: NeuPSIG recommendations. Pain 2013;154(11):2249-61.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intrathecal corticosteroid injections	Control	Relative (95% CI)	Absolute		
pain and safety												
4	randomised trials	serious[1]	serious[2]	no serious indirectness	no serious imprecision	none	-	-	-	-	⊕⊕OO LOW	CRITICAL
								0%		-		

[1] Trials have problems with adminstration including one trial stopped early; safety concerns exist
[2] Trials have conflicting conclusions

Author(s): Jos Kleijnen
Date: 2017-05-04
Question: Should epidural corticosteroid injections vs combined therapy with midazolam be used for post herpetic neuralgia?
Settings: Treatment by anaesthetists
Bibliography: Dureja GP, Usmani H, Khan M, Tahseen M, Jamal A. Efficacy of intrathecal midazolam with or without epidural methylprednisolone for management of post-herpetic neuralgia involving lumbosacral dermatomes. Pain Physician 2010;13(3):213-221.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Epidural corticosteroid injections**	**Combined therapy with midazolam**	**Relative (95% CI)**	**Absolute**		
Pain												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	-	-	-	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		

[1] No information about allocation concealment or caregivers blinding

Author(s): Jos Kleijnen
Date: 2017-05-04
Question: Should sympathetic nerve block be used for post herpetic neuralgia?
Settings: Treatment by anaesthetists
Bibliography: Dworkin RH, O'Connor AB, Kent J, Mackey SC, Raja SN, Stacey BR, et al. Interventional management of neuropathic pain: NeuPSIG recommendations. Pain 2013;154(11):2249-61.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Sympathetic nerve block**	**Control**	**Relative (95% CI)**	**Absolute**		
Pain												
2	observational studies	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	-	-	-	⊕OOO VERY LOW	CRITICAL
								0%		-		

[1] Unclear number of observational studies reporting no improvement

Author(s): Jos Kleijnen
Date: 2017-05-04
Question: Should spinal cord stimulation be used for post herpetic neuralgia?
Settings: Treatment by anaesthetists
Bibliography: Dworkin RH, O'Connor AB, Kent J, Mackey SC, Raja SN, Stacey BR, et al. Interventional management of neuropathic pain: NeuPSIG recommendations. Pain 2013;154(11):2249-61.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Spinal cord stimulation**	**Control**	**Relative (95% CI)**	**Absolute**		
Pain												
1	observational studies[1]	serious	no serious inconsistency	no serious indirectness	serious[1]	none	-	-	-	-	⊕OOO VERY LOW	CRITICAL
								0%		-		

[1] case series with 28 patients

Author(s): Jos Kleijnen
Date: 2017-05-04
Question: Should pulsed radiofrequency be used for post herpetic neuralgia?
Settings: Treatment by anaesthetists
Bibliography: Ke, M, Yinghui, F, Yi, J, Xuehua, H, Xiaoming, L, Zhijun, C, Chao, H, Yingwei, W. Efficacy of pulsed radiofrequency in the treatment of thoracic postherpetic neuralgia from the angulus costae: A randomized, double-blinded, controlled trial. Pain Physician 2013;16(1):15-25

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Pulsed radiofrequency**	**Control**	**Relative (95% CI)**	**Absolute**		
Pain and quality of life (follow-up mean 6 months; assessed with: VAS and SF-36)												
1	randomized trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	-	-	-	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		

[1] Only one single-center randomized trial from China found; 48 patients per group.

Author(s): Jos Kleijnen
Date: 2017-05-04
Question: Should transcutaneous nerve stimulation be used for post herpetic neuralgia?
Settings: Treatment by anesthetists
Bibliography: Barbarisi M, Pace MC, Passavanti MB, Maisto M, Mazzariello L, Pota V, et al. Pregabalin and transcutaneous electrical nerve stimulation for postherpetic neuralgia treatment. Clin J Pain 2010;26(7):567-72.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Transcutaneous nerve stimulation	Control	Relative (95% CI)	Absolute		
Pain (follow-up mean 4 weeks; assessed with: VAS)												
1	randomized trials	serious[1]	no serious inconsistency	no serious indirectness	serious[1]	none	-	-	-	-	⊕⊕OO LOW	CRITICAL
								0%		-		

[1] Small trial with 16 patients in the TENS group. No blinding.

Author(s): Jos Kleijnen
Date: 2017-05-04
Question: Should drezectomy be used for post herpetic neuralgia?
Settings: Treatment by anaesthetists
Bibliography: Chivukula S, Tempel ZJ, Chen CJ, Shin SS, Gande AV, Moossy JJ. Spinal and nucleus caudalis dorsal root entry zone lesioning for chronic pain: efficacy and outcomes. World Neurosurg 2015;84(2):494-504. Liu MX, Zhong J, Zhu J, Xia L, Dou NN. Treatment of postherpetic neuralgia using drezotomy guided by spinal cord stimulation. Stereotact Funct Neurosurg 2015;93(3):178-181.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Drezectomy	Control	Relative (95% CI)	Absolute		
Pain												
2	observational studies[1]	serious[1]	no serious inconsistency	no serious indirectness	serious[1]	none	-	-	-	-	⊕OOO VERY LOW	CRITICAL
								0%		-		

[1] small case series with 22 and 5 patients

18. Painful Diabetic Polyneuropathy

SYSTEMATIC REVIEWS IDENTIFIED

We identified one review published between 2010 and 2015 of spinal cord stimulation for painful diabetic polyneuropathy. See table.

Intervention	Relevant Review (s)	Search end date	Studies included	Meta-analysis
Spinal cord stimulation	Pluijms (2011)	March 2010	4 observational studies	No

ASSESSMENT OF THE REVIEW EVIDENCE

Spinal Cord stimulation

Study Reference	Participants	Interventions	Comparators	Outcomes	Study Designs
Pluijms (2011)	Adult patients (≥18 years) with chronic pain(duration ≥6 months)in the lower limbs due to painful diabetic polyneuropathy	Spinal cord stimulation	NR	Primary: Pain measured by direct statement, visual analogue scale/numeric rating scale), % of patients achieving > 50% relevant pain relief Secondary: Indirect measures of pain relief, adverse events, health related QoL	Case series Cohort studies

Results
Pain relief > 50% was observed in 63 % of patients across 4 observational studies (25 patients) at the end of one year of spinal cord stimulation. No major adverse events were reported.

Last Search date	Studies identified in review	Bottom Line
March 2010	4	This review demonstrated the very limited evidence available to suggest a pain-relieving effect of spinal cord stimulation in painful diabetic polyneuropathy. Future randomized controlled studies are needed before it can be considered as an integrated treatment option for this condition.

RELEVANT TRIALS PUBLISHED SUBSEQUENT TO THE SYSTEMATIC REVIEW

We identified two trials published subsequent to this review. See Table.

Intervention	Study
Spinal cord stimulation	De Vos (2014)
	Slangen (2014)

Study Details

Study	De Vos (2014)	Slangen (2014)
Country	The Netherlands, Denmark, Belgium and Germany (7 centres)	The Netherlands (2 centres)
Study Funder	St Jude Medical	Medtronic
Study Design	RCT	RCT
Recruitment dates	Nov 2008 to Oct 2012	1 Feb 2010 to 28 Feb 2013
Patient inclusion criteria	> 18 years of age, refractory diabetic pain in lower extremities for > 1 year (at least 50 on VAS),	Aged 18 to 80 with PDPN in lower limbs, insufficient pain relief and / or unacceptable side effects with drug treatment, pain > 12 months, mean pain intensity ≥ 5 on NRS
Patient exclusion criteria	Pain due to atherosclerotic lesions, infection, neuropathic pain in upper extremities, anticoagulant medication or known coagulant irregularities, psychiatric problems requiring treatment or addiction to drugs / alcohol or unable to participate	Neuropathic pain worse in upper limbs, recent neuromodulation therapy, drug or alcohol abuse, lack of patient cooperation, blood clotting disorder, immune deficiency, peripheral vascular disease with no palpable foot pulses at both feet, active foot ulceration, life expectancy < 1 year, pacemaker, infection or skin disorder at incision site, psychiatric problems, pregnancy, severe cardiac or pulmonary failure, unstable blood glucose control and use of oral anticoagulants that could not be stopped before procedure
Mean age (SD)	Int: 58 (11), Control: 61 (12)	Int: 57.1 (12.4), Control: 56.5 (8.0)
Total no (% male)	60 (63%)	36 (67%)
Diabetes type	Type I: 15 (25%), Type II: 45 (75%)	Type I: 4 (11%), Type II: 32 (88%)
Mean (SD) pain at baseline	Int: 73 (16), Control: 67 (18) on VAS 0 to 100	NR
Mean (SD) duration of pain	7 (6) years in both groups	Int: 6 (5.1), Control: 4.9 (3.6) years

Treatment and Outcome Details

Study	De Vos (2014)	Slangen (2014)
No in intervention	40 Spinal Cord Stimulation + Best Conventional Practice	22 Spinal cord Stimulation + Best Medical Treatment
No in control	20 Best conventional Practice only	14 Best Medical treatment only
Length of trial stimulation	7 days maximum	2 weeks
Treatment details	Implantation of SCS system according to each pain clinic's practice. Antibiotic prophylaxis followed by trial stimulation period max 7 days. If successful, pulse generator implanted subcutaneously (EonC, Eon or Eon Mini, St Jude Medical).	Implantation of SCS lead performed using local anesthesia and antibiotic prophylaxis. Patients admitted to hospital for 24 hours followed by a 2 week trial. If pain intensity for last 4 days of the trial was ≥ 50% lower than baseline or if ≥ 6 on Patient Global Impression of Change (PGIC) scale for pain and sleep the stimulator was implanted (Synergy Versitrel or PrimeAdvanced, Medtronic).
Conservative treatments allowed	Yes, at discretion of treating physician and these were registered	Yes
Primary Efficacy outcome	Percentage of patients with >50% pain reduction at 6 months. Assessed using VAS 0 to 100 scale	Treatment success – defined as ≥ 50% pain relief in pain intensity on NRS during day or night or a score of ≥ 6 in PGIC.
Safety assessed?	Yes. Treatment-emergent adverse events, device complications and early withdrawal from trial reported	Yes, Complications and adverse events reported
Length of follow up	6 months	6 months

Results of trials

De Vos (2014)[4]	Slangen (2014)
37 of 40 patients had a successful trial stimulation (93%). 25 (60%) patients in the intervention group had > 50% pain reduction at 6 months compared to 1 (5%) patient in the control group. Secondary outcomes were also generally more favorable in the intervention group. Adverse events unrelated to the procedure occurred in both groups at similar rates: SCS - 2 infections causing unstable blood glucose levels, 1 femur fracture and 1 cardiac arrest, Control – 2 infections, 1 carotid artery stenosis, 1 MI, 1 AF episode and 1 coronary bypass surgery. All were treated and improved or resolved during study period. Adverse events related to implantation were usually resolved by device repositioning: 2 Pain due to pulse generator, 1	Trial stimulation was successful in 17 of 22 SCS patients (77%). Treatment success was noted in 13 of 22 SCS patients (59%) and 1 of 14 BMT patients (7%), p < 0.009. Nine patients (41%) reported ≥ 50% pain relief during daytime compared to 0 in the BMT group (p < 0.003). Eight SCS patients (36%) showed ≥ 50% pain relief at night compared to 7% in the BMT group. Secondary outcomes generally supported these findings but quality of life was not significantly different between groups.

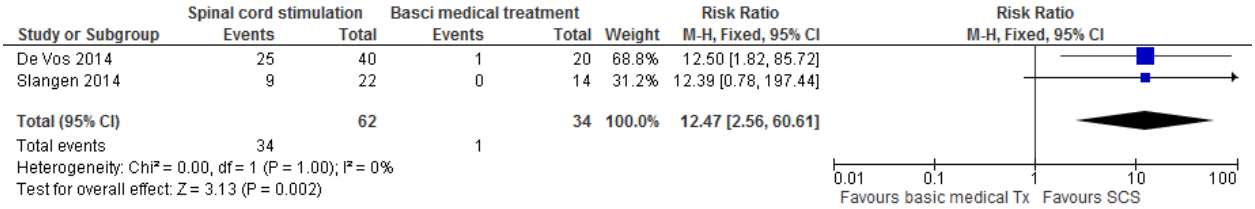
Electrode lead migration, 2 needed 2nd electrode lead directly placed, 1 infection, 1 prolonged hospitalization due to erroneous inclusion of patient with coagulopathy	Serious adverse events were noted in 2 patients. One SCS patient died of a subdural hematoma subsequent to implantation of the lead for test stimulation. A further patient contracted an infection of the SCS system 6 weeks after implantation with SCS which was subsequently removed. Patient did not recover completely and developed an autonomic neuropathy. SCS was not re-implanted.

Cochrane Risk of Bias

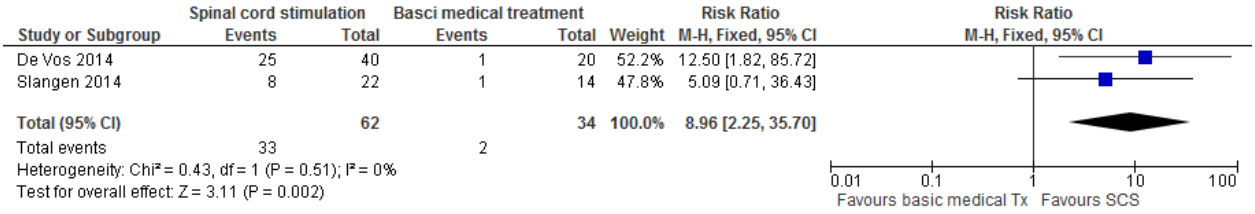
	De Vos (2014)		**Slangen (2014)**	
Randomization	Low	Performed by third party	Low	Independently managed
Allocation Concealment	Low	Performed by third party	Low	Independently managed
Blinding of participants	High	Not possible	High	Not possible
Blinding of caregivers	High	Not possible	High	Not possible
Blinding of assessors	Low	Assessed by third party	Unclear	Assessed by caregivers?
Incomplete outcome data	Low	ITT analysis	Low	ITT analysis (dropouts classified as treatment failures)
Selective reporting	Low	All outcomes reported	Low	All outcomes reported
Other Biases	Low	None detected	Low	None detected

Meta-analysis

The following fixed effect meta-analysis shows the pooled effect for the outcome of >50% pain relief using daytime data from Slangen.



The following meta-analysis shows a pooled effect for the outcome of >50% pain relief using night time data from Slangen.



Both analyses favour Spinal Cord Stimulation for pain relief. However the pooled results in both cases should be treated with some caution; pain was measured on different scales.

Author(s): Jos Kleijnen
Date: 2016-11-14
Question: Should spinal cord stimulation be used for painful diabetic ploy neuropathy?
Settings: Treatment by anesthetists
Bibliography: Pluijms WA, Slangen R, Joosten EA, Kessels AG, Merkies ISJ, Schaper NC, et al. Electrical spinal cord stimulation in painful diabetic polyneuropathy, a systematic review on treatment efficacy and safety. Eur J Pain 2011;15(8):783-8. de Vos CC, Meier K, Zaalberg PB, Nijhuis HJ, Duyvendak W, Vesper J, et al. Spinal cord stimulation in patients with painful diabetic neuropathy: a multicentre randomized clinical trial. Pain 2014;155(11):2426-31 Slangen R, Schaper NC, Faber CG, Joosten EA, Dirksen CD, Van Dongen RT, et al. Spinal cord stimulation and pain relief in painful diabetic peripheral neuropathy: a prospective two-center randomized controlled trial. Diabetes Care 2014;37(11):3016-3024

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Spinal cord stimulation	Control	Relative (95% CI)	Absolute		
Pain relief >= 50% at 6 months (follow-up mean 6 months; assessed with: VAS/NRS)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	strong association[3]	34/62 (54.8%)	1/34 (2.9%)	RR 12.47 (2.56 to 60.61)	337 more per 1000 (from 46 more to 1000 more)	⊕⊕⊕O MODERATE	CRITICAL
								2.9%		333 more per 1000 (from 45 more to 1000 more)		

[1] Blinding not possible
[2] Imprecision due to small numbers of patients
[3] Large effect RR 12.47

19. Carpal Tunnel Syndrome

SYSTEMATIC REVIEWS IDENTIFIED

We identified the most up to date reviews published between 2010 and 2015 of local injections with corticosteroids or pulsed RF treatment for carpal tunnel syndrome..

Intervention	Relevant Review (s)	Search end date	Studies included	Meta-analysis
Local injections with corticosteroids	Huisstede (2010)	Jan 2010	15 RCTs	N
Pulsed RF treatment of the median nerve	No reviews identified			

No reviews were identified for pulsed radiofrequency of the median nerve so we searched for RCTs published since the previous guidance.[1]

ASSESSMENT OF THE REVIEW EVIDENCE

Local injection of corticosteroids

Study Reference	Participants	Interventions	Comparators	Outcomes	Study Designs
Huistede (2010)	Patients with Carpal Tunnel Syndrome not caused by an acute trauma or any systemic disease	Any nonsurgical intervention	Not pre-specified. Review included both placebo and active treatment comparators.	Pain, function or recovery	Systematic reviews and randomised controlled trials

Results (Corticosteroid injection only)

A systematic review of 12 studies was included and the authors identified three further RCTs investigating corticosteroid injections.

Corticosteroid injection versus placebo:

Significant clinical improvement was found in one RCT (n=60) in patients given local corticosteroid (40mg methylprednisolone) compared with placebo injection one month after injection. (RR=3.83; 95%CI, 1.82 to 8.05). When 1.5 mg betamethasone was compared with placebo (n=81) significant clinical improvement was found two weeks after injection. (RR=2.04; 95%CI, 1.26 to 3.31).

Local versus systemic Corticosteroid injection

Better rate of improvement was seen in one trial (n = 37) with a local corticosteroid injection (betamethasone 1.5 mg) than with a systemic corticosteroid injection (betamethasone 1.5 mg) (RR=3.17; 95%CI, 1.02 to 9.87) at one month.

Corticosteroid injection versus oral steroid

One high quality trial (n=60) showed significant improvement on the global symptom score when corticosteroid injections (15mg methylprednisolone) were compared with oral steroids (25mg methylprednisolone). (WMD=-7.16, 95%CI, -11.46 to -2.86 at 8 weeks; and WMD =-7.10; 95%CI, -11.68 to -2.52 at 12 weeks). One trial found no difference between injection and oral steroids at 80 weeks of follow up.

Corticosteroid Injection Versus Anti-inflammatory Medication Plus Splinting
No significant differences in pain (VAS) at 2 or 8 week follow up and no significant improvement in symptoms (one high quality trial, n = 23)

Corticosteroid Injection Versus Helium-Neon Laser Treatment

In a low-quality study (n = 40), at 20 days of follow-up, significant differences were found in favour of corticosteroid injections with 20mg methylprednisolone compared with helium-neon laser on symptom improvement (RR = 1.89; 95% CI, 1.12 to 3.17). However, significant effects were not reported at 6 months.

Last search date	**Number of studies**	**Bottom line**
January 2010	53 (of which 15 relevant)	The authors stated that strong and moderate evidence for effectiveness was found for corticosteroids (oral or injected), and that a corticosteroid injection seems to be the most effective. However, the included studies that presented long-term results of steroids compared with other interventions found that the positive results for the effectiveness of steroids were not maintained in the long term. This review was at low risk of bias so conclusions are likely to be reliable.

RELEVANT RANDOMISED CONTROLLED TRIALS

In addition to the review identified, we located the following randomised controlled trials. See Table.

Intervention	**Study**
Local injection of corticosteroids	Ly-Pen (2012)
	Atroshi (2013), (Flondell (2010) *
	Dewi (2009)
	Gurcay (2009)
	Ismatullah (2013)
	Karadas (2012)
	Peters-Veluthamaningal (2010)

	Seok (2013)
	Soltani (2014)
Pulsed RF of the median nerve	Chen (2015)
	Ozyuvaci (2012) **

*Protocol for trial

**conference abstract only

EVIDENCE FROM RANDOMISED TRIALS

Local injection of corticosteroids

Steroids versus placebo

Study	**Atroshi (2013)**	**Karadas (2012)**	**Peters-Veluthamaningal (2010)**
Country	Sweden	Turkey	The Netherlands
Study Design	RCT	RCT	RCT
Study population	111 patients aged 18 to 70 years with primary idiopathic CTS. No thenar atrophy or sensory loss. No previous steroid injections but wrist splinting had failed.	57 patients (90 median nerves) > 18 with CTS symptoms < one year, both hands included in study where necessary. Patients without, and patients with serious electromyographic abnormalities were excluded.	69 patients presenting to GPs with symptoms of CTS. Prior treatment with steroid in past 6 months not allowed.
Patient details	30M, 81F, Mean age 47 (SD 11)	7M, 50F, Mean age 47	16M, 53F, Mean age 57
Intervention 1	37 patients received a single injection of 80mg methylprednisone	20 patients (30 median nerves) received 40 mg triamcinolone acetonide. All groups had one injection only.	36 patients received one or two intracarpal injections of 1 ml triamcinolonacetonide 10 mg/ml (11 had one injection and 24 had two)
Intervention 2	37 patients received a single injection of 40mg methylprednisone	18 patients (30 median nerves) received 4 ml 1% procaine HCl	N/A
Control	37 patients received a single injection of placebo.	19 patients (30 median nerves) received placebo (saline)	33 patients received one or two placebo injections (1 ml NaCl 0.9%)
Outcomes	Primary outcomes: change in CTS symptom severity scores at 10 weeks and rate of surgery at 1 year. Adverse events.	Nerve conduction measures, BCTQ symptom severity and functional disability scales and VAS (pain)	Immediate treatment response (4-point scale, physician-patient consensus), subjective improvement, Symptom Severity Scale (SSS) and

			Functional Status Scale (FSS) of the BCTQ, proportion of participants with recurrences.
Follow up duration	One year	Six months	2 weeks (RCT) or 4 weeks (if two injections). One year follow-up for steroid responders (direct or after crossing over at 4 weeks) only.
Brief results	Improvement in CTS symptom severity scores at 10 weeks was greater in patients who received methylprednisolone rather than placebo (difference in change from baseline, 80mg -0.64 (95% CI: -1.06 to -0.21), 40mg -0.88 (95%CI: -1.30 to -0.46)) but there were no significant differences at 1 year. The 1-year rates of surgery were 73%, 81%, and 92% in the 80-mg methylprednisolone, 40-mg methylprednisolone, and placebo groups, respectively. Compared with patients who received placebo, those who received 80 mg of methylprednisolone were less likely to have surgery (odds ratio, 0.24 (95%CI, 0.06 to 0.95). A difference between 40 mg and placebo was not found (OR 0.38 (0.09 to 1.59))	The steroid group had lower VAS pain scores than the placebo group at 6 months: 4.76 (SD 1.04) vs. 6.08 (SD 0.65), $p < 0.001$. Differences in BCTQ scales were less clear, in electrophysiologic outcomes the steroid group was generally better again. No differences were found between the steroid and procaine groups. No adverse events were observed.	Intervention patients had better immediate treatment response than control patients: 17/35 complete or satisfactory partial response vs. 5/31, $p = 0.013$. They had higher subjective improvement and improved more on BCTQ scales too. 49% Of TCA-responders (17/35) had recurrences during follow-up.

Study	Randomization	Allocation Concealment	Blinding of participants	Blinding of caregivers	Blinding of assessors	Incomplete outcome data	Selective reporting	Other Biases
Atroshi (2013)	Low	Low	Low	Low	Low	Low	Low	Low
Karadas (2012)	Unclear	Unclear	Low	High	High	Unclear	Low	Low
Peters-Veluthamaningal (2010)	Low	Low	Low	High	Low	Low	Low	Low*

*but for short-term outcomes only: other treatments offered after four weeks.

Steroids versus extracorporeal shock wave therapy

Study	Seok (2013)
Country	Korea
Study Design	RCT
Study population	36 patients ≥ 19 years with mild to moderately severe CTS, confirmed by electrophysiological studies
Patient details	11M, 25F. Mean age 51.8 (19.1), 3 ESWT and 2 steroid patients dropped out during follow-up: results for 31 patients.
Intervention 1	15 patients: one session of ESWT that comprised 1000 shocks at a frequency of 360 shocks/minute. The energy level was set at the maximum level tolerated by the patient.
Intervention 2	16 patients: One steroid injection under US guidance. 1 ml triamcinolone acetonide (40 mg) was injected into the area surrounding the median nerve.
Outcomes	10-cm VAS, Levine Self-assessment Questionnaire treatment (LSQ) and electrophysiology studies
Follow up duration	Up to 3 months
Brief results	Improvement in VAS scores in the ESWT group was 4.18 (SD 1.05), in the CS group 3.31 (SD 1.82), difference not significant. Differences in 3-month improvements in LSQ scores and electrophysiological measures were not found either.

Study	Randomisation	Allocation Concealment	Blinding of participants	Blinding of caregivers	Blinding of assessors	Incomplete outcome data	Selective reporting	Other Biases
Seok (2013)	Low	Unclear	High	High	Low*	High	Low	Low

* but primary outcome variables were patient-directed, except the electrophysiological measures.

Steroids versus Low-level laser therapy

Study	Soltani (2014)
Country	Iran
Study Design	RCT
Study population	38 patients (50 CTS-affected hands)
Patient details	6 M, 32 F, Mean age 47.4 (SD 10)
Intervention 1	16 (21 hands) received laser therapy in the physiotherapy ward. A low potent laser with amplitude of 775 nm, frequency of 6500 Hz and an intensity of 20 j/cm2*, at five points over 11 seconds along the median nerve passage, above the carpal tunnel was used. A total of 10 laser therapy sessions were performed every other day for 3 weeks.
Intervention2	17 (23 hands) received single local corticosteroid injection of hydrocortisone 50mg (2 ml) into the carpal tunnel via a 25- gauge needle.
Outcomes	Primary outcome: severity of disease, based on electrophysiological findings: symptom free / mild / moderate / severe. Secondary: VAS Pain scale, electrophysiological measures.
Follow up duration	8 weeks
Brief results	No differences were found in change of disease severity (laser: 19.0 % unchanged, 47.6 % improved 1 point, 33.3 % two points, CS 37.5 / 33.3 / 29.2 % respectively, p = 0.28, nor in VAS pain (p = 0.45 Both steroid injection and laser improved VAS for the severity of pain, and disease severity. However, sensory and motor amplitudes did not show any significant change, irrespective of the initial treatment. 'No reported or recognisable side effect' was reported.

*Description of the laser therapy is incomplete and/or incorrect. Text was 'amplitude of 775 nm', this must be an error. It must be wavelength 775 nm (near-infrared). Frequency: pulsed laser? Pulse width? Intensity is in watts/cm^2 (= Joules/sec/cm^2)

Study	Randomisation	Allocation Concealment	Blinding of participants	Blinding of caregivers	Blinding of assessors	Incomplete outcome data	Selective reporting	Other Biases
Soltani (2014)	Low	Low	High	High	Low	Low	Low	Unclear*

*5 Patients were unaccounted for: 38 were available for randomisation, but only 33 were actually randomised.

Steroids versus NSAIDS

Study	Gurcay (2009)
Country	Turkey
Study Design	RCT
Study population	32 patients with clinically and electromyographically diagnosed mild to moderate CTS, lasting 3 to 56 months, all except one in right hand.
Patient details	0M, 32F. Mean age 40.8 (SD 11.2)
Intervention 1	18 patients received local injection of 6 mg betamethasone through a 25-gauge needle. All patients in both groups were advised to apply wrist splints in a neutral position at night, for three weeks.
Intervention2	14 patients were given NSAIDs (meloxicam 15 mg/day, PO, for three weeks)
Outcomes	Functional Status Scale (FSS), Jebsen Taylor Test (JTT) was used to evaluate the patient's hand dexterity. Nerve conduction studies
Follow up duration	3 months
Brief results	No significant differences were found between the groups on any outcome variable. Patients improved in functional status, some JTT variables and in some electrophysiological measures. No complications or side effects of treatment were noted.

Study	Randomisation	Allocation Concealment	Blinding of participants	Blinding of caregivers	Blinding of assessors	Incomplete outcome data	Selective reporting	Other Biases
Gurcay (2009)	Low	Low	High	High	High	Unclear	Low	Low

Steroids versus surgery

Study	**Ly-Pen (2012)**	**Ismatullah (2013)**
Country	Spain	Pakistan
Study Design	RCT	RCT
Study population	101 patients > 18 (163 wrists) with symptoms of CTS for ≥ 3 months and inadequate response to splinting and NSAIDS. No thenar atrophy, previous surgery or injections.	40 patients > 3 months of CTS, no thenar atrophy, previous surgery or injections.
Patient details	8M, 93F, Mean age Surgery 50 (SD 10), Injection 53 (SD 14)	11M, 29F, Mean age 45.35 (SD 11.65)
Intervention 1	56 patients had surgical decompression using the limited palmar incision technique.	20 had Open Carpal Tunnel Release
Intervention2	49 patients local steroid injections of paramethasone acetonide, 20mg in 1 ml. Repeat injection after two weeks if nocturnal paraesthesia had not completely disappeared (13 wrists one injection, 69 wrists two).	20 Local injection with 40mg methyl-prednisolone (Depomedrol)
Outcomes	Percentage of wrists that reached ≥ 20% improvement in VAS for nocturnal paraesthesias	Global Symptoms Score (GSS)
Follow up duration	Up to 2 years	12 weeks
Brief results	At 3-months follow-up, 94 % of wrists in the injection groups had $\geq$ 20 % improvement in nocturnal paraesthesias against 75 % in the surgery group (p = 0.001), at later time points no significant differences were found. At 24-month follow-up, 60% of the wrists in the injection group vs 69% in the surgery group had $\geq$ 20% response (p = 0.256).	Four weeks after treatment, mean GSS for the steroid group was 9.85+6.39 and for the surgery group 7.30+5.68 (p = 0.190). Twelve weeks after treatment, mean GSS for the steroid group was 22.10+6.90 and for the surgery group 5.45+6.90 (p = 0.000). There were no major complications in either of the two groups. A case of cellulitis was found with LSI and a case of reflex sympathetic of CTS dystrophy was found with CTR.

Study	Randomisation	Allocation Concealment	Blinding of participants	Blinding of caregivers	Blinding of assessors	Incomplete outcome data	Selective reporting	Other Biases
Ly-Pen (2012)	Low	Low	High	High	High	Low	Low	High*
Ismatullah (2013)	Unclear	Unclear	High	High	High	Low	Low	Low

*Analysis by wrists. There was a high rejection of surgery which in ITT analysis counted as treatment failure.

Oral steroids versus local injections

Study	Dewi (2009)
Country	Indonesia
Study Design	RCT
Study population	50 patients with CTS, no thenar atrophy, not previously received oral corticosteroid therapy or local injection of corticosteroid within the last 3 months
Patient details	16M, 34F. Mean age Injection Group 53.6 (SD 7.62), Oral Group 51.3 (7.56)
Intervention 1	25 patients were given oral 16 mg triamcinolone daily for 2 weeks followed by 8 mg daily for the next 2 weeks and local placebo injection.
Intervention2	25 patients were given local injection of 15 mg triamcinolone and oral placebo for 4 weeks.
Outcomes	Global symptom score and nerve conduction studies
Follow up duration	Up to 4 weeks
Brief results	At 4 weeks, the injection group GSS improved 16.19 (SD 8.10) points, in the oral group 13.50 (SD 5.77) points ($p = 0.186$) Nerve conduction measures improved more in the injection group ($p < 0.05$)

Study	Randomization	Allocation Concealment	Blinding of participants	Blinding of caregivers	Blinding of assessors	Incomplete outcome data	Selective reporting	Other Biases
Dewi (2009)	Unclear	Unclear	Low	High	High*	Low	Low	Low

*Outcome assessor only blinded for nerve conduction outcomes.

Pulsed radiofrequency

Study	**Chen (2015)**
Country	Taiwan
Study Design	RCT (single center)
Study population	44 patients with typical symptoms and signs of CTS, such as positive Tinel's sign, Phalen's test, numbness, or tingling in at least two digits of the hand, and were confirmed with CTS by electrophysiological tests.
Patient details	1M, 43F, Mean age 56.1 (4.7)
Intervention 1	Ultrasound-guided PRF of the median nerve, probe with 4-mm active tip, at the proximal carpal tunnel (pisiform level). Electrode position checked with sensory and motor stimulation, PRF for 120 seconds, 2 Hz, pulse width 20 msec, at 42 °C. Patients were also prescribed night splint.
Control	Night splint alone
Outcomes	Primary: time to significant ($\geq$ 40 %) pain relief. Secondary: BCTQ, Median nerve cross-sectional area, electrophysiology, finger pinch strength.
Follow up duration	Up to 12 weeks of 36 patients
Brief results	Median onset of significant pain relief was 2 days in the PRF group vs 14 in the control groups. At 12 weeks, VAS Pain had decreased 4.2 (95 % CI 3.2 to 5.2) points in the PRF group vs 2.0 (1.1 to 2.9) in the control group ($p < 0.001$) Highly significant differences in BCTQ scales were found too (but not in electrophysiological measures or pinch strength)

Study	Randomisation	Allocation Concealment	Blinding of participants	Blinding of caregivers	Blinding of assessors	Incomplete outcome data	Selective reporting	Other Biases
Low	Low	High	High	High	Low	Low	Low	Low

Pulsed radiofrequency versus steroids

Study	**Ozyuvaci (2012) ***
Country	Not reported
Study Design	RCT
Study population	50 patients with CTS
Patient details	Not reported
Intervention 1	Steroids (unspecified) , then after 3 weeks a second dose of steroids (unspecified)
Intervention 2	Steroids (unspecified), then after 3 weeks 120 sec pulse radiofrequency
Outcomes	Not reported
Follow up duration	Unclear
Results	There were significant reductions in pain and disability scores between the baseline and follow-up periods. There was not a significant difference between the groups.

*conference abstract only

Author(s): Jos Kleijnen
Date: 2017-01-17
Question: Should Local injections with corticosteroids be used for carpal tunnel syndrome?
Settings: Treatment by anaesthetists
Bibliography: Huisstede BM, Hoogvliet P, Randsdorp MS, Glerum S, van Middelkoop M, Koes BW. Carpal tunnel syndrome. Part I: effectiveness of nonsurgical treatments - a systematic review. Arch Phys Med Rehabil 2010;91(7):981-1004.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Local injections with corticosteroids**	**Control**	**Relative (95% CI)**	**Absolute**		
Clinical improvement (follow-up 2-4 weeks)												
2	randomised trials	no serious risk of bias[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	53/73 (72.6%)	19/68 (27.9%)	RR 2.58 (1.72 to 3.87)	441 more per 1000 (from 201 more to 802 more)	⊕⊕⊕⊕ HIGH	CRITICAL
								27.9%		441 more per 1000 (from 201 more to 801 more)		

[1] Two randomised trials of corticosteroids versus placebo

Author(s): Jos Kleijnen
Date: 2017-01-17
Question: Should Pulsed RF treatment of the median nerve be used for carpal tunnel syndrome?
Settings: Treatment by anaesthetists
Bibliography: Chen LC, Ho CW, Sun CH, Lee JT, Li TY, Shih FM, et al. Ultrasound-Guided Pulsed Radiofrequency for Carpal Tunnel Syndrome: A Single-Blinded Randomized Controlled Study. PLoS One 2015;10(6):e0129918.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pulsed RF treatment of the median nerve	Control	Relative (95% CI)	Absolute		
Onset time of significant pain relief (follow-up mean 12 weeks; measured with: VAS 0-10[1]; Better indicated by lower values)												
1	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	18	18	-	HR 7.37 higher (3.04 to 17.87 higher)	⊕OOO VERY LOW	CRITICAL

[1] Effect on main outcome of onset time of pain relief measured on VAS but analysed as hazard ratio. Mean onset time of pain relief on PRF 2 days, on control 14 days.
[2] Inadequate allocation concealment and issues with blinding, also unclear whether appropriate intention to treat analyses were done, probably not.
[3] Small study with 18 patients analysed in each group

20. Meralgia Parasthetica

SYSTEMATIC REVIEWS IDENTIFIED

We identified the following review relevant to Lateral femoral cutaneous nerve (LFCN) infiltration with local anesthetic with / without corticosteroid published between 2010 and 2015. No reviews of pulsed RF or spinal cord stimulation were identified. See table for details.

Intervention	Relevant Review(s)	Search date	Studies Identified in review	Meta-analysis
Lateral femoral cutaneous nerve (LFCN) infiltration with local anesthetic ± corticosteroid	Khalil (2012) (Cochrane Review)	Up to Oct 2012	4 obs studies	No
Pulsed RF of LFCN	No reviews identified			
Spinal cord stimulation	No reviews identified			

ASSESSMENT OF THE REVIEW EVIDENCE

Study Reference	Participants	Interventions	Comparators	Outcomes	Study Designs
Khalil (2012)[3]	Participants with a clinical diagnosis of meralgia paraesthetica regardless of etiology	Conservative measures, local injection with steroids + local anesthetic and surgery (decompression or neurectomy)	No intervention, local anesthetic and nerve section	Symptom improvement (sustained for at least three months after the intervention)	RCTs, quasi-RCTs And observational studies > 5 cases of meralgia paraesthetica with a follow up ≥ 3 months of 80% of cases

Results

No RCTs or quasi-RCTs were identified. All studies were case series.

Four studies (n=157 participants) evaluated the injection of corticosteroid and local anesthetic and found cure or improvement in 130 (83%) cases.

A single study published in 1938 (n=29) found spontaneous improvement of meralgia paraesthetica in 20 (69%) cases.

Nine studies (n=300) assessed decompression and showed beneficial effects in 264 (88%) patients.

Three studies (n=48) found that treatment was beneficial for 45 (94%) of cases treated with neurectomy.

Last Search date	Studies identified in review	Bottom Line
October 2012	20 (4 relevant)	High quality observational studies reported comparable high improvement rates for meralgia paraesthetica following local injection of corticosteroid and surgical interventions. A similar

		outcome was reported without any intervention in a single natural history study. The evidence is weak. High quality randomised controlled trials are needed to determine whether corticosteroid injections are superior to conservative treatment. Long-term follow-up is needed to assess the recurrence rate after injection and the number of injections needed for long-term benefit. Surgical procedures need to be compared to corticosteroids in randomised controlled trials.

RELEVANT TRIALS PUBLISHED SUBSEQUENT TO THE SYSTEMATIC REVIEWS

We did not identify any RCTs published subsequent to the systematic review by Khalil[3] or any RCTs for the two interventions with no systematic review (pulsed RF of the lateral femoral cutaneous nerve and spinal cord stimulation).

OBSERVATIONAL STUDIES

In a targeted search we failed to identify any observational studies for pulsed RF of the lateral femoral cutaneous nerve and for spinal cord stimulation.

Author(s): Jos Kleijnen
Date: 2017-05-04
Question: Should lateral femoral cutaneous nerve injections with local anaesthetic ± corticosteroids be used for meralgia paresthetica?
Settings: Treatment by anaesthetists
Bibliography: Khalil N, Nicotra A, Rakowicz W. Treatment for meralgia paraesthetica. Cochrane Database of Systematic Reviews 2012, Issue 12. Art. No.: CD004159. DOI: 10.1002/14651858.CD004159.pub3.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Lateral femoral cutaneous nerve injections with local anaesthetic ± corticosteroids	Control	Relative (95% CI)	Absolute		
Symptom improvement												
4	observational studies[1]	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	-	-	-	⊕OOO VERY LOW	CRITICAL
								0%		-		

[1] Four case series with a total of 157 patients

Author(s): Jos Kleijnen
Date: 2017-05-04
Question: Should pulsed RF of the lateral femoral cutaneous nerve be used for meralgia paresthetica?
Settings: Treatment by anaesthetists
Bibliography: Patijn J, Van Zundert J. Meralgia Paraesthetica. In: Van Zundert J, Huygen F, Patijn J, van Kleef M, editors. Praktische richtlijnen anesthesiologische pijnbestrijding, gebaseerd op klinische diagnosen. Maastricht: NVA, VAVP, PKZ; 2009. p. 255-60. Choi HJ, Choi SK, Kim TS, Lim YJ. Pulsed radiofrequency neuromodulation treatment on the lateral femoral cutaneous nerve for the treatment of meralgia paresthetica. J Korean Neurosurg Soc. 2011;50(2):151-3. Fowler IM, Tucker AA, Mendez RJ. Treatment of meralgia paresthetica with ultrasound-guided pulsed radiofrequency ablation of the lateral femoral cutaneous nerve. Pain Pract. 2012;12(5):394-8

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Pulsed RF of the lateral femoral cutaneous nerve**	**Control**	**Relative (95% CI)**	**Absolute**		
Pain relief												
4	observational studies[1]	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	-	-	-	-	⊕OOO VERY LOW	CRITICAL
								0%		-		

[1] Only 4 case reports found

Author(s): Jos Kleijnen
Date: 2017-05-04
Question: Should spinal cord stimulation be used for meralgia paresthetica?
Settings: Treatment by anaesthetists
Bibliography: Patijn J, Van Zundert J. Meralgia Paraesthetica. In: Van Zundert J, Huygen F, Patijn J, van Kleef M, editors. Praktische richtlijnen anesthesiologische pijnbestrijding, gebaseerd op klinische diagnosen. Maastricht: NVA, VAVP, PKZ; 2009. p. 255-60

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Spinal cord stimulation	Control	Relative (95% CI)	Absolute		
Pain												
1	observational studies[1,2]	serious[1]	no serious inconsistency	no serious indirectness	very serious[1]	none	-	-	-	-	⊕OOO VERY LOW	CRITICAL
								0%		-		

[1] Only one case report found
[2] case reports

21. Phantom Pain

SYSTEMATIC REVIEWS

No relevant systematic reviews including the relevant interventions for phantom pain were identified. Studies of phantom pain appeared to be eligible in a review of dorsal root ganglion therapies to treat chronic pain.[3] However no relevant studies were identified.

RANDOMISED CONTROLLED TRIALS

No relevant randomized controlled trials were identified for any of the interventions.

OBSERVATIONAL STUDIES

A targeted search for observational studies on the above interventions published since the previous guidance identified the following studies:

Intervention	**Studies**
Pulsed RF treatment of the stump neuroma	West (2010)
Pulsed RF treatment adjacent to the spinal ganglion	Imani (2012)
Spinal cord stimulation	McAuley (2013)
Dorsal Root Ganglion stimulation	Eldabe (2015)

We also identified two abstracts related to dorsal root ganglion stimulation but it was unclear if these patients formed part of the series evaluated by Eldabe so these have not been extracted.

EVIDENCE FROM OBSERVATIONAL STUDIES

Pulsed RF treatment of the stump neuroma

Study	**West (2010)**
Setting	Department of Physical Medicine and Rehabilitation, Milwaukee, USA
Study Design	Case series
Study population	4 amputees with unbearable residual limb pain and phantom limb pain despite conservative management. All patients had evidence of neuroma formation. Residual limb pain was more important than phantom limb pain in at least three of them.
Patient details	4 men, aged 34 to 45 where reported, 2 bilateral above knee amputation, 1 left above-knee, 1 right above elbow. All had> 50% pain relief after a diagnostic local block of neuroma at area of maximal tenderness, returning to baseline within hours, on two separate occasions.
Intervention details	After local anaesthesia a 20G RF needle, 10 cm long cannula with a 10mm active curved tip was placed in most tender part of neuroma. Sensory stimulation was obtained at < 0.5 V in all cases with impedance ranging from 140 to 250 Ohms. PRFA used 2 Hz frequency, 20ms pulses in a 1 second cycle, 120 seconds duration, 42◦C with repeat cycle. The procedure was repeated four times, resulting in a total of 720 second of PRF: 3 times after 90° rotation of the curved tip, once with a straight tip. Afterwards, 1.5 ml of 1 % lidocaine with 20 mg of Depo-Medrol was injected.
Outcomes	Relief of residual limb pain and phantom pain and sensations, overall function and use of medication
Follow up duration	Six to seven months (3 patients), unspecified (1 patient).
Results	All four demonstrated ≥ 80% relief of residual limb pain over six months. One patient had complete resolution of phantom sensation and a further patient had decreased frequency of spontaneous phantom limb pain and resolution of evoked phantom limb pain. Two patients did not show any significant differences in their PLP or phantom sensation. All four reported improved overall function including increased prosthetic tolerance and decreased oral pain medications.

Pulsed RF treatment adjacent to the spinal ganglion

Study	**Imani (2012)**
Setting	Tehran University of Medical Sciences, Iran
Study Design	Case series
Study population	Two patients with phantom pain > 3 months unresponsive to conservative treatment
Patient details	2 women, Ages 25 and 35. Both patients had VAS > 5 with pain beginning from stump and radiating to lumbar and to leg. Sciatic nerve found to be cause of pain
Intervention details	Two weeks after diagnostic blockade (3 ml ropivacaine 0.2 % and triamcinolone 40 mg) PRF was performed with curved-tip RF needle (22 G, 150mm with 10mm active tip). Sensory stimulation was made (50 Hz, 0.4-0.6 voltage, 1-ms pulse width), which resulted in paraesthesia in the

	stump or the amputated leg. PRF was conducted on the DRG in two cycles, 42 °C, 120 seconds in both L4 and L5. Then ropivacaine (0.2%, 3 mL) and triamcinolone (40 mg) were again injected. In one patient, PRF was performed in L4 only because of changed anatomy after an earlier hemipelvectomy.
Outcomes	VAS (0 to 10?)
Follow up duration	Four or six months
Results	One patient had a 40% decrease in pain on VAS in six months. The second patient had a 30% decrease in pain scores in four months.

Spinal cord stimulation

Study	**McAuley (2013)**
Setting	Department of Neurostimulation, Royal London Hospital, UK
Study Design	Consecutive case series
Study population	12 patients who had received implantation of SCS devices for amputation-related pain over a period of 20 years. Four had phantom limb pain as a primary symptom, two had it as an additional symptom.
Patient details	8M, 4F (for the whole group). Mean age 60.5 (SD 12.2) years.
Intervention details	Quadripolar paddle electrode (Resume, Medtronic Inc, USA) with implanted programmable generator (several types). The electrode was implanted under general anesthesia epidurally via laminectomy to lie on the dorsal columns at a cervical (for upper limb pain) or thoracic (for lower limb pain) level and stitched to the surrounding tissue to minimize movement. The stimulator was controlled by patients (on / off and to adjust stimulation). At initial and subsequent neurostimulator clinic assessments the combination of electrodes and settings were tested and pulse amplitude, frequency and width adjusted to the patient. Mean setting used by the patients (all 12) was 2.8 (SD 1.9) V, pulse width 240 (210 to 450) and pulse frequency 100 (30 to 100) Hz. Great efforts were made to ensure proper stimulator after care: Electrode revision was done in six (of the 12) patients, there were two connector/lead fractures. Modal battery life was eight years (range 5 – 10 years).
Outcomes	Benefit of stimulation was expressed as percentage of pain relief. Furthermore, 'worthwhile benefit' was defined as 'pain relief that was meaningful and worthwhile to the patient (typically meaning that replacing the IPG was warranted when battery failure occurred).' In patients continuing to have benefit and receiving ongoing follow up VAS 0 to 10 scores were followed up to five years.
Follow up duration	Up to 20 years.
Results	Eleven of 12 patients reported an initial worthwhile benefit with a mean of 65% (SD 15.0%). Two patients were lost to follow up after one year. One further patient had spontaneous resolution of phantom pain and one could not achieve adequate stimulation despite electrode revisions. One of the remaining seven patients benefited for two years until lead fracture. One experienced waning benefit over 19 years at which point stimulation became painful. Five patients were followed for a median of 11 years with a benefit of 66% (SD 18.2%). Both phantom limb and stump pain responded to stimulation. However stimulation had to reach the

	phantom limb rather than just the stump to relieve phantom pain. Technical problems included electrode / lead fractures, control box failures and pain at the battery site (two cases each).

Dorsal Root Ganglion stimulation

Study	**Eldabe (2015)**
Setting	Multiple European sites
Study Design	Retrospective chart review
Study population	All eight patients treated with an Axium device (Spinal Modulation, Inc. USA) for phantom limb pain with or without stump pain. Patient selection criteria for this treatment not stated, nor is entirely clear whether the Axium is the only DRG neuromodulation device used in these centres. Patients with amputation of digits were excluded.
Patient details	2M, 5F, 1NR. Mean age of 5 of 8 patients 52.2 (SD 20.0) years (3 data not available). Six patients had amputation of their foot or leg, two of their arm. Patients were between 1 and 15 years post-amputation. Patients had failed pharmacological and other interventional therapy.
Intervention details	Under fluoroscopic guidance a narrow quadripolar neurostimulation lead was implanted using an epidural approach near relevant DRGs based on individual pain distributions. DRG neuromodulation (Axiom®, Spinal Modulation Inc. Menlo Park, CA, USA). All patients had a trial stimulation where ≥ 50% pain relief in the primary pain area indicated success. A fully implantable neurostimulator was placed under standard surgical procedures. The device was programmed to obtain the best pain / paraesthesia overlap and / or best pain relief with patient controlled stimulation intensity.
Outcomes	Pain ratings on VAS 0 - 100mm, quality of life with EQ-5D (two patients) and medication intake (six patients).
Follow up duration	Mean 14.4 months, Range five to 24 months
Results	All eight patients had a successful trial of DRG neuromodulation and received the permanent system. The mean pain reduction at follow up was 52.0% (SD 31.9). At last follow up pain was rated at 38.9mm (SD 27.1) compared to a baseline mean VAS 83.5mm (SD 10.5). In one case stimulation eliminated PLP as well as non-painful phantom sensations. Three patients experienced a lessening of pain relief despite good initial outcomes. In two of these cases pain relief lessened over 24 months and it was found that leads were placed sub optimally. In the third case excellent pain relief was obtained for one month at which point pain returned to baseline levels. No complications were reported for any patients.

Author(s): Jos Kleijnen
Date: 2017-01-18
Question: Should pulsed RF treatment of the stump neuroma be used for phantom pain?
Settings: Treatment by anesthetists
Bibliography: West M, Wu H. Pulsed radiofrequency ablation for residual and phantom limb pain: a case series. Pain Pract 2010;10(5):485-91.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pulsed RF treatment of the stump neuroma	Control	Relative (95% CI)	Absolute		
Relief of residual limb pain and phantom pain and sensations (follow-up 6-7 months)												
1	observational studies[1]	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	4/4 (100%)[3]	-	-	-	⊕OOO VERY LOW	CRITICAL

[1] case series
[2] 4 patients included
[3] All 4 patients had successful outcomes

Author(s): Jos Kleijnen
Date: 2017-01-18
Question: Should pulsed RF treatment adjacent to the spinal ganglion be used for phantom pain?
Settings: Treatment by anaesthetists
Bibliography: Imani F, Gharaei H, Rezvani M. Pulsed radiofrequency of lumbar dorsal root ganglion for chronic postamputation phantom pain. Anesthesiology and Pain Medicine 2012;1(3):194-7

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pulsed RF treatment adjacent to the spinal ganglion	Control	Relative (95% CI)	Absolute		
Pain (follow-up 4-6 months; assessed with: VAS)												
1	observational studies[1]	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	2/2 (100%)	-	-	-	⊕OOO VERY LOW	CRITICAL

[1] case series
[2] Only 2 patients

Author(s): Jos Kleijnen
Date: 2017-01-18
Question: Should spinal cord stimulation be used for phantom pain?
Settings: Treatment by anaesthetists
Bibliography: McAuley J, van Groningen R, Green C. Spinal cord stimulation for intractable pain following limb amputation. Neuromodulation 2013;16(6):530-6.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Spinal cord stimulation	Control	Relative (95% CI)	Absolute		
Pain relief (follow-up 0-20 years; assessed with: VAS)												
1	observational studies[1]	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	11/12 (91.7%)	-	-	-	⊕OOO VERY LOW	CRITICAL

[1] case series
[2] Only 12 patients with some lost to follow-up

Author(s): Jos Kleijnen
Date: 2017-01-18
Question: Should dorsal root ganglion stimulation be used for phantom pain?
Settings: Treatment by anaesthetists
Bibliography: Eldabe S, Burger K, Moser H, Klase D, Schu S, Wahlstedt A, et al. Dorsal root ganglion (DRG) stimulation in the treatment of phantom limb pain (PLP). Neuromodulation 2015;18(7):610-7.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Dorsal root ganglion stimulation	Control	Relative (95% CI)	Absolute		
Percent pain reduction (follow-up 5-24 months; measured with: VAS; range of scores: 0-100; Better indicated by higher values)												
1	observational studies[1]	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	8	-	-	-[3]	⊕OOO VERY LOW	CRITICAL

[1] case series
[2] Case series of 8 patients
[3] Mean pain reduction was 52%

23. Traumatic Plexus Lesion

SYSTEMATIC REVIEWS IDENTIFIED

We did not identify any systematic reviews published between 2010 and 2015 of spinal cord stimulation or of dorsal root ganglion stimulation for traumatic plexus lesion.

RELEVANT TRIALS PUBLISHED SUBSEQUENT TO THE SYSTEMATIC REVIEW

We did not identify any randomised controlled trials (RCTs) relevant to the two specified interventions for traumatic plexus lesion.

We searched for observational studies and identified the following published subsequent to the previous guidance. See Table.

Intervention	**Study**
Spinal cord stimulation	Chivukula (2014)
	Lai (2009) *

*Single case report

Data from Observational Studies

	Chivulula (2014)	**Lai (2009)**
Relevant Cases	8 patients with brachial plexus lesions within a series of 121 patients	1 brachial plexus avulsion
Male / Female	NR	1 / 0
Age (years)	NR	70
Intervention	Spinal cord stimulation	Spinal cord stimulation
Outcome	Mean pain reduction of 52.3% (11.9) at a mean follow-up of 4.2 years. Pain relief lasted an average of 3.1 (1.8) years.	At 1 year after surgery he did not use any analgesic medication.
Complications	0 revisions 1 CSF leak 0 infections 0 persistent pain / numbness	Initial mild right limb numbness

Author(s): Jos Kleijnen
Date: 2017-05-16
Question: Should dorsal root ganglion stimulation be used for traumatic plexus lesion?
Settings: Treatment by anesthetists
Bibliography: No evidence found

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Dorsal root ganglion stimulation	Control	Relative (95% CI)	Absolute		
Pain relief												
0[1]	No evidence available					none	-	-	-	-		CRITICAL
								0%		-		

[1] No evidence found

Author(s): Jos Kleijnen
Date: 2017-05-16
Question: Should spinal cord stimulation be used for traumatic plexus lesion?
Settings: Treatment by anesthetists
Bibliography: Chivukula S, Tempel ZJ, Weiner GM, Gande AV, Chen CJ, Ding D, et al. Cervical and cervicomedullary spinal cord stimulation for chronic pain: efficacy and outcomes. Clin Neurol Neurosurg 2014;127:33-41. Lai HY, Lee CY, Lee ST. High cervical spinal cord stimulation after failed dorsal root entry zone surgery for brachial plexus avulsion pain. Surg Neurol 2009;72(3):286-289.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Spinal cord stimulation	Control	Relative (95% CI)	Absolute		
Pain relief												
2	observational studies[1]	serious	no serious inconsistency	no serious indirectness	serious[1]	none	-	-	-	-	⊕OOO VERY LOW	CRITICAL

[1] One case series of 8 patients and one case report

24. Pain in Patients with Cancer

SYSTEMATIC REVIEWS IDENTIFIED

The following table lists the reviews and any gaps in the review evidence.

Intervention	Relevant Review (s)	Search end date	Cancer site(s)	Meta-analysis
Intrathecal medication (delivery)	Hayek (2011)	Dec 2010	General	No
Epidural medication (delivery)	Kurita (2011)	2009	General	No
Neuromodulation	Lihua (2013)	July 2012	General	Yes
Cervical (percutaneous)(surgical) cordotomy	France (2014)	March 2012	Mesothelioma	Yes
Neurolytic plexus coeliacus block	Nagels (2013)	May 2011	Abdominal	No
	Zhong (2014)	Nov 2012	Pancreatic	Yes
	Arcidiacono (2011)	Dec 2010	Pancreatic	Yes
	Kaufman (2010)	Dec 2007	Pancreatic	Yes
Neurolytic nervus splanchnicus block	No reviews identified			
Radiofrequency treatment splanchnic nerve	No reviews identified			
Neurolytic plexus hypogastricus block	No reviews identified			
Paravertebral block	Andreae (2012)	May 2012	Breast	Yes
	Thavaneswaran (2010)	May 2008	Breast	No
	Tahiri (2011)	June 2010	Breast	No
	Schnabel (2010)	2009	Breast	No
	Wijayasinghe (2014)	March 2014	Breast	No
Intercostals block	Wijayasinghe (2014)	March 2014	Breast	No
Neurolytic peripheral nerve block	No reviews identified			
Intrathecal phenolization of lower sacral roots of cauda equine	No reviews identified			
Vertebroplasty	No reviews identified			
Kyphoplasty	No reviews identified			
Drez lesion	Gadgil (2012)	Unclear	General	No

No systematic reviews were identified for seven of the requested interventions:

- Neurolytic nervus splanchnicus block
- Radiofrequency treatment splanchnic nerve

- Neurolytic plexus hypogastricus block
- Neurolytic peripheral nerve block
- Intrathecal phenolization of lower sacral roots of cauda equine
- Vertebroplasty
- Kyphoplasty

ASSESSMENT OF THE REVIEW EVIDENCE

Paravertebral block (4 reviews)

Review 1

Study Reference	Participants	Interventions	Comparators	Outcomes	Study Designs
Schnabel (2010)	Women undergoing breast surgery	Paravertebral block	Sham, any other analgesic modality	Acute postoperative pain scores (<2, 2 - 24, and 24 - 48 h), chronic postoperative pain (6 and 12 months), need for and time to rescue analgesics, adverse events	Randomized controlled trials

Results

- Five trials (n=284) reported that paravertebral block (PVB) alone resulted a significant improvement in worst postoperative pain score at <2 hour (mean difference [MD]: -2.47; 95% confidence interval [CI] - 3.06 to -1.88), when compared to general anesthesia (GA).
- Five trials (n=314) demonstrated that PVB as single technique resulted a significant improvement in worst postoperative pain score at 2 - 24 hour (MD: -1.77; 95%CI -2.42 to -1.12), when compared with general anasthesia.
- Three trials (n=168) PVB showed a significant improvement in worst postoperative pain scores when compared with GA at, 24 - 48 hour (MD: -1.75; 95%CI -3.19 to -0.31).
- Five trials (n=215) found that PVB with GA produced a significant improvement in worst postoperative pain scores at <2 hour (MD: -1.87; 95%CI -2.53 to -1.21) when compared with GA alone.
- Four trials (n=136) demonstrated a significant improvement in worst postoperative pain score between PVB with GA and GA alone at, 2- 24 hours (MD: -2.21; 95%CI -3.07 to -1.35).

Last Search date	Studies identified in review	Bottom Line
2009	15	Evidence suggests that paravertebral block in addition to general anesthesia or alone provides a better postoperative pain control

		with few adverse effects compared with other analgesic treatment strategies in women undergoing breast surgery.

Paravertebral block Review 2

Study Reference	Participants	Interventions	Comparators	Outcomes	Study Designs
Tahiri (2011)	Adults (18 years and over) undergoing breast surgery	Thoracic paravertebral block alone or compared with general anesthesia	NR	Efficacy (defined as requirement of additional anesthetic/sedation and conversion to general anesthesia); intra and postoperative complications; length of hospital stay (LOS); postoperative pain; postoperative narcotic use; and postoperative nausea/vomiting (PONV)	Randomized controlled trials, retrospective studies, and case series

Results

- The rate of complications in patients undergoing thoracic paravertebral block (TPVB) ranged between 0 and 12% as reported in 11 studies.
- Pain scores in patients undergoing TPVB were reported in 5 studies. At 1 h after surgery, the pain scores showed a mean difference of 2.48 (95% confidence interval [CI]: 2.20 to 2.75) across the two groups, and clearly favored TPVB over general anesthesia (GA). At 6 h after surgery, mean difference in pain across the groups was 1.71 (95%CI: 1.64 to 1.78) and also favored TPVB over GA.
- The use of postoperative analgesics (non-steroidal anti-inflammatory drugs [NSAIDs] and/or opioids) was reported in 10 studies. The use of postoperative analgesics was less frequent in patients who had received TPVB compared with GA (relative risk [RR]: 0.23; 95%CI: 0.15 to 0.37).
- The incidence of post-operative nausea and vomiting was considerably lower in patients who received TPVB as compared with patients who received GA (RR: 0.27; 95% CI: 0.12 to 0.61).
- In terms of patient satisfaction, a statistically significant (p=0.008) number of patients were satisfied with the use of TPVB as compared with placebo.
- Commonly reported adverse events included hypotension/bradycardia, epidural spread, and pneumothorax.

Last Search date	Studies identified in review	Bottom Line
June 2010	11	Present evidence indicates that thoracic paravertebral block provides effective anesthesia for ambulatory breast surgery and

		can result in significant benefits over general anesthesia in terms of post-operative analgesia, postoperative nausea/vomiting, opioid consumption and length of hospital stay.

Paravertebral block Review 3

Study Reference	Participants	Interventions	Comparators	Outcomes	Study Designs
Thavaneswaran (2010)	Patients undergoing surgery	Thoracic or lumbar paravertebral blocks	General anesthesia, epidural anesthesia, other regional anesthetic techniques	Ability to achieve effective surgical anesthesia, postoperative pain, length of hospital stay, patient satisfaction, intraoperative and postoperative complications, postoperative nausea and vomiting	Randomized controlled trials

Results

- Seven randomized controlled trials (RCTs) reported on the rate of effective block for paravertebral blocks (PVB) which ranged from 87% to 100%.
- Two studies reported that patients were more satisfied with PVB than with general anesthesia (GA).
- Meta-analysis of three studies showed significant less risk of postoperative nausea and vomiting in PVB group compare to general anesthesia group (relative risk [RR] 0.25, 95% confidence interval [CI] 0.13 to 0.50), although it does carry a risk of pleural puncture and epidural spread of local anesthetic.

Last Search date	Studies identified in review	Bottom Line
May 2008	8	Present evidence suggests that paravertebral blocks for surgical anesthesia at the level of the thoracic and lumbar vertebrae are associated with less pain during the immediate postoperative period, as well as less postoperative nausea and vomiting, and greater patient satisfaction compared with general anesthesia. Further methodologically rigorous, prospective trials with larger sample sizes and longer follow-up of patients are needed.

Paravertebral block Review 4

Study Reference	Participants	Interventions	Comparators	Outcomes	Study Designs

Andreae (2012)	Adults and children undergoing elective surgical procedures	Local anesthetics, regional anesthesia and paravertebral block	Conventional pain control	Persistent pain (chronic pain) at six or 12 months after surgery, allodynia, hyperalgesia, and use of pain medication.	Randomized controlled trials

Results
Regional anesthesia was effective in the prevention of chronic pain, at six months, after thoracotomy (Odds Ratio [OR] 0.33, 95% Confidence Interval [CI] 0.20 to 0.56). Two studies (n=89) reported that paravertebral block was beneficial in reducing pain after breast cancer surgery for five to six months (OR = 0.37, 95% CI 0.14 to 0.94). Surgical and anesthetic complications were sparsely and inconsistently reported.

Last Search date	Studies identified in review	Bottom Line
May 2012	23	Evidence supported the use of local anesthetics and regional anesthesia for reducing the risk of developing chronic pain after surgery. This finding is likely to be reliable. More clinical trials are required to strengthen the evidence.

Intercostal Block (1 Review)

Study Reference	Participants	Interventions	Comparators	Outcomes	Study Designs
Wijayasinghe(2014)	Patients who had undergone breast cancer surgery, had developed persistent pain and received a local anesthetic block as part of their pain treatment	Local anesthetic block excluding neural blockade in the perioperative period and treatments that did not target nerves.	Not pre-specified. Two studies had a comparator group (with or without gabapentin and different approaches of the same block)	Pain relief	Not pre-specified. Two of the seven included studies were RCTs.

Results
Four case series (15 patients) received intercostal nerve blocks. Overall 8 of 15 patients had complete pain relief from the local anesthetic blockade but the aim of all four studies was to help with future treatment options. The two studies of stellate ganglion block showed statistically significant reductions in pain scores for up to 3 months after the blocks but 8 of 75 patients (11%)

did not respond to the block. In the sole study of paravertebral block, 2 of 10 patients were pain-free after 5 months

Last Search date	Studies identified in review	Bottom Line
March 2014	7 (N=135)	This review found the evidence for neural blockade to be of low quality and inconclusive and recommended that high quality studies should be conducted. Although the review was at risk of bias in the selection and evaluation of studies, this conclusion is likely to be appropriate. All intercostal studies were diagnostic rather than treatment. While this is an indicator that an intercostal block may be a useful treatment option, it is not appropriate to extrapolate from these studies to a treatment effect.

Neurolytic plexus coeliacus block (4 reviews)
Review 1

Study Reference	Participants	Interventions	Comparators	Outcomes	Study Designs
Zhong (2014)	Patients with pancreatic cancer and refractory pain	Patients receiving a coeliac plexus block for pain management via the following procedures. percutaneous CPB, intraoperative CPB, endoscopic ultrasonography–assisted CPB	Patients receiving medical management only	Pain score and drug usage at 4 weeks, 8 weeks and at last report	Randomized controlled trials

Results Patients in the CPB groups had a significantly lower pain score at 4 weeks (Mean difference =-0.382 (SE 0.136) p = 0.005) (4 RCTs, 197 patients) but results were not statistically significant at 8 weeks (Mean difference = -0.265 (SE 0.217) p = 0.223) (6 RCTs, 379 patients). CPB groups required fewer drugs compared to control groups at 4 weeks (Mean difference = -0.49.765 (SE 15.242) p = 0.001) (5 RCTs, 231 patients) and at last report (Mean difference = -0.48.290 (SE 10.238) p < 0.001) (5 RCTs, 231 patients).

Last Search date	Studies identified in review	Bottom Line
Nov 2012	7	This meta-analysis identified and compared seven randomized controlled trials of pain relief from pancreatic cancer, by treatment with medical management alone to celiac plexus

		blockade with medical management. This review, which had some methodological limitations found that patients with pancreatic cancer treated with CPB experienced lower levels of pain and required less opioid medication than patients receiving standard analgesics.

Neurolytic plexus coeliacus block Review 2

Study Reference	Participants	Interventions	Comparators	Outcomes	Study Designs
Arcidiacono (2011) [8]	Adults (18 or over) with abdominal or back pain due to pancreatic cancer at any stage, confirmed by computed tomography (CT) or ultrasound, endoscopic ultrasonography (EUS) and clinical criteria. Patients with pain due to chronic inflammation (pancreatitis) were excluded.	Percutaneous celiac plexus block (CPB), the surgical approach, and EUS-guided neurolysis	Non-steroidal anti-inflammatory drugs (NSAIDs) and morphine	Reduction in pain intensity using a visual analogue scale (VAS) or other pain relief scales, consumption of analgesics; overall patient satisfaction after the procedure; adverse effects including the following (hypotension; diarrhoea; haematoma; procedure-related pain; neurologic complications; severe bleeding; infection; and mortality)	Randomized controlled trials (RCTs) with a minimum duration of four weeks' follow-up

Results

- At four and eight weeks pain scores were significantly lower in the celiac plexus block (CPB) group (four weeks: mean difference [MD] -0.42, 95% confidence interval [CI] -0.70 to - 0.13 and eight weeks: - 0.44 (95% CI -0.89 to - 0.01) as compared to the control group.

- Opioid consumption was also significantly lower than in the control group. The main adverse effects (diarrhea or constipation) were significantly more likely in the control group, where opioid consumption was higher.

Last Search date	Studies identified in review	Bottom Line
Dec 2010	6	There is limited evidence for the superiority of pain relief over analgesic therapy. The fact that celiac plexus block causes fewer adverse effects than opioids is important for patients. Further studies and randomized controlled trials are recommended to demonstrate the potential efficacy of a less invasive technique under endoscopic ultrasonography guidance.

Neurolytic plexus coeliacus block Review 3

Study Reference	Participants	Interventions	Comparators	Outcomes	Study Designs
Nagels (2013)	Patients with abdominal cancer pain. Studies were excluded if patients less than 18 years old or with non-cancer pain were included. Altogether the studies included 2,675 participants.	Celiac plexus neurolysis (CPN)	Any comparator or no comparator. Only studies comparing with systemic analgesic therapy were eligible for meta-analysis	Effects on pain, opioid use, quality of life (QoL), adverse effects.	All study designs and case reports.

Results
Percutaneous CPN significantly improves pain in patients with upper abdominal cancer, with a decrease in opioid consumption and side effects. It is unclear whether there is any change in quality of life. Case series suggest that EUS CPN improves pain. No conclusion can be made about EUS CPNs influence on opioid consumption. Although CPN is a safe procedure, side effects and complications can occur with both the percutaneous and EUS techniques.

Last Search date	Studies identified in review	Bottom Line
May 2011	66	The authors conclude that CPN should be considered in patients with upper abdominal cancer where the pain is not adequately controlled with systemic analgesics or when significant opioid-induced side effects are present; and that the percutaneous approach remains the standard technique as robust evidence for EUS CPN is lacking.

Neurolytic plexus coeliacus block Review 4

Study Reference	Participants	Interventions	Comparators	Outcomes	Study Designs
Kaufman (2010)	Patients (>18 years age) with unremitting chronic abdominal pain due to	Endoscopic ultrasound (EUS)-guided celiac plexus block (CPB) and celiac plexus	nr	Pain assessment and adverse effects	Prospective and retrospective studies

	pancreatic cancer or unresectable pancreatic cancer and requiring narcotic analgesics for pain control.	neurolysis (CPN)			

Results

- Pooled analysis of six studies (221 patients) reported that the proportion of patients with pain relief from Endoscopic ultrasound (EUS)-guided celiac plexus block (CPB) for chronic pancreatitis (CP) was 51.46%
- Pooled analysis of three studies (119 patients) reported that proportion of patients with pain relief from EUS-guided celiac plexus neurolysis (CPN) for pancreatic cancer (PC) was 72.54%
- Transient diarrhea, transient orthostatic hypotension, transient pain and abscess formation were commonly reported adverse events.

Last Search date	Studies identified in review	Bottom Line
Dec 2007	9	Present evidence based on small number of studies with limited sample size suggests Endoscopic ultrasound guided celiac plexus block and celiac plexus neurolysis is effective in pain management associated with chronic pancreatitis and pancreatic cancer. Further prospective randomized controlled studies are needed to evaluate quality of life.

Author(s): Jos Kleijnen
Date: 2016-11-14
Question: Should neurolytic plexus coeliacus block be used for pain due to cancer?
Settings: Treatment by anesthetists
Bibliography: Zhong W, Yu Z, Zeng JX, Lin Y, Yu T, Min XH, et al. Celiac plexus block for treatment of pain associated with pancreatic cancer: a meta-analysis. Pain Pract 2014;14(1):43-51. Nagels W, Pease N, Bekkering G, Cools F, Dobbels P. Celiac plexus neurolysis for abdominal cancer pain: a systematic review. Pain Med 2013;14(8):1140-63. Doi S, Yasuda I, Kawakami H, Hayashi T, Hisai H, Irisawa A, et al. Endoscopic ultrasound-guided celiac ganglia neurolysis vs. celiac plexus neurolysis: a randomized multicenter trial. Endoscopy 2013;45(5):362-9 Eisendrath P, Paquin SC, Delhaye M, Deviere JM, Sahai A. A randomize, double-blinded, multi-center, sham-controlled trial of EUS-guided celiac plexus block for pain due to chronic pancreatitis. Gastrointestinal Endoscopy. Conference: Digestive Diease Week, DDW 2014 ASGE Chicago, IL United States. Conference Start: 20140503 Conference End: 20140506. Conference Publication: (var.pagings). 79 (5 SUPPL. 1) (pp AB168), 2014. Date of Publication: May 2014. 2014. Gao L, Yang YJ, Xu HY, Zhou J, Hong H, Wang YL, et al. A randomized clinical trial of nerve block to manage end-stage pancreatic cancerous pain. Tumour Biol 2014;35(3):2297-301. LeBlanc JK, Al-Haddad M, McHenry L, Sherman S, Juan M, McGreevy K, et al. A prospective, randomized study of EUS-guided celiac plexus neurolysis for pancreatic cancer: one injection or two? Gastrointest Endosc 2011;74(6):1300-7.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Neurolytic plexus coeliacus block	Control	Relative (95% CI)	Absolute		
Pain (follow-up mean 8 weeks; assessed with: Various[1,2])												
11	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	-	-	-	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		

[1] Patients in the CPB groups had a significantly lower pain score at 4 weeks (Mean difference =-0.382 (SE 0.136) p = 0.005) (4 RCTs, 197 patients) but results were not statistically significant at 8 weeks (Mean difference = -0.265 (SE 0.217) p = 0.223) (6 RCTs, 379 patients). CPB groups required fewer drugs compared to control groups at 4 weeks (Mean difference = -0.49.765 (SE 15.242) p = 0.001) (5 RCTs, 231 patients) and at last report (Mean difference = -0.48.290 (SE 10.238) p < 0.001) (5 RCTs, 231 patients).
[2] When compared to medical management alone or pain management using nonsteroidal anti-inflammatories or morphine, the use of a coeliac plexus block was associated with better short term pain relief and significantly lower drug use. While side effects and complications occur with coeliac plexus block, side effects are generally less common and less severe than in the comparator groups.

DREZotomy (1 review)

Study Reference	Participants	Interventions	Comparators	Outcomes	Study Designs
Gadgil (2012)	Various cancer patients treated with DREZotomy	DREZotomy	NR	Pain (visual analogue scale)	Case reports and case series

Results

- In a series of 13 patients with pancoast tumors treated with microsurgical DREZotomy, of them two patients died in the postoperative period, and of the 11 survivors, 10 experienced good pain relief.
- In a series of 367 patients, 81 were treated for cancer pain, a good result (>75% pain relief) was obtained in 87% of patients operated at the cervicothoracic level and 78% of the patients operated at the lumbosacral level with the median postoperative survival of 13 months.

Last Search date	Studies identified in review	Bottom Line
Not reported	14	Available evidence indicates that DREZotomy is a viable treatment option for patients with well localized neuropathic cancer pain intractable to medical and first-line surgical management. Further prospective studies are needed to evaluate the outcomes of this procedure.

Intrathecal medication delivery (1 review)

Study Reference	Participants	Interventions	Comparators	Outcomes	Study Designs
Hayek (2011)	Participants with chronic pain including cancer and non-cancer pain	Intrathecal drug delivery system implant	NR	Primary outcome: Pain assessment (significant pain relief defined as a minimum of 2-point drop on an 11 pain numerical pain scale or a decrease of baseline pain intensity by 30%) Secondary outcome measure: Functional disability, amount of oral medication, side effects from systemic drugs, and improvement in quality of life (QOL).	All designs (prospective, retrospective, technical reports, randomized clinical trials)

Results
▪ The level of evidence for non-cancer pain studies and cancer-related pain studies meeting inclusion criteria of continuous use of an intrathecal drug delivery system for at least 12 and 3 months duration with 25 patients each in the cohort, are at Level II-3 and Level II-2 based on U.S. Preventive Services Task Force respectively. ▪ Insufficient information was available for adequate comparison to other routes of delivery. In addition, there was significant lack of data in regard to the multitude of combinations possible between hydrophilic and lipophilic opioids, local anesthetics, clonidine, baclofen, and ziconotide. ▪ Based on the reviewed evidence, intrathecal therapy is moderately effective and safe in controlling refractory painful conditions that have failed multiple other treatment modalities, both in cancer and non-cancer related conditions. ▪ However, there are significant limitations to these inferences. Significant variability in study design, patient selection, concomitant oral or transdermal opioid use and technical parameters may have important effects on outcomes of intrathecal therapies. ▪ Differences in patient selection, catheter location, medications used, complication rate, and location/type of pain treated may greatly affect outcomes and responses to therapy.

Last Search date	**Studies identified in review**	**Bottom Line**
Oct 2010	1 RCT, 4 observational studies	Intrathecal therapy is moderately effective and safe in controlling refractory painful conditions including cancer. Restriction to English language studies in this review means that eligible studies may have been missed.

Author(s): Jos Kleijnen
Date: 2016-11-14
Question: Should intrathecal medication be used for pain due to cancer?
Settings: Treatment by anesthetists
Bibliography: Hayek SM, Deer TR, Pope JE, Panchal SJ, Patel VB. Intrathecal therapy for cancer and non-cancer pain. Pain Physician 2011;14(3):219-48.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intrathecal medication	Control	Relative (95% CI)	Absolute		
Pain relief (follow-up mean 4 weeks; assessed with: Improvement in VAS)												
1	randomized trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	60/71 (84.5%)	51/72 (70.8%)	RR 1.19 (1 to 1.43)	135 more per 1000 (from 0 more to 305 more)	⊕⊕⊕O MODERATE	CRITICAL
								70.8%		135 more per 1000 (from 0 more to 304 more)		

[1] 4 observational studies and one randomised trial were available. The randomised trial was well performed, but blinding was not possible

Epidural medication delivery (1 review)

Study Reference	Participants	Interventions	Comparators	Outcomes	Study Designs
Kurita (2011)	Adults with cancer pain and healthy volunteers	Spinal opioids inc. epidural morphine, epidural sulfentanil	Opioids, placebo, control group, comprehensive medical management	Pain intensity and adverse events	Randomized controlled trials, non-randomized cohort studies, uncontrolled prospective studies, case series

Results
▪ Spinal opioid therapy might be useful for treating cancer pain that was not adequately controlled by systemic treatment. One study (n=85) reported that use of epidural morphine combination with clonidine showed most prominent effect in reducing neuropathic pain when compared with placebo. ▪ One study (n=28) found that use of epidural morphine showed superior effect in somatic pain. One study (n=20) reported the use of epidural morphine improved pain relief. The most common side effects reported were urinary retention, pruritus, nausea and vomiting.

Last Search date	Studies identified in review	Bottom Line
2009	11 studies	The studies analyzed provide very low quality of evidence and weak recommendation for using spinal opioids alone or in combination with other drugs in adult cancer patients. Future research on spinal therapy is needed to support the current findings.

Author(s): Jos Kleijnen
Date: 2016-11-14
Question: Should epidural medication be used for pain due to cancer?
Settings: Treatment by anesthetists
Bibliography: Kurita GP, Kaasa S, Sjogren P, European Palliative Care Research C. Spinal opioids in adult patients with cancer pain: a systematic review: a European Palliative Care Research Collaborative (EPCRC) opioid guidelines project. Palliat Med 2011;25(5):560-77. He QH, Liu QL, Li Z, Li KZ, Xie YG. Impact of Epidural Analgesia on Quality of Life and Pain in Advanced Cancer Patients. Pain management nursing : official journal of the American Society of Pain Management Nurses 2014. Lauretti GR, Rizzo CC, Mattos AL, Rodrigues SW. Epidural methadone results in dose-dependent analgesia in cancer pain, further enhanced by epidural dexamethasone. Br J Cancer 2013;108(2):259-64.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Epidural medication	Control	Relative (95% CI)	Absolute		
Pain relief (assessed with: VAS)												
4	randomized trials	very serious[1]	serious[2]	no serious indirectness	serious[3]	none	-	-	-	-	⊕OOO VERY LOW	CRITICAL
								0%		-		

[1] 4 small randomized trials comparing different dosages or drugs (3 trials) or same drug epidural versus intravenous
[2] No trials had the same comparisons
[3] Small trials

Neuromodulation (1 review)

Study Reference	Participants	Interventions	Comparators	Outcomes	Study Designs
Lihua (2013) *	Adults aged 18 to 80 with cancer-related pain eligible for Spinal cord Stimulation (SCS)	Spinal cord stimulation	Conventional medicine, physical therapies, complementary therapies, surgery or neuro-ablation techniques	At least 50% pain reduction Health-related quality of life Physical and functional abilities Pain-related anxiety and depression Rate of procedural complications Incidence of technical failures and withdrawal rate Treatment-related mortality	RCTs and non-randomized controlled trials. Only case series were identified

Results
Across four case series over 80% of patients reported at least a 50% reduction in pain intensity. More than 50% of patients reported decreased use of opioid medications. Major complications identified in a small number of patients in two studies included: implantation site infections, cerebrospinal fluid leakage, pain at the sites of the electrodes, dislodgement of the electrodes and system failure.

Last Search date	Studies identified in review	Bottom Line
July 2012	4 case series	This well-conducted review found insufficient evidence to establish the role of SCS in treating refractory cancer-related pain in relation to other interventions. Evidence from case series was generally positive and consistent with the stronger evidence base in non-cancer pain.

*Cochrane Review

Author(s): Jos Kleijnen
Date: 2016-11-14
Question: Should neuromodulation be used for pain due to cancer?
Settings: Treatment by anesthetists
Bibliography: Peng L, Min S, Zejun Z, Wei K, Bennett MI. Spinal cord stimulation for cancer-related pain in adults. Cochrane Database Syst Rev. 2015 Jun 29;6:CD009389. doi: 10.1002/14651858.CD009389.pub3.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Neuromodulation	Control	Relative (95% CI)	Absolute		
Pain												
4	observational studies[1]	serious[1]	no serious inconsistency	no serious indirectness	serious[1]	none	-	-	-	-	⨁OOO VERY LOW	CRITICAL

[1] 4 case series with 92 patients

Cervical cordotomy (1 review)

Study Reference	Participants	Interventions	Comparators	Outcomes	Study Designs
France (2014)	Patients with mesothelioma with intractable pain	Cordotomy (open or percutaneous)	Treatment for pain using other modalities (pharmacotherapy or other neuro-invasive or neuroablative procedures).	Effectiveness in relieving pain and adverse effects.	Any, except reviews and single case reports

Results

- All studies demonstrated good pain relief in the majority of patients. Initial post-procedure measurements showed the greatest reduction in pain.
- Some side effects (headache, mirror pain, motor weakness) occurred relatively frequently but were mostly transient. Respiratory dysfunction post-PCC was rare.
- No deaths were directly ascribed to cordotomy.

Last Search date	Studies identified in review	Bottom Line
March 2012	9 case series	According to the authors, "the available evidence is significantly limited in quantity and quality. Although it seems to suggest that cordotomy might be safe and effective in this setting, more reliable evidence is needed to aid decision making on continued provision. Given the overall low risk of bias in the ROBIS assessment this conclusion is likely to be supported by the evidence.

Author(s): Jos Kleijnen
Date: 2016-11-14
Question: Should cervical (percutaneous)(surgical) cordotomy be used for pain due to cancer?
Settings: Treatment by anaesthetists
Bibliography: France BD, Lewis RA, Sharma ML, Poolman M. Cordotomy in mesothelioma-related pain: a systematic review. BMJ Support Palliat Care 2014;4(1):19-29.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cervical (percutaneous)(surgical) cordotomy	Control	Relative (95% CI)	Absolute		
Pain (follow-up 2-26 weeks; assessed with: Various measures[1])												
9	observational studies[2]	serious[2,3]	no serious inconsistency	no serious indirectness	serious[4]	none	-	-	-	-	⊕OOO VERY LOW	CRITICAL

[1] All studies reported good pain relief in the majority of patients
[2] case series
[3] All studies had one or more shortcomings in the quality assessment
[4] All were small studies ranging from 3 - 53 patients. Only two studies included more than 20 patients.

Author(s): Jos Kleijnen
Date: 2016-11-14
Question: Should neurolytic plexus hypogastricus block be used for pain due to cancer?
Settings: Treatment by anesthetists
Bibliography: Mishra S, Bhatnagar S, Rana SP, Khurana D, Thulkar S. Efficacy of the anterior ultrasound-guided superior hypogastric plexus neurolysis in pelvic cancer pain in advanced gynecological cancer patients. Pain Med. 2013;14(6):837-42. doi: 10.1111/pme.12106.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Neurolytic plexus hypogastricus block	Control	Relative (95% CI)	Absolute		
Global pain intensity[1] (follow-up 1-13 weeks; assessed with: 10cm VAS)												
1	randomized trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	-	-	-	-	⊕⊕OO LOW	CRITICAL
								0%		-		

[1] The VAS-scores in the hypogastric-block-group had decreased significantly after 1 week, 1 and 2 months (about 20 at all times vs. 55, 45 and 35 respectively in the control group). At 3 months, there was no difference in pain scores. No numeric results were given, the data have to be estimated from a figure.
[2] Doubts about adequate blinding
[3] Small trail with 25 patients per group

Intrathecal phenolization of lower sacral roots of cauda equina (lower end block)

Author(s): Jos Kleijnen
Date: 2016-11-14
Question: Should intrathecal phenolisation of lower sacral roots of cauda equina (lower end block) be used for pain due to cancer?
Settings: Treatment by anesthetists
Bibliography: Ischia S, Luzzani A, Ischia A, Magon F, Toscano D. Subarachnoid neurolytic block (L5-S1) and unilateral percutaneous cervical cordotomy in the treatment of pain secondary to pelvic malignant disease. Pain. 1984 Oct;20(2):139-49.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intrathecal phenolisation of lower sacral roots of cauda equina (lower end block)	Control	Relative (95% CI)	Absolute		
Pain relief												
1	observational studies[1,2]	serious[1]	no serious inconsistency	no serious indirectness	serious[1]	none	-	-	-	-	⊕OOO VERY LOW	CRITICAL
								0%		-		

[1] Small case series in 37 patients
[2] 38% of patients treated with phenol 7,5% had complete or partial pain relief, while 80% of the patients treated with 10 and 15% fenol had this effect. Urinary retention, the only complication mentioned, occurred in 17, 60 and 50% respectively. No motor weakness occurred. The analgesic effect was long-lived, i.e. mostly more than 3 months.

POTENTIALLY RELEVANT TRIALS PUBLISHED SUBSEQUENT TO REVIEWS

Intervention	**Study**
Cordotomy	Fitzgibbon (2009)
Coeliac plexus block	Doi (2013)
	Eisendrath (2014)
	Gao (2014)
	LeBlanc (2011)
Epidural medication	Belavy (2013)
	Bertoglio (2012)
	He (2014)
	Lauretti (2013)[2]
Intrathecal medication	Cao (2014)
	Fares (2014)
	Kara (2012)
	Liu (2014)
	Malhotra (2013)
	Mohamed (2012)
Paravertebral block	Bhuvaneswari (2012)
	Chiu (2014)
	Faria (2015)
	Karmakar (2014)
	Yilmaz (2014)
	Zhang (2014)

POTENTIALLY RELEVANT STUDIES WHERE THERE WAS NO SYSTEMATIC REVIEW PUBLISHED BETWEEN 2010 AND 2014

Intervention	Study
Kyphoplasty	Bastian (2012) Berenson (2011) Jarzem (2010) Kurth (2012)
Vertebroplasty	Huang (2014) Li (2013) Orgera (2014) Yang (2012) Yang (2013)
Radiofrequent splanchnic block / Neurolytic nervus splanchnic block	Johnson (2009) Radpay (2009)
Neurolytic plexus hypogastricus block	Ahmed (2015) Huang (2014) Mishra (2013)
Neurolytic peripheral nerve block	No primary studies identified that are published since 2008
Intrathecal phenolization of lower sacral roots of cauda equine	No primary studies identified that are published since 2008

25. Chronic Refractory Angina Pectoris

SYSTEMATIC REVIEWS IDENTIFIED

We identified one review published between 2010 and 2015 of spinal cord stimulation for chronic refractory angina pectoris. See table.

Intervention	Relevant Review (s)	Search end date	Studies included	Meta-analysis
Spinal cord stimulation	Tsigaridas (2015)	April 2014	9 RCTs	No

ASSESSMENT OF THE REVIEW EVIDENCE

Spinal Cord stimulation

Study Reference	Participants	Interventions	Comparators	Outcomes	Study Designs
Tsigaridas (2015)	Patients with refractory angina	Spinal cord stimulation	Not pre-specified. Active, inactive and no treatment comparators were included.	Not pre-specified. Exercise capacity, angina symptoms, health-related quality of life, ischemic burden, complications and mortality were reported.	Randomized Controlled Trials (RCTs)

Results
7 RCTs (186 patients) compared SCS to either optimal medical treatment or inactive mode or low stimulation SCS. In just one of these were all patients to be followed up for 6 months. All trials were small and there were differences in participant characteristics, interventions, comparators, outcomes and length of follow up. Results regarding the benefits of SCS over control for angina symptoms and exercise capacity were inconsistent. Quality of life was measured in different ways with most (but not all) trials showing a statistically significant improvement. Complications were described in two trials, one of which reported mainly undesirable changes in stimulation and another reporting electrode dislocations. 2 RCTs compared SCS to alternative therapeutic interventions. In one trial (104 patients), those receiving a CABG showed improved exercise capacity and ST-segment depression during exercise compared to the SCS group. In this study, apart from lower mortality at 6 months in the SCS group (but not at 5 years) no statistically significant differences were found between treatment groups. One infection and 3 electrode dislocations occurred. In the second trial (68 patients) time to angina during exercise and improvement in CCS angina class in the SCS group was noted but no differences between groups were found at 12 and 24 month follow-up. Twenty-five SCS-related and 4 PMR-related events were reported.

Last Search date	Studies identified in review	Bottom Line
April 2014	9 RCTs	Although this review had a number of methodological limitations, it highlighted the limitations and inconsistencies in the existing evidence base for spinal cord stimulation for the treatment of refractory angina. The recommendation for a larger, well designed RCT appears to be appropriate to determine the role of spinal cord stimulation in refractory angina.

RELEVANT TRIALS PUBLISHED SUBSEQUENT TO THE SYSTEMATIC REVIEW

We identified one trial published subsequent to this review. See Table.

Intervention	Study
Spinal cord stimulation	Eldabe (2015)

Study and Patient Details

Study	Eldabe (2015)
Country	UK
Study Funder	SCS device materials supplied by Medtronic and Boston Scientific
Study Design	RCT
Recruitment dates	Jan 2011 to June 2014
Patient inclusion criteria	≥ 18 years of age, limiting angina despite optimal anti-angina therapy, Canadian Cardiovascular Society functional classification of angina of Class III or IV and angiographically documented CAD considered unsuitable for revascularization by referring cardiologist or cardiothoracic surgeon. Also demonstrable ischemia on functional testing.
Patient exclusion criteria	Comorbidity considered by assessing clinician to render patient unsuitable for neuromodulation, a pacemaker or implanted defibrillator, poor cognitive ability, ongoing anticoagulant therapy were all exclusion criteria.
Mean age (SD)	66
Total no (% male)	29 (72%)
CCS Classification	Class III (18), class IV (11)
Previous treatment	CABG (24), TENS (7), Stents (14), PCI (6), Stellate ganglion blocks (3), anti-angina medications (29) 22 of 29 (76%) were taking 8 or more different cardiovascular medications

Treatment Details

No in intervention	15
No in control	14
Length of trial stimulation	Acute on-table. Trial failure was defined as ≤ 80% paresthesia or painful sensations when temporary stimulator switched on
Treatment details	Treatment performed by health professional with ≥ 15 SCS implants in previous 12 months using local anesthetic. If trial was successful, leads were anchored to

	spine with small incision and connected subcutaneously to implanted pulse generator placed in anterior abdominal wall or buttock. Patients were instructed to adjust SCS device to generate comfortable level of paraesthesia for two hours three times a day, to terminate an angina attack, for as long as necessary or before exertion that might generate angina pain. Patients also received usual care standardised across the four sites. See below for details.
Control details	Usual care standardised for delivery across the four sites. The following was given sequentially from the day of randomisation as clinically appropriate: an education session with a pain consultant; a trial of a TENS; serial thoracic sympathectomy; and oral or systemic analgesics and adjuvant analgesia. Participants who had already failed to obtain pain relief from any of the sequence were moved onto the next therapy. Following completion of the sequence, the physician could use any therapy except repeat CABG, percutaneous revascularisation, percutaneous myocardial laser revascularisation or enhanced counterpulsation.

Outcome Details

Primary Efficacy outcome	This was a pilot, pragmatic trial aiming to address uncertainties before conducting a multicentre, definitive effectiveness trial. Outcomes were gathered relating to trial recruitment and retention, feasibility of trial, feasibility and acceptability of treatment, feasibility and acceptability. The primary patient outcome was disease-specific HRQoL assessed by UK version of Seattle Angina Questionnaire (SAQ) (0 to 100 with higher scores indicating better function). The study was not intended to be powered for this outcome.
Safety assessed?	The nature and frequency of device-specific and non-device complications and adverse events (serious and not serious) were collected at each follow up and between visits.
Length of follow up	6 months

Results

	SCS group	**UC group**	**Mean difference***
SAQ Quality of life 6 months	Mean (SD) 63.5 (21.9)	Mean (SD) 42.8 (22.8)	-22.3 (95% CI: -39.2 to -5.3)
Device-related adverse events	4 (2 superficial infection, 1 pain over implant, one inadequate paraesthesia)	NA	NA
Serious adverse events	2 deaths (judged unrelated to study procedures) 6 hospitalisations (1 SCS-related infection)	0 deaths 6 hospitalisations	NA NA

*adjusted for baseline score and stratification variables

Cochrane Risk of Bias

	Eldabe (2015)	
Randomisation	Low	Computer-generated
Allocation Concealment	Low	Independently managed
Blinding of participants	High	Not possible
Blinding of caregivers	High	Not possible
Blinding of assessors	Low	Nurses conducting exercise assessment blinded
Incomplete outcome data	Low	Treatment failure inc in analysis
Selective reporting	Low	No evidence of this
Other Biases	Low	No evidence of other bias

26. Ischemic Pain in the Extremities and Raynaud's Phenomenon

SYSTEMATIC REVIEWS IDENTIFIED

We identified the following relevant systematic reviews published between 2010 and 2015.

Intervention	Relevant Review(s)	Condition	Search date	Studies Identified in review	Meta-analysis
Sympathectomy	Huisstede (2011)	Raynaud's Phenomenon	Dec 2010	1 of 19 RCTs relevant	N
Spinal cord stimulation	Ubbink (2013) *	Critical leg ischaemia	Jan 2013	5 RCTs and 1 CCT	Y

ASSESSMENT OF THE REVIEW EVIDENCE

Sympathectomy

Study Reference	Participants	Interventions	Comparators	Outcomes	Study Designs
Huisstede (2011)	Patients with secondary Raynaud's phenomenon	Any	Any	Pain, function or recovery with a follow-up time of at least 2 weeks	Systematic reviews and RCTs

Results:

Five reviews and nineteen trials of non-surgical interventions were identified. One trial of percutaneous radiofrequency thoracic sympathectomy was identified. The trial was considered to be of low quality and had 50 participants. T2 and T3 thoracic radiofrequency thoracic sympathectomy was compared to a T2 thermolesion with local application of 0.5mL of 6% phenol. At 3-months follow-up, pain and quality of life improved in both groups but between group differences were not found.

Last Search date	Studies identified in review	Bottom Line
Dec 2010	1 of 19 trials relevant	There is no evidence for effectiveness that T2 and T3 thoracic radiofrequency is better than T2 thermolesion with a local application of phenol to treat secondary Raynaud's phenomenon. The review had a number of limitations, but this overall conclusion appears to be fair.

Spinal Cord Stimulation

Study Reference	Participants	Interventions	Comparators	Outcomes	Study Designs
Ubbink (2013)	Men and women aged > 18 with atherosclerotic nonreconstructable chronic critical leg ischaemia (NR-CCLI)	Spinal cord stimulation	Non-surgical treatment, such as analgesics, vasodilatory or anticoagulant medications and local wound care.	Primary outcome: Limb salvage Secondary outcomes: Pain relief, wound healing, SCS complications, quality of life, and costs	RCTs and Controlled clinical trials

Results:

Six studies (444 patients) were included. In general the quality of the studies was good. Limb salvage after 12 months was significantly higher in the SCS group (risk ratio (RR) 0.71, 95% confidence interval (CI) 0.56 to 0.90; risk difference (RD) -0.11, 95% CI -0.20 to -0.02). The main complications of SCS treatment were implantation problems (9%, 95% CI 4 to 15%) and changes in stimulation requiring re-intervention (15%, 95% CI 10 to 20%). Overall risk of complications with additional SCS treatment was 17% (95% CI 12 to 22).

Last Search date	Studies identified in review	Bottom Line
Jan 2013	5 RCTs and 1 CCT	This review found evidence in favor of spinal cord stimulation when compared to standard conservative treatment in terms of limb salvage for patients with non-reconstructable chronic critical leg ischemia. The authors stated that the benefits must be considered against the possible harms of relatively mild complications and the cost. This Cochrane review was at low risk of bias so conclusions are likely to be reliable.

RELEVANT TRIALS PUBLISHED SUBSEQUENT TO THE SYSTEMATIC REVIEW

We did not identify any RCTs published subsequent to the systematic reviews.

Author(s): Jos Kleijnen
Date: 2017-05-09
Question: Should radiofrequency sympathectomy vs thermolesion sympathectomy be used for Raynaud's phenomenon?
Settings: Treatment by anesthetists
Bibliography: Huisstede BM, Hoogvliet P, Paulis WD, van Middelkoop M, Hausman M, Coert JH, et al. Effectiveness of interventions for secondary Raynaud's phenomenon: a systematic review. Arch Phys Med Rehabil 2011;92(7):1166-80.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Radiofrequency sympathectomy	Thermolesion sympathectomy	Relative (95% CI)	Absolute		
Pain and quality of life (follow-up mean 3 months)												
1	randomized trials	serious[1]	no serious inconsistency	serious[2]	serious[1]	none	-	-	-	-	⊕OOO VERY LOW	CRITICAL
								0%		-		

[1] Small trial in 50 patients, rated as low quality in existing systematic review
[2] Comparison of two methods for same intervention

Author(s): Jos Kleijnen
Date: 2017-05-09
Question: Should spinal cord stimulation vs non-surgical treatments be used for critical leg ischaemia?
Settings: Treatment by anaesthetists
Bibliography: Ubbink DT, Vermeulen H. Spinal cord stimulation for non-reconstructable chronic critical leg ischaemia. Cochrane Database of Systematic Reviews 2013, Issue 2. Art. No.: CD004001. DOI: 10.1002/14651858.CD004001.pub3. 2013.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Spinal cord stimulation**	**Non-surgical treatments**	**Relative (95% CI)**	**Absolute**		
Limb salvage (follow-up mean 12 months[1])												
5	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	-	-	-	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		

[1] At 12 month follow-up, risk ratio (RR) for limb salvage was 0.71, 95% confidence interval (CI) 0.56 to 0.90; risk difference (RD) was -0.11, 95% CI -0.20 to -0.02

28. Pain in Chronic Pancreatitis

SYSTEMATIC REVIEWS / GUIDELINES IDENTIFIED

We identified the most up to date reviews published between 2010 and 2016 of RF nervus splanchnicus block, Spinal cord stimulation or Plexus coeliacus blockade (denervation pharmacological and RF) for chronic pancreatitis. See table.

Intervention	Relevant Review (s)	Search end date	Studies included	Meta-analysis
RF nervus splanchnicus	None identified			
Spinal cord stimulation	None identified			
Plexus coeliacus blockade	Moura (2015)[3]	November 2014	2	Y

The review by Moura aimed to compare endoscopic-ultrasound (EUS) versus percutaneous-guided celiac plexus block.[3]

A review by Kocher and colleagues was found to be out of date. A review by D'Haese covered all treatment options for pancreatitis but did not identify any studies of RF nervus splanchnicus or Spinal cord stimulation. Furthermore, the review did not report findings systematically so was not used to inform results on CPB.
We also identified two possibly relevant guidelines. Both were considered to be out of date.

EVIDENCE FROM SYSTEMATIC REVIEWS

Study Reference	Participants	Interventions	Comparators	Outcomes	Study Designs
Moura (2015)	Patients of any age with pain due to CP based on clinical and radiological criteria	EUS and percutaneous-guided CPB	EUS and percutaneous-guided CPB	Primary outcome: pain relief based on VAS 0-10 before and after procedure (up to 12 weeks). Secondary outcome: Procedure-related complications	RCTs

Results: Two trials were included. Both trials assessed the effect of 10ml bupivacaine followed by 3ml triamcinolone (40mg) on pain and assessed adverse effects. One trial was conducted in the USA and used CT guidance[8] and the other was conducted in India and used a fluoroscopy-guided technique.[9] The total number of participants was 74. Overall, with the exception of pain scores at 4 weeks (in favour of EUS), no differences were identified between EUS and percutaneous CPB for pain relief and rates of complication.

Last search date	Studies identified in review	Bottom Line
Nov 2014	2	According to this review no statistically significant difference was found between EUS and percutaneous CPB for pain relief and complications in chronic pancreatitis. This finding is not robust due to differences between the included trials that were pooled together. Additionally the total number of participants overall was small.

RELEVANT TRIALS

We did not identify any randomized controlled trials of the three interventions published since the previous guidance / systematic review.

OBSERVATIONAL STUDIES

We searched for observational studies published since the previous guidance.[1] The studies we identified can be seen in the table.

Intervention	Study
RF nervus splanchnicus block	DeJean (2013) *
	Verhaegh (2013)[11] and Keulemans (2009)
Spinal cord stimulation	Kapural (2011)

*****conference abstract only

EVIDENCE FROM OBSERVATIONAL STUDIES

RF nervus splanchnicus block

Study	**Verhaegh (2013) (**preliminary results in **Keulemans 2009)**
Setting	Hospital and university hospital, in Belgium and The Netherlands, respectively
Study Design	Case series
Study population	Patients with chronic pancreatitis based on history, calcifications and/or main pancreatic duct deviations on CT, US or MRI. Exocrine insufficiency supported the diagnosis if present.
Patient details	8 male, 3 female, mean age 50 (39 to 59). Upper abdominal pain, eventually radiating into the back. Pain had to be significant, that is: >= 3 episodes requiring opioid analgesics, or >= 1 episode requiring

	hospitalization in the previous 3 months. Pain had to be insufficiently controlled with analgesics (both NSAIDs and opioids). Other upper gastrointestinal pathology excluded. At least 50% pain relief after a diagnostic test block with 0.5% bupivacaine.
Intervention details	Under fluoroscopic guidance a 15-cm 22-G curved RF needle with 10 mm active tip was introduced. Placement was confirmed with contrast and with sensory (50 Hz < 1 V) and motor (2 Hz, < 2 V) stimulation. Two lesions were made at Th11 level, 60 seconds at 80°C, and another two at Th12. The procedure was repeated on the opposite side in case of bilateral pain.
Comparator details	NA
Outcomes	NRS (0-10), duration of effect
Follow up duration	Mean 19 months (1.5 to 55)
Results	11 patients were included, with 18 procedures total. Pain decreased from 7.7 $\underline{+}$ 0.9 to 2.8 ± 2.7 ($p \leq 0.001$). Five patients had a second procedure, two had a third. Pain reduction after the procedures was comparable after the first, second and third procedure. In responders, alleviation of pain persisted for median 45 weeks.

Study	**Dejean (2013)**
Setting	Not reported
Study Design	Case series
Study population	Chronic abdominal non-cancer pain of predominantly visceral origin (determined with epidural differential nerve block) with > 50% improvement after a splanchnic nerve block. No addiction disorder or severe untreated depression.
Patient details	Three patients, 2 female, 1 male, average age 25. One had intractable chronic pancreatitis pain, two had 'dysfunctional chronic abdominal pain'.
Intervention details	Bilateral percutaneous splanchnic nerve radiofrequency ablation at T12. Further details not reported.
Comparator details	NA
Outcomes	Absolute pain relief (baseline minus follow-up), opioid requirement, duration of effect
Follow up duration	6 months
Results	VAS score decreased 4.2 $\underline{+}$2.8 points (baseline 6 $\underline{+}$0.8 to 2.2 $\underline{+}$ 2.7 at one week). Opioid requirement decreased (no data). Average duration of effect 5 months.

Spinal Cord Stimulation

Study	**Kapural (2011)**
Setting	Pain clinics United States
Study Design	Case series (chart review)
Study population	Patients with 'established diagnosis of chronic pancreatitis'.
Patient details	Epidural retrograde differential block suggesting visceral origin of pain, >= 50% pain reduction after splanchnic or celiac sympathetic blocks. Psychological evaluation for implantable devices. There were 30 patients, 20 women and 10 men, average age 44 $\underline{+}$ 15 years, chronic pain duration 7.8 $\underline{+}$ 5 years.

Intervention details	SCS trial for 7-14 days, with SCS system implantation if effective (>= 50% pain relief). 17 patients had one lead implanted, the rest of them two. Lead tip was positioned at T5 (n=10), T6 (n=10), T4 (n=4). Octrode leads were used
Comparator details	NA
Outcomes	VAS (0-10), opioid use
Follow up duration	12 months
Results	24 Patients reported >= 50% pain reduction and had an SCS system implanted. They had pre-trial VAS scores 8 $\pm$ 1.6. One patient was lost to follow-up, in three patients the system had to be removed due to infection (2) or lead migration (1). In the 20 patients with one-year follow-up, pain decreased from baseline and remained low: 3.6 $\pm$ 2, $p < 0.001$. Opioid use decreased significantly and stayed low (p 0.016)

Author(s): Jos Kleijnen
Date: 2017-05-16
Question: Should spinal cord stimulation be used for chronic pancreatitis?
Settings: Treatment by anaesthetists
Bibliography: van Zundert J, Patijn J, Hartrick CT, Lataster A, Huygen FJPM, Mekhail N, et al., eds. Evidence-based interventional pain medicine: according to clinical diagnoses Chichester: Wiley-Blackwell, 2012. Kapural L, Cywinski JB, Sparks DA. Spinal cord stimulation for visceral pain from chronic pancreatitis. Neuromodulation 2011;14(5):423-6; discussion 426-7.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Spinal cord stimulation	Control	Relative (95% CI)	Absolute		
Pain (assessed with: VAS 0-10)												
1	observational studies[1]	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	-	-	-	-	⊕OOO VERY LOW	CRITICAL

[1] In addition to case series described in the previous guideline, one small additional case series was identified.
[2] Case series
[3] Small numbers of patients. In the latest study 30 patients in total.

Author(s): Jos Kleijnen
Date: 2017-05-16
Question: Should endoscopic ultrasound celiac plexus block vs percutaneous guided celiac plexus block be used for chronic pancreatitis?
Settings: Treatment by anaesthetists
Bibliography: Moura RN, De Moura EG, Bernardo WM, Otoch JP, Bustamante FA, Albers DV, et al. [Endoscopic-ultrasound versus percutaneous-guided celiac plexus block for chronic pancreatitis pain. A systematic review and meta-analysis]. Rev Gastroenterol Peru 2015;35(4):333-341.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Endoscopic ultrasound celiac plexus block**	**Percutaneous guided celiac plexus block**	**Relative (95% CI)**	**Absolute**		
Pain[1] (follow-up mean 12 weeks; assessed with: VAS)												
2	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	-	-	-	-	⊕⊕OO LOW	CRITICAL
								0%		-		

[1] The systematic review had a number of statistical errors.
[2] Each study scored 3 out of 5 on the JADAD risk of bias scale.
[3] Two small RCTs with 10/8 and 27/29 people in each group

Author(s): Jos Kleijnen
Date: 2017-05-16
Question: Should nervus splanchnicus block be used for chronic pancreatitis?
Settings: Treatment by anaesthetists
Bibliography: Dejean CN, Veizi IE, Hayek SM, James J. Percutaneous splanchnic nerve radiofrequency ablation in visceral pain: A case series. Reg Anesth Pain Med 2013. Verhaegh BPM, van Kleef M, Geurts JW, Puylaert M, van Zundert J, Kessels AGH, et al. Percutaneous radiofrequency ablation of the splanchnic nerves in patients with chronic pancreatitis: Results of single and repeated procedures in 11 patients. Pain Pract 2013;13(8):621-626. Keulemans Y, Puylaert M, Van Zundert J, Kessels F, Masclee A, Van Kleef M. Percutaneous radiofrequent lesioning of the splanchnic nerves (PRFLSN) in patients with chronic pancreatitis. Results of twelve procedures in eight patients. In: European Journal of Pain. Conference: 6th Congress of the European Federation of IASP Chapters: Pain in Europe 6th, EFIC Lisbon Portugal. Conference Start: 20090909 Conference End: 20090912. Conference Publication: (var.pagings). 13 (pp S45), 2009.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Nervus splanchnicus block	Control	Relative (95% CI)	Absolute		
Pain												
3	observational studies[1]	serious[1]	no serious inconsistency	no serious indirectness	serious[1]	none	-	-	-	-	⊕OOO VERY LOW	CRITICAL
								0%		-		

[1] Very small case series, 11 or fewer patients