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Interventional management of neuropathic pain: NeuPSIG recommendations

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Abstract

Neuropathic pain (NP) is often refractory to pharmacologic and non-interventional treatment. On behalf of the International Association for the Study of Pain Neuropathic Pain Special Interest Group (NeuPSIG), the authors evaluated systematic reviews, clinical trials, and existing guidelines for the interventional management of NP. Evidence is summarized and presented for neural blockade, spinal cord stimulation (SCS), intrathecal medication, and neurosurgical interventions in patients with the following peripheral and central NP conditions: herpes zoster and postherpetic neuralgia (PHN); painful diabetic and other peripheral neuropathies; spinal cord injury NP; central post-stroke pain; radiculopathy and failed back surgery syndrome (FBSS); complex regional pain syndrome (CRPS); and trigeminal neuralgia and neuropathy. Due to the paucity of high-quality clinical trials, no strong recommendations can be made. Four weak recommendations based on the amount and consistency of evidence, including degree of efficacy and safety, are: (1) epidural injections for herpes zoster; (2) steroid injections for radiculopathy; (3) SCS for FBSS; and (4) SCS for CRPS type 1. Based on the available data, we recommend *not* to use sympathetic blocks for PHN *nor* RF lesions for radiculopathy. No other conclusive recommendations can be made due to the poor quality of available of data. Whenever possible, these interventions should either be part of randomized clinical trials or documented in pain registries. Priorities for future research include randomized clinical trials; long-term studies; and head-to-head comparisons among different interventional and non-interventional treatments.

Keywords

Neuropathic pain; Evidence-based recommendations; Neural blockade; Spinal cord stimulation; Intrathecal medication; Neurosurgery; Clinical trials

1. Introduction

Neuropathic pain (NP) afflicts millions of people worldwide and has been estimated to occur in as much as 7% of the population [13]. Many common diseases, injuries, and interventions cause NP by producing lesions in somatosensory pathways in the peripheral or central nervous system [127]. Evidence-based recommendations for pharmacologic treatment have been published [7,37,90], but the management of patients with chronic NP can be complex, and many patients do not respond to treatment, obtain only partial relief of their pain, or experience intolerable adverse effects. The efficacy of non-pharmacologic non-interventional treatments, such as transcutaneous electrical nerve stimulation and cognitive-behavioral therapy, has not been well studied in NP, and their role in patient management therefore remains unclear.

For these reasons, interventional treatments, defined here as “invasive procedures involving delivery of drugs into targeted areas, or ablation/modulation of targeted nerves” for the treatment of pain [2], are often considered for patients with refractory NP. There are large gaps and controversies in the literature describing these interventions. The objective of this article is to present an up-to-date summary of the evidence and to describe recommendations that can be made based on the available evidence

2. Methods

The preparation of this article was conducted under the auspices of the International Association for the Study of Pain (IASP) Neuropathic Pain Special Interest Group (NeuPSIG) with additional support provided by the Neuropathic Pain Institute, both of which have received unrestricted support for their activities from multiple pharmaceutical and device companies. No individuals primarily employed by pharmaceutical or device companies participated in the preparation of this article.

The individuals involved in developing the present recommendations were chosen by the NeuPSIG Executive Committee and Treatment Guidelines Subcommittee to include a representative set of experts in NP and its treatment drawn from a broad array of fields, including anesthesiology, internal medicine, neurology, neurosurgery, and psychology; the size of the group was intentionally limited to promote discussion. Following literature searches, all participants were provided with copies of existing treatment guidelines, systematic reviews, meta-analyses, and clinical trials prior to an in-person meeting, and similar materials published subsequent to the meeting were circulated by e-mail and reviewed [20,25,28,29,34,60,93,100,107,123,129,130,133,137,140,143]. Targeted reviews of the literature on the treatment of NP with nerve blocks (S. Raja), spinal cord stimulation (SCS) (B. Stacey), implantable treatments (S. Mackey), and neurosurgical interventions (R. Levy) were presented during the meeting. Evidence tables for each of these interventions were then completed following the meeting and distributed to all authors. The presentations, the materials distributed before and after the meeting, and the authors' clinical and research experience provide the basis for the recommendations in this article.

Because pediatric NP was not specifically considered, these recommendations may not apply to the treatment of NP in children and adolescents. Surgical decompression for acute and chronic radicular NP was also not evaluated as developing recommendations for this procedure was considered beyond the scope of this article.

NP has recently been defined as "pain caused by a lesion or disease of the somatosensory system" [55]. On the basis of this definition, we evaluated the effects of interventional treatments on disorders or conditions that involve defined pathology of the somatosensory system. For peripheral NP, this includes diagnoses such as postherpetic neuralgia (PHN) and painful diabetic peripheral neuropathy (DPN). For central NP, prime examples are central post-stroke pain and spinal cord injury pain. We also included two diagnoses that are not usually considered to be purely neuropathic: complex regional pain syndrome (CRPS) and failed back surgery syndrome (FBSS). CRPS was included because CRPS type II—formerly called causalgia—is a NP condition that follows nerve injury, and CRPS type I—formerly called reflex sympathetic dystrophy—has a similar clinical presentation except that there is no evidence of injury to a major nerve [11,45,119]. We included FBSS with prominent radicular symptoms. FBSS itself appears to represent a mixed pain syndrome with a strong neuropathic component [10], and radicular symptoms associated with FBSS are likely to be neuropathic in etiology; previous high quality studies have focused on patients with FBSS with prominent radicular symptoms [70,97].

2.1. Search strategy and literature evaluation criteria

Relevant publications were identified through Medline searches (1966–2013), examination of reference lists of relevant published articles and book chapters, and personal knowledge of the authors. In evaluating the literature and developing recommendations, the Cochrane Database and other recent systematic reviews were emphasized [1,4,12,14,15,17–19,24,27,29,39,41,46,51,71,77,78,80–82,97,122–124,129,135]. Evidence of treatment efficacy (generally some form of pain intensity improvement or pain relief) was assessed on the basis of the results of clinical trials, which were evaluated and scored according to the Oxford Centre for Evidence-based Medicine levels of evidence [104]. Given the paucity of high-quality clinical trials evaluating interventional NP treatments, only case reports of 5 or fewer patients were excluded from consideration for these recommendations. Evidence tables were prepared that included: (1) prior systematic reviews of the relevant literature; (2) randomized clinical trials; (3) cohort studies; (4) case-control studies that are both prospective and include at least 20 patients; and (5) any additional study that contributes important information beyond that provided by the previous studies.

Published data were used to evaluate each intervention in terms of efficacy and effectiveness, safety, tolerability [53], and ease of use. The strength of evidence supporting the efficacy and safety of an intervention was summarized in accordance with the Grading of Recommendations Assessment, Development and Evaluation (GRADE) guidelines [47] (Table 1). The authors' recommendations for specific treatments are based on the apparent balance between desirable and undesirable effects; the quality of the evidence; and what is known about the values and preferences of patients regarding the risks and benefits involved, such as how consistently different patients weigh the importance of pain relief against the potential risks of the procedure in question, as per GRADE recommendations [48]. Generally, we did not consider the costs of procedures. The strength of recommendation categories and their intended interpretation are summarized in Table 1.

3. General considerations and recommendations

NeuPSIG recommendations for the pharmacologic treatment of NP [37] considered only treatments with at least two high-quality randomized clinical trials (RCTs). However, there are few RCTs assessing interventional treatments for NP, and many interventions used in clinical practice to treat NP in refractory patients are supported by weak, if any, evidence. Nevertheless, frequently patients with severe NP do not respond adequately to non-interventional treatments. In these guidelines, we have attempted to describe the strength of evidence supporting different interventional treatment options. It is important to emphasize that because of the major limitations of available research, our recommendations should not be used as a basis for reimbursement decisions by third-party payers or other organizations providing coverage of health care costs.

Clinical trials of interventional treatments are particularly challenging to conduct for several reasons. Recruiting well-defined patient samples that are appropriate for and willing to undergo investigation of an invasive therapy and yet are representative of a broader, generalizable patient population is especially difficult. The placebo response, which is substantial in pain trials in general, may be even larger in response to sham surgery and

sham interventions [76]. For example, an intervention, such as arthroscopic surgery for knee osteoarthritis, that seems to improve pain in about half of patients in observational studies, was shown to produce no improvements beyond sham surgery [40,89]. This critical observation should be remembered when interpreting the findings of observational studies and case series. Unfortunately, adequately blinding subjects and investigators to interventional treatments can be very challenging, and even impossible in certain circumstances. Furthermore, the ethics of performing sham procedures on control subjects continues to be debated [88].

The methodology used in existing studies of interventional treatments for NP has varied greatly, and few if any RCTs have been conducted for several of the interventions we discuss. The literature is limited by the lack of double-blind methods, randomization, patient samples with homogeneous diagnoses, appropriate comparison groups, standardized assessment of treatment outcomes, and agreement on the definition of a successful treatment response. The variability in assessed outcomes, particularly how and when pain intensity or disability is measured, is especially problematic since it precludes combining data across studies with different methods in a meaningful way.

In addition, there has been limited attention to demonstrating the impact of these interventions on health-related quality of life, including physical and emotional functioning [38,128]. Moreover, there are few head-to-head comparisons of interventional treatments, not only compared with each other but also with pharmacologic and non-pharmacologic, non-interventional treatments. This makes it difficult to evaluate the relative efficacy and safety of different interventions.

The duration of patient follow up across studies has varied greatly. Unfortunately, there are no standard definitions of short-term and long-term response to guide investigators when designing clinical trials. In some cases, such as certain types of injections, a single treatment may provide short-term benefit, but whether long-term benefit can be achieved by repeated injections spaced over varying time intervals has not been demonstrated. In general, more invasive interventions (such as device implantation or surgery) should be studied for longer periods of time, with several years of follow up typically needed to determine whether the benefits are likely to outweigh the risks over time.

All therapeutic interventions have potential risks, but invasive interventions, as a group, carry additional potential risks from the procedure including, for example, local infection, hematoma, and short or long-term nerve damage. In addition, interventions with implantable devices, such as spinal cord stimulation and intrathecal medication delivery, carry additional longer-term risks, such as elevated ongoing infection risk, local scarring, and increased pain over time. Unfortunately, there is generally very little evidence to define the long-term complication risk from the invasive treatment options for NP. Recent complications from invasive procedures, including fungal meningitis following intrathecal injection of contaminated steroid [www.fda.gov/Drugs/DrugSafety/FungalMeningitis/ucm325037.htm] and the recall of hip prostheses due to unexpected local and systemic inflammatory reactions to the prosthesis [e.g., http://www.fda.gov/safety/recalls/ucm311043.htm], highlight the possibility of severe and unexpected reactions to invasive procedures and implants.

4. Peripheral NP conditions

4.1. Herpes zoster

The role of neural blockade in the treatment of herpes zoster has been reviewed [71]. Two RCTs [105,142] suggest that epidural blocks with local anesthetics combined with steroids soon after the onset of herpes zoster can result in a decrease in pain and allodynia. Another RCT found that paravertebral block with local anesthetics and steroids improved pain from herpes zoster [56]. In one of these studies, a single epidural injection of methylprednisolone and bupivacaine resulted in a modest benefit at 1 month (48% with pain in epidural steroid group vs. 58% with standard therapy) [142] whereas paravertebral injections every 48 hours for 1 week resulted in a larger benefit (13% with pain in the paravertebral injections group vs. 45% with standard therapy) [56]. At 3, 6, and 12 months post-therapy, the incidence of PHN continued to be significantly lower in the paravertebral group than in the standard therapy group [56].

Studies of neural blockade in herpes zoster vary in the number, frequency, and duration of the blocks and hence are difficult to interpret with regard to the optimal number and frequency of the procedures. Available evidence indicates that serious adverse events in these studies are uncommon. The results of RCTs are consistent with the results of several observational and cohort studies of epidural local anesthetics alone or combined with steroids in herpes zoster [71]. Considered together, the moderate quality of the evidence provides the basis for a weak recommendation for epidural or paravertebral local anesthetic and steroid nerve blocks as a symptomatic treatment for relief of acute pain associated with herpes zoster. The authors suggest reserving nerve blocks for patients who fail aggressive oral pharmacotherapy, although there is no evidence that they have efficacy in these specific patients; the number of procedures and interval between them should be guided by the clinical response of the patient.

The results of recent RCTs [56,105] suggest that neural blockade – including repeated epidural injections and paravertebral injections of local anesthetics and steroids early in herpes zoster – may prevent PHN. However, a single epidural injection within 7 days of the onset of herpes zoster did not significantly reduce the prevalence of chronic pain over a six-month follow-up [142].

4.2. Postherpetic neuralgia (PHN)

Some non-randomized trials assessing sympathetic blockade in PHN have failed to demonstrate benefit, and there is very little data to suggest a beneficial effect [71,103,149]. Based on the available evidence, we recommend that the use of sympathetic nerve blocks in PHN should generally be avoided (recommendation against use on the basis of generally consistent low quality evidence indicating no benefit) [cf. 142]. There are inadequate data to draw any conclusion regarding the use of peripheral somatic nerve blocks in the treatment of PHN.

The efficacy of intrathecal methylprednisolone has been examined in three RCTs. In the first, intrathecal administration of methylprednisolone was more effective than epidural administration [66], but the sample size was only 25 patients divided into the two arms.

Subsequently, the same researchers reported efficacy over 1–2 years for four intrathecal injections of methylprednisolone and lidocaine performed over one month compared with lidocaine alone and with a no treatment control group [69]. The reported results of this trial are striking, and inconsistent with other studies of PHN and with clinical experience. A number of important criticisms of the study methodology have been described, including inability to solubilize the methylprednisolone in the described solution [118], patient difficulty tolerating the injections in the described position [74,95,151] and a lack of biological plausibility [94]. Since that trial, an independent research group attempted to replicate the findings but the trial was terminated early after all 6 patients randomized to intrathecal methylprednisolone experienced an increase in pain at 8 weeks (compared to 1 of 4 in the control group) [111]. Despite the previous favorable results [69], the authors believe that concerns about the reproducibility of the results of this single RCT and the potential risk of adhesive arachnoiditis [75,110,148] and other serious complications, such as fungal meningitis [www.fda.gov/Drugs/DrugSafety/FungalMeningitis/ucm325037.htm], warrant an "inconclusive" recommendation, with any use of this treatment approach limited to formal clinical trials and not routine clinical care.

Deer et al. [34] reviewed a considerable number of trials examining the effectiveness of various opioid and non-opioid medications with implantable intrathecal medication delivery (IMD) in the treatment of refractory NP. Unfortunately, there are no studies evaluating these therapies specifically in patients with PHN. Likewise, randomized trials of SCS for the treatment of PHN have also not been reported, although a prospective case series of patients with either herpes zoster or PHN has appeared [49]. The use of deep brain stimulation (DBS) has been described in a limited number of patients with PHN, with four of 11 patients being considered responders [29].

A recent double-blind RCT compared pulsed radiofrequency (PRF) treatment with sham therapy in 96 patients with PHN affecting the thoracic dermatomes [59]. PRF treatment of the intercostal nerve at the level of the zoster lesion, and the segments above and below, was done once a week for three weeks. Post-procedure pain scores and tramadol use were decreased, and several health-related quality of life domains were significantly improved through 6 months after treatment in the PRF group compared to the sham group. These results are similar to the reports from open-label studies of a reduction in pain during a 12-week follow up period after PRF treatment of the affected cervical, thoracic, or lumbar DRG in patients with PHN [67]. No complications were encountered in these studies. Although these preliminary studies are encouraging, the results need to be replicated and the recommendation for the role of PRF for PHN was considered "inconclusive."

Given the low quality of the available evidence and the potential for adverse events, further research will be needed before IMD, SCS, and DBS can be recommended for PHN ("inconclusive" recommendation).

4.3. Painful diabetic and other peripheral neuropathies

Neural blockade has not been studied in patients with painful DPN and other polyneuropathies. Very small, prospective trials have evaluated the effects of SCS on pain in patients with refractory DPN [31,36,125], often demonstrating large benefits although the

complication rate was 33% in one of the trials [36]. There is additional indirect support from studies examining patients with peripheral vascular disease, including patients with DPN [131,132]. As with PHN, there have been no clinical trials that have specifically evaluated the efficacy of IMD with implantable pumps in patients with painful DPN [34]. A systematic review by the EFNS found weak but positive results for DBS in peripheral NP, with 70% of the small number of patients showing long-term benefit [29]. Given the low quality of the available evidence and the potential for adverse events, additional clinical trials are necessary before SCS, IMD, and DBS can be recommended for painful DPN and other polyneuropathies ("inconclusive" recommendation) [cf. 107].

A recent high-quality systematic review found 11 case series examining surgical decompression in patients with DPN [20,28]. Eight of the 11 studies reported pain score improvements among patients undergoing decompression. Lee et al. [72] found that good outcomes were predicted by the presence of a positive Tinel sign pre-operatively in both diabetic and non-diabetic patients. Because of the low methodologic quality of the studies and the variability in the characteristics of included patients, surgical approaches, and reported outcomes [20], this intervention cannot be recommended as a treatment for painful peripheral neuropathy until high quality studies are conducted in which pain relief is a primary outcome measure, perhaps especially in patients with electrophysiologic evidence of nerve compression.

4.4. Peripheral nerve injury and brachial plexus avulsion

In certain rare instances (e.g., if pain is experienced within the sensory territory of a single nerve and that nerve is both distal and purely sensory in function or if a neuroma has formed as a result of nerve injury) ablative procedures of a peripheral nerve may be considered as a treatment for chronic NP [9,120]. Dorsal root entry zone (DREZ) lesioning is considered by some to be the procedure of choice for the treatment of NP due to brachial or lumbosacral plexus nerve root avulsion [6]. More than a dozen case series have been published with success rates of between 54 and 100% [18], but rigorous clinical trials are absent from the literature. Unfortunately, the quality of the evidence supporting these surgical procedures is low and consistent with an "inconclusive" recommendation.

5. Central NP conditions

5.1. Spinal cord injury NP

SCS has established efficacy in other chronic NP conditions and is among the more reversible of interventions. However, there are only low quality case series of SCS for patients with NP associated with spinal cord injury [29,100]. As noted previously, most of the trials examining the effectiveness of IMD in chronic pain have included heterogeneous groups of patients, making it difficult to know how applicable the results are to specific NP conditions. One very small, proof-of-concept randomized crossover trial assessed outcomes 6 hours after different intrathecal treatments in 15 patients with NP following spinal cord injury, but the trial was inconclusive and its results cannot be extrapolated to chronic management [113]. The available evidence regarding the use of DBS and DREZ lesioning in NP associated with spinal cord injury also consists of only case series, with relatively

unimpressive reported outcomes [5,29]. These low quality data are consistent with "inconclusive" recommendations for the use of SCS, IMD, DBS, and DREZ lesioning in spinal cord injury pain.

5.2. Central post-stroke pain

A rigorous systematic review granted a weak recommendation for the use of MCS in central post-stroke pain [29]; however, we consider the evidence base weak because it consists of case series [102] and a brief report in which patients who failed SCS were treated with either MCS or DBS [58]. There have been a number of case series examining motor cortex stimulation (MCS) and DBS for the treatment of central post-stroke pain with relatively unimpressive results [29,58]. This low quality evidence is consistent with an "inconclusive" recommendation for MCS and DBS in the treatment of central post-stroke pain.

SCS was evaluated in a series of 45 patients with refractory post-stroke pain, with only 3 achieving a 60% pain score reduction [58]. Although the quality of the evidence is low and only consistent with an "inconclusive" recommendation, the authors believe that SCS should generally not be used in post-stroke pain given the unfavorable case series results, with use of this treatment approach generally limited to research studies.

6. Radiculopathy and failed back surgery syndrome

6.1. Lumbosacral and cervical radiculopathy

Epidural steroid injection is a commonly used intervention for the treatment of chronic spinal pain in patients with radiculopathy. Epidural steroids have been administered using various approaches, such as the interlaminar, transforaminal, and caudal routes, as well as at varying sites along the neuraxis depending on the symptomatic region. This variability in treatment approaches, along with widely variable trial methodology, patient populations, and results, combine to make it challenging to draw definitive conclusions from the evidence [27].

A recent high-quality systematic review, commissioned by the American Pain Society (APS), gave a weak recommendation for the use of epidural steroid injection for patients with radiculopathy with prolapsed lumbar disc, based on fair evidence of moderate benefit for short-term (≤3 months) outcomes; shared decision-making was also recommended, given inconsistencies in evidence and the lack of demonstration of long-term benefits [23]. It was also concluded that there is insufficient evidence to recommend a specific treatment strategy (e.g., route of approach, type of steroid, or number of treatments). Since the completion of this guideline, Iversen and colleagues [54] published the results of a high-quality RCT showing no significant benefits of caudal injection of epidural steroids for chronic lumbar radiculopathy compared to saline epidural injection or subcutaneous saline injection. In an accompanying editorial, Cohen remarks on the inconsistency of the evidence across trials, but notes that the entirety of evidence supports the conclusion that some patients benefit from epidural steroid injection [26].

The American Society of Interventional Pain Physicians (ASIPP) grouped epidural injections for disc herniation or radiculitis into three categories: caudal, interlaminar, and

transforaminal [79]. On the basis of a systematic review for lumbar disc herniation with or without radiculitis, the ASIPP guidelines give a strong recommendation based on strong/moderate quality evidence for caudal epidural injections; a strong recommendation based on low quality evidence for short-term relief and a weak recommendation based on moderate quality evidence for long-term relief with interlaminar epidural steroid injection; a strong recommendation based on low quality evidence for lumbar transforaminal injection; and a strong recommendation based on low quality evidence for the use of cervical interlaminar steroid injection [84]. Some of the authors of the ASIPP guideline subsequently published a lengthy critique of the APS guideline [85], which was said to contain numerous inaccuracies [22]. The cause of several discrepancies between the guidelines are discussed in the APS authors' rebuttal to the ASIPP critique [22].

Another systematic review focused on placebo-controlled RCTs in spine patients and concluded that transforaminal epidural steroid injection for acute or subacute radicular pain has beneficial short-term effects and possibly also long-term benefits on pain and prevention of future spine surgery [73]. A critique of this review suggested that the author focused too much on positive results from RCTs and under-represented the effects of negative trials and inconsistent outcomes from different trials [21]. An additional review gave a weak positive recommendation for transforaminal corticosteroid injection [133]. Two more recent systematic review and meta-analysis of RCTs concluded that transforaminal injections of corticosteroids produce modest pain score reductions at 3 months, but no significant differences at 12 months [106,108]. Cohen et al. [27] systematically reviewed the literature and reported that RCTs were more likely to demonstrate a positive effect when the transforaminal technique was used (>70%) as compared to caudal (~60%) and interlaminar (50%) techniques. These authors also reported that there was a very strong association between the specialty of the author and the results of both RCTs and review articles, with 75% or more of RCTs and reviews conducted by pain physicians being positive, compared to only ~30% of RCTs and review articles authored by non-pain physicians [27].

Considering the available evidence, our assessment of the literature is consistent with the APS guidelines. We believe the evidence of benefit is moderate and supports a weak recommendation for the use of epidural injection for short-term benefits, although there is insufficient evidence regarding pain relief beyond 12 weeks or for prevention of future spine surgery.

An important possible pitfall of interlaminar epidural steroid injection is that the injectate can miss the targeted ventral epidural space in up to 40% of cases [147]. Recently, a transforaminal approach has been advocated based on the observation that when the needle is appropriately placed under fluoroscopic guidance, the injectate spreads to the ventral epidural space in almost all cases [79]. RCTs comparing the effects of transforaminal with interlaminar epidural steroid injections have produced mixed results [3,68,109,126]. As noted previously, Cohen and colleagues reported that a higher percentage of RCTs assessing the transforaminal technique have been positive compared to RCTs assessing the interlaminar technique [27].

Cervical epidural steroid injection can be effective [84]. However, this approach should be used with considerable caution due to reports of such adverse events as spinal cord and brainstem injury and persistent neurological complications [91].

Potential complications of these procedures include inadvertent dural puncture, epidural hematoma, infection, epidural abscess, intracranial air injection, nerve injury, intravascular injection, and spinal cord injury. These complications are relatively infrequent when experienced clinicians perform the procedures, although considerable caution should be exercised when utilizing the transforaminal technique in the cervical region. It is possible that transforaminal injections conducted under fluoroscopic guidance are more effective than interlaminar epidural approaches, but this has not been established definitively in controlled trials. Unfortunately, the literature fails to provide clarity regarding the optimal frequency, timing, and number of epidural steroid injections for the treatment of radicular neuropathic pain in the extremities [23,101].

Radiofrequency (RF) denervation (or lesioning) is a procedure where a peripheral nerve or sensory ganglion is ablated using the heat generated from a continuous high frequency alternating current. Although RF lesioning of nerves has been primarily examined for the relief of pain of zygapophyseal joint origin, a few trials have examined its efficacy in radicular pain at cervical and lumbar levels [14,82,135]. In contrast, the pulsed radiofrequency (PRF) technique is considered to be non-destructive, exposing the neural tissue to a high-frequency electric field without raising the temperature of the electrode tip beyond 42°C. Several uncontrolled trials suggest a beneficial effect of continuous and PRF treatment near the dorsal root ganglion for radicular pain, but few RCTs have been reported.

The initial optimism for the role of RF lesioning of the DRG for lumbosacral radiculopathy has not been supported by the results of RCTs. RF treatment adjacent to the cervical dorsal root ganglion as a treatment for cervical radicular pain has been examined in two RCTs. Van Kleef et al. [139] compared RF lesioning to sham therapy in 20 patients and reported a higher rate of successful outcome in the RF group compared to the sham group two months after treatment. Slappendel et al. [116] compared the effects of RF lesioning with electrode tip temperatures of 40°C vs 67°C in 61 patients with cervical radicular pain and observed similar success rates in the two groups 3 months after therapy. Because the study lacked a control group and RF was compared to historical controls, the lack of a difference between the two groups does not provide convincing evidence for a benefit of RF treatment. In a double-blind RCT, RF lesioning of the DRG was compared to sham therapy and failed to demonstrate any significant benefit in 83 patients with lumbosacral radicular pain [44].

The beneficial effect of PRF therapy for the treatment of lumbosacral radiculopathy has been described in case reports, clinical audits, and retrospective and prospective studies [92,134]. An RCT with a small sample size suggested that PRF treatment of the DRG and segmental nerve roots was more effective in reducing pain up to 12 months after treatment compared to a control group that received nerve root block with local anesthetics [43]. A case series [144] and one small RCT [145] in 23 patients with cervical radicular pain by the same group of investigators suggest that PRF may have a short-term (i.e., 3 months) beneficial effect in select patients with cervical brachialgia.

In summary, there is limited evidence of a potential short-term benefit of RF lesioning and PRF therapy in the treatment of chronic cervical radicular pain ("inconclusive" recommendation). These recommendations are similar to that of van Boxem et al. [135] who concluded that PRF of the DRG for cervical radicular pain may be indicated for a selected group of patients with chronic cervical brachialgia. For the treatment of lumbar radiculopathy, there is limited evidence for the beneficial effects of PRF of DRG and segmental nerve roots ("inconclusive" recommendation), and no evidence of benefit of RF lesioning (recommendation "against") [23].

Adhesiolysis, via a percutaneous or a spinal epiduroscopic approach, has been studied in patients with low back pain and radiculopathy. This procedure is based on the hypothesis that epidural adhesions contribute to the generation of pain and/or limits access of pain-relieving drugs to their intended sites of action. Studies have compared the benefits of adhesiolysis with varying combinations of saline or hypertonic saline, hyalurinodase, and steroids, using a fluoroscopic guided percutaneous catheter or epiduroscopic visualization of the adhesions. Although observational studies reported short and longer term benefits, the results of controlled trials have yielded contradictory results. One RCT found significant reductions in pain and disability scores at 3 months, but concerns about the design of this trial limit the confidence in its conclusions [146]. A recent critical review of the evidence led the authors to conclude that there is insufficient evidence to warrant a recommendation for the use of adhesiolysis outside of the context of a research study [133]. Overall, the evidence is of low quality, and an "inconclusive" recommendation is given.

6.2. Failed back surgery syndrome (FBSS) with prominent radicular symptoms

FBSS is a heterogeneous condition, and patients present with different types of pain that reflect a wide variety of potential pathophysiologic mechanisms, including persistent spinal or foraminal stenosis, surgery-associated root or other injuries to nerves, and nerve entrapment in scar tissue. Axial low back pain in FBSS is at least partly non-neuropathic in origin; we therefore focus on the management of FBSS with prominent radicular symptoms.

We did not find studies assessing the efficacy of epidural steroid injection for treating patients with FBSS who have prominent radicular symptoms ("inconclusive" recommendation). However, on the basis of the evidence reviewed above for the efficacy of epidural steroid injections in the treatment of radiculopathy and their relative safety and ease of application, the authors believe epidural steroid injections are a reasonable treatment option for clinicians and patients to consider when a patient has failed to respond to less invasive treatments and prior to considering more invasive treatments, such as SCS.

Adhesiolysis has been studied in patients with FBSS. A recent systematic review concluded that there is "fair evidence that percutaneous adhesiolysis is effective in relieving low back and/or leg pain due to post lumbar surgery syndrome or spinal stenosis" [52]. Manchikanti et al. [83,86,87] reported improved pain and disability following adhesiolysis for patients with FBSS with leg pain, but these studies do not report the effects on the neuropathic (i.e., radicular leg) pain (as opposed to the back pain, which is not necessarily neuropathic). Hence, it is unclear what effect adhesiolysis has on NP associated with FBSS. Although

adhesiolysis may help some patients with FBSS, we conclude that the evidence of efficacy for NP associated with FBSS is uncertain and give an “inconclusive” recommendation.

There are two RCTs evaluating SCS for patients with treatment-refractory FBSS with prominent radicular symptoms. In the first, North et al. [97] studied 50 patients with leg pain greater than back pain who were considered to be candidates for reoperation following spinal surgery. Patients were randomized to reoperation or treatment with SCS and were allowed to cross over to the other treatment if they were not satisfied with the results of treatment, with “success” defined as patient satisfaction with treatment and a 50% or greater reduction in pain. Forty-five patients were available for evaluation an average of 3 years postoperatively. A successful outcome occurred in 9/19 SCS patients versus 3/26 of the reoperation patients, and the rate of crossover to alternative treatment was lower in the SCS patients (5/24) than in the reoperation patients (14/26); both of these group differences were statistically significant. The study had a high crossover rate and the sample may not be representative of FBSS patients as a whole given wide variability in coverage of these procedures.

In the second RCT of SCS in patients with FBSS, 100 patients with leg pain greater than back pain were randomized to conventional medical management (CMM) alone or CMM with SCS. The primary outcome measure was the proportion of patients obtaining at least 50% relief of leg pain at 6 months [70], after which patients were allowed to cross over. Eighty-eight patients were available for analysis, with 28/52 subjects originally assigned to CMM crossing to SCS and 5/28 SCS patients crossing to CMM. Intention-to-treat analyses yielded 48% success for SCS and 9% success for CMM at 6 months, and 34% and 7% success respectively at 1 year. Of concern, thirty-one percent of the SCS patients available at 2 years had required device-related surgical revision. Limitations of this study include the lack of standardized definition of NP, the lack of standardized CMM, a relatively short duration of primary assessment, and the high crossover rate. Based on the strength of these trials, an independent systematic review concluded that SCS appears to be more effective than CMM and reoperation [115]. The EFNS guidelines for neurostimulation for NP gave SCS a weak recommendation for FBSS [29].

Other prospective studies have compared percutaneous to laminectomy electrodes [99] and dual-lead to single-lead systems [98], and multiple case series have reported favorable outcomes with SCS in FBSS. The results of the RCTs summarized above and these studies [100] support a weak recommendation. Based on the degree of invasiveness, risk of complications, and the relatively low response rate of SCS, the authors suggest reserving SCS for patients who fail less invasive treatment options, including consideration of a trial of epidural steroid injections. New stimulation parameters, such as high frequency stimulation [136], burst stimulation [35], and anatomical sites, such as dorsal root or dorsal root ganglion stimulation, are being explored as potential strategies to improve the efficacy of neuromodulation at the level of the spinal cord. The long-term effectiveness of these strategies needs to be determined with further studies.

As noted above, various opioid and nonopioid medications with implantable IMD in the treatment of refractory chronic pain have been examined in multiple studies, but the lack of

long-term RCTs and the heterogeneity of the patients studied and the treatments used makes it difficult to draw conclusions for FBSS with radiculopathy [32–34] (“inconclusive” recommendation).

There have been no randomized, prospective studies of DBS in patients with FBSS, but a total of 59 patients have been described in case series with a long-term success rate of 78% [29]. The available data are of low quality and warrant an “inconclusive” recommendation.

7. Complex regional pain syndrome (CRPS)

The potential benefits of sympathetic blockade with local anesthetics in patients with CRPS have been systematically reviewed [17,121]. Two very small, randomized crossover studies, only one of which has been published, showed modest benefits 2 days after a local anesthetic sympathetic block. However, no RCTs have evaluated benefits of sympathetic blockade over weeks or months. A case series of 25 subjects who had 3 stellate ganglion blocks at weekly intervals for upper extremity CRPS reported that 40% of patients had complete pain relief, 36% had partial pain relief and 24% had no pain relief over a six-month observation period [4]. There may be a correlation between shorter duration of symptoms and greater efficacy of sympathetic blockade, but further study of this is required. Although the quality of evidence is low, justifying an “inconclusive” recommendation, the treatment options for CRPS refractory to other management strategies are limited. Given ease of application, relative safety, and their clinical experience, the authors consider sympathetic blocks a reasonable treatment option to consider for patients refractory to pharmacologic and non-pharmacologic non-interventional treatments, especially when conducted early in the disease course and when the patient favors such treatment before consideration of the more invasive SCS.

SCS has demonstrated efficacy in CRPS type 1. Kemler et al. [60] reported a prospective, randomized trial of 54 patients with CRPS type 1 randomized on a 2:1 basis to SCS with physical therapy or physical therapy alone. Two-thirds of the patients randomized to a trial of SCS went on to implantation. At 6 months, pain was reduced in the SCS group by 2.4 cm on a 10-cm visual analogue scale of pain intensity versus a 0.2 cm increase in the comparison group. Furthermore, 39% of SCS patients compared to 6% of control patients rated themselves as “much improved.” Subsequent reports of this sample revealed that vasodilation was not associated with pain relief [61], sensory characteristics of CRPS other than pain did not change with treatment [65], and cervical and lumbar devices were equally effective [42]. Follow-up data at 2 years revealed continued benefit of SCS [62] but subsequent evaluations at 3, 4, and 5 year follow ups failed to demonstrate outcome differences between the groups [63], suggesting that the benefit of SCS may diminish with time. However, an analysis of the 5-year data from those patients who were actually implanted with an SCS system (mirroring the clinical practice of excluding those who did not have a positive trial) showed improvements in pain relief and global perceived effect. Ten of 24 (42%) implanted patients underwent reoperation by 5 years for a total of 29 complications, but 95% of those implanted indicated that they would repeat the procedure with the knowledge that they would have the same outcome [64].

In a prospective trial of 29 patients with CRPS type 1 who had temporary pain relief with a sympathetic block, Harke et al. [50] demonstrated numerous benefits after an average of 3 years, including reduced pain, improved function, and reduced medication. Pain relief in these patients was much greater with the stimulator on than during comparative periods in which the stimulator was switched off.

An independent systematic review concluded that there was evidence of efficacy of SCS relative to CMM in patients with CRPS type 1 [115]. The EFNS gave a weak recommendation for SCS for CRPS type 1 [29]. We agree that the moderate quality evidence in support of SCS as an interventional treatment for CRPS type 1 supports a weak recommendation, while the lack of evidence for patients with CRPS type 2 warrants an "inconclusive" recommendation. The authors suggest reserving SCS for patients with CRPS who do not respond adequately to non-invasive treatments and sympathetic nerve blocks or for whom nerve blocks are determined to be inappropriate.

Two small studies have shown benefit of intrathecal baclofen for the treatment of dystonia associated with CRPS [138,141], although, similar to other IMD studies, a large number of adverse events occurred with treatment. Taking into consideration available evidence and the potential for complications, intrathecal medication for CRPS is given an "inconclusive" recommendation for patients with CRPS.

Favorable responses associated with local anesthetic sympathetic blockade have led some clinicians to perform destructive procedures targeting the autonomic nervous system in an effort to produce a permanent interruption in the transmission of sympathetically-maintained pain. Multiple techniques have been employed to accomplish this, including chemical neurolysis (usually performed with phenol or alcohol), and radiofrequency or surgical ablation. Available literature describing these techniques consists of either uncontrolled case series or poorly controlled comparison studies [121]. Furthermore, there is a significant risk of patients developing post-ablation pain conditions that are often worse than the original pain [57]. The authors believe that ablative procedures of autonomic structures for NP should be avoided given the weak evidence and potential for serious sequelae associated with these interventions.

Finally, the use of repeated ketamine infusions in patients with CRPS has recently received considerable attention. A recent systematic review [8] identified two randomized trials [112,114] and several case series of repeated ketamine infusons. Despite positive results from moderate quality studies, the authors believe that concerns about the risks of this treatment – including drug-induced liver injury [96] – have not yet been adequately addressed and provide the basis for our "inconclusive" recommendation, with use ideally occurring in clinical settings that can enroll patients in prospective studies that include careful evaluation of effectiveness and safety.

8. Trigeminal neuralgia (TN) and trigeminal neuropathy

Systematic reviews of interventional treatments for patients with medically-refractory TN have been published recently [18,30,46,77,78,150]. There are few RCTs or prospective cohort studies and very few direct comparisons of the effectiveness and safety of different

procedures; most studies of interventional treatments for TN are uncontrolled case series. Considered together, these evidence-based reviews conclude that surgical procedures directed at the peripheral trigeminal nerve are either ineffective or that there is insufficient evidence to demonstrate their effectiveness. Although the reviews differed somewhat regarding their ratings of the quality of the studies of percutaneous procedures directed at the trigeminal ganglion, there was agreement that the available evidence suggests benefit from these procedures. The evidence for microvascular decompression (MVD) and radiosurgery also suggests potential for benefit among medically-refractory TN. Among surgical interventions for TN, MVD appears to provide the longest duration of pain control and greatest long-term patient satisfaction [46,122,140].

Considering the available systematic reviews and clinical trials [18,30,46,77,78,150], the low quality evidence is consistent with an “inconclusive” recommendation for MVD, radiofrequency rhizotomy, glycerol rhizotomy, balloon compression, and stereotactic radiosurgery in the treatment of patients with TN. Nevertheless, many medically-refractory patients with TN seem to benefit from these treatments. The authors suggest that consideration should be given to using interventional treatments in patients who are refractory to pharmacologic treatment for TN. Because direct comparisons of the efficacy of these different interventions are lacking [46], choosing among them involves considerations of patient age, history of previous surgical procedures, characteristic symptoms and severity of pain, medical comorbidities (especially multiple sclerosis or other conditions that can cause TN), the presence or absence of a compressive vessel demonstrated on MRI, and physician and patient preference [117].

8.1. Trigeminal neuropathy

There are multiple small case series of MCS in patients with peripheral neuropathic facial pain that have generally reported clinically meaningful pain relief in a majority of patients treated with this intervention [29]. As with MCS, there have been several small case series describing the treatment of facial NP with DBS. Although these data include very early experience with this therapy and the contemporary rate of success may be higher, the available evidence for MCS and DBS in patients with facial NP is low quality and can only support an “inconclusive” recommendation.

9. Conclusions

Interventional management is often considered for patients with NP who have not responded adequately to pharmacologic treatments used alone or in combination with non-pharmacologic treatments. It is important to emphasize that the interventional management of patients with chronic NP should be considered an integral component of a more comprehensive approach that also includes pharmacologic and non-pharmacologic, non-interventional treatments. Although the evidence for the efficacy of various pharmacologic treatments in patients with NP is considerable [7,37,90], this is much less true for non-pharmacologic treatments for NP, which require evaluation in RCTs.

Because of the important limitations of the evidence on which our recommendations are based, interventional treatments for the management of NP should ideally be offered in

clinical and research settings that will collect and report data on patient outcomes. This will make it possible to greatly improve the evidence on which future recommendations are based.

There are many areas of the literature that require additional research and that would benefit from standardization of approaches across research centers. Some of these issues include greater use of sham procedures for control groups, given the large placebo effect resulting from surgery and invasive procedures [40]; defining the most appropriate control group(s) for interventions for which sham surgery or procedure is not possible, such as “usual care” or an alternative, well-defined, clinically-relevant treatment control group; defining the duration of time required to have demonstrated short-term and long-term effects; and standardizing the outcomes reported, including pain outcomes, health-related quality of life, and adverse effects. In addition, it is imperative that long-term outcomes be reported following irreversible treatments, such as nerve ablation or surgery.

The effectiveness of interventional management of NP is often limited, with most interventions being associated with no more than 40–60% of patients obtaining lasting, albeit partial, relief of their pain. Continued development of new treatment approaches, additional trials involving existing interventional treatments alone and in combination, efforts to identify characteristics of treatment responders, and attention to functional and emotional outcomes are therefore needed to advance the treatment of NP [16]. Because the management of NP is expected to evolve as a result of ongoing translational and treatment studies, these recommendations should be updated within six years.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Abdi S, Datta S, Lucas LF. Role of epidural steroids in the management of chronic spinal pain: a systematic review of effectiveness and complications. Pain Physician. 2005; 8:127–43. [PubMed: 16850050]
2. Accident Compensation Corporation. Interventional guidelines for pain management. May 21. 2012 Accessed at: http://www.acc.co.nz/for-providers/clinical-best-practice/interventional-pain-management/interventions/intervention-index/WCM1_034233
3. Ackerman WE III, Ahmad M. The efficacy of lumbar epidural steroid injections in patients with lumbar disc herniations. Anesth Analg. 2007; 104:1217–22. [PubMed: 17456677]
4. Ackerman WE, Zhang JM. Efficacy of stellate ganglion blockade for the management of type 1 complex regional pain syndrome. South Med J. 2006; 99:1084–8. [PubMed: 17100029]
5. Agency for Healthcare Research and Quality. Management of chronic central neuropathic pain following traumatic spinal cord injury: summary. Rockville, MD: Agency for Healthcare Research and Quality; 2001. Evidence Report/Technology Assessment Number 45; AHRQ Publication Number 01-E062http://www.ahrq.gov/clinic/epcsums/neurosum.htm

6. Anderson VC, Burchiel KJ. A prospective study of long-term intrathecal morphine in the management of chronic nonmalignant pain. Neurosurgery. 1999; 44:289–300. [PubMed: 9932882]
7. Attal N, Cruccu G, Haanpaa M, Hansson P, Jensen TS, Nurmikko T, Sampaio C, Sindrup S, Wiffen P. EFNS Task Force. EFNS guidelines on pharmacological treatment of neuropathic pain. Eur J Neurol. 2006; 13:1153–69. [PubMed: 17038030]
8. Azari P, Lindsay DR, Briones D, Clarke C, Buchheit T, Pyati S. Efficacy and safety of ketamine in patients with complex regional pain syndrome: a systematic review. CNS Drugs. 2012; 26:215–28. [PubMed: 22136149]
9. Balcin H, Erba P, Wettstein R, Schaefer DJ, Peirer G, Kalbermatten DF. A comparative study of two methods of surgical treatment for painful neuroma. J Bone Joint Surg Br. 2009; 91:803–8. [PubMed: 19483236]
10. Baron R, Binder A. How neuropathic is sciatica? The mixed pain concept. Orthopäde. 2004; 33:568–75. [PubMed: 15067505]
11. Baron R, Janig W. Complex regional pain syndromes–how do we escape the diagnostic trap? Lancet. 2004; 364:1739–41. [PubMed: 15541435]
12. Boswell MV, Trescot AM, Datta S, Schultz DM, Hansen HC, Abdi S, Sehgal N, Shah RV, Singh V, Benyamin RM, Patel VB, Buenaventura RM, Colson JD, Cordner HJ, Epter RS, Jasper JF, Dunbar EE, Atluri SL, Bowman RC, Deer TR, Swicegood JR, Staats PS, Smith HS, Burton AW, Kloth DS, Giordano J, Manchikanti L. American Society of Interventional Pain Physicians. Interventional techniques: evidence-based practice guidelines in the management of chronic spinal pain. Pain Physician. 2007; 10:7–111. [PubMed: 17256025]
13. Bouhassira D, Lanteri-Minet M, Attal N, Laurent B, Touboul C. Prevalence of chronic pain with neuropathic characteristics in the general population. Pain. 2008; 136:380–7. [PubMed: 17888574]
14. Byrd D, Mackey S. Pulsed radiofrequency for chronic pain. Curr Pain Headache Rep. 2008; 12:37–41. [PubMed: 18417022]
15. Cameron T. Safety and efficacy of spinal cord stimulation for the treatment of chronic pain: a 20-year literature review. J Neurosurg. 2004; 100:254–67. [PubMed: 15029914]
16. Campbell, JN.; Basbaum, AI.; Dray, A.; Dubner, R.; Dworkin, RH.; Sang, CN., editors. Emerging strategies for the treatment of neuropathic pain. Seattle: IASP Press; 2006.
17. Cepeda MS, Carr DB, Lau J. Local anesthetic sympathetic blockade for complex regional pain syndrome (review). Cochrane Database Syst Rev. 2005:CD004598. [PubMed: 16235369]
18. Cetas JS, Saedi T, Burchiel KJ. Destructive procedures for the treatment of nonmalignant pain: a structured literature review. J Neurosurg. 2008; 109:389–404. [PubMed: 18759567]
19. Challapalli V, Tremont-Lukats IW, McNicol ED, Lau J, Carr DB. Systemic administration of local anesthetic agents to relieve neuropathic pain (review). Cochrane Database Syst Rev. 2005:CD003345. [PubMed: 16235318]
20. Chaudhry V, Stevens JC, Kincaid J, So YT. Practice advisory: utility of surgical decompression for treatment of diabetic neuropathy: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology. 2006; 66:1805–8. [PubMed: 16801641]
21. Chou R. Same trials, different conclusions: sorting out discrepancies between reviews on interventional procedures of the spine. Spine J. 2009; 9:679–89. [PubMed: 19540814]
22. Chou R, Atlas SJ, Loeser JD, Rosenquist RW, Stanos SP. Guideline warfare over interventional therapies for low back pain: can we raise the level of discourse? J Pain. 2011; 12:833–9. [PubMed: 21742563]
23. Chou R, Loeser JD, Owens DK, Rosenquist RW, Atlas SJ, Baisden J, Carragee EJ, Grabois M, Murphy DR, Resnick DK, Stanos SP, Shaffer WO, Wall EM. Interventional therapies, surgery, and interdisciplinary rehabilitation for low back pain: an evidence-based clinical practice guideline from the American Pain Society. Spine. 2009; 34:1066–77. [PubMed: 19363457]
24. Chou R, Qaseem A, Snow V, Casey D, Cross JT Jr, Shekelle P, Owens DK. Clinical Efficacy Assessment Subcommittee of the American College of Physicians, American College of Physicians, American Pain Society Low Back Pain Guidelines Panel. Diagnosis and treatment of low back pain: a joint clinical practice guideline from the American College of Physicians and the American Pain Society. Ann Intern Med. 2007; 147:478–91. [PubMed: 17909209]

25. Coffey RJ, Lozano AM. Neurostimulation for chronic noncancer pain: an evaluation of the clinical evidence and recommendations for future trial designs. J Neurosurg. 2006; 105:175–89. [PubMed: 17219820]
26. Cohen SP. Epidural steroid injections for low back pain: overall the evidence is weak, but some may benefit. BMJ. 2011; 343:d5310. [PubMed: 21914757]
27. Cohen SP, Bicket MC, Jamison D, Wilkinson I, Rathmell JP. Epidural steroids: a comprehensive, evidence-based review. Reg Anesth Pain Med. 2013; 38:175–200. [PubMed: 23598728]
28. Cornblath DR, Vinik A, Feldman E, Freeman R, Boulton AJ. Surgical decompression for diabetic sensorimotor polyneuropathy. Diabetes Care. 2007; 30:421–2. [PubMed: 17259523]
29. Cruccu G, Aziz TZ, Garcia-Larrea L, Hansson P, Jensen TS, Lefaucheur JP, Simpson BA, Taylor RS. EFNS guidelines on neurostimulation therapy for neuropathic pain. Eur J Neurol. 2007; 14:952–70. [PubMed: 17718686]
30. Cruccu G, Gronseth G, Alksne J, Argoff C, Brainin M, Burchiel K, Nurmikko T, Zakrzewska JM. AAN-EFNS guidelines on trigeminal neuralgia management. Eur J Neurol. 2008; 15:1013–28. [PubMed: 18721143]
31. Daousi C, Benbow SJ, MacFarlane IA. Electrical spinal cord stimulation in the long-term treatment of chronic painful diabetic neuropathy. Diabet Med. 2005; 22:393–8. [PubMed: 15787662]
32. Deer TR, Caraway DL, Kim CK, Dempsey CD, Stewart CD, McNeil KF. Clinical experience with intrathecal bupivacaine in combination with opioid for the treatment of chronic pain related to failed back surgery syndrome and metastatic cancer pain of the spine. Spine J. 2002; 2:274–8. [PubMed: 14589479]
33. Deer T, Chapple I, Classen A, Javery K, Stoker V, Tonder L, Burchiel K. Intrathecal drug delivery for treatment of chronic low back pain: report from the National Outcomes Registry for Low Back Pain. Pain Med. 2004; 5:6–13. [PubMed: 14996232]
34. Deer T, Krames ES, Hassenbusch SJ, Burton A, Caraway D, Dupen S, Eisenach J, Erdek M, Grigsby E, Kim P, Levy R, McDowell G, Mekhail N, Panchal S, Prager J, Rauck R, Saulino M, Sitzman T, Staats P, Stanton-Hicks M, Sterns L, Willis K, Witt W, Follett K, Huntoon M, Liem L, Rathmell J, Wallace M, Buchser E, Cousins M, Ver Donck A. Polyanalgesic consensus conference 2007: recommendations for the management of pain by intrathecal (intraspinal) drug delivery: report of an interdisciplinary expert panel. Neuromodulation. 2007; 10:300–28. [PubMed: 22150890]
35. DeRidder D, Plazier M, Kamerling N, Menovsky T, Vanneste S. Spinal cord stimulation for limb and back pain. World Neurosurgery. in press. 10.1016/j.wneu.2013.01.040
36. de Vos CC, Rajan V, Steenbergen W, van der Aa HE, Buschman HP. Effect and safety of spinal cord stimulation for treatment of chronic pain caused by diabetic neuropathy. J Diabetes Complications. 2009; 23:40–5. [PubMed: 18413161]
37. Dworkin RH, O'Connor AB, Backonja M, Farrar JT, Finnerup NB, Jensen TS, Kalso EA, Loeser JD, Miakowski C, Nurmikko TJ, Portenoy RK, Rice AS, Stacey BR, Treede RD, Turk DC, Wallace MS. Pharmacologic management of neuropathic pain: evidence-based recommendations. Pain. 2007; 132:237–51. [PubMed: 17920770]
38. Dworkin RH, Turk DC, Farrar JT, Haythornthwaite JA, Jensen MP, Katz NP, Kerns RD, Stucki G, Allen RR, Bellamy N, Carr DB, Chandler J, Cowan P, Dionne R, Galer BS, Hertz S, Jadad AR, Kramer LD, Manning DC, Martin S, McCormick CG, McDermott MP, McGrath P, Quessy S, Rappaport BA, Robbins W, Robinson JP, Rothman M, Royal MA, Simon L, Stauffer JW, Stein W, Tollett J, Wernicke J, Witter J, IMMPACT. Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. Pain. 2005; 113:9–19. [PubMed: 15621359]
39. Fisher R, Hassenbusch S, Krames E, Leong M, Minehart M, Prager J, Staats P, Webster L, Willis K. A consensus statement regarding the present suggested titration for Prialt (ziconotide). Neuromodulation. 2005; 8:153–4. [PubMed: 22151483]
40. Flum DR. Interpreting surgical trials with subjective outcomes: avoiding unSPORTsmanlike conduct. JAMA. 2006; 296:2483–5. [PubMed: 17119146]
41. Foletti A, Durrer A, Buchser E. Neurostimulation technology for the treatment of chronic pain: a focus on spinal cord stimulation. Expert Rev Med Devices. 2007; 4:201–14. [PubMed: 17359225]

42. Forouzanfar T, Kemler MA, Weber WE, Kessels AG, van Kleef M. Spinal cord stimulation in complex regional pain syndrome: cervical and lumbar devices are comparably effective. Br J Anaesth. 2004; 92:348–53. [PubMed: 14742334]
43. Fujii H, Kosogabe Y, Kajiki H. Long-term effects of pulsed radiofrequency on the dorsal root ganglion and segmental nerve roots for lumbosacral radicular pain: a prospective controlled randomized trial with nerve root block. Matsui. 2012; 61:790–3.
44. Geurts JWM, van Wijk RMAW, Wynne HJ, Hammink E, Buskens E, Lousberg R, Knape JTA, Groen GJ. Radiofrequency lesioning of dorsal root ganglia for chronic lumbosacral radicular pain: a randomised, double-blind, controlled trial. Lancet. 2003; 361:21–6. [PubMed: 12517462]
45. Gierthmühlen J, Maier C, Baron R, Tölle T, Treede RD, Birmbaumer N, Huge V, Koroschetz J, Krumova EK, Lauchart M, Maihöfner C, Richter H, Westermann A, the German Research Network on Neuropathic Pain (DFNS) study group. Sensory signs in complex regional pain syndrome and peripheral nerve injury. Pain. 2012; 153:765–74. [PubMed: 22154921]
46. Gronseth G, Cruccu G, Alksne J, Argoff C, Brainin M, Burchiel K, Nurmikko T, Zakrzewska JM. Practice Parameter: the diagnostic evaluation and treatment of trigeminal neuralgia (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology and the European Federation of Neurological Sciences. Neurology. 2008; 71:1183–90. [PubMed: 18716236]
47. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Schünemann HJ, GRADE working group. GRADE: what is “quality of evidence” and why is it important to clinicians? BMJ. 2008; 336:995–8. [PubMed: 18456631]
48. Guyatt GH, Oxman AD, Kunz R, Falck-Ytter Y, Vist GE, Liberati A, Schünemann HJ, GRADE working group. GRADE: going from evidence to recommendations. BMJ. 2008; 336:1049–51. [PubMed: 18467413]
49. Harke H, Gretenkort P, Ladleif HU, Koester P, Rahman S. Spinal cord stimulation in postherpetic neuralgia and in acute herpes zoster pain. Anesth Analg. 2002; 94:694–700. [PubMed: 11867400]
50. Harke H, Gretenkort P, Ladleif HU, Rahman S. Spinal cord stimulation in sympathetically maintained complex regional pain syndrome type I with severe disability: a prospective clinical study. Eur J Pain. 2005; 9:363–73. [PubMed: 15979016]
51. Hassenbusch SJ, Portenoy RK, Cousins M, Buchser E, Deer TR, Du Pen SL, Eisenach J, Follett KA, Hildebrand KR, Krames ES, Levy RM, Palmer PP, Rathmell JP, Rauck RL, Staats PS, Stearns L, Willis KD. Polyanalgesic Consensus Conference 2003: an update on the management of pain by intraspinal drug delivery: report of an expert panel. J Pain Symptom Manage. 2004; 27:540–63. [PubMed: 15165652]
52. Helm S, Benyamin RM, Chopra P, Deer TR, Justiz R. Percutaneous adhesiolysis in the management of chronic low back pain in post lumbar surgery syndrome and spinal stenosis: a systematic review. Pain Physician. 2012; 15:E435–62. [PubMed: 22828693]
53. Ioannidis JP, Evans SJ, Gotzsche PC, O’Neill RT, Altman DG, Schulz K, Moher D. Better reporting of harms in randomized trials: an extension of the CONSORT statement. Ann Intern Med. 2004; 141:781–8. [PubMed: 15545678]
54. Iversen T, Solberg TK, Romber B, Wilsgaard T, Twisk J, Anke A, Nygaard O, Hasvold T, Ingebrigtsen T. Effect of caudal epidural steroid or saline injection in chronic lumbar radiculopathy: multicentre, blinded, randomised controlled trial. BMJ. 2011; 343:d5278. [PubMed: 21914755]
55. Jensen TS, Baron R, Haanpää M, Kalso E, Loeser JD, Rice ASC, Treede RD. A new definition of neuropathic pain. Pain. 2011; 152:2204–5. [PubMed: 21764514]
56. Ji G, Niu J, Shi Y, Hou L, Lu Y, Xiong L. The effectiveness of repetitive paravertebral injections with local anesthetics and steroids for the prevention of postherpetic neuralgia in patients with acute herpes zoster. Anesth Analg. 2009; 109:1651–5. [PubMed: 19713253]
57. Kapetanos AT, Furlan AD, Mailis-Gagnon A. Characteristics and associated features ofpersistent post-sympathectomy pain. Clin J Pain. 2003; 19:192–9. [PubMed: 12792558]
58. Katayama Y, Yamamoto T, Kobayashi K, Kasai M, Oshima H, Fukaya C. Motor cortex stimulation for post-stroke pain: comparison of spinal cord and thalamic stimulation. Stereotact Funct Neurosurg. 2001; 77:183–6. [PubMed: 12378074]

59. Ke M, Yinghui F, Xeuhua 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; 16:15–25. [PubMed: 23340530]
60. Kemler MA, Barendse GA, van Kleef M, de Vet HC, Rijks CP, Furnee CA, van den Wildenberg FA. Spinal cord stimulation in patients with chronic reflex sympathetic dystrophy. N Engl J Med. 2000; 343:618–24. [PubMed: 10965008]
61. Kemler MA, Barendse GA, van Kleef M, Egbrink MG. Pain relief in complex regional pain syndrome due to spinal cord stimulation does not depend on vasodilation. Anesthesiology. 2000; 92:1653–60. [PubMed: 10839916]
62. Kemler MA, de Vet HC, Barendse GA, van Den Wildenberg FA, van Kleef M. The effect of spinal cord stimulation in patients with chronic reflex sympathetic dystrophy: two years' follow-up of the randomized controlled trial. Ann Neurol. 2004; 55:13–8. [PubMed: 14705107]
63. Kemler MA, de Vet HC, Barendse GA, van den Wildenberg FA, van Kleef M. Spinal cord stimulation for chronic reflex sympathetic dystrophy: five-year follow-up. N Engl J Med. 2006; 354:2394–6. [PubMed: 16738284]
64. Kemler MA, de Vet HC, Barendse GA, van den Wildenberg FA, van Kleef M. Effect of spinal cord stimulation for chronic complex regional pain syndrome Type I: five-year final follow-up of patients in a randomized controlled trial. J Neurosurg. 2008; 108:292–8. [PubMed: 18240925]
65. Kemler MA, Reulen JP, Barendse GA, van Kleef M, de Vet HC, van den Wildenberg FA. Impact of spinal cord stimulation on sensory characteristics in complex regional pain syndrome type I: a randomized trial. Anesthesiology. 2001; 95:72–80. [PubMed: 11465587]
66. Kikuchi A, Kotani N, Sato T, Takamura K, Sakai I, Matsuki A. Comparative therapeutic evaluation of intrathecal versus epidural methylprednisolone for long-term analgesia in patients with intractable postherpetic neuralgia. Reg Anesth Pain Med. 1999; 24:287–93. [PubMed: 10445766]
67. Kim YH, Lee CJ, Lee SC, Huh J, Nahm FS, Kim HZ, Lee MK. Effect of pulsed radiofrequency for postherpetic neuralgia. Acta Anaesthesiol Scand. 2008; 52:1140–3. [PubMed: 18840116]
68. Kolsi I, Delecrin J, Berthelot JM, Thomas L, Prost A, Maugars Y. Efficacy of nerve root versus interspinous injections of glucocorticoids in the treatment of disk-related sciatica. J Bone Joint Surg. 2000; 67:113–8.
69. Kotani N, Kushikata T, Hashimoto H, Kimura F, Muraoka M, Yodono M, Asai M, Matsuki A. Intrathecal methylprednisolone for intractable postherpetic neuralgia. N Engl J Med. 2000; 343:1514–9. [PubMed: 11087880]
70. Kumar K, Taylor RS, Jacques L, Eldabe S, Meglio M, Molet J, Thomson S, O'Callaghan J, Eisenberg E, Milbouw G, Buchser E, Fortini G, Richardson J, North RB. Spinal cord stimulation versus conventional medical management for neuropathic pain: a multicentre randomised controlled trial in patients with failed back surgery syndrome. Pain. 2007; 132:179–88. [PubMed: 17845835]
71. Kumar V, Krone K, Mathieu A. Neuraxial and sympathetic blocks in herpes zoster and postherpetic neuralgia: an appraisal of current evidence. Reg Anesth Pain Med. 2004; 29:454–61. [PubMed: 15372391]
72. Lee CH, Dellon AL. Prognostic ability of Tinel Sign in determining outcome for decompression surgery in diabetic and nondiabetic neuropathy. Ann Plast Surg. 2004; 53:523–7. [PubMed: 15602246]
73. Levin JH. Prospective, double-blind, randomized placebo-controlled trials in interventional spine: what the highest quality literature tells us. Spine J. 2009; 9:690–703. [PubMed: 18789773]
74. Lewis G. Intrathecal methylprednisolone for postherpetic neuralgia. N Engl J Med. 2001; 344:1020. [PubMed: 11280322]
75. Lima RM, Navarro LH, Carness JM, Barros GA, Marques ME, Solanki D, Ganem EM. Clinical and histological effects of the intrathecal administration of methylprednisolone in dogs. Pain Physician. 2010; 13:493–501. [PubMed: 20859319]
76. Liu T, Yu CP. Placebo analgesia, acupuncture and sham surgery. Evid Based Complement Alternat Med. 2011; 2011:943–7.

77. Lopez BC, Hamlyn PJ, Zakrzewska JM. Systematic review of ablative neurosurgical techniques for the treatment of trigeminal neuralgia. Neurosurgery. 2004; 54:973–83. [PubMed: 15046666]

78. Lopez BC, Hamlyn PJ, Zakrzewska JM. Stereotactic radiosurgery for primary trigeminal neuralgia: state of the evidence and recommendations for future reports. J Neurol Neurosurg Psychiatry. 2004; 75:1019–24. [PubMed: 15201363]

79. Lutz GE, Vad VB, Wisneski RJ. Fluoroscopic transforaminal lumbar epidural steroids: an outcome study. Arch Phys Med Rehabil. 1998; 79:1362–6. [PubMed: 9821894]

80. Mailis-Gagnon A, Furlan A. Sympathectomy for neuropathic pain (review). Cochrane Database Syst Rev. 2002:CD002918.

81. Mailis-Gagnon A, Furlan AD, Sandoval JA, Taylor R. Spinal cord stimulation for chronic pain (review). Cochrane Database Syst Rev. 2004:CD003783. [PubMed: 15266501]

82. Malik K, Benzon HT. Radiofrequency applications to dorsal root ganglia: a literature review. Anesthesiology. 2008; 109:527–42. [PubMed: 18719452]

83. Manchikanti L, Boswell MV, Rivera JJ, Pampati V, Damron KS, McManus CD, Brandon DE, Wilson SR. A randomized, controlled trial of spinal endoscopic adhesiolysis in chronic refractory low back and lower extremity pain. BMC Anesthesiology. 2005; 5:10. [PubMed: 16000173]

84. Manchikanti L, Boswell MV, Singh V, Benyamin RM, Fellows B, Abdi S, Buenventura RM, Conn A, Datta S, Derby R, Falco FJ, Erhart S, Diwan S, Hayek SM, Helm S, Parr AT, Schultz DM, Smith HS, Wolfer LR, Hirsch JA. Comprehensive evidence-based guidelines for interventional techniques in the management of chronic spinal pain. Pain Physician. 2009; 12:699–802. [PubMed: 19644537]

85. Manchikanti L, Datta S, Gupta S, Munglani R, Bryce DA, Ward SP, Benyamin RM, Sharma ML, Helm S, Fellows B, Hirsh JA. A critical review of the American Pain Society clinical practice guidelines for interventional techniques: Part 2. Therapeutic interventions. Pain Physician. 2010; 13:E215–64. [PubMed: 20648212]

86. Manchikanti L, Rivera JJ, Pampati V, Damron KS, McManus CD, Brandon DE, Wilson SR. One day lumbar epidural adhesiolysis and hypertonic saline neurolysis in treatment of chronic low back pain: a randomized, double-blind trial. Pain Physician. 2004; 7:177–86. [PubMed: 16868590]

87. Manchikanti L, Singh V, Cash KA, Pampati V, Datta S. A comparative effectiveness evaluation of percutaneous adhesiolysis and epidural steroid injections in managaing lumbar post surgery syndrome: a randomized, equivalence trial. Pain Physician. 2009; 12:E355–68. [PubMed: 19935992]

88. McGuirk S, Fahy C, Costi D, Cyna AM. Use of invasive placebos in research on local anaesthetic interventions. Anesth. 2011; 66:84–91.

89. Moseley JB, O'Malley KO, Petersen NJ, Menke TJ, Brody BA, Kuykendall DH, Hollingsworth JC, Ashton CM, Wray NP. A controlled trial of arthroscopic surgery for osteoarthritis of the knee. N Engl J Med. 2002; 347:81–8. [PubMed: 12110735]

90. Moulin DE, Clark AJ, Gilron I, Ware MA, Watson CPN, Sessle BJ, Coderre T, Morley-Forster PK, Stinson J, Boulanger A, Peng P, Finley GA, Taenzer P, Squire P, Dion D, Cholkan A, Gilani A, Gordon A, Henry J, Jovey R, Lynch M, Mailis-Gagnon A, Panju A, Rollman GB, Velly A, Canadian Pain Society. Pharmacological management of chronic neuropathic pain: consensus statement and guidelines from the Canadian Pain Society. Pain Res Manage. 2007; 12:13–21.

91. Muro K, O'Shaughnessy B, Ganju A. Infarction of the cervical spinal cord following multilevel transforaminal epidural steroid injection: case report and review of the literature. J Spinal Cord Med. 2007; 30:385–8. [PubMed: 17853663]

92. Nagda JV, Davis CW, Bajwa ZH, Simopoulos TT. Retrospective review of the efficacy and safety of repeated pulsed and continuous radiofrequency lesioning of the dorsal root ganglion/segmental nerve for lumbar radicular pain. Pain Physician. 2011; 14:371–6. [PubMed: 21785480]

93. National Institute for Health and Clinical Excellence. Spinal cord stimulation for chronic pain of neuropathic or ischaemic origin. 2008. available at: www.nice.org.uk/nicemedia/pdf/TA159Guidance.pdf

94. Nelson DA, Landau WM. Intrathecal methylprednisolone for postherpetic neuralgia. N Engl J Med. 2001; 344:1019. [PubMed: 11280320]

95. Niebergall H, Priebe HJ. Intrathecal methylprednisolone for postherpetic neuralgia. N Engl J Med. 2001; 344:1020. [PubMed: 11280323]

96. Noppers IM, Niesters M, Aarts LPHJ, Bauer MCR, Drewes AM, Dahan A, Sarton EY. Drug-induced liver injury following a repeated course of ketamine treatment for chronic pain in CRPS type 1 patients: a report of 3 cases. Pain. 2011; 152:2173–8. [PubMed: 21546160]

97. North RB, Kidd DH, Farrokhi F, Piantadosi SA. Spinal cord stimulation versus repeated lumbosacral spine surgery for chronic pain: a randomized, controlled trial. Neurosurgery. 2005; 56:98–106. [PubMed: 15617591]

98. North RB, Kidd DH, Olin J, Sieracki JM, Farrokhi F, Petrucci L, Cutchis PN. Spinal cord stimulation for axial low back pain: a prospective, controlled trial comparing dual with single percutaneous electrodes. Spine. 2005; 30:1412–8. [PubMed: 15959371]

99. North RB, Kidd DH, Petrucci L, Dorsi MJ. Spinal cord stimulation electrode design: a prospective, randomized, controlled trial comparing percutaneous with laminectomy electrodes: part II-clinical outcomes. Neurosurgery. 2005; 57:990–6. [PubMed: 16284568]

100. North RB, Shipley J. Practice parameters for the use of spinal cord stimulation in the treatment of chronic neuropathic pain. Pain Med. 2007; 8:S200–75. [PubMed: 17995571]

101. Novak S, Nemeth WC. The basis for recommending repeating epidural steroid injections for radical low back pain: a literature review. Arch Phys Med Rehabil. 2008; 89:543–52. [PubMed: 18295635]

102. Nuti C, Peyron R, Garcia-Larrea L, Brunon J, Laurent B, Sindou M, Mertens P. Motor cortex stimulation for refractory neuropathic pain: four year outcome and predictors of efficacy. Pain. 2005; 118:43–52. [PubMed: 16214292]

103. Opstelten W, van Wijck AJ, Stolker RJ. Interventions to prevent postherpetic neuralgia: cutaneous and percutaneous techniques. Pain. 2004; 107:202–6. [PubMed: 14736581]

104. Oxford Centre for Evidence-based Medicine. Levels of evidence (March 2009). May 22. 2012 Accessed at http://www.cebm.net/index.aspx?o=1025

105. Pasqualucci A, Pasqualucci V, Galla F, De Angelis V, Marzocchi V, Colussi R, Paoletti F, Girardis M, Lugano M, Del Sindaco F. Prevention of post-herpetic neuralgia: acyclovir and prednisolone versus epidural local anesthetic and methylprednisolone. Acta Anaesthesiol Scand. 2000; 44:910–8. [PubMed: 10981565]

106. Pinto RZ, Maher CG, Ferreira ML, Hancock M, Oliveira VC, McLachlan AJ, Koes B, Ferreira PH. Epidural corticosteroid injections in the management of sciatica: a systematic review and meta-analysis. Ann Intern Med. 2012; 157:865–77. [PubMed: 23362516]

107. Pluijms W, Huygen F, Cheng J, Mekhail N, van Kleef M, Van Zundert J, van Dongen R. 18. Painful diabetic polyneuropathy. Pain Pract. 2011; 11:191–8. [PubMed: 21199315]

108. Quraishi NA. Transforaminal injection of corticosteroids for lumbar radiculopathy: systematic review and meta-analysis. Eur Spine J. 2012; 21:214–9. [PubMed: 21892774]

109. Rados I, Sakic K, Fingler M, Kapural L. Efficacy of interlaminar vs transforaminal epidural steroid injection for the treatment of chronic unilateral radicular pain: prospective, randomize study. Pain Med. 2011; 12:1316–21. [PubMed: 21914118]

110. Rijsdijk M, van Wijck AJ, Kalkman CJ, Meulenhoff PC, Grafe MR, Steinauer J, Yaksh TL. Safety assessment and pharmacokinetics of intrathecal methylprednisolone acetate in dogs. Anesthesiology. 2012; 116:170–81. [PubMed: 22139590]

111. 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; 17:714–23. [PubMed: 23059790]

112. Schwartzman RJ, Alexander GM, Grothusen JR, Paylor T, Reichenberger E, Perreault M. Outpatient intravenous ketamine for the treatment of complex regional pain syndrome: a double-blind placebo controlled study. Pain. 2009; 147:107–15. [PubMed: 19783371]

113. Siddall PJ, Molloy AR, Walker S, Mather LE, Rutkowski SB, Cousins MJ. The efficacy of intrathecal morphine and clonidine in the treatment of pain after spinal cord injury. Anesth Analg. 2000; 91:1493–8. [PubMed: 11094007]

114. Sigtermans MJ, van Hilten JJ, Bauer MCR, Arbous MS, Marinus J, Sarton EY, Dahan A. Ketmaine produces effective and long-term pain relief in patients with Complex Regional Pain Syndrome Type 1. Pain. 2009; 145:304–11. [PubMed: 19604642]
115. Simpson EL, Duenas A, Holmes MW, Papaioannou D, Chilcott J. Spinal cord stimulation for chronic pain of neuropathic or ischaemic origin: systematic review and economic evaluation. Health Technol Assess. 2009; 13:1–154.
116. Slappendel R, Crul BJP, Braak GJJ, Geurts JWM, Booij LHDJ, Voerman VF, de Boo T. The efficacy of radiofrequency lesioning of the cervical spinal dorsal root ganglion in a double blinded randomized study: no difference between 40°C and 67°C treatments. Pain. 1997; 73:159–63. [PubMed: 9415501]
117. Spatz AL, Zakrzewska JM, Kay EJ. Decision analysis of medical and surgical treatments for trigeminal neuralgia: How patient evaluations of benefits and risks affect the utility of treatment decisions. Pain. 2007; 131:302–10. [PubMed: 17451880]
118. Srinivasan B. Intrathecal methylprednisolone for postherpetic neuralgia. N Engl J Med. 2001; 344:1021. [PubMed: 11280324]
119. Stanton-Hicks M, Janig W, Hassenbusch S, Haddox JD, Boas R, Wilson P. Reflex sympathetic dystrophy: changing concepts and taxonomy. Pain. 1995; 63:127–33. [PubMed: 8577483]
120. Stokvis A, van der Avoort DJ, van Neck JW, Hovius SE, Coert JH. Surgical management of neuroma pain: a prospective follow-up study. Pain. 2010; 151:862–9. [PubMed: 20974520]
121. Straube S, Derry S, Moore RA, McQuay HJ. Cervico-thoracic or lumbar sympathectomy for neuropathic pain and complex regional pain syndrome. Cochrane Database Syst Rev. 2010 Jul. 7:CD002918. [PubMed: 20614432]
122. Tatli M, Satici O, Kanpolat Y, Sindou M. Various surgical Modalities for trigeminal Neuralgia: Literature Study of respective long-term Outcomes. Acta Neurochirurgica. 2008; 150:243–55. [PubMed: 18193149]
123. Taylor RS. Spinal cord stimulation in complex regional pain syndrome and refractory neuropathic back and leg pain/failed back surgery syndrome: results of a systematic review and meta-analysis. J Pain Symptom Manage. 2006; 31:S13–9. [PubMed: 16647590]
124. Taylor RS, Van Buyten JP, Buchser E. Spinal cord stimulation for complex regional pain syndrome: a systematic review of the clinical and cost-effectiveness literature and assessment of prognostic factors. Eur J Pain. 2006; 10:91–101. [PubMed: 16310712]
125. Tesfaye S, Watt J, Benbow SJ, Pang KA, Miles J, MacFarlane IA. Electrical spinal-cord stimulation for painful diabetic peripheral neuropathy. Lancet. 1996; 348:1698–701. [PubMed: 8973433]
126. Thomas E, Cyteval C, Abiad L, Picot MC, Taourel P, Blotman F. Efficacy of transforaminal versus interspinous corticosteroid injectionin discal radiculalgia: a prospective, randomised, double-blind study. Clin Rheumatol. 2003; 22:299–304. [PubMed: 14579160]
127. Treede RD, Jensen TS, Campbell JN, Cruccu G, Dostrovsky JO, Griffin JW, Hansson P, Hughes R, Nurmikko T, Serra J. Neuropathic pain: redefinition and a grading system for clinical and research purposes. Neurology. 2008; 70:1630–5. [PubMed: 18003941]
128. Turk DC, Dworkin RH, Allen RR, Bellamy N, Brandenburg N, Carr DB, Cleeland C, Dionne R, Farrar JT, Galer BS, Hewitt DJ, Jadad AR, Katz NP, Kramer LD, Manning DC, McCormick CG, McDermott MP, McGrath P, Quessy S, Rappaport BA, Robinson JP, Royal MA, Simon L, Stauffer JW, Stein W, Tollett J, Witter J. Core outcome domains for chronic pain clinical trials: IMMPACT recommendations. Pain. 2003; 106:337–45. [PubMed: 14659516]
129. Turner JA, Loeser JD, Deyo RA, Sanders SB. Spinal cord stimulation for patients with failed back surgery syndrome or complex regional pain syndrome: a systematic review of effectiveness and complications. Pain. 2004; 108:137–47. [PubMed: 15109517]
130. Turner JA, Sears JM, Loeser JD. Programmable intrathecal opioid delivery systems for chronic noncancer pain: a systematic review of effectiveness and complications. Clin J Pain. 2007; 23:180–95. [PubMed: 17237668]
131. Ubbink DT, Vermeulen H. Spinal cord stimulation for non-reconstructable chronic critical leg ischaemia. Cochrane Database Syst Rev. 2005:CD004001. [PubMed: 16034919]

132. Ubbink DT, Vermeulen H. Spinal cord stimulation for critical leg ischemia: a review of effectiveness and optimal patient selection. J Pain Symptom Manage. 2006; 31:S30–5. [PubMed: 16647594]
133. van Boxem K, Cheng J, Patijn J, van Kleef M, Lataster A, Mekhail N, Van Zundert J. 11. Lumbosacral radicular pain. Pain Pract. 2010; 10:339–58. [PubMed: 20492580]
134. van Boxem K, van Bilsen J, de Meij N, Herrier A, Kessels F, van Zundert J, van Kleef M. Pulsed radiofrequency treatment adjacent to the lumbar dorsal root ganglion for the management of lumbosacral radicular syndrome: a clinical audit. Pain Med. 2011; 12:1322–30. [PubMed: 21812907]
135. van Boxem K, van Eerd M, Brinkhuize T, Patijn J, van Kleef M, van Zundert J. Radiofrequency and pulsed radiofrequency treatment of chronic pain syndromes: the available evidence. Pain Pract. 2008; 8:385–93. [PubMed: 18721175]
136. Van Buyten JP, Al-Kaisy A, Smet I, Palmisani S, Smith T. High-frequency spinal cord stimulation for the treatment of chronic back pain patients: results of a prospective multicenter European clinical study. Neuromodulation. 2013; 16:59–66. [PubMed: 23199157]
137. Van Eijs F, Stanton-Hicks M, Van Zundert J, Faber CG, Lubenow TR, Mekhail N, van Kleef M, Huygen F. 16. Complex regional pain syndrome. Pain Pract. 2011; 11:70–87. [PubMed: 20807353]
138. van Hilten BJ, van de Beek WJ, Hoff JI, Voormolen JH, Delhaas EM. Intrathecal baclofen for the treatment of dystonia in patients with reflex sympathetic dystrophy. N Engl J Med. 2000; 343:625–30. [PubMed: 10965009]
139. van Kleef M, Liem L, Lousberg R, Kessels F, Sluijter M. Radiofrequency lesion adjacent to the dorsal root ganglion for cervicobrachial pain: a prospective double blind randomized study. Neurosurgery. 1996; 38:1127–31. [PubMed: 8727142]
140. van Kleef M, van Genderen WE, Narouze S, Nurmikko TJ, van Zundert J, Geurts JW, Mekhail N. 1. Trigeminal neuralgia. Pain Pract. 2009; 9:252–9. [PubMed: 19619267]
141. van Rijn MA, Munts AG, Marinus J, Voormolen JHC, de Boer KS, Teepe-Twiss IM, van Dasselaar NT, Delhaas EM, van Hilten JJ. Intrathecal baclofen for dystonia of complex regional pain syndrome. Pain. in press.
142. van Wijck AJ, Opstelten W, Moons KG, van Essen GA, Stolker RJ, Kalkman CJ, Verheij TJ. The PINE study of epidural steroids and local anaesthetics to prevent postherpetic neuralgia: a randomised controlled trial. Lancet. 2006; 367:219–24. [PubMed: 16427490]
143. Van Wijck AJ, Wallace M, Mekhail N, van Kleef M. 17. Herpes zoster and post-herpetic neuralgia. Pain Pract. 2011; 11:88–97. [PubMed: 21114617]
144. van Zundert J, Lame IE, de Louw A, Jansen J, Kessels F, Patijn J, van Kleef M. 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. [PubMed: 22150908]
145. van Zundert J, Patijn J, Kessels A, Lamé 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; 127:173–82. [PubMed: 17055165]
146. Veihelmann A, Devens C, Trouillier H, Birkenmaier C, Gerdesmeyer L, Refior HJ. Epidural neuroplasty versus physiotherapy to relieve pain in patients with sciatica: a prospective randomized blinded clinical trial. J Orthop Sci. 2006; 11:365–9. [PubMed: 16897200]
147. Weinstein SM, Herring SA, Derby R. Contemporary concepts in spine care: epidural steroid injections. Spine. 1995; 20:1842–6. [PubMed: 7502144]
148. Wilkinson HA. Intrathecal depo-medrol: a literature review. Clin J Pain. 1992; 8:49–56. [PubMed: 1533555]
149. Wu CL, Marsh A, Dworkin RH. The role of sympathetic nerve blocks in herpes zoster and postherpetic neuralgia. Pain. 2000; 87:121–9. [PubMed: 10924805]
150. Zakrzewska JM, Akram H. Neurosurgical interventions for the treatment of classical trigeminal neuralgia. Cochrane Database Syst Rev. 2011; 9:CD007312. [PubMed: 21901707]
151. Zetlaoui JT, Cosserat J. Intrathecal methylprednisolone for postherpetic neuralgia. N Engl J Med. 2001; 344:1020–1. [PubMed: 11280321]

Table 1

Criteria for rating quality of evidence and strength of treatment recommendations [adapted from 23,47]

Quality of Evidence	
High quality	At least 2 high quality, directly applicable randomized, controlled trials with consistent results.
Moderate quality	At least 1 high quality randomized, controlled trial or 2 or more high quality observational studies with consistent results, or reasonable extrapolation of 2 or more high quality randomized, controlled trials.
Low quality	Some evidence of effect, but conclusions limited by study design limitations, inconsistent results, or extrapolation of questionable reliability.
Strength of Recommendation	
“Strong” recommendation for using the intervention	The balance of desirable effects vs harmful effects substantially favors the desirable effects. Most patients would want and should receive the intervention.
“Weak” recommendation for using the intervention	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”	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.

Table 2

Summary of quality of evidence and strength of recommendations for interventions for different types of neuropathic pain

Indication/Intervention	Quality of Evidence	Strength of Recommendation	Additional Comments
Herpes zoster			
Epidural or paravertebral nerve block(s) for treatment of pain	Moderate	Weak	Provides relief of acute pain, but has not been compared against less invasive treatments, such as oral pharmacotherapy
PHN (truncal)			
SCS	Low	Inconclusive	Weak evidence, but positive case series results in refractory PHN
IMD	Low	Inconclusive	Somewhat promising results in other types of chronic pain
Intrathecal steroid and local anesthetic injections	Low	Inconclusive	Unreplicated positive RCT, but concerns about the RCT and about safety (see text)
PRF treatment	Low	Inconclusive	Single RCT showing efficacy until 6 months
Sympathetic nerve blocks	Moderate	Against	Non-randomized studies have not shown benefit
Painful DPN and other peripheral neuropathies			
SCS	Low	Inconclusive	Weak evidence with small, positive case series with large effects in refractory DPN over long-term follow-up
IMD	Low	Inconclusive	Somewhat promising results in other types of chronic pain
DBS	Low	Inconclusive	Weak evidence but promising results in small, uncontrolled series
Surgical decompression	Low	Inconclusive	Most likely to be beneficial in patients with evidence of peripheral nerve compression
Peripheral nerve injury and brachial plexus avulsion			
Neuroma resection and relocation	Low	Inconclusive	Weak evidence in peripheral nerve injury
DREZ lesion	Low	Inconclusive	Weak evidence in brachial plexus avulsion
Spinal cord injury neuropathic pain			
SCS	Low	Inconclusive	Weak evidence, but positive case series results in refractory spinal cord injury NP
IMD	Low	Inconclusive	Very weak evidence in refractory spinal cord injury NP, but somewhat promising results in other types of chronic pain
DREZ lesion	Low	Inconclusive	Weak evidence in refractory spinal cord injury NP
DBS	Low	Inconclusive	Weak evidence in refractory spinal cord injury NP with lower published rates of success than DREZ lesioning, concerns about potential for adverse effects
Central post-stroke pain			
SCS	Low	Inconclusive	Very weak evidence, poor response rate in a single case series

Indication/Intervention	Quality of Evidence	Strength of Recommendation	Additional Comments
MCS	Low	Inconclusive	Weak evidence, but a number of case series have demonstrated ~50% response among refractory patients
DBS	Low	Inconclusive	Weak evidence in refractory patients with central post-stroke pain
Radiculopathy			
Epidural steroid injection(s)	Moderate	Weak	Short-term benefit for patients with prolapsed lumbar disc
PRF therapy for cervical or lumbar radiculopathy	Low	Inconclusive	Weak evidence of short-term benefit
RF lesioning for cervical radiculopathy	Low	Inconclusive	Weak evidence of short-term benefit
RF lesioning for lumbar radiculopathy	Moderate	Against	High-quality RCT failed to show benefit over sham radiofrequency lesioning
Adhesiolysis	Low	Inconclusive	Single RCT showed efficacy of adhesiolysis, but the study design limits confidence in conclusions of this study
FBSS with radiculopathy			
SCS	Moderate	Weak	Based on two RCTs appears to be better than reoperation and conventional medical management, but response rate relatively low and complication rate relatively high
Epidural steroid injection(s)	Low	Inconclusive	Weak evidence, but the authors consider a treatment trial prior to SCS a reasonable option for medically refractory patients given the evidence in radiculopathy, low risk, low cost, and higher complication risk with SCS
Adhesiolysis	Low	Inconclusive	Three RCTs have demonstrated pain score improvement with adhesiolysis, but the possible effects on the neuropathic (radicular) component of the pain are not described
IMD	Low	Inconclusive	Weak evidence in FBSS with radicular symptoms
DBS	Low	Inconclusive	Weak evidence, with few patients in case series with promising results
CRPS			
SCS for CRPS 1	Moderate	Weak	Long-term benefit demonstrated in CRPS type 1 patients, reoperation rate for complications 42% at 5 years, but 95% would undergo implantation again for the same result
SCS for CRPS 2	Low	Inconclusive	Very limited evidence
Sympathetic nerve block	Low	Inconclusive	Very limited evidence, but low risk; may be more beneficial early in disease
IMD	Low	Inconclusive	Little evidence for the treatment of CRPS except some evidence suggesting benefit of baclofen for treatment of dystonia associated with CRPS
Repeated ketamine infusions	Low	Inconclusive	Evidence of benefit in small RCTs, but administration protocol and long-term benefits and especially risks remain unclear
Trigeminal neuralgia			

Indication/Intervention	Quality of Evidence	Strength of Recommendation	Additional Comments
MVD, radiofrequency rhizotomy, glycerol rhizotomy, balloon compression or stereotactic radiosurgery	Low	Inconclusive	There is a lot of low quality evidence suggesting significant benefit from these procedures in patients refractory to medical treatment. MVD is the most invasive but may offer the longest benefits.
Trigeminal neuropathy			
MCS	Low	Inconclusive	Weak evidence of benefit, may be the best option for patients with pain refractory to non-interventional treatments
DBS	Low	Inconclusive	Less evidence than MCS of benefit

CRPS = complex regional pain syndrome; DBS = deep brain stimulation; DPN = diabetic peripheral neuropathy; DREZ = dorsal root entry zone; FBSS = failed back surgery syndrome; IMD = intrathecal medication delivery; MCS = motor cortex stimulation; MVD = microvascular decompression; NP = neuropathic pain; PHN = postherpetic neuralgia; PRF= pulsed radiofrequency; RCT = randomized clinical trial; RF= radiofrequency; SCS = spinal cord stimulation.