EAN guidelines on central neurostimulation therapy in chronic pain conditions

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Background and purpose: Our aim was to update previous European Federation of Neurological Societies guidelines on neurostimulation for neuropathic pain, expanding the search to new techniques and to chronic pain conditions other than neuropathic pain, and assessing the evidence with the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system.

Methods: A systematic review and meta-analysis of trials published between 2006 and December 2014 was conducted. Pain conditions included neuropathic pain, fibromyalgia, complex regional pain syndrome (CRPS) type I and post-surgical chronic back and leg pain (CBLP). Spinal cord stimulation (SCS), deep brain stimulation (DBS), epidural motor cortex stimulation (MCS), repetitive transcranial magnetic stimulation (rTMS) and transcranial direct electrical stimulation (tDCS) of the primary motor cortex (M1) or dorsolateral prefrontal cortex (DLPFC) were assessed. The GRADE system was used to assess quality of evidence and propose recommendations.

Results: The following recommendations were reached: 'weak' for SCS added to conventional medical management in diabetic painful neuropathy, CBLP and CRPS, for SCS versus reoperation in CBLP, for MCS in neuropathic pain, for rTMS of M1 in neuropathic pain and fibromyalgia and for tDCS of M1 in neuropathic pain; 'inconclusive' for DBS in neuropathic pain, rTMS and tDCS of the DLPFC, and for motor cortex tDCS in fibromyalgia and spinal cord injury pain.

Conclusions: Given the poor to moderate quality of evidence identified by this review, future large-scale multicentre studies of non-invasive and invasive neurostimulation are encouraged. The collection of higher quality evidence of the predictive factors for the efficacy of these techniques, such as the duration, quality and severity of pain, is also recommended.

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Introduction

Few evidence-based recommendations have been produced regarding the efficacy and safety of neurostimulation for chronic pain conditions. The most recent evidence-based recommendations concerned interventional management for neuropathic pain but did not

EUROPEAN JOURNAL OF NEUROLOGY

consider other types of pain or non-invasive techniques [1]. In 2007 the European Federation of Neurological Societies (EFNS) published the first evidence-based guidelines on neurostimulation for neuropathic pain [2]. Interventions included peripheral nerve stimulation, spinal cord stimulation (SCS), deep brain stimulation (DBS), epidural motor cortex stimulation (MCS) and repetitive transcranial magnetic stimulation (rTMS). These recommendations used the former guidance for the preparation of guidelines by EFNS task forces [3]. In the interim, new trials and techniques of neurostimulation such as transcranial direct current stimulation (tDCS) have been conducted in chronic pain. The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) has been established [4] and endorsed by the European Academy of Neurology (EAN) [5] as the method of choice to establish recommendations.

Here our aim was to update the EFNS guidelines on central neurostimulation for neuropathic pain. Contrary to prior guidelines or systematic reviews (e.g. [6]), the GRADE system was used and our search was extended to other chronic pain conditions, i.e. fibromyalgia, complex regional pain syndrome type I (CRPS I) and post-surgical chronic back and leg pain (CBLP) (formerly called failed back surgery syndrome or FBSS), for which central neurostimulation has been largely assessed. Our recommendations were restricted to central neurostimulation because trials on peripheral stimulations are characterized by a great heterogeneity of methods.

Methods

The preparation of these guidelines was conducted under the auspices of EFNS/EAN following an initial face-to-face meeting in Paris in November 2013.

The clinical question

The following 10 clinical questions (PICO: patients, intervention, comparison and outcome) were addressed.

1. Should SCS be added to conventional medical management versus conventional medical management alone in patients who have intractable peripheral neuropathic pain?
2. Should SCS be added to conventional medical management versus conventional medical management alone in patients who have CRPS I?
3. Should SCS be added to conventional medical management versus conventional medical management alone in patients who have post-surgical CBLP?
4. Should SCS be used instead of lumbar reoperation in patients who have post-surgical CBLP?
5. Should DBS be used to reduce pain in patients who have intractable neuropathic pain?
6. Should MCS be used to reduce pain in patients who have intractable neuropathic pain?
7. Should rTMS be used to reduce pain in patients with neuropathic pain?
8. Should rTMS be used to reduce pain in patients with fibromyalgia?
9. Should tDCS be used to reduce pain in patients with neuropathic pain?
10. Should tDCS be used to reduce pain in patients with fibromyalgia?

Search strategy

The full reports of prospective clinical trials published in peer-reviewed journals were identified using PubMed/MEDLINE, the Cochrane Library and Embase. The following neurostimulation techniques were assessed: SCS, DBS, MCS, rTMS and tDCS. Consistent with the former EFNS guidelines, our search was restricted to conventional SCS methods and therefore did not include more recently developed SCS variants such as burst and high frequency stimulation. Chronic pain assessed included neuropathic pain, fibromyalgia, CRPS I and post-surgical CBLP. In the case of rTMS and tDCS, studies included randomized placebo-controlled trials (RCTs) when available. For all the other procedures open RCTs (in the case of SCS) and non-randomized prospective or retrospective case series in the lack of comparative studies (in the case of MCS and DBS) were considered. Studies published only as abstracts were excluded. The study outcome (positive, negative, inconclusive) was based on the effect on pain intensity or proportion of responders. The time span of the search ranged from May 2006 (last date of search of prior EFNS guidelines [2]) to December 2014, except for tDCS and SCS which were assessed from 1966 for the following reasons: (i) tDCS was not included in prior guidelines; (ii) the use of the GRADE, which takes into account other parameters than blinding (which is impossible in SCS studies because of the paraesthesia induced by the stimulation), might impact the new level of recommendations for SCS.

Evidence summary, reporting and statistics

Where appropriate, a meta-analysis of studies based on the overall estimate effect of the intervention on pain intensity (and its 95% confidence interval) was undertaken and the level of statistical heterogeneity

(I^2 statistic, chi-squared test for heterogeneity) was calculated and risk of bias assessed using the Cochrane criteria [7]. Definition of the outcome was mean pain relief assessed on visual analogue (VAS) or numerical rating scales, expressed as difference of pain intensity at baseline and follow-up. The GRADE classification was used to assess recommendations based on a group of trials pertaining to the same stimulation technique. Final quality of evidence was rated as strong, moderate, low or very low (based on risk of bias, indirectness, inconsistency, imprecision and publication bias) and then the direction of recommendations (for, against, inconclusive) was based on the balance between desirable and undesirable effects (effect size, tolerability and safety), values and preferences for patients and costs when available. Once the relevant literature was identified for each neurostimulation technique, a preliminary analysis of the evidence was assigned to two members of the task force and then a GRADE classification was performed by MK, an EAN collaborator, with the help and supervision of NA. After results of these analyses were circulated, a second face-to-face meeting was convened in Nice in May 2015, where the final recommendations were endorsed by all the members of the task force.

Results

Full results of the meta-analysis (forest plots, tables) and of the GRADE are provided as supporting information for each of the five neurostimulation techniques. Summary results are reported in Table 1.

Spinal cord stimulation

Spinal cord stimulation uses a device that delivers electrical stimuli to the spinal cord in order to control chronic pain. SCS is mostly used for the treatment of post-surgical CBLP, CRPS and peripheral vascular disease. In traditional SCS, which is the focus of this systematic review, the frequency of stimulation ranges between 20 and 120 Hz. Stimulation at frequencies below 300 Hz typically induces paraesthesias (often described as tingling) projected to the caudal territories. There is a large consensus that pain relief is associated with paraesthesias covering the area of pain; this entails an accurate placement of the epidural electrode [8] but makes it impossible to compare conventional SCS with sham stimulation. Mechanisms of action are not fully understood. In neuropathic pain, experimental evidence shows that SCS alters local neurochemistry in the dorsal horn, suppressing central neuronal hyperexcitability [9,10].

Table 1 Summary of GRADE results in neurostimulation studies of neuropathic pain, CRPS I and fibromyalgia

Procedure	Neuropathic pain				Complex regional pain syndrome type I				Fibromyalgia			
Assessment	Final quality of evidence	Effect size	Tolerability/ safety	Values and preferences	Final quality of evidence	Effect size	Tolerability/safety	Values and preferences	Final quality of evidence	Effect size	Tolerability/ safety	Values and preferences
SCS[a]	Low	Low	Moderate	ND	Low	Low	Moderate	ND				
DBS	Very low	Very low	Moderate	ND								
MCS	Very low	Low	Moderate	High[b]								
rTMS of M1	Low	Low	High	ND	Very low	Low	High	ND	Low	Low	High	ND
rTMS of DLPFC	Very low	Low	High	ND					Very low	Low	High	ND
tDCS of M1	Low	Low	High	ND					Low	Low	High	ND
tDCS of DLPFC	Very low	Low	High	ND					Very low	Low	High	ND

CRPS I, complex regional pain syndrome type I; DBS, deep brain stimulation; DLPFC, dorsolateral prefrontal cortex; M1, primary motor cortex; MCS, epidural motor cortex stimulation; ND, not determined; rTMS, repetitive transcranial magnetic stimulation; SCS, spinal cord stimulation; tDCS, transcranial direct current stimulation.

[a]SCS is the only procedure that was studied specifically in post-surgical chronic back and leg pain (two randomized controlled studies); final quality of evidence was low, effect size was moderate, tolerability/safety was moderate and patients' preferences compared to reoperation or standard of care were high; [b]in one study, a number of patients with insignificant pain relief were willing to be reoperated for the same outcome [14].

In a pooled safety analysis of SCS across post-surgical CBLP and other chronic low back pain conditions [11,12], the adverse events mostly included lead migration (13.2%), lead breakage (9.1%) and other minor hardware problems. Medical complications were always minor and usually solved, such as hardware problems improved by removing the device. The overall infection rate was 3.4%.

Spinal cord stimulation added to conventional medical management versus conventional management alone or versus reoperation in post-surgical CBLP

Two RCTs were identified in post-surgical CBLP with predominantly leg pain. One showed that SCS added to medical management was more effective than conventional medical care alone [13]. The other found that SCS was more effective than reoperation [14] and that patients generally preferred SCS compared to reoperation. In both trials the proportion of responders (pain relief >50%) to SCS was 47%–48% versus 9%–12% with comparator at 6–24 months. These studies provided moderate quality of evidence for efficacy.

Spinal cord stimulation added to conventional medical management versus conventional management alone in CRPS and neuropathic pain

In one RCT comparing SCS with conventional care alone in CRPS I [15,16], SCS reduced pain intensity (10 cm VAS) by an average of 2.6 cm more than the control group at 6 months and 1.7 cm at 5 years. This study was of moderate quality. Two RCTs compared SCS to conventional medical management in painful diabetic neuropathy. Both trials showed a superiority of SCS over the control group on pain relief with a low quality of evidence.

Recommendations

There is weak recommendation for the use of SCS added to conventional medical management versus conventional medical management in painful diabetic neuropathy, CLBP and CRPS I and for the use of SCS as an alternative to reoperation in post-surgical CBLP (low or moderate quality of evidence).

Deep brain stimulation

The concept of relieving pain with DBS appeared in the 1950s [17]. Since then, many studies have investigated DBS efficacy in chronic pain, stimulation targets including the diencephalic periventricular gray (PVG), the mesencephalic periaqueductal gray (PAG), the sensory thalamus contralateral to pain and the anterior cingulate cortex. It is currently believed that stimulation of ventral PVG and PAG triggers non-opioid analgesia and may act through autonomic mechanisms, whereas stimulation of dorsal PVG involves endogenous opioids [18].

Deep brain stimulation is generally safe, with an overall frequency of adverse events of 8%–9%. These include lead fractures, wound infections, intra-operative seizure and postoperative burr hole site erosion [2]. Contraindications include psychiatric condition, coagulopathy and ventriculomegaly precluding direct electrode passage to the surgical target.

Deep brain stimulation therapy for intractable neuropathic pain

Seven studies including 163 patients with heterogeneous conditions, mostly dominated by peripheral or central neuropathic pain, were identified. All were case series with major limitations, such as retrospective data collection, poor selection criteria, lack of accurate diagnosis of neuropathic pain and poor reporting of adverse events. They used heterogeneous methodological approaches and targeted structures. Although the mean pain intensity reduction approached 50%, results were imprecise (large confidence intervals) and inconsistent, with large variations in reported pain relief across studies. It was also impossible to define subgroups according to specific diseases. However, the best DBS results (effect exceeding 50%, with relatively narrow confidence intervals) were obtained with stimulation of the somatosensory thalamus in patients with peripheral neuropathic pain [19,20].

Recommendations

Given the very low quality of evidence and the current uncertainty on DBS effects, the recommendation for DBS in neuropathic pain is inconclusive. It is recommended (i) to conduct prospective randomized and controlled studies providing reliable evidence on DBS efficacy; (ii) to define the safest and most efficacious DBS method, especially regarding the target; (iii) to use diagnostic algorithms and screening tools to better characterize the type of pain in order to improve selection criteria; (iv) to include a large sample of patients with homogeneous painful conditions to determine which conditions are more likely to respond to DBS.

Epidural motor cortex stimulation

Stimulation of central motor systems (cerebral cortex, pyramidal tracts) has long been shown to exert descending inhibitory influences upon nociceptive spinal and thalamic transmission and occasional

reports described its analgesic effects in man [21]. The clinical use of MCS for pain control was not documented, however, until the early 1990s [22]. Since then, MCS has been increasingly used for the treatment of drug-resistant chronic neuropathic pain.

The mechanisms underlying the analgesic effects of MCS remain incompletely elucidated. Studies in patients and animal models have shown extensive changes at various levels of the central nervous system, with a likely entry point at thalamic level [23–26] triggering distant effects on limbic and mid-frontal cortices [25,27,28] as well as descending modulation reaching the spinal horn [24,26,29]. The activation of the endogenous opioid system in the above areas has been involved in MCS-induced long-term pain relief in both patients [30,31] and animal models [32].

Motor cortex stimulation in refractory neuropathic pain
Seventeen studies (12 of them with follow-up <12 months) reporting data from 311 patients were identified. Most were observational prospective or case series and had low to very low quality. Although three studies were partially designed as crossover trials, they did not offer the necessary information to be processed as such and were treated as case series. Sensitivity analyses yielded high inconsistency in results due to heterogeneity in reports of pain intensity amongst studies. Imprecision was generally high with very large confidence intervals. The final quality of evidence was therefore downgraded as very low. However, several confounders may have contributed to underestimate the efficacy of MCS. First, contrary to most therapies with rapid and stable effects, MCS seems to display delayed and fluctuating analgesic effects which were not taken into account in the analysis of the primary outcome. For instance, in one RCT [33] two out of 12 patients (17%) who were initially good responders to MCS became poor responders at 12 months, whilst two patients considered as non-responders during the first month declared to be greatly relieved at 1 year. This may have led to an underestimation of the analgesic effects in 34% of the sample. Similar results were reported in two patients from another study [34]. Discrepancy between quantitative scores and patients' satisfaction was another potential confounder: in two studies [35,36], one of which was included in the present analyses [35], a number of patients agreed to be reoperated for the same outcome, although they were declared as having 'insignificant' pain relief. Such discordance suggests high values and preferences for MCS and was also reported for SCS [37]. Inconsistencies in pain intensity (leading to downgrading of evidence) might reflect suboptimal timing and/or distinct patients' estimates compared to quantitative scales. Finally, five studies (n = 110 patients) reported a positive significant relationship between preoperative response to motor cortex rTMS and postoperative response to MCS [34,35,38–40]. Studies with preoperative rTMS sessions [38,40] achieved better results than studies without them. This suggests that significant pain relief to preoperative non-invasive rTMS tests increases the probability of good MCS results, whilst lack of efficacy of rTMS decreases it. Similarly one study reported that the preoperative density of opioid receptors predicted the efficacy of MCS, but this result was found in *post hoc* analyses and thus patients were operated without consideration of their receptor status [31]. Altogether these results suggest that the overall MCS efficacy was probably underestimated and that a better selection of patients might increase the effect size of MCS studies.

Recommendations

A weak recommendation is proposed for the use of MCS in chronic refractory neuropathic pain. Our decision is based on the consideration of plausible confounders and potentially high values and preferences by patients (see above), although the level of evidence is very low. In future prospective trials, our recommendation is to better evaluate predictive factors of MCS outcome, particularly the response to rTMS and the density of opioid receptors.

Repetitive transcranial magnetic stimulation

Numerous studies have shown the value of rTMS to relieve various types of pain, including experimental pain [41] and neuropathic or non-neuropathic chronic pain conditions [42]. In most studies, the primary motor cortex (M1) was the stimulation target, but other targets have been investigated, mainly the dorsolateral prefrontal cortex (DLPFC).

Stimulation frequency is considered one of the most crucial rTMS parameters. Focal neuropathic pain can be relieved by high frequency (5–20 Hz) but not low frequency (0.5–1 Hz) stimulation of the contralateral M1 area [43]. Another important methodological point is the type and orientation of the stimulating coil. When using a figure-of-eight coil over M1, the handle of the coil needs to have an orientation parallel to the hemispheric midline to produce analgesia [44]. The value of other types of coils, producing more widespread or deeper cortical stimulation, remains to be determined.

High frequency M1 rTMS studies were initially based on single sessions, which produced delayed

analgesic effects (by 2–4 days) lasting only 6–8 days [45], which is too short-lasting to be compatible with therapeutic application. The repetition of daily rTMS sessions for at least 1 week can produce cumulative effects, lasting for more than 1 week beyond the time of stimulation [46,47]. However, for therapeutic purposes, a maintenance treatment (i.e. additional rTMS sessions performed at regular intervals) is required [47,48]. In this respect, Hodaj *et al*. [49] showed a significant relief of refractory facial pain, including cluster headache, following 19 sessions of high frequency M1 rTMS performed over a 6-month period, with still 40% of responders at the end of follow-up. In this study, the analgesic effect was reduced when session duration was shortened from 20 min to 10 min, despite the same number of 2000 pulses per session.

Safety is generally excellent, the main side effect of rTMS being transient headache. Contraindications include mainly epilepsy, brain tumour and cardiac pace-maker.

Primary motor cortex rTMS in neuropathic pain

Nine RCTs were identified: three had major limitations, including the number of pulses per session less than 1000 [50–52]. The most recent studies used 5-day or 10-day stimulations [46,53]. High frequency (5–20 Hz) M1 rTMS was found to be effective at short-term assessment (within 1 week beyond the time of stimulation) and mid-term assessment (from 1 to 6 weeks beyond the time of stimulation). Pain scores were reduced by 20%–45% following active stimulation with 35%–60% of responders (>30% pain relief). These analgesic effects were obtained whatever the anatomical origin of neuropathic pain, involving either the central or the peripheral nervous system, and seem to be similar in various neuropathic pain conditions.

Primary motor cortex rTMS in fibromyalgia

Five RCTs were identified: two were issued from the same group and two had poor methodological quality. High frequency (10 Hz) M1 rTMS was found to be effective at short term but not at mid-term. One study was negative on pain intensity but positive on quality of life [54]. One study showed that 14 sessions of left M1 rTMS over a 21-week period reduced pain for up to 1 month beyond the stimulation [48].

Primary motor cortex rTMS in CRPS I

Only one RCT [55] was found using 10 daily sessions of 10 Hz rTMS in 23 patients with refractory pain due to CRPS I concomitantly treated by the best medical treatment. Active rTMS produced significantly greater analgesic effects than sham rTMS over the 3 weeks of treatment. This study suggests the relevance of rTMS combined with the best medical or physical therapy in chronic pain.

Dorsolateral prefrontal cortex rTMS

Most studies were conducted in fibromyalgia. Several case reports of low frequency (1 Hz) rTMS of the right DLPFC [56] or high frequency (10–20 Hz) rTMS of the left DLPFC [57,58] suggested that analgesic effects were independent of antidepressant effects. Two studies of poor methodological quality using repeated sessions of low frequency (1 Hz) rTMS over the right DLFPC reported contradictory results. The best quality study was a randomized placebo-controlled 2-week trial of left DLPFC rTMS and showed durable and clinically relevant pain reduction, preceding an improvement in depression in 20 patients with fibromyalgia [59]. However, this study awaits replication.

There are very few data regarding rTMS of the DLPFC in neuropathic pain. Few clinical cases reported analgesia after low frequency (1 Hz) rTMS of the right DLPFC [60] or high frequency (10 Hz) rTMS of the left DLPFC [61]. Only one sham-controlled study was published to date and showed lack of efficacy of 10 days of high frequency (10 Hz) rTMS of the left DLPFC in 23 patients with central post-stroke pain [62].

Recommendations

Weak recommendations are provided for the use of M1 rTMS in neuropathic pain and fibromyalgia and inconclusive recommendations regarding CRPS (one study). rTMS should be applied contralaterally to localized neuropathic pain or on the left hemisphere in widespread neuropathic pain or fibromyalgia, using high frequency (5 Hz or more) stimulation, and should be delivered by a figure-of-eight coil oriented parallel to the midline over M1 for at least 1 week with at least 1000 pulses per session [42]. Increasing the total number of pulses per session and repeating the sessions for several days or weeks might enhance rTMS analgesia. There are inconclusive recommendations regarding rTMS of the DLPFC in fibromyalgia and neuropathic pain.

Transcranial direct current stimulation

Transcranial direct current stimulation is a widely used non-invasive technique for modulating neuronal excitability. It applies weak electric current of 0.5–3 mA to the skin in order to depolarize or hyperpolarize neurons in the brain [63]. Anodal stimulation

at the target electrode classically excites neuronal function whereas cathodal stimulation inhibits it, and a minimum duration of 5-min stimulation is needed to produce biological effects.

In recent years several studies have investigated tDCS in analgesia [64]. The mechanisms underlying tDCS effect on pain perception are unclear. Many animal studies and human observations nevertheless showed that M1 stimulation reduces the thalamic and brainstem nuclei hyperactivity underlying pain [29]. DLPFC stimulation probably mediates analgesic effects by modulating affective-emotional networks related to pain.

Safety is generally excellent, the main side effect of tDCS being a transient skin reaction below the stimulating electrodes. Rare cases of small skin burns below the cathode that recovered spontaneously have been reported. The safety of tDCS is also supported by the fact that it does not increase markers of neuronal damage, such as neuron specific enolase or brain *N*-acetyl-aspartate [65].

Fourteen studies were identified of tDCS in chronic pain, using mainly multiple sessions, including neuropathic pain and fibromyalgia.

Transcranial direct current stimulation in neuropathic pain

Twelve studies were conducted in neuropathic pain and used mainly repeated sessions (usually one per day for 5 days) (10 studies). All were RCTs and reported generally weakly positive results, but three studies conducted in spinal cord injury (SCI) pain were negative. All these studies had many limitations (small sample sizes, blinding issues, very short follow-up in many cases) and high inconsistency with large confidence intervals and heterogeneous results. For these reasons the final quality of evidence was downgraded to low.

Transcranial direct current stimulation in fibromyalgia

Three studies were conducted in fibromyalgia, of which two used repeated sessions. All were randomized sham-controlled trials accounting for an initial high quality of evidence. However, they had many limitations (small sample sizes, unblinding issues, randomization often not described, short follow-up in all cases), and their results were modest with high confidence intervals. These studies were therefore downgraded to low quality.

Recommendations

Due to low quality of evidence and marginally positive results, inconclusive recommendations for the use of tDCS in fibromyalgia are provided. A weak positive recommendation for the use of tDCS in peripheral neuropathic pain is provided but inconclusive recommendations in SCI pain (three negative studies with very low quality of evidence). Further studies are needed to clarify the effect of tDCS on chronic pain particularly with regard to potential distinct efficacy in various pain conditions and to the stimulation target.

Discussion

The updated guidelines for central neurostimulation techniques in chronic pain are presented here, based on a new systematic review and meta-analysis. Unlike prior EFNS guidelines [2], which were restricted to neuropathic pain, our recommendations extend to fibromyalgia, CRPS and post-surgical CBLP. In both fibromyalgia and CRPS I, the involvement of the peripheral and central nervous system has been demonstrated, although it is still unclear whether these findings indicate a general pathophysiological role or only concern a subset of patients [66,67]. In addition, patients suffering from these painful conditions are often refractory to conventional medical management and may therefore be candidates for neurostimulation therapy. Most SCS trials conducted in post-surgical CBLP only considered patients with leg pain, but it is not clear whether this corresponded to radiculopathy or to referred pain from the lower back. Thus post-surgical CBLP embraces a heterogeneous group of patients in which the presence and severity of nociceptive and neuropathic components may vary greatly.

One major advantage of the GRADE [4] in the case of neurostimulation techniques is that the final level of recommendation is not limited to the assessment of the design of the trial. RCTs, which are generally considered as the gold standard to assess treatments, have seldom been conducted with invasive neurostimulation techniques. However, the quality of RCTs may be downgraded to low or very low quality in cases of imprecision, indirectness or study limitations. Conversely open randomized prospective studies, which have been most commonly conducted with these techniques, may be upgraded in cases of large effect size. For example, traditional SCS has never been assessed in placebo-controlled RCTs because it induces paraesthesias in the area of pain, thus making blinding impossible; however, the GRADE analysis allowed a moderate quality of evidence to be reached for SCS due to the relatively large effect size and high values of preferences for the treatment.

A weak recommendation for the use of SCS in neuropathic pain and post-surgical CBLP, MCS in neuropathic pain, rTMS of M1 in neuropathic pain and fibromyalgia, and tDCS of M1 in peripheral

neuropathic pain is proposed. Inconclusive recommendations for DBS in neuropathic pain, rTMS of the DLPFC in fibromyalgia and neuropathic pain, and tDCS of M1 or DLPFC in fibromyalgia and SCI pain are provided (Table 2). Strong recommendations are not proposed for the use of any of these techniques, contrary to guidelines regarding pharmacotherapy [68]. One reason is the generally low to moderate final quality of the neurostimulation trials. Although the lack of placebo-controlled trials of traditional SCS stems from the difficulty of blinding, MCS studies in which sham stimulations are possible were mostly open-labelled and DBS studies were rather small case reports with major limitations. Non-invasive techniques (rTMS and tDCS) have been more often randomized and placebo-controlled, but also suffer from limitations such as small sample sizes and blinding issues (because of the poor credibility of the sham in most cases). Another reason for the lack of strong recommendation is the high level of inconsistency and imprecision in most studies with wide confidence intervals. This may be due to several factors, such as the small sample size, the inclusion of heterogeneous pain conditions (due to the lack of accurate diagnostic criteria), the variability of target definitions and the insufficient consideration of potential predictive positive factors, such as the positive response to rTMS in MCS.

All neurostimulation techniques including invasive procedures were found to be safe to very safe in our systematic review. Reports of deaths or even major adverse events after invasive procedures in thousands of patients are conspicuously few. By far the most common side effects of invasive techniques concerned malfunctioning of the stimulating apparatus or electrode movement. However, being invasive in nature, implanted neurostimulation techniques should be considered only in patients who are refractory, cannot tolerate or have contraindications to conventional medical management, with clearly defined pain condition after an optimal selection process.

For future trials of central neurostimulation, it is recommended to use larger sample sizes and in particular conduct multicentre studies of non-invasive and invasive neurostimulation in neuropathic pain, CRPS and fibromyalgia. In addition to pain, these studies should collect patient reported outcomes of quality of life and satisfaction with treatment. For neuropathic pain, it is also recommended to focus on more specific and homogeneous populations. For brain stimulation techniques, it is strongly recommended to better define the best targets of stimulation within cortical regions through image-guided navigation using morphological or functional brain imaging. High quality prospective studies of the predictive factors of these techniques with predefined assessment of potential predictors, such as duration, severity and quality of pain, are encouraged.

Novel techniques are rapidly being introduced in the field of neurostimulation. In particular high frequency or burst SCS [69–71] and dorsal root ganglion stimulation [72] have the advantage of not being perceived, whilst H-coil rTMS allows non-invasive stimulation of deeper brain structures such as the lower leg area on the medial aspect of M1 [73]. The implementation of new RCTs aiming to convey the necessary evidence of benefit for these promising techniques is encouraged.

Future update

After discussions between the Chairs of the EAN Scientific Panel Pain and the Chair of the IASP Neuromodulation SIG, it has been agreed that these guidelines will be formally updated in 5 years (i.e. 2020).

Table 2 Summary of GRADE recommendations for neurostimulation in chronic pain

Procedure	Neuropathic pain	Post-surgical chronic back and leg pain	CRPS I	Fibromyalgia
Spinal cord stimulation				
SCS versus conventional management	Weak for	Weak for	Weak for	
SCS versus reoperation		Weak for		
Deep brain stimulation	Inconclusive			
Epidural motor cortex stimulation	Weak for			
Repetitive transcranial magnetic stimulation				
rTMS of M1	Weak for		Inconclusive	Weak for
rTMS of DLPFC	Inconclusive			Inconclusive
Transcranial direct current stimulation				
tDCS of M1	Weak for (inconclusive in SCI)			Inconclusive
tDCS of DLPFC	Inconclusive			Inconclusive

CRPS I, complex regional pain syndrome type I; DLPFC, dorsolateral prefrontal cortex; M1, primary motor cortex; rTMS, repetitive transcranial magnetic stimulation; SCI, spinal cord injury; SCS, spinal cord stimulation; tDCS, transcranial direct current stimulation.

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GC, LGL, JPL, MK, PH, AT and NA declare no conflict of interest related to this study. WP is on the scientific advisory board of EBS technologies. RT is a consultant advisor to Medtronic and is currently a member of the Trial Steering Committee on two ongoing Medtronic trials (PROMISE and SubQStim). VT received honoraria from Codman, St Jude and Medtronic for giving lectures and being a member of advisory boards not related to this study.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Data S1. Supplementary material including characteristics of the studies, forest plots, GRADE evidence profile tables and GRADE recommendations for all neurostimulation techniques.

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