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CME ARTICLE

EFNS guidelines on neurostimulation therapy for neuropathic pain

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Pharmacological relief of neuropathic pain is often insufficient. Electrical neurostimulation is efficacious in chronic neuropathic pain and other neurological diseases. European Federation of Neurological Societies (EFNS) launched a Task Force to evaluate the evidence for these techniques and to produce relevant recommendations. We searched the literature from 1968 to 2006, looking for neurostimulation in neuropathic pain conditions, and classified the trials according to the EFNS scheme of evidence for therapeutic interventions. Spinal cord stimulation (SCS) is efficacious in failed back surgery syndrome (FBSS) and complex regional pain syndrome (CRPS) type I (level B recommendation). High-frequency transcutaneous electrical nerve stimulation (TENS) may be better than placebo (level C) although worse than electroacupuncture (level B). One kind of repetitive transcranial magnetic stimulation (rTMS) has transient efficacy in central and peripheral neuropathic pains (level B). Motor cortex stimulation (MCS) is efficacious in central post-stroke and facial pain (level C). Deep brain stimulation (DBS) should only be performed in experienced centres. Evidence for implanted peripheral stimulations is inadequate. TENS and r-TMS are non-invasive and suitable as preliminary or add-on therapies. Further controlled trials are warranted for SCS in conditions other than failed back surgery syndrome and CRPS and for MCS and DBS in general. These chronically implanted techniques provide satisfactory pain relief in many patients, including those resistant to medication or other means.

Background and objectives

Although pharmacological research is making major efforts in the field of neuropathic pain, a considerable number of patients do not achieve sufficient pain relief with medication alone. In real life, a sufficient level of pain relief is probably one that allows the patient to have an acceptable quality of life. In evidence-based studies on pain it is customary to consider as 'responders' to treatment those patients that report a pain relief $>50\%$. On that basis, it would appear from the most recent reviews and the European Federation of Neurological Societies (EFNS) guidelines that only 30–40% of the patients with chronic neuropathic pain achieve that target with pharmacotherapy [1,2]. However, the 50% rule is being increasingly argued because in many patients objective markers of satisfactory improvement may co-exist with nominal levels of scaled pain relief much $<50\%$ [3,4]. It was thereby proposed that a clinically meaningful reduction of chronic pain in placebo-controlled trials would be a two-point decrease or 30% reduction on a 0–10 numerical rating scale [5].

Ancillary treatments that are harmless, such as physical and psychological therapies, are often used. Although they may help them to cope, this is often not enough for the patients with severe pain. Amongst the alternatives, a number of previously common surgical lesions aimed at relieving neuropathic pain (such as neurotomies) have now been abandoned.

Neurostimulation therapy is increasingly being used either as a substitute for surgical lesions or in addition to the current medical therapy in several conditions, including Parkinson's disease, dystonia, obsessive-compulsive disorder and refractory pain, whilst trials

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are in progress in other movement and psychiatric disorders, epilepsy and migraine. The neurostimulation techniques proposed for treating pain are: transcutaneous electrical nerve stimulation (TENS), peripheral nerve stimulation (PNS), nerve root stimulation (NRS), spinal cord stimulation (SCS), deep brain stimulation (DBS), epidural motor cortex stimulation (MCS), and repetitive transcranial magnetic stimulation (rTMS). These techniques vary greatly in their degree of invasiveness, stimulated structures and rationale, but they are all adjustable and reversible.

Our Task Force aimed at providing the neurologist with evidence-based recommendations that may help to determine when a patient with neuropathic pain should try a neurostimulation procedure. To provide a better understanding, the results are preceded by a description of the procedure and its supposed rationale.

Search methods

Task Force participants were divided into subgroups and assigned the search for specific neurostimulation procedures, with two persons carrying out an independent search for each procedure. A two-stage approach to the relevant literature search was undertaken. First the MEDLINE, EMBASE and Cochrane databases were searched for systematic reviews, from inception date to May 2006. Detailed searches are listed in Appendix 1 (Supplementary Material). Recent textbooks known to the authors were also examined for relevant references. These reviews and books were used to identify the primary literature. Secondly, given the search cut off dates of previous systematic reviews, an update search for primary studies (randomized controlled trials, non-randomized controlled trials, observational comparative studies and case series) was undertaken. Studies identified by this updated search were added to the body of evidence for each neurostimulation procedure under each indication heading.

All study designs were included except case reports and very small case series (< 8). In addition, we excluded those multiple-indication case series without disaggregated reported outcomes. Both reviewers undertook the study selection. For each indication, the number and type of studies was indicated and a summary of efficacy and harm findings given. Where there was more than one systematic review or primary publication on the same series of patients, we took the most comprehensive analysis. The evidence was graded and a recommendation for each indication applied according to the EFNS guidelines [6]. The full list of references of all the assessed studies can be found in Appendix 2 (Supplementary material).

Results

Peripheral stimulations (TENS, PNS and NRS)

Derived from folk tradition, the notion that rubbing the skin over a painful area relieves pain, found scientific support in the gate-control theory proposed by Melzack and Wall [7]. Since then, electrical stimulations for pain relief have spread worldwide. The most known technique is TENS. Surface electrodes are placed over the painful area or the nerve that innervates it and the stimulation is delivered at high frequency and low intensity (below pain threshold), to produce an intense activation of Aβ afferents and to evoke paresthesiae that cover the painful area. A completely different approach is that of using low-frequency, high-intensity stimuli that do elicit painful sensations (this technique is also called 'acupuncture-like' or—when delivered through needle-electrodes—'electro-acupuncture'). In both cases, stimulation sessions of very variable duration (often 20–30 min) are repeated at variable intervals. Because the pain relief is immediate but short-lasting, many patients use a portable stimulator, which can be kept on for hours or switched on during intermittent aggravations. To provide a more stable and efficient stimulation, electrodes can be percutaneously implanted to contact the nerve (usually the main limb nerves but also branches of the trigeminal or occipital nerves) and connected subcutaneously to a stimulation unit (PNS). To cover the painful areas that are not accessible from the surface, such as pelvic viscera, a lead for SCS can be implanted deeply at the root exit from the spine (NRS) or into Meckel's cave to stimulate the Gasserian ganglion.

For all these techniques, when the currents are applied at high frequency and low intensity, the accepted mechanism is that of the homotopical inhibition exerted by large-size afferents on spinothalamic pathways. Whether this inhibition is exerted mostly on pre-synaptic terminals or second-order neurons, or involves long-loops, or whether it is more efficacious on lamina I or lamina V neurons, is of no consequence from the practical point of view. It is important to know that inhibition is strictly homotopical (i.e. the large-fibre input must generate paresthesiae covering the entire painful territory) and that pain relief rapidly declines after stimulation is stopped. The less used low-frequency high-intensity stimulation ('acupuncture-like') is thought to activate, through a long-loop, the antinociceptive systems; because it is at least partly naloxone-reversible, the analgesic effect is thought to be also mediated by the opioid system [8,9]. Hence, in theory, it may also be effective in central pain. Importantly, the peripheral stimulation must be pain-

ful, can be heterotopic, and has long-lasting effects. Rather than the diagnosis, the main indications are derived from the therapeutic rationale. In the standard TENS, pain must be confined to a relatively small area or a territory that is innervated by an easily accessible nerve. Another important condition regards the sparing of Aβ-fibre function: patients with severe loss of such fibres (as easily assessed by the TENS-evoked sensation) are unsuitable. Finally, because transcutaneous stimulations are virtually harmless (apart from possible interferences with cardiac pacemakers), TENS is often used as an ancillary support to the drug or other physical treatments, in a large variety of conditions. In contrast, PNS/NRS have more restricted indications and are used in pharmacoresistant patients.

Evidence identified

Whereas there is plenty of controlled studies and meta-analyses in nociceptive pains, the search on neuropathic pain yielded disappointing results. We identified one systematic review on outpatient services for chronic pain [10], which analysed 38 RCTs (only two studies dealing with neuropathic pains), and came to the conclusion that clearly the pain-relieving effect of TENS increases with dose (duration of the session $\times$ frequency of sessions $\times$ total duration).

Our search on TENS in neuropathic pain (Table 1) found nine controlled trials (classes II–IV) that, although not all dealing exclusively with neuropathic pain, allowed us to extract data for about 200 patients with pain of ascertained neuropathic origin. Four studies dealt with painful diabetic neuropathy: one class-II study found very-high-frequency stimulation of the lower-limb muscles more efficacious than standard TENS [11]; the others (all class III) found low-frequency TENS or acupuncture-like more efficacious than sham stimulations [12–14]. Two class-III studies dealt with peripheral mononeuropathies: both found standard TENS better than placebo [15,16]. One small RCT in post-herpetic neuralgia (PHN) found conventional TENS to have little effect whilst electroacupuncture was decidedly better [17]. One crossover, small-sample study (class III) in painful cervical radiculopathy found that standard TENS applied to the cervical back was better than placebo but a TENS with random frequency variation was superior (Table 1) [18]. Regarding PNS, we found six clinical trials (no RCT), in 202 patients with various kinds of peripheral neuropathy or mixed pains. These studies, none having an adequate control, reported an average success rate of 60%. Regarding NRS, we only found two class IV studies in patients with pelvic pains or interstitial cystitis (Table 1).

Recommendations

We cannot draw any conclusion for PNS and NRS. Even for TENS, it is difficult to come to conclusive recommendations. The total number of patients with ascertained neuropathic pain was only some 200, with diseases, comparators, and results varying considerably from study to study. Stimulation parameters also vary considerably between the studies, using different pulse waveforms and a wide range of frequencies, not to mention number and duration of the sessions. In conclusion, standard high-frequency TENS is possibly better than placebo (level C) though probably worse than acupuncture-like or any other kind of electrical stimulation (level B).

Spinal cord stimulation

This technique consists of inserting electrodes into the posterior epidural space of the thoracic or cervical spine ipsilateral to the pain (if unilateral) and at an appropriate rostro-caudal level to evoke the topographically appropriate paraesthesiae which are a pre-requisite for (but not a guarantee of) success. Catheter or wire electrodes can be inserted percutaneously under local or general anaesthesia; plate ('surgical') electrode systems require an open operation but may perform better. Power is supplied by an implanted pulse generator (IPG).

The introduction of SCS followed from the gate-control theory [7] of 'pain transmission' but SCS does not have a simple antinociceptive action. It can modulate the spontaneous and evoked elements of neuropathic pain, including allodynia, it has an antiischaemic action, both cardiac and in the periphery, and other autonomic effects including the normalization of the autonomic manifestations of complex regional pain syndromes (CRPS). The relative contributions of local segmental actions in the spinal cord and long-loop effects have not yet been elucidated. It is known that the effect of SCS is mediated by large-myelinated Aß afferents, whose collaterals ascend in the dorsal columns. Whereas sensory loss because of distal axonopathy or peripheral nerve lesion is not an exclusion criterion, sparing of the dorsal columns is probably necessary [19].

Patient selection is mostly based on diagnosis. It is recognized that SCS may be effective against various ischaemic and specific neuropathic pain syndromes. Additional tests may be useful to confirm SCS indication, such as somatosensory evoked potentials (SEPs) [19], whereas the response to TENS does not seem to be a reliable guide. Trial stimulation via externalized leads is widely employed: it will identify the patients who do not like the sensation from SCS and those in whom

Table 1 Summary of efficacy and safety of peripheral stimulations (TENS, PNS, and NRS)

Technique/condition	Available evidence	No. patients	Summary of efficacy	Summary of harms	Comparator	Blind	Random	EFNS class	Comments
TENS/chronic pain	One meta-analysis [10], analysing 38 RCTs; only two on neuropathic pain: Thorsteinsson 1977 and Rutgers 1988 [16,17]	–	There is no evidence; but it is clear that effect increases with dose (duration of the session × frequency of sessions × total duration)	Practically nothing	Various	Yes	Yes	I	
TENS/NeP Painful diabetic neuropathy	Reichstein 2005 [11]	25	TENS compared with HF muscle: 25% success with TENS and 69% with HF	Practically nothing	High-frequency muscle s timulation	Yes	Yes	II	Reichstein [11] has no placebo, TENS goes far worse than HF muscle stimulation
Diabetic neuropathy	Forst 2004 [14]	19	LF TENS reduced VAS by 23%, significant difference from placebo	Practically nothing	Placebo	Yes	Yes	III	
Painful diabetic neuropathy	Hamza 2000 [13]	50	Painful PENS reduced VAS by 60%, significant difference from sham, and improved QoL	Practically nothing	Sham		Yes	III	Crossover with an inadequate comparator (needles with no current)
Diabetic neuropathy	Kumar 1997 [12]	35	LF TENS with biphasic stimuli exponentially decaying was significantly better than sham in reducing neuropathic symptoms	Practically nothing	Sham		Yes	III	Sham inadequate and report of improvement of all symptoms.
Traumatic neuropathy	Cheing 2005 [15]	19	Significantly better than placebo	Practically nothing	Placebo	Yes	Yes	II	
Radiculopathy	Bloodworth 2004 [18]	11	Random TENS and TENS on the cervical back were significantly better than placebo, with R-TENS better than TENS	Practically nothing	Placebo and Random-TENS	Yes	Yes	III	Few patients and crossover
Mixed pains	CT Tulgar 1991 (internal control)	8	Two did not get sufficient pain relief; one received prolonged pain relief; three went better with 'burst', one with high-rate and one with low-rate modulated TENS	Practically nothing	Four modes of TENS stimulation	Yes	No	IV	Few patients who chose which mode of TENS they preferred

Table 1 (Continued)

Technique/condition	Available evidence	No. patients	Summary of efficacy	Summary of harms	Comparator	Blind	Random	EFNS class	Comments
PHN	RCT Rutgers 1988 [17]	few		Practically nothing	Acupuncture	See McQuay *et al.* 1997 [10]			
Peripheral neuropathy	RCT Thorsteinsson 1977 [16]	24	Significantly better than placebo	Practically nothing	Placebo	Yes	Yes	III	
PNS/NeP	No meta-analyses, no RCTs			Sometimes need for reoperation	None	No	No	Class IV not enough evidence for any recommendation	Very few and old papers, this technique does not seem to be getting popular
CRPS II	Buschmann 1999	52	Successful in 47						
Peripheral (*n*)	Nashold 1982	35	Successful in 15						
Post-traumatic	Law 1980	22	Successful in 13						
Mixed/various	Picaza 1977	37	Successful in 18						
Mixed/various	Campbell 1976	33	Successful in eight						
Peripheral (*n*) radiculopathy, amputation	Picaza 1975	23	Successful in 20						
Totals		202	Successful in 121 (60%)						
NRS/NeP	No meta-analyses, no RCTs			Sometimes need for reoperation	None	No	No	Class IV not enough evidence for any recommendation	
Neuropathic pelvic pain	CT Everaert 2001	26	Successful in 16						
Interstitial cystitis	Whitmore 2003, no control	33	Significant improvement						

TENS, transcutaneous electrical nerve stimulation; LF TENS, low-frequency, high-intensity TENS, also called acupuncture-like; PNS, peripheral nerve stimulation with implanted electrodes; NRS, nerve root stimulation with implanted electrodes; QoL, quality of life; CT, controlled trial; HF, high frequency; PENS, percutaneous electrical nerve stimulation.

Table 2 Summary of efficacy and safety of spinal cord stimulation (SCS)

Indication	Volume of evidence [no. trials (no. patients)]	EFNS class	Summary of efficacy	Summary of harms	EFNS grade	Comments
FBSS	**Systematic review and meta-analysis** Taylor *et al.* 2005 [21] and Cameron 2004 [20] [1 RCT (60)] (SCS vs. reoperation) [1 cohort study (44)] [72 case series (2956)] **New primary studies** [1 RCT (100)] (SCS vs. CMM) 'PROCESS' Kumar *et al.* (2005, 2007) [27,28] [6 cases series (361)] Kumar *et al.* 2006; North *et al.* 2005i&ii [26]; Spincemaille *et al.* 2005; Van Buyten *et al,* 2003; May *et al.* 2002	II	**RCTs** *Pain relief ≥50%*: SCS 9/24 (37.5%) vs. reop. 3/26 (11.5%) ($P = 0.475$) at 2 years SCS 24/48 (48%) vs. CMM 4/52 (9%) $P < 0.0001$ at 6-months *Use of opioids*: SCS 3/23 vs. reop. 11/16 ($P = 0.0005$) at 2-years SCS 25/48 (50%) vs. CMM 31/52 (70%) ($P = 0.058$) at 6 months **Case series** *Pain relief ≥50%*: 62% (95% CI: 56–72) *Disability* Pooled results across two case series show significant improvement in ODI following SCS with mean follow-up of 6 months *Quality of life* Pooled results across two case series show significant improvement in SIP following SCS with mean follow-up of 6 months	*Most common complications were*: Lead migration 361/2753 (13.2%) Infection 100/2972 (3.4%) Lead breakage 250/2753 (9.1%) Hardware malfunction 80/2753 (2.9%) Battery failure 35/2107 (1.6%) Unwanted stimulation 65/2753 (2.4%) 'Most complications were not life threatening and could usually be resolved by removing the device'. Overall 43% of patients experience one or more complications	B	*PROCESS study*: Trial protocol published [27] First oral presentation at EFIC Istanbul, Sept. 2006 Final results in press [28]
Failed neck surgery syndrome	No evidence found			As FBSS		

Table 2 (*Continued*)

Indication	Volume of evidence [no. trials (no. patients)]	EFNS class	Summary of efficacy	Summary of harms	EFNS grade	Comments
CRPS	**Systematic review/ meta-analysis** Taylor *et al.* 2006 and Cameron 2004 [20,21] [1RCT (54)] – type I CRPS Overall [25 cases series (500)] (12 case series type I, eight cases series in type II, five case series in both I and II) **New primary studies** 5-year follow-up on above RCT Kemler *et al.* 2006 [30] [2 cases series (61)] Kumar *et al.* 2006; Harke *et al.* 2005	Type I: II Type II: IV	**RCT** (at 6 and 12 months and 5-years) *Change in VAS pain*: SCS + physical therapy −2.4 (SD 2.5) vs. physical therapy: 0.2 (1.6) $P < 0.0001$ at 6-months *Quality of life (EQ-5D)*: −2.7 (SD 2.8) vs. 0.4 (1.8) $P < 0.001$ at 6-months **Case series** *Pain relief ≥50*: 67% (95% CI: 51–74) *Disability*: 3/3 studies showed a significant improve in functional capacity following SCS *Quality of life*: 2/2 studies showed a significant improvement in HRQoL following SCS Some evidence that level of pain relief with SCS in CRPS type II patients > CRPS type I	As FBSS Overall 33% of patients experience one or more complications	CRPS type I: B CRPS type II; D	
Peripheral nerve injury	One retrospective 2-centre mixed case series [$n = 152$] Lazorthes *et al.* 1995	IV	85% good and excellent at ≥2 years.	Not disaggregated. Transient paraparesis in 1/692 (whole series)	D	Pain NRS, activity and analgesic drug intake scored

Table 2 (*Continued*)

Indication	Volume of evidence [no. trials (no. patients)]	EFNS class	Summary of efficacy	Summary of harms	EFNS grade	Comments
Diabetic neuropathy	One prospective case series [$n = 8$] Tesfaye *et al.* 1996; Daousi *et al.* 2004 One retrospective mixed case series [$n = 14$] Kumar *et al.* 2006	IV IV	*Pain relief* >50% pain relief in 6/8 at 14 months (6/7: one died at 2 months) >50% relief in 5/6 at 3 years (background and peak pain) >50% relief in 4/4 at 7 years (background pain) >50% relief in 3/4 at 7 years (peak pain) *Exercise tolerance* Increased by 150% in 6/6 *Pain relief* >50% relief in 12/14 'long-term'	Lead migration in 2/8 Superficial infection in 2/8 Skin reaction in 1/8	D	Prospective VAS + McGill Sep. pain elements Preservation of large fibre (vibration and joint position) function essential Five outcome measures Third party assessor Follow-up unclear
Other peripheral neuropathy	One retrospective mixed case series [$n = 23$] Kim *et al.* 2001	IV	*Pain relief* >50% relief in 10/23 (43.5%) at 1 year	Not disaggregated	D	
Post-herpetic neuralgia	Four retrospective case series (3 mixed) [10; 28; 8; 4 (50)] Kumar *et al.* 2006; Harke *et al.* 2002; Meglio *et al.* 1989; Sanchez-Ledesma *et al.* 1989	IV	*Pain relief* Significant long-term in 38/50 (pooled) Medication stopped in 21/31 Opioids stopped in 18/19	Lead fracture in one Receiver failure in one Leads replaced in three to improve coverage	D	Success varies between series due to variable deafferentation
Intercostal neuralgia	No evidence found relating to this specific diagnosis					
Brachial plexus damage/avulsion	Two retrospective case series (2 mixed) [8; 8 (16)] Simpson *et al.* 2003 Hood; Siegfried 1984	IV	*Pain relief* Significant relief in 8/16	Nil, or not disaggregated	D	Different scoring methods Evidence of full avulsion (cf damage) of specific relevant nerve roots not always given

Table 2 (*Continued*)

Indication	Volume of evidence [no. trials (no. patients)]	EFNS class	Summary of efficacy	Summary of harms	EFNS grade	Comments
Amputation pain (phantom and stump)	Three retrospective case series [25; 9; 61 (95)] Lazorthes *et al.* 1995; Simpson 1991 Krainick + Thoden 1989; Krainick *et al.* 1975	IV	*Phantom pain* Significant relief in 7/14 *Stump pain* Significant relief in 5/9 *Mixed – stump/phantom not specified* *Krainick's series*: 56% of 61 had >50% relief (early), dropping to 43% (late). Reduced drug intake correlated *Lazorthes*: 60% of 25 good or excellent long-term (≥2 years)	Infection 1.6% Surgical revisions 31%	D	Phantom and stump pains not always distinguished
Facial pain (trigeminopathic)	Insufficient evidence					
Central pain of spinal cord origin	Five retrospective case series (4 mixed) [19; 11; 101; 9; 35 (175)] Kumar *et al.* 2006; Barolat *et al.* 1998; Lazorthes *et al.* 1995; Cioni *et al.* 1995; Meglio *et al.* 1989; Tasker *et al.* 1992	IV	*Pain relief* a) *cord injury*: 15/62 significant long term pain relief overall incomplete: 11/33 significant relief complete: 0/11 significant relief b) *MS*: long-term pain relief on five outcome measures in 15/19 (Kumar) bowel/sphincter function improved in 16/28 Gait improved in 15/19 (no details) c) *mixed incl trauma, tumour surgery, viral etc*: 34% good/ excellent at ≥2 years (Lazorthes; $n = 101$). Pain relief, analgesic drug intake and activity	Not stated/not disaggregated in four studies Aseptic meningitis 1/9 Superficial infection 1/9 Electrode dislodgement 1/9	D	Completeness of lesion not always stated Much greater success where clinically incomplete lesion Success correlates with sensory status: the less sensory deficit the better the results
Central pain of brain origin	Two retrospective case series (1 mixed) [45; 10 (55)] Katayama *et al.* 2001; Simpson 1991 [39]	IV	*Pain relief* Significant in 6/55 >60% reduction in VAS in 3/45	Not stated/not disaggregated	D	

CMM, conventional medical management; ODI, Oswestry Disability Index; SIP, sickness impact profile; VAS, visual analogue scale; HRQoL, health-related quality of life; NRS, numerical rating scale; MS, multiple sclerosis.

appropriate stimulation cannot be achieved. However, this testing is not a guarantee of long-term success in neuropathic pain.

Evidence identified

We identified a number of systematic reviews and meta-analyses [20–22] and a few narrative but detailed reviews [23–25]. The majority of systematic reviews, as well as primary studies, to date have focused on patients with failed back surgery syndrome (FBSS) or complex regional pain syndrome (CRPS). Concerning FBSS there are two class-II RCTs, the first showing that SCS is more effective than reoperation [26] and the second that its addition is more effective than conventional medical care alone [27,28]. In these trials the responders (pain relief > 50%) to SCS were 47–48% vs. 9–12% with comparator, at 6–24 months. In the pooled data from case series in 3307 FBSS patients, the proportion of responders was 62%. In CRPS type I, results and evidence level are also good, with a single class-II RCT of SCS compared with conventional care alone [29,30]. In this RCT, SCS reduced the visual analogue scale score by a mean 2.6 cm more than comparator at 6 months and by 1.7 cm at 5 years. In the pooled data from case series ($n = 561$) in CRPS I and II, the proportion of responders was 67%. Both RCTs and case series have also found significant improvement in functional capacity and quality of life. In a pooled safety analysis of SCS across all indications, the undesired events were mostly dysfunction in the stimulating apparatus: lead migration (13.2%), lead breakage (9.1%), and other minor hardware problems [20]. Also the medical complications were minor and never life threatening and were usually solved, like the hardware problems, by removing the device. The overall infection rate was 3.4%.

The effect of SCS has also been studied in many other conditions. We found positive case series evidence for CRPS II, peripheral nerve injury, diabetic neuropathy, PHN, brachial plexus damage, amputation (stump and phantom pains) and partial spinal cord injury, and negative evidence for central pain of brain origin, nerve root avulsion and complete spinal cord transection. However, all reports are class IV, thus preventing any firm conclusion. The efficacy and safety outcomes of SCS are detailed by indication in Table 2.

Recommendations

We found level B evidence for the effectiveness of SCS in FBSS and CRPS I. The available evidence is also positive for CRPS II, peripheral nerve injury, diabetic neuropathy, PHN, brachial plexus lesion, amputation (stump and phantom pains) and partial spinal cord injury, but still requires confirmatory comparative trials before the use of SCS can be unreservedly recommended in these conditions.

Deep brain stimulation

Deep brain stimulation for the treatment of medically refractory chronic pain preceded the gate theory [31]. Deep brain targets in current use include the sensory (ventral posterior) thalamus and periventricular gray matter (PVG) contralateral to the pain if unilateral, or bilaterally if indicated. Both sites have been targets of analgesic DBS for three decades [32,33]. After accurate target localization using MRI, stereotactic computerized tomography and brain atlas co-registration as appropriate, an electrode is stereotactically inserted into subcortical cerebrum under local anesthesia. The electrodes are connected to a subcutaneous IPG, placed in the chest or abdomen.

The mechanisms by which DBS relieves pain remain unclear. Animal experiments have shown that thalamic stimulation suppressed deafferentation pain, most probably via thalamo-corticofugal descending pathways. Autonomic effects of PVG stimulation are under investigation, a positive correlation between analgesic efficacy and magnitude of blood pressure reduction have been demonstrated in humans [34]. It is currently believed that stimulation of ventral PVG engages non-opioid dependent analgesia commensurate with passive coping behaviour whereas stimulation of dorsal PVG involves opioid-related 'fight or flight' analgesia with associated autonomic effects [34]. The effect of frequency, lower frequencies (5–50 Hz) being analgesic and higher frequencies (> 70 Hz) pain-provoking, suggests a dynamic model whereby synchronous oscillations modulate pain perception.

As with any implanted technique of neurostimulation for treating pain, patient selection is a major challenge. Trial stimulation via externalized leads can identify those in whom DBS is not efficacious or poorly tolerated [35,36]. However, successful trial stimulation has not resulted in long-term success for up to half of cases. Contraindications include psychiatric illness, uncorrectable coagulopathy, and ventriculomegaly precluding direct electrode passage to the surgical target [37].

Evidence identified

We identified several reviews and one meta-analysis [37], which conclude that DBS is more effective for nociceptive pain than for neuropathic pain (63% vs. 47% long-term success). In patients with neuropathic pain, moderately higher rates of success were seen in patients with peripheral lesions (phantom limb pain, radiculopathies, plexopathies and neuropathies) [37]. We identified a number of primary studies, for 623

patients and a mean success rate of 46% at long-term (Table 3). However, most studies, were class-IV case series. Amongst these, two studies (Table 4) targeted the somatosensory thalamus or PAG/PVG, using current standards of MRI in target localization and current DBS devices: one study, in 15 patients with central post-stroke pain (CPSP), considered DBS successful (pain relief >30%) in 67% of patients at long-term [36]; the other, in 21 patients with various neuropathic pain conditions, concluded that DBS had low efficacy, with only 24% of patients maintaining long-term benefit (i.e. they were willing to keep using DBS after 5 years) none of these patients having CPSP [38]. Another study, comparing the efficacy of SCS, DBS (targeting the thalamus) and MCS in 45 patients with CPSP, reported DBS success in only 25% of patients [39]. The other studies were more than a decade old and had various targets; their results are summarized by clinical indication in Table 5 and by stimulation target in Table 6.

Recommendations

For the use of DBS there is weak positive evidence in peripheral neuropathic pain including pain after amputation and facial pain (expert opinion requiring confirmatory trials). In CPSP, DBS results are equivocal and require further comparative trials.

Motor cortex stimulation

During the past decade MCS has emerged as a promising tool for the treatment of patients with drug-resistant neuropathic pain. The technique consists in implanting epidural electrodes over the motor strip. Electrodes are most commonly introduced through a frontoparietal craniotomy (40 × 50 mm) over the central area, under general anaesthesia, or through a simple burr hole under local anaesthesia. The craniotomy technique minimizes the risk for epidural haematoma and renders easier the use of electrophysiological techniques to localize the central sulcus, usually with SEPs

Table 3 Summary of deep brain stimulation studies

Study	Type of study	Number of patients implanted	Number successful at long-term follow-up (%)	Follow-up time (months); range (mean)	EFNS class
Richardson & Akil (1977) [33]	Prospective case series	30	18 (60)	1–46	IV
Plotkin (1980)		10	40	36	IV
Shulman *et al.* (1982)		24	11 (46)	(>24)	IV
Young *et al.* (1985)		48	35 (73)	2–60 (20)	IV
Hosobuchi (1986)		122	94 (77)	24–168	IV
Levy *et al.* (1987) [53]		141	42 (12)	24–168 (80)	IV
Siegfried (1987)		89	38 (43)	<24	IV
Gybels *et al.* (1993)		36	11 (31)	48	IV
Kumar *et al.* (1997) [12]		68	42 (62)	6–180 (78)	IV
Katayama *et al.* (2001) [39]		45	11 (25)	N/A	III
Hamani *et al.* (2006) [38]		21	5 (24)	2–108 (24)	IV
Owen *et al.* (2006) [35]		34	12 (35)	1–44 (19)	IV

Table 4 Summary of efficacy and safety of deep brain stimulation by indication from recent and currently applicable studies

Indication	Volume of evidence no. trials (no. patients)	EFNS class	Summary of efficacy (%)	Summary of safety
Amputation pain (phantom and stump)	2 (5; 1)	IV	100; 100	No indication specific complications: four wound infections; two DBS lead fractures; one intra-operative seizure; one post-operative burr hole site erosion
Post-stroke	2 (16; 8)	IV	69; 0	
Facial pain (trigeminopathic)	2 (4; 4)	IV	100; 25	
Cephalalgia not including trigeminopathic facial pain	2 (3; 1)	IV	100; N/A	
Central pain of spinal cord origin	2 (2; 4)	IV	0; 25	
Multiple sclerosis pain	1 (2)	IV	50	
Other and trauma	2 (4; 1)	IV	75; 100	

Pain assessment used at least one of VAS (visual analogue scale); MPQ (McGill pain questionnaire); N1T (N-of-1 trial); HRQoL, health-related quality of life; NRS, numerical rating scale. Only VAS-related outcomes using a threshold of >50% improvement are shown here.

Table 5 Summary of efficacy and safety of deep brain stimulation by indication from other, older studies (after Bittar *et al.* 2005) [37]

Indication	Volume of evidence (no. patients)	Success on initial stimulation	Success on chronic stimulation	Long-term percentage success
Amputation pain (phantom and stump)	9	7	4	44
Post-stroke pain	45	24	14	31
FBSS	59	54	46	78
Peripheral nerve injury	44	36	31	70
Post-herpetic neuralgia	11	6	4	36
Intercostal neuralgia	4	3	1	25
Brachial plexus damage/avulsion	12	9	6	50
Malignancy pain	23	19	15	65
Facial pain (trigeminopathic)	32	21	12	38
Central pain of spinal cord origin	47	28	20	43
Other	35	28	22	63

Table 6 Summary of efficacy and anatomical targets from other, older studies (after Bittar *et al.* 2005 [5])

Anatomical site of DBS	Volume of evidence no. patients	Number successful long-term	Percentage success
PVG	148	117	79
PVG and ST or IC	55	48	87
ST	100	58	58
ST or IC	16	6	38

PVG, periventricular gray matter; ST, sensory thalamus; IC, internal capsule.

concomitant to MRI-guided 'neuronavigation'. Intraoperative cortical stimulation with clinical assessment or EMG recordings can help to determine the position of the electrodes. One or two quadripolar electrodes are implanted over the motor representation of the painful area, either parallel or orthogonal to the central sulcus. The electrode is connected to a subcutaneous IPG. The stimulation parameters are optimized post-operatively, keeping the intensity below motor threshold, and the stimulation is usually set on cyclic mode (alternating 'on' and 'off' periods).

The mechanism of action of MCS remains hypothetical. Tsubokawa *et al.* [40] showed that MCS attenuated abnormal thalamic hyperactivity after spinothalamic transection in cats, and considered that such effect involved retrograde activation of somatosensory cortex by cortico-cortical axons [41]. However, positron-emission tomography and SEPs failed to show any significant activation of sensory-motor cortex during MCS, whilst a strong focal activation was observed in thalamus, insula, cingulate-orbitofrontal junction and brainstem [42,43], suggesting that MCS-induced pain relief may relate to (i) top-down activation of descending pain control systems going from motor cortex to thalamus, and perhaps to motor brainstem nuclei and (ii) blunting of affective reactions to pain via activation of orbitofrontal-perigenual cingulate cortex [43]. Both hypotheses have received recent support from studies in animals and in humans [44–46]. The fact that many of the regions activated by MCS contain high levels of opioid receptors suggests that long-lasting MCS effects may also involve secretion of endogenous opioids.

Eligible patients should be resistant or intolerant to main drugs used for neuropathic pain [1,2]. Some studies include pre-operative sessions of transcranial magnetic stimulation, which is regarded predictive of the MCS outcome (see Repetitive transcranial magnetic stimulation). Candidates to MCS have sometimes experienced failure of other neurosurgical procedures, such as radicellectomy (DREZ-lesion), anterolateral cordotomy, trigeminal nerve surgery or SCS.

Evidence identified

Our search disclosed no systematic review or meta-analysis, but found a relatively large number of studies (mostly case series) on CPSP and facial neuropathic pain. In CPSP, we extracted 143 non-overlapping patients from 20 case series: the average proportion of success was about 50%. Slightly better results (60% of responders, based on 60 patients from eight series) were obtained in facial neuropathic pain, central or peripheral. Most of these case series were class IV. Two studies can be classified as class III, because they had a comparator (results of other treatments, surgical or pharmacological), and outcome assessment and treatment were dissociated: Katayama *et al.* [39]. had a 48% success rate in patients with CPSP and Nuti *et al.* [4]. A 52% success rate in 31 patients with various neuropathic pain conditions, mostly CPSP. One of these papers provided follow-up results up to

4 years [4]. In phantom pain, brachial plexus or nerve trunk lesion, spinal cord lesions or CRPS, we only found case reports. Most common undesired events were related to some malfunction of the stimulating apparatus (e.g. unexpected battery depletion). Seizures, wound infection, sepsis, extradural haematoma, and pain induced by MCS have also been reported. Overall 20% of patients experience one or more complications, in general of benign nature. Details of the search with summary of benefits/harms can be found in Table 7 and 8.

Recommendations

There is level C evidence (two convincing class III studies, 15–20 convergent class IV series) that MCS is useful in 50–60% of patients with CPSP and central or peripheral facial neuropathic pain, with small risk of medical complications. The evidence about any other condition remains insufficient.

Repetitive transcranial magnetic stimulation

The use of rTMS in patients with chronic pain aims at producing analgesic effects by means of a non-invasive cortical stimulation [47]. The stimulation is performed by applying on the scalp, above a targeted cortical region, the coil of a magnetic stimulator. A focal stimulation using a figure-of-eight coil is mandatory. The intensity of stimulation is expressed as a percentage of the motor threshold of a muscle at rest in the painful territory. The stimulation is performed just below motor threshold. The frequency and the total number of delivered pulses depend on the study. One single session should last at least 20 min and should include at least 1000 pulses. Daily sessions can be repeated for one or several weeks. There is no induced pain and no need for anaesthesia or for hospital stay during the treatment.

The rationale is the same as for implanted MCS. The stimulation is thought to activate some fibres that run

Table 7 Summary of efficacy and safety of MCS in CPSP

Indication	Volume of evidence [no. trials (no. patients)]	EFNS class	Summary of efficacy	Summary of harms	Comments
CPSP	Systematic review and meta-analysis None Primary studies (1991–2006) No RCT [20 cases series, with much overlap (143 non-overlapping patients)] Rasche *et al.* 2006, Nuti *et al.* 2005 [4] (+Mertens *et al.* 1999 +G-Larrea *et al.* 1999) [43] Saitoh *et al.* 2003 (+Saitoh *et al.* 2001) Fukaya *et al.* 2003 +Katayama *et al.* 2001 [39] +Katayama *et al.* 1998 +Yamamoto *et al.* 1997 Nguyen *et al.* 2000 +Nguyen *et al.* 2000 +Nguyen *et al.* 1999 +Nguyen *et al.* 1997 Nandi *et al.* 2002 Carroll *et al.* 2000 Fujii *et al.* 1997 Katayama *et al.* 1994 Tsubokawa *et al.* 1993 +Tsubokaw *et al.* 1991 Drouot *et al.* 2002	All class IV (unless indicated otherwise) III III	Case series (8–45 cases) Satisfactory pain relief (≥50%) reported in 0–100% of cases (all series) In series with $n >$ 20 cases satisfactory pain relief in 48–52% of patients	Most common complications: 26% (battery failure, seizures, wound infection and sepsis) Pain induced by MCS Phantom pain Extradural haematoma Seizures Hardware malfunction Overall 20% of patients experience one or more complications and in general of benign nature	Many patient duplications or reinterventions making total nb of cases difficult to calculate. Reports with duplicated data were pooled Efficacy related to pre-operative response to drugs? (Yamamoto 1997, $n = 28$) Efficacy related to sensory symptoms? (Druot 2002, $n = 11$) Efficacy related to motor symptoms? (Katayama 1998, $n = 31$)

CPSP, central post-stroke pain; MCS, motor cortex stimulation.

Table 8 Summary of efficacy and safety of motor cortex stimulation in facial pain

Indication	Volume of evidence [no. trials (no. patients)]	EFNS class	Summary of efficacy	Summary of harms	Comments
Facial pain	Systematic review and meta-analysis: None Primary studies (1991–2006) No RCT *Case series (60 patients)* Rasche *et al*. 2006 (3/50) Brown Ptiliss 2005 (10/60) Nuti *et al*. 2005 [4] (5/60) Drouot *et al*. 2002 (15) Nguyen *et al*. 2000a (12/83) +Nguyen *et al*. 2000b same +Nguyen *et al*. 1999 same +Nguyen *et al*. 1997 (7/100) Ebel *et al*. 1996 (7/43) Katayama *et al*. 1994 (3/66) Meyersonl 1993 (5/100)	All class IV	Case series Satisfactory pain relief (≥50%) reported in 43–100% of cases (all series) No series with $n > 20$ cases Mean percent of patients with satisfactory pain relief: 66%	Most common complications: 26% (battery failure, seizures, wound infection and sepsis) Pain induced by MCS Extradural haematoma Seizures Hardware malfunction Overall 20% of patients experience one or more complications, in general of benign nature	Many patient duplications or reinterventions making total nb of cases difficult to calculate. Reports with duplicated data were pooled. Small series but sometimes long follow-up: 72 m

MCS, motor cortex stimulation.

through the motor cortex and project to remote structures involved in some aspects of neuropathic pain processing (emotional or sensori-discriminative components). The method is non-invasive and can be applied to any patient with drug-resistant, chronic neuropathic pain, who could be candidate for the implantation of a cortical stimulator. As the clinical effects are rather modest and short-lasting beyond the time of a single session of stimulation, this method cannot be considered a therapy, except if the sessions of stimulation are repeated for several days or weeks.

Evidence identified

We identified some reviews, none systematic, and 14 controlled studies that used sham stimulations in crossover or parallel groups, 280 patients with definite neuropathic pain (CPSP, spinal cord lesions, trigeminal nerve, brachial plexus, or limb nerve lesions, phantom pain and CRPS II). Efficacy, rather than varying between pain conditions, mostly depends on stimulation parameters. There is consensus from two RCTs in patients with CPSP or various peripheral nerve lesions that rTMS of the primary motor cortex, when applied at low-frequency (i.e. 1 Hz or less), is ineffective (class II) [48,49]. Focal-coil stimulations at high-rate (5–20 Hz), of long-duration (at least 1000 pulses) and possibly repeated sessions, induce pain relief ($>30\%$) in about 50% of patients (class II/III) [50–52]. The effect begins a few days later and its duration is short, <1 week after a single session. Another important aspect is that a positive response to high-frequency rTMS is probably predictive of a positive outcome of subsequent chronic epidural MCS (class II) [49].

There is insufficient evidence for other indications or other techniques, including magnetic stimulation of the dorsolateral prefrontal cortex or the parietal cortex, as well as transcranial direct current stimulation. The efficacy and safety outcomes of transcranial magnetic stimulation are detailed in Table 9 and 10.

Recommendations

There is moderate evidence that rTMS of the motor cortex, using a figure-of-eight coil and high frequency (5–20 Hz) induces significant pain relief in CPSP and several other neuropathic pain conditions (level B). However, because the effect is modest and short-lasting, rTMS should not be used as the sole treatment in chronic neuropathic pain. It may be proposed for short-lasting pains or to identify suitable candidates for an epidural implant (MCS). In contrast, in the same pain conditions, low-frequency rTMS is probably ineffective (level B).

General comments

Most trials on neurostimulation for pain relief did not comply with the requirements of evidence-based medicine (EBM), often because of the difficulty in using an adequate comparator for these stimulations. Level-B recommendations could however be drawn for some procedures in some pain conditions. Naturally, some neurostimulation procedures are relatively new, thus the available evidence is still sparse and it would be pre-mature to draw negative conclusions (Fig. 1).

Peripheral stimulations have been used very little in neuropathic pain. Acupuncture-like stimulations are

Table 9 Summary of efficacy and safety of rTMS, primary motor cortex stimulation, 1 Hz or less

Indication	Volume of evidence [no. trials (no. patients)]	EFNS class	Summary of efficacy	Summary of harms	EFNS grade	Comments
Stroke ($n = 32$), Spinal cord lesion ($n = 4$), Trigeminal nerve lesion ($n = 1$), Brachial plexus or limb nerve lesion ($n = 8$), Phantom limb pain ($n = 14$)	New primary studies Three sham-controlled trials All negative (59 p.) Lefaucheur *et al.* 2001a André-Obadia *et al.* 2006 Irlbacher *et al.* 2006	 II II III	No efficacy *Pain relief* ≥*30%*: 5% (mean pain relief: 4%)	No reported complications	B	No significant effect compared with sham stimulation

Table 10 Summary of efficacy and safety of rTMS, primary motor cortex stimulation, 5 Hz or more

Indication	Volume of evidence [no. trials (no. patients)	EFNS class	Summary of efficacy	Summary of harms	EFNS grade	Comments
Stroke ($n = 98$), Spinal cord lesion ($n = 24$), Trigeminal nerve lesion ($n = 60$), Brachial plexus or limb nerve lesion ($n = 36$) CRPS ($n = 10$)	New primary studies [11 sham-controlled trial (281 p.)] Positive studies (228 p.) Lefaucheur *et al.* 2001a Lefaucheur *et al.* 2001b Lefaucheur *et al.* 2004a Pleger *et al.* 2004 Khedr *et al.* 2005 Hirayama *et al.* 2006 Lefaucheur *et al.* 2006a Lefaucheur *et al.* 2006b	 II II II III II II II II	*Pain relief* ≥*30%*: 46% (mean pain relief: 26%) 104 responders/206 patients. Efficacy regarding indication: idem for stroke vs. trigeminal nerve lesion (Lefaucheur *et al.* 2004; Khedr *et al.* 2005) or brachial plexus lesion (Lefaucheur *et al.* 2004); better for thalamic vs. brainstem stroke (Lefaucheur *et al.* 2004) poorer results for spinal cord lesion (Lefaucheur *et al.* 2004) CRPS: no significant difference with the other causes (Pleger *et al.* 2004)	No reported complications	B	No significant effect compared to sham stimulation in case of circular coil (Rollnik *et al.* 2002) or 5 Hz-rTMS (Irlbacher *et al.* 2006) and < 1000 pulses per session (Rollnik *et al.* 2002; Irlbacher *et al.* 2006) Better pain relief in case of repeated sessions (Khedr *et al.* 2005) or stimulation of adjacent cortical area (Lefaucheur *et al.* 2006b) Pain relief duration: less than one week after a single session; about two weeks after one week of stimulation
Stroke ($n = 20$), Spinal cord lesion ($n = 6$), Trigeminal nerve lesion ($n = 1$), Brachial plexus or limb nerve lesion ($n = 8$) Phantom limb pain ($n = 15$), CRPS ($n = 2$), non-neuropathic ($n = 1$)	Negative studies (53 p.): Rollnik *et al.* 2002 André-Obadia *et al.* 2006 Irlbacher *et al.* 2006	 III II III				

rTMS, repetitive transcranial magnetic stimulation; CRPS, complex regional pain syndrome.

probably more efficacious than high-frequency TENS, but we do not have strong evidence. Unlike some other neurostimulation procedures, TENS is extremely easy to apply and devoid of any risk. This is why TENS is so widely used in acute and chronic pain patients, with little concern whether the improvements are because of

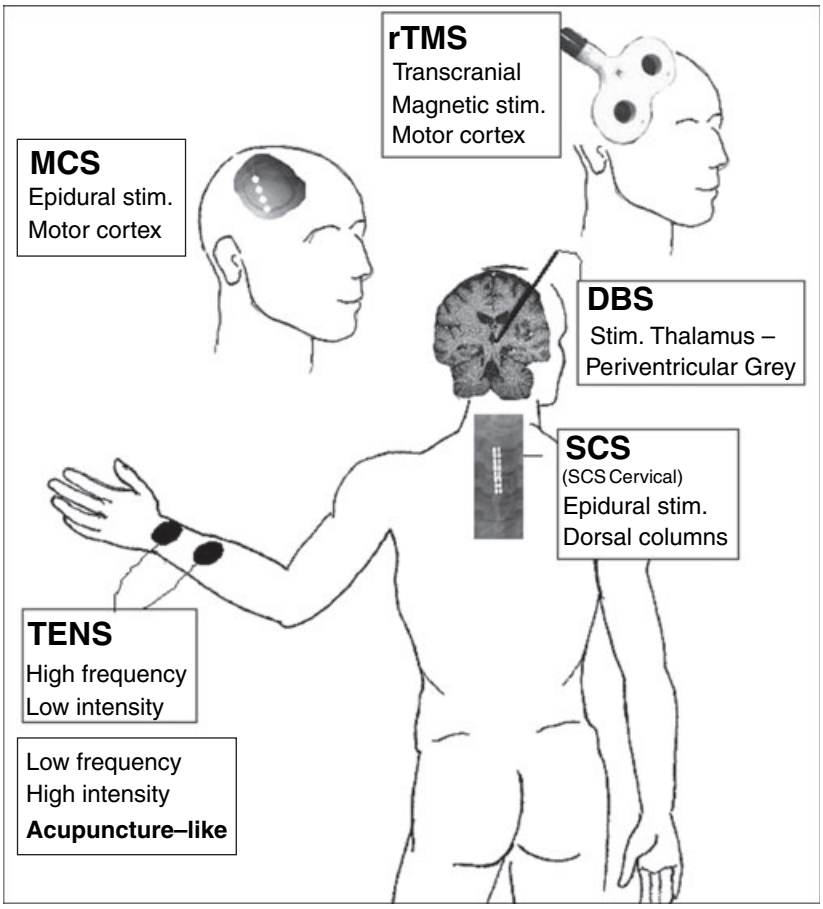

Figure 1 Schematic representation of different neurostimulation procedures, e.g. for a patient with pain in the left hand because of peripheral nerve injury.

a placebo effect or not. This may also hold true for neuropathic pain patients. SCS has class II RCT evidence. Its efficacy has been so far demonstrated in two conditions, which are not 'definitely neuropathic': FBSS and CRPS type I. Pain in FBSS is usually mixed and it is difficult to extract the neuropathic component, and CRPS I is still a 'putative neuropathic' pain.

Spinal cord stimulation, DBS and MCS are typically used when all other treatments have failed. This context should be taken into account when making recommendations. We analysed only published evidence. Thousands of stimulators are implanted every year and only a tiny minority appears in published studies. Absence of evidence is not evidence of absence of effect, and low-level evidence (i.e. case series) should be given some credence. For some indications, there was a considerable body of 'positive' case series findings, sometimes over long periods of time. Furthermore, the whole field has been largely characterized by a heavy dependence on the outcome measure '50% pain relief' as a threshold indicator of success, after both trial and definitive stimulation, which may distort the true picture. Others have found a 30% pain relief to correspond to a clinically meaningful success [5], and factors beyond changes in pain intensity are also relevant.

Although not a new therapy, DBS has metamorphosed considerably over the last decade, concomitantly with advances in both stimulator technology and neuroimaging techniques, leading to improved efficacy and reduced complications. DBS should be performed in experienced, specialist centres, using established outcome measures and willing to publish their results. Whereas its efficacy in CPSP is controversial, DBS appears more promising for phantom limb pain and trigeminal neuropathic pains.

Motor cortex stimulation is useful in CPSP and in central or peripheral facial pain. Interestingly, the proportion of good and excellent results increases consistently in patients with facial pain relative to all other classes. The reason is not yet established. Candidates for MCS have neuropathic pain that has been resistant to drugs and often to other interventions. In view of the potential development of this method, it is of the utmost importance that placebo-

controlled, double-blind studies are produced to increase the level of evidence, particularly because of MCS, not being perceived by the patient, allows a perfect placebo.

As with TENS, the efficacy of rTMS seems to increase with dose: higher frequency, longer duration of the session, and more sessions tend to yield better results. Because the clinical effects are rather modest and short-lasting, rTMS cannot be considered as a therapeutic method for the long term, except if the sessions of stimulation are repeated for several days or weeks. Currently, rTMS can be proposed as a non-invasive pre-operative therapeutic test for patients with drug-resistant chronic pain who are candidates for surgically-implanted chronic MCS.

Concerning harms (detailed in the Tables), TENS and rTMS are virtually harmless. SCS, DBS and MCS do entail adverse events in a large proportion of patients (up to 20% with MCS and 40% with SCS experience one or more complications). However, most of these are simple lead migration or battery depletion that do not produce physical harm and can usually be solved. Real harms are few, usually wound infection (3.4% with SCS, 7.3% with DBS and 2.2% with MCS) and very rare cases—often single cases—of aseptic meningitis, transient paraparesis, epidural haematoma, epileptic seizures and skin reactions, none being life-threatening. Our search disclosed one case only of pre-operative death 20 years ago [53]. Indeed, one of the reasons for the use of neurostimulation therapy is that the application of low-intensity electrical currents is not associated with any of the side effects entailed by drugs.

Finally, we feel that neurostimulation therapy will prove to be useful for a broader indication than is suggested by our search. We hope that future trials are designed bearing in mind the EBM requirements. Although it is admittedly difficult to find a credible placebo for neurostimulation therapy, the investigators may compare their procedure to other treatments. Furthermore, we recommend that investigators pay attention to definition of diagnosis, inclusion criteria, blind assessment of the outcomes, and impact on patient-related variables such as quality of life and daily living activities.

Declaration conflict of interest

RST has a consultant contract with Medtronic, as an expert in Health Care Policy and Clinical Trial Design. PH, LGL, JPL and BS received honorarium from Medtronic for lectures or advisory boards. The other authors have nothing to declare.

Supplementary Materials

The following supplementary material is available for this article:

Appendix 1. SCS search strategies

Appendix 2. Full list of studies

This material is available as part of the online article from:

http://www.blackwell-synergy.com/doi/abs/10.1111/j.1468-1331.2007.01916.x

(This link will take you to the article abstract).

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