Implantable technology for pain management

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Abstract

Neuropathic pain is a well-recognized chronic pain condition. This can have a significant impact in patients' quality of life. Neuromodulation is defined by the International Neuromodulation Society as 'the therapeutic alteration of activity in the central or peripheral nervous system either electrically or pharmacologically'. Electrical stimulation can be performed at the motor cortex, deep brain, spinal cord, dorsal root ganglion, peripheral nerve and peripheral nerve field. Pharmacological modulation is achieved by directly infusing drugs to the central nervous system. Although neuromodulation has become increasing popular, it is still currently believed to be underused in treating neuropathic pain. This modality has provided us with a non-pharmacological approach to manage patients with neuropathic pain. Patients should have been assessed by a multidisciplinary team before undergoing neuromodulation. This review highlights the present and future management of patients with chronic intractable pain using neuromodulation.

Keywords Burst stimulation; dorsal root ganglion stimulation; high-frequency stimulation; neuromodulation; spinal cord stimulation; wireless spinal cord stimulation

Royal College of Anaesthetists CPD Matrix: 1D02, 3E00

Introduction

Neuromodulation is a rapidly expanding field of medicine to treat pain, functional disorders such as epilepsy, rectal and urinary incontinence. National Institute of Health and Care Excellence (NICE) technology assessment has recommended neuromodulation as a cost effective modality in managing certain neuropathic pain conditions.[1] The strengths of neuromodulation are its specificity, reversibility and programmability. Its benefits are long-term improvement in functional status, pain relief and reduction in the demand for healthcare resources. Thus, its superior clinical results, along with its long-term cost-effectiveness, demonstrate that neuromodulation has many clinical and economic benefits in an era of rising healthcare costs.

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Learning objectives

After reading this article, you should be able to:

- explain the difference between electrical and chemical neuromodulation
- understand the patient selection and role of neuromodulation in managing chronic intractable pain
- explain the different theories underlying the mechanism of action of neuromodulation
- explain the different types of spinal cord stimulators, such as dorsal root ganglion stimulator, high-frequency stimulator and burst stimulator

The present conception of neuromodulation originated over half a century ago, in the mid 1960s, when Melzack and Wall's gate-control theory was proposed. This theory is based on the idea of a gate that is controlled by large and small fibers of pain neurons depending on their activation. In 1967, Shealy successfully managed to implant a platinum electrode in the subarachnoid space, which was attached to an external power source supplying electrical stimulation. A year later, Medtronic was the first company to introduce spinal cord stimulation (SCS) at a commercial scale using radiofrequency.

Neuromodulation for treating chronic debilitating pain can be classified into two forms, electrical and chemical. Electrical neuromodulation is achieved by placing an electrode at a target nerve both central and peripheral and connected to implantable pulse generator (IPG), whereas spinal chemical neuromodulation involves placing one or more drugs directly into the central nervous system such as epidural, intraventricular and intrathecal. Intrathecal drug delivery system (ITDD) involves placing a catheter in the cerebral spinal fluid, allowing the medication to be administered directly into the central nervous system and therefore reducing the side effects.

Intrathecal drug delivery (Figure 1)

ITDD involves a pump acting as a drug reservoir that is placed in the subcutaneous tissue and connected to the intrathecal space via a catheter. The pump is powered by a computer-programmed rotor or a hydraulic-driven continuous flow pump.

Although there are no international criteria for selecting patients for ITDD, patients can generally be divided into cancer and non-cancer pain. Cancer pain is fundamentally different from non-cancer pain; for example, patients with cancer often have a poor prognosis (shorter life span), different pain modalities/sites and lower quality of life. Previous studies have only considered cancer patients with a life expectancy of more than 3 months; however, in 2012, the Polyanalgesic Consensus Committee (PACC) revisited their previous recommendations and urged clinicians to meticulously consider those with a life expectancy less than 3 months for ITDD. In 2016 PACC recommended many indications for using ITDD in non-cancer pain, primarily pain originating from the spine (failed back surgery syndrome, spondylosis, compression fracture, discogenic), complex regional pain syndrome, abdomen/pelvis (visceral, somatic), extremity (radicular, joint) and trunk (post-herpetic neuralgia, post-thoracotomy syndromes).

Implantable drug delivery systems

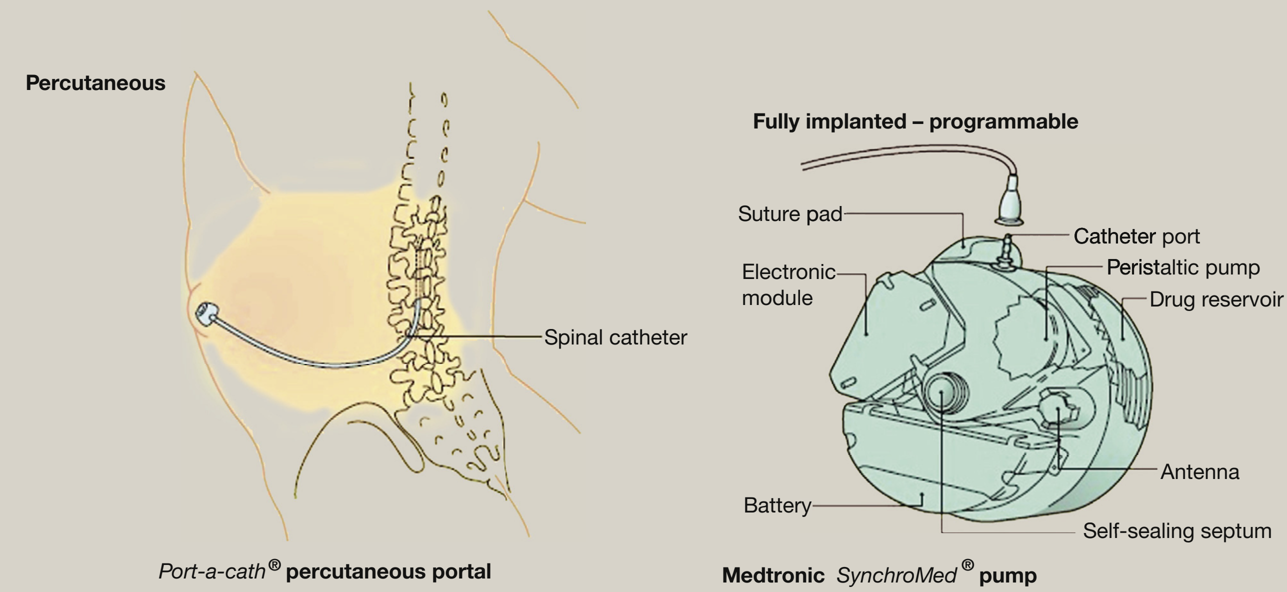

Figure 1

The PACC panel have suggested the recommended medications to treat patients with chronic pain (Table 1).[2]

Contraindications for ITDD

- Systemic infection.
- Bleeding diathesis.
- Failure to obtain consent.
- Altered spinal anatomy (relative).
- Local infection (relative).
- Pre-existing leg oedema (relative).

Complications of ITDD (specific)

- Intrathecal granulomas: can be avoided by adhering to concentrations and rate recommended by the PCC.
- MRI scanning issues: the magnetic field can stop the rotary pump or gives a big bolus. The pump needs to be emptied and stopped before MRI and rechecked and restarted after the MRI.
- Leg oedema.

Vigilance for catheter obstruction, dislodgement, migration and drug related complications such as long-term opioid use and other pharmacological agent related complications should be monitored.

Recommendations of PACC for managing chronic pain using intrathecal drug delivery

Drug	Recommendation for starting dose	Maximum concentration	Maximum dose per day
Morphine	0.1–0.5 mg/day	20 mg/ml	15 mg
Hydromorphone	0.01–0.15 mg/day	15 mg/ml	10 mg
Fentanyl	25–75 μg/day	10 mg/ml	1000 μg
Sufentanil	10–20 μg/day	5 mg/ml	500 μg
Bupivacaine	0.01–4 mg/day	30 mg/ml	15–20 mg
Clonidine	20–100 μg/day	1000 μg/ml	600 μg
Ziconotide	0.5–1.2 μg/day (to 2.4 μg/day per product labelling)	100 μg/ml	19.2 μg

Table 1

Spinal cord stimulation

Mechanism of action[3]

The mechanism of SCS in treating chronic refractory pain has not yet been fully elucidated and the exact mechanism still remains unknown. There are theories proposed based on animal work.

- Gate-control theory: this mechanism was first proposed by Melzack and Wall, whereby activating the dorsal column nerves inhibits nociceptive pain impulses in the dorsal horn, was eventually found to be partially true, due to the fact the acute nociceptive pain is not completely inhibited by SCS.
- Supraspinal inhibition: supraspinal centres are involved in the effects of implantable spinal stimulators, in which the dorsal column brainstem loop is the key factor. Barchini et al. studied the underlying mechanism of the supraspinal and spinal segmental role in neuropathic SCS pain relieving effects.[4] This was done by using SCS rostral and caudal to the level of dorsal column injury under various receptors antagonists. Their findings proved that both supraspinal and spinal effects contributed to the effects of SCS in alleviating pain and that different synaptic circuits and transmitter systems were involved in supraspinal and spinal pain relieving effect.
- Neurophysiological mechanisms:
    - SCS inhibits the activation of the abnormally hyperactive wide dynamic range (WDR) neurons in the dorsal horn of the spinal cord.

 - The anti-dromic stimulation of the SCS in the dorsal horn seems to inhibit the peripheral nerves that usually maintain the hyperactivity of WDR neurons.
 - Inhibition of the spinothalamic tract.
- Neurochemical mechanisms: SCS is also involved in altering the neurotransmitters in the central nervous system, in which the over excitability of wide dynamic range neurons found in the dorsal root ganglion can be counteracted using SCS by increasing GABA release and decreasing glutamate concentration in the extracellular space of the dorsal horn. Furthermore, the release of acetylcholine was observed in rats under the effects of SCS, leading to the activation of muscarinic receptors. Along with the involvement of the aforementioned neurotransmitters, there seems to be an adenosine dependent mechanism, all of which could play a role in potentiating the effects of SCS.
- Anti-ischaemic mechanisms: SCS application result in improvement of balance between cardiac tissue oxygen supply and demand, a useful effect in patients with angina pectoris secondary to coronary hypo perfusion. This is thought to be related to altering the neuronal activity of the heart, by minimizing consequences of coronary hypo perfusion such as arrthymia. In peripheral vascular disease SCS can be useful by inhibiting the sympathetic nervous system and causing peripheral vasodilation by anti-dromic release of substances such as nitric oxide.

Patient selection

SCS is indicated in patients with intractable neuropathic pain syndromes (Box 1). Although it is suggested that SCS is less effective in treating nociceptive pain than neuropathic pain, it can sometimes be challenging to differentiate the degree of involvement of nociceptive and neuropathic pain; as such, an SCS trial is justified in these cases. With newer innovative technologies, some of the indications such as post amputation pain, post thoracotomy pain and post hernia repair pain can be treated successfully. As our understanding increases, we are able to treat more neuropathic conditions successfully.

Contraindications for SCS:

- coagulopathy
- sepsis (localized or systemic)
- immune suppression (relative contraindication)
- presence of pacemaker or implantable defibrillator (relative contraindication).

SCS is not contraindicated in patients with psychological comorbidity. Multidisciplinary assessment is warranted for patients with mental illness, cognitive impairment, communication problems, or learning difficulty. A psychological screening is essential in some patients along with pain management program and individual psychology sessions before implantation. However, it remains unclear whether patients with mild/moderate psychological disorders should be considered for SCS (Box 1).

Indications for spinal cord stimulation (British Pain Society Guidelines 2009)

Good indications for SCS (likely to respond)
Neuropathic pain in leg or arm following lumbar or cervical spine surgery (FBSS/FNSS)
Complex regional pain syndrome (CRPS)
Neuropathic pain secondary to peripheral nerve damage
Pain associated with peripheral vascular disease
Refractory angina pectoris (RAP)
Brachial plexopathy: traumatic (partial, not avulsion), post-irradiation

Intermediate indications for SCS (may respond)
Amputation pain (stump pain responds better than phantom pain)
Axial pain following spinal surgery
Intercostal neuralgia, such as post-thoracotomy or post-herpetic neuralgia
Pain associated with spinal cord damage
(other peripheral neuropathic pain syndromes, such as those following trauma may respond)

Poor indications for SCS (rarely respond)
Central pain of non-spinal cord origin
Spinal cord injury with clinically complete loss of posterior column function
Perineal or anorectal pain

Unresponsive to SCS
Complete spinal cord transection
Non-ischaemic nociceptive pain
Nerve root avulsion

Box 1

Procedure (Figure 2)

An electrode is inserted into the epidural space either percutaneously under fluoroscopic guidance or open via mini laminotomy or laminectomy. These electrodes are connected to an implantable pulse generator (IPG) using either extension. Adjustments can be made to the frequency, amplitude and pulse width to achieve pleasant paraesthesia in the area of the pain. The patients are then allowed to trial this for 1–4 weeks to assess the efficacy and the ease of use. A trial is successful on achieving more than 50% pain relief and improvement in quality of life. This will be followed by implanting an IPG in the subcutaneous tissue of abdomen or buttock or thoracic rib cage.

As an invasive procedure, SCS carries risks such as dural puncture, lead fracture, migration and infection. Newer anchoring tools and better precautions to prevent infection including administration of intravenous antibiotics have helped in reducing these complications considerably.

NICE has appraised the SCS. The guidelines NICE Tag 0159, suggest the use of SCS as a cost-effective treatment in refractory pain secondary to failed back surgery syndrome (FBSS), CRPS and other neuropathic pain.[1]

Complications of SCS

- Lead migration requiring revision.
- Lead fracture requiring revision.
- Dural puncture (with Tuohy needle or electrode).
- Infection (rare).
- Neurological injury due to direct trauma, haematoma or abscess (rare).

Device-related complications are decreasing due to the advancement in the technology of electrodes, anchors and IPGs.[5]

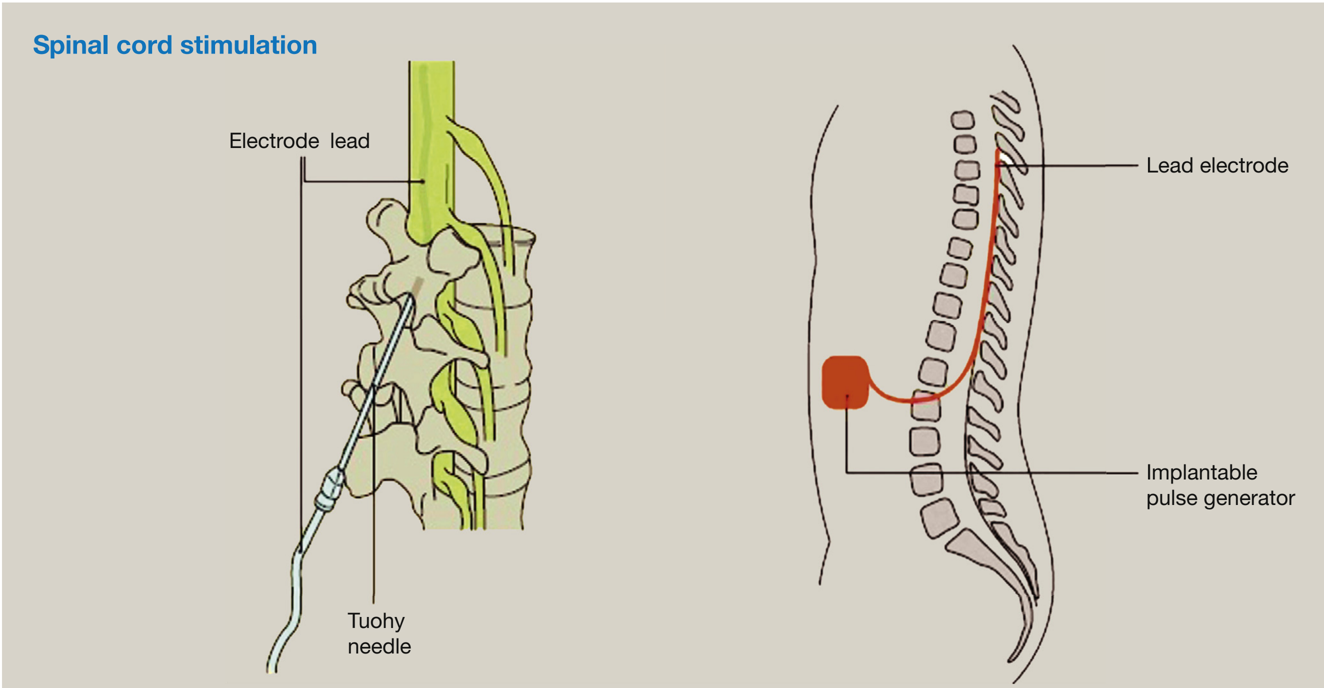

Figure 2

Surgical insertion of electrodes warrants special considerations as given the larger size compared to percutaneous electrodes, care must be taken to avoid cord compression in patients with spinal canal stenosis. Extensive laminectomy should be considered carefully as it can lead to morbidity in the cervical spine and pain lasting for months in the thoracic spine.

Special precautions in patients with SCS in situ include:

- Use of diathermy: unipolar diathermy carries the risk of passing electricity through SCS components therefore avoid use or if must ensure reference plate is away from SCS site.
- MRI scan: can be challenging due to interaction with SCS components. SCS maybe compatible with MRI and if not other imaging modalities such CT can be performed instead.
- Security systems: such as in airports can be activated
- Antibiotic prophylaxis: not warranted in patients undergoing surgical procedures.

Dorsal root ganglion stimulation (Figure 3)

The dorsal root ganglion (DRG), a collection of visceral and somatic cell bodies conveying sensation for all sensory modalities, has recently become an appealing site for treating intractable chronic neuropathic pain. Similar to the traditional SCS, neurostimulation at this site involves both the spinal and supraspinal mechanisms, providing a platform for modulating the C and Ad type neurons responsible for transmitting nociceptive pain.

The DRG is an anatomical organ present under the pedicles in the spine. This target has been made accessible by the development of a special delivery sheath and a small electrode. As the DRG has minimal or no CSF, the current required to stimulate this structure is far less and this also has a focused stimulation on a dermatomal distribution allowing to focus the therapy.

In 2013, Liem et al.[6] conducted a prospective, multicentre observational study in which 39 patients underwent DRG neurostimulation and were followed for 6 months. This trial included a variety of neuropathic pain syndromes, including failed back surgery syndrome, lumbar stenosis, CRPS and radiculopathy. The DRG stimulators were turned off at two time points for 7 days acting as a control group. The primary aim was to assess the feasibility and safety of DRG neurostimulation. The authors found that the pain was reduced (by at least 50%) in 57%, 70% and 89% for back, leg and foot pain, respectively. Of note, the authors acknowledged the fact that

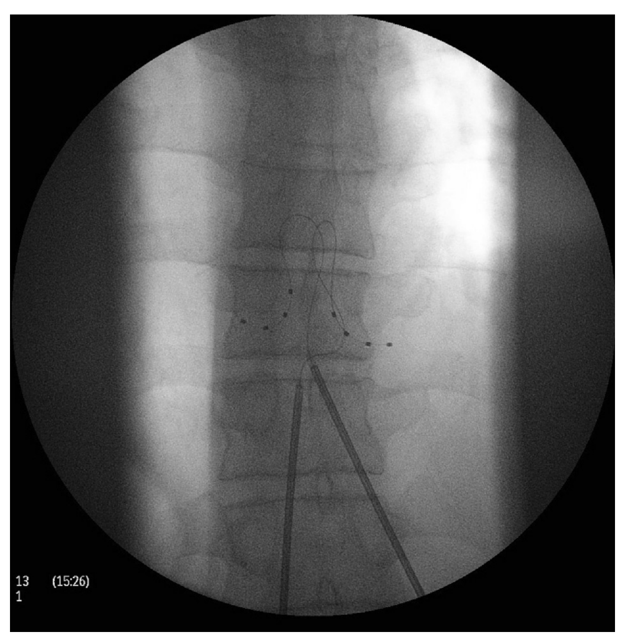

Figure 3 Dorsal root ganglion electrodes in position with a slack created in the epidural space.

the placebo effect could potentially be a source of bias during the control period time frame, influencing the end results of the trial. In terms of complications, it was reported that 10% of the participants had infection, 9% had cerebrospinal fluid leak, and fewer than 5% experienced uncomfortable stimulation or lead migration.

A multicentre, prospective, randomized control trial ACCURATE study,[7] aims to assess the efficacy and safety of DRG stimulators by comparing it to traditional SCS. A total of 152 patients diagnosed with CRPS/peripheral causalgia were recruited for the trial; of these, half were randomized to DRG stimulation and the other half to traditional SCS. The technical responsibility of the therapy, either DRG stimulation or traditional SCS, were the representatives of the company. In other words, the devices were optimized and programmed by the representatives from that company, thus minimizing bias and providing the best effect of the stimulators. At the end of 12 months, 72.3 % DRG and 65.7% SCS arm achieved the study end point. Treatment success at primary end point of 3 months was defined as ≥50 % reduction in pain using VAS score. DRG stimulation resulted in higher treatment success rate of 81.2% compared to 55.7% in traditional SCS (P <0.001). Similar pattern continued up to the trial secondary end point of 12 months. Changes in paraesthesia secondary to posture was significantly lower in DRG implanted subjects compared to SCS. In Addition, improvement on measures of quality of life, functional status and psychological disposition was demonstrated on DRG stimulation in contrast to SCS. Safety profile was similar in both DRG and SCS. Limitations to this trial exist. The success rate was not only based on achieving ≥50% pain reduction, but also on continuing in the study (dropouts counted as failures). In addition, a specific regime for pain killers was only in place for the first 3 months and therefore variation in this after that period may have affected the results at 12 months. SCS programming had limitation as the accelometer function was disabled which may have had an effect on postural related changes in parasthaesia.

Waveforms

Some elements of SCS have been unchanged since this technique was employed nearly fifty years ago. Traditional SCS involves the production of electrical impulses (within a narrow frequency range) in an isochronous fashion, which is therefore associated with paraesthesia. These aspects (low frequency, paraesthesia, regular pattern) of conventional SCS have been consistently challenged over the years as a necessity for a pain-relieving effect in patients with chronic pain. Traditional SCS with a clinically acceptable frequency (1–200 Hz) does not relieve chronic pain without being associated with paraesthesia, creating the need for paraesthesia mapping, which involves interacting with patients while implanting the electrodes. However, when the frequency was increased to 10 KHz using 30-ms electrical impulses, pain relief can still be achieved, but in the absence of paraesthesia. Using this concept, high-frequency stimulators have proven their superiority over traditional SCS in terms of magnitude of pain relief, onset of effect and convenience for patients.[5] It is important to highlight, however, that high-frequency stimulators require recharging once per day due to high power consumption. A further anticipated development will be to introduce long lasting batteries associated with these devices.

Another new stimulation paradigm is burst stimulation, which emits a short surge of high frequency impulses to the spinal cord. This burst surge of impulses delivers five 1 ms spikes at a rate of 500 Hz per second. These impulse episodes are delivered forty times per second, resulting in a 40 Hz burst mode. The underlying rationale for introducing the 40 Hz burst mode was related to the nature of the human thalamus that releases impulses in a burst and tonic modes to activate the cortex of the brain.

High-frequency stimulators

High-frequency spinal cord stimulation is indicated to provide a paraesthesia free analgesic effect and remove the need for paraesthesia mapping. It is designed to deliver 1000–10,000 Hz compared to the 50–100 Hz delivered by traditional SCS. In this new technique, electrodes are positioned based on anatomical landmarks only. Electrodes are placed in a staggered fashion in order to maximize coverage and provide contiguous stimulation of different dermatomes. Patients with chronic back and leg pain are treated by placing one electrode at the level of T8 and the other at the level of T9 to enable stimulation of the dorsal column of levels T9–T11 (Figure 4).

Kapural et al.[5] presented a multicentre randomized controlled trial (SENZA-RCT study) to assess the effectiveness and safety of 10 kHz high-frequency stimulators (HF-10 SCS) compared to the traditional SCS therapy for patients with recurrent back and leg pain. The authors assessed the pre and post implantation pain score (using the VAS scale), the functional capacity of the participants and their satisfaction. This study recruited 171 participants, of whom 90 had the HF-10 SCS implanted while 81 were treated with the traditional SCS. They found that 84% of the participants with back pain responded (≥50% reduction in VAS score relative to baseline score) to HF–SCS, compared to 44% in the other group, at 3 months. Furthermore, over 78% of patients treated for back pain with HF- 10 SCS responded to treatment, versus 51.3% in the traditional SCS group, at 12 months. HF-10 SCS was also found to be superior to the traditional treatment

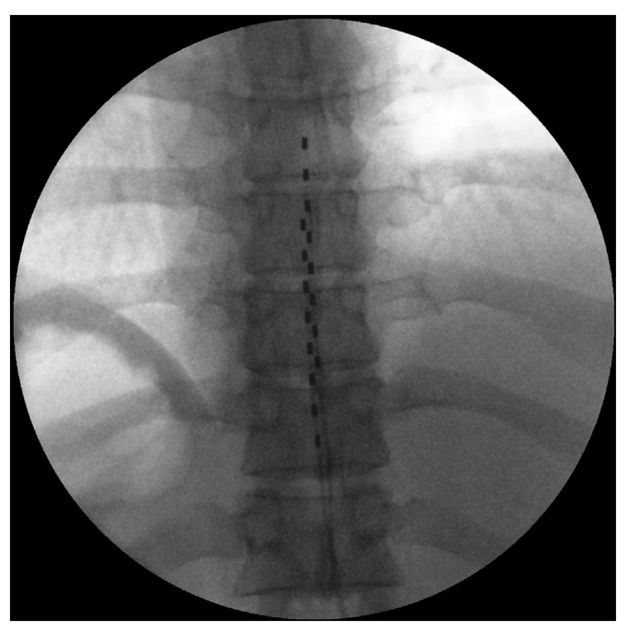

Figure 4 Two electrodes in place covering T8-T11.

in terms of leg pain; 83.1% versus 55% at 3 months and 78.7% versus 51% at 12 months. In addition, HF-10 SCS subjects showed favorable results in terms of functional capacity as measured by Oswestry Disability Index ODI) scale by an average improvement of 16.5 in HF-10 SCS, versus 13 in those treated with traditional SCS. The 24-months results haven't shown much change from the 12-month data.

Burst neurostimulation

Despite the efficacy of traditional SCS in treating chronic pain, there is still a high level of heterogeneity with regards to the degree of pain reduction. Some evidence suggests that up to 30% of patients treated for chronic pain can be classified as non-responders. An alternative mode of SCS, burst stimulation, which employs the use of series of impulses (as opposed to a single pulse), may address many of the challenges that physicians face when dealing with traditional SCS, including the inability to cover certain areas and intolerance to the paraesthesia effect of traditional SCS that can lead to a failed SCS trial.

De Ridder et al.[8] conducted a randomized double-blinded controlled study comparing three different pain relief models (burst, tonic and placebo-effect pain relief) on 15 patients with intractable chronic pain. As opposed to tonic stimulators, the authors found that burst stimulators did not result in more paraesthesia compared to the placebo stimulators. Furthermore, burst stimulators were found to have a profound pain relief effect superior to that of both tonic and placebo stimulators, in terms of back and generalized pain perceived by the participants. Tonic stimulation, however, did not suppress back pain significantly when compared to placebo stimulators, nor did it have better pain relief results when pain was at its worst.

In the same trial, De Ridder et al. studied the underlying mechanism of their findings by comparing the data from a source localized electroencephalogram, in which they found that burst stimulators had a significant increase in the activation of dorsal lateral prefrontal cortex and anterior cingulate cortex.[8] It was previously shown that attention to pain is regulated and modulated through the anterior cingulate cortex, which is part of the medial intentional pain system; as such, they have hypothesized that burst stimulation regulates the medial system along with lateral discriminatory pain. In other words, the clinical effects of burst stimulation could replicate how pain is perceived after undergoing a frontal lobectomy, resulting in a substantial effect on the attention paid to pain. It is important to highlight that only burst stimulation had superior results to placebo stimulators by changing the participant's attention to pain. Burst stimulation, therefore, might not necessarily have a stronger pain suppressing effect, but rather by having an attention modulating effect, as evident from the clinical and pathophysiological evidence.

Peripheral nerve stimulation (PNS)

As opposed to other types of neurostimulation, peripheral nerve stimulation (PNS) involves directly stimulating peripheral nerves and inhibiting primary afferent nerves. PNS seems to be useful in treating neuropathic pain, especially in the limbs, as long as the sensation is preserved in the affected region. Its efficacy, however, is not yet fully conclusive, and therefore it is necessary to conduct a randomized control trial to assess the efficacy of the PNS technique in the long-term.

PNS for chronic headaches

Refractory headache is a worldwide health problem affecting up to 5% of the population. The majority of headaches are often treated with medical treatment alone; however, a few remain intractable despite optimal medical treatment. Understanding the craniocervical nociceptive system is essential in managing chronic headaches. The anatomy of the occipital region is well understood: three main nerves – least, lesser and greater occipital nerves – innervate the occipital region; all three supply the posterior aspect of the head and originate from the cervical spinal roots. Furthermore, there is a well-established connection between the cervical nerve roots and the trigeminal nerve, or the so-called trigeminocervical system. This underlying connection is the main reason why pain is referred from the cervical to the frontal region, explaining the mechanism by which the stimulation of the occipital nerve modulates pain in the occipital region as well as the trigeminal nerve innervation distribution.

Occipital nerve stimulation

Occipital nerve stimulation (ONS) has been used to treat an array of primary headache syndromes, such as cluster headaches and migraines. ONS can also be used to treat secondary headaches, including occipital neuralgia and traumatic headaches. This procedure involves placing an electrode subcutaneously close to the occipital nerve and connected to an IPG (Figure 5).

The positive results published by small studies have encouraged the three primary manufacturers of ONS to conduct multicentre, prospective, double-blinded, randomized control

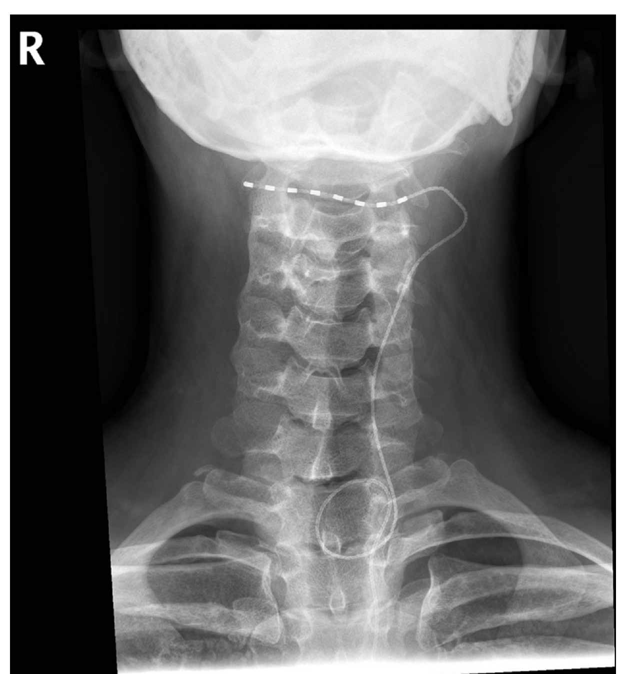

Figure 5 Anteroposterior view of an occipital nerve stimulator in position.

trials, including the St. Jude's study (157 patients), ONSTIM study (67 patients) and PRISM study (125 patients).[9] Unfortunately, the PRISM and St. Jude's studies did not find a significant post therapeutic response in patients recruited in their trials, according to the historical standardized positive response of $\geq$50% in terms of pain relief or reduction in frequency of migraine episodes. The St. Jude study, however, found that over 50% of the participants were satisfied with the device 12 weeks post implantation and that about 60% of the patients experienced a pain reduction of $\geq$30% of the threshold level. The ONSTIM study was the only trial in which patients had a significant result, with about 39% of the participants responding to treatment at 3 months. It should be noted that these results should be interpreted with care, as a positive therapeutic response was defined as pain reduction of $\geq$30%, rather than the historical standardized 50%, compared to their initial baseline score.

These promising results, along with the level of optimism regarding the use of this treatment modality to treat intractable headaches, have urged St. Jude to carry out a long-term 40 week follow-up on their previous study, in which almost 60% of patients achieved 30% or greater reduction in pain intensity and/or headache frequency, and about half of the participants achieved a 50% pain reduction.[4] However, these results should be interpreted within the context of our patients' safety. For example, over 70% of the patients experienced at least one complication after having had the stimulator implanted, such as lead migration, infection and persistent pain and/or numbness at the site of lead. Moreover, almost 40% of the patients needed to have an additional surgery due to device-related adverse events.

Further trials are needed to assess the complications of ONS, as the complications are still high, and therefore refinement may be needed in the implantation technique and/or technology of ONS in order to assess whether it is safe to use on a wide-scale commercial level.

Sphenopalatine ganglion stimulation

The sphenopalatine ganglion (SPG), also referred to as the pterygopalatine ganglion, is considered to be one of the biggest of the parasympathetic ganglions that supply the cerebral vasculature, meninges, lacrimal glands, pharangeal glands and nasal mucosa. The SPG is known to have numerous nerve roots, including sensory, autonomic and motor nerves. It is suggested that SPG stimulation can treat chronic headaches by innervating the post-ganglionic parasympathetic nerves of SPG and thwarting the sensory processing in the trigeminal nucleus caudalis. These post-ganglionic parasympathetic nerves arising from the SPG are distributed to the maxillary and ophthalmic divisions of the trigeminal nerve. As such, the activation of the trigeminal autonomic reflex is thought to have a major role in autonomic symptoms and pain, which are often associated with cluster headaches. Activating the parasympathetic outflow of the SPG, supplying the cerebral blood vessels and meninges, results in dilation of the cerebral blood vessels as well as activation of the nociceptive fibers of the meninges, which is manifested as referred pain from the head. Therefore, SPG stimulation has been used for clinical treatment of patients with chronic pain, particularly cluster headaches.

In a multicentre randomized control trial, Schoenen et al.[10] demonstrated the efficacy and safety of SPG stimulation in treating refractory cluster headaches by comparing SPG stimulation to sham-treated participants. Pain relief was observed in 76% of patients treated with SPG stimulation versus sham-treated patients. Furthermore, SPG stimulation was found to be superior to that of sham-treated patients, with about 70% of the SPG stimulated participants demonstrating a significant improvement of their symptoms; of those, 25% had pain relief of $\geq$50% from headache attacks, and 36% had a reduction in the frequency of headache attacks. ◆

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