Invasive Neurostimulation in the Management of Chronic Neuropathic Pain Syndromes

a report by

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Historical Perspective
The analgesic effect of electricity has been exploited for thousands of years (electric fish, static electricity) but it has been controllable only since the introduction of the Leyden jar in 1745. Electro-acupuncture was introduced in 1823. Peripheral nerve stimulation was also developed in the 19th century, but its misuse (‘the golden age of medical electricity’) led to its ban in the US in 1910. The modern era of therapeutic neurostimulation was launched by the gate control theory of pain transmission, although deep brain stimulation (DBS) had already been used for pain control. It was also driven by the dawning awareness that damage to the nervous system, including therapeutic damage, could itself generate pain – neuropathic pain. The first human application of spinal cord stimulation (SCS) was in 1967.

General Considerations
Physical treatments such as electrical neurostimulation have clear advantages over pharmacotherapy in terms of adverse side effects. Despite this and the fact that fewer than half of patients with chronic neuropathic pain obtain worthwhile long-term pain relief from drugs, implanted neurostimulators are regarded as a treatment of last resort. This is only partly due to the high initial cost involved; cost-effectiveness studies are consistently positive, with a crossover point in less than three years (probably a little later, but with greater long-term benefit, in the case of the more expensive recently introduced rechargeable systems).

The biggest hurdle facing the field is the issue of evidence. There is a large body of positive but uncontrolled published evidence and enormous unpublished positive experience, but very little ‘level one’ evidence. Not only does this provide the financially constrained healthcare commissioners and insurers with an excuse, but it is also relevant to the key factor of case selection.

There are remarkably few contraindications: the presence of an implanted cardiac defibrillator or a demand-type cardiac pacemaker, uncontrolled coagulopathy, sepsis and, to a variable extent, cognitive impairment.

Spinal Cord Stimulation

General Comments
This is the most widely and commonly used form of internal neurostimulation. The epidural electrodes are placed ipsilateral to the pain, because it is necessary to activate the collaterals of the large Aβ afferents that ascend in the posterior columns of the spinal cord. The rostro-caudal and lateral positioning of the electrode system must be appropriate so that the gentle evoked paraesthesiae cover the painful area. Originally, monopolar systems were used, then bipolar and now 16 contacts are commonly available, requiring computer assistance for programming. Dual-channel and multichannel programming permit electronic steering of the stimulation topography, greatly reducing the need for physical repositioning of the electrodes. Electrodes are either of the wire/catheter type, which can be inserted percutaneously via a Tuohy needle under local anaesthesia or in the form of a paddle, which requires an open operation. The former are less invasive but are electrically inefficient and more prone to dislodgement than ‘surgical’ systems. The latter perform better but require both a surgeon and a bigger procedure for insertion. The power comes from an implanted pulse generator similar to a cardiac pacemaker and the electronic parameters are programmed by telemetry. External power sources coupled to an implanted receiver–transducer by radiofrequency are available for cases in which power demand is high, but the recent introduction of rechargeable implantable systems avoids the need for frequent replacements in a more elegant way.

Indications
In broad terms, SCS is effective for neuropathic and ischaemic pain and does not influence nociceptive pain (e.g. arthritis, acute wound pain, etc.). The most common applications, which have also provided the best evidence for efficacy, are complex regional pain syndrome (CRPS) and the poorly named failed back surgery syndrome (FBSS). FBSS, i.e. pain in the leg and/or back persisting after one or more lumbar spine operations, is...
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One demonstrated superiority of SCS over re-operation and the other supported the addition of SCS over conventional medical management alone. Overall, the success rate appears to be around 60–65%.

CRPS, characterised by severe pain, allodynia and autonomic, trophic and motor abnormalities following almost any injury (type I) or a specific nerve injury (type II), also responds well to SCS. A significant degree of pain relief occurs in approximately 70% of cases and the allodynia (pain induced by normally innocuous stimuli) and other elements are also often normalised. CRPS remains poorly understood and even its classification as a neuropathic syndrome is controversial. The biggest puzzle is why it should develop after one particular injury, having not emerged previously in the same (predisposed) individual. One published RCT showed a significantly greater degree of pain relief when SCS was added to physiotherapy.

A large body of less robust published evidence also supports the use of SCS in FBSS, CRPS and pain without the features of CRPS following peripheral nerve injury, as well as in diabetic neuropathy, post-herpetic neuralgia, brachial plexus damage, amputation pain (stump and phantom pains) and partial spinal cord injury. It will not work for pain caused by complete avulsion of the brachial plexus or complete transection of the spinal cord or for pain following a stroke.

**Selection of Cases**

Diagnosis alone is clearly insufficient, otherwise success rates would be higher. It is not yet understood why some patients with an appropriate diagnosis do not respond. The response to transcutaneous electrical nerve stimulation (TENS) is not a reliable guide. Trial SCS via a temporary externalised lead is very commonly employed but, although it will identify the small minority who do not like the sensation of SCS, it does not reliably predict long-term success. Large series with thoroughly conducted preliminary trials have typically not yielded success rates above about 70%. This may be partly due to the placebo effect of the trial, but the criterion of success used in most trials – typically a 50% reduction in pain intensity on a visual analogue scale (VAS) – may also be partly to blame. Some have used somatosensory evoked potentials as a guide, as well as the response to sympathetic blocks, but these have not yet entered routine practice. A better understanding of the pathophysiology of the target conditions may improve case selection and thereby success rates in the future.

**Mechanism of Action**

The relative contributions of long-loop effects via the brainstem and thalamus and local segmental effects in the spinal cord have not yet been elucidated. It is not known whether the necessary evoked paraesthesiae represent an epiphenomenon. SCS does not simply ‘close the gate’, as it is not effective against nociceptive pain. Animal models suggest that allodynia is associated with reduced release of gamma aminobutyric acid (GABA) in the dorsal horn of the spinal cord and that effective SCS increases its release, along with a decreased release of excitatory amino acids. However, there are no animal models of spontaneous pain, one of the hallmarks of neuropathic pain syndromes. A better understanding of the mechanism of action will improve both case selection and the credibility of the treatment in the eyes of commissioners and reimbursers. It may also shed light on the pathophysiology of the conditions it modifies.

**Other Methods of Neurostimulation**

**Motor Cortex Stimulation**

The relationship between sensory and motor functions is complex and fundamental, and there must be a point in cerebral activity at which the distinction is lost. It is therefore fascinating to reflect on the fact that stimulating the motor cortex with surface (epidural) electrodes can control neuropathic pain of central origin – in particular, central post-stroke pain and trigeminal de-afferentation pain – in approximately 50% and 70% of patients respectively. These two conditions are extremely difficult to treat effectively by other means. The position of the electrode contacts appears to be critically important and may be relevant to some of the failures. Identifying the optimum electrical parameters can be time-consuming and is hampered by the absence of evoked paraesthesiae (c.f. SCS) and by the slow effect of MCS. There is also a variable after-effect that permits cyclical stimulation patterns – e.g. three hours on and three hours off – and can last for 12 hours or more. The mechanism of action is not understood, but neurophysiological and positron-emission tomography (PET) evidence suggest both an activation of descending intrinsic pain control systems and an effect on limbic, affective activity. Stimulation of the sensory cortex (post-central gyrus) is usually unpleasant.

**Deep Brain Stimulation**

Deep brain stimulation (DBS) via implanted electrodes preceded the gate theory and the introduction of SCS, but has never been carried out in significant numbers for pain. In the wake of the rapid development of DBS for movement disorders over the past two decades and with the benefit of modern imaging and other technology, DBS for pain has to some extent been revisited. The previously proposed dichotomy, supported by animal experiments, of thalamic and internal capsule stimulation for neuropathic pain versus (opioid-rich) periventricular and periaqueductal grey stimulation for nociceptive pain has not been sustained completely in clinical practice. Case selection is of paramount importance and is not informed reliably...
by trial stimulation. Reported outcomes have varied quite widely, but the long-term success rate has been lower for neuropathic pain than for nociceptive pain and has not exceeded 50%. An apparent exception is the recently introduced hypothalamic stimulation for cluster headache, which appears to have a much higher success rate. In general, neuropathic pain of peripheral origin has fared better with deep brain stimulation than has central (post-stroke) pain.

Peripheral Nerve Stimulation
Peripheral nerve stimulation (PNS) boomed in the second half of the 19th century and auto-PNS by Wall and the neurosurgeon Sweet helped develop and test the gate control theory, but therapeutic invasive PNS has not yet become re-established in the modern era. Initially, technical factors led to nerve damage and only short-term success, but recently interest has been renewed, particularly for indications such as CRPS. In general, high-frequency, low-intensity stimulation has been employed, acting to inhibit spinothalamic transmission by activating large, myelinated, afferent neurones. Occipital nerve stimulation for cervicogenic headache, occipital neuralgia and possibly migraine is also currently receiving attention. Sensory field stimulation achieved by simply inserting the electrodes subcutaneously into the painful area, rather than in direct contact with the nerve trunk, is also a promising but not yet fully evaluated innovation.

Sacral Root Stimulation
Sacral motor (ventral) root stimulation has been used for three decades to improve bladder and erectile function in paraplegics. It is only recently, however, that the therapeutic value of sacral sensory root stimulation has been appreciated, particularly for interstitial cystitis and urge incontinence. The published evidence remains sparse but encouraging at present and the techniques are relatively simple, without the need for major surgery.

Conclusion
As I write this, in March 2007, it is 40 years almost to the day since the first spinal cord stimulator was implanted in a human; DBS is in its sixth decade. The pressure to justify the use of neurostimulation, however, remains considerable, with increasing demands for ‘evidence’ by financially constrained healthcare systems. At least 20,000 new units are implanted annually worldwide and the number is steadily increasing. Neuromodulation is highly successful commercially, which would be unusual if the products did not work. Patients demand surgical operations to replace depleted power sources, strongly implying benefit. Reported success rates in case series are fairly consistent. Yet we are increasingly reminded that there is very little ‘level one’ evidence of efficacy. We have to ask what constitutes appropriate evidence in such a field, including cost-effectiveness data.

Exciting new indications are appearing and the technology is always improving, but these factors must be complemented by better case selection. Better case selection depends upon three things: better ways of assessing outcomes; better understanding of the pathophysiology of the target disorders; and better understanding of the mechanism(s) of action. In turn, it will lead to better outcomes, reduced cost per successful case and the opportunity to treat more patients earlier. Earlier treatment may itself improve outcomes and may modify the disease process.