

Historical and Present State of Neuromodulation in Chronic Pain

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Abstract Neuromodulation is based on the revolutionary concept that paresthesia-inducing electrical stimulation could be analgesic. Its historical basis emanates from Melzack and Wall's gate control theory of pain proposed in 1965. Neuromodulation has given us ready access to the systems of pain modulation and helped mature the understanding of the pathophysiology of pain. Physiologic studies highlight the complex ascending influence of neurostimulation on sensory processing. However, the present understanding of pain is rudimentary and evidence that neuromodulation works is modest. This paper emphasizes the historical antecedents, present state, and emerging future of 3 commonly applied neuromodulatory techniques—spinal cord stimulation, peripheral nerve and field stimulation, and deep brain stimulation—for chronic pain. It is hoped this article will enhance the understanding of neuromodulation and its role in pain management.

Keywords Neuromodulation · Spinal cord stimulation · Peripheral nerve stimulation · Peripheral field nerve stimulation · Deep brain stimulation · Historical overview · Chronic pain · Failed back surgery syndrome · Complex regional pain syndrome · Refractory angina pectoris · Peripheral vascular disease · Neuropathic pain · Movement disorders · Minimally invasive · Effectiveness · Quality of life · Analgesia

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Introduction

The modern history of neuromodulation spans over half a century, during which the transition from nascent offering to mature, evidence-based medical subspecialty was made. Neuromodulation continues to evolve, shaped by rapid innovation in science and technology. Its strengths are its reversibility, programmability, low risk, and specificity. Its benefits are evidenced by improved pain relief, functional status, health-related quality of life, and reduced demand for health-care resources [1, 2, 3•, 4–6].

Neuromodulation has demonstrated efficacy in the treatment of pain pathologies resistant to conventional medical management (CMM) or surgery; in doing so it has become the approach of choice for improving quality of life at minimal risk. The key to success with neuromodulation is careful patient selection and recognizing pathologies that yield a higher success rate. The challenge for neuromodulatory therapies is 2-fold: (1) justifying the value of technological innovation, and associated expenditures, in the form of robust randomized controlled trials (RCTs) and physiological models that adequately explain pain relief; and (2) generating awareness and uptake amongst patients, payers, and health-care professionals in a financial landscape characterized by cost-cutting.

Spinal Cord Stimulation (SCS)

The earliest recorded use of neuromodulation for the treatment of pain dates back to 15 AD when Scribonius, after observing that gout pain had been relieved by the accidental contact with torpedo fish, recommended this treatment for pain in general [7]. The present conception of neuromodulation took shape in the 1965 with the publication of Melzack and Wall's gate control theory of pain. It proposed the existence of a gate involved in pain perception that could be opened or closed depending on the differential activation of small and large

neural fibers [8]. Two years later, Shealy and Mortimer designed an electrode and successfully implanted it in a patient to alleviate cancer-related pain [9]. These leads consisted of plate-style, platinum electrodes and were placed in the spinal subarachnoid space. These leads required an external power supply connected by needles passed through the skin. Implantation techniques were fraught with complications such as cerebrospinal fluid leak, arachnoiditis, and infection. The first SCS systems were modifications of pre-existing stimulators used for cardiovascular conditions. Medtronic Inc. (Minneapolis, MN) introduced the first commercially available SCS system in 1968, which used radiofrequency coupled with dorsal-column stimulators.

The architecture of the present-day SCS originated in the 1970s–1980s with the creation of permanently implantable percutaneous leads for epidural placement [10, 11]. In 1981, Medtronic provided the first fully implantable SCS system and the first rechargeable implantable pulse generator (IPG) was released by Boston Scientific in 2004 [12]. The ability to capture dermatomal pain distributions and maximize paresthesia coverage has been further augmented by the development of multicontact leads and ability to implant multilead arrays. More recently, innovative lead delivery systems, such as the Epiducer (St. Jude Medical Inc, Plano, TX) [13] have enabled percutaneous placement of narrow paddle leads (S-Series paddle leads; St. Jude Medical Inc) [14].

Present State

SCS is the dominant segment of the neuromodulation sector. Its wide-spread acceptance is attributable to low morbidity and simplicity of implantation, burgeoning clinical indications for use, and robust evidence of efficacy [2, 4] and cost-effectiveness [3••]. By the end of this year, it is estimated that over 50,000 SCS units will be sold globally [12].

Initially conceived of as a therapy of last resort [15•, 16••], SCS has gradually acquired first-line status for the treatment of chronic neuropathic pain [17, 18]. SCS buttressed its legitimacy in the scientific and public arenas in the 2007, when Kumar and associates published results from the multicenter PROCESS RCT, providing Class I evidence of efficacy for the use of SCS in failed back surgery syndrome (FBSS) [1]. There is widespread agreement among experts that patients presenting with neuropathic pain who do not respond to CMM by 12 to 16 weeks should be offered a trial of SCS [17, 18].

SCS is Food and Drug Administration (FDA) approved for chronic pain of the trunk and limbs. Several RCTs support its use in chronic neuropathic pain pathologies such as FBSS and complex regional pain syndrome (CRPS), which constitute the overwhelming majority of implants. In the United States, it is also used off-label for refractory angina pectoris and peripheral vascular disease.

Current systems tend to employ multilead arrays—each lead may contain up to 20 contact points—connected to a rechargeable IPG. Multicolumn leads facilitate improved current steering and paresthesia coverage. The advent of multicontact leads (≥ 8 contacts) has lowered surgical revision rates from 22% to $\leq 5\%$ [6, 16••]. The incidence of lead fracture has also declined from 6% [6] to $< 3\%$ [2] with improved manufacturing methods.

Contact points per lead continue to increase in conjunction with price, in the notable absence of evidence of superiority. Commonly used cylindrical leads have 4, 8, or 16 contacts while paddle leads are available in configuration of 2, 3, and 5 columns with contacts ranging from 4, 8, 16–20 [16••].

Kumar et al previously demonstrated that efficacy of SCS treatment is time dependent with success rates exceeding 85% if implantation occurs within 2 years of symptom onset.

The long-term success rate of SCS is inversely proportional to the time delay between the onset of the chronic pain syndrome to SCS implantation. Present mean wait-times of 65.4 months roughly translate into a long-term success rate of 47%. This implies that the key to optimizing success is to employ strict patient selection criteria and to offer SCS earlier [6, 19••].

Emerging Stimulation Targets

Capitalizing on the recognition of dorsal root ganglion hyperexcitability in pain transduction and maintenance of chronic pain, Spinal Modulation (Menlo Park, CA) has released its Axiom neurostimulator in Europe and Australia [20]. Advantages are durable pain, technical ease of lead placement, and ability to provide sub-dermatomal specificity while retaining multidermatome coverage.

Novel Modes of Stimulation

A departure from low-frequency stimulation parameters—a staple of SCS since its conception—is underway. High-frequency SCS (HFS) operates at 5–10 kHz. The notable advantage is absence of paresthesia, which at times can be annoying to some patients when using conventional SCS. In a recent study, HFS provided significant low back and leg pain relief to more than 70% of patients [21•]. A phase III pivotal trial of HFS vs conventional SCS recently completed enrollment, results are anticipated shortly (SENZA-RCT; Nevro Corp, Menlo Park CA) [16••].

De Ridder et al have demonstrated that burst stimulation (BrS) delivering square waves (40 Hz bursts with 5 spikes at 500 Hz per burst) can produce equivalent or better pain relief

than conventional tonic stimulation. BrS appears to suppress pain without the induction of paresthesia, possibly because significantly more charge per second is delivered over tonic stimulation but at lower amplitudes, resulting in sub-threshold stimulation of A β fibers [22].

Technology: Perils and Promise

MRI Computability

MRI incompatibility is a significant concern for patients and clinicians [23]. Through its SureScan program, Medtronic Inc. has launched the first implantable SCS solution compatible with full-body 1.5 Tesla MRI. These leads incorporate a braided body that acts as radio-frequency shield and dissipation surface. Filtered feed-through capacitors built into the neurostimulator output channels shunt high frequency energy to the neurostimulator case, preventing damage to internal circuitry. The use of ferrous materials is also minimized. Other manufacturers are racing to produce MRI-compatible equipment [24, 25].

IPG Design

Just as dual-channel IPGs replaced single-channel stimulators, 4-, 8-, and 16-channel devices have followed. Boston Scientific (Valencia, CA) recently introduced 16-contact leads and is expected to soon release a 32-channel IPG in the United States. It is not yet known, however, if the increased number of lead contacts and IPG channels potentiate analgesic effect [16••].

Medtronic Inc. (Minneapolis MN) has recently integrated accelerometers (AdaptivStim; RestoreSensor) to allow the IPG to sense whether the patient is sitting or lying and to automatically adjust programs that have been pre-selected for each position or activity [16••]. Ethical considerations include security, privacy, and conditions of data release to third parties.

The hunt for alternative power sources continues; a more radical approach involves radio-frequency and microwave technology [24].

Programming

With increasing contact points per lead and utilization of multiple lead arrays, the number of possible configurations is nearly infinite, making manual combination determination time-consuming and tiring to both clinician and patient. Advanced automated programming algorithms have been developed with the goal of reducing programming effort (Precision Spectra Boston Scientific; Valencia, CA) [16••].

Axial Back Pain and Multicolumn Stimulation

To date, axial back pain has evaded the grasp of SCS. This reality may be altered by multicolumn stimulation, which effectively harnesses axial low back pain. The Specify 5-6-5 lead (Medtronic Inc., Minneapolis, MN) and 5-column Penta lead (St. Jude Medical Inc., Plano, TX) enable SCS programming in both medial/lateral and rostral/caudal orientations. The rationale for this approach is based on computer modeling by Holsheimer et al, which proposes that transverse tripolar stimulation provides superior current steering [26].

Unresolved Questions

While the technological SCS revolution continues unabated, fundamental questions of biophysical and clinical relevance have not been satisfactorily addressed. For example, the relationship between number of contact points and patient outcomes is unclear, as is the relevance of contact spacing and multiple independent current controls or the advantages of constant current vs constant voltage strategies. The ideal number or configuration of leads required for harnessing back pain with uni- or bilateral leg pain requires elaboration [27].

Peripheral Nerve Stimulation (PNS)

Despite considerable development, PNS continues to suffer from underutilization, limited commercial support, paucity of clinical and basic research, reimbursement challenges, and a lack of regulatory approval for existing devices [28••].

The genesis of the Electreat in the early 20th century, a consumer electrical device, represents the historical antecedent of peripheral electrical stimulation. This device subsequently morphed into the technology for transcutaneous electrical nerve stimulation. PNS originated in the 1960s, when Wall and Sweet inserted an electrode into their own infraorbital foramina and obtained analgesia during the period of electrical stimulation. The first PNS surgery was performed on a 26-year-old woman with CRPS on October 9, 1965. During this operation, Wall and Sweet implanted a pair of silastic split-ring platinum electrodes around the ulnar and another pair around the median nerve in the arm with externalization of the electrodes at the mid-forearm [29]. In 1967, the duo published the first article documenting the idea of PNS with implantable devices [30].

In 1976, Campbell et al demonstrated a tentative role of PNS in the treatment of chronic pain in a study of 23 patients. However, they documented that patients treated with a sciatic implant for low back pain had suboptimal outcomes [31]. Presently, for PNS the targets are greater occipital, trunk,

and extremity peripheral nerves. Common cranial nerve targets are the trigeminal and vagus nerves [32].

PNS was initially achieved using cuff-type electrodes, which were later superseded by button-type (paddle) electrodes. The major limitations of these techniques included surgical nerve exposure, difficulty in achieving and maintaining adequate positioning of contacts for optimal paresthesia coverage, and declining pain relief over time. Multiple reports of nerve injury from electrode insertion and electrode-related fibrosis dampened the appeal of PNS [28•, 29].

Paddle electrodes are suitable for stimulation of large peripheral nerves, and occipital nerve stimulation (ONS) for relief of occipital neuralgia (ON) or migraine. As is the case with SCS and other neuromodulating methods, the utility of cylindrical vs paddle leads for PNS is debated. The benefits of paddle design include the unidirectional stimulation, greater electrical efficiency, and lowered incidence of lead migration [28•].

In the 1980s, the advent of IPGs enabled neuromodulators to forgo radiofrequency-coupled devices, thus making long-term stimulation easier. To help maintain contact between the paddle electrode and peripheral nerve, a dedicated PNS paddle electrode with integrated-mesh was developed in the early 1990s (On-Point, Medtronic Inc., Minneapolis, MN). This lead has been approved by FDA for PNS. However, despite increased clinical use there was a lack of interest in obtaining FDA approval for IPGs [28•]. Eventually manufacturing of RF generators was discontinued and the whole field of PNS became off-labeled.

The use of PNS for craniofacial neuropathic pain was resurrected in 1999 by a report from Weiner and Reed that cited durable pain relief in 12 patients undergoing percutaneous electrode insertion in the vicinity of the occipital nerves for treatment of ON [33]. Subsequently, Slavin et al extended this technique for craniofacial pain in the trigeminal distribution by placing electrodes over the supra and infra-orbital nerves [34].

In contrast to other forms of neurostimulation, the appeal of PNS is a direct stimulation of peripheral nerves and inhibition of primary afferents, thus producing nociceptive blockade. The recent introduction of the peripheral nerve field stimulation (PNFS; also known as subcutaneous stimulation) represents an evolution of PNS. As the name implies, small nerve endings within the subcutaneous tissue are stimulated. An advantage of PNFS over SCS or PNS is its technical ease and ability to place the lead directly in the affected painful area [29, 35].

Indications

Headache and Occipital Neuralgia

The strongest interest in PNS centers on the treatment of intractable headache. Current efforts have developed along 2

streams: cephalic neuralgia and primary headache. Several case series have reported impressive success rate in the range of 70%–100% for ONS in occipital neuralgia and cervicogenic headaches. More recently, investigators have successfully applied supraorbital nerve stimulation for neuropathic pain and postherpetic neuralgia in the V₁ distribution of the trigeminal nerve. Yakolev et al have extended its use for the atypical facial pain. In our experience, however, the atypical facial pain responds poorly to PNS [36•].

Ultimately, the 3 device manufacturers undertook RCTs to evaluate the effectiveness of ONS in chronic migraine. Both the Boston Scientific [37] and St. Jude [38•] trials found no evidence for a significant therapeutic effect. The ONSTIM trial (Medtronic Inc., Minneapolis, MN) [39•] achieved its primary endpoint. However, a 30% improvement in pain was used to define a responder, rather than the standard 50%.

Traumatic and Postsurgical Neuropathies

Percutaneously inserted PNS electrodes were used for control of inguinal pain after herniorrhaphy, genitofemoral neuralgic pain, thoracic postherpetic or post-thoracotomy pain, and CRPS II. In addition, PNFS has been applied in the treatment of abdominal wall, low back, and neck pain [28•].

Chronic Low Back Pain

In November of 2012, Medtronic Inc. launched that the SubQStim II study, the first RCT comparing the clinical effectiveness of PNFS and CMM vs CMM alone for the management of the back pain following FBSS [36•]. This trial is in its recruitment phase.

In many ways, PNS is complementary to SCS. In cases where dorsal-column SCS fails to adequately relieve back pain, PNFS is a useful adjunct. Mironer and colleagues demonstrated that combination SCS-PNFS provided wider coverage of axial pain with an overall success of 90% [40].

Deep Brain Stimulation (DBS)

Horsley and Clarke invented animal stereotaxic techniques in 1908 and concurrently introduced stereotactically localized stimulation of deep brain structures [41]. The first stereotactic procedure in humans was reported by Spiegel and Wycis [42], and has become a staple of neurosurgery ever since. In 1969 Reynolds [43] observed that stimulation of the periventricular area of rats produced profound analgesia such that they could undergo surgery with no apparent pain. Similar stimulation was provided to patients with chronic pain by Richardson and Akil in 1977 [44, 45]. The following year, the duo linked this area to endorphin release [46]. The genesis of modern DBS occurred in 1973, the result of a report by Hosobuchi [47]

describing successful use of chronic thalamic stimulation for the treatment of anesthesia dolorosa.

The momentum behind neuromodulation prompted the FDA to sponsor a symposium on safety and efficacy in 1977 [48], which culminated in the determination that further studies were needed to prove the efficacy of DBS. Two industry-sponsored open-label multicenter trials of 246 enrollees from 1989 to 1995, in which investigators implanted electrodes within the somesthetic system (ventral posterior medial or ventral posterior lateral thalamic nuclei or internal capsule) and/or the periaqueductal/periventricular gray (PAG/PVG), failed to achieve their primary endpoints of $\geq 50\%$ pain relief in $\geq 50\%$ of patients [49]. On the basis of these trials, the FDA did not approve DBS for pain [50]. Over time, there has been a decline in the number of published studies and patients treated with DBS for pain. This is attributable to its off-label status and development of less invasive alternatives [50, 51].

DBS for pain, being an off-label indication in the United States, is practiced in a handful of specialized neurosurgical centers. Its present clinical use is best accomplished in the academic setting, within the construct of ongoing research. Salvaging DBS for pain is linked to bench and bedside efforts establishing biological models of plausibility and demonstration of efficacy in well-designed RCTs [28•]. Presently, DBS is gaining traction in other areas, notably in the movement disorders, neuropsychiatry, and epilepsy domains [51]. A recrudescence of DBS for pain could materialize if its usefulness in headache disorders such as cluster headache, hemicrania continua is substantiated [51].

DBS remains the subject of investigational interest. The benefit varies depending upon length of follow-up, condition treated, definition of adequate pain relief, and the site of stimulation [52]. DBS can be effective when combined with rigorous patient selection. A meta-analysis of 6 studies revealed that the long-term pain alleviation rate was highest with DBS of the PAG/PVG (79%), or the PAG/PVG plus sensory thalamus/internal capsule (87%). Stimulation of the sensory thalamus alone was less effective (58%). DBS was more effective for nociceptive than deafferentation pain (63% vs 47% long-term success; $P < 0.01$) [52]. However, in the review of 141 patients, Levy et al documented initial pain relief in only 83 (59%). With the mean follow-up of 80 months, only 42 patients (31%) continued to report significant pain relief. Some pain states, particularly anesthesia dolorosa and the spinal cord injury pain, did not seem to respond to DBS [53]. Much of the recent research has originated from Tipu Aziz of Oxford. Their latest findings describe 85 patients who underwent DBS for neuropathic pain, of which 66% gained benefit (average follow-up 19.6 months). On long-term follow-up of 42 months, an improvement of 30% in pain and quality of life was observed in 15 patients [54•].

Stimulation Targets

It is thought that stimulation of the PAG/PVG is efficacious for nociceptive pain, whereas DBS of the sensory thalamus is more advantageous for deafferentation pain such as thalamic pain and phantom-limb syndrome [52, 53]. It is suggested that DBS of the ipsilateral ventroposterior hypothalamus decreases attack frequency in cluster headache [51].

Conclusions

Neuropathic pain is complex and common. It is frequently resistant to conventional medical therapies and surgical approaches. A paradigm shift is underway, as neuromodulatory techniques begin to acquire first-line treatment status. The outlook for neuromodulation is optimistic and the field maintains a strong development pipeline, with novel solutions and new indications constantly emerging. Focused healthcare allocation coupled with growing disease burden and advances in translational and clinical research will drive future adoption.

Compliance with Ethics Guidelines

Conflict of Interest Kirshna Kumar is a consultant for Medtronic Inc. and Boston Scientific and has received research grants from Medtronic in the past. Syed Rizvi declares that he has no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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