NEUROMODULATION AND CHRONIC PAIN

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«Neuromodulation is a field of science, medicine, and bioengineering that encompasses implantable and non-implantable technologies, electrical and chemical, that improves life for humanity. Neuromodulation is technology that impacts upon the neural interface.»

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ABSTRACT

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Chronic pain causes extreme suffering for millions of people worldwide. It is the leading cause for lost workdays and patients often undergo expensive courses of treatment. Because chronic pain is often difficult to relieve for sustained periods of time, it can have a significant impact on person's quality of life. Current primary methods for treatment include drugs (usually opioids or anti-inflammatory medications), surgical intervention, physical therapy and psychotherapy. However, more invasive treatments may be needed for patients with severe intractable pain who do not respond to these less invasive treatments.

Since Melzack and Wall's Gate Theory of Pain was first proposed, an improved understanding of neuroscience has lead to development of implantable 'neuromodulatory' technologies for refractory pain. Simply put, such technologies involve drug delivery to, electrical stimulation of neural pathways. In the pain management context, neuromodulation aims to reduce afferent activity within pain pathways by targeted electrical neurostimulation or drug delivery into CSF. Targets for implanted neurostimulators include the spinal cord, peripheral nerves or brain, while implantable pumps deliver analgesic drugs to intrathecal or intracerebroventricular sites. Implantable neuromodulation therapies are expensive, invasive and prone to side effects and complications. Clinicians and health professionals involved with implantation and aftercare of such devices require a high level of expertise. In spite of these challenges the uptake of these therapies continues to rise worldwide as does the evidence for cost effectiveness due to reduced expenditure on conventional medical management.

This article will describe types of electrical neurostimulation in terms of "neuromodulation techniques" such as spinal cord stimulation, peripheral nerve stimulation, targeted stimulation and external neuromodulation procedures.

Neuromodulation includes two groups of therapies: electrical modulation by stimulation of the central or peripheral nervous system for the purpose of modulating or modifying a function, such as the perception of pain, and drug delivery systems administering drugs to the intrathecal space around the spinal cord and occasionally intraventricularly to control pain in patients suffering from chronic non-malignant pain,

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cancer pain and spasticity. In this paper we will focus only in the first group of neuromodulation therapies.

"Chronic pain" as used herein, is pain that lasts a long time, regardless of the etiology, and includes cancer pain as well as pain of non cancer origin. It must be recognized that the physiology of each of those two types of pain is different in that cancer pain ordinarily involves noxious stimulation of tissues or involvement of nerves, whereas chronic pain may involve pathology of particularly nerve tissue or most commonly muscle, or may not involve any identifiable tissue pathology at all. Such chronic pain is a perception rather than a sensation per se, but may attenuate by the neuromodulation techniques discussed below.

HISTORY

The dramatic effects of stimulation of the body or nervous system have long been recognized and the use of neuromodulation has grown from those observations. It is said that from circa 9000 BC, bracelets and necklaces of magnetite and amber were used to prevent headache and arthritis[1]. The Roman writer, Pliny the Elder, mentioned in his Historica Naturalis that circa 1000 BC a Greek shepherd´s walking on mountain Ida noticed that the iron nails of his sandals were strongly drawn to some black rocks. That type of rock was then named magnesian from "Magnes", the shepherds name, and is now known as magnetite[2,3]. The ancient Greeks called a fossilized resin today known as amber (from the old Arabic ambar) "electron". As early as 600BC, a Greek philosopher and mathematician, Thales of Melitus, noted the peculiar property of amber for attracting small pieces of material when rubbed with fur[2]. Thales believed that the amber became magnetic with friction because magnetic would attract iron without having to be rubbed. The observation remained a mystery for more than two millennia until the Italian mathematician and physician Girolamo Cardano realized, in 1551, that "the magnet stone" and the amber do not attract in the same way[2]. Half a century later the physician of Queen Elizabeth I, William Gilbert, widely regarded as "the original electrician", pointed out that amber was not the only substance that, when rubbed, attracted light objects, and revealed the nature of electrostatic electricity and magnetism. He also introduced the term "electric force"[4].

Much of ancient peoples were allured by the properties of the animated minerals, to a greater extend they stood in awe of the astounding forces discharged by certain fish. The ichthyological fauna comprises fish capable of discharging electrical current to sun or kill their prey. The freshwater, strongly electrogenic species include the electric catfish, which lives in the rivers of tropical Africa and the Nile valley, and the electric eel, which inhabits the rivers of South America. The saltwater, strongly electrogenic species include the electric rays, which are found in all tropical and temperate seas. The ancient Egyptians acknowledged the power of the Nile catfish in tomb paintings and in hieroglyphs, describing it as the fish that 'releases the troupes", an implication that the fishe's jolt of electricity forced fishermen to release the net so that the enmeshed fish could escape[5]. The Greeks called the electric ray *narke* or 'numbness-producing' from which the word *nercosis* was coined[1]. The Romans called it 'torpedo' from the word *torpor* as the name was synonymous with the effects. The ancient Egyptians apparently used the shocks from the Nile catfish for the treatment of neuralgia, headache and other painful disorders[6]. However, the first written document on medical application of electricity dates to AD 46 when Roman physician, Stribonius Largus, mentioned in his work *Compositiones Medicae* the use of torpedo's discharge to treat gout and headache[5]. Electroichthyotherapy continued to be used in Europe until the middle of the 19th century[7]. We now know that the electrogenic organs consist of stacks of vertically oriented cells and that each cell acts like miniature battery[8].

The age of man-made electricity began in 1672 with the prototype of an electrostatic generator constructed by the German engineer, Otto von Guericke. The Leyden jar (forerunner of the electrical capacitor) invented in 1745, extended the application of electricity for the treatment of

pain by enabling energy to be stored and discharged for later use[9]. From then on the history of electrotherapy may be divided into define periods demarcated by landmark discoveries of electromagnetism[10].

The first stage of modern electrotherapy dates from the invention of the rotating-disc static-electricity machine invented by the English toolmaker, Jesse Ramsden, in 1766[11]. The therapeutic application of static electricity was named 'Franklinism' after the American statesman and scientist, Benjamin Franklin, who with his famous kite experiment in 1775, proved that lighting and electrostatic charge on a Leyden jar were identical. The most spectacular of the static electric therapies was the electric air-bath which was used, among other indications, for obstinate pain, particularly from rheumatism, and was recommended by Althaus for headache and neuralgia[11].

The second stage of modern electrotherapy started with the Galvani-Volta controversy, which led to the discovery of the electrochemical battery in 1800.

The third stage was reached with the discovery of electromagnetic induction. In 1831 an English chemist and physicist, Michael Faraday, showed that a changing current in one coil induced a voltage in a second coil. This paved the way for the introduction of the electric generator in 1848 by Du Bois-Raymond which became the essential tool for stimulating excitable tissue[11].

The 19th century became known as 'the golden age of medical electricity' but was also referred to as "the electromagnetic era of medical quackery'[12,13].

It is very interesting that in states by the turn of 19th century most doctors in U.S.A were using electrical machines in their offices without blessing of science. This came to an end in 1910 when electrotherapy was legally excluded from clinical practice following the Flexner report, which triggered reforms in the standard of medical education. Electrical machines were removed from doctors' offices and were relegated to 'museum of quackery'[14]. The Golden age of electro-analgesia was also ended in Europe in the early 20th century. The association with quackery, the establishment of the drug industry and the appearance of X-ray treatment were the probable reasons for the loss of interest[15].

Electrophysiological experiments in the early 1930s led to the development of induction coil techniques for 'remote' transfer of electrical energy through the intact body[16,17]. An efficient variation employing radio-frequency as an induction method was adopted by clinicians for cardiac pacing[18]. Subsequently produced neural stimulators were a spin-off of this technology.

No single event had more impact on electro-analgesia than the Gate Theory of Pain[19]. The theory postulated central inhibition of pain by non-painful stimuli, a concept that had been predicted half a century earlier by Sir Henry Head, an English neurologist. Wall and Melzac experimented on their own infra-orbital nerves using needle-stimulating electrodes, and on superficial nerves such as the ulnar nerve, using surface electrodes. They then used transcutaneous or percutaneous stimulation in three patients who experienced partial or total relief of pain during stimulation[20,21]. Shortly after the first peripheral nerve stimulator was implanted around the median nerve using a pair of split-ring platinum electrodes[22].

The first dorsal column stimulating device was implanted by N. Shealy in 1967[23]. The electrode was placed subdurally and maintained close to the cord by suturing it to the dura. During the past years many implantations took place but, due to technical problems and surgical complications such as CSF leak, cord compression and adhesive fibrosis, as well as widespread use by inexpert implanters and uncritical selection of patients, resulted in an initial high rate of failure of dorsal column stimulation.

Improved methods of implantation and screening contributed to a later resurgence of interest among pain doctors in Europe and USA[24].

The contribution of private industry in the development of medical equipment used for neuromodulation was of paramanount importance:

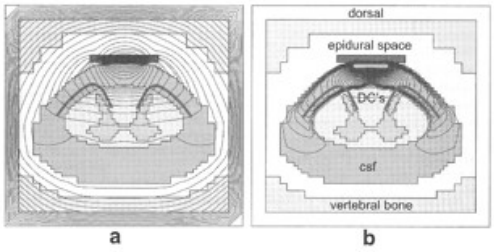
various choice of material for electrodes, lead wires and coatings, digital circuitry and high-density, long life implantable batteries. There was also progressive advance in the design of electrode arrays and to the programming capacity of the stimulation devices. The initially radio-frequency activated passive systems, with hard-wired contact combinations, gave way to multipolar, multi-channel, multiprogrammable neural stimulators[24]. Advanced cardiac pacemaker technology provided the basis for the development of non-invasively programmable, totally implantable pulse generators (IPGs)[25].

Over time the electrode arrays for peripheral nerve stimulation evolved from 'split-cylinder' or 'wrap-around' designs to 'self-sizing spiral cuffs'. But they were all found to cause neural damage by compression, surgical trauma, lead migration or tension and movement[26]. Eventually, a surgical implantation technique was developed that prevents direct contact with the nerve by using a quadripolar plate-like and putting a thin flap of fascia between the electrodes and the nerve. This has become an established routine implantation for peripheral nerve stimulation[27].

There were also changes in terminology; the term "dorsal column stimulation' replaced by the term 'spinal cord stimulation' (SCS) because it appeared that structures other than the dorsal columns are involved in the analgesic effect[28].

As the methods of neurostimulation became more complex, computer modeling of SCS was used and patient interactive computerized programming of stimulation was developed[29-31]. The areas of stimulation expanded from the spinal cord and peripheral nerves to the sensory nuclei of the thalamus[32-34] to the periaqueductal and periventricular gray matter [35,36] and of late to the motor cortex[37-39]. The field of application of this modality also extended beyond the initial indication of failed back surgery syndrome[40-42] to a wide range of conditions including ischaemic peripheral vascular disease[43,44], atypical trigeminal neuralgia[45,46], refractory angina pectoris [47,48], reflex sympathetic dystrophy[49,50], interstitial cystitis[51,52], occipital neuralgia[53,54], ilioinguinal neuralgia[55], postherpetic neuralgia[56], diabetic neuropathy[57] and epilepsy[58].

Figure 1: Isopotential lines (a) and isocurrent lines (b) in a transverse section of the 3-dimensional cervical SCS model including the mid-dorsal, epidural cathode; stimulation is applied monopolarly



(modified from Jan Holsheimer : Principles of neurostimulation. In Electrical Stimulation and the Relief of Pain, Pain Research and Clinical Managment, Vol. 15, Edited by Brian A. Simpson, 2003, Elsevier Science B.V, Amsterdam, The Netherlands)

PHYSIOLOGY OF NEUROMODULATION. MECHANISM OF ACTION

As discussed above, spinal cord stimulation, for the clinical control of pain, was first introduced in 1967 by Shealy and collegues[23] in response to the publication of the gate control theory of pain by Melzack and Wall in 1965[19]. The gate control theory, as first published, without benefit of later refinements, stated that painful "electro-chemical" nociceptive information in the periphery is transmitted to the spinal cord in small diameter, unmyelinated c-fibers, and lightly myelinated A-delta fibers. These fibers would also, in turn, terminate at the substantia gelatinosa of the dorsal horn, "the gate", of the spinal cord (Figure 1). At the same time other sensory information such as touch or vibration, carried in large myelinated A-delta fibers, would also converge and terminate at this gate of the spinal cord. The basic premise of this theory is that reception of large fiber information, such as touch or vibration turn off or closes the gate to reception of small fiber information.

Shealy et al theorized that the electrical stimulation of large A-beta fibers of the dorsal co-

lumns would antidromically inhibit reception of painful small fiber information at that stimulated spinal segment and all other information "downstream" from the area of stimulation. Since it is now known that this electrical stimulation inhibition of pain occurs, not only at the dorsal columns, but also at the dorsal root entry zones and other regions of the spinal cord, at the term dorsal column stimulation is now supplanted by the more accurate term of spinal cord stimulation.

Figure 2: An implanted generator with one tri-polar electrode lead, a patient's programmer and a physician's handheld programmer unit

Although the "gate control theory" seemed to fully explain the effectiveness of SCS, further experiments and clinical evidence also support the existence of other mechanisms contributing to its antinociceptive effects[59,60]. These mechanisms are separated into: (1) mild neurophysiological modulation of acute nociception as a sensory function; (2) inhibition of neuronal activity in the dorsal horn of spinal cord evoked by painful stimuli in the periphery; (3) activation of descending pain-control pathways and supraspinal structures; (4) attenuation of dorsal horn wide dynamic receptor (WDR) neuronal hyperactivity; (5) blockade of supraspinal sympathetic mechanisms; (6) modulation of abnormally activated A-beta neurons related to the perception of pain neurochemists restoration of normal GABA levels in the dorsal horn and possible release of adenosine with evidences going against an action through the endogenous opioid system; (7) secondary suppression of sympathoadrenal output associated with Beta endorphin release and finally the Calcitonin Gene-Related Peptide release (endogenous vasodilator) from origin of afferent fibres in response to "antidromic" stimulation.

Figure 3: Examples of existing leads

SPINAL CORD STIMULATION (SCS)

Spinal cord stimulation for pain control is therapy based on producing an electrical filed over the spinal cord of neuropathic origin, not pain of nociceptive origin. The electric field is propagated by either an external neuropulse generator which transmits an electric pulse via cable, to an externally worn antennae that is radio-coupled to an implanted receiving device or by an implanted, programmable neuropulse generator that contains a battery pack, an antennae and a computer module that allows for programming externally (Figure 2). After generation, the electrical pulse is transmitted to its

intended target, the spinal cord, via an implanted electrical cable connected to a surgically (mini-laminotomy electrodes or percutaneously) implanted arrays of electrodes (Figure 3). These electrodes are placed directly into the epidural space either over the spinal cord segment processing the patients pain or from a retrograde direction over the nerve roots conducting the patients pain[61].

Very early in the development of this therapy intrathecally placed monopolar or non–programmable bipolar SCS leads were placed, but after the development of early problems and therapy limiting complications, these intrathecal leads were supplanted by quadropolar and octapolar leads there were able to be programmed at the time of the initial surgery. Still later on, due to advances in technology, multichannel quadropolar and octapolar leads were implanted epidurally and utilizing bipopar or multipolar stimulation were introduced and were found to be superior to single channel devices[62].

Prior to the early 1990's most, if not almost all, electrode arrays were single quadripolar or single octapolar electrodes. Today multiple electrodes arrays with multiple contacts placed either percutaneously into the epidural space through an appropiate needle or directly through a laminotomy incision have been developed. These electrode arrays for, at least, bipolar stimulation and for the external reprogramming of these devices. These four-contact quatrodes and eight-contact octrodes provide the ability to change the cathode-anode combinations to better locate affected painful areas, as well as accommodate for electrode migration. It has been calculated that with a longitudinal lead of four contacts, 65 different anode-cathode combinations can be programmed and in a lead with eight contacts, 6000 combinations are possible. Advances in programming technology also allow for the independent programming of multiple (up to 24) differing programs. This complex, advanced programming is facilitated by the use of a computer program.

Lastly, patients should be fully informed of the benefits and burdens of SCS before implantation and should receive specific outcome and complication rates relating to the unit where the procedure is being performed.

Patient selection for SCS, indications, contraindications and timing

Patients must have an up to date assessment in relation to the indication for SCS. History and physical examination should be detailed, and include in relevant cases an assessment of posterior column function[63].

Indications for spinal cord stimulation

Good indications (likely to respond)
- neuropathic pain in leg or arm following lumbar or cervical spine surgery (FBSS/FNSS)
- complex regional pain syndrome
- neuropathic pain secondary to peripheral nerve damage
- pain associated with peripheral vascular disease
- refractory angina
- 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 e.g. post-thoracotomy or post-herpetic neuralgia
- pain associated with spinal cord damage
- (other peripheral neuropathic pain syndromes e.g. 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, anorectal pain

Unresponsive to SCS
- complete cord transection
- non-ischaemic nociceptive pain
- nerve root avulsion

Medical contraindication for SCS

- uncontrolled bleeding disorder/ongoing anticoagulant therapy
- systemic or local sepsis
- presence of a demand pacemaker or implanted defibrillator

- immunosupression (this is a relative contra-indication)

NB Cognitive impairment resulting in failure to understand the therapy is not a reason to exclude patients from SCS but these patients must have a cognizant carrier and adequate social support.

Timing

SCS may be delivered in parallel with other therapies, e.g. medication and psychologically based therapies. For indications strongly supported by evidence, i.e. CRPS, neuropathic pain following spinal surgery, peripheral vascular disease and refractory angina, SCS should be considered early in the patient's management when simple first line therapies have failed. SCS should not necessarily be considered a treatment of last resort.

Especially, for or patients with refractory angina pectoris, the European Society of Cardiology recommends that:

1. An interventional cardiologist with experience in managing patients with refractory angina should review the patient
2. There should be documented evidence of reversible myocardial ischaemia.

SCS should be considered only if the patient continues to suffer from disabling angina despite cognitive behavioral intervention and the use of transcutaneous nerve stimulation (TENS)

NEUROSTIMULATION SYSTEM COMPONENTS AND IMPLANTATION

Techniques of Implantation

Electrodes may be inserted percutaneously via an epidural needle or plate electrodes may be surgically implanted via laminotomy. Electrodes may be bipolar or multipolar and multiple electrodes may be used. Pulse generation is achieved by either a fully implantable battery powered device (similar to a cardiac pacemaker) or a smaller implantable radiofrequency receiver powered by an external battery source. Radiofrequency systems are indicated for some patients, e.g. those with a high current use, including those with multiple electrodes and are preferred by some patients.

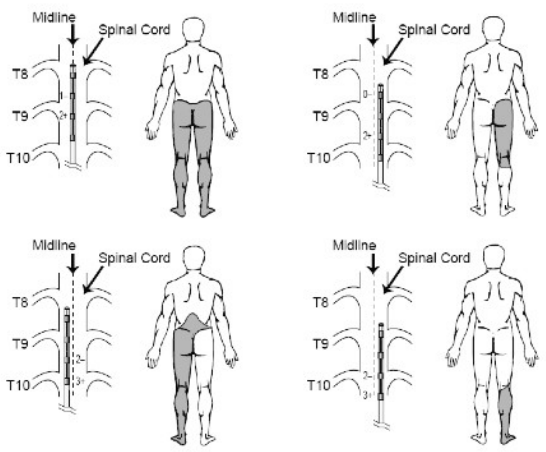
Percutaneous Lead Placement

Percutaneous lead placement is a safer, less invasive, technically easier procedure compared with hemilaminectomy lead placement[64]. Physician variation exists in methods of percutaneous placement. The technique outlined represents an acceptable method. The placement of the trial lead is performed under local anesthesia with intravenous sedation. Prior to initiating the procedure, antibiotics are given, and proper positioning is obtained. A third generation cephalosporin is the drug of choice in patients allergic to cephalosporins, but also a combination of an aminoglycoside and Vancomycin is acceptable. A sterile operating theatre and a dedicated anesthesiologist are required. The patient is placed in the prone position and fluoroscopic imaging is used to facilitate lead placement. The needle entry point is determined at this time and local anesthetics are placed. A paramedian approach is used two to three levels below the entry level. The 15-gauge Tuohy needle should enter the intralaminal space at an angle of 30^{o} to 45^{o} by the loss of resistance technique. An epidurogram may be performed prior to lead placement with a preservative-free contrast. This will confirm the epidural space and reduce the risk of erroneous lead placement. Anterioposterior, and lateral fluoroscopic views are essential in correct lead placement. The lead should be placed two to three levels above the epidural needle entry site. This provides a margin of error for mild cephalocaudal migration. Once the Tuohy needle is confirmed to be in the epidural space, the lead is placed to the ipsilateral side of the pain generator. Manipulation of the needle bevel, rotation of the lead clockwise and counterclockwise, and the use of a curved or straight stylet influence lead placement. These characteristics allow for fine manipulation to an acceptable position.

To stimulate the lower extremity or lower back for axial pain, the desired lead placement is at the T9 to T12 position. Above the T9 level, patients often experience nerve root irritation into the abdomen or intercostal nerves. Foot pain is best treated at the T12 level, while but-

tock pain is best treated at the T9 level. Axial analgesia is difficult to obtain, but has been described with dual lead configurations at the T9 level[65]. Cervical spine stimulation is obtained by entering the skin at T2 or T3 and entering the interlaminal space at C7 to T1 or T1 to T2. The lead is placed at the C3 to C7 level in most cases. As with lumbar entry, an anterioposterior and lateral view is obtained for proper placement. Thoracic placement is used for angina pectoris at the T1 level. For SCS treatment of postherpetic neuralgia, the lead is placed into the lateral gutter. Sacral nerve root stimulation is achieved at the S3 neural foramen[66].

Figure 4: lead placement and area of stimulation



In U.S the Food and Drug Administration (FDA) have recently approved urge incontinence as an indication for a trial of spinal cord stimulation. Once the radiologic position of the lead is acceptable, the patient sedation is decreased to enhance communication. Because of this need for abrupt changes in sedation level, Propofol or Remifentanil are often the drugs of choice. The intravenous drugs are preferably given by infusion and doses vary based upon individual patient needs. At this time, the lead is connected to a screening wire and an assistant, trained in stimulation programming, produces an electrical impulse by a hand-held generator. A minimum of one positive and one negative electrode are required to create a current field to affect neural pathways. The negative electrode should be placed at the level most applicable to the pain generator because a more effective impulse is created. The stimulating pattern is more effective if the lead is in close proximity to the spinal cord, therefore, lead manipulation may be helpful if a good pattern is not obtained because of epidural fat or fibrotic tissue[67]. The paraesthesia obtained on the operating table must be within the pain topography and be perceived as pleasant. When this goal is achieved, the physician must determine the method of trial. The needle may be removed under fluoroscopic guidance, and the lead secured to the skin. With this method the trial lead is removed in a few days, and, if successful, must be replaced at the time of permanent system placement. If the initial lead is to be used permanently, a cut down to the level of the supraspinous ligament is performed. The needle and stylet are then removed and the wound is irrigated with antibiotics. A silastic anchor is used to secure the lead with a non-absorbable suture. A small subcutaneous pocket is made and a trial wire is tunneled to the side opposite the planned permanent generator. The same lead is then used for permanent stimulation if the trial succeeds.

Table 1: Evaluation checklist prior to scheduling a trial lead implantation and subsequent lead placement

1. A documented physiological pain generator exists*
2. Reasonable conservative therapies have been exhausted or are unacceptable
3. No psychological contraindications exist
4. No infection is present at implant site
5. No widespread systemic infections exist
6. No active coagulopathies exist
7. No untreated addictions exist
8. A trial stimulation lead produces a paresthesia in the topography of the pain
9. The trial paresthesia is pleasant
10. Objective improvements are seen during the trial period **
11. Subjective improvement is seen during the trial period
12. A reasonable time of temporary trial (stimulation exists >48 hours)

*By diagnostic study, diagnostic block or physical evaluation, a physiologic defect exists, which most likely accounts for the pain.

**If improved function as measured by exam, such as range of motion, blood flow, gait, grip strength.

The Trial Period

A successful trial is determined by several factors:

1. *A pleasant paraesthesia is obtained in the topography of the pain 50% or more of the baseline pain level is relieved*
2. *Objective improvement is documented (i.e., Improved gait, sleep, blood flow, range of movement)*
3. *The patient wishes to proceed with permanent system placement*
4. *An acceptable time period is allowed (i.e., >48 hours) to determine success*

Selection

Patient selection is the most important aspect of establishing a successful interventional pain program. When a patient has a condition that merits SCS consideration, several selection criteria must be evaluated.

Table 1 presents an evaluation checklist to be reviewed prior to scheduling a trial lead implantation and subsequent lead placement:

Psychological assessment for patient selection is complex and requires a psychologist or psychiatrist, who is experienced in pain medicine in order to identify several risk factors that should exclude patients from implantable pain therapy[68]. Such factors are summarized below:

1. Active psychosis
2. Uncontrolled or untreated major affective disorder
3. Active suicidal behavior
4. Active homicidal behavior
5. Serious alcohol or drug addiction problems
6. Dementia and serious cognitive deficits

NOTE: Certain personality disorders, such as borderline personality, have been shown to be negative predictive outcome factors, but do not exclude the patient from this procedure.

Other psychological factors should be considered, such as pain ratings over the given scale (greater than 10/10), personality disorders, inadequate social support, unrealistic expectations, inability to understand the computer equipment, and litigation or secondary gain[68]. Litigation and Workers' Compensation have not been shown to be a negative indicator in these cases, although this remains controversial[69].

Permanent System Placement

When criteria for a successful trial are met, a permanent system is implanted. The procedure is performed with local anesthesia and monitored sedation in the lateral decubitus position. If a trial lead was secured to the skin, it must be removed. Once a successful lead is in place, a preoperative antibiotic is given and a sterile environment is obtained. A third generation cephalosporin is commonly used, but a combination of an aminoglycoside and Vancomycin may be substituted. The dose is dependent on patient size. The previous incision is opened and dissection is made to the implanted lead. The temporary connection is disconnected in a sterile manner and then pulled from the field by an assistant. Antibiotic irrigation and a glove change occur. A subcutaneous incision is made at a previously chosen site in the lower abdominal wall or buttock, and a small 4-cm subcutaneous pocket is created. A permanent connection system is tunneled from the dorsal to ventral incision. The generator placed may be either totally implantable with an internal power source (A) or a partially externalized system with an external power source (B) may be used.

(A)-Totally implantable neurostimulation system

The fully implanted neurostimulation system consists of an implantable neurostimulator and an implantable lead and extension, a programmer used by physicians, a patient programmer and an external control magnet that turns the system on or off.

1. **Neurostimulator**. The implantable neurostimulator is the device that generates the exact electrical impulses that are sent to your spinal cord to control your pain. The neurostimulator contains a special battery and electronics to create these impulses. The device is most frequently placed under the skin in your abdomen.
2. **Lead**. Neurostimulation leads are special insulated wires designed to deliver neurostimulation to the spinal cord. A neurosti-

mulation system may use one lead (single-channel) or two leads (dual-channel). The lead is about 11 inches long and is placed under the skin near your spine. It contains a set of electrodes through which the electrical stimulation is delivered to the spinal cord.

3. **Extension**. The extension is a small cable about 20 inches long that is placed under the skin and connects the lead to the neurostimulator used by physicians Programmer.
4. The **programmer** let the physician to adjust the neurostimulation system to the appropriate level for your pain. This programmer consists of a computer, programming head, and a printer. The programming head is placed over the area where the neurostimulator is implanted to program the settings by use of radio waves. This procedure is done through the skin and is generally considered to be painless.
5. After implantation the **neurostimulation system** can be programmed to more effectively deal with pain. For example, the multiple electrodes on leads can be readjusted to provide differing patterns of pain coverage. The strength of the pain coverage can be altered to accommodate lesser or greater pain.
6. **Patient Programmer**. The hand-held patient programmer allows the patient to program his/her own stimulation (within the settings his/her physician has selected). The patient programmer allows the adjustment of stimulation according to pain between visits to the doctor's office. Depending on the need for pain control, the patient used the programmer to turn the system off and back on. The patient also directs the system to provide greater or lesser pain relief (by increasing or decreasing the tingling) within limits set by the physician. The patient is not able to change his/her limits by his/herself but may discuss the need for possible changes with the physician. The 9-volt battery is required to operate the programmer"..
7. **Control Magnet**. The control magnet is an optional accessory used to turn the stimulation ON and OFF as needed. This magnet should be kept away from items such as credit cards, computers, videotapes etc, which can be demagnetized.

(B)-Partially externalized system with an external power source.

The externally powered system consists of an implantable receiver (1), an implantable lead (2) and extension (3), an external transmitter (4) and an external antenna (5).

1. **Receiver**. The receiver is implanted in the same manner as the neurostimulator of the internal system. The receiver contains electronic circuits but no batteries. The receiver is connected to the extension, which is connected to the lead. It sends neurostimulation to the spinal cord.
2. **Lead**. The lead is an insulated wire about 11 inches long that is placed under the skin near your spine. It contains a set of electrodes through which the neurostimulation is delivered to the spinal cord.
3. **Extension**. The extension is an insulated wire about 20 inches long that is placed under the skin and connects the lead to the receiver.
4. **External Transmitter**. The external transmitter is the power source of the externally powered system. This component transmits radio-frequency signals painlessly through the skin to the receiver. The external transmitter can be worn on a belt. A 9-volt battery is required to operate the transmitter and may need to be replaced every few days depending on use.
5. **Antenna**. The antenna is placed on the skin over the receiver with tape patches. It sends power in the form of radio waves to the receiver. The antenna must be taped (with medical tape) to the skin while the system is turned on.

Immediately following implantation, patient should avoid lifting, bending, stretching, and twisting. However light exercise, such as walking, is encouraged to build strength and help relieve pain.

Regarding infection of the implantable device the commonest organism to infect spinal cord stimulating systems is *staphylococcus aureus*. Where practicable, patients scheduled for SCS should be screened for methicillin-resistant *staphylococcus aureus* no longer than four weeks before the procedure. This will allow rational choice of antibiotic prophylaxis at the time of surgery.

Patients should be fully informed of the benefits and burdens of SCS before implantation and should receive specific outcome and complication rates relating to the unit where the procedure is being performed. Special considerations arise for patients with a spinal cord stimulator in situ who require an MRI scan. Experienced radiological advice must be sought in these circumstances.

COMPLICATIONS OF SCS

Major complications of SCS are rare. SCS has been used in many thousands of patients worldwide; some clinical centers have reported follow up of greater than 10 years.

Common complications and rare, but serious, adverse effects must be discussed during the consent process; this must be documented. Patients should be told about the complication rates in the unit where the procedure is to be carried out.

1. Neurological damage relating to epidural electrode placement is a rare complication, and may occur with both percutaneous and plate electrodes. Damage may occur directly, or via unrecognised epidural haematoma or from infection. These latter complications are reversible if diagnosed and treated promptly, emphasizing the importance of postoperative neurological observations. Vigilance and access to early imaging are essential.
2. Dural puncture may occur during percutaneous insertion of electrodes. This happens most frequently with the Tuohy needle, but may occur with the guide wire or the stimulating electrode.
3. Infection of implanted neurostimulators is a potentially serious problem and must never be ignored: in many cases the infection will not resolve unless the stimulating system is explanted. Infection of the entire system is rare but can result in epidural abscess formation with potentially disastrous neuro-logical consequences. Explantation in this circumstance is mandatory. However, su-perficial low grade infections of the IPG/receiver pocket are more common and, although there is no published evidence, considerable anecdotal evidence does exist for the efficacy of conservative manage-ment in some cases and for the temporary explantation of just the IPG/receiver (pre-ferably reimplanted in a fresh pocket) in others.
4. Patients should be aware that not only surgery will be necessary to replace a depleted IPG but that it may also be necessary to revise the electrodes or connections.
5. Electrode migration may occur immediately following the procedure or at any time during the trial period (if used) or following IPG and receiver insertion. Cervical electrodes are more likely to be dislodged than those in the thoracic region. Migration is less likely with plate electrodes.
6. Other potential problems include ingress of fluid into the connectors or electrode, lead breakage and disconnection.

EFFICASY OF SCS

In the field of spinal cord stimulation there are numerous retrospective studies that tout the efficacy of spinal cord stimulation[62,70]. These studies or reports usually lump patients together that have varied and differing pain syndromes. The take home message of most of these reports is that there appears to be approximately a 60% efficacy rate that lasts approximately 2 years. After 2 years, for whatever reason, there appears to be a fall off of efficacy in some patients.

As stated above, spinal cord stimulation, not

only has efficacy in neuropathic pain of appendicular origin, but has known efficacy in patients with back pain secondary to failed back surgery syndrome, degenerative disk disease, and chronic arachnoiditis, CRPS, peripheral vascular disease, and in patients with intractable angina.

Failed back surgery syndrome (FBSS) is a commonly recognized indication for spinal cord stimulation[40,42,71]. Some authors have suggested that mixed neuropathic and nociceptive processes associated with failed back surgery syndrome is the most common indication for this modality[72-74]. Using the most common criteria for "success" after spinal cord stimulation implantation, which is greater than or equal to 50% pain relief, pain relief has been experienced in 11-70% of patients with FBSS [75]. An explanation for this wide range of success rates may have to do with the difficulty in alleviating the back pain, which is often associated with leg pain in the FBSS patient. In fact this back pain after back surgery may be due to nociceptive processes and not to neuropathic processes. As we have seen, SCS does not relieve pain of nociceptive origin. Some authors have suggested that dual SCS electrodes on both sides of the midline can relieve axial low back pain[74]. However a follow up study by North et al demonstrated no difference with regard to decreasing back and leg pain when using either single or dual spinal cord stimulating electrodes[76]. While the issue of concurrently treating low back associated with limb pain with single or dual electrodes persists, most practitioners continue to favor dual electrodes in those patients with bilateral lower extremity pain. In general, a decrease in the need for oral pain medications and an improvement in function can be attained in a successful trial of spinal cord stimulation.

Success rates with spinal cord stimulation and angina pectoris have been reported[48,77-80]. The pain associated with peripheral vascular disease is also well documented[61,81-83]. Studies have supported the use of spinal cord stimulation in treating the neuropathic components as well as the swelling components of complex regional pain syndrome (CRPS) Types I and II[84]. Others, however, have shown variable result[49,75].

PERIPHERAL NERVE STIMULATION (PNS)

Although peripheral nerve stimulation (PNS) is not something new, the interest has been increased over the last few years. As previously discussed, Wall and Sweet tried to find a new approach for suppression of neuropathic pain by inserting an electrode into their own infraorbital foramina and obtained decrease in pain perception during the entire episode of electrical stimulation[20,85]. More over in the first article on PNS with implantable devices (even before the dorsal column stimulation was introduced), one of the eight patients with neuropathic pain presented severe facial pain and had an electrode inserted deep into the infraorbital foramen: the stimulation resulted in lasting pain suppression as long as the stimulator was on [85].

Based on the “gate control theory”[19], PNS was used by many centers and in most cases, implantation involved surgical exploration of the peripheral nerve and placement of the flat plate multi contact electrode immediately next to it[86].

The initial enthusiasm was tempered by the morbidity associated with the electrode design and with the surgical techniques that were used for their implantation[87]. Nerve injury from electrode insertion or stimulation-related fibrosis, made PNS approach less attractive, particularly since the SCS approach became universally accepted as means of long term treatment of medically intractable neuropathic pain of various etiologies[88].

A few enthusiastic centers continued using PNS for certain neuropathic pain syndromes, but the lack of wide interest among implanters resulted in little effort on the part of device manufacturers in getting appropriate approval from the U.S. Food and Drug Administration (FDA) for use of their implantable generators in PNS. Even now, according to the manufacturers’ manuals the only device specifically approved for peripheral nerve stimulation is a radio-

frequency system made by Medtronic (Minneapolis, MN); all other systems, including implantable pulse generators made by Medtronic, as well as devices made by Advanced Neuromodulation Systems (ANS, Plano, TX) and Advanced Bionics (Sylmar, CA), are used for PNS on an off-label basis.

Resurgence of the PNS approach may be credited to pioneering work of Weiner and Reed[89], who described the percutaneous technique of electrode insertion in the vicinity of the occipital nerves to treat occipital neuralgia.

Soon after, Slavin and Burchiel[90,91] described the use of this technique in both occipital and trigeminal areas, and thereafter the approach was modified by many implanters in term of the electrode type, insertion procedure, indications, and the like[92-96].

From the early experience it is clear that PNS can be useful if:

1. Electrophysiologic studies-electromyography (EMG) or somatosensory evoked potentials (SSEP) – can demonstrate abnormalities in the distribution of a peripheral nerve.
2. Repeated nerve blocks are effective in relieving pain distal and in the region subserved.
3. A percutaneous trial stimulation proximal to the peripheral nerve lesion provides 50% relief of symptoms.
4. If pain relief in the nerve distribution is less than 50%, but there is a significant improvement in function, blood flow, control of allodynia/hyperalgesia and use of the extremity.
5. The patient understands the limitations and objectives of the therapy and is motivated for success.
6. Psychological testing excluded psychiatric pathology or specific pain related behavior.
7. The patient understands that the modality will reduce, but probable not eliminate his pain and that it will not cure the condition.

Indications and pain conditions for which PNS have been reported are: 1) neuropathic pain[97]; 2) postherpetic neuralgia [56,94,98]; 3) post traumatic or postsurgical neuropathic pain that is related to underlying dysfunction of particular nerves, including the infraorbital, supraorbital and occipital nerves[46,98,99]; 4)classic migrai-ne, transformed migraine presenting with occi-pital pain and discomfort, and hemicrania con-tinua[100-103]; 5)occipital neuralgia or cervico-genic occipital pain[53,104,105]; 6)complex re-gional pain syndrome[27,106,107]; 7)cluster headaches[107,108]; 8)chronic daily headaches[100,109]; 9)inguinal pain after herniorrhaphy[110]; 10)coccygodynia[96,111]; 11)fibromyalgia[112,113]; 12)sacroiliac pain[14]; 13)Interstitial Cystitis, Pelvic Pain, Urinary Incontinence[51,115,116]; 14)Stimulation for Visceral Pain and Gastrointestinal Pain: Pancreatitis, Inflammatory Bowel Disease, Others [117]; 15)facial pain[99];

Due to the relatively simple and nontraumatic nature of PNS, the list of contraindications is short and is based predominantly on common sense considerations. For example, PNS would be contraindicated in patients with bleeding disorders and active anticoagulation that cannot be stopped for a few days close to the time of the surgical procedure; in patients with active infection, particularly if there is bacteraemia or direct involvement of the surgical region; in patients with major cognitive impairment, untreated depression or malingering; and in patients with unsuccessful PNS trial.

In addition, given that no devices on the market today have been cleared for routine MRI testing, those patients who require follow-up MRI studies (e.g., patients with tumors) should not be implanted with PNS.

Regarding the mechanism of PNS, actually is still largely unknown. Several animal studies have suggested explanations that are related to direct excitation of central pain-processing system and increase in the excitability of the system[118,119]; limited human research has indicated activation of the dorsal rostral pons, anterior cingulate cortex, and cuneus in response to PNS in suboccipital area[102]. Better understanding of PNS mechanism may result in refinement of surgical indications, individual

tailoring of appropriate treatment approach, and perhaps optimization of the hardware choice.

Development of special devices for PNS is yet another potential direction of progress in this rapidly growing area. New electrodes with different spacing options and lower profile may be particularly useful for PNS. Significant research in the area of nerve-electrode interface is currently taking place[120], but the devices for PNS have not been developed or approved for widespread clinical use. It is possible that newly developed electrodes will be used not only for PNS in the strict sense of its definition but also in the neighboring area of stimulation of spinal nerves[121] and gasserian ganglion[122].

Undoubtedly, BION[123,124] and similar devices dedicated to PNS may broaden the indications and further decrease the rate of complications and side effects. Acquiring approval for these devices to be used for PNS procedures may in turn facilitate the acceptance of the approach and better reimbursement of those procedures that are done at present only under research protocols or on an off-label basis.

The opportunities for growth in PNS field are endless; it appears that the current state of PNS represents only a tip of the iceberg, and its full role in the pain management continuum is still to be discovered.

EXTERNAL AND TARGETED NEUROMODULATION.

Last but not least, the target and external neuromodulation techniques have risen in some centers just recently. Although new they have shown good results especially in the management of neuropathic pain.

1) External neuromodulation.

External Neuromodulation (EN) involves application of electrical stimulation via an external nerve mapping probe connected to an impulse generator, to the nerves covering distribution of the painful area or directly to the epicenter of the painful area. The effects of external stimulation do not correlate with TENS applied externally over the same area. The External application allows the procedure to be performed on an outpatient basis.

External Neuromodulation, a noninvasive modality, is not only an effective initial indicator prior to permanent percutaneous peripheral neuromodulation implantation but also plays a role as a sole therapeutic intervention in management of chronic intractable pain[125,126].

2) Targeted neuromodulation

In this technique, a current is applied through a needle (a plain regional anesthesia needle) or an electrode, subcutaneously in the center of the painful area, and it can eliminate neuropathic pain of various origin[128].

The proposed mechanisms are the same as PNS:

Central mechanisms
- ✓ Gate control theory
- ✓ Release of endogenous opioids and neurotransmitters
- ✓ Modulation of supra spinal structures
- ✓ Depression of sympathetic hyperactivity

Peripheral mechanisms
- ✓ Peripheral axonal blockade
- ✓ Excitation failure of C fibres and to lesser extent, A fibres under-stimulation and subsequent loss of sensory perception

The introduction of a stimulating electrode directly to the center of peripherally affected painful areas, either subcutaneously or externally over the skin, (thereby bypassing the spinal cord and peripheral nerves), is a novel, simple, and effective procedure in the control of intractable neuropathic pain. Development of newer devices and miniaturization of electrodes will play a role in refinement and further simplification of subcutaneous neurostimulation. The described approach of percutaneous permanent subcutaneous neuromodulating implant is a promising tool in the management of neuropathic pain; however, further studies are needed to support these initial observations.

SUMMARY

Management of chronic pain has over the years progressed from simple treatment of symptoms to a refined application of several different modalities based on improved understanding of the

mechanisms that cause and maintain pain. There are further exciting prospects on the horizon and future pharmacological, electrophysiological, and psychological developments are likely to have a major impact on how treatment is delivered.

The future of SCS and related techniques is dependent on a variety of scientific, technical, social and economic factors; each of these is essential but will probably have relatively little impact if considered separately. Research in the mechanisms of pain, of diseases and of the action of SCS is likely to result in a broadening of the indications therapeutic neuromodulation, not only for pain management but also for the control of functional disorders.

Technological improvements of the equipment will improve treatment reliability and ease of application. This should eventually decrease the total cost by reducing the need for revision and device replacement as well as the recourse to expensive and time-consuming procedures.

Cost-effectiveness and efficacy are key issues in the acceptance of the therapy and proper studies as well as adequate information for the public, the physicians and the healthcare decision makers are crucial.

The ultimate goal, however, will be to find ways to tackle pain early to prevent the development of chronic pain. This will undoubtedly mean substantial attitudinal and practical changes across the whole of the healthcare system.

For neuromodulation to expand it must be shown to be effective but also be perceived that way if physicians are to recommend the treatments and patients are to be willing to accept them.

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