Surgical Treatment for Neuropathic Pain

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Educational Objectives

1. Review the background and rational use of interventional pain techniques.
2. Assess adequate patient selection, indications, and the evidence to support the use of surgical interventional therapies for neuropathic pain.
3. Identify pros and cons of different surgical ablative and functional neurosurgical interventional therapies to help determine the proper choice of technique for the treatment of chronic neuropathic pain.

Introduction

“Any professional who handles pain patients should be familiar with all therapeutic modalities currently available”

– John Bonica

According to the definition by the International Association for the Study of Pain (IASP), neuropathic pain is caused by a lesion or disease of the somatosensory nervous system. Its treatment may be difficult. Medications and psychotherapy are often insufficient to reduce the pain to a tolerable level. In some well-defined circumstances, functional neurosurgery may provide an alternative treatment strategy. Before deciding on the most appropriate surgical procedure for a particular patient with neuropathic pain, the anatomical and physiological mechanisms involved in the pain must be analyzed carefully. Analgesic surgery, a branch of functional neurosurgery, provides some effective strategies for those patients in whom less invasive conservative treatment has failed or in cases in which medication causes significant adverse effects. The fundamental principle to keep in mind is that any indication for an invasive procedure must arise from an interdisciplinary consensus, taking into account a comprehensive evaluation of pain characteristics and the psychological condition of the patient. Neurosurgical procedures available for the treatment of chronic neuropathic pain can be divided into three broad groups, as follows:

- Anatomical procedures treating the pain etiology.
- Lesional or ablative procedures making selective therapeutic lesions in well-defined and identified targets demonstrated to sustain pain.
- Neuromodulation techniques using electrical stimulation or implanted drug delivery systems.

We will describe each of these groups below.

Anatomical Procedures

In those cases in which neuropathic pain is due to an identifiable anatomical cause, a treatment option is to perform a procedure to correct the disturbance and thus control the symptoms. This procedure should
achieve its goal (pain relief) without any impact on other neurological functions. Unfortunately, there are few neuropathic pain conditions secondary to a specific anatomical disorder that is easily amenable to surgical intervention. A typical example may be trigeminal neuralgia (TN) caused by nerve compression owing to an expansive lesion or secondary to a neurovascular anomaly in the posterior fossa, a situation that is resolved by microsurgical resection of the lesion or reducing the arterial loop responsible for trigeminal irritation, respectively (Fig. 1). Another typical example is compressive radiculopathy secondary to disc herniation that is refractory to conservative treatment. In this case, relief of pain is achieved by radicular decompression by microdiscectomy.

Ablative or Lesional Procedures

“Pain may seem to run in front of the knife”
– Otfrid Foerster

The mechanism of action of ablative procedures is based on the interruption of a nociceptive pathway at any of its levels, or of those structures related to the origin and/or maintenance of the pain. The interruption of nociceptive information is performed via various ablative techniques such as the use of surgical sections, neurolytic agents (phenol, alcohol, etc.), radiofrequency (RF), cryosurgery, and radiosurgery, among others. Whereas ablative techniques were commonly used during the past century, particularly for cancer pain management, their use has been limited today owing to their irreversibility, morbidity, the high incidence of deafferentation pain, and the emergence of modern, less risky, and more effective options.

From a topographic point of view, ablative procedures can be grouped into peripheral procedures (neurectomy, gangliectomy, rhizotomy, and sympathectomy), spinal cord procedures (dorsal root entry zone [DREZ] lesion, cordotomy, commissurotomy, extralemniscal myelotomy, commissural myelotomy, and cordectomy), and encephalic/cranial procedures (trigeminal nucleotomy, bulbar and pontine spinothalamic tractotomy, mesencephalic tractotomy, thalamotomy, hypothalamotomy, cingulotomy, and hypophysectomy). Presently, there are few ablative procedures that can be considered useful in the treatment of specific neuropathic pain conditions. The following is a discussion of some important conditions for which surgical therapies may be indicated:

Trigeminal Rhizotomy

Idiopathic TN refractory to medical therapy is, undoubtedly, one of the best examples of neuropathic pain for which ablative procedures remain extremely useful, effective, and carry very low risk. Percutaneous RF trigeminal rhizotomy is a remarkably effective treatment option, after which most patients are free of pain and can discard the medications they take for this condition. The procedure relies on the application of RF electric current to a portion of the trigeminal root, either
in or just behind the gasserian ganglion, to generate heat locally in order to destroy some of the nerve fibers within it, predominantly nociceptive fibers, because of their greater susceptibility to heat. The aim is to achieve a total or almost total analgesia in the cutaneous area that corresponds to the heated portion of the trigeminal root, accompanied by only partial hypoesthesia in the same area.

The approach is essentially the same as that described by Härtel in 1914 for injection treatments [26]. Under fluoroscopy guidance, the needle is inserted 2–3 cm lateral to the corner of the mouth on the symptomatic side of the face and then advanced in a superior, posterior, and medial direction to reach the foramen ovale and the gasserian ganglion while always remaining under the mucosa. Once the tip of the needle has passed through the foramen ovale, it is advanced further until it just overlies the clival line under lateral fluoroscopic view (Fig. 2). The guide needle is removed, and a few drops of cerebrospinal fluid (CSF) generally emerge from the needle. By this time, a stimulation test is performed to elicit paresthesia in the area of pain. Taha and Tew [88] state that the electrode tip should be 5 mm beyond the clival line for V1 stimulation, just at the clival line for V2 stimulation, and 5 mm in front of the clival line for V3 stimulation. Once the needle position has been confirmed, RF lesions are performed, usually at 65°C for 1 minute each. The endpoint is the achievement of hypoalgesia or analgesia in the initially painful area, with no more than partial hypoesthesia.

Gybels and Sweet [24], and more recently Kanpolat et al. [36] evaluated the results of large series that had been published emphasizing that early complete relief of pain was obtained in more than 95% of patients in all series. The rate of late recurrence requiring reoperation was generally in the range of 20% to 30%. Dysesthesia in the treated area is a common postoperative phenomenon (5% to 24% in various series) that sometimes requires treatment with medication. Anesthesia dolorosa is defined as dysesthesia arising in a totally anesthetic area and is much more rare (1.2%).

In addition to RF techniques, other ablative procedures are used to control pain secondary to trigeminal neuralgia with satisfactory results. In 1971, Lars Leksell published the results of two patients with trigeminal neuralgia treated with his pioneering

![Fig. 2. Intraoperative fluoroscopic image during percutaneous trigeminal rhizotomy: (a) lateral view, (b) head-on view of the foramen ovale. ST, sella turcica; CL, clival line; FO, foramen ovale.](image-url)
technique of stereotactic radiosurgery in 1953 [42]. This technique is now accepted as the least invasive of all surgical procedures for the treatment of TN. However, it is more expensive than percutaneous techniques. Results vary among publications; however, it is estimated that approximately 75% of patients are pain free initially, but less than 60% maintain this outcome after 2 years, and just over half of treated patients remain pain free on or off medications at a 3-year follow-up [47].

In 1981, Sten Hakanson reported the retroganglionic glycerol rhizolysis technique for treating TN via glycerol injection into the trigeminal cistern, a minimally invasive method with low surgical risk and little impact on facial sensibility [25]. In 1983, Mullan and Lichtor pioneered the concept of percutaneous balloon compression for trigeminal neuralgia [51]. This procedure is especially useful in patients with first division pain because it does not injure the myelinated fibers that mediate the blink reflex, providing relative protection of corneal sensation. It is also greatly helpful in patients with pain across multiple trigeminal branch divisions because it does not require multiple lesions. Furthermore, it is advantageous in elderly patients with whom it would be difficult to communicate during selective thermal rhizotomy. It is relatively inexpensive and is a technically and technologically simple operation.

**Stereotactic Trigeminal Nucleotomy**

Dysesthetic neuropathic or deafferentation facial pain still poses a challenge for the neurosurgeon. Surgical attempts to further interrupt the already damaged primary afferent neuron at any site, including trigeminal tractotomy, have consistently failed. In fact, they usually aggravate rather than ameliorate the pain [23,68]. In contrast, lesioning the second-order neurons at the nucleus caudalis, that is, at the putative focus of denervation neuronal hyperactivity, appears to be a rational approach [72]. Stereotactic trigeminal nucleotomy presumably removes the segmental pool of hyperexcitable neurons and denervation hypersensitivity, eliminating convergence and severing the ascending intranuclear pathways. The technique has been well described [31]. In brief, patients undergo surgery under neuroleptic analgesia, with the head fully flexed within a stereotactic frame. Electrical stimulation clearly identifies the trigeminal region, with its rostral dermatome located ventrolaterally and its caudal dermatome dorsomedially. It is usually possible to further define the dorsal border of the nucleus by ipsilateral responses induced from the cuneatus tract and its ventral border by contralateral responses elicited from the spinothalamic tract, or at times by motor responses obtained from a posteriorly located corticospinal tract [68].

In addition, threshold stimulation often mimics the patient’s neuropathic pain. This procedure allows for the placement of accurate stereotactic lesions with concomitant electrophysiological control of cranial nerves V, VII, IX, and X, as well as of the second and third cervical roots, at the nucleus caudalis (Fig. 3). Schwarcz has used this technique since 1971, terming the

![Fig. 3. Postsurgical magnetic resonance image after stereotactic trigeminal nucleotomy. Arrows show that the radiofrequency lesion is entirely within the nucleus caudalis area: (a) axial view, (b) coronal view.](image-url)
procedure trigeminal nucleotomy to emphasize the significance of lesioning primarily the second-order neurons at the oral pole of the nucleus caudalis, which are heavily involved in intrinsic mechanisms pertaining to dysesthetic facial pain [65,71]. From a series of 204 consecutive nucleotomies performed on 196 patients, 143 underwent this procedure for deafferentation pain [57]. In this study, Piedimonte and Schvarcz reported abolition of allodynia and a marked reduction of deep background pain in 75.0% of patients with postherpetic dysesthesia, 71.7% of those with dysesthesia, 66.7% of those with anesthesia dolorosa, and 77.8% of those with posttraumatic neuropathy [57].

Siqueira described a method for open surgical trigeminal nucleotomy [84], and Kanpolat et al. developed an elegant computed tomography–guided percutaneous technique for trigeminal nucleotomy [35]; both of these methods were for deafferentation pain. Grigorian and Slavin also reported good results with ultrasound-guided trigeminal nucleotomy for deafferentation pain [21]. Even though stereotactic trigeminal nucleotomy is a reasonably straightforward technique, especially suitable for elusive dysesthetic facial pain phenomena, its use has been diminished with the development of neuromodulation techniques.

Dorsal Root Entry Zone Lesions

In the 1960s, several neurophysiological investigations showed that the dorsal horn is the first, and an important, level of modulation for pain sensation. This was popularized in 1965 by the gate-control theory [49], which drew neurosurgeons’ attention to this area as a possible target for augmentative (spinal cord stimulation) and ablative pain surgery.

Sindou and colleagues have attempted a microsurgical DREZotomy procedure in patients with neuropathic pain syndromes, such as those associated with paraplegia and brachial plexus avulsion, since 1972, owing to encouraging early results with malignancies (mainly Pancoast syndrome) [82,83]. Soon thereafter, Nashold and colleagues began to perform DREZ lesions via RF thermocoagulation in the substantia gelatinosa of the dorsal horn [55] and later along the entire DREZ [54], especially for pain caused by brachial plexus avulsion. More recently, DREZ procedures have been performed via CO₂ and argon laser by Levy et al. [45] and Powers et al. [59], respectively.

The microsurgical DREZotomy procedure consists of a longitudinal incision of the dorsolateral sulcus, ventrolaterally at the entrance of the rootlets into the sulcus, and microbipolar coagulations performed continuously down to the apex of the dorsal horn, along all of the spinal cord segments selected for surgery. The average lesion is 2–3 mm deep and is made at a 35° angle medially and ventrally. This method was conceived with the aim of preventing complete abolition of tactile and proprioceptive sensations and avoiding deafferentation phenomena [33].

DREZ procedures, whatever their modality, are effective for pain developing after brachial plexus avulsion [61,80,95], pain caused by spinal cord and/or cauda equina lesions [52,61,64,81], pain related to peripheral nerve injuries, and pain after limb amputation resulting in phantom limb pain and/or pain in the stump. Few groups have reported results for postherpetic pain. Only superficial pain, especially of the allodynic type, in the affected dermatome(s) is significantly improved [18,61].

Neuromodulation Techniques

The growing knowledge of pain mechanisms makes it clear that simple interruption of the peripheral or central nervous system does not necessarily prevent an impulse from reaching the brain [7]. In addition, the limited efficacy and significant potential complications associated with neuroablative procedures have led to the development of neuroaugmentative techniques including electrical stimulation of the brain, spinal cord, and peripheral nerves, as well as chronic infusion of analgesic substances into the lumbar spinal and intraventricular CSF. It has been shown that these procedures are more effective than conventional destructive operations, with extremely low morbidity.

It is essential to be aware of the criteria for success, among which are as follows:

- Failure of less expensive and invasive therapies.
- The existence of an objective pathology consistent with the pain reported by the patient.
- Further surgical interventions are not indicated.
- There is no serious untreated habit of drug abuse.
- There are no psychological barriers to a successful outcome.
- There is no absolute contraindication for implantation.
- A trial has been conducted to test efficacy (chemical and electrical neuromodulation) and to rule out toxicity (chemical neuromodulation).
Chemical Neuromodulation

Morphine, known since ancient times and considered by the Sumerian culture more than 5000 years ago [10], is an extremely effective analgesic agent. Unfortunately, systemic administration tends to cause side effects, and its use for prolonged periods can result in tolerance and the potential for opioid addiction.

The discovery of opioid receptors in the substantia gelatinosa of the spinal cord led to the recognition that opioids have both spinal and supraspinal analgesic action. Fields and Basbaum in the United States, and subsequently Besson in France, elucidated and described the descending inhibitory pain system. This pathway begins with projections from the frontal cortex and hypothalamus to the midbrain periaqueductal gray, which then projects to the dorsal pons and dorsalventral medulla and end in the substantia gelatinosa of the spinal cord dorsal horn. These efferent pathways inhibit ascending nociceptive second-order neurons, thus blocking the transmission of pain. Understanding the mechanism by which opioids exert their antinociceptive activity at the spinal level led to the first trials of spinal administration of these agents, with morphine administered epidurally [9] and intrathecally [105] for the treatment of cancer pain. The advantage of intrathecal drug therapy for treating pain is that the effects of the drug are restricted to the specific area related to the conduction of nociceptive input. Thus, a significantly lower total dose is required to produce analgesia, and the systemic effects of the drug are greatly diminished. Morphine is particularly suitable for this application because of its hydrophilicity and resulting low absorption from the CSF. Thus, it is not uncommon for the effects of intrathecal morphine analgesia to last up to 24 hours [9].

The discovery of multiple receptor systems involved in nociceptive transmission and modulation at the spinal level has allowed for the evaluation and application of specific drugs such as opioid receptor agonists, \( \alpha_2 \)-adrenoceptor agonists, gamma aminobutyric acid B (GABA B) agonists, calcitonin, and somatostatin and its analog octreotide, among others. There are more than 100 open studies (of which at least 16 have evaluated scales to measure pain pre- and postintervention) supporting the use of intrathecal drug delivery for long-term pain relief and improvement of quality of life. Four of these obtained good results for quality of life according to the guidelines of the University of York, United Kingdom [5,28,99,108]. However, controlled blinded trials are still lacking, and hence the role of intrathecal therapies for chronic, noncancer, neuropathic pain requires further investigation.

For all indications, patient selection is extremely important and should include a multidisciplinary and comprehensive assessment of symptoms, illness, psychological and social factors, current and previous treatments, and other treatment options. Intrathecal administration of drugs may be concurrent and adjuvant with other forms of pain management. Not all patients with neuropathic pain benefit from intrathegal drug delivery. For this reason, it is essential to perform a prior therapeutic trial with predictive purpose. Various approaches have been proposed for intrathecal drug testing, including single versus multiple injections, administration via catheter versus lumbar puncture, epidural versus intrathecal routes, and bolus drug administration versus continuous infusion. The test with a single intraspinal dose of an active agent poses a significant possibility of placebo effect, which can occur in at least 30% of cases.

Robert Levy has developed a quantitative, crossover, double-blind protocol to identify preimplant candidates for the chronic infusion of drugs for the control of refractory pain [44]. The implementation of this protocol has resulted in the elimination of approximately 30% of potential candidates. Of those patients with successful detection, 70% have had long-term pain relief ranging from good to excellent. This detection paradigm appears to be both reliable and easily applicable [44].

Several studies have demonstrated the cost-effectiveness of intrathecal therapy with implantable devices. These studies have analyzed all of the costs related to intrathecal drug infusion therapy [86]. The results suggest that this therapy is more cost effective than systemic medication beyond 11–22 months for noncancer pain.

Routes of Administration

The opioid epidural equianalgesic dose is almost 10 times greater than the intrathecal dose. Since 80% to 90% of the epidural dose is absorbed systemically, the larger dose requirement may lead to more systemic side effects including constipation and urinary retention. These larger doses increase even more the likelihood of developing opioid tolerance. In addition, because there is a fixed maximum solubility of morphine in saline of
approximately 55 mg/mL, and pump reservoirs are of limited size, the larger dose requirement implies the need to fill the reservoir more frequently. Furthermore, epidural catheter placement has been associated with epidural fibrosis, resulting in failure owing to catheter occlusion, torsion, or displacement.

Although intrathecal drug administration avoids these complications, it carries the disadvantage of potential loss of postural spinal CSF and associated spinal headache, respiratory depression owing to opiate supraspinal distribution, and increased risk of meningeal infection or neural damage. However, the advantages of the intrathecal route, including the requirement of lower dose, leading to increased intervals between pump refilling; the low risk of catheter failure; and the low potential complication rate, suggest that this is the favored route for intraspinal drug delivery.

**Drug Options**

Drugs can be used individually or in combination to maximize analgesic effects and minimize side effects. The most commonly used intrathecal pharmacological agents are listed below.

**Opioids**

Morphine is considered the gold standard drug owing to its stability, affinity for receptors, and extensive experience with its use for this route of administration [56]. Hydromorphone is approximately five times more potent than morphine and is used when there is intolerance to morphine. The adverse effect profile of hydromorphone is equivalent to, or more favorable than, that of morphine [5]. Diacetylmorphine (diamorphine) is highly soluble in saline and with bupivacaine and/or clonidine, making it attractive for use in a combination of drugs intrathecally.

The central side effects of intrathecal opioids include delayed respiratory depression [20], itching, nausea, vomiting, urinary retention, sedation, constipation, edema, weight gain, excessive sweating, changes in memory and mood, and headache. Endocrine effects include hypogonadism, loss of libido, and hypocortisolism [1]. Inflammatory granuloma of the catheter tip has been described in recent years. It occurs between the spinal cord and the dura, mostly in the chest area, with an estimated incidence of 0.5% per patient. Inflammatory granuloma can cause compression of the spinal cord and roots, producing irradiating pain and progressive neurological deficit. It is usually associated with failure of analgesia because the infusion is unable to reach the neural tissue target. The etiology is unknown, but it could be due to a reaction to the catheter tip, low-grade infection, or be related to the infused medication. Animal models suggest that the cause could be high opioid concentration. Granulomatous masses have been reported with morphine, hydromorphone, and baclofen, and low-flow pumps could be a risk factor. In some cases, assessment or even withdrawal of the catheter is necessary. In the situation of systematic spinal cord compression, urgent simple decompression may be indicated [27].

There are several studies on the efficacy of morphine administered via the subarachnoid spinal route for the treatment of pain. Auld et al. reported two studies of intraspinal narcotics for the treatment of nonmalignant pain. In the first, 21 of 32 patients achieved adequate pain relief [7]; in the second, 14 of 20 patients achieved satisfactory pain relief with intraspinal morphine [8].

**Local Anesthetics**

Intrathecal bupivacaine is usually used in combination with morphine to provide better pain control in patients with neuropathic pain. There is evidence that bupivacaine acts synergistically with morphine, reducing the need to increase the dose of intrathecal morphine [3,100]. Local anesthetics can cause sensory deficit, motor disturbances, signs of autonomic dysfunction, and neurotoxicity. There is less likely to be a problem if continuous infusions are used instead of a bolus. Clinically relevant side effects do not appear with bupivacaine doses less than 25 mg/day. Urinary retention, weakness, drowsiness, and paresthesia have been reported with larger doses.

**Clonidine**

Clonidine has been shown to be effective in the treatment of neuropathic pain [17]. It is generally used in combination with morphine and/or bupivacaine. The synergistic combination of morphine and clonidine has proved to be effective in patients with pain as a result of spinal cord injury [78]. The most common side effects of intrathecal clonidine are hypotension, bradycardia, and sedation. Tamsen and Gordh originally studied two patients with pain of nonmalignant origin [90]. The first patient received an epidural infusion of 150 mg clonidine and 5 mg morphine. Analgesia lasted for more than 9 hours compared to less than 3 hours for each
drug separately. The second patient received epidural clonidine, which provided analgesia equivalent to that obtained with epidural narcotic alone or in combination with clonidine. No side effects were reported.

In contrast to clonidine, the α₂-adrenergic agonist tizanidine does not appear to induce hypotension. This agent has proved to be an effective analgesic when administered intrathecally in experimental chronic neuropathic pain [41]. Tizanidine appears to be particularly useful in treating neuropathic pain syndromes refractory to narcotics.

**Baclofen**

Intrathecal baclofen has been established for the relief of severe spasticity. There may be some analgesic effects [89]. Although it is rarely used for chronic pain not related to spasticity, there are a small number of case series documenting its effectiveness in the treatment of nonmalignant chronic pain such as phantom pain, failed back surgery syndrome (FBSS), peripheral nerve injury, and complex regional pain syndrome (CRPS) [101,109]. Side effects associated with continuous infusion of baclofen are rare but include sedation, dizziness, and constipation. Lesser degrees of overdose may cause ataxia, dizziness, and mental confusion. These effects are more common after a bolus dose compared to continuous infusion. Excessive muscular hypotonia may result in unwanted or even dangerous weakness, owing to a reduction in respiratory muscle tone. Physostigmine has been used for overdose, but a ventilation period may be required; central effects should resolve within 24 hours. Withdrawal can occur if the pump is not properly refilled or if there are malfunctions of the pump or catheter, and may result in rebound spasticity, motor hyperactivity, headache, drowsiness, disorientation, hallucinations, rhabdomyolysis, seizures, or even death.

**Ziconotide**

Ziconotide produces its analgesic effect via specific blockade of N-type calcium channels located in presynaptic terminals of the dorsal horn [12]. Side effects include dizziness, nausea, nystagmus, abnormal gait, confusion, and urinary retention. Serious but rare side effects include psychosis, suicide, and rhabdomyolysis. Ziconotide may be initiated at 2.4 μg/day and subsequently titrated according to the analgesic response and adverse effects. Increases must be ≤2.4 μg/day to a maximum dose of 21.6 μg/day. The minimum interval between dose increments is 24 hours. For safety reasons, the recommended interval is 48 hours or longer [62].

Two randomized, double-blind, placebo-controlled studies support the use of ziconotide in the treatment of chronic nonmalignant pain; although the clinical significance was modest, side effects were problematic, and experience with use of this drug is limited [62,104]. The combination of intrathecal ziconotide with other intrathecal drugs, including morphine, hydromorphone, clonidine, or baclofen, is associated with a reduction in the concentration of ziconotide of approximately 20% within a few weeks [75–77].

**Infusion System Options**

Despite the popularity of implantable pumps, there are a significant number of methods by which intraspinal drug administration can be achieved. These systems include percutaneous epidural catheters coupled to external pumps, internalized passive reservoirs and catheters requiring percutaneous administration of drugs, mechanical systems activated by the patient, constant-flow infusion pumps, and programmable infusion pumps. Taking into account the significant cost of the implantable device and the surgical procedure, the choice of delivery system should be made with careful consideration of the benefits of continuous infusion versus bolus infusion, the patient’s general medical condition, the outpatient condition, and estimated life expectancy.

It has been suggested that continuous infusion may result in a reduced rate of opioid receptor tachyphylaxis [14] and a lower risk of tardive respiratory depression [13]. Clinical studies have not clearly confirmed the superiority of continuous versus bolus intraspinal infusion. Gourlay et al. reported that epidural administration morphine of both continuous infusion and intermittent bolus provided equivalent pain relief, and there was no consistent difference in depression or neuropsychological function [19]. Other researchers have similarly reported that either infusion method provides analgesia without significant effect on the level of consciousness, with a low complication rate and probably not resulting in addiction [13].

Fixed-rate delivery systems are less expensive than programmable-rate delivery systems but lack flexibility in terms of delivery. Dose changes are made by modifying the concentration of the solution to be infused. Thus, there is increased patient discomfort and cost when dose modifications are indicated. In addition, these devices are subject to slight variations in the rates
of drug release with changes in temperature and atmospheric pressure. Because the system does not depend on a power source, it should last the life of the patient.

Programmable pumps allow for telemetric, transcutaneous, and noninvasive modification of the drug dose, as well as sophisticated drug-dosing regimens. Because these pumps are battery run, they require surgical replacement; under normal conditions, this occurs approximately every 4 to 6 years. Both types of systems, fixed-flow pumps and programmable pumps, need to be refilled every 1 to 3 months depending on the rate of release and stability of the drug used.

**Electrical Neuromodulation**

Electricity has been used to treat a variety of human pain conditions for many centuries. Therapeutic effects of electric discharges from the electric ray *Torpedo* were well known in ancient times and described by Scribonius Largus for the treatment of patients with gout or headaches. In 1860, Julius Althaus wrote on pain control with electricity applied directly to a peripheral sensory nerve [4]. There are presently diverse and clinically useful structures for electrical neurostimulation, the most important of which are described below.

**Peripheral Nerve Stimulation**

In 1967, Wall and Sweet reported that nonpainful electrical stimulation of peripheral nerve does indeed suppress pain perception in the area that it innervates. They confirmed their experimental findings by inserting electrodes into their own infraorbital foramina [103]. The exact mechanism by which peripheral nerve stimulation (PNS) reduces chronic pain remains unknown. Experimental evidence suggests that it may have both a central effect and a peripheral effect on acute pain perception by acting at multiple sites and via various mechanisms. In an early report by Nashold et al., distinguished by its lengthy follow-up (4–9 years), patients reported more than 90% subjective pain relief [53]. A total of 35 patients were implanted over a period of 8 years. The patients were off all analgesic medications and continued to use the stimulator regularly. The long-term success rate for patients with upper-extremity pain secondary to peripheral nerve injury was 53% (9 of 17 patients).

In 1997, Shetter et al. described one of the largest experiences with PNS [74]. A total of 125 nerve implants were performed for stimulation in 117 patients. Two-thirds of the patients had pain in an upper extremity, owing to injury of a peripheral nerve. There were 101 patients available to follow-up at postoperative intervals of 1 to 53 months. A total of 78 patients (77%) were described as having good to excellent pain relief.

Hassenbusch et al. prospectively evaluated 34 patients with reflex sympathetic dystrophy or CRPS type II [29]. During the trial, 32 patients experienced more than 50% pain reduction. At a mean follow-up of 2.2 years, 63% were considered to have a good or fair outcome characterized by pain reduction of at least 25% associated with improvement in vasomotor tone, trophic changes, or motor function.

In 1999, Weiner and Reed [107] described a percutaneous technique of electrode insertion in the vicinity of the greater and lesser occipital nerves to treat occipital neuralgia, with successful results. Since then, the use of this technique has increased and its indications have expanded to include cervicogenic headache, transformed migraine, cluster headache, and tension headache, among others. Weiner [106] reported 75% good to excellent long-term pain control in more than 150 patients treated during the period 1993 to 2005. The good results achieved with occipital nerve stimulation have encouraged other physicians to attempt percutaneous electrode placement adjacent to the supraorbital and infraorbital nerves for the treatment of postherpetic and posttraumatic trigeminal neuropathy. Good outcomes have been described in several small series [34,85]. More recently, synergistic stimulation, approaching more than one target involved in pain genesis or maintenance, was described for different complex neuropathic pain conditions (Fig. 4).

**Spinal Cord Stimulation**

Spinal cord stimulation (SCS) is an exceptionally good example of translational pain research. In fact, in the gate-control theory published in 1965, Melzack and Wall explicitly stated that the theory could have therapeutic implications by means of selectively activating large-diameter fiber systems for the control of pain [49]. Based on this theory, Shealy et al. reported the first trials with SCS as a clinical pain therapy [73]. Presently, SCS is presumably the most commonly practiced neuromodulation technique for neuropathic pain. The mechanism of action of SCS in neuropathic pain is incompletely understood. The original conceptual basis presupposes antidromic activation of ascending dorsal column fibers. The presence of paresthesia-coverage of the painful area, indicating the activation of the dorsal
column, is a prerequisite for pain relief. Pain associated with extensive deafferentation or direct injury of dorsal column fibers (where it is not possible to obtain paresthesia at the painful site) fails to respond to SCS. There is some evidence that SCS increases the substance P content in human CSF and the spinal release of substance P and serotonin in cats [46] and reduces the release of excitatory amino acids (glutamate, aspartate) while at the same time augmenting GABA release [16].

At present, various forms of neuropathic pain conditions are the main indications for SCS therapy. The favorable experience of SCS as a unique treatment option has materialized in two consensus documents [15,22]. The beneficial effect of SCS may persist for a long time. Several literature reports have documented that patients continue to experience good relief from pain for many years, even decades [39]. The most common indication for SCS is lumbar radicular pain after FBSS, presented as irradiating pain in one or both legs. Low back pain, also present in FBSS, is much more difficult to alleviate, owing to the fact that it is difficult to produce paresthesia in the lumbar area and because of its predominantly nociceptive nature.

The Prospective Randomised Controlled Multicentre Trial of the Effectiveness of Spinal Cord Stimulation (PROCESS, ISRCTN 77527324) recruited 100 patients in a total of 12 centers in Europe, Canada, Australia, and Israel. A total of 52 patients were assigned to the SCS group and 48 to the conventional medical management group. Results of this international, multicenter, prospective, randomized controlled trial show that SCS provides pain relief and improves health-related quality of life and functional capacity in patients with neuropathic pain secondary to FBSS. In contrast, conventional medical management alone provided little or no pain relief or no other outcome benefit [38].

The other principal indication for SCS is CRPS type I. This is the only diagnosis for which the efficacy of SCS has attained the highest degree of evidence level. Taylor et al. analyzed data from 25 case studies on SCS treatment of CRPS, with a mean follow-up of 33 months [92,93]. They found that 67% of the patients were reported to have a >50% relief from pain. A similar result was reported by a European task force for evaluation of neurostimulation, but the evidence quality has been ranked as low (grade C) [15].

The usefulness of SCS for other neuropathic pain indications is substantiated only in retrospective case series and observational studies, among which include CRPS type II, peripheral nerve injury, diabetic neuropathy, brachial plexus injury (partial), cauda equina injury, phantom limb and stump pain, intercostal neuralgia, postherpetic neuralgia [79], and painful legs and moving toes [60].

The majority of electrode leads selected for implant are percutaneous. Surgical leads (plate electrodes) are considered to be less likely to dislocate and are greatly preferred when a percutaneous cable lead has been dislocated several times or when scar tissue prevents the passing of such an electrode to the target area (Fig. 5). A stimulation trial using temporary percutaneous extension cables is an indispensable step.

Fig. 4. Postsurgical frontal (a) and lateral (b) X-ray control images showing tetrapolar electrodes for the synergic stimulation of the sphenopalatine ganglion (SPG) and great occipital nerve (GON).
in deciding whether or not a complete stimulation system should be permanently implanted [22]. In many countries, a period of trial stimulation is required for reimbursement.

**Motor Cortex Stimulation**

The use of motor cortex stimulation (MCS) to control central pain was introduced by Tsubokawa et al. especially for poststroke pain in 1991 [96], by Meyerson et al. for trigeminal neuropathic pain in 1993 [50], and by Katayama et al. for Wallenberg syndrome in 1994 [37]. Despite encouraging results, the mechanisms of MCS have yet to be elucidated. The surgical technique consists of a small craniotomy performed around the area identified as the precentral gyrus during preoperative planning. Somatosensory evoked potentials are obtained with the use of electrode grids to identify the central sulcus and its orientation via the detection of N20-P20 phase reversal. Stimulation is attempted with individual contacts of the grid. The goal is to locate the contact that produces motor responses in the painful area. The positions of the identified electrodes can be marked on the corresponding dura mater, indicating the position and orientation for electrodes to be implanted.

According to Tsubokawa et al., the best location and orientation of the electrode array corresponds to the site where bipolar stimulation produces muscle twitches in the painful area with the lowest threshold [97]. After identification of the appropriate location, the electrode array is sutured tightly on the dural surface, and the stimulation system is internalized. On the following days, the parameters for chronic stimulation are selected to achieve optimal pain control. Outcomes from series in the literature indicate that positive results can be accomplished with this method and may be long lasting.

Sindou et al. reported the results of 127 operations from diverse published series [80]. A total of 86 patients had pain after stroke, 29 presented with trigeminal neuropathic pain, and 12 experienced pain of miscellaneous origin. Pain relief of >50% was obtained after a 1-year follow-up in two-thirds of the patients with poststroke pain and in patients with neuropathic trigeminal pain. In most patients, relief persisted on long-term follow-up (1–6 years; average 2 years).
A double-blind assessment of a group of patients with implanted motor cortex stimulators has corroborated the efficacy of this method [102]. In this study, stimulation was randomized to the off mode for a period of 30 days at 60 or 90 days post-implantation with active stimulation, and pain levels were reassessed. The results indicated that pain levels were significantly reduced by stimulation and significantly increased when the stimulation was turned off. In all series, complications were limited to occasional seizures by the time intensity parameters were adjusted. In conclusion, MCS is recommended for treating poststroke pain and trigeminal pain of neuropathic origin.

**Deep Brain Stimulation**

Deep brain stimulation (DBS) has been used to treat intractable pain for more than 50 years. Heath and Mickle [30] and Pool et al. [58] reported analgesic effects in patients receiving stimulation in the septal region. By the 1970s and 1980s, thalamic and periaqueductal gray/periventricular gray stimulation were commonly used for the treatment of chronic refractory pain [32,48,63,91,98]. Though no proper studies comparing the outcomes of DBS in different targets have been conducted, the general consensus is that neuropathic pain is more likely to respond to stimulation of the sensory thalamus, whereas nociceptive pain responds better to periaqueductal gray/periventricular gray stimulation [43]. Patients with mixed pain may be implanted with electrodes in both structures.

In addition to these more common targets, DBS of the internal capsule has been routinely offered to poststroke patients with significant thalamic atrophy [2,40]. Other targets leading to good outcomes in small clinical series or case reports are the septal region [67,69], medial thalamus (including the centromedian-parafascicular nuclei) [66,94], and cingulate gyrus [87]. Within the past decades, there has been a progressive decrease in the number of published studies and the number of patients with chronic pain treated with DBS. This has been partially attributed to the development and use of less-invasive alternatives for the management of neuropathic pain including catheters and pumps for drug administration, new pharmacological agents, and spinal cord and motor cortex stimulation. Despite these facts, DBS continues to be offered routinely to patients with chronic refractory neuropathic pain.

Boccard et al. recently reported 85 patients who underwent DBS for chronic neuropathic pain of different etiologies, targeting the periventricular gray area in 33 patients, the ventral posterior nuclei of the thalamus in 15, or both in 37. Almost 70% of the patients retained implants 6 months after surgery. A total of 39 of 59 (66%) of those who retained implants gained benefit and efficacy, depending on etiology, improving outcomes by 89% for amputation pain and 70% for stroke pain [11].

**Final Remarks**

As John Bonica presciently expressed, we should try to know all the therapeutic options available for pain control, even if we are not the ones who will carry out these techniques. Functional neurosurgery provides the necessary tools for those complex cases that have not found the solution with pharmacological treatment or less-invasive techniques. Success depends on accurate diagnosis, adequate patient selection, proper choice of the technique to be used, and its correct implementation.

**References**

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