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Neurosurg Clin N Am 15 (2004) 343–357

NEUROSURGERY
CLINICS
OF NORTH AMERICA

Deep brain stimulation for the treatment of chronic, intractable pain

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Neurosurgical treatment of pain began with ablative techniques. Through technologic advances, improved neuroanatomic and physiologic understanding, and the realization that interruption of direct pain pathways eventually fails, neurostimulation emerged and ultimately superseded ablative techniques. During the past decade, however, deep brain stimulation (DBS) for pain has largely been supplanted by other forms of neurostimulation, namely, precentral or motor cortex stimulation (MCS) and spinal cord stimulation (SCS).

A crude but effective means of assessing the general frequency with which each of these three modalities is currently used can be achieved by surveying the number of articles published on each modality during the past 5 years. The results of a PubMed search limited to human subjects since 1999 was filtered to include only articles specifically addressing the treatment of pain by these three forms of neurostimulation. SCS had the highest number (42 articles), followed by MCS (31 articles), leaving DBS with the fewest (11 articles). Although SCS is generally not used to treat central neuropathic pain, MCS and DBS are competing modalities used at slightly different levels of the neuraxis to treat the same types of pain. Why DBS has given way to other forms of stimulation does not seem to be based on efficacy alone. Although the consensus seems to be that MCS is more efficacious than DBS, the fact is that both lack prospective studies and their overall reported long-term outcomes (~50%–75%) are comparable. This leaves other factors, such as perceived efficacy, safety, and novelty, to potentially explain why DBS has been supplanted by alternative modalities in the field of pain.

The current article presents the history, indications, technical aspects, and retrospective outcomes of DBS for pain.

History of deep brain stimulation for chronic intractable pain

The first deep brain structure reported to provide pain relief when electrically stimulated was the septal region by Heath [1] in 1954 for the treatment of schizophrenia. Two years later, Pool et al [2] reported pain relief from septal region stimulation also performed in the setting of psychiatric disease. In 1960, Heath and Mickle [3] went on to successfully stimulate the septal region exclusively for the treatment of pain. In 1966, Ervin et al [4] reported pain relief from caudate stimulation. One year later, Gol [5]

All three authors have professional relationships and either currently or previously received grant funding from Medtronic (Minneapolis, MN).

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doi:10.1016/j.nec.2004.03.004

reported pain relief by stimulation of the caudate and the septal region.

Thalamic stimulation for pain was first reported by Mazars et al [6] in the ventroposterolateral nucleus (VPL) for bodily pain and by White [7] in the ventralis posteromedialis (VPM) for facial pain. These early cases used acute stimulation only, however. In 1973, the VPL and VPM were chronically stimulated for the first time by Mazars et al [8] and Hosobuchi et al [9], respectively. Numerous other groups have since confirmed the benefit of chronic stimulation of the somatosensory thalamus and internal capsule (IC) [8–19].

Stimulation of the periaqueductal gray matter (PAG) and periventricular gray matter (PVG) in human beings as a treatment for pain was begun in 1977 by two groups: Richardson and Akil [20,21] and Hosobuchi et al [22]. These initial trials were based on Reynold's 1969 discovery that low-frequency PAG stimulation produced analgesia in rats [23], a finding that ultimately led to the discovery of the brain's endogenous opioids and their receptors.

Most recently, Franzini et al [27] reported the successful treatment of cluster headaches (CHs) using stimulation of the posteroinferior hypothalamus. This work was based on evidence that CHs may be the manifestation of posterior hypothalamic hyperactivity [24–26]. Knowing that high-frequency stimulation (HFS) was effective in treating movement disorders involving hyperactive nuclei, it was postulated that the same principle might also apply to hyperactive hypothalamic nuclei [27,28].

Since the inception of stimulation for the treatment of pain, numerous other deep brain nuclei have been assessed for pain-relieving properties. These include the parabrachial region [29,30]; the Kolliker-Fuse nucleus [31,32]; and several other thalamic nuclei, including the dorsal medial nucleus, the parafascicular nucleus, and the centromedian nucleus [33–35].

Classification of pain

In the treatment of pain using DBS, target selection is guided by the specific type of pain being treated. The importance of this was illustrated by Levy [36] in his recent meta-analysis, which showed that long-term success rates are strongly correlated with selecting the target appropriate for the type of pain. Thus, the first step in successful DBS treatment of pain is the correct classification of the patient's pain.

Although numerous classification schemes exist, for the purpose of DBS treatment, pain can be classified into two major categories: nociceptive pain and neuropathic pain. CH is discussed separately because it is a specific pain syndrome that currently has a unique DBS target.

Nociceptive pain

Nociceptive pain is pain secondary to potential tissue damage in the setting of a functionally normal nervous system. The perception of potential tissue damage is relayed through pain pathways by activation of peripheral nociceptors in response to noxious somatic or visceral stimuli. Somatic nociceptive pain is often well localized and described as sharp, aching, or throbbing. Visceral nociceptive pain is less well localized and may include a cramping component if hollow viscera are involved. Pharmacologically, nociceptive pain is responsive to opioids, and its optimal target for DBS treatment is the PVG/PAG. Specific examples of nociceptive pain include the nonradicular component of lumbar disk disease or failed back syndrome and cancer pain among others.

Neuropathic pain

Neuropathic pain is pain resulting from an insult to the nervous system itself. The International Association for the Study of Pain (IASP) defined it as pain "initiated or caused by a primary lesion or dysfunction of the nervous system" [37]. The two major subtypes of neuropathic pain are deafferentation pain and central pain [38]. One possible mechanism is that neural injury or irritation leads to abnormal somatosensory processing in the peripheral or central nervous system. Another possible mechanism is that abnormal processing may arise from the loss of innervation from central pathways. Increased bursting of thalamic neurons in rats was noted after deafferentation [39] Additionally, several groups have reported abnormal firing of somatosensory thalamic neurons during intraoperative recordings of patients being treated for neuropathic pain [39–41]. Loss of peripheral input can lead to abnormal signal amplification by a process known as "central sensitization," leading to allodynia [42].

Clinically, neuropathic pain is diverse. It may be characterized as burning, lancinating, shock-like, tingling, or shooting. It may be constant or episodic. When episodic, it may occur spontaneously or in

response to nonpainful stimuli (allodynia). There may be associated focal neurologic deficits, such as weakness or autonomic changes. Trophic skin changes have also been described [42]. Pharmacologically, this type of pain is responsive to antiepileptic drugs or antidepressants and is classically refractory to standard opioid treatment. The optimal target for DBS treatment is the VPL or VPM for bodily or facial pain, respectively. Specific examples of neuropathic pain include poststroke pain, thalamic pain, pain from multiple sclerosis, pain from Parkinson's disease, spinal cord injury, syringomyelia, plexus avulsion, phantom pain after amputation, and painful mononeuropathies (eg, radicular component of low back pain, lancinating neuralgias, entrapment neuropathies). Although controversial, complex regional pain syndrome is often included in this category [42].

Cluster headache

CH is a unique pain syndrome comprising the sudden onset of severe unilateral pain involving the eye, temple, and cheek, and it may include signs of autonomic dysfunction. Patients often have daily attacks for a period of 6 to 12 weeks, followed by a variable period of complete remission. Recurrences classically have a seasonal pattern. Although the origin of CHs was previously thought to be exclusively vascular, recent evidence involving positron emission tomography (PET) scanning [24,25,43], functional MRI, and electrophysiologic recordings [27] has implicated hyperactivity of the dorsal hypothalamus as playing a key role in CH. Although most CHs are successfully treated with medications [44,45], approximately 4% may be completely refractory to medical management [46]. Although numerous ablative techniques have been used to treat CHs [47], they have a high incidence of associated sensory loss and recurrence [45]. The only known DBS target for CH is the ipsilateral posteroinferior hypothalamus recently described by Franzini et al [27].

Difficulties in classifying pain

Pain classification may be clouded by ambiguous clinical presentations. The most commonly used tool to help classify difficult cases is the morphine naloxone test; until recently, this test was considered a valuable aid in classifying pain to select the appropriate target for stimulation [22,48–50]. The test consists of administering 5-mg increments of morphine sulfate or saline intravenously every 10 minutes in a double-blinded manner. If the patient has significant pain relief after receiving between 10 and 25 mg of morphine, which is then reversed by naloxone, the pain is classified as nociceptive. Pain relief with less than 10 mg is indicative of inadequate pharmacologic management. Pain unresponsive to greater than 25 mg of morphine and having qualities consistent with neuropathic pain is diagnosed as such. Patients with pain that does not respond to high-dose morphine and has questionable characteristics can be weaned off morphine using l-tryptophan and reassessed to ensure that the initial failure is not secondary to opiate tolerance [50]. In 1987, Young and Chambi [51] reported that the morphine naloxone test did not predict successful PVG stimulation. More recently, in an unpublished study by Young and Kroening, further doubt was cast on the validity of the morphine naloxone test, reporting no statistically significant difference in outcomes between groups using and not using the test [36]. Notably, the l-tryptophan portion of this test has been completely abandoned because it is no longer deemed medically safe [36].

Patient selection and indications for treatment

The first step is to ensure that the patient fulfills the general criteria used to screen candidates for any neurosurgical pain intervention. The second step is to determine if DBS, as opposed to other neurosurgical pain procedures, is the most appropriate treatment modality. Once DBS has been deemed appropriate, the final step is choosing the optimal DBS target for the patient's pain.

General selection criteria

The pain

The pain must be incapacitating and refractory to maximum conservative management and other less invasive yet effective treatment modalities if available. The pain must be chronic. Patients generally should have pain for a minimum of 1 year, with at least 6 months of maximal nonneurosurgical pain management before consideration of any intervention. The pain must have a clearly defined cause.

The patient

The influence of patient selection on the outcome of neurosurgical pain management should not be underestimated. The patient's general

medical condition should be adequate to tolerate the lengthy procedure required for implantation of a deep brain stimulator. Significant comorbidities, such as cardiovascular disease or bleeding diatheses, must be addressed before surgery. The importance of age or life expectancy should be considered in the context of the indications for treatment. Additionally, consideration should be given to leaving the intermittent pulse generator externalized in the setting of terminal cancer pain. Cognitive status should be adequate to permit the patient's cooperation during intraoperative testing.

Pain is a subjective complaint that is directly assessable only by the patient. Socioeconomic factors, interindividual variability in pain tolerance, psychologic factors, and the possibility of secondary gain must all be considered. As a result, numerous attempts have been made to quantify or classify pain. Although pain patients commonly suffer from minor psychiatric problems, such as anxiety and mild depression, the patient should be free of any major psychiatric illnesses, including severe untreated depression. Tests such as the Minnesota Multiphasic Personality Inventory (MMPI) should be used to screen for certain personality traits that are associated with less favorable outcomes. Patients identified as having strong psychologic components to their pain should be treated appropriately before surgical decision making. For the purpose of assessing DBS outcomes, clinical pain scales, such as the McGill Pain Questionnaire [52] and a visual analog scale [53], should be used before and after surgery. Although pain patients may have undergone numerous surgical procedures to alleviate their pain, a history of overly excessive or unnecessary surgeries should raise suspicion. Finally, the patient should be able and willing to give informed consent with realistic expectations of the potential risks, benefits, and shortcomings of DBS treatment for pain.

The team

The decision to perform DBS for the treatment of pain should always be made in the setting of a multidisciplinary pain team. In addition to the neurosurgeon, the team should include a pain specialist to confirm that the patient is truly refractory to maximal conservative pain management and to assist with continued postimplantation pharmacologic treatment if necessary. Psychiatrists and psychologists are necessary to identify contraindicated psychologic issues and to treat them appropriately if possible. In the setting of CHs, the team should include a neurologist with experience in headache treatment.

Deep brain stimulation target selection

Two major areas have evolved to become the primary targets in contemporary DBS treatment of chronic pain. These are the paresthesia-producing areas (somatosensory thalamus, medial lemniscus, or thalamic radiations) for the treatment of neuropathic pain and the medial areas (PAG/PVG) for the treatment of nociceptive pain [54].

Paresthesia-producing stimulation

Theoretic basis and supporting evidence

The origin of paresthesia-producing stimulation lies in the Melzack-Wall gate control theory of pain, which states that threshold stimulation applied to large peripheral nerve fibers causes suppression of conduction in small nociceptive fibers through opioid-dependent mechanisms involving activation of met-enkephalinergic interneurons in the dorsal horn of the spinal cord [55]. Wall and Sweet [56] confirmed that nociceptive fiber inputs could be suppressed through such a mechanism, and the neurosurgical community began to apply the principle. This first included stimulating the dorsal columns of the spinal cord, later moving rostrally to the brain's lemniscal pathways (ventrocaudal nucleus, medial lemniscus, or thalamic radiations) in an attempt to induce paresthesias chronically in the distribution of the patient's pain. With experience, it became evident that such stimulation was effective primarily for neuropathic pain versus nociceptive pain. Investigation revealed abnormal neuronal activity of the somatosensory thalamus in the setting of neuropathic pain [39,40]. Hypothetically, electrical stimulation of the brain's lemniscal pathways may alter the brain's complex processing of such signals rather than simply blocking transmission of pain along pathways. Animal studies have supported this theory. VPL stimulation in primates may inhibit spinothalamic tract neurons of the dorsal horn of the spinal cord [57–59]. In rats, VPL stimulation has been shown to inhibit neuronal activity in the centromedian-parafascicular (CM-Pf) complex [60].

Specific paresthesia producing deep brain targets

The primary deep brain targets for neuropathic pain lie in the somatosensory thalamus. They are

the VPL for bodily pain and the VPM nucleus for facial pain. There are two situations in which stimulation of the thalamic radiations in the IC may be more efficacious than direct stimulation of the VPL/VPM, however. The first is when paresthesia-producing stimulation over a wide area of the body is needed to treat a large pain distribution. The second is in the setting of postthalamic infarct pain in which the remaining thalamic substrate may be insufficient for effective thalamic stimulation. Even IC (or attempted thalamic) stimulation in the setting of thalamic pain syndrome has produced poor outcomes [50], however, and more promising therapies, such as precentral cortical stimulation, should be considered.

Medial stimulation

In 1969, Reynolds [23] observed that electrical stimulation of PAG/PVG produced analgesia in rats. Based on this work, stimulation of the PAG/PVG in human patients as a treatment for pain was first performed in 1977 by two groups: Richardson and Akil [20,21] and Hosobuchi et al [22]. In addition to demonstrating effective pain relief, both groups demonstrated a rise in cerebrospinal fluid (CSF) endogenous opioid levels. This rise in CSF β-endorphin and met-enkephalin levels was later confirmed by several groups [21,51,61–63] The underlying mechanism is believed to involve activation of opioid pathways that interact with serotonergic neurons descending from the nucleus raphe magnus (NRM) to the dorsal horn of the spinal cord [62–66]. This theory is supported by the existence of cross-tolerance between PAG/PVG stimulation and opioids as well as the suppression of PAG/PVG's effect by the administration of naloxone [22,67]. More recently, Nandi et al [68] implicated a thalamic role in PVG stimulation by describing a reduction in pain-related thalamic field potentials in response to low-frequency (5–35 Hz) PVG stimulation. Medial stimulation is primarily used for nociceptive pain. Although some believe it is also effective for selected cases of neuropathic pain, this is controversial.

Specific targets for medial stimulation

The primary targets for medial stimulation are the PAG and the PVG. Although low-frequency stimulation of either the PAG or PVG is capable of effective pain relief, the threshold for evoking unpleasant sensations (eg, fear, nervousness, doom) is lower with PVG stimulation than with PAG stimulation. Additionally, only the ventral PAG is targeted, because dorsal PAG stimulation almost universally induces unpleasant sensations, even at low amplitudes [36], but ventral PAG stimulation induces visual side effects, such as oscillopsia.

Hypothalamic stimulation

Stimulation of the posterior hypothalamus exclusively for the treatment of intractable CH was recently reported [27,28]. This target was selected based on reports of posteroinferior hypothalamic hyperactivity seen on PET scans, functional MRI, and electrophysiologic recordings of the area [25–27,69]. The posteroinferior hypothalamus is believed to be the source of CH. HFS may inhibit hyperactive hypothalamic neurons. An alternative explanation is stimulation-induced activation of pain-modulating pathways [27]. CH is the only pain condition currently treated with posteroinferior hypothalamic stimulation. The original and characteristic feature of this target is that DBS is meant to inhibit its hyperactivity by HFS, whereas all the other above-mentioned targets were meant to be activated through low-frequency stimulation.

Multitarget implantation

In some cases, patients may present with pain that legitimately involves neuropathic and nociceptive components, or definitive classification of the pain is not possible. Such mixed presentations are commonly encountered in patients with low back pain or failed back syndrome in which clinicians often classify the midline component as nociceptive and the radicular component as neuropathic. Patients presenting with combined or ambiguous pain types may be best treated with combined implantations of the PAG/PVG and VPL/VPM targets.

When to consider deep brain stimulation: consideration of alternative neurosurgical pain interventions

The goal of neurosurgical pain management is to provide the patient with maximum pain relief using the least invasive and safest technique available. The following are examples of alternative neurosurgical pain interventions that should be considered in specified cases.

Ablative techniques

Although ablative techniques have largely been replaced with neuromodulation, some continue to

be used. Tasker and Filho [54] reported that although the steady pain component associated with spinal cord injury may benefit from VPL DBS, the lancinating and evoked elements may be better treated with ablative techniques. Additionally, bilateral cordotomy provides immediate but short-lived (less than 2 years) pain relief and may be a safer and more cost-effective alternative in the setting of intractable cancer pain. Other ablative techniques still used for the treatment of cancer pain include mesencephalotomy, myelotomy, and cingulotomy. As discussed later in this article, however, intrathecal drug delivery is more commonly used for cancer pain because it is nondestructive and potentially more efficacious. Finally, endoscopically performed sympathectomies provide pain relief in approximately one third of those with complex regional pain syndrome (CRPS) type I or II [70].

Spinal cord stimulation

SCS is the caudal analogue of VPL stimulation for the treatment of bodily neuropathic pain. Its mechanism of action is also putatively based on Melzack and Wall's gate control theory of pain. SCS should be considered as a less invasive but equally efficacious alternative to thalamic/IC DBS for the treatment of neuropathic pain secondary to peripheral nerve or nerve root injury. SCS is contraindicated by obliteration of the spinal epidural space or previous SCS failure. Note, however, that regarding previous SCS failure, a correlation is believed to exist between the results of SCS and thalamic/IC DBS. Thus, if SCS does not alleviate peripheral nerve or nerve root pain, it is likely that DBS of the sensory thalamus will also fail [54]. The success rate for CRPS types I and II is around 80% to 90% and is around 60% to 70% for persistent radicular pain after spinal surgery [71]. Notably, the efficacy of contemporary SCS may be greater than previously reported because of recent improvements in technique and hardware [72,73].

Intrathecal/intraventricular drug delivery

The most common use of intraventricular drug delivery (IDD) systems (usually infusing opioids) is in the treatment of terminal cancer pain and should be strongly considered when life expectancy is limited. A recent randomized trial found intrathecal drug delivery to be superior (52% decrease) to comprehensive medical management in pain control (39% reduction) [74]. In recent years, a large number of studies have reported a benefit from the use of IDD in nonmalignant pain, primarily in failed back syndrome. Roberts et al [75] reported a mean reduction in pain of 60% at 3 years of follow-up. A prior prospective study assessing IDD in nonmalignant pain reported less dramatic results, however, with 36% of patients having 50% or greater pain reduction at 2 years [76].

Motor cortex simulation (precentral simulation)

MCS, also known as precentral stimulation, was first reported by Tsubokawa et al [77] in 1991. Although lacking controlled studies, precentral stimulation seems to be as efficacious as thalamic DBS in the treatment of a wide variety of neuropathic pain types, with successful outcomes typically in 50% to 75% of cases [77–81].

It has been suggested as a potentially superior treatment relative to all other forms of chronic stimulation used to treat poststroke pain. This may be explained by the fact that thalamic stimulation has been reported to yield painful effects in the setting of poststroke pain. Katayama et al [80] performed the only comparison between thalamic DBS and precentral stimulation for poststroke pain. Although this was not a prospective study, these investigators reported that precentral stimulation achieved excellent pain control in 50% of cases, whereas thalamic or IC DBS actually increased the pain. Conversely, another group reported poor outcomes in the treatment of thalamic pain syndromes using precentral stimulation [79]. Nevertheless, numerous subsequent studies have reported good to excellent outcomes using precentral stimulation for thalamic pain syndrome [78,82,83].

MCS also seems to be particularly efficacious for facial central pain, with outcomes as high as an 83% reduction achieved in 77% of patients [78]. Finally, from a safety perspective, although electrode grid placement requires a craniotomy, the procedure is often entirely extradural and thus less invasive than DBS. To date, there has been no published report of neurologic injury occurring secondary to MCS placement [84]. This may be explained by the easily accessible and proportionately large area of facial representation on the cortical convexity.

Two situations in which precentral stimulation is relatively contraindicated are large cortical strokes with significant encephalomalacia in the intended region of stimulation and the presence of

significant weakness in the distribution of the pain. The treatment of leg pain has been difficult using precentral stimulation simply because of the interhemispheric location of the corresponding cortex. Recently, however, Saitoh et al [85] have reported effective treatment of leg pain by placing electrodes subdurally in the interhemispheric fissure.

Surgical technique

General stereotactic technique

The general stereotactic technique used for the DBS treatment of pain is the same used in the DBS treatment of other indications. First, stereotactic imaging is performed using one of several imaging modalities: MRI, CT, ventriculography, or some combination of the three. The advantages and disadvantages of each remain topics of debate [86]. Regardless of imaging modality, almost all groups use indirect targeting for initial localization. Indirect imaging involves defining the target in relation to third ventricular landmarks, primarily the anterior commissure (AC) and posterior commissure (PC), as opposed to direct visualization of the target itself. Additionally, these targets are always incompletely defined; even MRI fails to identify the thalamic subdivisions clearly. The patient is then taken to the operating room with a stereotactic frame fixed to the head maintaining the identical stereotactic relations present during image acquisition. Electrophysiologic refinement of the target, followed by definitive electrode implantation, is then performed via a precoronal parasagittal burr hole using local anesthesia. It is important that the patient remains coherent during the procedure so as to provide valuable feedback regarding the effects of intraoperative stimulation. A plethora of electrophysiology systems are commercially available.

Electrophysiologic localization comprises recording (detection of neuronal activity) and stimulation. Electrophysiology involves recording cellular activity along the potential track of implantation to map the borders of the target and define surrounding structures. Stimulation is performed using either micro- or macrostimulation. The goal is twofold: to assess for the positive effects of stimulation (reduction in pain or other known prognostically positive signs) and to assess for adverse stimulation effects (eg, undesirable sensations, muscular contractions). Note that the parameters of intraoperative stimulation should be compatible with those used for chronic stimulation specific to the type of pain being treated. Once the optimal placement site is found, the microelectrode is replaced with the permanent electrode, which is then secured in place. Although many groups secure the electrode using commercially available plates or caps, the authors prefer using suture tied in serial knots to attach the electrode to the perimeter of the burr hole, which is then embedded in a low-profile layer of methyl methacrylate. The electrode is then attached to an extension cable, which is externalized through a second stab incision for trial stimulation. Postoperative MRI or CT allows for assessment of postoperative perielectrode edema or hematoma. Once these resolve, if present, and trial stimulation proves efficacious, the intermittent pulse generator (IPG) is implanted. The IPG is implanted through an infraclavicular incision and should be secured directly to the surface of the pectoralis fascia. Cables are passed subcutaneously to connect the generator and electrodes, resulting in a permanent fully enclosed system that is transcutaneously programmable via telemetry.

Paresthesia-producing targets

Ventroposterolateral nucleus, ventralis posteromedialis, and internal capsule

Electrodes implanted in the somatosensory thalamic nuclei are placed in the somatotopic area corresponding to the location of the pain in the contralateral body near the entry site of the medial lemniscus. Electrodes implanted in the IC are placed in its posterior limb. The VPM is targeted for facial pain, the VPL for bodily pain, and the IC when inadequate tissue remains after thalamic infarction. For these targets, pain relief is produced only on the side contralateral to implantation. Therefore, implantations can either be unilateral (contralateral to the side of unilateral pain) or bilateral (for bilateral pain). Stereotactic coordinates for each target are shown in Table 1. Physiologic localization for all three should be performed from 10 mm above to 6 mm below the AC-PC plane in 2-mm steps [15]. Final electrode position along the dorsoventral plane is determined by the location of optimal stimulation results, specifically, the area where the voltage threshold for producing paresthesias in the distribution of pain is lowest and the threshold for producing adverse effects is highest. Stimulation-induced muscle contractions are usually caused by involvement of the corticospinal tract in the posterior limb of the IC [86]. Although electrophysiology may help to identify entry into the

Table 1
Stereotactic coordinates of deep brain stimulation targets for the treatment of pain

Target	Stereotactic coordinates
VPM	X: 8–10 mm lateral to midline Y: 8–10 mm posterior to AC-$PC_{midpoint}$ Z: 10 mm above AC-PC to 6 mm below AC-PC in 2-mm steps
VPL	X: 14–16 mm lateral to midline Y: 10–12 mm posterior to AC-$PC_{midpoint}$ Z: 10 mm above AC-PC to 6 mm below AC-PC in 2-mm steps
IC	X: 25 mm lateral to midline Y: 12–14 mm posterior to AC-$PC_{midpoint}$ Z: 10 mm above AC-PC to 6 mm below AC-PC in 2-mm steps
PVG	X: 2–3 mm lateral to wall of 3V Y: 2 mm anterior to PC Z: start 2 mm above target
Hypothalamus	X: 2 mm lateral to midline Y: 2 mm posterior to AC-$PC_{midpoint}$ Z: 5 mm below AC-$PC_{midpoint}$

Abbreviations: AC, anterior commissure; IC, internal Capsule; PC, posterior commissure; PVG, periventricular gray mutter; VPL, ventropostero latteral nucleus; VPM, ventralis posteromedialis; 3V, —.

somatosensory thalamus, the area of stimulation-produced paresthesias and cellular receptive fields do not always match [36]. Because stimulation delivery is the sole clinically effective component in the end, stimulation results should always take precedence over electrophysiology results in determining the final electrode position. Typical long-term stimulation parameters for the VPL and VPM are an amplitude (Amp) of 2 to 8 V, a frequency (Freq) of 50 to 100 Hz, and a pulse width (PW) of 0.2 to 0.8 milliseconds [50].

Medial targets

Periaqueductal gray matter and periventricular gray matter

Electrodes implanted in the PAG and PVG are placed at the level of the diencephalic-mesencephalic transition. Although some advocate bilateral implantation [87,88], numerous reports indicate that unilateral implantation is sufficient to relieve even bilateral pain [49,89–91]. The topic remains controversial. Stereotactic coordinates for each target are shown in Table 1. Physiologic localization should start 2 mm above the target and continue until the optimal location is found [89]. Electrophysiology is valuable for PVG implantation by helping to place the electrode in close proximity to several adjacent nuclei that some believe to be correlated with superior outcomes. These nuclei are the dorsomedial nucleus (DM), the Pf nucleus, and the endymalis nucleus [33,86]. Stimulation effects that are positive prognosticators include a feeling of warmth or cold either contralateral or globally, pleasure, and relaxation. These sensations are usually achieved at threshold amplitude using a frequency of 50 Hz and pulse durations between 0.2 and 1.0 milliseconds [36]. Pain reduction is commonly reported but typically with a delay of 10 minutes after the onset of stimulation [50]. Hosobuchi [87] reported that the single best predictor of correct electrode placement is stimulation-induced inhibition of conjugate upgaze; however, this is potentially associated with oscillopsia, making the setting range narrow. Young and Rinaldi [86] and Young [92] reported characteristic changes of baseline vital signs in response to stimulation when the appropriate target is encountered. These include an increase of heart rate by 32 ± 12, beats per minute, an increase in mean systolic blood pressure by 72 ± 21 mm Hg, and an increase in mean diastolic blood pressure by 47 ± 10 mm Hg. Eighty-seven percent of patients with these changes ultimately had pain relief versus 26% of patients who did not have these cardiovascular changes [86,92] Negative effects of stimulation include the following: blurred vision, oscillopsia, and nystagmus caused by involvement of the nearby Edinger-Westphal and third cranial nerve nuclei; sympathetic responses, such as fear and anxiety, when placed too anterior; and sensations of vertigo, nausea, and suffocation when placed too posterior or deep [50,89,93,94]. Undesirable sensations of fear, anxiety, and burning are encountered with progressively higher amplitudes in the PVG and anterior PAG and are easily evoked during dorsal PAG stimulation, making it a less desirable target. Additionally, PAG or PVG stimulation below the AC-PC plane has been noted to induce such effects commonly [54]. Typical long-term stimulation parameters for PVG stimulation are an Amp of 1 to 5 V, a Freq of 25 to 50 Hz, and a PW of 0.1 to 0.5 milliseconds [50]. Furthermore, higher frequency PVG stimulation (frequency of 50–100 Hz) has been reported to actually worsen pain [68].

Posteroinferior hypothalamic target

Electrodes are implanted in the posteroinferior hypothalamus ipsilateral to the symptoms of the

CH. Stereotactic coordinates are shown in Table 1. Physiologic localization begins 10 mm above the target and continues until the optimal location is found. Electrophysiology may demonstrate hyperactive hypothalamic neuronal firing. Notably, stimulation-induced pain relief has a lag time between several hours and several weeks after initiation of stimulation [69]. As a result, final electrode placement is largely guided by stimulation-induced side effects. At the optimal site, stimulation greater than 4 V elicited conjugate ocular deviation in all cases and was often accompanied by undesirable feelings of near death, whereas no additional side effects were present at routine stimulation parameters: an Amp of 0.7 to 3 V, a Freq of 180 Hz, and a PW of 60 milliseconds [27,28,69].

Putative new targets

To date, DBS for pain has not been one of the most successful areas of functional neurosurgery. As a result, pharmacologic, psychotherapeutic, and palliative approaches are taking an increasingly important place. Not all deep brain targets have been fully explored, however. In the past three decades, the properties of a descending inhibitory system that originates in the PAG and rostral ventral medulla, an area that includes the NRM and paragigantocellularis, have been well documented [95–97]. Furthermore, it has been demonstrated that electrical and chemical stimulation of these sites produces analgesia and inhibition of spinal cord nociceptive neurons [98–101]. Revival of DBS for pain might arise from the development or use of new targets, such as the NRM [64,65] or the lateral habenula [102,103].

Trial stimulation and implantation of intermittent pulse generator

Regardless of the pain type or target, a period of trial stimulation beginning several days after implantation and lasting approximately 1 week is used by virtually all groups. The purpose of trial stimulation is to determine if efficacy is possible, and if so, at what stimulation parameters. Stimulation is usually deemed successful if it can improve the patient's pain by 50% or greater. If the trial period demonstrates effective pain relief from stimulation, the IPG is implanted. If stimulation is not efficacious, the IPG is not implanted and the electrodes may be removed. Kumar et al [50] reported satisfactory trial stimulation and subsequent IPG implantation in 78% of 68 patients. The rate of success in stimulation trials is correlated with the quality of patient selection.

Complications

Overall, complications of DBS for pain are no different than those seen in DBS for movement disorders. Although complications do vary according to target, implanting the VPL nucleus for pain is likely comparable to implanting the nucleus ventralis intermedius for tremor. DBS complications can be divided into two categories: perioperative and long term. The most common perioperative complication is hemorrhage. Terao et al [104] recently reported that hemorrhages were seen on the CT scans of 3.4% of 59 patients who received subthalamic nucleus implantations for the treatment of Parkinson's disease. This is in agreement with the hemorrhage rates reported by Bendok and Levy [105]: 1.6% to 4.1% in their meta-analysis of the literature. The rate of hemorrhage resulting in neurologic deficits, however, was only 0.02%. Regarding overall complication rates, Beric et al [106] reported that 26 of 86 patients undergoing electrode implantation for movement disorders had an untoward event related to their procedure. Of these, 6% had persistent neurologic sequelae.

Excluding the development of tolerance, most long-term or delayed complications are related to hardware. In the multicenter United States and European Tremor Trials (n = 197 patients), adverse events related to the device included lead migration or dislodgment (1.0%), lead fracture (0.5%), infection (1.5%), erosion (2.5%), electrical short circuit or open circuit (1.0%), and component malfunction (1.5%) [107]. Oh et al [108] reported the hardware complications of 79 patients implanted with 124 electrodes during a mean follow-up period of 33 months. Overall, 20 patients (25.3%) had 26 hardware-related complications involving 23 (18.5%) of the electrodes. A significant finding was a high number of complications involving erosions or infections, which occurred in 7 of 12 instances as a late complication (beyond 12 months).

Outcomes

Outcomes by pain type and target

The general consensus regarding target selection is that neuropathic pain should be treated with VPM/VPL stimulation, nociceptive pain with

PAG/PVG stimulation, and mixed pain with implantation of both target areas. Although there was previously considerable debate concerning the importance of target-pain type matching in predicting outcomes, Levy's recent meta-analysis of all reported cases in the literature concluded that it is indeed extremely important [36]. In summary, Levy normalized the long-term outcomes of 13 studies in which 1114 patients were treated with DBS for pain [19,48,49,86,109–115]. Long-term success criteria included greater than 50% pain reduction, greater than 1 year of stimulator use, and an outcome description of "good, excellent, total, moderate, or complete." Failure criteria included less than 50% pain reduction, discontinuation of the stimulator, and an outcome description of "fair, poor, none, slight, or partial." He found a long-term success rate of 50% (range: 19%–79%) for all cases, 47% for neuropathic pain cases, and 61% for nociceptive pain cases. Additionally, the success rates for each pain type were evaluated according to whether the VPL/VPM or the PAG/PVG was targeted. For neuropathic pain, the long-term success rate was 56% using VPL/VPM and 23% using PAG/PVG. For nociceptive pain, the long-term success rate was 0% using VPL/VPM and 59% using PAG/PVG.

In interpreting these results, two opposing factors must be considered. First, a large percentage of the reported outcomes represent patients operated on during the early stages of DBS for pain. Assuming that improvements in outcomes accompany the significant technical advances made in the field, one would expect that the outcomes reported here underestimate the reality of the current state. Second, follow-up periods were variable among the outcomes reported by various groups. Although Levy's normalization criteria [36] included continued use of the stimulator for longer than 1 year, tolerance to DBS has been reported to occur after the first year of use. Because patients developing tolerance after 1 year would have been considered to have successful outcomes, one would expect that the outcomes reported here might be better than reality.

Outcomes of hypothalamic stimulation for intractable CH are presented separately because they have only recently been reported by a single group and represent the treatment of a relatively unique type of pain. Six of the seven patients treated maintained complete pain relief with follow-up periods as long as 3 years. The seventh patient had a recurrence of symptoms at 18 months for which medical management was resumed. No adverse effects were noted in any of the patients, all had intact trigeminal sensation, and the benefit of stimulation was universally reversible [27,28,69].

Tolerance

Tolerance is the term used to describe the loss of stimulation-induced benefit over time. The pathophysiology underlying tolerance remains unknown but is often attributed to a cross-tolerance to opioids. Exhaustion of the serotonergic pathway has been considered in both situations, and high-dose l-tryptophan administration has been used to reverse it, with mixed results. High-dose l-tryptophan is no longer used, however, because it may present a risk of adverse side effects [116]. What degree of loss and over what period of time are variable. Although tolerance often develops during the first year, Kumar et al [50] reported a mean onset of tolerance for PVG stimulation at 7.1 years and for thalamic stimulation at 3.8 years. Several methods have been used to remedy the problem of tolerance. They include altering stimulation parameters, stimulation holidays, stimulation ramping (gradual augmentation of stimulation intensity in a cyclic manner), and implanting a second electrode in an alternative target or in the same target contralaterally if not already done [50]. Of these remedies, implantation of a second electrode proved most effective. As stated previously, tolerance of hypothalamic stimulation was observed in only one of seven cases [28].

Discussion and summary

Neuromodulation for pain has evolved enormously over the past decade. The general technique of electrode implantation into the deep brain has become widespread, in part, because of its application in the field of movement disorders. As is true for most aspects of neurosurgery, one of the most difficult decisions is determining the right operation for the right patient. Unfortunately, in the treatment of pain, patient and procedure selection are often clouded by multiple variables. As a result, implementation of DBS for pain should be limited to experienced multidisciplinary teams.

The fact that pain is a subjective complaint, directly accessible only by the patient himself and subject to multiple factors, including socioeconomic background, psychological status, and potential for secondary gain, makes outcome

assessment particularly difficult. As a means to quantify outcomes, a variety of pain questionnaires and visual analog scales, along with productivity measures and quality of life assessments, have been used. The tools employed vary among groups, however. Furthermore, although typically described as 50% pain reduction for greater than 1 year, the definition of long-term success is also variable. The lack of clear definition in outcome measures, combined with the absence of controlled studies, makes an accurate comparison among pain interventions extremely difficult.

Over the past decade, the pain community has moved away from DBS and toward newer alternative therapies, namely, MCS for central neuropathic pain and SCS for peripheral neuropathic pain. Although this may, in fact, prove to be a justified move, it is currently a relatively unfounded one. There are several major potential reasons underlying this move. First and foremost is a potential perception of superior efficacy associated with MCS and SCS. Although this may be true, because of the limitations in outcome analysis, the only currently available information is the nonstandardized outcome data pieced together in literature reviews. Interestingly, the average outcomes for all three modalities (50%–75%) fall within a range whose difference is possibly attributable to the confounding variables introduced by nonuniform outcome measures and definitions of success. The second reason may be the perception of the relative degree of safety or invasiveness associated with each procedure. MCS and SCS are typically extradural procedures, whereas DBS, by nature, is not. Although all have an associated risk for complications, none is considered a high-risk procedure. Should efficacy prove comparable, however, a significant safety differential would certainly justify selecting one procedure over another. The third and final reason may stem from the relative novelty of alternative procedures, particularly MCS. Pain is difficult to treat, and outcomes of surgical treatments have been historically undesirable. A new less invasive procedure with seemingly comparable efficacy in an armamentarium of tools producing suboptimal outcomes is palatable. To reiterate, MCS and SCS may indeed prove to be superior treatments for chronic intractable pain, but without standardized outcome measures and controlled studies, it is too soon to know.

Finally, DBS for pain is currently available only as an off-label treatment. DBS for pain began in 1969 before the US Congress passed the Medical Device Act regulating implantable medical devices. In the mid-1970s, DBS for pain was officially brought to the market just before the law was put into effect. The law allowed all market-released devices to remain on the market through a grandfather clause for a period of time. The law also required the US Food and Drug Administration (FDA) to call for a premarket approval application, which was effective in 1989. At that time, there was not sufficient FDA quality data, so the products were taken off the market and an investigational device exemption (IDE) was filed to study the therapy/systems. The study struggled along for a few years, not enrolling sufficient patients to file a premarket approval, and eventually was stopped, with the therapy effectively removed from the market in the early 1990s. From that point until the Activa (Medtronic, Minneapolis, Minnesota) therapy was released for tremor, no DBS system was available for pain in the United States. Presently, there is no commercially available system specifically for pain, meaning that other systems must be used off-label for DBS treatment of pain (Mullett K, PhD, Medtronic, personal communication, 2003).

In summary, although neurostimulation offers the significant advantage of producing reversible effects in all targets, one must also consider the relative disadvantages of cost, risk of hardware implantation, and specialized follow-up care required for IPG programming and replacement. This being said, however, neuromodulation offers selected patients an effective and safe solution for their legitimate quest of intractable pain relief.

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