DEEP BRAIN STIMULATION:

AN OFF-LABEL SURGICAL THERAPY FOR REFRACTORY CHRONIC PAIN

LAURA SPERRY MSN RN ANP-C,
LIN ZHANG MD PHD, KIA SHAHLAIE

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Abstract

Deep brain stimulation (DBS) may provide an alternative therapy for chronic pain in patients who have failed pharmaceutical and more conservative therapies. This paper is intended to build upon the introductions to DBS in the management of movement disorders as well as its future applications published in the Summer 2012 and Spring 2014 JNLCP and to discuss the need for further research on DBS managing chronic pain syndromes. Readers are expected to understand the patient selection process, procedure and risks and complications. The efficacy of DBS in pain management is summarized and the rationale behind the lack of availability and need for further research is discussed.

According to the 2008 Medical Expenditure Panel Survey, chronic pain affects approximately 100 million adults in the United States and the impact on function and quality of life can be significant. Based on this data, the total financial cost of pain to society, combining health care costs and productivity estimates, ranged from $560-635 billion per year; greater than the annual costs of heart disease, cancer and diabetes (Institute of Medicine Committee on Advancing Pain Research, Care, and Education, 2011). Pain is often complex in nature, requiring multiple modalities, including pharmaceutical, physiotherapeutic and invasive therapies to target the symptoms. For example, patients with failed back surgery syndrome (FBSS) have combined lower back pain and radicular pain. Because spinal cord stimulation (SCS) only relieves the radicular aspect of pain and intrathecal opioids are better for the low-back aspect of pain, these patients traditionally would be treated with both SCS and intrathecal opioids (Rasche, Rinaldi, Young, & Tronnier, 2006). While most cases of chronic pain can be treated medically, about 10% of patients are refractory to these therapies (NHS England Specialised Commissioning Team, 2015, July). For those who fail pharmaceutical and more conservative therapies, deep brain stimulation (DBS) may provide some relief from their chronic discomfort.

DBS is a neurosurgical procedure that implants a brain pacemaker device to deliver electrical stimulation to specific targets in the brain. Leads are placed in specific areas of the brain according to the symptoms involved (Figure 1). DBS is widely used in movement disorders but has also shown effectiveness in epilepsy, obsessive compulsive disorders, cluster headache, and Tourette's syndrome (Boccard, Pereir, & Aziz, 2015).

Patient Selection and Procedure

A detailed description of DBS patient selection and procedure was discussed in the Summer 2012 issue of the Journal of Nurse Life Care Planning (Zhang, Sperry, & Shahlaie). According to Pereira, Green, & Aziz (2013), there are two challenges in identifying appropriate surgical candidates: first, the pain must be characterized as neuropathic and not factitious or psychogenic in origin and second, the team must identify which patients with neuropathic pain will likely benefit from DBS. Due to the challenging nature of these decisions, it is essential that the DBS team consists of a pain specialist, a neurosurgeon and a neuropsychologist. The symptoms such as hyperalgesia, allodynia, and hyperpathia appear more important than the specific etiology of chronic pain in determining potential benefit.

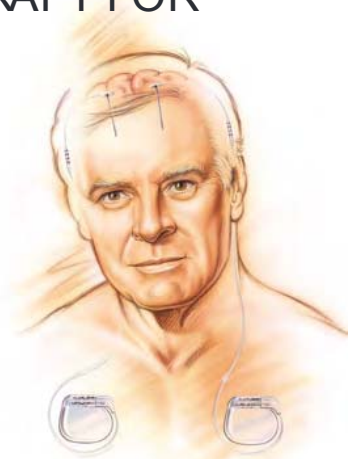

Figure 1: Bilateral DBS electrode, lead extender and IPG placement (Medtronic Inc., 2012)

DBS for chronic pain should only be considered once a patient has tried and failed, or at least reasonably considered, all other conventional therapies (NHS England Specialised Services Clinical Reference Group for Specialised Pain, n.d.). The NHS England lists involvement in ongoing litigation or compensation claims as an additional exclusion criteria based on data that shows that this situation negatively impacts response to pain treatments. They require these situations to be resolved before a patient proceeds with any neuromodulation therapy including DBS.

While the general selection process and procedure are similar whether DBS is being used to treat a movement disorder or a pain syndrome, the target of the stimulation field is unique. Leads are typically implanted into the periaqueductal gray (PAG)/periventricular gray (PVG) matter for nociceptive pain and the ventroposterolateral/ventroposteromedial (VPL/VPM) sensory thalamus for neuropathic pain (Levy, Deer, & Henderson, 2010). The PAG is located in the midbrain and is the primary control center for descending modulation of pain causing release of endogenous opioid neurotransmitters that signal to the spinal cord and dampen incoming pain messages. The PVG matter is located in the thalamus and upper midbrain. The VPL and VPM are relay nuclei in the thalamus that are a part of the somatosensory system and work through non-opioid mechanisms offering relief in central pain (Rasche et al., 2006; Pereira et al., 2013; Boccard et al., 2015). As many people have combined pain syndromes with both neuropathic and nociceptive components, surgeons will often implant both the PAG/PVG and sensory thalamus simultaneously (Levy et al., 2010). The anterior cingulate cortex is a newer target that targets the affective component of pain and targets hemi- or whole-body post-stroke pain (Periera et al., 2013; Boccard et al., 2014; Boccard et al., 2015) (Figure 2; Table 1). More recently, the Cleveland Clinic completed a prospective, randomized, double-blind, controlled trial of DBS for thalamic pain syndrome targeting the ventral striatum/anterior limb of the internal capsule, a new target which impacts the emotional and affective components of pain. They are currently looking for funding to expand this into a larger, long-term, multicenter study (Machado, 2015) (Table 2).

Different from the procedure for DBS in movement disorders, many programs will leave the leads externalized for at least a week after the initial implantation to determine efficacy. If the patient obtains adequate pain relief, the leads are then permanently implanted and the DBS is programmed to optimized settings (Pereira et al., 2013).

Risks and Complications

As previously reviewed by Zhang et al., (2012), while DBS is supposed to be minimally invasive and non-ablative, it is associated with several concerning complications, some of which are irreversible. Rates of complications are quite variable from site to site (Bronstein et al., 2011). Patient selection, surgical methods and surgical team experience are critical components in minimizing these risks (Hariz, 2002).

Accurate stereotactic radiological studies and intraoperative physiologic corroboration of the target site (s) are critical pieces that help limit the number of necessary exploratory tracks and limit surgical time, thus, reducing hemorrhage and device-related infection risk (Hariz, 2002). Symptomatic hemorrhage risk is 1.5-3% per lead implant. The risk of a hemorrhage resulting in permanent morbidity is 0.5-1.0% per lead (Marks, 2011). Serious infection related to the device insertion is approximately 10% per device (Weaver et al. 2009). Transient headache occurred in over 50% of cases but most of these resolve by the time of discharge. PAV/PVG stimulation can cause transient side effects including diplopia (14.2%), nausea (10.6%), vertical gaze palsies (9.9%), blurred vision (9.2%), horizontal nystagmus (4.3%), and persistent oscillopsia (3.5%) (Levy et al., 2010). Device-related complications including infection, skin erosion (1-2.5%), electrode migration (019%), electrode fracture (0-15%) and hardware failure may occur at any time following the device insertion (Hariz, 2002; Bronstein et al., 2011).

Finally, even when DBS is truly efficacious, tolerance may manifest after several years. Adjustments in stimulation settings or periodic interruption of stimulation can be effective means of addressing this issue. Newer advances in technology, such as so-called smart adaptive stimulation, may further assist patients in better controlling their pain

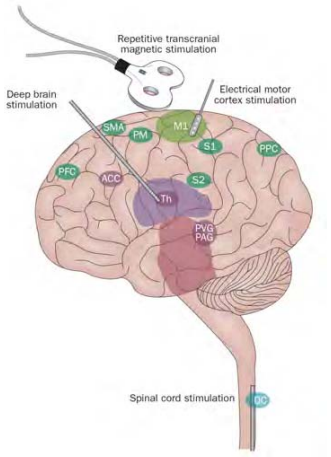

Figure 2: There are several neurosurgical stimulation therapies available to treat intractable pain. This image shows the various targets. In particular, DBS targets the sensory thalamus (Th) (VPL/VPM), periventricular grey matter (PVG), periaqueductal grey matter (PAG), and the anterior cingulate cortex (ACC). Reprinted by permission from Macmillan Publishers Ltd: Hosomi, K, Seymour, B, & Saitoh, Y. (2015, April). Modulating the pain network—neurostimulation for central poststroke pain. Nature Reviews Neurology, 11, 290–299. Published online 21 April 2015; doi:10.1038/nrneurol.2015.58.

and reducing tolerance to stimulation (Boccard et al., 2015; Pereira et al., 2013). Another challenge is that improvement in one type of pain may unmask other bothersome types or regions of pain to which the individual was not previously focused, such as treatment of burning hyperesthesia may unmask muscular allodynia (Periera et al., 2013).

Access Challenges

Using neurostimulation to target intractable pain first appeared in the 1950s (Boccard et al, 2015; Heath, 1954; Pool, 1954). By the mid-1970s, DBS for pain was determined to be safe and effective. However, due to legislative changes, the FDA shortly thereafter requested the 3 existing manufacturers to conduct comprehensive safety and efficacy trials on DBS and chronic pain. Only one company complied with this request and its studies showed only limited efficacy. As a result, the FDA rescinded the approval for DBS and pain and it is still considered an "off label" use, limiting reimbursement by insurers and its availability (Boccard et al., 2015; Pereira et al., 2013; Levy et al., 2010).

Currently, only a small handful of academic hospitals in the U.S. offer DBS as an off-label therapy for chronic pain. While most U.S. payers consider this use experimental and investigational, some do have a provision for covering it in specific cases (Health Net, 2015). Coding and reimbursement data for DBS and chronic pain is not easily found but the cost is likely similar to DBS for movement disorders. The National Parkinson Foundation estimates a DBS surgery to cost between $35,000-$50,000 per side (Okun & Zeilman, n.d.). Without third party coverage, this procedure becomes cost prohibitive for most.

While DBS for pain is not readily available in the U.S., the European Federation of Neurological Societies and the United Kingdom National Institute for Health and Clinical Excellence (NICE) have previously approved DBS for refractory chronic pain syndromes (Boccard et al., 2015; NICE, 2011). A preliminary draft of the 2015 NHS England commissioning report for DBS and chronic pain initially recommended continued commissioning of DBS for chronic pain at specified centers (n.d.). Unfortunately, based on the lack of additional economic data since the 2011 NICE publication, the NHS England ultimately declined routine commissioning of this procedure for chronic pain (2015, July).

Table 1: Types of pain. (IASP, 2014, October 6; Boccard et al., 2015; Pereira et al., 2013)

Types of Pain	Description	Surgical Target
Nociceptive Pain	Pain that occurs due to actual damage to the non-neural tissue. The somatosensory nervous system is functioning normally	PAG/ PVG
Neuropathic Pain	Pain that occurs due to actual nerve damage. There may be a lesion or disease of the somatosensory nervous system	VPL/ VPM
Affective Component of pain	This addresses the individual's perception of pain rather than the sensory components.	ACC

Efficacy

It is difficult to conduct a comparative analysis of DBS verses other treatments in treating chronic pain because of the highly varied pathologies. Rasche et al. (2006) found that most of the published reports on DBS and chronic pain were level V, historic case-control studies. Few studies used an independent examiner for evaluation of results and there were no standardized patient selection or evaluation criteria in the published studies. Blinded stimulation had not been done and a pharmaceutical dose-response relationship had not been examined. Rasche et al. (2006) thus performed a double-blind study on 56 patients with various neuropathic and mixed nociceptive/neuropathy pain syndromes where they implanted DBS leads into the somatosensory thalamus or the PVG or a combination of both regions. The best long-term results were attained in patients with chronic low-back and leg pain, for example, FBSS. Patients with neuropathic pain of peripheral origin (such as complex regional pain syndrome (CRPS) Type II) also responded well to DBS. Disappointing results were documented in patients with central pain syndromes, such as pain due to spinal cord injury and post-stroke pain. In general, combined stimulation of PVG and VPL was superior to single-lead stimulation.

Recent publications suggest that DBS can be effective for phantom limb pain, brachial plexus injury, central post-stroke pain, reflex sympathetic dystrophy, complex regional pain syndrome, face pain, spinal injuries, failed back surgery syndrome, occipital neuralgia and cluster headaches and migraines (Boccard et al., 2015). Fontaine et al. (2009) did not find that DBS improved chronic cluster headache compared to sham stimulation but they question that their study design may have impacted their findings and recommended further evaluation (Table 2). Targeting the sensory pathways seems to be less effective in treating thalamic pain syndromes and paraplegia pain, leading researchers to consider affective targets (Machado, 2015; Levy et al., 2010; Rasche et al., 2006).

In a recent review, Boccard et al. (2015) discussed the limitation of several of the larger publis hed studies on DBS and pain. Lack of randomization and case controls, poor enrollment and loss to follow-up, and heterogeneity in DBS efficacy possibly due to variance in study designs and pain etiologies resulted in significant limitations in this

data. In addition, there are few studies that compared neurosurgical options for treating refractory pain syndromes, leaving questions as to the comparative effectiveness of these options. There are currently two clinical studies listed on www.clinicaltrials.gov addressing DBS and pain that are actively recruiting (Table 2).

Conclusion

In conclusion, DBS for pain has been shown to be effective in several patient series. However, additional clinical trials are required to more robustly demonstrate the efficacy of DBS to treat intractable chronic pain and regain FDA approval. The NHS England recommends additional trials to 1) confirm the outcome findings that currently are only published via cohort studies and case-series; 2) to address concerns about tolerance and attrition rate in the long-term studies; and 3) to identify predictors of long-term efficacy (NHS England Specialised Services Clinical Reference Group for Specialised Pain, n.d.). In order for third-party payers to fund this procedure, further research is necessary to prove the cost benefit. While the subset of patients who would ultimately qualify for this procedure is relatively small, the impact of their chronic pain on their quality of life, healthcare costs, and society is significant and mandates further exploration of neuromodulation, in particular DBS, as a therapeutic option. results?term=deep+brain+stimulation+pain&pg=1.

Table 2: Current studies on DBS and chronic pain (U.S. National Institutes of Health (n.d.)

Study Title	Status	Start Date	Completion Date	Study Design	Sponsors & Collaborators
Treatment of Pain and Autonomic Dysrexia in Spinal Cord Injury With Deep Brain Stimulation ClinicalTrials.gov Identifier: NCT02006433	Recruiting	December 2013	December 2015	Phase 1 Allocation: Non-Randomized Endpoint Classification: Safety/Efficacy Study Intervention Model: Single Group Assignment Masking: Open Label Primary Purpose: Treatment	Sponsor: Jonathan R Jagid, M.D., University of Miami Collaborator: United States Department of Defense
Towards Individualized Deep Brain Stimulation Treatment of Chronic Neuropathic Pain (DBSforPain) ClinicalTrials.gov Identifier: NCT01899170	Recruiting	April 2014	August 2022	Phase 2 Allocation: Randomized Endpoint Classification: Safety/Efficacy Study Intervention Model: Parallel Assignment Masking: Double Blind (Subject, Investigator, Outcomes Assessor) Primary Purpose: Treatment	Sponsor: University of Aarhus, Denmark Collaborators: Stanford University California Pacific Medical Center Research Institute
Safety Study of Deep Brain Stimulation to Manage Thalamic Pain Syndrome (DBS) ClinicalTrials.gov Identifier: NCT01072656	Active, Not recruiting	May 2010	August 2014	Phase 1 Allocation: Randomized Endpoint Classification: Safety/Efficacy Study Intervention Model: Crossover Assignment Masking: Double Blind (Subject, Caregiver, Investigator) Primary Purpose: Treatment	Sponsor: The Cleveland Clinic Collaborator: National Institutes of Health (NIH)
Evaluation of Efficacity and Safety of Deep Brain Stimulation (DBS) in Chronic and Treatment-Resistant Cluster Headache(CH) ClinicalTrials.gov Identifier: NCT00662935	Completed	May 2005	March 2008	Allocation: Randomized Endpoint Classification: Safety/Efficacy Study Intervention Model: Crossover Assignment Masking: Double-Blind Primary Purpose: Treatment	Sponsor: Centre Hospitalier Universitaire de Nice Collaborator: Medtronic

LAURA SPERRY, MSN, ANP-C

is the Clinical Coordinator for the Deep Brain Stimulation (DBS) Program at the University of California, Davis Medical Center in Sacramento, CA. She collaborates with the other regional DBS programs in facilitating a post-DBS support group for patients with Parkinson's disease. Ms. Sperry is nationally certified as an Adult Nurse Practitioner with the American Nurses Credentialing Center. She has co-authored several journal articles on DBS and has lectured at an international nursing conference. She can be contacted at lmsperry@ucdavis.edu.

LIN ZHANG, MD, PhD

is an Associate Professor in the Departments of Neurology and Neurological Surgery and the co-Director for the Deep Brain Stimulation Program at the University of California, Davis Medical Center in Sacramento, CA. Dr. Zhang's clinical and research interests focus primarily on Parkinson's disease, including its epidemiology and the association between past nutritional deficiency and current prevalence of the disease. He is testing new drugs with neuroprotective properties that may slow down the progression of Parkinson's. He also is investigating the clinical manifestation of the disease in patients with atypical Parkinson's disease, and those with a family history of permutation for Fragile X Syndrome, a genetic disorder that typically affects children. He can be reached at mdzhang@ucdavis.edu.

KIARASH SHAHLAIE, MD, PhD

is Associate Professor in Neurological Surgery and Neurology and Co-Director of the Deep Brain Stimulation Program at the University of California, Davis Medical Center, Sacramento, CA. Dr. Shahlaie's philosophy of care is minimizing surgery risk and facilitating rapid recovery with minimally invasive surgical techniques; providing innovative surgical treatment options for Parkinson's disease, essential tremor, dystonia, and other movement disorders, and certain psychiatric and pain conditions; and closely involving the families and caretakers of patients with severe traumatic brain injury during acute and chronic stages of recovery. He is the Bronte Endowed Chair of Research and conducts ongoing laboratory and clinical trials of neuromodulation and neurorestoration therapies. He can be reached at krshahlaie@ucdavis.edu.

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