NEUROMODULATION: TECHNOLOGY AT THE NEURAL INTERFACE

Volume 12 • Number 2 • 2009
http://www.blackwell-synergy.com/loi/ner

MEDICAL COMMENTARY

Implementing the SAFE Principles for the Development of Pain Medicine Therapeutic Algorithms That Include Neuromodulation Techniques

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ABSTRACT

Currently accepted chronic pain treatment algorithms have positioned therapies according to levels of invasiveness and up-front costs. After reviewing updated literature on efficacy and cost outcomes of care for patients with chronic pain that include interventional implantable technologies, we offer a new model of thinking when formulating algorithms of care that might include more invasive and costly interventions such as spinal cord stimulation, the SAFE principles. These SAFE principles include "safety," "appropriateness," "fiscal neutrality," and "efficacy."

KEY WORDS: *Algorithm, appropriateness, chronic pain, efficacy, fiscal neutrality, neuromodulation, principles, spinal cord stimulation, safety, spinal cord stimulation.*

Introduction

The traditional role of the physician is to heal patients. To accomplish this goal, the physician synthesizes his or her knowledge base derived from education, experience, and extrapolation of the medical and scientific literature into an appropriate treatment plan. In this traditional model, accepted medical treatment is based on safety of the intervention, appropriateness to the diagnosis and individual patient, and effectiveness. In today's world of rapidly growing therapeutic options and increasing medical cost, the role of the physician has expanded to encompass consideration of cost-utility in an attempt to maximize the benefit for their patients in an environment of limited healthcare resources.

In government-sponsored healthcare systems, government agencies dictate the allocation of care based on known efficacy data/safety, cost, and available resources. In the United States, health care for the insured patient is also limited by cost. Hospitals routinely deny certain therapies and technologies because of inadequate reimbursement, and third-party payers, including private and public payers; for example, the Centers for Medicare and Medicaid Services use cost to dictate the spectrum of medical coverage.

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Since 1960, third-party payment for health care has increased dramatically. The share paid directly "out of pocket" by consumers fell from 49% in 1960 to 21% in 1988 (1). At the same time, healthcare costs have escalated and are forecasted to reach 20% of the U.S. gross domestic product by 2015 (2–4). While the determinates of increased medical cost are multifaceted, many health economists point to the development and diffusion of medical technology as the primary factor for rising healthcare cost. In a report issued by the Centers for Medicare and Medicaid Services, an expert panel estimated that new medical technology may account for more than half of long-term spending growth of heath care by providing new treatments for previously untreatable or poorly treated conditions (5). Similarly, DiMatteo, in 2005, evaluated the determinants of healthcare cost in both the United States and Canada over a 20-year period and found that, in both government-sponsored and free market healthcare systems, technological change accounted for approximately two-thirds of healthcare expenditure increases whereas the aging population accounted for only 10% of the increase (6). These findings along with the fact that, in the United States, the medical care for people with chronic disease accounts for more than 75% of the nation's $2 trillion medical care costs, will certainly cause payers to have concern about the financial implications of emerging technologies for the treatment of chronic pain (7). While justification for implementing these technologies will certainly depend on the evaluation of various outcome measures that include years of potential life lost (8), quality-adjusted life years (9), and disability-adjusted life years (10), the evaluation of these outcomes variables is not the scope of this paper. Instead, this paper will propose a set of principles that should be considered when developing treatment algorithms for chronic pain management, taking into account the socioeconomic constraints on health care. We contend that implementation of a broad set of principles for evaluation of therapies allows for balancing of competing interest in an environment of limited resources. In this paper, neuromodulation technologies such as spinal cord stimulation (SCS) will be used as an example of a new technology that can be appropriately positioned in a continuum of care available for management of chronic pain using the principles outlined below.

An early chronic pain treatment algorithm offered by one of these authors (Krames) had proposed that neuromodulation therapies, such as SCS, peripheral nerve stimulation, and intrathecal drug delivery systems (IDDS), be final options after all other therapies had been exhausted (11). Because of the multiple treatment options for chronic pain, it was proposed that therapies should be used in an algorithmic and logical approach in order of their level of invasiveness and up-front cost with design simplicity being a key goal (see Fig. 1) (11). In this algorithm, based on the "KISS" principle ("keep it sweet and simple"), for the treatment

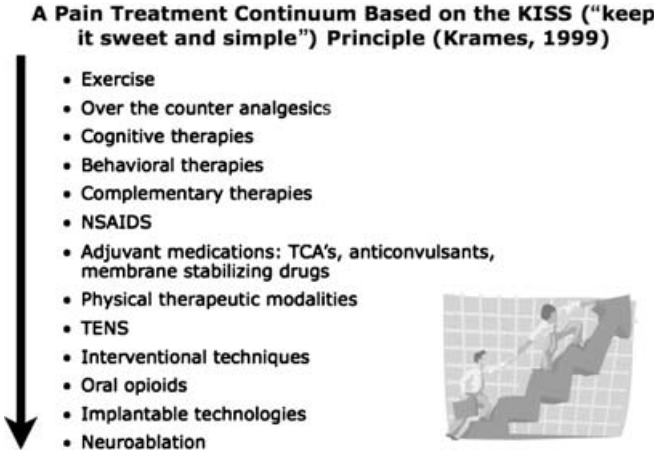

FIGURE 1. In this algorithm, based on the KISS principle ("Keep It Sweet and Simple"), it was proposed that therapies proven to be efficacious with less propensity to do harm and less costly be used before therapies proven to be efficacious with greater propensities to do harm and more costly. As each therapy tried failed to provide efficacy for any one patient, that therapy would be, as the algorithm suggested, discarded for a more invasive and more costly therapy (11).

of pain, it was proposed that therapies, proven to be efficacious with less propensity to do harm and less costly, be used before therapies proven to be efficacious with greater propensities to do harm and more costly. If a given therapy failed to provide efficacy for any one patient, that therapy would be discarded for a more invasive and more costly therapy. As such, SCS or IDDS, invasive therapies with large up-front costs, using this form of algorithmic thinking, would be relegated to "last resort" therapy.

While this approach may have been appropriate during the early development and introduction of a given neuromodulation technology such as SCS and the early development of algorithms of care for patients in pain, it may not be, today, in the best interest of the patient or even a third-party payer to wait until all other possible treatment options have failed before initiating neuromodulation therapies. SCS may be more costly up front than less costly therapies, such as initiating oral opioid therapy, but if equally or more effective than oral opioid maintenance and less costly over time, it may actually be best to offer this therapy earlier in a treatment algorithm rather than later.

It is in the this context and certainly others like it, such as the practice of performing numerous procedures without long-term benefit where long-standing practice styles may be challenged in favor of appropriately positioned neuromodulation therapies. For example, North et al. showed, in a randomized, controlled study (RCT), that those patients with persistent neuropathic leg pain treated with SCS after appropriate neural decompression did better when comparing efficacy outcome and cost than those treated with repeat surgery (12). These authors analyzed the cost-effectiveness and cost-utility of treating failed back surgery

syndrome (FBSS) using SCS vs. reoperation. They analyzed the patient-charge data with respect to intention to treat (costs and outcomes as a randomized group), treated as intended (costs as randomized; crossover failure assigned to a randomized group), and final treatment costs and outcomes. These authors found that by their mean 3.1-year follow-up, 13 of 21 patients (62%) reoperated upon crossed to SCS vs. 5 of 19 patients (26%) with SCS who crossed to reoperation ($p < 0.025$). The mean cost per success was $117,901 for crossovers to SCS. No crossovers to reoperation achieved success despite a mean per-patient expenditure of $260,584. The mean per-patient costs were $31,530 for SCS vs. $38,160 for reoperation (intention to treat), $48,357 for SCS vs. $105,928 for reoperation (treated as intended), and $34,371 for SCS vs. $36,341 for reoperation (final treatment). The authors concluded that "SCS was less expensive and more effective than reoperation in selected FBSS patients, and should be the initial therapy of choice and that when SCS failed, reoperation was unlikely to succeed."

While many neuromodulation therapies may initially be more expensive than some more conventional therapies, such as physical therapy and medication management, they can be more cost-effective over time (13,14). For example, Taylor et al., in 2005, developed a decision-analytic model to assess the cost-effectiveness of SCS relative to nonsurgical conventional medical management (CMM) for patients with FBSS (15). Outcome data of SCS and CMM were extracted from 2-year follow-up data of two RCTs. Treatment effects were measured as levels of pain relief. Short- (2 years) and long-term (lifetime) healthcare costs were obtained from a detailed Canadian costing study in FBSS patients. Results were presented as incremental cost per quality-adjusted life year and expressed in 2003 euros. These authors found that when compared to CMM, SCS was more costly before two years but, over the lifetime of the patient, SCS was cost-saving and resulted in more health gain relative to CMM. Kemler and Furnee, in Holland, studied the costs over time of SCS vs. physical therapy in a group of patients with complex regional pain syndrome (CRPS) (16). The per-patient cost of treatment for CRPS in the first year after implantation was $4000 higher for SCS than for physical therapy; however, in the lifetime analyses, SCS was $60,000 less expensive per patient than the control therapy. In addition, at 1-year follow-up, pain relief ($p < 0.001$) and health-related QOL ($p = 0.004$) were both significantly better for the SCS patients. A British RCT of patients treated for CRPS I by Taylor et al. found a lifetime cost saving of approximately $60,800 for the SCS group when compared to the physical therapy group (17). It is the superior effectiveness and long-term cost-effectiveness of SCS in these studies that challenges the notion that neuromodulation techniques should be at the end of a treatment algorithm (11).

Medical Algorithms

Unlike a mathematical algorithm that is a well-defined series of instructions for completing a task designed to solve a problem and lead to a specific endpoint, a medical algorithm that guides the treatment of persistent pain must have the flexibility to accommodate the medical needs, goals, and circumstances of an individual patient and treating physician while simultaneously accommodating the cost–benefit constraints of the medical system in which the patient and the physician both exist. As such, an algorithm for the treatment of pain may need to contain parallel pathways to accommodate these various circumstances and goals while still providing rational guidance to the clinician. At times these parallel pathways may have divergent endpoints. Thus, a valuable algorithm will help the clinician balance these divergent goals. For example, a patient with cancer pain who has significant side-effects from high dose systemic opioid medications to the point of significantly interfering with his or her activities of daily living may be able to achieve the goal of improved analgesia with less side-effects through the implantation of an IDDS. However, a third-party payer may not deem such an intervention cost-effective if a patient has a short life expectancy. Likewise, if young patient has a long life expectancy, a physician may decide not to use an IDDS, even if the patient had failed all prior analgesic therapies and this was the only option left for the patient because of the unacceptable risk of long-term neurotoxicity. The need for balance between invasive treatments that might be more effective than less invasive treatments is at the heart of why rational algorithms are needed to help clinicians, patients, and payers appropriately position neuromodulation techniques within a treatment plan for pain management. While a published algorithm is by nature static, the underlining principles of a given algorithm can be adapted to the individual medical and socioeconomic circumstances of a specific patient and practitioner.

Barriers to Neuromodulation Therapy

While neuromodulation therapies are familiar to most pain physicians and neurosurgeons, the majority of patients with persistent pain are seen and treated by providers who may not be aware of neuromodulation technology as a treatment option. Thus, implementation of a successful algorithm to treat patients with persistent pain with neuromodulation therapies such as SCS will certainly require widespread patient, physician, and third-party payer education. Once familiarity with the technology is achieved, the attitudes of patients, physicians, and third-party payers regarding neuromodulation will also certainly need to be addressed. Specifically, physicians and patients will need to be convinced that an algorithm encompassing neuromodulation will lead to the desired outcome of reduced

pain and improved quality of life and third-party payers will need to be convinced that there is a cost advantage over time of neuromodulation when compared to less up-front costly therapies before implementing such an algorithm.

To improve the probability of successful implementation, an algorithm also must not significantly interfere with the habits and routines of a physician's practice. If the algorithm is viewed as too rigid or difficult to apply, it most likely will not be implemented. For neuromodulation, this may be manifested as impediments to access to the technology by the treating physician or access to colleagues who are skilled at using neuromodulation technologies. While access should not be a barrier in most western urban settings, skilled practitioners may not always be available in rural settings and certainly not in developing countries.

Other barriers include hospital and physician resistance to implementing these therapies due to concern about adequate reimbursement and patient reluctance to implanted technology. Patient reluctance may be addressed by introducing smaller and more user-friendly devices and opportunities for prospective patients to interact with patients already implanted with neuromodulation devices. Certainly, the impact of mass media and direct marketing on patient acceptance cannot be underestimated as evidenced by the impact mass media has had on the usage of drugs aimed at treating erectile dysfunction (18). Physician and hospital reimbursement barriers are more difficult to address and certainly efforts to improve reimbursement may also adversely affect the cost utility of a given technology.

The SAFE Principles: Towards a Balanced Approach for Development of Algorithms Utilizing Neuromodulation Therapies

This manuscript proposes a set of principles that should be considered when developing treatment algorithms for patients with chronic pain that might or might not include invasive implantable technologies. These evaluative principles are more relevant today than the previous evaluative "KISS" principle to establish relevant and more appropriate algorithms of care for pain disorders. More is known today regarding therapies offered and used than 20 years previous. These principles can be more easily recalled by using the acronym SAFE (safety, appropriateness, fiscal neutrality, and effectiveness).

Principle of Safety

Persistent chronic pain is rarely life threatening and, thus, treatments for chronic pain should be held to a higher standard of safety than treatments for life-threatening illness, such as advanced cardiac life support. As with all invasive procedures, neuromodulation technologies are inherently associated with biological and surgical risks, including infection, bleeding, and injury to neural tissues. As such, the positioning of neuromodulation technologies in an algorithm to treat persistent chronic pain has traditionally come after trials of less invasive treatments such as medication management (11). While medications are certainly less invasive and may be safer for short-term management of patients with acute pain, their long-term use for chronic pain may be associated with greater biological risk than neuromodulation interventions. Chronic use of nonsteroidal anti-inflammatory drugs (NSAID) is an example of a conservative therapy that has increased risk of injury over time. Chronic use of NSAIDs for pain management is associated with a 17–31% incidence of gastric ulcer formation, leading to 16,500 deaths and more than 100,000 hospitalizations every year in the estimated 20 million patients taking chronic NSAIDs in the United States (19–21). In a 10-year period, this would give rise to a million hospitalizations for NSAID-induced gastritis. By comparison, the greatest biological risks of SCS for chronic pain occurs during the operative and postoperative periods with infection and seroma being the most common complications. In a 10-year retrospective study of 160 patients treated with SCS, Kumar et al. al reported a total of 7.5% biological adverse events with 4.4% incidence of infection and a 3.1% incidence of seroma, and no neural injury or death (22). While this sample size is smaller compared to those evaluating chronic NSAID use, these results nonetheless, in our estimation, support the hypothesis that the risk of injury from chronic usage of NSAIDs is greater than the risk of injury caused by long-term treatment with SCS. Similarly, patients treated with chronic opioids are at risk of a variety of adverse events including endocrinopathy (23–25) bowel obstruction (26), cognitive impairment (27–30), and respiratory depression (31). Thus, when comparing the relative safety of various treatments for chronic pain, it is essential to assess the risks of each comparator therapy over the same duration of time.

Principle of Appropriateness

> It is much more important to know what sort of a patient has a disease than what sort of a disease a patient has.
>
> —Sir William Osler (1849–1910)

This statement is as true today as it was when Sir William Osler made it over a century ago (32). Certainly, when determining if a given treatment is appropriate for inclusion in a medical algorithm to treat persistent pain, it is of equal importance to secure the diagnosis as well as confirm the absence of any pertinent medical or psychosocial contraindications. Everyone would agree that patients with peptic ulcer disease or those with renal failure should not be treated with NSAIDs or that chronic opioid therapies

should be avoided if possible in patients with underlying drug addictions. Likewise, systemic infections and coagulopathies are medical contraindications and that premorbid psychiatric illness such as schizophrenia or conversion disorders are psychiatric barriers to performing elective invasive procedures. Disregarding these contraindications increases the risk of injury to patients and may result in additional cost to treat these added complications.

Likewise, patients with significant psychosocial comorbidities such as active psychosis, unresolved psychoemotional traumas, certain personality disorders, unresolved pain related litigation, untreated severe mood disorders, and serious untreated drug addictions, to name a few, may all be at increased risk of treatment failure with implanted technology. Disregarding these psychosocial factors may also increase the risk of injury to patients and result in failure of therapeutic interventions and unnecessary cost. According to the National Institutes of Health, it is estimated that over $100 billion is spent on treatment for persistent pain, which exceeds the combined expenditure for heart disease, cancer, and AIDS (33,34). Thus, it is critical for the future viability of neuromodulation that appropriate measures be taken to ensure that only suitable patients be provided with these advanced technologies. When Shealy first described the use of SCS for the treatment of persistent pain, he recommended that appropriate patients be emotionally stable and have limited elevations in the Minnesota Multiphasic Personality Inventory depression scale (35). Since his initial report, numerous investigators have addressed the importance of appropriate psychosocial evaluations and the risk of failure of neuromodulation technology when psychosocial comorbidities are not effectively addressed. Long et al. reported that neuromodulation technology in patients that did not have appropriate psychosocial evaluation prior to treatment had a long-term success rate of only 33% (36). This percentage increased to 70% in patients that were subjected to psychosocial evaluations and screening. This finding was supported by a later more extensive review in 1993 by De La Porte et al. (37). In their review they found that, in studies where good psychosocial screening was implemented, the initial SCS success rates were 85% and long-term success rates were 60%. Whereas, in studies where there was no psychosocial screening, initial success rates were 50% and long-term success rates were only 35% (26). While subsequent studies have confirmed these findings, standardization of the psychological screening tools and consensus of what psychosocial factors are contraindications to neuromodulation treatment remain elusive.

In 1998, the European Federation of International Association for the Study of Pain Chapters published a consensus document on neuromodulation of pain that included psychosocial exclusion criteria for implanted technologies (38). These included major psychiatric disorders; poor compliance and/or insufficient understanding of the therapy; lack of appropriate social support; substance abuse; and drug-seeking behavior. A later international consensus report added active homicidal or suicidal behavior; hypochondriasis, and psychopathologic somatization to the list of psychosocial exclusion criteria for neuromodulation technology (39). Yet, identifying psychosocial contraindications for neuromodulation interventions is not the only reason for performing a psychosocial evaluation. In a recent prospective study, Heckler et al. revealed that a presurgical behavioral medicine evaluation stratifying patients offered neuromodulation devices for pain control into different risk groups successfully predicted the long-term trend in emotional, functional, and pain status 1 year after the initial evaluation (40). Thus, when developing treatment algorithms that include neuromodulation technologies, it is clear that evaluating the appropriateness of a given treatment for a patient requires a psychosocial evaluation in addition to a pathophysiological evaluation. In the process of performing a psychosocial evaluation, one might even find that a patient is a better candidate for neuromodulation than medication management as might be the case for a patient with a distant history of opioid addiction who wishes to avoid opioid medications.

Principle of Fiscal Neutrality

As mentioned above, healthcare costs have steadily increased over the last few decades and are expected to continue to rise (2,3). While the high cost of and demand for medical technology is only one of many reasons for this increase, many physicians and policy-makers point to unnecessary use of medical technology as a major contributor to the rising cost of health care (41,42). With shrinking resources and increased demand, health administrators struggle to allocate appropriate resources while maintaining fiscal responsibility. As a result, third-party payers and non–pain management physicians are reluctant to authorize or refer patients for neuromodulation technology as part of a treatment algorithm for persistent pain. Thus, appropriate positioning of neuromodulation technology within a treatment algorithm for persistent pain must take into account the financial implications of this treatment with fiscal neutrality[1] being the financial goal for implementation. In this context, fiscal neutrality implies that the cost of implementing a new therapy does not result in greater financial expenditure than a current or comparator therapy over a given time period.

In the realm of chronic pain management, both the initial cost and the long-term cost must be accounted for. For example, Bedder et al. first reported that implanting

[1]Fiscal (cost) neutrality in the context of medical algorithms is the cost of the therapy over time when compared to the cost of the comparator therapy over time. Neutral in this context means that the initial cost of the therapy is neutralized by the cost savings of the therapy when compared to the comparator over time.

an initially more expensive intrathecal pump for opioid delivery as compared to delivery with an external pump for cancer pain management was cost neutral at 3 months and resulted in a cost savings thereafter (43). Similarly, when compared with conventional medical management strategies for chronic pain, some authors found that implanted intrathecal opioid delivery was cost neutral at 22–28 months after implant, and generated a cost savings thereafter (44–47). Fiscal neutrality may even be achieved on day 1 of the implant when compared to other surgeries as observed by North et al. in their study of SCS vs. conventional repeat spine surgery (reoperation) for treatment of FBSS and the study of Andrell et al. on SCS vs. coronary artery bypass surgery for intractable angina (48,49). In fact, in the studies of North and of Andrell, implementing SCS was actually a cost savings as compared with repeat spine surgery or cardiovascular surgery. Taylor and Taylor estimated that when compared to conventional medication management, SCS was also more effective and less costly when treating FBSS over the lifetime of a patient (50). As previously stated, shorter time to fiscal neutrality was observed for treatment of CRPS by Kemler and Furnee (16). SCS was found to be fiscally neutral in as little as 2.5 years after implantation when compared to standard focused physical therapy treatment alone. In a literature review, Taylor et al. reported that the time to fiscal neutrality when using SCS was 1–3 years in a variety of pain conditions (51).

The time to fiscal neutrality is influenced not only by the initial cost of implanting neuromodulation technology but also by the long-term cost of the technology, including end-of-life battery replacement, mechanical and biological complications, lead migration, and lead and catheter fracture. In addition to the biologic risks associated with neuromodulation technologies discussed above, there are also "hardware" complications of implanted devices that include system failure and system breakdown.

When occurring, these hardware complications add to the cost of the therapy and must be accounted for when evaluating the fiscal implications of implementing a given therapy. In a literature review of SCS, Cameron found a 13.2% incidence of lead migration and a 9.1% incidence of lead breakage following analysis of 2,972 patients from 51 papers (52) and in an analysis of 289 patients with SCS systems, Rosenow et al. found a 32% failure rate when using percutaneous-type leads placed in the thoracic spine and attached to a pulse generator placed in the gluteal region for the treatment of lower extremity pain (53). Turner et al., in a systematic review of the SCS literature for FBSS and CRPS, found 22 articles out of 583 that addressed complication rates (54). They found a mean of 10.2% of patients had some type of equipment failure, with 23.1% of patients undergoing revision of the stimulator for reasons other than battery change and 11.0% of patients undergoing removal of the stimulator for any reason.

Reducing these complications and thus the long-term cost associated with implementation of neuromodulation technology by improving surgical techniques, improving electrode design and programmability, all help to further reduce the time to fiscal neutrality (55–58).

Using rechargeable batteries to reduce costs over time actually may increase the time to fiscal neutrality because of their up-front increased costs, but over time, this advance in technology decreases the costs of SCS systems significantly. Hornberger et al. using a generalized state-transition probability framework to model costs found that a rechargeable SCS system is projected to require from 2.6 to 4.2 fewer battery generator replacements for battery depletion when compared to a nonrechargeable SCS system. The total lifetime savings of a rechargeable system ranged from $104,000 to $168,833. In all of the one-way sensitivity analyses conducted, a rechargeable system saved money. The authors concluded that a rechargeable SCS system is projected to save up to $100,000 over a patient's lifetime (59).

Principle of Effectiveness

> Efficiency is doing things right; effectiveness is doing the right things.
>
> Peter Drucker (1909–2005) (60)

Certainly "doing the right thing" is what clinicians hope to achieve for their patients; guiding their actions are training, experience, colleagues, and the medical literature. Alone, the medical literature is insufficient to guide clinical judgment, yet it is certainly essential when developing medical treatment algorithms of care.

Many treatment algorithms for the medication management of persistent pain conditions are developed after compiling data from a number of randomized, double-blinded, placebo-controlled clinical trials (61–63). Because these algorithms are often derived from evidence generated by employing strict scientific rigor, they are often regarded as being the best examples of evidence-based medicine. While many of these studies certainly show clinical efficacy of a given treatment, some would argue that because they are often conducted in academic centers of excellence by the best-trained physicians in optimal conditions in highly selected patients, they may not adequately demonstrate the true effectiveness of the treatment in the general population where patient selection may not be as rigorous and physician training more variable (64). In other words, these RCTs, although scientifically rigorous, may not have face validity.

In addition, demonstration of clinical efficacy alone is not sufficient to mandate implementation of a given treatment into a clinical algorithm. Indeed, third-party payers and government agencies may require a broader base of evidence to support implementation of a given treatment. Clearly, this was the case when former Secretary of Health

and Human Services Patricia Roberts Harris declared in 1980 that new health technologies must be evaluated not only on the basis of their medical efficacy but also on their "social consequences" before any consideration could be given to federal reimbursement for the new device or procedure (65,66). As such, implementation of a given therapy for pain should be judged by more than just a change in pain scores. The recent Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) recommends a core set of outcome measurements that include measurement not only of pain levels, but also change in functional status, frequency and severity of side-effects and adverse events, patient evaluation of global improvement, and overall patient satisfaction with the treatment (67). These added measurements provide a means to appropriately compare two treatments with equal efficacy in terms of pain reporting but with significantly different levels of side-effects (e.g., medication induced sedation, nausea, and constipation vs. minimal side-effects from SCS).

In addition to clearly establishing the appropriate outcome measures to be used when comparing various therapies, it is also critical to determine the appropriate level of evidence for comparing neuromodulation therapies with other treatment options. Typically, studies aimed at comparing different medication therapies are performed by utilizing RCTs. However, in clinical trials of neuromodulation, placebo-controlled, double-blind studies of implanted technologies are nearly, but not totally, impossible to conduct for both technical and ethical reasons (68). Certainly, the risks of surgical intervention are too great to justify sham surgeries for clinical design and this position is supported by the 2000 revision of the Declaration of Helsinki, which reinforces the prohibition against offering placebo instead of effective therapy (69). Blinding can also be difficult in clinical trials of neurostimulator devices as many of these devices, but not all, can and are sensed by the patient when turned on and likewise, sensed when turned off (70). In addition, limited number of cases per given institution make conducting trials on a large number of patients difficult. Furthermore, in the general medical community, training and expertise in neuromodulation implant techniques may be more variable than other type of surgeries as many implanters acquire their implant skills after their residency training.

Despite these caveats, there is still ample evidence to demonstrate the effectiveness of neuromodulation technology for the management of persistent pain, and implementation of this evidence certainly meets the definition of evidence-based medicine. According to the Center for Evidence Based Medicine, 'evidence-based medicine is the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients. The practice of evidence-based medicine means integrating individual clinical expertise with the best available external clinical evidence from systematic research" (71).

The Evidence Base for Neuromodulation

There are a number of RCTs that demonstrate greater effectiveness of implanted neuromodulation technology over conventional therapy for the treatment of persistent pain. The effectiveness of intrathecal medications delivered via an implanted intrathecal pump as compared to CMM was investigated by Smith et al. in a group of 200 cancer patients in a well-designed RCT (72). The study was designed to randomly assign patients to one of two treatment groups. The result of their studies revealed that patients treated with intrathecal therapy had better pain control with significantly fewer medication-induced toxic side-effects when compared to those randomized to CMM, and a totally unexpected outcome of this RCT was that the group randomized to intrathecal therapy had longer time to death than the group that was randomized to CMM. For patients with chronic noncancer pain, an RCT comparing intrathecal drug delivery to conventional pain therapy revealed that patients treated with an implanted intrathecal pump had greater pain control with less disability over a 3-year period (73).

Investigations of SCS were similar to those investigating intrathecal therapies. The effectiveness of SCS when compared to reoperation for persistent lumbar radicular pain after lumbosacral spine surgery was investigated by North et al. in an RCT (74). The results of this study revealed that SCS was more effective than reoperation during a 3-year follow-up period. In a multicenter, randomized clinical trial of SCS vs. CMM, Kumar et al. found that SCS was also more effective than CMM at reducing pain, improving the quality of life of, and increasing functional capacity in patients with persistent lumbar radicular pain after surgery (14). These are just a few examples of studies demonstrating superior effectiveness of neuromodulation therapy when compared to CMM. Certainly, more studies are needed to further advance the use of neuromodulation therapy.

Use of the SAFE Principles in Choosing Therapies for an Individual Patient

Positioning of neuromodulation technology within a treatment algorithm for persistent pain has traditionally been relegated to the end of an exhaustive list of more conventional therapies (11). This can sometimes lead to years or decades of poor pain control, prolonged medication toxicity, prolonged disability, excessive costs, countless interventional procedures, and increased risk of central nervous system reorganization before neuromodulation technology is offered. We propose that the SAFE principles be the foundation on which to build algorithms for the treatment of persistent pain with neuromodulation implantable technologies having an equal footing for evaluation as other therapies when developing these algorithms. Although the start-up costs for neuromodulation

therapies are high when compared to less invasive therapies, the total costs for care over time may be less with these neuromodulation therapies than their less costly (up-front) comparators. By subjecting all therapies to a comprehensive evaluation of the individual SAFE principles, we believe that neuromodulation will be appropriately positioned in the continuum of care and not arbitrarily relegated to the end of the treatment continuum.

As is the case today, at the onset of severe disabling pain, treatment is focused on aggressive use of all available conventional therapies. However, when left unabated, persistent severe pain can lead to peripheral and central sensitization, making pain management even more difficult to manage and treat while extending the duration of disability and increasing the cost of care. We suggest that neuromodulation technology be at least considered when conventional therapies no longer meet one or more of the SAFE principles. We believe using this approach will help to more appropriately position neuromodulation therapies within a continuum of care for specific pain disorders. In future articles, using these SAFE principles, we will present algorithms of care regarding the use of SCS for chronic FBSS and CRPS.

While we believe that the use of the SAFE principles will help in the development of treatment algorithms that include neuromodulation therapies, we recognize that the true value of a clinical treatment algorithm is judged, not by its design, but rather by its implementation. The barriers that impede implementation of medical algorithms have been reviewed by Cabana et al. (75), who performed a literature review of why physicians do not implement clinical guidelines. They identified three major obstacles to implementation: physician knowledge, attitudes, and behaviors. Lack of awareness and familiarity were the primary knowledge barriers to implementation, while lack of agreement, self-efficacy, outcome expectancy, and motivation were the primary attitude obstacles. Behavioral barriers included external environmental factors such as patient preferences, lack of time, lack of resources, lack of reimbursement, and perceived increase in malpractice liability. The McDonnell Norms Group expanded on this analysis and concluded that the general failure of clinical guideline implementation might also rest in more basic psychosocial motivators of human behavior, including fashion, convenience, functional simplicity, widespread acceptance, marketing, and public demand (76). Certainly, these factors must also be addressed when developing algorithms for specific disease processes.

Conflict of Interest

The authors, Drs Krames, Poree, Deer, and Levy, acknowledge that they have received no editorial or financial support for the writing of this manuscript.

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