Response to NICE Appraisal Consultation Document on Spinal Cord Stimulation for Chronic Pain of Neuropathic or Ischaemic Origin.

[redacted]
University Hospital of Wales
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Introduction

I am a member of the Clinical Advisory Group, representing the Society of British Neurological Surgeons and endorsed by the Welsh Assembly Government.

Spinal cord stimulation (SCS) was introduced in 1967 and I have been actively involved in its use since 1980 – 28 years – in London and Cardiff. As a consultant neurosurgeon since 1988 I have implanted spinal cord stimulators in 328 patients. Over the last 5 years I have implanted an average of 25 new units per annum, including in that period 45 (36%) for "Failed Back Surgery Syndrome" (FBSS); 41 (33%) for Complex Regional Pain Syndrome (CRPS), 31 (25%) for other neuropathic pain syndromes and a smaller number for ischaemic conditions. Some patients continue to enjoy effective stimulation for neuropathic syndromes after more than 15 years.

My publications on SCS (selected references appended chronologically, 1-23; other references are listed in the order in which they appear) include an early case series[(2)], and the first comprehensive literature review[(4)], both of which contributed to the recognition that SCS is effective in neuropathic and ischaemic pain but not in nociceptive pain. At the invitation of Prof. Patrick Wall I wrote the chapter on neurostimulation for the 4th edition of Wall and Melzack's Textbook of Pain[(8)] and co-wrote the chapter in the 5th edition[(14)]. It was his suggestion that I edited a book on neurostimulation for pain[(9)] and I have also co-edited a further, 2 volume, textbook on neurostimulation/ neuromodulation[(18,19)].

I was a member of the panel which published the UK guidelines for SCS in 2005[(24)], a member of the recent European Federation of Neurological Societies Task Force on neurostimulation for pain[(8)] and am European representative on the neuromodulation committee of the World Federation of Neurosurgical Societies. I was president of the International Neuromodulation Society (INS) 2000 – 2003.

I would not have persisted with these clinical and academic endeavours over a long period if SCS was not effective in a variety of chronic, intensely painful and disabling conditions. Various reviews of my case series have revealed very significant, often dramatic, benefit in approximately 60% of patients with a range of otherwise intractable neuropathic syndromes and a moderate but worthwhile benefit in a further 20%. In my experience more than 80% of patients with CRPS gain considerable benefit from SCS. Outcomes are improving with technological advances in the equipment.

Contextural comments

1) A very large body of RCT evidence indicates that drug therapy gives effective relief for less than 50% of patients with neuropathic pain.[25]

2) SCS is a long-term treatment for long-term conditions and therefore not appropriately assessed in the same way as acute treatments for short-term conditions (e.g postoperative analgesia).

3) The impossibility of blinding (evoked paraesthesia are essential), surgical considerations and the long time-course militate against acquisition of the highest level evidence in this field. Thus the paucity of RCTs contrasts with the position in, say, acute drug trials, which are comparatively straightforward. There is, however, a large body of lower level positive evidence as acknowledged by the EFNS Task Force[22].

4) Patients treated with SCS have generally failed to respond to all other treatment, physical, pharmacological, psychological and invasive, often over long periods.

5) These patients have, obviously, not recovered spontaneously, also over a long period of time.

6) Lower level evidence (e.g uncontrolled case series) is strengthened by, and should be given greater recognition for, the length of history prior to SCS combined with the duration of the response which are both typically measured in years, sometimes more than 20 years. This effectively eliminates placebo responses. The number and range of previous, ineffective, therapies are also relevant to this point.

7) A majority of patients not only return for pulse generator replacement and because of other equipment failures, but also typically demand urgent attention, thereby acting as their own controls.

> **Illustrative case:** I have a patient with severe Raynaud's disease (vasospastic disease) affecting all 4 extremities. Over 15 years prior to implantation she had had four vascular operations and had almost lost the use of her hands, as well as suffering severe pain and blistering. She has enjoyed spectacular control with SCS, both of pain and functionally, for 12 years. The relief is immediately lost when her pulse generators deplete and is restored when they are replaced (she has 2 systems). This "N of one trial" provides compelling evidence.

8) Critical limb ischaemia (CLI)

> **Illustrative case:** A 51 year old lady presented with severe rest pain and a deep ischaemic ulcer on one toe despite having undergone surgical sympathectomy and two bypass grafts in the previous two years. She was using a wheelchair. After a failed prostacyclin trial she was scheduled for above-knee amputation but decided to try SCS. After implantation in 1990 the foot immediately became warm, the rest pain was completely relieved, the ulcer healed and her walking distance increased to more than a mile. She took her granddaughters all round the world. The only time the pain returned was when a technical fault developed with the stimulator and it resolved when it was replaced. When she died from lung cancer 13 years later she had two comfortable legs and was still walking long distances.

9) I suspect that, almost paradoxically, the wealth of dramatically positive clinical experience, where nothing else works, is partly responsible for the relative paucity of RCTs, in the same way that nobody has invested in RCTs for fire extinguishers, parachutes and laparotomy for ruptured spleen.

10) **Outcome assessment** in patients with chronically painful neuropathic conditions is problematic and "50% pain relief", although almost universally used, is simplistic and misleading in this context.[10,26] Pain is inherently non-quantitative and the VAS is a subjective abstraction, not an objective measure. It is subject to many influences when used in the long term. Some patients who consistently report considerable degrees of pain relief yield percentage changes on VAS scores lower than 50%. [12, 27, 28]

> **Illustrative case**: One patient, a professional man with a young family who was disabled by FBSS, reported to me that his reduction in pain intensity was no more than 25% but SCS made the *quality* of the pain very different and much more bearable and that it made an enormous difference to his life. Such reports are not unusual.

More holistic outcome measures have been appearing in the literature only very recently.

11) In our study where the stimulator was switched off for a period [12], 34 out of 63 declined to take part. Ten (16%) explicitly did not wish to be without their stimulator even for one week and 15 (24%) gave no reason. The others declined for various reasons.

12) FBSS is just one representative or cause of neuropathic pain of peripheral origin (cf. spinal cord injury or stroke: central origin). The Assessment should be made in this context, i.e as assessing neuropathic pain of peripheral origin where the available published evidence happens to be mainly about the exemplar FBSS. Approval should logically be generalised to other cases including "Failed Neck Surgery Syndrome", amputation pain, post thoracotomy pain, various other post surgical peripheral syndromes, diabetic peripheral neuropathy etc.

13) With regard to angina pectoris, the question is not whether SCS is better than any comparator. It is whether SCS is *at least as good as* coronary artery bypass grafting (CABG), but with the advantage of being a much smaller procedure not requiring ITU/coronary unit admission etc, in high risk/unsuitable cases, and is it effective in patients unsuitable for stenting? You have the evidence for reduced hospital admission and improved cardiac function.

14) **Trial stimulation.** I am extremely uneasy about the recommendation that there should be a preliminary trial. This is advocated simply because that is what happened to be done in the RCTs being relied upon. You recommend trial stimulation with no comparative evidence, controlled or otherwise, which contrasts vividly with your general dependence upon RCTs. The efficacy of trial stimulation has never been tested in an appropriately constructed trial, so how do you justify supporting it?

Although trial stimulation may certainly detect the very small proportion of patients who do not like the sensation or whose pain is exacerbated by stimulation, overall it is a poor predictor of long-term success, leading to a failure rate of around 30% on average. See for example Van Buyten et al [29] whose long term success rate was 68% after a very thorough preliminary trial in a large series. Possible reasons for this include:

- it depends on percutaneous wire or "catheter" electrodes; surgically implanted paddle electrodes perform better[30, 31] and may work where percutaneous leads do not, but cannot be used for a trial.

- the biggest failure rate occurs early, suggesting a placebo response(see De la Porte and Van de Kelft[32]: 95% immediate success, 80% at one month, 58% at one year in FBSS). In the Tesfaye RCT on diabetic neuropathy [33] a dummy trial stimulator significantly improved the pain scores.
- most patients see this as their last hope and are desperate to "qualify". This will bias the outcome of the trial.
- selecting patients on the basis of a 50% change in VAS is completely unsatisfactory. A VAS score of 10/10 dropping to 5/10 is not the same as a score of 5/10 dropping to 2.5/10. It is 100% different! This is absurd. The worst cases have to score the biggest responses to proceed; a less severe case is more likely to get a stimulator.
- although the false positive rate of selecting cases IN is as high as 30% or more, little is known about the false negative rate, i.e patients who are wrongly rejected. There is some published evidence, however, indicating that patients who fail a trial can certainly benefit in the long term [34, 35].
- in some people the response increases over time, which would not be detected by a trial.

I have not used trial stimulation for several years yet my outcomes are comparable to those where a trial is used.

General

1) I have not raised specific points from the RCTs which are being relied upon but I refer to Dr Simon Thomson's comments on these, and those of NSUKI, which I fully endorse.

2) As Dr Simon Thomson explains in his submission, new calculations indicate that the ICER for CRPS is substantially less than £30,000 per QALY

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3) The extent of the dependence upon published RCTs appears excessive. I was very disturbed to read in the Technology Assessment Report produced for NICE by ScHARR, at pp22/23: "Data from non-randomised studies were not included as evidence was available from RCTs." The EFNS Task Force on stimulation for pain acknowledged that there was positive evidence for SCS in a range of neuropathic pain conditions, whilst acknowledging that further comparative trials were needed before SCS could be *unreservedly* recommended for these conditions [22].

4) A lack of *published* high level evidence is not, of course, evidence for lack of efficacy. The clinical evidence, both published and unpublished, relates to tens of thousands of cases implanted and sometimes reimplanted over several decades.

5) Many suitable patients have their conditions as a result of hospital treatment.

6) There is a cohort of patients with CRPS and various neuropathic and ischaemic conditions in whom the sustained response is dramatic and life-changing for them and their families.

7) The extent and duration of the unremitting suffering of people who may be greatly helped by SCS is generally not appreciated, including by the medical profession. It is dangerous and unconscionable to condemn many of these people to continue with their suffering because relatively few RCTs have been published, in a field in which there are barriers to obtaining the highest level evidence.

8) Whilst strongly endorsing the call for further research, I fear the proposal, that apart from FBSS SCS should be employed only as part of a research programme, is too restrictive and exclusive and will deny deserving patients appropriate therapy.

9) I have spent many years using SCS to treat patients with CRPS, a range of neuropathic pain aetiologies and vasospastic disease, very successfully and without a preliminary trial. Is NICE going to opine that most of my practice is invalid and should not continue and that these patients did not, or should not, have had years of pain relief and improved function?

[redacted]

Cardiff

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