Health Technology Appraisal of Spinal Cord Stimulation for Chronic Pain of Neuropathic or Ischaemic Origin (HTA 07/08)

This submission is being made on behalf of the Pain Relief Foundation (PRF) and the Walton Centre for Neurology and Neurosurgery (WCNN) in Liverpool. The PRF is a charitable organisation set up to facilitate research into the causes and treatment of chronic pain. It is closely associated with the Pain Clinic at WCNN and the team are directly involved in the work of the PRF. The centre's main experience is with spinal cord stimulation (SCS) for the treatment of chronic neuropathic pain. SCS for refractory angina pectoris and chronic critical limb ischemia is generally carried out at other specialist centres. The PRF / WCNN strongly support the use of SCS in both these conditions, but the main focus of our submission will be the use of SCS for chronic neuropathic pain.

What is the place of the technology in current practice?

In the NHS, chronic neuropathic pain is currently primarily treated using a pharmacological approach. Despite a considerable increase in randomised placebo-controlled trials in neuropathic pain over recent years, the medical treatment of neuropathic pain is still far from satisfactory, with less than half of the patients achieving significant benefit with any pharmacological drug (Attal et al, 2006).

SCS is an evidence-based therapy for the management of chronic neuropathic pain. Its use is advocated for patients who have failed conventional medical management. Randomised controlled trials (RCTs) of SCS have been undertaken for: failed back surgery syndrome (FBSS), complex regional pain syndrome (CRPS) (type I), refractory angina pectoris and chronic critical limb ischemia. However, other indications have emerged through clinical practice and experience (British Pain Society, 2005). SCS is not currently available to all patients who may benefit due to significant geographical variations in provision of service. The selection of patients for this treatment is currently limited by the experience / knowledge of the pain clinician involved in their care and availability of services in the local area. In areas where clinicians have not been exposed to the use of SCS, it may not even be considered as a treatment option.

The current alternative to SCS is the use of pharmacological agents. As stated earlier in the text, efficacy is limited in the drugs used to treat chronic neuropathic pain. Drug-related adverse effects are common, not only because of the specific medications used, but also because many of the patients with this condition are older, take multiple medications, and have co-morbid illnesses (Dworkin et al, 2003). Many patients fail pharmacotherapy because they are unable to tolerate the side effects.

Surgery attempting to treat the causes of chronic neuropathic pain is not advocated by pain management specialists and is generally actively

discouraged, because it can often make the situation worse rather than better. The amount of spinal surgery carried out purely for pain relief (eg spinal fusion procedures) has dropped dramatically due to this. A randomised controlled trial by North et al (2005), comparing re-operation with SCS in patients with FBSS, demonstrated that SCS provides effective pain relief for at least 3 years. Overall, in current clinical practice pharmacological approaches continue to be the main treatment method for chronic neuropathic pain.

The setting in which SCS is used is extremely important. All patients being considered for SCS should be carefully selected and undergo a full multidisciplinary assessment. The British Pain Society (2005) recommends that a multidisciplinary pain management team is the most appropriate context in which to provide SCS. Certain subgroups of patients may need careful consideration of their suitability for SCS, such as those with significant cognitive impairment, or physical and psychological co-morbidities. These issues do not preclude treatment with SCS, but patients will require full and detailed assessment, in conjunction with other relevant teams / specialists.

There are certain sub-groups of patients who may not be appropriate for SCS. It is widely accepted that some conditions will not respond to SCS, such as patients with: complete cord transaction, non-ischaemic nociceptive pain and nerve root avulsion (British Pain Society, 2005). In addition, there are certain groups with conditions that rarely respond to SCS who require very careful consideration, such as: central pain of non-spinal cord origin, spinal cord injury with clinically complete loss of posterior column function, perineal, anorectal pain (British Pain Society, 2005).

There are also certain subgroups that have contraindications / relative contraindications to SCS, such as patients with: uncontrolled bleeding disorder/ongoing anticoagulant therapy, systemic or local sepsis, presence of a demand pacemaker or implanted defibrillator, immunosupression (this is a relative contraindication) (British Pain Society, 2005).

The technology should be used in recognised centres, based in secondary care specialist clinic settings, with a full multidisciplinary team available. The team should comprise: Consultants in Pain Medicine, Neurosurgeons, and nurses, psychologists and physiotherapists specialising in pain management. Additional professional input may also be required from other specialities depending on the indication for SCS e.g. vascular surgeons, cardiologists. Occasional implanters are not acceptable and the British Pain Society (2005) recommends that centres should be implanting an average of 10 electrode systems per year to ensure competence.

SCS is already being widely used in certain centres. Since the British Pain Society Recommendations (2005) it is reported that the number of centres carrying out small numbers of SCS implants has reduced. However, there are still thought to be some centres implanting less than 10 electrode systems per year. At the WCNN, SCS has been used since the early 1990s and approximately 600 - 700 patients have been implanted since that time. The WCNN has successfully treated a large number of patients with SCS for some

of the conditions identified in the RCTs, but also for other conditions that do not have RCT evidence. These conditions include: neuropathic pain secondary to peripheral nerve damage (related to trauma or surgery), traumatic brachial plexopathy: (partial, not avulsion), post-amputation pain (stump and phantom pain), diabetic neuropathy, facial pain, neuropathic pain associated with MS, and post-herpetic neuralgia. It is essential that such patients are not denied treatment with SCS purely on the basis that an RCT has not been carried out for a particular condition, when there is strong clinical evidence to support its use.

The British Pain Society (2005) published recommendations for best clinical practice on spinal cord stimulation for the management of pain. The recommendations were produced by a consensus group of relevant healthcare professionals and patients' representatives. The guidelines make reference to the current body of evidence relating to spinal cord stimulation and this is used to underpin the recommendations. As previously discussed, certain key RCTs are considered and in addition many case reports, retrospective and prospective case series, and observational comparative studies of SCS, particularly for FBSS and CRPS. The recommendations are appropriate and evidence-based and have been adopted nationally to guide clinical practice.

There is currently some variation in how SCS is used in the NHS. The infrastructure can vary greatly between centres and in some settings an occasional implanter may be working in relative isolation without the support of a multidisciplinary team (despite the British Pain Society Guidelines, 2005). It appears the majority of implanting centres do carry out trials of SCS before proceeding to permanent implant, but there is some debate around this. The merits of trials are discussed later in the text. There is also variation in the types of electrodes that are used and this often reflects the infrastructure of the implanting centre. In centres where Neurosurgeons are actively involved with the provision of SCS, surgical plate electrodes are often used for the permanent implant. However, a number of these centres do use percutaneous electrodes for trials of SCS.

In centres where Pain Consultants are the main implanters, percutaneous electrodes tend to be used for both trial and permanent SCS, because without the input of a neurosurgeon there is no option to use a surgical electrode. The argument for the use of surgical plate electrodes is that the centres using them believe they are less prone to migration and are less positional (ie provide more consistent stimulation when the patient is moving around). However, there is no head to head data comparing the two types of electrode and it may be possible to argue that migration rates reduce for both percutaneous and surgical electrodes with increased experience and expertise of the implanter. At the WCNN, in our clinical experience the percutaneous electrodes used during trial of SCS are more prone to migration and positional stimulation than the surgical plate electrodes used for the permanent implants. In addition, we receive a number of referrals from centres that only use percutaneous electrodes, for patients who require

conversion to a surgical plate electrode due to ongoing problems with percutaneous electrode migration.

It is worth noting that centres should have direct access to a spinal surgeon or neurosurgeon competent to deal with the complications of SCS, as recommended in the British Pain Society Guidelines (2005). One concern would be whether centres that are only able to implant percutaneous electrodes do have this type of access to a neurosurgeon. It is essential that access to Neurosurgical Services is set up as part of the infrastructure of centres carrying out SCS. Both for emergency situations and also if conversion to a surgical plate electrode is required.

The advantages and disadvantages of the technology

SCS compares very favourably with the current pharmacological alternatives available to treat chronic neuropathic pain. As previously discussed, the medical treatment of neuropathic pain is still far from satisfactory, with less than half of the patients achieving significant benefit with any pharmacological drug (Attal et al, 2006). Kumar et al (2007) recently published a multi-centre, randomised controlled trial of SCS versus conventional medical management (CMM) for the treatment of FBSS. The primary outcome measure was the proportion of patients achieving 50% or more relief of their leg pain. At 6 months, 48% of the SCS patients, compared to only 9% of the CMM patients ($p < 0.001$), achieved the primary outcome. However, it is widely recognised that there are other important factors such as quality of life and level of function, and pain relief should not be considered in isolation. Kumar et al (2007) also found that the SCS group had significantly enhanced health-related quality of life on seven of the eight dimensions of the SF-36 ($p \leq 0.02$) and superior function of the Oswestry Disability Index ($p \leq 0.001$) compared to the CMM group.

In addition to significant pain relief, another advantage of SCS is the potential for patients to reduce their medication intake. In the clinical experience of the Pain and Neuromodulation Team at the WCNN, many patients are reluctant to take long-term medication, either due to concerns about long-term effects on health or due to side effects. Reduction of medication is frequently identified as a treatment goal when patients are assessed at the WCNN for SCS and many patients are able to achieve this. In the study by Kumar et al (2007), the SCS group exhibited a trend towards a decrease in analgesic drug intake.

Due to the fact that SCS involves the implantation of a fairly technical system with electrodes and wires and connections, one of the disadvantages is that a certain amount of system maintenance can be required. However, at the WCNN this is something that patients are informed about from the point of assessment and are generally prepared to accept if they are gaining significant pain relief from the SCS. The study by Kumar et al (2007) reported that 27 (32%) of patients experienced a total of 40 device-related complications, and for 20 patients (24%), surgery was required to correct this.

With any implanted system there is always a potential risk of infection. The Kumar et al (2007) study reported an 8% infection rate at 12 months. At the WCNN the infection rate for SCS has been approximately 3%. In an attempt to reduce this further, we have introduced an implant unit for SCS patients and other patients having systems implanted e.g. deep brain stimulators, vagal nerve stimulators. Patients are isolated on the unit during their admission and all staff and visitors are required to wear aprons (and gloves for direct patient contact). All patients are MRSA screened before admission to the unit and are required to wash in Octenisan solution the night before and the morning of surgery. At the WCNN we have managed to treat the majority of the small number of infections with IV antibiotics. Rarely, an SCS system may have to be explanted if an infection does not resolve. Clinical opinion differs on this issue and some centres will immediately remove infected systems. Clinical experience at the WCNN has demonstrated that it is possible to save the majority of infected systems with IV antibiotic treatment. However, due to the small number of cases involved it is not possible to draw firm conclusions as to the best course of action. Although from a humanitarian perspective, it is perhaps more appropriate to discuss the risks with the patient and offer the option of trying to save the system with antibiotics. Otherwise they may be without the benefits of their SCS for a number of months before the system can be re-implanted.

Any of the complications detailed above can have a significant impact on the patient if they are not dealt with appropriately. It is essential that centres are adequately resourced, with a dedicated team for the care of SCS patients. This means that complications can be dealt with swiftly and appropriately to minimise the impact on the patients' quality of life. Patients must be fully informed throughout the assessment and implant process that implantation of an SCS will require ongoing commitment from them due to routine maintenance (e.g. IPG changes, clinic appointments for battery checks) and potential complications. It is essential that patients are reviewed regularly in relation to the battery life of the IPG. Loss of therapy and return to pre-SCS pain levels can be very distressing for patients and have a significant impact and their quality of life. If patients are reviewed on a regular basis the battery end of life can often be pre-empted and the patient can be booked in for an IPG replacement before complete loss of therapy occurs. It is essential that centres have the infrastructure to support regular clinic appointments for patients with SCS. In addition, there must be enough theatre / bed capacity to facilitate admission in a timely fashion when IPG replacement or other system maintenance is required.

In relation to the evidence-base for SCS, the use of the technology in clinical practice does reflect that observed under clinical trial conditions. In the recent Kumar et al (2007) study, one of the study centres was based in the UK. Therefore, current UK practice was represented in the trial. The European Federation of Neurological Societies (EFNS) recently published guidelines on the use of neurostimulation therapy for neuropathic pain (Cruccu et al, 2007). They identified two class-II RCTs concerning FBSS (North et al, 2005; Kumar et al, 2005). The first showed that SCS is more effective than re-operation and the second that the addition of SCS is more effective than CMM alone. In

CRPS I they also identified one class-II RCT which showed that SCS is more effective when compared with conventional care alone (Kemler et al, 2000 and 2006). Cruccu et al (2007) also found positive case series evidence for CRPS II, peripheral nerve injury, diabetic neuropathy, post-herpetic neuralgia, brachial plexus damage, amputation (stump and phantom pains) and partial spinal cord injury.

It is essential that this additional case series evidence is taken into consideration and that treatment with SCS is not reserved solely for those conditions with RCT evidence. It would be reasonable for further research to be recommended, as long as treatment with SCS is not withheld from the wider range of neuropathic pain conditions known to respond to it in clinical practice. RCTs are not straightforward for this type of therapy and it is extremely difficult to provide any reasonable type of placebo control. However, comparison to standard treatment is not unreasonable; although this in itself proves a problem in many cases. For example, in the case of phantom limb pain there is no consensus as to the standard treatment and a wide range of therapies have been advocated over the years. A survey in 1980 identified 68 different methods, of which 50 were still in use (Sherman et al, 1980). As with pharmacological research, it may be that the results of RCTs in certain key conditions are then extrapolated to other similar conditions. For example, many of the studies of the newer anticonvulsant drugs were focussed on the treatment of painful diabetic neuropathy and post-herpetic neuralgia, but the drugs are licensed for the general treatment of neuropathic pain. Therefore, it could also be argued that if SCS has been demonstrated to be effective in certain key neuropathic pain conditions, the results could be extrapolated to other similar neuropathic pain conditions. This again strengthens the argument for carrying out trials of SCS before permanent implant, especially in those conditions without RCT evidence.

It is essential that certain rules / procedures are in place before patients receive SCS. As previously discussed, the British Pain Society (2005) recommends that a multidisciplinary pain management team is the most appropriate context in which to provide SCS. It is essential that centres have an appropriate infrastructure in place and that SCS implants are not carried out in a haphazard manner. This ensures that patients receive appropriate care both pre and post-implant and there is no risk of facilities no longer being available in the future should the patient require further surgery for IPG replacement or system maintenance. The majority of patients at the WCNN receive a full multidisciplinary assessment before being considered for a trial of SCS. Following a successful trial of SCS and implantation of a permanent system, the patient continues to be managed by the multidisciplinary team on a long-term basis.

At the Walton Centre, due to the wide range of conditions that have been seen to respond to SCS in clinical practice, it is deemed useful to have a trial before proceeding to full implant. This ensures that only patients who are going to have a significant response to SCS receive a permanent implant, which provides a more cost effective and appropriate use of resources. However, it must be noted that this is not routine practice in all implanting

centres and clinical opinions differ on the importance of this. However, local audit results detailed below support the case for trial of SCS before proceeding to permanent implant. Cruccu et al (2007) note that trial stimulation through externalised leads is widely employed. They suggest that this helps to identify patients who do not like the sensation from SCS and those in whom appropriate stimulation cannot be achieved. Our clinical experience would concur with this viewpoint and we have found that a small number of patients find the sensation of SCS unpleasant and do not wish to proceed to permanent implant. There are also some patients who do not gain significant pain relief, and / or have areas of numbness and are unable to detect the paraesthesia from the SCS.

Additional sources of evidence?

An additional source of evidence would be the local unpublished audit results and clinical experience at the WCNN, as a centre that has been treating patients with SCS since the early 1990s. As discussed earlier in the text, we now have approximately 600 – 700 patients with SCS. This volume of patients obviously provides a vast amount of clinical experience and follow up data. Due to the fact that the WCNN trials all patients before implanting a permanent SCS, the long-term success rate is high for a range of conditions. In a recent retrospective audit (2006) of 114 trials of SCS in 97 patients, the success rate of SCS trials was 66.6%. This demonstrates the value of a trial before proceeding to permanent implant. 79% of patients who received a permanent implant reported good long term pain relief of over 50% (≥ 6 months).

Implementation issues

The PRF / WCNN recommend that SCS should be delivered by regional centres with an appropriate infrastructure in place, as detailed earlier in the text. It is likely that there would need to be an increase in the provision of services in order to correct the current variations in availability of SCS. However, this should be achieved by the strengthening of regional centres, rather than by an increase in the number of centres providing this service.

SCS should not be delivered by occasional implanters working in isolation without a formal infrastructure in place. It is important that there are measures in place to ensure the level of competency in implanting centres. The requirement for regional centres implanting large numbers of SCS would help to ensure this. In addition, the focus of such expertise in regional centres could then be used to educate and train staff from newly proposed centres. If regional centres were nationally identified and promoted, this would raise awareness of the facilities available and ensure that patients were referred to the appropriate centre. This would reduce the current geographical variation in the provision of SCS.

The number of centres required would have to be judged on the maximum capacity of the centres currently implanting. If some centres are already functioning at capacity, this would indicate the need for a second centre to cover that particular geographical area. Another option is for specialist centres to focus on SCS for particular conditions. For example, the WCNN does not generally implant SCS for chronic refractory angina because SCS for this condition is carried out at the National Refractory Angina Centre at The Cardiothoracic Centre in Liverpool. This is appropriate because they have the other relevant specialists on-site to ensure that all aspects of the condition are managed effectively.

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