Systematic review to identify predictors of treatment response to neuromodulation in patients with neuropathic pain – protocol

Running title: Predictors of SCS treatment success

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Abstract

Objectives: Patients who suffer from long-term, neuropathic pain that proves refractory to conventional medical management are high consumers of health care resources, and experience poorer physical and mental health than people with other forms of pain. Pharmacological treatments have problematic side effects: non-pharmacological interventions have limitations. Spinal cord stimulation (SCS) is an effective treatment for neuropathic pain, although 30-40% of patients fail to achieve acceptable levels of pain relief. There are currently no objective methods to predict the success of SCS to treat neuropathic pain and therefore it is important to understand which patient factors which may be predictive of a lack of response to SCS, to inform future patient treatment options. This study proposes a protocol for a systematic review and meta-analysis of published studies to examine these predictive factors.

Methods: A number of bibliographic databases will be searched to identify relevant studies published since 2012 that provide data on patient characteristics (e.g., age, gender, pain severity) as predictors of SCS outcomes of pain, function and health related quality of life. Two independent reviewers will screen citations; data will be extracted following full text screening. Risk of bias will be assessed using the Quality In Prognosis Studies tool (QUIPS).

Results: A formal quantitative synthesis is planned; where data from studies with same predictive factors is available, this will be considered for pooling into separate meta-analyses. Where high heterogeneity or inconsistency in the data exists, subgroup analysis will be conducted.

Conclusions: This study seeks to provide a contemporary review of patient predictors of success of neuromodulation for neuropathic pain. We anticipate that findings may guide the

use of neuromodulation in patient subgroups and the design and reporting of future clinical studies in this field.

Key words: spinal cord stimulation; chronic pain; predictor; neuropathic pain; patient characteristics

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Introduction

Neuropathic pain (NeuP) is defined as pain arising as a direct consequence of a lesion or disease affecting the somatosensory system.[1] A recent review of the epidemiology of chronic pain found no single estimated population prevalence of NeuP[2] but instead a range from 1% to 11.4%. This variation reflects the differing ways in which NeuP is defined according to different assessment tool instruments, which were originally designed for clinical rather than research purposes. The current best population estimates for NeuP have been calculated using screening instruments that detect pain with probable neuropathic features.[3, 4]

An expert panel reached the consensus that the following six pain characteristics should be included in the definition of NeuP for epidemiological research: i) prickling, tingling, pins & needles; (ii) pain evoked by light touch; (iii) electric shocks or shooting pain; (iv) hot or burning pain; (v) a relevant patient history; and (vi) brush allodynia on self-examination. It is unknown what proportion of individuals experience clinically significant, long-term pain that has not responded to standard non-specialist treatment. These “refractory” cases of NeuP are clinically the most important to detect, as they are likely to be the most severe and difficult to treat and require greater use of healthcare resources. Consensus was reached to define “refractory NeuP” as having the following four components: (i) minimum duration (12 months); (ii) minimum number of trials of drugs of known effectiveness (four); (iii) adequate duration of these trials (3 months or maximum tolerated); and (iv) outcomes of treatment (pain severity, quality of life).

As with many chronic pain conditions, patients with NeuP are high consumers of health care resources, such as visits to medical professionals and use of prescription medications.[5, 6] The heterogeneity of its aetiologies, symptoms and underlying mechanisms renders it very challenging to manage.[7] There is evidence suggesting that people with NeuP experience poorer physical and mental health than people with other forms of pain, even when adjusted for pain intensity.[8, 9] Pharmacological treatments used to manage NeuP include antidepressants, anticonvulsant drugs, topical treatments and opioid analgesics.[6] However, these can have problematic side effects, and up to 50% of patients with NeuP fail to obtain pain relief from pharmacological treatments.[10] Gabapentinoids, a class of nerve painkillers are increasingly prescribed for low back pain and sciatica, despite being shown to be ineffective, potentially dangerous and addictive.[11, 12] The self-reported lifetime prevalence of misuse in the UK is 1.1% for gabapentin and 0.5% for pregabalin.[13] As a result, gabapentinoids were reclassified as Class C drugs under the Misuse of Drugs Act from April 2019. [14] Opioids, although effective in some cases of NeuP, are not routinely recommended due to a combination of tolerance, addictive potential and opioid-induced hyperalgesia.[15] Non-pharmacological interventions, including physiotherapy, acupuncture, trans-cutaneous electrical nerve stimulation, percutaneous electrical nerve stimulation, and psychological therapies have been trialled but all of which have many limitations.[16-18]

Findings from observational studies in the USA and Europe suggest that between 70% and 96% of people with NeuP who seek care, continue to experience moderate to severe pain,[19] despite available treatments. In summary, patients with NeuP have high disease burden and unmet treatment need.

Description of intervention

Spinal cord stimulation (SCS) has been shown to be an effective treatment for neuropathic pain refractory to conventional medical management in several randomized controlled trials (RCTs).[20-22] SCS provides important enhancement to function and health-related quality of life[23] by providing improved pain relief and has also been shown to be a cost-effective therapy in many studies.[24-26] Based on the evidence for clinical effectiveness and cost-effectiveness, the National Institute for Health and Care Excellence (NICE) recommended SCS as a treatment for patients suffering from refractory chronic neuropathic pain conditions including failed back surgery syndrome (FBSS).[27]

Currently in the UK, patients with NeuP are selected for SCS by a multidisciplinary team as recommended by NICE.[27] About 50% to 70% of patients receiving SCS experience good levels of pain relief (>30% reduction in pain). Complications occur in 30% to 40% of patients; these are frequently minor device-related issues, such as lead migration or lead breakage.[28] The incidence of infectious complications varies from 3.4% to 10%; such complications require prolonged antibiotics and device revision or removal.[28] Major complications such as post-dural puncture headache, haematoma formation and neurological injury are rare.[29] Nevertheless, typically 30% to 40% of patients who undergo SCS fail to achieve acceptable levels of pain relief (defined as 50% reduction in pain).[30, 31]

There are no objective methods allowing clinicians to predict the success of SCS for patients with neuropathic pain of FBSS. It is therefore important to understand the patient factors that might be predictive of a lack of response to SCS and may inform better patient selection for treatment.

Patient predictors for treatment response

Studies have identified several predictors which can be divided into modifiable and non-modifiable risk factors. Non-modifiable risk factors include age,[32] gender,[33, 34] aetiology of pain,[35] location of pain (predominantly leg or back),[32, 35, 36] and number of surgeries.[32, 35] In patients who have undergone previous surgical procedures, the shorter the duration of time from surgery to implantation, the greater the rate of success defined as ≥50% pain relief, i.e. 93% for those with less than a 3-year waiting period versus 9% for those with greater than a 12-year waiting period ($p < 0.001$).[35] Those patients whose pain did not follow a previous surgical procedure had better responses to SCS than patients who had multiple surgical procedures prior to their first implant (68% success rate with SCS in patients without prior surgical procedures versus 53% with prior surgeries).[35] It is also believed that SCS may be a more successful therapy (defined as ≥50% continued pain relief combined with patient satisfaction with treatment) for those who present with chronic pain predominantly in the legs rather than the lower back, perhaps partly because back pain has a nociceptive component.[37]

Modifiable risk factors include psychological status, smoking,[38] and body mass index. [39] Current literature suggests that psychological factors such as somatization, depression, anxiety, and poor coping are important predictors of poor outcome (where successful outcome was defined as decreased pain, increased function, return to work, and reduced medical treatment).[39] In a systematic review, 92% of studies (out of 25 studies reviewed) exhibited a positive relationship between one or more psychological factors and poor treatment outcome, where successful treatment outcome was defined as decreased pain, increased function, return to work and reduced medical treatment.[39] Evidence also

suggests that longer pain duration prior to intervention was predictive of poorer outcomes, with each 12-month increase in the duration of pain reducing the level of pain relief by ~2.0%.[40] In other studies, patients with high BMI were found to have less functional improvement at 6 months with SCS, with less improvement on the Beck Depression Inventory at 6 months and one year post-SCS, and less improvement in pain at one year measured by the Pain Catastrophizing Scale.[41] Tobacco use was also found to correlate with lead migration, revision due to new pain symptoms and a rating of <5 on the Global Outcome Rating scale, as graded by care providers. [42]

Why is this review required?

Several RCTs have compared SCS to usual conventional medical management in the last few decades.[21, 22, 43] Although the individual studies have demonstrated the clinical effectiveness and cost-effectiveness of SCS in this group, unfortunately they are limited by small sample size, and therefore have inadequate statistical power to meaningfully quantify predictors of treatment effect.

Review aim

A previous systemic review and meta-analysis[40] found evidence of substantial statistical heterogeneity ($P < 0.0001$) in level of pain relief following SCS. The mean level of pain relief across studies was 58% (95% CI: 53% to 64%) at an average follow-up of 24 months using a random effects method. Multivariable meta-regression analysis showed no predictive patient or technology factors. The review authors concluded that SCS was effective in

reducing pain irrespective of the location of chronic back and leg pain (CBLP). The review supported SCS as an effective pain-relieving treatment for CBLP with predominant leg pain with or without a prior history of back surgery. We aim to update this previous systematic review and meta-analysis to examine the effect of patient characteristics on outcomes of neuromodulation in patients with neuropathic pain.

Review question and objectives

This review will address the key question: *What are the patient characteristics that predict the success of SCS?* The objectives of the review are to identify predictors of improvement in pain relief, function and health-related quality of life (HRQoL) following treatment with SCS.

Methods

This systematic review will be conducted in accordance with The Cochrane Collaboration principles of Systematic Reviews and reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[44, 45] The protocol for this study is registered with the International Prospective Register of Systematic Reviews (PROSPERO) database (CRD42022306871).

Eligibility Criteria

The inclusion and exclusion criteria for this review are summarized in table 1.

Outcomes

We will focus on patient characteristics as potential predictors of the outcomes of SCS. The primary outcome is pain, with secondary outcomes of function and HRQoL. We will include all reported measures of these three outcomes, assessed at any post-treatment follow-up time. We aim to develop a set of core outcomes for design of future studies.

The potential patient predictor outcomes that will be considered are listed in table 2.

Search strategy

We will identify all relevant published studies (excluding unpublished trials, case reports and studies published only in abstract form or as conference proceedings). We will focus our search strategy on the population and the interventions components of our review question. It will not be limited by outcome in order to broaden the scope of eligible studies.

A comprehensive search strategy will be developed and implemented with the assistance of an experienced health information specialist. The search strategy will combine terms relating to or describing SCS with terms for pain and will incorporate terms for predictors and outcome. This strategy is expected to identify the publications that will address the principal elements of the systematic review question. The search strategy will be adapted for use with each bibliographic database to be searched.

There will be language restrictions due to resource limitation; we will include trials published in English, Hindi, French and Portuguese, as these languages are spoken by the review team. As this is being carried out as an update to a previous systematic review, [40]

and there have been significant changes in technology since then (e.g., new devices, new programming), we will search for studies published since the searches in that review were performed (2012 to date). The searches will be re-run just before the final analyses and further studies retrieved for inclusion.

Database searches

We will search MEDLINE (OVID), Embase (OVID), CINAHL, APA PsycInfo and Wikistim databases using the search terms described in Supplementary Materials file 1. Identified studies published since 2012 will be included. Reference lists of reviews and retrieved articles will be checked for additional studies and citation searches performed on key articles. Following this, we will send the list of included studies to other experts in the field to ask whether they are aware of any other potentially available studies that are not included in the list.

Citation management and study selection

Citations from electronic database searches will be exported to EndNote. Duplicate citations will be removed using the automated features of EndNote before screening. Two reviewers will independently screen all the titles and abstracts identified by the electronic searches to identify potentially relevant articles to be retrieved. Full-text copies of potentially relevant studies will be obtained and assessed independently by two reviewers for inclusion using the eligibility criteria. Differences will be resolved through discussion, and if necessary, by consultation with a third reviewer.

A PRISMA flow chart will detail the screening process for the review and reasons for exclusion will be documented.

Data extraction and management

Following full text screening, data will be extracted from eligible studies using a data extraction form. Data extracted will include:

- general information
- study design
- patient demographics (potential predictors of outcome as mentioned above)
- indication for intervention (including all indications such as CRPS, FBSS, neck and arm pain, diabetic neuropathy)
- type of intervention
- comparator
- study population
- study period
- number of participants included in the analysis
- follow-up duration
- efficacy outcomes

This will be performed by one reviewer and checked for accuracy by a second reviewer. Inconsistencies will be resolved through discussion, and, if necessary, in consultation with a third reviewer. If clarification is necessary or insufficient data are presented, we will attempt to contact the authors for further information. If an answer cannot be obtained from authors, the impact will be discussed as a limitation of the review. All the data will be assessed in sufficient detail to complete a table of included studies in the full review.

Risk of bias (quality) assessment

Risk of bias will be assessed using the Quality In Prognosis Studies (QUIPS) tool.[46] Six domains will be considered when evaluating validity and bias in studies of prognostic factors: study participation, study attrition, prognostic factor measurement, confounding measurement and account, outcome measurement, and analysis and reporting.[47] The QUIPS tool includes questions related to these areas that can inform judgments of risk of bias in prognostic research. Quality assessment of the included studies will be undertaken by one reviewer (AK) and checked for agreement by a second reviewer. Any disagreements will be resolved by discussion, and, if necessary, a third reviewer will be consulted.

This process will identifythe important experimental design characteristics of studies which evaluate predictors for SCS outcome and to evaluate the clarity of reporting of these trials.

Analysis plan

Measures of treatment effect

A detailed summary of included studies will be tabulated, structured around the target population characteristics, type of outcomes assessed, and nature of reporting. A description of all included studies will be provided in table forms and discussed in the text.[48]

Success criteria will be determined by the included studies.

A formal quantitative synthesis is planned. We anticipate that there will be a limited scope for a meta-analysis because of the range of different patient characteristics and outcomes measured across the existing trials.

Where data is available, results from studies with similar predictive factors and outcome measures such as pain and disability will be considered for pooling into separate meta-analyses using a random-effects model, with standardized mean differences for continuous outcomes, results will be reported with 95% confidence intervals and two-sided P values for each pooled estimate. Otherwise, subgroup analysis will be conducted in case of high heterogeneity or inconsistency. For each study, the follow-up time points will be collated and for each outcome, results will be pooled using data from the time point most frequently reported, or the closest time point available within a specific study, with +/- 1 month precision for follow-up up to 3 months or +/- 2 months for follow-up from 4 to 12 months.

We have three clinical outcomes: (i) pain (primary outcome; (ii) function; and (iii) health-related quality of life (HRQoL). For each of these outcomes, we will ascertain for each study whether the outcome was reported, and if so, the measurement tool used. If there is variation in the measurement tools used, we will consider for each outcome whether it is appropriate to perform a meta-analysis combining results from studies where different measurement tools are used to measure the same outcome. If it is not considered

appropriate to combine results from studies that report results using different measurement tools, we will perform subgroup analyses combining data only from those studies using the same measurement tool. A minimum of two studies will be required for pooled analysis of results. For each of the three clinical outcomes, we will perform a series of meta-analyses to investigate the potential effect of patient characteristics, both modifiable and non-modifiable, that may predict the specified outcome.

To investigate the potential effect of patient characteristics on outcomes, we will perform meta-regression or stratified meta-analysis as appropriate. For example, the effect of sex could be investigated by meta-regression using percentage male as a covariate, or by performing stratified meta-analysis if the necessary data is provided by the study.

Using aggregate level data, we will perform random effects meta-analyses using the DerSimonian and Laird model, as clinical heterogeneity between the studies is anticipated. We will report heterogeneity using the I^2 statistic. All outcomes are reported as continuous measurements and will be pooled using a standardized mean difference (SMD; Cohen's d). The Cohen's d estimate will be interpreted as 'small' (<0.20),'medium' (0.20–0.50), or 'large' (>0.50). The SMD will be reported with a 95% confidence interval. All analyses will be performed using Stata v.17.

Discussion

This updated systematic review and meta-analysis seeks to provide a contemporary review of patient predictors of the success of neuromodulation for NeuP.

The same group has already investigated the role of screening trials of SCS for the treatment of neuropathic pain and found that despite limited diagnostic utility, screening trials do not improve patient outcomes,[49] therefore an analysis of patient predictors becomes central to patient selection and improving the long-term outcomes of this therapy.

Given the significant inter-patient variability in treatment outcomes, further studies to understand predictors of outcome after SCS are desirable, in order to identify in advance who is most and least likely to benefit from such interventions. The identification of such predictive factors would have important implications for selection of the patients to undergo SCS. The probability of treatment success and the impact of lifestyle changes (such as smoking) can be discussed with patients as they choose from the various treatment options.

We anticipate that this review will inform future clinical guidance on the use of neuromodulation in patient subgroups and the design and reporting of future clinical studies in this field. We are planning to publish this review in key clinical journals and present at clinical meetings and conferences to maximize its impact and accessibility. We are in the process of accessing data from published trials in order to perform Individual Patient Data meta-analysis to further analyze any possible patient predictive factors impacting on patient outcome.

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Table 1

Inclusion criteria (if all of the following met)	Exclusion criteria (if any of the following met)
Population comprised patients with neuropathic pain ≥ 6 months	Population comprised patients with ischemic pain
Adult patients (aged 16 years or over)	SCS used for conditions other than pain (e.g., urinary incontinence)
Intervention was SCS (any modality of treatment e.g., burst, conventional, high frequency, high density etc.)	Patients younger than 16 years old
Any comparator/ No comparator	Trials including patients during pregnancy
Randomised controlled trials (parallel or crossover), prospective studies (single arm, case control, cohort), retrospective studies (case control, cohort), registry studies	
Sample size ≥30	Abstracts/ conference proceedings, case reports/series
Any patient related outcomes (includes pain intensity or proportion of pain relief, function, quality of life, etc.)	
Follow up ≥ 6 month	
Studies with quantitative analysis	Studies with qualitative analysis only (i.e., it is acceptable to have quantitative + qualitative, but not qualitative only)
Human studies only	
Studies written in English, Hindi, French, or Portuguese languages	

RCT=randomised controlled trial; SCS=spinal cord stimulation; CRPS=Chronic Regional Pain Syndrome; FBSS=Failed Back Surgery Syndrome

Table 2

Non-modifiable predictors	Modifiable predictors
Age at recruitment	Body mass index (BMI)
Gender	Smoking status
Educational status	Baseline function status (mobility, mood, sleep)
Employment status	Class and dosage of concomitant analgesics
Co-morbidities number and type including other pain conditions	Opioid doses
Compensation/legal situation related to pain	Other non-pharmacological treatment
Type of pain (neuropathic/non-neuropathic)	
Duration of pain	
Initial diagnosis of pain	
Location of pain (back/leg)	
Pain scores	
Previous surgery for pain (yes/no)	
Time since last surgery for pain (only if at least one previous surgical procedure for pain)	
Baseline quality of life	

Supplementary materials file 1

Search Strategy

Five separate databases (MEDLINE, CINAH, Embase, APA PsycInfo and WIKI+STIM) were searched from 2012 to 8-10/09/2020. Language restrictions were specified to include English, Arabic, French, Hindi or Portuguese. In addition, a cited reference search was completed using Google Scholar and the reference lists of included studies were hand searched for relevant publications missed by the search strategy.

The following search strategy was conducted on EMBASE, MEDLINE, CINAHL and APA PsycInfo

(((((electrical stimulation therapy).ti,ab AND ((spine OR spinal OR spines).ti,ab OR (spinal cord).ti,ab)) OR (spinal cord stimulat*).ti,ab OR exp "SPINAL CORD STIMULATION"/ OR (dorsal column stimulat*).ti,ab OR (neurostimulat*).ti,ab OR exp "IMPLANTABLE NEUROSTIMULATORS"/ OR (neuromodulation).ti,ab) AND ((low back pain).ti,ab OR exp "LOW BACK PAIN"/ OR (failed back surgery syndrome).ti,ab OR exp "FAILED BACK SURGERY SYNDROME"/ OR (FBSS).ti,ab OR (back pain).ti,ab OR exp "BACK PAIN"/ OR (chronic leg pain).ti,ab OR (chronic back AND leg pain).ti,ab OR (post laminectomy pain).ti,ab OR (radicular pain).ti,ab OR (axial pain).ti,ab OR (sciatica).ti,ab OR exp SCIATICA/ OR exp "SCIATIC NEUROPATHY"/ OR (neuropathic pain).ti,ab OR (nerve pain).ti,ab)) AND ((predict*).ti,ab OR (prognos*).ti,ab OR (outcome*).ti,ab)) [DT 2011-2020] [Languages English OR Arabic OR French OR Hindi OR Portuguese]

Wikistim was searched under the category of SCS, with the following search terms:

predict* OR outcome* OR prognos*