

Brain and spinal stimulation therapies for phantom limb pain: a systematic review

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Declared competing interests of authors: Sam Eldabe reports grants and personal fees from Medtronic plc (Minneapolis, MN, USA) and personal fees from Abbott Laboratories (Chicago, IL, USA) and Boston Scientific (Marlborough, MA, USA) outside the submitted work.

Published November 2018

DOI: 10.3310/hta22620

Scientific summary

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Health Technology Assessment 2018; Vol. 22: No. 62

DOI: 10.3310/hta22620

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Background

Phantom limb pain (PLP) is defined as persistent painful sensations perceived in the missing portion of an amputated limb. It is experienced by around 60–80% of amputees but the intensity, frequency, nature and duration of PLP can vary widely. There appears to be no single best treatment for PLP, although the options are numerous and varied. A pharmacological focus prevails in primary care settings, but patients rarely report satisfactory pain management. Other interventions include transcutaneous electrical nerve stimulation (TENS), acupuncture, mirror therapy, cognitive–behavioural therapy (CBT), perioperative interventions, and myoelectric and body-powered prostheses.

Brain, spinal cord and dorsal root ganglion (DRG) neuromodulation (or neurostimulation) therapies are targeted at patients with chronic pain that is refractory to pharmacological treatment. Deep brain stimulation (DBS) is a neurosurgical procedure in which electrodes are implanted into certain parts of the brain with stimulation controlled by a pacemaker-like device, called a neurostimulator (implanted under the skin in the chest or abdomen). The stimulation may alter the electrical signals in the brain that are responsible for pain. Motor cortex stimulation (MCS) involves placing electrodes on the surface of the brain and is equally as invasive as DBS. Non-invasive brain stimulation therapies, such as repetitive transcranial magnetic stimulation (rTMS) and transcranial current stimulation, also exist. In spinal cord stimulation (SCS), and DRG stimulation, electrodes are implanted near the spinal cord or the DRG and are connected to a neurostimulator. This generates an electrical pulse, which can provide analgesia through different mechanisms. No fully systematic review of neuromodulation therapies has previously been published; reviews of other PLP treatments report that the evidence is generally limited. The combination of limited evidence and a lack of guidelines for the management of PLP represents a major challenge for the clinician.

Objectives

The objective was to determine which types of brain and spinal stimulation therapy are likely to be the most promising for treating chronic PLP. This was done by undertaking a systematic review to assess the evidence on treatment effectiveness and safety and a systematic review of the epidemiology of chronic PLP. A survey of practising NHS clinicians was also undertaken to obtain information on which treatments are used to treat chronic PLP in the NHS and how effective they are perceived to be, and to elicit opinions regarding future research studies.

Methods

Systematic reviews

A systematic review of the clinical literature on the effectiveness and safety of brain and spinal stimulation therapies for PLP was undertaken and registered on PROSPERO (registration number CRD42017065387). Searches were carried out during May 2017 using a broad search strategy, without date or language restrictions. Twelve databases (including MEDLINE and EMBASE) were searched as well as several clinical trial registries. Eligible studies were of patients with PLP resulting from amputation. For studies of intervention effectiveness and safety, the eligible interventions were DBS, MCS, rTMS, transcranial current stimulation, SCS (also referred to as dorsal column stimulation) and DRG stimulation. Any comparator treatment was eligible. Studies had to report quantitative results on PLP intensity (either continuous or categorical data). Only comparative trials were eligible for the non-invasive therapies, but uncontrolled studies were also eligible for the invasive therapies.

Studies that reported data relevant to the epidemiology of chronic PLP were also identified from the same broad database search results. Eligible studies had to report data on the level or severity of PLP (either continuous or categorical data). Studies also had to report using patient inclusion criteria of either ≥ 6 months since amputation or a mean or median time since amputation of ≥ 1 year. Prospective studies that recruited patients prior to amputation were eligible if they reported relevant PLP data for ≥ 6 months post amputation.

Two reviewers independently screened all titles and abstracts and full papers. Discrepancies were resolved by consensus or via a third reviewer. Comparative trials were quality assessed using the Cochrane risk-of-bias tool. Uncontrolled studies were quality assessed using specific items from the PROCESS (preferred reporting of case series in surgery) checklist. Invasive surgical interventions were also evaluated based on key aspects of the stages of Innovation, Development, Exploration, Assessment, and Long-term study (the IDEAL model). Data extraction and quality assessments were conducted by one reviewer and checked by a second, with any discrepancies resolved by discussion or via a third reviewer.

Data on patient characteristics, interventions and outcomes were tabulated and a narrative synthesis was undertaken. Results were interpreted in the context of the results of study quality assessments. The possibility of pooling randomised controlled trial (RCT) data using meta-analysis was explored, but was not possible owing to heterogeneity of outcome data.

Survey

A questionnaire on the frequency of use of specific PLP treatments, their perceived effectiveness and the viability of future research studies was distributed between September and November 2017 via the e-mail lists of the British Society for Stereotactic and Functional Neurosurgery and the Neuromodulation Society of the United Kingdom and Ireland. Results were analysed and presented narratively with accompanying tables when appropriate (see *Chapter 3, Results*).

Results

Overall, 6082 titles and abstracts were screened for inclusion and the full texts of 303 papers were assessed against the review eligibility criteria. Seven RCTs, 30 non-comparative group studies, 18 case reports and 21 epidemiology studies were included.

Studies of efficacy, effectiveness and safety

Results from a randomised trial (with a low overall risk of bias) of 54 PLP patients suggested worthwhile short-term benefits of rTMS in reducing PLP, but not in reducing anxiety or depression. However, the PLP benefit seen 2 weeks after the end of treatment was no longer evident 4 weeks after the end of treatment. The two other RCTs of rTMS were smaller; one had a very short follow-up duration and the other had a high overall risk of bias. Small randomised trials of transcranial direct current stimulation (tDCS) suggest the possibility of modest, short-term reductions in PLP. Both tDCS and rTMS appeared safe in the short term.

All the evidence on invasive neuromodulation therapies was derived from uncontrolled group studies (case series) or case reports. Overall, there were four group studies of MCS, eight of DBS, three of DRG stimulation and 14 of SCS. Although several studies reported results that appeared impressive in the short term, the effects diminished over time in some patients, with implants sometimes having to be removed. Nevertheless, it appears that some patients do benefit in the longer term from invasive neuromodulation therapies, although most studies did not have follow-up data beyond around 2 years.

Many of the non-comparative group studies had important methodological and/or reporting limitations. All the studies were small, few studies recruited patients consecutively or used a prospective design and only three studies were multicentred. Some studies did not present results for outcomes mentioned in their

methods sections (so selective outcome reporting may have biased the study results) and few studies reported data on outcomes important to patients, such as quality of life. Many publications reported on mixed cohorts of patients, with some data not reported separately for the subgroup of patients with PLP.

Epidemiology

Eight epidemiology studies had a longitudinal design and 13 had a cross-sectional design. The evidence on prognostic factors for the development of chronic PLP from the longitudinal studies had important limitations, including small sample sizes and short follow-up durations. The longitudinal study results suggested that both pre-amputation pain and early PLP intensity are good predictors of chronic PLP up to 2 years after amputation. Neither level of amputation nor early stump pain seem to be correlated with PLP intensity at later follow-ups.

Results from the cross-sectional studies suggested that the proportion of patients with severe chronic PLP is between around 30% and 40% of the chronic PLP population, whereas the proportion of patients with moderate chronic PLP is around 25%. From the studies reporting data on how chronic PLP affects patients' daily lives, it appears that around one-quarter of chronic PLP patients find their PLP to be either moderately or severely limiting or bothersome. Considerable variation was reported across studies regarding the frequency and duration of PLP episodes. Although many of the cross-sectional studies had large sample sizes, many also had participation rates of between around 50% and 70%. Therefore, it is possible that the results of these studies were subject to non-response bias, which might limit their generalisability to the broader chronic PLP population.

Survey

A total of 37 online questionnaire responses were received from 30 different hospitals: 67% from pain management clinics, 30% from neurosurgery units and 3% from a rehabilitation unit. Most responders were either pain physicians (62%) or neurosurgeons (30%). Results indicated a very high use of pharmacological treatments in the chronic PLP population, with CBT and mirror therapy or graded motor imagery also being frequently used. Of the invasive neuromodulation therapies, SCS and DRG stimulation were frequently used. The prevalence of the use of DBS and MCS was quite low, as would be expected given the current lack of NHS funding for these treatments.

Most clinicians considered pharmacological treatments and CBT to be at least sometimes effective for chronic PLP. TENS was not thought to be very effective by most clinicians, but around two-thirds of neurosurgeons considered acupuncture to sometimes be effective. Pain physicians considered mirror therapy and graded motor imagery interventions to be more frequently effective than did neurosurgeons. A large majority of responders considered SCS and DRG stimulation to be either mostly or sometimes effective, but neurosurgeons were split in their opinions on how frequently DBS is effective. Most neurosurgeons considered MCS to rarely be effective.

Nineteen of the 24 responders who had administered neuromodulation therapies thought that a randomised trial design could be successfully used to study neuromodulation therapies for PLP. Problems with patient recruitment were foreseen by two responders. Of the therapies that could be studied in a RCT, pain physicians reported that they would most like to see SCS and DRG stimulation studied, whereas neurosurgeons reported that they would most like to see DRG stimulation and DBS studied.

Conclusions

The studies of the efficacy, effectiveness and safety of neuromodulation treatments do not provide robust, reliable results, largely owing to a combination of study design and reporting limitations, small sample sizes and short follow-up durations. Consequently, there is much uncertainty about which neuromodulation treatments are best for treating chronic PLP, hindering informed treatment decisions in clinical practice.

Many of the epidemiological studies that included chronic PLP patients also yielded limited data, although they indicated that PLP that substantially affects quality of life is not a rare condition. Although these data, along with the views of NHS clinicians derived from our survey, suggest that recruitment to a randomised trial may be viable, there are credible concerns (from neuromodulation studies of other types of chronic pain) that recruitment and retention might be problematic. Randomised crossover or randomised N-of-1 trial designs may be the most viable approaches. An alternative study design could be a prospective registry study that incorporates N-of-1 trials. Among NHS clinicians, SCS, DRG stimulation and DBS were the interventions most frequently chosen for evaluation in RCTs. Regardless of the study design adopted, long-term evaluation of quality-of-life outcomes would be important, as would broader assessments of pain that go beyond pain intensity alone.

Study registration

This study is registered as PROSPERO CRD42017065387.

Funding

Funding for this study was provided by the Health Technology Assessment programme of the National Institute for Health Research.

ISSN 1366-5278 (Print)

ISSN 2046-4924 (Online)

Impact factor: 4.513

Health Technology Assessment is indexed in MEDLINE, CINAHL, EMBASE, The Cochrane Library and the Clarivate Analytics Science Citation Index.

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This report

The research reported in this issue of the journal was funded by the HTA programme as project number 16/58/02. The contractual start date was in May 2017. The draft report began editorial review in January 2018 and was accepted for publication in May 2018. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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