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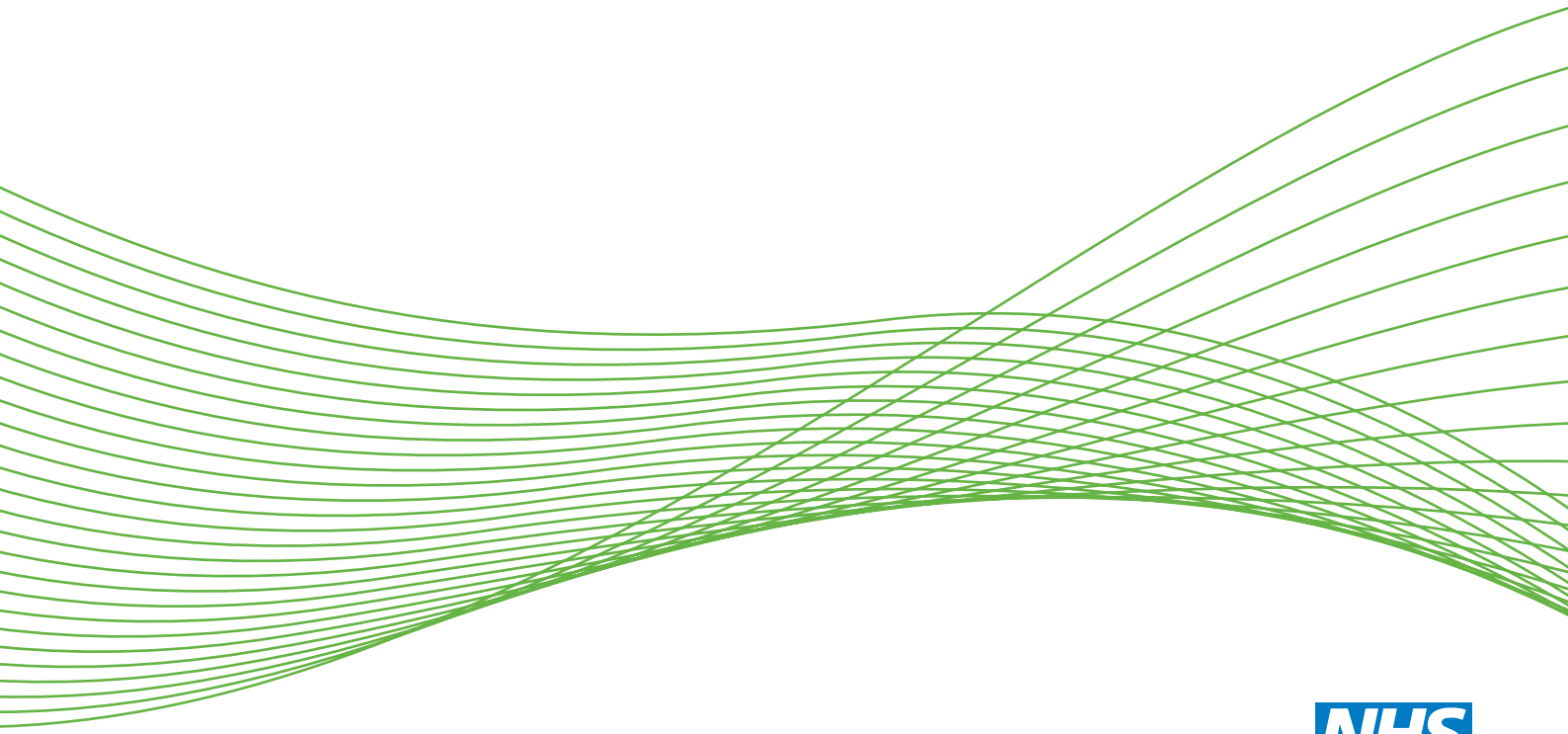

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Brain and spinal stimulation therapies for phantom limb pain: a systematic review

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Abstract

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

Mark Corbett,[1]* Emily South,[1] Melissa Harden,[1] Sam Eldabe,[2] Erlick Pereira,[3] Imad Sedki,[4] Neil Hall[2] and Nerys Woolacott[1]

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Background: Although many treatments exist for phantom limb pain (PLP), the evidence supporting them is limited and there are no guidelines for PLP management. Brain and spinal cord neurostimulation therapies are targeted at patients with chronic PLP but have yet to be systematically reviewed.

Objective: To determine which types of brain and spinal stimulation therapy appear to be the best for treating chronic PLP.

Design: Systematic reviews of effectiveness and epidemiology studies, and a survey of NHS practice.

Population: All patients with PLP.

Interventions: Invasive interventions – deep brain stimulation (DBS), motor cortex stimulation (MCS), spinal cord stimulation (SCS) and dorsal root ganglion (DRG) stimulation. Non-invasive interventions – repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS).

Main outcome measures: Phantom limb pain and quality of life.

Data sources: Twelve databases (including MEDLINE and EMBASE) and clinical trial registries were searched in May 2017, with no date limits applied.

Review methods: Two reviewers screened titles and abstracts and full texts. Data extraction and quality assessments were undertaken by one reviewer and checked by another. A questionnaire was distributed to clinicians via established e-mail lists of two relevant clinical societies. All results were presented narratively with accompanying tables.

Results: Seven randomised controlled trials (RCTs), 30 non-comparative group studies, 18 case reports and 21 epidemiology studies were included. Results from a good-quality RCT suggested short-term benefits of rTMS in reducing PLP, but not in reducing anxiety or depression. Small randomised trials of tDCS suggested the possibility of modest, short-term reductions in PLP. No RCTs of invasive therapies were identified. Results from small, non-comparative group studies suggested that, although many patients benefited from short-term pain reduction, far fewer maintained their benefits. Most studies had important methodological or reporting limitations and few studies reported quality-of-life data. The evidence on prognostic factors for the development of chronic PLP from the longitudinal studies also had important limitations. The results from these studies suggested that pre-amputation pain and early PLP intensity are good predictors of chronic PLP. 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, and that around one-quarter

of chronic PLP patients find their PLP to be either moderately or severely limiting or bothersome. There were 37 responses to the questionnaire distributed to clinicians. SCS and DRG stimulation are frequently used in the NHS but the prevalence of use of DBS and MCS was low. Most responders considered SCS and DRG stimulation to be at least sometimes effective. Neurosurgeons had mixed views on DBS, but most considered MCS to rarely be effective. Most clinicians thought that a randomised trial design could be successfully used to study neurostimulation therapies.

Limitation: There was a lack of robust research studies.

Conclusions: Currently available studies of the efficacy, effectiveness and safety of neurostimulation treatments do not provide robust, reliable results. Therefore, it is uncertain which treatments are best for chronic PLP.

Future work: Randomised crossover trials, randomised N-of-1 trials and prospective registry trials are viable study designs for future research.

Study registration: The study is registered as PROSPERO CRD42017065387.

Funding: The National Institute for Health Research Health Technology Assessment programme.

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Supplementary material can be found on the NIHR Journals Library report project page (www.journalslibrary.nihr.ac.uk/programmes/hta/165802/#/documentation).

Supplementary material has been provided by the authors to support the report and any files provided at submission will have been seen by peer reviewers, but not extensively reviewed. Any supplementary material provided at a later stage in the process may not have been peer reviewed.

List of abbreviations

CBT	cognitive–behavioural therapy
DBS	deep brain stimulation
DREZ	dorsal root entry zone lesioning
DRG	dorsal root ganglion
EQ-5D	EuroQol-5 Dimensions
IDEAL	Innovation, Development, Exploration, Assessment, and Long-term study
M1	primary motor cortex
MCID	minimum clinically important difference
MCS	motor cortex stimulation
MPQ	McGill Pain Questionnaire
NICE	National Institute for Health and Care Excellence
PLP	phantom limb pain
PPC	posterior parietal cortex
RCT	randomised controlled trial
rTMS	repetitive transcranial magnetic stimulation
SCS	spinal cord stimulation
SF-36	Short Form questionnaire – 36 items
tDCS	transcranial direct current stimulation
TENS	transcutaneous electrical nerve stimulation
VAS	visual analogue scale

Plain English summary

Phantom limb pain (PLP) is pain perceived by amputees in the missing part of their limb. Electrical stimulation of the brain or spine can be used to treat long-term PLP when other treatments have not worked, but there is limited knowledge on how effective it is. Brain stimulation can be non-invasive (electrodes placed on the scalp) or invasive (electrodes inserted into the brain during an operation). Stimulation of the spine is an invasive therapy. This project aimed to find out which types of brain and spine stimulation seem likely to be best for treating PLP.

We identified and studied all the key data from all relevant research publications and also asked NHS clinicians for their views. Results from studies of non-invasive brain stimulation treatments showed that they may improve PLP for a short time after treatment, but there were no long-term data. Results from studies of invasive stimulation treatments suggested that, although many patients benefited from short-term pain reduction, far fewer had long-term benefit.

Other types of study showed that around one-quarter of patients with chronic PLP found their pain to be either moderately or severely limiting or bothersome. The survey of clinicians suggested that spinal stimulation is often used for PLP in the NHS, with most of the clinicians considering it to be at least sometimes effective. There were fewer positive views on how well brain stimulation worked.

Based on all these findings, specific recommendations were made for conducting future research studies that should produce much more reliable results.

Scientific summary

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.

Chapter 1 Background

Phantom limb pain (PLP) is defined as persistent painful sensations perceived in the missing portion of an amputated limb. Common reasons for limb amputations include circulatory disorders, severe trauma events, cancer and persistent limb infections. Although not fully understood, it is thought that PLP is caused by cortical changes in the brain (i.e. by disorganised brain mapping), with alterations at other levels of the central nervous system, such as the dorsal root ganglion (DRG), having a role.[1] As the nerves heal following amputation, the 'wrong connections' can be formed such that the sense of touch is perceived as pain, and this in turn can result in central sensitisation.[2,3]

Postamputation phenomena can comprise three elements:[4]

1. phantom limb pain – painful sensations referred to the absent limb
2. phantom limb sensation – any sensation in the absent limb, except pain
3. stump pain – pain localised in the stump.

Phantom limb pain occurs in around 60% to 80% of amputees, but the intensity, frequency and duration of PLP can vary widely.[5] Risk factors have been reported to include female sex,[6,7] pre-amputation pain[8] and depression.[9] PLP may be severe in around one-third of patients;[9,10] however, for many patients, the pain may be episodic and not particularly disabling. For example, in one survey, half of patients with PLP reported one or fewer episodes of PLP per week, with most episodes lasting between a few minutes and 1 hour.[10] Another survey reported that around one-fifth of patients always experience PLP.[9] The presence, duration and severity of PLP are, therefore, all-important determinants of health-related quality of life.[11,12]

There appears to be no single best treatment for PLP, although the options seem numerous and varied. As far back as 1980, a literature review and survey identified 68 different methods of treating PLP, 50 of which were still in use at that time.[13] A pharmacological focus on treatment prevails in primary care settings, although amputees with PLP rarely report satisfactory pain management.[14] A recent systematic review[15] of pharmacological interventions found the randomised trial evidence for the medications reviewed to be inconclusive. This was mainly a result of the limited outcomes reported and the small trial sample sizes: 14 trials were identified, covering seven different types of treatment, and the total number of participants across all trials was only 269 (sample sizes ranged from 8 to 36).[15]

Other treatments have also been studied in systematic reviews, although they are often based on even more limited evidence. They include perioperative interventions,[16] transcutaneous electrical nerve stimulation (TENS),[17,18] acupuncture,[19] mirror therapy[20] and myoelectric and body-powered prostheses.[21] This combination of limited evidence and a lack of guidelines for the management of PLP represents a major challenge for clinicians.

Brain, spinal cord and DRG 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. The amount of stimulation the brain receives is controlled by a pacemaker-like device, called a neurostimulator, which is 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) – a therapy that is equally as invasive as DBS – involves placing electrodes on the surface of the brain. Other brain stimulation therapies are non-invasive, such as repetitive transcranial magnetic stimulation (rTMS) and transcranial current stimulation.

In spinal cord stimulation (SCS) and DRG stimulation, electrodes are implanted near the spinal cord or the DRG and connected to a neurostimulator that is inserted under the skin in the abdomen, chest wall or in the buttock area. This generates an electrical pulse that can provide analgesia through different mechanisms.

The National Institute for Health and Care Excellence (NICE)[22,23] recommends that:

> *DBS should only be used in patients with refractory chronic pain syndromes that other treatments have failed to control; patient selection should be carried out by a multidisciplinary team specialising in pain management.*
>
> *© NICE [2011]* Deep Brain Stimulation for Refractory Chronic Pain Syndromes (Excluding Headache).[22] *Available from www.nice.org.uk/guidance/ipg382. All rights reserved. Subject to Notice of rights. NICE guidance is prepared for the National Health Service in England. All NICE guidance is subject to regular review and may be updated or withdrawn. NICE accepts no responsibility for the use of its content in this product/publication*

> *SCS should only be used in adults with chronic pain of neuropathic origin if they continue to experience chronic pain (measuring at least 50 mm on a 0–100 mm visual analogue scale) for at least 6 months despite appropriate conventional medical management and who have had a successful trial of SCS. This is providing that patients are assessed by a multidisciplinary team experienced in chronic pain assessment and management of people with SCS devices.*
>
> *© NICE [2008]* Spinal Cord Stimulation for Chronic Pain of Neuropathic or Ischaemic Origin.[23] *Available from www.nice.org.uk/guidance/ta159. All rights reserved. Subject to Notice of rights. NICE guidance is prepared for the National Health Service in England. All NICE guidance is subject to regular review and may be updated or withdrawn. NICE accepts no responsibility for the use of its content in this product/publication*

Although there are other neurosurgical means of relieving PLP, such as dorsal root entry zone lesioning (DREZ), these surgeries are irreversible and have higher-risk profiles. They should only be considered for patients refractory to the reversible neurostimulation therapies outlined earlier in this section, and are therefore beyond the scope of this review.

Scope of the existing research for stimulation therapies

In order to scope the need for further secondary research, we initially conducted a preliminary search of the published literature. The results indicated that the evidence base for neurostimulation therapies appeared limited.

Invasive brain stimulation therapies

There were no systematic reviews of studies of brain stimulation for PLP. Literature reviews of DBS in patients with chronic pain conditions have included some small studies of PLP patients, with results suggesting beneficial and clinically important pain reduction in some patients.[24–26] However, these three studies were not systematic reviews and the scope of the patient populations studied was broad. Consequently, the data presented were sometimes limited in terms of intervention parameters, patient characteristics and results/numbers of outcomes. This is important because there is no consensus on how DBS operations should be undertaken – slight differences in surgical technique or postoperative stimulation parameters may have important effects on pain; there is also no agreement on how the outcomes of DBS treatment should be evaluated.[27]

Non-invasive brain stimulation therapies

A 2014 Cochrane Database Systematic Review[28] of randomised controlled trials (RCTs) and quasi-RCTs of non-invasive brain stimulation techniques for any chronic pain condition identified two small trials ($n = 27$ and $n = 14$) of rTMS that recruited patients with PLP. Our preliminary literature search identified two further trials of rTMS for PLP: one published in 2016, which was a placebo-controlled double-blind RCT with 54 participants,[29] and one published in 2013, which was a randomised crossover trial with eight participants.[30]

Spinal stimulation therapies

Spinal stimulation therapies include SCS and DRG stimulation therapies. A 2010 literature review of SCS therapies for PLP[31] concluded that for patients in whom medical management has proven inadequate, SCS is a low-risk intervention that can lead to decreased pain, decreased overall symptomology and improved functional outcome. A recently published systematic review of SCS for PLP[32] identified 12 studies that were mostly small case series. However, the review reported limited patient, intervention and outcome data, making interpretation of the study results difficult. DRG stimulation devices have only become available quite recently.

In summary, studies of stimulation therapies for PLP have not been subject to robust systematic review. Such a review was therefore warranted to align the evidence base for these therapies with many of the other treatments for PLP.

Overall aims and objectives of the study

The overall aims and objectives of this study were to determine which types of brain and spinal stimulation therapy are likely to be the most promising for treating PLP. This was done by undertaking a systematic review to assess the research evidence on treatment effectiveness and safety. Given the anticipated limitations of the evidence base, a systematic review of the epidemiology of chronic PLP and a survey of practising NHS clinicians were also undertaken to help inform future research recommendations.

Chapter 2 Systematic review

Methods

A systematic review of the clinical literature was undertaken to identify the existing evidence on the effectiveness and safety of brain and spinal stimulation therapies for PLP. A review of the evidence on the epidemiology and characteristics of patients with chronic PLP was also undertaken. The review protocol was registered on PROSPERO (registration number CRD42017065387), an international database of prospectively registered systematic reviews.

Literature searching

The aim of the literature search was to identify studies of brain and spinal stimulation therapies for PLP and studies of the epidemiology of PLP.

An information specialist developed the search strategy in MEDLINE (via Ovid). A broad search strategy was employed based around terms for PLP. To ensure maximal retrieval of relevant studies, the search was not restricted to brain or spinal stimulation therapies. The MEDLINE strategy was adapted for use in all resources searched.

The searches were carried out in May 2017. No date, language, geographical or study design limits were applied to the strategy. The following databases were searched: MEDLINE (including Epub Ahead of Print, In-Process & Other Non-Indexed Citations, via Ovid MEDLINE Daily and via Ovid MEDLINE), Allied and Complementary Medicine Database, British Nursing Index, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Cumulative Index to Nursing & Allied Health Plus, Database of Abstracts of Reviews of Effects, EMBASE, Health Technology Assessment database, PsycINFO, PubMed and the Science Citation Index.

In addition, the following resources were searched for ongoing, unpublished or grey literature: PROSPERO, Conference Proceedings Citation Index: Science, ClinicalTrials.gov, the EU Clinical Trials Register and the World Health Organization's International Clinical Trials Registry Platform portal.

The search results were imported into EndNote X8 [Clarivate Analytics (formerly Thomson Reuters), Philadelphia, PA, USA] and deduplicated. The complete search strategies can be found in *Report Supplementary Material 1*.

Supplementary search methods were used to identify intervention studies in broad patient populations (i.e. those with chronic pain conditions), which may have contained data on patients with PLP. These methods included forward citation searches and reference checking of key studies and reviews. Clinical experts were asked about the possibility of any relevant studies or data not picked up using other search methods.

Study selection

Two reviewers independently screened all titles and abstracts obtained through the searches. Full papers of potentially relevant studies were obtained wherever possible. Two reviewers independently assessed the relevance of each study using predefined eligibility criteria. Discrepancies were resolved by consensus, or via a third reviewer when necessary.

The eligibility criteria used to select studies of intervention effectiveness were:

- Population – all patients with PLP resulting from amputation.
- Interventions – DBS, MCS, rTMS, transcranial current stimulation, SCS (also referred to as dorsal column stimulation) and DRG stimulation. Studies of treatments that combine different types of neurostimulation therapy were also eligible.

- Comparators – any comparator treatment was eligible.
- Outcomes – eligible studies had to report quantitative results for the review's primary outcome, which was PLP intensity (either continuous or categorical data).
- Secondary review outcomes included –

    - frequency and duration of PLP episodes
    - stump pain
    - health-related quality of life
    - level of disability/daily activities
    - anxiety or depression, if assessed using a validated measure
    - complications and adverse effects of neurostimulation therapy.

- Study designs – based on the results of the scoping exercise of existing research, only comparative trials (prospective randomised and quasi-randomised) were eligible for the non-invasive treatments. Prospective comparative trials and uncontrolled studies were eligible for the invasive therapies. Studies of heterogeneous cohorts of patients, such as patients with other types of chronic pain, were only included if results were reported separately for the patients with PLP.

Data extraction and quality assessment

Data extraction forms were piloted and refined as necessary prior to full data extraction. Randomised trials and quasi-randomised trials were quality assessed using the Cochrane risk-of-bias tool[33] and by consideration of trial external validity. To enhance judgements on selection bias, baseline data were assessed for group imbalances in PLP intensity, frequency or duration, time since amputation and sizeable imbalances in the numbers randomised.[34]

Studies of two or more patients without a control group were quality assessed using the following items from the PROCESS (preferred reporting of case series in surgery) checklist:[35] whether the study was prospective or retrospective in design, whether participants were consecutively or non-consecutively recruited and whether the study was single or multicentre. Adequacy of reporting of population and intervention details was also considered when synthesising results.

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), as described by the IDEAL collaboration framework for evidence-based surgery.[36]

Data extraction and quality assessment were conducted by one reviewer and checked by a second reviewer for accuracy; any discrepancies were resolved by discussion or via a third reviewer if necessary.

Synthesis

A narrative synthesis was undertaken. Data on key characteristics of patients, interventions and outcomes were tabulated to provide clear summaries of the included studies. Studies were grouped by design and by intervention. Differences between studies were discussed in the text, and the potential impact of these differences on outcomes was explored. Results were interpreted in the context of the results of the study quality assessments. Pooling of RCTs using meta-analysis was not possible because of heterogeneity of outcome data.

Review of epidemiology of chronic phantom limb pain

An assessment of the available data on the epidemiology and characteristics of patients with chronic PLP was undertaken. Survey or registry studies reporting data on the epidemiology and/or characteristics of patients with chronic, refractory or severe PLP were eligible. To ensure a focus on these patients, studies had to report data on the level or severity of PLP and include patient inclusion criteria of either ≥ 6 months since amputation (or start of prosthesis use) or a mean or median time since amputation (or start of prosthesis use) of ≥ 1 year. In addition, prospective studies that recruited patients prior to amputation were

eligible if they reported relevant PLP data at or beyond the 6-month time point. To ensure that the number of included studies would be manageable, cross-sectional studies were only included if they had a sample of ≥ 100 patients (or 50 patients in studies of bilateral amputees); there were no limits on sample size for longitudinal studies. The literature searching was conducted as part of that for the review of efficacy and safety (see *Literature searching*). Data extraction and synthesis were also as described in *Data extraction and quality assessment* and *Synthesis*.

Results

Quantity and quality of research available

Overall, 11,557 records were retrieved from the searches of the electronic databases and three studies were identified from other sources (citation searching). *Figure 1* shows details of the number of references excluded at each stage. After removal of duplicates, 6082 titles and abstracts were screened for inclusion. Of these, 333 records were included based on the title and abstract. The full texts of 303 papers were assessed against the review eligibility criteria, with 223 excluded at this stage. The full texts of 30 records were not screened because they were either unobtainable, could not be translated or were identified as

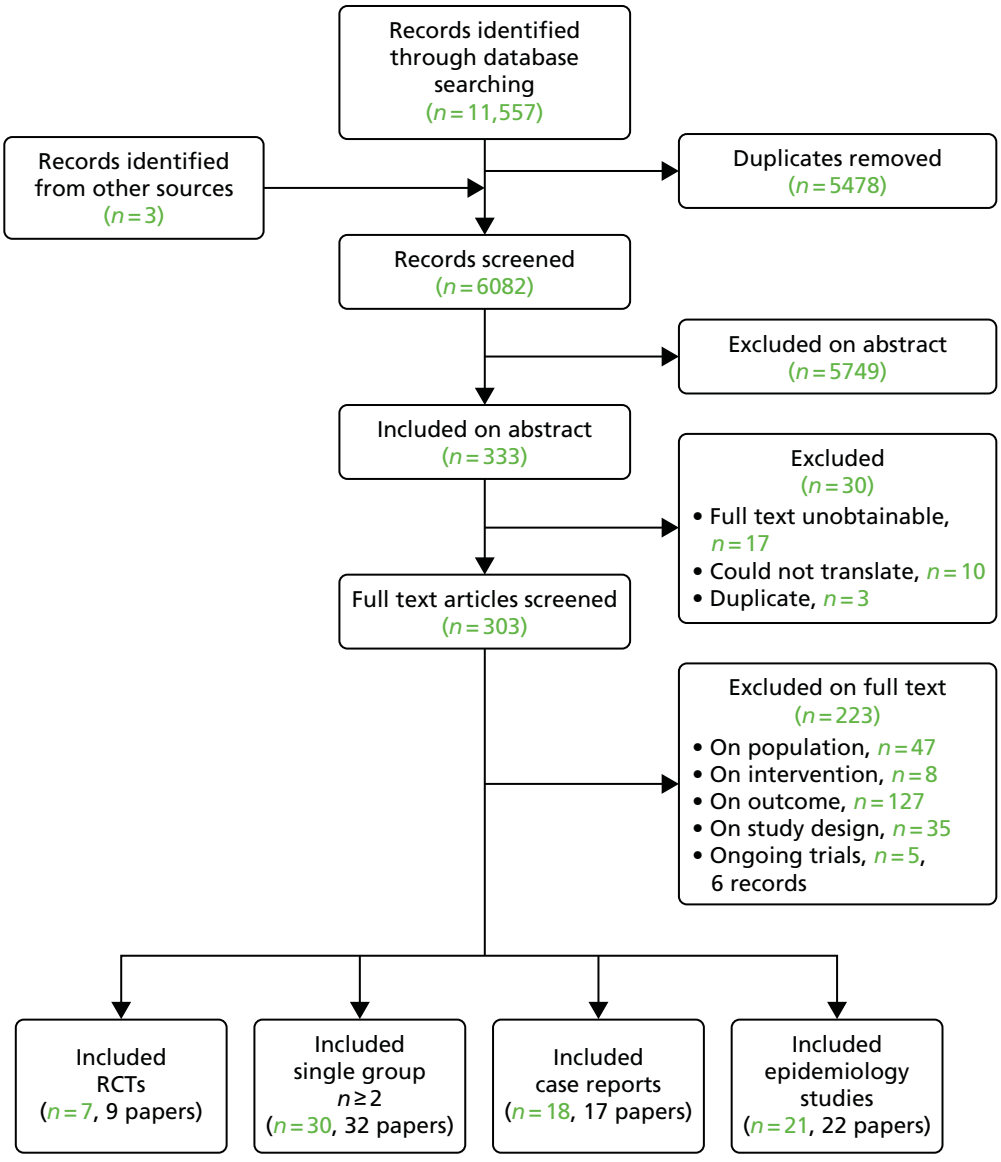

FIGURE 1 Flow diagram of studies through the review.

duplicates. In total, nine records on seven RCTs, 32 papers on 30 non-comparative group studies, 22 papers on 21 epidemiology studies and 17 papers on 18 case reports met the eligibility criteria. Of those excluded based on the full text, 127 were excluded on outcome, 47 on population, 35 on study design and 8 on intervention. There were also five relevant trials that were still ongoing (i.e. results were not yet available).

Ongoing trials

Details of the five ongoing trials are shown in *Table 1*. In terms of invasive treatments, there are two single-group studies of SCS[37,38] and a randomised crossover trial of MCS,[39] which planned to include patients with chronic neuropathic pain including PLP. For non-invasive treatments, there is a randomised crossover trial of transcranial direct current stimulation (tDCS)[40] and a RCT of tDCS and mirror therapy,[41] which has a factorial design.

Studies of efficacy, effectiveness and safety

Randomised controlled trials

Characteristics of randomised controlled trials

There were nine records reporting on a total of seven separate RCTs that met the inclusion criteria. Three RCTS were of rTMS,[29,43,44] three were of tDCS[30,45] and one was of MCS.[46] One of the papers on tDCS described two different RCTs conducted with the same cohort of patients.[30] *Tables 2* and *3* show baseline patient characteristics for the included RCTs. *Tables 4* and *5* show details of the interventions. The patient selection criteria used in the RCTs are listed in *Report Supplementary Material 2*.

TABLE 1 Ongoing trials of neurostimulation that include PLP participants

ClinicalTrials.gov identifier and title	Intervention	Study design	Participants	Location	Status (November 2017)
NCT02684201; *Epidural Spinal Cord Stimulation for Sensory Restoration and Phantom Limb Pain in Upper-Limb Amputees*[37]	SCS	Single-group study	PLP	USA	Recruiting participants
NCT03027947; *Spinal Root and Spinal Cord Stimulation for Restoration of Function in Lower-Limb Amputees*[38]	SCS	Single-group study	PLP	USA	Recruiting participants
NCT01554332; *Motor Cortex Stimulation for Chronic Neuropathic Pain*[39]	MCS	Randomised crossover trial	Chronic neuropathic pain, including PLP	Brazil	Ongoing but not recruiting participants
NCT02051959; *Long-Term Treatment of Patients Experiencing Phantom Limb Pain With Transcranial Direct Current Stimulation (tDCS)*[40]	tDCS	Randomised crossover trial	PLP	Israel	Suspended participant recruitment
NCT02487966; *Optimizing Rehabilitation for Phantom Limb Pain Using Mirror Therapy and Transcranial Direct Current Stimulation (tDCS)*[41,42]	tDCS and mirror therapy	RCT with factorial assignment	PLP	USA	Recruiting participants

TABLE 2 Baseline characteristics of participants in the RCTs of non-invasive therapies

Study	Country	Interventions studied	Number of PLP patients randomised	Mean age (years)	% male	Unilateral/ bilateral amputation	Amputation site	Amputation cause	Mean time since amputation (years)	Prosthesis use (%)	Comorbidities	PLP at baseline (mean VAS score)	Duration/frequency of PLP episodes
Ahmed *et al.* 2011[43]	Egypt	rTMS vs. sham	27	52.5	70	Unilateral	60% below knee, 37% above elbow and 3% below elbow	22% traumatic, 30% ischaemic and unclear for remainder	Unclear mean 'duration of illness' of 2.7 years	NR	All participants had diabetes mellitus	7.5	NR
Bolognini *et al.* 2013[30]	Italy	tDCS vs. sham	8	59.0	38	Unilateral	62% upper leg, 25% lower leg and 13% upper arm	75% blood vessel disease and 25% accident	1.6	63	NR	Mean scores ranged between 2.5 and 3.3 over the two studies	NR
Bolognini *et al.* 2015[45]	Italy	tDCS vs. sham	8	60.8	75	Unilateral	50% upper leg, 38% lower leg and 12% upper arm	63% blood vessel disease, 25% trauma and 12% cancer	4.6	50	NR	5.6	Average frequency of PLP paroxysms[a] (above background level): 6.4
Malavera *et al.* 2016[29] and 2013[47,48]	Colombia	rTMS vs. sham	54	33.9	93	Unilateral	Lower limb	Landmine	7.8	NR	NR	4.9	NR
Irlbacher *et al.* 2006[44]	Germany	rTMS vs. sham	14	46.6	57	Unilateral	50% upper limb	NR	15.2	NR	NR	NR	

NR, not reported; VAS, visual analogue scale.
a Scale of 0 (never during the day) to 10 (very frequent).

TABLE 3 Baseline characteristics of participants in the RCT of MCS

Study	Country	Interventions studied	Number of PLP patients randomised	Mean age (years)	% male	Amputation site	Amputation cause	Mean time since amputation (years)	Prosthesis use (%), comorbidities, PLP at baseline (mean VAS score) and duration/frequency of PLP episodes
Radic *et al.* 2015[46,49]	Canada	MCS, high vs. low intensity (subtherapeutic) stimulation	2[a] (subgroup of $n = 12$ with different neuropathic pain syndromes)	36.5	100	Second finger in both patients	NR	Mean duration of pain: 4.9 years	All NR

NR, not reported; VAS, visual analogue scale.
a One patient withdrew because of a protocol breach (stimulator stopped working).

TABLE 4 Intervention details for the RCTs of non-invasive therapies

Study	Intervention	Control	Location of stimulation	Stimulation parameters	Notes
Ahmed *et al.* 2011[43]	rTMS	Sham stimulation: coil elevated and angled away from the head	Optimal scalp position determined from where transcranial magnetic stimulation evoked motor potentials of maximum peak-to-peak amplitude in muscle proximal to the stump	High frequency: 20 Hz 10-second trains (200 pulses) every 1 minute Intensity of stimulation: 80% of resting motor threshold 10-minute session daily for 5 consecutive days	
Bolognini *et al.* 2013[30]	Trial 1: • anodal tDCS	Sham stimulation (stimulator turned off after 30 seconds)	M1 Anodal electrode placed over C3 or C4 to target hemisphere contralateral to amputation Cathode electrode placed over contralateral supraorbital area	Frequency NR 15-minute sessions Intensity: 2 mA	Crossover design Paper reported two trials undertaken in the same cohort. One trial targeted the M1, the other targeted the PPC
	Trial 2: • anodal tDCS • cathodal tDCS	Sham stimulation (stimulator turned off after 30 seconds)	PPC Hemisphere contralateral to amputation Active electrode placed over P3 or P4 Reference electrode placed over contralateral supraorbital area	Frequency NR 15-minute sessions Intensity: 2 mA	
Bolognini *et al.* 2015[45]	Anodal tDCS	Sham stimulation (current lasted for 30 seconds)	Motor cortex Anodal electrode placed over C3 or C4 to stimulate M1 contralateral to the amputation Cathode electrode over the contralateral supraorbital area	15-minute session Ramping period of 10 seconds at beginning and end Intensity: 1.5 mA 5 consecutive days	Crossover design

Study	Intervention	Control	Location of stimulation	Stimulation parameters	Notes
Malavera *et al.* 2016[29] and 2013[47,48]	rTMS	Sham stimulation (sham coil)	M1 contralateral to the amputated leg (corresponding to the first dorsal interosseous muscle of the hand contralateral to pain)	Frequency: 10 Hz 20-minute sessions – 20 trains of 6 seconds (54-second intertrain interval) Intensity of stimulation: 90% of motor threshold Daily session for 10 days during a 2-week period	
Irlbacher *et al.* 2006[44]	rTMS	Sham stimulation Identical placement of coil that looks and sounds identical and produces same scalp sensation but does not activate cortex	M1 area corresponding to affected phantom limb. Optimal placement defined by maximal motor response	Frequency: rTMS 1 Hz, 5 Hz Sham: 2 Hz 1 Hz: ≈8 minutes 2 Hz: ≈4 minutes 5 Hz: ≈1.5 minutes 500 pulses per session Intensity of stimulation: 95% of the intensity that evoked electromyographic response ≥ 0.1 mV in 5 out of 10 trials when stimulating unaffected 'mirrored' M1 area of phantom limb Daily session for 5 consecutive days (see notes)	Three 28-consecutive-day treatment blocks: 5 days of baseline metrics, 5 days of treatment, 5 days of observation, 18-day wash-out period, then next block Not all patients completed the planned three blocks: six completed one block, three completed two blocks and five completed all three blocks

M1, primary motor cortex; NR, not reported; PPC, posterior parietal cortex.

TABLE 5 Intervention details for the RCT of MCS

Study	Intervention	Control	Surgical methods	Location of stimulation	Stimulation parameters
Radic *et al.* 2015[46,49]	High-intensity MCS	Low-intensity MCS (subtherapeutic)	A four-contact electrode was placed in epidural space through burr hole No mention of trial period	Contralateral motor cortex Electrode aligned parallel or perpendicular to the central sulcus. Intraoperative stimulation used to check location	Stimulation applied in cycling mode. High intensity: on for 10 minutes, off for 2 hours. Low intensity on for 1 minute, off for 6 hours Amplitude and pulse width set to 70% motor threshold Motor threshold: 3.9, amplitude 2.7 V, pulse width 450 microseconds in one patient Motor threshold: 4, amplitude 2.8 V, pulse width 210 microseconds in other patient Frequency: 50 Hz

Four studies were conducted in Europe,[30,44,45] one was conducted in Canada,[46] one was conducted in Egypt[43] and one was conducted in Colombia.[29] The six RCTs of non-invasive interventions used sham stimulation as a control. The other RCT[46] used high-frequency MCS as the intervention, with low-frequency stimulation (at a subtherapeutic level) as a placebo treatment. Five of the RCTs had a crossover design,[30,44–46] including two crossover trials undertaken on the same cohort but with different targets for tDCS;[30] one of these trials included two active treatments (anodal tDCS and cathodal tDCS) as well as sham stimulation so patients went through three phases. Similarly, in the crossover trial on rTMS, patients underwent three different interventions: stimulation at 1 Hz, 5 Hz and sham stimulation.[44] The two trials reported in Bolognini *et al.*[30] differed in design from the other RCTs of non-invasive treatments as patients underwent just one session of each intervention, separated by ≥ 3 hours, with outcome assessments made immediately and after 90 minutes. The other non-invasive trials involved daily sessions for a period of 5–10 days and longer follow-up periods (except for one[44] in which measurements were taken 15 minutes after the intervention).

Some trials included patients with chronic pain conditions other than PLP, but data were only extracted on PLP patients. The RCT of MCS[46] included only two patients with PLP, one of whom withdrew from the study. Sample sizes of PLP patients in the RCTs of non-invasive treatments varied, ranging from 8 to 54 participants. Participant mean ages ranged from 33.9 to 60.8 years. Over 70% of patients were male in all but one study,[30] in which 38% were male.

All the RCTs included only patients with unilateral amputations. Five of the studies included patients with upper or lower-limb amputations,[30,43–45] whereas one included only lower-limb amputees.[29] Both of the patients in the RCT of MCS[46] had finger amputations. Causes of amputation varied and were not reported in two trials.[44,46] One RCT specifically included only landmine victims.[29] In the remaining four RCTs,[30,43,45] 22% to 25% of amputations resulted from trauma or accident. Blood vessel disease accounted for the majority of amputations in three of these trials.[30,45] The mean time since amputation was reported in five trials[29,30,44,45] and ranged from 1.6 to 15.2 years. The other trials reported a mean duration of pain of 4.9 years[46] and a mean duration of illness of 2.7 years, respectively,[43] although it was not clear in the latter study whether illness referred to PLP or diabetes mellitus (which all participants had).

Baseline PLP intensity ranged from 4.9 to 7.5 on a visual analogue scale (VAS) (scale of 0–10) in the three trials that reported it.[29,43,45] One publication reported the mean VAS score before tDCS in each of two different trials on the same patients, which was much lower than the other studies, ranging from 2.5 to 3.3.[30] One trial reported the average frequency of PLP episodes above the background level as 6.4 on a 0–10 scale (0 = never during the day, 10 = very frequent),[45] but neither mean duration nor frequency of PLP episodes at baseline were reported in any other trial.

Trial risk-of-bias assessment results

The results of the risk-of-bias assessments are presented in *Table 6*. The Bolognini *et al.*[30] paper had results for two distinct but closely related trials; for the purposes of this risk-of-bias assessment, these two trials were sufficiently similar to record the results as one trial. Three of the five trials that were assessed for risk of bias had a crossover design, in which patients acted as their own controls,[30,44,45] and two trials had a parallel-group design.[29,43]

One trial[43] had a high-risk judgement for overall risk of bias owing to the use of quasi-randomisation: patients were allocated treatments on the basis of the day of the week. This may be the reason for the large imbalance in patient numbers across treatment groups seen in this trial (17 were allocated to the active treatment group and 10 were allocated to the sham group). One trial[45] had an unclear risk judgement for overall risk of bias because of the lack of detail on whether or not the trial had missing data (i.e. it was unclear whether or not patients dropped out of the trial and how any such missing data were handled in the analyses). This trial was a crossover trial and the risk of selection bias was likely to be low; it reported that the same number of participants were randomised to the two intervention sequences, which would eliminate the impact of any period effects (i.e. differences between responses in the second period compared with responses in the first period that were not caused by the interventions being trialled).[45]

The remaining three trials[29,30,44] had low risk judgements for overall risk of bias. Although the randomisation method details were not well reported for two of these trials,[30,44] their crossover designs meant that the risk of selection bias was likely to be low; in one trial,[30] there was no follow-up (i.e. assessments were immediately after treatment) and the gap between interventions was very short, ruling out the possibility of period effects. Both trials[30,44] reported the use of designs that would minimise carry-over effects between treatments: one[30] stated that the different treatment sessions were separated by > 3 hours, during which time PLP had returned to baseline, and one[44] reported the use of 18-day wash-out phases.

Randomised controlled trial results for non-invasive treatments

Results from the randomised and quasi-randomised trials of non-invasive treatments (tDCS and rTMS) are presented in *Table 7*.

Transcranial direct current stimulation Two publications – both by Bolognini *et al.*[30,45] – reported on trials of the efficacy and safety of tDCS for PLP. Bolognini *et al.*[30] studied the immediate effects of two variants of tDCS in the same cohort of patients: tDCS to the primary motor cortex (M1) and tDCS to the posterior parietal cortex (PPC). This study found a significant but very short-term benefit (of < 90 seconds) of tDCS to M1 on the pain of PLP but no benefit on pain from tDCS to the PPC. The other Bolognini *et al.*[45] publication reported on a trial of the effects of 1 week of treatment with tDCS in M1 and found a significant benefit at the end of treatment, with the benefit sustained for a further week of (no treatment) follow-up. The Bolognini *et al.*[45] trial also evaluated depression as an outcome, reporting a statistically significant effect favouring tDCS. Baseline data identified the trial population as being mostly comprised of patients with mild depression.[45] No significant differences were reported for stump pain in the Bolognini *et al.*[45] trial. Clearly, these trials are limited by their small sample sizes and short follow-up periods. Moreover, the baseline data suggest that the trial results should only be viewed as being applicable to patients with quite mild PLP.

Across all the tDCS trials, there was little difference between active tDCS and sham in terms of the summary scores of the specific types of adverse effects that were evaluated.

TABLE 6 Results of randomised and quasi-randomised trial risk-of-bias assessments

Study	Sequence generation	Allocation concealment	Important baseline imbalance	Blinding of participants and researchers	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Overall judgement
Ahmed *et al.* 2011[43]								
Judgement	High risk	High risk	High risk	Low risk	Low risk	Unclear risk	Low risk	High risk
Support	Allocation on the basis of day of the week		Large imbalance in group numbers: 17 in intervention vs. 10 in sham	Patients blinded. Researcher giving treatment not blinded but clinic time only 10 minutes	Patient self-assessment. Realistic sham stimulation	No CONSORT diagram or description of patient flow through trial	Relevant pain outcomes reported	
Bolognini *et al.* 2013[30]								
Judgement	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Support	No details other than 'randomised' but this was a crossover trial. Treatment sessions were short, as were the gaps between treatments. The follow-up time point was immediately after the intervention, so minimal risk of period effects		Patients acted as their own control (crossover study)	Patients blinded. Sham stimulator turned off after 30 seconds Assessments were either immediately after or 90 minutes after treatment	Blinded patient self-assessment. Validation reference cited in paper	Number randomised not totally clear but attrition very unlikely owing to very short follow-up	Review-relevant outcomes reported	Methods also suggested low risk of carryover effects
Bolognini *et al.* 2015[45]								
Judgement	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear risk	Low risk	Unclear risk
Support	Few randomisation details. But this was a crossover trial and the same number of participants were randomised to the two intervention sequences (i.e. active then sham, and sham then active). This would eliminate the impact of any period effects		Crossover design	Patients blinded. Sham stimulator turned off after 30 seconds. Sessions were short so unlikely to be differences in cointerventions from carers	Blinded patient self-assessment. Validation reference cited in paper	No details provided	Review-relevant outcomes reported	Based primarily on lack of detail on patient flow through trial
Irlbacher *et al.* 2006[44]								
Judgement	Low risk (probably)	Low risk (probably)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Support	No details other than 'randomised' but crossover design used so likely to be low risk		Crossover design	Participants blinded. Sham device realistic. Caregivers not blinded but sessions were short so unlikely to be differences in cointerventions from carers	All outcomes were patient self-assessed and patients were blinded	Dropouts evenly distributed across groups: $n = 9$ for all three treatment groups. 14 patients were recruited	No protocol, but no obvious discrepancy or omission or logical non-consistency between design and reported outcomes	18-day wash-out phase between treatments

Study	Sequence generation	Allocation concealment	Important baseline imbalance	Blinding of participants and researchers	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Overall judgement
Malavera *et al.* 2016[29]								
Judgement	Low risk	Low risk	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk
Support	A computer-generated randomisation method with a permuted block size of six was used. The randomisation code was only given to the treating investigator on the first day of treatment session by an independent investigator not involved with any other aspect of the trial		Frequency and duration of PLP not reported	Patients blinded. Sessions were short so unlikely to be differences in cointerventions from carers	Patient self-assessment. When asked, patients were not able to tell which treatment they were on	Low risk for 15-day results. Six patients with missing data at day 30 – some uncertainty whether or not imputation methods were appropriate	Review-relevant (primary) outcome reported as stated on trial registry	

CONSORT, Consolidated Standards of Reporting Trials.

TABLE 7 Randomised and quasi-randomised trial results of non-invasive brain stimulation therapies for PLP

Study	Outcome measure	Results[a]
Trials of tDCS		
Bolognini *et al.* 2013[30] (trial 1, $n = 8$ crossover; tDCS in M1)	PLP: VAS 0–10	*p*-values for this study are for comparisons between follow-up time point and baseline; the follow-up time point was immediately after the intervention
		Anodal tDCS of M1: baseline 2.6 vs. post tDCS 0.8; $p < 0.02$
		Sham: baseline 3.3 vs. post tDCS 2.6; $p = 0.3$
		PLP returned to near-baseline levels after 90 minutes
	Stump pain VAS	No significant effect reported for stump pain ($p = 0.8$). Results presented only as a graph
	Adverse effects: 0–27 score[b]	tDCS of M1 2.6, sham 2.1; $p = 0.36$
Bolognini *et al.* 2013[30] (trial 2, $n = 7$ crossover; tDCS in PPC)	PLP: VAS 0–10	No significant differences, ANOVA $p = 0.7$. Results presented only as a graph
	Stump pain VAS	No significant differences, ANOVA $p = 0.1$. Results presented only as a graph
	Adverse effects: 0–27 score[b]	tDCS 2.43, sham 2.13; $p = 0.45$
Bolognini *et al.* 2015[45] (crossover, $n = 8$; tDCS in M1)	PLP: VAS 0–10, % change from baseline	ANOVA showed significant effect of the tDCS week (sham or active); $p = 0.04$
		tDCS –28%, sham –9%; $p = 0.04$
		Difference compared with sham week: immediately after 1 week of active tDCS –42%; $p = 0.04$. Follow-up week (i.e. 1 week following active/sham weeks) –41%; $p = 0.04$
	PLP: frequency of paroxysms (0–10 VAS), % change from baseline	Main effect of week showed a significant reduction during the week of active tDCS –33%; $p = 0.03$
		Significant reduction during follow-up week –44%; $p = 0.01$. Sham week –9%
	Beck Depression Inventory	Prior to tDCS, 14; after final tDCS (and sham), 11; $p = 0.05$
	Adverse effects: 0–27 score[b]	tDCS, 3.22; sham, 2.74; $p = 0.31$
		No adverse effects reported

TABLE 7 Randomised and quasi-randomised trial results of non-invasive brain stimulation therapies for PLP (*continued*)

Study	Outcome measure	Results[a]
Trials of rTMS		
Ahmed *et al.* 2011[43] (rTMS, $n = 17$; sham, $n = 10$)	PLP: VAS 0–10	*p*-values for this study are for comparisons between follow-up time point and baseline Baseline: • rTMS, 7.4 (1.3) • sham, 7.6 (0.84) After one session: • rTMS, 7.1 (2.1); $p = 0.40$ • sham, 7.80 (0.91); $p = 0.59$ After five sessions: • rTMS, 3.4 (1.2); $p = 0.001$ • sham, 7.40 (0.84); $p = 0.59$ 1 month (from final session): • rTMS, 3.4 (1.7); $p = 0.001$ • sham, 7.3 (0.8); $p = 0.46$ 2 months (from final session): • rTMS, 4.5 (2.2); $p = 0.001$ • sham, 7.6 (1.0); $p = 1.0$
	Pain: Leeds assessment of neuropathic symptoms and signs	Baseline: • rTMS, 17.2 (3.7) • sham, 18.10 (1.9) After one session: • rTMS, 16.8 (3.4); $p = 0.38$ • sham, 17.30 (1.9); $p = 0.11$ After five sessions: • rTMS, 8.4 (3.7); $p = 0.001$ • sham, 17.8 (2.3); $p = 0.49$ 1 month (from final session): • rTMS: 7.6 (2.7); $p = 0.001$ • sham: 17.4 (2.2); $p = 0.19$ 2 months (from final session): • rTMS: 9.5 (3.7); $p = 0.001$ • sham: 16.8 (1.7); $p = 0.04$

continued

TABLE 7 Randomised and quasi-randomised trial results of non-invasive brain stimulation therapies for PLP (*continued*)

Study	Outcome measure	Results[a]
	Hamilton Rating Scale for Depression score	rTMS: • before 19.5 (6.7), after 10.4 (4.6); $p = 0.0001$. Follow-up time point was not specified Sham: • before 17.1 (1.6), after 15.4 (2.4); $p = 0.07$
	Hamilton Anxiety Rating Scale score	rTMS: • before 15.8 (3.4), after 9.6 (2.9); $p = 0.0001$. Follow-up time point was not specified Sham: • before 15.8 (1.7), after 16.2 (1.5); $p = 0.39$
Malavera *et al.* 2016[29] and 2013[47,48] (rTMS, $n = 27$; sham, $n = 27$)	PLP: number with ≥ 30% reduction in VAS score compared with baseline; primary outcome	15 days (after end of treatment): rTMS 19 (70.3%) vs. sham 11 (40.7%), RR = 1.72, 95% CI 1.03 to 2.89 30 days: rTMS 15 (55.5%) vs. sham 9 (33.3%), RR = 1.66, 95% CI 0.88 to 3.13
	PLP: absolute VAS scores	Baseline: rTMS 4.98 (1.97), sham 4.82 (1.98) 15 days: rTMS 2.3 (2.5), sham 3.7 (3.0). Mean between group difference = 1.4, 95% CI –0.07 to 2.93; $p = 0.06$ 30 days: rTMS 3.0 (2.6), sham 3.9 (2.7). Mean between group difference = 0.9, 95% CI –0.59 to 2.31; $p = 0.24$
	Zung self-rating depression scale	Baseline: rTMS 26.7 (5.7), sham 25.6 (6.8) 15 days: rTMS 25.1 (5.9), sham 24.2 (4.4) 30 days: rTMS 24.9 (9.1), sham 23.2 (3.0) No statistically significant between-group differences
	Zung self-rating anxiety scale	Baseline: rTMS 27.8 (7.7), sham 26.9 (9.3) 15 days: rTMS 25.8 (7.0), sham 25.1 (5.5) 30 days: rTMS 23.8 (7.3), sham 24.4 (4.2) No statistically significant between-group differences
	Adverse effects	No significant differences between groups in minor adverse effects, such as headache, neck pain and sleepiness. No serious adverse effects were reported

TABLE 7 Randomised and quasi-randomised trial results of non-invasive brain stimulation therapies for PLP (*continued*)

Study	Outcome measure	Results[a]
Irlbacher *et al.* 2006[44] ($n = 14$ crossover; rTMS)	PLP: VAS 0–100 Pre and post scores are separately averaged over five measurements (daily measurements taken over 5 consecutive treatment-days)	Immediately before treatment (mean, over 5 days): • rTMS 1 Hz, 43.8 (29.3) • rTMS 5 Hz, 53.0 (25.5) • sham 2 Hz, 45.9 (28.7) 15 minutes after treatment (mean, over 5 days), $n = 9$: • rTMS 1 Hz, 42.2 (27.9) • rTMS 5 Hz, 49.9 (23.3) • sham 2 Hz, 43.7 (29.7)

ANOVA, analysis of variance; CI, confidence interval; M1, primary motor cortex; PPC, posterior parietal cortex; RR, risk ratio; SD, standard deviation.
a Mean (SD) unless otherwise stated.
b Calculated as the sum of intensity rating (0–3) for nine separate items (headache, neck pain, scalp pain, scalp burn, prickle, reddened skin, drowsiness, difficult concentration and mood changes).

Repetitive transcranial magnetic stimulation Three trials compared rTMS with sham rTMS.[29,43,44] The largest trial,[29] which randomised 54 participants with PLP, was rated as having a low overall risk of bias. Results for the trial's primary outcome – the number of patients with a ≥ 30% PLP reduction from baseline, at 2 weeks after the end of treatment – demonstrated a statistically significant difference favouring rTMS over sham. However, the result was not statistically significantly different at 1 month after the end of treatment, and no statistically significant between-group differences were seen at either of these time points when absolute PLP VAS data were used in the analyses. No statistically significant between-group differences were seen for the trial's anxiety, depression and adverse effects outcomes.

A small, quasi-randomised trial[43] reported statistically significant improvements in PLP directly after five rTMS sessions and at both 1 month and 2 months after the final session. This trial also reported statistically significant improvements in depression and anxiety, although the relevant follow-up time points for these results were not stated. However, this trial reported its analyses as comparisons between follow-up time points and baseline for each intervention (rTMS and sham), rather than as comparisons between the intervention groups. More importantly, this trial's results were judged to be at a high risk of bias and, therefore, they should not be considered as reliable estimates of effect.

The third trial was a small study of 5 days of treatment reported by Irlbacher *et al.*[44] It found similar PLP reductions immediately after stimulation across groups, including sham stimulation. It was judged to have a low risk of bias, but the sample size was small (only 14 patients). The authors concluded that, at present, rTMS should not be recommended as a standard therapy for PLP.

Two of the three rTMS trials[29,43] reported data on PLP intensity 1 month after the end of treatment. The two results are presented in a forest plot (*Figure 2*), although they were too different to justify pooling. The result from the trial that was rated as having a low risk of bias, reported by Malavera *et al.*,[29] shows no statistically significant difference between rTMS and sham, whereas the result from the quasi-randomised trial reported by Ahmed *et al.*,[43] which has been rated as having a high risk of bias, shows quite a large and statistically significant effect favouring rTMS.

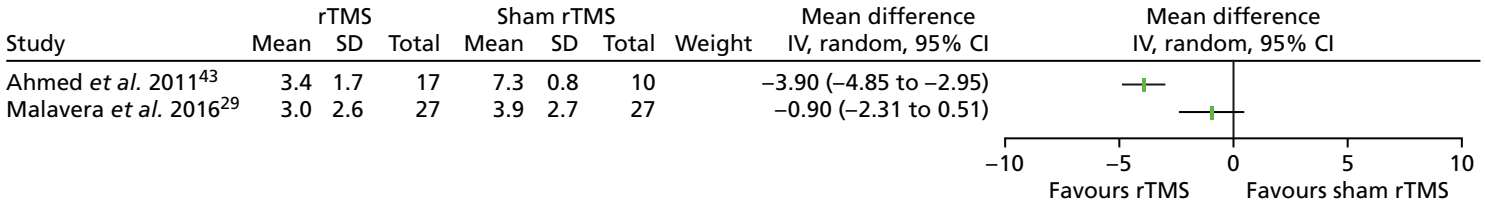

FIGURE 2 Forest plot of rTMS trial results for PLP intensity (VAS 0–10 scores) 1 month after the end of treatment. CI, confidence interval; IV, instrumental variable; SD, standard deviation.

Results for invasive treatments

Although one randomised trial[46] was identified that recruited patients with PLP, it provided outcome data for only a single PLP patient and so cannot be evaluated as a RCT in the present context. This study was of MCS and recruited patients with a range of different neuropathic pain conditions. Only two patients had PLP, both with phantom finger pain. After recruiting 12 patients, the trial was stopped early owing to a lack of efficacy. One PLP patient was among the six patients who completed the trial: for this patient, the stimulator was explanted owing to a lack of benefit at 33 months (*Table 8*). Six patients withdrew early from the trial.

Summary

Results from a good-quality randomised trial[29] of 54 PLP patients suggest worthwhile benefits of rTMS in reducing PLP, but not in reducing anxiety or depression. However, the PLP benefit seen at 2 weeks after the end of treatment was no longer evident at 4 weeks after the end of treatment. Small randomised trials[30,45] of tDCS to M1 suggest the possibility of modest, short-term reductions in PLP. Although both interventions appear safe, larger trials with longer follow-up periods would be needed to resolve the considerable uncertainty about the true potential of these non-invasive treatments for PLP. There is no RCT evidence available for invasive neurostimulation treatments for PLP.

TABLE 8 The RCT results for invasive treatments

Study	Outcome measure	Results[a]
Radic *et al.* 2015[46,49] (MCS; $n = 2$ with PLP, crossover trial; one PLP patient withdrew)	PLP VAS % change	At 12 weeks' follow-up, with high-intensity stimulation compared with low-intensity stimulation, there was no change in VAS score during activities or the 'most pain' VAS score. There was a reduction in VAS score during rest of around 23% and a reduction in the 'least pain' of around 17%
	McGill Pain Questionnaire absolute scores	Small decrease (< 5) from baseline in total score for low-intensity stimulation. No change for high-intensity stimulation
		Increase from baseline in miscellaneous score for low- (1-point increase) and high-intensity stimulation (2-point increase)
	SF-36	With high-intensity stimulation compared with low-intensity stimulation, there was around a 15% reduction in the mental summary score, and no change in the physical summary score
	BDI II	Small increase from baseline in BDI score for low- (around 5 points) and high-intensity stimulation (around 2 points)
	Standard 7-point Patient Global Impression of Change	No difference between low- and high-intensity stimulation: Patient Global Impression of Change score of 4
	Long-term follow-up	At 33 months' follow-up, the stimulator was explanted because of the lack of benefit
	Adverse events	The PLP patient who withdrew did so because their stimulator turned off unexpectedly

BDI, Beck Depression Inventory; SF-36, Short Form questionnaire – 36 items.
a For the PLP patient, data are presented only in graphs.
Note
Follow-up time points of 12 weeks for both the intervention and the control.

Non-comparative group studies

Characteristics of non-comparative group studies

Thirty non-comparative group studies, which were mostly case series, met the inclusion criteria. Nine studies were of DBS,[50–58] four were of MCS,[59–62] three were of DRG stimulation[63–65] and 14 were of SCS.[66–78]

Some study cohorts overlapped. Five patients treated with DBS in a single-centre case series[51] were all included in a cohort of 14 patients treated at two centres reported in another publication.[52] The five patients were also included in a further paper with 3-year follow-up results, with the addition of one patient to the cohort.[58] One study of SCS[76] probably includes results for patients already reported in an earlier paper,[77] but not enough information was available to be sure these are all the same patients. Five studies were reported only as conference abstracts.[52,53,63,65,72] *Tables 9–11* outline the basic design characteristics of the non-comparative group studies; many papers did not report adequate details. Of those that reported design methods, seven were prospective[50–52,54,58,61,63] and eight were retrospective studies.[59,64–66,71,72,75] Fifteen studies were conducted at a single centre[50,51,54,58,61,62,65,68,69,73–77] and three reported data from multiple centres.[52,66,79] Patient recruitment was reported as being consecutive in nine studies.[50–52,58,59,64,65,69,75]

Tables 12–14 present the baseline characteristics of patients included in the non-comparative group studies. The number of patients with PLP ranged from 2 to 26, with most studies including fewer than 10 PLP patients. Baseline characteristics for the subgroups of patients with PLP were not available in many of the publications that reported on mixed cohorts of chronic pain patients. When reported, the mean age of patients with PLP ranged from 38.8 to 74.7 years. In most studies, most patients were male.

The site of amputation varied: in 10 papers,[50,51,56,59,62,64,68,73,78] all or most patients had lower-limb amputation; in four papers[57,60,61,70] all or most had upper-limb amputations; and there were equal numbers in two papers.[58,65] In seven of the studies that reported cause of amputation,[51,52,56,58,70,71,78] all or most patients had undergone amputation because of trauma. Three studies[67,68] only included patients who had undergone amputation as a result of disease (including cancer) and the remainder had mixed causes or the cause was unreported.

Few studies reported the mean time since amputation, although some reported the duration of pain. The mean duration of pain patients had experienced prior to the intervention ranged from 2.6 to 23.0 years. Baseline intensity of PLP was not reported in most studies and different measurements were used in the few studies that did report it. In those studies that reported PLP on a VAS, mean scores were > 7 (on a VAS of

TABLE 9 Motor cortex stimulation: key design characteristics of non-comparative group studies

Study	Design characteristics
Carroll *et al.* 2000[61]	Prospective, single-centre audit of neuropathic pain cases (1995–8) NR whether consecutive or non-consecutive
Hosomi *et al.* 2008[59]	Retrospective, consecutive case series of neuropathic pain patients NR whether single or multicentre
Saitoh *et al.* 2000[62]	Single-centre case series of deafferentation pain patients (1996–8) Unclear whether consecutive or non-consecutive NR whether retrospective or prospective
Sol *et al.* 2001[60]	Details NR

NR, not reported.

TABLE 10 Deep brain stimulation: key design characteristics of non-comparative group studies

Study	Design characteristics
Abreu *et al.* 2017[58] (same cohort as Pereira *et al.* 2013,[51] with one additional patient)	Prospective, single-centre, consecutive case series of patients with chronic neuropathic pain after amputation or BPA (2009–12)
Bittar *et al.* 2005[56]	Case series; method details NR
Boccard *et al.* 2013[50]	Prospective, single-centre, consecutive case series of chronic neuropathic pain patients over 12 years (1999–2011)
Chamadoira *et al.* 2011[53] (conference abstract)	Case series; NR whether prospective or retrospective, single or multicentre, or consecutive or non-consecutive recruitment
Mundinger and Salomão 1980[57]	Study of chronic pain patients NR whether single or multicentre, or consecutive or non-consecutive recruitment Unclear whether retrospective or prospective
Owen *et al.* 2007[54]	Prospective, single-centre study of neuropathic pain patients NR whether consecutive or non-consecutive recruitment
Pereira *et al.* 2012[52] (conference abstract)	Prospective study of consecutive patients treated in two European centres (2003–11)
Pereira *et al.* 2013[51] (from same cohort as Pereira *et al.* 2012[52])	Prospective, single-centre, consecutive case series of patients with chronic neuropathic pain after amputation or BPA (2009–11)
Yamamoto *et al.* 2006[55]	Method details NR

BPA, brachial plexus avulsion; NR, not reported.

TABLE 11 Spinal stimulation therapies: key design characteristics of non-comparative group studies

Study	Design characteristics
Dorsal root ganglion stimulation	
Eldabe *et al.* 2015[64,79]	Retrospective review of records of all patients receiving DRG stimulation at multiple European sites
Love-Jones *et al.*[63] (conference abstract)	Prospective series of patients with PLP and/or stump pain enrolled in five clinical trials
Wahlstedt and Leljevahl 2013[65] (conference abstract)	Retrospective, single-centre, consecutive case series
Spinal cord stimulation	
Broggi *et al.* 1994[66]	Retrospective, multicentre study of chronic pain patients in 23 Italian centres NR whether consecutive or non-consecutive recruitment
Claeys and Horsch 1997[67]	Case series (1986–92) Method details NR
De Caridi *et al.* 2016[68]	Multiple case report from a single centre NR whether retrospective or prospective, or consecutive or non-consecutive recruitment Patients with both PLP and lower-limb ischaemia

continued

TABLE 11 Spinal stimulation therapies: key design characteristics of non-comparative group studies (*continued*)

Study	Design characteristics
Devulder *et al.* 1990[69]	Review of consecutive patients in a single centre
	NR whether prospective or retrospective
Garcia-March *et al.* 1987[70]	Study of BPA patients; method details NR
Katayama *et al.* 2001[71]	SCS, DBS and MCS
	Retrospective review of patients
	NR whether single centre or multicentre, or consecutive or non-consecutive recruitment
	Eligibility criteria allowed patients with pain in a non-existing limb regardless of whether the original limb had been amputated or not; 11 of 19 patients had BPA; most of these had undergone arm amputation but some had not so only data for the eight non-BPA patients are extracted here
Krainick *et al.* 1975[78]	Method details NR
Miles *et al.* 1974[77]	Single-centre study
	NR whether retrospective or prospective, or consecutive or non-consecutive recruitment
Miles and Lipton 1978[76]	Single-centre case series
	Unclear whether retrospective or prospective, or consecutive or non-consecutive
Naidu *et al.* 2013[72] (conference abstract)	Retrospective review of clinical records (2010–12)
	NR whether single centre or multicentre, or consecutive or non-consecutive recruitment
	Cases included that used specific method for spinal target selection
Nittner 1982[73]	Single-centre study; NR whether retrospective or prospective, or consecutive or non-consecutive recruitment
Sánchez-Ledesma *et al.* 1989[74]	Single-centre case series of deafferentation pain patients
	Unclear whether retrospective or prospective, or consecutive or non-consecutive recruitment
Viswanathan *et al.* 2010[31]	Retrospective review of prospectively collected data (patient records) at single centre (2003–8)
	Unclear whether consecutive or non-consecutive recruitment
Wester 1987[75]	Retrospective, single-centre, consecutive study of chronic pain patients (1978–84)

BPA, brachial plexus avulsion; NR, not reported.

TABLE 12 Motor cortex stimulation: baseline characteristics of non-comparative group studies

Study	Number with		Mean age (years)	Sex	Amputation sites and causes	Time since amputation	Baseline PLP	Duration/frequency of PLP
	PLP	Stump pain[a]						
Carroll *et al.* 2000[61]	3	1	47.7	Two males, one female	Two upper limb, one lower limb Causes NR	Mean of approximately 15 years of pain duration (range 5–22 years) (estimate based on year of pain onset and year of intervention)	NR	Constant pain in all patients
Hosomi *et al.* 2008[59]	4	1	58.5	Four males	All lower limb (one bilateral) Causes NR	Mean of 5.5 years of pain duration	NR	NR
Saitoh *et al.* 2000[62]	2	1	57.5	Two males	Both lower limb	NR	VAS score of 10 in both patients	NR
Sol *et al.* 2001[60]	3	NR	Individual ages and mean NR Range 44–52	Three males	All upper limb Causes NR	Mean of 11 years of pain duration (range 2–27 years)	NR	Constant pain in all patients

NR, not reported.
a In addition to PLP.

TABLE 13 Deep brain stimulation: baseline characteristics of non-comparative group studies

Study	Number with		Mean age (years)	Sex	Amputation sites and causes	Time since amputation	Baseline PLP	Duration/ frequency of PLP
	PLP	Stump pain[a]						
Abreu *et al.* 2017[58] (same cohort as Pereira *et al.* 2013,[51] with one additional patient)	6	NR	55.7	Four males, two females	Three above elbow, two above knee, one below knee All trauma	Mean 23.0 years of pain duration	Median VAS score: 6 Median UWNPS: 63 Median BPI score: 11.5	NR
Bittar *et al.* 2005[56]	3	NR	55.7	Three males	Two lower limb, one upper limb Two trauma, one vascular insufficiency	NR	NR	NR
Boccard *et al.* 2013[50]	9	NR (some had stump pain)	51.8	Seven males, one female	One upper limb, eight lower limb, including one bilateral lower limb Causes NR	NR	NR	NR
Chamadoira *et al.* 2011[53] (conference abstract)	4	NR	NR	NR	NR	NR	NR	NR
Mundinger and Salomão 1980[57]	7	4	47.9	Seven males	Four upper limb (one above elbow, one below elbow, two not specified), three lower limb (two above knee, one not specified) Causes NR	NR	NR	NR
Owen *et al.* 2007[54]	7	NR	NR	NR	NR	NR	NR	NR
Pereira *et al.* 2012[52] (conference abstract)	14	NR	52	11 males, three females	Amputation site NR (one bilateral) 11 trauma, three ischaemia, one infection	NR	NR	NR
Pereira *et al.* 2013[51] (from same cohort as Pereira *et al.* 2012[52])	5	NR	54.2	Three males, two females	Two above knee, two above elbow, one below knee All trauma	Mean 19.6 years of pain duration	Mean VAS score: 7.0 (SD 2.8) Mean UWNPS: 72.2 (SD 17.3) Mean BPI score 13.6 (SD 3.8)	NR
Yamamoto *et al.* 2006[55]	11	NR	NR	NR	NR	NR	NR	NR

BPI, Brief Pain Inventory; NR, not reported (for PLP subgroup); SD, standard deviation; UWNPS, Median University of Washington Neuropathic Pain Score.
a In addition to PLP.

TABLE 14 Spinal stimulation therapies: baseline characteristics of non-comparative group studies

Study	Number with		Mean age (years)	Sex	Amputation sites and causes	Time since amputation	Baseline PLP	Duration/ frequency of PLP
	PLP	Stump pain[a]						
Dorsal root ganglion stimulation								
Eldabe *et al.* 2015[64,79]	8	3	52.2 (based on $n = 5$ only)	Five females, two males, one NR	Four leg, two arm, two foot; wide variation in causes	Mean 7.9 years, $n = 7 + 1$ NR (range 1 to 18 years)	Mean VAS score 83.5 (SD 10.5)	NR
Love-Jones *et al.*[63] (conference abstract)	NR but 22 with PLP and/or stump pain		NR	NR	NR	NR	Mean VAS score 86.1 (SD 10.5, $n = 14$). Includes some patients with only stump pain	NR
Wahlstedt and Leljevahl 2013[65] (conference abstract)	2	2	NR	NR	One hand, one foot	NR	NR	NR
Spinal cord stimulation								
Broggi *et al.* 1994[66]	26	NR	NR	NR	NR	NR	NR	NR
Claeys and Horsch 1997[67]	7	NR	64.1	Five males, two females	Amputation site NR All chronic limb ischaemia	Mean 2.6 years (SD 0.6 years) pain duration	NR	NR
De Caridi *et al.* 2016[68]	3	0	74.7	Two males, one female	All lower limb All peripheral arterial disease	Two patients: ≈6 months One patient: < 4 months	VAS score of > 90 in one patient NR in two patients	NR
Devulder *et al.* 1990[69]	5	NR	NR	NR	NR	NR	NR	NR
Garcia-March *et al.* 1987[70]	2	2	40.5	Two males	All upper limb All brachial plexus avulsion (owing to trauma)	Mean 15.5 months of pain duration	NR	NR
Katayama *et al.* 2001[71]	8	NR	NR	NR	Amputation site NR All trauma, neoplasms or infections	NR	NR	NR

continued

TABLE 14 Spinal stimulation therapies: baseline characteristics of non-comparative group studies (*continued*)

Study	Number with		Mean age (years)	Sex	Amputation sites and causes	Time since amputation	Baseline PLP	Duration/ frequency of PLP
	PLP	Stump pain[a]						
Krainick *et al.* 1975[78]	4[b]	1	NR	NR	Three above knee, one above elbow Three trauma, one vascular	NR	NR	NR
Miles *et al.* 1974[77]	5	NR	43.8	Four males, one female	NR	Mean 18.1 years of pain duration	NR	NR
Miles and Lipton 1978[76]	9	NR	NR	NR	NR (minimum of two upper limb)	NR	NR	NR
Naidu *et al.* 2013[72] (conference abstract)	5	NR	NR	NR	NR	NR	VAS scores of > 7.5 in all patients	NR
Nittner 1982[73]	7 (unclear if all had amputation)	3	57.4	Six males, one female	All lower limb Causes not clear	NR	NR	NR
Sanchez-Ledesma *et al.* 1989[74]	6	NR	NR	NR	NR	NR	NR	NR
Viswanathan *et al.* 2010[31]	4	NR	38.8	Three males, one female	Two above knee, one hip disarticulation, one hemisacrectomy All cancer	One patient: ≥ 30 years Three patients: < 7 years	NR	NR
Wester 1987[75]	5	NR	NR	NR	NR	NR	1–3 scale (3 = strong pain, 2 = moderate pain, 1 = weak pain); average of 2.50 ($n = 4$)	

NR, not reported (for PLP patients); SD, standard deviation.
a In addition to PLP.
b Included 52 patients with PLP or stump pain but data were only reported separately for four PLP patients.

1–10) or > 70 (on a VAS of 0–100) in all cases, except in one study that reported a median score of 6.[58] Only two studies[60,61] reported any information on the duration or frequency of PLP episodes, both specifying that pain was constant in all patients.

Results of non-comparative group studies

Motor cortex stimulation All four of the included MCS studies were small, each reporting on four or fewer patients. Across all four studies, 12 patients were studied in total. The quality assessment results are presented in *Table 15*. One study was prospective,[61] one was retrospective[59] and the method of recruitment was unclear in two studies.[60,62] One study[59] reported that consecutive patient data were used and three studies[60–62] did not clearly report how patients were selected. Two studies[61,62] were based on experience at a single centre but these details were not reported in the other studies.[59,60] In terms of the IDEAL stages, MCS research has not progressed beyond the development/exploration stage. In two studies,[60,61] all the patients had constant PLP before intervention with MCS.

TABLE 15 Quality assessment results for the non-comparative group studies

Study	IDEAL stage[a]	Prospective or retrospective design	Single centre/multicentre	Recruitment
Motor cortex stimulation				
Carroll *et al.* 2000[61]	2a	Prospective	Single	NR
Hosomi *et al.* 2008[59]	2a	Retrospective	NR	Consecutive
Saitoh *et al.* 2000[62]	2a	NR	Single	NR
Sol *et al.* 2001[60]	1/2a	NR	NR	NR
Deep brain stimulation				
Abreu *et al.* 2017[58]	2b/3	Prospective	Single	Consecutive
Bittar *et al.* 2005[56]	1/2a	NR	NR	NR
Boccard *et al.* 2013[50]	2b/3	Prospective	Single	Consecutive
Chamadoira *et al.* 2011[53] (conference abstract)	2a	NR	NR	NR
Mundinger and Salomão 1980[57]	2a/b	NR	NR	NR
Owen *et al.* 2007[54]	2a/b	Prospective	Single	NR
Pereira *et al.* 2013[51]	2b/3	Prospective	Single	Consecutive
Pereira *et al.* 2012[52] (conference abstract)	2a	Prospective	Multicentre	Consecutive
Yamamoto *et al.* 2006[55]	2a	NR	NR	NR
Dorsal root ganglion stimulation				
Eldabe *et al.* 2015[64,79]	1/2a	Retrospective	Multicentre	Consecutive: 'all patients treated with DRG neuromodulation'
Love-Jones *et al.* 2015[63] (conference abstract)	2a/b	Prospective	NR	NR
Wahlstedt and Leljevahl 2013[65] (conference abstract)	2b	Retrospective	Single	Appears to be consecutive: 'first 5 patients' treated

continued

TABLE 15 Quality assessment results for the non-comparative group studies (*continued*)

Study	IDEAL stage[a]	Prospective or retrospective design	Single centre/multicentre	Recruitment
Spinal cord stimulation				
Broggi *et al.* 1994[66]	4 (included a large cohort and long-term follow-up)	Retrospective	Multicentre	NR
Claeys & Horsch 1997[67]	2a/b	NR	NR	NR
De Caridi *et al.* 2016[68]	2a/b	NR	Single	NR
Devulder *et al.* 1990[69]	2a	NR – probably Retrospective	Single	Consecutive
Garcia-March *et al.* 1987[70]	2b	NR	NR	NR
Katayama *et al.* 2001[71]	–	Retrospective	NR	NR
Krainick *et al.* 1975[78]	2b	NR	NR	NR
Miles *et al.* 1974[77]	2a	NR	Single	NR
Miles and Lipton 1978[76]	2a	NR	Single	NR
Nittner 1982[73] (conference abstract)	2a	NR	Single	NR
Sanchez-Ledesma *et al.* 1989[74]	2b	Unclear – probably retrospective	Single	NR
Viswanathan *et al.* 2010[31]	2a	Retrospective	Single	NR
Wester 1987[75]	2a/b	Retrospective	Single	Consecutive

NR, not reported.
a A loose estimate of the stage of research, based on the IDEAL recommendation stages of surgical innovation.[80]

Study intervention details and results are presented in *Table 16*. Only one[61] of the three studies reported on the frequency of stimulation used. Two studies[59,60] reported using trial periods to evaluate MCS before decisions were made on permanent implantation; both reported trial success in all patients. Across all three studies in which there were around 2 years of follow-up, six patients were reported to have PLP reductions of $\geq 70\%$, although in one patient pain relief was achieved only after repositioning of the electrodes. In the study that reported separate results data for PLP 'at rest' and PLP 'during activity',[60] the reductions for the latter were notably lower. Three patients did not have an adequate response to MCS; the electrodes were removed in two patients, and one patient discontinued treatment. Data were not reported for one patient, who was at the 6-month follow-up point. Few data were reported on other outcomes. One study[60] reported 'significant improvement' in the activities of daily living scores in two patients, although no actual results data were provided.

Deep brain stimulation The eight included DBS studies covered 55 PLP patients in total (see *Table 13*). Sample sizes ranged from 3 to 14 patients. Most publications reported on studies that recruited patients covering two or more chronic pain conditions, of which PLP patients were a subgroup.[50,51,53–55,57] Consequently, PLP-specific data were sometimes not available for several baseline parameters (see *Table 13*) and for some results; baseline PLP levels were available in only one study.[51] In one of the SCS studies,[71] two patients were treated with DBS, having failed treatment with SCS (see *Spinal cord stimulation*).

TABLE 16 Motor cortex stimulation: intervention parameters and results of non-comparative group studies

Study	Intervention parameters	Results

Carroll *et al.* 2000[61]	• Implantation of quadripolar electrode by means of a two-stage surgical procedure
	• Craniotomy undertaken 1 week before definitive procedure
	• Electrodes implanted extradurally. Bipolar stimulation at 15–25 Hz used to identify optimum position for electrodes
	• Stimulation tested intraoperatively but no trial period. Initial titration to determine optimum stimulation parameters done 4–6 weeks after implantation
	• Mean frequency (in two patients with pain relief at titration): 50 Hz
		• Two of three patients experienced pain relief during postoperative titration of stimulation parameters (4–6 weeks after surgery)
		• Patient 5: 70% PLP relief at 23 months' follow-up; 0% relief of stump pain. 'Good' pain relief (3) on a 0–5 scale
		• Patient 8: 75% PLP relief in arm, 5% relief in hand at 21 months' follow-up
		• Patient 9: no pain relief – discontinued owing to technical failure
		• Four-point verbal rating scale of pain intensity and five-point rating scale of pain relief scale measured but results not reported for all patients
		• Adverse effects/complications:
		  ○ Patient 5: unacceptable tightness in phantom leg when amplitude increased (despite 100% relief of pain at higher amplitude). Electrodes re-sited 1 year 7 months after intervention owing to fractured lead because of trauma sustained while rapidly elevating arms above head
		  ○ Patient 8: faulty IPG replaced 7 months after intervention. Electrodes replaced 1 year after intervention owing to fractured leads. Secondary wound infection of neck and scalp after electrode revision, required antibiotics
		  ○ Patient 9: electrodes re-sited 6 months after intervention. Technical failure because of poor patient compliance. Patient had contact with large magnetic field causing ID number to be wiped from stimulator. Caused damage to the IPG by repeatedly rotating the pulse generator under his skin for first titration session

Hosomi *et al.* 2008[59]	• Test stimulation for 1 or 2 weeks before permanent implantation • Grid electrodes used to determine optimal site for pain relief (M1 in all patients). Resume electrodes implanted in interhemispheric fissure for two patients, subdural precentral gyrus surface for one patient and both sites for one patient	• 90% VAS score reduction in one patient at 54 months' follow-up. Electrodes removed in two patients (at 6 months and 5 months). < 6 months' follow-up data available for one patient • Short-form MPQ also measured but results not reported for PLP patients
Saitoh *et al.* 2000[62]	• Craniotomy undertaken overlying the SSS • Placement of four-electrode array in the interhemispheric fissure. In one patient, a second four-electrode array was placed beside the SSS. Positioned in proximity to the motor cortex that corresponded to the affected limb • Test period before permanent implantation (length unclear). Stimulation delivered to various areas no more than three times a day. Monophasic square-wave pulses. 25–50 Hz. Usually applied continuously for 30 minutes	• VAS and MPQ classified as follows: excellent = reduction in PLP by 80–100%; good = reduction in PLP by 60–79%; fair = reduction in PLP by 40–59%; poor = < 40% reduction • Both patients received permanent implant after trial period • Follow-up duration ranged from 6 to 26 months for all patients (not just PLP) • Patient 6: during test stimulation VAS = 2 (excellent). After 20 months, outcome recorded as good • Patient 8: during test stimulation VAS = 6 (fair). After 6 months, outcome recorded as fair

continued

TABLE 16 Motor cortex stimulation: intervention parameters and results of non-comparative group studies (*continued*)

Study	Intervention parameters	Results

Sol *et al.* 2001[60]	• Craniotomy flap undertaken to expose the dura overlying the sensorimotor cortex. Four-contact electrode tightly sutured to the dura at the location of the central sulcus and functional motor area
	• 1-week period of testing undertaken
		• Mean follow-up duration: 27.3 months
		• All patients obtained complete initial improvement of PLP. At follow-up:
		  ○ Patient 1: progressive loss of effect after 4 months. Following repositioning of electrode, patient had 80% pain relief on VAS at rest, 20% during activity
		  ○ Patient 2: 100% pain relief on VAS at rest, 80% during activity
		  ○ Patient 3: 70% pain relief on VAS at rest, 40% during activity
		  ○ Patients 2 and 3 had 'significant improvement' in activities of daily living scores at follow-up (actual data were not reported). No patients had postoperative complications or side effects

ID, identification; IPG, implantable pulse generator; MPQ, McGill Pain Questionnaire; SSS, superior sagittal sinus.

The quality assessment results for the DBS studies are presented in *Table 15*. Five studies were undertaken prospectively;[50–52,54,58] although three of these studies were closely related, reporting on cohorts that overlapped.[51,52,58] Abreu *et al.*'s[58] paper provides longer-term follow-up data for the Pereira *et al.*[51] cohort (and also adds a single patient). In four studies,[53,55–57] it was unclear whether the studies were undertaken prospectively or retrospectively. In four studies, patients[50–52,58] were recruited consecutively. Only one study[52] was reported as being multicentre. In terms of the IDEAL stages, most of the studies of DBS were at the development/exploration stage, although three[50,51,58] included some elements of the assessment stage.

Study intervention details and results are presented in *Table 17*. Five[50–52,54,55] of the eight studies reported stimulation frequency details. Seven studies[50–54,56,58] used trial periods to evaluate DBS before decisions were made on permanent implantation. In the remaining two studies,[55,57] information on trial periods was not reported. Most of the studies that mentioned trial periods reported on success rates – all were 100%. For the four studies[50–52,58] that prospectively recruited consecutive patients, the mean improvements in VAS pain score in PLP patients after 1 year of follow-up ranged from 39% to 90%; three[50–52] of these studies reported on mean Short Form questionnaire – 36 items (SF-36) improvements, which ranged from 13% to 58%. It should be noted that the extremes of the ranges of these results are from the two related studies by Pereira *et al.*;[51,52] this notable difference in results may be attributable to greater clinician experience and better patient selection in the smaller group that was studied later (see *Table 17*). One study[58] followed patients for 3 years, reporting a statistically significant 67% median improvement in VAS pain score (from baseline); SF-36 median improvement was 17% and was not statistically significant.

All of the other studies reported data on the number of PLP patients achieving a $\geq$ 50% improvement in pain (or $\geq$ 60% in one study).[55] Across these studies, after 1 or 2 years of follow-up, the proportion of patients achieving a $\geq$ 50% improvement ranged from 50% to 100%. In the study that used the $\geq$ 60% cut-off point, 8 out of 11 patients (73%) were responding to DBS at 1 year.[55] Complication and adverse event data, which were reported for whole study cohorts (rather than specifically for PLP), revealed variation in incidence, ranging from no significant adverse events[51] to 18% of patients needing lead revisions.[50]

Spinal stimulation therapies

Of the interventions targeting the spinal area, we identified three studies of DRG stimulation[63–65] and 14 studies of SCS.[66–78]

TABLE 17 Deep brain stimulation: intervention parameters and results of non-comparative group studies

Study	Intervention parameters	Results
Abreu *et al.* 2017[58] (same cohort as Pereira *et al.* 2013,[51] with one additional patient)	• Contralateral, ventroposterolateral nucleus of the sensory thalamus targeted. Effect of macrostimulation assessed from 2 mm above to 5 mm below the calculated target to elicit paraesthesia or analgesia • Quadripolar electrodes. Final electrode position determined by intraoperative clinical assessment that relied on subjective reporting by awake patient • 48-hour period of postoperative clinical assessment before decision on whether or not to permanently implant electrodes • Initial frequency: 10 Hz in three patients, 20 Hz in two patients, 30 Hz in one patient • Frequency at 3 years: 10 Hz in four patients, 15 Hz in one patient, 20 Hz in one patient	• Follow-up duration of 3 years. All patients received permanent implant (100% trial success rate) • At 1 year: o median VAS score decreased from 6 to 1, median improvement of 80% from baseline; $p = 0.02$ o median UNWPS decreased from 63 to 9, median improvement of 83% from baseline; $p = 0.04$ o median BPI decreased from 11.5 to 2, median improvement of 90% from baseline; $p = 0.02$ o median SF-36 increased from 462 to 618, median improvement of 34% from baseline; $p = 0.40$ • At 2 years: o median VAS score = 0.3, median improvement of 83% from baseline; $p = 0.003$ o median UNWPS = 9, median improvement of 83% from baseline; $p = 0.03$ o median BPI = 1, median improvement of 91% from baseline; $p = 0.003$ o median SF-36 = 576, median improvement of 23% from baseline; $p = 0.29$ • At 3 years: o median VAS score = 2, median improvement of 67% from baseline; $p = 0.049$ o median UNWPS = 31, median improvement of 51% from baseline; $p = 0.32$ o median BPI = 4, median improvement of 65% from baseline; $p = 0.16$ o median SF-36 = 655, median improvement of 17% from baseline; $p = 0.24$ • No surgical complications or side effects and no need for electrode or implantable pulse generator revisions up to 3 years
Bittar *et al.* 2005[56]	• DBS of PVG and somatosensory thalamus. Two patients: PVG only. One patient: PVG and thalamic stimulation • Implanted electrodes had four exposed contacts, each 1.5 mm long, arranged linearly with 1.5 mm in between. Location adjusted to find site of greatest pain relief • Several days of testing before generator implanted	• At mean follow-up duration of 13.3 months, the mean reduction of pain intensity was 62% (SD 7.4%, range 55–70%). Satisfactory pain relief (≥ 50%) in all three patients. Burning component of pain completely alleviated in all three patients • Statistically significant improvement in quality-of-life measures (EQ-5D VAS 0–100). Mean preoperative value: 43, mean postoperative value: 68; $p = 0.02$ • SF-36 v-2 questionnaire and MPQ also assessed – results not reported

continued

TABLE 17 Deep brain stimulation: intervention parameters and results of non-comparative group studies (*continued*)

Study	Intervention parameters	Results

Boccard *et al.* 2013[50]	• DBS of either PVG or VPL thalamic nuclei or both targets (contralateral to the painful side)
	• Quadripolar electrodes with 1.5 mm spacing implanted. Final position determined by intraoperative clinical assessment reliant on subjective reporting by awake patient
	• Initial stimulation at 5–50 Hz
	• 1-week trial, with targets trialled individually then together for 1–2 days
		• Mean follow-up duration: 32 months
		• Nine of nine patients received a permanent implant (100% trial success rate)
		• After 3 months, mean pain reduction on VAS was 52.5% (SD 30.3%; $p = 0.06$)
		• Mean improvements at 1-year follow-up (p-values for baseline comparisons):
		  ○ VAS score ($n = 7$) 38.7% (SD 20.5%, $p = 0.004$)
		  ○ MPQ score ($n = 7$) 31.8% (SD 38.5%, $p = 0.04$)
		  ○ SF-36 score ($n = 8$) 17.6% (SD 24.2%, $p = 0.09$)
		  ○ EQ-5D score ($n = 8$) 31.7% (SD 11.0%, $p = 0.01$)
		  ○ Health state ($n = 7$) 81.5% (SD 120.0%, $p = 0.005$)
		• Adverse event rates (in the broader cohort of chronic pain patients): 42% needed implantable pulse generator changes, 18% had lead revisions, 9% had infections, 7% needed device removal

Chamadoira *et al.* 2011[53] (conference abstract)	• Electrodes implanted in somatosensory thalamus • Double-blind evaluation to test effect of each electrode on its own as well as combined stimulation with different parameter settings before implantation of stimulation device	• Two of the four PLP patients (50%) had > 50% pain relief at 1 year. Other two patients had 'similar results' at 6 months. VAS, BPI, SF-36, MPQ and UWNPS all measured but unclear which of these measurements pain relief results referred to • Quality of life: 'a significant improvement in all patients'
Mundinger and Salomão 1980[57]	• DBS of lemniscus medialis with inclusion of the specific and unspecific somatosensory nuclei in four patients • DBS of centrum medianum in two patients • DBS of medial pulvinar in one patient	• Mean follow-up duration for PLP patients: 21.4 months • One of seven patients practically free of pain (> 70% improvement), no analgesics, completely fit to work, good general condition (PLP and stump pain together) • Four of seven patients had up to 70% pain improvement, no analgesics but still slightly handicapped owing to pain, fit to work (PLP and stump pain together in one patient) • Two of seven patients had up to 50% pain improvement, no more analgesics or only occasionally (PLP and stump pain together in both patients) • Complications in the broader group ($n = 32$): six 'technical' and five 'neurological'. Further details provided in the publication
Owen *et al.* 2007[54]	• DBS of the sensory thalamus and/or the periventricular and periaqueductal grey area • 1-week trial stimulation before permanent implantation. Stimulation frequency for all patients (not available for just PLP) ranged between 5 Hz and 50 Hz	• Follow-up duration for PLP patients not reported; for all patients, mean was 44.5 months • Seven of seven patients received permanent implant (100% trial success rate) • Mean improvement in VAS score of 51% (SD 14%, range 18–74%) in six patients

TABLE 17 Deep brain stimulation: intervention parameters and results of non-comparative group studies (*continued*)

Study	Intervention parameters	Results
		• Four of six patients (67%) had ≥ 50% improvement • MPQ also measured but results not reported • Four-tiered categorisation of pain outcomes not reported separately for PLP • It appeared that one of the seven patients was lost to follow-up • Adverse events for whole cohort ($n = 38$): wound infection needing prolonged course of antibiotics in two patients. Electrode lead fracture in one patient

Pereira *et al.* 2013[51] [patients are from the same cohort as Pereira *et al.* 2012[52] (conference abstract)]	• Contralateral ventroposterolateral nucleus of the sensory thalamus targeted
	• After burr hole exposure, a radiofrequency electrode impedance check was undertaken to 10 mm above target, then DBS electrode insertion to target and intraoperative C-arm radiographic target confirmation
	• Quadripolar electrodes with 0.5-mm contacts spaced 1.5 mm apart. Final electrode position determined by intraoperative clinical assessment that relied on subjective reporting by awake patient
	• Frequency: two patients, 10 Hz; two patients, 20 Hz; one patient, 30 Hz
	• 48-hour trial undertaken before decision on permanent implantation
		• Follow-up at 1 month, 3 months, 6 months and 12 months
		• Five of five patients received permanent implant (100% trial success rate)
		• Mean VAS score before DBS was 7.4; at 12 months it was 3
		• Mean improvements at 12 month follow-up:
		  ○ VAS score: 90% (SD 10%; $p < 0.001$)
		  ○ SF-36: 58% (SD 97.9; $p = 0.127$)
		  ○ UWNPS: 80% (SD 13%; $p < 0.001$)
		  ○ BPI: 80% (SD 15%; $p < 0.001$)
		• Statistically significant improvements in VAS score at 1 and 6 months, in UWNPS at all follow-up points and in BPI at all follow-up points
		• SF-36 statistically significantly improved by 71% at 1 month ($p = 0.013$) but non-significant results at all other follow-up points
		• No significant surgical complications. Side effects were 'unremarkable'

Pereira *et al.* 2012[52] (conference abstract)	• DBS of the ventral posterolateral thalamus and periaqueductal grey. In contralateral positions in most patients • Mean frequency: 22 Hz	• Follow-up at 1–3 months, 6 months and 12 months. 4-year follow-up for some patients • All patients received permanent implant • Mean VAS score reductions were 61% at 1–3 months and 57% at 1 year • Mean SF-36 improvements were 22% at 1–3 months and 13% at 1 year • 4-year data for four patients: improvements of 36% for VAS and 11% for SF-36 • 'Additional outcome scores' also measured, but results not reported • Adverse effects: there were no operative complications. Three patients received electrode revisions (two owing to electrode damage, one owing to overcome tolerance)
Yamamoto *et al.* 2006[55]	• DBS of thalamic nucleus VC • Implantation through burr hole. Electrodes with four contact points placed so that the most distal contact point was in the VC and the most proximal in the thalamic nucleus ventralis intermedius • Stimulation frequency: 20–135 Hz	• Follow-up duration of 1 year • 8 out of 11 patients (73%) achieved > 60% pain reduction in VAS score • Mean reduction in VAS score was 69% • In two cases, pain completely disappeared after long-term stimulation. It reappeared after long-term cessation of DBS and patients underwent DBS again which subsequently reduced the pain

BPI, Brief Pain Inventory; EQ-5D, EuroQol-5 Dimensions; MPQ, McGill Pain Questionnaire; PVG, periventricular grey matter; SD, standard deviation; UWNPS, University of Washington Neuropathic Pain Score; VC, ventralis caudalis; VPL, ventral posterior lateral.

Dorsal root ganglion stimulation

The largest of the three studies of DRG stimulation (see *Table 14*),[63] which was available only as a conference abstract, reported on patients with PLP and/or stump pain but data were not reported separately for PLP and stump pain patients. This somewhat limits the applicability of this study's results to a PLP population (as it appears likely that some patients did not have PLP, only stump pain). However, the mean baseline pain in this study (86 on a 0–100 VAS) was similar to the mean baseline pain in a study in which all eight patients had PLP (84 on a 0–100 VAS).[64] The remaining study was of two patients.[65] The quality assessment results are presented in *Table 15*. One study recruited patients prospectively,[63] one was retrospective[64] and the recruitment method details were not reported in one study.[65] Two of the three studies reported recruiting patients consecutively.[64,65] One study was multicentre,[64] one was based at a single centre[65] and one did not report details.[63] In terms of the IDEAL stages, all three studies of DRG were at the development/exploration stage.

Study intervention details and results are presented in *Table 18*. Only one study[64] reported on the frequency of stimulation used. All three studies reported use of a trial period before full implantation. Two studies reported on the results of trial periods, with high success rates of 73%[63] and 100%.[64] One study[64] reported results showing that the amount of pain relief from DRG stimulation varied widely across patients, and sometimes waned over time. In the study that presented results of stump-pain-only patients together with PLP patients,[63] 6 out of 16 permanently implanted patients (38%) had ≥ 50% pain relief at 6 months. Quality of life was assessed in two studies, both using the EuroQol-5 Dimensions (EQ-5D). The retrospective study[64] had data available for two of the eight patients, reporting only that 'significant improvement' was observed. The other study[63] reported that at 6 months the mean EQ-5D index score improved by around 0.3, although more patients contributed data to the before-treatment mean score than to the after-treatment mean score so the result is likely to have been affected by attrition bias. A conference abstract[65] reported on DRG stimulation used in patients with various pain conditions. Two patients had PLP and stump pain, but results were only reported for one patient, and only up to 1 week of follow-up. Overall, very few complications were reported across studies.

Spinal cord stimulation

Sample sizes across the 14 studies of SCS ranged from 2 to 26 patients, although all but the largest study had sample sizes of < 10 patients. Ninety-six patients were studied in total. Baseline pain was only clearly reported in one study.[75] In another study,[72] reported as a conference abstract, baseline VAS scores were reported on a graph and were > 7.5 for all five patients. The quality assessment results are presented in *Table 15*. Five studies were retrospective[66,71,72,75] and the timing of recruitment was unclear in six studies.[67–70,73,74] Only two studies reported that patients were included consecutively.[69,75] One publication was based on a multicentre study[66] and eight were single-centre studies.[68,69,73–77] Although it appeared that several of the remaining studies were at single centres, this was not clearly reported as such. Despite the fact that the earliest of these studies was published in 1974, in terms of the IDEAL stages, most of the studies of SCS were at the development/exploration stage, with the exception of one retrospective multicentre study of epidural SCS published in 1994,[66] which included a large cohort and long-term follow-up.

Study intervention details and results are presented in *Table 19*. Only 2[67,70] of the 14 studies reported on the frequency of stimulation used. Few studies reported on trial period success rates. Three studies,[71,72] all with follow-up durations of ≥ 1 year, reported that all or most patients had positive results with PLP reductions of ≥ 60% or ≥ 80%. Five studies,[67,70,73,74,77] reporting at varying follow-up time points, had more mixed results with variation in responses across and within patients (i.e. pain relief waning over time). Six studies[66,68,69,75,76,78] reported either very limited or very short-term results data on PLP reduction.

TABLE 18 Dorsal root ganglion stimulation: intervention parameters and results of non-comparative group studies

Study	Intervention parameters	Results
Eldabe *et al.* 2015[64,79]	Narrow quadripolar neurostimulation leads using an epidural approach and curved stylets. Stimulating contacts placed near relevant DRGs based on individual pain distributions. All patients underwent a multiple-day period of trial stimulation: ≥ 50% pain relief was considered successful. Frequency: 20–40 Hz	Mean follow-up duration: 14.4 months. Mean VAS score at last follow-up was 38.9 (SD 27.1). Mean of 52.0% (SD 31.9%) pain reduction (stump and/or PLP) Eight out of eight patients received a permanent implant (100% trial success rate) % pain relief for the four patients who had only PLP: 0% (at 24 months), < 20% (at 24 months), 29% (at 13 months), 100% (at 5 months) Five patients had good pain relief outcomes. Three patients experienced poor outcomes, despite good initial results EQ-5D assessed in two patients: 'significant improvement' reported but numbers not presented. No complications were reported for any of the patients
Love-Jones *et al.* 2015[63] (conference abstract)	Specifically designed quadripolar leads placed in the epidural space near the relevant DRG following standard procedures Patients underwent trial period	Results not reported separately for PLP and stump pain 16 of 22 patients received a permanent implant (73% trial success rate) At 6 months, VAS score was reduced to 37.8 (SD 35.4) ($n = 10$) Six of 16 permanently implanted patients reported ≥ 50% pain relief EQ-5D index score improved from 0.27 (SD 0.29) ($n = 14$) to 0.60 (SD 0.28) ($n = 10$); $p < 0.05$ Total weighted rank and number of words chosen in MPQ improved from 44.9 (SD 13.4) to 19.0 (SD 17.3) and 14.9 (SD 4.61) to 7.3 (SD 5.7), respectively; $p < 0.05$ One patient was explanted for inadequate pain relief after 6 months
Wahlstedt and Leljevahl 2013[65] (conference abstract)	Patients underwent a trial in which specifically designed leads were implanted at the target DRGs. Following successful trial, patients received a fully implantable neuromodulation device	After 1 week, PLP improved in one patient by 100%; results not reported for 1-month time point Results not reported for the second PLP patient

EQ-5D, EuroQol-5 Dimensions; MPQ, McGill Pain Questionnaire; SD, standard deviation.

TABLE 19 Spinal cord stimulation: intervention parameters and results of non-comparative group studies

Study	Intervention parameters	Results
Broggi *et al.* 1994[66]	Epidural SCS Unipolar or multipolar lead implant to dorsal or cervical area. Stimulation test period: mean 17 days, range 8–42 days (for all chronic pain patients)	Verbal pain intensity scale (mild to excruciating), VAS and 'life standard' all measured, but very limited data reported specifically for PLP patients 88.5% of PLP patients had pain relief and requested system internalisation Complication rate in whole cohort (non-malignant chronic pain) ($n = 410$): dislocation of leads 4%, lead breakage 2%, infections 1%
Claeys and Horsch 1997[67]	Quadripolar lead placed into epidural space by percutaneous lumbar puncture. Lead advanced under radioscopic control to level of T11–12 1-week trial period before implantation of IPG if adequate pain relief Usual initial frequency settings: 70–120 Hz Stimulation could be given continuously or intermittently	At 3 months' follow-up, pain relief on VAS was 77.6% in five patients and 57.3% in other two patients At mean follow-up duration of 29.5 months: • Stable successful results in three patients (mean 78.7% pain relief), diminished positive effects in two patients (mean 56.6%), poor pain relief in two patients (mean 24.3%) • 'Same effects on pain relief recorded by a verbal scale' • No implantation-related complications
De Caridi *et al.* 2016[68]	2-octrode electrode lead placed in median peridural space. Double paramedian approach with a C-arm Test stimulation performed for 1 week. Permanent SCS therapy if pain maintained to within 20–30/100 mm on VAS, use of opiate analgesics decreased by 50%, increase in transcutaneous oxygen pressure of > 75% on the right foot	Patient 1: > 90/100 mm before intervention. 3 months after intervention, pain was 'maintained within 30/100 mm' Patient 2: baseline PLP NR. 3 months after intervention, pain 'maintained within 30/100 mm' Patient 3: baseline PLP NR. 3 months after intervention, pain 'maintained within 30/100 mm'
Devulder *et al.* 1990[69]	Minimum 2-week trial procedure. Monopolar electrodes introduced percutaneously in the epidural space during trial. Located at a level that produced electrical stimulation paraesthesia in the painful area If trial procedure was positive after at least 2 weeks, multipolar Resume electrodes were neurosurgically implanted for permanent system	Follow-up duration not reported Three of five patients had good pain relief with no need for medication One of five patients had little pain relief and needed narcotic analgesics One of five patients no longer used the stimulation system Complications in the broader population ($n = 45$): 23 patients required reintervention, with migration and breakage of the electrode being the commonest causes
Garcia-March *et al.* 1987[70]	Bipolar stimulation used. Two stimulating electrodes percutaneously introduced into epidural space and advanced to a cervical level where stimulation provoked a tingling sensation in the painful region Trial stimulation for 2 weeks at 80–120 Hz Permanently implanted if pain relief experienced	Two of two patients received permanent implant (100% trial success rate) 'Fair' defined as 25–75% pain relief, analgesics required, unable to return to work or social life. 'Poor' defined as < 25% pain relief, narcotics required and other invasive neurosurgical treatment required Fair early results in both patients, with poor results at 19 months' follow-up for one patient and 14 months for the other There were no adverse effects

TABLE 19 Spinal cord stimulation: intervention parameters and results of non-comparative group studies (*continued*)

Study	Intervention parameters	Results
Katayama *et al.* 2001[71]	All patients tried percutaneous SCS. If it failed to reduce pain, patients were considered for DBS of thalamic nucleus ventralis caudalis or MCS DBS performed with four contact electrodes, 1.5 mm in length, each separated by 1.5 mm SCS and MCS both performed with four plate electrodes, 5 mm in diameter, each separated by 5 mm, placed epidurally through a small laminectomy or craniotomy If pain control was achieved, chronic stimulation was performed	Follow-up duration range (for all 19 patients, not just non-BPA group): 2–18 years Six of eight patients achieved satisfactory pain control (defined as ≥ 80% pain reduction on VAS) with SCS Two of two patients achieved satisfactory pain control with DBS One patient underwent DBS and MCS, with 30–100% pain reduction on VAS with DBS and 10–20% pain reduction with MCS
Krainick *et al.* 1975[78]	Test procedure of percutaneous stimulation of the spinal cord using floating electrode for 3 days. Puncture done mostly in lumbar area and threaded upwards to the desired level. Electrodes implanted subdurally or endodurally	DCS implanted after trial in three of four patients (75% trial success rate). One of four patients experienced no pain relief Postoperative results at discharge: • 50–75% pain relief in one of three patients (PLP and stump pain) • 75–100% pain relief in one of three patients • The other patient experienced operative complications and the DCS was explanted
Miles *et al.* 1974[77]	Posterior column implantation. Electrode site was cervical (four patients) or thoracic (one patient). Some patients had a trial period (details unclear)	Mean follow-up duration: 5.8 months No pain relief in two of five patients Good relief and no analgesics in three of five patients
Miles and Lipton 1978[76]	Stimulation done percutaneously during test period, with electrode(s) inserted into the extradural space (two electrodes with tips 2–5 cm apart) or subarachnoid space. Tested for up to several weeks in extradural position or 2–3 days in subarachnoid space Decision to perform implant based on several tests	Six of nine patients had excellent relief of pain with the requirement of no analgesics One of nine patients had some relief of pain with the need for occasional simple analgesics Two of nine patients had no relief of pain The follow-up time point for these results was not reported
Naidu *et al.* 2013[72] (conference abstract)	Clinical examination to map out the dermatome, target selection entirely directed by segment that would refer sensation to the phantom Multicolumn paddle electrodes. Multiple stimulation configuration options used	Average follow-up duration of approximately 12 months All patients experienced a > 60% reduction in VAS score Mean VAS (0–10) score reduction was 7.3 No serious complications were reported

continued

TABLE 19 Spinal cord stimulation: intervention parameters and results of non-comparative group studies (*continued*)

Study	Intervention parameters	Results
Nittner 1982[73]	Epidural implantation of electrodes Location of electrodes varied. Authors found optimal results when tip of active electrode was between D10 and L1. Unipolar or bipolar implantation of electrodes depending on case	Six of seven patients had 'excellent' results and the other patient had 'good' results at time of operation. Postsurgery pain results: • Patient 1: 'satisfactory' at 3 weeks, < 30% improvement • Patient 2: 'satisfactory' at 1-month follow-up, < 30% improvement. Removal of electrodes at 2 months • Patient 3: 'good' at 1 month, 70% improvement • Patient 4: 'good' at 3 months, 50% improvement. Recurrence at 6 months • Patient 5: 'excellent' at 3 months, 100% improvement. < 30% improvement at 1 year • Patient 6: 'excellent' at 9 months, 100% improvement • Patient 7: no follow-up results recorded
Sanchez-Ledesma *et al.* 1989[74]	One or two standard SCS leads introduced percutaneously into the epidural space Patients underwent 2 weeks of trial stimulation. If patients had a positive response involving pain remission > 50%, the device was permanently implanted	Follow-up duration for PLP patients not reported; for all patients, mean of 5.5 years Three of six patients had positive response to trial stimulation and were permanently implanted Two of three patients had 0–25% long-lasting pain relief One of three patients had 50–75% long-lasting pain relief There were no serious complications and two minor complications in the broader population ($n = 49$)
Viswanathan *et al.* 2010[31]	Percutaneous octopolar leads All patients underwent a 1-week trial of stimulation. Permanent implantation was performed if 50% reduction in pain experienced	All patients reported pain relief of > 80% postoperatively Mean follow-up duration was 28 months Three patients reported a 2-point decrease in their usual amount of pain on numerical pain scale and one patient reported no change On 11-point BPI scale assessing other symptomology along 10 dimensions, three patients had a decrease in their total symptom score by 13, 14 and 4 points, respectively. One patient reported an increase by 5 points in total symptom score (owing to recurrent cancer and treatment) Complications: one patient developed an allergic dermatitis to the generator requiring revision with a GORE-TEX® (W.L. Core & Associates, Inc., Flagstaff, AZ, USA) pouch. One patient had a surgical site infection following routine changing of the implantable pulse generator. It required removal of the SCS system and treatment with antibiotics

TABLE 19 Spinal cord stimulation: intervention parameters and results of non-comparative group studies (*continued*)

Study	Intervention parameters	Results
Wester 1987[75]	Wire electrodes introduced into dorsal epidural space through epidural needles. Located to give tingling sensation in the pain area Trial period of 1 week. If patient reported promising pain reduction, the system was internalised	Follow-up duration for PLP patients not reported. For all patients, median of 15 months, range 4–60 months Five of five patients received permanent implant (100% trial success rate) Four PLP patients were still wearing the system at follow-up (one of them regularly). One patient died before follow-up In the four patients alive at follow-up, pain intensity before surgery was 2.5 (on a scale of 3 = strong, 2 = moderate, 1 = weak). At follow-up, pain intensity was 2.1 with DCS and 2.6 without DCS. The 'pain reducing effect' was rated as 0.5 on a scale of 0 (no effect) to 3 (good effect) Complications in broader population ($n = 30$): reoperation in 13 patients owing to technical issues

BPA, brachial plexus avulsion; BPI, Brief Pain Inventory; DCS, dorsal column stimulation; IPG, implantable pulse generator; NR, not reported.

None of the studies reported on quality-of-life measures, although one study's[70] assessment of treatment response broadly considered whether or not patients had 'returned to work or social life' (both patients studied achieved 'poor' results). When reported, complications were infrequent in most studies, although one study[69] reported that in the broader chronic pain population of 45 patients, just over half required reintervention, mostly owing to migration and breakage of the electrode. Another publication[75] reported that in its broader study population, 13 out of 30 patients needed reoperation owing to technical issues.

Summary

Although several of the non-comparative group studies reported results that appeared impressive in the short term (many patients had reductions in PLP sufficient to warrant permanent implantation), the effects diminish 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 neurostimulation therapies, although most studies did not have follow-up data beyond around 2 years.

Notwithstanding these results, their meaning – to the wider chronic PLP population – should be interpreted with caution because many studies had important methodological and/or reporting limitations. Results from uncontrolled studies are often inherently unreliable, being prone to several types of bias. For example, few studies reported recruiting patients consecutively, a useful method for minimising selection bias. Within this fundamental limitation, there were further methodological issues. Few studies reported having a prospective design, which would ensure consistency of outcome data. Only three studies were multicentred; the results of single-centre studies have limited generalisability to other centres, particularly for surgical interventions such as these, in which factors (such as surgeon experience and parameter preferences) can affect results considerably. Some studies did not present results for outcomes that were mentioned in their methods sections. Although such suboptimal reporting of results could be attributable to a lack of space (especially in older publications), it may also indicate the presence of reporting biases that highlight more impressive results and suppress less impressive ones. Few studies reported data on quality of life or activities of daily living – outcomes that are key in demonstrating the true value of interventions for chronic pain. Adequate stimulation parameter data were sometimes not reported, making the replication of procedures by other investigators difficult. Reflecting the limitations of these studies in terms of the IDEAL stages, none of these neurostimulation therapy interventions has been fully developed and properly evaluated for clinical effectiveness.

The reporting issues were not helped by the fact that many studies were of heterogeneous populations with chronic pain, only a subgroup of which had PLP. Consequently, in many studies, baseline data on important variables, such as time since amputation and PLP intensity, were not available, making it difficult to interpret results. Results data specific to PLP patients were also sometimes minimally reported. Moreover, even when it was clear that patients had PLP, many studies were not clear on whether or not patients also had stump pain (in addition to PLP). It is likely that in some studies patients were reporting on overall pain relief reductions (i.e. PLP and stump pain together). This is important because neurostimulation interventions may have different effects on PLP compared with stump pain, and results from the larger epidemiology studies in our review indicated that stump pain may be prevalent in around half to two-thirds of amputees (whose amputations were undertaken many years ago). The complexities involved in assessing and interpreting pain outcomes further highlight the importance of the need to also assess quality-of-life outcomes.

The limitations evident in most of the non-comparative studies make it very difficult to attempt to compare results across interventions and studies. Differences in results might be a consequence of variation in patient, intervention or methodological parameters, rather than differences in treatment effect.

Case reports

There were 18 individual cases of PLP patients treated with an invasive brain or spinal stimulation therapy reported in 17 papers that met the inclusion criteria (*Table 20*). Most were published as individual case reports, although several were part of larger single-group studies (including multiple case reports) that included only one patient with PLP.[81,83,85,96] Five of the cases[84,89–91,97] were reported only as conference abstracts.

There were six case reports on SCS,[82,84,88,90–92] six on MCS[81,86,93–96] and four on DBS.[83,85,87,97] There was also one case report of SCS and DRG stimulation being undertaken simultaneously[89] and one of MCS followed by DBS.[92] Follow-up time was at least a few months in most reports and several years in many. There was one study of DBS that had only 1 week of follow-up.[97] The follow-up time was 6 weeks in both a study of MCS[86] and the study of simultaneous SCS and DRG stimulation.[89]

The results of the case reports were generally positive, as would be expected with individual cases that the authors have selected to publish. A few studies reported adverse events. One patient undergoing SCS experienced pain caused by lead disposition.[91] Complications associated with MCS were reported: one patient experienced severe dysarthria and dysesthesias a few days after the operation, until modifications to the stimulation were made;[96] in another case, a patient experienced wound infection complications from the replacement of an electrode 1 year after the initial surgery and vocal arrest and seizure during high-voltage stimulation 2 years after surgery.[93] One further study reported that electrode revision was needed after SCS.[82]

Epidemiology studies

Of the 21 epidemiology studies of amputees included in the review, eight had a longitudinal design[98–105] and 13 had a cross-sectional design.[9,10,106–116]

Longitudinal studies

Characteristics of longitudinal studies

Table 21 shows the characteristics of the populations in the longitudinal studies. Six studies had a prospective design[98,100,102–105] and two were retrospective.[99,101] In the prospective studies, patients were mostly recruited via hospitals and prosthetic fitting centres. Other than one retrospective mailed survey,[99] all studies involved interviews, sometimes combined with measurement or review of medical records. Three of the studies took place in the UK,[99,103,105] two in the rest of Europe[102,104] and one each in Canada,[100] the USA[98] and Turkey.[101] The number of participants varied from 11 in one study[100] to 176 in the mailed survey,[99] although most studies included > 50 participants. The proportion of amputees who had PLP varied between studies (and across time points) and ranged from 45% to 92%.

TABLE 20 Details of case report studies

Study	Characteristics (age, time since amputation, baseline PLP)	Intervention	Duration of treatment follow-up	Results
Buchanan *et al.* 2014[81]	Age (years): 56 Male Above elbow amputation as a result of trauma Time since amputation NR Medically refractory pain, 2 years Baseline PLP on VAS (0–10): 9	MCS	3 months	3-month follow-up postoperative VAS scores = 6.5, –0.28% change from preoperative VAS
Bunch *et al.* 2015[82]	Age (years): 57 Male Bilateral lower-limb amputation as a result of infection Time since amputation NR Baseline PLP and stump pain on VAS (0–10): 6	SCS (SCS system implanted pre amputation for back pain did not provide PLP relief and was changed to constant current system with additional leads)	12 months	90% pain reduction (PLP, stump pain and back pain) during stimulation immediately after operation and at 14-day follow-up Lead migration leading to lack of coverage in one limb at 3 months 90% pain reduction after revision Sustained coverage of painful areas at 12 months (NR if 12 months after initial procedure or revision)
Green *et al.* 2004[83]	Age (years): 53 Male Lower-limb amputation Time since amputation NR Baseline PLP on VAS (0–100): 81	DBS (PVG)	6 months	PLP on VAS at 6 months reduced from 81 to 68 ($p < 0.01$ between baseline and 6 months) MPQ score reduced from 26 at baseline to 19 at 6 months ($p > 0.05$) Randomised N-of-1 trial results: mean PLP on VAS was 48 when stimulator on, 46 when stimulator off ($p = 0.89$) Patient correctly guessed whether stimulator was on or off 5 out of 10 times. No complications

continued

TABLE 20 Details of case report studies (*continued*)

Study	Characteristics (age, time since amputation, baseline PLP)	Intervention	Duration of treatment follow-up	Results
Hoffman and Sachdeva 2015[84] (conference abstract)	Age (years): 52 Male Lower-limb amputation as a result of infection Time since amputation NR Baseline PLP NR	SCS	> 1 year	80% pain relief of residual limb pain and PLP at postoperative visit Ongoing relief at approximately 1 year, except for phantom foot > 80% pain relief after implantation of additional lead
Hollingworth *et al.* 2017[85]	Age (years): 35 Female Above elbow amputation as a result of trauma Time since amputation NR Baseline PLP on VAS (0–100): 94	DBS	3 years	VAS score at 3 years' follow-up: 56 Patient no longer reliant on hot compress, allowing return to independent living
Koppelstaetter *et al.* 2007[86]	Age (years): 49 Male 30 years since amputation Duration of pain: 28 years Baseline PLP on VAS: 8 (assume out of 10)	MCS	6 weeks	70% pain reduction on VAS Effect immediate and persisting up to longest follow-up (6 weeks)

Study	Characteristics (age, time since amputation, baseline PLP)	Intervention	Duration of treatment follow-up	Results
Kringelbach *et al.* 2007[87]	Age (years): 58 Male Above the knee amputation as a result of infection 4 years since amputation Baseline PLP NR	DBS (PVG/PAG)	NR	Post-treatment improvement measured by MPQ – reduction in pain score by 74% With stimulation on VAS = 4.68
Lee *et al.* 2016[88]	Age (years): 46 Male Above knee amputation as a result of infection 3 years since amputation Baseline PLP on VAS (0–10): 7–8	SCS (specifically spinal cauda equina stimulation)	5 months	PLP maintained at 2–3 on VAS during 5 months' follow-up PLP sometimes increased to 4–5 on VAS
Mills and Helm 2016[89] (conference abstract)	Age (years): 56 Female Below knee amputation as a result of trauma Duration of PLP: 3 years Baseline PLP NR	SCS and DRG stimulation (simultaneously)	6 weeks	During 5-day trial, 50% relief of PLP with SCS and 80% with DRG 75% improvement with DRG at 6 weeks' follow-up

continued

TABLE 20 Details of case report studies (*continued*)

Study	Characteristics (age, time since amputation, baseline PLP)	Intervention	Duration of treatment follow-up	Results
Mubarak *et al.* 2011[90] (conference abstract)	Age (years): 35 Male Hand amputation as a result of trauma Refractory to treatment for 5 months including stellate ganglion blocks Baseline PLP NR	SCS	6 months	Patient-reported PLP (VAS) reduced by > 50% at 1, 3 and 6 months
Mudrakouski *et al.* 2016[91] (conference abstract)	Age (years): 36 Male Below elbow amputation as a result of trauma 8 years since amputation Baseline PLP NR	SCS	2 years	100% pain relief for 6 months Effect gradually diminished with no pain control after 2 years and stimulation causing excruciating pain owing to lead disposition Very good pain control from trial of high-frequency stimulation despite lead disposition
Nandi *et al.* 2004[92]	Age (years): 56 Female Above knee amputation for infection ≈4 years since amputation Baseline PLP on VAS (0–10): 9.4	SCS	2 years	VAS score improved from 9.4 (SD 0.89) to 1.0 (SD 0.7); $p < 0.001$. Time of poststimulation VAS measurement not reported but pain relief was 'sustained' at time of last follow-up 2 years after intervention

Study	Characteristics (age, time since amputation, baseline PLP)	Intervention	Duration of treatment follow-up	Results
Nandi *et al.* 2004[92]	Age (years): 51 Male Below knee amputation for peripheral vascular disease ≈4 years since amputation (MCS), ≈8 years since amputation (DBS) Baseline PLP on VAS (0–10): 8.9 before MCS, 8.4 before DBS	MCS followed by DBS	4 years of MCS NR for DBS	With MCS, VAS score improved from 8.9 (SD 0.73) to 1.9 (SD 0.56) ($p < 0.001$) (time of measurement NR). Rapid decrease in pain relief occurred over 1 month after 4 years of MCS With DBS, VAS score improved from 8.4 (SD 0.96) to 2 (SD 0.81) ($p < 0.001$). Effect has been 'stable' for 1 year at last follow-up
Pereira *et al.* 2015[93]	Age (years): 56 Female Amputation at shoulder for chronic pain (trauma?) > 10 years since amputation Baseline PLP on VAS (0–10): 9	MCS	16 years	PLP reduced by 78% to 2 on VAS at 6 months Pain reduced by 75% from 8 with stimulation off to 2 with stimulation on at 16 years Improvements in MPQ and activities of daily living Adverse events: • Electrode replacement at 1 year with wound infection complications • Vocal arrest and seizure with high voltage stimulation at 2 years • Several revisions and replacements of electrodes/IPG required
Roux *et al.* 2001[94]	Age (years): 45 Male Above elbow amputation as a result of trauma 2 years since amputation Baseline PLP NR	MCS	10 months	VAS measure for pain reduction. Baseline VAS score NR Postoperatively reported 70% reduction in PLP VAS score, and remained stable with adjustment to follow-up at 3 and 10 months

continued

TABLE 20 Details of case report studies (*continued*)

Study	Characteristics (age, time since amputation, baseline PLP)	Intervention	Duration of treatment follow-up	Results
Saitoh *et al.* 1999[95]	Age (years): 62 Male Lower leg amputation resulting from trauma and subsequent necrosis 6.5 years since amputation Baseline PLP on VAS (0–10) = 9	MCS	1 year	Test stimulation produced a reduction in PLP VAS score from baseline = 9 to post treatment = 2 At 12-month follow-up, pain relief was still effective
Sakas *et al.* 2011[96]	Age (years): 44 Male Above elbow amputation as a result of trauma 11 years since amputation Previous cervical cord stimulation unsuccessful and removed after 5 months Baseline PLP NR	MCS	9 months	2 days postoperative PLP improved by 60% Modifications required owing to severe dysarthria and dysesthesias Day 10 postoperative bifocal stimulation resulted in 90% improvement in PLP At 9-month follow-up, patient virtually pain free
Sims-Williams *et al.* 2013[97] (conference abstract)	Female Further characteristics NR	DBS (combined PVG/PAG)	1 week	Created warmth that completely resolved the cold pain felt Parafascicular stimulation resulted in telescoping of phantom limb from its previously contracted flexed position Pain and amputation stump allodynia improved by 50% (method of measurement NR)

IPG, implantable pulse generator; MPQ, McGill Pain Questionnaire; NR, not reported; PAG periaqueductal grey; PVG, periventricular grey matter; SD, standard deviation.

TABLE 21 Characteristics of longitudinal epidemiology studies

Study	Type of study	Population (means unless otherwise indicated)
Hanley *et al.* 2007[98]	Prospective study Recruitment from consecutive admissions to trauma hospital, as part of RCT Face-to-face interviews and telephone interviews	Setting: USA *N* included (participation rate): 57 (66%) % with PLP: for 4–5 days, 67%; for 6 months, 69%; for 1 year, 73%; for 2 years, 62% Age (years): 44 % male: 68 Amputation sites: below knee, 74%; above knee, 14%; midfoot, 5%; through knee, 4%; other, 3% Amputation causes: trauma, 70%; diabetes mellitus, 16%; infection, 5%; vascular disease, 4%; other, 5% Time since amputation: 2 years of follow-up % with prosthesis: NR Comorbidities: 66% had chronic residual limb pain
Houghton *et al.* 1994[99]	Retrospective, mailed survey	Setting: UK *N* included (participation rate): 176 (52%) % with PLP: 78 Age (years): around 70 % male: NR Amputation sites: below knee, 55%; above knee, 42%; through knee, 3% Amputation causes: trauma (including surgery for tumours), 56%; vascular, 44% Time since amputation (years): above knee, 10;[a] below knee, 6.8;[a] through knee, 9.5[a] % with prosthesis: 100 Comorbidities: NR
Hunter *et al.* 2008[100]	Prospective study but initial measurements taken as part of other studies Face-to-face interviews and measurement	Setting: Canada *N* included (participation rate): 11 (79%) % with PLP: initial, 72%; follow-up, 63% Age (years): 35 % male: 91 Amputation site: below shoulder, 100% Amputation cause: trauma, 100%

continued

TABLE 21 Characteristics of longitudinal epidemiology studies (*continued*)

Study	Type of study	Population (means unless otherwise indicated)
		Time since amputation (mean, years): 2.4 (at follow-up) % with prosthesis: 100 (at follow-up) Comorbidities: 91% had stump pain
Kelle *et al.* 2017[101]	Retrospective review of records combined with cross-sectional interviews	Setting: Turkey *N* included (participation rate): 101 (47%) % with PLP: EPP, 90%; 6 months, 45% Age (years): 58 % male: 77 Amputation sites: above knee, including knee disarticulation, 25%; below knee to ankle, 40%; below ankle, 35% Amputation causes: diabetes mellitus, 38%; trauma, 37%; vascular disease, 12%; cancer, 6%; infection, 4%; other, 3% Time since amputation (years): not clear but between 6 months and 3 years before interview % with prosthesis: NR Comorbidities: 27% had stump pain at 6 months
Nikolajsen *et al.* 1997[102]	Prospective study (although pain questions were retrospective for time period since last interview) Recruitment from RCT cohort. Interviews	Setting: Denmark *N* included (participation rate): 56 (36%). 17 patients (30%) died during follow-up. Four patients excluded from analysis – had re-amputation after first follow-up % with PLP: 1 week ($n = 54$), 67%; 3 months ($n = 37$), 68%; 6 months ($n = 36$), 75% Age (years): 72[a] % male: 59 Amputation sites: below knee, 55%; above knee, 32%; through knee, 13% Amputation causes: all peripheral vascular disease or diabetic ulcers Time since amputation (years): 0.5 (follow-up) % with prosthesis: NR Comorbidities: 43% diabetes mellitus, 18% previous amputation, 19% stump pain (at 3 months)
Parkes 1973[103]	Prospective study Recruitment from limb fitting centre. Face-to-face interviews	Setting: UK *N* included (participation rate): 46 (87%) % with PLP: 3–4 weeks, 85%; 13 months, 61% Age (years): NR (all under 70 years)

TABLE 21 Characteristics of longitudinal epidemiology studies (*continued*)

Study	Type of study	Population (means unless otherwise indicated)
		% male: 80 Amputation site: NR Amputation cause: NR Time since amputation (years): 1.1 (follow-up) % with prosthesis: 100 Comorbidities: NR
Pohjolainen 1991[104]	Prospective study Recruitment of consecutive patients sent for prosthetic fitting Face-to-face interviews, examinations and evaluation of medical records	Setting: Finland *N* included (participation rate): 155 (NR). 16 patients (10%) died before follow-up % with PLP: initial assessment, 59%; 1 year ($n = 124$), 53% Age (years): 63 % male: 72 Amputation sites: below knee, 60%; above knee, 40% Amputation causes: vascular disease, 81%; trauma, 10%; tumour, 6%; other, 3% Time since amputation (years): 1 (follow-up) % with prosthesis: 100 Comorbidities: 30% had problems in contralateral leg at initial assessment
Richardson *et al.* 2006[105]	Prospective study. Recruitment from one hospital prior to amputation. Interviews	Setting: UK *N* included (participation rate): 59 (89%). Seven patients (12%) died before follow-up % with PLP: week 1, 92%; 6 months ($n = 52$), 79% Age (years): 64 % male: 63 Amputation sites: below knee, 46%; above knee, 49%; bilateral below knee, 3%; bilateral above knee, 2% Amputation cause: all peripheral vascular disease Time since amputation (years): 0.5 (follow-up) % with prosthesis: NR Comorbidities: 51% had stump pain (at 6 months)

EPP, early postoperative period; *N*, number of amputees; NR, not reported.
a Median.

When reported, the average age of participants ranged from 35 to 72 years and most were male (ranging from 59% to 91% of study participants). Most of the studies included only patients with lower-limb amputation, except for one study that included patients with only below-shoulder amputations[100] and one that did not report this information.[103] All or most patients had amputations caused by trauma in three studies,[98–100] and all or most amputations were caused by vascular disease (vascular disease or diabetic ulcers in one case) in another three studies.[102,104,105] One study did not report on amputation causes[103] and in another the majority had been either caused by trauma or diabetes mellitus.[101] When reported, the overall mean time since amputation at the most recent follow-up ranged from 6 months to 2.4 years. In three of the studies,[99,100,104] all participants used a prosthesis, whereas the remainder did not report this information. Five studies[98,100–102,105] reported the proportion of participants with stump pain, ranging from 19% to 91%.

Results of longitudinal studies

Results from the longitudinal studies are presented in *Table 22*. At the population level, PLP intensity recorded up to 1 week post amputation ranged from 1.6 to 5.9 on a VAS scale (of 0–10). At later follow-ups, PLP intensity in most studies was quite low with mean (or median) 0–10 VAS scores ranging from 1.8 to 3.7 at 6 months post amputation, 2.4 to 3.0 at 1 year and 2.1 to 6.0 at 2 years. Three studies[98,103,104] reported data on subcategories of pain intensity (all three reported data at, or around, 1 year post amputation). One study[98] reported that 35% of patients had a PLP of > 3 (on a 0–10 VAS). The other two studies[103,104] used mild, moderate and severe pain categories and reported that around 25% of patients had moderate pain. There were notable differences in the proportions for mild PLP (50% and 73%) and severe PLP (25% and 0%). Two studies[101,105] reported on duration or frequency of PLP episodes, both at 6 months. Richardson *et al.*[105] reported that around two-thirds of patients had PLP episodes lasting between 1 and 29 minutes and 44% of patients had between two and nine episodes per day; 2% had continuous PLP. Kelle *et al.*[101] reported much lower episode frequencies, with 56% of patients having an episode once every 10–15 days. One study[102] reported that intensity of PLP did not decrease with time but duration of PLP attacks was significantly shorter after 6 months than after 3 months ($p = 0.001$).

Two studies[98,100] reported that early residual limb pain (stump pain) was not correlated with PLP intensity at later follow-ups. However, these studies did find that early PLP intensity was a predictor of chronic PLP at 6 months and 1 year.[98,100] Two further studies identified an association between early and later PLP, but the analyses did not relate to intensity of PLP: one study[102] found that early PLP predicted the presence of PLP at 6 months and another[103] reported associations between PLP at 13 months and PLP during the first month after the operation.

Three studies[98,99,102] identified associations between pre-amputation pain and PLP. Hanley *et al.*[98] found pre-amputation pain to be a significant predictor of chronic PLP at 2 years. Similarly, Houghton *et al.*[99] found the level of preoperative pain in vascular amputees – but not in trauma amputees – to be correlated with the level of PLP at periods up to and including 2 years after amputation, but there was no correlation at 5 years. This study also reported no significant difference in levels of PLP experienced by vascular and traumatic amputees at any time. However, the Houghton *et al.*[99] study was retrospective. In retrospective studies, it would be very difficult for patients to provide accurate data on pre-amputation pain intensity and PLP intensity experienced in previous years. Results from Nikolajsen *et al.*[102] suggested that pre-amputation pain may influence PLP early (at 3 months) but not later (at 6 months) in patients with amputations as a result of peripheral vascular disease or diabetic ulcers. However, the results of this study were based on using a cut-off point for 'clinically relevant' pain of ≥ 20 (on a 0–100 scale). Therefore, the relevance of this study's results to a population with moderate to severe PLP is somewhat uncertain as this population normally has VAS score ranges of between 5 and 10 (on a 0–10 scale).

Kelle *et al.*[101] reported a retrospective study of 101 patients not receiving medical treatment for PLP. Results indicated that level of amputation has no impact on level of PLP. Across the longitudinal studies identified, there were very few data published on associations between PLP and quality of life, daily activities, anxiety or depression. The only relevant results (associations between PLP and reduced walking distance and reduced outdoor walking) were briefly reported in a Finnish study.[104]

TABLE 22 Methods and results of longitudinal epidemiology studies

Study and number with PLP	Method details	PLP intensity (mean) and prevalence by severity	Associations between PLP and patient characteristics, quality of life, daily activities, anxiety or depression
Hanley *et al.* 2007[98] • Days 4–5: 38 • 6 months: 39 • 12 months: 42 • 24 months: 35	Duration of follow-up: 2 years after amputation Initial measurement: before amputation (median 2 days, range 0–14 days) Follow-up time points post amputation: days 4 and 5 (averaged), 6 months, 12 months, 24 months Recall period: initial assessment and post amputation = 24 hours. ≥ 6 months = average of ratings from three times within 1-week period Method of PLP assessment: 0–10 numeric rating scale	Intensity of PLP: • Days 4–5 – 2.1 • 6 months – 2.4 • 1 year – 2.4 • 2 years – 2.1 Prevalence of PLP by severity: • % with pain score – > 3 • Days 4–5 – 32%, 6 months – 33%, 1 year – 35%, 2 years – 30%	Pre-amputation pain intensity was a significant predictor of PLP intensity at 2 years ($p < 0.05$) Early PLP intensity was the only significant independent predictor of PLP intensity at 6 ($p < 0.01$) and 12 ($p < 0.001$) months after amputation; greater acute PLP (4–5 days after amputation) was associated with higher intensity PLP Early residual limb pain was not a significant independent predictor of PLP intensity at any follow-up point
Houghton *et al.* 1994[99] • 137	Duration of retrospective follow-up: varied by patient Initial measurement: before amputation Follow-up time points post amputation: immediately after amputation, 6 months, 1 year, 2 years, 5 years and current pain at time of survey Recall period: between 6 months and over 5 years Method of PLP assessment: VAS 0–10 scale	Intensity of PLP: • Immediately after amputation – 4[a] • 6 months – 3[a] • 1 year – 3[a] • 2 years – 2[a] • 5 years – 1[a] Prevalence of PLP by severity: • NE	In vascular amputees, level of preoperative pain was correlated with level of phantom pain: immediately after amputation ($p < 0.005$), at 6 months ($p < 0.0005$), 1 year ($p < 0.005$), 2 years ($p < 0.005$) after amputation and at the time of answering the questionnaire ($p < 0.0005$). No correlation at 5 years ($p = 0.19$) In trauma amputees, there was a significant correlation between level of preoperative and level of phantom pain only immediately after surgery ($p < 0.005$) Preoperative pain was more severe in vascular than in trauma amputees (median 7 vs. median 2.5; $p < 0.0005$) No significant difference in levels of PLP experienced by vascular and traumatic amputees at any time

continued

TABLE 22 Methods and results of longitudinal epidemiology studies (*continued*)

Study and number with PLP	Method details	PLP intensity (mean) and prevalence by severity	Associations between PLP and patient characteristics, quality of life, daily activities, anxiety or depression
Hunter *et al.* 2008[100] • Initial assessment: 8 • Follow-up: 7	Duration of follow-up: mean 28.3 months after amputation Initial measurement: < 6 months after amputation (mean 4.6 months) Follow-up time points: one session ≥ 11.5 months after initial measurement (means of 28.3 months since amputation, 24 months since initial measurement) Recall period: within the previous week Method of PLP assessment: VAS 0–10 scale	Intensity of PLP • Initial – 5.9 • Follow-up – 6.0 Prevalence of PLP by severity: • NE	Significant relationship between initial PLP intensity and follow-up PLP intensity ($p < 0.001$) Initial stump pain not correlated with PLP at follow-up
Kelle *et al.* 2017[101] • EPP: 91 • 6 months: 45	Duration of retrospective follow-up: 6 months after amputation Initial measurement: 'Early postoperative period' Follow-up time points: 6 months post amputation Recall period: unclear Method of PLP assessment: VAS 0–10 scale	Intensity of PLP: • EPP – 6.8 • 6 months – 3.7 Prevalence of PLP by severity: • At EPP ($n = 67$ with data), 67% had permanent PLP, 33% had PLP every day (on and off). There were significantly more permanent PLP patients in group I • At 6 months ($n = 45$), none had permanent or everyday PLP, 7% once every 3 days, 16% once a week, 56% once every 10–15 days, 22 once a month	PLP analysed by groups based on site of amputation. Group 1, above knee and knee; group II: below knee to ankle; group III, below ankle. Analysis did not control for cause of amputation; trauma was the most common cause in group I, diabetes mellitus in group III Significant difference between groups in PLP intensity at EPP with highest VAS score in group I ($p = 0.02$); no significant differences after 6 months ($p = 0.58$)

Study and number with PLP	Method details	PLP intensity (mean) and prevalence by severity	Associations between PLP and patient characteristics, quality of life, daily activities, anxiety or depression
Nikolajsen *et al.* 1997[102] • 1 week: 36 • 3 months: 24 • 6 months: 27	Duration of follow-up: 6 months after amputation Initial measurement: day before amputation Follow-up time points post amputation: 1 week, 3 months, 6 months Recall period: since amputation or since previous interview Method of PLP assessment: VAS 0–100 scale (clinically relevant if ≥ 20 mm); also MPQ	Intensity of PLP: • 1 week – 15.5[a] • 3 months – 24[a] • 6 months – 22[a] Prevalence of PLP by severity: • NE	Significant association between pre-amputation VAS pain of ≥ 20 mm and PLP of ≥ 20 mm during first 3 months, but not for 6-month time point ($p = 0.1$) Intensity of PLP did not decrease with time but duration of PLP attacks was significantly shorter after 6 months than after 3 months ($p = 0.001$) PLP presence at 1 week associated with PLP presence at 6 months ($p = 0.002$)
Parkes 1973[103] • 3–4 weeks: 39 • 13 months: 28	Duration of follow-up: 13 months after amputation Initial measurement: 3–4 weeks post amputation Follow-up time points: 13 months post amputation Recall period: 3–4 weeks, since amputation; 13 months, NR Method of PLP assessment: categorical – none, mild, moderate or severe	Intensity of PLP: • NE Prevalence of PLP by severity: • At 13 months, 28/46 still had some PLP – severe, 7 (25%); moderate, 7 (25%); mild, 14 (50%)	Association between PLP at 13 months and: illness that lasted for more than a year before amputation ($p < 0.05$), illness that persisted after operation to produce a threat to life or the remaining limb ($p < 0.05$), rigid personality ($p > 0.02$), compulsively self-reliant personality ($p < 0.02$), PLP during first month after operation ($p < 0.05$), unemployment or retirement at 13 months ($p < 0.02$)
Pohjolainen 1991[104] • Initial assessment: 91 • 1 year: 66	Duration of follow-up: 1 year after amputation Initial measurement: at prosthetic fitting (maximum of 16 weeks after amputation) Follow-up time points: 1 year post amputation Recall period: NR Method of PLP assessment: categorical – mild, moderate, severe	Intensity of PLP: • NE Prevalence of PLP by severity: • At initial assessment – mild, 73%; moderate, 27%; severe, 0% • 1 year – mild, 70%; moderate, 30%; severe, 0%	Association between PLP and reduced walking distance and reduced outdoor walking (both $p < 0.05$)

continued

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TABLE 22 Methods and results of longitudinal epidemiology studies (*continued*)

Study and number with PLP	Method details	PLP intensity (mean) and prevalence by severity	Associations between PLP and patient characteristics, quality of life, daily activities, anxiety or depression
Richardson *et al.* 2006[105] • First week: 54 • 6 months: 41	Duration of follow-up: 6 months after amputation Initial measurement: first week post amputation Follow-up time points: 6 months post amputation Recall period: NR Method of PLP assessment: VAS 0–100; MPQ; 0–5 scale (Present Pain Intensity)	Intensity of PLP: • VAS score at 6 months – 27 • PPI – first week, 3.0; 6 months, 1.8 Prevalence of PLP by severity: • At 6 months, 64% of amputees had attacks lasting between 1 and 29 minutes, 10% for 1 hour, 12% for > 1 hour • 44% had between 2 and 9 attacks per day, 12% had > 10 per day	NE

EPP, early postoperative period; MPQ, McGill Pain Questionnaire; NE, not evaluated; NR, not reported; PPI, present pain intensity.
a Median.

Cross-sectional studies

Characteristics of cross-sectional studies

Table 23 shows the characteristics of the amputee populations in the cross-sectional epidemiology studies. In most studies, questionnaires were mailed to participants or distributed by co-operating organisations. Data were collected through face-to-face interviews in three studies[106,109,110] and through telephone interviews in one study.[9] Of those studies that reported a method of selecting participants, two used random sampling[10,112] and one used census sampling.[109] The sample for four surveys was either self-selected or partially self-selected (including through membership of an amputee organisation).[9,111,113,116] One study[107] included a mix of participants selected through both random sampling and self-selection, and another study[115] distributed surveys through co-operating organisations.

Almost half of the studies took place in the USA,[9,10,107,111–113] with three in Iran,[106,109,110] one in the UK,[116] and two in the rest of Europe[114,115] (one study did not specify a location but appears likely to have been set in the USA[108]).

TABLE 23 Characteristics of cross-sectional epidemiology studies

Study	Type of data collection	Population (means unless otherwise specified)
Ehde *et al.* 2000[10] (cohort also reported in Hanley *et al.* 2006[117])	Mailed survey, selection by random number generator	Setting: USA *N* included (participation rate): 255 (56%) % with PLP: 72 Age (years): 55 % male: 8 Amputation sites: below knee, 54%; above knee, 30%; other (hip, toes), 8%; knee disarticulation, 5%; ankle disarticulation, 3% Amputation cause: trauma, 53%; vascular disease, 20%; infection, 23%; gangrene, 21%; diabetes mellitus, 13%; congenital problem, 2%; tumour, 5%; other, 19% (multiple answers allowed) Time since amputation (years): 14.2 % with prosthesis: 83 Comorbidities: 74% stump pain, 52% back pain, 43% pain in other leg/foot
Ephraim *et al.* 2005[9]	Telephone interviews, sample stratified by amputation aetiology (from those who contacted Amputee Coalition of America)	Setting: USA *N* included (participation rate): 914 (67%) % with PLP: 80 Age (years): 50 % male: 60

continued

TABLE 23 Characteristics of cross-sectional epidemiology studies (*continued*)

Study	Type of data collection	Population (means unless otherwise specified)
		Amputation sites: below knee, 41%; above knee, 38%; bilateral lower limb, 10%; above elbow, 5%; below elbow, 5%; bilateral upper limb, 1% Amputation cause: peripheral vascular disease, 37%; trauma, 39%; cancer, 24% Time since amputation (years): 4[a] (0–66 range) % with prosthesis: 80 Comorbidities: 68% stump pain, 62% back pain
Hirsh *et al.* 2010[108]	Mailed survey	Setting: NR (USA?) *N* included (participation rate): 335 (56.2%) % with PLP: 83 Age (years): 59 % male: 72 Amputation sites: lower limb, 99%; upper limb, 5% (11 participants had both) Amputation cause: trauma, 78%; other causes NR Time since amputation (years): 19 % with prosthesis: NR Comorbidities: 64% stump pain
Modirian *et al.* 2009[106]	Interviews in a medical setting	Setting: Iran *N* included (participation rate): 103 (74%) % with PLP: 54 (% of limbs) Age (years): 38 % male: 99 Amputation sites: bilateral. Finger/wrist, 52%; at elbow, 40%; above elbow, 8% Amputation cause: all war injuries Time since amputation (years): 17.1 % with prosthesis: NR Comorbidities: 40% overweight, 8% obese

TABLE 23 Characteristics of cross-sectional epidemiology studies (*continued*)

Study	Type of data collection	Population (means unless otherwise specified)
Molton *et al.* 2007[107] (some overlap of patients with Ehde *et al.* 2000[10])	Mailed survey, selection by random number generator and some self-selecting – responses to flyers/ advertisements	Setting: USA *N* included (participation rate): 375 (51%) % with PLP: 100 Age (years): 54 % male: 67 Amputation sites: below knee, 55% Amputation cause: injury, 52%; vascular disease, 24%; infection, 24% Time since amputation (years): 11.0 % with prosthesis: NR Comorbidities: NR
Rahimi *et al.* 2012[109]	Face-to-face interviews, census sampling for selection	Setting: Iran *N* included (participation rate): 335 (58%) % with PLP: 67 Age (years): 42 % male: 97 Amputation sites: bilateral. 38% below knee, 22% above knee, 34% above and below knee, 6% NR Amputation cause: all war injuries Time since amputation (years): 20 % with prosthesis: 80 Comorbidities: 61% vertebral column pain
Rayegani *et al.* 2010[110]	Face-to-face interviews by medical professional	Setting: Iran *N* included (participation rate): 335 (84%) % with PLP: 64 Age (years): 42 % male: 98

continued

TABLE 23 Characteristics of cross-sectional epidemiology studies (*continued*)

Study	Type of data collection	Population (means unless otherwise specified)
		Amputation sites: bilateral. By limb: below knee, 53%; above knee, 36%; knee disarticulation, 7%; other, 4% Amputation cause: all war injuries Time since amputation (years): NR % with prosthesis: 79 Comorbidities: 53% low back pain, 22% neck pain, 9% thoracic spine pain
Sherman and Sherman 1983[111]	Mailed survey, partially self-selected (members of society of veteran amputees)	Setting: USA *N* included (participation rate): 764 (61%) % with PLP: 85 Age (years) 51 % male: NR Amputation sites: lower limb, 82%; upper limb, 14%; bilateral upper and lower limbs, 4% Amputation cause: all related to military service. Combat related, 85%; accidents, 6%; other causes NR Time since amputation (years): 28.2 % with prosthesis: > 90 Comorbidities: 58% stump pain
Sherman and Sherman 1985[113]	Mailed survey, self-selecting sample in response to requests in newspapers	Setting: USA *N* included (participation rate): 436 (85%) % with PLP: 100 Age (years): 59 % male: 89 Amputation sites: NR Amputation cause: all unrelated to military service. Accidents, 50%; disease, 46% Time since amputation (years): 14 % with prosthesis: NR Comorbidities: 58% stump pain

TABLE 23 Characteristics of cross-sectional epidemiology studies (*continued*)

Study	Type of data collection	Population (means unless otherwise specified)
Sherman *et al.* 1984[112]	Mailed survey, random selection	Setting: USA *N* included (participation rate): 2694 (55%) % with PLP: 78 Age (years): 53 % male: 100 Amputation sites: NR Amputation cause: all related to military service. Direct combat injuries, 42%; combat-associated problems, 34%; accidents, 18%; disease, 6% Time since amputation (years): 26.9 % with prosthesis: NR Comorbidities: 62% stump pain
Solonen 1962[114]	Sample of first 1000 completed of 4000 distributed surveys	Setting: Finland *N* included (participation rate): 1000 (N/A) % with PLP: 68 Age (years): 42 % male: 100 Amputation sites: below knee, 43%; above knee, 27%; above elbow, 16%; below elbow, 10%; bilateral, 3%; foot, 1% Amputation cause: all war injuries Time since amputation (years): 14 % with prosthesis: 99 Comorbidities: 42% stump pain
Streit *et al.* 2015[115]	Surveys distributed by co-operating organisations	Setting: Germany *N* included (participation rate): 122 (NR for bilateral amputees) % with PLP: 74% (lifetime), 56% of limbs (last 3 months) Age (years): 65 % male: 76 Amputation sites: bilateral. Lower limb, 73%; upper limb, 13%; upper and lower limb, 14%

continued

TABLE 23 Characteristics of cross-sectional epidemiology studies (*continued*)

Study	Type of data collection	Population (means unless otherwise specified)
		Amputation cause: by limb – trauma, 66%; vascular disease, 24%; infection, 7%; tumour, 0.4%; other, 7% (multiple answers allowed) Time since amputation (years): 31.2 % with prosthesis: NR Comorbidities: 60% (of limbs) stump pain
Wartan *et al.* 1997[116]	Mailed survey to the British Limbless Ex-Servicemen's Association (now known as Blesma, The Limbless Veterans) Selection by random number generator	Setting: UK *N* included (participation rate): 526 (89%) % with PLP: 62% (lifetime), 52% (current) Age (years): 73[a] % male: 100 Amputation sites: below knee, 48%; above knee, 42%; above elbow, 10%; below elbow, 9% (includes some amputees with amputations at more than one site) Amputation cause: all trauma. Active military service, 89% Time since amputation (years): 50[a] % with prosthesis: 96 Comorbidities: 57% stump pain

N, number of amputees; N/A, not applicable; NR, not reported.
a Median.

The number of participants ranged from 103 to 2694, with most studies including < 1000 participants. There was some overlap in the cohorts of patients included in two of the studies,[10,107] although it is not reported how many patients were included in both of them. The proportion of participants with PLP ranged from 52% to 82%, except for two studies[107,113] in which only participants with PLP were included. Mean ages ranged from 38 to 72 years. In all studies, most participants were male (when reported).

Four studies[106,109,110,115] only included participants with bilateral amputations. One study[106] included only upper-limb amputees and two studies[112,113] did not report on amputation site. The remaining studies included either only lower-limb amputees or cohorts in which most patients were lower-limb amputees. Seven studies[106,109–112,114,116] were of military veterans or those injured at war. The remainder of studies included participants with different amputation causes, the most common being trauma. Time since amputation (mean or median) ranged from 4 to 50 years. Prosthesis use was high in those studies that reported it (79% to 99%). In studies that reported on comorbidities, 42% to 75% of participants reported stump pain and 52% to 62% of participants reported back pain.

Results of cross-sectional studies

The results of the cross-sectional studies are reported in *Table 24*. Six of the cross-sectional studies[9,10,107,108,113,115] reported population mean VAS scores for PLP. The range of means was quite narrow, being between 4.6 and 6.1 (out of 10) and notably higher than was seen in the longitudinal studies (range 2.4 to 3 at 1 year post amputation).

Seven studies[9,10,106,109,110,112,114] reported data on categories of pain intensity. The proportions of patients with 'severe' PLP – usually defined as being between scores of 7 and 10 on a VAS – ranged between 13% and 39% across five studies: 30%,[10] 39%,[9] 38%,[109] 13%[110] and 29%.[112] The proportions of patients with 'moderate' PLP (between 5 and 6 on a VAS) ranged between 23% and 29% across three studies.[9,110,112] The proportions of patients with 'mild' PLP (between 0 or 1 and 4 on a VAS) ranged between 35% and 64% across three studies.[9,110,112] Modirian *et al.*[106] reported the proportion with 'discomforting' PLP as 26%, the proportion with 'distressing' PLP as 35% and the proportion with 'excruciating' PLP as 38%.

Two studies provided data on the 'bothersomeness' of PLP.[9,10] The study by Ephraim *et al.*[9] reported that the pain was not bothersome for 19% of participants, the pain was somewhat bothersome for 54% of participants and the pain was extremely bothersome for 27% of participants. The Ehde *et al.*[10] study reported that 10% of participants found PLP to be not at all bothersome, 42% of participants found PLP to be mildly bothersome, 16% of participants found PLP to be moderately bothersome and 32% of participants found PLP to be severely bothersome.

Only one study (Ehde *et al.*[10]) reported data on how pain intensity related to pain-related disability using the Chronic Pain Grade Classification: 47% of patients had low pain intensity and low disability, 28% of patients had high pain intensity and low disability, 9% of patients had high disability that was moderately limiting and 14% of patients had high disability that was severely limiting. In 1962, Solonen[114] reported a 3% rate for patients with severe, persistently incapacitating PLP.

Six studies[10,109,110,112,113,116] reported on frequency of PLP attacks, although the categorisation of frequencies varied across studies. Two related studies by Sherman *et al.*[112] and Sherman and Sherman[113] reported that just under half of patients have PLP attacks on between 1 and 5 days every month and around one-third have PLP attacks on > 20 days per month. One study[116] reported that 40% of patients had PLP a few times per month and that 28% of patients had continuous PLP. Another study[10] reported that half of patients had one or fewer episodes of PLP per week. Rahimi *et al.*[109] reported that 21% of patients said that they always or usually suffered with PLP, and Rayegani *et al.*[110] reported that 5% of patients 'always' have PLP, 13% 'often' have PLP, 37% 'sometimes' have PLP and 44% 'rarely' have PLP.

Two related studies[112,113] reported on duration of PLP attacks. Around one-third of patients had attacks lasting 'seconds', and around one-third of patients had attacks lasting 'hours'. Around 10–20% of patients had continuous PLP; although respondents could answer this duration question with free text, 'minutes' was not listed as an example option.

Four studies[9,107–109] reported on associations relating to populations with chronic PLP. The study by Molton *et al.*[107] concluded that, in a population with lower extremity amputations, the relationship between pain intensity and pain-related interference with daily living was stronger in younger adults than in older adults and that this was driven by greater time since injury in older adults. The study (which undertook analyses that controlled for variables, such as type of injury and baseline pain severity) also found that neither reason for amputation nor amputation location was significantly associated with PLP severity or interference with daily living (except for a subgroup of gangrene amputation patients). A larger study[9] found no association for time since amputation when comparing severe PLP with mild PLP, although the time since amputation (median of 4 years) was notably shorter than in the Molton *et al.*[107] study (mean of 11 years). There were also no significant associations for sex, age or aetiology of amputation. Severe PLP was significantly associated with depressed mood and lower-limb amputation. This study also reported that extremely

TABLE 24 Methods and results of large cross-sectional epidemiology studies

Study	Amputees with PLP	Method details	Intensity of PLP (mean)	Results: PLP prevalence by severity and associations between PLP and patient characteristics, quality of life, daily activities, anxiety or depression
Modirian *et al.* 2009[106]	Unclear, but 112 limbs	Recall period: NR Method of PLP assessment: categorical	NE	Prevalence of PLP by severity: by limb ($n = 112$) – mild, 1%; discomforting, 26%; distressing, 35%; excruciating, 38% Associations: NE
Molton 2007[107]	375	Recall period: 3 months Method of PLP assessment: 0–10 scale	4.6	Prevalence of PLP by severity: NR Associations: the relationship between PLP severity and pain-related interference with daily living was moderated by age ($p < 0.05$). Analysis of age group differences in pain-related interference by pain level showed a large effect when pain was moderate/severe, but not when mild/moderate; younger adults had much higher pain-related interference ($p < 0.001$) than older adults. Time since amputation was a significant predictor of pain interference above and beyond chronological age. Neither reason for amputation nor amputation location was significantly associated with PLP severity or interference, except for gangrene amputation patients ($n = 78$) reporting greater PLP intensity than patients with other causes of amputation; $p < 0.05$ Note that some patients in this study overlap with the Ehde *et al.* 2000[10] cohort described below
Ehde *et al.* 2000[10] (cohort also reported in Hanley *et al.* 2006[117])	183	Recall period: 3 months Method of PLP assessment: 0–10 scale	5.1 Half reported ≤ 1 episode per week	Prevalence of PLP by severity: 30% reported mean PLP of severe intensity (i.e. between 7 and 10). Not at all bothersome, 10%; mildly bothersome (1–4 on scale), 42%; moderately bothersome (5–6), 16%; severely bothersome (7–10), 32%. Chronic pain grade classification: pain free, 2%; grade I (low disability, low pain intensity), 47%; grade II (low disability, high pain intensity), 28%; grade III (high disability – moderately limiting), 9%; grade IV (high disability – severely limiting), 14% Associations: NE

Study	Amputees with PLP	Method details	Intensity of PLP (mean)	Results: PLP prevalence by severity and associations between PLP and patient characteristics, quality of life, daily activities, anxiety or depression
Ephraim *et al.* 2005[9]	727	Recall period: 4 weeks Method of PLP assessment: 1–10 scale	5.5	Prevalence of PLP by severity: mild (1–4 on scale), 35%; moderate (5–6), 26%; severe (7–10), 39%. Pain not bothersome, 19%; somewhat bothersome, 54%; extremely bothersome, 27% Associations: severe (vs. mild) PLP significantly associated ($p < 0.05$) with depressed mood score of ≥ 10 on CES-D scale and lower-limb amputation, but no associations for time since amputation, sex, age and aetiology of amputation. Extremely bothersome (vs. not bothersome) PLP significantly associated ($p < 0.05$) with younger age (less likely in 55- to 64-year age group than in 18- to 44-year age group), ≥ 2 comorbid conditions, CES-D score of ≥ 10 and not wearing a prosthesis (vs. ≥ 9 hours of daily wear). Somewhat bothersome (vs. not bothersome) PLP significantly associated ($p < 0.05$) with CES-D score of ≥ 10
Hirsh *et al.* 2010[108]	279	Recall period: 1 week Method of PLP assessment: 0–10 scale	5.3	Prevalence of PLP by severity: NR Associations: no difference between the sexes found for the intensity or presence of PLP
Rahimi *et al.* 2012[109]	223	Recall period: NR Method of PLP assessment: categorical	NE	Prevalence of PLP by severity: severe, 38%; 21% said they always or usually suffered with PLP Associations: significant relationship ($p < 0.05$) between severe phantom pain (vs. not severe) and lower scores on SF-36 domains of physical functioning, general health and physical component scale
Rayegani *et al.* 2010[110]	214	Recall period: 4 weeks Method of PLP assessment: 0–10 scale	NR	Prevalence of PLP by severity: by limb ($n = 426$) – very mild (1–2 on scale), 40%; mild (3–4), 24%; moderate (5–6), 23%; severe (7–10), 13%. 5% 'always' have PLP, 13% 'often' (> 8 hours/day), 37% 'sometimes', 44% 'rarely' Associations: NE
Sherman and Sherman 1983[111]	648	Recall period: NR Method of PLP assessment: 0–100 scale	'Worst': 68.7 'Least usual': 18.0	Prevalence of PLP by severity: NE Associations: NE (comparisons only for PLP vs. no PLP populations)

continued

TABLE 24 Methods and results of large cross-sectional epidemiology studies (*continued*)

Study	Amputees with PLP	Method details	Intensity of PLP (mean)	Results: PLP prevalence by severity and associations between PLP and patient characteristics, quality of life, daily activities, anxiety or depression
Sherman *et al.* 1984[112]	2101	Recall period: not specified on questionnaire Method of PLP assessment: 0–10 scale	Usual: 5.3 Worst: 7.7 Least: 2.9	Prevalence of PLP by severity: usual pain intensity rating – 0 = 1.4%, 1 = 6.2%, 2 = 10.9%, 3 = 12.7%, 4 = 10.5%, 5 = 19.1%, 6 = 9.9%, 7 = 7.3%, 8 = 10.5%, 9 = 2.9%, 10 = 8.4%. Days per month of PLP – 27% over 20 days, 10% 11–20 days, 14% 6–10 days, 35% 2–5 day, 14% 1 day. Hours per day of PLP – 27% > 15 hours, 7% 11–15 hours, 14% 6–10 hours, 32% 2–5 hours, 20% ≤ 1 hour. Length of episodes – 'seconds', 38%; 'hours', 37%; 'days', 11%; 'months', 2%; 'continuous', 12% Associations: NE (comparisons only for PLP vs. no PLP populations)
Sherman and Sherman 1985[113]	436	Recall period: NR Method of PLP assessment: 0–10 scale	Mean: 5.0 Worst: 7.4 Least: 2.4	Prevalence of PLP by severity: days per month of PLP – 40% over 20 days, 7% 11–20 days, 8% 6–10 days, 31% 2–5 day, 13% 1 day, 1% < 1 day. Hours per day of PLP – 35% > 15 hours, 7% 11–15 hours, 11% 6–10 hours, 29% 2–5 hours, 18% ≤ 1 hour. Length of episodes – 'seconds', 37%; 'hours', 33%; 'days', 8%; 'months', 1%; 'continuous', 20% Associations: NE
Solonen 1962[114]	678	Recall period: NR Method of PLP assessment: categorical	NE	Prevalence of PLP by severity: 3% had severe, persistently incapacitating PLP Associations: NE
Streit *et al.* 2015[115]	68	Recall period: intensity – 4 weeks Method of PLP assessment: 0–10 scale	6.14	Prevalence of PLP by severity: NE Associations: only reported for a broader population (of around 90 patients) with a lifetime history of PLP – this included patients in remission (i.e. no PLP in previous 3 months)
Wartan *et al.* 1997[116]	144 (patients with stable, chronic PLP)	Recall period: not specified on questionnaire Method of PLP assessment: 0–10 scale	NR for chronic population	Prevalence of PLP by severity: 15 (10%) had a few PLP attacks per year, 58 (40%) had PLP a few times per month, 27 (19%) had a few PLP attacks per day, 5 (3%) had a few attacks per hour and 39 (28%) reported that PLP was always present Associations: NE (comparisons only for any PLP vs. no PLP populations)

CES-D, Centre for Epidemiologic Studies Depression scale (range 0–30); NE, not evaluated; NR, not reported.

bothersome PLP (vs. not bothersome) was significantly associated with younger age, depressed mood, having comorbidities and not wearing a prosthesis.

In the remaining two studies, which looked at associations with PLP, one[109] identified a significant relationship between severe PLP (vs. not severe) and lower scores on SF-36 domains of physical functioning, general health and physical component scale, and one[108] reported no difference between the sexes for the intensity or presence of PLP.

Summary

The evidence on prognostic factors for the development of chronic PLP in patients with PLP following amputation has important limitations. Although the literature searches identified numerous epidemiological studies that reported results for chronic PLP cohorts, fewer than one-third of the studies had a prospective design. Moreover, only one of the prospective studies had a sample size of > 100 (so some results may have been prone to chance effects), and follow-up durations were generally limited to between 6 months and 2 years. Mean VAS scores indicated that most patients had quite mild PLP. 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.

Most of the epidemiology studies had a cross-sectional design, in which each patient's data were collected at a single point in time. Results from such studies often cannot establish the direction and causality of any associations found. For example, the reported association between chronic severe PLP and depression might imply that severe PLP is a risk factor for developing depression (implying that treatment for severe PLP is paramount). Alternatively, it may be that existing depression is a risk factor for severe PLP (implying that treatment for depression is more urgent). Longitudinal cohort studies could answer such questions but none of the longitudinal studies in our review addressed outcomes, such as depression, anxiety and quality of life. Although many of the cross-sectional studies had large sample sizes, many of them also had participation rates of between around 50% and 70%. Therefore, it is possible that these studies' results were subject to non-response bias, which might limit their generalisibility to the broader chronic PLP population.

Nevertheless, cross-sectional studies may be useful for estimating disease prevalence.[118] Results suggest that the proportion of patients with chronic PLP that is severe lies between around 30% and 40%, 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 25% 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 attacks; for example, estimates of the proportion of patients with continuous PLP range from around 2% to 20%.

Chapter 3 Survey of NHS practice

The aims of the survey were (1) to provide the views of clinicians who deliver neurostimulation therapies regarding which treatments are being used to treat chronic PLP in NHS patients and how effective those treatments are perceived to be, and (2) to elicit opinions regarding future research studies.

Methods

A questionnaire was designed and distributed using Qualtrics® software (May 2017 version; Qualtrics®, Provo, UT, USA). The questionnaire was first piloted by clinical members of the review team. We distributed the survey via the e-mail lists of the British Society for Stereotactic and Functional Neurosurgery and the Neuromodulation Society of the United Kingdom and Ireland. The survey was distributed between September and November 2017. Responses were made anonymously, although responders had the option of providing an e-mail address, should they wish to be notified about the publication of this report. It was not possible to calculate an overall response rate as we did not have direct access to the e-mail distribution lists.

The survey asked questions about the frequency of use of specific treatments and their perceived effectiveness. Questions were also asked about the viability of future research studies and treatment preferences in these studies. The full questionnaire content can be found in *Report Supplementary Material 3*. No imputations were used for missing data in partially completed questionnaires. Data were assumed to be missing at random, with the most probable reasons for missing data assumed to be lack of time (e.g. the questionnaire had been started but the respondent did not have time to complete it) and a lack of information or knowledge (to hand) to complete the survey. Results were analysed and narratively presented with accompanying tables when appropriate. The unit of analysis was at the individual level (rather than at the unit level) for all questions.

Results

A total of 37 questionnaires were received from 30 different hospitals. Thirty-four questionnaires (92%) were fully completed and three (8%) were partially completed. Key summary results relating to each question are presented in the following sections.

Respondent characteristics

Thirty-four questionnaires were received from respondents in England, and one questionnaire each was received from respondents in Wales, Northern Ireland and the Republic of Ireland. Twenty-five responses (68%) were from pain management clinics, 11 were from neurosurgery units and one (3%) response was from a rehabilitation unit. Responders were either pain physicians (23 responders, 62%), neurosurgeons (11 responders, 30%), anaesthetists (two responders, 5%) or rehabilitation physicians (one response, 3%).

Questions and responses

Please consider the list below of 12 types of treatment. How frequently would you estimate that each of them is used in your unit in patients who have chronic phantom limb pain?

The responses to this question are summarised in *Table 25*, which provides both overall results and results split by the main clinician subgroups: pain physicians and neurosurgeons.

The results indicate a very high use of pharmacological treatments in the chronic PLP population. Cognitive–behavioural therapy (CBT) and mirror therapy or graded motor imagery are frequently used interventions, but opinions on the frequency of use of acupuncture and TENS were much more variable. Relatively few patients receive myoelectric prostheses, DREZ and transcranial stimulation therapies. Of the

TABLE 25 Clinician estimates of prevalence of intervention use in patients with chronic PLP

Intervention	Prevalence, *n* (%)					
	Always used	Usually used	Sometimes used	Rarely used	Never used	Do not know
Pharmacologics						
Full sample (*N* = 35)	24 (69)	8 (23)	0	2 (6)	1 (3)	0
Pain physicians (*N* = 22)	16 (73)	4 (18)	0	2 (9)	0	0
Neurosurgeons (*N* = 10)	7 (70)	2 (20)	0	0	1 (10)	0
TENS						
Full sample (*N* = 37)	4 (11)	2 (5)	17 (46)	10 (27)	3 (8)	1 (3)
Pain physicians (*N* = 23)	2 (9)	1 (4)	11 (48)	8 (35)	1 (4)	0
Neurosurgeons (*N* = 11)	2 (18)	1 (9)	4 (36)	2 (18)	1 (9)	1 (9)
Acupuncture						
Full sample (*N* = 37)	1 (3)	6 (16)	10 (27)	12 (32)	7 (19)	1 (3)
Pain physicians (*N* = 23)	0	2 (9)	8 (35)	10 (43)	3 (13)	0
Neurosurgeons (*N* = 11)	1 (9)	4 (36)	0	2 (18)	3 (27)	1 (9)
Mirror therapy/graded motor imagery						
Full sample (*N* = 37)	5 (14)	13 (35)	8 (22)	7 (19)	2 (5)	2 (5)
Pain physicians (*N* = 23)	4 (17)	9 (39)	5 (22)	5 (22)	0	0
Neurosurgeons (*N* = 11)	1 (9)	3 (27)	1 (9)	2 (18)	2 (18)	2 (18)
CBT						
Full sample (*N* = 37)	13 (35)	10 (27)	7 (19)	1 (3)	5 (14)	1 (3)
Pain physicians (*N* = 23)	8 (35)	8 (35)	4 (17)	1 (4)	2 (9)	0
Neurosurgeons (*N* = 11)	5 (45)	2 (18)	1 (9)	0	2 (18)	1 (9)
Myoelectric prosthesis						
Full sample (*N* = 37)	0	2 (5)	5 (14)	4 (11)	22 (59)	4 (11)
Pain physicians (*N* = 23)	0	0	3 (13)	4 (17)	15 (65)	1 (4)
Neurosurgeons (*N* = 11)	0	2 (18)	1 (9)	0	5 (45)	3 (27)
Spinal cord stimulation						
Full sample (*N* = 37)	1 (3)	7 (19)	21 (57)	1 (3)	7 (19)	0
Pain physicians (*N* = 23)	0	6 (26)	11 (48)	1 (4)	5 (22)	0
Neurosurgeons (*N* = 11)	1 (9)	1 (9)	8 (73)	0	1 (9)	0
Dorsal root ganglion stimulation						
Full sample (*N* = 36)	2 (6)	11 (31)	11 (31)	2 (6)	7 (19)	3 (8)
Pain physicians (*N* = 23)	1 (4)	7 (30)	9 (39)	1 (4)	5 (22)	0
Neurosurgeons (*N* = 11)	1 (9)	4 (36)	1 (9)	1 (9)	2 (18)	2 (18)
Deep brain stimulation						
Full sample (*N* = 37)	0	2 (5)	6 (16)	4 (11)	23 (62)	2 (5)
Pain physicians (*N* = 23)	0	0	2 (9)	3 (13)	16 (70)	2 (9)
Neurosurgeons (*N* = 11)	0	2 (18)	4 (36)	1 (9)	4 (36)	0

TABLE 25 Clinician estimates of prevalence of intervention use in patients with chronic PLP (*continued*)

Intervention	Prevalence, *n* (%)					
	Always used	Usually used	Sometimes used	Rarely used	Never used	Do not know
Motor cortex stimulation						
Full sample (*N* = 37)	1 (3)	1 (3)	1 (3)	3 (8)	29 (78)	2 (5)
Pain physicians (*N* = 23)	0	1 (4)	0	1 (4)	19 (83)	2 (9)
Neurosurgeons (*N* = 11)	1 (9)	0	1 (9)	2 (18)	7 (64)	0
Transcranial magnetic/current stimulation						
Full sample (*N* = 37)	0	2 (5)	2 (5)	1 (3)	27 (73)	5 (14)
Pain physicians (*N* = 23)	0	1 (4)	0	1 (4)	17 (74)	4 (17)
Neurosurgeons (*N* = 11)	0	1 (9)	2 (18)	0	7 (64)	1 (9)
DREZ						
Full sample (*N* = 37)	0	2 (5)	0	5 (14)	27 (73)	3 (8)
Pain physicians (*N* = 23)	0	2 (9)	0	4 (17)	15 (65)	2 (9)
Neurosurgeons (*N* = 11)	0	0	0	1 (9)	9 (82)	1 (9)

CBT, cognitive–behavioural therapy.
Note
Percentages are of the response total for each intervention.

invasive neurostimulation therapies, SCS seems to be the most prevalent, with around three-quarters of both pain physicians and neurosurgeons indicating that their patients usually or sometimes use SCS. DRG stimulation is also frequently used (although a little less so than SCS). The prevalence of the use of DBS and MCS was quite low, as would be expected given the current lack of funding for these treatments. The use of DBS was higher in patients attending neurosurgery units than in patients attending pain management clinics.

Based on your experience of patients with chronic phantom limb pain, how do you rate the effectiveness – in terms of pain relief – of the same 12 types of treatment listed below?

The responses to this question are summarised in *Table 26*.

Most clinicians considered pharmacological treatments and CBT to be at least sometimes effective for alleviating pain in chronic PLP patients. TENS was not thought to be very effective by most clinicians, but around two-thirds of neurosurgeons considered acupuncture to be sometimes 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 both SCS and DRG stimulation to be either mostly effective or sometimes effective for reducing PLP. Neurosurgeons were split in their opinions on how frequently DBS is effective: one-third thought that it was mostly effective, one-third thought that it was sometimes effective and one-third thought that it was rarely effective. A majority of neurosurgeons considered MCS to be rarely effective. Most pain physicians selected ‘Don’t know’ when asked about how frequently DBS and MCS were effective.

TABLE 26 Clinician opinions on intervention effectiveness for pain relief in chronic PLP patients

Intervention	Clinician opinions, *n* (%)			
	Mostly effective	Sometimes effective	Rarely effective	Do not know
Pharmacologics				
Full sample (*N* = 34)	5 (15)	21 (62)	7 (21)	1 (3)
Pain physicians (*N* = 22)	4 (18)	13 (59)	5 (23)	0
Neurosurgeons (*N* = 9)	0	6 (67)	2 (22)	1 (11)
TENS				
Full sample (*N* = 34)	0	10 (29)	20 (59)	4 (12)
Pain physicians (*N* = 22)	0	6 (27)	13 (59)	3 (14)
Neurosurgeons (*N* = 9)	0	3 (33)	5 (56)	1 (11)
Acupuncture				
Full sample (*N* = 34)	0	11 (32)	21 (62)	2 (6)
Pain physicians (*N* = 22)	0	3 (14)	17 (77)	2 (9)
Neurosurgeons (*N* = 9)	0	6 (67)	3 (33)	0
Mirror therapy/graded motor imagery				
Full sample (*N* = 34)	3 (9)	19 (56)	11 (32)	1 (3)
Pain physicians (*N* = 22)	3 (14)	13 (59)	6 (27)	0
Neurosurgeons (*N* = 9)	0	3 (33)	5 (56)	1 (11)
CBT				
Full sample (*N* = 34)	3 (9)	21 (62)	9 (26)	1 (3)
Pain physicians (*N* = 22)	3 (14)	12 (55)	7 (32)	0
Neurosurgeons (*N* = 9)	0	7 (78)	2 (22)	0
Myoelectric prosthesis				
Full sample (*N* = 33)	0	8 (24)	1 (3)	24 (73)
Pain physicians (*N* = 22)	0	5 (23)	0	17 (77)
Neurosurgeons (*N* = 8)	0	2 (25)	1 (13)	5 (63)
Spinal cord stimulation				
Full sample (*N* = 33)	3 (9)	23 (70)	1 (3)	6 (18)
Pain physicians (*N* = 22)	1 (5)	16 (73)	0	5 (23)
Neurosurgeons (*N* = 8)	2 (25)	5 (63)	1 (13)	0
Dorsal root ganglion stimulation				
Full sample (*N* = 34)	6 (18)	19 (56)	1 (3)	8 (24)
Pain physicians (*N* = 22)	3 (14)	14 (64)	1 (5)	4 (18)
Neurosurgeons (*N* = 9)	3 (33)	4 (44)	0	2 (22)
Deep brain stimulation				
Full sample (*N* = 34)	3 (9)	5 (15)	5 (15)	21 (62)
Pain physicians (*N* = 22)	0	2 (9)	2 (9)	18 (82)
Neurosurgeons (*N* = 9)	3 (33)	3 (33)	3 (33)	0

TABLE 26 Clinician opinions on intervention effectiveness for pain relief in chronic PLP patients (*continued*)

Intervention	Clinician opinions, *n* (%)			
	Mostly effective	Sometimes effective	Rarely effective	Do not know
Motor cortex stimulation				
Full sample (*N* = 34)	1 (3)	2 (6)	6 (18)	25 (74)
Pain physicians (*N* = 22)	0	0	2 (9)	20 (91)
Neurosurgeons (*N* = 9)	1 (11)	2 (22)	4 (44)	2 (22)
Transcranial magnetic/current stimulation				
Full sample (*N* = 34)	0	4 (12)	3 (9)	27 (79)
Pain physicians (*N* = 22)	0	0	2 (9)	20 (91)
Neurosurgeons (*N* = 9)	0	4 (44)	1 (11)	4 (44)
DREZ				
Full sample (*N* = 33)	0	3 (9)	4 (12)	26 (79)
Pain physicians (*N* = 22)	0	2 (9)	3 (14)	17 (77)
Neurosurgeons (*N* = 9)	0	1 (11)	1 (11)	7 (78)

CBT, cognitive–behavioural therapy.

Have you ever administered any of the following treatments to patients with phantom limb pain?

The responses to this question are summarised in *Table 27*. This illustrates the broader experience of neurosurgeons in delivering a range of neurostimulation treatments.

Regarding a future research study, do you think that a randomised trial design can be successfully used to study neuromodulation therapies for chronic phantom limb pain? (Only responders who indicated that they had administered one of the neuromodulation therapies listed in the previous question were asked this question)

From 24 responses, 19 responders stated 'Yes', three stated 'No' and two stated 'Don't know'.

It would be helpful if you could say why a randomised trial design might not be viable. If you have any thoughts on alternative study designs you think might be more appropriate, and thoughts on which neuromodulation treatments you would like to see studied, please also state them here

Of the three responders who foresaw difficulties with conducting a RCT, two mentioned problems in recruiting enough participants. One of these responders added that 'heterogeneity' and the 'nature of pain research' would be an issue but did not elaborate further. One responder said that double blinding would be difficult.

Please select which neuromodulation therapy or therapies you would like to see studied in a randomised trial (Only responders who said that they thought that a randomised controlled trial design could be used to study neuromodulation therapies for chronic PLP were asked this question)

The responses to this question are summarised in *Table 28*. Pain physicians would most like to see SCS and DRG stimulation studied in a RCT. Neurosurgeons would most like to see DRG stimulation and DBS studied in a RCT.

TABLE 27 Numbers of clinicians who have administered neurostimulation therapies

Intervention	Clinicians who have/have not administered neurostimulation therapies, *n* (%)	
	Yes	No
Spinal cord stimulation		
Full sample (*N* = 34)	23 (68)	11 (32)
Pain physicians (*N* = 22)	14 (64)	8 (36)
Neurosurgeons (*N* = 9)	8 (89)	1 (11)
Dorsal root ganglion stimulation		
Full sample (*N* = 34)	17 (50)	17 (50)
Pain physicians (*N* = 22)	11 (50)	11 (50)
Neurosurgeons (*N* = 9)	6 (67)	3 (33)
Deep brain stimulation		
Full sample (*N* = 34)	8 (24)	26 (76)
Pain physicians (*N* = 22)	0	22 (100)
Neurosurgeons (*N* = 9)	8 (89)	1 (11)
Motor cortex stimulation		
Full sample (*N* = 34)	3 (9)	31 (91)
Pain physicians (*N* = 22)	0	22 (100)
Neurosurgeons (*N* = 9)	3 (33)	6 (67)
Transcranial magnetic/current stimulation		
Full sample (*N* = 34)	2 (6)	32 (94)
Pain physicians (*N* = 22)	0	22 (100)
Neurosurgeons (*N* = 9)	2 (22)	7 (78)

TABLE 28 Clinician intervention preferences for a future randomised trial

Intervention	Counts, *n* (% of total counts)		
	All responses	Pain physicians	Neurosurgeons
SCS	15 (31)	10 (40)	4 (19)
Dorsal root ganglion stimulation	18 (38)	10 (40)	7 (33)
DBS	8 (17)	2 (8)	6 (29)
MCS	3 (6)	1 (4)	2 (10)
Transcranial magnetic/current stimulation	4 (8)	2 (8)	2 (10)
Total	48 (100)	25 (100)	21 (100)

Are you aware of any summary data on the effectiveness or safety of neuromodulation therapies for phantom limb pain that we are unlikely to have identified in our searches of literature databases (e.g. unpublished data and very recent conference abstracts)? (Only responders who had administered a neuromodulation treatment were asked this question)

Two responders said 'Yes': one mentioned a conference abstract (which we had identified in our previous searches) and one provided their e-mail address but did not respond when details were requested. Sixteen responders replied 'No' and six stated 'Don't know'.

Summary of survey findings

The survey results indicated that SCS seems to be the most frequently used neuromodulation therapy in the NHS: around three-quarters of both pain physicians and neurosurgeons indicated that their patients usually or sometimes use SCS. DRG stimulation is also frequently used. The prevalence of the use of DBS and MCS was quite low, as would be expected given the current lack of funding for these treatments in the NHS. Most responders thought both SCS and DRG stimulation to be either mostly or sometimes effective for reducing PLP. Although neurosurgeons were split in their opinions on how frequently DBS is effective, most considered MCS to rarely be effective. Most clinicians thought that a randomised trial design was viable to study neuromodulation therapies, although recruiting enough participants was raised as a concern. Pain physicians most wanted to see SCS and DRG stimulation studied in a RCT, whereas neurosurgeons most wanted to see DRG stimulation and DBS studied in a RCT.

Chapter 4 Discussion

Statement of principal findings

For non-invasive neurostimulation treatments, results from a good-quality randomised trial[29] suggest short-term benefits of rTMS in reducing PLP but not in reducing anxiety or depression. Small randomised trials of tDCS[30,45] suggest only the possibility of modest, short-term reductions in PLP. Both of these interventions appear safe, but only larger trials with longer follow-up periods will resolve the considerable uncertainty about their true potential for treating PLP.

For invasive neurostimulation treatments – DBS, MCS, SCS and DRG stimulation – all the available evidence was derived from small, uncontrolled group studies or case reports. Although several studies reported results that appeared impressive in the short term (many patients had reductions in PLP sufficient to warrant permanent implantation), the effects diminished over time in some patients, with implants sometimes having to be removed. Most studies did not have follow-up data beyond 2 to 3 years, although it is evident that some patients still derived worthwhile benefits at these time points. Nevertheless, results from uncontrolled studies are inherently unreliable and, aside from the problems with interpreting results that arise from not having control data, many of these studies had other important methodological and/or reporting limitations. Few studies recruited patients prospectively and consecutively. In terms of outcomes, many studies focused on evaluating only pain intensity, using a visual analogue or numerical rating scale, and did not evaluate pain frequency or duration. Although several studies used the McGill Pain Questionnaire (MPQ) – which utilises information on more descriptive, qualitative aspects of pain – in many of them, results were not presented. Few studies reported data on quality-of-life outcomes, which are very important when evaluating effects on chronic pain. The consequences of these methodological and reporting limitations are that the results and conclusions of most of these studies should not be considered robust. Given that invasive neuromodulation is often used for only severe PLP and often as a late treatment option, the applicability of the results to a broader chronic PLP population is limited. Therefore, there is still much uncertainty as to which neurostimulation treatments are best for treating chronic PLP.

Although we identified numerous epidemiological studies, much of the evidence on prognostic factors for the development of chronic PLP had important limitations. The longitudinal studies we identified were quite small with limited follow-up periods; none addressed outcomes such as depression, anxiety and quality of life, and most patients had quite mild PLP. Both pre-amputation pain and early PLP intensity appear to be 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. We also identified many cross-sectional studies, which were useful for providing estimates of disease prevalence. Results suggested that the proportion of chronic PLP patients with severe PLP lies between 30% and 40%, whereas the proportion with moderate PLP is around 25%. From the studies reporting data on how chronic PLP affects patients' daily lives, it appears that around 25% of chronic PLP patients find their PLP to be either moderately or severely limiting or bothersome. Much variation was reported across studies regarding the frequency and duration of PLP attacks.

Our survey of the views of NHS clinicians indicated that SCS seems to be the most frequently used neurostimulation therapy: around three-quarters of both pain physicians and neurosurgeons indicated that their patients usually or sometimes use SCS. DRG stimulation is also frequently used. The prevalence of the use of DBS and MCS was quite low, as would be expected given the current lack of funding for these treatments in the NHS. The survey results also indicated a very high use of pharmacological treatments. TENS was not thought to be very effective by most clinicians, although most considered cognitive–behavioural therapy to be at least sometimes effective and most neurosurgeons considered acupuncture to be sometimes effective for reducing chronic PLP. Most responders considered both SCS and DRG stimulation to be either mostly or

sometimes effective. Although neurosurgeons were split in their opinions on how frequently DBS is effective, most considered MCS to rarely be effective. A large majority of clinicians thought that a RCT design was viable to study neurostimulation therapies, although recruiting enough participants was raised as a concern. Pain physicians most wanted to see SCS and DRG stimulation studied in a RCT, whereas neurosurgeons most wanted to see DRG stimulation and DBS studied in a RCT.

Strengths and limitations of the assessment

This study was designed to be broad in scope because we anticipated a sparse evidence base. We conducted a systematic review of epidemiology studies in addition to a systematic review of effectiveness studies, which was not restricted by study design for the invasive therapy studies. Moreover, these reviews were augmented by a survey of relevant NHS clinicians. We adopted this approach in order to provide further data to best inform our recommendations for future research.

The systematic reviews were undertaken using robust and transparent methods. The bibliographic database searches were comprehensive, allowing identification of all relevant studies. Searches were also made to identify any unpublished studies. The possibility of publication or language biases affecting the review was, therefore, minimised. Similarly, the possibility of reviewer errors and biases affecting our review was reduced by duplicating review processes, such as study eligibility screening. Thorough risk-of-bias evaluations were made of the RCTs, and the single-group studies were evaluated on key aspects of study design. The sample for our NHS survey was large and diverse enough to be representative of NHS staff who treat PLP using neurostimulation treatments. The survey was circulated via two specialist e-mailing lists that were known to the clinicians in the review team. Our estimates are that there are approximately 30 neurostimulation centres in the UK (we had responses from 30 different hospitals), and that there are around 10–20 relevant neurosurgeons (11 neurosurgeons responded). Therefore, we think that the survey results are broadly representative of the views and practices of NHS clinicians.

The main limitation of the systematic review was the evidence that was identified. The RCTs were small, with short-term data. The studies of invasive treatments were small, and lacked control groups; few studies recruited patients prospectively and consecutively. For the epidemiology studies, although several aspects of study quality, such as participation rates, were recorded and discussed in the review, this was done only informally, which is a limitation. Although a number of relevant assessment tools exist, there is a need for agreement on critical elements for assessing susceptibility to bias in epidemiology studies, and to develop appropriate evaluation tools.[119]

Future research

Study design

The lack of controlled studies of invasive treatments for PLP presents a problem for decision-makers. Although controlled studies are needed, the viability of possibly relevant study designs warrants careful thought. Although there have been no RCTs of invasive treatments in a PLP population, a RCT of DBS has recently been published on patients with post-stroke pain syndrome.[120] This double-blinded, crossover RCT recruited 10 patients at a single centre in the USA. After implantation of DBS leads, patients were randomised to active or sham DBS for a period of 3 months, followed by crossover to the other study intervention for 3 months. Patients then underwent an 18-month open-label phase of DBS. The primary end point was a $\geq$ 50% improvement on the Pain Disability Index. During the randomised phase of the trial, patients were followed up at 1, 2 and 3 months after randomisation and crossover. One patient withdrew from the study before randomisation. No statistically significant differences were found between active DBS and sham in scores for the Pain Disability Index, VAS or the Sensory Pain Rating Index of the MPQ.

In considering the viability of this study design for trialling DBS for chronic PLP, it is noteworthy that 36 of the initial cohort of 69 patients identified as potential participants declined consent to be screened for eligibility. Of the 33 who did consent to eligibility screening, 13 did not meet the eligibility criteria, six did not give consent for further study and four were lost to follow-up. Therefore, in this particular RCT of DBS in patients with chronic pain, around seven potential participants had to be identified in order to randomise one. Moreover, although it was encouraging that 9 of the 10 randomised patients completed both blinded intervention phases (i.e. they were followed up for 6 months), four participants withdrew consent prior to completing the open-label phase, leaving only five participants with 18-month data.

All of the RCTs in our review were of non-invasive treatments and all were small. Three had a crossover design and two had a parallel-group design. The largest trial, reported by Malavera *et al.*,[29] was a parallel-group trial that recruited 54 PLP patients from one centre in Columbia, although over one-quarter of eligible patients declined participation. Although we identified five relevant ongoing trials in our searches, the proposed sample sizes are generally small and two are uncontrolled (single-group) studies; therefore, the results of these five trials (if published) may have only a minor impact on resolving uncertainty about which neurostimulation treatments are most effective.

It seems clear that strategies to maximise patient recruitment and retention are key. A randomised crossover design is useful in this respect because fewer patients are needed when compared with a parallel-group trial; this is because patients act as their own control in a crossover trial. Crossover trials may also be more appealing than parallel-group trials to both patients and ethics committees because patients are guaranteed to receive an active treatment (providing they can complete both phases). In parallel-group trials, patients can experience 'resentful demoralisation' if they think that they have been allocated an inert or standard intervention, which may increase withdrawal rates. If a particular neurostimulation therapy produces a clear sensation in the user, the use of sham stimulation, using parameters sufficient to give a subtherapeutic sensation, should ensure that patients are adequately blinded in a crossover trial. Blinding of caregivers and evaluators has been raised as an important design issue.[121] The use of crossover designs is often not a viable option in clinical research but they are viable in this area of research. This is because chronic PLP is a stable condition and the effects of neurostimulation therapies are reversible (i.e. therapies can be turned on and off). Although the duration of the carry-over effects of neurostimulation are unknown with any precision, they are not thought to exceed several days at most.

Another study design that could be considered in a chronic PLP population, and that has similarities to a crossover trial, is the N-of-1 trial design. The difference between the designs is that N-of-1 trials study single participants, who typically receive more than one 'cycle' of treatments. Consequently, the unit of randomisation is the treatment order within a treatment cycle for a patient. In a crossover trial, the patient is the unit of randomisation, with one cycle of treatment normally given.[122] The N-of-1 design has been used to study DBS for neuropathic pain using five 'pairs of treatments': the stimulator being turned on and off.[83] N-of-1 trials are a very efficient and less costly way to gain insights into comparative treatment effectiveness in a range of patients. Although they are most often used to derive comparative data for different active treatments in single patients, in chronic PLP neurostimulation research they are more likely to be used to compare the impact of several on/off phases. Furthermore, it is possible to meta-analyse data from multiple N-of-1 trials investigating the same sets of interventions, which can be useful in identifying clinical characteristics that are predictors of treatment response.[123]

Recruitment and retention of participants in a trial might be maximised by using eligibility criteria that specify thresholds for PLP (e.g. a minimum mean VAS score of 5 on a 0–10 scale) and quality of life, which reflect the subgroup of chronic PLP patients most in need of intervention. Eligible patients should have tried and failed other relevant interventions from earlier in the treatment pathway. If recruitment is anticipated to be the major obstacle, a prospective observational database or registry study could be considered. Although this approach should maximise patient numbers, its results would inherently be subject to uncertainty owing to confounding. It should be acknowledged that RCTs that do not recruit enough participants may also produce unreliable results, being prone to chance effects. In the UK,

neuromodulation registries exist for SCS and DBS. A hybrid design might also be practicable, whereby N-of-1 trials are incorporated into clinical databases or registries, ensuring consistent approaches in patient selection, interventions, outcome measures and data collection.

Regardless of the study design adopted, a collaborative approach between rehabilitation physicians and implanting physicians will be important. Long-term assessment would also be needed, particularly of quality-of-life outcomes and broader assessments of pain that go beyond pain intensity alone (such as the MPQ).[124] Long-term assessments would also provide valuable data on the development of tolerance of neurostimulation therapy, about which little is known in the chronic PLP population. Both short- and long-term data on adjustment of intervention parameters will be required, as will safety data. Concurrent economic evaluation of therapies should be strongly considered in any future study of effectiveness. Because learning curves can have an important impact on surgery study outcomes, it is recommended that research studies are conducted at established centres with experienced surgeons.

Categorising and interpreting pain data

Many of the effectiveness studies in our review used thresholds to categorise treatment success, such as a 50% or a greater reduction in pain. Such thresholds may be quite arbitrary and not necessarily evidence-based. Similarly, some of the epidemiology studies also categorised PLP as being mild, moderate or severe, based on pain score. However, there is evidence suggesting that the cut-off scores used for these types of categorisations, derived from research on patients with cancer pain, may not be optimal for studying PLP.[125]

In many areas of pain research, studies are conducted to determine 'minimum clinically important differences' (MCIDs): the smallest improvement in pain score perceived by patients as being beneficial. 'Substantial' clinically relevant differences are also sometimes used to interpret results of studies of effectiveness. Determination of MCID for chronic PLP would help with interpreting results of efficacy studies. A systematic review of 37 empirical studies that estimated MCID in acute pain found both wide variation in MCIDs (8–40 mm on a 100-mm scale) and that baseline pain was strongly associated with absolute, but not relative, MCID (patients with higher baseline pain needed more pain reduction to perceive relief).[126] The authors concluded that MCID is context-specific and potentially misguiding if determined, applied or interpreted inappropriately. Even more relevant to future studies of chronic PLP, the authors stated that they were due to publish a systematic review of the MCID in chronic pain, which indicated similar issues of high study variability. For many conditions, MCIDs have also been calculated for quality-of-life outcomes.[127,128]

Quality-of-life measures

Careful thought should also be given to the type of quality-of-life assessment tool used. The limited scope and content of generic health-related quality-of-life measures may mean that, for some conditions, generic tools may not be sensitive enough to detect meaningful changes resulting from treatment. However, generic measures are useful in other ways: for example, in allowing easier comparison of results across different patient groups. Generic and specific quality-of-life dimensions may be assessed simultaneously. For patients with chronic pain, a pain and discomfort module has been developed to increase the specificity and sensitivity of the generic core WHOQOL-100 (World Health Organization's Quality of Life – 100 questions) instrument. This was done because the pain and discomfort facet in the original instrument was found to under-represent the impact of chronic pain on quality of life. The module relates most strongly to the physical, psychological and level-of-independence domains, and less to social relationships, the environment or spirituality.[129]

Conclusions

The studies of the efficacy, effectiveness and safety of neurostimulation 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 periods. Consequently, there is much uncertainty about which neurostimulation 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 did indicate that PLP that substantially affects quality of life is not a rare condition among amputees. 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 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 the NHS clinicians responding to our survey, 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 is important, as are broader assessments of pain that go beyond pain intensity alone.

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Contributions of authors

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Mark Corbett (Research Fellow) wrote the first draft of the protocol, led on designing and undertaking the reviews, wrote the survey and contributed to the writing of the report.

Emily South (Research Fellow) conducted many of the review processes (screening studies, extracting data and risk-of-bias evaluations) and contributed to the writing of the report.

Melissa Harden (Information Specialist) contributed to the protocol, developed the search strategies, conducted a range of searches to locate studies and wrote the sections of the report relating to the literature searches.

Sam Eldabe (Consultant in Pain Medicine and Anaesthesia) contributed to the protocol, the survey design and distribution and the writing of the report.

Erlick Pereira (Consultant Neurosurgeon and Spinal Surgeon) contributed to the protocol, the survey design and distribution and the writing of the report.

Imad Sedki (Consultant in Rehabilitation Medicine) contributed to the protocol, the survey design and distribution and the writing of the report.

Neil Hall (Consultant in Pain Management and Anaesthesia) contributed to the protocol, the survey design and distribution and the writing of the report.

Nerys Woolacott (Reader Emerita) contributed to the protocol, the survey design, some of the review processes and the writing of the report.

Data-sharing statement

All the available review data and the survey questionnaire results summary data are included in the report. There are no further data suitable for sharing. All queries should be submitted to the corresponding author in the first instance.

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