Assessment of Low-Frequency Nerve Stimulation for Peripheral Neuropathic Pain.

Thesis submitted in accordance with the requirements of the University of Liverpool for the degree of doctor in philosophy by

Selina Johnson.

January 2022.

Academic Honesty Declaration

I confirm that:

- I have read and understood the University's PGR Policy on Plagiarism and Dishonest Use of Data (Appendix 4 of the PGR Code of Practice).
- I have acted honestly, ethically, and professionally in conduct leading to assessment for the programme of study.
- I have not copied material from another source nor committed plagiarism nor fabricated, falsified, or embellished data when completing the attached material.
- I have not copied material from another source, nor colluded with any other student in the preparation and production of this material.
- If an allegation of suspected academic malpractice is made, I give permission to the University to use source-matching software to ensure that the submitted material is all my own work.

Selina Johnson

Table of contents.

Abstract

Low-Frequency Nerve Stimulation for Peripheral Neuropathic Pain

Selina Johnson

Neuropathic pain can arise either peripherally or centrally as a direct consequence of a lesion or disease affecting the somatosensory system. It can persist long after the initial cause has resolved. Persistent (chronic) neuropathic pain affects 8% of people in the UK and is often severely debilitating, affecting patients' physical, economic, and emotional wellbeing. Current neuropathic pain management guidelines are heavily weighted on pharmacotherapy, but often with only modest outcomes and for many, there is no effective treatment. Therefore, there is a need for alternative approaches to support this patient group.

Following nerve injury, abnormal impulses arising from peripheral nociceptors can lead to an amplification of synaptic transmission in dorsal horn neurons termed 'nociceptive long-term potentiation' (LTP). Low-frequency electrical nerve stimulation (LFS) has been shown to reduce the efficacy of synaptic transmission and thereby reverse this process by inducing 'long-term depression' (LTD). LFS to induce LTD, therefore, represents a potential treatment for neuropathic pain where LTP is a feature.

Surgical and invasive devices that deliver electrical stimulation do not consistently utilise LFS, whilst the designs of many non-invasive devices fail to achieve a sufficient current density to induce LTD. We had previously conducted a small observational study that provided proof of concept for reduction in nerve injury pain using a low-frequency stimulation device that uses a small spherical electrode potentially capable of inducing LTD. A further observational study supported our results, however, this needed further evaluation in randomised controlled trials.

To conduct a robust trial, we explored the issues relating to the use of sham devices in interventional trials to inform our study. We then conducted a single site, blinded, randomised sham-controlled trial. 76 patients with longstanding localised neuropathic pain following peripheral nerve injury were randomised to receive either active or control treatment, followed by an optional treatment extension or treatment switch to the alternative treatment arm. The primary outcome was average of 24-h pain intensity recorded on an 11-point (0–10) numerical rating scale, averaged over the last 7 days of treatment.

The trial results indicated there was no statistically significant difference in the primary outcome between the two study groups with pain scores at 3 months being on average 0.3 units lower in the active group (95% CI -1.0, 0.3; p=0.30). Significant improvement was observed for the surface area of allodynia following active treatment with a difference of 74 cm^2 between groups (95% CI -126, -22; p=0.006), indicating a reduction in enhanced skin sensitivity. Across all outcomes, the number of patients achieving minimally clinically important difference was significantly higher in the active group compared to the sham group (33% ±11 Vs 19% ±7.1, p=0.005, u=10 Mann Whitney test). The treatment was well tolerated with a low side effect profile. Post hoc patient interviews indicated that many patients were often stimulating at a suboptimal dose.

Although the primary outcome failed to achieve significance, a positive trend was observed across all domains in favour of active treatment indicating a biological effect. Results, therefore, highlight LFS as a potential treatment, however, they also show the necessity for refinement of its delivery to facilitate optimal LTD and therapeutic benefit. The results highlight we need to ensure treatment efficacy, patients need to fully understand the tools or modality they have been given and this needs to be an integral part of treatment evaluation. We, therefore, believe this thesis provides important

practical considerations in terms of the conduct of mechanism driven therapy and adds to the body of evidence regarding LFS and LTD.

List of tables

List of Figures

Chapter 1 Introduction, Neuropathic Pain.

Chapter sub-sections:

1. Definition
2. Aetiology of peripheral neuropathic pain
3. Background mechanisms
4. Clinical presentation
5. Diagnosis
6. Epidemiology
7. The Impact of Neuropathic pain

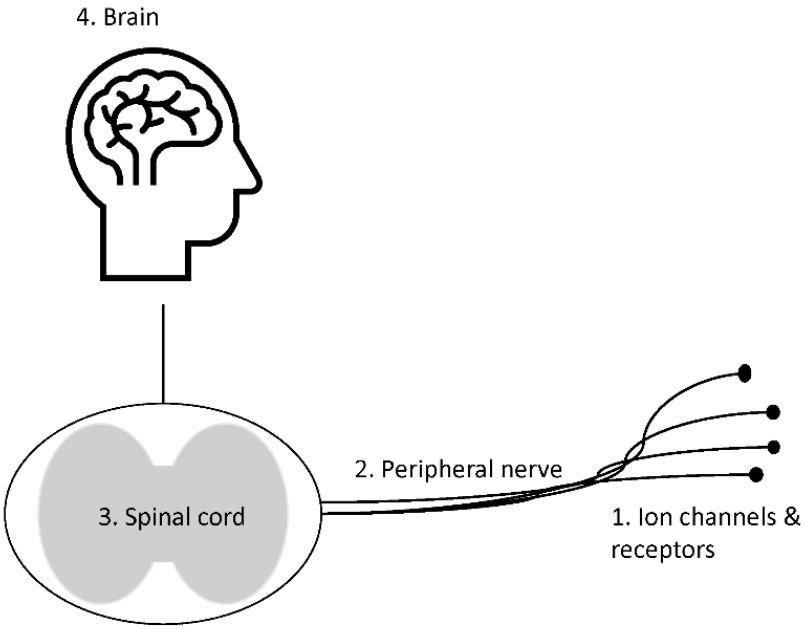
1. Definition

Neuropathic pain (NP) has been defined by the International Association for the Study of Pain (IASP) as 'pain arising as a direct consequence of a lesion or disease of the somatosensory nervous system' [1]. The somatosensory system allows for the perception of touch, movement, vibration, pressure and pain, temperature and position sense [2]. It comprises of specialised sensory neurons found in the muscles, joints, skin, and fascia, that convey information by specific nerve fibres to the spinal cord and then onto the brain for processing. These specialised sensory neurons include thermoreceptors that respond to changes in temperature, mechanoreceptors that transduce mechanical stimulus, chemoreceptors that transduce chemical signals, pruriceptors that transduce itchy sensations and nociceptors that encode and transduce painful stimulus. Disease or damage to the somatosensory system will cause complex changes in how somatosensory information is processed in those body parts that correspond to the peripheral, spinal or brain territory that has been damaged [3].

Given this definition outlined above, neuropathic pain can encompass a very large number of aetiologies and is often further categorised as either peripheral or central neuropathic pain dependent on the location of the lesion or disease. As illustrated in figure (Fig) 1.1. Central neuropathic pain is the result of a central lesion or disease which affects processing at the level of the spinal cord or brain or diseases such as strokes, Parkinson's disease, multiple sclerosis, or spinal cord injury [2,4]. Peripheral neuropathic pain, which will be the focus of this thesis, occurs from disease

or damage to peripheral nerves, predominantly the lightly myelinated Aδ fibres and small unmyelinated C-fibres where nociceptors are located[2,3].

Figure 1.1 Illustration of possible lesion locations associated with neuropathic pain.



Peripheral lesions cause 1) Damage to receptors and ion channels, 2) damage to the peripheral nerve, or central lesions such as 3) lesions of the spinal cord 4) lesions within the brain i.e., ischaemic stroke or multiple sclerosis.

2. Aetiology of peripheral neuropathic pain

Peripheral neuropathic pain can either be a result of systemic processes or secondary to local damage. Aetiologies for systemic processes include diabetic neuropathic pain, post herpetic neuralgia, immune-mediated conditions or exposure to toxic substances including alcohol and chemotherapeutics induced neuropathies. Systemic processes are associated with regional symptoms as a consequence of metabolic changes[5]. Pain secondary to local damage such as trauma or surgery is more commonly referred to as peripheral nerve injury pain (PPNI). PPNI is the most common cause of single-nerve injury and localised symptoms. PPNI is commonly attributed to three basic types of injury: (i) stretch-related, (ii) lacerations, and (iii) compressions [6]. Of these three types, stretch related is suggested to be the most common followed by lacerations and compressions [7]. The type of injury can be further classified based on the degree of demyelination and the extent of

damage to the axons as either neurapraxia, axonotmesis, or neurotmesis using the Seddon criteria [8]. The mildest form of injury is called *neurapraxia*, which typically occurs from mild compression or traction of the nerve, resulting in reduced nerve conduction velocity because of segmental demyelination. The second level *axonotmesis* additionally includes direct damage to the axon. Whilst the most severe form of injury called *neurotmesis* describes complete discontinuity of the nerve as there is full transection of the axons and connective tissue layers. Further criteria called the Sunderland criteria,[9,10]expands on this to include damage to connective tissues and include five subclassifications, as illustrated by Vijayavenkataraman,[9](page 57, Fig 3), and is shown in figure 1.2.

Whilst each neuropathic pain condition is triggered by different precipitating events and natural histories, many of the features and symptoms of persistent neuropathic pain overlap between conditions.

Figure 1.2 Peripheral nerve Injury classifications.

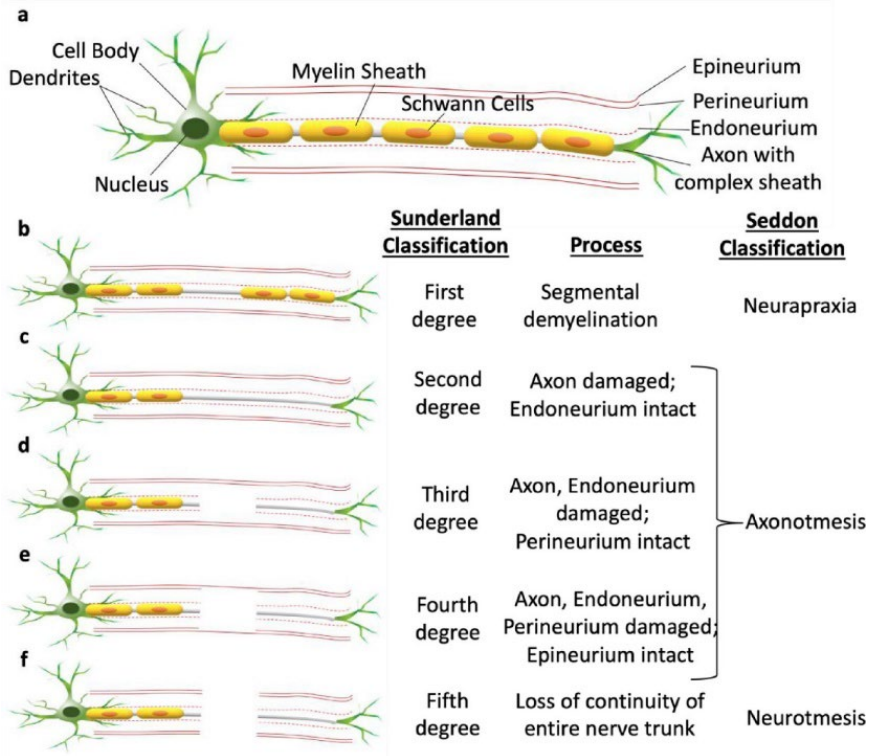


Illustration by Vijayavenkataraman [9] (page 57, Fig 3), reproduced with permission from Elsevier.

3. Background mechanisms.

When a peripheral nerve is damaged, it behaves differently. Negative symptoms such as numbness and hypoesthesia are associated with the loss of afferent input. However, we also see positive phenomena such as spontaneous pain and heightened painful responses to normally innocuous stimuli. Peripheral neuropathic pain results from pathophysiological changes in primary sensory afferents triggered by the injury, that cause consequent changes in nerve transmission and central nervous system processing. Persistent pain reflects a faulty maladaptive functioning pain system that has been damaged [11].

Whilst there is a consensus that both peripheral and central nervous system changes play a role in persistent peripheral neuropathic pain, it is also proposed that many of the central adaptations are driven by changes in the peripheral nervous system [12–14]. Additionally, peripheral processes tend to be more accessible to clinical treatments. Therefore, the purpose of this section will provide a brief background overview of some of the relevant peripheral pathophysiological processes associated with peripheral neuropathic pain.

Peripheral neuropathic pain is induced by partial nerve damage, implicating two classes of nociceptors as potential causes of ongoing pain: damaged or undamaged nociceptors[15]. Changes in both damaged and undamaged nociceptors can occur at multiple sites along the neural axis and lead to and cause imbalances in excitatory and inhibitory processes contributing to central sensitisation, altered sensory function and persisting pain as illustrated by Campbel [16] (page 81, Fig 2), and is shown in figure 1.3.

These changes can be broadly classed into 4 conceptual models/ mechanisms of change which will be discussed, however, there is also considerable overlap between them:

I. Denervation.
II. Ectopic activity (spontaneous firing),
III. Sensitisation of surviving neurons -peripheral sensitisation,
IV. Central sensitisation,

Figure 1.3 Changes at different sites along the neural axis for pain following spinal nerve injury.

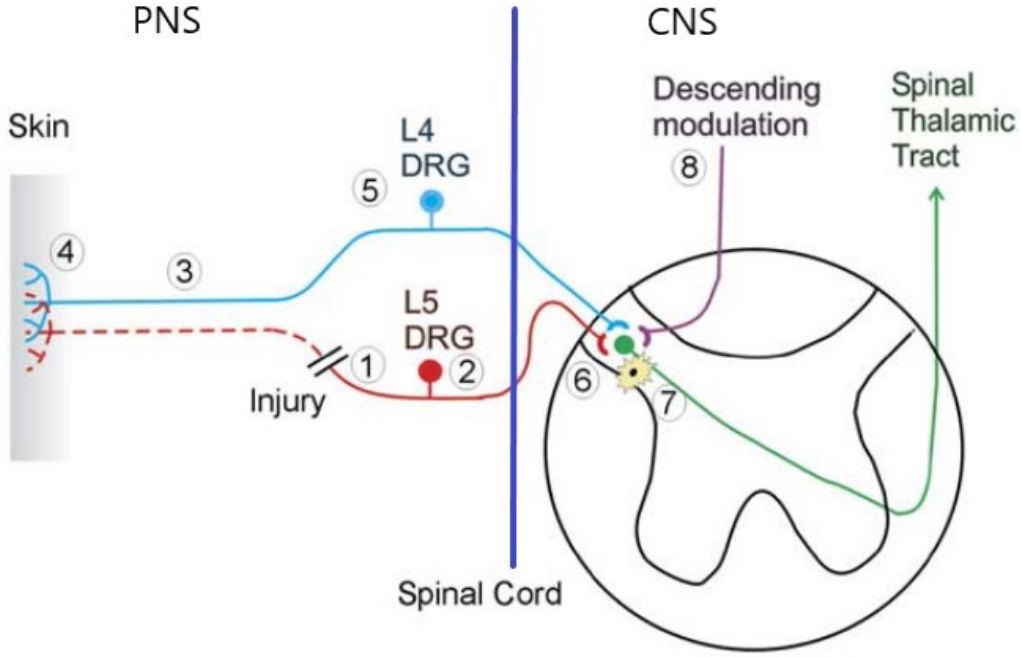


Illustration by Campbel [16](page 81, figure 2), reproduced with permission from Elsevier.
Damaged sites: *1) spontaneous neuronal activity and ectopic sensitivity at the site of injury. 2) Loss of trophic support from the periphery leads to up or down-regulation of activity at the dorsal root ganglion, 3) the distal part of the injured nerve undergoes Wallerian denervation (retrograde degeneration because of nerve lesion).*
Undamaged sites: *4) partial denervation of the peripheral tissues leads to changes in ion channels and axon structure that sensitise the surviving primary afferent nociceptor. 5) As a consequence, activity at the dorsal horn is affected and is up or downregulated.*
Changes in the dorsal horn*: 6) sensitisation of the postsynaptic dorsal horn (DH) augmentation of responses to cutaneous stimulation. 7) microglial cells become activated and can contribute to sensitisation. 8) Changes in descending modulation can further add to the DH sensitisation.*

i. Denervation

Denervation describes when there is a loss of a nerve supply [17]. The disconnection of that afferent from the periphery will be associated with a sensory deficit reflecting the loss of that specific afferent. For example, light touch for Aβ-fibres, pain and cold for A-δ fibres and C-fibres for non-painful warm and cold sensation as well as pain from acid burn[3]. However, there will also be other structural changes that can lead to heightened sensations in addition to sensory loss. Some examples of common structural changes associated with denervation are:

Peripheral changes associated with denervation.

With denervation there is a disruption to the integrity of the nerve for example, with axonotmesis, we see disruption of the axon and surrounding myelin and some preservation of either the endoneurium or perineurium or both. In response to damage, the tips of the axon grow sprouts to regenerate but can tangle forming neuromas [12]. These changes interfere with how the cell can regulate its baseline sensitivity, and activation thresholds, therefore, giving rise to abnormal sensitivity in the areas affected (Fig 1.3. Point 2) [16]. These changes have an impact on the affected afferent and the neighbouring afferents. For instance, significant losses in protective myelin between neighbouring neurons have been shown to induce changes in ion expression and cause excitation of neighbouring afferents with different functions (cross excitation) [15,17].

Central changes associated with denervation

Structural changes will also be seen in the spinal cord. For instance, peripheral nerve damage is associated with substantial degeneration of C-fibre primary afferent terminals in laminae II (Fig 1.4) [11]. Because of this loss, central terminals from intact Aβ-fibres that normally terminate in laminae III and IV grow into laminae II and so 'sprout' to form connections with other central nociceptive neurons which is another form of cross excitation. This leads to mechanoreceptive Aβ-fibre stimulation being perceived as pain, whilst there is a loss in temperature sensation that was regulated by the now lost C-fibres. The extent of resprouting depends on the degree of C-fibre loss [18].

Denervation can also result in reduced inhibition. For example, cold specific Aδ-fibres produce cold sensations but also inhibit central responses to the C-fibre nociceptors that respond to cold pain. Therefore, when these fibres are lost, this inhibitory response is also lost and the threshold for C-fibre evoked sensation is decreased resulting in cold hyperalgesia [15]. In addition to hyperalgesia following the loss of peripheral afferents, cold hyperalgesia is also seen in central neuropathic pain

conditions and may be mediated by misinterpretation of peripheral sensory input by sensitized central/ cortical neurons [19].

Therefore, denervation will affect both peripheral and central nociceptive communication which can cause imbalances in excitatory and inhibitory pain processes (as described below).

ii Ectopic activity.

Ectopic activity describes action potential generation within the nociceptive pathways independent of stimulus [11]. Action potentials are an electrical event in which the cell membrane resting potential rapidly falls (depolarisation) to transmit an electrical signal from one cell to another [20]. Spontaneous ectopic activity following nerve injury can be generated at multiple sites, including at the site of injury, the cell body, the dorsal root ganglion and in neighbouring intact afferents [11]. The term 'ectopic pacemaker site' is often used to describe the sites of spontaneous firing and is strongly influenced by the voltage-gated ion channels[3].

Ion channels are membrane proteins that allow ions to pass through the channel pore. By regulating the flow of ions across the cell membrane, they control the electrical charge inside and on the outside of the cell. This dictates the resting membrane potential of the cell and the generation of action potentials. Ion channels, therefore, play an important role in how molecules are transported (trafficked) and changes can alter the primary afferent function [2].

Role of sodium channels in ectopic activity

Sodium-ion channels (Na+) are considered to play a major role in terms of ectopic activity due to their role in regulating membrane resting potentials and cell excitability[21]. There are nine widely recognised subtypes of voltage-gated Na+ channels, which are designated NaV1.1-1.9 [15]. After nerve injury, sodium channels that are usually transported and recycled, begin to accumulate in remaining areas of the cell such as neuromas, and patches of demyelination where myelin, which would normally suppress their insertion, is no longer present [11]. The increased expression of Na+ increases the trafficking of sodium ions and cell excitability. Changes in Na+ expression have been linked to the

spontaneous firing of Aδ-, C- and also Aβ- fibres activation in various pain conditions [11,15]. Paraesthesia and dysesthesia are associated with the ectopic activity of Aβ-fibres, whilst ectopic activity of C- and Aδ-fibres is associated with lancinating and burning pain [15]. Such changes have been reversed by drugs that target sodium channels confirming their involvement in peripheral nerve excitation e.g., local anaesthetics like lidocaine or bupivacaine and antiepileptics such as carbamazepine and oxcarbazepine. Unfortunately, many sodium blockers are not selective and will act on fibres other than sensory pain fibres. For example, sodium channel blockers can act on motor fibres and in extreme cases affect locomotion, breathing and cardiovascular function effects [21–23]. Na(v)1.7, Na(v)1.8, and Na(v)1.9, sodium channels are expressed in peripheral sensory neurons and therefore selective blockers have been a target for pharmacological treatments[21].

Other ion channels

Research has helped identify many other ectopic ion channel drivers that alter membrane excitability and there are likely many more. For example, calcium channels have also been implicated and are expressed at higher levels following nerve injury [15]. There are a variety of calcium channels, like Na+ channels, that help determine membrane excitability and regulate gene expression. In response to depolarisation, voltage-gated calcium channels (CaV) open and increase intracellular calcium. The rate of the calcium influx determines the calcium concentration at the post synaptic terminal and can either increase or decrease synaptic strength (see LTD chapter). Generally speaking, low concentrations of calcium reduces the availability of receptors and consequently weaken the synapse [24,25] and higher concentrations enhance synaptic strength and the release of excitatory neurotransmitters. Medications developed to target this include gabapentin and pregabalin which bind to the α2-δ subunit of these channels and reduce the synaptic excitability[26]. Other ion channels that have been implicated in chronic pain include K+ channels, TRP channel family and hyperpolarisation-activated and cyclic nucleotide-gates (HCN) channels. The change in ion expression following nerve injury, therefore, is associated with the development of ectopic pacemaker sites. What triggers the changes in sensory neuron ion channel expression is not entirely

clear but is likely to be controlled by transcription factors that bring about transcriptional changes including changes in ion channel expression [2].

iii Peripheral sensitisation

Peripheral sensitisation describes increased responsiveness and reduced threshold for stimulation of the peripheral ends of nociceptors [15]. It can arise from various mechanisms including changes in voltage-gated ion channels.

Sensitisation of nociceptors

The primary afferent nociceptors can be activated by exogenous (external origin from outside the nerve-such as mechanical pressure) or endogenous substances (from within the nerve itself)[15]. Endogenous substances comprise neurotransmitters, which are membrane receptor proteins such as amino acids, and neurokinins, inflammatory mediators (bradykinin and prostaglandins), and nerve growth factors (NGF) [15].

Phenotypic switching

Neurotransmitters and proteins help maintain the neuronal phenotype of a nerve. Injury or damage to a nerve will disrupt the communication between the primary afferent and the sensory cell body [27]. This alters how these proteins and neurotransmitters are produced by the cell body and transported both peripherally and centrally (Fig 1.3. point 2) [27,28]. This can lead to an up-regulation or down-regulation of what molecules are expressed. If this alters the way the nerve functions and communicates with other cells, we can see a change in neuronal phenotype which can further drive neuronal sensitivity [2,3,11]. For example, following nerve axotomy Aβ-fibres can change their neurotransmitter and protein expression and begin to change and release peptides that would normally mediate C-fibre and Aδ-fibre induced pain, such as substance P and calcitonin gene-related peptide (CGRP)[29,30].

Inflammatory mediators

Wallerian degeneration occurs when the section of the axon distal to the injury degenerates, and the axon and myelin sheath is degraded (Fig 1.3. point 3). Normally Schwann cells insulate the axon but following nerve injury they switch from producing myelin to synthesising growth factors and inflammatory mediators [31]. These changes promote hyperalgesia and allodynia. In animal studies, peripheral nerve injury is associated with the upregulation of various chemical mediators and proteins, such as tumour necrosis factor-alpha (TNF-α) and polymorphonuclear leucocytes (IL-1β) immunoreactivity in the dorsal root ganglia of injured cells, but also the injured neighbouring neurons [32]. This is associated with mechanical and thermal hyperalgesia, which has been demonstrated in animal models of experimental pain as increased thermal and mechanical withdrawal [33]. The presence of these inflammatory mediators, therefore, sensitises both damaged and intact neurones and helps drive and maintain chronic peripheral sensitisation (Fig 1.3. Point 4)[2,11].

There are various mediators to peripheral sensitisation, and current research is revealing further classes of sensory afferents with the potential for additional influence via different targets, such as C-tactile afferents and autoantibodies[34,35,36]. Understanding the precise contributions of different mediators and different sensory afferents relative to presenting symptoms can help improve the efficacy of both pharmacological and neuromodulatory pain treatments.

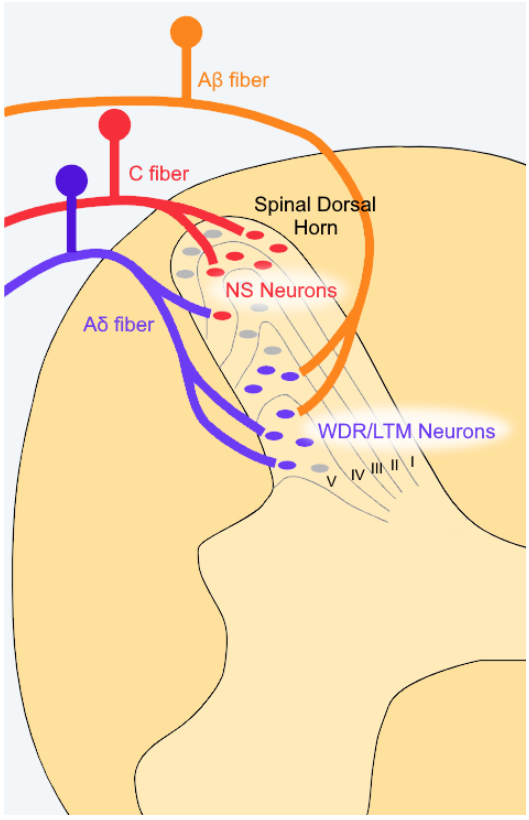
iv Central sensitisation

Central sensitisation describes the increased responsiveness of nociceptive neurons in the central nervous system to their normal or subthreshold afferent input [1]. The following text will briefly describe changes relating to the dorsal horn.

Interneurons within the dorsal horn play a role in modulating and gating afferent input and can be either nociceptive specific neurons or wide dynamic range neurons (WDR) [20,37]. Nociceptive specific neurons convey noxious information from Aδ- and C-fibres and terminate in the outer layers and have localised receptive fields (laminae I-III). WDR can be excited by both noxious and non-noxious

stimuli and therefore receive information from Aβ-, Aδ- and C-fibres and have large receptive fields [38] (Fig 1.4).

Figure 1.4: Dorsal horn structure illustrating where the sensory afferents terminate.



Nociceptive specific neurons (NS) convey noxious information from Aδ- and C-fibres and terminate in the outer layers (laminae I-III). Wide dynamic range (WDR) can be excited by both noxious and non-noxious stimuli and therefore receive information from Aβ-fibres and Aδ-fibres and C-fibres and terminate in the deep laminae (III-VI), they also contain low threshold mechanoreceptive (LTM) neurons that receive input from Aδ-fibres and Aβ-fibres, adapted from [38].

Excitatory nociceptive facilitation at the dorsal horn.

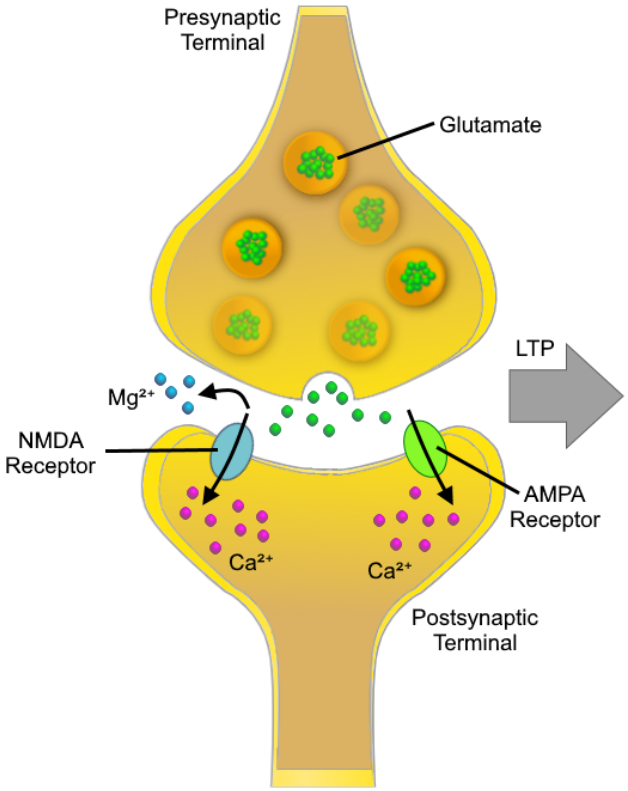
Dependent on what neurotransmitters they produce, interneurons can either be excitatory interneurons (releasing glutamate) or inhibitory (releasing GABA and/ or glycerine)[39].

Excitatory interneurons

Glutamate is the most widely distributed excitatory neurotransmitter in the CNS binds to either ionotropic receptors (ligand-gated ion channels) or metabotropic G-glutamate receptors (mGluR)[15,40].

Two well researched ionotropic receptors are α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) and N-methyl-D-aspartic acid channels (NMDA)[40]. AMPA allows for the influx of sodium and potassium whilst NMDA controls the influx of calcium [41]. It has also been shown that nerve injury can alter both AMPA and NMDA trafficking, and hence contribute to central sensitisation via increasing permeability to Na+ and Ca2+ entry [3], (Fig 1.5). NMDA blockage has been examined for the treatment of neuropathic pain with some efficacy demonstrated for drugs such as ketamine [3,42].

Figure 1.5: Inotropic glutamate receptors and their role in central sensitisation.



Following peripheral nerve injury, α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) and N-methyl-D-aspartic acid channels (NMDA) show increased permeability to calcium Ca2+. This enhances synaptic connections and can lead to a long-lasting increase in signal transmission of noxious output (long term potentiation– LTP).

Metabolic glutamate receptors

There are different groups of metabotropic glutamate receptors, with some enhancing synaptic transmission (Group 1- mGluR1) whilst others inhibit (Group II mGluR2 and 3, and Group III mGluR4,5,6,7 and 8)[15]. Increased expression of glutamate following nerve injury can lead to

increased excitability of nociceptive neurons in the dorsal horn and expansion of their receptive fields within the dorsal horn (Fig 1.3. Point 6) [43]. This means that low-level stimulation of Aβ-fibres can now excite Aδ-fibres and C-fibres [15,44]. Clinically this can be seen as increased stimulus-evoked pain, for example pin prick hyperalgesia and dynamic mechanical allodynia.

Recent studies have also revealed the role of other excitatory neurotransmitters such as the peptides somatostatin (SOM+), VGLUT3, and calretinin protein kinase C(PKC). How these different neurons interact and work together is yet to be determined [3].

Inhibitory interneurons

There are many inhibitory interneurons in the dorsal horn, such as serotonergic, noradrenergic, and opioid receptors in addition to GABAergic and glycinergic interneurons.

GABAergic interneurons are more prevalent in the deeper dorsal horn and glycinergic neurons are more prevalent in superficial laminae. Inhibitory transmission of these receptors has been shown to drop in chronic neuropathic pain [15]. As such, the loss of disinhibition of nociceptive input leads to increased pain sensitivity [15].

It is assumed that other mechanisms, beyond the remit of this thesis, such as supraspinal mechanisms are additionally involved in central sensitisation.

Mechanism's synthesis

This section was intended to provide a background rather than be a comprehensive review, and supraspinal mechanisms such as descending pathway modulation, spinal glia and cortical reorganisation were not discussed as they were beyond the remit of this thesis[2,3]. One can see from this brief review that peripheral neuropathic pain is a complex integration of many different mechanisms following nerve injury. In many patients, the peripheral drive of nociception is thought essential to initiate central sensitisation and also maintain and modulate it, [13,14]with reported studies demonstrating that peripheral targets can reduce evoked hypersensitivity thought to be associated

with central sensitisation [13,14]. This peripheral-central interaction suggests that therapeutic approaches in the periphery will not only influence peripheral drivers but also influence aspects of central sensitisation in the central nervous system (CNS).

4. Clinical presentation

People with neuropathic pain frequently use characteristic pain descriptors to describe their pain including burning, cold, electric shock type pain, tingling, pins and needles, numbness, itching, and stabbing. These descriptors help to distinguish it from other types of chronic pain [45]. In addition to spontaneous pain which can be ongoing or intermittent, patients also experience symptoms of sensory loss (negative phenomena) alongside paradoxical symptoms of sensory gain (positive phenomena) and paroxysmal [4,46]. Symptoms of sensory loss would include loss of or reduced appreciation of sensations such as light touch, painful pressure, temperature etc. Symptoms of sensory gain can include heightened evoked pain responses including dysesthesia which refers to an unpleasant sensation to touch, allodynia which is a pain in response to a normally non-painful stimulus and hyperalgesia which is an exaggerated response to a normally noxious stimulus [47]. Paroxysmal pain refers to severe pain of sudden onset that is often brief and well localised that can occur spontaneously with no obvious trigger [3]. Pain mechanisms maintaining these characteristic symptoms will vary depending on whether the neuropathic pain is of central or peripheral origin. There is growing evidence that the pathophysiological concepts discussed above can be linked and correlated with clinical signs [47–49]. Attempts to select and match treatments and patients based on potential pathophysiological mechanisms may help to individualise treatment and improve the efficacy of new and available neuropathic pain treatments.

5. Diagnosis.

For neuropathic pain there is no specific diagnostic tool, instead, a grading system is recommended to guide decisions on the level of certainty with which neuropathic pain can be determined in an individual patient [4]. This grading system was first published in 2008, [50] and has more recently been

updated in 2016 [4]. The grading system proposes three levels of certainty: i) possible, ii) probable, and iii) definite neuropathic pain as illustrated by Finnerup et al[4] (Fig 2, page 1601), and shown in Figure 1.6. These levels are determined by evidence from the patient history, examination, and confirmatory tests. Possible neuropathic pain is confirmed through the patient's pain history, which should include pain descriptors, the presence of non-painful sensory symptoms, and aggravating and alleviating factors, suggestive of pain being related to a neurological lesion and not another cause. Additionally, the pain distribution should be consistent with the suspected lesion or disease. Probable neuropathic pain would be proposed based on evidence from the examination of sensory signs in the same neuroanatomically plausible distribution. In some cases, although the nature of the lesion has been confirmed by a diagnostic test, sensory signs may be difficult to demonstrate, and for these cases, the level "probable" continues to be appropriate [4]. Whilst definite neuropathic pain would describe probable neuropathic pain with confirmatory diagnostic tests that confirm the location and nature of the lesion or disease to be able to explain the pain [4]. Diagnosis of peripheral neuropathic pain would need to confirm the neuroanatomical distribution and the lesion within peripheral nerves. Although the grading system provides some consistency and consensus regarding the measurement and definition of neuropathic pain, diagnosis is still largely based on clinical judgement, interpretation of tests and subjective history.

Figure 1.6: Flow chart illustrated representation of updated grading system for neuropathic pain.

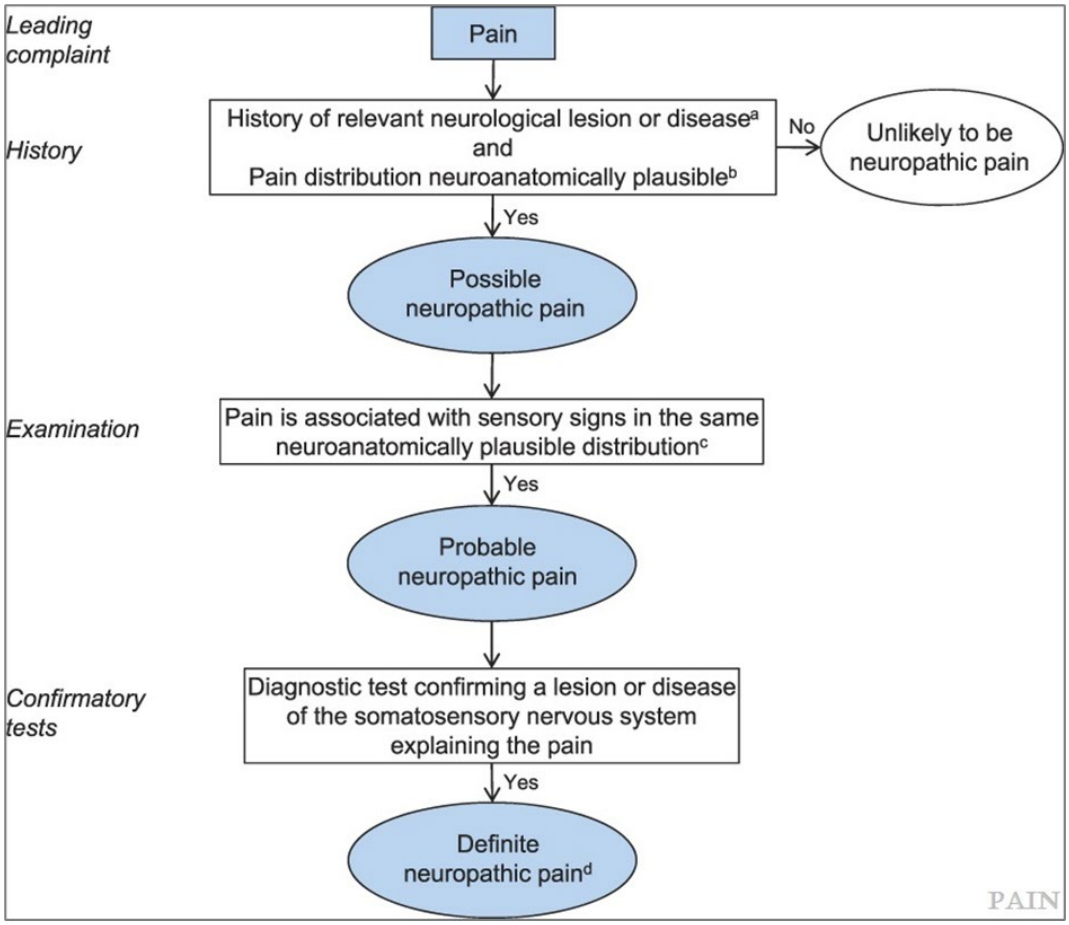


Illustration by Finnerup[4], (Figure 2, page 1601), reproduced with permission from Wolters Kluwer.

6. Epidemiology.

An accurate estimation of the true incidence and prevalence of neuropathic pain is made difficult because of the lack of simple diagnostic criteria. Many epidemiology studies were published before the grading system and thus, it is difficult to obtain a true estimate due to epidemiological studies using different methods of assessment and different definitions of neuropathic pain.

The incidence of neuropathic pain is likely to grow owing to an ageing global population, increases in diseases such as diabetes and improvements in survival rates following radiotherapy and chemotherapy [11].

In addition to the grading system for neuropathic pain, various clinical tools in the form of questionnaires have been developed over the last twenty years. These use the common verbal pain

descriptors described above such as burning, electric shocks, tingling, pricking, pins and needles, numbness, itch, and pain evoked by brushing. These questionnaires have been found by validation studies to show excellent sensitivity (ranging from 74% to 85%) and specificity (ranging from 76% to 90%) for discriminating between neuropathic and non-neuropathic pain [51]. These questionnaires have been used by several large epidemiological surveys in different countries to estimate the prevalence of neuropathic pain, the most commonly cited being the Douleur Neuropathique en 4 questions [52] and the Leeds assessment of neuropathic symptoms and signs (S-LANSS) [53]. Van Hecke et al conducted a systematic review which examined the incidence of neuropathic pain in the general population in which many such studies are summarised [54]. Within the review, the prevalence of neuropathic pain as a feature of chronic pain (or pain of predominantly neuropathic origin) was examined by 8 studies and ranged from 1% to 17.9%. In studies that used questionnaire-based case ascertainment tools such as the DN4 and S-LANSS [53], the range of prevalence estimates was wide from 3.3–to 17.9%. However, including only studies that administered measures precisely as they were designed and validated, the range of prevalence rates was much narrower 6.9–10% [55–58]. Examples of where tools were not used as designed and validated included where the complete questionnaire was not used but instead items were selected, or where patients were screened before administration leading to overinflated estimates. The review additionally highlighted that many studies did not provide a working definition for neuropathic pain as a starting point and also highlighted a general lack of consensus regarding the agreed definition of neuropathic pain [54]. They call for future studies to recognise the revised grading system to help achieve better standardisation and consistency moving forward.

Since this review, similar population prevalence estimates (i.e. 6–10%) have been reported in studies using the DN4 questionnaire in other non-European countries including Benin [59] and Morocco [60]. Other large-scale studies population-based studies have also been conducted with other questionnaires. In Libya, the LANSS questionnaire suggested the incidence of neuropathic pain to be 19.7% [61], whilst the PainDetect in Japan suggested a lower incidence of 3.2% [62]. These results

suggest variations in incidence rates could be associated with the chosen tool but also with how it is utilised. Additionally, health systems and health profiles can be geographically very different which may further compound variations in reported incidence rates.

Included in the Van Heck review were two large scale epidemiological studies conducted in Northern Europe, one conducted in the United Kingdom (UK) [57] and one in France [55]. One would assume health care systems and health profiles in these two countries would be relatively similar. In support, the EuroQol group which developed the EQ-5D (an instrument which evaluates the generic quality of life) has provided population reference data indicating that health profiles are broadly similar across northern European countries [63].

The UK study administered the S-LANSS questionnaire [53] in six general practitioner practices in three UK cities [57]. Based on a 52.5% return rate (n=2957) they estimated the prevalence of chronic pain (> 3 months) of predominantly neuropathic origin within these cities to be 8.2% (95% CI 7.2% to 9.2%) defined as a LANSS score ≥ 12. One must note that this sample is representative of the general population in three large cities rather than the entire UK population. The French study was larger and employed a nationwide postal survey which included the DN4 [52] and had a greater return rate of 81.2% (n=23712)[55]. The estimated prevalence of chronic neuropathic pain (> 3 months) within this study was about 6.9% [95%CI: 6.6-7.2] based on a DN4 score ≥ 3. The prevalence in the general population of symptoms of neuropathic pain in western Europe based on these studies suggests between 6.9-8.2% incidence [55,57].

It is hard to determine from these studies how many neuropathic pain patients would have specifically had peripheral neuropathic pain and population-based studies examining this differentiation are lacking. One study was identified that attempted further to differentiate the incidence of neuropathic pain based on classifications of central and peripheral neuropathic pain [64]. They performed a cross-sectional study and examined the incidence of neuropathic pain within chronic pain patients in 104 Spanish pain clinics (n=2173). Patients were additionally classified using

the revised grading scale for neuropathic pain [4]. The selected cohort had chronic pain and therefore represents a sample with higher prevalence rates when compared to the general population studies. The prevalence of neuropathic pain for central neuropathic pain and peripheral neuropathic pain amongst chronic pain patients was 2.4% (95% CI: 1.7;3.1) and 12.9% (95% CI: 1.5;14.3), respectively. Although this study only reflects a chronic pain cohort, it does help to illustrate that neuropathic pain, particularly peripheral neuropathic pain, accounts for a significant proportion of all chronic pain patients that will attend a pain clinic.

7. The Impact of Neuropathic pain.

Neuropathic pain has a high impact as well as prevalence. The literature measuring the impact of neuropathic pain reflects that this is multifaceted and measures various outcomes including function, emotional impact, and costs which include direct (relating to health care utilisation) and indirect costs (relating to work status), quality of life and treatment failure/limitations.

Function

Persistent neuropathic pain can make it very difficult for a patient to maintain normal functional activities. This has been well documented with various studies reporting consistent evidence that neuropathic pain is negatively associated with physical functioning [65]. Patients with neuropathic pain have also been shown to be more severely compromised in terms of functional ability when compared to persons with chronic pain without neuropathic features [66–68]. For example, the large beforementioned UK prevalence study by Torrance et al [57], also captured information regarding function[58]. Respondents were categorised as either having; 1) no chronic pain (NCP) (n=1537), 2) chronic pain of non-neuropathic origin (CP) (n=1179) and 3) chronic pain of neuropathic origin (CNP) (n=241). CNP patients were found to have significantly poorer scores for all interference items of the Brief pain inventory (BPI) than those with CP (P<0.001). Additionally, function, as measured by domains included in the SF-36 (a generic health status measure), was also significantly lower for patients with chronic neuropathic pain than for the other two groups (P<0.001). After adjusting for

pain severity, age, and gender, the CNP group was still found to have poorer scores than the other groups in all domains of the SF-36 and all interference items in the BPI, indicating poorer health function and greater disability compared to other groups.

Emotional functioning

Numerous studies report negative impact in terms of emotional functioning associated with NP, but many do not include control or comparison populations [57,65,69–71]. Attal et al in a follow on from the beforementioned French nationwide survey evaluated emotional functioning [72]. They measured anxiety and depression using the Hospital Anxiety and Depression Symptom Scale (HADS)[73]. This was administered to a representative sample of previous study respondents (n=2957 based on an 85.6% response rate). HADS scores for people with neuropathic pain (A= 17 (0.3), D= 9.7 (0.1), n=241) were significantly higher than for those with chronic pain and no neuropathic features (A= 14.1 (0.3), D 8.2 (0.1), n=1179) and people with no pain (A= 9.7 (0.2), D 6.0 (0.1), n=1537). Figures in parenthesis denote SEM. Therefore, results illustrate those patients with features of neuropathic pain, as identified via the DN4, reported a significantly higher degree of anxiety and depression than without NP characteristics ($P < .01$). Additionally, they found NP patients have greater use of health care facilities (21% vs 9%; $P < .01$) than those with pain and no NP features. One limitation of the study is its reliance on a measure of self-report, the DN4, to determine neuropathic pain characteristics. Other non-neuropathic conditions such as fibromyalgia for example, often display some features of neuropathic pain such as burning pain. Results, therefore, were not able to rule out that conditions such as fibromyalgia were not included in what is described as neuropathic pain. They do comment, however, that less than 5% of the subjects presented with diffuse widespread pain which they suggest makes this perspective unlikely. Similarly, other studies have reported similar findings indicating that persons with chronic NP have higher degrees of anxiety and depression scores, and use of health care when compared with patients with non-neuropathic chronic pain, and patients without chronic pain [68,74,72].

Quality of life.

The impact of neuropathic pain on health-related quality of life (HRQoL) has also been measured within many studies [65,75]. A high-quality systematic review conducted by Jensen et al included 52 studies that assessed HR-QOL in six different NP conditions and found consistent evidence that chronic neuropathic pain is associated with important impairments across a broad spectrum of HRQoL domains, including physical, emotional, role, and social functioning [65]. How quality of life was measured varied across studies, but the most commonly included measures were the EQ5D (EuroQol- 5 dimension quality of life instrument) [76] and the SF 36 (short form 36 health survey questionnaire)[77]. Both can be used to calculate a health utility score. Generally, health utility measures evaluate patients' subjective preferences on a scale where 0 represents death and 1 represents full health. Utility scores are frequently used to quantify the cost-effectiveness of therapies and are therefore often required by health policy makers.

To get a sense of the impact of NP in relation to other health conditions, it is useful to understand these utility scores relative to other conditions.

Doth et al conducted a systematic review and meta-analysis to test the hypothesis that NP is associated with low levels of health utility [78]. The review included 24 studies and reported an average EQ-5D health utility score of 0.43 (95% confidence interval [CI]: 0.41–0.46) for mixed neuropathic pain populations. The review also conducted a search for systematic reviews of HRQoL utility in selected chronic diseases and conditions and where they were unable to identify a systematic review and values from published health technology assessments were used. Results illustrated that NP utilities were generally lower (i.e., lower levels of HRQoL) than these other chronic conditions that included cancer, heart failure, chronic obstructive pulmonary disease, motor neurone disease, type 2 diabetes, Parkinson's disease and stroke [78]. For example, average utility scores for chronic heart failure and Parkinson's disease were 0.6 and 0.62 respectively. The review concludes that NP is associated with lower levels of health utility and notes that the key drivers of health utility appear to be NP condition and disease severity. The review describes health utility

scores for neuropathic pain subtypes of painful diabetic peripheral neuropathy (DMN), central neuropathic pain (CNP), chronic low back pain with a neuropathic component (CLBP-NeP), postherpetic neuralgia (PHN), and mixed neuropathic pain. Therefore, it is not possible to deduce from these results possible health utility scores relative to painful peripheral nerve injury (PPNI), but the mixed neuropathic pain subgroup is the most likely to reflect this pain type.

A more recent cross-sectional study examined the prevalence of probable NeP among chronic pain patients attending Brazilian hospitals and pain clinics in São Paulo, Ceara, and Bahia[79]. Neuropathic pain prevalence was reported as 14.5% of all chronic pain patients (n=307/2118). The investigators further assessed the clinical characteristics of six NP subtypes which included the four subtypes included in the latter review (DMN, CNP, CLBP-NeP and PHN), but additionally included a further two subtypes of post-traumatic neuropathic pain (PTN), and post-surgical neuropathic pain (PSN). These latter two, therefore, reflect the classification of PPNI that we are interested in. PTN and PSN patients were reported to have the least favourable EQ-5D index scores (M=0.42, SD=0.19) across all NP subtypes. Therefore, results support similar health utility scores to the previous review but also highlight that there is some variation between neuropathic pain subtypes with conditions classed as PPNI being amongst the lowest scoring in terms of HRQoL.

Costs

The burden of suffering that pain imposes on individuals will affect healthcare utilisation and work-related issues which can be associated with significant costs that society must share.

Moore et al in a systematic review examined the societal and healthcare costs associated with chronic noncancer and neuropathic pain [70]. The review included 43 studies which examined the quality of life and impact on work (collective n= 540,000). Using studies that compared the healthcare resources used by those in chronic pain relative to those with no pain, the indication was that for every £1 spent on healthcare services for patients without chronic pain, the amount of expenditure incurred by patients with chronic pain was as follows: GP consultations: range from

£1.59 to £1.93, In-patient days: range from £2.07 to £4.75, Outpatient attendances: £3.61, Medication: £2.53, Emergency attendances: £1.89, Total utilisation: £3.03. This, therefore, shows the costs for patients with chronic pain on health care resources are almost three times more than for persons without pain. The review reports on all chronic non-cancer pain conditions, therefore, from these costs related findings it is not possible to determine the costs incurred by patients solely with neuropathic pain.

A more recent study aimed at providing insight on the burden of neuropathic pain specifically across France, Germany, Italy, Spain, and the UK by considering direct and indirect costs, productivity loss, and humanistic impact on patients and their families [80]. 3965 patients with neuropathic pain seen within pain clinics were asked to complete assessments to provide information regarding sick leave and retirement, number of health care consultations, drug treatments, and surgical procedures. Patients provided further demographic and disease-related data and completed the Work Productivity and Activity Impairment (WPAI), the EuroQol 5-Dimension (EQ-5D), and the Brief Pain Inventory (BPI) questionnaires.

The costs associated with managing neuropathic pain were calculated as direct (relating to health care utilisation) and indirect costs (relating to work status). The direct health care costs were taken as the sum of consultations, prescribed drugs, and surgical and nonsurgical procedures undertaken for the management of NP. Relevant country-specific sources were used to calculate these costs.

The average number of consultations per annum was considered high across the five countries, with patients typically attending 3.5 GP visits (range 3-4, UK=3) and 5.5 (range 4-7, UK=4) specialized care reviews specifically for their neuropathic pain. Across the whole sample, the mean number of prescribed drugs for neuropathic pain per patient was 1.8 (1.7 in France and Germany, 1.8 in the UK and Italy, and 2.1 in Spain). Around two-thirds of patients received an anticonvulsant, whilst opioids were the second most used analgesic analgesics for ~25% of the total sample. On average 8% of patients had received surgery with peripheral nerve decompression being the most common surgical

intervention, whilst 14% had a non-surgical intervention such as steroid injection and nerve blocks. Total annual direct health-care costs per patient ranged from €1,939 (Italy) to €3,131 (Spain) (UK=€2,951) and therefore illustrate considerable annual costs associated with the treatment of neuropathic pain.

Additionally, the direct non-health-related impact in terms of support provided by caregivers was considered. To quantify this the number of hours of care provided by friends and family each week was recorded. However, as this care is usually provided at no cost it is noted that this form of support is not routinely captured by traditional health care analysis quantifying the cost associated with a condition. On average, persons with neuropathic pain required 27.5hrs care per week (SD 13.76) and 31.3 hrs in the UK. This highlights the significant societal burden of NP that is not captured by standard analysis of health- care resources.

Indirect costs (work-related costs) included salary and time adjustment of patients due to sick leave. Across all countries, approximately 1/3 of people were described as employed and 20% of patients were described to be on sick leave. Indirect costs (i.e., sick leave) constituted most costs in all five countries: €7,098 in France, €11,232 in Germany, €6,382 in Italy, €7,066 in Spain, and €5,492 in the UK.

In addition to costs associated with sick leave, impairment while at work was recorded using the Work Productivity and Activity Impairment questionnaire (WPAI). A score of 0 would indicate no impairment, and a score of 100 would indicate that the patient could not undertake any work at all. The results suggest that a significant proportion of the patient's work time in the previous week was affected by NP (mean WPAI score range was 34.4–56.1, UK= 44.3). These scores were relatively high when compared to reported scores for other diseases such as diabetes, respiratory conditions, and arthritis.

Overall, the study highlights that despite differences in practice between countries, the cost for society in terms of lost work and productivity due to NP is high[80]. It also illustrates the wider costs to

patients, carers and families demonstrating the wider societal costs associated with neuropathic pain.

Pharmacological treatments.

Given the evident and significant impact associated with neuropathic pain, there is a need to find effective treatments. Current guidelines for the management of neuropathic pain are heavily weighted toward pharmacological management [42,81–83]. However, although medications are the most common treatment method many patients do not achieve satisfactory pain relief with current evidence-based treatment or do not tolerate effective doses because of unwanted side effects [81].

For example, a Canadian study illustrated that significant improvement in pain and function was achieved for less than ¼ (23.7%) of neuropathic pain patients managed according to standard guidelines within tertiary care pain clinics [84]. This echoes the findings of previously reported studies that demonstrated poor HRQoL and functional interference despite large numbers of visits to pain physicians and a high level of prescriptions for pain [72,80]. The side effects of available medications are also not innocuous, for example, treatment using opioids has been linked with death due to overdose, addiction and suicide [85].

Conclusion.

Neuropathic pain affects between 6.9-8.2% of people in western Europe [55,57]. It is associated with significant pain-related disability [57,65], poor quality of life [78], and high levels of anxiety and depression [72]. The average health care costs of managing neuropathic pain are estimated to be £2512 (€2,951) per patient per annum and can further increase with pain severity[80]. This does not include the costs associated with salary losses and works time adjustments due to sick leave that is said to be even higher[80]. The overall burden of neuropathic pain is only likely to increase further owing to an ageing global population[11]. An understanding of maintaining mechanisms of action is essential for providing effective treatment and improving the management of this condition[3]. Current understanding of mechanisms suggests that therapeutic approaches targeting peripheral drivers will influence

peripheral aspects of neuropathic pain but can also influence aspects of central sensitisation in the CNS[13,14]. Many pharmacological treatments have been developed with this in mind and recommended as part of guidelines for the management of peripheral neuropathic pain [42,81–83]. However, the evidence suggests that subjects with peripheral neuropathic pain are far from optimally managed by medications, despite large numbers of visits to pain physicians and a high level of prescriptions for pain[72,80]. Other techniques, such as neuromodulation, have been considered third-line treatment options, however, there is limited evidence to support such third line approaches currently in the management of peripheral neuropathic pain [86,87]. Because of the limitations of the current pharmacological treatments, peripheral neuropathic pain is still considered an unmet clinical need and therefore it is necessary to understand how it can be better managed [3,81]. Therefore, there is a need to identify safe, well-tolerated, and effective pharmacological and nonpharmacological treatments to support better management of peripheral neuropathic pain in those who fail to respond to current guideline recommendations.

Chapter 1 References

1. IASP Task Force on Taxonomy. *IASP Taxonomy 2012 Update*. Second. (Merskey H, Bogduk N, eds.). Seattle: IASP Press; 1994. https://www.iasp-pain.org/resources/terminology/.

2. Colloca L, Ludman T, Bouhassira D, et al. Neuropathic pain. *Nat Rev Dis Prim*. 2017;3. doi:10.1038/nrdp.2017.2

3. Finnerup NB, Kuner R, Jensen TS. Neuropathic Pain: From Mechanisms to Treatment. *Physiol Rev*. 2020;101(1):259-301. doi:10.1152/PHYSREV.00045.2019

4. Finnerup NB, Haroutounian S, Kamerman P, et al. Neuropathic pain: An updated grading system for research and clinical practice. *Pain*. 2016;157(8):1599-1606. doi:10.1097/j.pain.0000000000000492

5. Lehmann HC, Wunderlich G, Fink GR, Sommer C. Diagnosis of peripheral neuropathy. *Neurol Res Pract*. 2020;2(1):1-7. doi:10.1186/S42466-020-00064-2/FIGURES/2

6. Burnett MG, Zager EL. Pathophysiology of peripheral nerve injury: a brief review. *Neurosurg Focus*. 2004;16(5):1-7. doi:10.3171/FOC.2004.16.5.2

7. Campbell WW. Evaluation and management of peripheral nerve injury. *Clin Neurophysiol*. 2008;119(9):1951-1965.

8. Seddon HJ, Medawar PB SH. Rate of regeneration of peripheral nerves in man. *J Physiol*. 1943;102(2):191-215. doi:10.1113/JPHYSIOL.1943.SP004027

9. Vijayavenkataraman S. Nerve guide conduits for peripheral nerve injury repair: A review on design, materials and fabrication methods. *Acta Biomater*. 2020;106:54-69. doi:10.1016/J.ACTBIO.2020.02.003

10. SUNDERLAND S. A classification of peripheral nerve injuries producing loss of function. *Brain*. 1951;74(4):491-516. doi:10.1093/BRAIN/74.4.491

11. Costigan M, Scholz J, Woolf C. Neuropathic pain: a maladaptive response of the nervous system to damage. *Annu Rev Neurosci*. 2009;32:1-32. doi:10.1146/ANNUREV.NEURO.051508.135531

12. Devor M. Peripheral Neuropathic Pain. In: *Encyclopedia of Pain*. Springer, Berlin, Heidelberg; 2007:1791-1800. doi:10.1007/978-3-540-29805-2_3279

13. Haroutounian, S., Nikolajsen, L., Bendtsen, T. F., Finnerup, N. B., Kristensen, A. D., Hasselstrøm, J. B., & Jensen TS. Primary afferent input is critical for maintaining spontaneous pain in peripheral neuropathy. *Pain*. 2014;155(7):1272-1279. doi:10.1016/J.PAIN.2014.03.022

14. Baron R, Hans G D, AH. Peripheral input and its importance for central sensitization. *Ann Neurol*. 2013;74(5):630-636. doi:10.1002/ANA.24017

15. Nickel FT, Seifert F, Lanz S, Maihöfner C. Mechanisms of neuropathic pain. *Eur Neuropsychopharmacol*. 2012;22(2):81-91. doi:10.1016/j.euroneuro.2011.05.005

16. Campbell JN, Meyer RA. Mechanisms of Neuropathic Pain. *Neuron*. 2006;52(1):77-92. doi:10.1016/j.neuron.2006.09.021

17. Devor M. Neuropathic pain: pathophysiological response of nerves to injury. In: Mcmahon S, Koltzenburg M, Tracey I, Turk D, eds. *Wall and Melzacks Textbook of Pain*. 6th ed. Philadelphia: Elsevier; 2013:861-889.

18. Fields HL, Rowbotham M BR. Postherpetic Neuralgia: Irritable Nociceptors and Deafferentation | Elsevier Enhanced Reader. *Neurobiol Dis*. 1998;5(4):209-227. doi:10.1006/nbdi.1998.0204.

19. Haroutounian S, Ford AL, Frey K, et al. How central is central poststroke pain? The role of afferent input in poststroke neuropathic pain: a prospective, open-label pilot study. *Pain*. 2018;159(7):1317-1324. doi:10.1097/J.PAIN.0000000000001213

20. Ringkamp M, Raja SN, Campbell JN, Meyer RA. Peripheral mechanisms of cutaneous nociception. In: McMahon S, Koltzenburg M, Tracey I, Turk D, eds. *Wall and Melzacks Textbook of Pain*. 6th ed. Philadelphia: Elsevier; 2013:1-30.

21. Dib-Hajj SD, Waxman SG. Sodium Channels in Human Pain Disorders: Genetics and Pharmacogenomics. *Annu Rev Neurosci*. 2019;42:87-106. doi:10.1146/ANNUREV-NEURO-070918-050144

22. Alles SRA, Smith PA. Etiology and pharmacology of neuropathic pain. *Pharmacol Rev*. 2018;70(2):315-347. doi:10.1124/pr.117.014399

23. Dib-Hajj SD, Cummins TR, Black JA, Waxman SG. Sodium channels in normal and pathological pain. *Annu Rev Neurosci*. 2010;33:325-347. doi:10.1146/ANNUREV-NEURO-060909-153234

24. Bear MF, Malenka RC. Synaptic plasticity: LTP and LTD. *Curr Opin Neurobiol*. 1994;4(3):389-399. doi:10.1016/0959-4388(94)90101-5

25. Cooke SF, Bliss TVP. Plasticity in the human central nervous system. *Brain*. 2006;129(7):1659-1673. doi:10.1093/brain/awl082

26. Taylor CP. Mechanisms of analgesia by gabapentin and pregabalin - Calcium channel α2-δ [Cavα2-δ] ligands. *Pain*. 2009;142(1-2):13-16. doi:10.1016/j.pain.2008.11.019

27. Amir R, Michaelis M, Devor M. Membrane Potential Oscillations in Dorsal Root Ganglion Neurons: Role in Normal Electrogenesis and Neuropathic Pain. *J Neurosci*. 1999;19(19):8589. doi:10.1523/JNEUROSCI.19-19-08589.1999

28. Boucher TJ, McMahon SB. Neurotrophic factors and neuropathic pain. *Curr Opin Pharmacol*. 2001;1(1):66-72. doi:10.1016/S1471-4892(01)00010-8

29. Löken L, Braz J, Etlin A, et al. Contribution of dorsal horn CGRP-expressing interneurons to mechanical sensitivity. *Elife*. 2021;10. doi:10.7554/ELIFE.59751

30. Liu C-N, Wall PD, Ben-Dor E, Michaelis M, Amir R, Devor M. Tactile allodynia in the absence of C-fiber activation: altered firing properties of DRG neurons following spinal nerve injury. *Pain*. 2000;85(3):503-521. doi:https://doi.org/10.1016/s0304-3959(00)00251-7

31. Woolf CJ. Neuropathic pain is a pathological pain Aetiology of neuropathic pain. *the Lancet @Bullet*. 1999;353:1959-1964. doi:10.1016/S0140-6736(99)01307-0

32. Schäfers M, Sorkin L. Effect of cytokines on neuronal excitability. *Neurosci Lett*. 2008;437(3):188-193. doi:10.1016/J.NEULET.2008.03.052

33. Sandkühler J, Sandkuhler J. Models and mechanisms of hyperalgesia and allodynia. *Physiol Rev*. 2009;89(2):707-758. doi:10.1152/physrev.00025.2008

34. Gossrau G, Klimova A, Lapp HS, et al. C-tactile touch perception in patients with chronic pain disorders. *Pain reports*. 2021;6(2):e941. doi:10.1097/PR9.0000000000000941

35. Liljencrantz J, Olausson H. Tactile C fibres and their contributions to pleasant sensations and tactile allodynia. *Front Behav Neurosci*. 2014;8(MAR). doi:10.3389/FNBEH.2014.00037

36. Dawes JM, Weir GA, Middleton SJ, et al. Immune or Genetic-Mediated Disruption of CASPR2 Causes Pain Hypersensitivity Due to Enhanced Primary Afferent Excitability. *Neuron*. 2018;97(4):806-822.e10. doi:10.1016/J.NEURON.2018.01.033

37. Latremoliere A, Woolf CJ. Central Sensitization: A Generator of Pain Hypersensitivity by Central Neural Plasticity. *J Pain*. 2009;10(9):895-926. doi:10.1016/j.jpain.2009.06.012

38. Basbaum AI, Bautista DM, Scherrer G, Julius D. Cellular and Molecular Mechanisms of Pain. *Cell*. 2009;139(2):267. doi:10.1016/J.CELL.2009.09.028

39. Hughes DI, Todd AJ. Central Nervous System Targets: Inhibitory Interneurons in the Spinal Cord. *Neurotherapeutics*. 2020;17(3):874-885. doi:10.1007/S13311-020-00936-0

40. Bleakman D, Alt A, Nisenbaum ES. Glutamate receptors and pain. *Semin Cell Dev Biol*. 2006;17(5):592-604. doi:10.1016/J.SEMCDB.2006.10.008

41. Yoshimura M, Yonehara N. Alteration in sensitivity of ionotropic glutamate receptors and tachykinin receptors in spinal cord contribute to development and maintenance of nerve injury-evoked neuropathic pain. *Neurosci Res*. 2006;56(1):21-28. doi:10.1016/J.NEURES.2006.04.015

42. Finnerup NB, Attal N, Haroutounian S, et al. Pharmacotherapy for neuropathic pain in adults: A systematic review and meta-analysis. *Lancet Neurol*. 2015;14(2):162-173. doi:10.1016/S1474-4422(14)70251-0

43. D'Mello R, Dickenson A. Spinal cord mechanisms of pain. *Br J Anaesth*. 2008;101(1):8-16. doi:10.1093/BJA/AEN088

44. Zhu Y, Henry JL. Excitability of Aβ sensory neurons is altered in an animal model of peripheral neuropathy. *BMC Neurosci*. 2012;13(1):15. doi:10.1186/1471-2202-13-15

45. Attal N, Bouhassira D, Baron R. Diagnosis and assessment of neuropathic pain through questionnaires. *Lancet Neurol*. 2018;17(5). doi:10.1016/S1474-4422(18)30071-1

46. Magerl W, Krumova EK, Baron R, Tölle T, Treede RD, Maier C. Reference data for quantitative sensory testing (QST): Refined stratification for age and a novel method for statistical comparison of group data. *Pain*. 2010;151(3):598-605. doi:10.1016/j.pain.2010.07.026

47. Baron R, Maier C, Attal N, et al. Peripheral neuropathic pain: A mechanism-related organizing principle based on sensory profiles. *Pain*. 2017;158(2):261-272. doi:10.1097/j.pain.0000000000000753

48. Vollert J, Magerl W, Baron R, et al. Pathophysiological mechanisms of neuropathic pain: Comparison of sensory phenotypes in patients and human surrogate pain models. *Pain*. 2018;159(6):1090-1102. doi:10.1097/j.pain.0000000000001190

49. Vollert J, Maier C, Attal N, et al. Stratifying patients with peripheral neuropathic pain based on sensory profiles: Algorithm and sample size recommendations. *Pain*. 2017;158(8). doi:10.1097/j.pain.0000000000000935

50. Treede R-D, Jensen TS, Campbell JN, et al. Neuropathic pain redefinition and a grading system for clinical and research purposes. *Neurology*. 2008;70(18):1630-1635.

doi:doi:10.1212/01.wnl.0000282763.29778.59

51. Bouhassira D. Neuropathic pain: Definition, assessment and epidemiology. *Rev Neurol (Paris)*. 2019;175(1-2):16-25. doi:10.1016/J.NEUROL.2018.09.016

52. Bouhassira D, Attal N, Alchaar H, et al. Comparison of pain syndromes associated with nervous or somatic lesions and development of a new neuropathic pain diagnostic questionnaire (DN4). *Pain*. 2005;114(1-2):29-36. doi:10.1016/J.PAIN.2004.12.010

53. Bennett MI, Smith BH, Torrance N, Potter J. The S-LANSS score for identifying pain of predominantly neuropathic origin: validation for use in clinical and postal research. *J Pain*. 2005;6(3):149-158. doi:10.1016/j.jpain.2004.11.007

54. Van Hecke O, Austin SK, Khan RA, Smith BH, Torrance N. Neuropathic pain in the general population: A systematic review of epidemiological studies. *Pain*. 2014;155(4):654-662. doi:10.1016/j.pain.2013.11.013

55. Bouhassira D, Lanteri-Minet M, Attal N, Laurent B, Touboul C. Prevalence of chronic pain with neuropathic characteristics in the general population. *Pain*. 2008;136(3):380-387. doi:10.1016/j.pain.2007.08.013

56. De Moraes Vieira ÉB, Garcia JBS, Da Silva AAM, Mualem Araújo RLT, Jansen RCS. Prevalence, Characteristics, and Factors Associated With Chronic Pain With and Without Neuropathic Characteristics in São Luís, Brazil. *J Pain Symptom Manage*. 2012;44(2):239-251. doi:10.1016/J.JPAINSYMMAN.2011.08.014

57. Torrance N, Smith BH, Bennett MI, Lee AJ. The Epidemiology of Chronic Pain of Predominantly Neuropathic Origin. Results From a General Population Survey. *J Pain*. 2006;7(4):281-289. doi:10.1016/j.jpain.2005.11.008

58. Yawn BP, Wollan PC, Weingarten TN, Watson JC, Hooten WM, Melton LJ. The Prevalence of Neuropathic Pain: Clinical Evaluation Compared with Screening Tools in a Community Population. *Pain Med*. 2009;10(3):586-593. doi:10.1111/J.1526-4637.2009.00588.X

59. Adoukonou T, Gnonlonfoun D, Kpozehouen A, et al. [Prevalence and characteristics of chronic pain with a neuropathic component at Parakou in northern Benin in 2012]. *Rev Neurol (Paris)*. 2014;170(11):703-711. doi:10.1016/J.NEUROL.2014.07.013

60. Harifi G, Amine M, Ait Ouazar M, et al. Prevalence of Chronic Pain with Neuropathic Characteristics in the Moroccan General Population: A National Survey. *Pain Med*. 2013;14(2):287-292. doi:10.1111/PME.12009

61. Elzahaf RA, Johnson MI, Tashani OA. The epidemiology of chronic pain in Libya: a cross-sectional telephone survey. *BMC Public Heal 2016 161*. 2016;16(1):1-14. doi:10.1186/S12889-016-3349-6

62. Inoue S, Taguchi T, Yamashita T, Nakamura M, Ushida T. The prevalence and impact of chronic neuropathic pain on daily and social life: A nationwide study in a Japanese population. *Eur J Pain*. 2017;21(4):727-737. doi:10.1002/EJP.977

63. Szende A, Janssen B, Cabasés J. *Self-Reported Population Health: An International Perspective Based on EQ-5D*. 1st ed. Dordrecht: Springer Netherlands; 2014. doi:10.1007/978-94-007-7596-1

64. Failde I, Dueñas M, Ribera MV, et al. Prevalence of central and peripheral neuropathic pain in patients attending pain clinics in Spain: factors related to the intensity of pain and quality of life. *J Pain Res*. 2018;11:1835-1847. doi:10.2147/JPR.S159729

65. Jensen MP, Chodroff MJ, Dworkin RH. The impact of neuropathic pain on health-related quality of life. *Neurology*. 2007;68(15):1178-1182. doi:10.1212/01.WNL.0000259085.61898.9E

66. Djordjevic OC, Konstantinovic M, Miljkovic N. Difference between subjects in the early chronic phase of low back pain with and without neuropathic component: an observational cross-sectional study. *Eur J Phys Rehabil Med*. 2018;55(2):217-224. doi:10.23736/S1973

67. Blyth FM. Global burden of neuropathic pain. *Pain*. 2018;159(3):614-617. doi:10.1097/j.pain.0000000000001127

68. Smith BH, Torrance N, Bennett MI, Lee AJ. Health and quality of life are associated with chronic pain of predominantly neuropathic origin in the community. *Clin J Pain*. 2007;23(2):143-149. doi:10.1097/01.AJP.0000210956.31997.89

69. Gierthmühlen J, Böhmer J, Attal N, et al. Association of sensory phenotype with quality of life, functionality, and emotional well-being in patients suffering from neuropathic pain. *Pain*. 2021; doi:10.1097/j.pain.0000000000002501

70. Moore R, Derry S, Taylor RS, Straube S, Phillips CJ. The costs and consequences of adequately managed chronic non-cancer pain and chronic neuropathic pain. *Pain Pract*. 2014;14(1):79-94. doi:10.1111/papr.12050

71. McDermott AM, Toelle TR, Rowbotham DJ, Schaefer CP, Dukes EM. The burden of neuropathic pain: Results from a cross-sectional survey. *Eur J Pain*. 2006;10(2):127. doi:10.1016/j.ejpain.2005.01.014

72. Attal N, Lanteri-Minet M, Laurent B, Fermanian J, Bouhassira D. The specific disease burden of neuropathic pain: Results of a French nationwide survey. *Pain*. 2011;152(12):2836-2843. doi:10.1016/j.pain.2011.09.014

73. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand*. 1983;67(6):361-370. doi:10.1111/j.1600-0447.1983.tb09716.x.

74. Smith BH, Torrance N. Epidemiology of Neuropathic Pain and Its Impact on Quality of Life. *Curr Pain Headache Rep*. 2012;16(3):191-198. doi:10.1007/S11916-012-0256-0

75. O'Connor AB. Neuropathic pain: Quality-of-life impact, costs and cost-effectiveness of therapy. *Pharmacoeconomics*. 2009;27(2):95-112. doi:10.2165/00019053-200927020-00002

76. Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res*. 2011;20(10):1727. doi:10.1007/S11136-011-9903-X

77. Ware JJ, Sherbourne C. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care*. 1992;30(6):473-483. https://pubmed.ncbi.nlm.nih.gov/1593914/. Accessed April 7, 2022.

78. Doth AH, Hansson PT, Jensen MP, Taylor RS. The burden of neuropathic pain: A systematic review and meta-analysis of health utilities. *Pain*. 2010;149(2):338-344. doi:10.1016/j.pain.2010.02.034

79. Udall M, Kudel. I, Cappelleri J, et al. Epidemiology of physician-diagnosed neuropathic pain in Brazil. *J Pain Res*. 2019;12:243-253. doi:10.2147/JPR.S160504

80. De Courcy J, Liedgens H, Obradovic M, Holbrook T, Jakubanis R. A burden of illness study for neuropathic pain in Europe. *Clin Outcomes Res*. 2016;8:113-126. doi:10.2147/CEOR.S81396

81. Moisset X, Bouhassira D, Attal N. French guidelines for neuropathic pain: An update and commentary. *Rev Neurol (Paris)*. 2021;177:834-837. doi:10.1016/j.neurol.2021.07.004

82. De Moulin D, Boulanger A, Clark AJ, et al. Pharmacological Management of Chronic Neuropathic Pain: Revised Consensus Statement from the Canadian Pain Society. *Pain Res Manag*. 2014;19(6):328-335. doi:10.1155/2014/754693

83. Centre CPAN. Neuropathic Pain: The Pharmacological Management of Neuropathic Pain in Adults in Non-Specialist Settings. *NICE Clin Guidel*. 2010;2015(March):1-155. https://pubmed.ncbi.nlm.nih.gov/22319807/. Accessed November 13, 2021.

84. Moulin DE, Clark AJ, Gordon A, et al. Long-Term Outcome of the Management of Chronic Neuropathic Pain: A Prospective Observational Study. *J Pain*. 2015;16(9):852-861. doi:10.1016/j.jpain.2015.05.011

85. Wen LS, Sadeghi NB. The opioid crisis and the 2020 US election: crossroads for a national epidemic. *Lancet*. 2020;396(10259):1316-1318. doi:10.1016/S0140-6736(20)32113-9

86. National Institute for Clinical Excellence NI advisory committee (IPAC). *Systematic Review of Stimulation of Peripheral Nerves for the Treatment of Refractory Pain (Including Peripheral Nerve Field Stimulation)*. NICE; 2012. http://guidance.nice.org.uk/IPG450/Overview/pdf/English.

87. National Institute for Clinical Excellence N. Percutaneous electrical nerve stimulation for refractory neuropathic pain (IPG450). Interventional procedures guidance IPG450. http://guidance.nice.org.uk/IPG450. Published 2013. Accessed August 12, 2021.

Chapter 2: Long term synaptic depression as a possible treatment mechanism for neuropathic pain.

Long Term synaptic Depression (LTD) has been suggested as a potential mechanism for the treatment of neuropathic pain. It describes a state where there is a long-lasting (hours) reduction in synaptic efficacy. The counterbalancing process is termed Long Term Potentiation (LTP), where there is an enhancement of synaptic connections and synaptic transmission is upregulated and amplified. LTP and LTD have been demonstrated as mechanisms underlying synaptic plasticity throughout the whole central nervous system and are thought to be associated with learning and memory formation [1].

Within central pain pathways, the modulation of nociceptive synaptic transmission that leads to either diminished or enhanced synaptic communication between spinal horn neurons has been termed 'nociceptive or spinal LTD and LTP' [2]. Nociceptive LTD and LTP can be induced in an *'activity-dependent'* manner by strong or lasting discharges in C-fibres, generating a central depression or amplification of nociceptive responses following trauma, inflammation, or injury [3,4]. Conversely, induction can also be achieved in an *'activity-independent'* manner in the absence of any preconditioning activity in nociceptive nerve fibres. A clinically relevant example of the latter is LTP and hyperalgesia which develops after the abrupt withdrawal from opioids. Opioids normally depress synaptic strength at C-fibres. On withdrawal of opioids, synaptic strength not only returns to normal very quickly but becomes potentiated for prolonged periods of time[3]. Activity independent *mechanisms* of LTP include non-Hebbian and glycogenic LTP which are outside the remit of this thesis.

Neuropathic pain, as previously discussed, leads to a disruption of pain pathways with abnormal peripheral nociceptor impulses being generated by either damaged or surviving undamaged nociceptors [5]. These abnormal impulses from peripheral nociceptors following nerve injury have

been shown, in animal models, to induce in an *'activity dependent'* manner nociceptive LTP and consequently lead to enhanced responsiveness of spinal horn neurons and central sensitisation [6]. Central sensitisation, as illustrated in the previous chapter, refers to the enhanced responsiveness of spinal horn neurons to normal afferent input; and is a well-recognized mediator of chronic pain states [5]. Thus, nociceptive LTP has been suggested to be a mediating mechanism of painful central sensitisation in the spinal cord following nerve injury [6,7].

In animal models, high-frequency electrical stimulation (HFS) of primary nociceptive C-fibre afferents has been used to simulate atypical synchronous nociceptor discharges and consequently induce nociceptive LTP and central sensitisation [8,9]. Animal models have also demonstrated that low-frequency stimulation (LFS) can reverse the effects of LTP via the induction of lasting long-term depression (LTD) or depotentiation of synaptic transmission in the spinal cord [8,10].

While LTP cannot be directly measured in healthy human subjects, its consequence, central sensitisation, can be assessed. In healthy humans' the application of electrical stimulation equivalent to the above-cited rodent studies induces prolonged enhancement of somatosensory evoked potentials and pain response to cutaneous stimulus and thus provides a perceptual correlate for human nociceptive LTP [6,11]. LFS has been shown to reverse the effects of LTP in healthy individuals resulting in reductions in somatosensory evoked potentials and pain responses to cutaneous stimulus, and thereby, provides a model for human nociceptive LTD [11–15]. Recent research has also demonstrated that LFS of the radial nerve in healthy volunteers not only reduces pain evoked potentials but is also associated with reductions in the central processing of SEPs [16].

The existing research, therefore, supports the concept that induction of LTD via LFS could provide a possible target for the treatment of chronic neuropathic pain following nerve injury via its ability to reduce the enhanced synaptic transmission associated with LTP and its consequence, central sensitisation [11–13]. Current knowledge concerning the use of electrical stimulation to influence LTP

and LTD has come from animal studies and experimental induction in man. Therefore, further research is required to understand and explore possible clinical applications of LTD.

Some of the salient findings from existing research and their implications, for the development and evaluation of clinical applications of LTD, will be discussed.

Molecular mechanisms

Both LTP and LTD processes are suggested to be calcium ion (Ca2+) dependent and both require an elevation of intracellular calcium to occur[17,18]. However, the mechanisms underlying the dual role of calcium, triggering either LTP or LTD, are still largely unclear and multiple types of LTP and LTD have been studied[19]. These include N-methyl-d-aspartate receptor (NMDAR) dependent, mGluR-Dependent LTD and endocannabinoid-Mediated LTD[18,20]. N-methyl-d-aspartate receptor (NMDAR) dependent LTP and LTD represent the most studied forms of LTP and LTD[18,20,21]. In this model, the activation of NMDARs causes a change in Ca2+ levels which triggers LTP or LTD. NMDARs are glutamate-gated cation channels that allow pre- to postsynaptic permeation of calcium and other cations. At resting potentials, NMDARs allow external magnesium ions to enter the NMDA pore, which binds tightly and prevents further ion permeation, such as Ca2+ entry. However, if the postsynaptic membrane is sufficiently depolarized, NMDARs become activated and allow Ca2+ to flow into the cell, to relieve the magnesium ion block from the NMDAR pore.

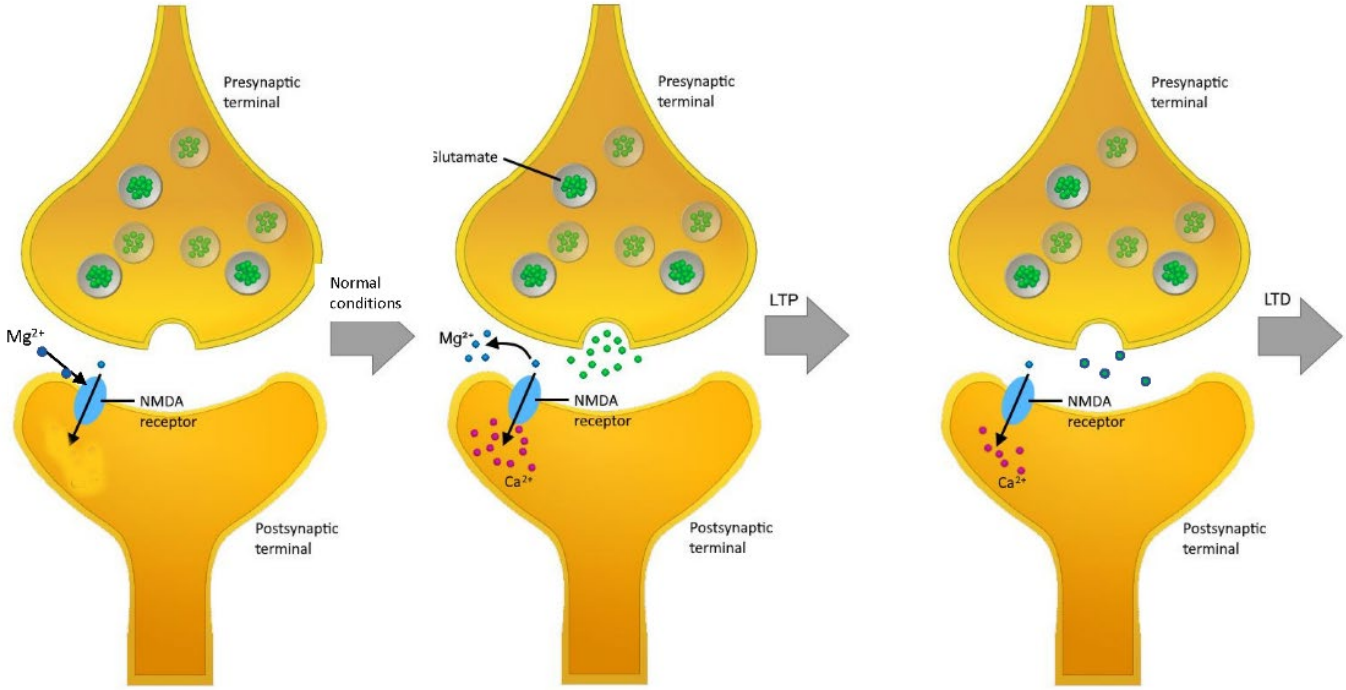
This can be triggered by the release of glutamate from the presynaptic terminal following peripheral noxious stimulation of A-δ and C-fibres. Glutamate diffuses across the synaptic cleft and binds to post synaptic NMDARs and depolarises the cell [18,20]. The level of depolarisation is important as to whether the synaptic transmission is potentiated or depressed. For example, strong depolarisation induced by fast high frequency (100Hz) stimulation causes the ejection of Mg2+ ions unblocking the NMDA ion pore, allowing higher concentrations of Ca2+ to permutate to the post synaptic cell, which enhances synaptic strength and stimulates the release of further excitatory neurotransmitters such as substance P and glutamate post synaptically [22]. Whereas conditions such as LTD, are typically

triggered by prolonged repetitive low-frequency (1 Hz) stimulation[18]. In this scenario, the degree of depolarisation is insufficient to remove the Mg2+ ions that block NMDA receptors (see Fig 2.1). Therefore, only a small volume of calcium permeates into the post synaptic cell. This low concentration of calcium reduces the availability of receptors and consequently weakens the synapse [23,24]. The modest increase in Ca2+ preferentially activates calcineurin which is associated with dephosphorylation (removal of phosphates) which in turn can further weaken synaptic strength.

Hebbian synaptic LTP and LTD

Hebbian LTP and LTD have been defined as synapse-specific changes in strength driven by the coordination of pre- synaptic input and post synaptic depolarisation, as described above [25]. If LTP is expressed at only stimulated synapses it provides a mechanism for primary hyperalgesia but does not account for pain amplification in surrounding areas outside the primary lesion (secondary hyperalgesia) or remotely (widespread hyperalgesia) where neither nociceptor activation nor peripheral sensitisation occurs. *Non-Hebbian LTP and LTD* conversely describe postsynaptic output that is not paired to presynaptic activation and therefore represents a form of *'activity independent'* LTP and LTD [25].

Figure 2.1 Illustration of LTP and LTD



Normal conditions: *The Mg^{2+} the NMDA pore and bind tightly preventing further ion permeation such as Ca2+ entry.* ***LTP:*** *The NMDA is activated by the release of presynaptic glutamate, and the post synaptic membrane is sufficiently depolarised to allow the ejection of Mg2+ ions which block the NMDA ion pore, which now allows Ca2+ to enter the cell. High concentrations of Ca2+ increase the availability of receptors and strengthen the synapse.* ***LTD:*** *The post-synaptic depolarisation is insufficient to remove the Mg2+ ions that block NMDA receptors. Therefore, only a small volume of calcium permeates into the post synaptic cell and reduces the availability of receptors weakening the synapse.*

Pharmacological manipulation of the LTP/LTD system

Based on the current molecular understanding of LTP and LTD induction in animal models, a variety of pharmacological treatment targets have been evaluated to prevent LTP induction and stimulate LTD induction. These can be divided into four basic categories of intervention:

1) Drugs which interfere with postsynaptic depolarisation such as α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptor antagonists. AMPA are a subtype of the ionotropic glutamate receptor that modulates cell excitability by gating the flow of calcium and sodium ions into the cell [20], thus inhibiting their function and preventing excitatory neurotransmission[26]. An example would be the anti-epileptic drug Perampanel which has limited evidence for neuropathic pain in animal models[27,28].

2) Drugs directly interfere with NMDA receptor activation e.g. NMDA receptor antagonists such as ketamine have been shown to interfere with LTP induction [29] and continuous infusion to interfere with established secondary hyperalgesia [30,31].

3) Drugs that interfere with additional sources of activity-dependent intracellular calcium rise e.g. antagonists of T-type voltage-gated calcium channels (VGCCs), activators of intracellular calcium stores [32,33] or metabotropic glutamate receptors (mGluRIs) receptors [34,35].

4) Drugs that interfere with descending control mechanisms [26]. For example, prolonged burst stimulation of the sciatic nerve at Aδ-fibre strength produces LTD of C-fibre-evoked field potentials in rats, but when descending control is inhibited by spinalisation it induces LTP [36]. These results demonstrate that the descending control systems can influence LTP and LTD.

In animal models, a variety of the above interventions have been found to either prevent experimentally induced LTP induction or reverse its effects, and their actions have then been replicated in human models. In human models, spinal synaptic strength cannot be directly measured and therefore, results have only inferred experimental induction of LTP by drawing upon animal model data or modification of human clinical symptoms such as secondary hyperalgesia.

Manipulation of LTP/LTD system by electrical stimulation

Low-frequency stimulation at 1Hz with stimulus trains of 1000 pulses has been demonstrated to reverse the effects of LTP via the induction of long-lasting long-term depression at primary afferent synapses with neurons of lamina II of the rat spinal cord [8,37]. Studies such as this demonstrate the potential of LTD induction via low-frequency electrical stimulation as a therapeutic target. Numerous LTD studies in healthy human subjects have adopted these stimulation parameters, demonstrating reductions in sensory evoked potentials in response to a painful stimulus, corresponding with LTD as a working mechanism[12,16,38,39]. The results of these studies have also shown that specific stimulation parameters such as the number of impulses (pulse duration), stimulation frequency, stimulation

strength and electrode shape all significantly influence the degree of LTD and are discussed below [12–15].

Stimulation frequency

LTD has been demonstrated using stimulation frequencies of 1-4Hz[11,12,14], although most consistently using frequencies of 1-2Hz [11,12,15,39]. Dudek and Bear examined LTD and LTP in response to electrical stimulation of rat hippocampal slices at frequencies ranging from 0.5 to 50Hz[40]. The results illustrated that stimulation at frequencies of 1-3Hz, in a normal system without a pre-existing state of LTP, consistently induced LTD. The strength of LTD declined considerably outside of this range, with stimulation at 10Hz or 0.5Hz producing no notable change, and at higher frequencies, there was a shift from LTD to LTP induction. The most pronounced LTD was induced at stimulation frequencies of 1Hz, suggesting an optimal range of LTD induction lies between 1-2Hz and diminishes outside of this range. Jung et al tested the hypothesis that LTD of spinal nociception and pain in man depends on LFS frequency, the number of electrical pulses and stimulation intensity[12]. Painful electrical test stimulation (0.125Hz) and conditioning LFS were applied to the right-hand dorsum. Somatosensory evoked cortical potentials (SEP) were recorded, and volunteers rated stimulus intensity. Results suggested that frequencies of 1Hz and 2Hz were associated with a more pronounced reduction in SEPs than frequencies of 0.5Hz.

The importance of stimulation frequency has been suggested to relate to the activation thresholds of different calcium-binding proteins[19]. In in vitro studies higher frequencies of between 10 and 200Hz have been demonstrated to activate calmodulin (CaMKII an LTP facilitating molecule), while lower frequencies between 1 and 3Hz activated calcineurin (an LTD facilitating molecule) [19,41].

Duration of stimulation

There is evidence from rodent studies that long-lasting stimulation of at least 900 pulses is required to activate calcineurin. Calcineurin is a calcium-dependent phosphate implicated in LTD and needs a

prolonged rise in calcium to be activated [42,43]. Noxious LFS stimulation for shorter durations has conversely been associated with LTP [33,44]. In human studies, reduction of enhanced evoked pain responses using the same stimulation parameters has been demonstrated [13,38]. Further studies have examined the influence of varying pulse durations of between 300 and 1200 pulses [11,12,38]. Pulse durations of at least 900 - 1200 pulses have been shown to produce the most pronounced reduction in pain responses, with some suggestion that even longer pulse durations, if tolerated, would be even more beneficial [12]. This supports the findings from rodent studies where duration of at least 900 - 1200 pulses was deemed essential to influence the intracellular Ca2+ concentration and phosphate binding that is important to LTD induction.

Stimulation strength

Stimulation strength has also been suggested to be important in terms of LTD induction via electrical stimulation. There is evidence from animal studies that excitation of A-δ fibres is necessary to induce LTD[37,45]. A-δ fibres are preferentially activated at stimulus intensities perceived as sharp and painful [12,13], whereas stimulation at lower intensities has been suggested to mainly activate Aβ fibres not associated with LTD [37]. In studies in healthy human subjects, stimulation strengths of 2- 4 times pain perception threshold are associated with sustained depression of pain perception, whilst stimulation at 1 times pain threshold is not[12,13]. Pain perception threshold is defined as the minimum intensity of a stimulus that is perceived to be painful[46]. Further evidence in healthy human subjects suggests strengths below 1-time pain perception threshold and above 5 times pain threshold produce less pronounced LTD than strengths between 2-5 times pain perception threshold [47]. These combined results are suggestive of a u-shaped relationship in respect to intensity of stimulation, optimal A-δ stimulation and the strength of LTD. They suggest stimulation should be above what is perceived as minimally painful but not too painful.

Electrode shape

The shape of the electrode has also been identified to be important with LTD induction. As already mentioned, excitation of A-δ fibres is necessary to induce LTD[37,45]. Experiments applying local cutaneous stimulation in healthy subjects have provided evidence that preferential activation of cutaneous A-δ fibres can be achieved using a concentric electrode that creates a high current density [48,49]. In contrast, larger diameter surface electrodes, such as TENS electrodes, do not generate the required current density to preferentially activate A-δ fibres, unless used at very high intensities, which evidence shows few patients can tolerate [50,51]. Therefore, TENS typically activates the whole A- fibre spectrum without any preference[50,51].

The above literature describes the influence of different stimulation paradigms on Hebbian forms of electrically induced LTD.

Sensory characteristics relevant to LTP and LTD

Nociceptive LTP induced via high-frequency stimulation appears to enhance A-beta and A-delta fibre mediated cutaneous sensations, specifically A-delta fibre high threshold mechanoreceptors for punctate hyperalgesia and A-beta low threshold mechanoreceptors for dynamic mechanical allodynia [38]. This supports the understanding that LTP and conversely LTD influence synaptic transmission via centrally mediated mechanisms, such as central sensitisation, rather than peripheral mechanisms. Therefore, it follows that LTD induced by LFS as a method of pain relief will be most appropriate for persons with neuropathic pain who display sensory features more typical of central sensitisation versus peripheral sensitisation.

Quantitative sensory testing has been extensively used to evaluate the sensory features associated with different neuropathic pain syndromes. Results have defined patterns of loss or gain of function across multiple sensory modalities (‘somatosensory profiles’), which likely reflect underlying pain generating mechanisms such as peripheral and central sensitisation [52]. Studies examining similarities in terms of dominant sensory features across different neuropathic pain conditions, have identified

3 distinct clusters or sensory phenotypes for patients with neuropathic pain [52,53]; 'sensory loss', 'thermal hyperalgesia' and 'mechanical hyperalgesia'. The 'sensory loss' cluster is characterised by loss of small and large diameter nerve function with patients demonstrating loss of temperature sensation and mechanical pressure sensation. Elements of this phenotype have been observed in experimentally induced pain following a compression nerve block. Within the 'thermal hyperalgesia' cluster there is a preservation of sensory function and prominent features of heat and cold hyperalgesia and mild dynamic allodynia. This sensory profile resembles that seen in experimentally induced pain following UVB burn and has previously been described as the 'irritable nociceptor' sensory profile, which is considered to reflect more prominent features of peripheral sensitisation. The mechanical hyperalgesia subgroup exhibits loss of small fibre function, pin prick hyperalgesia and dynamic allodynia. This phenotype, therefore, shows similarities to experimentally induced pain via high-frequency electrical stimulation, and the previously described 'models of central sensitisation'. Therefore, patients displaying this later sensory phenotype could respond to LFS aimed at inducing LTD related analgesia.

Conclusion

The current body of literature provides evidence that LTD is a plausible mechanism for the treatment of some types of neuropathic pain. Results from studies examining the different sensory phenotypes of patients with neuropathic pain would suggest that LTP and LTD are likely to have greater relevance for patients displaying a predominant 'mechanical-hyperalgesia' sensory phenotype, i.e. who specifically demonstrate mechanical dynamic allodynia and punctate hyperalgesia[52,53]. This is because these features characterise painful conditions with prominent spinal cord sensitisation, which is the anticipated target of LTD interventions. Patients with peripheral nerve injury demonstrate high rates of positive sensory signs associated with this phenotype, specifically dynamic mechanical allodynia and pinprick hyperalgesia [53].

Pharmacological agents are often associated with side effects and, therefore, there is an argument, as previously discussed, to explore well-tolerated non-pharmacological modalities. LFS in both animal and human studies is an appropriate technology to induce nociceptive LTD within the territory of the stimulated nerve in conditions which are of a mechanical hyperalgesia phentotype[8,13,37,38]. LFS delivered to induce LTD would, therefore, seem appropriate for patients with localised pain following peripheral nerve injury. However, these results in experimental models have not been replicated in patients with ongoing chronic neuropathic pain. Therefore, it remains unclear as to whether LFS can indeed induce LTD in persons with persistent LTP and can therefore be applied therapeutically in a clinical setting.

Chapter 2 References

1. Bliss TVP, Collingridge GL. A synaptic model of memory: Long-term potentiation in the hippocampus. *Nature*. 1993;361(6407):31-39. doi:10.1038/361031a0

2. Ikeda H. Synaptic Plasticity in Spinal Lamina I Projection Neurons That Mediate Hyperalgesia. *Science (80-)*. 2003;299(5610):1237-1240. doi:10.1126/science.1080659

3. Sandkühler J, Gruber-Schoffnegger D. Hyperalgesia by synaptic long-term potentiation (LTP): An update. *Curr Opin Pharmacol*. 2012;12(1):18-27. doi:10.1016/j.coph.2011.10.018

4. Jensen TS, Baron R. Translation of symptoms and signs into mechanisms in neuropathic pain. *Pain*. 2003;102(1-2):1-8. doi:10.1016/s0304-3959(03)00006-x

5. Woolf CJ. Neuropathic pain is a pathological pain Aetiology of neuropathic pain. *the Lancet @Bullet*. 1999;353:1959-1964. doi:10.1016/S0140-6736(99)01307-0

6. Sandkühler J, Sandkuhler J. Models and mechanisms of hyperalgesia and allodynia. *Physiol Rev*. 2009;89(2):707-758. doi:10.1152/physrev.00025.2008

7. Magerl W, Klein T. Chapter 33 Experimental human models of neuropathic pain. In: Cervero F JT., ed. *Handbook of Clinical Neurology, Pain*. volume 81. Elsevier; 2006:503-516. doi:10.1016/S0072-9752(06)80037-0

8. Liu, X. G. Morton CR, Azkue JJ, Zimmermann M S. Long-term depression of C-fibre-evoked spinal field potentials by stimulation of primary afferent Aδ-fibres in the adult rat. *Eur J Neurosci*. 1998;10(10):3069-75. doi:10.1046/j.1460-9568.1998.00310.x

9. Liu XG, Sandkühler J. Characterization of long-term potentiation of C-fiber-evoked potentials in the spinal dorsal horn of adult rat: Essential role of NK1 and NK2 receptors. *J Neurophysiol*. 1997;78(4):1973-1982. doi:10.1152/jn.1997.78.4.1973

10. Sandkühler J. Understanding LTP in pain pathways. *Mol Pain*. 2007;3(9). doi:10.1186/1744-8069-3-9

11. Klein T, Magerl W, Hopf H-C, Sandkühler J, Treede R-D. Perceptual correlates of nociceptive long-term potentiation and long-term depression in humans. *J Neurosci*. 2004;24(4):964-971. doi:10.1523/JNEUROSCI.1222-03.2004

12. Jung K, Rottmann S, Ellrich J. Long-term depression of spinal nociception and pain in man: Influence of varying stimulation parameters. *Eur J Pain*. 2009;13(2):161-170. doi:10.1016/j.ejpain.2008.04.001

13. Rottmann S, Jung K, Ellrich J. Electrical low-frequency stimulation induces homotopic long-term depression of nociception and pain from hand in man. *Clin Neurophysiol*. 2008;119(8):1895-1904. doi:10.1016/j.clinph.2008.02.022

14. Mücke M, Cuhls H, Radbruch L, Weigl T, Rolke R. Evidence of heterosynaptic LTD in the human nociceptive system: Superficial skin neuromodulation using a matrix electrode reduces deep pain sensitivity. *PLoS One*. 2014;9(9). doi:10.1371/journal.pone.0107718

15. Ellrich J, Schorr A. Low-frequency stimulation of trigeminal afferents induces long-term depression of human sensory processing. *Brain Res*. 2004;996(2):255-258.

doi:10.1016/j.brainres.2003.08.068

16. Hewitt D, Byrne A, Henderson J, et al. Inhibition of cortical somatosensory processing during and after low-frequency peripheral nerve stimulation in humans. *Clin Neurophysiol*. 2021;132(7):1481-1495. doi:10.1016/J.CLINPH.2021.03.024

17. Evans RC, Blackwell KT. Calcium: amplitude, duration, or location? *Biol Bull*. 2015;228(1):75-83. doi:10.1086/BBLV228N1P75

18. Citri A, Malenka RC. Synaptic Plasticity: Multiple Forms, Functions, and Mechanisms. *Neuropsychopharmacol 2008 331*. 2007;33(1):18-41. doi:10.1038/sj.npp.1301559

19. Li L, Stefan MI, Le Novère N. Calcium Input Frequency, Duration and Amplitude Differentially Modulate the Relative Activation of Calcineurin and CaMKII. *PLoS One*. 2012;7(9):e43810. doi:10.1371/JOURNAL.PONE.0043810

20. Malenka RC, Bear MF. Review LTP and LTD: An Embarrassment of Riches is useful to conceptualize LTP and LTD as a general class of cellular/synaptic phenomena. Just as different neurons express different complements of ion channels. *Neuron*. 2004;44:5-21. doi:10.1016/j.neuron.2004.09.012 20.

21. Bliss TVP, Cooke SF. Long-term potentiation and long-term depression: A clinical perspective. *Clin (Sao Paulo)*. 2011;66(Suppl 1(Suppl 1)):3-17. doi:10.1590/S1807-59322011001300002

22. Ruppersberg JP, Kitzing E V., Schoepfer R. The mechanism of magnesium block of NMDA receptors. *Semin Neurosci*. 1994;6(2):87-96. doi:10.1006/SMNS.1994.1012

23. Bear MF, Malenka RC. Synaptic plasticity: LTP and LTD. *Curr Opin Neurobiol*. 1994;4(3):389-399. doi:10.1016/0959-4388(94)90101-5

24. Cooke SF, Bliss TVP. Plasticity in the human central nervous system. *Brain*. 2006;129(7):1659-1673. doi:10.1093/brain/awl082

25. Naka A, Gruber-Schoffnegger D, Sandkühler J. Non-Hebbian plasticity at C-fiber synapses in rat spinal cord lamina i neurons. *Pain*. 2013;154(8):1333-1342. doi:10.1016/j.pain.2013.04.011

26. Ruscheweyh R, Wilder-Smith O, Drdla R, Liu X-G, Sandkühler J. Long-term potentiation in spinal nociceptive pathways as a novel target for pain therapy. *Mol Pain*. 2011;7(20). doi:10.1186/1744-8069-7-20

27. Hara K, Haranishi Y, Terada T. Intrathecally administered perampanel alleviates neuropathic and inflammatory pain in rats. *Eur J Pharmacol*. 2020;872:172949. doi:10.1016/J.EJPHAR.2020.172949

28. Khangura RK, Bali A, Kaur G, Singh N, Jaggi AS. Neuropathic pain attenuating effects of perampanel in an experimental model of chronic constriction injury in rats. *Biomed Pharmacother*. 2017;94:557-563. doi:10.1016/J.BIOPHA.2017.07.137

29. Klein T, Magerl W, Nickel U, Hopf HC, Sandkühler J, Treede RD. Effects of the NMDA-receptor antagonist ketamine on perceptual correlates of long-term potentiation within the nociceptive system. *Neuropharmacology*. 2007;52(2):655-61. doi:10.1016/j.neuropharm.2006.09.008

30. Gottrup H, Bach FW, Juhl G, Jensen TS. Differential effects of ketamine and lidocaine on spontaneous and mechanical evoked pain in patients with nerve injury pain. *Anesthesiology*. 2006;104(3):527-536. doi:10.1097/00000542-200603000-00021

31. Leung A, Wallace MS, Ridgeway B, Yaksh T. Concentration-effect relationship of intravenous alfentanil and ketamine on peripheral neurosensory thresholds, allodynia and hyperalgesia of neuropathic pain. *Pain*. 2001;91(1-2):177-87. doi:10.1016/S0304-3959(00)00433-4

32. Drdla R, Sandkühler J. Long-term potentiation at C-fibre synapses by low-level presynaptic activity in vivo. *Mol Pain*. 2008;28(4):18. doi:10.1186/1744-8069-4-18

33. Ikeda H, Stark J, Fischer H, et al. Synaptic amplifier of inflammatory pain in the spinal dorsal horn. *Science (80-)*. 2006;312(5780):1659-1662. doi:10.1126/science.1127233

34. Jung SJ, Kim SJ, Park YK, Oh SB, Cho K, Kim J. Group I mGluR regulates the polarity of spike-timing-dependent plasticity in substantia gelatinosa neurons. *Biochem Biophys Res Commun*. 2006;25(347(2)):509-16. doi:10.1016/j.bbrc.2006.06.134

35. Azkue JJ, Liu XG, Zimmermann M, Sandkühler J. Induction of long-term potentiation of C fibre-evoked spinal field potentials requires recruitment of group I, but not group II/III metabotropic glutamate receptors. *Pain*. 2003;106(3):373-379. doi:10.1016/j.pain.2003.08.007

36. Liu XG, Sandkühler J. Long-term potentiation of C-fiber-evoked potentials in the rat spinal dorsal horn is prevented by spinal N-methyl-d-aspartic acid receptor blockage. *Neurosci Lett*. 1995;191(1-2):43-46. doi:10.1016/0304-3940(95)11553-0

37. Sandkühler J, Chen JG, Cheng G, Randić M. Low-frequency stimulation of afferent aδ-fibres induces long-term depression at primary afferent synapses with substantia gelatinosa neurons in the rat. *J Neurosci*. 1997;17(16):6483-6491. doi:10.1523/jneurosci.17-16-06483.1997

38. Lang S, Klein T, Magerl W, Treede RD. Modality-specific sensory changes in humans after the induction of long-term potentiation (LTP) in cutaneous nociceptive pathways. *Pain*. 2007;128(3):254-263. doi:10.1016/j.pain.2006.09.026

39. Rottmann S, Jung K, Ellrich J. Electrical low-frequency stimulation induces long-term depression of sensory and affective components of pain in healthy man. *Eur J Pain*. 2010;14(4):359-365. doi:10.1016/j.ejpain.2009.06.001. Epub 2009 Jul 14.

40. Dudek SM, Bear MF. Homosynaptic long-term depression in area CA1 of hippocampus and effects of N-methyl-D-aspartate receptor blockade. *Proc Natl Acad Sci U S A*. 1992;89(10):4363-4367. doi:10.1073/PNAS.89.10.4363

41. Li L, Lai M, Cole S, Le Novère N, Edelstein SJ. Neurogranin stimulates Ca2+/calmodulin-dependent kinase II by suppressing calcineurin activity at specific calcium spike frequencies. *PLoS Comput Biol*. 2020;16(2). doi:10.1371/JOURNAL.PCBI.1006991

42. Xia Z, Storm DR. The role of calmodulin as a signal integrator for synaptic plasticity. *Nat Rev Neurosci*. 2005;6(4):267-276. doi:10.1038/nrn1647

43. Yasuda H, Higashi H, Kudo Y, et al. Imaging of calcineurin activated by long-term depression-inducing synaptic inputs in living neurons of rat visual cortex. *Eur J Neurosci*. 2003;17(2):287-297. doi:10.1046/j.1460-9568.2003.02449.x

44. Kim HY oun., Jun J, Wang J, Bittar A, Chung K, Chung JM o. Induction of long-term potentiation and long-term depression is cell-type specific in the spinal cord. *Pain*. 2015;156(4):618-625. doi:10.1097/01.J.PAIN.0000460354.09622.EC

45. Randic M, Jiang MC, Cerne R. Long-term potentiation and long-term depression of primary afferent neurotransmission in the rat spinal cord. *J Neurosci*. 1993;13(12):5228-5241.

doi:10.1523/JNEUROSCI.13-12-05228.1993.

46. Coons MJ, Steglitz J. Pain Threshold. In: *Encyclopedia of Behavioral Medicine*. Springer, New York, NY; 2013:1427-1428. doi:10.1007/978-1-4419-1005-9_1160

47. W. Magerl, F. Henrich, L. Röhring, D. Pfau, T. Klein RT. Poster PF0343 : Reversal of LTP-like hyperalgesia by low-frequency electrical stimulation. *16th World Congress On Pain, Yokohama 2016 Abstracts,* https://event.crowdcompass.com/wcp2016/activity/ozu0y7GLko. Accessed January 19, 2021.

48. Kaube H, Katsarava Z, Käufer T, Diener HC, Ellrich J. A new method to increase nociception specificity of the human blink reflex. *Clin Neurophysiol*. 2000;111(3):413-416. doi:10.1016/S1388-2457(99)00295-3

49. Katsarava Z, Ayzenberg I, Sack F, Limmroth V, Diener HC, Kaube H. A novel method of eliciting pain-related potentials by transcutaneous electrical stimulation. *Headache*. 2006;46(10):1511-1517. doi:10.1111/J.1526-4610.2006.00446.X

50. Gibson W, Wand BM, O'Connell NE. Transcutaneous electrical nerve stimulation (TENS) for neuropathic pain in adults. *Cochrane Database Syst Rev*. 2017. doi:10.1002/14651858.CD011976.pub2

51. Sluka KA, Bjordal JM, Marchand S, Rakel BA. What Makes Transcutaneous Electrical Nerve Stimulation Work? Making Sense of the Mixed Results in the Clinical Literature. *Phys Ther*. 2013;93(10):1397-1402. doi:10.2522/PTJ.20120281

52. Baron R, Maier C, Attal N, et al. Peripheral neuropathic pain: A mechanism-related organizing principle based on sensory profiles. *Pain*. 2017;158(2):261-272. doi:10.1097/j.pain.0000000000000753

53. Vollert J, Maier C, Attal N, et al. Stratifying patients with peripheral neuropathic pain based on sensory profiles: Algorithm and sample size recommendations. *Pain*. 2017;158(8). doi:10.1097/j.pain.0000000000000935

Chapter 3: Long term depression via low-frequency neurostimulation for chronic/ neuropathic pain – A systematic review.

As illustrated in the previous chapters long term potentiation (LTP) is a molecular mechanism that leads to the enhancement of nociceptive activity[1,2]. While LTP cannot be directly measured in human subjects, its consequence, central sensitisation can be assessed[3,4]. Low-frequency electrical nerve stimulation (LFS) of 1-2 Hertz (Hz) has been shown to induce long term depression (LTD) by reversing the effects of experimentally induced LTP[4–6], thus reducing heightened somatosensory evoked potentials and pain responses to cutaneous stimulus [4–6]. Induction of LTD via LFS, therefore, represents a potential neurostimulation treatment target for chronic pain conditions that exhibit signs of central sensitisation, such as peripheral neuropathic pain. There are a variety of neurostimulation therapies used to manage various chronic pain conditions including spinal cord stimulation, dorsal root ganglion stimulation, peripheral nerve stimulation, and transcutaneous electrical nerve stimulation. However, there is no current review that considers low-frequency stimulation modalities where LTD induction may be the mechanism of action.

The objective of this chapter is to describe the LFS literature for chronic neuropathic pain and examine whether long-term synaptic depression could be considered the working mechanism.

Methods

A systematic review of the literature was conducted, focusing on the effectiveness of interventions for chronic neuropathic pain where LTD may be the underpinning mechanism of action.
The protocol for this review was registered with Prospero: CRD42021241762.

Search strategy

Electronic databases Pubmed, MEDLINE, Embase, CINAHL and the Cochrane register of controlled trials and references were searched with no date limits. An example search strategy was developed as below following consultation with a medical librarian. Searches were conducted in April 2021.

Example Search Strategy –Pubmed

1. Neuropathic pain
2. Chronic pain
3. 1 or 2
4. Nerve stim*
5. Peripheral nerve stim*
6. Electrical stim*
7. Long term depression
8. Long-term depression
9. Low frequency stim*
10. Low-frequency stim*
11. A delta 'adj3' stim*
12. Synaptic transmission
13. Intracellular ca*
14. 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13
15. 3 AND 14
16. Limit (English language and humans)

* Denotes were truncation was used to broaden search.

Selection of studies

Study eligibility was constructed using PICO components (see Table 3.1).

Table 3. 1: A PICO table illustrating review inclusion criteria.

Population	Adults and children with chronic neuropathic pain. Chronic pain will be defined as pain persisting for 6 months or longer.	
Intervention	Any form of Low-frequency nerve stimulation, with LFS defined as using descriptor of 'low frequency' or stating ≤10 Hz frequency	
Comparator	Sham, dummy stimulation, comparator treatment, no treatment control.	
Outcomes	Objective or self-reported measures are acceptable for the following outcomes:	
	Primary outcomes: • Pain reduction • Quality of pain/ psychophysical parameters	Secondary outcomes: • Pain • Quality of life • Function • Mood-Psychological PROMS • Self-efficacy • Medication reduction • Frequency of flare-ups • Health Care Utilisation • Safety
Setting	Primary, secondary, or tertiary healthcare. Inpatient, outpatient, or community settings.	
Study design	All Excluding single case series	

All abstracts were reviewed using an inclusion/ exclusion screening tool (Table 3.2). As discussed in the previous chapter, evidence suggests that LTD is a plausible mechanism for the treatment of some types of neuropathic pain. Based on this understanding, the review's inclusion criteria were limited to neuropathic pain studies. Studies were excluded if the stimulation target was outside of the territory of the affected nerve. In such circumstances, it is unlikely that LTD induced by LFS would be the predominant working mechanism.

Studies were included if they used 'low-frequency stimulation' which was defined for the review as stimulation of <10Hz. This was because the review of literature for the LTD chapter illustrated LTD in experimental research is optimally achieved at 1-2Hz stimulation, with declining effect outside of this range and no effect observed at frequencies of 10Hz[5,7].

LTD studies have demonstrated that a sustained, long-lasting, low-frequency stimulation of *at least* 900 pulses is required to activate calcineurin [8,9]. As discussed in the previous chapter, calcineurin is a calcium-dependent phosphate implicated in LTD and needs a prolonged rise in calcium to be activated [8,9]. Alternating currents would not provide sustained long-lasting low-frequency stimulation capable of achieving this and therefore these studies were additionally excluded.

A further required parameter for induction of LTD is stimulation strength. As discussed in the previous chapter, stimulation strengths of 2- 4 times the pain perception threshold are required to activate A-δ fibres that are necessary to induce LTD[10,11]. An initial scoping review of the literature highlighted that very few studies described stimulation intensity and therefore this was not included as an inclusion/ exclusion criterion.

Studies only available in abstract form, reviews, single case studies, and animal studies were excluded. Language limits of English only articles were also applied.

Table 3.2: Inclusion criteria screening tool

	Include	Exclude
Population	☐ Adults with chronic (>6 months) pain	☐ Acute pain - defined as fewer than 6 months duration. ☐ Pain not in the sensory distribution of stimulation target
Intervention	☐ Nerve stimulation ☐ Peripheral nerve stimulation ☐ Electrical nerve stimulation ☐ Low frequency stimulation ☐ Low-frequency stimulation ☐ Long term depression ☐ A-delta fibre 'adj3' stimulation ☐ Synaptic transmission ☐ Intracellular calcium	☐ Either stimulation not described as 'Low frequency stimulation' or <10 Hz is not described. ☐ Alternating frequency current.
Comparator	☐ Any and none	☐ n/a
Outcomes	Primary outcomes: ☐ Pain ☐ Pain quality/ psychophysical parameters	
Study design	☐ Any investigational study	☐ Reports of studies* ☐ Single case study ☐ Abstract only
Language	☐ English	☐ Non-English
Overall decision	☐ INCLUDED	☐ EXCLUDED
Notes	*Whilst reports and reviews of studies were excluded reviews were used to identify studies and obtain information about studies and their results.	

Data extraction

Included abstracts proceeded to a full-text review. Extracted data included study characteristics, pain conditions, and stimulation parameters. LTD is an activity-dependent weakening of synaptic activity, therefore measurements of pain quality that demonstrated a reduction in aspects of the sensory gain would be considered most relevant. It was presumed, however, that change in stimulus-evoked pain would not have been measured by all clinical studies and therefore change in spontaneous pain intensity was also reported.

Quality assessment

The quality of included studies was assessed by two authors with any conflicts being resolved by a third, using the Cochrane Risk of Bias tool (RoB 2) for Randomised Controlled Trials (RCTs) [12] and for the case-series reviews -The Joanna Briggs Institute Critical Appraisal tool for Case Series Studies [13].

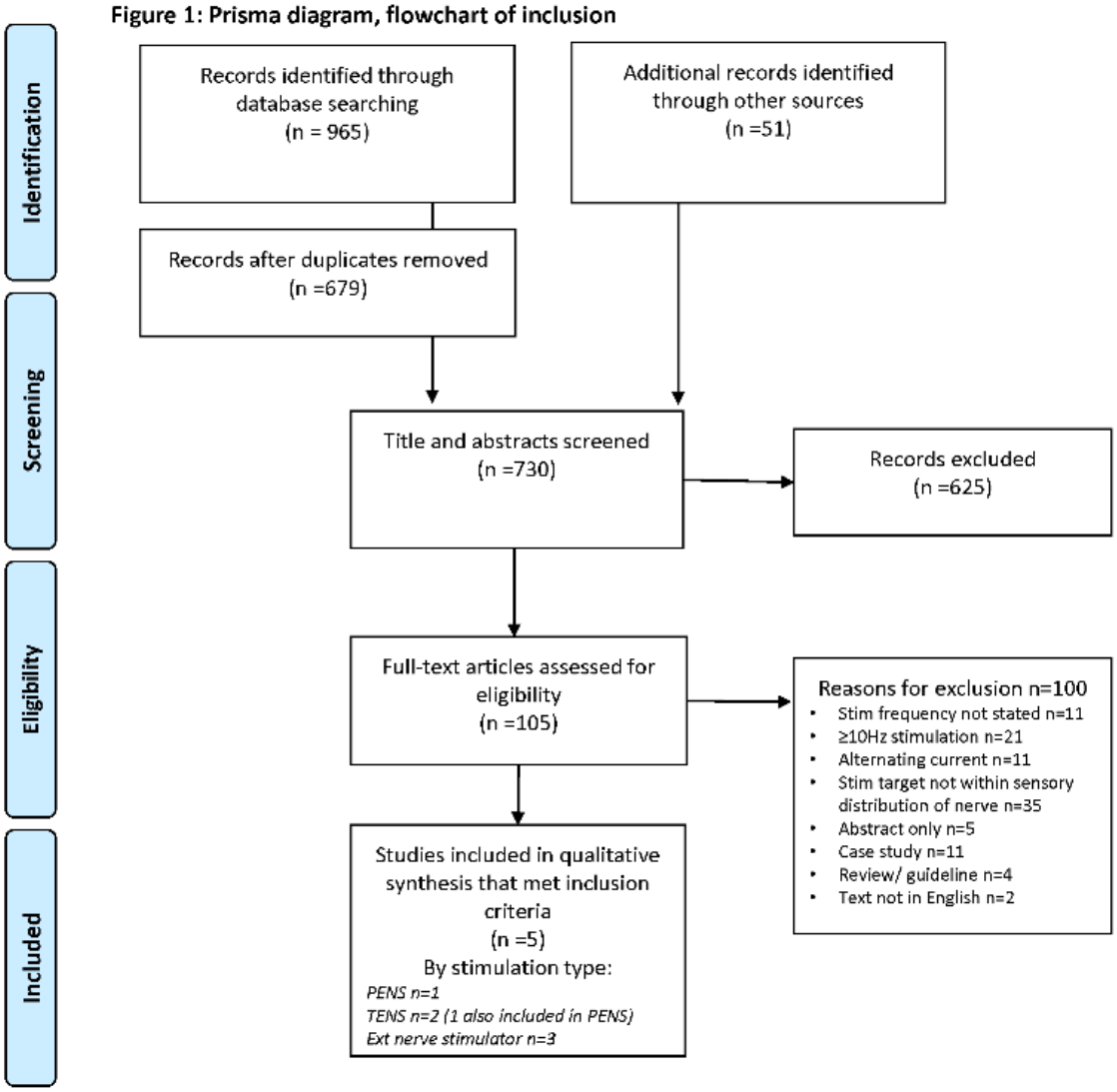
Data synthesis

Due to methodological heterogeneity, a quantitative review was not attempted. Data were synthesised according to the stimulator device, relevant stimulation parameters and outcomes of pain or stimulus-evoked pain.

Results

Searches of electronic databases returned 961 records, and 679 abstracts after removing duplicates. 51 additional articles were identified via references of which 625 were excluded resulting in 105 full-text review articles. The final narrative represents the inclusion of 5 studies, of which two were by our team (Fig 3.1), reasons for the exclusion of neurostimulation types are listed in table 3.3. Modalities of spinal cord stimulation (SCS), dorsal root ganglion stimulation, deep brain stimulation, and transcranial magnetic stimulation were additionally excluded as they were stimulated over the 10Hz frequency. Study characteristics are provided in table 3.4. No literature was found that described stimulation between 4-10Hz. Therefore, within the results, the term low frequency refers to stimulation delivered at ≤4Hz.

Figure 3.1 Prisma diagram of LFS



Neurostimulator	Description	Reasons for exclusion
Percutaneous peripheral nerve stimulation (PNS)	Stimulation of peripheral nerves using implanted devices	Stimulation frequency either >10 Hz or described only as a wide frequency range that would be unlikely to reflect consistent use of low-frequency stimulation e.g., 1-200Hz.
Occipital nerve stimulation	Electrical stimulation of the	No description of stimulation frequency,

(ONS)	greater occipital nerve	or range described as 60-130Hz
Trigeminal nerve stimulation	Electrical stimulation to branches of the trigeminal nerve either using implantable or external electrodes.	No description of stimulation frequency, or frequency described as high-frequency stimulation.
Peripheral nerve field stimulation (PNFS)	Placement of PNS leads within subcutaneous peripheral receptive “fields” of a single nerve.	No description of stimulation frequency, or range described as 15Hz-120Hz
Transcranial magnetic stimulation (TMS)	A non-invasive procedure that uses magnetic fields to stimulate a specific area of the brain	Stimulation frequency >10 Hz
Deep Brain stimulation (DBS)	Electrical stimulation to specific targets in the brain by implantable electrodes	Stimulation frequency >10 Hz
Spinal cord stimulation (SCS)	Electrical stimulation of the spinal cord by implantable electrodes	Stimulation frequency >10 Hz
Dorsal root ganglion stimulation (DRG)	Electrical stimulation of the dorsal root ganglion by implantable electrodes	Stimulation frequency >10 Hz

Table 3.3: Summary of neurostimulation devices *not* included in this review

Table 3.4: LFS study characteristics

	Sample and Method	Stimulation Parameters	Stimulation Intensity	Duration and frequency of treatment	Outcomes
Ghoname 1999[14]	64 patients with sciatica in a single-blind randomized sham-controlled cross over trial comparing sham-PENS, PENS, TENS, and exercise therapies	0 Hz Sham PENS 4 Hz PENS 4 Hz TENS	Highest tolerable amplitude without muscle contractions	30 mins, 3 x week for 3 weeks- with 1 week 'off' between treatments	VAS pain- VAS activity VAS sleep SF-36 *24hrs after treatment*
Forst 2004[15]	19 patients with DPN in a randomized double-blind parallel-group design comparing TENS to sham TENS	Active= 4 Hz Sham = 0Hz	Not described	20-30 mins x 6 weeks, daily frequency unclear	NTSS-6 VAS post-treatment
Sierakowski 2016[16]	72 patients with neuropathic pain in the upper limb were treated with external noninvasive peripheral nerve stimulation in a single site prospective non-controlled study.	2Hz	Just below the level of discomfort	10 mins 1x week for up to 8 sessions	VAS post-treatment Duration of pain relief
Johnson 2015a[17]	20 patients with either complex regional pain syndrome or neuropathic pain following nerve injury were treated with external noninvasive peripheral nerve stimulation in a 3-stage single-site prospective non-controlled study. Stage 1= treatment 1 x week for 6 weeks, stage 2= 6-week home loan, stage 3 = 6 weeks of no treatment.	2Hz	Maximal tolerable level	Stage 1: 10 mins 1x week Stage 2: 10 mins duration frequency determined by the patient Stage 3: no treatment	NRS BPI Duration of pain relief The surface area of allodynia EQ-5D-3L
Johnson 2015b [18]	Long term follow up of 5 patients from [17], average follow of 3.5 years.	2 Hz	Maximal tolerable level	Minimum of 10 minutes and frequency determined by the patient.	NRS average and worst pain

Key: CLBP= chronic low back pain, PENS= percutaneous electrical nerve stimulation, TENS = transcutaneous electrical nerve stimulation, Hz= hertz, mA= milli amps DPN= diabetic peripheral neuropathy, LFS= low-frequency nerve stimulation, Mins= minutes, VAS= visual analogue scale, NTSS-6= neuropathy total symptom score, NRS= numerical rating scale, BPI= brief pain inventory, EQ-5D-3L= Euroqol quality of life measure.

Quality

Study quality was variable overall; the main identified limitations are listed below.

Quality assessment of RCTs (n=2).

Table 3.5: Quality assessment of included RCTs using Cochrane Risk of bias tool 2.

First Author[(ref)]	Bias arising from randomisation	Bias due to deviations from intended interventions	Bias due to missing outcome data	Bias in measurement of outcome	Bias in selection of reported result	Final bias assessment	Study quality is limited by the small sample size
Ghoname [14]	SOME	SOME	SOME	HIGH	HIGH	HIGH	NO
Forst [15]	LOW	HIGH	SOME	HIGH	SOME	HIGH	YES

i) *Randomisation bias* was described as some with the Ghoname et al trial as allocation concealment was unclear.

ii) In both studies, *Bias associated with deviations from intended interventions* was also found. Within the Forst et al[15] study this was considered high as blinding was not described, whilst within the Ghoname et al[14] study description of blinding was unclear.

iii) *Missing outcome data bias*: Neither study included a description of sensitivity analysis or reasons for withdrawal.

iv) *Measurement of outcome bias* was associated with the following:

   a. Patients were not excluded that had prior subject knowledge and control was used that produced no active stimulation.

   b. Assessment of blinding was not described.

v) *Reported outcome bias* was high in the Ghoname study[14] as reported outcomes were not stated in the statistical methods section therefore it could not be determined whether these were pre or post protocol additions. Whilst in both studies missing data was not accounted for or described.

vi) In the Forst et al study [15], sample size n=19 was considered to limit quality. Small sizes ≤20 were considered too small to draw yield reliable or precise estimates [19].

Quality assessment of case series n=3.

Table 3.6: Quality assessment of non-randomized trials using The Joanna Briggs Institute Critical Appraisal tool for Case series studies.

Intervention type	Ext non-invasive low-frequency nerve stimulation		
Authors	Sierakowski [16]	Johnson [17]	Johnson [18]
Major components			
1. Were there clear criteria for inclusion in the case series?	Y	Y	N
2. Was the condition measured in a standard, reliable way for all participants included in the case series?	N	Y	N
3. Were valid methods used for identification of the condition for all participants included in the case series?	N	Y	N
4. Did the case series have consecutive inclusion of participants?	Y	Y	N
5. Did the case series have the complete inclusion of participants?	Y	Y	N
6. Was there clear reporting of the demographics of the participants in the study?	N	Y	N
7. Was there clear reporting of clinical information of the participants?	N	Y	N
8. Were the outcomes or follow up results of cases clearly reported?	N	Y	N
9. Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	Y	Y	Y
10. Was statistical analysis appropriate?	N	Y	N
11. Study quality is limited by the small sample size	U	Y	Y
N= No, Y= yes, N/A= not applicable or not relevant in terms of study design, U= unclear.			

i) *Condition measurement bias* was found for both Johnson [18] and Sierakowski [16] due to limited description of the patient's baseline characteristics and previous treatments.

ii) Moderate *identification bias* was found for Johnson [18] and Sierakowski [16] as patient identification did not include a standardised measurement.

iii) Statistical analysis was not considered appropriate when:

   a. Missing data were not accounted for or described (Johnson [18] and Sierakowski [16])

   b. Studies did not adequately describe statistical methods (Johnson [18] and Sierakowski [16])

iv) A high attrition rate (> 20%) was described by Johnson [17], however, this was the only study to describe reasons for withdrawal.

v) Study quality was also often limited by small sample sizes (≤20) in both of the Johnson et al studies.

Percutaneous electrical nerve stimulation (PENS)

PENS involves the electrical stimulation of individual nerves or dermatomes via fine gauge needles inserted near the nerve or dermatome associated with the pain.

One study met the inclusion criteria [14].

Pain outcomes and stimulation parameters.

Ghoname et al conducted a single-blinded (investigator) randomized sham-controlled cross-over trial comparing low frequency percutaneous electrical nerve stimulation (PENS), and low-frequency transcutaneous electrical nerve stimulation (TENS) to sham PENS (n=64) for the treatment of sciatica[14]. All patients received the three modalities according to one of three different sequences: (1) Sham ± PENS ± TENS; (2) PENS ± TENS ± Sham; or (3) TENS ± Sham ± PENS. Each treatment was administered for 30 min, three times per week, for 3 weeks, with 1 week *'off'* between each modality. All patients received all three modalities over the 11 weeks. Both PENS and TENS treatments were delivered at a stimulation frequency of 4 Hz, a pulse width of 0.1m/s and were adjusted to produce the highest tolerable amplitude without muscle contractions. The sham PENS delivered no electrical output. The sham PENS and active PENS were connected to 5 bipolar leads (with each lead connected to 1 positive and 1 negative probe) and therefore used a total of 10 needles placed in the territory of the sciatic nerve. The TENS used 4 medium-sized (2.5-cm) cutaneous electrode pads placed along the course of the sciatic nerve. A visual analogue scale (VAS) scores for pain intensity, level of activity and quality of sleep 24hr before receiving the first treatment (before) and 24hr after the last treatment (after) were assessed for each modality, with 0= best and 10= worst. For spontaneous pain intensity, they report for both PENS and TENS significant improvements in before and after scores $p<0.05$ (PENS= 7.2 - 4.1, ±1.6, TENS =7.0-5.4 ±1.9), and minimal change for sham PENS (6.6 - 6.1, ±1.9). For the level of activity and quality of sleep, they also report for both PENS and TENS significant improvements in before and after scores

p<0.05 (PENS= activity 6.4 - 4.0, ±1.9; sleep 5.5 - 3.1, ±1.9, TENS = activity 5.8 – 4.5 ±1.7, sleep 5.0-4.0 ±2), and minimal change for sham PENS (activity 6.0 – 5.5, ±2; sleep 5.2-4.9, ± 1.9). Across all these outcome domains PENS was significantly different from sham-PENS and TENS, P< 0.01, and confidence intervals were not described.

TENS

TENS involves the application of variable electrical frequencies typically using adhesive electrodes and transcutaneous electrodes placed directly on the skin surface. One study was found that met the inclusion criteria[15].

Pain outcomes and stimulation parameters.

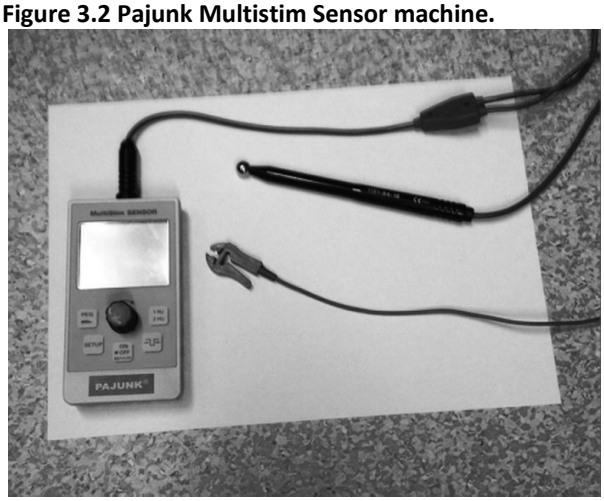
Forst et al conducted a double-blind, randomised study that compared TENS with a placebo TENS, in 19 patients (8 patients per group) suffering from mild-to-moderate symptomatic diabetic neuropathy affecting the feet [15]. The severity of neuropathy was defined using the neuropathy total symptom score (NTSS-6), with the total symptom score ranging between 4 and 16. Stimulation pads were placed at the anatomical localisation of the peroneal nerve and stimulation was performed either using the 2Hz stimulation or an electrically inactive device for periods of 30minutes once a day. Further stimulation parameters were not described. At baseline, after 6, and 12 weeks of treatment, the patients' symptoms were registered using the new total symptom score (NTSS-6) and a visual analogue scale (VAS). They reported significant improvement in NTSS-6 score after 6 weeks (-42 %) and after 12 weeks (-32 %) of treatment for the active TENS group but no significant change associated with the sham treatment (baseline: 10.0±3.3, 6 weeks: 5.8± 5.0, p<0.05; 12 weeks: 6.8±3.9, p=0.05; placebo group: baseline: 7.6±3.1; 6 weeks: 8.1±5.1, n.s.; 12 weeks: 6.5±6.1, non-significant). A significant improvement in the VAS rating was found after 6 weeks of TENS therapy (19.8±5.0 to 14.4±9.6; p<0.05), which was maintained at 12 weeks, while no change was observed in the placebo arm. Sub analysis of the different qualities of the NTSS-score revealed an improvement in allodynia (1.4±1.6 to 0.5±1.0; p<0.05), but also numbness (2.2±1.0 to 1.6±1.3; p<0.03) and

lancinating pain (1.6±1.1 to 0.6±0.9; p<0.02) at 12 weeks, while no change was observed in the placebo arm. The observed reduction in reported allodynia would support LTD induction.

External noninvasive low-frequency nerve stimulation

Two prospective studies and one retrospective follow-up, using a spherical nerve-mapping probe that is placed over the skin to electrically stimulate the peripheral nerve, were identified [16–18] as illustrated in Figure 3.2.

Figure 3.2 Pajunk Multistim Sensor machine.



A retrospective follow-up study was considered too small and problematic in terms of potential bias to provide any useful evidence.

Pain outcomes and stimulation parameters.

Both prospective studies used the same device (Pajunk multistim sensor, Pajunk Germany- Fig 3.2) and were stimulated at frequencies of 2 Hz for periods of 10 minutes. Sierakowski et al evaluated response in 72 consecutive patients with neuropathic pain in the upper limb [16]. Patients were treated once a week for an average of 8 weeks. Stimulation was delivered in the territory of the affected nerve at a frequency of 2 Hz, at an intensity just below the level of discomfort. Following all treatments, the largest recorded pain reduction for each patient was used to calculate overall improvement (range or variation in this score is not provided). An overall pain reduction from 8.4 (SD 1.6) before treatment to 4.2 (SD 3.5) afterwards ($p < 0.001$) was reported. The study also used a

grading system to quantify the duration of pain relief. 'Cure' occurred in 8/72 (11%) cases and describes complete pain resolution with no recurrence during the follow-up period. 39% (28/72) of cases experienced pain relief lasting between 1 day to 1 week, whilst 51% (37/72) of patients had no benefit (< 1-day relief). All patients with a positive effect were followed up for 6 months, 77% of these (28/36) had ongoing benefit whilst 8 had terminated their follow up (reasons not stated).

The smaller study by Johnson et al recruited 20 patients referred to a tertiary pain clinic with a diagnosis of either complex regional pain syndrome or neuropathic pain after peripheral nerve injury [17]. Participants completed three stages of treatment: stage 1, six weekly treatment sessions; stage 2, six-week equipment home loan; stage 3, six weeks of no treatment. Stimulation was delivered in the territory of the affected nerve using a frequency of 2Hz and a pulse width of 1.0m/s. The intensity was gradually increased from 0 mA to the maximum level tolerable (motor responses were accepted). Results show a significant reduction of 2.8 NRS, 95% CI 1.6–4.0, $p < 0.001$, intention-to-treat analysis), with 55% (11/20) of patients reporting ≥50% pain reduction. The treatment effect durations were relatively stable throughout the study period and no cumulative effect with treatment was observed. Within stage 3 (no treatment) a trend toward baseline mean scores was observed, suggesting some treatment frequency is needed to maintain efficacy. Significant reduction in surface areas of allodynia following stage 1 ($p=0.001$; the sum of positive and negative ranks: 131, −22.00), and stage 2 ($p=0.008$; the sum of positive and negative ranks: 133, −20.00). A reduction in surface areas of allodynia would be in keeping with the possible induction of LTD.

Discussion

The objective of this systematic review was to consider potential neurostimulator therapies for neuropathic pain where induction of LTD via LFS may be a possible working mechanism. All 5 studies showed a reduction in pain intensity following repeated treatment using stimulation of ≤4Hz for periods of 10- 30 minutes or longer. The evidence from these 5 studies, therefore, suggests that LFS is effective in terms of pain reduction for chronic neuropathic pain. The magnitude of effect appears

to vary greatly across studies, and between-study comparisons were limited by the heterogeneity of study methods. Evidence to support LTD as the working mechanism underpinning therapeutical success was limited and further evidence of effect is required.

Measurement of LTD

LTD describes a reduction in synaptic efficacy[20]. LTD in response to LFS has been demonstrated as a reduction in heightened somatosensory evoked potentials and pain responses to a cutaneous stimulus in experimentally induced pain states [4–6]. This review highlights that for most clinical studies the primary outcome was the reduction in spontaneous pain intensity. Although a reduction in spontaneous pain may follow a reduction in stimulus-evoked pain, it does not necessarily demonstrate a reduction in synaptic efficacy and may also reflect effects other than LTD. Therefore, to confidently evaluate whether LTD is a plausible mechanism of action, the additional inclusion of an outcome measure that illustrates a reduction in pain sensitivity to evoked painful stimulus studies would be needed. Two out of the five included LFS studies contained measures that quantified a change in evoked pain responses [15,17]. In both of these studies, a reduction of allodynia was measured [15,17], one included an objective measure[17], whilst the other reported change in subjective measures of pain quality including reported allodynia[15]. The inclusion of these outcomes in both studies demonstrated that LFS suppressed heightened pain responses and would support the presence of LTD. Therefore, assessments that additionally measure changes in evoked pain responses should be considered for trials where LTD could be considered the mechanism of action.

Stimulation parameters and delivery

Stimulation frequency

LTD in experimental research is optimally achieved at 1-2 Hz stimulation, with declining effect outside of this range and no effect observed at frequencies of 10 Hz[4,5,21]. Hence, frequencies of <10Hz were considered plausible for induction of LTD. No literature was found that described

stimulation between 4-10Hz and therefore LFS within this review refers to stimulation delivered at ≤4Hz.

One of the included studies stimulated using PENS and TENS at 4 Hz whilst for the further 4 studies stimulation using TENS or external peripheral nerve stimulation was described at 2 Hz. The small number of studies identified reflects that LFS is currently not widely considered. Within the screened literature the term low frequency stimulation referred to stimulation delivered at a frequency of 4 Hz for studies examining PENS, and no studies were identified that explored stimulation below this frequency. Further studies examining the use of PENS in other pain conditions have suggested that improved analgesic responses may be achieved by using higher frequencies of 50-100 Hz[22,23]. Higher frequency stimulation would involve mechanisms other than LTD. The LTD literature suggests LTD is optimally achieved at 1-2 Hz stimulation, with declining effects below and above these frequencies[4,5,21]. Therefore, it is possible within these studies stimulation was not within the optimal range to induce LTD and future studies could consider lower frequencies with LTD optimisation in mind.

Stimulation electrode

Experimental induction of LTD via LFS has illustrated that the shape of the electrode is of importance. This is because LTD is associated with the preferential activation of A-δ fibre afferents, which typically require high current density to achieve adequate depth of penetration [6]. Studies examining different electrode shapes have found intraepidermal electrodes or small spherical percutaneous electrodes best achieve the required current density to activate the A-δ fibre afferents required to induce LTD[21,24]. Therefore, PENS therapy and the spherical pen-shaped electrode used for external peripheral nerve stimulation would both theoretically be capable of achieving the high current density required to induce LTD. Conversely, the flat surface electrodes used with TENS would make it challenging to achieve the required current density to adequately stimulate A-δ fibres and induce LTD without using a very high stimulation strength, which evidence shows few patients can

tolerate [25,26]. Consequently, TENS has been shown in experimentally induced neuropathic pain models to be more typically associated with activation of larger diameter A-beta nerve fibres that do not require high current density stimulation [27,28]. It is therefore unlikely that low-frequency TENS therapy was associated with LTD.

Stimulation intensity

The strength of stimulation has additionally been found to be important in terms of LTD induction. A-δ fibres are preferentially activated at intensities perceived as sharp and painful [5,6], whereas stimulation at lower intensities has been suggested to mainly activate Aβ fibres not associated with LTD [10]. Some degree of pain with the electrical stimulus is thus required to obtain LTD [2]. Evidence from studies in healthy human subjects suggests stimulation strengths of 2- 4 times pain perception are associated with sustained depression of pain perception[5,6]. Pain threshold is defined as the minimum intensity of a stimulus that is perceived to be painful[29]. Further evidence in healthy human subjects suggests strengths below 1-time pain threshold and above 5 times pain threshold produce less pronounced LTD than strengths between 2-5 times pain threshold [30]. These combined results are suggestive of a u-shaped relationship concerning the intensity of stimulation and the strength of LTD. Out of the five included studies, 3 included some description of stimulation strength. Ghoname et al in the PENS study described stimulation intensity was delivered at the highest tolerable amplitude without muscle contractions[14]. In the external non-invasive nerve stimulation studies; Johnson et al stimulated at the maximum level tolerable (motor responses were accepted)[17], whilst Sierakowski et al describe stimulation just below the level of discomfort[16]. These descriptions would imply that a degree of painfulness was associated with stimulation for both the Ghoname et al and Johnson et al studies, however, it is also possible that stimulation was too strong in some cases to achieve optimal LTD. The Sierakowski study stimulated just below discomfort, and therefore it is unlikely the stimulus was perceived as painful, which is considered necessary for induction of LTD. Within the Sierakowski study, the primary outcome was pain reduction on an NRS following treatment compared to baseline. The post-treatment score was taken as the largest recorded pain

reduction out of a total of 8 treatment sessions. The range or variation in the post-treatment scores following each treatment is not provided, and therefore, it is not clear whether pain reduction was consistent following each treatment session. Additionally, a strong placebo response cannot be excluded in the absence of a control group.

Future trials need to consider how optimal stimulation strength is achieved and how this is described. This is more challenging for trials where the control has no perceivable output.

Stimulation duration

There is evidence from animal studies that stimulation of at least 900 pulses is required to achieve the prolonged rise in calcium to activate calcineurin. Calcineurin is a calcium-dependent phosphate implicated in LTD [8,9]. In human studies pulse durations of at least, 900 - 1200 pulses have been shown to produce the most pronounced reduction in pain responses, with some suggestion that even longer pulse durations if tolerated would be beneficial [5]. The two non-invasive peripheral nerve stimulation trials stimulated for 10 mins [16,17], whilst the TENS study stimulated for 20-30 mins and the PENS study stimulated for 30 min periods. Therefore, all included studies would have achieved the required 900 pulses deemed essential to influence the intracellular Ca2+ concentration and phosphate binding that is important to LTD induction.

Summary of stimulation parameters and delivery

Stimulation parameters conducive to LTD induction in experimental studies were observed in four of the five reviewed neurostimulation studies [14,16–18], two of which were uncontrolled trials of external non-invasive peripheral nerve stimulation (2Hz), with a high risk of bias in many areas including high attrition[16,17]. The third retrospective follow-up study was considered too small and problematic in terms of potential bias to provide any useful evidence[18]. The fourth study was a controlled study examining minimally invasive PENS (4Hz) [14]. All studies support that significant and stable pain reduction can be achieved in response to LFS. There is, therefore, limited evidence supporting

treatments where LTD could be plausible and merits further exploration alongside other established stimulation methods.

Limitations

The review highlighted several methodological limitations in the literature, such as high bias related to reporting of outcomes and handling of outcomes.

A further limitation of the controlled trials was that both utilised a device with no stimulation output. How the absence of paresthesia was explained to patients and the success of blinding is not described, therefore, it is not possible to evaluate the success of the intended sham. The creation of a valid sham that produces some sensation of paresthesia without providing the therapeutic benefit is a challenging area for all controlled trials of neurostimulation but is needed to improve the quality of future studies[31]. Additionally, this may also help reduce the high attrition rates that were seen in many studies.

A large number of trials were excluded from the current review on the basis that stimulation parameters were not adequately described, and this was considered a major limitation of the general neurostimulation literature. The manipulation of programming parameters has the potential for preferential targeting of different fibres to produce different effects [32,33]. Therefore, to improve outcomes, consideration should be given to programming parameters and potential mechanisms of action. Failure to describe programming parameters in the neuromodulation literature has been recognised and there have been recent calls for future neuromodulation studies to provide more detail regarding programming parameters [31,34].

Evidence implies that mechanisms of LTP and LTD reflect centrally mediated mechanisms such as central sensitisation rather than peripheral mechanisms[2]. Therefore. LTD is likely to have greater relevance for patients displaying a predominant 'mechanical hyperalgesia' sensory phenotype and who specifically demonstrated mechanical dynamic allodynia and secondary hyperalgesia [30,31]. Patients with peripheral nerve injury demonstrate high rates of positive sensory signs associated

with this phenotype, specifically dynamic mechanical allodynia and pinprick hyperalgesia [35]. Therefore, patients with this pain type may be more receptive to treatment where LTD is the proposed working mechanism. Stratification of patients, according to specific sensory profiles based on mechanistic understanding of sensory profiles, could therefore be helpful to future studies but is generally not considered within the current neuromodulation literature. The idea of stratifying patients with neuropathic pain based on sensory profiles is not new and seminal work has already commenced in this area [35,36]. Trials designed with this in mind may also demonstrate even better outcomes as treatment becomes more personalized and appropriate.

Conclusion

We found evidence to support pain reduction associated with LFS, whilst evidence to support LTD in chronic neuropathic pain was limited. The review highlights that few studies justify treatment either based on the mechanism of action or stimulation parameters. Future neurostimulation trials that additionally consider the mechanism of action have the potential to help better stratify patients and treatment selection and improve outcomes. The need to improve currently poor treatment outcomes for patients with peripheral neuropathic pain has already been described as a clinically unmet need [37,38]. Therefore, there is good justification to further explore neurostimulation treatments that could be associated with benefits for this pain group. This systematic review identified four studies that potentially support LTD as a working mechanism. One evaluated the use of 4Hz PENS for sciatica. As suggested, lower frequency stimulation is generally considered optimal for the induction of LTD, however, there is currently no evidence for PENS at delivered at lower frequencies. PENS is a minimally invasive form of treatment, and therefore, requires repeated hospital visits to administer treatment. Two prospective case series studies treated neuropathic pain conditions where LTD would be considered a relevant mechanism and provided promising results in terms of efficacy [16,17]. A further retrospective follow-up study that utilised similar parameters was considered too small and problematic in terms of potential bias to provide any useful evidence[18].

Neither of the prospective studies employed a control arm, therefore, the review highlights a gap in current evidence, and future studies are needed that a) confirm LTD is the working mechanism and ii) confirm efficacy with RCTs.

Chapter 3 References

1. Sandkühler J. Understanding LTP in pain pathways. *Mol Pain*. 2007;3:9. Published 2007 Apr 3. doi:10.1186/1744-8069-3-9

2. Lang S, Klein T, Magerl W, Treede RD. Modality-specific sensory changes in humans after the induction of long-term potentiation (LTP) in cutaneous nociceptive pathways. *Pain*. 2007;128(3):254-263. doi:10.1016/j.pain.2006.09.026

3. Sandkühler J, Sandkuhler J. Models and mechanisms of hyperalgesia and allodynia. *Physiol Rev*. 2009;89(2):707-758. doi:10.1152/physrev.00025.2008

4. Klein T, Magerl W, Hopf HC, Sandkühler J, Treede RD. Perceptual correlates of nociceptive long-term potentiation and long-term depression in humans. *J Neurosci*. 2004;24(4):964-971. doi:10.1523/JNEUROSCI.1222-03.2004

5. Jung K, Rottmann S, Ellrich J. Long-term depression of spinal nociception and pain in man: Influence of varying stimulation parameters. *Eur J Pain*. 2009;13(2):161-170. doi: 10.1016/j.ejpain.2008.04.001

6. Rottmann S, Jung K, Ellrich J. Electrical low-frequency stimulation induces homotopic long-term depression of nociception and pain from hand in man. *Clin Neurophysiol*. 2008;119(8):1895-1904.doi:10.1016/j.clinph.2008.02.022

7. Mücke M, Cuhls H, Radbruch L, Weigl T, Rolke R. Evidence of heterosynaptic LTD in the human nociceptive system: Superficial skin neuromodulation using a matrix electrode reduces deep pain sensitivity. *PLoS One*. 2014;9(9). doi:10.1371/journal.pone.0107718

8. Xia Z, Storm DR. The role of calmodulin as a signal integrator for synaptic plasticity. *Nat Rev Neurosci*. 2005;6(4):267-276. doi:10.1038/nrn1647

9. Yasuda H, Higashi H, Kudo Y, et al. Imaging of calcineurin activated by long-term depression-inducing synaptic inputs in living neurons of rat visual cortex. *Eur J Neurosci*. 2003;17(2):287-297. doi:10.1046/j.1460-9568.2003.02449.x

10. Sandkühler J, Chen JG, Cheng G, Randić M. Low-frequency stimulation of afferent aδ-fibres induces long-term depression at primary afferent synapses with substantia gelatinosa neurons in the rat. *J Neurosci*. 1997. doi:10.1523/jneurosci.17-16-06483.1997

11. Randic M, Jiang MC, Cerne R. Long-term potentiation and long-term depression of primary afferent neurotransmission in the rat spinal cord. *J Neurosci*. 1993;13(12):5228-5241. doi: 10.1523/JNEUROSCI.13-12-05228.1993.

12. Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing the risk of bias in randomised trials. *BMJ*. 2019;366:l4898. Published 2019 Aug 28. doi:10.1136/BMJ.l4898

13. Moola, S., Munn, Z., Tufanaru, C., Aromataris, E., Sears, K., Sfetcu, R., Currie, M., Qureshi, R., Mattis, P. and Lisy, K., 2022. [online] Reviewersmanual.joannabriggs.org. Available at: <https://reviewersmanual.joannabriggs.org/.> [Accessed 12 January 2022].

14. Ghoname ESA, White PF, Ahmed HE, Hamza MA, Craig WF, Noe CE. Percutaneous electrical nerve stimulation: an alternative to TENS in the management of sciatica. *Pain*. 1999;83(2):193-199. doi:10.1016/S0304-3959(99)00097-4

15. Forst T, Nguyen M, Forst S, Disselhoff B, Pohlmann T, Pfützner A. Impact of low frequency transcutaneous electrical nerve stimulation on symptomatic diabetic neuropathy using the new Salutaris device. *Diabetes Nutr Metab*. 2004;17(3):163-168.

16. Sierakowski A, Jing SS, Poel J, Elliot D. Transcutaneous Peripheral Nerve Stimulation for the Treatment of Neuropathic Pain in the Upper Limb. *J Hand Surg Asian-Pacific*. 2016;21(1):37-43. doi:10.1142/S2424835516500041

17. Johnson S, Ayling H, Sharma M, Goebel A. External Noninvasive Peripheral Nerve Stimulation Treatment of Neuropathic Pain: A Prospective Audit. *Neuromodulation*. 2015;18(5):384-391. doi:10.1111/ner.12244

18. Johnson S, Goebel A. Long-Term Treatment of Chronic Neuropathic Pain Using External Noninvasive External Peripheral Nerve Stimulation in Five Patients. *Neuromodulation*. 2015;18(5):384-391. doi:10.1111/ner.12365

19. Hackshaw A. Small studies: strengths and limitations. *Eur Respir J*. 2008;32(5):1141-1143. doi:10.1183/09031936.00136408

20. Ikeda H, Stark J, Fischer H, et al. Synaptic amplifier of inflammatory pain in the spinal dorsal horn. *Science (80-)*. 2006;312(5780):1659-1662. doi:10.1126/science.1127233

21. Ghoname ESA, Craig WF, White PF, et al. The effect of stimulus frequency on the analgesic response to percutaneous electrical nerve stimulation in patients with chronic low back pain. *Anesth Analg*. 1999;88(4):841-846. doi:10.1213/00000539-199904000-00030

22. Ahmed HE, Craig WF, White PF, et al. Percutaneous electrical nerve stimulation: an alternative to antiviral drugs for acute herpes zoster. *Anesth Analg*. 1998;87(4):911-914. doi:10.1097/00000539-199810000-00031

23. Mouraux A, Iannetti GD, Plaghki L. Low intensity intra-epidermal electrical stimulation can activate Aδ-nociceptors selectively. *Pain*. 2010;150(1):199-207. doi:10.1016/j.pain.2010.04.026

24. Gibson W, Wand BM, O'Connell NE. Transcutaneous electrical nerve stimulation (TENS) for neuropathic pain in adults. *Cochrane Database Syst Rev*. 2017;9(9): CD011976. Published 2017 Sep 14. doi:10.1002/14651858.CD011976.pub2

25. Sluka KA, Bjordal JM, Marchand S, Rakel BA. What Makes Transcutaneous Electrical Nerve Stimulation Work? Making Sense of the Mixed Results in the Clinical Literature. *Phys Ther*. 2013;93(10):1397-1402. doi:10.2522/PTJ.20120281

26. Nilsson H-J, Levinsson A, Schouenborg J. Cutaneous field stimulation (CFS): a new powerful method to combat itch. *Pain*. 1997;71(1):49-55. doi: 10.1016/s0304-3959(97)03339-3.

27. Vera-Portocarrero LP, Cordero T, Billstrom T, Swearingen K, Wacnik PW, Johanek LM. Differential effects of subcutaneous electrical stimulation (SQS) and transcutaneous electrical nerve stimulation (TENS) in rodent models of chronic neuropathic or inflammatory pain. *Neuromodulation*. 2013;16(4):328-335. doi:10.1111/ner.12037

28. Coons MJ, Steglitz J. Pain Threshold. In: *Encyclopedia of Behavioral Medicine*. Springer, New York, NY; 2013:1427-1428. doi:10.1007/978-1-4419-1005-9_1160

29. W. Magerl, F. Henrich, L. Röhring, D. Pfau, T. Klein RT. Poster PF0343 : Reversal of LTP-like hyperalgesia by low-frequency electrical stimulation - 16th World Congress on Pain - Built with CrowdCompass by Cvent. In: *16th World Congress On Pain, Yokohama 2016 Abstracts*; 2016. https://event.crowdcompass.com/wcp2016/activity/ozu0y7GLko. Accessed January 19,

2021.

30. Katz N, Dworkin RH, North R, et al. Research design considerations for randomized controlled trials of spinal cord stimulation for pain. *Pain*. 2021;162(7):1935-1956. doi:10.1097/j.pain.0000000000002204

31. Linderoth, B & Foreman, RD. Conventional and Novel Spinal Stimulation Algorithms: Hypothetical Mechanisms of Action and Comments on Outcomes. *Neuromodulation*. 2017;20(6):525-533. doi:10.1111/NER.12624

32. Caylor J, Reddy R, Yin S, et al. Spinal cord stimulation in chronic pain: evidence and theory for mechanisms of action. *Bioelectron Med*. 2019;5(1). doi:10.1186/S42234-019-0023-1

33. Hofmeister M, Memedovich A, Brown S, et al. Effectiveness of Neurostimulation Technologies for the Management of Chronic Pain: A Systematic Review. *Neuromodulation*. 2020;23(2):150-157. doi:10.1111/NER.13020

34. Vollert J, Maier C, Attal N, et al. Stratifying patients with peripheral neuropathic pain based on sensory profiles: Algorithm and sample size recommendations. *Pain*. 2017;158(8). doi:10.1097/j.pain.0000000000000935

35. Baron R, Maier C, Attal N, et al. Peripheral neuropathic pain: A mechanism-related organizing principle based on sensory profiles. *Pain*. 2017;158(2):261-272. doi:10.1097/j.pain.0000000000000753

36. Moisset X, Bouhassira D, Attal N. French guidelines for neuropathic pain: An update and commentary. *Rev Neurol (Paris)*. 2021;177:834-837. doi:10.1016/j.neurol.2021.07.004

37. Finnerup NB, Kuner R, Jensen TS. Neuropathic Pain: From Mechanisms to Treatment. *Physiol Rev*. 2020;101(1):259-301. doi:10.1152/PHYSREV.00045.2019

Chapter 4: Sham controls in interventional pain trials – tricky in practice

Introduction

The previous chapter highlighted that a limitation in many neurostimulation trials is the absence of a credible and valid sham control. This chapter, therefore, considers some of the issues surrounding the use of sham-controlled trials within interventional pain trials. When considering this issue, it is important to recognize why a trial would require a sham control.

To ensure patients receive the best available care for their condition and to limit the potential harms associated with patients being exposed to ineffective treatments high-quality evidence is required. Randomised controlled trials (RCTs) are considered the 'gold standard' in research in terms of demonstrating treatment efficacy and producing high-quality evidence [1]. Within an RCT subjects are randomly allocated to either an experimental group or a control group and assessed for outcomes of interest. The most rigorous type of RCT is a 'double-blind RCT', where clinicians and participants are unaware of the treatment received. Within trials of this type, any bias that may arise from knowledge of treatment is presumably eliminated and any unspecified effects are fairly reflected[2].

A placebo control describes a treatment that is similar in every respect to the treatment being tested except that it does not contain the active component that is thought to be associated with the therapeutic effect [3]. Similarly, a sham control describes a procedure/ intervention designed to resemble the procedure or intervention being tested but that does not contain the component thought to be associated with a therapeutic effect [3,4]. Typically, the term 'placebo control' is used in pharmacological interventional trials where common placebos include inert tablets (like sugar pills) or inert injections (like physiological saline solution). Whilst the term 'sham control' is retained for interventional trials that examine devices, psychological and physical treatments (such as sham-controlled nerve stimulation or acupuncture).

The use of a sham-controlled randomised trial design, therefore, lends itself well to the conduct of double-blind RCTs as it facilitates high-quality evidence free of many forms of bias. However, a recent search of the Medline database revealed that of 8,233 interventional chronic pain studies only 340 (4%) employed a sham control [5]. One suggested reason for the low number of such trials is the understanding that the development of credible sham procedures is often challenging and may also require considerable resources [6]. Initial scoping searches of the literature suggested that there was a need for a comprehensive overview that synthesises all the available evidence to guide researchers in this area. Therefore, a narrative review was conducted to summarise relevant literature that describes the key issues and considerations relevant to researchers when designing sham-controlled interventional pain trials.

Methods

To describe the key issues and considerations in justifying the use of and designing a sham-control in interventional pain trials, we conducted a literature review. Databases searched were MEDLINE and Science Direct in addition to references to identified articles. Searches were limited to English and human studies with no date limits. An example search strategy was developed as below following consultation with a medical librarian Table 4.1.

Table 4.1. Example search strategy

Databases searched	Science direct and Medline
Search strategy	**Search Strategy – Medline (Ovid)** 1. Sham 2. control 3. device 4. intervent* 5. intervention* 6. 1 and 2 7. 3 or 4 or 5 8. 6 and 7 9. evaluat* 10. issue* 11. design 12. consideration* 13. problem* 14. 9 or 10 or 11 or 12 or 13 15. 8 and 14 Limit to (English language and humans)
* Denote where truncation was used as part of searches	

Searches were originally conducted in January 2019 and re-run and updated in April 2021. Articles were included if they described or discussed issues relating to the conduct or design of a sham-controlled trial. All abstracts identified from the database search were independently reviewed and screened by one reviewer. Data extraction included article characteristics of author, year, identified considerations for use of sham controls and main themes.

Results

Searches of electronic databases returned 499 records and 15 additional articles were identified via article references; 481 of these abstracts were excluded as not relevant, resulting in 43 articles which have informed the narrative review (Fig 4.1). The review has been sub-sectioned by the main identified themes and relevant subthemes (Table 4.2).

Figure 4.1 PRISMA flow chart

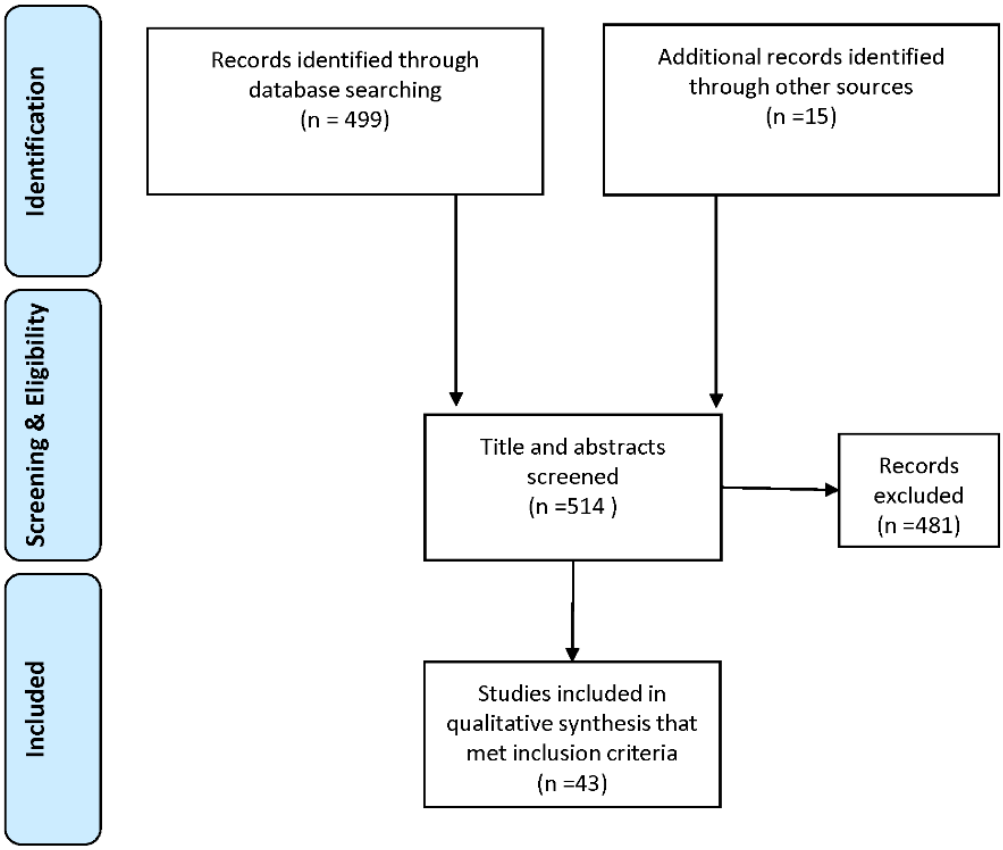


Table 4.2. Identified themes relevant to sham trial design and conduct.

Main Identified Themes	Sub- Themes
Study design	Parallel Group
	Cross-over design
	Enriched enrolment
Design issues relating to sham	Mechanism of action
	No perceivable output
	Sub-therapeutic dosing
	Testing of sham
Sources of bias and mitigating bias in sham trials	Blinding
	Assessment of blinding
	Clinical interactions
	Expectation
Study population	Placebo effects
Ethics	Equipoise
	Risk-benefit balance
	Informed consent
	Deliberate deception

Study design

The choice of study design has a significant bearing on the conduct of sham-controlled studies. The literature describes several study designs that include sham-controls, such as 'parallel-group', 'cross-over', and 'enriched-enrolment'. For each of these study designs, we discuss some of the highlighted issues relevant to the use of a sham control.

Parallel group

Within this study design patients are randomly assigned to either only the sham or active treatment arm[7]. The design facilitates subject blinding to treatment allocation because subjects can't directly compare active with sham treatments provided, they have no prior experience of the intervention or contact with other study patients. A limitation of this study design is that not all patients will receive the active treatment, which may adversely impact a patient's willingness to participate and needs to, therefore, be ethically justifiable. To aid study recruitment or retention an open-label extension after completion of the main study is desirable [8–10]. An open extension may sometimes also allow for extended evaluation of treatment effects; however, many patients may withdraw before this follow-on period if they experience adverse events, lack of treatment efficacy, or they may opt not to

continue treatment for other reasons [11,12]. Therefore, careful attention to biases such as patient selection bias needs to be considered as part of the method of analysis and study attrition needs to be clearly described and managed where open-label extension is used [12].

Cross-over design

In cross-over design studies patients are randomised to the active and sham treatment arms and subsequently cross-over to the alternative treatment following completion of the initial treatment [9,13]. The influence of inter-individual variability is minimised as subjects act as their own control. As all subjects are exposed to both active and control treatments, cross-over studies typically require fewer subjects to achieve the same statistical power as parallel designs and therefore are less costly. However, as subjects can compare their experience of both interventions there is a risk of subjects becoming effectively unblinded following cross-over. This is particularly salient for neurostimulation trials which involve an active device that produces a perceivable sensation, and a sham device produces no perceivable output. In an extreme example of such issues all patients correctly guessed their treatment allocation following cross-over, rendering the use of 'sham' pointless [14]. Attrition rates may also be high in the active-sham group with patients dropping out after crossing over [15].

Enriched enrolment

For most chronic pain treatments, profound clinical response is confined to a minority of patients and there will be subgroups that have no response at all [16]. There is therefore a danger that some treatments that potentially work well for subgroups of patients are dismissed as non-effective based on the results of conventional trials. Enriched enrolment studies exploit the observation that some treatments work better in some individuals than in others, by first exposing all patients to treatment and then only randomising patients who have demonstrated a good response to treatment [17]. As such it has been proposed that enrolment studies can help to identify the subgroups of patients who benefit from treatment and hence provide information relevant to clinical practice[16,17]. Currently, this method has been used mostly in drug trials. For example, enriched enrolment has been used in

several studies to evaluate the efficacy of opioids in comparison to placebo treatment within non-cancer pain trials [17,18]. Conversely, several systematic reviews have suggested that there is no difference in terms of pain outcomes between trials of this type and non-enriched studies in this area, creating some uncertainty regarding the value of an enrichment trial design [17,18]. A further caution suggested with this type of trial is that as the unblinded phase of an enriched enrolment study familiarises all participants with the treatment effects there is a significant risk of unblinding in the randomisation phase [18]. For sham-controlled device trials, this would require careful consideration in terms of what stimulation parameters could be used to maintain blinding whilst providing no therapeutic effect (see also design of the sham device).

Design of the sham device

The literature discusses various issues surrounding the design of a sham intervention which relate to the mechanism of action of the active intervention, the use of sham controls with no perceivable output and subtherapeutic stimulation and feasibility testing.

Mechanism of action

Establishing a sham treatment that does not contain the component thought to be associated with the therapeutic effect is difficult to achieve when the working mechanisms of the active treatment are not clearly understood. This issue was highlighted by the international group of experts and stakeholders who developed the Template for Intervention Description and Replication (TIDieR) checklist and guide [19]. They reported that for too many sham-controlled trials the supposed mechanisms for the active treatment were unclear, and therefore, it also remained unclear as to whether the proposed sham was truly 'inactive'. They recommended that a suitable description of mechanisms should be included with study methods and attempts should be made to understand which specific components of the 'active' arm thereby need to be controlled [19].

No perceivable output

A favoured method due to its simplicity in numerous device trials is to use the same device for both the active and sham arm but simply disconnect the sham device from its power source creating an inactive control [14,20,21]. Whilst this purports to be a simple solution, this type of sham fails to replicate often expected sensations or side effects associated with the active treatment. This can jeopardise treatment credibility [22–26]and as previously highlighted inadvertently lead to unblinding [14]. Common recommendations when utilising a device with no perceivable effect are to exclude patients with previous experience of the intervention and avoid cross-over designs [14,27].

Subtherapeutic dosing

An alternative sham design involved the delivery of subtherapeutic doses such as shorter duration or lower strength version of a neuromodulation paradigm. A recent systematic review of randomized sham-controlled trials of spinal cord stimulation (SCS) describes four studies that used lower intensity tonic stimulation as sham control [28]. A highlighted limitation of these studies was that in the absence of pre-trial testing of the sham, the absence of a true, albeit perhaps smaller therapeutic benefit cannot be confidently excluded which may have led to an underestimation of the active treatment effect. Given that pre-trial testing will be subject to similar bias parameters as trial intervention, understanding of and ideally monitoring the application of the active mechanism is again important (see also next paragraph).

Testing of the sham

A study by Sheffer et al [25] looked specifically at the development of a sham technique for high-frequency repetitive transcranial magnetic stimulation (rTMS). In this study, the sensation produced by the active device was considered an important factor that needed to be replicated by an adequate sham to prevent unblinding. The group developed a sham that used focal stimulation of the scalp and used brain imaging to confirm that this stimulation was not associated with cortex

activation. Following patient evaluation, they concluded that focal electrical stimulation can be an effective sham control for high-frequency rTMS. Such studies are rare, and it is widely recognised that very few studies report how the sham has been tested/ developed or how treatment credibility was assessed [6]. The development of a sham intervention itself may be facilitated by the involvement of other agencies such as industry and patient groups to overcome these various challenges.

Sources of bias and mitigating bias in sham trials

Bias refers to a type of error that affects how a result is interpreted due to the way the study was designed or conducted [29]. Where bias is large, the results of a sham-controlled study may be inaccurately interpreted. There are various issues surrounding bias in sham-controlled trials such as blinding, assessment of blinding, observer bias and expectations.

Blinding

Bias associated with inadequate blinding of treatment allocation is cited as one of the major sources of bias in sham RCTs [6,30,31]. Although sham-controlled studies in theory reduce the risk of bias by facilitating blinding to treatment allocation, it can be difficult to blind treatment allocation fully. In certain cases, to ensure an intervention is delivered safely and accurately it may not be possible for the clinician delivering the treatment to be blinded to treatment allocation. For example, for surgical procedures, it would be necessary in most cases for the surgeon to be aware of the differences between active and sham treatments. Equally, it would be hard to blind a clinician delivering treatment when there are evident differences in treatment response between sham and active treatments. In cases such as these, it is strongly advised to limit detection bias (i.e. say what that is) that independent, blinded assessors of outcome are involved [19,32]. It is recommended that all double-blind trials adequately describe all measures used to blind participants and researchers to allow confident interpretation of the risk of unblinding bias within a given study [2,19]. However, it has been illustrated by various systematic reviews of sham-controlled studies that adequate description of study blinding is generally poor [28,33–35].

Assessment of blinding

In addition to considering how blinding is achieved, it has also been highlighted that studies need to consider how it is assessed [2,36]. An early review conducted by Hrobjartsson analysed a random sample of blinded randomized clinical trials indexed in The Cochrane Central Register of Controlled Trials [31]. They identified 1599 blinded trials and found only 31(2%) of those trials reported tests for the success of blinding. In most cases, assessment of blinding was only conducted for patients, and they conclude that to demonstrate successful blinding, assessment should ideally include all individuals that are described as blinded (e.g., including the assessors of outcomes). Furthermore, they highlight that there is also uncertainty around the best way to assess blinding and a lack of formal measures to do this. Most studies ask people to guess between the experimental and control arm and there is some debate as to whether an additional 'don't know' category should also be included [31,32]. Further variation exists concerning when to assess. A positive test conducted during, or after the end of the trial cannot be interpreted as a clear indication of bias, as 'unblinding' may be caused by the experience of a true treatment effect [31]. Assessment immediately after an intervention may provide information regarding the credibility of the sham, but it does not assess how blinding was maintained during the study. There is therefore huge potential for variation across studies in how assessment of blinding is conducted. The literature generally describes that assessment of blinding is poorly considered, and 1/3 of studies that assess blinding contain no clear information concerning the result of any assessment [31].

Clinical interactions

Clinical interactions have additionally been found to strongly affect treatment response and can inadvertently lead to unblinding of subjects by clinicians, either consciously or subconsciously [37–39]. To mitigate this type of bias, clinicians must consider how information is delivered and presented to ensure both the active and sham treatments are delivered in an equal and comparable way. TIDieR guides researchers in this area and asks for studies to provide detailed documentation and reporting

of key study elements, such as patient monitoring, study procedures, and verbal and written instructions [19].

Expectations

What we think or expect about treatment has also been shown to strongly impact treatment response [40–42]. Bingel et al in a study using functional magnetic resonance imaging found that positive and negative treatment expectation was related to the activation of different areas of the cortex[43]. They found positive expectancy was associated with activity within the endogenous opioid system and enhanced analgesic effect, and that negative expectancy impacts the hippocampus and abolished analgesic response [43]. The power of expectation is especially significant for sham-controlled trials, as both patients and clinicians expect that half the sample will receive the sham intervention. It has therefore been proposed that patient expectation of benefit is assessed before they commence a trial, and that perception of effectiveness is assessed on trial completion [44,45]. An important implication of the above findings is the weight of verbal and nonverbal communication concerning expectation. This will include not only how researchers communicate but also how participants talk to one another [46]. This will involve considering not just what happens in the clinic/treatment room but also what can be communicated within waiting areas and via the web and social media.

Study population

Placebo effect

Many randomized, double-blind clinical trials in neuropathic pain have failed to demonstrate a significant difference between active treatment and sham treatments, despite previous positive results of pre-clinical studies [47–49]. This has in part been attributed to strong placebo responses in chronic pain states as compared to other conditions. The degree of placebo response varies greatly across different chronic pain conditions [47,50,51]. A systematic review by Arakawa considered variation in placebo responses in neuropathic pain syndromes [52]. They demonstrate that the proportion of

patients expected to have a 50% or better pain reduction in placebo control groups can be hugely different depending on the type of neuropathic pain syndrome. For example, a response rate of 23% was reported for trials of peripheral neuropathic pain, 15% for posttraumatic peripheral neuropathic pain and 26% for painful diabetic peripheral neuropathy (95% CI) [52]. It has also been demonstrated that even within syndromes the presence of certain symptom characteristics can also influence the 'response rate', response rate (the number of patients that show a positive response to treatment). For example, studies that include symptoms of hyperalgesia have been suggested to have amongst the largest placebo responses [51,53,54]. This highlights how variable individual responses can be, even within similar conditions and the need to carefully consider how diagnostically homogenous a population may need to be to demonstrate treatment efficacy [13]. For chronic pain trials, this is not without challenges as not all types of chronic pain have well-accepted diagnostic criteria. For example, chronic low back pain, although very common, can have variable characteristics depending on whether one is examining non-neuropathic or neuropathic symptoms.

Ethics

Within the literature, the most frequent *objections* to the use of sham-controlled studies come from the potential ethical concerns that are associated with their conduct, including equipoise, risk-benefit evaluation and deliberate deception [4,55–57].

Equipoise

An ethical concern is created around whether it is ethically acceptable to allow patients to have an inferior treatment if researchers know one arm is superior. In a seminal paper in the New England Journal of medicine, Benjamin Freedman proposed the concept of equipoise [58]. He debated that it is ethical to subject patients to an inferior treatment if the requirement for equipoise could be satisfied. He stated that "the requirement is satisfied if there is genuine uncertainty within the expert medical community about the preferred treatment- not necessarily on the part of the individual investigator-about the preferred treatment". For example, although clinicians may feel

peripheral nerve stimulation (PENS) is beneficial for neuropathic pain, NICE guidelines [59] suggest there is currently insufficient evidence of efficacy to support its use, therefore, a trial comparing PENS to sham PENS would be considered to have equipoise. It is therefore important that any research establishes that there is adequate uncertainty regarding the relative efficacy of an intervention.

Risk-benefit balance

Critics argue that sham-controlled trials are unethical because participants assigned to the control group have no prospect of benefit from the trial, yet they are exposed to all the risks of the sham intervention. Conversely, when the efficacy of an intervention is not established or is under question it could be argued there are clear benefits from being assigned to the sham control. The use of a sham intervention should therefore involve weighing up the relative risks and harms associated with its use as part of a risk-benefit analysis [56,57,60]. The literature suggests that risk-benefit analysis should consider; 1) the risk has been minimized for the scientific question to be answered, 2) the risk is not excessive, and 3) the risk is justified by important knowledge to be gained [56,60,61].

Informed consent

It has been suggested that it may be more difficult to obtain informed consent in sham-controlled trials because subjects within these trials have a greater risk of not appreciating or understanding all the potential implications of a sham control [56,61,62]. Whilst it has also been suggested patients may participate in a sham-controlled trial believing it improves their ability to access further treatments in the future [62]. Others have hypothesized that for interventional sham-controlled trials, the study subjects' participants may think that an invasive intervention will not be performed if it does not have any potential benefits [63]. Therefore, to meet the requirement of informed consent, sham-controlled studies need to ensure and demonstrate that the purpose and nature of the sham intervention are understood by all study participants.

Deliberate deception

In studies that use blinding of treatment allocation, study subjects are led to believe that the control could plausibly be the active treatment and therefore subjects are deliberately deceived to reduce bias [64]. Deliberate deception has conversely been suggested unethical as it violates the principles of patient autonomy and may cause clinicians to feel a moral discomfort [55,61]. Proposed ethical frameworks suggest that to justify the use of deliberate deception the following requirements should be shown to have been met; 1) deliberate deception is required to obtain valid data, 2) there is full disclosure to subjects regarding the use of deliberate deception, 3) subjects are aware they may receive a sham procedure 4) subjects are debriefed when the blind is broken [56,61].

Discussion

In a world that requires increasing reassurances to implement and develop evidence-based treatments, researchers need to convince funders, governance frameworks such as ethics, and patients concerning treatment efficacy. They must balance these issues to produce well designed and appropriately conducted trials. The inclusion of a sham control in a device trial can reduce bias by facilitating the conduct of double-blinded trials and therefore aid the conduct of high-quality research. Conversely, amongst published studies, the quality of identified sham-controlled trials was limited as methods relating to the conduct of sham-controlled were often poorly described.

Several major and subcategory themes have been identified that describe quality items which if considered could improve the conduct of future sham-controlled interventional pain trials.

Design and testing of sham

Although guidelines call for studies to adequately describe how sham treatments have been tested and developed [19,64], what is striking from the literature is that very few studies do so [23,65,66]. Testing of sham interventions adds additional time and cost to the conduct of a study. If a new interventional device or sham device is developed it must conform to medical devices regulation

policy. This will include consideration of UKCA (UK Conformity Assessed) or CE (European Conformity) marking and ensuring adequate indemnity insurances are in place. The most utilised form of sham controls in neurostimulation trials appears to be an active device that is disconnected from any power source and therefore produces no output. This design negates some of the policy processes such as CE marking just discussed, however, as highlighted in the review, carries a high risk of unblinding [15]. Further design options, such as lower dose or subthreshold stimulation, fall short when the mechanisms of action for the active treatment are not fully understood as possible treatment effects cannot be excluded. To overcome such issues, future studies could consider and explore basic science and industry partnerships to develop valid and robust sham interventions. As part of this process, patient and public involvement are further recommended to ensure shams are developed that are deemed relevant and credible to the subjects they are evaluated on. This aligns with the increasing requirement of research funders for research to demonstrate patient involvement at every stage of research to improve research design and outcomes [67].

Sources of bias and mitigating bias

Under this theme, blinding was a predominant issue. Overall, blinding was found to be one aspect of trial conduct that was typically found to be poorly described in published trials [27,30,31]. Unblinding due to perceivable differences between sham and active interventions was cited as one of the most common sources of unblinding. To overcome unblinding, where this could be an issue, several papers recommended that patients with previous experience of the intervention should be excluded, cross over designs should be avoided and providing partial disclosure in terms of expected side effects of treatment should be considered [13,19]. Many trials published after such recommendations appear to have incorporated many of these suggestions. Although most studies explained the differences between the sham and active devices, few described how these differences were explained and understood by both patients and clinicians. Conversely in clinical practice patient education is well recognised as an important aspect of any treatment procedure.

Therefore, there seems to be some disparity as to what is acceptable research practice and what is acceptable clinical practice. Additionally, there was much variation in how and when blinding was assessed, with many reviews concluding that the success of blinding was often unclear [2,68]. Whilst this seems a common critique of the literature, recommendations about how and when blinding could be assessed are equally lacking. It is recommended that future studies provide an adequate description of measures taken to maintain blinding and justify when and how assessments are made [19,28,68].

Expectation

The use of a sham control facilitates the conduct of double-blind trials to establish the efficacy of treatment over and above expectancy and other forms of bias [69]. Participants and clinicians within sham-controlled trials may validly question treatment allocation which may affect expectations relative to treatment and outcome response. Blinding and assessment of blinding as discussed are undoubtedly important in terms of assessing the impact of expectations associated with treatment allocation [6,30]. Whilst assessment of treatment allocation is commonly recommended but poorly implemented, assessment of treatment expectations appears to be less commonly considered. Deliberate manipulation of expectation relative to treatment efficacy has been demonstrated to enhance and diminish the effects of treatment and placebo responses [43,45,53]. It is also recognised treatment expectations can be unintentionally manipulated via social and interpersonal interactions [37,45]. Treatment expectation therefore can be influenced by many factors which are associated with considerable ambiguity in terms of how best to assess and measure its influence within RCTs [70]. Whilst most studies assess treatment expectations before treatment it is also suggested that expectations might be influenced by the course of treatment [44,45,70]. Consequently, there are calls for studies to consider the assessment of treatment expectations at multiple time points (before, during, and after a procedure) [44,45,70]. However, the effects of different assessment timing remain unclear and there is little evidence examining this in a systematic way [45]. Treatment expectation,

therefore, represents an important multifactorial covariant. Studies should include a minimum assessment of expectation relative to treatment allocation and treatment efficacy, pre and post treatment, for patients but also clinicians and who are blinded.

Study population- placebo effects

The placebo effect is a powerful psycho-neurobiological mechanism for modulating clinical outcomes [45]. Placebo effects as suggested can be influenced by expectation but have also been demonstrated to vary considerably between and within different pain conditions [47,50,51]. Accurate estimates relative to potential placebo responses are required to inform study design in terms of power calculations and statically analysis. Therefore, researchers need to understand the relative magnitude of placebo responses relative to the study population. A systematic review has demonstrated significant variation in placebo responses between different types of neuropathic pain [52]. Additionally, the literature also illustrates there is further variation between placebo responses relative to different sensory symptoms [51,53,54]. Quantitative sensory testing has been extensively used to evaluate the sensory features associated with different neuropathic pain syndromes. Results have defined patterns of loss or gain of function across multiple sensory modalities ('somatosensory profiles'), which likely reflect underlying pain generating mechanisms such as peripheral, central sensitisation and potentially placebo potentials [71]. Stratification of patients by sensory phenotype has been suggested, which could improve treatment selection and outcomes by allowing for mechanistically informed treatment selection. On this basis stratification of patients by pain type and additionally, sensory phenotype could also help in terms of understanding and evaluating placebo response and informing study design.

Ethics

The most well-documented areas surrounding the conduct of sham-controlled trials are the ethical considerations of conducting such trials. Various frameworks have been developed to help guide researchers through salient ethical issues such as equipoise, risk-benefit response, informed

consent, deliberate deception and moral discomfort [60,61]. The consensus shared by the ethical literature surrounding the conduct of sham-controlled trials is not whether it is ethical to conduct a sham, but rather consider whether conditions that make it ethical have been met.

Therefore, there are various issues to consider when conducting a sham-controlled trial and a holistic appreciation of these multiple factors are required to conduct good quality sham-controlled research studies.

Conclusion

Good quality sham-controlled trials are needed to support the efficacy of untested or unproven treatments. Currently, the methods used concerning sham-controlled trials are not always clearly described, which limits the quality and validity of findings. This chapter highlights some of the salient issues and provides recommendations for the conduct and reporting of future sham-controlled interventional pain trials.

Chapter 4 References

1. Heneghan C. EBM Guidelines: Evidence-Based Medicine. *Evid Based Med*. 2004;9(2):61-61. doi:10.1136/ebm.9.2.61

2. Higgins JPT, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing the risk of bias in randomised trials. *BMJ*. 2011;343(7829). doi:10.1136/bmj.d5928

3. Sedgwick P. Placebos and sham treatments. *BMJ*. 2015;351:h3755. doi:10.1136/bmj.h3755

4. Brim RL, Miller FG. The potential benefit of the placebo effect in sham-controlled trials: Implications for risk-benefit assessments and informed consent. *J Med Ethics*. 2013. doi:10.1136/med ethics-2012-101045

5. Johnson S. Medline database search. https://hdas.nice.org.uk/strategy/1034502/#show-searches. Published 2021. Accessed June 7, 2021.

6. Katz N, Dworkin RH, North R, et al. Research design considerations for randomized controlled trials of spinal cord stimulation for pain. *Pain*. 2021;162(7):1935-1956. doi:10.1097/j.pain.0000000000002204

7. Staudacher HM, Irving PM, Lomer MCE, Whelan K. The challenges of control groups, placebos and blinding in clinical trials of dietary interventions. *Proc Nutr Soc*. 2017;76(3):203-212. doi:10.1017/S0029665117000350

8. Kallmes DF, Comstock B a, Heagerty PJ, et al. A randomized trial of vertebroplasty for osteoporotic spinal fractures. *N Engl J Med*. 2009;361(6):569-579. doi:10.1056/NEJMoa0900563

9. Gewandter JS, Dworkin RH, Turk DC, et al. Research designs for proof-of-concept chronic pain clinical trials: IMMPACT recommendations. *PAIN®*. 2014;155(9):1683-1695. doi:10.1016/j.pain.2014.05.025. Epub 2014 May 24.

10. Taylor WJ, Weatherall M. What are open-label extension studies for? *J Rheumatol*. 2006;3333(334):642-643. http://www.jrheum.org/content/33/4/642.citation. Accessed December 22, 2016.

11. Bialas P, Maier C, Klose P, Häuser W. Efficacy and harms of long-term opioid therapy in chronic non-cancer pain: Systematic review and meta-analysis of open-label extension trials with a study duration ≥26 weeks. *Eur J Pain (United Kingdom)*. 2020;24(2):265-278. doi:10.1002/ejp.1496

12. Hemming K, Hutton JL, Maguire MJ, Marson AG. Open-label extension studies and patient selection biases. *J Eval Clin Pract*. 2008;14(1):141-144. doi:10.1111/j.1365-2753.2007.00821.x

13. Dworkin RH, Turk DC, Peirce-Sandner S, et al. Research design considerations for confirmatory chronic pain clinical trials: IMMPACT recommendations. *Pain*. 2010;149(2):177-193. doi:10.1016/j.pain.2010.02.018

14. Raphael JH, Raheem TA, Southall JL, Bennett A, Ashford RL, Williams S. Randomized Double-Blind Sham-Controlled Crossover Study of Short-Term Effect of Percutaneous Electrical Nerve Stimulation in Neuropathic Pain. *Pain Med*. 2011;12(10):1515-1522.

15. Hui D, Zhukovsky DS, Bruera E. Which treatment is better? Ascertaining patient preferences with crossover randomized controlled trials. *J Pain Symptom Manage*. 2015;49(3):625-631. doi:10.1016/j.jpainsymman.2014.11.294

16. Moore A, Derry S, Eccleston C, Kalso E. Expect analgesic failure; pursue analgesic success. *BMJ*. 2013;3(346):f2690. doi:10.1136/bmj.f2690

17. Moore RA, Wiffen PJ, Eccleston C, et al. Systematic review of enriched enrolment, randomised withdrawal trial designs in chronic pain: A new framework for design and reporting. *Pain*. 2015;156(8):1382-1395. doi:10.1097/j.pain.0000000000000088

18. Furlan AD, Chaparro LE, Ba EI, Mailis-Gagnon A. A comparison between enriched and nonenriched enrollment randomized withdrawal trials of opioids for chronic noncancer pain. *Pain Res Manag*. 2011;16(5):337-351.

19. Hoffmann TC, Glasziou PP, Boutron I, et al. Better reporting of interventions: Template for intervention description and replication (TIDieR) checklist and guide. *BMJ*. 2014;348:g1687. doi:10.1136/bmj.g1687

20. Hamza MA, White PF, Craig WF, et al. Percutaneous electrical nerve stimulation: a novel analgesic therapy for diabetic neuropathic pain. *Diabetes Care*. 2000;23(3):365-370. doi:10.2337/diacare.23.3.365.

21. Ghoname EA, Craig WF, White PF, et al. Percutaneous electrical nerve stimulation for low back pain: a randomized crossover study. *JAMA*. 1999;281(9):818-823. doi:jpc90000 [pii]

22. Dworkin RH, Turk DC, Farrar JT, et al. Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. *Pain*. 2005;113(1-2):9-19. doi:10.1016/j.pain.2004.09.012.

23. Brunoni AR, Nitsche MA, Bolognini N, et al. Clinical research with transcranial direct current stimulation (tDCS): Challenges and future directions. *Brain Stimul*. 2012;5(3):175-195. doi:10.1016/j.brs.2011.03.002

24. George MS, Padberg F, Schlaepfer TE, et al. Controversy: Repetitive transcranial magnetic stimulation or transcranial direct current stimulation shows efficacy in treating psychiatric diseases (depression, mania, schizophrenia, obsessive-compulsive disorder, panic, posttraumatic stress disorder). *Brain Stimul*. 2009;2(1):14-21. doi:10.1016/j.brs.2008.06.001

25. Sheffer CE, Mennemeier MS, Landes RD, et al. Focal electrical stimulation as an effective sham control for active rTMS and biofeedback treatments. *Appl Psychophysiol Biofeedback*. 2013;38(3):171-176. doi:10.1007/s10484-013-9221-x

26. White ARR, Filshie J, Cummings TMM. Clinical trials of acupuncture: consensus recommendations for optimal treatment, sham controls and blinding. *Complement Ther Med*. 2001;9(4):237-245. doi:10.1054/ctim.2001.0489

27. Boutron I, Estellat C, Ravaud P, et al. A review of blinding in randomized controlled trials found results inconsistent and questionable. *J Clin Epidemiol*. 2005;58(12):1220-1226. doi:10.1016/j.jclinepi.2005.04.006

28. Duarte R V., McNicol E, Colloca L, Taylor RS, North RB, Eldabe S. Randomized Placebo-/Sham-Controlled Trials of Spinal Cord Stimulation: A Systematic Review and Methodological Appraisal. *Neuromodulation*. 2020;23(1):10-18. doi:10.1111/ner.13018

29. Vetter TR, Mascha EJ. Bias, Confounding, and Interaction: Lions and Tigers, and Bears, Oh My! *Anesth Analg*. 2017;125(3):1042-1048. doi:10.1213/ANE.0000000000002332

30. Haahr MT, Hróbjartsson A. Who is blinded in randomized clinical trials? A study of 200 trials

and a survey of authors. *Clin Trials*. 2006;3(4):360-365. doi:10.1177/1740774506069153

31. Hróbjartsson A, Forfang E, Haahr MT, Als-Nielsen B, Brorson S. Blinded trials taken to the test: An analysis of randomized clinical trials that report tests for the success of blinding. *Int J Epidemiol*. 2007;36(3):654-663. doi:10.1093/ije/dym020

32. Boutron I, Guittet L, Estellat C, Moher D, Hróbjartsson A, Ravaud P. Reporting methods of blinding in randomized trials assessing nonpharmacological treatments. *PLoS Med*. 2007;4(2):e61. doi:10.1371/journal.pmed.0040061

33. Boutron I, Dutton S, Ravaud P, Altman DG. Reporting and interpretation of randomized controlled trials with statistically nonsignificant results for primary outcomes. *JAMA - J Am Med Assoc*. 2010;303(20):2058-64. doi:10.1001/jama.2010.651

34. Carroll D, Moore RA, McQuay HJ, Fairman F, Tramer M, Leijon G. Transcutaneous electrical nerve stimulation (TENS) for chronic pain. *Cochrane Libr*. 2000.

35. Gibson W, Wand BM, O'Connell NE. Transcutaneous electrical nerve stimulation (TENS) for neuropathic pain in adults. *Cochrane Database Syst Rev*. 2017. doi:10.1002/14651858.CD011976.pub2

36. Sterne JA, Hernán MA, Reeves BC, et al. ROBINS-I: A tool for assessing the risk of bias in non-randomised studies of interventions. *BMJ*. 2016;355. doi:10.1136/bmj.i4919

37. Chen PHA, Cheong JH, Jolly E, Elhence H, Wager TD, Chang LJ. Socially transmitted placebo effects. *Nat Hum Behav*. 2019;3(12):1295-1305. doi:10.1038/s41562-019-0749-5

38. Di Blasi Z, Harkness E, Ernst E, Georgiou A, Kleijnen J. Influence of context effects on health outcomes: A systematic review. *Lancet*. 2001;357(9258):757-762. doi:10.1016/S0140-6736(00)04169-6

39. Rief W, Glombiewski JA. The hidden effects of blinded, placebo-controlled randomized trials: An experimental investigation. *Pain*. 2012;153(12):2473-2477. doi:10.1016/j.pain.2012.09.007

40. Enck P, Bingel U, Schedlowski M, Rief W. The placebo response in medicine: minimize, maximize or personalize? *Nat Rev Drug Discov*. 2013;12(3):191-204. doi:10.1038/nrd3923

41. Enck P, Benedetti F, Schedlowski M. New Insights into the Placebo and Nocebo Responses. *Neuron*. 2008;59(2):195-206. doi:10.1016/j.neuron.2008.06.030

42. Benedetti F. *Placebo Effects: Understanding the Mechanisms in Health and Disease*.; 2009. doi:10.1093/acprof:oso/9780199559121.001.0001

43. Bingel U, Wanigasekera V, Wiech K, et al. The effect of treatment expectation on drug efficacy: imaging the analgesic benefit of the opioid remifentanil. *Sci Transl Med*. 2011;3(70):70ra14. doi:10.1126/scitranslmed.3001244

44. Frisaldi E, Shaibani A, Benedetti F. Why We should Assess Patients' Expectations in Clinical Trials. *Pain Ther*. 2017;6(1):107-110. doi:10.1007/s40122-017-0071-8

45. Colloca L. The Placebo Effect in Pain Therapies. *Annu Rev Pharmacol Toxicol Annu Rev Pharmacol Toxicol*. 2019;59:191-211. doi:10.1146/annurev-pharmtox

46. Hróbjartsson A, Gøtzsche PC. Placebo interventions for all clinical conditions. *Cochrane Database Syst Rev*. 2010;2010(1). doi:10.1002/14651858.CD003974.pub3

47. Dworkin RH, Turk DC, Peirce-Sandner S, et al. Placebo and treatment group responses in

postherpetic neuralgia vs. painful diabetic peripheral neuropathy clinical trials in the REPORT database. *Pain*. 2010;150(1):12-16. doi:10.1016/j.pain.2010.02.002

48. Freeman R, Emir B, Parsons B. Predictors of placebo response in peripheral neuropathic pain: insights from pregabalin clinical trials. *J Pain Res*. 2015;8:257-268. doi:10.2147/JPR.S78303

49. Thienel U, Neto W, Schwabe SK, Vijapurkar U. Topiramate in painful diabetic polyneuropathy: findings from three double-blind placebo-controlled trials. *Acta Neurol Scand*. 2004;110(4):221-231. doi:10.1111/j.1600-0404.2004.00338.x

50. Mbizvo GK, Nolan SJ, Nurmikko TJ, Goebel A. Placebo responses in long-standing complex regional pain syndrome: a systematic review and meta-analysis. *J Pain*. 2015;16(2):99-115. doi:10.1016/j.jpain.2014.11.008

51. Skyt I, Vase L. Placebo effects in chronic pain conditions : can placebo components enhance the efficacy of active treatments? *Tidsskr Forsk i Sygd og Samf*. 2015:63-88. http://ojs.statsbiblioteket.dk/index.php/sygdomogsamfund/article/download/22895/20017.

52. Arakawa A, Kaneko M, Narukawa M. An Investigation of Factors Contributing to Higher Levels of Placebo Response in Clinical Trials in Neuropathic Pain: A Systematic Review and Meta-Analysis. *Clin Drug Investig*. 2015;35(2):67-81. doi:10.1007/s40261-014-0259-1

53. Vase L, Skyt I, Hall KT. Placebo, nocebo, and neuropathic pain. *Pain*. 2016;157(1):98-105. doi:10.1097/j.pain.0000000000000445

54. Vase L, Petersen GL, Lund K. Placebo Effects in Idiopathic and Neuropathic Pain Conditions. In: F. Benedetti et al. (eds.), ed. *Handbook of Experimental Pharmacology*. Berlin Heidelberg: Springer-Verlag; 2014:121-136. doi:10.1007/978-3-662-44519-8_7

55. Macklin R. The Ethical Problems with Sham Surgery in Clinical Research. *N Engl J Med*. 1999;23(341(13)):992-6. doi:10.1056/nejm199909233411312

56. Niemansburg SL, Van Delden JJM, Dhert WJA, Bredenoord AL. Reconsidering the ethics of sham interventions in an era of emerging technologies. *Surg (United States)*. 2015;157(4):801-810. doi:10.1016/j.surg.2014.12.001

57. Miller FG, Kaptchuk TJ. Sham procedures and the ethics of clinical trials. *J R Soc Med*. 2004;97:576-578. doi:10.1258/jrsm.97.12.576

58. Freedman B. Equipoise and the ethics of clinical research. *N Engl J Med*. 1987. doi:10.1056/NEJM198707163170304

59. National Institute for Health and Care Excellence. Percutaneous electrical nerve stimulation for refractory neuropathic pain. *NICE Interv Proced Guide 450*. 2013;(March):1-6. https://www.nice.org.uk/guidance/ipg450.

60. Tambone V, Sacchini D, Spagnolo AG, et al. A proposed road map for the ethical evaluation of sham (placebo) surgery. *Ann Surg*. 2017;265(4):658-661. doi:10.1097/SLA.0000000000002007

61. Horng S, Miller FG. Ethical framework for the use of sham procedures in clinical trials. *Crit Care Med*. 2003;31(3 Suppl): S126-S130. doi:10.1097/01.CCM.0000054906.49187.67

62. Dekkers W, Boer G. Sham neurosurgery in patients with Parkinson's disease: Is it morally acceptable? *J Med Ethics*. 2001;27(3):151-6. doi:10.1136/jme.27.3.151

63. Gillett GR. Unnecessary holes in the head. *IRB Ethics Hum Res*. 2001;23(6):1-6.

64. Altman DG, Schulz KF, Moher D, et al. The revised CONSORT statement for reporting randomized trials: explanation and elaboration. *Ann Intern Med*. 2001;134(8):663-694. doi:doi: 10.7326/0003-4819-134-8-200104170-00012.

65. Kriek N, Groeneweg JG, Stronks DL, de Ridder D, Huygen FJPM. Preferred frequencies and waveforms for spinal cord stimulation in patients with complex regional pain syndrome: A multicentre, double-blind, randomized and placebo-controlled crossover trial. *Eur J Pain*. 2017;21(3):507-519. doi:10.1002/ejp.944

66. Schulz KF, Altman DG, Moher D, for the CONSORT Group. CONSORT 2010 statement: updated guidelines for reporting parallel group randomized trials. *Ann Intern Med*. 2010;152(11):727-732. doi:10.7326/0003-4819-152-11-201006010-00232

67. Boivin A, Richards T, Forsythe L, et al. Evaluating patient and public involvement in research. *BMJ*. 2018;363. doi:10.1136/bmj.k5147

68. Sterne JAC, Savović J, Page MJ, et al. RoB 2: A revised tool for assessing the risk of bias in randomised trials. *BMJ*. 2019;366. doi:10.1136/bmj.l4898

69. Colagiuri B. Participant expectancies in double-blind randomized placebo-controlled trials: potential limitations to trial validity. *Clin Trials*. 2010;7(3):246-255. doi:10.1177/1740774510367916

70. Laferton JAC, Kube T, Salzmann S, Auer CJ, Shedden-Mora MC. Patients' Expectations Regarding Medical Treatment: A Critical Review of Concepts and Their Assessment. *Front Psychol*. 2017;8(FEB). doi:10.3389/FPSYG.2017.00233

71. Baron R, Maier C, Attal N, et al. Peripheral neuropathic pain: A mechanism-related organizing principle based on sensory profiles. *Pain*. 2017;158(2):261-272. doi:10.1097/j.pain.0000000000000753

Chapter 5: Methods

We have seen that chronic neuropathic pain is a very challenging condition to manage and is associated with poor quality of life and function. Current management guidelines are heavily weighted on pharmacotherapy, often with modest outcomes [1,2]. When pharmacotherapy management is measured as sub-optimal, either due to adverse events or insufficient pain relief, next-line therapy options include surgical lesioning or neuromodulation therapy [3]. A disadvantage of surgical lesioning is that it is non-adjustable and not reversible. Neuromodulation therapy involves using electrical or chemical technology that acts directly upon nerves to alter or modulate nerve activity. Most neuromodulation technologies are invasive.

Enhanced pain responses are common features of neuropathic pain and have been associated with the amplification of synaptic transmission in nociceptive pathways termed 'nociceptive Long-Term Potentiation' (LTP). It has been shown that Long Term Depression (LTD), the counterbalancing process of LTP, can be induced using low-frequency peripheral nerve stimulation at high current density[4–7]. Given the psychophysical features of neuropathic pain following peripheral nerve injury described in chapters 1 and 2, induction of LTD, via low-frequency stimulation, should therefore aptly target this type of pain through lowering enhanced gain in the nociceptive pathways [8]. The use of low-frequency stimulation (LFS) to induce LTD as a treatment for neuropathic pain within clinical populations has however yet not been extensively explored. Evidence to support the clinical use of LFS in neuropathic pain stems from observational studies that suggest that external non-invasive peripheral nerve stimulation may relieve pain for people with localised neuropathic pain [9–13]. There is currently no evidence from controlled trials to confirm this. Therefore, there is good justification to explore the efficacy of low-frequency nerve stimulation in a randomised controlled trial (RCT). The current research sought to explore the potential efficacy of a non-invasive approach to elicit LTD-related pain suppression in peripheral neuropathic pain. Previous open study results do not allow for

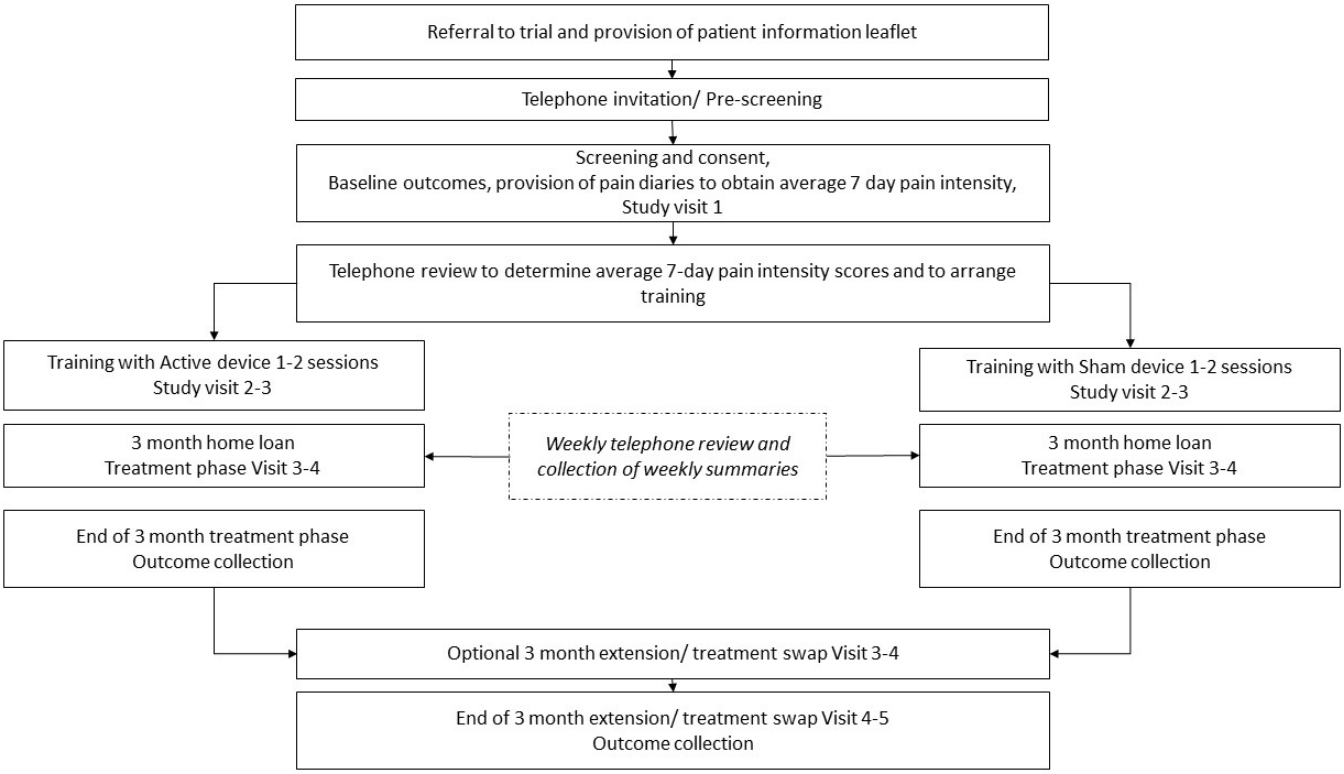
the exclusion of possible moderate long-lasting changes in the pain intensity after stopping treatment [14]; therefore, a crossover RCT design was not feasible.

A parallel-group, double-blinded, sham-controlled randomised trial was designed and conducted.

Study design

The EN-PENS trial was a single-site, blinded, randomised controlled parallel-group superiority add-on trial with a 1:1 allocation ratio. Following the screening, patients were randomised to receive either active or control (sham) treatment. Participants and the research nurses providing the training and undertaking the study assessments were blinded. Participants received training and supportive materials on the use of the neuromodulation stimulator (active or control). Once competent at using the EN-PENS machine, participants entered a 3-month treatment phase. At the end of the treatment phase, a 3-month optional choice of treatment extension or swap to the other treatment was offered (see the flow diagram of Fig. 5.1). Patient and public involvement were integral to the design of the study as described at the end of the chapter.

Figure 5.1 ENPENS study flow chart



Setting

This was a single-site study conducted at a neurosciences research centre in a tertiary specialist neurosciences hospital providing a pain management service with a catchment area of 3.2 million.

Study Objectives

The primary objective of this RCT was to establish clinical efficacy and provide a confident estimate of the effect size of electrical non-invasive peripheral electrical nerve stimulation (EN-PENS) treatment to reduce pain in patients with moderate to severe neuropathic pain associated with definite or probable peripheral nerve injury. The secondary objectives were to evaluate the impact of this treatment in terms of QOL and day-to-day function. Further objectives were to gain a better understanding of the effects of this treatment concerning mood, self-efficacy (confidence to perform abilities in the presence of pain), reduction of allodynia, potential mode of action, cost-effectiveness, and health care resource use (e.g., whether treatment can reduce the need for drug treatment).

Hypothesis

A significant difference ($p < 0.05$) in terms of average 24h pain intensity recorded on an 11-point (0-10, 0=no pain & 10= worse pain imaginable) numerical rating scale (NRS), averaged over the last 7 days of the 3-month treatment phase in favour of the active treatment would be observed.

Participants

Patient identification

In routine, clinical practice, all referrals of patients with chronic pain to the study site (Walton Centre) are placed on a pooled list for review and most are then triaged by a pain consultant; a proportion is instead triaged by a pain specialist triage physiotherapist. For the trial, the principal investigator (PI) (SJ) regularly reviewed this pain pooled list by reading all referral letters to identify potentially eligible patients for the study. The PI kept a database of all potentially suitable patients and contacted the consultants before the patients scheduled an initial consultation with them to prompt them to consider study eligibility during the clinic consultation. The PI also contacted consultants following the consultation for clinical outcomes and the patient's potential suitability for the trial. To clarify whether this strategy would be sufficient to meet the recruitment target of 76 patients over 24 months, or 3 patients per month, a feasibility audit was conducted by the PI before conducting the study. As part of this audit, the PI identified all patients coded at the first pain clinic assessment as having neuropathic pain for 3 months (May- July) over 2 consecutive years 2013 (n=285) and 2014 (n=273). Patient letters were then screened to identify patients who fulfilled inclusion criteria; 2013=29, 2014=27. Based on these results an average of 28 eligible patients within 3 months is assumed, or 214/24 months, i.e., 9 per month and therefore, allowing for a refusal rate of just over 60%.

Patient identification by internal referral

The study centre pain physiotherapists who currently review the pain consultant's pooled list to identify patients for physiotherapy triage clinic were also asked to identify suitable patients and inform the PI following the same procedure as consultants.

Patients with this condition are often eligible for invasive neuromodulation. The neuromodulation multi-disciplinary team (MDT) complete a comprehensive assessment of patients referred to them for the assessment of suitability for invasive neuromodulation. It was expected that some patients who presented as being suitable for invasive neuromodulation would also be suitable for EN-PENS. This referral pathway receives referrals from the pain consultants 'pooled list' but also directly from neurosurgeons. The team were asked to monitor patients referred to this service and contact the PI if they identified potentially suitable patients.

The centre, had at the time of the study, an active nurse-led high dose capsaicin service. It was considered that some patients referred to this service would also be suitable for the trial. The PI, therefore, made regular contact with this team asking them to identify and highlight potentially suitable patients to the PI.

The established pain management programme (PMP) patient registry was also searched to identify potentially eligible patients that have undergone PMP treatment within the last 2 years. Potentially suitable patients were contacted via telephone to ascertain whether they would like to learn about being involved in a research study. Those who expressed an interest were sent a patient information leaflet asking them to contact the study team if they were interested in enrolling (Appendix 1). If patients had not made contact within 1 week of receiving the leaflet the study team contacted the patient to ascertain if they had any questions, require any further information, and wanted to be involved.

Study posters and e-posters were used to advertise the study to clinicians and patients within outpatient clinic departments at the study site.

Identification by external referral

The study centre works closely with primary and secondary care satellite sites within the Northwest. These sites routinely refer pain patients to the study centre in its capacity as a tertiary pain centre. Referral to the centre is often for consideration of treatments not provided within primary and

secondary care. Whilst preparing the study protocol other sites within the Northwest were contacted and the study proposal was described; these sites agreed to refer patients directly to the study centre for possible inclusion in the study. The PI visited nine of these external departments to provide presentations regarding the study and provided monthly study recruitment updates which outlined recruitment rates, recruitment targets and examples of cases found eligible.

If a patient was deemed as potentially eligible, they were asked to refer the patient to the study centre pain clinic and highlight in the referral letter that they may be suitable for the EN-PENS trial.

Patient screening

Once identified as potentially eligible and were happy to be contacted the PI contacted the patient to discuss the study, answer questions and conduct an initial telephone pre-screen of the study inclusion and exclusion criteria. If a patient was found suitable, then a date was arranged with the patient to attend a face-to-face screening appointment where written informed consent was obtained by the study PI (Study Visit one), (Appendix 2).

Study inclusion criteria

- Chronic neuropathic pain following peripheral nerve injury, *definite or probable*[15].
    1. Pain with a distinct neuroanatomically plausible distribution
    2. A history suggestive of a relevant lesion or disease affecting the peripheral or central somatosensory system
    3. Demonstration of the distinct neuroanatomically plausible distribution by at least one confirmatory test
    4. Demonstration of the relevant lesion or disease by at least one confirmatory test

  Grading of certainty for the presence of neuropathic pain: definite neuropathic pain: all (1 to 4); *probable* neuropathic pain: 1 and 2, plus either 3 or 4 [15].

- ≥ 12 months duration of pain. Post-traumatic nerve regeneration is usually complete at 12 months, so the inclusion of this group will reduce the likelihood of pain relief due to nerve regeneration [16].
- Adults were aged 18 or above.
- Moderate to severe pain intensity: Average 24-hour pain intensity over 7-days at baseline of ≥ 5/10 but not dropping below 4 on any single day, on an 11-point (0-10) numerical rating scale, with 0 being *'no pain'* and 10 being *'the worst pain imaginable'* (NRS). This is under recommendations that trials evaluating the efficacy of neuropathic pain treatments should include a minimum pain inclusion criterion of 4 (rather than a lower pain intensity) or above on a 0 to 10 scale, to improve assay sensitivity and reduce the likelihood of falsely negative outcomes[17].
- Pain localized to the distribution of 1-2 peripheral nerves. To ensure that the area of pain can be covered with 10 minutes of stimulation at each point to limit the time burden for patients to complete treatment.
- Distribution of pain that will allow for the nerve to be stimulated proximally from the areas of pain. This would exclude, for example, some types of neuropathic facial pain. Invasive PNS trial evidence suggests analgesia is maximized when stimulation is used in this way [18].
- Medications that numb affected areas should be discontinued before the study to enable stimulation of the peripheral nerves. Lidocaine patches were discontinued 2 weeks prior, and Capsaicin treatments (both low-, and high concentration) 4 months before EN-PENS to allow nerve endings to grow back.
- To ensure patients' care was not disadvantaged via inclusion in the study, patients should have trialled first-line pharmacotherapy in keeping with current management guidelines for the treatment of neuropathic pain. First-line treatment includes either tricyclic antidepressants or serotonin-noradrenaline reuptake inhibitors, pregabalin or gabapentin [1].
- Moderate- severe brush stroke allodynia. This was originally defined as pain of ≥ 5/10 on an 11-point (0-10) numerical rating scale (NRS) when a brush stroke is applied to the affected area

(average of 3 strokes over the affected area). As previously discussed, long term potentiation (LTP) and long-term depression (LTD) have been shown to enhance and diminish centrally mediated evoked cutaneous responses, specifically punctate and dynamic allodynia [19]. To test the ability to induce LTD via LFS as a method of pain relief for persons with neuropathic pain, it is, therefore, necessary to select patients with sensory features that have been described experimentally to be associated with LTP and conversely LTD. The required intensity of allodynia was lowered from 5/10 to 3/10 following an ethical amendment within the first 6 months of the study. This change was implemented to aid recruitment because the outcome assessment was not evaluating the change in intensity of allodynia but rather change in the area of allodynia.

- Willing to not commence any new medications/ treatments for their neuropathic pain whilst involved in the trial so as not to confuse patient evaluation of treatment efficacy.
- Women of childbearing potential could participate providing they were using adequate birth control methods for the duration of the trial, Including accepted methods of contraception such as barrier methods, intrauterine device IUD, contraceptive implant, depot injection, oral contraception, and abstinence (as part of lifestyle choice). This was a safety inclusion.

Study exclusion criteria

- Absolute numbness- This suggests sufficient nerve damage to render EN-PENS unlikely to work [6,7].
- Known EN-PENS contraindications:
  - Pregnancy. Non-pregnancy was confirmed by urine test at baseline and treatment end (12 weeks).
  - Cardiac pacemakers.
- Other chronic pains, or unstable medical conditions, which in the opinion of the PI in consultation with the studies medical doctors would make the trial unsuitable for the patient.

- Strong fluctuating pain intensity or the dose of utilised pain medications, during the 6 weeks before the study, which in the judgement of the PI would interfere with the assessment of outcomes.
- Persons participating in an interventional trial within the past 3 months so as not to compromise the assessment of EN-PENS efficacy due to carry over from a prior intervention.
- Persons participating in a non-interventional trial completed within the past 2 weeks, except for quantity sensory testing, to avoid interference with the assessment of EN-PENS efficacy by any carryover from a prior intervention.
- Diagnosed psychiatric or mental health disorder, which could in the judgment of the PI, interfere with successful study participation. This was assessed via patient self-report or from case notes. Commonly reported mental health problems such as anxiety or depression were not routinely excluded. The only exception was if the subject was receiving or awaiting active psychological treatment for anxiety and depression.
- Inability to comply with the study protocol for the trial period of 3 months.
- Inability to complete outcome measures.
- Incapacity to understand the information necessary to provide informed consent.
- Other implanted devices for the same pain complaints such as spinal cord stimulation, dorsal root ganglion stimulation or deep brain stimulator.
- Phantom limb pain, as this type of pain is suggested to be largely driven by changes in cortical processes which could not be targeted by peripheral nerve stimulation [20,21]. Stump pain was considered a potentially suitable target.

Ethics approval

Ethics approval was obtained through the National Research Ethics Service (NRES) Committee Northwest Coast - Preston (Ref: 16/NW/0273).

The trial was registered with the ISRCTN: ISRCTN53432663. The full trial protocol was published before the trial started and was conducted in accordance with this, except for the ethical amendments discussed at the end of chapter [22].

Trial procedures

Screening & consent

Screening concerning inclusion and exclusion criteria and consent was completed by the study PI. All baseline outcomes were then taken for patients who were found to be suitable.

At the end of this visit, patients were given a seven-day pain diary to complete over a week. Patients were asked to record their daily average pain score (over 24hrs) on an 11-point NRS (0-10), with 0 being *'no pain'* and 10 being *'the worst pain imaginable'*, to ascertain the baseline average pain scores.

Patients were telephoned the following week to ascertain their average 24-hour pain intensities. Average 7-day pain scores were calculated to confirm the presence of moderate to severe pain intensity as stipulated in the inclusion criteria. This telephone call eliminated unnecessary travel to the randomisation visit for those who do not fulfil this inclusion criterion. Screen failures could be rescreened only where there was a short-term reason for ineligibility, such as an ongoing acute illness. A screening log was kept on site and maintained by the PI to document details of patients invited to be screened for participation in the study.

Randomisation

Randomisation was conducted by an independent randomisation service via an online system based at the King's Clinical Trials Unit (King's CTU) based at the Institute of Psychiatry. Randomisation used a 1:1 allocation by a computer-generated randomisation schedule (concealed), based on random permuted blocks of varying size to ensure a balance between the numbers in the two groups.

Only the PI was authorised to request randomisation. Study trial nurses were told the assigned allocation of the patient to either 'flat electrode' (sham) or 'pen electrode' (active) so that they could assign the appropriate machine to the patient to commence training.

Randomisation took place one week after the initial screening. Pain diaries provided the baseline average pain scores for inclusion.

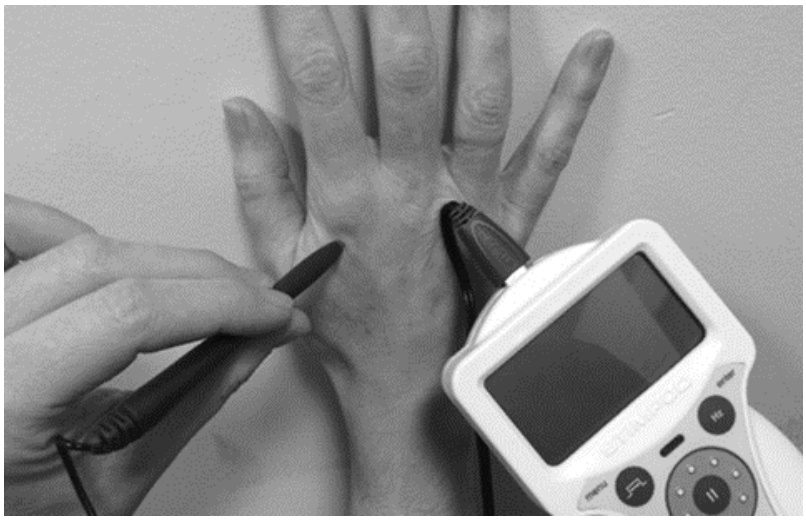
Stimulation interventions

To maintain blinding, the control stimulation needed to produce a perceivable but non-therapeutic electrical stimulation (patient focus group feedback- see PPI section below). Control and active stimulation parameters were developed in discussion with the collaborator Professor Magerl (the University of Heidelberg, Centre for Biomedicine and Medical Technology Mannheim, Germany). As the sham control machine delivered a small current, to exclude an active effect the control stimulation parameters were trialled on known EN-PENS responsive patients (n=6) before the trial. All active and sham machines were supplied without cost by Xavant medical LTD who played no part in the study concept or design. All active devices were CE marked, whilst all sham devices were not CE marked. Legal contracts between Xavant medical LTD and the sponsor site relating to indemnity insurance for both devices were agreed upon as part of sponsorship approvals.

Active device (Pen electrode)

XAVANT STIMPOD NMS460 device was using a frequency of 2 hertz (Hz), 1.0 millisecond (ms) pulse width and maximal amplitude of 30 milliamps (mA) and delivered stimulation via a ball-shaped electrode (Fig 5.2).

Figure 5.2 XAVANT STIMPOD NMS460 device



The electrode shape creates a high current density, [7] which when used in combination with the specified stimulation parameters, as described in chapters 2 and 3, achieves analgesia through induction of long-term depression (LTD) of synaptic strength [6–8].

Sham device (Flat electrode)

The machine looked identical and used a frequency of 2 Hz, 0.1 ms pulse width and maximal amplitude of 6mA, although the display appeared to allow stimulation to be increased by 30 mA. Stimulation was delivered via a 5 cm^2 square adhesive electrode, the combination of the electrode shape and the low pulse width produced a lower current density so as not to elicit LTD [19].

Blinding

Research nurses and patients were blinded to active and sham allocation.

Blinding considerations

To maintain blinding, research nurses and patients were informed that the purpose of the trial was to compare two types of electrical stimulation and that the interventions' effectiveness is determined by the electrical field rather than by any particular sensation or strength of perceived stimulation; it was posited to them that therefore it is not possible to conclude from using the machine how likely the intervention is to cause any benefit.

During training, the amplitude and stimulation time were limited (5mA and <5mins) to ensure any LTD effect would not be obtained which could lead to unbinding of research nurses or participants through observation of LTD pain reduction. LTD requires delivery of ≥1200 pulses, typically obtained from 10 minutes of treatment at 2HZ [7,23]. Patients and research nurses were also informed that the duration of training will be too short to achieve any effect. Additionally, no pain scores were recorded pre or post-treatment during training sessions.

Differences in respect to perceived stimulation

In preliminary experiments before the trial (see PPI section) it was noted that sensations produced by both devices differed. Stimulation via the pen electrode stimulation was generally felt throughout the distribution of the targeted nerve and patients could experience a motor response within this distribution. For the flat electrode group, patients felt a more localised stimulation, and would not generally experience any motor response.

To support the preservation of blinding throughout the trial, patient information material and research nurse instruction, therefore, stated that: 'Stimulation may in some cases elicit a referred stimulation pattern and a motor response. These effects will vary greatly between patients, and although these effects will be sought to ensure optimal and correct stimulation, these effects are not necessary for attaining treatment benefit.'

Stimulation training

Stimulation training took place on the same day as randomisation and was provided by the research nurses. To ensure accurate nerve identification, a physiotherapist independent of the trial with experience with nerve stimulation, determined the stimulation target but had no further patient contact during the trial. During training, a photograph was taken to record the correct placement of the electrode and was given to the patient to aid stimulation location at home. During training, subjects in both groups were advised to increase the stimulation amplitude to just above a perceivable level. The LTD effect was not obtained within training even if the active machine was used, because effective LTD requires delivery of about 1200 pulses, typically obtained from 10 minutes of treatment [5,19]. No pain scores were recorded pre-or post-treatment during training sessions. Patients were provided with a photograph taken as part of the training to take home, aiding replication of stimulation location.

Treatment phase

Once patients were able to demonstrate independent usage of the device to the research nurse on the same day of randomisation, they were deemed device competent and were loaned a device for 3 months. The length of this treatment phase was reduced from 6 months to 3 months following initial PPI feedback. It was felt that a period of 6 months would adversely affect retention in those patients without treatment benefits.

Treatment dosage

Patients were advised to stimulate for a minimum of ten minutes once a day, at an amplitude that was mildly painful but not intolerable to achieve LTD effect, whilst pulse width and frequency were fixed (sham = 2Hz, 0.1m/s, active= 2Hz, 1.0 m/s). Patients determined the frequency and timings of stimulation. Weekly telephone calls monitored treatment compliance and obtained health care utilisation data.

Optional treatment extension/ swap

Post-treatment phase participants were offered the choice of an optional treatment-extension/ treatment -swap, or termination of the study to aid study recruitment and retention; this measure had been introduced following PPI feedback (see PPI section).

Definition of end of the study

The end of the study was the last participant's final study contact at day 196 (+/–14 days) following completion of the open extension/treatment swap.

Summary of adherence/ retention strategies

- Weekly phone calls during the home loan period.
- Optional treatment extension/swap.
- Patient Information clarified that a beneficial response may not always be immediate, and effects sometimes increase with time.
- Study visits were offered within relatively wide time windows to maximize convenience.
- Patients were able to claim travel expenses for all study visits.

Outcomes

Outcomes were considered to reflect meaningful changes important to patients suffering from neuropathic pain (patient focus group). All study outcomes were further reviewed concerning patient burden and appropriateness by members of a local chronic pain patient support group (self-motivation in lasting endorphins -SMILE*) n= 25. A patient outcome pack is provided in appendix 3 to provide an understanding of all outcome questionnaires.

**SMILE is a registered charity set up to support chronic pain sufferers, helping them to live their lives despite their pain http://www.smileliverpool.co.uk.*

Primary outcome

The primary study endpoint is the average 24h pain intensity recorded on an 11-point (0-10, 0=no pain & 10= worse pain imaginable) numerical rating scale (NRS), averaged over the last 7 days of the 3-month treatment phase [24].

Further outcomes are listed below with text in brackets indicating what this measure was intended to capture.

Secondary outcomes

Were determined as important endpoints that were expected to show a treatment effect.

- Brief pain inventory (BPI) interference subscale (functional interference of pain with daily living) [25]. This scale measures how much pain has interfered with nine daily activities, including general activity, walking, work, mood, enjoyment of life, relations with others, sleep, ability to concentrate and appetite. Each item is rated on a scale of 0-10 (0 denotes pain does not interfere, 10 indicates pain completely interferes). BPI pain interference is scored as the mean of the nine interference items.
- Health-related quality of life (Euroqol EQ-5D-5L) [26]. The EQ-5D-5L is a self-assessed, health-related, quality of life questionnaire. It includes a scale which measures the quality of life on a 5-component scale including mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. It also includes a 0-100 visual analogue where patients are asked to rate their general health status on that day (0= worst possible health and 100= best possible health).
- A modified Client Service Receipt Inventory (CSRI) (health care resource use) [27], supported by a regular telephone questionnaire [28]).

Exploratory outcomes

Were determined as clinically important events that were considered less likely to show a treatment effect.

- Hospital Anxiety and Depression Scale [29] (emotional function). This is a 14-item measure designed to assess anxiety and depression symptoms. The questionnaire comprises seven questions for anxiety and seven questions for depression. The questions relating to anxiety and depression are scored separately to give a total possible score of 21 for each.
- The pain self-efficacy questionnaire [30] (perceived confidence to function despite the pain). The Pain Self-Efficacy Questionnaire (PSEQ) measures a person's confidence to perform activity despite the pain. It includes ten items across a range of functions, including household chores, socialising, work, as well as coping with pain without medication.
- Worst pain as measured by the BPI [25]. Worst pain over the last 24 hours was recorded on an 11-point (0-10, 0=no pain & 10= worse pain imaginable) numerical rating scale (NRS).
- Dynamically mapped allodynia (DMA) (change in the Surface area of allodynia [31]). To measure and quantify sensory changes and plausible LTD, **Method of mapping*
- The neuropathic pain symptom inventory (NPSI) [32] (Quality of pain). The NPSI is a self-rated questionnaire that includes 10 items corresponding to sensory descriptors (each rated on a numeric scale from 0 to 10- 0= no symptom and 1=worst symptom imaginable), which can be grouped into 5 dimensions (burning pain, paroxysmal pain, pressing pain, evoked pain, paresthesia/dysesthesia), and 2 temporal items assessing pain duration and the number of pain paroxysms.

All measures were recorded at baseline, 3 months and following completion of optional treatment extension/swap. EuroQOL-5D-5L VAS scale was recorded at baseline, 1, 2 and 3 months.

Pain diaries:

Pain intensity and treatment frequency were also captured by completion of weekly patient diaries during the home loan phase. For each day of treatment subjects were asked to record 24h pain

intensity recorded on an 11-point (0-10, 0=no pain & 10= worse pain imaginable) numerical rating scale (NRS), and the number of times they used the device. Daily pain scores were averaged over each week of treatment to provide an average 7-day score for each week of treatment. Patients were provided with stamped addressed envelopes and returned these diaries via post at 1 month and 2 months. For diaries completed in the third month of treatment, subjects returned these as part of their 3-month (end of treatment phase) study visit. As part of the weekly phone calls, patients were reminded to complete their diaries and return them.

* *Method of DMA mapping: short strokes of 1 sec were applied using a cotton wool ball held at its end. Mapping started from outside the tender/painful area identified by the patient and moved in a radial trajectory toward the presumed epicentre of the pain. The border of identified allodynia was identified as an abrupt increase in painfulness of the strokes. The border was then marked with a soft tip surgical marker. An acetate sheet was then used to map the outline of this border. The surface area was calculated by placing the acetate on a squared cutting mat and counting the number of* $1cm^2$ *squares.*

On completion of the study only

- Patient perceived global impression of change (PGIC) [33].
- Patient perception regarding treatment allocation [34].
- Suitability for neuromodulation, a named pain consultant (MLS) was asked to review case notes and clinical assessment letters of all study patients for potential medical suitability for invasive neuromodulation. They were asked to indicate whether they deemed the patient based on this information to be a medically suitable candidate for future neuromodulation treatment. Via this process, we hoped to gauge the number of patients where successful EN-PENS might prevent the need for invasive neuromodulation.
- A semi-structured telephone interview of a proportion of patients within the active group to obtain qualitative data regarding treatment experience and efficacy (appendix 4).

Safety outcomes

Serious Adverse Events (SAEs), Suspected Unexpected Serious Adverse Reaction (SUSARs) and Serious Adverse Events (SARs) were recorded at every point of patient contact. Relationship to the treatment was assessed by the trials' pain consultants. As this was a blinded trial involving control and active treatment, seriousness, causality and expectedness were evaluated as though the patient were on the active treatment. The Sponsor reported SUSARs and other SARs to the regulatory authority Medicines and Healthcare Regulatory Authority (MHRA) following the reporting timelines. The PI reported to the Northwest Coast - Preston ethics committee.

Withdrawal of participants

The study treatment was discontinued, and patients withdrew if:

- Participants decided they no longer wished to continue (see also below)
- It was recommended by the Investigator or another clinician (e.g., due to intercurrent illness during the study or increased pain following repeated stimulation)
- The trial was terminated if deemed appropriate by the study staff in consultation with the study's PI and pain consultant.

Where appropriate, patients who wished to discontinue their study intervention or for whom discontinuation was advised, were asked whether they would still be willing to continue weekly diaries.

Patients were also withdrawn if:

- They were randomized but never received any treatment (i.e., the first training session was never started — this is also termed 'non-compliance').
- They failed to complete weekly pain diary reports on three consecutive occasions or 4 non-consecutive weeks that include the last month of treatment (this is also termed 'missing data').

All data from patients randomised to treatment were included in the intention-to-treat analysis (see statistical analysis). Participants had the right to withdraw from the study at any time without

providing a reason; the Investigator also had the right to withdraw a participant from the study if they considered that it was in the best interests of the participant (adverse events). Following withdrawal, patients were asked to volunteer a reason for withdrawal. Subjects who withdrew from treatment early were encouraged to nevertheless return to the study site to have follow-up outcomes (week 13), providing that consent was not withdrawn. Participants who withdraw early were expected to return all study equipment within 2 weeks of ending the study.

Sample size

The trial sample size was calculated to show a difference between the two groups for the primary outcome. A previously published case series without a control group on the use of this treatment method observed a pre-to-post treatment reduction in patients with peripheral neuropathic pain from 6.4 to 3.6 (mean reduction of 2.8 units) [9]. The literature search did not identify studies that would provide a reliable estimate for the control (sham) group response. Data from a systematic review and meta-analysis in a different post-traumatic neuropathic pain condition, complex regional pain syndrome [35] reported a pooled sham response as being negligible. For this study, the sample size calculations were based on a between-group difference of 1. 5. This was a conservative estimate based on the available preliminary and placebo data[9,35]. A previous review of similar interventions suggested a standard deviation for the post-treatment pains score of 1.9 [9]. A correlation of 0.5 between the baseline and outcome pain scores was assumed. Based on a 5% significance level and a 90% power, and allowing for an attrition rate of 30%, it was calculated using the Stata statistics software (version 15.1), that 38 participants per group were required.

Statistical Analysis

The primary study analysis and safety analysis were performed using intention to treat analysis (ITT) based on all randomized, eligible patients with outcomes measured at the end of the study. A Per Protocol patient population analysis was also conducted for the primary outcome. This consisted of those patients who received the treatment that they were randomized to. Patients receiving

treatment different to their allocation, or not receiving treatment as set out in the protocol, were excluded from this population.

Primary outcome

The primary outcome was compared between groups using Analysis of Covariance (ANCOVA) with baseline pain scores as a covariate.

Secondary analysis of the primary outcome

The proportion of patients in each arm that achieved >2 points NRS improvement, 30% and 50% pain relief were reported. Minimally meaningful average pain intensity was defined as ≥ 2 points OR ≥ 30% [36].

Secondary and Exploratory outcomes

The secondary and exploratory outcomes were also compared between groups using Analysis of Covariance (ANCOVA) for all outcomes measured on a continuous scale. The Mann-Whitney test was used to compare between-group differences for exploratory outcomes measured on an ordinal scale such as PGIC. For binary outcomes, such as allocation prediction, the Chi-square test was used to compare between groups. The number and percentage of patients in each outcome category for each treatment arm were presented.

Minimally Clinical Important Difference Change (MCID)

The proportion of patients within each group obtaining a clinically meaningful change, as determined by existing literature (listed below), was also described for all outcomes. From this, the number and proportion of patients obtaining successful outcomes were determined per group.

Clinically meaningful change criteria for outcomes:

1. A 2-point reduction in the average 24h pain intensity over the last 7 days of the 3-month home-loan (primary endpoint) [37].
2. 3-point decrease on Brief Pain Inventory worst pain intensity (0-10 scale). This change represents moderate clinically important improvement [37].

3. Reduction of 2 points on the BPI interference subscale [37].
4. Increase of 7 or more points on PSEQ, plus movement to a different severity category (Categories: <20, 20-30, 31-40, >40) [38].
5. Reduction of 20% in DMA [31].
6. Reduction of 4 points on HADS anxiety, plus movement to different between severity categories (categories: normal (0–7) mild (8–10) moderate (11–14) severe (15–21)) [39].
7. Reduction of 4 points on HADS depression, plus movement to a different severity category (categories: normal (0–7) mild (8–10) moderate (11–14) severe (15–21)) [39].
8. Increase of 11 points on EQ-5D-5L VAS scale [40].
9. Increase of 0.145 units on the EQ-5D-5L QoL health index. The figure is derived from unpublished data from the Oxford pain rehab unit that indicated a median change of 0.145 (n=491) in response to attending a 16-day pain management programme (L Heeles 2019, personal communication, 11 October). Although this is a more comprehensive treatment than the RCT delivered, this provides a comparable disease group and population comparison.
10. NPSI- clinically meaningful change was not considered as we were unable to identify any relevant literature or samples allowing us to determine the relevant effect size.

Sensitivity analyses

All data analysis including sensitivity analyses was done together with an independent statistician. Sensitivity analysis was performed to assess the impact of missing values in primary and secondary outcomes as potential attrition rates were unknown. For this, Multiple Imputation (MI) was applied, using methods based on multivariate normal distribution [41]. The distribution of all outcomes was examined to check that the data assumptions were met. For each analysis, 20 imputed samples were created and analysed simultaneously.

Safety analysis

The total number of adverse events and the number of patients who experienced an adverse event were summarized descriptively. The safety population consisted of all patients recruited into the study

who participated for at least one week of the study. Descriptive summaries of the numbers of AEs per patient were also made. Summaries were described as:

- Seriousness (serious, not serious)
- Intensity (Mild, Moderate, Severe)
- Related to study participation (definite, probable, possible, remote, not related)
- Description of adverse events

Data from the optional extension/ treatment swap

For patients choosing to continue to the extension period, a comparison was made between outcomes from the end of the main trial period and the end of the extension period. Comparisons were made for 4 subgroups of patients separately: 1. Randomised to sham, continued with a sham device, 2. Randomised to sham, switched to an active device, 3. Randomised to active, continued with an active device, 4. Randomised to active, switched to a sham device. Outcomes of average 24h pain intensity over the last 7-day period (primary endpoint), Quality of life, DMA, and frequency of machine use were analysed. Within-group comparisons were performed using the paired t-test if the change in scores was found to be normally distributed and Wilcoxon matched-pairs test where it was not.

Factors associated with favourable outcomes

Linear regression was used to examine which demographic/baseline factors were associated with the following outcomes:

- change in the primary outcome measure
- number of favourable outcomes
- change in quality-of-life health status scale

For all outcomes, a series of univariable linear regression was performed to examine the association of each factor with the outcomes. This was followed by a multiple regression analysis to examine the joint association between factors and outcome. To restrict the number of variables in the multiple regression, only factors with a significant univariable p-value of <0.1 were included. The following

factors were considered as predictor variables in these analyses: trial group, age, gender, duration of pain, sub-categories of NPSI at baseline, baseline pain score and frequency of use during the home loan.

Health economic analysis

Health economic analysis was conducted by the Bangor health economics department. Costs of treatment, procedures and investigations, contact with primary and secondary care services and personal social services were all captured as part of this analysis.

Post hoc study telephone survey

A semi-structured telephone interview (n=12) for patients within the active group was conducted following completion of all study interventions and after database lock. The telephone questionnaire utilised was submitted and approved as an ethical amendment. The interview aimed to provide qualitative data to help understand patients' experience of treatment, particularly how they evaluated the efficacy or lack of efficacy and how they used the device. The questions were formulated as part of a consultative process with the study PPI members, the study PI, a health psychologist from the University of Liverpool and the study medical supervisor. The questions were then approved by the study trial management group (see below) and sponsor site representatives.

Trial organisation and monitoring

The EN-PENS protocol had been extensively reviewed by clinicians, statisticians, and patient groups. The trial was registered with an International Standard Randomised Controlled Trial Number (ISRCTN), registration number ISRCTN53432663. All aspects of trial administration were conducted by the Sponsor site Neurosciences Research Unit and finance departments. An external project monitor was also appointed as part of data quality assurance. The Neurosciences Research Unit trials manager supervised Neurosciences Research Unit staff. Day-to-day trial management by the Trial Manager (TM) and PI included establishing and carrying out the trial following international, national, and local laws and regulations and good clinical practice (GCP). All staff training and supervision concerning study procedures were provided by the PI and reviewed on a 6 monthly

basis. Appointment and recruitment for the TM position were coordinated by the PI who also acted as the TM line manager and supervisor. The study PI received mentorship and support from pain consultants AG and TJN.

Trial management group.

Quarterly trial management meetings reviewed the day-to-day running and management of the trial. Members included the PI, trial manager, health economists (DH and EH), trial statistician and consumer representative (WH), lead research nurse and a member of the trial's unit management team from the sponsor site. This group met quarterly to oversee the day-to-day study running and management. This group oversaw the review of all study documentation, protocol deviations, amendments, trial targets, timelines, study close, dissemination, and outputs, and reported to the trial steering group (TSG).

The trial steering group.

The TSG met every 6 months. The group comprised; one independent academic researcher who acted as TSG chair, a further independent clinical researcher, and an independent patient representative who sat on the TSG and the study PI. Independence was defined as follows:

- Not part of the same institution as any of the applicants or members of the project team.
- Not part of the same institution that is acting as a recruitment or investigative centre.
- Not related to any of the applicants or project team members.
- No other perceived conflicts of interest.

The role of the TSG was to provide overall supervision of the trial, ensure milestones were met, provide recommendations to the sponsor and TMG, and ensure the trial adhered to Medical Research Council (MRC) Guidelines for Good Clinical Practice in Clinical Trials[42].

Annual reports were provided by the PI to the centres, research governance committee and pain services management group and National Institute for Health Research (NIHR) funders.

Confidentiality and data protection

All data were pseudonymised. The links between the artificial and the normal identifiers were stored separately and securely on password-protected research databases protected by file-level encryption (subject to NHS access controls). All paper copies of questionnaires and outcomes with identifiable patient details were filed and stored in a locked filing cabinet within the sponsor site's Neuroscience Research Unit and kept in adherence to Caldicott principles [43].

All electronic data was stored on a password protected research database protected by file-level encryption (subject to NHS access controls). Offsite information was encrypted and was subject to the Trust's IT and Information governance standard operating procedures.

Role of funding sources

This work was funded by The NIHR Research for Patient Benefit award grant number PB-PG-0215-36039. All active and sham machines were supplied by a commercial manufacturer (Xavant medical Ltd) free of charge (Xavant medical Ltd have played no part in the study concept or design, data analysis or study write up).

Patient and public involvement.

Patient and public involvement were very important to ensure and safeguard the quality, effectiveness, credibility, and impact of the planned study. PPI involvement helped to shape every stage of the study from initial concept, design, implementation and though to evaluation.

Endorsing study concept

Patients involved in a prior audit using external non-invasive peripheral nerve stimulation (EN-PENS) with >50% pain relief [14] were contacted (n=9), and a semi-structured interview was conducted by the

PI under the supervision of a health psychologist. Most patients contacted commented without prompt that they felt EN-PENS should have been offered sooner with their pain management and strongly endorsed the need for evidence to support its use within the NHS. This validated the initial study concept and need.

Informing study design

Following this, a small patient focus group comprising of individuals with neuropathic pain and one individual with experience of EN-PENS (n=3) was conducted (Dec 2013), which helped refine the trial design. Monies to run this group were awarded from The Research Design Services Northwest PPI Bursary Scheme. The group was facilitated by a health psychologist. The group viewed the establishment of treatment efficacy as a primary aim, and they endorsed the study as 'worthwhile' and important to achieve this. People commented that an important strength of the treatment was that it could be self-administered and therefore treatment could be tailored (through variation of frequency and stimulus intensity) to what suited the individual in terms of effect and convenience. They reported that this independence in terms of treatment administration was important to feelings of control. The group proposed several major methodological changes which included: the exclusion of a third comparator arm using transcutaneous electrical nerve stimulation (TENS) as, like the audit patients, most trial participants would have already unsuccessfully trialled TENS, reduction of the length of the treatment period (the originally proposed length of 6 months was felt would adversely affect retention in the absence of treatment effect). They also prioritised outcome measures and methods of outcome collection to ensure they captured 'meaningful' change for the study population.

Design of sham intervention

A further patient consultation group (n=6) compromising of known EN-PENS responsive patients tested and evaluated the sham device and trialled different pulse width settings to confirm the feasibility and acceptability of the sham device.

Patient burden and questionnaire acceptability

To review the patient-facing content of the study, a local chronic pain support group called SMILE was invited to review patient questionnaires and patient-facing materials. 25 members of this group were kind enough to do so and provided feedback concerning wording, relevance, and potential burden.

Study governance and dissemination

Two patient representatives were also recruited to the study management committees. One patient with experience with the device agreed to join the trial management group (TMG).

Ethically approved methodological changes

Three study amendments were submitted during the study.

Ethics amendment 1

June 2016 before the commencement of study. This amendment addressed the correction of minor errors in the study supporting paperwork such as the trial protocol and the device instructions provided before the study started.

Ethics non-substantial amendment

August 2017. This amendment requested revision of the inclusion criteria to include a DMA of ≥ 3/10 NRS rather than ≥ 5/10 NRS. The study did include a reduction in the intensity of allodynia as a study outcome, therefore, this request did not affect outcomes. The amendment was made to aid recruitment, following several patient exclusions due to DMA being <5/10 NRS.

Ethics amendment 3

April 2020. Study enrolment and participation had been completed after the database lock had occurred. The amendment requested permission to conduct a semi-structured telephone interview (n=12) on patients within the active group who had completed the study. The interview aimed to provide qualitative contextual data to help understand the patients' experiences of treatment, how they evaluated the efficacy of the intervention and how they used the device.

Chapter 5 References

1. Attal N, Cruccu G, Baron R al, et al. EFNS guidelines on the pharmacological treatment of neuropathic pain: 2010 revision. *Eur J Neurol*. 2010;17(9):1113-e88. doi:10.1111/j.1468-1331.2010.02999.x

2. Finnerup NB, Attal N, Haroutounian S, et al. Pharmacotherapy for neuropathic pain in adults: A systematic review and meta-analysis. *Lancet Neurol*. 2015;14(2):162-173. doi:10.1016/S1474-4422(14)70251-0

3. Cruccu G, Garcia-Larrea L, Hansson P, et al. EAN guidelines on central neurostimulation therapy in chronic pain conditions. *Eur J Neurol*. 2016;23(10):1489-1499. doi:10.1111/ENE.13103

4. Cruccu G, Truini A. Neurostimulation therapy (acupuncture-like) and long-term depression: A challenge for the clinical neurophysiologist. *Clin Neurophysiol*. 2009;120(12):2004-2005. doi:10.1016/j.clinph.2009.09.017

5. Klein T, Magerl W, Hopf H-C, Sandkühler J, Treede R-D. Perceptual correlates of nociceptive long-term potentiation and long-term depression in humans. *J Neurosci*. 2004;24(4):964-971. doi: 10.1523/JNEUROSCI.1222-03.2004.

6. Jung K, Rottmann S, Ellrich J. Long-term depression of spinal nociception and pain in man: Influence of varying stimulation parameters. *Eur J Pain*. 2009;13(2):161-170. doi:10.1016/j.ejpain.2008.04.001

7. Rottmann S, Jung K, Ellrich J. Electrical low-frequency stimulation induces homotopic long-term depression of nociception and pain from hand in man. *Clin Neurophysiol*. 2008;119(8):1895-1904. doi:10.1016/j.clinph.2008.02.022

8. Rottmann S, Jung K, Ellrich J. Electrical low-frequency stimulation induces long-term depression of sensory and affective components of pain in healthy man. *Eur J Pain*. 2010;14(4):359-365. doi: 10.1016/j.ejpain.2009.06.001. Epub 2009 Jul 14.

9. Johnson S, Ayling H, Sharma M, Goebel A. External Noninvasive Peripheral Nerve Stimulation Treatment of Neuropathic Pain: A Prospective Audit. *Neuromodulation*. 2015;18(5):384-391. doi:10.1111/ner.12244

10. Kothari S, Goroszeniuk T, Reddy R, Khan R. Neuromodulation (NM) of the Distal Sciatic/Popliteal Nerve for Neuropathic Pain of Leg, Foot and Ankle. *Reg Anesth Pain Med*. 2008;33(5):e211.

11. Athmaja. Azzopardi, J., Goroseniuk, T. & Kothari, s. T. External neuromodulation for “little big sting” CRPS following post phlebotomy nerve injury. *Reg Anesth Pain Med*. 2009;34(5):1-193.

12. Goroszeniuk T, Kothari S. Targeted external area stimulation: 240. *Reg Anesth Pain Med*. 2004;29(5):98.

13. Kothari S, Goroszeniuk T. 602 EXTERNAL NEUROMODULATION (EN) AS A DIAGNOSTIC TEST AND THERAPEUTIC PROCEDURE. *Eur J Pain*. 2006;10:S158.

14. Johnson S, Goebel A. Long-Term Treatment of Chronic Neuropathic Pain Using External

Noninvasive External Peripheral Nerve Stimulation in Five Patients. *Neuromodulation*. 2015;18(5):384-391. doi:10.1111/ner.12365

15. Treede R-D, Jensen TS, Campbell JN, et al. Neuropathic pain redefinition and a grading system for clinical and research purposes. *Neurology*. 2008;70(18):1630-1635. doi:doi:10.1212/01.wnl.0000282763.29778.59

16. Campbell WW. Evaluation and management of peripheral nerve injury. *Clin Neurophysiol*. 2008;119(9):1951-1965.doi: 10.1016/j.clinph.2008.03.018

17. Dworkin RH, Turk DC, Peirce-Sandner S, et al. Assay sensitivity and study features in neuropathic pain trials: An ACTION meta-analysis. *Neurology*. 2013;81(1):67. doi:10.1212/WNL.0B013E318297EE69

18. Hassenbusch SJS, Stanton-Hicks M, Schoppa D, Walsh JJG, Covington ECE. Long-term results of peripheral nerve stimulation for reflex sympathetic dystrophy. *J Neurosurg*. 1996;84(3):415-423. doi: 10.3171/jns.1996.84.3.0415.

19. Lang S, Klein T, Magerl W, Treede RD. Modality-specific sensory changes in humans after the induction of long-term potentiation (LTP) in cutaneous nociceptive pathways. *Pain*. 2007;128(3):254-263. doi:10.1016/j.pain.2006.09.026

20. Flor H. Phantom-limb pain: characteristics, causes, and treatment. *Lancet Neurol*. 2002;1(3):182-189. doi:10.1016/s1474-4422(02)00074-1

21. Flor H, Nikolajsen L, Staehelin Jensen T. Phantom limb pain: a case of maladaptive CNS plasticity?. *Nat Rev Neurosci*. 2006;7(11):873-881. doi:10.1038/nrn1991

22. Johnson S, Goebel A, Richey R, Holmes E, Hughes D. A randomised, patient-assessor blinded, sham-controlled trial of external non-invasive peripheral nerve stimulation for chronic neuropathic pain following peripheral nerve injury (EN-PENS trial): study protocol for a randomised controlled trial. *Trials*. 2016;17(1):574. doi:10.1186/s13063-016-1709-2

23. Ellrich J, Schorr A. Low-frequency stimulation of trigeminal afferents induces long-term depression of human sensory processing. *Brain Res*. 2004;996(2):255-258. doi:10.1016/j.brainres.2003.08.068

24. Dworkin RH, Turk DC, Farrar JT, et al. Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. *Pain*. 2005;113(1-2):9-19. doi:doi: 10.1016/j.pain.2004.09.012.

25. Cleeland CS, Ryan KM. Pain assessment: global use of the Brief Pain Inventory. *Ann Acad Med Singapore*. 1994;23(2):129-138.

26. Group TE. EuroQol-a new facility for the measurement of health-related quality of life. *Health Policy (New York)*. 1990;16(3):199-208.

27. Curtis L, Netten A. *Unit Costs of Health and Social Care*. University of Kent; 2005.

28. Beecham, Jennifer and Knapp, Martin (2001) *Costing psychiatric interventions.* In: Thornicroft, Graham, (ed.) Measuring Mental Health Needs. Gaskell, London, UK, pp. 200-224. ISBN 9781901242607

29. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand*.

1983;67(6):361-370. doi: 10.1111/j.1600-0447.1983.tb09716.x.

30. Anderson KO, Dowds BN, Pelletz RE, Edwards WT, Peeters-Asdourian C. Development and initial validation of a scale to measure self-efficacy beliefs in patients with chronic pain. *Pain*. 1995;63(1):77-83. doi: 10.1016/0304-3959(95)00021-J.

31. Love-Jones SJ, Besson M, Steeds CE, Brook P, Chizh BA, Pickering AE. Homotopic stimulation can reduce the area of allodynia in patients with neuropathic pain. *Eur J Pain*. 2009;13(9):942-948. doi: 10.1016/j.ejpain.2008.11.018.

32. Bouhassira D, Attal N, Fermanian J, et al. Development and validation of the neuropathic pain symptom inventory. *Pain*. 2004;108(3):248-257. doi: 10.1016/j.pain.2003.12.024.

33. Hurst H, Bolton J. Assessing the clinical significance of change scores recorded on subjective outcome measures. *J Manipulative Physiol Ther*. 2004;27(1):26-35. doi: 10.1016/j.jmpt.2003.11.003

34. Altman DG, Schulz KF, Moher D, et al. The revised CONSORT statement for reporting randomized trials: explanation and elaboration. *Ann Intern Med*. 2001;134(8):663-694. doi:doi: 10.7326/0003-4819-134-8-200104170-00012.

35. Mbizvo GK, Nolan SJ, Nurmikko TJ, Goebel A. Placebo responses in long-standing complex regional pain syndrome: a systematic review and meta-analysis. *J Pain*. 2015;16(2):99-115. doi:10.1016/j.jpain.2014.11.008

36. Dworkin RH, Turk DC, Wyrwich KW, et al. Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. *J Pain*. 2008;9(2):105-121. doi: 10.1016/j.jpain.2007.09.005. Epub 2007 Dec 11.

37. Dworkin RH, Turk DC, McDermott MP, et al. Interpreting the clinical importance of group differences in chronic pain clinical trials: IMMPACT recommendations. *Pain*. 2009;146(3):238-244. doi:10.1016/j.pain.2009.08.019

38. Nicholas MK. The pain self-efficacy questionnaire: Taking pain into account. *Eur J Pain*. 2007;11(2):153-163. doi:10.1016/j.ejpain.2005.12.008

39. Bjelland I, Dahl AA, Haug TT, Neckelmann D. The validity of the Hospital Anxiety and Depression Scale: An updated literature review. *J Psychosom Res*. 2002;52(2):69–77. doi:10.1016/S0022-3999(01)00296-3

40. Janssen MF, Pickard AS, Golicki D, et al. Measurement properties of the EQ-5D-5L compared to the EQ-5D-3L across eight patient groups: A multi-country study. *Qual Life Res*. 2013;22(7):1717-27. doi:10.1007/s11136-012-0322-4

41. Royston P. Multiple imputations of missing values: update of ice. *Stata J*. 2005;5(4):527.

42. Good Clinical Practice. Health Research Authority. https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/good-clinical-practice/. Published 2022. Accessed January 12, 2022.

43. The Caldicott Report. *IHRIM*. 1999;40(2):17-19.

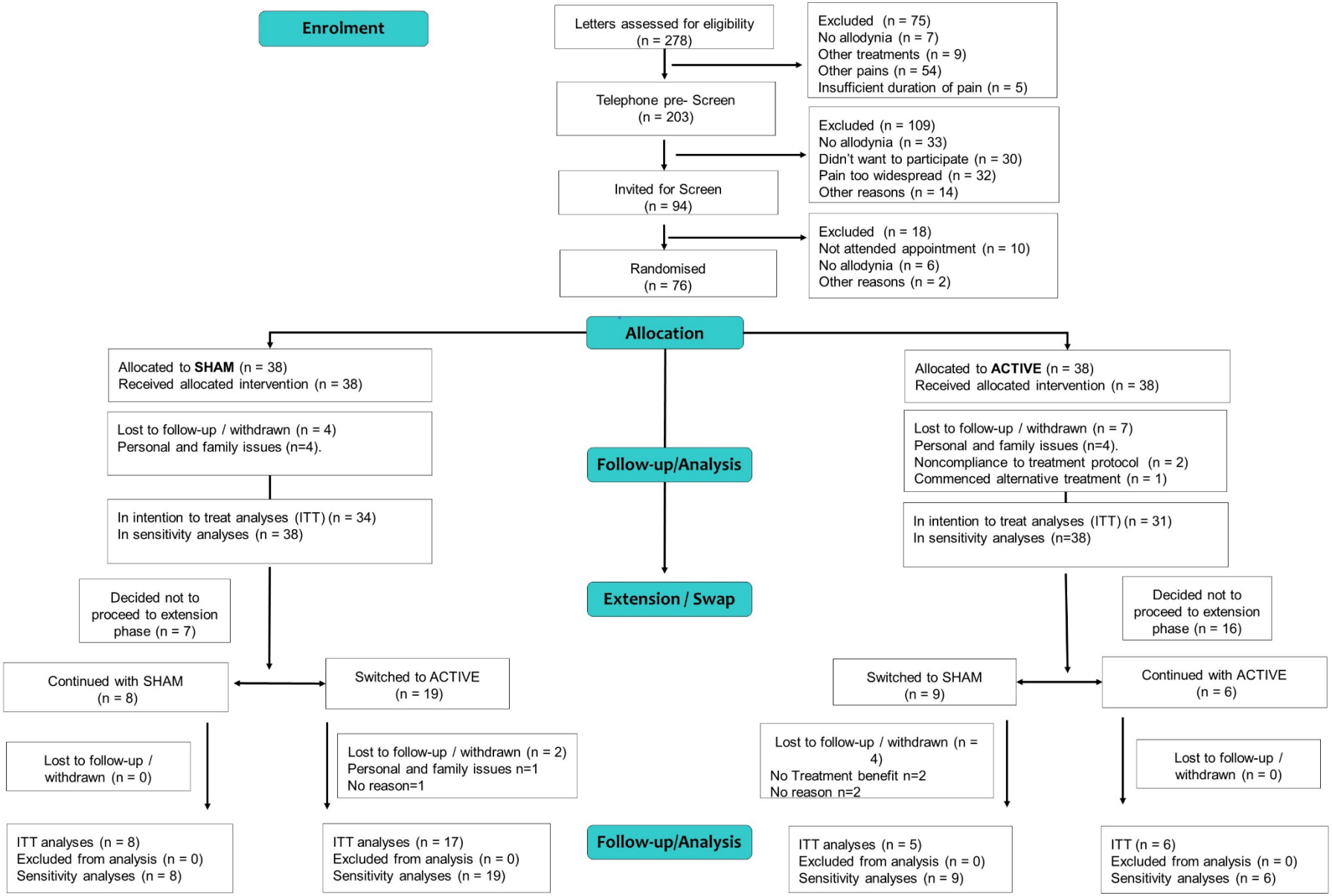
Chapter 6 Results

Participants

Participant flow

Participants were recruited for the EN-PENS trial between January 26, 2017, and July 11, 2019. All patients had completed treatment by January 16, 2020. All referral letters received by the study centre's pain clinic during this period were screened by the study's principal investigator (PI). Two hundred and seventy-eight referral letters mentioning a diagnosis of neuropathic pain were identified. Of these, it was felt that 203 could be potentially eligible for inclusion and received a telephone pre-screen from which 96 patients were invited for screening. Seventy-six of these ninety-six patients were found eligible following the screening. Reasons for exclusion included; n=18 did not meet the inclusion criteria, n=10 did not attend the screening, n=6 had no allodynia and a further 2 were excluded for other reasons (see Fig 6.1). Seventy-six patients were randomised to treatment (38 per group), and 65 patients contributed to the protocol analysis (34 sham, 31 active).
Eleven patients (14%, active n= 7/38, sham n=4/38) withdrew from the main treatment phase (reasons for withdrawal are defined within the methods chapter). Reasons for withdrawal included personal and family issues (n=8), non-compliance to treatment protocol (n=2), and one patient discontinued undergoing alternative treatment. Forty-two patients (55%) entered the optional treatment extension/ swap phase, and 6 patients withdrew during this phase. Reasons for withdrawal included personal and family issues (n=1), no reason (n=3) and no treatment benefit (n=3). An illustration of the flow of patients throughout the study is shown in figure 6.1.

Figure 6.1: EN-PENS trial profile (CONSORT diagram)



Baseline characteristics

	Category	Active (n=38)	Sham (n=38)	All Patients (n=76)	Between group p value

The mean age of all 76 patients was 50.4 years (SD 15.9) and 35/76 (47%) were men. The average pain duration was 47 months with an interquartile range of [27,87]. The predominant mechanism of injury was peripheral nerve injury following surgery n=54 (71%). Fifty-nine per cent (n=44/76) of patients were potentially suitable for invasive neuromodulation (for all baseline demographic variables and outcomes per group refer to table 6.1). All patients were taking some form of regular pain medications, 1.7 on average (SD 1.4), a full list of previous pain treatments is provided in table 6.2.

Age		47·3 ± 15·9	53·6 ± 12·2	50·4 ± 14·0	0.06
Gender	Female	22 (58%)	18 (47%)	40 (53%)	0.36†
	Male	16 (42%)	20 (53%)	36 (47%)	-
Duration Pain (months)		44 [27, 96]	48 [26, 72]	47 [27, 87]	0.75‡
Mechanism of Injury	Nerve entrapment	1 (3%)	2 (5%)	3 (4%)	-
	Nerve injury:				
	- Surgery	29 (76%)	25 (66%)	54 (71%)	-
	- Other mech. Trauma	6 (16%)	7 (18%)	13 (17%)	-
	- Radiotherapy	2 (5%)	0 (0%)	2 (3%)	-
	- Medication	0 (0%)	1 (3%)	1 (1%)	-
	Post-herpetic neuralgia	0 (0%)	3 (8%)	3 (4%)	-
Number pain meds		1·6 ± 1·5	1·7 ± 1·4	1·7 ± 1·4	0.76
Pain medications (+)	General pain meds	18 (58%)	24 (69%)	42 (64%)	-
	NSAIDs	9 (29%)	13 (37%)	22 (33%)	-
	Opioids	9 (29%)	7 (20%)	16 (24%)	-
	Anti-Epileptics	15 (48%)	20 (57%)	35 (53%)	-
	Anti-Depressants	16 (52%)	11 (31%)	27 (41%)	-
	Muscle relaxants	1 (3%)	2 (6%)	3 (5%)	-
Baseline assessments:					
Primary	Pain in last seven days #	7·2 ± 1·2	7·5 ± 1·4	7·3 ± 1·3	0.32
Variability pain (*)		0·85 ± 0·51	0·84 ± 0·44	0·85 ± 0·47	0.93
Secondary	EQ VAS	51 ± 18	57 ± 25	54 ± 22	0.23
	EQ-5D index	0·35 ± 0·23	0·34 ± 0·29	0·35 ± 0·26	0.87
	BPI I	6·2 ± 1·9	6·4 ± 2·0	6·3 ± 1·9	0.66
Exploratory	BPI W	8·4 ± 1·1	8·2 ± 1·4	8·3 ± 1·2	0.49
	HADS anxiety	10·7 ± 4·3	10·4 ± 5·2	10·5 ± 4·8	0.78
	HADS depression	9·3 ± 4·6	9·0 ± 4·5	9·1 ± 4·5	0.77
	PESQ	24 ± 14	23 ± 14	24 ± 14	0.75
	DMA mapped area	207 ± 192	175 ± 141	191 ± 168	0.41
	NPSI total score	63 ± 15	61 ± 19	62 ± 15	0.61

Summary statistics are mean ± standard deviation, median [inter-quartile range] or number (percentage). There were no significant differences in any baseline measures between active and sham groups. For all measures of continuous data between group differences were compared using t-tests, † denotes ordinal data, that was compared using the chi square test, ‡ denotes continuous skewed data, were the means were compared using Mann Whitney u test.

(#) Denotes the average of the recorded 7-day pain intensities

(*) Measured by the standard deviation of the baseline daily pain scores in the week prior to randomisation

(+) Patients could be on more than one type of pain medication. Percentage values may not add up to 100%

EQ-VAS = EuroQol visual analogue score, EQ-5D Index = EQ-5D-5L index score (utility), BPI I =Brief pain inventory interference subscale, BPI W= Brief pain inventory worst pain intensity, HADS anxiety= Hospital anxiety scale anxiety subscale, HADS depression= Hospital anxiety scale depression subscale, PSEQ= Pain self-efficacy questionnaire, DMA mapped area = Dynamic allodynia mapped area, NPSI total= Neuropathic pain symptom inventory subscale total score.

Table 6.1 Patient demographics & baseline characteristics of the Intention to Treat analysis population.

Table 6.2: Previous medical treatments

	Sham n (%)	Active n (%)	All Patients n (%)
Acupuncture	7 (18%)	6 (16%)	13 (17%)
Botox	1 (3%)	0 (0%)	1 (1%)
Capsaicin high dose patches	8 (21%)	5 (13%)	13 (17%)
Capsaicin cream	5 (13%)	5 (13%)	10 (13%)
Cognitive behavioural therapy	1 (3%)	0 (0%)	1 (1%)
Hydrotherapy	1 (3%)	2 (5%)	3 (4%)
Hypnosis	1 (3%)	0 (0%)	1 (1%)
Laser treatment	2 (5%)	0 (0%)	2 (3%)
Lidocaine	17 (45%)	13 (34%)	30 (39%)
Mirror box	1 (3%)	0 (0%)	1 (1%)
Nerve block	10 (26%)	10 (26%)	20 (26%)
Nerve decompression	1 (3%)	1 (3%)	2 (3%)
Nerve exploration	5 (13%)	3 (8%)	8 (11%)
Neuromodulation	0 (0%)	1 (3%)	1 (1%)
Opioids	5 (13%)	3 (8%)	8 (11%)
Orthotic	1 (3%)	0 (0%)	1 (1%)
Physiotherapy	15 (39%)	17 (44%)	32 (42%)
PMP (pain management programme)	3 (8%)	3 (8%)	6 (8%)
Psychological therapy	0 (0%)	1 (3%)	1 (1%)
Pulsed radiofrequency	3 (8%)	1 (3%)	4 (5%)
Steroid injection	0 (0%)	1 (3%)	1 (1%)
TENS	7 (18%)	9 (24%)	16 (21%)
TMS	0 (0%)	1 (3%)	1 (1%)
Trigger point injections	1 (3%)	1 (3%)	2 (3%)
Note: Patients could have more than one type of previous management. Percentage values may not add up to 100%			

Baseline outcome characteristics

Concerning baseline outcome characteristics (see table 6.1), the average 24 hr pain intensity (averaged over the 7 days before randomisation) was 7.3 (SD 1.3), average variability of this score over the 7 days was 0.85 (SD 0.47). Mean EQ-5D-5L VAS perceived overall health status was 54/100 (SD 22) and the health utility score was 0.35 (SD 0.26). Average Brief pain inventory interference (BPI I) baseline scores indicating moderate levels of functional impairment, 6.3/10 (SD 1.9). Mean worst pain intensity was high scoring 8.3/10 (SD 1.2), whilst the Hospital Anxiety and Depression Scale (HADS) anxiety score were 10.5 (SD 4.8), and the HADS depression score was 9.1 (SD 4.5). Scores were within the mild category. Pain Self-efficacy Questionnaire (PSEQ) scores were at the lower end of the range of 24/60 (SD 14), indicating low perceived confidence to perform an activity in the presence of pain. Dynamically mapped allodynia (DMA) varied greatly across individuals with an

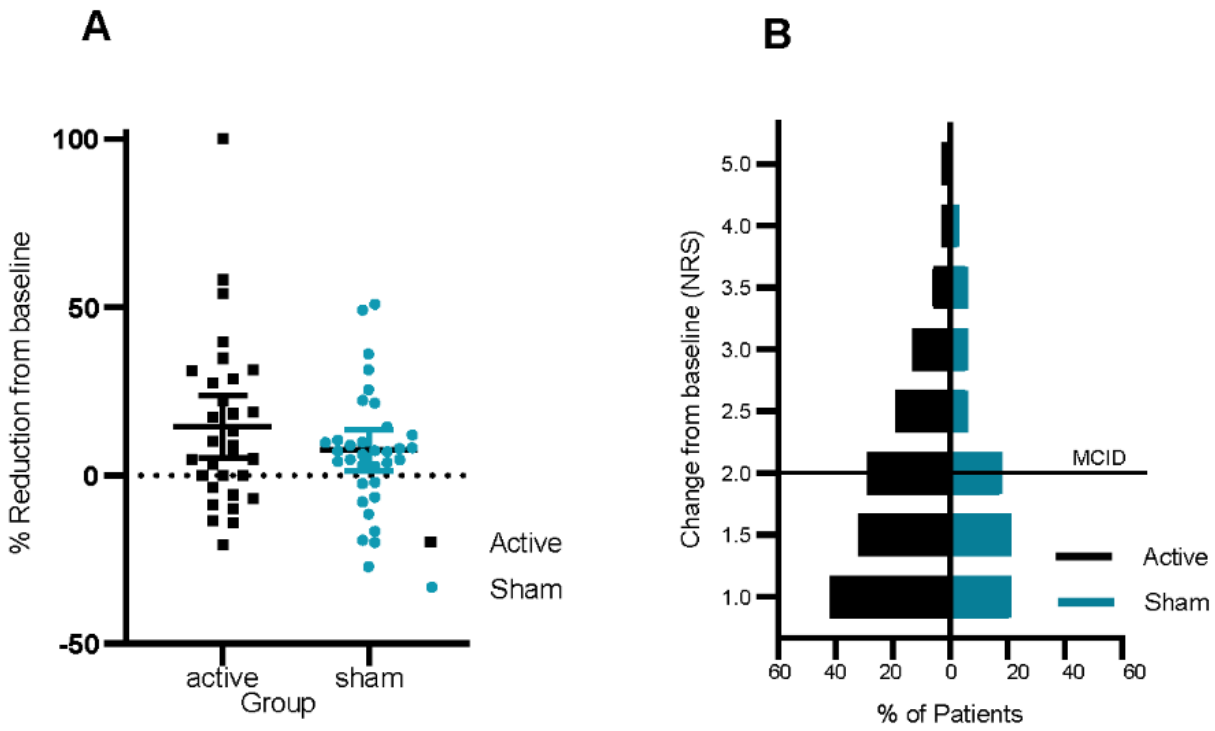
average score of 191cm^3 (SD 168) for the group, whilst the neuropathic pain symptom inventory (NPSI) total subscore was at the higher end of the pain symptom range at 62/100 (SD 1.5). This would indicate that patients had high incidence and severity in terms of features of neuropathic pain. Baseline demographics and baseline outcomes were statistically comparable between groups.

Primary outcome

Intention to treat analysis

This was based on all randomized eligible patients and suggested no evidence of a statistically significant difference in the primary outcome between study groups (Fig 6.2 A, Table 6.3). The data for the primary outcome met the assumptions of the statistical methods (e.g., normal distribution of residuals and homogeneity of variance), thus, no data transformation of the outcome was required. After accounting for baseline scores, the pain scores at 3 months were 0.3 units lower in the active group (95% CI -1.0, 0.3; p=0.30) giving an effect size of 0.19 (Cohens D).

Figure 6.2 Average spontaneous pain reduction at an individual level, and in discrete improvement intervals.



A Percentage reduction in the average NRS pain intensity from baseline to end of treatment. Negative scores denote worsening; B Percentage of patients achieving step-reductions in their average NRS scores from baseline to the end of treatment, where MCID denotes the minimal clinically important difference of equal to 2; n = 31 active, n = 34 sham, error bars show mean and 95% confidence intervals.

Table 6.3: Study Outcomes (Intention to treat).

	Group	N	Baseline Mean ± SD	3 months Mean ± SD	Trt effect (*) Mean (95% CI)	P-value	t value
Primary Outcome							
Average NRS (over 7 days)	Sham	34	7.3 ± 1.4	6.7 ± 1.7	0	0.30	-1.04
	Active	31	7.1 ± 1.3	6.2 ± 1.9	-0.3 (-1.0, 0.3)		
Secondary outcomes							
EQ-5D-5L VAS	Sham	34	57 ± 25	56 ± 24	0	**0.05**	2.04
	Active	31	48 ± 18	61 ± 20	10 (0, 19)		
EQ-5D-5L Health Index	Sham	34	0.35 ± 0.29	0.41 ± 0.31	0	0.40	0.84
	Active	31	0.36 ± 0.25	0.46 ± 0.29	0.04 (-0.06, 0.14)		
BPI	Sham	34	6.3 ± 2.0	5.8 ± 2.3	0	0.06	-1.96
Interference	Active	31	6.3 ± 1.9	4.9 ± 2.6	-0.9 (-1.7, 0.0)		
Exploratory Outcomes							
BPI worst pain	Sham	34	8.0 ± 3.0	7.4 ± 1.9	0	0.07	-1.84
	Active	31	8.4 ± 1.0	7.0 ± 1.9	-0.8 (-1.6, 0.1)		
HADS anxiety	Sham	34	10.6 ± 5.1	9.7 ± 4.5	0	0.22	-1.24
	Active	31	11.0 ± 4.7	9.2 ± 5.1	-0.9 (-2.3, 0.5)		
HADS depression	Sham	34	9.0 ± 4.5	9.0 ± 5.0	0	0.13	-1.54
	Active	31	9.4 ± 4.9	8.3 ± 4.9	-1.1 (-2.4, 0.3)		
PESQ	Sham	34	24 ± 15	27 ± 16	0	0.46	0.75
	Active	31	23 ± 13	28 ± 15	1 (-2, 5)		
DMA	Sham	34	180 ± 145	215 ± 202	0	**0.006**	-2.85
	Active	31	211 ± 204	173 ± 215	-74 (-126, -22)		
NPSI total	Sham	34	59 ± 18	55 ± 16	0	0.13	-1.54
	Active	31	63 ± 15	52 ± 19	-5 (-12, 2)		

** Trt effect =Treatment effect is the difference in outcome between treatment groups, adjusted for outcome at baseline. All analyses using ANCOVA. The figures highlighted in bold indicate a significant level <0.05.n= the number of patients with both baseline and end of treatment outcomes, Average NRS= Average pain intensity, EQ-VAS = EuroQol visual analogue score, EQ-5D Index = EQ-5D-5L index score (utility), BPI I =Brief pain inventory interference subscale, BPI W= Brief pain inventory worst pain intensity, HADS anxiety= Hospital anxiety and depression scale anxiety subscale, HADS depression= depression subscale, PSEQ= Pain self-efficacy questionnaire, DMA mapped area = Dynamic allodynia mapped area, NPSI total= Neuropathic pain symptom inventory subscale total score. No correction for multiple analyses took place.*

In a secondary analysis of the primary outcome, the proportion of patients exceeding the threshold of minimally meaningful pain reduction (≥ 2 points OR ≥ 30%) was 29% in the active group, compared to 18% in the sham group (table 6.4, Fig 6.2 B).

Table 6.4: Secondary analysis of the primary outcome, the proportion of patients achieving defined pain reduction.

	Sham		Active	
	N	**n (%)**	**N**	**n (%)**
Primary Outcomes				
≥ 2 points	34	6 (18%)	31	9 (29%)
≥ 30% (*)	34	4 (12%)	31	7 (23%)
≥ 50% (*)	34	1 (3%)	31	3 (10%)
≥ 2 points OR ≥ 30% (*)	34	6 (18%)	31	9 (29%)
(*) % change based on pain score at baseline				

Per protocol analysis

The analysis for the primary outcome, average 24h pain intensity over the last 7 days of the 3-month home-loan, was repeated for the per-protocol population (PP). One patient in the sham group did not use the machine throughout the 3-month study period and was thus excluded from the PP population. Aside from this one patient, the PP population was equivalent to the full analysis population. The results of the ANCOVA per-protocol analysis are listed in table 6.5.

Table 6.5: Primary outcome – Per Protocol population

Outcome	**Group**	**N**	**Baseline Mean ± SD**	**3 months Mean ± SD**	**Trt effect (*) Mean (95% CI)**	**P-value**	**t value**
Pain in last	Sham	33	7.4 ± 1.4	6.8 ± 1.7	0	0.34	-0.97
7 days	Active	31	7.1 ± 1.3	6.2 ± 1.9	-0.3 (-1.0, 0.4)		
Analysis using ANCOVA (*) Difference adjusted for outcome at baseline							

The data suggested no evidence of a statistically significant difference in the primary outcome between the two study groups. The size of the difference between treatment groups was equivalent to that observed for the intention to treat analysis.

The number of patients meeting pre-determined targets for the improvement in the primary outcome was also quantified (The information is summarised in Table 6.6).

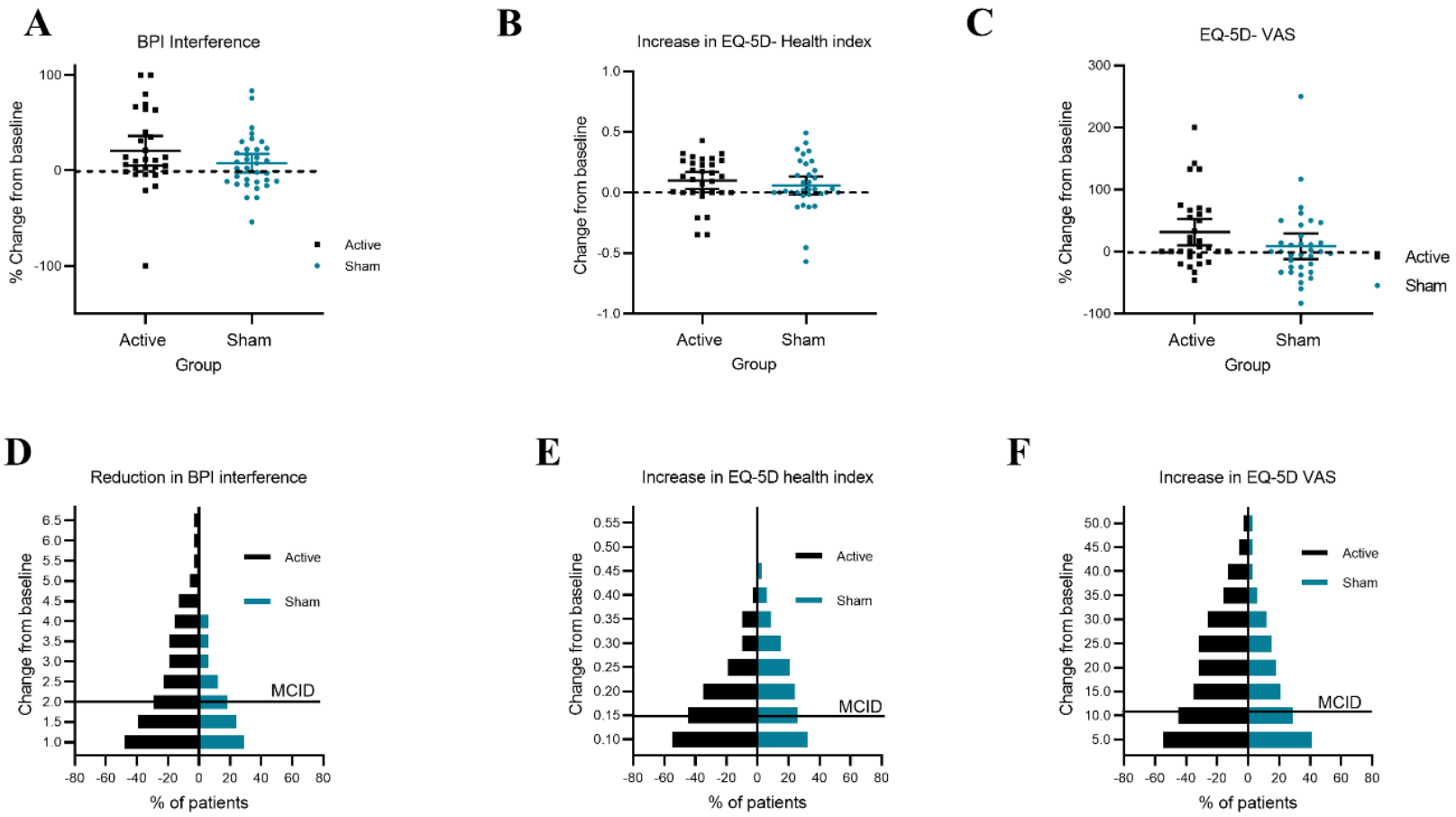
Table 6.6: Improvement in the primary outcome – Per Protocol population

Pain Improvement	**Sham**		**Active**	
	N	n (%)	N	n (%)
≥ 2 points	33	6 (18%)	31	9 (29%)
≥ 30% (*)	33	4 (12%)	31	7 (23%)
≥ 50% (*)	33	1 (3%)	31	3 (10%)
≥ 2 points OR ≥ 30% (*)	33	6 (18%)	31	9 (29%)
(*) % change based on pain score at baseline				

Secondary Outcome measures

There was some evidence of a difference between groups for 2/3 of the secondary outcomes (Table 6.3, Fig 6.3). Quality of life ratings (EQ5D-5L VAS) was on average 10 points higher in the active group (95% CI 0, 19; p=0.05). The BPI interference subscale values were on average 0.9 points lower (BPI interference subscale) (95 % CI -1.7, 0.0; p=0.06). It should be noted that EQ-5D- Health index score is weighted by population preferences, unlike the EQ-VAS which reflects individual patient changes in outcome.

Figure 6.3 Secondary outcomes.



A- Percentage improvement in the average BPI interference from baseline to end of treatment; B- Score change in Eq-5D health index from baseline to end of treatment; C Percentage improvement in Eq-5D VAS. For A, B and C Negative scores denote worsening; D, E &F illustrate the percentage of patients achieving step-reductions in the presented outcome from baseline to the end of treatment, where MCID denotes minimal clinically important difference relative to that outcome; n = 31 active, n = 34 sham. For A, B and C Negative scores denote worsening; error bars show mean and 95% confidence intervals, D, E &F illustrate the percentage of patients achieving step-reductions in the presented outcome from baseline to the end of treatment, where MCID denotes minimal clinically important difference relative to that outcome; n = 31 active, n = 34 sham.

Sensitivity analysis

Before the study started attrition rates were unknown. Therefore, sensitivity analysis using multiple imputations was built into the statistical analysis plan to assess the impact of missing values. Attrition rates on study completion were very low. For primary outcomes, the multiple imputation analysis suggested that the active group had pain scores that were, on average, 0.4 (95% CI) units lower than the sham group and were not found to be statistically significant (p=0.2). For secondary outcomes, there was no strong evidence of a difference between groups for any of the secondary outcomes (see Table 6.7).

Table 6.7: Sensitivity Analysis using multiple imputation methods.

	Group	**N**	**Baseline (+) Mean ± SD**	**3 months (#) Mean (95% CI)**	**Trt effect (*) (#) Mean (95% CI)**	**P-value**	**t value**
Primary outcome 7 days	Sham	38	7.5 ± 1.4	6.9 (6.3, 7.6)	0	0.22	-1.23
	Active	38	7.2 ± 1.2	6.2 (5.6, 6.9)	-0.4 (-1.1, 0.3)		
EQ VAS	Sham	38	58 ± 25	57 (49, 64)	0	0.10	1.70
	Active	38	50 ± 18	61 (53, 69)	8 (-1, 18)		
EQ-5D	Sham	38	0.34 ± 0.29	0.40 (0.31, 0.50)	0	0.49	0.70
	Active	38	0.35 ± 0.23	0.45 (0.35, 0.55)	0.03 (-0.06, 0.13)		
BPI Interference	Sham	38	6.4 ± 2.0	5.9 (5.1, 6.7)	0	0.11	-1.65
	Active	38	6.2 ± 1.9	4.9 (4.0, 5.7)	-0.8 (-1.7, 0.2)		
All analyses using ANCOVA, (+) Observed data, (#) Values after multiple imputations, (*) Treatment effect is the difference in outcome between treatment groups, adjusted for outcome at baseline. No correction for multiple analyses took place.							

Exploratory Efficacy Analyses

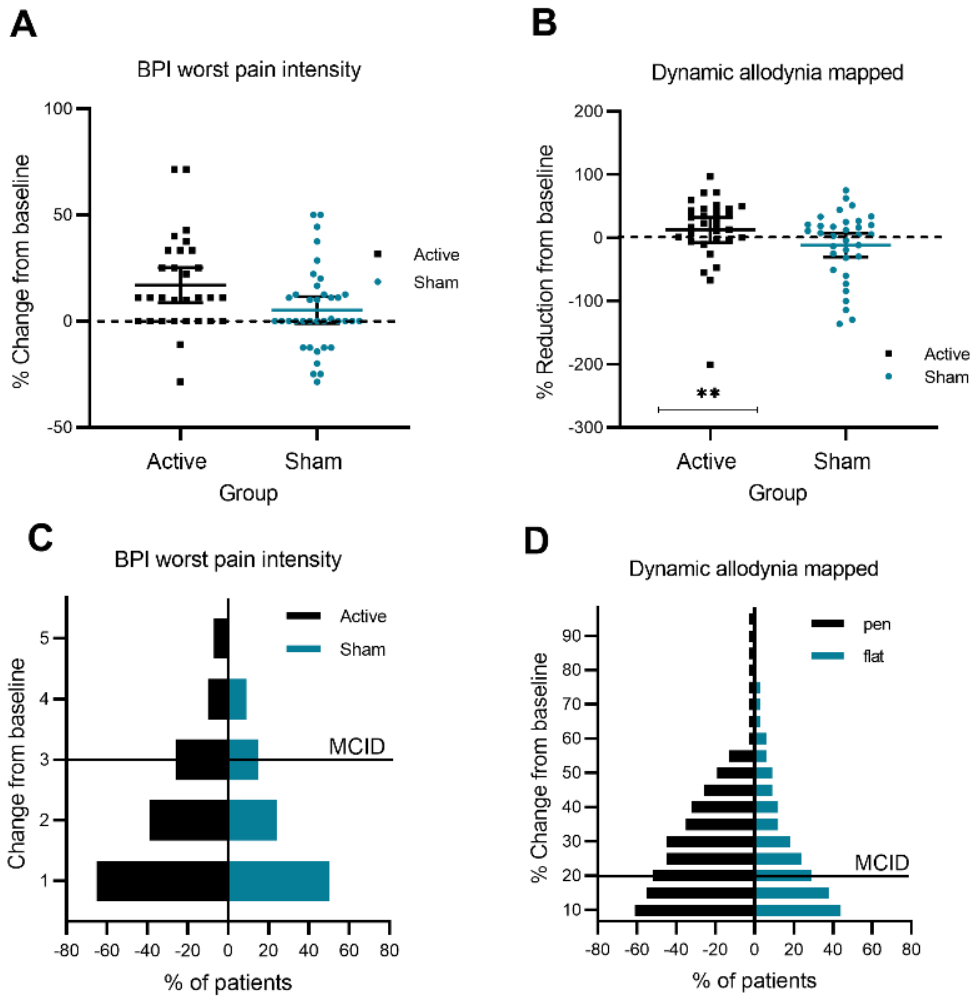
The only outcome within the EN-PENS trial to demonstrate significant change between groups was DMA (95% CI: 22 to 126 units lower; p=0.006). This measured 74 units lower in the active group compared to the sham group. BPI worst pain scores were on average, 0.8 units lower in the active group following treatment (table 6.3, Fig 6.4), but this difference was only of borderline statistical

significance (p=0.07). Several of the exploratory outcomes were measured on a categorical or ordinal scale. The analysis results for these outcomes are summarised in Table 6.8. Patients perceived global impression of change did not differ between groups. More patients in the active group felt they had been allocated a more effective vs less effective treatment (18 (64%) vs 10 (36%)) compared to the sham group (11 (37%) vs 19 (63%)).

Table 6.8: Exploratory outcomes on categorical/ordinal scale

Outcome	**Category**	**Sham**		**Active**		**P-**
		N	n (%)	N	n (%)	value
PGIC	Much worse	33	1 (3%)	31	0 (0%)	0.36
	Minimally worse		1 (3%)		1 (3%)	
	No change		19 (58%)		16 (52%)	
	Minimally improved		7 (21%)		7 (23%)	
	Much improved		5 (15%)		6 (19%)	
	V. much improved		0 (0%)		1 (3%)	
Allocation prediction	Square electrode	30	19 (63%)	28	10 (36%)	**0.04**
	Active electrode		11 (37%)		18 (64%)	
Allocation Result	Incorrect	30	11 (37%)	28	10 (36%)	0.94
	Correct		19 (63%)		18 (64%)	
Continued to extension	No	34	7 (21%)	30	15 (50%)	**0.01**
	Yes		27 (79%)		15 (50%)	
Swap to other device (+)	No	27	8 (30%)	15	6 (40%)	0.50
	Yes		19 (70%)		9 (60%)	
(+) Figures for those continuing to the extension period only						

Figure 6.4 Exploratory outcomes demonstrating positive change.



A- Percentage improvement in the average BPI worse pain intensity from baseline to end of treatment; B- Percentage improvement in the average Dynamic allodynia mapped (DMA) from baseline to end of treatment; For A & B Negative scores denote worsening, error bars show mean and 95% confidence intervals; D & E illustrate the percentage of patients achieving step-reductions in the presented outcome from baseline to the end of treatment, where MCID denotes minimal clinically important difference relative to that outcome; n = 31 active, n = 34 sham.

Minimally Clinical Important Difference Change (MCID)

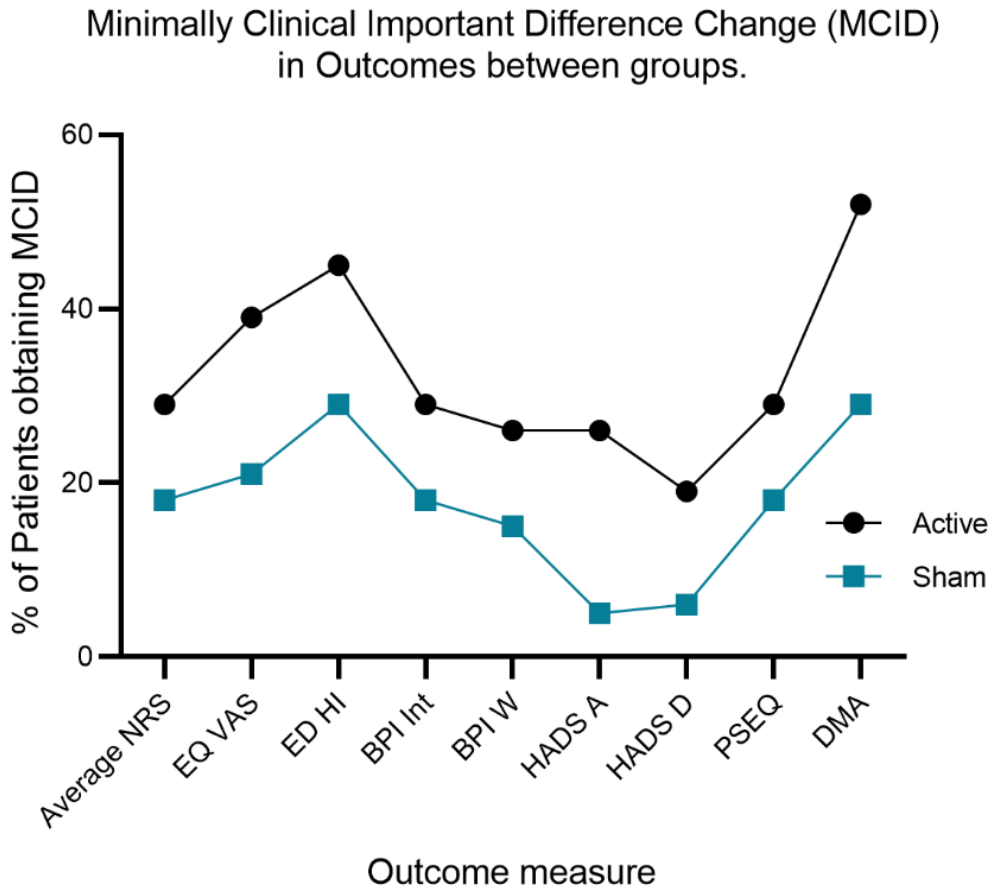
For the average pain intensity (primary outcome) the number of patients experiencing ≥ 2 points OR ≥ 30% NRS reduction was 29% of patients in the active group, compared to 18% of the sham group (table 6.9, Fig 6.2B). For the EQ-5D-5L VAS health status score, 39% in the active group reported a clinically meaningful improvement compared to 21% in the sham group (Table 6.9, Fig 6.3F). The health index subscale of the EQ-5D-5L demonstrated that 45% of persons in the active group demonstrated MCID compared to 29% in the sham group (table 6.9, Fig 6.3E). In terms of functional interference, 29% of patients in the active group reported MCID compared to 18% in the sham group (Table 6.9, Fig 6.3D). For all exploratory outcomes, the number of patients achieving minimally clinical important difference (MCID) change in outcomes was proportionally higher in favour of the active group across all outcome domains (Table 6.9, Fig 6.5).

Table 6.9: Minimally clinical important difference (MCID) change for outcomes.

	Sham		Active		Fisher's exact P-value
	N	**n (%)**	**N**	**n (%)**	
Primary Outcomes					
≥ 2 points OR ≥ 30% (*)	34	6 (18%)	31	9 (29%)	0.131
Secondary outcomes					
EQVAS ≥ 11	34	7 (21%)	31	12 (39%)	0.061
EQ-5d ≥ 0.145	34	10 (29%)	31	14 (45%)	0.088
Interference ≥ 2	34	6 (18%)	31	9 (29%)	0.131
Exploratory outcomes					
BPI worst pain ≥ 3	34	5 (15%)	31	8 (26%)	0.134
Anxiety ≥ 4 (**)	34	5 (15%)	31	8 (26%)	0.134
Depression ≥ 4 (**)	34	2 (6%)	31	6 (19%)	0.082
PESQ ≥ 7 (**)	34	6 (18%)	31	9 (29%)	0.131
DMA ≥ (***)	34	10 (29%)	31	16 (52%)	**0.039**
Total mean	34	19% (±7.1)	31	33% (± 11)	**0.005¥**

** % change based on pain score at baseline*
*** Also met additional criteria of movement to different severity category*
**** >20 % change based on the area at baseline, EQ-VAS = EuroQol visual analogue score, EQ-5D Index = EQ-5D-5L index score (utility), BPI I =Brief pain inventory interference subscale, BPI W= Brief pain inventory worst pain intensity, HADS anxiety= Hospital anxiety scale anxiety subscale, HADS depression= Hospital anxiety scale depression subscale, PSEQ= Pain self-efficacy questionnaire, DMA mapped area = Dynamic allodynia mapped area, ± standard deviation, ¥ Mann Whitney.*

Figure 6.5 Minimally Clinical Important Difference Change (MCID) in Outcomes between groups.



Plotted scores indicate the average percentage of patients achieving MCID for each respective outcome. Key: NRS= numerical rating scale, EQ-VAS = EuroQol visual analogue score, EQ-5D HI = EQ-5D-5L index score (utility), BPI Int =Brief pain inventory interference subscale, BPI W= Brief pain inventory worst pain intensity, HADS A= Hospital anxiety scale anxiety subscale, HADS D= Hospital anxiety scale depression subscale, PSEQ= Pain self-efficacy questionnaire, DMA = Dynamic allodynia mapped area; n = 31 active, n = 34 sham.

Number of prespecified successful outcomes

The number of prespecified successful outcomes (n=9) (as defined by MCID) was also compared between the two groups. The analysis results are summarised in Table 6.10.

Table 6.10: Number of successful outcomes

Outcome	Group	N	Mean ± SD	Median [IQR]	P-value
Prim/Secondary Outcomes	Sham	34	0.9 ± 1.1	0.5 [0, 1]	0.05
	Active	31	1.4 ± 1.3	1 [0, 2]	
All outcomes	Sham	34	1.7 ± 1.4	1.5 [1, 2]	**0.03**
	Active	31	2.9 ± 2.4	3 [1, 4]	
Summary statistics are mean ± standard deviation, median [interquartile range]					

The group difference achieved statistical significance when just the primary and secondary outcomes were included and additionally when all outcomes were included in the outcome definition.
The number of successful outcomes achieved was higher in the active group than in the sham group. When all outcomes were considered, the active group met a mean of 2.9 outcomes (out of 9), compared to a mean of 1.7 (out of 9) in the sham group.

Safety analysis

A total of 101 AEs were reported in the sham group (average 2.7 +/-2.0 per patient in this group) compared to 103 in the active group (average 2.7 +/- 1.9 per patient in this group) and two SAEs events were reported overall. The SAEs considered not to be related were viral meningitis and shingles. Three AEs were evaluated as definitely related to the device (active n=2 and sham n=1) and were reported as increased pain during stimulation, whilst 10 were evaluated as probably related (active= 3 and sham n=7) and were reported as temporary bruising, redness, and pain during stimulation (Table 6.11).

Table 6.11 Safety Analysis Information

	Category	Sham n events (%)	Active n events (%)
Total number of Adverse events		101	103
Number of patients experiencing AEs		31 (82%)	34 (89%)
AEs per patient		2.7 ± 2.0	2.7 ± 1.9
AE seriousness	Not serious	101 (100%)	101 (98%)
	Serious	0 (0%)	2 (2%)
AE intensity	Mild	36 (38%)	44 (45%)
	Moderate	55 (58%)	50 (51%)
	Severe	4 (4%)	4 (4%)
Relatedness to	Definite	2 (2%)	1 (1%)
study treatment	Probable	7 (7%)	3 (3%)
	Possible	15 (15%)	27 (26%)
	Remote	16 (16%)	9 (9%)
	Not related	60 (60%)	63 (61%)
SAE details	Shingles	-	1 (50%)
	Viral Meningitis	-	1 (50%)
AE details	Musculoskeletal system	28 (28%)	22 (21%)
	Renal system problem	7 (7%)	2 (2%)
	Digestive system problem	2 (2%)	9 (9%)
	Psychological	1 (1%)	2 (2%)
	Respiratory	21 (21%)	17 (17%)
	Cardiac	2 (2%)	1 (1%)
	Infection and infestation	4 (4%)	13 (13%)
	Eye disorder	1 (1%)	4 (4%)
	Ear/ labrythinitis disorder	0 (0%)	1 (1%)
	Injury, procedural complications	24 (24%)	27 (26%)
	Headache	6 (6%)	4 (4%)
	Other	5 (5%)	1 (1%)

n= number of patients, % represents % of patients as a proportion of the total number of AEs per group. AE= adverse event, AEs- adverse events, SAE= serious adverse event

Data from the optional extension period

Average NRS dropped by 1.0 points (n=5, 95% CI -3.3, 1.3, p=0.28) for those that continued with the active treatment. Those that switched from sham to active or that continued with sham did not exceed an improvement of 0.3 points. Those that switched from active to sham experienced a worsening of pain by 1.5 points n=5 (95% CI 0.4, 2.6, p=0.02). There were no significant changes in

other outcomes from the end of the main trial phase to the end of the extension period in the various study subgroups (Table 6.12). It is noted that the results here should be treated with some caution, as they were based on small numbers in subgroups.

Table 6.12: Changes from the end of the main study to the end of the extension

	Subgroup	N	Main study Mean ± SD	End Extension Mean ± SD	Change (*) Mean (95% CI)	P-value
Pain in last	Sham/Sham	6	6.0 ± 1.7	5.9 ± 2.3	0.0 (-0.9, 0.8)	0.89
7 days	Sham/Active	17	6.8 ± 1.8	6.5 ± 2.1	-0.3 (-1.1, 0.6)	0.51
	Active/Active	5	5.7 ± 0.8	4.7 ± 1.1	-1.0 (-3.3, 1.3)	0.28
	Active/Sham	5	4.7 ± 2.4	6.3 ± 2.2	1.5 (0.4, 2.6)	**0.02**
EQ-5D HI	Sham/Sham	6	0.57 ± 0.24	0.53 ± 0.31	-0.04 (-0.21, 0.13)	0.58
	Sham/Active	17	0.36 ± 0.31	0.29 ± 0.31	-0.07 (-0.15, 0.01)	0.07
	Active/Active	5	0.69 ± 0.07	0.65 ± 0.15	-0.04 (-0.23, 0.15)	0.60
	Active/Sham	7	0.55 ± 0.24	0.54 ± 0.28	-0.01 (-0.17, 0.15	0.92
DMA	Sham/Sham	6	227 ± 223	126 ± 96	-101 (-268, 66)	0.18
	Sham/Active	16	231 ± 213	227 ± 221	4 (-39, 48)	0.83
	Active/Active	6	139 ± 139	161 ± 142	22 (-21, 64)	0.25
	Active/Sham	7	160 ± 70	237 ± 191	77 (-54, 207)	0.20
Frequency	Sham/Sham	4	2.5 ± 0.6	2.3 ± 1.0	-0.2 (-1.0, 0.5)	0.39
of use	Sham/Active	13	2.1 ± 1.3	1.9 ± 16	-0.2 (-1.0, 0.7)	0.71
	Active/Active	6	1.5 ± 0.5	1.5 ± 0.5	0.0 (0.0, 0.0) (+)	1.00
	Active/Sham	5	2.8 ± 2.2	2.2 ± 1.3	-0.6 (-1.7, 0.5)	0.21

The within-group comparisons were performed using the paired t-test, as the change in scores was found to follow a normal distribution for all outcomes. (*) Change calculated as values at end of extension minus end of the main trial,
(+) The confidence interval of zero width as all patients had the same frequency of use at both timepoints,
EQ-5D HI = EQ-5D-5L index score (utility), DMA= dynamic allodynia mapped.

Factors associated with favourable outcomes

Further analyses were performed to examine associations between patient baseline factors and three key study outcomes; 1. primary study outcome, 2. EQ-5D-5L VAS health status scale and 3. number of successful outcomes. Each patient/baseline factor was considered separately in a series of univariable linear regressions. The analysis results are summarised in Table 6.13. The figures are the regression coefficients, along with corresponding confidence intervals, and associated p-value indicating the significance of the results. For the categorical factors, the regression coefficients represent the difference in pain scores between each category and a baseline category. For the continuous factors, the regression coefficients represent the change in pain score for a one-unit increase in each factor. The number of successful outcomes was found to have a strongly positively

skewed distribution and was thus analysed on the log scale. The results are presented in terms of ratios.

Table 6.13: Univariable Linear regression results

Baseline factor	Category	Study factor	Unadjusted for baseline (*)		Adjusted for baseline (*)	
	Term		Coefficient (95% CI)	P-value	Coefficient (95% CI)	P-value
Baseline pain	-	1	0.9 (0.6, 1.2)	**<0.001**	-	
		2	-8 (-11, -4)	**<0.001**	-6 (-9, -2)	**0.004**
		3	0.92 (0.82, 1.04)	0.18		
Age (+)	Linear term Squared term	1	2.4 (0.4, 4.4) -0.2 (-0.5, 0.0)	0.05	1.4 (-0.1, 3.0) -0.2 (-0.3, 0.0)	0.16
	Linear term Squared term	2	-33 (-57, -9) 3 (1, 6)	**0.03**	-25 (-46, -3) 2 (0, 5)	**0.05**
	Linear term Squared term	3	0.88 (0.79, 0.99)	**0.03**		
Gender	Female Male	1	0 0.5 (-0.3, 1.4)	0.23	0 0.6 (-0.1, 1.3)	0.07
	Female Male	2	0 -3 (-14, 8)	0.64	0 0 (-10, 9)	0.93
	Female Male	3	1 0.77 (0.56, 1.04)	0.09		**
Duration of pain	≤ 3 years 3-6 years >6 years	1	0 -0.6 (-1.6, 0.5) 0.0 (-1.1, 1.2)	0.49	0 -0.5 (-1.3, 0.3) 0.0 (-0.8, 0.9)	0.35
	≤ 3 years 3-6 years >6 years	2	0 6 (-6, 18) -9 (-23, 5)	0.11	0 1 (-10, 13) -8 (-20, 5)	0.31
	≤ 3 years 3-6 years >6 years	3	1 0.98 (0.68, 1.41) 0.77 (0.52, 1.15)	0.39		
NPSI baseline						
Burning	-	1	0.12 (-0.01, 0.26)	0.07	0.03 (-0.07, 0.14)	0.52
		2	-2.5 (-4.0, -0.9)	**0.003**	-1.5 (-3.0, 0.1)	0.06
		3	0.96 (0.91, 1.00)	0.07		**
Pressing	-	1	0.10 (-0.04, 0.24)	0.17	0.08 (-0.03, 0.18)	0.16
		2	-1.2 (-3.0, 0.5)	0.17	-0.4 (-2.0, 1.2)	0.60
		3	0.98 (0.93, 1.03)	0.34		
Paroxysmal	-	1	0.07 (-0.09, 0.24)	0.37	-0.01 (-0.13, 0.12)	0.92
		2	-1.1 (-3.1, 0.9)	0.27	-0.7 (-2.5, 1.1)	0.43
		3	1.03 (0.98, 1.10)	0.25		
Evoked	-	1	0.21 (-0.05, 0.47)	0.12	0.00 (-0.21, 0.21)	0.98
		2	-2.9 (-6.1, 0.3)	0.07	-2.1 (-5.0, 0.7)	0.14
		3	1.05 (0.96, 1.15)	0.29		
Paraesthesia	-	1	-0.05 (-0.19, 0.10)	0.55	-0.05 (-0.16, 0.06)	0.40
		2	-0.8 (-2.7, 1.0)	0.36	-0.3 (-1.9, 1.3)	0.71
		3	1.02 (0.97, 1.08)	0.39		
Frequency of use (#)		1	0.2 (-0.2, 0.7)	0.26	-0.0 (-0.4, 0.3)	0.83
		2	-1 (-6, 4)	0.72	-3 (-8, 1)	0.14
		3	0.89 (0.77, 1.03)	0.12		

*(*) Unadjusted / adjusted for average pain score at baseline, (+) Regression coefficients reported for a 10-year increase in age, (#) an Average number of uses per day, and Factors demonstrating the significance of <0.05 are highlighted in bold. ** indicates scores with a significance of <0.1 that were also included in multiple regression, NPSI= neuropathic pain symptom inventory. Study factor 1= primary study outcome, 2= EQ-5D-5L VAS health status scale and 3=number of successful outcomes.*

Where the primary outcome was the dependent variable, the results suggested that, as might be expected, there was a strong association between baseline pain and pain at 3-months. Apart from baseline score, after accounting for baseline scores there were no factors strongly associated with the primary outcome. Therefore, no factors associated with the primary outcome were considered for multiple regression. Where EQ-5D VAS was the dependent variable in the linear regression factors of baseline pain score, age and NPSI burning score at baseline were significantly associated with EQ-5D VAS at 3 months. Where the numbers of successful outcomes were the dependent variable, the factors of age were significantly associated with the number of successful outcomes, with the number of successful outcomes decreasing with age. A 10-year increase in age was associated with a 12% reduction in the number of successful outcomes.

A backwards selection procedure was performed to retain only factors significantly <0.05 (or almost significant) associated with the outcome as part of the multiple regression. The results of these multiple regressions are summarised in table 6.14.

Table 6.14: Association between patient/baseline characteristics and the study factors of EQ-5D VAS score and number of favourable outcomes – Multiple Linear regression

Study factor	Baseline Factor	Term	Coefficient (95% CI) (*)	P-value
EQ-5D VAS score	Baseline pain	-	-5 (-9, -1)	**0.008**
EQ-5D VAS score	Age (+)	Linear term Squared term	-21 (-42, 0) 2 (0, 4)	0.08
EQ-5D VAS score	NPSI Burning (baseline)			
Number of favourable outcomes	Age (+)	-	0.90 (0.81, 1.01)	0.07
Number of favourable outcomes	Gender	Female Male	1 0.74 (0.56, 0.99)	**0.04**
Number of favourable outcomes	NPSI Burning (baseline)	-	0.95 (0.91, 0.99)	**0.02**
Number of favourable outcomes	Treatment group	Sham Electrode Active Electrode	1 1.29 (0.96, 1.74)	0.09
(*) Adjusted for study factor score at baseline (+) Regression coefficients reported for a 10-year increase in age, NPSI= neuropathic pain symptom inventory, EQ-5D VAS- health status visual analogue score, figures highlighted in bold denote a significant p-value of <0.5.				

The multiple regression where EQ-5D VAS was the dependent factor suggested that baseline pain score was still significantly associated with EQ-5D VAS. Higher pain scores at baseline were again

associated with lower VAS scores (B=-5, 95% CI (-9, -1) p<0.008). There was also some evidence of an association between age and the outcome, although again this result did not quite reach statistical significance. After adjusting for these two variables, NPSI burning score was no longer found to be significant.

Where the number of successful outcomes was the dependent factor, multiple regressions included baseline factors of age, gender and NPSI burning pain. The treatment group was also included, as the number of successful outcomes was previously found to vary between groups.

The multivariable analyses suggested that both gender (B=0.74, 95% CI (0.56, 0.99) p=0.04) and NPSI burning score (B=0.95, 95% CI (0.91, 0.99) p=0.02) were significantly associated with the number of successful outcomes. The results showed males had fewer successful outcomes than females, a higher NPSI baseline score was also associated with fewer successful outcomes, whilst age was no longer significant.

Health economic outcomes

The economic analysis was conducted by the Bangor health economics department to estimate the incremental cost per quality adjusted-life-year of EN-PNS compared to the sham device. The incremental QALY difference in 3-month costs between the active electrode and the sham electrode was 0.0035 (95% CI (-0.0167, 0.0246), which is equivalent to approximately 3 additional days of perfect health over 3-months. The active device was associated with more QALYs, but at a higher cost and was not found to be cost-effective when compared to the sham intervention.

Table 6.15: Economic outcomes; CI=confidence interval, QALY= quality-adjusted life years, ICER=Institute for clinical and economic review threshold.

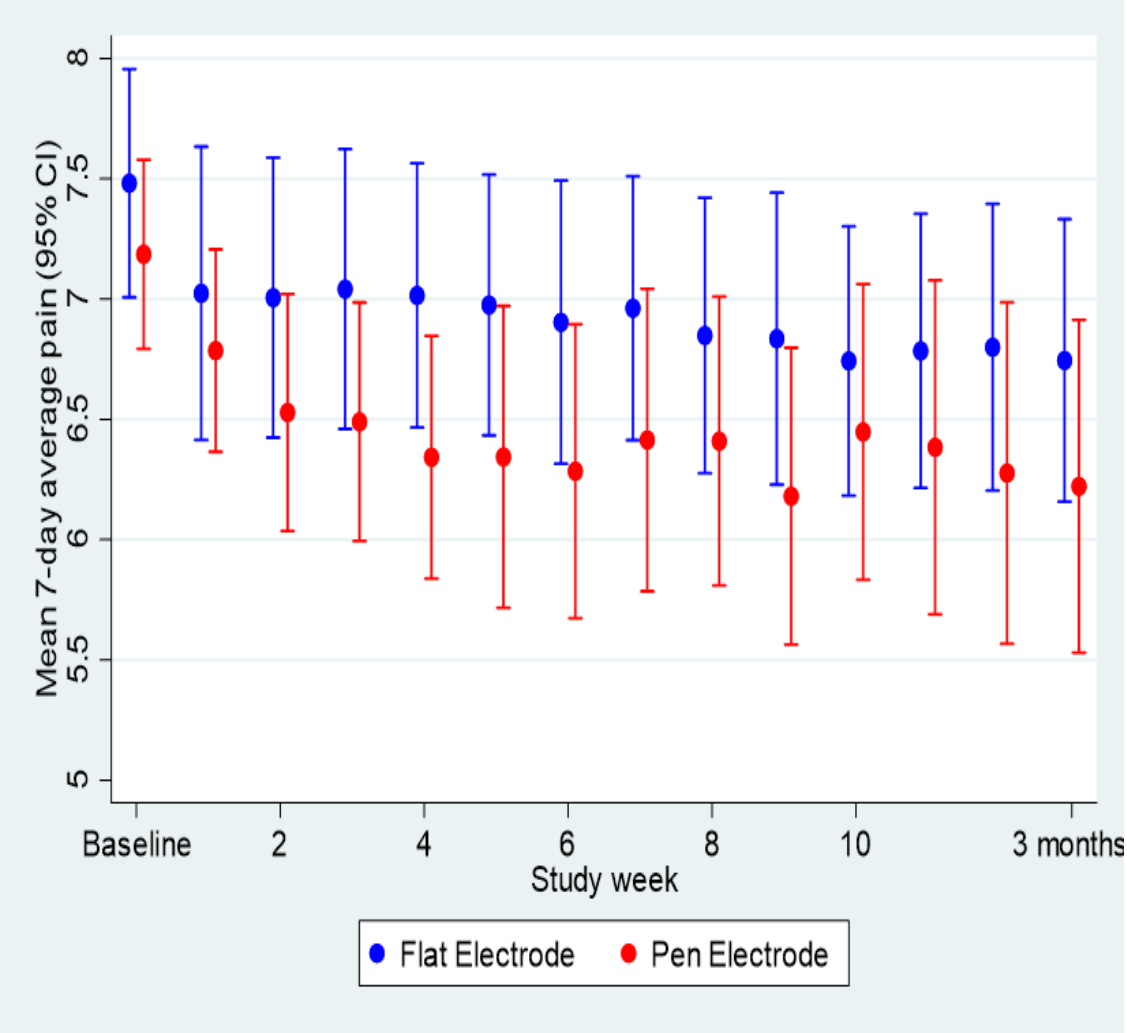
ADJUSTED					
	Mean total costs (95% CI)	**Mean total QALYs (95% CI)**	**Incremental Costs (95% CI)**	**Incremental QALYs (95% CI)**	**ICER**
Sham	£524 (305, 828)	0.1221 (0.1008, 0.1403)			
Active	£2372 (2174, 2577)	0.1255 (0.1000, 0.1481)	£1848 (1481, 2152)	0.0035 (-0.0167, 0.0246)	£528,040/QALY

Further exploratory analysis

Additional exploratory measure analysis

An additional exploratory outcome was the 7-day average pain scores throughout the study. These were analysed graphically by plotting the scores in each treatment group over time. This information is shown in figure 2. The figures reported are the mean score in each treatment group over time, with the error bars indicating the 95% confidence interval of the mean. Seven-day average pain scores in each treatment group over time graphically illustrate both treatment groups undergo a reduction in scores from the baseline time point to 1 week, with some further reductions at week 2 for the active group which remain consistently lower throughout (Fig 6.6).

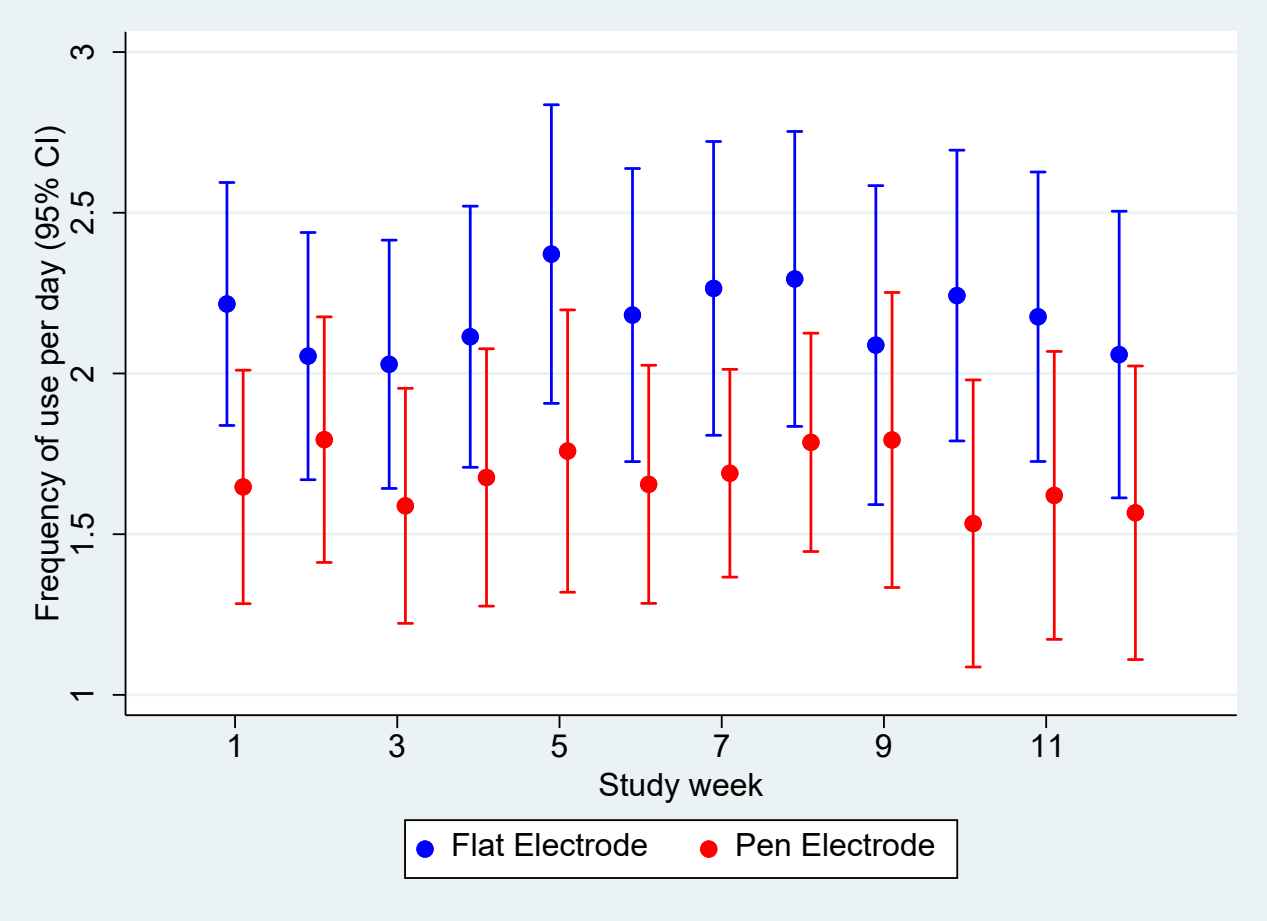
Figure 6.6. Mean 7-day average pain intensity over the treatment phase.



The figures reported are the mean score in each treatment group over time, with the error bars indicating the 95% confidence interval of the mean.

Also, of interest was the frequency of use of the device throughout the study in the two treatment groups. This was also examined graphically, and the summary data for this measure is summarised in figure 6.7.

Figure 6.7: Frequency of device use throughout the study



Post hoc telephone survey results

Post-hoc interview with 12 patients within the active treatment group was conducted to understand how patients used and experienced the treatment (Appendix 4, Post hoc telephone questionnaire). The first question asked patients how the stimulation felt. Patients who perceived the stimulation as painful n=6, all perceived the treatment as beneficial, whilst those who described the treatment as uncomfortable or not painful did not perceive any benefit n=6 (Fig 6.8, Q1a and Q1b).

All patients who did not find stimulation painful were asked in question 2 whether they could have tolerated higher intensity stimulation (Fig 6.8, Q2). Of these, n=2 reported they did not attempt higher intensity because they had been advised not to, n=1 reported mood prevented them from trying a higher intensity, n=1 tried it but found higher intensity stimulation uncomfortable and n=2 found higher intensity stimulation irritated their pain (Table 6.16).

Table 6.16- Responses to post hoc telephone survey question 2

Stimulation level	Q2, could you have tolerated higher Y/N and the reasons why (= number of patients).
Painful	N=5 already high Y=1 but did not increase as it was helping
Uncomfortable	N=2 tried but it aggravated the pain
Not painful	N=1 Tried but it was uncomfortable N=3 Did not attempt to (2- advised not to, 1 mood).

In response to question 3 which asked about how often and for how long patients used the stimulator, all 12 patients reported stimulating daily for the specified duration of 10 minutes. The only exception to this, was in two cases when the device was not used on a few days when they were unwell for reasons other than pain. Only 3 patients considered using the device to manage spikes of pain.

In terms of stimulator use (question 4), n=7 (4 reporting treatment benefit) patients indicated they chose to use the device at a set time each day irrespective of pain levels, whilst n=3 (1 reporting treatment benefit) reported they used it when they were relaxed and comfortable, n=2 due to the location of pain stimulated when they were dressing to expose the area and n=1 use was determined by free time who also reported treatment benefit (Fig 6.8 Q4). All patients felt confident using the device (question 5). Patients were asked if anyone had helped them to consider how and when the device might work best for them (question 6). Two patients felt further information on accurate location of stimulation would have been helpful, five commented they felt they felt confident they could contact the team with any questions and therefore felt reassured through the study.

Most patients (n=8) reported that pain reduction was important to how they evaluated treatment effect (question 7, Fig 6.8 Q7). In response to how they would have liked the treatment to help (question 8), all patients referred to the question before in their response.

All patients reported feeling that they had alternative options available to them should the stimulation not be helpful in response (question 9, Fig 6.8 Q9).

Patients provided mixed responses concerning what they would like to change about the device (question 10, Fig 6.8 Q10). Most responses related to the practicalities of using the device, with 4 patients reporting holding the pen was difficult, 2 reporting it was hard to undress to expose the area, 1 found using it in the workplace was awkward, 1 felt it was too complicated, 1 found the reference electrode uncomfortable, whilst one found identifying the target for stimulation could be challenging.

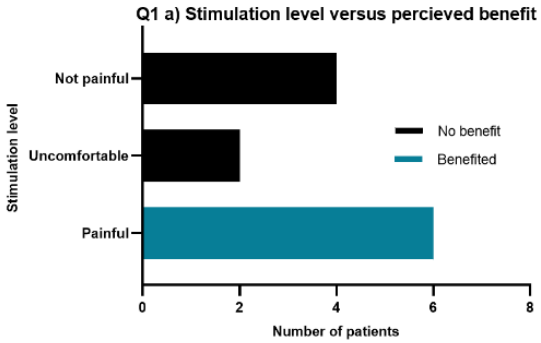
The final question asked patients to rate on a scale of 1-10 how likely they would be to continue with stimulator use if they were provided with a machine, with 0= unlikely and 10= highly likely. Five of the patients who reported treatment benefits gave responses ≥5 indicating they would be highly likely to continue with treatment, compared to 3 who perceived no treatment benefit (Fig 6.8 Q11).

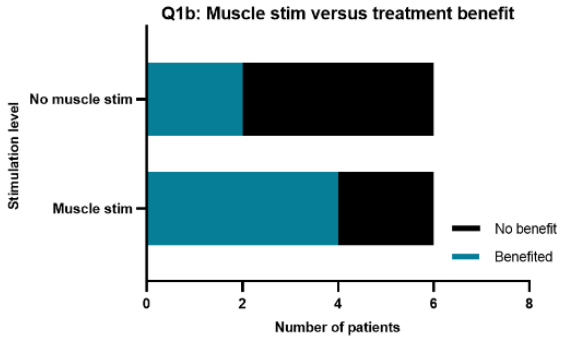
Patients were asked to clarify their responses to this question (Table 6.17).

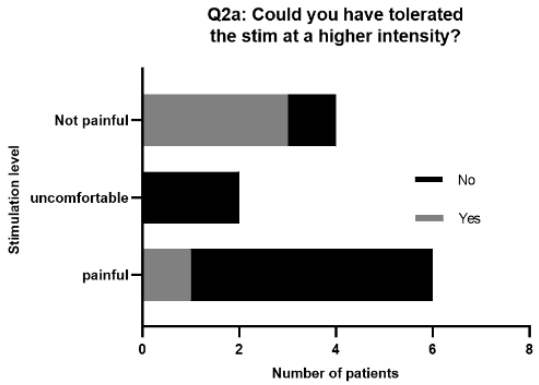
Table 6.17- Responses to post hoc telephone survey question 11

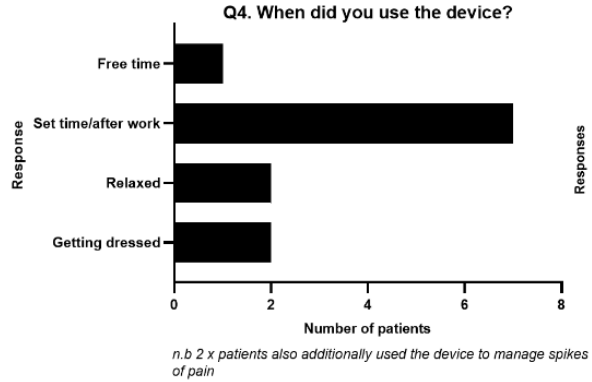
Comments were provided relating to scores		
Score	Comments	Responder
10	Their mood had limited ability to judge response during trial	N
7	Pain has now changed following surgery since the trial.	N
8	Would like longer to evaluate the response	N
4	Benefited but hard to maintain the position of stim	Y

Figure 6.8: Graphical representations of responses to specific questions of the post hoc telephone survey

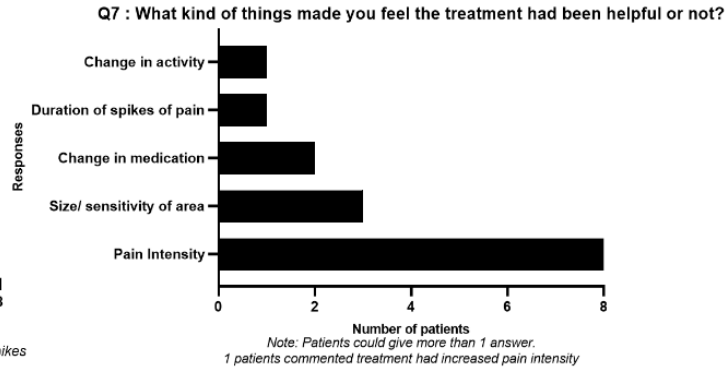




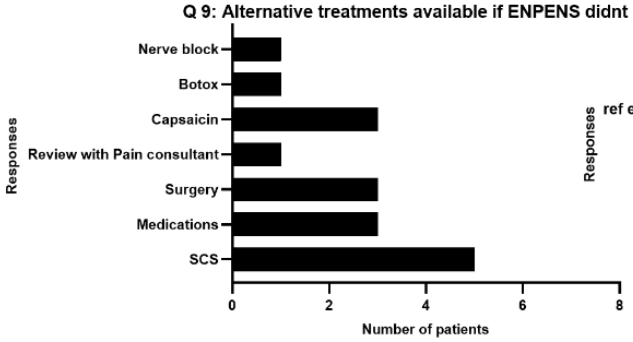




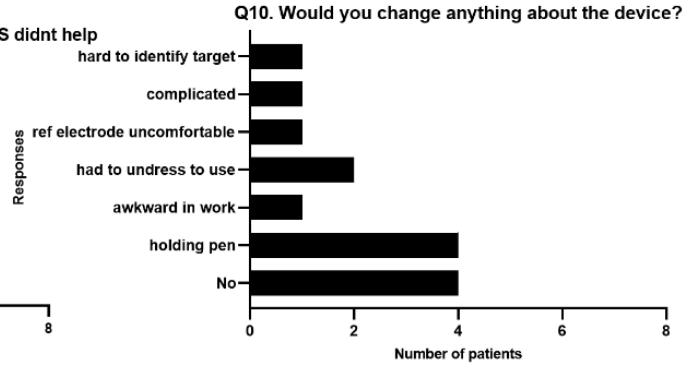
n.b 2 x patients also additionally used the device to manage spikes of pain



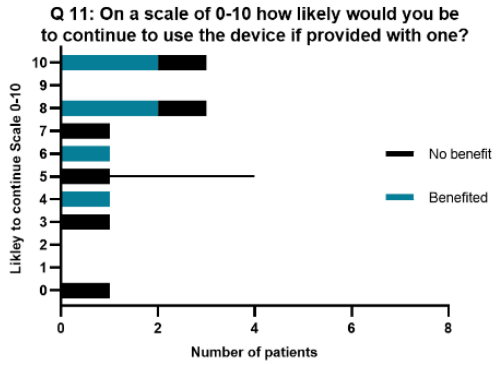
Note: Patients could give more than 1 answer.
1 patients commented treatment had increased pain intensity



Note patients could give more than 1 response



Note patients could give more than one response.



Chapter 7 Discussion

Research problem

The evidence suggests that subjects with neuropathic pain are far from optimally managed by medications, despite large numbers of visits to pain physicians and a high level of prescriptions for pain[1,2]. Other techniques, such as neuromodulation, have been considered third-line treatment options, however, there is limited evidence to support such third line approaches currently in the management of persistent painful peripheral nerve injury (PPNI) [3,4]. Because of the limitations of currently available treatments, neuropathic pain is still considered an unmet clinical need and therefore, there is a need to understand how it can be better managed [5,6].

Amplification of synaptic transmission in nociceptive pathways, termed 'nociceptive long-term potentiation (LTP), has been associated with neuropathic pain following peripheral nerve injury[7]. The use of low-frequency electrical stimulation delivered at a high current density has been shown to induce long term depression (LTD,) the counterbalancing process of LTP [8–11]. Induction of LTD via low-frequency stimulation should therefore aptly target PPNI by lowering enhanced gain in nociceptive pathways[11]. Evidence to support the clinical use of LFS where LTD may be a working mechanism for PPNI is limited to observational studies. These studies suggest that external non-invasive peripheral nerve may relieve pain for people with localised neuropathic pain [12–14]. There is currently no evidence from controlled trials to confirm this.

Research question

The current work sought to explore the potential efficacy of a non-invasive approach to elicit LTD-related pain suppression. The primary objective of this research was to establish clinical efficacy and provide a confident estimate of the effect size of low frequency electrical non-invasive peripheral electrical nerve stimulation (EN-PENS) treatment to reduce pain in patients with moderate to severe neuropathic pain associated with definite or probable peripheral nerve injury. The secondary

objectives were to evaluate the impact of this treatment in terms of QOL and day-to-day function. Further objectives were to gain a better understanding of this modality concerning mood, self-efficacy (confidence to perform abilities in the presence of pain), reduction of allodynia, potential mode of action and cost-effectiveness based on health resource use. We hypothesised that a significant difference (p=< 0.05) in terms of reduction of average pain intensity would be demonstrated in favour of the active treatment.

Summary of key findings

The data illustrated that treatment was not associated with a significant change in pain intensity. Results demonstrated that there was no statistically significant difference in the primary outcome between the two study groups with pain scores at 3 months being on average 0.3 units lower in the active group (95% CI -1.0, 0.3; p=0.30) giving an effect size of 0.19 (Cohens D). The number of patients experiencing ≥ 2 points OR ≥ 30% NRS reduction was 29% of patients in the active group, compared to 18% of the sham group. There was evidence of improvement for 2/3 of the secondary outcomes; quality of life ratings (EQ5D-5L VAS) was on average 10 points higher (95% CI 0, 19; p=0.05), whilst functional change was on average improved by 0.9 points (BPI interference subscale) (95 % CI -1.7, 0.0; p=0.06) in the active group.

Analysis of exploratory outcomes supported significant improvement in dynamic mechanical allodynia (DMA) following active treatment with a difference of 74 cm^2 between groups (95% CI -126, -22; p=0.006, i.e., the allodynia area was reduced by 74cm2 more in the active group).

Across all other outcome domains, a trend in terms of positive effect was observed for the active treatment which is suggestive of a biological effect. The number of outcomes achieving minimally important clinical change per patient was on average higher in the active group compared to the sham (2.9 outcomes versus 1.7 outcomes, p=0.03). Multivariable analyses suggested that both gender (B=0.74, 95% CI (0.56, 0.99) p=0.04) and neuropathic pain symptom inventory (NPSI) burning score (B=0.95, 95% CI (0.91, 0.99) p=0.02) were significantly associated with the number of

successful outcomes. Males had fewer successful outcomes than females, whilst a higher NPSI baseline score was also associated with fewer successful outcomes.

Post hoc telephone interviews indicated that all patients who observed the stimulation as painful (n = 6/12) reported an analgesic effect, but those who observed the treatment as either 'uncomfortable' or 'not painful' (n = 6/12) experienced no analgesic benefit. Patients additionally indicated that the timing of their stimulator use was not influenced by their pain experiences, but more frequently conducted at a set time of day. The intervention was well tolerated.

Interpretation of findings

The only outcomes to demonstrate significant improvement associated with active treatment were change in dynamic mechanical allodynia (DMA) (p=0.006) and EQ-5D VAS (p=0.05). The positive change in DMA reflects a change in stimulus-evoked pain in the affected area, which would support LTD as a plausible mechanism of action. The underpinning mechanism for pain-LTD is an intermediate rise of postsynaptic calcium concentration in nociceptive dorsal horn neurons (> 1 µM/L) inducing long-lasting depotentiation of synaptic transmission via increased phosphatase activity, diminishing postsynaptic LTP maintenance mechanisms. Under conditions of LTD, only a small volume of calcium permeates into the postsynaptic cell, which reduces the availability of receptors by translocation and consequently weakens synaptic efficacy[15]. The principle that LFS can induce pain-related LTD to treat established pain-LTP had earlier been established in healthy volunteers[16]. This study is the first randomised controlled trial (RCT) to examine LFS with LTD as a proposed working mechanism in a neuropathic pain population.

Unlike in preliminary open-labelled studies using the same type of stimulator device[12–14], reduction of stimulus-evoked pain was not paralleled by significantly reduced spontaneous pain. Although LFS may not potentially reduce spontaneous pain intensity, several lines of evidence suggest that this outcome may reflect both sub-optimal stimulation intensity and frequency. Evidence from volunteer studies indicates that a just noticeably painful stimulus strength of 2-10 x detection threshold is

effective for induction of LTD, while weaker or stronger stimuli are either less effective or completely ineffective[9,16]. Thus it is suggested that the painfulness of an electrical stimulus is a function of the stimulus strength[17]. Within the trial, patients determined stimulus strength ad libitum, and therefore it was not possible to determine whether patients were stimulating within an effective amplitude range. Patients had been advised to stimulate at an intensity perceived as mildly painful but not intolerable. Post-hoc telephone interviews illustrated only patients who experienced the stimulation in the active arm as painful, but none of the other patients found the treatment beneficial. It is likely, therefore, that for maximal effect, clinically the LFS intensity should be mildly painful and that adherence to initial instructions was not consistently followed but, also that advice regarding stimulation was not precise enough. Furthermore, post-hoc telephone interviews indicated that most patients used the stimulator once a day, at a set time of day regardless of their actual pain experiences. This would suggest that patients viewed treatment as something that acted over a 24-hr period (like a drug). As the duration of the LTD effect is unlikely to exceed a few hours[13], patients may therefore have missed out on the potential of using the treatment to target either spontaneous- or activity-induced pain increases that would be variable during the day. Experimental studies have additionally indicated that repeated application of LFS (within 40 mins of the first application) can enhance and prolong LTD [10]. Therefore, as patients were only stimulated once a day the potential to further enhance the treatment effect by repeating stimulation was not optimised. Patient education about treatment mechanisms, required stimulation strength, timing and frequency of treatment may therefore optimize clinical benefit by individually tailoring the stimulation and thus requires further evaluation.

It is, however, also possible that reduction in this type of stimulus-evoked pain in some patients does not fully translate into a reduction of their spontaneous pain. A potential disconnect between spontaneous and stimulus-evoked neuropathic pain has been illustrated elsewhere[18,19]. Topical lidocaine has been shown to reduce DMA for up to 3 months in patients with neuropathic pain after

knee surgery, without global pain reduction[18]; and mechanical allodynia has been demonstrated in the absence of spontaneous pain[19].

The findings demonstrate a reduction in enhanced pain sensitivity following low-frequency nerve stimulation. This finding is supportive of previous studies' findings and appears to be a consistent effect associated with low-frequency nerve stimulation[7,10,13]. A decrease in marked skin sensitivity represents an important change in pain presentation and may still be considered/ desired as a meaningful effect for patients in the absence of spontaneous pain reduction.

In addition to purely mechanistic factors that may explain a disconnect between spontaneous pain and evoked pain, there may be other biopsychosocial or contextual factors that exhibit an influence. For example, how pain is evaluated will be influenced by contextual factors such as emotional wellbeing, physical functioning, and social occupational factors[20–22]. It is difficult for studies to measure relevant contextual factors, and whilst the exploratory measures within the trial in part attempted to do this, an association between exploratory outcome measures and pain outcomes was not found.

Multivariable analyses suggested that gender (B=0.74, 95% CI (0.56, 0.99) p=0.04) and NPSI baseline burning score (B=0.95, 95% CI (0.91, 0.99) p=0.02) were significantly associated with the number of successful outcomes. Males and patients with higher NPSI baseline burning scores had fewer successful outcomes. High baseline burning pain scores would indicate sensory features relating to sensory phenotypes of thermal hyperalgesia and sensory loss [23]. LTP and LTD are thought to be most closely associated with aspects of central sensitisation for which punctate hyperalgesia and dynamic mechanical allodynia are hallmark signs and are most strongly associated with mechanical hyperalgesia sensory phenotype[23–25]. Therefore, the presence of strong burning sensory characteristics suggests that these patients *also* had characteristics fitting with thermal hyperalgesia and sensory loss phenotypes and therefore may have been less responsive to LTD as a treatment mechanism.

Previous epidemiological studies have indicated that persons with chronic pain with features of neuropathic pain typically have moderate or severe levels of anxiety and depression[2]. Conversely within the current study baseline hospital anxiety and depression (HADS) questionnaire scores (Anxiety= 10·5 ± 4·8 and depression=9·1 ± 4·5), fell within the mild symptom severity catergory[26]. All other outcome measures indicate moderate levels of severity in terms of the domains measured. This was an unexpected finding, and we are unsure as to why this group exhibited only mild emotional distress. Our inclusion criteria reflected the inclusion of very localised pain versus more widespread pain where high levels of emotional distress are well documented[27]. Whether lower levels of distress are typical for a highly localised neuropathic pain condition in comparison to a more widespread neuropathic pain condition would require further exploration.

The use of an optional treatment extension/ treatment swap was utilised principally as a study retention aid but also provided further long-term outcome information for a small proportion of subjects. During this phase, extended use of the active device was associated with a further reduction of 1.0 points in average pain intensity (n=5, 95% CI -3.3, 1.3, p=0.28), whilst only minimal improvement (not exceeding 0.3 points) was reported for those who switched to active or continued with sham. A significant worsening in average pain intensity by 1.5 points n=5 (95% CI 0.4, 2.6, p=0.02) was observed for patients who switched from active treatment to sham. These results provide some suggestion that treatment efficacy improves with extended use but requires further validation with larger numbers. A longer period of follow up (6 months) was originally considered as part of the study design but was reduced to 3 months following PPI consultation. PPI members strongly felt that a longer follow up of 6 months would be too burdensome for patients in the absence of treatment efficacy and would negatively influence study attrition. The suggestive evidence that prolonged use further improves efficacy however merits further exploration and long term follow up studies are recommended.

Strengths

As identified the evidence to support LTD via LFS largely relates to results from experimental studies in healthy subjects[8–11,28]. Therefore, this study builds on this evidence by considering the necessary stimulation paradigm requirements to achieve LTD mechanistically in a clinical population. The required stimulation paradigm includes stimulation frequency (1-2Hz)[10,29,30], stimulation strength (between 1-4 x pain perception threshold) [31,32], pulse duration (1200 pulses) [10,33,34], and electrode shape (concentric electrode to preferentially activate Aδ fibres) [35,36]. Observational studies support that these stimulation paradigms could be associated with clinical effects[13,14]. The current study builds on this evidence by evaluating efficacy as part of an RCT. Therefore, this study addresses current known gaps in the existing research and is the first mechanistically informed RCT to examine LFS for the treatment of neuropathic pain. The study provides clear justification for stimulation parameters that can be used to inform future study design.

In the absence of a specific diagnostic tool for neuropathic pain, the study used the neuropathic grading scale to ensure only patients with probable or definite neuropathic pain were recruited[37]. This can be considered a further strength of the study by ensuring patient selection was supported by a standardised, validated tool and supported by a mechanistic rationale.

Quantitative sensory testing with different neuropathic pain syndromes has defined patterns of loss or gain of function across multiple sensory modalities ('somatosensory profiles') which likely reflect underlying pain generating mechanisms [23]. Results from studies examining the different sensory profiles of patients with neuropathic pain would suggest that mechanisms of LTP and LTD are likely to have greater relevance for patients displaying a predominant 'mechanical-hyperalgesia' sensory phenotype, i.e. who specifically demonstrate mechanical dynamic allodynia and punctate hyperalgesia[23,38]. To additionally support the mechanistic rationale the inclusion criteria therefore also required DMA to reflect a mechanical hyperalgesia sensory profile. The study was therefore successful in terms of recruitment and retention of a very specific group of patients.

It has been suggested stratification of patients by sensory profiles could improve both patient selection and treatment outcomes by improving mechanistically informed treatment rationale [38]. Future studies could additionally consider the inclusion of neuropathic pain-specific screening questionnaires and inclusion of comprehensive sensory testing to better stratify patients by neuropathic pain sensory characteristics.

The development and use of a true sham intervention with some perceivable but inefficient stimulation parameters is a further strength – the lack of credible sham intervention has previously been noted as a limitation in neuromodulation trials[39,40]. The sham intervention was developed through collaborative consultation with both neurophysiologists and patients. This dual type of collaboration is recommended for future research studies to ensure intended sham interventions are supported by robust mechanistically informed evidence and are adequately tested before investigation.

The sham device used a conventional 5x5 cm^2 TENS electrode whereas the active device used a small concentrically shaped electrode. Experimental studies using cutaneous stimulation, have provided evidence that preferential activation of cutaneous A-δ fibres can be achieved using a concentric electrode that creates a high current density[35,36]. In contrast, larger diameter surface electrodes, such as TENS electrodes, do not generate the required current density to preferentially activate A-δ fibres, required for LTD induction unless used at very high intensities [41,42]. Therefore, TENS even when used at a low frequency typically activates the whole A- fibre spectrum without any preference [41,42]. The justification of electrode design, therefore, helps to highlight a fundamental difference between conventional LFS TENS and the LFS used within this study.

Strong PPI involvement throughout the study process was an additional strength of the study. PPI involvement helped to shape every stage of the study from the endorsement of the initial concept, design, implementation, governance, and evaluation. This ensured the study was relevant and

helped to improve the study design. Such processes contributed to the study achieving a high level of patient adherence resulting in high data quality and reducing uncertainty.

The selection of outcomes reflected domains considered and prioritised by both clinicians and patients and was supported by outcome recommendations[43]. The study further included successful randomisation with active and comparator groups being well balanced.

Limitations

Average 24 hrs pain intensity was chosen as the primary outcome measure for this study on the basis that it was prioritised highly by clinicians and patients. In experimental studies, the effect of LTD has been largely demonstrated by reduced sensory and evoked potentials [7,10]. To potentially demonstrate a change supportive of LTD induction we included a reduction in DMA as an exploratory outcome. Reduced DMA however on its own is also not confirmatory of LTD, which can be considered a limitation of the current study. A more comprehensive evaluation of sensory testing is recommended for future studies to provide evidence supportive of LTD as a mechanism of action. A comprehensive evaluation of sensory responses could additionally enhance understanding of response profiles and help to improve patient and treatment selection in future studies.

Although a reduction in sensory evoked potentials has been suggested correlate of LTD, the neurobiological basis of LTD which is *reduced synaptic activity* cannot be directly accessed in humans. This remains a limitation for all human studies.

The study protocol allowed patients to continue treatment without further advice or corrections after initial training. Post-hoc interviews have highlighted that this approach might have diminished the intervention's effectiveness. Evaluation of stimulator use was limited as devices were not equipped with a system to monitor compliance or stimulation parameters. It is now becoming more common practice to use smartphone applications as part of trial design[44]. Therefore, future trials could consider smartphone applications that require participants to input data relating to

stimulation. This would help to encourage compliance but also provide an opportunity to monitor and evaluate compliance.

In normal practice, suboptimal stimulation may be improved with education relating to stimulation electrode positioning and coverage, but due to blinding, this was not possible. To overcome this in future the use of additional stimulation optimisation sessions could be delivered by clinicians independent of the study, to ensure within both groups patients were supported to achieve optimal stimulation.

The study considered localised peripheral neuropathic pain and as discussed utilised the neuropathic grading scale to ensure measurement of neuropathic pain was standardised. However, we did not consider classification by type of injury. Peripheral neuropathic pain can be further classified based on the degree of demyelination and the extent of damage to the axons as either neurapraxia, axonotmesis, or neurotmesis using the Seddon or Sunderland criteria [45,46]. Further classification by type of injury could be useful in future studies to consider whether the degree of injury influences response and improve patient selection.

Data from a systematic review and meta-analysis in a different post-traumatic neuropathic pain condition, complex regional pain syndrome reported a pooled sham response as being negligible [47]. For the ENPENS study, the sample size calculations were based on a between-group difference of 1. 5. This was a conservative estimate based on the available preliminary and placebo data[13,47]. Within the current study patients within the sham group experienced on average a reduction in the primary outcome of 0.6 points versus 0.9 points within the active group (95% CI -1.0, 0.3; p=0.30). Therefore, the current study would suggest that reported sham responses are not negligible and this is an important consideration for future studies and should be used to inform future study design.

The sham device used a standard TENS electrode and therefore had some visual similarities to a conventional TENS device. Patients with previous experience with TENS were included in the current study but the outcome of this experience was not ascertained. This may have influenced the results

we observed within the sham group. Future studies should consider whether patients perceive similarities to previous treatments and how this may shape their experience and expectations concerning planned research treatments.

The inclusion of patients who may not have benefited from treatment such as patients with psychological co-morbidities or who had pain conditions that were potentially unresponsive to single nerve stimulation may have inadvertently underpowered the study. For example, radiotherapy-induced nerve pain (n=2, active) and medication-induced nerve pain (n=1, sham) were included. Radiotherapy and medication-induced nerve pain is rarely confined to the distribution of one nerve. The three patients included with these indications all experienced hand pain and only reported pain in the radial or ulnar nerve territory following said treatments but, minor contributions from other segments can perhaps not be excluded.

Although patient medications and changes in medications were recorded the study did not consider the potential mechanism of action of different drugs and whether this could interfere with LTD. For example, gabapentin and pregabalin bind to the α2-δ subunit of calcium channels and therefore also interfere with Ca influx which may compromise further reduction in synaptic excitability by LTD[48]. Patients were asked to indicate if they felt that they had been assigned to a more or less effective intervention. Within the active group, most patients correctly identified that they had received the more effective treatment which may reflect that more patients experienced treatment benefits. A formal assessment of blinding, however, was not included during initial training, i.e., before delivery of any effective stimulation and therefore it is not possible to confidently exclude any unaccounted-for unblinding effect and its impact on the outcome.

Recommendations for implementation of future research

Experimental studies have demonstrated that LFS can reduce enhanced evoked sensory responses[8–11]. Further research is required to confirm whether suggested enhancements would improve efficacy and provide definite conclusions regarding the potential clinical utility of LTD induced by LFS as a

treatment for PPNI. A starting point for future research would be to confirm within a clinical population whether LTD is a function of the painfulness of an electrical stimulus. Understanding this would enable better patient education about treatment use and treatment prescription.

In conjunction with understanding parameter requirements, it would also be important to appreciate from a patient's perspective whether they would engage with potential parameter refinements, such as painful stimulation or more frequent use. Further knowledge in both these areas is required to refine future therapies.

As highlighted the study illustrated a reduction in DMA in keeping with the mechanisms of LTD. However, to provide more robust evidence supportive of the LTD affect future studies should include a more comprehensive evaluation of change in sensory measures. Whilst this should include more extensive quantitative sensory testing it should not be limited to peripheral responses. For example, recent research has demonstrated that LFS of the radial nerve in healthy volunteers in addition to reducing sensory evoked potentials peripherally was also associated with reductions in the central processing of sensory evoked potentials [28]. Therefore, further research exploring both peripheral and cortical responses could further enhance the current mechanistic understanding of treatment effect, and response profiles, and help to inform patient stratification and treatment selection in future studies.

A classic parallel design RCT study was used to evaluate external non-invasive peripheral nerve stimulation. Such study designs have been critiqued for lacking sensitivity when intervention specific effect (active minus sham) approaches 10% unless the study is of exceptional size [49]. A specific effect of 11% was observed within the current trial and, therefore, may have lacked sensitivity due to a considerable analgesic response in the sham group (18% in the sham group experiencing a ≥2 NRS or 30% pain reduction compared to 29% of patients in the active group). Consequently, future research also should look toward alternative study designs where potential placebo effects can be reduced, and sensitivity could perhaps be improved with this in mind. Some of the specific challenges relating to the conduct of such trials were discussed as part of chapter 4. Enriched enrolment randomized

withdrawal (EERW) designs are one possible study design that could be considered EERW increases sensitivity by removing definite non-responders and; therefore, can give a useful indication of the overall proportion of patients who would benefit from treatment[50,51]. Currently, however, there are only a few good examples of EERW in chronic pain trials [52].

Conclusion

This study is the first randomised controlled trial to examine LFS with LTD as a proposed working mechanism in a neuropathic pain population. Evidence from the study regarding reduction in pain intensity, the primary outcome, failed to reach significance. The results suggest evidence for the reduction in evoked pain in keeping with LTD as a working mechanism. Results suggest further refinement of this modality is required, to enhance potential LTD, which will help inform future study design and approaches to LFS treatment. Low frequency stimulation is well-tolerated, comparing favourably with drug treatments for the same patient group [53].

Chapter 7 References

1. De Courcy J, Liedgens H, Obradovic M, Holbrook T, Jakubanis R. A burden of illness study for neuropathic pain in Europe. *Clin Outcomes Res*. 2016;8:113-126. doi:10.2147/CEOR.S81396

2. Attal N, Lanteri-Minet M, Laurent B, Fermanian J, Bouhassira D. The specific disease burden of neuropathic pain: Results of a French nationwide survey. *Pain*. 2011;152(12):2836-2843. doi:10.1016/j.pain.2011.09.014

3. National Institute for Clinical Excellence NI advisory committee (IPAC). *Systematic Review of Stimulation of Peripheral Nerves for the Treatment of Refractory Pain (Including Peripheral Nerve Field Stimulation)*. NICE; 2012. http://guidance.nice.org.uk/IPG450/Overview/pdf/English.

4. National Institute for Clinical Excellence N. Percutaneous electrical nerve stimulation for refractory neuropathic pain (IPG450). Interventional procedures guidance IPG450. http://guidance.nice.org.uk/IPG450. Published 2013. Accessed August 12, 2021.

5. Moisset X, Bouhassira D, Attal N. French guidelines for neuropathic pain: An update and commentary. *Rev Neurol (Paris)*. 2021;177:834-837. doi:10.1016/j.neurol.2021.07.004

6. Finnerup NB, Kuner R, Jensen TS. Neuropathic Pain: From Mechanisms to Treatment. *Physiol Rev*. 2020;101(1):259-301. doi:10.1152/PHYSREV.00045.2019

7. Rottmann S, Jung K, Ellrich J. Electrical low-frequency stimulation induces long-term depression of sensory and affective components of pain in healthy man. *Eur J Pain*. 2010;14(4):359-365. doi:10.1016/j.ejpain.2009.06.001. Epub 2009 Jul 14.

8. Cruccu G, Truini A. Neurostimulation therapy (acupuncture-like) and long-term depression: A challenge for the clinical neurophysiologist. *Clin Neurophysiol*. 2009;120(12):2004-2005. doi:10.1016/j.clinph.2009.09.017

9. Klein T, Magerl W, Hopf H-C, Sandkühler J, Treede R-D. Perceptual correlates of nociceptive long-term potentiation and long-term depression in humans. *J Neurosci*. 2004;24(4):964-971. doi:10.1523/JNEUROSCI.1222-03.2004

10. Jung K, Rottmann S, Ellrich J. Long-term depression of spinal nociception and pain in man: Influence of varying stimulation parameters. *Eur J Pain*. 2009;13(2):161-170. doi:10.1016/j.ejpain.2008.04.001

11. Rottmann S, Jung K, Ellrich J. Electrical low-frequency stimulation induces homotopic long-term depression of nociception and pain from hand in man. *Clin Neurophysiol*. 2008;119(8):1895-1904. doi:10.1016/j.clinph.2008.02.022

12. Johnson S, Goebel A. Long-Term Treatment of Chronic Neuropathic Pain Using External Noninvasive External Peripheral Nerve Stimulation in Five Patients. *Neuromodulation*. 2015;18(5):384-391. doi:10.1111/ner.12365

13. Johnson S, Ayling H, Sharma M, Goebel A. External Noninvasive Peripheral Nerve Stimulation

Treatment of Neuropathic Pain: A Prospective Audit. *Neuromodulation*. 2015;18(5):384-391. doi:10.1111/ner.12244

14. Sierakowski A, Jing SS, Poel J, Elliot D. Transcutaneous Peripheral Nerve Stimulation for the Treatment of Neuropathic Pain in the Upper Limb. *J Hand Surg Asian-Pacific Vol*. 2016;21(1):37-43. doi:10.1142/S2424835516500041

15. Price TJ, Inyang KE. Commonalities between pain and memory mechanisms and their meaning for understanding chronic pain. *Prog Mol Biol Transl Sci*. 2015;131:409-34. doi:10.1016/bs.pmbts.2014.11.010

16. W. Magerl, F. Henrich, L. Röhring, D. Pfau, T. Klein RT. Poster PF0343 : Reversal of LTP-like hyperalgesia by low-frequency electrical stimulation - 16th World Congress on Pain - Built with CrowdCompass by Cvent. In: *16th World Congress On Pain, Yokohama 2016 Abstracts,*. ; 2016. https://event.crowdcompass.com/wcp2016/activity/ozu0y7GLko. Accessed January 19, 2021.

17. Lang S, Klein T, Magerl W, Treede RD. Modality-specific sensory changes in humans after the induction of long-term potentiation (LTP) in cutaneous nociceptive pathways. *Pain*. 2007;128(3):254-263. doi:10.1016/j.pain.2006.09.026

18. Pickering G, Voute M, Macian N, Ganry H, Pereira B. Effectiveness and safety of 5% lidocaine-medicated plaster on localized neuropathic pain after knee surgery: a randomized, double-blind controlled trial. *Pain*. 2019;160(5):1186-1195. doi:10.1097/j.pain.0000000000001502

19. Forstenpointner J, Ruscheweyh R, Attal N, et al. No pain, still gain (of function): the relation between sensory profiles and the presence or absence of self-reported pain in a large multicenter cohort of patients with neuropathy. *Pain*. 2020;162(3):718-727. doi:10.1097/j.pain.0000000000002058

20. Anderson KO, Dowds BN, Pelletz RE, Edwards WT, Peeters-Asdourian C. Development and initial validation of a scale to measure self-efficacy beliefs in patients with chronic pain. *Pain*. 1995;63(1):77-83. doi:10.1016/0304-3959(95)00021-J.

21. Dworkin RH, Turk DC, McDermott MP, et al. Interpreting the clinical importance of group differences in chronic pain clinical trials: IMMPACT recommendations. *Pain*. 2009;146(3):238-244. doi:10.1016/j.pain.2009.08.019

22. Nicholas MK. The pain self-efficacy questionnaire: Taking pain into account. *Eur J Pain*. 2007;11(2):153-163. doi:10.1016/j.ejpain.2005.12.008

23. Baron R, Maier C, Attal N, et al. Peripheral neuropathic pain: A mechanism-related organizing principle based on sensory profiles. *Pain*. 2017;158(2):261-272. doi:10.1097/j.pain.0000000000000753

24. Baumgärtner U, Magerl W, Klein T, Hopf HC, Treede R-D. Neurogenic hyperalgesia versus painful hypoalgesia: two distinct mechanisms of neuropathic pain. *Pain*. 96(1):141-151. doi:10.1016/s0304-3959(01)00438-9.

25. Fields HL, Rowbotham M BR. Postherpetic Neuralgia: Irritable Nociceptors and Deafferentation | Elsevier Enhanced Reader. *Neurobiol Dis*. 1998;5(4):209-227. doi:10.1006/nbdi.1998.0204.

26. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand*. 1983;67(6):361-370. doi:10.1111/j.1600-0447.1983.tb09716.x.

27. Mills SEE, Nicolson KP, Smith BH. Chronic pain: a review of its epidemiology and associated factors in population-based studies. *Br J Anaesth*. 2019;123(2):e273-e283. doi:10.1016/J.BJA.2019.03.023

28. Hewitt D, Byrne A, Henderson J, et al. Inhibition of cortical somatosensory processing during and after low-frequency peripheral nerve stimulation in humans. *Clin Neurophysiol*. 2021;132(7):1481-1495. doi:10.1016/J.CLINPH.2021.03.024

29. Li L, Lai M, Cole S, Le Novère N, Edelstein SJ. Neurogranin stimulates Ca2+/calmodulin-dependent kinase II by suppressing calcineurin activity at specific calcium spike frequencies. *PLoS Comput Biol*. 2020;16(2). doi:10.1371/JOURNAL.PCBI.1006991

30. Dudek SM, Bear MF. Homosynaptic long-term depression in area CA1 of hippocampus and effects of N-methyl-D-aspartate receptor blockade. *Proc Natl Acad Sci U S A*. 1992;89(10):4363-4367. doi:10.1073/PNAS.89.10.4363

31. Sandkühler J, Chen JG, Cheng G, Randić M. Low-frequency stimulation of afferent aδ-fibres induces long-term depression at primary afferent synapses with substantia gelatinosa neurons in the rat. *J Neurosci*. 1997;17(16):6483-6491. doi:10.1523/jneurosci.17-16-06483.1997

32. Randic M, Jiang MC, Cerne R. Long-term potentiation and long-term depression of primary afferent neurotransmission in the rat spinal cord. *J Neurosci*. 1993;13(12):5228-5241. doi:10.1523/JNEUROSCI.13-12-05228.1993.

33. Xia Z, Storm DR. The role of calmodulin as a signal integrator for synaptic plasticity. *Nat Rev Neurosci*. 2005;6(4):267-276. doi:10.1038/nrn1647

34. Yasuda H, Higashi H, Kudo Y, et al. Imaging of calcineurin activated by long-term depression-inducing synaptic inputs in living neurons of rat visual cortex. *Eur J Neurosci*. 2003;17(2):287-297. doi:10.1046/j.1460-9568.2003.02449.x

35. Kaube H, Katsarava Z, Käufer T, Diener HC, Ellrich J. A new method to increase nociception specificity of the human blink reflex. *Clin Neurophysiol*. 2000;111(3):413-416. doi:10.1016/S1388-2457(99)00295-3

36. Katsarava Z, Ayzenberg I, Sack F, Limmroth V, Diener HC, Kaube H. A novel method of eliciting pain-related potentials by transcutaneous electrical stimulation. *Headache*. 2006;46(10):1511-1517. doi:10.1111/J.1526-4610.2006.00446.X

37. Finnerup NB, Haroutounian S, Kamerman P, et al. Neuropathic pain: An updated grading system for research and clinical practice. *Pain*. 2016;157(8):1599-1606. doi:10.1097/j.pain.0000000000000492

38. Vollert J, Maier C, Attal N, et al. Stratifying patients with peripheral neuropathic pain based on sensory profiles: Algorithm and sample size recommendations. *Pain*. 2017;158(8). doi:10.1097/j.pain.0000000000000935

39. Katz N, Dworkin RH, North R, et al. Research design considerations for randomized controlled trials of spinal cord stimulation for pain. *Pain*. 2021;162(7):1935-1956.

doi:10.1097/j.pain.0000000000002204

40. Kjær SW, Rice ASC, Wartolowska K, Vase L. Neuromodulation: more than a placebo effect? *Pain*. 2020;161(3):491-495. doi:10.1097/j.pain.0000000000001727

41. Gibson W, Wand BM, O'Connell NE. Transcutaneous electrical nerve stimulation (TENS) for neuropathic pain in adults. *Cochrane Database Syst Rev*. 2017. doi:10.1002/14651858.CD011976.pub2

42. Sluka KA, Bjordal JM, Marchand S, Rakel BA. What Makes Transcutaneous Electrical Nerve Stimulation Work? Making Sense of the Mixed Results in the Clinical Literature. *Phys Ther*. 2013;93(10):1397-1402. doi:10.2522/PTJ.20120281

43. Dworkin RH, Turk DC, Farrar JT, et al. Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. *Pain*. 2005;113(1-2):9-19. doi:10.1016/j.pain.2004.09.012.

44. Romeo A, Edney S, Plotnikoff R, et al. Can Smartphone Apps Increase Physical Activity? Systematic Review and Meta-Analysis. *J Med Internet Res*. 2019;21(3):e12053. doi:10.2196/12053

45. Seddon HJ, Medawar PB SH. Rate of regeneration of peripheral nerves in man. *J Physiol*. 1943;102(2):191-215. doi:10.1113/JPHYSIOL.1943.SP004027

46. SUNDERLAND S. A classification of peripheral nerve injuries producing loss of function. *Brain*. 1951;74(4):491-516. doi:10.1093/BRAIN/74.4.491

47. Mbizvo GK, Nolan SJ, Nurmikko TJ, Goebel A. Placebo responses in long-standing complex regional pain syndrome: a systematic review and meta-analysis. *J Pain*. 2015;16(2):99-115. doi:10.1016/j.jpain.2014.11.008

48. Taylor CP. Mechanisms of analgesia by gabapentin and pregabalin - Calcium channel α2-δ [Cavα2-δ] ligands. *Pain*. 2009;142(1-2):13-16. doi:10.1016/j.pain.2008.11.019

49. Moore RA, Derry S, Wiffen PJ. Challenges in design and interpretation of chronic pain trials. *Br J Anaesth*. 2013;111(1):38-45. doi:10.1093/bja/aet126

50. Straube S, Derry S, McQuay HJ, Moore RA. Enriched enrolment: Definition and effects of enrichment and dose in trials of pregabalin and gabapentin in neuropathic pain. A systematic review. *Br J Clin Pharmacol*. 2008;66(2):266-75. doi:10.1111/j.1365-2125.2008.03200.x

51. Katz N. Enriched enrollment randomized withdrawal trial designs of analgesics: Focus on methodology. *Clin J Pain*. 2009;25(9):797-807. doi:10.1097/AJP.0b013e3181b12dec

52. Moore RA, Wiffen PJ, Eccleston C, et al. Systematic review of enriched enrolment, randomised withdrawal trial designs in chronic pain: A new framework for design and reporting. *Pain*. 2015;156(8):1382-1395. doi:10.1097/j.pain.0000000000000088

53. Finnerup NB, Attal N, Haroutounian S, et al. Pharmacotherapy for neuropathic pain in adults: A systematic review and meta-analysis. *Lancet Neurol*. 2015;14(2):162-173. doi:10.1016/S1474-4422(14)70251-0

Acknowledgments/ Dedications page

The author would like to thank:

- The pain research institute for their ongoing help and supporting the author to pursue her research interests.
- Her primary supervisor Dr Andreas Goebel for the patience and mentorship he has provided throughout this PhD and in terms of career development and direction.
- Professor Turo Nurmikko for providing additional mentorship and support.
- Walter Magerl, Dr Andy Marshall and Dr Anne Marshal for their involvement and work around LTD working mechanisms.
- Her husband and family for always being supportive, providing time to complete the work and proofreading.

Appendix 1 ENPENS Participant Information Sheet

Participant Information Leaflet Version 3; 27/06/18 (with HRA approved GDPR wording) IRAS NO. 197139

Participant Information Sheet

Title of Project: A randomised controlled trial of External non-invasive peripheral nerve stimulation for chronic neuropathic pain following peripheral nerve injury (EN-PENS trial).

Investigators: Ms S Johnson, Dr. A Goebel; Prof. T.J. Nurmikko; Mr D Watling, Prof. D Hughes; Mr P Bassett, Ms W Hall, Ms E Burraston.

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and talk about it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

Thank you for taking the time to read this leaflet.

What is the purpose of the study?
Neuropathic pain is a pain that comes from problems with signals from the nerves. Eight percent of people in the UK are estimated to have persistent (chronic) neuropathic pain and for many there is no effective treatment. External non-invasive peripheral nerve stimulation (EN-PNS) is a form of electrical stimulation that involves placing an electrode onto the skin, which can be easily self-administered by patients. We have found EN-PNS can provide pain relief for people with neuropathic pain, however there is currently no evidence from controlled studies, needed to support its use within the NHS.

The study aims to establish whether EN-PNS is effective in reducing pain for people with long-standing neuropathic pain following peripheral nerve injury.

Further aims are to assess:
Benefits to other commonly affected areas such as quality of life, function, mood and whether treatment can help reduce medications and/or avoid surgical interventions.

What are the alternatives for treatment?
Medications are the most common treatment method but often have limited benefit or unwanted side effects. Surgical treatments such as spinal cord stimulation are then often considered.

The study:
This is a randomized, controlled trial of EN-PNS. Patients will randomly receive one of two forms of EN-PENS treatment (both forms of EN-PENS will look the same however the stimulation frequency will differ). Patients will be trained to deliver their own treatment and then continue treatment for 3 months at home. Outcomes will be taken at the start and end

The EN-PENS trial is funded by the National Institute for Health Research

of treatment. At the end of 3 months home loan all participants will be offered the opportunity to extend treatment or swap treatment and try the alternative EN-PENS treatment for a further 3 months. You will also be asked whether you wish to take part in a specially designed additional outcome that involves testing sensation in areas of pain and areas that are not painful. This additional testing will help us to understand how exactly EN-PENS works and thereby who it will benefit. This additional outcome is optional and you can take part in this as well or instead of the main study (see separate information leaflet).
Patients with neuropathic pain have helped develop the study and will also support study management.

Are there any side effects or risks?
EN-PENS is generally considered a safe treatment option for a variety of pain conditions. Persons with a cardiac pacemaker, spinal cord stimulator or are known to be pregnant should not use EN-PENS. Other than these exclusions the only reported side effect in a minority of cases is short lived increases in pain following stimulation.

What if I am pregnant or plan to become pregnant?
If you are pregnant or planning a pregnancy you will not be able to take part in this study. To ensure reduce any risk to you will be asked to have a urine test to ensure you are not pregnant at the start of the study (Visit 1) and at the end of the study (visit 5). No urine samples will be kept. To make sure you do not become pregnant during the course of the study you will also be asked to use adequate birth control methods for the duration of the trial.
Why have I been chosen?
You have long-standing neuropathic pain following a peripheral nerve injury and have been reviewed within the pain clinic of the Walton Centre NHS Trust.

Do I have to take part?
Taking part is voluntary. It is up to you to decide whether or not you want to take part. If you choose to take part you can also choose to stop at any time without giving a reason. The standard of care you receive now or in the future will be the same whether you take part or not.

What will happen to me if I take part?
You will be contacted by the research team who will check whether you are interested in taking part and complete a check list with you to ensure that for you the treatment is safe and suitable.

If you wish to take part you will be sent a paper or electronic pain diary. Someone will explain how to complete this. This diary will ask you to note down your average and worst pain scores over the period of a week. You will be asked to return this at your first visit (screening visit). You will also be given contact information should you wish to ask any further questions before the screening appointment.

Visit 1: The screening visit. You will be asked to give consent to the study, sign a consent form and screened for suitability.
Visits 2-4: You will be randomised to receive one of two forms of EN-PENS treatment and then trained how to use it over 1-3 training sessions. Once you feel you can use the

The EN-PENS trial is funded by the National Institute for Health Research

machine yourself without further instruction you will be loaned the machine to use at home for 3 months.

Visit 4 or 5: Following 3 months of using the stimulator at home you will be offered the opportunity to either continue with the treatment for a further 3 months, switch to the alternative EN-PENS for a further 3 months or discontinue the trial.

You will be expected to return equipment on the final study visit. If you finish the study early you will be expected to return equipment within 2 weeks of ending the study.

Outcome measures:
At the initial screening (visit 1) and at the end of treatment (visit 5) you will be asked to complete some outcome measures that will help us measure changes associated with treatment. The measures will include questionnaires and measures that will show any changes in sensation in the painful area. These measures should take no longer than 30 minutes to complete.

How will the EN-PENS feel?
Both forms of EN-PENS will give you an electrical current to the nerve supplying the area of pain. The purpose of this trial is to compare two types of electrical stimulation and find out how much they relieve pain. We anticipate that one of these may be more effective than the other, but it is also possible that both are effective, or neither. The stimulator's effectiveness is determined by the electrical field, and therefore it is not possible to conclude from using the machine which of the two stimulators has been assigned. Stimulation may in some cases be felt throughout the area of pain or cause muscles to twitch. These effects will vary greatly between patients, and are not necessary in order to achieve treatment benefit.

During the home loan period we will ask you to continue treatment yourself, but when and how often is up to you. We suggest that treatment periods are at least ten minutes long in order to obtaining pain relief. You can vary the strength of the stimulus however, we would advise that a stimulation should be mildly painful but not exceed an unpleasant level. We will ask you to keep a diary to record your treatments.

What support will I receive?
We will telephone you once a week during the home loan to check you have no problems and answer any questions you may have. You will also be provided with contact information should you require any further support or wish to arrange an appointment.

What are the possible disadvantages and risks of taking part?

There are no known side effects associated with treatment other than in some cases a temporary increase in pain associated with treatment. If you are taking any medications that numb the affected area such as capsaicin or lidocaine plasters you will be asked to discontinue these during the course of the trial.

What are the possible benefits of taking part?
For patients who benefit from treatment we would expect them to experience a reduction in pain intensity. Additionally patients may report reduced sensitivity in the area of pain and improvements to everyday activities that have been limited by pain.

The EN-PENS trial is funded by the National Institute for Health Research

By taking part in the study you will help to provide information that will inform whether the NHS should support the use of ENPNS for patients with neuropathic pain. If the trial is positive this may benefit other patients with neuropathic pain in the future by helping them to reduce medications or avoid more invasive surgical treatments such as spinal cord stimulation.

Currently as there is no good quality evidence to support EN-PNS and therefore treatment cannot be continued long-term (i.e. Provision of a machine) unless a 'special funding' request is made to their commissioning health board or people purchase their own machine.

What if there is a problem?
If you have a concern about any aspect of this study, you should ask to speak with one of your research team who will do their best to answer your questions.

If you are still unhappy and wish to complain formally, you can do this through the NHS Complaints Procedure. Details can be found at the bottom of the leaflet. If you are harmed by taking part in this research project, there are no special compensation arrangements. If you are harmed and this is due to someone's negligence, then you may have grounds for a legal action for compensation against the NHS Trust where you are being treated but you may have to pay for your legal costs. The normal National Health Service complaints mechanisms should be available to you.

What happens if I change my mind?
If at any time you decide to stop taking part in the study we will stop the treatment. If you do decide to stop taking part we will ask you if you would like to:

- Continue to complete follow up visits for the study or
- Stop taking part with no more study visits.

We will use any study information collected up until the time you stop taking part unless you ask us not to, this information will be anonymised so you cannot be identified.

Will my taking part in this study be kept confidential?
We will follow ethical and legal practice and all information which is collected about you during the course of the study will be kept strictly confidential. With your consent, we will send a letter to your GP to let them know you are taking part. Any data collected we will use a study number and initials and anonymised data where relevant.

What will happen to the results of the trial?
The results will be published in scientific journals and we will make a summary available on The Walton Centre website. We will not use your name in any publications and we will ensure that all information about you is kept confidential. You will be able to see the results on the website.

Additional information about the study
The Walton Centre NHS FT is the sponsor for this study based in the United Kingdom. We will be using information from you and/or your medical records in order to undertake this study and will act as the data controller for this study. This means that we are responsible for looking after your information and using it properly. The Walton Centre NH FT will keep identifiable information about you for 5 years after the study has finished.

The EN-PENS trial is funded by the National Institute for Health Research

Your rights to access change or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate.

If you withdraw from the study, we will keep the information about you that we have already obtained. To safeguard your rights, we will use the minimum personally-identifiable information possible.
You can find out more about how we use your information at
http://www.thewaltoncentre.nhs.uk
or by contacting the Neuroscience Research Centre 0151 529 5666.
The Walton Centre is responsible for managing this study. This study is funded by The National Institute for Health Research.

Expenses and payments
You will have to attend additional clinics for the purpose of the project. Reasonable costs incurred by you to attend this appointment can be claimed back, your healthcare team should be able to explain the process. You will be able to claim an average of £30+VAT per patient per visit with a maximum number of 6 clinical visits.

What happens next?
If you wish to participate we would ask you to contact the study team within 1 week of receiving this leaflet.

Telephone number: **0151 5295666**

If you do not make contact a member of the study team will contact you to ask if you have any further unanswered questions and wish to participate.

Thank you for reading this information sheet.

If you would like more information or have any questions about the EN-PENS trial please contact:
Telephone number: **0151 5295666 (24hrs in case of emergency)**

If you wish to discuss the study with someone independent of the research team you can contact the local NHS Patient Advice and Liaison Service(PALS) on: **0151 556 3090/3089**

Complaints: If you wish to make a complaint you can contact the Patient Experience Team on: **0151 556 3090/3091,** or write to them at; Patient Experience Team, Sid Watkins Building, The Walton Centre NHS Foundation Trust, Lower Lane, Fazakerley, Liverpool, L9 7LJ or Email: PatientExperienceTeam@thewaltoncentre.nhs.uk

The EN-PENS trial is funded by the National Institute for Health Research

Appendix 2 ENPENS Consent form

A randomised controlled trial of External non-invasive peripheral nerve stimulation for chronic neuropathic pain following peripheral nerve injury (EN-PENS trial).

The Walton Centre NHS Foundation Trust

Excellence in Neuroscience

Please initial all boxes

1. I confirm that I have read and understand the 'Participant Information Sheet, version 3' for the above study. I have had the opportunity to consider the Information, ask questions and have had these answered satisfactorily. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected. ☐

3. I understand that relevant sections of my medical notes and any data collected during the study may be looked at by authorised individuals from the research team, regulatory authorities or from the NHS trust, where is relevant to my taking part in this research. I give permission for these individuals to have access to my record for this purpose. ☐

4. I agree that my telephone number can be used by the research team to contact me during the trial at agreed weekly intervals to monitor my progress with treatment. ☐

5. I agree that my anonymised data can be stored on a secure electronic database held at the Walton Centre. ☐

6. I agree that an authorised person who is bound by confidentiality (e.g. the project lead or members of the research team at The Walton Centre NHS Foundation Trust) can view the personal data recorded as far as it is necessary for data control of the project. ☐

7. I agree to my GP being informed of my participation in the study. ☐

8. I agree that the EN-PENS device will not be used by anyone other than myself. ☐

9. I agree to return all trial equipment within 2 weeks of study completion irrespective of whether the trial ended prematurely. ☐

10. <u>Optional Components:</u>

.

<u>i Future Research Projects</u> I give my permission for the Walton Centre to contact me in the future regarding using my anonymous data in further research studies or regarding my participation in future research studies for which I would be eligible and for which I may want to consider participation. ☐

Please sign 3 copies, keeping 1 for yourself , one will be filed in your medical notes and one will be retained by the researchers.

Appendix 3 Patient outcomes pack

EN-PENS TRIAL PATIENT OUTCOME PACK IRAS NO. 197139
Version 1 17/03/16

Patient details: attach sticker

Date:

Please circle:

Baseline Final Optional ext.

WCNN BPI-SF

1. Please rate your pain by circling the one number that best describes your pain at its **worst** in the past 24 hours

0 1 2 3 4 5 6 7 8 9 10

NO PAIN — PAIN AS BAD AS YOU CAN IMAGINE

2. Please rate your pain by circling the one number that best describes your pain at its **least** in the past 24 hours

0 1 2 3 4 5 6 7 8 9 10

NO PAIN — PAIN AS BAD AS YOU CAN IMAGINE

3. Please rate your pain by circling the one number that best describes your pain on **average**

0 1 2 3 4 5 6 7 8 9 10

NO PAIN — PAIN AS BAD AS YOU CAN IMAGINE

4. Please rate your pain by circling the one number that tells how much pain you have right **now**

0 1 2 3 4 5 6 7 8 9 10

NO PAIN — PAIN AS BAD AS YOU CAN IMAGINE

5. Circle the one number that describes how, during the past 24 hours, pain has interfered with:

A. General Activity

0 1 2 3 4 5 6 7 8 9 10

DOES NOT INTERFERE — COMPLETELY INTERFERES

B. Mood

0 1 2 3 4 5 6 7 8 9 10

DOES NOT INTERFERE — COMPLETELY INTERFERES

C. Walking Ability

0 1 2 3 4 5 6 7 8 9 10

DOES NOT INTERFERE — COMPLETELY INTERFERES

D. Normal work (includes both work outside the home and housework)

0 1 2 3 4 5 6 7 8 9 10

DOES NOT INTERFERE — COMPLETELY INTERFERES

E. Relations with other people

0 1 2 3 4 5 6 7 8 9 10

DOES NOT INTERFERE — COMPLETELY INTERFERES

F. Sleep

0 1 2 3 4 5 6 7 8 9 10

DOES NOT INTERFERE — COMPLETELY INTERFERES

G. Enjoyment of life

0 1 2 3 4 5 6 7 8 9 10

DOES NOT INTERFERE — COMPLETELY INTERFERES

H. Ability to concentrate

0 1 2 3 4 5 6 7 8 9 10

DOES NOT INTERFERE — COMPLETELY INTERFERES

I. Appetite

0 1 2 3 4 5 6 7 8 9 10

DOES NOT INTERFERE — COMPLETELY INTERFERES

6. Before your onset of pain did you have trouble telling your right from your left? YES / NO

MEDICATIONS:

Name	dose	frequency

NOTED SIDE EFFECTS WITH STIMULATION TREATMENT: (free text)

TREATMENT ALLOCATION (circle as appropriate):

PEN

FLAT

Surface area of allodynia:_____cm^2

The EN-PENS trial is funded by the National Institute for Health Research

*We wish to know if you feel pain provoked or increased by brushing, pressure, contact with something cold on the painful area. For each of the following questions, please circle the number that best describes the **average severity of your provoked pain during the past 24 hours**. Circle the number 0 if you have not felt such pain. (Circle one number only.)*

Q8/. Is your pain provoked or increased by brushing on the painful area?

No pain	0	1	2	3	4	5	6	7	8	9	10	Worst pain imaginable

Q9/. Is your pain provoked or increased by pressure on the painful area?

No pain	0	1	2	3	4	5	6	7	8	9	10	Worst pain imaginable

Q10/. Is your pain provoked or increased by **contact** with something cold on the painful area?

No pain	0	1	2	3	4	5	6	7	8	9	10	Worst pain imaginable

*We wish to know if you feel abnormal sensations **in the painful area**. For each of the following questions, please circle the number that best describes the **average severity of your abnormal sensations during the past 24 hours**. Circle the number 0 if you have not felt such sensations. (Circle one number only.)*

Q11/. Do you feel pins and needles?

No pins & needles	0	1	2	3	4	5	6	7	8	9	10	Worst pins & needles imaginable

Q12/. Do you feel tingling?

No tingling	0	1	2	3	4	5	6	7	8	9	10	Worst tingling imaginable

RESULTS

TOTAL SCORE	SUBSCORES
1 – Q1 = ...	(SUPERFICIAL SPONTANEOUS) BURNING PAIN: Q1= ...../10
2 – (Q2+Q3) = ...	(DEEP SPONTANEOUS) PRESSING PAIN: (Q2+Q3)/2 = .../10
3 – (Q5+Q6) = ...	PAROXYSMAL PAIN: (Q5+Q6)/2 = .../10
4 – (Q8+Q9+Q10) = ...	EVOKED PAIN: (Q8+Q9+Q10)/3= ...../10
5 – (Q11+Q12) = ...	PARESTHESIA/DYSESTHESIA: (Q11+Q12)/2 = .../10
(1+2+3+4+5) = .../100	

The EN-PENS trial is funded by the National Institute for Health Research

NPSI:

*We wish to know if you feel spontaneous pain, that is pain without any stimulation. For each of the following questions, please circle the number that best describes the **average severity of your spontaneous pain during the past 24 hours**. Circle the number 0 if you have not felt such pain. (Circle one number only.)*

Q1/. Does your pain feel like burning?

No burning	0	1	2	3	4	5	6	7	8	9	10	Worst burning imaginable

Q2/. Does your pain feel like squeezing?

No squeezing	0	1	2	3	4	5	6	7	8	9	10	Worst squeezing imaginable

Q3/. Does your pain feel like pressure?

No pressure	0	1	2	3	4	5	6	7	8	9	10	Worst pressure imaginable

Q4/. **During the past 24 hours**, your spontaneous pain has been present:

Tick the response that best describes your case.

Permanently	/_/
Between 8 and 12 hours	/_/
Between 4 and 7 hours	/_/
Between 1 and 3 hours	/_/
Less than 1 hour	/_/

*We wish to know if you have brief attacks of pain. For each of the following questions, please circle the number that best describes the **average severity of your painful attacks during the past 24 hours**. Circle the number 0 if you have not felt such pain. (Circle one number only.)*

Q5/. Does your pain feel like electric shocks?

No electric shocks	0	1	2	3	4	5	6	7	8	9	10	Worst electric shocks imaginable

Q6/. Does your pain feel like stabbing?

No stabbing	0	1	2	3	4	5	6	7	8	9	10	Worst stabbing imaginable

Q7/. **During the past 24 hours**, how many of these pain attacks have you had?

Tick the response that best describes your case.

More than 20	/_/
Between 11 and 20	/_/
Between 6 and 10	/_/
Between 1 and 5	/_/
No pain attack	/_/

The EN-PENS trial is funded by the National Institute for Health Research

SELF EFFICACY QUESTIONNAIRE

Please rate how confident you are that you can do the following at present, DESPITE YOUR PAIN. Circle a number for each item where **0 = Not at all confident and 6 = completely confident.**

	Circle a number where 0 = Not Confident						6 = Completely Confident
1. I can enjoy things despite the pain	0	1	2	3	4	5	6
2. I can do most of the household chores (tidying up, washing dishes) despite the pain	0	1	2	3	4	5	6
3. I can socialise with my friends or family as often as I used to despite the pain	0	1	2	3	4	5	6
4. I can cope with my pain in most situations	0	1	2	3	4	5	6
5. I can do some form of work (including housework, paid and unpaid work) despite the pain	0	1	2	3	4	5	6
6. I can still do most of the things I enjoy, such as hobbies or leisure activities despite the pain	0	1	2	3	4	5	6
7. I can cope with my pain without medication	0	1	2	3	4	5	6
8. I can accomplish most of my goals in life despite the pain	0	1	2	3	4	5	6
9. I can lead a normal lifestyle despite the pain	0	1	2	3	4	5	6
10. I can gradually become more active despite the pain	0	1	2	3	4	5	6

Total score:

The EN-PENS trial is funded by the National Institute for Health Research

EQ-5D-5L
Under each heading, please tick the **ONE box that best describes your health TODAY**

MOBILITY
I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE
I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

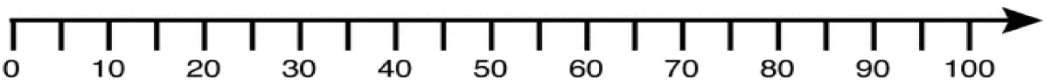
USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*
I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION
I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

We would like to know **how good or bad your health is TODAY**.

- mark an X on the scale to indicate how your health is TODAY



The worst health you can imagine — The best health you can imagine

The EN-PENS trial is funded by the National Institute for Health Research

HADS

This questionnaire is designed to help your clinician to know how you feel. Read each item below and underline the reply which comes closest to how you have been feeling in the past week.

Don't take too long over your replies; your immediate reaction to each item will probably be more accurate than a long, thought-out response.

I feel tense or wound up
- Most of the time
- A lot of the time
- From time to time (occasionally)
- Not at all

I still enjoy the things I used to enjoy
- Definitely as much
- Not quite as much
- Only a little
- Hardly at all

I get a sort of frightening feeling as if something awful is about to happen
- Very definitely and quite badly
- Yes, but not too badly
- A little, but it doesn't worry me
- Not at all

I can laugh and see the funny side of things
- As much as I always could
- Not quite so much now
- Definitely not so much now
- Not at all

Worrying thoughts go through my mind
- A great deal of the time
- A lot of the time
- Not too often
- Very little

I feel cheerful
- Never
- Not often
- Sometimes
- Most of the time

I can sit at ease and feel relaxed
- Definitely
- Usually
- Not often
- Not at all

I feel as if I am slowed down
- Nearly all the time
- Very often
- Sometimes
- Not at all

I get a sort of frightened feeling like butterflies in the stomach
- Not at all
- Occasionally
- Quite often
- Very often

I have lost interest in my appearance
- Definitely
- I don't take as much care as I should
- I may not take quite as much care
- I take just as much care as ever

I feel restless as if I have to be on the move
- Very much indeed
- Quite a lot
- Not very much
- Not at all

I look forward with enjoyment to things
- As much as I ever did
- Rather less than I used to
- Definitely less than I used to
- Hardly at all

I get sudden feeling of panic
- Very often indeed
- Quite often
- Not very often
- Not at all

I can enjoy a good book or radio or television programme
- Often
- Sometimes
- Not often
- Very Seldom

The EN-PENS trial is funded by the National Institute for Health Research

To be completed at study end only.

Please rate, with a tick, how much better or worse you feel with this treatment:	
3	Very much improved
2	Much improved
1	Minimally improved
0	No change
-1	Minimally worse
-2	Much Worse
-3	Very Much Worse

Did you feel you were given a MORE or LESS active treatment? (Circle as appropriate)

1 MORE

2 LESS

Please state your reason for this:

.....
.....
.....
.....
.....
.....
.....

The EN-PENS trial is funded by the National Institute for Health Research

Appendix 4 Posthoc telephone questionnaire

ENPENS STUDY SEMI STRUCTURED TELEPHONE SURVEY
Version 2 22/04/20

Hi there, is that [name]? My name is... I am a researcher at... We are calling you because...Is now a good time to speak?

Thank you very much for your involvement in the ENPENS research study. We very much appreciate your time and feedback and therefore would value your thoughts and answers regarding your use and experience of the device.

It would be helpful and if you could take the time to answer some questions regarding the study. It is entirely optional and if now not a good time is we can arrange a more convenient time. I would also like to reassure you all answers will remain anonymised and confidential.

If you prefer not to answer certain questions, just let me know and we'll move on to the next question. There are no right or wrong answers, we are just interested in your feedback and experience in taking part in the study. All answers will remain anonymised and confidential.

If now is not a good time to speak can arrange a time that perhaps will be?

1. Did you find the stimulation itself uncomfortable or painful, either during or after your treatment?
    a. Did you notice any muscle twitching?

    b. Did this affect how you used the device?

2. Can you remember how high you turned up the device?
    a. Do you think you could have tolerated it at a higher intensity?
    b. What were some of the reasons that made you stick with the level you chose?

3. How often did you use the device and for how long?
    a. Were there days when you did not use the device?
    b. (contingent on question 3a) Can you tell about some of the reasons that stopped you from using the device on certain days?

4. How did you decide when you would use the device? (i.e. after work, first thing in the morning, when your pain was bad).

5. Did you feel confident you were using the device correctly? Did you talk to anyone about how you used the device, or did you look it up online?

6. Did anyone help you to find out how and when the device might work best for you? Would this have been helpful?

7. What kinds of things made you think the treatment had been helpful or not?

8. Can you briefly tell me how would you have liked it to help? Or what would have made you feel like it had helped more?

9. What did you feel your treatment options could be if ENPENS didn't help?

10. Is there anything you feel needs to be changed about the device? We cant promise anything but can pass on your suggestions.

11. On a scale from 1 to 10, how likely would you be to continue to use the device if you were provided with one?

12. Is there anything else you would like us to know? Or anything you would like to ask us about the study?

Thank you very much for your time today, we really appreciate it. Your feedback will help us to better understand how people experience using the device.