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EXTERNAL NON-INVASIVE PERIPHERAL NERVE STIMULATION FOR CHRONIC PERIPHERAL NEUROPATHIC PAIN FOLLOWING PERIPHERAL NERVE INJURY- A RANDOMIZED SHAM-CONTROLLED TRIAL

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Introduction

Eight percent of people in the UK are estimated to have chronic neuropathic pain [1]. Current management guidelines are heavily weighted on pharmacotherapy with modest outcomes [2].

External non-invasive peripheral nerve stimulation (EN-PNS) is a neuromodulation technology where a ball shaped electrode is positioned over the injured nerve, and low-frequency stimulation (1-2Hz) is applied. This stimulation mode achieves long-lasting analgesia through a specific mechanism, preferential activation of superficial nociceptive A-delta fibres inducing long-term depression (LTD) of synaptic strength [4].

Observational studies suggest that EN-PENS may relieve pain for people with localised neuropathic pain [5,6]; however, there is currently no evidence from controlled trials to confirm the efficacy for patients with longstanding neuropathic pain.

https://pubmed.ncbi.nlm.nih.gov/25308421/

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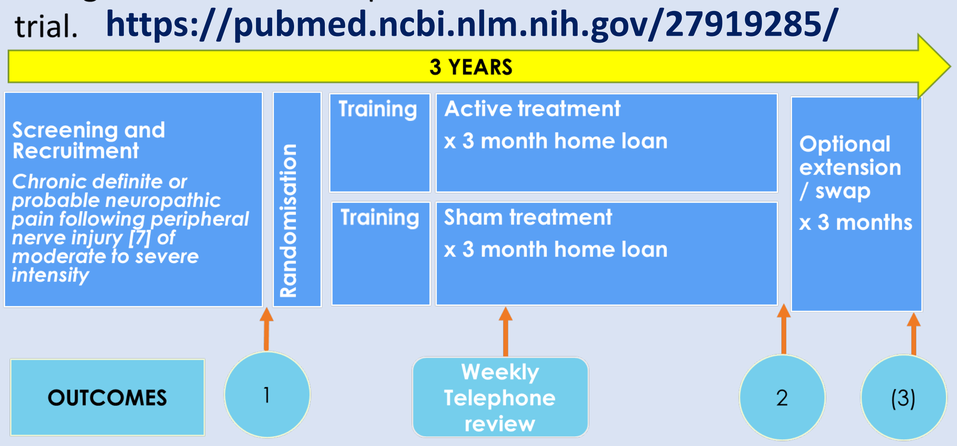
Method

A single site randomised patient-assessor blinded sham controlled trial. **https://pubmed.ncbi.nlm.nih.gov/27919285/**



Primary outcome - Average 24-h pain intensity recorded on an 11-point (0–10) numerical rating scale, averaged over the last 7 days of treatment, at three months, compared between study groups

Results-1.

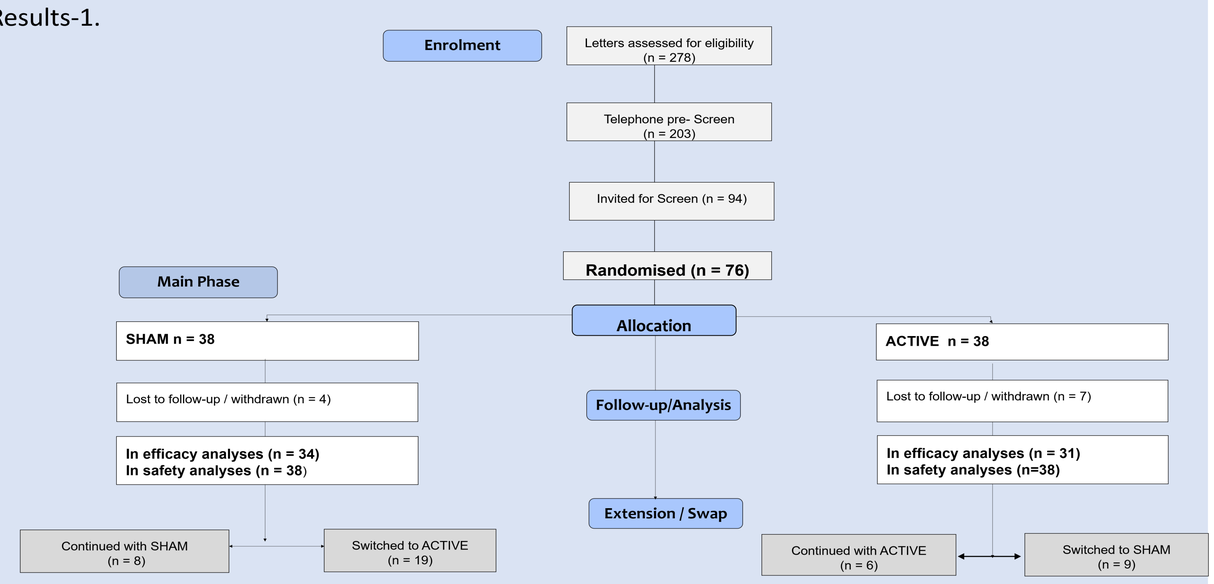
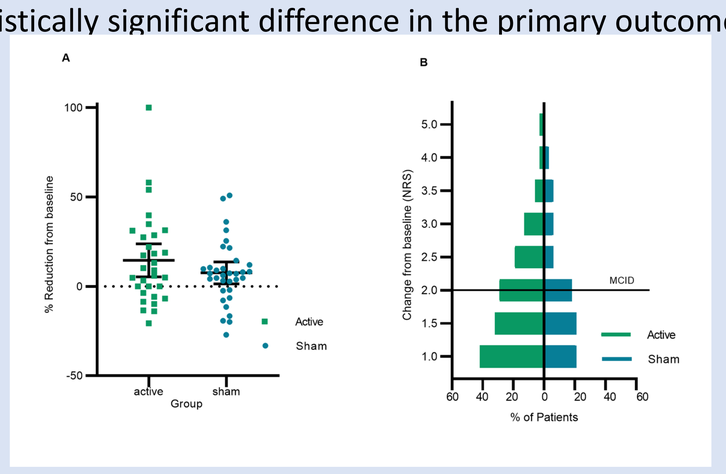


Figure 1: Simplified ENPENS Trial Profile (CONSORT Diagram).

Results 2: Primary outcome

There was no statistically significant difference in the primary outcome between the study groups.



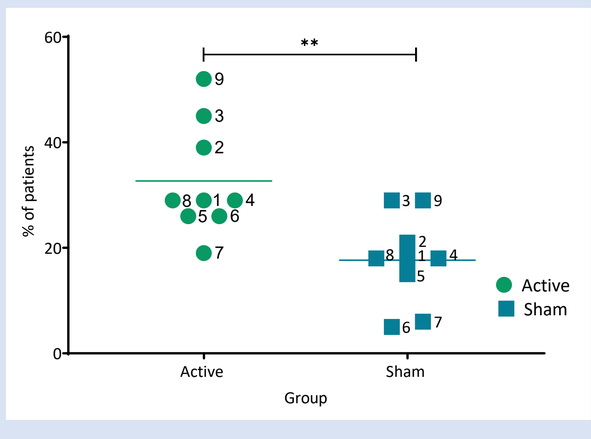
Pain scores were 0·3 units lower in active group (95% CI -1·0, 0·3; p=0·30) giving an effect size of 0·19 (Cohen's D).

Results 3:

Secondary outcomes: EQ-VAS scores were on average ten points higher (=better) in the active group (95% CI 0, 19; p=0·05), and BPI interference subscale values were on average 0·9 points lower (=better) (95 % CI -1·7, 0·0; p=0·06). Other outcomes did not significantly change.

Exploratory outcomes: Dynamic surface area of allodynia area – the only objective measure of **stimulus evoked pain-** demonstrated significant change between groups, being on average 74 cm2 lower within active group compared to sham (95% CI: 22 to 126 cm2 lower; **p=0·006**).
More sham group patients demonstrated enlargement of the DMA area following treatment, (47%, n=16 vs 29 %, n=9, p=0·14 (chi square test)).

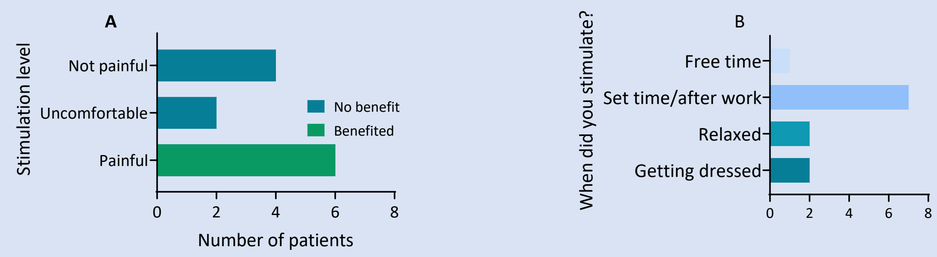
Minimally important clinical difference:
The average percentage of patients achieving MCID in any given outcome domain was significantly higher in the active group compared to the sham group
(33% ±11 Vs 19% ±7.1, p=0.005, u=10 Mann Whitney test).



Key: 1= Average Pain intensity (NRS) , 2= EQ-5D-5L VAS descriptor, 3 = EQ-5D-5L health Index
4 = Brief pain inventory interference subscale, 5= Brief pain inventory worst pain intensity
6= Hospital anxiety scale anxiety subscale, 7= Hospital anxiety scale depression subscale
*8= Pain self-efficacy questionnaire, 9= Dynamic allodynia mapped area, **P=≤.01*

Post hoc: Understanding patient experience of treatment.

Research indicates that to induce optimal LTD stimulus strength should be delivered at 2-5 x electrical detection threshold (which is usually perceived as painful).



Conclusions

This was a negative study, but results illustrate a trend toward positive outcome change within the active group compared to the sham group. Significant reduction of stimulus-evoked pain was observed, supporting effective induction of long-term depression for patients with pain after peripheral nerve injury and highlights the therapeutic potential of low frequency stimulation. The failure to reach significant change illustrates further optimization of low frequency nerve stimulation as a treatment modality is required. Based on post hoc questions we would suggest further optimization regarding patient education in respect to mechanistic objectives, strengthening of measures of adherence and fidelity and understanding of barriers and facilitators in terms of patient use.

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