INPLASY PROTOCOL

To cite: Burkey et al. Painful Peripheral Neuropathies of the Lower Limbs and/or Lower Extremities Treated with Spinal Cord Stimulation: A Systematic Review with Narrative Synthesis. Inplasy protocol 202310001. doi: 10.37766/inplasy2023.1.0001

Received: 01 January 2023

Published: 01 January 2023

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Support: **Nevro Corp.**

Review Stage at time of this submission: **Completed but not published.**

Painful Peripheral Neuropathies of the Lower Limbs and/or Lower Extremities Treated with Spinal Cord Stimulation: A Systematic Review with Narrative Synthesis

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Review question / Objective: **For patients with lower limb pain due to painful peripheral neuropathy (PPN), how effective is spinal cord stimulation (SCS) as measured by pain intensity and responder rate outcomes?**
Eligibility criteria: **Study reported pain-related outcomes from a prospective or retrospective study of SCS (or a related spinal stimulation technology) used to treat at least 3 human subjects with PPN of the lower limbs and/or lower extremities. Exclusions: Study report not peer-reviewed; study has no full-text manuscript available (eg, conference proceedings); study does not report original data; data cannot be extracted for the population of interest; data were presented for 2 or fewer human subjects (ie, case studies).**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 01 January 2023 and was last updated on 01 January 2023 (registration number INPLASY202310004).

INTRODUCTION

Review question / Objective: **For patients with lower limb pain due to painful peripheral neuropathy (PPN), how effective is spinal cord stimulation (SCS) as measured by pain intensity and responder rate outcomes?**

Rationale: **Recent reviews of SCS in the painful peripheral neuropathy (PPN) area have focused on patients with painful diabetic neuropathy (PDN). However, increasing evidence suggests that the therapy may be beneficial in other PPN indications. Therefore, a comprehensive and systematic review of SCS across all PPN indications is needed to collate and summarize the latest evidence. In addition, given the prevalence of sensorimotor symptoms in PPN patients, a summary of the evidence relating to neurological changes after SCS may be useful to clinicians.**

Condition being studied: Painful peripheral neuropathy (PPN).

METHODS

Search strategy: #1. “spinal cord”[tiab] OR spine[tiab] OR spinal[tiab] OR epidural[tiab] OR “dorsal column*”[tiab] OR invasive[tiab] OR implant*[tiab] OR “spinal nerve*”[tiab] OR “spinal gangli*"[tiab] OR "spinal root*"[tiab] OR "nerve root*"[tiab] OR "dorsal gangli*"[tiab] OR "dorsal root*” [tiab]
#2. stimulation[tiab] OR stimulator[tiab] OR neuromodulation[tiab] OR neurostimulator[tiab]
#3. #1 AND #2
#4. "spinal cord stimulation"[mesh] OR "electric stimulation therapy"[mesh] OR scs[tiab] OR drg[tiab]
#5. #3 OR #4
#6. "Diabetic Neuropathies”[mesh]
#7. diabet*[tiab] AND (neuropath*[tiab] OR amyotroph*[tiab] OR polyneuropath*[tiab] OR mononeuropath*[tiab] OR neuralg*[tiab] OR pain*[tiab])
#8. #6 OR #7
#9. neuropathy[tiab] OR neuropathies[tiab] OR polyneuropath*[tiab] OR mononeuropath*[tiab]
#10. #8 OR #9
#11. #5 AND #10.

Participant or population: Painful peripheral neuropathy patients with pain in the lower limbs and/or lower extremities.

Intervention: Spinal cord stimulation (SCS). During traditional SCS (t-SCS), electrical pulses are applied to the spinal cord at a frequency between 40 Hz and 60 Hz. Paresthesia is elicited in the painful area by the electrical stimulation and masks the sensation of pain. During 10 kHz SCS, no paresthesia is felt or required for pain relief. Other forms of SCS, such as burst SCS and dorsal root ganglion stimulation (DRGS), induce paresthesia in a subset of patients.

Comparator: N/A.

Study designs to be included: Prospective or retrospective study of SCS (or a related spinal stimulation technology).

Eligibility criteria: Study reported pain-related outcomes from a prospective or retrospective study of SCS (or a related spinal stimulation technology) used to treat at least 3 human subjects with PPN of the lower limbs and/or lower extremities. Exclusions: Study report not peer-reviewed; study has no full-text manuscript available (eg, conference proceedings); study does not report original data; data cannot be extracted for the population of interest; data were presented for 2 or fewer human subjects (ie, case studies).

Information sources: PubMed database.

Main outcome(s): Two standard SCS efficacy outcomes were defined: (1) mean pain intensity reduction from baseline (2) responder rate, defined as the proportion of subjects with at least a 50% reduction in pain intensity from baseline.

Additional outcome(s): Secondary outcomes of interest included neurological assessment outcomes, changes in function, and health-related quality of life (HR-QoL) improvement.

Data management: Data were captured in an Excel spreadsheet to standardize group quantitative and qualitative outcomes.

Quality assessment / Risk of bias analysis: A single reviewer assessed the risk of bias for each included RCT using the Cochrane Risk of Bias tool (RoB 2) tool. The assessment considered: (1) Bias arising from the randomization process; (2) Bias due to deviations from intended interventions; (3) Bias due to missing outcome data; (4) Bias in measurement of the outcome; (5) Bias in selection of the reported result. Each domain was graded as low risk, high risk, or with some concerns.

Strategy of data synthesis: Meta-analysis was not considered appropriate for the included studies due to the heterogeneous disease etiologies, interventions, and study methodologies. Therefore, we prepared a narrative description of the data and a tabulated summary of pain measures and

other outcomes. The tabulated summary and narrative outline grouped studies principally by etiology, SCS modality, and study type. A separate tabulated summary of neurological data was also presented.

Subgroup analysis: N/A.

Sensitivity analysis: N/A.

Language restriction: No.

Country(ies) involved: UK and USA.

Keywords: Painful diabetic neuropathy; peripheral neuropathy; spinal cord stimulation; 10 kHz SCS; diabetes; neuropathic pain; systematic review.

Contributions of each author:

Author 1 - Adam Burkey - The author was involved in the conceptualization of the study and reviewing /editing of the manuscript.
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Author 4 - Deborah Edgar - The author was involved in the conceptualization of the study, the development of the study methodology, and the analysis. She also prepared the original manuscript draft and worked on reviewing /editing of the manuscript.
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Conflicts of interest: ARB has received consulting fees from Nevro and research support from Nevro. JLC has received consulting fees from Vertos and research support from Nevro. CEA has received consulting fees from Nevro, Vertex, Amgen, Lundbeck, Collegium, Gene Pharma, Clexio Biosciences, Biohaven, Teva and research support from Abbvie, Amgen, Lilly and Teva. DRE received a fee from Nevro in her capacity as an independent medical writer. EAP has received consulting fees from Abbott Neuromodulation, Biotronik, Boston Scientific, Medtronic Neuromodulation, Nalu, Neuros Medical, Nevro, Presidio Medical, Saluda, and Vertos; research support from Mainstay, Medtronic Neuromodulation, Nalu, Neuros Medical, Nevro, ReNeuron, Saluda, and SPR; and stock options from neuro42 and SynerFuse.