ONTARIO HEALTH TECHNOLOGY ASSESSMENT SERIES

Peripheral Nerve Stimulation for Chronic Neuropathic Pain

A Health Technology Assessment

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Ontario Health

Key Messages

What Is This Health Technology Assessment About?

Chronic neuropathic pain is long-term nerve pain in the shoulders, trunk, arms, or legs. It is a major contributor to disability. It affects people's physical and mental well-being, and their quality of life. Treatment options for chronic neuropathic pain range from nonopioid medications to surgery.

One treatment option for chronic neuropathic pain is called percutaneous peripheral nerve stimulation, or PNS. Modern PNS involves implanting a small electrical device (a wire-like lead or electrode) under the skin near the affected nerves. The device then delivers electric signals, stimulating the nerves and blocking pain signals from going to the brain. There are 2 types of percutaneous PNS: permanent and temporary (up to 60 days). PNS may be helpful for people with chronic neuropathic pain when pain medications or other noninvasive treatments do not provide enough pain relief. People who use PNS may be able to reduce or discontinue their use of opioid medications.

This health technology assessment looked at how safe, effective, and cost-effective PNS is for adults with chronic neuropathic pain. It also looked at the budget impact of publicly funding PNS and at the experiences, preferences, and values of adults with chronic neuropathic pain.

What Did This Health Technology Assessment Find?

Compared to people who did not receive PNS, permanent PNS improved people's pain, functioning, and health-related quality of life, but it had little to no effect on their use of pain medications. Temporary PNS may improve pain, functioning, and health-related quality of life, and it may reduce the use of pain medications. Implantation of a permanent or temporary PNS system is reasonably safe.

Compared with standard care alone, PNS in addition to standard care may be cost-effective. We estimate that publicly funding PNS in addition to standard care for people with chronic neuropathic pain in Ontario over the next 5 years would cost an additional $10.09 million.

People with chronic pain and care partners described how difficult it was to live with chronic pain and how it negatively affected their quality of life and mental health. They also spoke about the challenges and frustration of trying many pain management options to find something that worked for them. People who had direct experience with permanent PNS spoke about its effectiveness in managing pain and its positive impact on their quality of life and mental health.

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Abstract

Background

Chronic neuropathic pain is a major health problem that adversely affects people's physical and mental well-being, as well as their quality of life. Percutaneous peripheral nerve stimulation (PNS) may offer a minimally invasive option earlier in the treatment continuum for adults with chronic neuropathic pain that is refractory to conventional medical management. We conducted a health technology assessment of PNS for adults with chronic neuropathic pain, which included an evaluation of effectiveness, safety, cost-effectiveness, the budget impact of publicly funding PNS, and patient preferences and values.

Methods

We performed a systematic literature search of the clinical evidence. We assessed the risk of bias of each included study using the Cochrane risk-of-bias tool for randomized controlled trials and the Risk of Bias in Non-randomized Studies – of Interventions for observational studies, and the quality of the body of evidence according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Working Group criteria. We performed a systematic economic literature search and conducted a cost–utility analysis with a 3-year horizon from a public payer perspective. We also analyzed the budget impact of publicly funding PNS in adults with chronic neuropathic pain in Ontario. To contextualize the potential value of PNS, we spoke to people with chronic pain, and to care partners of patients with chronic pain.

Results

We included 17 publications (2 randomized controlled trials and 12 nonrandomized studies) in the clinical evidence review. These studies included chronic neuropathic pain in the trunk and the upper and lower extremities. Compared with placebo controls in adults with chronic neuropathic pain that is refractory to conventional medical management, permanent PNS likely decreases pain scores, likely improves functional outcomes, and likely improves health-related quality of life, but it has little to no effect on the use of pain medications (all GRADEs: Moderate). Compared with before implantation in adults with chronic neuropathic pain, permanent PNS may decrease pain scores, may decrease the use of pain medications, may improve functional outcomes, and may improve health-related quality of life (all GRADEs: Low). Compared with placebo controls in adults with chronic postamputation pain, temporary PNS may decrease pain scores, may decrease use of pain medications, may improve functional outcomes, and may improve health-related quality of life (all GRADEs: Low). Compared with before implantation in adults with chronic postamputation pain, temporary PNS may decrease pain scores, may decrease the use of pain medications, may improve functional outcomes, and may improve health-related quality of life (all GRADEs: Low). We did not find any studies that compared permanent PNS to temporary PNS. Implantation of a PNS system is a reasonably safe procedure; most adverse events were localized and mild in intensity (GRADEs: Moderate to Low).

The incremental cost-effectiveness ratio of PNS in addition to standard care compared with standard care alone is $87,211 per quality-adjusted life-year (QALY) gained. The probability of PNS in addition to standard care being cost-effective versus standard care alone is 1.02% at a willingness-to-pay of $50,000 per QALY gained and 64.88% at a willingness-to-pay of $100,000 per QALY gained. The annual budget impact of publicly funding PNS in Ontario over the next 5 years ranges from an additional $0.97 million

in year 1, increasing to $3.15 million in year 5, for a total of $10.09 million over 5 years. People with chronic pain and their family members and care partners viewed PNS favourably. Those who had direct experience with permanent PNS perceived it to be effective in reducing their pain levels, leading to a positive impact on their quality of life and mental health. Current barriers to accessing PNS include lack of awareness, cost, and geography.

Conclusions

In adults with chronic neuropathic pain that is refractory to conventional medical management, permanent PNS likely improves pain outcomes, functional outcomes, and health-related quality of life but has little to no effect on the use of pain medications compared with placebo controls. Temporary PNS may improve pain outcomes, functional outcomes, and health-related quality of life, and it may reduce the use of pain medications. Implantation of a permanent or temporary PNS system is reasonably safe. The incremental cost-effectiveness ratio of PNS in addition to standard care compared with standard care alone is $87,211 per QALY gained. We estimate that publicly funding PNS in Ontario would result in additional costs of $10.09 million over the next 5 years. People who had direct experience with permanent PNS spoke of its effectiveness in reducing their pain levels and its positive impact on their quality of life and mental health. Barriers to accessing PNS include lack of awareness, cost, and geography.

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Objective

This health technology assessment evaluates the effectiveness, safety, and cost-effectiveness of minimally invasive percutaneous peripheral nerve stimulation (PNS) for the treatment of chronic neuropathic pain in adults. It also evaluates the budget impact of publicly funding minimally invasive percutaneous PNS and the experiences, preferences, and values of adults with chronic neuropathic pain.

Background

Health Condition

Neuropathic pain is defined as pain caused by a lesion or disease of the somatosensory system, including the peripheral fibres (Aβ, Aδ, and C) and central neurons.[1] Common conditions associated with neuropathic pain include postherpetic neuralgia (pain that continues after a bout of shingles), occipital neuralgia (burning or throbbing pain that starts at the base of the head and goes to the scalp), painful radiculopathy (a pinched nerve in the spine causing pain in the arms or the legs), diabetic neuropathy, HIV infection, leprosy, limb amputation, stroke, and peripheral nerve injury from surgery, radiation, or trauma.

Patients with neuropathic pain experience symptoms such as burning and electricity-like sensations, as well as pain resulting from nonpainful stimulation, such as light touch.[1] These symptoms often persist, becoming chronic and responding less and less to pain medications. People's quality of life is impaired as a result of sleep disturbances, anxiety, and depression, as well as morbidity from the pain itself and its underlying cause.

Clinical Need and Population of Interest

Chronic neuropathic pain is a major global health problem.[2] The Canadian prevalence of likely neuropathic pain is 1.9% to 3.4%.[3] As of October 2023, the population of Ontario was 15.8 million,[4] meaning that approximately 302,000 to 537,000 people in Ontario have chronic neuropathic pain.

Current Treatment Options

Conservative treatments, such as physical therapy and nonopioid medications, provide few analgesic benefits for severe cases of chronic neuropathic pain.[5] Opioid medications are a last resort – often used when other therapies provide inadequate pain relief – but prolonged use of opioid medications carries risks of dependence and abuse. Interventional treatments, such as steroid or anesthetic injections, transcutaneous electrical nerve stimulation, or radiofrequency ablation, have limited short-term efficacy. More invasive interventions, including spinal cord stimulation and dorsal root ganglion stimulation, are expensive and carry risks of infection and lead migration. In addition, some peripheral targets are not amenable to these invasive interventions.

Health Technology Under Review

Compared with other interventional pain management options, percutaneous PNS may offer greater selectivity and accuracy for chronic neuropathic pain that has well-defined nerve targets.[6] Modern PNS refers to the placement of a wire-like electrode next to 1 or more peripheral nerves. The electrode is connected to an external device, which will induce paresthesia (a tingling feeling) in the form of rapid electrical pulses to relieve pain. Patients can adjust the stimulation parameters to fit their needs.[7] The proposed mechanism for pain relief with PNS is modulation of inflammatory pathways, the autonomic nervous system, and endogenous pain-inhibition pathways.[8] The therapeutic goal is to avoid starting opioids or to taper opioid doses. While they are receiving PNS, some patients may still need nonopioid medications (e.g., gabapentinoids, anticonvulsants, antidepressants) or even opioids at a reduced dose.

According to an international survey of pain medicine experts, PNS should be offered early in the treatment of chronic neuropathic pain.[5] Specifically, PNS should be considered after less invasive interventions (such as epidural or peripheral steroid injection, transcutaneous electrical nerve stimulation, pulsed radiofrequency, or radiofrequency ablation or denervation) but before opioid medications, spinal cord stimulation, or other more invasive interventions. In addition, a comprehensive treatment algorithm for neuropathic pain based on international guidelines, published data, and best practices recommended that neuromodulation (e.g., PNS) should be offered before low-dose opioids and target drug delivery (e.g., spinal cord stimulation).[9]

Historically, PNS used leads adapted from devices meant for spinal cord stimulation, instead of leads designed specifically for peripheral nerves.[10,11] This practice was limited by its complexity, and by the invasiveness of the open surgical implantation of a multicontact electrode (paddle) along or adjacent to the targeted nerves. Open surgeries were often complicated by iatrogenic nerve injury and lead migration, requiring revision. It was also difficult to find a peripheral pocket large enough to install the implantable pulse generator on the trunk, requiring a long tunnelling course.

The recent development of minimally invasive PNS devices that use percutaneously implanted leads designed for peripheral nerves along with an external pulse generator may overcome the limitations of these early devices.[10] In addition, advances in ultrasound and fluoroscopy to guide lead placement has not only increased precision and safety, but also captured more nerves. It has become possible to target large-diameter afferent sensory fibres at higher frequencies and efferent fibres at lower frequencies to achieve pain reduction.[12]

At the time of writing, 4 minimally invasive percutaneous PNS systems have regulatory approval in North America: StimRouter (Bioventus Inc.),[10] Freedom (Curonix Inc.),[13] Nalu (Nalu Medical),[14] and SPRINT (SPR Therapeutics).[15] All 4 systems are indicated for intractable chronic pain of peripheral nerve origin.[10,12] In addition, although the SPRINT PNS system is not intended to be placed in the region innervated by the cranial and facial nerves,[15] it can be used to treat headache pain in the occipital region and axial neck pain.[16]

The StimRouter, Freedom, and Nalu systems are permanent PNS systems. The SPRINT system is currently the only 60-day temporary system available for clinical use (i.e., leads are removed 60 days after initial implantation).

(Note: unless otherwise specified, all references to peripheral nerve stimulation or PNS in this health technology assessment refer to minimally invasive, percutaneous PNS.)

Regulatory Information

The StimRouter PNS system, manufactured by Bioventus Inc. (formerly Bioness Inc.), is licensed by Health Canada as a Class III device (licence number 100426). It is a permanent PNS system; no temporary PNS systems have been approved by Health Canada.

The other 3 PNS systems – Freedom (Curonix Inc.),[13] Nalu (Nalu Medical),[14] and SPRINT (SPR Therapeutics)[15] – are available in the United States and approved by the US Food and Drug Administration, but they have not been approved by Health Canada. Internationally, PNS devices are clinically approved and commercially available in Australia, and have received CE marks for Germany, France, Italy, Spain, Portugal, Belgium, the Netherlands, and the United Kingdom. Some PNS devices available in Europe (e.g., Neurimpulse) are not available in North America.

Ontario and Canadian Context

At present, StimRouter is the only PNS system available for clinical use in Ontario. Implantation of the StimRouter PNS system is performed mostly by pain medicine physicians experienced in ultrasound-guided procedures, under local anesthesia on an outpatient basis.[10] Prior to permanent implantation, an ultrasound-guided diagnostic nerve block is performed to identify target nerves and assess potential pain relief. Those who demonstrate pain reduction of greater than 50% with the nerve block then proceed to a permanent PNS implant. Two leads may be implanted around larger nerves (such as the sciatic nerve) to provide more complete nerve coverage; as well, 2 leads may be implanted on 2 nerves that are near one another, using a single external pulse transmitter.[10] The implantation procedure takes approximately 40 to 50 minutes. The PNS device is typically programmed on the same day as the implantation procedure, and patients can start using it immediately. Device programming is performed by the physician or by clinic staff (e.g., nurses, physician assistants) under the direction of the physician and with remote or onsite support of a device representative. The device is programmed in accordance with patients' preferences for the sensation of pain relief, using different waveforms, intensities, pulse rates, phase durations, and treatment times. Stimulation can be constant or intermittent.

Eligibility for PNS to treat chronic neuropathic pain is determined based on medical history, a physical examination, diagnostic tests (e.g., electromyography, nerve conduction velocity, magnetic resonance neurography nerve blocks), mental and cognitive conditions, and patient preferences.[17]

PNS devices are not publicly funded in Ontario, although Ontario Health Insurance Plan fee codes are available for clinicians to bill for implantation time. To our knowledge, 3 pain clinics in Ontario (1 in a hospital and 2 in the community) have implanted these devices funded by third-party insurance, self-pay, manufacturer pro bono, or philanthropic sources (personal communication, Bioventus Inc., July 20, 2023).

PNS devices are also not publicly funded in any Canadian province or territory. However, they have been used in Alberta, British Columbia, and Quebec, funded by third-party insurance or self-pay (personal communication, Bioventus Inc., July 20, 2023).

In 2020, the Ontario Health Technology Advisory Committee recommended publicly funding spinal cord stimulation at frequencies up to and including 10 kHz in adults with chronic noncancer pain that is refractory to conventional medical management.[18]

Equity Context

We use the PROGRESS-Plus framework to help explicitly consider health equity in our health technology assessments.[19] PROGRESS-Plus is a health equity framework used to identify population and individual characteristics across which health inequities may exist. These characteristics include place of residence; race or ethnicity, culture, or language; gender or sex; disability; occupation; religion; education; socioeconomic status; social capital; and other key characteristics that stratify health opportunities and outcomes.

Access to PNS devices for people with chronic neuropathic pain is currently limited to 3 clinics in Ontario (2 in the Greater Toronto Area and 1 in Kingston) that have adopted this technology. Effective public funding may improve equity in access to the technology.

Expert Consultation

We engaged with experts in the specialty areas of pain medicine to help inform our understanding of aspects of the health technology and our methodologies, and to contextualize the evidence.

PROSPERO Registration

This health technology assessment has been registered in PROSPERO, the international prospective register of systematic reviews (CRD# 42023481564), available at crd.york.ac.uk/PROSPERO.

Clinical Evidence

Research Question

What are the effectiveness and safety of minimally invasive percutaneous peripheral nerve stimulation (PNS) compared with non-PNS methods of pain management for the treatment of chronic neuropathic pain in adults?

Methods

Clinical Literature Search

We performed a clinical literature search on October 25, 2023, to retrieve studies published from January 1, 2013, until the search date. The rationale for the search date limit was that PNS was not mentioned in the 2013 International Association for the Study of Pain Neuropathic Pain Special Interest Group guidelines[20] and did not become widely available until after publication of those guidelines. We used the Ovid interface in the following databases: MEDLINE, Embase, the Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews, and the National Health Service Economic Evaluation Database (NHS EED).

A medical librarian developed the search strategies using controlled vocabulary (e.g., Medical Subject Headings) and relevant keywords. The final search strategy was peer-reviewed using the PRESS Checklist.[21]

We created database auto-alerts in MEDLINE and Embase and monitored them until May 24, 2024. We also performed a targeted grey literature search of the International HTA Database, the websites of health technology assessment organizations and regulatory agencies, and clinical trial and systematic review registries, following a standard list of sites developed internally. See Appendix 1 for our literature search strategies, including all search terms.

Eligibility Criteria

Studies

Inclusion Criteria

- English-language full-text publications
- Studies published from January 1, 2013, to the search date
- Health technology assessments, systematic reviews; randomized controlled trials (RCTs); nonrandomized comparative studies, including before-and-after studies, registries, and surveys
- Case series with 10 or more participants

Exclusion Criteria

- Animal and in vitro studies
- Narrative reviews, conference abstracts, case reports, editorials, commentaries, letters

Participants

Inclusion Criteria

- Adults with localized or regional chronic neuropathic pain of peripheral nerve origin, including the shoulders, trunk, and upper and lower extremities, as well as specific areas of the head and neck, depending on the PNS device (note: StimRouter [Bioventus Inc.] is not indicated for patients with pain of craniofacial nerve origin,[10] but SPRINT [SPR Therapeutics] is indicated for patients with headache in the occipital region and axial neck pain[16])

Exclusion Criteria

- Children
- Pregnant people

Interventions

Inclusion Criteria

- Minimally invasive percutaneous PNS systems with regulatory approval in North America, with or without conventional medical management (e.g., physical therapy, nonopioid medications, opioid medications)

Exclusion Criteria

- Early generations of PNS devices that require open surgical implantation of a stimulation lead or surgical placement of an implantable pulse generator
- Peripheral nerve field stimulation
- Transcutaneous electric nerve stimulation
- Spinal cord stimulation devices used for PNS

Comparators

Inclusion Criteria

- Conventional medical management (e.g., physical therapy, nonopioid medications, opioid medications)
- No intervention

Exclusion Criteria

- Interventions that include PNS

Outcome Measures

Primary Outcome

- Proportion of patients with a positive response to PNS
- Pain scores

Secondary Outcomes

- Use of pain medications
- Functional outcomes (e.g., activities of daily living, ambulatory abilities)
- Health-related quality of life
- Health services utilization
- Adverse events

Timing

- Presence of chronic neuropathic pain when conventional medical management (including physical therapy, opioid medications, nonopioid medications, and less invasive interventions such as injection therapy) does not provide sufficient pain relief[6]

Setting

- Outpatient

Literature Screening

Two reviewers screened titles and abstracts to assess the eligibility of a sample of 100 citations to validate the inclusion and exclusion criteria. A single reviewer then screened all remaining citations using Covidence[22] and obtained the full texts of studies that appeared eligible for review according to the inclusion criteria. The same reviewer then examined the full-text articles and selected studies eligible for inclusion. The reviewer also examined reference lists and consulted content experts for any additional relevant studies not identified through the search.

Data Extraction

We extracted data from the included studies on study populations, indications, target nerves, eligibility, follow-up duration, funding sources, and results.

Equity Considerations

In a broader sense, there are disparities in all aspects of pain management. These disparities have been identified for different racial and ethnic groups and vulnerable populations, including the 2SLGBTQIA+ community, those of low socioeconomic status, military veterans, older people, and those living in rural areas.[23] With advances in interventional pain procedures, disparity in access is expected to increase.

Specific to this health technology assessment, a cross-sectional survey conducted in Canada found that men who were economically disadvantaged had a higher burden of neuropathic pain.[3] If PNS is not publicly funded, lower socioeconomic status or financial barriers may further limit access to this technology for people with chronic neuropathic pain.

Equity considerations relevant to the use of PNS implants for chronic neuropathic pain across different populations (i.e., gender or sex, socioeconomic status) have been reported to the extent that the information was available in the included studies.

Statistical Analysis

We did not pool the results of the included studies because of differences in study populations and outcomes measurement. We have summarized the results in tables and described them in the text.

We were unable to undertake a subgroup analysis because information was unavailable on the effect of PNS implants for chronic neuropathic pain across different populations.

Critical Appraisal of Evidence

We assessed risk of bias using the Cochrane risk-of-bias tool for RCTs[24] and the Risk of Bias in Non-randomized Studies – of Interventions (ROBINS-I) tool for observational studies[25] (Appendix 2).

We evaluated the quality of the body of evidence for each outcome according to the *Grading of Recommendations Assessment, Development, and Evaluation* (GRADE) *Handbook*.[26] The body of evidence was assessed based on the following considerations: risk of bias, inconsistency, indirectness, imprecision, and publication bias. The overall rating reflects our certainty in the evidence.

Results

Clinical Literature Search

The clinical literature search yielded 2,150 citations, including grey literature searches and after removing duplicates, published from January 1, 2013, until October 25, 2023. We identified 1 additional eligible study from other sources, including database alerts (monitored throughout the assessment period). In total, we identified 17 publications (2 RCTs and 12 observational studies) that met our inclusion criteria. See Appendix 3 for a list of selected studies excluded after full-text review. Figure 1 presents the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram for the clinical literature search.

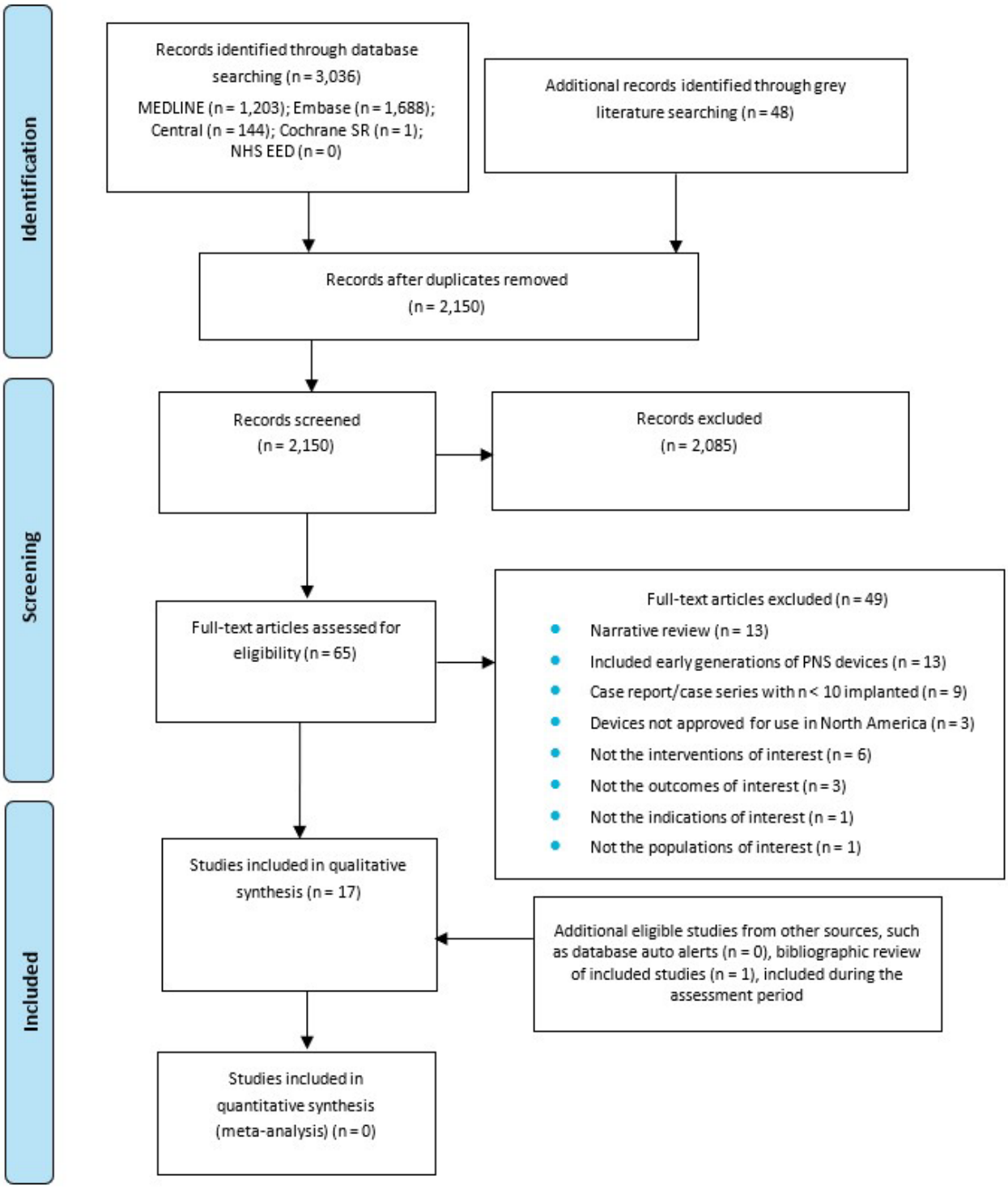

Figure 1: PRISMA Flow Diagram – Clinical Systematic Review

PRISMA flow diagram showing the clinical systematic review. The clinical literature search yielded 2,150 citations including grey literature results and after duplicates, published between January 1, 2013, and October 25, 2023. We screened the abstracts of the 2,150 identified studies and excluded 2,085. We assessed the full text of 65 articles and excluded a further 49. In the end, we included 17 articles in the qualitative synthesis, including 1 study identified from other sources.

Abbreviation: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses.

Source: Adapted from Page et al.[27]

Characteristics of Included Studies

The literature search identified 17 publications from 14 primary studies for inclusion in this clinical evidence review. Among the 14 studies:

- 1 RCT and 1 nonrandomized study investigated the StimRouter PNS system (permanent PNS)[11,28]
- 4 nonrandomized studies investigated the Freedom PNS system (permanent PNS)[29-32]
- 1 RCT[33,34] and 7 nonrandomized studies[35-43] investigated the SPRINT PNS system (temporary PNS)

No studies of the Nalu neurostimulation system met our inclusion criteria.

In the RCT of the StimRouter system,[28] 94 patients with chronic neuropathic pain in the trunk, upper extremities, or lower extremities underwent implantation and were randomized to receive PNS (intervention; n = 45) or no active stimulation (placebo controls; n = 49) for 90 days. The authors assessed primary efficacy outcomes at the end of the 90-day intervention. After the primary intervention period, 30 patients in the control group crossed over to receive active stimulation and were followed for another 90 days in a secondary efficacy analysis.

In the nonrandomized study of StimRouter,[11] 39 patients with focal mononeuropathy were surveyed by the manufacturer before and 3 to 6 months after device implantation.

The 4 nonrandomized studies of the Freedom PNS system were retrospective, with sample sizes of 11 to 57.[29-32] All studies had a before-and-after design, using patients as their own controls. Patients were followed for up to 12 months after permanent PNS implantation. Two studies examined chronic neuropathic pain in general,[29,30] 1 examined chronic knee pain,[31] and 1 examined chronic foot pain.[32]

In the RCT of the SPRINT system, 28 patients with chronic postamputation pain were randomized to receive PNS (intervention; n = 14) or no active stimulation (placebo controls; n = 14) for 4 weeks.[33,34] At the end of the 4 weeks, the entire placebo control group crossed over to the intervention group. All patients then received PNS for an additional 4 weeks. Primary outcomes were ascertained at 4 weeks (i.e., 4-week PNS vs. 4-week placebo), 8 weeks (8-week PNS vs. 4-week placebo + 4-week PNS), and 12 months. The 12-month follow-up demonstrated the sustained effects of temporary intervention, because all PNS leads were explanted after 60 days.

Among the 7 nonrandomized studies of the SPRINT PNS system, 1 was a prospective, multicentre cohort study of 74 patients with chronic axial back pain; this cohort also included a substudy of patients who had previous radiofrequency ablation of the medial branch nerves.[36,38,44] Three studies reported real-world evidence for patients with a variety of chronic neuropathic pain conditions; these retrospective studies used different research methods (including an analysis of 6,106 records in the manufacturer's database,[40] a cross-sectional follow-up survey of 252 patients linked to baseline data in the manufacturer's database,[41] and a review of 89 electronic medical records[35]) and different follow-up durations for each patient. Two studies were retrospective cohort studies of 15 patients with cancer pain[42] and 19 patients with chronic pain from nonoperative knee osteoarthritis.[43] One study was a retrospective chart review of the incidence of lead tip retention in 50 patients who underwent 80 temporary PNS lead placements.[39]

We did not identify any studies that reported on health service utilization. Table 1 describes the characteristics of the included studies.

Table 1: Characteristics of Studies Included in the Clinical Literature Review

Author, year, device (manufacturer)	Study design	Population	Intervention(s) and comparator(s)	Indications, target nerves, eligibility	Follow-up duration	Funding source(s)
Permanent PNS						
Deer et al, 2016[28] StimRouter (Bioventus Inc.)	Prospective, multicentre, partial cross-over RCT 13 study centres	I: n = 45 (M/F = 20/25); mean age 52.8 ± 10.0 y C: n = 49 (M/F 19/30); mean age 53.2 ± 12.1 y	I: 90-day PNS stimulation C: No stimulation (control) After 90 days of treatment, 30 patients in the control group crossed over to the intervention group	Chronic pain of peripheral nerve origin (trunk, upper extremities, and lower extremities)	30, 60, and 90 days for primary treatment effects 6 and 12 months after partial crossover from control to intervention	Bioventus Inc. (formerly Bioness Inc.)
Oswald et al, 2019[11] StimRouter (Bioventus Inc.)	Prospective case series 18 study centres Survey conducted by manufacturer before and 3 to 6 months after implantation	N = 39 (M/F = 18/21); mean age M/F: 61/59 y	I: PNS C: NA	Chronic mononeuropathic pain: axillary nerve, genital femoral nerve, intercostal nerve, ilioinguinal nerve, lateral femoral cutaneous nerve, peroneal nerve, saphenous nerve, suprascapular nerve, sural nerve, tibial nerve Most participants received a preprocedure test block along the suspected nerve, with > 50% pain reduction	3 to 6 months	Bioventus Inc. (formerly Bioness Inc.)
Abd-Elsayed et al, 2023[29] Freedom (Curonix Inc.)	Retrospective chart review	N = 57 (M/F = 13/44); mean age 66.6 ± 11.0 y	I: PNS C: NA	Chronic pain: genicular nerves, superior cluneal nerves, posterior tibial nerve ± sural nerve, middle cluneal nerves, radial and ulnar nerves, right common peroneal nerves	1, 3, 6, 9, 12, and 24 months	None
Chahadeh et al, 2021[30] Freedom (Curonix Inc.)	Retrospective case series 6 study centres	N = 11; age range 53–94 y	I: PNS C: NA	Chronic peripheral neuropathic pain: superior cluneal nerve, superior gluteal nerve, genicular nerve, suprascapular nerve, tibial nerve 1-week trial after diagnostic nerve block; patients with a temporary response of > 50% pain relief would receive a permanent implant	1, 3, 6, and 12 months	None

Author, year, device (manufacturer)	Study design	Population	Intervention(s) and comparator(s)	Indications, target nerves, eligibility	Follow-up duration	Funding source(s)
Fruh et al, 2023[31] Freedom (Curonix Inc.)	Retrospective cohort study	N = 25 (M/F = 11/14) with PNS results; median age 57 y (IQR 50–67 y) Initial population was 33; 6 were explanted due to nonsufficient benefits within the first 4 weeks, and 2 were explanted due to wound infection	I: PNS C: NA	Chronic knee pain: saphenous nerve branches No trial; eligible patients were implanted, and then explanted if they did not have sufficient pain relief in the first 4 weeks	Postoperative and at 3, 6, and 12 months	Open-access funding enabled and organized by Projekt DEAL
Pollina et al, 2024[32] Freedom (Curonix Inc.)	Retrospective chart review for baseline data; prospective follow-up data collection at least 12 months after PNS implantation	N = 15 (M/F = 8/7); mean age 65 ± 9.3 y	I: PNS C: NA	Chronic foot pain: posterior tibial nerve Successful trial with > 50% improvement in pain	At least 12 months	None
Temporary PNS						
Gilmore et al, 2019[33] (1–8 weeks' follow-up) Gilmore et al, 2019[34] (12-month follow-up) SPRINT (SPR Therapeutics)	Multicentre, double-blind, crossover RCT 6 study centres	I: n = 12 (M/F = 10/2); mean age 48.3 ± 12.3 y C: n = 14 (M/F = 10/4); mean age 45.0 ± 13.2 y	I: 60-day PNS C: Sham stimulation (placebo control) 4-week sham stimulation, then crossover for 4-week PNS	Chronic neuropathic postamputation pain: femoral and sciatic nerves	4 weeks, 8 weeks, 3 months, 6 months, and 12 months	US Department of Defense

Author, year, device (manufacturer)	Study design	Population	Intervention(s) and comparator(s)	Indications, target nerves, eligibility	Follow-up duration	Funding source(s)
Abd-Elsayed et al, 2023[35] SPRINT (SPR Therapeutics)	Retrospective chart review	N = 89 (M/F = 39/50); mean age 62.2 ± 14.3 y	I: 60-day PNS C: NA	Chronic pain: C2 medial branch nerve, T9 nerve, T10 intercostal nerve, L3 nerve, L4 nerve, L5 medial branch nerve, brachial plexus along the interscalene groove, supraclavicular nerve, suprascapular nerve, radial nerve, median nerve, ilioinguinal nerve, genitofemoral nerve, iliohypogastric nerve, cluneal nerve, lateral femoral nerve, popliteal nerve, tibial nerve, posterior tibial nerve, saphenous nerve, infrapatellar branch of the saphenous nerve, peroneal nerve, superficial peroneal nerve, sural nerve A nerve-specific diagnostic block was performed; an improvement in pain > 50% was considered as eligibility for implantation	Average duration of improvement: 123 ± 126 days (minimum = 6 days, maximum = 683 days)	None
Gilmore et al, 2021[38] (end of 2-month treatment) Gilmore et al, 2023[44] (up to 12 months after treatment) Deer et al, 2021[36] (substudy of patients after RFA treatment) SPRINT (SPR Therapeutics)	Prospective, multicentre cohort study Before-and-after design	*Main cohort* N = 74 (M/F = 35/39); mean age 56.3 ± 13.5 y *Substudy* N = 15 (M/F = 8/7); mean age: 57.5 ± 17.4 y	I: 60-day PNS C: NA	Chronic axial low back pain; lumbar medial branch nerves Successful lead implantation and stimulation evidenced by selective activation of lumbar multifidi and visualization of multifidi contraction under ultrasound	*Main cohort* 2, 5, 8, 11, and 14 months after the start of the intervention *Substudy* 5 months after the start of the intervention	SPR Therapeutics Inc.
Hoffmann et al, 2021[39] SPRINT (SPR Therapeutics)	Retrospective review	N = 50 patients with 80 PNS leads implanted	I: 60-day PNS C: NA	Lead tip retention rates	60 days	None
Huntoon et al, 2023[40] SPRINT (SPR Therapeutics)	Retrospective review of device-manufacturer's database	N = 6,160	I: 60-day PNS C: NA	Chronic pain: lumbar medial branches, femoral nerve and branches (e.g., saphenous), sciatic nerve and branches (e.g., tibial, common peroneal), suprascapular nerve and axillary nerve	60 days	SPR Therapeutics Inc.

Author, year, device (manufacturer)	Study design	Population	Intervention(s) and comparator(s)	Indications, target nerves, eligibility	Follow-up duration	Funding source(s)
Pingree et al, 2022[41] SPRINT (SPR Therapeutics)	Cross-sectional follow-up survey (compared with existing database collected at baseline and at the end of 60-day PNS treatment)	N = 252 who completed initial and follow-up surveys	I: 60-day PNS C: NA	Chronic pain: medial branch of dorsal ramus, and suprascapular, axillary, femoral, sciatic, saphenous, common peroneal, tibial, ulnar, median, radial brachial plexus, ilioinguinal, intercostal, pudendal, occipital, lateral femoral cutaneous nerves	3–30 months' follow-up at the time of survey completion: 75% within the first year; 21% between 1 and 2 years; 4% > 2 years from start of treatment	SPR Therapeutics Inc.
Sudek et al, 2024[42] SPRINT (SPR Therapeutics)	Retrospective chart review	N = 15	I: 60-day PNS C: NA	Oncologic-related pain (tumour-related cancer pain, treatment-related cancer pain, pain due to cancer-associated conditions, cancer-independent pain), including shoulder pain, low back pain, upper-extremity neuropathy, lower-extremity neuropathy, intercostal neuralgia, abdominal pain; intercostal nerves, lumbar medial branches, cluneal, ilioinguinal, iliohypogastric, axillary, suprascapular, supraclavicular nerves and spinal nerve roots	30 and/or 60 days after implantation	None
Vangeison et al, 2023[43] SPRINT (SPR Therapeutics)	Retrospective chart review	N = 19	I: 60-day PNS C: NA	Refractory nonsurgical knee pain: saphenous nerve, superior lateral genicular nerve, superior medial genicular nerve, common peritoneal nerve, sciatic nerve	30 days and 60 days after implantation; 30 days and 60 days after explantation	None

Abbreviations: C, comparator; I, intervention; IQR, interquartile range; NA, not applicable; PNS, peripheral nerve stimulation; RCT, randomized controlled trial; RFA, radiofrequency ablation.
Note: In this table and other tables in this section, studies are grouped by device and by study type. Outcomes are presented in the subsequent sections.

Risk of Bias in the Included Studies

Results of the risk of bias assessment for the included studies can be found in Appendix 2, Tables A1 and A2. The RCTs were at risk of bias due to large attrition rates and selective reporting. The nonrandomized studies had a number of potential sources of bias: confounding due to lack of randomization; selection bias from retrospective study designs; information bias from using data in medical records or manufacturers' databases; reporting bias due to lack of blinding and lack of separate control groups; and missing data because of loss to follow-up.

Pain Outcomes

Pain outcomes were reported as the proportion of patients with a positive response to PNS, the magnitude of pain reduction, or both. Definitions of pain response differed between studies, and the magnitude of pain reduction was measured using various pain scales.

Proportion of Patients With a Positive Response to PNS

Table 2 summarizes the results for the proportion of patients with a positive response to PNS.

Table 2: Proportion of Patients With a Positive Response to PNS

Author, year	Results
Permanent PNS	
Deer et al, 2016[28] StimRouter (Bioventus Inc.) Randomized controlled trial	Proportion of patients who responded to 90-day treatment (defined as ≥ 30% decrease in pain without an increase in pain medications), intervention vs. control: 38% (n = 17/45) vs. 10% (n = 5/49); *P* = .005 After the 90-day treatment, 30/49 patients in the control group crossed over to the treatment group; 30% (n = 9/30) of those responded to treatment
Temporary PNS	
Gilmore et al, 2019[33] (1–8 weeks' follow-up) Gilmore et al, 2019[34] (12-month follow-up) SPRINT (SPR Therapeutics) Randomized controlled trial	Proportion of patients with ≥ 50% pain relief compared to baseline in all qualifying regions of residual limb pain and phantom limb pain, intervention vs. control: • 4 weeks: 58% (n = 7/12) vs. 14% (n = 2/14); *P* = .037 • 8 weeks (end of treatment): 67% (n = 8/12) vs. 14% (n = 2/14); *P* = .014 • 12 months: 67% (n = 8/12) vs. 0% (n = 0/14); *P* = .001
Abd-Elsayed et al, 2023[35] SPRINT (SPR Therapeutics) Retrospective chart review	76% (n = 68/89) reported pain relief on a VAS after a 60-day intervention

Author, year	Results
Gilmore et al, 2021[38] (end of 2-month treatment) Gilmore et al, 2023[44] (up to 12 months after treatment) Deer et al, 2021[36] (substudy of patients after RFA treatment) SPRINT (SPR Therapeutics) Prospective, multicentre cohort study	*Main cohort* Proportion of patients with a ≥ 30% reduction on the BPI-5[a] compared with baseline • 2 months (end of 60-day intervention): 73% • 5 months: 59% • 8 months: 53% • 11 months: 58% • 14 months: 58% *Substudy* Proportion of patients with a ≥ 50% reduction on the BPI-5[a] (a highly clinically meaningful reduction) • At the end of 60-day intervention: 67% (n = 10/15) • 3 months after PNS lead removal: 80% (n = 8/10) Proportion of patients with a ≥ 30% reduction on the BPI-5[a] (a clinically meaningful reduction) • At the end of 60-day intervention: 87% (n = 13/15) • 3 months after PNS lead removal: 73% (n = 13/15)
Huntoon et al, 2023[40] SPRINT (SPR Therapeutics) Retrospective review of device-manufacturer's database	At the end of 60-day intervention: • 71% (n = 4,348/6,160) reported a ≥ 50% pain reduction on the BPI [a] and/or improvement in quality of life on the PGIC scale • 55% (n = 3,275/5,968) reported a ≥ 50% reduction on the BPI[a] (substantial pain relief) • 66% (n = 3,925/5,968) reported a ≥ 30% reduction on the BPI[a] (clinically significant pain relief)
Pingree et al, 2022[41] SPRINT (SPR Therapeutics) Cross-sectional follow-up survey	At the end of 60-day treatment, 73% (n = 185/252) reported a ≥ 50% reduction on the BPI[a] (substantial pain relief) and/or improvement in quality of life on the PGIC scale At the time of the follow-up survey, 50% (n = 125/252) reported a sustained ≥ 50% reduction on the BPI[a] (substantial pain relief) and/or improvement in quality of life on the PGIC scale
Sudek et al, 2024[42] SPRINT (SPR Therapeutics) Retrospective chart review	60% (n = 9/15) achieved pain relief (defined as a pain reduction of > 2 points on a VAS scale) at 30 or 60 days after PNS implantation

Abbreviations: BPI, Brief Pain Inventory; BPI-5, Brief Pain Inventory, question 5; PGIC, Patient Global Impression of Change; PNS, peripheral nerve stimulation; RFA, radiofrequency ablation; VAS, visual analog scale.

[a] The Brief Pain Inventory assesses pain at its "worst," "least," "average," and "now". It also measures how much pain has interfered with 7 daily activities, including general activity, walking, work, mood, enjoyment of life, relations with others, and sleep. It uses a numerical rating scale from 0 to 10: the higher the score, the higher the pain severity or pain interference.

Permanent PNS

An RCT of StimRouter[28] demonstrated that patients with chronic neuropathic pain who received PNS achieved a higher response rate (38%) than placebo controls (10%) after a 90-day intervention (response rate was defined as a ≥ 30% decrease in pain without an increase in the use of pain medications); this finding was statistically significant. After the 90-day intervention, 30 patients in the control group crossed over to receive active stimulation, and the response rate in that group was 30%.

Based on 1 RCT,[28] the GRADE quality of the evidence for this outcome was Moderate (downgraded due to risk of bias; Appendix 2, Table A3). We did not find any nonrandomized studies for this outcome (Appendix 2, Table A4).

Temporary PNS

An RCT of SPRINT[33,34] for chronic postamputation pain reported statistically significant differences between the PNS and placebo control groups. After a 4-week PNS intervention, 58% of patients in the PNS group demonstrated a pain reduction of 50% or greater, compared to 14% of placebo controls.

Then, the entire placebo control group crossed over and began receiving active PNS. At the end of the 60-day intervention, 67% in the intervention group (who received 8 weeks of PNS) and 14% in the placebo control group (who received 4 weeks of PNS) maintained the pain reduction. The pain response was sustained at 12-month follow-up for those who received 8 weeks of PNS.

In the nonrandomized studies,[35,36,38,40-42,44] a majority of patients achieved a 30% to 50% pain reduction after a 60-day PNS intervention; this magnitude of pain reduction is generally considered to be clinically meaningful.[45] However, in a retrospective chart review of patients who underwent a temporary PNS intervention at different anatomical locations for different nerve targets, 24% of patients experienced no improvement in pain scores, despite the fact that all of them had received a confirmatory nerve-specific diagnostic block prior to the study.[35] Another retrospective chart review in oncology populations showed that temporary PNS provided pain relief to patients with cancer- and noncancer-related pain localized to a specific nerve distribution, but not to patients with pain related to cancer treatment.[42]

Based on 1 RCT (2 publications)[33,34] and 5 nonrandomized studies (7 publications),[35,36,38,40-42,44] the GRADE quality of the evidence for this outcome was Low (downgraded due to risk of bias and imprecision; Appendix 2, Tables A5 and A6).

Pain Scores

Table 3 summarizes the results for pain scores.

Table 3: Pain Scores

Author, year	Results[a]
Permanent PNS	
Deer et al, 2016[28] StimRouter (Bioventus Inc.) Randomized controlled trial	Mean reduction in NRS pain score at 3 months, intervention vs. control: 27.2% (n = 45) vs. 2.3% (n = 49) Mean difference between intervention and control groups: 24.9%, *P* < .001 Difference in pain reduction at 3 months by anatomical location, mean NRS score ± SD, intervention vs. control • Upper extremities: 29.2 ± 33.3 (n = 12) vs. 6.5 ± 20.2 (n = 14) • Lower extremities: 21.0 ± 30.8 (n = 13) vs. 1.2 ± 31.8 (n = 14) • Trunk: 30.1 ± 30.6 (n = 20) vs. 0.2 ± 26.8 (n = 21)
Oswald et al, 2019[11] StimRouter (Bioventus Inc.) Prospective case series	Average VAS pain score, before PNS vs. after PNS (n = 39): 8.2 vs. 2.4; 70.8% pain reduction By peripheral nerve stimulated, before PNS vs. after PNS: • Lateral femoral cutaneous (n = 3): 8.3 vs. 0.0; 100% pain reduction • Genitofemoral (n = 1): 10.0 vs. 1.0; 90% pain reduction • Ilioinguinal (n = 1): 10.0 vs. 1.0; 90% pain reduction • Sural (n = 1): 8.0 vs. 2.0; 75% pain reduction • Peroneal (n = 3): 9.0 vs. 2.3; 74.1% pain reduction • Axillary nerve (n = 18): 8.0 vs. 2.4; 70.1% pain reduction • Suprascapular (n = 1): 9.0 vs. 3.0; 66.7% pain reduction • Saphenous (n = 3): 7.7 vs. 2.7; 65.2% pain reduction • Tibial (n = 5): 7.8 vs. 2.6; 66.7% pain reduction • Brachial plexus (n = 2): 9.5 vs. 4.5; 52.6% pain reduction • Intercostal (n = 1): 7.0 vs. 5.0; 28.6% pain reduction

Author, year	Results[a]
Abd-Elsayed et al, 2023[29] Freedom (Curonix Inc.) Retrospective chart review	Pain scores pre-implant vs. follow-up, mean ± SD • 1 month: 7.44 ± 1.48 vs. 1.60 ± 1.49 (n = 57); *P* < .001 • 3 months: 7.42 ± 1.50 vs. 1.60 ± 1.50 (n = 56); *P* < .001 • 6 months: 7.52 ± 1.50 vs. 1.72 ± 1.57 (n = 50); *P* < .001 • 9 months: 7.41 ± 1.53 vs. 1.70 ± 1.55 (n = 44); *P* < .001 • 12 months: 7.41 ± 1.58 vs. 1.76 ± 1.63 (n = 34); *P* < .001 • 15 months: 7.38 ± 1.59 vs. 1.69 ± 1.56 (n = 29); *P* < .001 • 24 months: 7.50 ± 1.70 vs. 1.45 ± 1.57 (n = 20); *P* < .001 Patients reported more than 70% improvement in pain at all follow-ups
Chahadeh et al, 2021[30] Freedom (Curonix Inc.) Retrospective case series	Mean VAS scores (n = 11): baseline, 85.5; 1 month, 19.3; 3 months, 15.6; 6 months, 11.8 Mean VAS score decreased by 78% at 1 month (n = 11); 91% at 6 months (n = 5); and 76% at 12 months (n = 1)
Fruh et al, 2023[31] Freedom (Curonix Inc.) Retrospective cohort	Median (IQR) NRS scores at rest (n = 25) • Before PNS implantation: 8 (7–9) • After PNS implantation: 3 (2–4); *P* < .01 • 3 months: 2 (2–3); *P* < .01 • 6 months: 2 (1–4); *P* < .01 An additional 12-month follow-up in 9 patients showed a persistent, statistically significant decrease in knee pain (*P* < .01)
Pollina et al, 2024[32] Freedom (Curonix Inc.) Retrospective chart review	VRS scores, mean ± SD (n = 15) • Before PNS implantation: 8.6 ± 1.2 • > 12 months' follow-up: 3.0 ± 1.8; *P* < .001
Temporary PNS	
Gilmore et al, 2019[33] (1–8 weeks' follow-up) Gilmore et al, 2019[34] (12-month follow-up) SPRINT (SPR Therapeutics) Randomized controlled trial	Reduction in residual limb pain score from baseline, PNS vs. placebo, mean ± SD • 4 weeks: 2.1 ± 2.6 (n = 7) vs. 1.7 ± 1.6 (n = 11) • 8 weeks (end of 60-day intervention): 2.5 ± 2.2 (n = 7) vs. 1.7 ± 1.8 (n = 11) • 3 months: 4.0 ± 1.2 (n = 5) vs. 1.0 ± 2.9 (n = 8); *P* < .05[b] • 12 months: 4.3 ± 1.5 (n = 3) vs. 1.0 ± 2.0 (n = 4); *P* < .05[b] Reduction in phantom limb pain score from baseline, PNS vs. placebo, mean ± SD • 4 weeks: 3.3 ± 1.9 (n = 11) vs. 1.5 ± 1.4 (n = 13) • 8 weeks (end of 60-day intervention): 3.8 ± 2.2 (n = 11) vs. 2.2 ± 1.7[b] (n = 13); *P* < .05[b] • 3 months: 3.5 ± 2.3 (n = 10) vs. 1.7 ± 2.4 (n = 10); *P* < .05[b] • 12 months: 2.6 ± 3.7 (n = 8) vs. 2.0 ± 2.2 (n = 4)

Author, year	Results[a]
Abd-Elsayed et al, 2023[35] SPRINT (SPR Therapeutics) Retrospective chart review	VAS pain scores, before vs. after PNS, mean ± SD: 6.36 ± 2.18 vs. 4.19 ± 2.70; 34% pain improvement; *P* < .001 By diagnosis (% pain score improvement on VAS): • Cervical facet arthropathy and bilateral occipital neuralgia (n = 4): 39% • Low back pain (n = 2): 95% • Thoracic back pain (n = 2): 74% • Lumbar disc disease (n = 1): 50% • Lumbar neuropathy (n = 1): 0% • Lumbar spondylosis without myelopathy (n = 9): 28% • Lumbar facet arthropathy (n = 6): 43% • Suprascapular neuropathy (n = 19): 62% • Chronic chemotherapy-induced neuropathy (n = 1): 50% • Chronic headaches (n = 1): 70% • Diabetic polyneuropathy (n = 1): 0% • Brachial plexopathy (n = 5): 46% • Radial neuropathy (n = 3): 65% • Median neuropathy of the hands (n = 2): 5% • Neuroma of upper extremity amputation (n = 1): 50% • Intercostal neuralgia (n = 1): 0% • Ilioinguinal and iliohypogastric neuropathies (n = 2): 78% • Peroneal neuropathy (n = 6): 80% • Peroneal and tibial neuropathies (n = 2): 50% • Peroneal and sural neuropathies (n = 2): 70% • Sciatic neuropathy (n = 5): 14% • Cluneal neuralgia (n = 1): 75% • Femoral artery injury (n = 1): 20% • Femoral cutaneous neuropathy (n = 1): 0% • Saphenous neuropathy (n = 6): 58% • Knee osteoarthritis (n = 1): 65% • Posterior tibial neuropathy (n = 2): 50% • Foot neuropathy (n = 1): 50%
Gilmore et al, 2021,[38] (end of 2-month treatment) Gilmore et al, 2023,[44] (up to 12 months after treatment) Deer et al, 2021,[36] (substudy of patients after RFA treatment) SPRINT (SPR Therapeutics) Prospective, multicentre cohort study	*Main cohort* Pain scores on the BPI-5,[c] mean ± SEM • Baseline: 6.08 ± 0.14 (n = 74) • 2 months (end of 60-day intervention): 3.59 ± 0.22 (n = 74); *P* < .001 • 5 months: 3.59 ± 0.25 (n = 70); *P* < .001 • 8 months: 3.89 ± 0.26 (n = 66); *P* < .001 • 11 months: 4.04 ± 0.30 (n = 62); *P* < .001 • 14 months: 3.87 ± 0.27 (n = 62); *P* < .001 *Substudy* Pain scores in on the BPI-5,[c] mean ± SD • Baseline: 6.3 ± 1.0 • 2 months (end of 60-day intervention): 2.4 ± 1.6; *P* < .001 • 5 months: 3.1 ± 1.9; *P* < .001
Huntoon et al, 2023[40] SPRINT (SPR Therapeutics) Retrospective review of device-manufacturer's database	63% mean pain reduction among 71% responders with a ≥ 50% pain reduction on the BPI[c] and/or improvement in quality of life on the PGIC scale 73% mean pain reduction among 55% responders with a ≥ 50% reduction on the BPI[c] 67% mean pain reduction among 66% responders with a ≥ 30% reduction on the BPI[c]
Sudek et al, 2024[42] SPRINT (SPR Therapeutics) Retrospective chart review	Average decrease in VAS pain score • Tumour-related cancer pain: 3 points (n = 4) • Cancer-associated conditions: 3 points (n = 1) • Treatment-related cancer pain: 0.3 points (n = 6) • Cancer-independent pain: 2 points (n = 4)

Author, year	Results[a]
Vangeison et al, 2023[43] SPRINT (SPR Therapeutics) Retrospective chart review	% pain reduction compared with baseline • 30 days after PNS implantation: 57.9%; *P* = .76 • 60 days after PNS implantation to end of 60-day intervention: 67.5%; *P* = .39 • 30 days after PNS explantation: 50.0%; *P* = .89 • 60 days after PNS explantation: 63.2%; *P* = .97

Abbreviations: BPI, Brief Pain Inventory; BPI-5, Brief Pain Inventory, question 5; IQR, interquartile range; NRS, numerical rating scale; PGIC, Patient Global Impression of Change; PNS, peripheral nerve stimulation; RFA, radiofrequency ablation; SD, standard deviation; SEM, standard error of the mean; VAS, visual analog scale; VRS, verbal rating scale.

[a] For all pain scores used in the included studies, the higher the score, the more intense the pain.

[b] Compared with placebo group at the end of placebo period at week 4.

[c] The Brief Pain Inventory assesses pain at its "worst," "least," "average," and "now". It also measures how much pain has interfered with 7 daily activities, including general activity, walking, work, mood, enjoyment of life, relations with others, and sleep. It uses a numerical rating scale from 0 to 10: the higher the score, the higher the pain severity or pain interference.

Permanent PNS

In an RCT of StimRouter,[28] the mean reduction in pain score was 27.2% in the PNS group and 2.3% in the placebo control group at 3 months' follow-up. The mean difference between the PNS and placebo control groups was 24.9% ($P < .001$). Stratified by anatomical location, pain reduction was greater in the trunk than in the lower extremities.

A nonrandomized study of StimRouter[11] showed a 70.8% reduction in pain scores 3 to 6 months after PNS implantation. However, the extent of the pain relief varied by the peripheral nerve stimulated, most ranging from 52.6% for the brachial plexus nerve to 100% for the lateral femoral cutaneous nerve; PNS to the intercostal nerves resulted in only a 28.6% pain reduction.

Four nonrandomized studies of the Freedom PNS system showed reductions in pain scores of over 60% after PNS implantation.[29-32] Pain reduction was sustained until 6 to 24 months' follow-up.

Based on 1 RCT[28] and 5 nonrandomized studies,[11,29-32] the GRADE quality of the evidence for this outcome was Moderate for the RCT (downgraded due to risk of bias) and Low for the nonrandomized studies (downgraded due to risk of bias and imprecision; Appendix 2, Tables A3 and A4).

Temporary PNS

In an RCT of PNS for chronic postamputation pain,[33,34] the authors found no statistically significant difference between the PNS group and the placebo control group in terms of mean reduction of residual limb pain score (2.1 vs. 1.7) or phantom limb pain score (3.3 vs. 1.5) after 4 weeks of the intervention. After 4 weeks, the placebo control group crossed over to the PNS group and both groups received active stimulation for an additional 4 weeks until the end of the 60-day study. Using difference in pain scores for the placebo controls at 4 weeks as the comparator, the authors found a higher pain reduction in the intervention group for residual limb pain at 3- and 12-month follow-up, and for phantom limb pain at 8-week and 3-month follow-up; these findings were statistically significant.

A prospective, multicentre cohort study of PNS for patients with chronic axial back pain[38,44] showed a statistically significant lower pain score after a 60-day PNS intervention, and the pain relief was sustained up to 12-month follow-up. A subgroup of patients who received radiofrequency ablation before PNS also experienced statistically significant pain relief after the PNS intervention.[36]

Three retrospective chart reviews also evaluated temporary PNS. In a review of 89 patients with chronic neuropathic pain, the average reduction in pain score was approximately 35%; when stratified by diagnosis, the pain score reduction ranged from 0% to 100%.[35] In a review of 15 patients with cancer pain, approximately 60% reported a response to PNS.[42] Patients with pain related to cancer treatment did not respond. Among the responders, pain relief ranged from 40% to 100%. A review of 19 patients with chronic knee pain showed a 50% pain reduction from 1 to 3 months after PNS implantation.[43]

Real-world evidence from analyses of manufacturers' databases did not report specific inclusion or exclusion criteria for patient selection.[35,36,40] However, a majority of the study populations responded to the PNS intervention, obtaining clinically meaningful pain relief (≥ 50% reduction in pain score).

Based on 1 RCT (2 publications)[33,34] and 5 nonrandomized studies (7 publications),[35,36,38,40,42-44] the GRADE quality of the evidence for this outcome was Low (downgraded due to risk of bias and imprecision; Appendix 2, Tables A5 and A6).

Secondary Outcomes

Secondary outcomes reported in the included studies were use of pain medications, functional outcomes (e.g., activities of daily living, ambulatory abilities), health-related quality of life, and adverse events. No studies reported on health services utilization.

Use of Pain Medications

Table 4 summarizes the results for the use of pain medications.

Table 4: Use of Pain Medications

Author, year	Results
Permanent PNS	
Deer et al, 2016[28] StimRouter (Bioventus Inc.) Randomized controlled trial	No increase in pain medications at 3 months, PNS vs. controls: 97.8% (n = 44/46) vs. 95.9% (n = 47/49); *P* = .61
Oswald et al, 2019[11] StimRouter (Bioventus Inc.) Prospective case series	89% of patients with PNS experienced a > 50% reduction in opioid use
Abd-Elsayed et al, 2023[29] Freedom (Curonix Inc.) Retrospective chart review	MME of opioids, pre-implant vs. follow-up, mean ± SD • 6 months: 47.75 ± 45.25 vs. 37.92 ± 43.51 (n = 57); *P* = .002 • 12 months: 42.72 ± 43.19 vs. 30.38 ± 41.62 (n = 42); *P* = .003 • 24 months: 41.20 ± 46.12 vs. 21.19 ± 40.88 (n = 27); *P* ≤ .001
Chahadeh et al, 2021[30] Freedom (Curonix Inc.) Retrospective case series	9% (n = 1/11) of patients stopped all pain medications 91% (n = 10/11) of patients reduced their pain medications by at least 50%
Fruh et al, 2023[31] Freedom (Curonix Inc.) Retrospective cohort	Median (IQR) MME of opioids (n = 25) • Pre-implant: 80 (50–150) • 3 months: 20 (5–45) • 6 months: 20 (0–25)

Author, year	Results
Temporary PNS	
Gilmore et al, 2019[33] (1–8 weeks' follow-up) Gilmore et al, 2019[34] (12-month follow-up) SPRINT (SPR Therapeutics) Randomized controlled trial	Daily MED at baseline, PNS vs. placebo, mean ± SD: 86.9 ± 105.2 (n = 4) vs. 46.8 ± 70.8 (n = 5) Reduction of MED: 29.2 ± 24.6 at 4 weeks (PNS) and 37.4 ± 18.0 at 8 weeks (PNS) vs. 15.6 ± 36.7 at follow-up (placebo; time not specified) Proportion of patients who reduced or stopped opioid and/or nonopioid medication use • PNS: 50% (n = 6/12) after 8 weeks of treatment • Placebo: 43% (n = 6/14) after 4 weeks of placebo
Gilmore et al, 2021[38] (end of 2-month treatment) Gilmore et al, 2023[44] (up to 12 months after treatment) SPRINT (SPR Therapeutics) Prospective, multicentre cohort study	At baseline, 20 patients reported opioid consumption After a 60-day intervention, 63% (n = 12/19) reported a reduction in opioid use, with an average 65% reduction, equivalent to an average 15.1 MME decrease, from 28.5 MME to 13.4 MME At 5-month follow-up (3 months after explantation), 65% (n = 13/20) reported a reduction in opioid use, with an average 65% reduction, equivalent to an average 15.6 MME decrease, from 25.9 MME to 10.4 MME At 8-month follow-up (6 months after explantation), 61% (n = 11/18) reported a reduction in opioid use, with an average 62% reduction, equivalent to an average 18.6 MME decrease, from 25.4 MME to 6.8 MME Complete cessation of opioid analgesic consumption • After 60-day intervention: 21% (n = 4/19) • At 5-month follow-up (3 months after explantation): 21% (n = 4/20) • At 8-month follow-up (6 months after explantation): 17% (n = 3/18) • At 14-month follow-up (12 months after explantation): 21% (n = 3/14)
Pingree et al, 2022[41] SPRINT (SPR Therapeutics) Cross-sectional follow-up survey	35% (n = 44/126) who used opioids before PNS reported reducing or ceasing usage at the time of survey completion
Vangeison et al, 2023[43] SPRINT (SPR Therapeutics) Retrospective chart review	No appreciable change in overall opioid medication use (*P* = .26) during follow-up intervals

Abbreviations: IQR, interquartile range; MED, morphine equivalent dose; MME, mg morphine equivalent; PNS, peripheral nerve stimulation; SD, standard deviation.

Permanent PNS

In an RCT of StimRouter,[28] neither the PNS treatment group nor the placebo control group showed an increase in use of pain medications at 3-month follow-up. However, 4 nonrandomized studies of the StimRouter or Freedom PNS systems showed that most patients had a substantial reduction in the use of pain medications or opioids after PNS implantation.[11,29-31]

Based on 1 RCT[28] and 4 nonrandomized studies,[11,29-31] the GRADE quality of evidence for this outcome was Moderate for the RCT (downgraded due to risk of bias) and Low for the nonrandomized studies (downgraded due to risk of bias and imprecision; Appendix 2, Tables A3 and A4).

Temporary PNS

An RCT in patients with chronic postamputation pain who were using opioids before the study[33,34] found a greater reduction in opioid usage in the PNS group than in the placebo control group, although the opioid dosage at baseline was higher in the PNS group than in the placebo control group. The proportion of patients who stopped or reduced their opioid or nonopioid pain medications was similar for the PNS (50%) and placebo groups (43%).

In a prospective cohort study of patients with chronic axial back pain who were using opioids before the study,[38,44] approximately 60% reported to have 60% reduction in opioid dosage after a 60-day PNS intervention. This reduction was stable at 3 and 6 months after explantation. The results from 2 retrospective studies were mixed: one showed reduced opioid use,[41] but the other found no change in overall use after the PNS intervention.[43]

Based on 1 RCT (2 publications)[33,34] and 3 nonrandomized studies (4 publications),[38,41,43,44] the GRADE quality of the evidence for this outcome was Low for the RCT (downgraded due to risk of bias and imprecision) and Low for the nonrandomized studies (downgraded due to risk of bias and inconsistency; Appendix 2, Tables A5 and A6).

Functional Outcomes

Table 5 summarizes the results for functional outcomes.

Table 5: Functional Outcomes

Author, year	Results
Permanent PNS	
Deer et al, 2016[28] StimRouter (Bioventus Inc.) Randomized controlled trial	Change (difference between baseline and 3 months) in BPI[a] average score, PNS vs. control, mean ± SD • Worse pain score: −2.4 ± 2.3 vs. −0.3 ± 1.6; *P* < .001 • General activity: −2.3 ± 2.7 vs. −0.4 ± 2.0; *P* = .001 • Mood: −2.2 ± 3.1 vs. −0.6 ± 2.1; *P* = .012 • Walking ability: −2.4 ± 3.0 vs. −0.1 ± 1.9; *P* < .001 • Normal work: −2.4 ± 2.6 vs. −0.3 ± 2.1; *P* < .001 • Relations with other people: −2.0 ± 3.1 vs. −0.3 ± 2.0; *P* = .007 • Sleep: −2.1 ± 2.8 vs. 0.3 ± 2.2; *P* < .001 • Enjoyment of life: −2.5 ± 2.9 vs. −0.1 ± 2.0; *P* < .001
Oswald et al, 2019[11] StimRouter (Bioventus Inc.) Prospective case series	100% of respondents to a questionnaire reported an improvement in activity % improvement in activity after PNS implant • All: 72% (n = 27) • Axillary: 73.5% (n = 14) • Brachial plexus: 80% (n = 1) • Genitofemoral: 75% (n = 1) • Ilioinguinal: 75% (n = 1) • Intercostal: 40% (n = 1) • Lateral femoral cutaneous: 70% (n = 2) • Peroneal: 75% (n = 2) • Suprascapular: 80% (n = 1) • Sural: 60% (n = 1) • Tibial: 73.3% (n = 3)
Temporary PNS	
Gilmore et al, 2019,[33] (1–8 weeks' follow-up) Gilmore et al, 2019,[34] (12-month follow-up) SPRINT (SPR Therapeutics) Randomized controlled trial	Proportion of patients with a ≥ 50% reduction in the interference of pain in activities of daily living, PNS vs. placebo • 8 weeks (end of intervention): 80% vs. 15%; *P* = .003 • 12 months: 56% vs. 18%; *P* = .07
Abd-Elsayed et al, 2023[35] SPRINT (SPR Therapeutics) Retrospective chart review	"Patients reported improved sleep, mood, and ability to perform daily activities"

Author, year	Results
Gilmore et al, 2021[38] (end of 2-month treatment) Gilmore et al, 2023[44] (up to 12 months after treatment SPRINT (SPR Therapeutics) Prospective, multicentre cohort study	Proportion of patients who experienced a ≥ 30% reduction in back-pain-related disability compared with baseline, as measured by the ODI[b] • 2 months (end of 60-day intervention): 73% • 5 months: 60% • 8 months: 54% • 11 months: 49% • 14 months: 50% Back-pain-related disability as measured by the ODI,[b] mean ± SEM • Baseline: 38.33 ± 1.45 (n = 74) at baseline • 2 months (end of 60-day intervention): 23.30 ± 1.50 (n = 74); *P* < .001 • 5 months: 25.01 ± 1.76 (n = 70); *P* < .001 • 8 months: 27.46 ± 1.86 (n = 65); *P* < .002 • 11 months: 28.74 ± 2.03 (n = 61); *P* = .002 • 14 months: 28.86 ± 1.97 (n = 62); *P* = .002 Proportion of patients who experienced a ≥ 30% reduction in pain interference compared with baseline, as measured by the BPI-9[a] • 2 months (end of 60-day intervention): 73% • 5 months: 69% • 8 months: 62% • 11 months: 58% • 14 months: 56% Pain interference as measured by the BPI-9,[a] mean ± SEM • Baseline: 5.61 ± 0.88 (n = 74) • 2 months (end of 60-day intervention): 2.72 ± 0.24 (n = 73); *P* < .001 • 5 months: 3.04 ± 0.28 (n = 70); *P* < .001 • 8 months: 3.32 ± 0.30 (n = 65); *P* < .001 • 11 months: 3.68 ± 0.32 (n = 60); *P* < .001 • 14 months: 3.63 ± 0.29 (n = 61); *P* < .001
Deer et al, 2021[36] (substudy of patients after RFA treatment) SPRINT (SPR Therapeutics) Prospective, multicentre cohort study	87% (n = 13/15) reported a clinically meaningful reduction in back-pain-related disability (≥ 10-point decrease in ODI[b] score) 80% (n = 12/15) reported a clinically meaningful reduction in pain interference with activities of daily living (≥ 30% decrease in BPI[a] score) Back-pain-related disability as measured by the ODI,[b] mean ± SD • Baseline: 43.1 ± 12.7 • 2 months (end of 60-day intervention): 21.8 ± 13.9; *P* < .001 • 5 months: 26.1 ± 13.2; *P* = .003 Pain interference as measured by the BPI-9,[a] mean ± SD • Baseline: 6.2 ± 1.8 • 2 months (end of 60-day intervention): 2.4 ± 2.1; *P* < .001 • 5 months: 3.2 ± 2.7; *P* = .002

Abbreviations: BPI, Brief Pain Inventory; BPI-9, Brief Pain Inventory, 9-item self-administered questionnaire; ODI, Oswestry Disability Index; PNS, peripheral nerve stimulation; RFA, radiofrequency ablation; SD, standard deviation; SEM, standard error of mean.

[a] The Brief Pain Inventory assesses pain at its "worst," "least," "average," and "now." It also measures how much pain has interfered with 7 daily activities, including general activity, walking, work, mood, enjoyment of life, relations with others, and sleep. It uses a numerical rating scale from 0 to 10: the higher the score, the higher the pain severity or pain interference.

[b] The Oswestry Disability Index measures a patient's permanent functional disability. It includes the domains of pain intensity, personal care, lifting, walking, sitting, standing, sleeping, sex life, social life, and travelling. The higher the score, the more severe the disability.

Permanent PNS

One RCT[28] and 1 nonrandomized study[11] of StimRouter showed substantial improvements in functional outcomes after PNS implantation, including activity, walking ability, ability to do normal work, and enjoyment of life.[11,28]

Based on 1 RCT[28] and 1 nonrandomized study,[11] the GRADE quality of the evidence for this outcome was Moderate for the RCT (downgraded due to risk of bias) and Low for the nonrandomized study (downgraded due to risk of bias and imprecision; Appendix 2, Tables A3 and A4).

Temporary PNS

In an RCT of patients with chronic postamputation pain,[33,34] pain interference with activities of daily living was less in the PNS intervention group after a 60-day intervention compared with the placebo group at the end of the 4-week placebo period; this finding was statistically significant. However, the difference was not statistically significant at 12-month follow-up.

In a prospective cohort of patients with chronic axial back pain,[36,38,44] back-pain-related disabilities and pain interference with daily activities were lower after a 60-day PNS intervention; these findings were statistically significant. This functional improvement was sustained until 12 months in the primary cohort and 3 months in a subgroup of patients with previous radiofrequency ablation.

Based on 1 RCT (2 publications)[33,34] and 2 nonrandomized studies (4 publications),[35,36,38,44] the GRADE quality of the evidence for this outcome was Low for the RCT and nonrandomized studies (downgraded due to risk of bias and imprecision; Appendix 2, Tables A5 and A6).

Health-Related Quality of Life

Table 6 summarizes the results for health-related quality of life.

Table 6: Health-Related Quality of Life

Author, year	Results
Permanent PNS	
Deer et al, 2016[28] StimRouter (Bioventus Inc.) Randomized controlled trial	Change (difference between baseline and 3 months) in quality of life measured with the SF-12 version 2 health survey, PNS vs. control, mean ± SD: 1.4 ± 5.9 vs. −0.2 ± 3.4; *P* = .037 PGIC[a] in activity limitations, symptoms, emotions, and overall quality of life related to painful condition at 3 months, PNS vs. control, mean ± SD: 4.8 ± 1.5 vs. 2.5 ± 1.9; *P* < .001 PGIC[b] since the beginning of care at the clinic at 3 months, PNS vs. control, mean ± SD: 2.8 ± 1.6 vs. 5.0 ± 2.4; *P* < .001 Patient satisfaction with the PNS device[c] at 3 months, PNS vs. control, mean ± SD: 7.3 ± 2.9 vs. 3.0 ± 3.6; *P* < .001
Chahadeh et al, 2021[30] Freedom (Curonix Inc.) Retrospective case series	Median PGIC score: 7 out of 7 total – "a great deal better" "There was an important improvement in quality of life and sleep reported by all patients"
Fruh et al, 2023[31] Freedom (Curonix Inc.) Retrospective cohort	Median PCS[d] score, SF-36, pre-PNS vs. follow-up (n = 11): 23.05 vs. 38.42[e]; *P* < .01 Median MCS[d] score, SF-36, pre-PNS vs. follow-up (n = 11): 50.42 vs. 57.50[e]; *P* = .039 Participants "reported a significant improvement as related to mood state (*P* < .01) and quality of sleep (*P* < .01)"
Pollina et al, 2024[32] Freedom (Curonix Inc.) Retrospective chart review	Median satisfaction on the PGIC at > 12 months (n = 15): 7 out of 7, with most patients reporting a 6 (better) or a 7 (a great deal better) Participants "reported a considerable improvement in mobility and quality of life"
Temporary PNS	
Gilmore et al, 2019[33] (1–8 weeks' follow-up) Gilmore et al, 2019[34] (12-month follow-up) SPRINT (SPR Therapeutics) Randomized controlled trial	Average PGIC scores, PNS vs. placebo, mean ± SD • 4 weeks: 1.4 ± 1.1 (n = 11) vs. 0.6 ± 1.3 (n = 13) • 8 weeks (end of 60-day intervention): 2.2 ± 0.9 (n = 10) vs. 1.3 ± 1.0 (n = 11); *P* < .05[f] • 3 months: 1.9 ± 0.9 (n = 10) vs. 1.0 ± 0.8 (n = 10); *P* < .05[f] • 12 months: 1.8 ± 1.3 (n = 8) vs. 1.2 ± 1.5 (n = 4) at 12 months Average reduction in BDI-II[g] score from baseline, PNS vs. placebo, mean ± SD • 4 weeks: 1.8 ± 4.4 (n = 11) vs. −0.2 ± 7.3 (n = 13); *P* < .05[f] • 8 weeks (end of 60-day intervention): 4.2 ± 6.5 (n = 10) vs. −1.7 ± 9.8 (n = 11); *P* < .05[f] • 3 months: 1.3 ± 8.3 (n = 10) vs. −2.4 ± 9.7 (n = 10); *P* < .05[f] • 12 months: 2.5 ± 6.1 (n = 8) vs. 2.2 ± 17.8 (n = 4); *P* < .05[f]
Gilmore et al, 2021[38] (end of 2-month treatment) Gilmore et al, 2023[44] (up to 12 months after treatment) SPRINT (SPR Therapeutics) Prospective, multicentre cohort study	PGIC scores • After the 60-day PNS intervention: among 74 patients, 91% (95% CI 81.5%–96.1%) reported that their quality of life was improved; 59% (95% CI 47.4%–70.7%) reported that they were at least "much improved" compared with baseline. Mean scores for quality of life were "much improved" • At 14-month follow-up: among 51 patients who had completed long-term follow-up, 51% (95% CI 36.6%–65.3%) continued to report quality-of-life improvement attributed to PNS compared with baseline BDI-II scores, mean ± SD • Baseline: 8.5 ± 5.4 • After the 60-day PNS intervention: 5.3 ± 5.2; *P* < .001 RAND-36 survey[h] after the 60-day PNS intervention vs. baseline, mean ± SD • Physical functioning: 56.8 ± 24.0 vs. 42.8 ± 22.6; improved by 33%; *P* < .001 vs. baseline • Role limitations, physical health: 50.0 ± 40.4 vs. 21.9 ± 35.6; improved by 128%; *P* < .001 vs. baseline • Role limitations, emotional problems: 74.0 ± 39.8 vs. 63.0 ± 43.2; improved by 17% • Energy or fatigue: 53.9 ± 19.8 vs. 40.8 ± 20.6; improved by 32%; *P* < .001 vs. baseline • Emotional well-being: 79.7± 15.0 vs. 72.5 ± 17.2; improved by 10%; *P* < .05 vs. baseline • Social functioning: 74.7 ± 22.6 vs. 57.2 ± 26.2; improved by 31%; *P* < .001 vs. baseline • Pain: 57.6 ± 20.6 vs. 35.5 ± 17.2; improved by 62%; *P* < .001 vs. baseline • General health: 69.5 ± 19.8 vs. 64.2 ± 21.8; improved by 8%

Author, year	Results
Huntoon et al, 2023[40] SPRINT (SPR Therapeutics) Retrospective review of device-manufacturer's database	Stratification of patient-reported % pain relief by PGIC response showed that reporting "minimally improved," "much improved," and "very much improved" each had a mean percentage of ≥ 30% pain reduction (i.e., in the clinically meaningful range)
Sudek et al, 2024[42] SPRINT (SPR Therapeutics) Retrospective chart review	Average change in ESAS[i] scores • Tumour-related cancer pain: increase of 7 points (n = 4) • Pain due to cancer-associated conditions: increase of 13 points (n = 1) • Treatment-related cancer pain: increase of 2 points (n = 6) • Cancer-independent pain: decrease of 21 points (n = 4)

Abbreviations: BDI-II, Beck Depression Inventory; ESAS, Edmonton Symptoms Assessment Scale; MCS, mental components summary score of the SF-36; PGIC, Patient Global Impression of Change; PCS, physical components summary score of the SF-36; PNS, peripheral nerve stimulation; SD, standard deviation; SF-12, 12-item Short Form Survey; SF-36, 36-item Short Form Survey.

[a] The PGIC scale evaluates overall health status as perceived by the patient. Each item scores from 1 to 7: 1 indicates no change, and 7 indicates a great deal better or considerable improvement.

[b] Scores ranged from 0 to 10; 0 indicated much better, 5 indicated no change, and 10 indicated much worse.

[c] Scores ranged from 0 to 10; 0 indicated not satisfied at all, and 10 indicated completely satisfied.

[d] The SF-36 questionnaire comprises a physical components summary (including physical functioning, physical role, bodily pain) and a mental components summary (including social functioning, emotional role, mental health). The higher the score, the better the quality of life.

[e] Median follow-up time was 13 months (interquartile range 12–16).

[f] Intervention group compared with the placebo group at the end of the placebo period (week 4).

[g] The BDI-II measures the presence and severity of depressive symptoms. Each item scores from 0 to 3; the higher the score, the more severe the symptoms.

[h] The RAND-36 survey measures health-related quality of life. It comprises 36 items that assess 8 health concepts: physical functioning, role limitations caused by physical health problems, role limitations caused by emotional problems, social function, emotional well-being, energy or fatigue, bodily pain, and general health perception. The higher the score, the better the health status.

[i] The ESAS assesses common symptoms experienced by cancer patients, including pain, tiredness, nausea, depression, anxiety, drowsiness, appetite, well-being, shortness of breath, and sleep. Each item scores from 0 to 10; an increase in score indicates worsened symptom burden and quality of life.

Permanent PNS

In an RCT of StimRouter,[28] patients who received PNS reported better health-related quality of life than the placebo group. In addition, 3 nonrandomized studies[30-32] showed an improvement in health-related quality of life after implantation of a Freedom PNS system. Most patients reported an improvement in factors related to sleep, mood, mental health, physical health, and overall well-being.

Based on 1 RCT[28] and 3 nonrandomized studies,[30-32] the GRADE quality of the evidence for this outcome was Moderate for the RCT (downgraded due to risk of bias) and Low for the nonrandomized studies (downgraded due to risk of bias and imprecision; Appendix 2, Tables A3 and A4).

Temporary PNS

An RCT[33,34] showed that a 60-day PNS intervention improved health-related quality of life (measured using the Patient Global Impression of Change scale) in patients with chronic postamputation pain compared with the placebo group, both at the end of the intervention and at 3-month follow-up. Scores on the Beck Depression Inventory were also improved in the PNS group from the 4-week to the 12-month follow-up.

In a prospective cohort of patients with chronic axial back pain,[38,44] 91% of patients reported improved health-related quality of life after a 60-day PNS intervention. The extent of the improvement for physical well-being was larger than that for emotional well-being, as measured using the RAND-36 survey. Approximately half of the patients showed sustained improvement at 12-month follow-up.

A retrospective review of a manufacturer's database[40] showed that the improvement in quality of life improvement was associated with pain reduction, as showed by the stratification of percent pain relief in responses on the Patient Global Impression of Change scale.

In a retrospective chart review of patients with cancer,[42] the authors found some inconsistencies in pain scores (measured using a visual analog scale) and quality-of-life outcomes (measured using the Edmonton Symptoms Assessment Scale). Patients reported improvements in pain scores, but worse quality-of-life outcomes for tumor-related cancer pain and pain due to cancer-associated conditions. The study authors suggested that this discordance was likely due to the medley of physical, social, and subjective well-being factors for these values as a result of the progression of cancer or the adverse effects of cancer treatment.

Based on 1 RCT (2 publications)[33,34] and 3 nonrandomized studies (4 publications),[38,40,42,44] the GRADE quality of the evidence for this outcome was Low for the RCT (downgraded due to risk of bias and imprecision) and Low for the nonrandomized studies (downgraded due to risk of bias and inconsistency; Appendix 2, Tables A5 and A6).

Adverse Events

Table 7 summarizes the results for adverse events.

Table 7: Adverse Events

Author, year	Results
Permanent PNS	
Deer et al, 2016[28] StimRouter (Bioventus Inc.) Randomized controlled trial	25 serious adverse events at 12-month follow-up, 0 device-related: 14 PNS, 11 control • Resulting in death: 0 PNS, 0 control • Life-threatening: 1 PNS, 0 control • Inpatient or prolonged hospitalization: 10 PNS, 7 control • Resulting in persistent or significant disability or incapability: 0 PNS, 0 control • Congenital anomaly or birth defect: 0 PNS, 0 control • Required intervention to avoid permanent damage or impairment: 3 PNS, 4 control 121 adverse events at 12-month follow-up, 51 device-related: 60 PNS, 61 control • Of the 51 device-related adverse events (28 PNS, 23 control), 80.4% were mild in intensity and most were superficial in nature (e.g., skin rash, redness, soreness) 7 patients (of 94 implanted in the PNS and control groups) were explanted • Dissatisfaction with pain relief (n = 5) • Chronic dermatitis or sensitivity to electrode patch (n = 1) • Rejected lead after picking at the initial implant site, creating a dehiscence near the knee (n = 1) All explantations were performed without complications
Abd-Elsayed et al, 2023[29] Freedom (Curonix Inc.) Retrospective chart review	PNS explantation (n = 1) Lead migration (n = 1)
Chahadeh et al, 2021[30] Freedom (Curonix Inc.) Retrospective case series	No adverse events reported
Fruh et al, 2023[31] Freedom (Curonix Inc.) Retrospective cohort	No intraoperative surgical complications Postoperative wound infection (n = 2)

Author, year	Results
Pollina et al, 2024[32] Freedom (Curonix Inc.) Retrospective chart review	Erosion required a single revision (n = 1)
Temporary PNS	
Gilmore et al, 2019[33] (1–8 weeks' follow-up) Gilmore et al, 2019[34] (12-month follow-up) SPRINT (SPR Therapeutics) Randomized controlled trial	At 8 weeks of treatment, 22 study-related events were reported in 46% (13/28) patients who underwent lead implantation (96% mild, 4% moderate, 0% severe) No additional adverse events at 12-month follow-up Mild adverse events • Skin irritation or redness at the lead exit site (n = 7) • Adhesive return electrode pad site (n = 3) or bandage site (n = 4) • Pain due to implantation (n = 4) • Pruritus at the pad site (n = 1) • Pruritus under the supporting belt (n = 1) • Fatigue (n = 1) Moderate adverse events: pain due to stimulation (n = 1), resolved by adjusting stimulation parameters No leads fractured during intervention Suspected lead fracture during explantation (n = 5)
Abd-Elsayed et al, 2023[35] SPRINT (SPR Therapeutics) Retrospective chart review	Among 89 patients: infection (n = 1), lead migration (n = 4)
Gilmore et al, 2021[38] (end of 2-month treatment) Gilmore et al, 2023[44] (up to 12 months after treatment) Deer et al, 2021[36] (substudy in patients after RFA treatment) SPRINT (SPR Therapeutics) Prospective, multicentre cohort study	*Main cohort, adverse events for the duration of the study* Dermatological adverse events • Skin irritation (n = 34; 27 mild, 7 moderate) • Pruritus (n = 21; 19 mild, 2 moderate) • Granuloma, discoloration, urticaria, or other (n = 8; 5 mild, 3 moderate) • Infection[a] (n = 2; 0 mild, 2 moderate) Neurological adverse events • New pain (n = 8; 6 mild, 2 moderate) • Worsening pain (n = 5; 5 mild, 0 moderate) • Discomfort (n = 5; 3 mild, 2 moderate) Other adverse events • Neurological or other (n = 2; 2 mild, 0 moderate) • Cardiovascular[b] (n =1; 1 mild, 0 moderate) • Unable to determine relationship (n = 5; 5 mild, 0 moderate) • Not study-related[c] (n = 22; 3 mild, 19 moderate) *Substudy* • Superficial skin infection (n = 1) • Lead migration or dislodgement (n = 4)
Hoffmann et al, 2022[39] SPRINT (SPR Therapeutics) Retrospective review	Retained lead tip fragments at the time of removal after 60-day treatment (n = 5; 6.25%)
Huntoon et al, 2023[40] SPRINT (SPR Therapeutics) Retrospective review of device-manufacturer's database	435 medical events reported in 369 (6%) patients • Skin irritation (n = 163) • Confirmed infection (n = 7) • Suspected infection (n = 73) • Pain or uncomfortable stimulation (n = 73) • Change in sensation/location of stimulation (n = 38) • Pain at lead exit site (n = 20) • Swelling (n = 11) • All other medical events (n = 50) Lead dislodgement in 6.0% patients; lead fracture in 8.1% patients

Author, year	Results
Sudek et al, 2024[42]	No complications reported
SPRINT (SPR Therapeutics)	Some patients experienced uncomfortable sensations during stimulation
Retrospective chart review	Patients commonly reported muscle fasciculations, soreness, or tenderness when PNS was occurring

Abbreviations: PNS, peripheral nerve stimulation; RFA, radiofrequency ablation.

[a] One superficial infection at a lead site was resolved with an oral antibiotic and the removal of the lead 1 week prior to the end of treatment. One skin infection at the location of the waterproof dressing was resolved with an oral antibiotic and discontinuation of benzoin tincture (used to increase dressing adhesion and suspected to be cause of the irritation).

[b] For example, temporary vasovagal response.

[c] For example, strep throat, urinary traction infection, other musculoskeletal, other pain, etc.

Permanent PNS

There was no mortality associated with permanent PNS implantation. In an RCT of StimRouter,[28] none of the serious adverse events in the intervention or control groups were related to the study intervention. Device-related adverse events were mostly mild in intensity, and similar in frequency for both the intervention and control groups. Events were localized to the stimulation area or the site of surgery.

For the Freedom PNS system,[29-32] only a few adverse events (e.g., lead migration and wound infection) were reported.

Based on 1 RCT[28] and 4 nonrandomized studies,[29-32] the GRADE quality of the evidence for this outcome was Moderate for the RCT (downgraded due to risk of bias) and Low for the nonrandomized studies (downgraded due to risk of bias and imprecision; Appendix 2, Tables A3 and A4).

Temporary PNS

In an RCT of the SPRINT PNS system for patients with chronic postamputation pain,[33,34] most study-related adverse events were mild in nature, such as skin irritation and itchiness.

In nonrandomized studies, common device-related adverse events were lead fractures or migration. Common medical adverse effects were skin irritation and local infection, which appeared to be mild in intensity and self-limiting.[35,36,38,40,42,44] A retrospective review of 80 temporary percutaneous PNS SPRINT lead placements[39] showed retained lead fragments in 6.25% of placements when the leads were removed at the end of the 60-day PNS intervention; the review authors stated that this retention rate was consistent with other published data, which showed lead fracture rates of 3% to 21%.

Based on 1 RCT (2 publications)[33,34] and 5 nonrandomized studies (7 publications),[35,36,38-40,42,44] the GRADE quality of the evidence for this outcome was Low for the RCT and nonrandomized studies (downgraded due to risk of bias and imprecision; Appendix 2, Tables A5 and A6).

Ongoing Studies

We are aware of 8 ongoing studies (4 RCTs and 4 observational studies) on ClinicalTrials.gov that have potential relevance to this review (Table 8).

Table 8: Ongoing Studies of Minimally Invasive Percutaneous PNS

PNS device	Trial number	Study title	Study design	Accrual start date	Estimated completion date
Freedom	NCT03877653	Double-blinded randomized control trial of knee pain using sub-threshold peripheral nerve stimulation	RCT	September 2021	June 2026
Nalu	NCT05287373	Clinical study of a micro-implantable pulse generator for the treatment of peripheral neuropathic pain (COMFORT)	RCT	January 2022	September 2024
Nalu	NCT05870124	Clinical study of a micro-implantable pulse generator for the treatment of peripheral neuropathic pain (COMFORT 2)	RCT	April 2023	April 2025
SPRINT	NCT04246281	A randomized, controlled, multicenter trial of percutaneous peripheral nerve stimulation for the treatment of back pain	RCT	June 2020	March 2026
SPRINT	NCT05649917	A post-market observational case series study of percutaneous peripheral nerve stimulation for the treatment of chronic shoulder pain	Observational study	July 2022	July 2024
SPRINT	NCT05491915	The MONARCH (Multicenter Occipital Neuralgia and Cervicogenic Headache) case series study: treatment of head pain with the SPRINT peripheral nerve stimulation system	Observational study	October 2022	August 2026
StimRouter	NCT05644639	StimRouter genicular neuromodulation for chronic knee osteoarthritic pain management (GLEAM)	Observational study	October 2022	January 2024
StimRouter	NCT03913689	A prospective, open-label, long-term, multi-center, registry to assess the safety and efficacy of the Bioness StimRouter neuromodulation system in subjects with chronic pain of peripheral nerve origin	Observational study	June 2019	April 2028

Abbreviation: PNS, peripheral nerve stimulation; RCT, randomized controlled trial.

Discussion

In this clinical evidence review, we found that percutaneous PNS reduced pain intensity in some adults with chronic neuropathic pain, depending on which nerves were targeted and at which anatomical locations the stimulation leads were placed. For patients who responded to the stimulation, the magnitude of pain reduction was generally clinically meaningful (≥ 30%–50% pain reduction),[45] and it was often achieved concurrently with functional improvements. These results were seen with both permanent and temporary implants. The main difference between permanent and temporary PNS lay in the duration of the treatment: patients with permanent implants received continuous treatment based on their needs, and patients with temporary implants received 60 days of treatment.

People who use percutaneous PNS may be able to reduce or discontinue their opioid use. In the RCT evidence we reviewed, there was a decrease in opioid use with the SPRINT temporary PNS system,[33,34] but not with the StimRouter permanent PNS system.[28] This inconsistency may be related to study populations, baseline opioid dosage, or delay or no response to PNS in some patients.[46]

At present, only the StimRouter permanent PNS system has been approved by Health Canada. Given the similar mechanisms of action for permanent and temporary and PNS systems, we reviewed both types of devices. Because PNS is indicated for use on different nerve targets in a variety of chronic pain conditions, the study populations in the literature were heterogeneous. We identified only 2 RCTs (1 on

StimRouter for chronic neuropathic pain and 1 on SPRINT for chronic postamputation pain). The rest of the evidence was of low quality, limited mostly by study design (e.g., retrospective reviews of medical records or manufacturers' databases). Although real-world evidence is being met with increased acceptance and application, it has inherent limitations, such as missing data; lack of randomization; and risk of selection, reporting, and information bias.[46]

Chronic neuropathic pain is a highly prevalent condition. In *Chronic Pain in Canada,*[47] published by the Canadian Pain Task Force in 2019, the authors noted that certain populations bear more of the pain burden, including older adults, Indigenous people, and veterans. In a cross-sectional survey conducted in Canada,[3] economically disadvantaged men had a higher burden of neuropathic pain. Health disparities also exist in terms of access to pain management for less-studied vulnerable populations.[23] We did not find evidence about percutaneous PNS for chronic neuropathic pain specific to these subgroups, but access to this neuromodulation treatment may address some of the current disparities in pain management. As well, we found no quantitative evidence on how PNS may affect health service utilization, although in theory it may reduce the number of visits to pain clinics for repeated interventions or follow-ups.

The minimally invasive procedure used to place PNS implants is reasonably safe. The existing evidence suggested that some diagnoses and nerve targets may be better suited for PNS than others. This finding highlighted the importance of careful patient selection, which should be a decision between clinicians and patients based on medical history, physical examination, diagnostic tests, and patient preference.

In the context of severe chronic neuropathic pain in adults with pain that is refractory to conventional medical management, PNS offers an alternative nonopioid neuromodulation option earlier in the treatment continuum, before the need to resort to higher doses of opioids or more invasive interventions.

Conclusions

Effectiveness of Permanent PNS

Compared with placebo controls in adults with chronic neuropathic pain, permanent PNS:

- Likely decreases pain scores (GRADE: Moderate)
- Likely does not change the use of pain medications (GRADE: Moderate)
- Likely improves functional outcomes (GRADE: Moderate)
- Likely improves health-related quality of life (GRADE: Moderate)

Compared with before implantation in adults with chronic neuropathic pain, permanent PNS:

- May decrease pain scores (GRADE: Low)
- May decrease the use of pain medications (GRADE: Low)
- May improve functional outcomes (GRADE: Low)
- May improve health-related quality of life (GRADE: Low)

Effectiveness of Temporary PNS

Compared with placebo controls in adults with chronic postamputation pain, temporary PNS:

- May decrease pain scores (GRADE: Low)
- May decrease the use of pain medications (GRADE: Low)
- May improve functional outcomes (GRADE: Low)
- May improve health-related quality of life (GRADE: Low)

Compared with before implantation in adults with chronic neuropathic pain, temporary PNS:

- May decrease pain scores (GRADE: Low)
- May decrease the use of pain medications (GRADE: Low)
- May improve functional outcomes (GRADE: Low)
- May improve health-related quality of life (GRADE: Low)

Safety of PNS for Chronic Neuropathic Pain

PNS implantation is a reasonably safe procedure; most adverse effects are localized and mild in intensity (GRADE: Moderate to Low).

Economic Evidence

Research Question

What is the cost-effectiveness of minimally invasive percutaneous peripheral nerve stimulation (PNS) compared with non-PNS methods of pain management for the treatment of chronic neuropathic pain in adults?

Methods

Economic Literature Search

We performed an economic literature search on October 26, 2023, to retrieve studies published from January 1, 2013, until the search date. To retrieve relevant studies, we developed a search using the clinical search strategy with an economic and costing filter applied.

We created database auto-alerts in MEDLINE and Embase and monitored them until September 1, 2024. We also performed a targeted grey literature search following a standard list of websites developed internally, which includes the International HTA Database and the Tufts Cost-Effectiveness Analysis Registry. See Clinical Literature Search, above, for further details on methods used. See Appendix 1 for our literature search strategies, including all search terms.

Eligibility Criteria

Studies

Inclusion Criteria

- English-language full-text publications
- Studies published from January 1, 2013, to the search date
- Cost–benefit analyses, cost-effectiveness analyses, cost-minimization analyses, or cost–utility analyses

Exclusion Criteria

- Narrative or systematic literature reviews, cost-of-illness studies, comparative or noncomparative costing analyses, letters or editorials, case reports, commentaries, abstracts, posters, unpublished studies

Participants

Inclusion Criteria

- Adults with localized or regional chronic neuropathic pain of peripheral nerve origin, including the shoulders, trunk, and upper and lower extremities, as well as specific areas of the head and neck,

depending on the PNS device (note: StimRouter [Bioventus Inc.] is not indicated for patients with pain of craniofacial nerve origin,[10] but SPRINT [SPR Therapeutics] is indicated for patients with headache in the occipital region and axial neck pain[16])

Exclusion Criteria

- Children
- Pregnant people

Interventions

Inclusion Criteria

- Minimally invasive percutaneous PNS systems with regulatory approval in North America, with or without conventional medical management (e.g., physical therapy, nonopioid medications, opioid medications)

Exclusion Criteria

- Early generations of PNS devices that require open surgical implantation of a stimulation lead or surgical placement of an implantable pulse generator
- Peripheral nerve field stimulation
- Transcutaneous electric nerve stimulation
- Spinal cord stimulation devices used for PNS

Comparators

Inclusion Criteria

- Conventional medical management (e.g., physical therapy, nonopioid medications, opioid medications)
- No intervention

Exclusion Criteria

- Interventions that include PNS

Outcome Measures

- Costs
- Health outcomes (e.g., quality-adjusted life-years)
- Incremental costs
- Incremental effectiveness
- Incremental cost-effectiveness ratios

Literature Screening

A single reviewer conducted an initial screening of titles and abstracts using Covidence[27] and then obtained the full texts of studies that appeared eligible for review according to the inclusion criteria. The same reviewer then examined the full-text articles and selected studies eligible for inclusion. The reviewer also examined reference lists and consulted content experts for any additional relevant studies not identified through the search.

Data Extraction

We extracted relevant data on study characteristics and outcomes to collect information about the following:

- Source (e.g., citation information, study type)
- Methods (e.g., study design, analytic technique, perspective, time horizon, population, intervention[s], comparator[s])
- Outcomes (e.g., health outcomes, costs, incremental cost-effectiveness ratios)

Study Applicability and Limitations

We determined the usefulness of each identified study for decision-making by applying a modified quality appraisal checklist for economic evaluations originally developed by the National Institute for Health and Care Excellence (NICE) in the United Kingdom.[48] The NICE checklist has 2 sections: the first is for assessing study applicability, and the second is for assessing study limitations. We modified the wording of the questions of the first section to make it specific to Ontario. Using this checklist, we assessed the applicability of each study to the research question (directly, partially, or not applicable). Next, we assessed the limitations (minor, potentially serious, or very serious) of the studies that we found to be applicable.

Results

Economic Literature Search

The economic literature search yielded 195 citations, including grey literature results and after removing duplicates, published between January 1, 2013, and October 26, 2023. We did not identify any additional eligible studies from other sources, including database alerts (monitored until September 1, 2024). We did not identify any studies that met our inclusion criteria. See Appendix 4 for a list of

selected studies excluded after full-text review. Figure 2 presents the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram for the economic literature search.

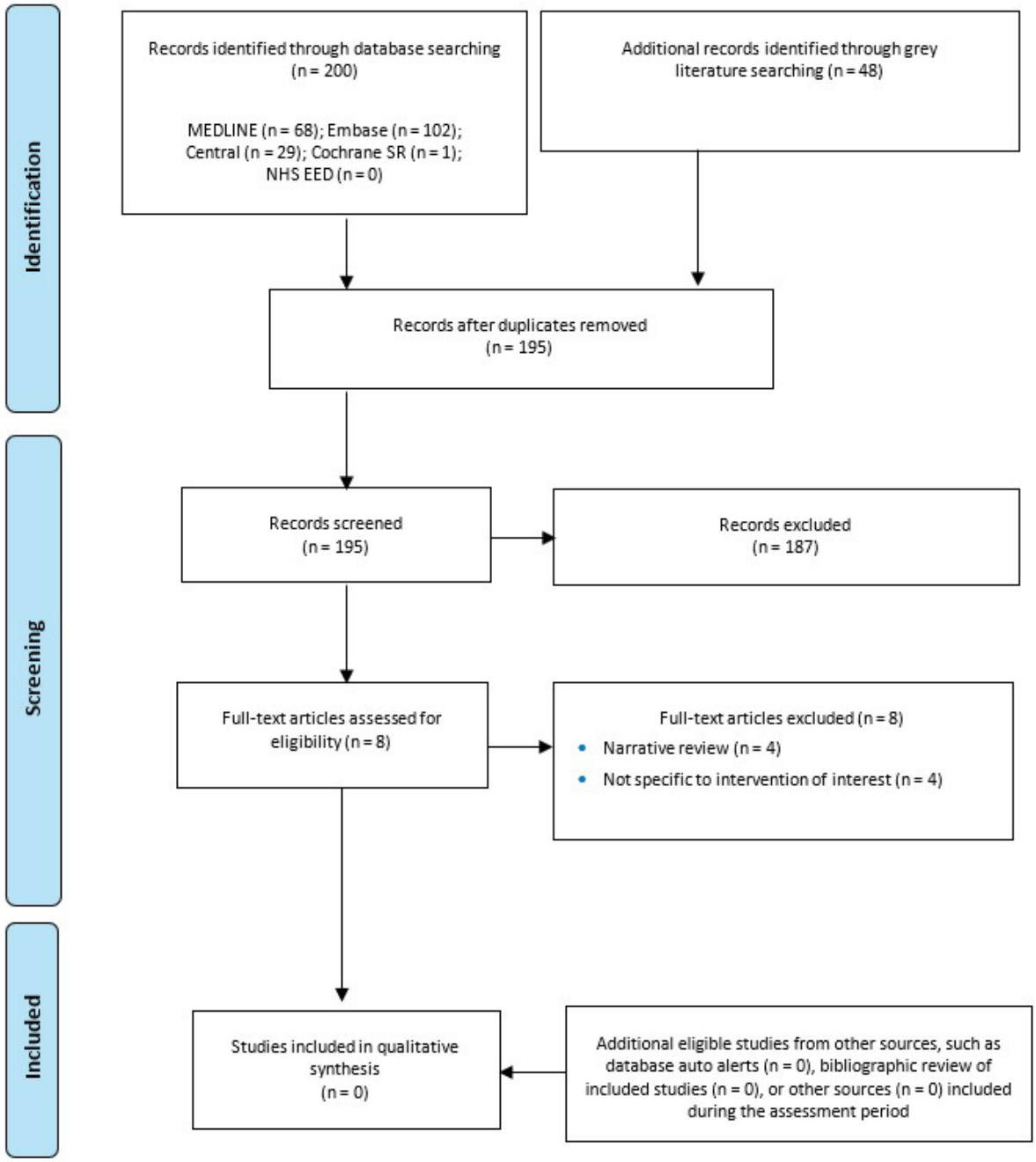

Figure 2: PRISMA Flow Diagram – Economic Systematic Review

PRISMA flow diagram showing the economic systematic review. The economic literature search yielded 195 citations, including grey literature results and after removing duplicates, published between January 1, 2013, and October 26, 2023. We screened the abstracts of the 195 identified studies and excluded 187. We assessed the full text of 8 articles and excluded all 8. In the end, we included no articles in the qualitative synthesis.

Abbreviation: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses.

Source: Adapted from Page et al.[27]

Overview of Included Economic Studies

We did not identify any studies on the cost-effectiveness of minimally invasive percutaneous PNS for the treatment of chronic neuropathic pain in adults. A list of excluded studies and reasons for exclusion can be found in Appendix 4.

Discussion

There is a paucity of economic evidence on minimally invasive PNS systems in the published literature. Cost-effectiveness studies have been conducted in other types of neurostimulation therapy for chronic pain, including spinal cord stimulation, dorsal root ganglion stimulation, transcutaneous electrical stimulation, and peripheral nerve field stimulation.

A recent review of the financial sustainability of neuromodulation for pain[49] found that the only available study on the cost-effectiveness of PNS was a French registry study of occipital nerve stimulation for refractory chronic cluster headache.

One study identified in our search evaluated the cost-effectiveness of peripheral nerve field stimulation plus spinal cord stimulation, compared to spinal cord stimulation alone.[50] This study found that the addition of peripheral nerve field stimulation was cost-effective, but because of the intervention and comparator used, it was not directly applicable to our research question. Peripheral nerve field stimulation is similar to PNS, but the leads are implanted in the subcutaneous tissues in the area of localized pain to stimulate a group of nerves rather than a single nerve target. As well, the devices used for peripheral nerve field stimulation (and more specifically, in the study described above) are not the same as the systems used for minimally invasive PNS that are the focus of this health technology assessment.

Conclusions

We did not identify any cost-effectiveness studies that met our inclusion criteria. Therefore, the cost-effectiveness of PNS remains unknown; further research is needed.

Primary Economic Evaluation

We did not identify any published economic evaluations in the economic literature review that addressed our specific research question. Owing to these limitations, we conducted a primary economic evaluation.

Research Question

What is the cost-effectiveness of minimally invasive percutaneous peripheral nerve stimulation (PNS) in addition to standard care compared with standard care alone for the treatment of chronic neuropathic pain in adults from the perspective of the Ontario Ministry of Health?

Methods

The information presented in this report follows the reporting standards set out by the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement.[51] The content of this report is based on a previously developed economic project plan.

Type of Analysis

We conducted a probabilistic cost–utility analysis, as recommended by the Canadian Agency for Drugs and Technologies in Health (CADTH) guidelines for economic evaluations.

Population of Interest

Our population of interest was adults with severe, refractory, chronic neuropathic pain of peripheral nerve origin who were eligible for treatment with PNS systems that have regulatory approval in North America. These were individuals with severe pain that was poorly managed despite appropriate medical therapy. The Ontario Health quality standard *Chronic Pain: Care for Adults, Adolescents, and Children*[52] defines chronic pain as pain that typically lasts longer than 3 months or that continues past the time of normal tissue healing.

Most PNS systems are not indicated for patients with pain of craniofacial nerve origin. As well, some PNS systems are contraindicated for patients with active implanted devices (e.g., a cardiac pacemaker or defibrillator), or any implanted devices or metallic implants within 15 cm of the intended lead implantation site. PNS systems are not indicated for pregnant people or children.

We based our population of interest on participants in the randomized controlled trial (RCT) of the StimRouter device,[28] identified in the clinical evidence review. In that trial, the average age of participants was 53 years, and 58.5% were female; participants had severe, intractable, chronic pain of peripheral nerve origin for 3 months or more, associated with post-traumatic or postsurgical neuralgia, excluding the craniofacial region.

Perspective

We conducted our reference case analysis from the perspective of the Ontario Ministry of Health.

Interventions and Comparators

We conducted evaluations for PNS in addition to non-PNS methods of pain management (referred to as "standard care"), compared with standard care alone. Table 9 summarizes the interventions evaluated in the economic model.

Table 9: Interventions and Comparators Evaluated in the Primary Economic Model

Intervention	Comparator	Population	Outcomes
PNS in addition to standard care • Permanent impant (reference case) • Temporary implant	Standard care alone (i.e., non-PNS methods of pain management)	Adults (≥ 18 years of age) with localized or regional chronic neuropathic pain of peripheral nerve origin, including the shoulders, trunk, and upper and lower extremities, as well as specific areas of the head and neck, depending on the PNS device	Total costs, QALYs, ICERs estimated as cost per QALY gained

Abbreviations: ICER, incremental cost-effectiveness ratio; PNS, peripheral nerve stimulation; QALY, quality-adjusted life-years.

Standard Care for the Management of Chronic Neuropathic Pain

Standard care for adults with chronic peripheral neuropathic pain includes noninvasive methods such as oral analgesics and nonsteroidal anti-inflammatory drugs, opioid medications, antiepileptic drugs and antidepressants, epidural steroid injections, transcutaneous electrical nerve stimulation, physical therapy, and exercise.[52] In patients with refractory chronic pain (i.e., pain that does not respond to conventional treatments), more invasive approaches can be considered, such as spinal cord stimulation, denervation surgery, and implantable drug delivery systems.

More invasive treatment approaches require periodic access to an interprofessional pain program, or to specialist care. Access to specialized pain care varies across Ontario: some locations have no pain specialists, and some pain management interventions might not be available or affordable for everyone.[52]

PNS in Addition to Standard Care

PNS involves implanting an electrode to deliver electrical stimulation to a target peripheral nerve.[7] According to experts, PNS should be offered early in the course of treatment: after less invasive interventions (such as epidural or peripheral steroid injections, or transcutaneous electrical nerve stimulation) but before starting or increasing doses of opioid medications, spinal cord stimulation, or other more invasive interventions.[5] PNS is indicated for pain management as an adjunct to other modes of therapy (e.g., medications).

Compared with other interventional pain management options, PNS may offer greater selectivity and accuracy for chronic neuropathic pain that has well-defined nerve targets.[6] Its proposed mechanism for pain relief is by direct inhibition of pain neurotransmission by changing local inflammatory mediators, and by elevating pain thresholds via stimulation.[35] The therapeutic goal of PNS is to relieve pain and help patients avoid starting opioids (or taper down their opioid doses). While they are receiving PNS, some patients may still need nonopioid medications (e.g., anticonvulsants, antidepressants) or opioids at a reduced dose.

PNS devices have been designed for temporary or permanent implantation. Temporary PNS systems are typically implanted for 60 days and then removed.[35] Permanent PNS devices are typically used to stimulate a nerve for a extended period of time to meet patients' pain-relief needs, after which the lead can be explanted or remain implanted for its lifespan in case restimulation is required (Michael Gofeld, MD, virtual communication, July 13, 2023).

As of the time of writing, 1 PNS system had Health Canada approval: the StimRouter PNS system, which is designed for permanent implantation. As such, local clinical expertise is only with a permanent PNS system, and we have conducted the reference case analysis for this type of system. Three other PNS systems have regulatory approval in North America (i.e., Sprint, Freedom, and Nalu). Of these, the Sprint PNS system is the only one designed for temporary implantation; we have conducted a scenario analysis for temporary PNS based on the Sprint PNS system.

Adults with refractory peripheral nerve pain are assessed by a pain specialist to determine their eligibility for PNS. Experts in Ontario often identify patients eligible for permanent PNS implantation based on the person's clinical picture and the results of nerve conduction studies, magnetic resonance neurography, ultrasonography, and/or needle stimulation. Those who are eligible then undergo the implantation procedure. This procedure involves percutaneous implantation of a lead containing stimulation electrodes adjacent to the target peripheral nerves, usually guided by ultrasound imaging. Generally, a transmitter provides energy to power the device and sends signals to the implanted lead to produce a nonpainful electrical stimulation that helps block pain perception. Once the device has been programmed by a clinician, the patient can turn the unit on and off, change programs, and titrate stimulation intensity at home.[28]

Time Horizon and Discounting

We used a 3-year time horizon in our reference case analysis. Most clinical trials identified in our preliminary search had short durations, with follow-up periods of up to 12 months. The evidence for the effectiveness of PNS beyond these trial periods is uncertain, but we assumed that effectiveness would continue for the 3-year time horizon. Although PNS devices may be implanted permanently and a longer time horizon may be appropriate, we conservatively chose a 3-year time horizon based on the length of clinical expertise with these devices in Ontario and given the limited clinical data. In accordance with CADTH guidelines,[53] we applied an annual discount rate of 1.5% to costs and quality-adjusted life-years (QALYs) incurred after the first year. We conducted scenario analyses exploring 1- and 5-year time horizons.

Main Assumptions

The model's main assumptions were as follows:

- The health utilities of people in the standard care cohort would remain unchanged from baseline (i.e., when they entered the model) until death. Given that people eligible for PNS are those whose pain is poorly managed despite appropriate medical therapy, we assumed that standard care would not provide further pain relief over time.
- Shortly after PNS implantation, those who responded to treatment (≥ 30% pain relief from baseline) would be in the optimal pain relief state (see Model Structure, below) and experience improved health utilities.

- Once a person moved to the suboptimal pain relief state, they could not move back to the optimal pain relief state (conservative assumption). It is possible that a person who had suboptimal pain relief with PNS treatment could achieve improved pain relief over time as a result of improved treatment adherence, resolution of technical issues, optimization of stimulation programming, neurophysiological factors such as progressive reconditioning of the pain state, or treatment of the underlying condition that caused pain (e.g. anti-cancer therapy).[36,54] However, we were unable to identify long-term studies that provided the data to demonstrate this or to derive probabilities from. We validated that this assumption was reasonable based on expert consultation (Michael Gofeld, MD, email communication, May 13, 2024).
- Those who received PNS and were in the suboptimal pain relief state would have a slightly higher health utility than those who received standard care alone. Based on expert opinion, we assumed that those in the PNS cohort would still experience benefits from improvement of other symptoms, even if they did not achieve pain relief of 30% or greater (Michael Gofeld, MD, email communication, May 13, 2024).
- After implantation of a permanent PNS system, most people would not require explantation for the model time horizon. Some would require device explantation because of failure to relieve pain, or because of a serious adverse event (e.g., lead fracture). Based on expert opinion and information from trials,[11,28] we assumed that many patients with reduced pain relief would elect to keep the stimulation leads in (James Khan, MD, email communication, February 2024).
- 10% of patients receiving PNS would have 2 leads implanted; the remaining 90% would have 1 lead implanted (based on information from trials[11] and local clinical experts: Michael Gofeld, MD email communication, February 23, 2024; James Khan, MD, email communication, February 23, 2024). Two leads may be implanted around larger nerves (such as the sciatic nerve) to provide more complete nerve coverage, or on 2 nerves that are close to one other. In either case, the patient would use 1 external pulse transmitter.
- We considered only adverse events that would require explantation, and we assumed that these would occur in the first year only. Adverse events associated with PNS for the treatment of chronic pain are generally mild and do not require hospitalization or treatment (see Table 7 in the clinical evidence review).
- There was no difference in mortality outcomes between treatment cohorts.

Model Structure

We developed a decision-analytic model to determine the incremental cost per QALY. People with chronic neuropathic pain could experience 1 of 4 mutually exclusive health states: optimal pain relief (≥ 30% pain relief from baseline), suboptimal pain relief (< 30% pain relief from baseline), explant, or dead (see Figure 3). We estimated the proportion of patients in the optimal and suboptimal pain relief states based on published clinical studies.[28]

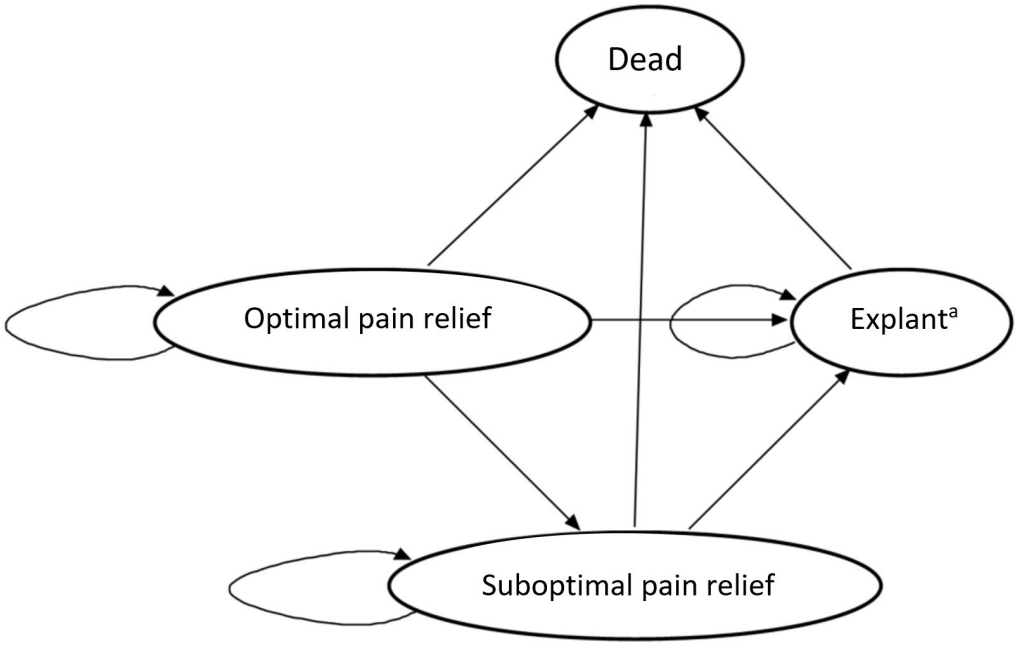

Figure 3: Model Structure

The model used for the primary economic evaluation. People in the PNS cohort who entered the optimal pain relief state would stay there until device explantation, loss of pain relief and move to the suboptimal pain relief state, or death. People in the PNS cohort who entered the suboptimal pain relief state would also stay there until device explantation or death. Those who had the device explanted would move to the standard care cohort.

Abbreviation: PNS, peripheral nerve stimulation.

[a] PNS systems can be explanted if the person experiences a complication requiring explanation or if they are dissatisfied with the pain relief and request explantation. Anyone in the PNS cohort who had the device explanted would receive standard care only.

People in the PNS cohort who entered the optimal pain relief state would remain there unless one of the following occurred: they experienced a complication requiring device explanation (e.g., lead fracture); they lost pain relief and moved to the suboptimal pain relief state; or they entered the dead state. Similarly, people in the PNS cohort who entered the suboptimal pain relief state remained there unless 1 of the following occurred: they experienced a complication requiring device explanation; they lost pain relief and requested explantation; or they entered the dead state. People in the PNS cohort who had the device explanted would move to the standard care cohort.

We assumed that all people in the standard care cohort would enter the suboptimal pain relief state and remain there for the duration of the model unless they entered the dead state.

We chose a cycle length of 3 months to represent a clinically meaningful time interval. Depending on the treatment a patient received, they would have different costs and utilities (i.e., health-related quality of life). At any point in the model, patients could die (any-cause mortality) and enter the absorbing dead state.

A successful response (achieving some pain reduction) to a preprocedure test block along the suspected nerve is often part of the selection criteria for PNS system implantation. We assumed that all patients entering the model were eligible for PNS and had had a successful response to a diagnostic nerve block.

Clinical Outcomes and Utility Parameters

We used several input parameters to populate the model:

- Variables to model the natural history of chronic pain of peripheral nerve origin
- Variables to modify the natural history model to account for the treatment effects of PNS
- Variables to capture health state utilities (i.e., quality of life)

We obtained clinical and utility parameters from the clinical evidence review whenever possible, and we validated them with clinical experts to ensure that they reflected real-world clinical practice in Ontario. Table 10 summarizes the clinical parameters for the reference case model.

Table 10: Summary Estimates Used in the Economic Model

Model parameter	Mean	Distribution[a]	Source
Standard care alone			
Percent of people who use an opioid analgesic	65%	Fixed	Oswald et al[11]
Probability of achieving optimal pain relief in the first 3 months	0%	–	Assumption
PNS in addition to standard care			
Probability of achieving optimal pain relief in the first 3 months	28%[b]	Beta (7.7; 19.8)	Deer et al[28]
Annual probability of complications requiring explantation	2%	Beta (2; 92)	Deer et al[28]
Probability of losing pain relief in the first year	7%	Beta (5; 70)	Deer et al[28]
Annual probability of losing pain relief after first year	3%	Beta (0.60; 17.78)	Kemler et al[55]

Abbreviations: PNS, peripheral nerve stimulation.

[a] Beta distribution: parameter 1 = alpha, parameter 2 = beta.

[b] Calculated by adjusting for the possibility of placebo effect. In Deer et al,[28] the probability of response was 10% in the control group and 38% in the treatment group; we calculated the distribution using the standard errors of the observed probabilities of responders in the control and treatment groups from this study.

Natural History

Given that people eligible for PNS are those whose pain is poorly managed despite appropriate medical treatment, we assumed that continuing with standard care would provide no further pain relief over time. Therefore, in the reference case we assumed that patients in the standard care cohort would stay in the suboptimal pain relief state for the duration of the model, unless they entered the absorbing dead state.

Impact of PNS on Natural History

Pain Intensity

Based on the findings of the clinical evidence review, we estimated that 28% of patients in the PNS cohort would achieve optimal pain relief. We derived this estimate from a randomized partial crossover trial of the StimRouter permanent PNS system[28]; the trial reported the percentage of study participants who achieved optimal pain relief in the first 3 months after PNS implantation. The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) quality of the evidence for this outcome was Moderate (Appendix 2, Table A3).

In the study, participants in the treatment and control groups were implanted with the PNS device, but stimulations were turned off for the control group. In total, 94 people were implanted: 45 in the treatment group and 49 in the control group. After 90 days, 30 members of the control group crossed over and started receiving stimulations. Responders were defined as those who experienced at least a 30% decrease in average pain at rest (using a numeric rating scale) and had no increase in use of pain medicine. The study authors found that 3 months after randomization, 38% of patients in the treatment group were responders, compared to 10% in the control group. Assuming that the responders in the control group experienced a placebo effect, we adjusted for this and derived the treatment effect as the difference between the 2 groups (i.e., 28%).

We used information from the same trial to estimate a 7% probability of losing pain relief in the first 12 months, based on the fact that 5 of 75 participants were dissatisfied with their pain relief and requested that the device be explanted.[28] For subsequent months, we derived the annual probability of losing pain relief (3.24%; range 0.0–0.1577) based on information from a long-term trial of spinal cord stimulation.[55] Given a lack of data on the probability of losing pain relief in the optimal pain relief state, we assumed that these probabilities would apply to both the optimal and suboptimal pain relief states. Patients in the optimal pain relief state who lost pain relief would move to the suboptimal pain relief state, and patients in the suboptimal pain relief state who lost pain relief would move to the explantation state and start receiving standard care only.

There was a lack of RCT evidence on sustained pain response with permanent PNS. However, 4 nonrandomized studies of the Freedom PNS system[11,29-31] showed a reduction in pain scores of greater than 60% after PNS implantation. Pain reduction was sustained until 6-month and 24-month follow-up (see Table 3 in the clinical evidence review; GRADE: Low).

Pain Medications

We considered the impact of PNS on acute medication use. People with chronic pain may use a wide range of opioid, nonopioid, and other medications to manage their pain; however, most clinical studies reported only on changes in opioid analgesic consumption from before to after PNS implantation.

The clinical evidence review found that in adults with chronic neuropathic pain, PNS likely led to similar use of pain medications compared with placebo controls (GRADE: Moderate). This finding was based on a study of the StimRouter system,[28] which found no increase in pain medications in the PNS treatment and placebo control groups at 3-month follow-up. We assumed that there would be no difference in use of pain medications for the PNS and standard care cohorts.

However, the clinical evidence review also found that in nonrandomized studies of the StimRouter or Freedom PNS systems, most patients had a substantial reduction in the use of pain medications or opioids after PNS implantation (see Table 4 in the clinical evidence review for overall difference in acute medication use between groups; GRADE: Low). Therefore, in scenario analyses we used information from a nonrandomized study of the StimRouter PNS system[56] to derive our estimate for average reduction in opioid doses. The authors of that study found that approximately 65% of participants (11 of 34 responders) were taking opioids prior to PNS implantation. After implantation, 89% of participants observed a reduction in opioid consumption of greater than 50%, with an average reduction of 68% at 3 to 6 months after implantation. Based on this study, we estimated that people in the PNS cohort would experience a 68% decrease in opioid use.

We assumed that the mean daily systemic opioid use for people in the standard care cohort would be 28.5 mg morphine milligram equivalent (MME), based on a study of the temporary Sprint PNS system.[44] This average MME reflects Ontario prescribing practices and the average daily MME for people with chronic pain who are candidates for PNS in Ontario (Anuj Bhatia, MD, email communication, February 2024).

Adverse Events

We calculated the probability of adverse events using the occurrence of any complication that would require device explanation, including biological and device-related complications.

The clinical evidence review found that PNS devices are generally well tolerated, and that most study-related adverse events were mild in nature, such as skin irritation and itchiness (see Table 7 in the clinical evidence review for a summary of the safety and adverse events associated with PNS use). We used information from the StimRouter RCT[28] and calculated the probability of adverse events to be 2%, based on the fact that 2 of 94 people had an adverse event requiring explantation over a 1-year follow-up period. Of those, 1 person developed chronic dermatitis or sensitivity, and 1 rejected the lead after agitating the initial implantation site. We applied this probability to people in the optimal and suboptimal pain relief states.

We conservatively assumed that no adverse events would be associated with standard care alone, although some well-documented risks are associated with certain treatments (e.g., the use of opioids may lead to nausea, sedation, physical dependence, and other symptoms).

Mortality and Life Expectancy

Given our 3-year time horizon, we assumed that mortality directly attributed to chronic neuropathic pain would be low; no clinical studies reported a change in mortality with PNS. In the model, people could transition to the dead state (background or all-cause mortality) every 3 months, which represented the length of a model cycle. We estimated the proportion of people who would transition to the dead state using survival estimates from the 2023 Ontario Life Tables.[57]

Health State Utilities

A health state utility represents a person's preference for a certain health state or outcome, such as chronic pain. Utilities are often measured on a scale ranging from 0 (death) to 1 (full health). We considered a person's health-related quality of life in the model. The utilities for different health states are presented in Table 11.

Table 11: Utilities Used in the Economic Model

Health state or treatment state	Utility or disutility, mean (SD)	Source
Optimal pain relief state	0.63 (0.27)	Torrance et al[58]
Suboptimal pain relief state, PNS in addition to standard care	0.36	Calculated
Suboptimal pain relief state, standard care alone	0.33 (0.36)	Torrance et al[58]
Disutility associated with adverse events	−0.05 (0.03)[a]	Kemler et al[55]

Abbreviation: PNS, peripheral nerve stimulation; SD, standard deviation.

[a] Standard error calculated from a range of 0.0 to 0.10.

Some of the studies identified in the clinical evidence review reported quality-of-life outcomes using different tools. No study reported EQ-5D index scores, which can be converted directly to health utilities in economic evaluations. In an RCT of the StimRouter system,[28] participants receiving PNS reported better health-related quality of life than the placebo group at 3 months post-implantation. Three nonrandomized studies also showed an improvement in health-related quality of life after implantation of the Freedom PNS system (see Table 6 in the clinical evidence review; GRADE, Low).

We identified utility inputs from a 2014 study by Torrance et al,[58] which assessed the health utility scores (EQ-5D and SF-6D) of 1,972 patients from the United Kingdom who reported mild, moderate, or severe chronic pain (Table 11). The study authors used the average pain intensity numeric rating scale of the Chronic Pain Grade to classify average pain severity based on previously established cut points of 0 to 3 for mild pain, 4 to 6 for moderate pain, and 7 to 10 for severe pain.[58] We used EQ-5D utility values for the reference case. Similar EQ-5D health utility values by severity of neuropathic pain have been reported in a systematic review of health utilities for neuropathic pain[59] and a Canadian spinal cord stimulation study by Kumar et al,[60] which collected EQ-5D utility scores directly from patients. Kumar et al[60] reported the following average utility values: standard care arm, 0.54 for the optimal health state and 0.32 for the suboptimal health state; spinal cord stimulation arm, 0.62 for the optimal health state and 0.41 for the suboptimal health state.

The majority of participants in the clinical trials of PNS rated their pain as moderate to severe. The average pain score at baseline in a nonrandomized study of StimRouter[11] was 8.2; we used this finding to assign a utility score for severe pain to the suboptimal pain relief state of the standard care cohort (mean 0.33, standard deviation 0.36). Based on expert consultation, we heard that people in the suboptimal pain relief state of the PNS cohort may still benefit from improvements in other symptoms (Michael Gofeld, MD, email communication, May 13, 2024). Therefore, we assumed that people in the suboptimal pain relief state in the PNS cohort would have a 10% higher health utility (mean 0.36) than those in the standard care cohort. This assumption aligns with findings from a study by Kumar et al,[60] which found that people in the suboptimal health state while receiving spinal cord stimulation still reported higher utility scores than people in the suboptimal health state while receiving standard care only.

Considering that a 30% reduction in pain would translate to an average pain score of 5.7 (i.e., moderate pain), we used the utility score for moderate pain for the optimal pain relief state (mean 0.63, standard deviation 0.27).

We assumed that a complication from PNS would have a negative effect on utility, leading to a 1-time disutility of −0.05.[55]

We assumed that those in the standard care cohort would remain at the baseline utility (0.33) throughout the model time horizon or until they transitioned to the dead state. This assumption may have overestimated the health utility gains associated with the use of PNS.

Cost Parameters

We obtained cost inputs from Ontario sources, published literature, and clinical experts. We obtained the fees for device implantation and professional visits from the Ontario Schedule of Benefits for Physician Services.[61] There is no guarantee that the fee codes are priced correctly; service may be included as part of an existing insured service, or it may require a new fee code (changes to the Schedule of Benefits are negotiated jointly between the Ministry of Health and the Ontario Medical Association). All costs are

reported in 2024 Canadian dollars. When costs in 2024 Canadian dollars were not available, we used the Statistics Canada Consumer Price Index[62] to adjust costs to 2024 Canadian dollars.

Cost of PNS

Table 12 summarizes the costs used in the economic model. The total cost of PNS in addition to standard care was the cost of surgeries and maintenance events (i.e., implants, physician visits, and complications associated with PNS).

Table 12: Costs Used in the Economic Model

Variable	Unit cost, $	Duration or quantity	Total cost, $	Source
Cost of standard care alone				
Annual cost of medications, opioid analgesics[a]	21.27 for 3 months	12 months	85.10	Ontario Drug Benefit Formulary[63]
Cost of PNS in addition to standard care				
Cost of initial PNS implant				
Diagnostic nerve block	34.10	1	34.10	Schedule of Benefits,[61] G231
PNS device[b]	12,500.00	1	12,500.00	BioVentus[c]
Additional lead	7,000.00	0–1	–	BioVentus[c]
Probability of additional lead	–	10%	13,200.00	Expert opinion[d]
Physician fees for implantation				
Lead physician fee	404.30	1	404.30	Schedule of Benefits,[61] Z823
Physician assistant fee	12.51	12 units[e]	150.12	Schedule of Benefits,[61] Z823
Anesthesiologist fee	15.29	12 units[e]	183.48	Schedule of Benefits,[61] Z823
Physician fee for follow-up	64.65	3	193.95	Schedule of Benefits,[61] A013
Physician fee for device programming	20.60	1	20.60	Schedule of Benefits,[61] G283/G284
Average annual maintenance costs				
Cost of electrode patches	10.00 (9.38–10.63)	93.6/year[f]	935.90	BioVentus[c]
Physician fee for device programming	20.60	2/year	41.20	Schedule of Benefits, [61] G283/G284
Cost of replacement EPT battery and patient programmer	5,200.00	1	5,200.00	BioVentus[g]
Cost of explantation	266.60	1	266.60	Schedule of Benefits,[61] Z824
Annual cost of medications, opioid analgesics[a]	21.27 for 3 months	12 months	85.10	Ontario Drug Benefit Formulary[63]

Abbreviations: EPT, external pulse transmitter; PNS, peripheral nerve stimulation.

[a] Assumes 65% of patients are taking opioid analgesics[56] and 24.1% are covered by a public drug plan.[64]

[b] PNS device starter kit includes leads and tools, external pulse transmitter, programmer, and 56 disposable electrode patches.

[c] BioVentus, virtual communication, July 20, 2023.

[d] Michael Gofeld, MD, email communication, February 23, 2024; James Khan, MD, email communication, February 23, 2024.

[e] 12 units: 8 basic units and 4 time units (assuming a 60-minute procedure time).

[f] Assumes patients need to change the patch every 2.6 to 5.2 days.

[g] BioVentus, virtual communication, May 2, 2024.

Device

We obtained the cost of a permanent PNS device from a manufacturer. A minimally invasive PNS system typically includes an electrical lead and receiver, a pulse transmitter, electrodes, and a programmer.

A StimRouter starter kit (including electrical leads and implantation tools, an external pulse transmitter, a patient programmer, and 56 electrode patches) costs $12,500. The cost of an additional electrical lead was estimated at $7,000. Two leads may be implanted around larger nerves (such as the sciatic nerve) to provide more complete nerve coverage, or on 2 nerves that are close to one another; in either case, 1 external pulse transmitter would be used. Based on information from trials[11] and local clinical experts (Michael Gofeld, MD, email communication, February 23, 2024; James Khan, MD, email communication, February 23, 2024), we assumed that 10% of people receiving PNS in Ontario would have 2 leads implanted.

An electrode patch is placed over the implanted lead and is replaced every 2 to 5 days. An electrode patch comes in 2 sizes (small or large), and a box of 8 patches costs $75 to $85 (BioVentus, virtual communication, July 20, 2023). This translates to a per-patch cost of $9.38 to $10.63. We estimated that the supply of patches in the starter kit would last approximately 8 months, and that the subsequent average annual cost of the patches would be $935.90.

Implantation

Minimally invasive PNS can typically be done in an outpatient setting, under local anaesthesia by a pain physician (Michael Gofeld, MD email communication, February 23, 2024; James Khan, MD, email communication, February 23, 2024). We estimated the cost of a preoperative diagnostic nerve block to be $34.10 (Schedule of Benefits,[61] code G231).

The implantation procedure takes approximately 40 to 50 minutes using ultrasound or fluoroscopic image guidance. Based on a procedure time of approximately 1 hour, we estimated that total physician fees for the initial procedure would be $737.90 (Schedule of Benefits[61] code Z823 for implantation or revision of stimulation pack or leads [peripheral nerve, brain]).

Based on consultation with experts, we assumed that physicians who have experience with neuromodulation would be qualified to implant the PNS device. Therefore, we did not include training costs in our analysis.

Post-implantation Visits

After the PNS device has been implanted, it can be programmed on the same day or in the following week, depending on inflammation at the implantation site (Michael Gofeld, MD, virtual communication, July 13, 2023). No physician fee code is available for PNS device programming and reprogramming. This service may be included as part of an existing insured service, or it may require its own fee code (changes to the Schedule of Benefits are negotiated jointly between the Ministry of Health and the Ontario Medical Association). Although programming can be done by the physician or by clinic staff, only physician services are eligible for payment by OHIP. To estimate the potential cost associated with PNS device programming for our analysis, we used the fee code for single chamber reprogramming (including electrocardiography) as a proxy (Schedule of Benefits[61] code G283/G284).

For permanent PNS systems, patients typically return to the clinic for follow-up at 1 to 2 weeks, 1 month, and 3 months after implantation. We estimated the cost of follow-up in the immediate postoperative period to be $214.55 (including 3 follow-up visits [Schedule of Benefits[61] code A013] and 1 charge for programming or adjusting the PNS device [Schedule of Benefits[61] code G283/G284]).

Long-Term Follow-Up and Maintenance

According to clinical experts, there is no standard frequency of long-term follow-up care after permanent PNS implantation (Michael Gofeld, MD, virtual communication, July 13, 2023). After the post-implantation checkup, patients can return to their physician as needed. If stimulation is lost, they may need to return to their physician for device troubleshooting and parameter adjustment or reprogramming. In the reference case, we assumed an average of 2 physician visits per year for periodic adjustment of stimulation parameters. We assumed that PNS reprogramming would be conducted during standard care physician visits, so we excluded the consultation or visit fee and included only the additional physician fee for programming or adjusting the PNS device (2 charges for programming or adjusting the PNS device [Schedule of Benefits[61] code G283/G284]).

For the permanent StimRouter PNS system, we obtained the cost of a "user kit" from the manufacturer (BioVentus, virtual communication, May 2, 2024). Costing approximately $5,200, the user kit has a replacement external pulse transmitter battery with a lifetime of 1 to 2 years and a patient programmer with a lifetime of 2 to 3 years. We assumed that 1 user kit would be required during the 3-year model time horizon.

Adverse Events or Explantation

We assumed that costs associated with complications requiring explantation, or explantation requested due to lack of pain relief would be limited to physician fees. We estimated the cost of explantation to be $266.60 (Schedule of Benefits[61] code Z824). We assumed conservatively that any complications incurred with standard care would not affect cost or quality of life.

Standard Care for Chronic Pain (Pain Medications)

Health resource use related to the management of chronic neuropathic pain typically includes physician visits, other health care provider visits, prescription medications, transcutaneous electrical nerve stimulation, outpatient tests and procedures, emergency room visits, hospital outpatient visits, and hospitalizations.[65] We did not identify any studies that reported the impact of PNS on health service utilization aside from opioid use. Therefore, we have not captured the costs of other therapies. The cost of standard care reported in this analysis includes only the average cost of opioid medications and should not be interpreted as the average cost of standard care for chronic neuropathic pain when taking into account all therapies available in Ontario.

For the standard care cohort, we assumed that the average use of systemic opioid medication by people with refractory peripheral nerve pain was 28.5 MME per day (see Pain Medications). To calculate the average monthly cost of opioid pain medications, we searched the unit prices of the most commonly recommended prescription opioids for moderate to severe peripheral nerve pain in the Ontario Drug Benefit formulary.[63] We multiplied the average dose by the unit price of each drug to obtain the daily cost, and multiplied the daily cost by 30.437 to approximate the monthly cost. For each drug, we also incorporated pharmacy markup and dispensing fees.

Table 12 presents the average cost of opioid medications for the standard care cohort. In this analysis, we evaluated costs from both a Ministry of Health perspective and a societal perspective. From a societal perspective, we calculated the total 3-month cost of opioid medications for chronic pain to be $135.80. From a Ministry of Health perspective, we assumed that 24.1% of people would be covered

under the public drug plan.[64] Given that only 65% of people in the cohort were likely to be taking opioid medications,[11] we calculated the average cost of opioid mediations for 3 months for the standard care cohort to be $21.27.

Internal Validation

The secondary health economist conducted formal internal validation. This process included testing the mathematical logic of the model, checking for errors, and ensuring the accuracy of parameter inputs and equations.

Equity Considerations

Economic evaluations inherently focus on horizontal equity (i.e., people with similar characteristics are treated in a similar way). Where possible, we conducted subgroup or scenario analyses to best address vertical equity, which allows for people with different characteristics to be treated differently according to their needs.

In our economic evaluation, the use of QALYs reflects horizontal equity because equal social value is assigned to each unit of health effect, regardless of the characteristics of the people who receive those effects, or the condition being treated.

We also considered equity in term of access to the technology, and potential additional costs borne by people living in remote northern communities, by conducting a scenario analysis using the Northern Health Travel Grant.

Analysis

Our reference case and sensitivity analyses adhered to the CADTH guidelines[53] when appropriate. The reference case represents the analysis with the most likely set of input parameters and model assumptions.

We calculated the reference case of this analysis by running 5,000 simulations (probabilistic analysis) that simultaneously captured the uncertainty in all parameters that were expected to vary. We set distributions for variables within the model. Tables 10, 11, and 12 list the model variables and corresponding distributions. We calculated mean costs and mean QALYs with credible intervals for each intervention assessed. We also calculated the mean incremental costs with credible intervals, incremental QALYs with credible intervals, and incremental cost-effectiveness ratios (ICERs) for PNS in addition to standard care versus standard care alone.

The results of the probabilistic analysis are presented in a scatter plot on a cost-effectiveness plane and in a cost-effectiveness acceptability curve. Although not used as definitive willingness-to-pay (WTP) thresholds, including graphical indications of the location of the results relative to guideposts of $50,000 per QALY and $100,000 per QALY facilitates interpretation of the findings and comparison with historical decisions. We also present uncertainty quantitatively as the probability that an intervention is cost-effective at previously mentioned WTP guideposts. This uncertainty is also presented qualitatively, in 1 of 5 categories defined by the Ontario Decision Framework[66]: highly likely to be cost-effective (80%–100% probability of being cost-effective), moderately likely to be cost-effective (60%–79% probability), uncertain if cost-effective (40%–59% probability), moderately likely to not be cost-effective (20%–39% probability), or highly likely not to be cost-effective (0%–19% probability).

Scenario Analyses

Table 13 summarizes the scenario analyses we explored.

- Scenario 1: temporary PNS implant; in this scenario, PNS was implanted for 60 days and then removed. Temporary PNS systems have not yet been used in Ontario, but they are typically implanted for 60 days and then explanted, unless a serious adverse event occurs that requires earlier explanation. For this analysis, we used clinical effectiveness data from studies of the temporary SPRINT PNS system.[44]
- Scenarios 2 and 3: change in time horizon; 1- and 5-year time horizons.
- Scenarios 4 and 5: cost of the PNS device increased or decreased by 10% (± $1,320).
- Scenario 6: PNS device price threshold; identifying at which threshold price of the PNS device the strategy would become cost-effective.
- Scenario 7: higher probability of response; assuming no adjustment or a 10% increase in the probability of response with PNS (38% probability of responders).
- Scenario 8: lower probability of response; assuming a 10% reduction in the probability of response with PNS (18% probability of responders).
- Scenario 9: opioid medication use; change opioid medication use based on information from Oswald et al[11] (68% reduction).
- Scenario 10: societal perspective; considering the cost of productivity loss due to chronic pain and change in activity with PNS. We also included the total cost of opioid medication. Not everyone is covered under a public drug plan; some would be covered under private insurance or pay out of pocket. We included opioid drug costs at a rate of 100%.
- Scenario 11: Northern Health Travel Grant; some financial assistance is available for Northern Ontario residents who travel long distances for medical specialist services. In this scenario, we included the cost of a grant for people in Northern communities, which is approximately 6% of Ontario's population.[67] We assumed a total payment to the patient of $455.00 for the trip: $205 for the calculated travel grant and $250 for an accommodation allowance of 3 lodging nights. There would also be a physician fee of $10.25 (Schedule of Benefits code K036) for completion of the Northern Health Travel Grant application form.
- Scenario 12: SF-6D utility values; we assigned SF-6D utility values of 0.58 (for severe pain) to the suboptimal pain relief state and 0.66 (for moderate pain) to the optimal pain relief state.
- Scenario 13: assumption about the long-term effectiveness of PNS; we assumed that all those in the suboptimal pain relief state would have the PNS system explanted and stop receiving PNS after 3 months.
- Scenario 14: assumption about the long-term stability of pain response from PNS; we assumed that after 1 year, pain relief would be stabilized, and that people would no longer move from the optimal to the suboptimal pain relief state.

Table 13: Variables Varied in Scenario Analyses

Parameter	Reference case	Scenario analysis
Scenario 1: temporary PNS implant	Everyone in the PNS cohort received treatment for the model time horizon (unless explantation was needed for an adverse event or no pain relief)	Everyone in the PNS cohort received treatment for 60 days (unless explantation was needed for an adverse event or no pain relief)
Scenarios 2 and 3: time horizon	3-year time horizon	1- and 5-year time horizons
Scenarios 4 and 5: PNS device costs	Using the list price provided by the manufacturer for the cost of the PNS system	Decreasing or increasing the total cost of the PNS system by 10% of the list price
Scenario 6: PNS device price threshold	Using the list price provided by the manufacturer for the cost of the PNS system	Using $4,212.91 as the price of the PNS device to meet the $50,000 WTP threshold
Scenarios 7 and 8: adjustment for PNS responders	Assuming an adjustment in the probability of response for PNS (28% responders)	Assuming no adjustment or a 10% increase in the probability of response for PNS (38% responders) Assuming a 10% decrease in the probability of response for PNS (18% responders)
Scenario 9: drug costs and effect	Using drug costs covered from a Ministry of Health perspective; no effect of PNS on opioid use	Assuming a 68% reduction in opioid use (Oswald et al[11]) and its effect on drug costs from a Ministry of Health perspective
Scenario 10: societal perspective	Including only costs incurred from a Ministry of Health perspective	Including the costs of productity loss and improvement in activity with PNS
Scenario 11: Northern Health Travel Grant	Not including the Northern Health Travel Grant	Assuming some travel grant payment for people from Northern communities
Scenario 12: utility values	Using EQ-5D utility values	Using SF-6D utility values
Scenario 13: response-dependent continuation of treatment	Everyone in the PNS cohort received treatment for 3 years, regardless of pain relief state, unless they had a serious adverse event or they requested explantation due to dissatisfaction with pain relief	Those in the suboptimal pain relief state stopped receiving PNS treatment after 3 months and had the device explanted
Scenario 14: long-term stability of pain response	People could continue moving from the optimal to the suboptimal pain relief state for the full model duration	After 1 year, pain relief stabilized and people stopped moving from the optimal to the suboptimal pain relief state

Abbreviations: PNS, peripheral nerve stimulation; WTP, willingness to pay.

Results

Reference Case Analysis

Table 14 provides results of the reference case analysis (permanent implant) from a Ministry of Health perspective. The mean total costs for PNS in addition to standard care and standard alone were $21,312.46 and $249.26, respectively. PNS in addition to standard care had a higher overall incremental cost of $21,063.20 because of device and maintenance costs. PNS in addition to standard care resulted in an increase of 0.24 QALYs. The mean total effect was 1.21 QALYs for PNS in addition to standard care and 0.97 QALYs for standard care alone. PNS in addition to standard care resulted in an ICER of $87,211 per QALY over 3 years compared with standard care alone. See Appendix 5, Table A7, for a breakdown of the costs by category.

Table 14: Reference Case Analysis Results – Adjusted Responder

Strategy	Average total cost, $	Incremental cost, $[a,b]	Average total effect, QALYs	Incremental effect, QALYs[b,c]	ICER, $/QALY[b]
Standard care alone	249.26	–	0.97 (0.89–1.04)	–	–
PNS in addition to standard care	21,312.46 (20,238.86–22,524.32)	21,063.20 (19,989.60–22,275.06)	1.21 (1.07–1.36)	0.24 (0.13–0.39)	87,211

Abbreviations: ICER, incremental cost-effectiveness ratio; PNS, peripheral nerve stimulation; QALY, quality-adjusted life-year.

[a] Incremental cost = average cost (strategy B) – average cost (strategy A).

[b] Results may appear inexact due to rounding.

[c] Incremental effect = average effect (strategy B) – average effect (strategy A).

The results of our probabilistic analysis are presented in a cost-effectiveness acceptability curve (Figure 4) and as a scatter plot on a cost-effectiveness plane (Figure 5). In the cost-effectiveness acceptability curve, a low WTP means that preference is driven by difference in cost; a high WTP means that preference is driven by difference in QALYs. In the cost-effectiveness plane, results from the 5,000 model iterations that fall to the right of or below the WTP line are considered to be cost-effective. The results of this analysis show that at commonly used WTP values of $50,000 and $100,000, the probability that PNS in addition to standard care would be cost-effective was 1.02% and 64.88%, respectively. This means that PNS in addition to standard care is highly unlikely to be cost-effective at a WTP value of $50,000, but moderately likely to be cost-effective at a WTP value of $100,000. The likelihood of PNS in addition to standard care being cost-effective increased greatly as the WTP value increased.

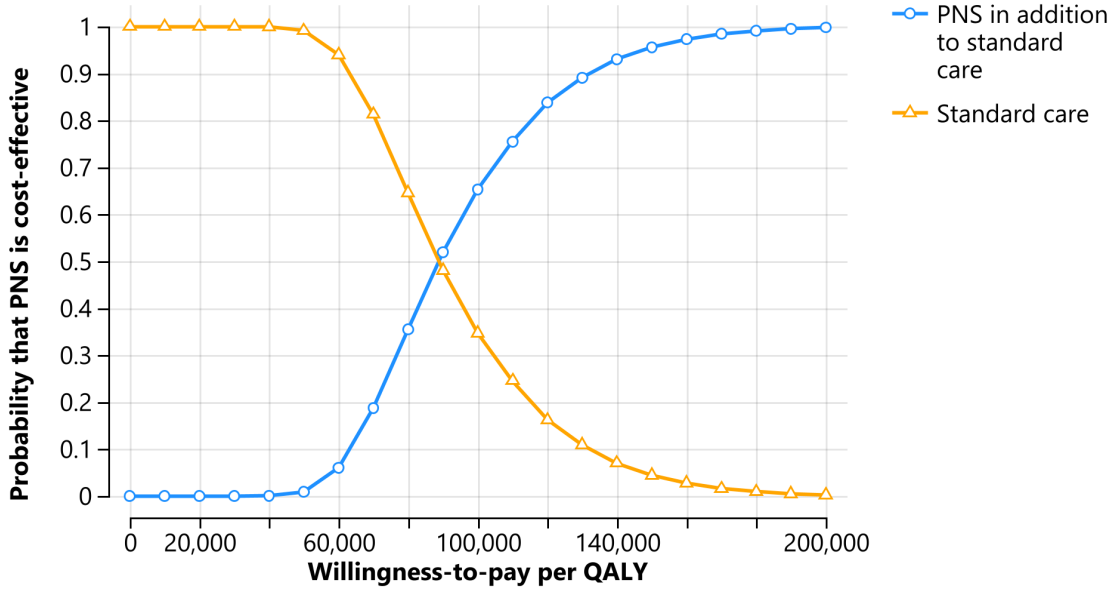

Figure 4: Cost-Effectiveness Acceptability Curve

A cost-effectiveness acceptability curve showing the results of the probabilistic analysis. PNS in addition to standard care was highly unlikely to be cost-effective at a WTP value of $50,000 but moderately likely to be cost-effective at a WTP value of $100,000.

Abbreviations: PNS, peripheral nerve stimulation; QALY, quality-adjusted life-year; WTP, willingness to pay.

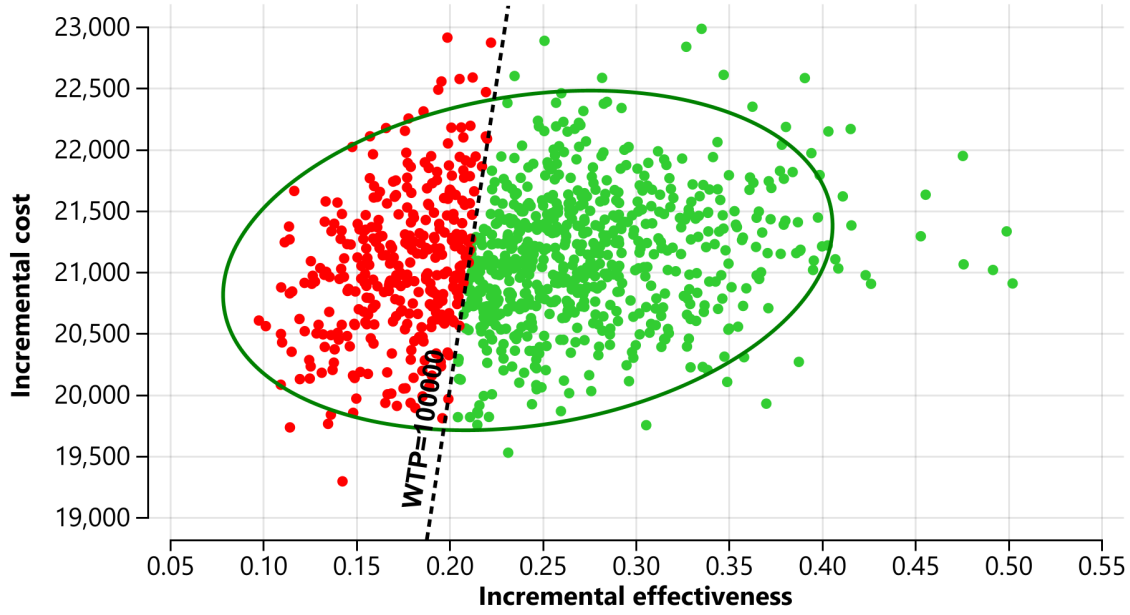

Figure 5: Scatter Plot of Probabilistic Results

A scatter plot of probabilistic results showing the findings from the 5,000 model iterations. Results that fall to the right of (or below) the WTP line (shown in green) are considered optimal. Results that fall to the left of (or above) the WTP line (shown in red) are considered suboptimal.
Abbreviations: PNS, peripheral nerve stimulation; QALY, quality-adjusted life-year; WTP, willingness to pay.

Scenario Analysis

Table 15 provides a summary of the results of the scenario analyses.

Table 15: Scenario Analysis Results

Strategy	Average total cost, $	Incremental cost, $[a,b]	Average total effect, QALYs	Incremental effect, QALYs[b,c]	ICER, $/QALY[b]
Reference case	SC: 249.26 PNS: 21,312.46	21,063.20	SC: 0.97 PNS: 1.21	0.24	87,211
Scenario 1: temporary PNS implant	SC: 249.26 PNS: 14,702.41	14,453.15	SC: 0.97 PNS: 1.49	0.52	27,841
Scenario 2: 1-year time horizon	SC: 84.42 PNS: 16,314.60	16,230.18	SC: 0.33 PNS: 0.42	0.09	172,284
Scenario 3: 5-year time horizon	SC: 408.88 PNS: 25,838.01	25,429.13	SC: 1.59 PNS: 1.95	0.37	69,455
Scenario 4: PNS device costs increased by 10%	SC: 249.26 PNS: 23,309.90	23,060.64	SC: 0.97 PNS: 1.21	0.24	95,481
Scenario 5: PNS device costs decreased by 10%	SC: 249.26 PNS: 19,315.02	19,065.76	SC: 0.97 PNS: 1.21	0.24	78,941
Scenario 6: PNS device price threshold	SC: 249.26 PNS: 12,325.37	12,076.11	SC: 0.97 PNS: 1.21	0.24	50,000

Strategy	Average total cost, $	Incremental cost, $[a,b]	Average total effect, QALYs	Incremental effect, QALYs[b,c]	ICER, $/QALY[b]
Scenario 7: 10% increase in PNS responders	SC: 249.26 PNS: 21,230.42	20,981.15	SC: 0.97 PNS: 1.28	0.31	66,734
Scenario 8: 10% decrease in PNS responders	SC: 249.26 PNS: 21,241.23	20,991.97	SC: 0.97 PNS: 1.13	0.17	125,984
Scenario 9: drug costs and effect	SC: 249.26 PNS: 21,241.48	20,992.22	SC: 0.97 PNS: 1.21	0.24	86,917
Scenario 10: societal perspective	SC: 24,836.25 PNS: 42,363.26	17,527.00	SC: 0.97 PNS: 1.21	0.24	72,569
Scenario 11: Northern Health Travel Grant	SC: 249.26 PNS: 21,340.38	21,091.11	SC: 0.97 PNS: 1.21	0.24	87,326
Scenario 12: SF-6D utility values	SC: 249.26 PNS: 21,313.08	21,063.82	SC: 1.70 PNS: 1.77	0.07	288,800
Scenario 13: response-dependent continuation of treatment	SC: 249.26 PNS: 16,150.27	15,901.00	SC: 0.97 PNS: 1.15	0.18	87,902
Scenario 14: no change in optimal state after 1 year	SC: 249.26 PNS: 21,487	21,237.68	SC: 0.97 PNS: 1.22	0.25	84,519

Abbreviations: ICER, incremental cost-effectiveness ratio; SC, standard care; PNS, peripheral nerve stimulation.

[a] Incremental cost = average cost (strategy B) – average cost (strategy A).

[b] Results may appear inexact due to rounding.

[c] Incremental effect = average effect (strategy B) – average effect (strategy A).

Our scenario analyses showed that some parameters affected the results more substantially than others. Six scenarios yielded results with higher ICERs than in the reference case: when the time horizon was shorter; when PNS device costs were increased 10%; when the probability of response to PNS was decreased by 10%; when a Northern Health Travel Grant was included; when higher baseline utility values were used; and when all people who did not meet the pain relief threshold (30% or greater) received explants.

Eight scenarios yielded results with lower ICERs than in the reference case: when the PNS system was implanted temporarily; when the model time horizon was increased; when PNS device costs were decreased 10% or at the threshold price of $4,212.91; when probability of response to PNS was as observed; when opioid medication use was reduced in the PNS cohort; considering productivity loss in the societal perspective; and when responders stabilized after 1 year.

Overall, the cost-effectiveness results were most sensitive to the following:

- Considering productivity loss in the societal perspective
- Considering the PNS implant to be temporary
- No adjustment to the probability of response to PNS (e.g., 38% vs. 28% responders)
- Reduction in the cost of the PNS device and consumables by 10% of the list price
- Increase in the model time horizon to 5 years

Discussion

Our reference case results show that the upfront costs associated with the PNS device are high, as are the long-term costs of the PNS disposable patches.

In our reference case analysis, we made conservative assumptions, including that PNS in addition to standard care would not be associated with a decrease in pain medication use, and that people receiving PNS would continue to take the same dose of opioid pain medications as those in the standard care cohort. In our scenario analysis, when we considered potential savings associated with a reduction in opioid medication use, we found that the impact on the overall cost of PNS was small. The estimated reduction in costs related to opioid use with PNS was $58.96 per person annually from a Ministry of Health perspective, considering a 68% reduction in opioid use reported in a nonrandomized study of the StimRouter[11] PNS system. We did not capture an anticipated decline in adverse events associated with a decrease in pain medication use. This is notable, because we anticipated that a decrease in opioid use may have led to an associated reduction in treatment-related adverse events, which could have improved quality-of-life outcomes and reduced the costs of adverse events related to standard care. This may mean that our analysis provides more conservative estimates of quality-of-life improvement and cost savings.

It is also important to note that our reference case results – which showed an increase in QALYs of 0.24 – were developed using EQ-5D utility values. We used EQ-5D utility values in the reference case because EQ-5D was the instrument used most commonly in previous spinal cord stimulation studies, and it is often used to assess cost-effectiveness for various health conditions across Canada. In a scenario analysis, we used utility values derived from the SF-6D instrument reported by Torrance et al.[58] Compared with EQ-5D utility values, the SF-6D utility value for severe chronic pain was much higher (0.58 vs. 0.33), but the utility value for moderate pain was similar (0.66 vs. 0.63). As a result, the incremental QALY gained with PNS using the higher baseline utility score from the SF-6D instrument was 0.07, and the resulting ICER was $288,800/QALY. However, Torrance et al[58] have suggested that it may be unreliable (perhaps even invalid) to compare studies of severe pain-related conditions that use different health utility measures.

When we compared our reference case analysis conducted over 3 years to a scenario analysis conducted over 5 years, PNS in addition to standard care had slightly more favourable results (the ICER decreased to $69,455/QALY). This scenario analysis showed that the benefit of PNS could be accrued over time to offset the high initial cost of the PNS device, and this may be a reasonable expectation, because PNS can be implanted permanently. However, the clinical evidence associated with PNS use comes from studies with short follow-up periods, so it is uncertain how pain response would be maintained. The findings of this scenario should be interpreted with caution.

The findings for scenario 1 (considering a temporary implant) should also be interpreted with substantial caution for several reasons. First, the temporary SPRINT PNS device is not licensed in Canada, and no local clinical experience was available to advise on the likely clinical pathway for temporary implants. The cost of the temporary SPRINT PNS device is also unknown; we used the cost for the permanent StimRouter device in our analysis. Furthermore, the clinical evidence review found only 1 RCT on temporary PNS conducted in adults with chronic post-amputation pain.[33,34] To capture potential outcomes for adults with more general chronic neuropathic pain and derive parameters for the scenario, we used a nonrandomized study[44]; the GRADE quality of evidence was Low. The study also defined responders to PNS as those with reductions in back pain intensity of 30% or greater, a broader

definition than that used in the StimRouter RCT,[28] which also required that patients have no increase in pain medicine use to be classified as responders.

It is also important to consider barriers to accessing specialized care for chronic pain in Ontario. As described in the clinical evidence review, it is likely that PNS would be performed at provincial neuromodulation centres (all of which are located in large urban areas), as well as at some private pain centres with expertise in ultrasound and fluoroscopic imaging. Access for some patients may be limited; however, if follow-up care (including device reprogramming) can take place at satellite centres by appropriately trained health care professionals, then some travel-related and out-of-pocket costs may be mitigated. Some of the experts we consulted also suggested that with the PNS device, patients can adjust the stimulation and manage their pain on their own, allowing for fewer follow-up visits. In a scenario analysis, we captured the cost of grants for travel and accommodation funding for people living in Northern regions who may have to travel to receive a PNS implant.

Equity Considerations

By conducting a scenario analysis from a societal perspective, we captured some of the costs of standard care that are borne by patients but are not captured from a Ministry of Health perspective, as well as the costs related to the productivity loss associated with living with chronic pain. We also captured some of the additional costs borne by patients living in remote Northern communities by conducting a scenario analysis using the Northern Health Travel Grant.

Public funding for PNS may improve access to effective treatment for those who cannot afford the treatment out of pocket or who do not have private insurance coverage. As well, funding this technology could reduce inequity as a result of improved access for people in remote areas who require treatments that are delivered at a physician's office (e.g., nerve block injections, botulinum toxin type A injections) or regular drug monitoring.

Strengths and Limitations

To our knowledge, our analysis is the first to evaluate the cost–utility of PNS in addition to standard care compared with standard care alone for chronic neuropathic pain in a Canadian context. We were able to capture QALY gains associated with the use of PNS. Before this analysis, no study has analyzed the costs and effectiveness of a minimally invasive PNS device approved by Health Canada or the US Food and Drug Administration.

Given the scarcity of rigorous evidence on this topic, we made conservative assumptions in our reference case. To ensure that our results were generalizable to the context of health care in Ontario and Canada, we ensured that our cost parameters were derived largely from local sources, including the Canadian PNS list price, the Ontario Schedule of Benefits, and the Ontario Drug Benefit formulary.

Some limitations of our analysis should be noted. First, because only 1 PNS device has been approved by Health Canada, the evidence used to generate our economic model was based on a single device and brand: the StimRouter device (Bioventus Inc.). As well, the definition of pain responses differed between studies used to derive our parameters, and the magnitude of pain reduction was measured using various pain scales. In the RCT used to derive information about pain response, responders were defined as people experiencing at least a 30% decrease in average pain at rest (using a numerical rating scale) and with no increase in pain medicine use. We were also unable to derive utility values from the clinical

studies assessing PNS. Therefore, there is considerable uncertainty in the correlations between pain response and improvements in health-related quality of life.

There was also a lack of evidence about health services utilization and the potential impact of PNS on other standard care interventions. We have heard from clinicians that there is a substantial economic burden associated with alternative therapies for chronic neuropathic pain – specifically nerve blocks – that could be reduced with the use of PNS. However, because of a lack of clinical evidence to support such a reduction, we did not include this potential impact in our analyses and our results may be viewed as conservative. The long-term efficacy of PNS use is also uncertain because of the short follow-up periods used in published RCTs. Our model time horizon of 3 years reflects this limitation. We may not have fully captured the potential benefits of PNS use for people with chronic neuropathic pain within and beyond 3 years.

Conclusions

In adults with chronic neuropathic pain, our primary economic evaluation showed that compared with standard care alone, PNS in addition to standard care was associated with 0.24 QALYs gained and an additional cost of $21,063 per person, resulting in an ICER of $87,211 per QALY over a 3-year time horizon. These results were most sensitive to time horizon and assumptions about response-dependent treatment continuation. Our findings should be interpreted with caution because of the moderate to low quality of the clinical inputs used to inform our modelling.

Budget Impact Analysis

Research Question

What is the potential 5-year budget impact for the Ontario Ministry of Health of publicly funding minimally invasive percutaneous peripheral nerve stimulation (PNS) for the treatment of chronic neuropathic pain in adults?

Methods

Analytic Framework

We estimated the budget impact of publicly funding minimally invasive PNS using the cost difference between 2 scenarios: (1) current clinical practice without public funding for minimally invasive percutaneous PNS (the current scenario), and (2) anticipated clinical practice with public funding for minimally invasive percutaneous PNS (the new scenario). Figure 6 presents the model schematic.

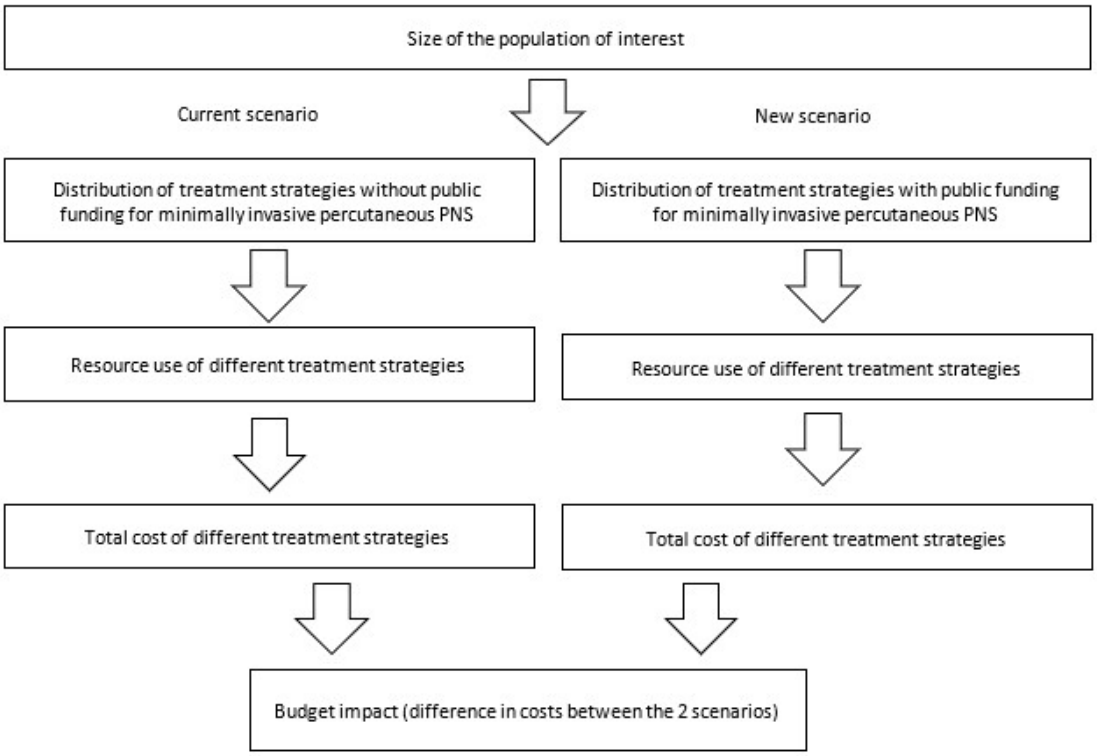

Figure 6: Schematic Model of Budget Impact

Flow chart describing the model for the budget impact analysis. Based on the size of the population of interest, we created 2 scenarios: the current scenario, which would explore the distribution of treatment strategies, resource use, and total costs without public funding for minimally invasive percutaneous PNS, and the new scenario, which would explore the distribution of treatment strategies, resource use, and total costs with public funding for minimally invasive percutaneous PNS. The budget impact would represent the difference in costs between the 2 scenarios.
Abbreviation: PNS, peripheral nerve stimulation.

Key Assumptions

- About 60 people would receive PNS in the first year.
- The number of people receiving PNS would increase annually by 20 over the next 5 years (assumption for simplicity).
- The cost of PNS would stay constant over the next 5 years. The price of the PNS system included start-up and implementation costs only (i.e., training was not included).
- Standard care and its costs for patients with chronic neuropathic pain would remain constant over the next 5 years. We estimated the cost of standard care to reflect only the average cost of opioid medications. Standard care for chronic neuropathic pain often includes visits to the pain clinic and the emergency room, repeat nerve blocks, other analgesic medications, and other modes of therapy, but we did not identify any studies that reported the impact of PNS on health service utilization aside from opioid use.

Population of Interest

Chronic neuropathic pain is a global health problem.[2] In 2016, a Canadian cross-sectional survey showed that the prevalence of likely neuropathic pain was 1.9% to 3.4%, and the prevalence of possible neuropathic pain was 5.8% to 8.1%, depending on the screening tools used.[3]

Of the patients who experience refractory chronic neuropathic pain despite receiving appropriate medical therapy (including medications, physical modalities, and interventional or injection options), PNS may be offered to achieve better pain management. However, eligibility for PNS should be assessed carefully by pain medicine specialists to increase the likelihood of treatment success.

Most people treated with PNS have neuropathic pain syndromes, including chronic neuropathic pelvic pain or complex regional pain syndrome. In these people, PNS is used as a treatment of last resort after all currently available noninvasive treatments have failed to provide pain relief. The population of interest for this analysis was adults (aged 18 years and older) with chronic neuropathic pain for whom the treatment options currently available in Ontario have not provided adequate pain relief and who become eligible for PNS.

Because of the complex interplay between variables when identifying potential candidates for PNS, we were unable to use administrative databases or the published literature to derive an estimated number of people eligible to undergo this treatment in Ontario. Therefore, we estimated our target population based on clinical expert opinion, determining that approximately 5% of patients with neuropathic pain may be eligible for PNS (Anuj Bhatia, MD, October 22, 2023). Using the prevalence of likely neuropathic pain, we estimated that approximately 12,104 to 21,659 people would be eligible for PNS, based on Ontario's adult population of 12.74 million in October 2023.[68] However, a limited number of practitioners can perform the implantation procedure; at present, it is being performed primarily by pain medicine specialists in outpatient clinics (level 2 out-of-hospital premises). For this reason, we estimated the budget impact based on the capacity of the system to perform PNS implantations (Table 16).

Table 16: Volume of Intervention

Scenario	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Current scenario						
Standard care alone, n	60	80	100	120	140	500
New scenario						
PNS in addition to standard care, n	60	80	100	120	140	500
Standard care alone, n	0	0	0	0	0	0

Abbreviation: PNS, peripheral nerve stimulation.

Current Intervention Mix

In the current scenario, standard care for adults with chronic peripheral neuropathic pain includes noninvasive methods such as oral analgesics and nonsteroidal anti-inflammatory drugs, opioid medications, antiepileptic drugs and antidepressants, epidural steroid injections, transcutaneous electrical nerve stimulation, physical therapy, and exercise.[52] In patients with refractory chronic pain (i.e., the pain does not respond to conventional treatments), more invasive approaches can be considered, such as spinal cord stimulation, denervation surgery, and implantable drug delivery systems.

According to experts, PNS should be offered early in the treatment of chronic neuropathic pain (Michael Gofeld, MD, virtual communication, July 13, 2023). Specifically, PNS should be considered after less invasive interventions have been attempted, such as epidural or peripheral steroid injection, transcutaneous electrical nerve stimulation, pulsed radiofrequency, and radiofrequency ablation or denervation, but before starting opioid medications (or increasing doses), spinal cord stimulation, or other more invasive interventions.[5]

Minimally invasive percutaneous PNS devices are not publicly funded in Ontario. There is a physician fee code for implantation, but the device is paid for by the patient (out of pocket) or by other payers (e.g., third-party insurance, manufacturer pro bono, or philanthropic sources).

Uptake of the New Intervention and New Intervention Mix

In the new scenario, adults with chronic refractory neuropathic pain may be eligible for PNS in addition to standard care. To our knowledge, 3 pain clinics in Ontario (1 in hospital and 2 in the community) have implanted these devices. To date, approximately 6 to 9 implants are being performed each year by 3 physicians in Ontario. If the PNS device were publicly funded, clinicians might expect to perform 10 to 25 implants per year (Joe Quigg, MD, email communication, July 24, 2023; Anuj Bhatia, MD, email communication, September 18, 2023).

If PNS were publicly funded, all implants would likely be performed at the current 3 sites at first, given their established expertise and the patient selection and care processes for this procedure. Over time, PNS implantation may become available at other sites with established pain centres. We estimated that all 6 neuromodulation centres (2 in Toronto and 1 each in Hamilton, Kingston, Ottawa, and London), as well as 10 to 20 private pain centres in Ontario would offer this treatment (Anuj Bhatia, MD, email communication, March 4, 2024).

If PNS were publicly funded, uptake in Ontario would depend on factors such as clinical capacity, patient preference, and awareness on the part of primary care clinicians. Given that awareness is currently limited, and rates of referrals are low (Michael Gofeld, MD, email communication, February 23, 2024; James Khan, MD, email communication, February 23, 2024; Joe Quigg, MD, email communication, March 13, 2024; Anuj Bhatia, MD, email communication, March 12, 2024; BioVentus virtual communication, July 20, 2023), we expect that initial uptake of PNS would also be low. We considered a higher volume of people eligible for PNS in a scenario analysis.

Resources and Costs

We included resources and costs associated with the health technology (i.e., direct costs of the PNS system only) and the disease (i.e., all health care costs). To determine resources and costs associated with the health technology, we included the mean costs associated with PNS. To obtain costs associated with the disease, we ran the companion cost-effectiveness analyses previously described (see the primary economic evaluation) over the time horizon of the budget impact analysis (without discounting).

In the future, the cost of PNS may be publicly funded indirectly through hospital global budgets. We accounted for device costs separately when generating our estimate of the total costs of PNS in addition to standard care.

Internal Validation

The secondary health economist conducted formal internal validation. This process included checking for errors and ensuring the accuracy of parameter inputs and equations in the budget impact analysis.

Analysis

We conducted a reference case analysis and sensitivity analyses. Our reference case analysis represents the analysis with the most likely set of input parameters and model assumptions. Our sensitivity analyses explored how the results were affected by varying input parameters and model assumptions.

The scenarios examined in our sensitivity analysis were as follows:

- Scenario 1: volume of PNS implantations increased by 50% of reference-case assumptions
- Scenario 2: volume of PNS implantations decreased by 50% of reference-case assumptions
- Scenario 3: volume of PNS implantations increased by 300% of reference-case assumptions
- Scenario 4: cost of the PNS device increased by 10% of its list price
- Scenario 5: cost of the PNS device decreased by 10% of its list price
- Scenario 6: temporary implant
- Scenario 7: Ministry of Health drug costs and effect
- Scenario 8: Northern Health Travel Grant

Results

Reference Case

Table 17 summarizes the potential budget impact of publicly funding minimally invasive percutaneous PNS for the treatment of chronic neuropathic pain in adults over the next 5 years. We estimated that public funding for PNS would lead to additional costs of $0.97 million in year 1, increasing to $3.15 million in year 5, for a total of $10.09 million over 5 years (for PNS implantations in a total of 500 people).

Table 17: Budget Impact Analysis Results

	Budget impact, $ million[a,b,c]					
Scenario	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Total**
Current scenario	0.01	0.01	0.02	0.03	0.04	0.11
Opioid costs	0.01	0.01	0.02	0.03	0.04	0.11
New scenario	0.98	1.46	1.99	2.57	3.19	10.20
PNS costs	0.91	1.37	1.87	2.41	2.99	9.55
Physician fees[d]	0.06	0.08	0.11	0.13	0.15	0.53
Opioid costs	0.01	0.01	0.02	0.03	0.04	0.11
Budget impact[b,c]	0.97	1.45	1.97	2.54	3.15	10.09

Abbreviation: PNS, peripheral nerve stimulation.

[a] In 2024 Canadian dollars.

[b] All costs were calculated using the mean cost from the probabilistic results of the primary economic evaluation.

[c] Results may appear inexact due to rounding.

[d] Only incremental physician fees directly related to PNS implantation or programming were included in the analysis.

Sensitivity Analysis

Table 18 summarizes the results of the 8 scenario analyses. Compared with the reference case, scenarios that considered an increase in PNS costs or volume resulted in a higher budget impact, and scenarios that considered a decrease in costs or volume resulted in a lower budget impact. The 8 scenarios yielded total 5-year budget impacts that ranged from 5.04 million to 30.27 million. Scenario 3 considered funding PNS for 1,500 people over 5 years and led to the greatest change in total budget impact.

Table 18: Budget Impact Analysis Results – Sensitivity Analyses

Scenario	Budget impact, $ million[a,b]					
	Year 1	Year 2	Year 3	Year 4	Year 5	Total[b]
Reference case	0.97	1.45	1.97	2.54	3.15	10.09
Scenario 1: volume of PNS implantations increased by 50%	1.46	2.18	2.96	3.81	4.72	15.13
Scenario 2: volume of PNS implantations decreased by 50%	0.49	0.73	0.99	1.27	1.57	5.04
Scenario 3: volume of PNS implantations increased by 300%	2.92	4.36	5.92	7.62	9.45	30.27
Scenario 4: cost of the PNS device increased by 10%	1.07	1.59	2.16	2.78	3.45	11.05
Scenario 5: cost of the PNS device decreased by 10%	0.88	1.32	1.79	2.30	2.85	9.13
Scenario 6: temporary implant	0.87	1.16	1.45	1.73	2.02	7.23
Scenario 7: Ministry of Health drug costs and effect	0.97	1.45	1.97	2.53	3.14	10.06
Scenario 8: Northern Health Travel Grant	0.98	1.45	1.98	2.54	3.15	10.10

Abbreviations: PNS, peripheral nerve stimulation.

[a] In 2024 Canadian dollars.

[b] Results may appear inexact due to rounding.

Discussion

PNS for chronic neuropathic pain is associated with the cost of the device, disposables, and follow-up care. These costs were not offset by reductions in acute medication use because no high-quality clinical evidence indicated this effect. In Scenario 7, our assumption about a potential reduction in medication use was based on low-quality evidence; these results need to be interpreted with caution.

The reference case budget impact reflects a smaller volume of patients with chronic pain who may be able to receive a PNS implant in the first 5 years of public funding because of resource constraints and slower uptake. As noted earlier, if PNS were publicly funded, uptake in Ontario would depend on factors such as clinical capacity, patient preference, and awareness on the part of primary care clinicians.

Based on expert opinion, we assumed that if PNS were publicly funded, about 60 implantation procedures would be performed in the first year, increasing by 20 per year for a total of 500 implants funded over 5 years. It is important to note that at present, many potentially eligible patients are not referred for PNS implantation because of a lack of awareness of this technology among health care professionals (James Khan, MD, email communication, February 2024). An increase in awareness may lead to an increase in the number of eligible patients referred for PNS implantation, as well as a subsequent increase in budget impact. In scenario 1, we considered a 50% increase in the volume assumed for the reference case (e.g., 90 implants in the first year, increasing by 30 each year for a total of 750 implants funded over 5 years) and found that the total budget impact would be 15.13 million over 5 years.

Equity Considerations

We conducted a scenario analysis that reflected a funding scenario in which Northern Health Travel Grants are provided for patients in northern communities, who would need to travel to receive PNS implantation. In this scenario, the change in the potential budget impact was minimal.

Strengths and Limitations

The estimates for our budget impact analysis were derived from our primary economic evaluation, which obtained its clinical parameters from the clinical evidence review and derived its cost parameters largely from Canadian sources. We were able to source the cost of a PNS device directly from a manufacturer. We validated our assumptions and estimates with clinical experts who have expertise in the use of PNS for chronic pain.

Our budget impact analysis was limited by some uncertainties. First, it was based on the economic model developed in our primary economic evaluation, so it contains the same parameter and structural uncertainties. Second, we estimated potential uptake in the next 5 years based on expert opinion, so our estimate is highly uncertain. Last, our budget impact estimates of PNS use were based on costs for a single PNS device (StimRouter). Should other PNS devices (with varying costs) become available in Ontario, the applicability of our analysis may be limited.

Conclusions

We estimated that publicly funding PNS in Ontario for the treatment of chronic neuropathic pain in adults would cost an additional $0.97 million in year 1, increasing to $3.15 million in year 5, for a total of $10.09 million over 5 years.

Preferences and Values Evidence

Objective

The objective of this analysis was to explore the underlying values, needs, and priorities of those who have lived experience of chronic neuropathic pain, as well as the preferences and perceptions of patients, care partners, and health care providers with respect to minimally invasive percutaneous peripheral nerve stimulation (PNS).

Background

Exploring patient preferences and values provides a unique source of information about people's experiences of a health condition and the health technologies or interventions used to manage or treat that health condition. It includes the impact of the condition and its treatment on the person with the health condition, their family and other care partners, and the person's personal environment. Engagement also provides insights into how a health condition is managed by the province's health system.

Information shared from lived experience can also identify gaps or limitations in published research (e.g., outcomes important to those with lived experience that are not reflected in the literature).[69-71] Additionally, lived experience can provide information and perspectives on the ethical and social values implications of health technologies or interventions.

Because the needs, preferences, priorities, and values of those with lived experience in Ontario are important to consider to understand the impact of the technology in people's lives, we may speak directly with people who live with a given health condition, including those with experience of the technology or intervention we are exploring.

For this analysis, we examined the preferences and values of people with chronic neuropathic pain, care partners, and health care providers in 2 ways:

- A review by Ontario Health of the quantitative evidence on patient, care partner, and health care provider preferences and values
- Direct engagement by Ontario Health with people with chronic pain through interviews

Quantitative Evidence

Research Question

What is the relative preference of patients and health care providers for minimally invasive percutaneous PNS for the treatment of chronic neuropathic pain in adults?

Methods

Literature Search

We performed a literature search for quantitative evidence of preferences and values on November 20, 2023, to retrieve studies published from database inception until the search date. We used the Ovid interface to search MEDLINE and the EBSCOhost interface to search the Cumulative Index to Nursing & Allied Health Literature (CINAHL). We also searched the International Network of Agencies for Health Technology Assessment (INAHTA) database of health technology assessments.

The search was based on the population and intervention of the clinical search strategy with a methodological filter applied to limit retrieval to quantitative evidence of preferences and values (modified from Selva et al[72]). The final search strategy was peer-reviewed using the PRESS Checklist.[21]

We created database auto-alerts in MEDLINE and CINAHL and monitored them until May 24, 2024. See Appendix 1 for our literature search strategies, including all search terms.

Eligibility Criteria

Studies

Inclusion Criteria

- English-language full-text publications
- Studies published since database inception
- Studies of patient and health care provider preferences for minimally invasive percutaneous PNS to manage chronic neuropathic pain that used quantitative measures:
  - Utility measures: direct techniques (standard gamble, time trade-off, rating scales), conjoint analysis (discrete choice experiment, contingent valuation and willingness-to-pay, probability trade-off), or indirect techniques (prescored multi-attributable instruments such as the 36-Item Short Form Health Survey, EQ-5D, Health Utilities Index)
  - Nonutility measures: direct-choice techniques, decision aids, surveys, questionnaires

Exclusion Criteria

- Animal and in vitro studies
- Qualitative studies, editorials, commentaries, case reports, conference abstracts, letters

Participants

Inclusion Criteria

- Adults with localized or regional chronic neuropathic pain of peripheral nerve origin, including the shoulders, trunk, and upper and lower extremities, as well as specific areas of the head and neck, depending on the PNS device (note: StimRouter [Bioventus Inc.] is not indicated for patients with pain of craniofacial nerve origin,[10] but SPRINT [SPR Therapeutics] is indicated for patients with headache in the occipital region or axial neck pain[16])

Exclusion Criteria

- Children
- Pregnant people

Interventions

Inclusion Criteria

- Minimally invasive percutaneous PNS systems that have regulatory approval in North America, with or without conventional medical management (e.g., physical therapy, nonopioid medications, opioid medications)

Exclusion Criteria

- Early generations of PNS devices that require open surgical implantation of a stimulation lead or surgical placement of an implantable pulse generator
- Peripheral nerve field stimulation
- Transcutaneous electric nerve stimulation (TENS)
- Spinal cord stimulation devices used for PNS

Comparators

Inclusion Criteria

- Conventional medical management (e.g., physical therapy, nonopioid medications, opioid medications)
- No intervention

Exclusion Criteria

- Interventions that include PNS

Outcome Measures

- Any outcomes related to satisfaction, preferences, and values

Timing

- Presence of chronic neuropathic pain when conventional medical treatments (including nonopioid medications, physical therapy, and less invasive interventions [e.g., injection therapy]) do not provide sufficient pain relief[6]

Setting

- Outpatient

Literature Screening

A single reviewer conducted an initial screening of titles and abstracts using Covidence[22] and then obtained the full texts of studies that appeared eligible for review according to the inclusion criteria. The same reviewer then examined the full-text articles and selected studies eligible for inclusion. The reviewer also examined reference lists and consulted content experts for any additional relevant studies not identified through the search.

Data Extraction

A single reviewer extracted relevant data on study design and characteristics, results, and PICOTS (population, intervention, comparator, timing, setting).

Statistical Analysis

Results are summarized narratively. No additional statistical analyses were conducted beyond those reported in the primary studies.

Critical Appraisal of Evidence

We did not undertake a formal critical appraisal of the included studies.

Results

Literature Search

The literature search of the quantitative evidence of preferences and values yielded 124 citations, including grey literature searches and after removing duplicates, published between database inception and November 21, 2023. We did not identify any additional studies from other sources, including database alerts monitored during the assessment period. In total, we identified 2 observational studies that met our inclusion criteria. Figure 7 presents the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram for the literature search for quantitative evidence of preferences and values.

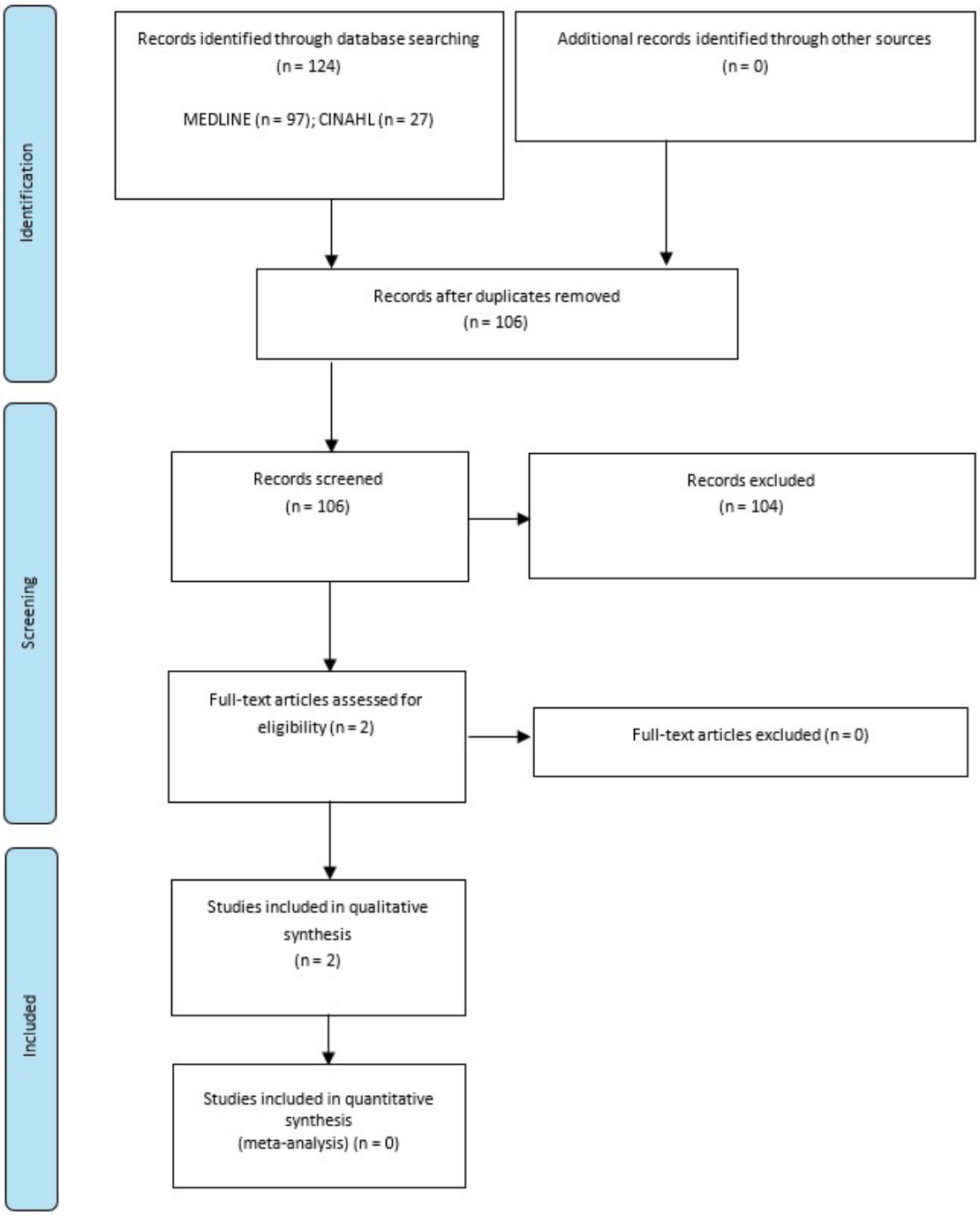

Figure 7: PRISMA Flow Diagram – Quantitative Evidence of Preferences and Values Review

PRISMA flow diagram showing the quantitative evidence of preferences and values review. The literature search for quantitative evidence of preferences and values yielded 124 citations, including grey literature searches and after removing duplicates, published between database inception and November 21, 2023. We screened the abstracts of the 124 identified studies and excluded 122. We assessed the full text of 2 articles. In the end, we included 2 articles in the qualitative synthesis.

Abbreviation: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses.

Source: Adapted from Page et al.[27]

Characteristics of Included Studies

Two survey-based studies met the inclusion criteria.[5,73]

A cross-sectional survey explored how pain medicine physicians perceived the role of PNS in treating chronic neuropathic pain.[5] The survey was emailed to 36 international neuropathic pain experts, including pain medicine physicians, researchers, and leaders of 11 professional pain societies in Canada, the United States, and the United Kingdom. Of the 36 surveys sent, 24 experts (67%) responded.

A consumer survey study characterized patient insights and preferences related to interventional pain management treatment options for chronic low back pain.[73] Two online surveys were included in this study. In the first survey, 2,402 panelists aged 34 to 75 years, with self-reported moderate to severe pain of at least 6 months' duration, were recruited from the American Consumer Opinion panel. Based on a set of screener questions on pain history and previous treatment, 129 eligible panelists completed the full survey to determine their preference for radiofrequency ablation, temporary (60-day) PNS, conventional PNS, spinal cord stimulation, or dorsal root ganglion stimulation. The second survey of 347 panelists assessed participants' preference for stimulation or ablation as a treatment option for chronic back pain.

Health Care Providers' Perspectives

The survey of international pain experts on the role of PNS in treating chronic neuropathic pain found that the most frequently targeted nerves were the distal common peroneal, tibial, and sural nerves, and the most common indication for PNS was persistent postsurgical pain of more than 3 months' duration.[5] Approximately half of the respondents preferred to trial non-neuromodulation treatment for 1 to 3 months before offering PNS. About 92% respondents agreed that PNS should be offered early in the treatment of neuropathic pain. The list below shows the aggregate neuropathic pain treatment algorithm in order of median rank:

- First line: nonopioid medications
- Second line: epidural or perineural steroid injections, TENS
- Third line: pulsed radiofrequency, radiofrequency ablation, or denervation
- Fourth line: temporary PNS, then permanent PNS
- Fifth line: spinal cord stimulation, dorsal root ganglion stimulation, opioid medications
- Sixth line: cryoablation, botulinum injection
- Seventh line: peripheral nerve field stimulation, intrathecal drug delivery
- Other: ketamine injection

The most common barriers to the use of PNS were a lack of high-quality evidence in support of its use, a lack of a standardized fellowship curriculum on neuromodulation, and different reimbursement systems across various countries.

Patient Preferences

Based on the findings of consumer-based online surveys that assessed patient preferences for interventional pain management options for chronic back pain,[73] the study authors inferred that treatment options that did not involve a permanent implant – such as temporary PNS or radiofrequency

ablation – were more desirable to patients. Participants also expressed a preference for stimulation-based versus ablative treatment. When participants were given scenarios describing the risks and benefits of each procedure, their preferred option was temporary PNS. It is important to note that the patient preferences expressed in these surveys may not correlate with physician preferences in treatment discussions.

Discussion

The preferences and perceptions of health care providers and patients are important considerations when selecting appropriate treatment modalities. From the perspectives of health care providers, barriers to the use and implementation of PNS in clinical practice include cost, training, and evidence. In their opinion, PNS should be offered before spinal cord stimulation or more invasive procedures for chronic neuropathic pain. Patients preferred stimulation over ablation to treat chronic back pain, but temporary PNS was more desirable than permanent PNS.

At present, only 1 PNS device (i.e., StimRouter) is available for clinical use in Ontario, and it is a permanent implant. Before proceeding with permanent PNS implantation, pain medicine physicians would attempt other nerve treatments that are publicly funded, such as pulsed radiofrequency neuromodulation. If patients receive extended pain relief from such treatments, then permanent PNS implantation would be unnecessary.

Conclusions

The quantitative preference and values evidence for PNS in the treatment of chronic neuropathic pain clarified its place among the available interventional pain management options, identified barriers to its use, and provided insights into patient preferences when risks and benefits were discussed.

Direct Patient Engagement

Methods

Partnership Plan

The partnership plan for this health technology assessment focused on consultation to examine the experiences of people with chronic neuropathic pain and those of their families and other care partners. We engaged people via telephone interviews.

We used a qualitative interview, as this method of engagement allowed us to explore the meaning of central themes in the experiences of people with chronic neuropathic pain, as well as those of their families and care partners.[74] The sensitive nature of exploring people's experiences of a health condition and their quality of life are other factors that support our choice of an interview methodology.

Participant Outreach

We used an approach called purposive sampling,[75-78] which involves actively reaching out to people with direct experience of the health condition and health technology or intervention being reviewed. We approached a variety of clinical experts to spread the word about this engagement activity and to contact people with chronic neuropathic pain, family members, and care partners, including those with experience of PNS.

Inclusion Criteria

We sought to speak with adults who had lived experience of chronic neuropathic pain. We included those with and without direct experience of PNS.

Exclusion Criteria

We did not set exclusion criteria.

Participants

For this project, we spoke with 18 people with chronic pain living in Ontario, as well as with 2 care partners. Some participants were unaware of the specific type of chronic pain they were experiencing, so we could not determine the number of participants with chronic neuropathic pain. Six participants had direct experience with permanent PNS, all of whom were diagnosed with chronic neuropathic pain.

Approach

At the beginning of the interview, we explained the role of our organization, the purpose of this health technology assessment, the risks of participation, and how participants' personal health information would be protected. We gave this information to participants both verbally and in a letter of information (Appendix 6). We then obtained participants' verbal consent before starting the interview. With participants' consent, we audio-recorded and then transcribed the interviews.

Interviews lasted approximately 30 to 60 minutes. The interview was semi-structured and consisted of a series of open-ended questions. Questions were based on a list developed by the Health Technology Assessment International Interest Group on Patient and Citizen Involvement in Health Technology Assessment.[79] Questions focused on the impact of chronic neuropathic pain on their quality of life, their experiences with treatments to manage chronic neuropathic pain, their experiences with PNS, their perceptions of the benefits or limitations of PNS, and the impact of the person's chronic neuropathic pain and treatments on family members and care partners. See Appendix 7 for our interview guide.

Data Extraction and Analysis

We used a modified version of a grounded-theory methodology to analyze interview transcripts. The grounded-theory approach allowed us to organize and compare information on experiences across participants. This method consists of a repetitive process of obtaining, documenting, and analyzing responses while simultaneously collecting, analyzing, and comparing information.[80,81] We used the qualitative data analysis software program NVivo[82] to identify and interpret patterns in the data. The patterns we identified allowed us to highlight the impacts of chronic pain and pain management on the people we interviewed.

Results

Impact of Chronic Pain

Participants spoke about their experience with chronic pain. The path and progression of the pain was unique to each individual, and participants reported a variety of experiences. Some had been living with pain for many years, but for others the pain was more recent. The origins of the chronic pain were

unique as well: for some, it developed following a traumatic injury, and for others, it was a symptom of an underlying disease or a side effect of surgery.

> *I had my first surgery … after that day, my health spiralled downhill with my pain.*
>
> *I have chronic regional pain syndrome that resulted from when I hit my ankle on my desk. A minor injury that caused severe nerve pain.*
>
> *The disease had spread quite extensively … my treatments have involved everything possible to reduce the ongoing spread of [the disease] and manage my pain.*

Participants emphasized the intensity of the pain and its debilitating effects. Participants spoke about the substantial negative impact the pain had on their day-to-day life. The pain affected all aspects of their life, including their physical and mental health. Living with chronic pain also affected health-promoting activities such as sleeping and exercise.

> *It really has affected every part of my life, from the social to the physical, to being able to do anything – to sleep, to just the quality of my life in general. And it's exhausting.*
>
> *[The pain] affects my ability to sleep through the night.*
>
> *I am in motion most nights. I'm on my left side, then I'm on my back, then I'm on my right side, on my back. I do this all night long.*

Most of the people we interviewed spoke about how the pain limited their mobility, making it difficult to walk, stand, or maintain balance. Participants spoke about their loss of independence as a result of the pain and its impact on their mobility, making it difficult to conduct day-to-day errands and tasks such as cleaning or cooking. They described an increased dependence on care partners and family members.

> *I went from being fully active to not being able to walk a block.*
>
> *I can't stand for any length of time without being in terrible agony.*
>
> *He hardly leaves his bed and got a nice fancy bed that you can angle up because he's bedridden most of the time, and he's bedridden because of the pain.*

Several participants described the impact of their chronic pain on employment; some had to quit their job, some were on modified duties, and some had to push through the pain while at work. Those who had to quit their job spoke about the financial strain this caused for their households.

> *I was gainfully employed, but I lost my job probably about a year after that.*
>
> *It has impacted my ability to change careers, to grow in my career.*
>
> *I had to go on permanent modified duties at work. I couldn't push or pull more than a small amount [of weight].*

We had to sell our house because financially we couldn't continue to keep it up.

Participants talked about the overwhelming toll of chronic pain on their mental health. Some reported depression, which often led to social isolation or suicidal thoughts. Some mentioned anxiety, especially with respect to the unpredictable severity of their pain, given its episodic nature. They also spoke about frustration and distress because of the limitations imposed by their pain.

> *I was definitely to the point where I was suicidal. The only thing that kept me going was the fact that I had 2 boys that I knew I had to take care of.*
>
> *I didn't know how to deal with the pain. I kind of honestly just hung out by myself. I started to get really depressed, lost all my friends, and just lost a grasp of the outside world.*
>
> *I never suffered from anxiety in my life, but I have terrible anxiety now and I go through periods of depression.*
>
> *We used to travel a lot. I can't tell you the last time I travelled. I don't have any social life at all. I don't entertain. In the past 6 months I have withdrawn from most of my volunteer work.*

Participants mentioned the impact of their pain on loved ones and care partners. Care partners had to take on increased responsibilities, including day-to-day tasks such as childcare and maintaining the household. Family relationships were negatively affected because people's pain caused them to withdraw from their family and from family social engagement.

> *I needed a lot of help from my husband, who is really good to be there for me, but he almost gave up in the end, too.*
>
> *I'm very dependent on my husband. If I didn't have my husband, at some point I would need some help. And I'm worried I'll have to go into long-term care.*
>
> *I'm a grandmother. I was overseeing my grandkids yesterday, and it's not the same as it used to be. I can't play with them the way I used to. I basically sit there, and they come and talk to me.*

Treatments for Chronic Pain

Participants had a great deal of experience with treatments for chronic pain. They spoke about their lengthy journey to find pain-management solutions, which included over-the-counter and prescription medications, as well as nonpharmacological treatments such as massage, chiropractic care, reflexology, and meditation. Participants felt that they had exhausted all options but still had not achieved adequate pain relief.

> *Over the past 12 years I have endured 30-plus forms of treatment, ranging from drug interventions to multiple major surgeries.*

I was being treated at a pain clinic for a good 2 years … I was going through a variety of options – different treatments at different times – to see if anything would work for me.

I tried many, many different things … we tried everything under the sun.

Some participants reflected on how they had to plan major life events around their pain treatments.

I literally plan vacations and events around my lidocaine, including my wedding. I had to plan my wedding around when I could get lidocaine so I could participate in my wedding.

I had to decide if I wanted to expose my baby to narcotics or if I wanted to be in extreme pain, and we split the difference … We stopped the medication before I went off work, so the baby wouldn't experience withdrawal when he was born."

Most participants reported that the treatments offered by care teams were ineffective, and they reported frustration with the fact that they had tried different options but were not finding an effective one. Some participants spoke about how their care teams did not provide them with adequate pain-management solutions and how they experienced stigma related to taking pain medication. In some cases, treatments would provide only temporary pain relief. Some had to self-advocate to receive a specialist referral. Most noted that their extended health benefits were insufficient to cover the cost of the extensive and complex pain management strategies they required.

I just kept fighting with my doctor, who finally said he would send me to a neurologist to see if there was something wrong. I ended up getting sent to 2 neurologists who did an MRI [magnetic resonance imaging].

I started doing ultrasound-guided nerve blocks, which were very, very helpful – which would definitely give me some relief. But then the problem was, it would still come back.

Participants also spoke about how the side effects of their pain medications (such as drowsiness, nausea, and not being alert) had a negative impact on their daily lives, especially when their dose was increased, leading to increased fatigue and time in bed. They raised concerns about the long-term effects of taking daily pain medication, as well as the possibility of addiction.

Some of those stronger meds have too many side effects. These drugs were awful. I remember at one point, I felt like I was hallucinating. It was just so many bad experiences with drugs. When you're on heavy-duty pain pills, you feel groggy and out of sorts. I was really scared that I was becoming addicted.

Some participants had medical conditions or other factors that limited the types of pain medication available to them. Because of the concerns described above, most expressed a preference for nonpharmacological pain-management options.

I'm on blood thinners, so my options for pain management are basically Tylenol and a patch that I can put on my skin.

I was breast feeding, so I chose not to go back on that medication. I ended up spending the first year of my baby's life in a lot of pain and not being able to do a lot.

Awareness of PNS

Most participants were unaware of PNS as a pain-management option. Those who had direct experience with permanent PNS learned about it from their care provider.

This was new for me. I'm not sure why, but I did not know about [PNS].

I guess I have heard of it, but not as something that would be implanted. I have heard of it being used in other ways kind of like the TENS unit.

The doctor brought me in as a potential patient to try [PNS] out.

Participants who had direct experience with permanent PNS spoke about their decision-making. They had exhausted all pain-management options and were open to trying other options to find relief. They looked to their care team for guidance about eligibility. Some expressed hesitation when they learned about the implantation procedure.

When I heard the news that I was accepted as a candidate for the nerve stimulator device, you could only imagine the relief that lifted away from me; it was literally the weight of the world.

My husband was very nervous about an implant. It means surgery.

Those who did not have experience with PNS said that they were open to trying the device if they met the eligibility criteria, but they also noted that they would consider other noninvasive options before trying PNS. Others expressed no hesitation in trying PNS because they had had such a long pain-management journey.

With anything new, I need more details – a lot more details – before I agree to anything.

I'm probably a little hesitant, but I would be open to it.

I would certainly look into it because I'm so limited as far as other options.

I would be willing to give it a try in a heartbeat. First off, it's something that I I've never tried before, never heard of even. From my perspective, it is new concept in in pain control. And I've tried so many different things that don't really work all that well.

PNS Implant Procedure

Participants who had undergone the PNS implant procedure spoke about their experiences and stated that it not overly burdensome. Some experienced a long procedure time, but recovery was quick.

I did not find it invasive whatsoever. I went home. I was fine.

I was awake. But sedated … I think I was in the surgery for 2½ hours.

It takes quite a while to put the thing in. The [doctor] did a wonderful job to get it in and put it where it needed to be … But it went very smoothly with minimal pain, and I was on antibiotics.

Participants reported that using the device day to day was straightforward and maintenance was minimal, requiring only that they charged the device and changed the adhesive patches every few days. In some cases, participants mentioned that they used their PNS device less over time.

I had 2 or 3 pain episodes a week. I could put it on, but [the episode] wouldn't last for 3 days anymore. So now I was like under a day, and the pain would be gone and less intense.

At the beginning I was wearing it 4 times a week for the day and now, I've gone like a week and a half without using it.

Impact of PNS

Those who had direct experience with permanent PNS spoke about the profoundly positive impact that it had on their quality of life. The greatest impact they mentioned was the reduction or complete elimination of pain when they were using the device. Many described PNS as having as a life-changing effect on their quality of life. Participants mentioned that they had regained their mobility and were able to sit, stand, and walk. In a few cases, they were able to participate in exercise and recreational sports.

I just find that it helps me to be able to function better and I do more things around the house.

I play volleyball now with my friends once a week. I play volleyball with my kids.

I can wrestle with my kids. I can play with my kids – I couldn't even wrestle with my children.

I haven't really had a day where I've had to phone in sick because of the pain.

Substantial decreases in pain levels also led to increases in independence. Participants regained the ability to manage their day-to-day activities without assistance, and that led to a decrease in care partner burden.

Participants also reported decreasing or completely eliminating their pain medication because the PNS provided the needed pain relief.

I use zero narcotics and just marijuana sometimes.

I can go for a walk outside. I was pretty much tied to a seat and doing nothing for a good 7 years.

My energy level is so much better than before. Little things like cleaning up, going to the park, is a lot easier. I'm enjoying my life with my son is so much easier now.

My work is better because to be really honest, I think the drugs were making me pretty foggy.

Barriers to Accessing PNS

One key barrier to accessing PNS is lack of awareness. Most participants were unaware of PNS as an option for managing pain, and those with experience of PNS only become aware of it when it was offered to them by their care team.

The cost of the device (approximately $12,000) poses another barrier. All participants mentioned the high cost of PNS, which meant that it was not financially feasible, and that it would cause financial strain to pay out of pocket. All of those who had experience with PNS had had their device donated, and they expressed gratitude for the donation. These participants also received refill patches for a period of time. Although most were still using the donated refill patches, some mentioned concerns about ongoing costs for the future.

It would be a financial burden. I wouldn't get it. I couldn't afford it.

I wish I could afford it, but I can't afford $12,000. There's no way I can do that.

There was a philanthropist or somebody who put money toward the program, and I didn't have to pay anything.

I just bought a whole bunch. I think I paid about $500, and I think it'll probably last me maybe 8 months.

We even tried to claim [the patches] through insurance, and insurance wouldn't even cover it.

Geography poses another important barrier. Participants spoke about the challenges of accessing specialists before even being considered eligible for PNS.

I got myself into a pain clinic, which is a 3-hour drive from my house.

I was travelling 2 hours to [another city] to get my treatment there.

I have been on the wait list [for a pain specialist] for 2 years. They have not called me yet.

Discussion

All participants reported a lengthy pain-management journey, which involved trying many pharmacological and nonpharmacological treatments, often without effective pain relief. As well, the pharmacological options came with unwanted side effects, and high doses of pain medication led to concerns about addiction. Those with experience of PNS reported its favourable impact on their pain, quality of life, and mental health.

There were some limitations to this work. Some participants were unaware of the specific type of chronic pain they were experiencing. For this reason, our findings are generalizable to those who experience chronic pain, but not to those with chronic neuropathic pain. Few participants had experience with PNS because of limited access to PNS in Ontario, as well as availability and cost. There was also a lack of geographic representation among participants: all of them lived in southern Ontario. However, we did speak with people who lived in urban and rural areas.

Conclusions

Participants spoke about the debilitating nature of chronic pain and its impact on their quality of life and mental health. All spoke about the frustration of having to try many options to find effective pain management. Participants were open to trying PNS to manage their pain because of a preference for nonpharmacological options, but some expressed hesitation because of the implantation procedure. Participants who had experience with permanent PNS emphasized the tremendous positive impact it had on their pain, quality of life, and mental health. Lack of awareness, cost, and geography pose substantial barriers to access for people with chronic neuropathic pain in Ontario.

Preferences and Values Evidence Discussion

The review of the quantitative evidence of preferences and values identified studies of temporary and permanent PNS devices, as well as other pain management options, whereas the interview questions in the direct patient engagement were focused on a permanent PNS device. The quantitative evidence showed that patients preferred stimulation-based over ablation-based treatments, and they preferred a temporary PNS device. These results align with the findings of the direct patient engagement, in which some participants expressed hesitation about using a permanent PNS device because of the invasiveness of the implantation procedure; they were more open to other noninvasive or nonpermanent options for managing their chronic pain.

Preferences and Values Evidence Conclusions

In the review of the quantitative evidence of preferences and values, health care providers specializing in pain medicine recommended that PNS be offered before more invasive interventions in the treatment of neuropathic pain. Patients preferred stimulation-based over ablation-based treatment, and temporary PNS devices over permanent PNS devices. Through direct engagement with patients and care partners, we learned about the positive impact of PNS on patients' pain, quality of life, and mental health. Lack of awareness about PNS, cost, and geography pose substantial barriers to accessing PNS for people with chronic pain in Ontario.

Conclusions of the Health Technology Assessment

Compared to people who did not receive peripheral nerve stimulation (PNS), permanent implanted PNS improved people's pain, functioning, and health-related quality of life, but it had little to no effect on their use of pain medications. Temporary PNS may improve pain, functioning, and health-related quality of life, and it may reduce the use of pain medications. Implantation of a permanent or temporary PNS system is reasonably safe.

The incremental cost-effectiveness ratio of PNS in addition to standard care compared with standard care alone is $87,211 per quality-adjusted life-year (QALY) gained. The probability that PNS in addition to standard care would be cost-effective compared with standard care alone is 1.02% at a willingness-to-pay of $50,000 per QALY gained and 64.88% at a willingness-to-pay of $100,000 per QALY gained. The annual budget impact of publicly funding PNS in Ontario over the next 5 years ranges from an additional $0.97 million in year 1, increasing to $3.15 million in year 5, for a total of $10.09 million over 5 years.

Participants spoke about the debilitating nature of chronic pain and its impact on their quality of life and mental health. Patients who had direct experience with permanent PNS spoke about its effectiveness in reducing their pain levels and its positive impact on their quality of life and mental health. Barriers to accessing PNS include lack of awareness, cost, and geography.

Abbreviations

CADTH: Canadian Agency for Drugs and Technologies in Health

CHEERS: Consolidated Health Economic Evaluation Reporting Standards

CINAHL: Cumulative Index to Nursing and Allied Health Literature

GRADE: Grading of Recommendations Assessment, Development, and Evaluation

ICER: incremental cost-effectiveness ratio

INAHTA: International Network of Agencies for Health Technology Assessment

MME: morphine milligram equivalent

NHS EED: National Health Service Economic Evaluation Database

NICE: National Institute for Health and Care Excellence

PNS: peripheral nerve stimulation

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-analyses

QALY: quality-adjusted life-year

RCT: randomized controlled trial

ROBINS-I: Risk of Bias in Non-randomized Studies–of Interventions

TENS: transcutaneous electrical nerve stimulation

WTP: willingness-to-pay

Glossary

Adverse event: An adverse event is an unexpected medical problem that happens during treatment for a health condition. Adverse events may be caused by something other than the treatment.

Budget impact analysis: A budget impact analysis estimates the financial impact of adopting a new health care intervention on the current budget (i.e., the affordability of the new intervention). It is based on predictions of how changes in the intervention mix will impact the level of health care spending for a specific population. Budget impact analyses are typically conducted for a short-term period (e.g., 5 years). The budget impact, sometimes referred to as the net budget impact, is the estimated cost difference between the current scenario (i.e., the anticipated amount of spending for a specific population without using the new intervention) and the new scenario (i.e., the anticipated amount of spending for a specific population following the introduction of the new intervention).

Cost-effective: A health care intervention is considered cost-effective when it provides additional benefits, compared with relevant alternatives, at an additional cost that is acceptable to a decision-maker based on the maximum willingness-to-pay value.

Cost-effectiveness acceptability curve: In economic evaluations, a cost-effectiveness acceptability curve is a graphical representation of the results of a probabilistic analysis. It illustrates the probability of health care interventions being cost-effective over a range of willingness-to-pay values. Willingness-to-pay values are plotted on the horizontal axis of the graph, and the probability of the intervention of interest and its comparator(s) being cost-effective at corresponding willingness-to-pay values is plotted on the vertical axis.

Cost-effectiveness analysis: Used broadly, "cost-effectiveness analysis" may refer to an economic evaluation used to compare the benefits of 2 or more health care interventions with their costs. It may encompass several types of analysis (e.g., cost-effectiveness analysis, cost–utility analysis). Used more specifically, "cost-effectiveness analysis" may refer to a type of economic evaluation in which the main outcome measure is the incremental cost per natural unit of health (e.g., life-year, symptom-free day) gained.

Cost-effectiveness plane: In economic evaluations, a cost-effectiveness plane is a graph used to show the differences in cost and effectiveness between a health care intervention and its comparator(s). Differences in effects are plotted on the horizontal axis, and differences in costs are plotted on the vertical axis.

Cost–utility analysis: A cost–utility analysis is a type of economic evaluation used to compare the benefits of 2 or more health care interventions with their costs. The benefits are measured using quality-adjusted life-years, which capture both the quality and quantity of life. In a cost–utility analysis, the main outcome measure is the incremental cost per quality-adjusted life-year gained.

Discounting: Discounting is a method used in economic evaluations to adjust for the differential timing of the costs incurred and the benefits generated by a health care intervention over time. Discounting reflects the concept of positive time preference, whereby future costs and benefits are reduced to reflect their present value. The health technology assessments conducted by Ontario Health use an annual discount rate of 1.5% for both future costs and future benefits.

Disutility: A disutility is a decrease in utility (i.e., a decrease in preference for a particular health outcome) typically resulting from a particular health condition (e.g., experiencing a symptom or complication).

EQ-5D: The EQ-5D is a generic health-related quality-of-life classification system widely used in clinical studies. In economic evaluations, it is used as an indirect method of obtaining health state preferences (i.e., utility values). The EQ-5D questionnaire consists of 5 questions relating to different domains of quality of life: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. For each domain, there are 3 response options: no problems, some problems, or severe problems. A newer instrument, the EQ-5D-5L, includes 5 response options for each domain. A scoring table is used to convert EQ-5D scores to utility values.

Equity: Unlike the notion of equality, equity is not about treating everyone the same way.[83] It denotes fairness and justice in process and in results. Equitable outcomes often require differential treatment and resource redistribution to achieve a level playing field among all individuals and communities. This requires recognizing and addressing barriers to opportunities for all to thrive in our society.

Health-related quality of life: Health-related quality of life is a measure of the impact of a health care intervention on a person's health. It includes the dimensions of physiology, function, social life, cognition, emotions, sleep and rest, energy and vitality, health perception, and general life satisfaction.

Health state: A health state is a particular status of health (e.g., sick, well, dead). A health state is associated with some amount of benefit and may be associated with specific costs. Benefit is captured through individual or societal preferences for the time spent in each health state and is expressed in quality-adjusted weights called utility values. In a Markov model, a finite number of mutually exclusive health states are used to represent discrete states of health.

Horizontal equity: Horizontal equity requires that people with like characteristics (of ethical relevance) be treated the same.

Incremental cost: The incremental cost is the additional cost, typically per person, of a health care intervention versus a comparator.

Incremental cost-effectiveness ratio (ICER): The incremental cost-effectiveness ratio (ICER) is a summary measure that indicates, for a given health care intervention, how much more a health care consumer must pay to get an additional unit of benefit relative to an alternative intervention. It is obtained by dividing the incremental cost by the incremental effectiveness. Incremental cost-effectiveness ratios are typically presented as the cost per life-year gained or the cost per quality-adjusted life-year gained.

Ministry of Health perspective: The perspective adopted in economic evaluations determines the types of costs and health benefits to include. Ontario Health develops health technology assessment reports from the perspective of the Ontario Ministry of Health. This perspective includes all costs and health benefits attributable to the Ministry of Health, such as treatment costs (e.g., drugs, administration, monitoring, hospital stays) and costs associated with managing adverse events caused by treatments. This perspective does not include out-of-pocket costs incurred by patients related to obtaining care (e.g., transportation) or loss of productivity (e.g., absenteeism).

Natural history of a disease: The natural history of a disease is the progression of a disease over time in the absence of any health care intervention.

Probabilistic analysis: A probabilistic analysis (also known as a probabilistic sensitivity analysis) is used in economic models to explore uncertainty in several parameters simultaneously and is done using Monte Carlo simulation. Model inputs are defined as a distribution of possible values. In each iteration, model inputs are obtained by randomly sampling from each distribution, and a single estimate of cost and effectiveness is generated. This process is repeated many times (e.g., 10,000 times) to estimate the number of times (i.e., the probability) that the health care intervention of interest is cost-effective.

Quality-adjusted life-year (QALY): The quality-adjusted life-year (QALY) is a generic health outcome measure commonly used in cost–utility analyses to reflect the quantity and quality of life-years lived. The life-years lived are adjusted for quality of life using individual or societal preferences (i.e., utility values) for being in a particular health state. One year of perfect health is represented by one quality-adjusted life-year.

Reference case: The reference case is a preferred set of methods and principles that provide the guidelines for economic evaluations. Its purpose is to standardize the approach of conducting and reporting economic evaluations, so that results can be compared across studies.

Scenario analysis: A scenario analysis is used to explore uncertainty in the results of an economic evaluation. It is done by observing the potential impact of different scenarios on the cost-effectiveness of a health care intervention. Scenario analyses include varying structural assumptions from the reference case.

Sensitivity analysis: Every economic evaluation contains some degree of uncertainty, and results can vary depending on the values taken by key parameters and the assumptions made. Sensitivity analysis allows these factors to be varied and shows the impact of these variations on the results of the evaluation. There are various types of sensitivity analysis, including deterministic, probabilistic, and scenario.

Short-Form–Six Dimensions (SF-6D): The SF-6D is a generic health-related quality-of-life classification system widely used in clinical studies. In economic evaluations, it is used as an indirect method of obtaining health state preferences (i.e., utility values). The classification system consists of 6 attributes (physical functioning, role limitations, social functioning, pain, mental health, and vitality), each associated with 4 to 6 levels, thus producing a total of 18,000 possible unique health states. A scoring table is used to convert SF-6D scores to health state values.

Societal perspective: The perspective adopted in an economic evaluation determines the types of costs and health benefits to include. The societal perspective reflects the broader economy and is the aggregation of all perspectives (e.g., health care payer and patient perspectives). It considers the full effect of a health condition on society, including all costs (regardless of who pays) and all benefits (regardless of who benefits).

Time horizon: In economic evaluations, the time horizon is the time frame over which costs and benefits are examined and calculated. The relevant time horizon is chosen based on the nature of the disease and health care intervention being assessed, as well as the purpose of the analysis. For instance, a lifetime horizon would be chosen to capture the long-term health and cost consequences over a patient's lifetime.

Utility: A utility is a value that represents a person's preference for various health states. Typically, utility values are anchored at 0 (death) and 1 (perfect health). In some scoring systems, a negative utility value indicates a state of health valued as being worse than death. Utility values can be aggregated over time to derive quality-adjusted life-years, a common outcome measure in economic evaluations.

Vertical equity: Vertical equity allows for people with different characteristics (of ethical relevance) to be treated differently.

Willingness-to-pay value: A willingness-to-pay value is the monetary value a health care consumer is willing to pay for added health benefits. When conducting a cost–utility analysis, the willingness-to-pay value represents the cost a consumer is willing to pay for an additional quality-adjusted life-year. If the incremental cost-effectiveness ratio is less than the willingness-to-pay value, the health care intervention of interest is considered cost-effective. If the incremental cost-effectiveness ratio is more than the willingness-to-pay value, the intervention is considered not to be cost-effective.

Appendices

Appendix 1: Literature Search Strategies

Clinical Evidence Search

Search date: October 25, 2023

Databases searched: Ovid MEDLINE, Embase, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, NHS Economic Evaluation Database

Database Segments: EBM Reviews - Cochrane Central Register of Controlled Trials <September 2023>, EBM Reviews - Cochrane Database of Systematic Reviews <2005 to October 18, 2023>, EBM Reviews - NHS Economic Evaluation Database <1st Quarter 2016>, Embase <1980 to 2023 Week 42>, Ovid MEDLINE(R) ALL <1946 to October 24, 2023>

Search Strategy:

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1 Peripheral Nerves/ (48691)
2 Peripheral Nervous System Diseases/ (55540)
3 Peripheral Nerve Injuries/ (15096)
4 exp Nerve Compression Syndromes/ (59665)
5 (((fiber* or fibre* or nerve* or neuropath* or disease* or disorder*) adj3 (peripheral or autonomic or somatosensor*)) or epineurium* or endoneurium* or autonomic pathway* or perineurium).ti,ab,kf. (334697)
6 exp Mononeuropathies/ (115025)
7 (mononeuropath* or mononeuriti* or ((carpal tunnel or femoral* or fibular* or median or medial or peroneal* or plantar* or popliteal* or radial* or sciatic* or tarsal* or thoracic* outlet* tibial* or ulnar*) adj3 (nerve* or neuropath*)) or thoracic outlet syndrome*).ti,ab,kf. (152312)
8 exp Lower Extremity/ (667539)
9 exp Upper Extremity/ (550356)
10 (((lower or upper) adj3 (extremit* or limb*)) or membrum inferius or membrum superius).ti,ab,kf. (463349)
11 (ankle* or buttock* or gluteal* or regio tarsalis or tarsus or knee or foot or feet or leg or legs or hip or hips or coxa or coxas or thigh* or arm or arms or brachium* or armpit* or underarm* or axilla* or elbow* or forearm* or antebrachium* or hand or hands or shoulder* or wrist*).ti,ab,kf. (3690045)
12 Torso/ (26024)
13 (torso or trunk).ti,ab,kf. (167406)
14 exp Back Pain/ (188455)
15 Facial Pain/ (16211)
16 Headache Disorders/ (3967)
17 Musculoskeletal Pain/ (20738)
18 Neck Pain/ (42135)
19 Shoulder Pain/ (28648)
20 ((back or face or facial* or headache* or musculoskeletal* or neck or shoulder*) adj3 pain*).ti,ab,kf. (291196)

21 or/1-20 (5059604)
22 Chronic Pain/ (104764)
23 ((chronic* or complex or intractable or refractory) adj3 pain*).ti,ab,kf. (256684)
24 Pain, Postoperative/ (109344)
25 ((post operati* or postop* or post surg* or postsurg*) adj3 pain*).ti,ab,kf. (149569)
26 Complex Regional Pain Syndromes/ (5664)
27 (((complex regional or locali#ed) adj3 pain*) or crps or reflex* sympathetic* dystroph* or post-trauma* dystroph* or algodystroph* or algoneurodystroph* or neuroalgodystroph*).ti,ab,kf. (23975)
28 or/22-27 (476652)
29 21 and 28 (173390)
30 ((chronic* or complex or intractable or refractory) adj3 neuropath* adj3 pain*).ti,ab,kf. (11540)
31 Causalgia/ (1578)
32 (causalgia* or (("type II" or "type 2") adj5 (regional pain* or crps))).ti,ab,kf. (1654)
33 Neuralgia/ (28246)
34 (neuralgia* or neuroma* or nerve* pain* or (neuropathic adj3 pain*) or neurodynia* or (piriformis adj2 syndrome*) or (pudendal adj2 neuropath*) or (nerve* adj2 entrapment) or impingement* or sciatic* or allodyni* or hyperalgesi*).ti,ab,kf. (267705)
35 or/29-34 (422652)
36 Electrodes, Implanted/ (24075)
37 (implant* adj3 (lead or leads or electrode* or percutaneous*)).ti,ab,kf. (47342)
38 Electric Stimulation Therapy/ (26801)
39 ((peripheral* adj3 nerve* adj3 stim*) or pn stim*).ti,ab,kf. (8183)
40 ((minimal* invasive* adj3 (percutaneous* or PNS)) or (percutaneous adj3 (PNS or nerve stim*))).ti,ab,kf. (6103)
41 (external* adj5 pulse* adj3 (generator* or transmitter*)).ti,ab,kf. (258)
42 (stimrouter* or bioventus* or sprint* pns* or spr therapeutics* or stimq* or curonix* or stimwave* or nalu or ((pns or neurostimulat* or neuro-stimulat*) adj3 (system* or device*))).ti,ab,kf. (8368)
43 or/36-42 (109644)
44 35 and 43 (7913)
45 exp Animals/ not Humans/ (16370128)
46 44 not 45 (5374)
47 46 use medall (2580)
48 (Comment or Editorial or (Letter not (Letter and Randomized Controlled Trial)) or Congress).pt. (4311290)
49 47 not 48 (2513)
50 46 use cctr,coch (479)
51 ((Letter not (Letter and Randomized Controlled Trial)) or Conference proceeding or Editorial or Comment or Trial Registry Record).pt. (4956833)
52 50 not 51 (291)
53 46 use cleed (1)
54 49 or 52 or 53 (2805)
55 limit 54 to english language [Limit not valid in CDSR; records were retained] (2551)
56 limit 55 to yr="2013 -Current" (1348)
57 peripheral nerve/ (48462)
58 peripheral neuropathy/ (79141)
59 exp nerve injury/ (99768)

60 (((fiber* or fibre* or nerve* or neuropath* or disease* or disorder*) adj3 (peripheral or autonomic or somatosensor*)) or epineurium* or endoneurium* or autonomic pathway* or perineurium).tw,kw,kf. (337181)
61 exp mononeuropathy/ (115000)
62 (mononeuropath* or mononeuriti* or ((carpal tunnel or femoral* or fibular* or median or medial or peroneal* or plantar* or popliteal* or radial* or sciatic* or tarsal* or thoracic* outlet* tibial* or ulnar*) adj3 (nerve* or neuropath*)) or thoracic outlet syndrome*).tw,kw,kf. (153052)
63 exp lower limb/ (667539)
64 exp upper limb/ (550356)
65 (((lower or upper) adj3 (extremit* or limb*)) or membrum inferius or membrum superius).tw,kw,kf. (464648)
66 (ankle* or buttock* or gluteal* or regio tarsalis or tarsus or knee or foot or feet or leg or legs or hip or hips or coxa or coxas or thigh* or arm or arms or brachium* or armpit* or underarm* or axilla* or elbow* or forearm* or antebrachium* or hand or hands or shoulder* or wrist*).tw,kw,kf. (3704402)
67 trunk/ (28485)
68 (torso or trunk).tw,kw,kf. (167834)
69 exp musculoskeletal pain/ (198128)
70 face pain/ (19666)
71 "headache and facial pain"/ (1976)
72 ((back or face or facial* or headache* or musculoskeletal* or neck or shoulder*) adj3 pain*).tw,kw,kf. (296109)
73 or/57-72 (5093924)
74 exp chronic pain/ (104872)
75 ((chronic* or complex or intractable or refractory) adj3 pain*).tw,kw,kf. (259118)
76 postoperative pain/ (138953)
77 ((post operati* or postop* or post surg* or postsurg*) adj3 pain*).tw,kw,kf. (154609)
78 complex regional pain syndrome/ (7500)
79 (((complex regional or locali#ed) adj3 pain*) or crps or reflex* sympathetic* dystroph* or post-trauma* dystroph* or algodystroph* or algoneurodystroph* or neuroalgodystroph*).tw,kw,kf. (24209)
80 or/74-79 (497439)
81 73 and 80 (181101)
82 neuropathic pain/ (60524)
83 ((chronic* or complex or intractable or refractory) adj3 neuropath* adj3 pain*).tw,kw,kf. (11891)
84 complex regional pain syndrome type II/ (1173)
85 (causalgia* or (("type II" or "type 2") adj5 (regional pain* or crps))).tw,kw,kf. (1698)
86 neuralgia/ (28246)
87 (neuralgia* or neuroma* or nerve* pain* or (neuropathic adj3 pain*) or neurodynia* or (piriformis adj2 syndrome*) or (pudendal adj2 neuropath*) or (nerve* adj2 entrapment) or impingement* or sciatic* or allodyni* or hyperalgesi*).tw,kw,kf. (269008)
88 or/81-87 (440048)
89 electrode implant/ (3501)
90 (implant* adj3 (lead or leads or electrode* or percutaneous*)).tw,kw,kf,dv. (47739)
91 nerve stimulation/ (38948)
92 ((peripheral* adj3 nerve* adj3 stim*) or pn stim*).tw,kw,kf,dv. (8275)
93 ((minimal* invasive* adj3 (percutaneous* or PNS)) or (percutaneous adj3 (PNS or nerve stim*))).tw,kw,kf,dv. (7704)
94 (external* adj5 pulse* adj3 (generator* or transmitter*)).tw,kw,kf,dv. (260)

95 (stimrouter* or bioventus* or sprint* pns* or spr therapeutics* or stimq* or curonix* or stimwave* or nalu or ((pns or neurostimulat* or neuro-stimulat*) adj3 (system* or device*))).tw,kw,kf,dv. (8472)
96 or/89-95 (107073)
97 88 and 96 (9485)
98 97 use emez (7011)
99 (exp animal/ or nonhuman/) not exp human/ (11935833)
100 98 not 99 (5160)
101 Comment/ or Editorial/ or (letter.pt. not (letter.pt. and randomized controlled trial/)) or conference abstract.pt. or conference review.pt. (9126371)
102 100 not 101 (3169)
103 limit 102 to english language [Limit not valid in CDSR; records were retained] (2932)
104 limit 103 to yr="2013 -Current" (1688)
105 56 or 104 (3036)
106 105 use medall (1203)
107 105 use emez (1688)
108 105 use coch (1)
109 105 use cctr (144)
110 105 use cleed (0)
111 remove duplicates from 105 (2134)

Economic Evidence Search

Search date: October 26, 2023

Databases searched: Ovid MEDLINE, Embase, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, NHS Economic Evaluation Database

Database segments: EBM Reviews - Cochrane Central Register of Controlled Trials <September 2023>, EBM Reviews - Cochrane Database of Systematic Reviews <2005 to October 18, 2023>, EBM Reviews - NHS Economic Evaluation Database <1st Quarter 2016>, Embase <1980 to 2023 Week 42>, Ovid MEDLINE(R) ALL <1946 to October 25, 2023>

Search Strategy:

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1 Peripheral Nerves/ (48690)
2 Peripheral Nervous System Diseases/ (55539)
3 Peripheral Nerve Injuries/ (15096)
4 exp Nerve Compression Syndromes/ (59663)
5 (((fiber* or fibre* or nerve* or neuropath* or disease* or disorder*) adj3 (peripheral or autonomic or somatosensor*)) or epineurium* or endoneurium* or autonomic pathway* or perineurium).ti,ab,kf. (334688)
6 exp Mononeuropathies/ (115023)
7 (mononeuropath* or mononeuriti* or ((carpal tunnel or femoral* or fibular* or median or medial or peroneal* or plantar* or popliteal* or radial* or sciatic* or tarsal* or thoracic* outlet* tibial* or ulnar*) adj3 (nerve* or neuropath*)) or thoracic outlet syndrome*).ti,ab,kf. (152312)
8 exp Lower Extremity/ (667511)
9 exp Upper Extremity/ (550335)

10 (((lower or upper) adj3 (extremit* or limb*)) or membrum inferius or membrum superius).ti,ab,kf. (463360)
11 (ankle* or buttock* or gluteal* or regio tarsalis or tarsus or knee or foot or feet or leg or legs or hip or hips or coxa or coxas or thigh* or arm or arms or brachium* or armpit* or underarm* or axilla* or elbow* or forearm* or antebrachium* or hand or hands or shoulder* or wrist*).ti,ab,kf. (3690054)
12 Torso/ (26024)
13 (torso or trunk).ti,ab,kf. (167415)
14 exp Back Pain/ (188446)
15 Facial Pain/ (16211)
16 Headache Disorders/ (3967)
17 Musculoskeletal Pain/ (20737)
18 Neck Pain/ (42131)
19 Shoulder Pain/ (28647)
20 ((back or face or facial* or headache* or musculoskeletal* or neck or shoulder*) adj3 pain*).ti,ab,kf. (291211)
21 or/1-20 (5059611)
22 Chronic Pain/ (104752)
23 ((chronic* or complex or intractable or refractory) adj3 pain*).ti,ab,kf. (256700)
24 Pain, Postoperative/ (109325)
25 ((post operati* or postop* or post surg* or postsurg*) adj3 pain*).ti,ab,kf. (149561)
26 Complex Regional Pain Syndromes/ (5664)
27 (((complex regional or locali#ed) adj3 pain*) or crps or reflex* sympathetic* dystroph* or post-trauma* dystroph* or algodystroph* or algoneurodystroph* or neuroalgodystroph*).ti,ab,kf. (23974)
28 or/22-27 (476658)
29 21 and 28 (173395)
30 ((chronic* or complex or intractable or refractory) adj3 neuropath* adj3 pain*).ti,ab,kf. (11543)
31 Causalgia/ (1578)
32 (causalgia* or (("type II" or "type 2") adj5 (regional pain* or crps))).ti,ab,kf. (1654)
33 Neuralgia/ (28242)
34 (neuralgia* or neuroma* or nerve* pain* or (neuropathic adj3 pain*) or neurodynia* or (piriformis adj2 syndrome*) or (pudendal adj2 neuropath*) or (nerve* adj2 entrapment) or impingement* or sciatic* or allodyni* or hyperalgesi*).ti,ab,kf. (267714)
35 or/29-34 (422660)
36 Electrodes, Implanted/ (24075)
37 (implant* adj3 (lead or leads or electrode* or percutaneous*)).ti,ab,kf. (47344)
38 Electric Stimulation Therapy/ (26800)
39 ((peripheral* adj3 nerve* adj3 stim*) or pn stim*).ti,ab,kf. (8183)
40 ((minimal* invasive* adj3 (percutaneous* or PNS)) or (percutaneous adj3 (PNS or nerve stim*))).ti,ab,kf. (6105)
41 (external* adj5 pulse* adj3 (generator* or transmitter*)).ti,ab,kf. (258)
42 (stimrouter* or bioventus* or sprint* pns* or spr therapeutics* or stimq* or curonix* or stimwave* or nalu or ((pns or neurostimulat* or neuro-stimulat*) adj3 (system* or device*))).ti,ab,kf. (8369)
43 or/36-42 (109648)
44 35 and 43 (7915)
45 exp Animals/ not Humans/ (16369646)
46 44 not 45 (5375)

47 (Comment or Editorial or (Letter not (Letter and Randomized Controlled Trial)) or Congress).pt. (4311364)
48 46 not 47 (5288)
49 48 use coch,cleed (6)
50 economics/ (264800)
51 economics, medical/ or economics, pharmaceutical/ or exp economics, hospital/ or economics, nursing/ or economics, dental/ (1063604)
52 economics.fs. (470349)
53 (econom* or price or prices or pricing or priced or discount* or expenditure* or budget* or pharmacoeconomic* or pharmaco-economic*).ti,ab,kf. (1299853)
54 exp "costs and cost analysis"/ (695371)
55 (cost or costs or costing or costly).ti. (336504)
56 cost effective*.ti,ab,kf. (459197)
57 (cost* adj2 (util* or efficacy* or benefit* or minimi* or analy* or saving* or estimate* or allocation or control or sharing or instrument* or technolog* or increment*)).ab,kf. (315030)
58 models, economic/ (16062)
59 markov chains/ or monte carlo method/ (108938)
60 (decision adj1 (tree* or analy* or model*)).ti,ab,kf. (68733)
61 (markov or markow or monte carlo).ti,ab,kf. (182135)
62 quality-adjusted life years/ (56467)
63 (QOLY or QOLYs or HRQOL or HRQOLs or QALY or QALYs or QALE or QALEs).ti,ab,kf. (114005)
64 ((adjusted adj1 (quality or life)) or (willing* adj2 pay) or sensitivity analys*s).ti,ab,kf. (198584)
65 or/50-64 (3426634)
66 48 and 65 (287)
67 66 use medall,cctr (160)
68 49 or 67 (166)
69 limit 68 to english language [Limit not valid in CDSR; records were retained] (159)
70 limit 69 to yr="2013 -Current" (98)
71 peripheral nerve/ (48461)
72 peripheral neuropathy/ (79140)
73 exp nerve injury/ (99768)
74 (((fiber* or fibre* or nerve* or neuropath* or disease* or disorder*) adj3 (peripheral or autonomic or somatosensor*)) or epineurium* or endoneurium* or autonomic pathway* or perineurium).tw,kw,kf. (337172)
75 exp mononeuropathy/ (114998)
76 (mononeuropath* or mononeuriti* or ((carpal tunnel or femoral* or fibular* or median or medial or peroneal* or plantar* or popliteal* or radial* or sciatic* or tarsal* or thoracic* outlet* tibial* or ulnar*) adj3 (nerve* or neuropath*)) or thoracic outlet syndrome*).tw,kw,kf. (153052)
77 exp lower limb/ (667511)
78 exp upper limb/ (550335)
79 (((lower or upper) adj3 (extremit* or limb*)) or membrum inferius or membrum superius).tw,kw,kf. (464659)
80 (ankle* or buttock* or gluteal* or regio tarsalis or tarsus or knee or foot or feet or leg or legs or hip or hips or coxa or coxas or thigh* or arm or arms or brachium* or armpit* or underarm* or axilla* or elbow* or forearm* or antebrachium* or hand or hands or shoulder* or wrist*).tw,kw,kf. (3704411)
81 trunk/ (28485)
82 (torso or trunk).tw,kw,kf. (167843)
83 exp musculoskeletal pain/ (198126)

84 face pain/ (19666)
85 "headache and facial pain"/ (1976)
86 ((back or face or facial* or headache* or musculoskeletal* or neck or shoulder*) adj3 pain*).tw,kw,kf. (296124)
87 or/71-86 (5093933)
88 exp chronic pain/ (104860)
89 ((chronic* or complex or intractable or refractory) adj3 pain*).tw,kw,kf. (259134)
90 postoperative pain/ (138934)
91 ((post operati* or postop* or post surg* or postsurg*) adj3 pain*).tw,kw,kf. (154601)
92 complex regional pain syndrome/ (7500)
93 (((complex regional or locali#ed) adj3 pain*) or crps or reflex* sympathetic* dystroph* or post-trauma* dystroph* or algodystroph* or algoneurodystroph* or neuroalgodystroph*).tw,kw,kf. (24208)
94 or/88-93 (497446)
95 87 and 94 (181107)
96 neuropathic pain/ (60520)
97 ((chronic* or complex or intractable or refractory) adj3 neuropath* adj3 pain*).tw,kw,kf. (11894)
98 complex regional pain syndrome type II/ (1173)
99 (causalgia* or (("type II" or "type 2") adj5 (regional pain* or crps))).tw,kw,kf. (1698)
100 neuralgia/ (28242)
101 (neuralgia* or neuroma* or nerve* pain* or (neuropathic adj3 pain*) or neurodynia* or (piriformis adj2 syndrome*) or (pudendal adj2 neuropath*) or (nerve* adj2 entrapment) or impingement* or sciatic* or allodyni* or hyperalgesi*).tw,kw,kf. (269017)
102 or/95-101 (440057)
103 electrode implant/ (3501)
104 (implant* adj3 (lead or leads or electrode* or percutaneous*)).tw,kw,kf,dv. (47741)
105 nerve stimulation/ (38948)
106 ((peripheral* adj3 nerve* adj3 stim*) or pn stim*).tw,kw,kf,dv. (8275)
107 ((minimal* invasive* adj3 (percutaneous* or PNS)) or (percutaneous adj3 (PNS or nerve stim*))).tw,kw,kf,dv. (7706)
108 (external* adj5 pulse* adj3 (generator* or transmitter*)).tw,kw,kf,dv. (260)
109 (stimrouter* or bioventus* or sprint* pns* or spr therapeutics* or stimq* or curonix* or stimwave* or nalu or ((pns or neurostimulat* or neuro-stimulat*) adj3 (system* or device*))).tw,kw,kf,dv. (8473)
110 or/103-109 (107078)
111 102 and 110 (9487)
112 (exp animal/ or nonhuman/) not exp human/ (11935351)
113 111 not 112 (6998)
114 Comment/ or Editorial/ or (letter.pt. not (letter.pt. and randomized controlled trial/)) or conference abstract.pt. or conference review.pt. (9126447)
115 113 not 114 (4990)
116 Economics/ (264800)
117 Health Economics/ or Pharmacoeconomics/ or Drug Cost/ or Drug Formulary/ (148324)
118 Economic Aspect/ or exp Economic Evaluation/ (558387)
119 (econom* or price or prices or pricing or priced or discount* or expenditure* or budget* or pharmacoeconomic* or pharmaco-economic*).tw,kw,kf. (1320207)
120 exp "Cost"/ (695371)
121 (cost or costs or costing or costly).ti. (336504)
122 cost effective*.tw,kw,kf. (468027)

123 (cost* adj2 (util* or efficac* or benefit* or minimi* or analy* or saving* or estimate* or allocation or control or sharing or instrument* or technolog* or increment*)).ab,kw,kf. (324738)
124 Monte Carlo Method/ (84596)
125 (decision adj1 (tree* or analy* or model*)).tw,kw,kf. (72141)
126 (markov or markow or monte carlo).tw,kw,kf. (185606)
127 Quality-Adjusted Life Years/ (56467)
128 (QOLY or QOLYs or HRQOL or HRQOLs or QALY or QALYs or QALE or QALEs).tw,kw,kf. (117355)
129 ((adjusted adj1 (quality or life)) or (willing* adj2 pay) or sensitivity analys*s).tw,kw,kf. (219357)
130 or/116-129 (2943966)
131 115 and 130 (284)
132 131 use emez (157)
133 limit 132 to english language [Limit not valid in CDSR; records were retained] (149)
134 limit 133 to yr="2013 -Current" (102)
135 70 or 134 (200)
136 135 use medall (68)
137 135 use emez (102)
138 135 use coch (1)
139 135 use cctr (29)
140 135 use cleed (0)
141 remove duplicates from 135 (147)

Quantitative Evidence of Preferences and Values Search

Search date: November 20, 2023

Databases searched: Ovid Medline, EBSCO CINAHL

Database Segment: Ovid MEDLINE(R) ALL <1946 to November 20, 2023>

Search Strategy:
1 Peripheral Nerves/ (24548)
2 Peripheral Nervous System Diseases/ (24967)
3 Peripheral Nerve Injuries/ (8047)
4 exp Nerve Compression Syndromes/ (24315)
5 (((fiber* or fibre* or nerve* or neuropath* or disease* or disorder*) adj3 (peripheral or autonomic or somatosensor*)) or epineurium* or endoneurium* or autonomic pathway* or perineurium).ti,ab,kf. (135963)
6 exp Mononeuropathies/ (22574)
7 (mononeuropath* or mononeuriti* or ((carpal tunnel or femoral* or fibular* or median or medial or peroneal* or plantar* or popliteal* or radial* or sciatic* or tarsal* or thoracic* outlet* tibial* or ulnar*) adj3 (nerve* or neuropath*)) or thoracic outlet syndrome*).ti,ab,kf. (66894)
8 exp Lower Extremity/ (188484)
9 exp Upper Extremity/ (188774)
10 (((lower or upper) adj3 (extremit* or limb*)) or membrum inferius or membrum superius).ti,ab,kf. (181538)
11 (ankle* or buttock* or gluteal* or regio tarsalis or tarsus or knee or foot or feet or leg or legs or hip or hips or coxa or coxas or thigh* or arm or arms or brachium* or armpit* or underarm* or axilla* or elbow* or forearm* or antebrachium* or hand or hands or shoulder* or wrist*).ti,ab,kf. (1487404)

12 Torso/ (5039)
13 (torso or trunk).ti,ab,kf. (69375)
14 exp Back Pain/ (45515)
15 Facial Pain/ (7214)
16 Headache Disorders/ (2739)
17 Musculoskeletal Pain/ (4678)
18 Neck Pain/ (8692)
19 Shoulder Pain/ (5987)
20 ((back or face or facial* or headache* or musculoskeletal* or neck or shoulder*) adj3 pain*).ti,ab,kf. (109220)
21 or/1-20 (1998019)
22 Chronic Pain/ (23280)
23 ((chronic* or complex or intractable or refractory) adj3 pain*).ti,ab,kf. (96190)
24 Pain, Postoperative/ (48994)
25 ((post operati* or postop* or post surg* or postsurg*) adj3 pain*).ti,ab,kf. (48136)
26 Complex Regional Pain Syndromes/ (1881)
27 (((complex regional or locali#ed) adj3 pain*) or crps or reflex* sympathetic* dystroph* or post-trauma* dystroph* or algodystroph* or algoneurodystroph* or neuroalgodystroph*).ti,ab,kf. (9316)
28 or/22-27 (171955)
29 21 and 28 (59391)
30 ((chronic* or complex or intractable or refractory) adj3 neuropath* adj3 pain*).ti,ab,kf. (4307)
31 Causalgia/ (692)
32 (causalgia* or (("type II" or "type 2") adj5 (regional pain* or crps))).ti,ab,kf. (734)
33 Neuralgia/ (17946)
34 (neuralgia* or neuroma* or nerve* pain* or (neuropathic adj3 pain*) or neurodynia* or (piriformis adj2 syndrome*) or (pudendal adj2 neuropath*) or (nerve* adj2 entrapment) or impingement* or sciatic* or allodyni* or hyperalgesi*).ti,ab,kf. (114019)
35 or/29-34 (167516)
36 Electrodes, Implanted/ (21485)
37 (implant* adj3 (lead or leads or electrode* or percutaneous*)).ti,ab,kf. (18561)
38 Electric Stimulation Therapy/ (22098)
39 ((peripheral* adj3 nerve* adj3 stim*) or pn stim*).ti,ab,kf. (3137)
40 ((minimal* invasive* adj3 (percutaneous* or PNS)) or (percutaneous adj3 (PNS or nerve stim*))).ti,ab,kf. (2233)
41 (external* adj5 pulse* adj3 (generator* or transmitter*)).ti,ab,kf. (88)
42 (stimrouter* or bioventus* or sprint* pns* or spr therapeutics* or stimq* or curonix* or stimwave* or nalu or ((pns or neurostimulat* or neuro-stimulat*) adj3 (system* or device*))).ti,ab,kf. (3310)
43 or/36-42 (61996)
44 35 and 43 (3423)
45 exp Animals/ not Humans/ (5173282)
46 44 not 45 (2592)
47 Attitude to Health/ (85453)
48 Health Knowledge, Attitudes, Practice/ (127377)
49 Patient Participation/ (29651)
50 Patient Preference/ (10791)
51 Attitude of Health Personnel/ (131952)
52 *Professional-Patient Relations/ (12512)

53 *Physician-Patient Relations/ (37349)
54 Choice Behavior/ (35039)
55 (choice or choices or value* or valuation* or knowledg*).ti. (328442)
56 (preference* or expectation* or attitude* or acceptab* or point of view).ti,ab,kf. (759825)
57 ((clinician* or doctor* or (health* adj2 worker*) or (pain adj3 (expert* or specialist*)) or patient*1 or personal or physician* or practitioner* or professional*1 or provider* or user*1 or women or men) adj2 (participation or perspective* or perception* or misperception* or perceiv* or view* or understand* or misunderstand* or value*1 or knowledg*)).ti,ab,kf. (190734)
58 health perception*.ti,ab,kf. (3436)
59 *Decision Making/ (46746)
60 (clinician* or doctor* or (health* adj2 worker*) or (pain adj3 (expert* or specialist*)) or patient*1 or personal or physician* or practitioner* or professional*1 or provider* or user*1 or women or men).ti. (3031105)
61 59 and 60 (8543)
62 (decision* and mak*).ti. (38763)
63 (decision mak* or decisions mak*).ti,ab,kf. (220125)
64 62 or 63 (221810)
65 (clinician* or doctor* or (health* adj2 worker*) or (pain adj3 (expert* or specialist*)) or patient*1 or personal or physician* or practitioner* or professional*1 or provider* or user*1 or women or men).ti,ab,kf. (10100786)
66 64 and 65 (139346)
67 (discrete choice* or decision board* or decision analy* or decision-support or decision tool* or decision aid* or latent class* or decision* conflict* or decision* regret*).ti,ab,kf. (53594)
68 Decision Support Techniques/ (22547)
69 (health and utilit*).ti. (2013)
70 (gamble* or prospect theory or health utilit* or utility value* or utility score* or utility estimate* or health state or feeling thermometer* or best-worst scaling or time trade-off or TTO or probability trade-off).ti,ab,kf. (17551)
71 (preference based or preference score* or preference elicitation or multiattribute or multi attribute).ti,ab,kf. (3960)
72 or/47-58,61,66-71 (1617666)
73 46 and 72 (104)
74 limit 73 to english language (97)

Database: CINAHL

 # Query Results

S1 (MH "Peripheral Nerves") 3,793
S2 (MH "Peripheral Nervous System Diseases") 6,206
S3 (MH "Nerve Compression Syndromes+") 5,368
S4 (((fiber* or fibre* or nerve* or neuropath* or disease* or disorder*) N3 (peripheral or autonomic or somatosensor*)) or epineurium* or endoneurium* or autonomic pathway* or perineurium) 33,917
S5 (MH "Mononeuropathies+") 548
S6 (mononeuropath* or mononeuriti* or ((carpal tunnel or femoral* or fibular* or median or medial or peroneal* or plantar* or popliteal* or radial* or sciatic* or tarsal* or thoracic* outlet* tibial* or ulnar*) N3 (nerve* or neuropath*)) or thoracic outlet syndrome*) 13,355
S7 (MH "Lower Extremity+") 55,339
S8 (MH "Upper Extremity+") 41,324
S9 (((lower or upper) n3 (extremit* or limb*)) or membrum inferius or membrum superius) 59,981

S10 (ankle* or buttock* or gluteal* or regio tarsalis or tarsus or knee or foot or feet or leg or legs or hip or hips or coxa or coxas or thigh* or arm or arms or brachium* or armpit* or underarm* or axilla* or elbow* or forearm* or antebrachium* or hand or hands or shoulder* or wrist*) 410,236
S11 (MH "Torso+") 8,492
S12 (torso or trunk) 15,836
S13 (MH "Back Pain+") 28,079
S14 (MH "Facial Pain") 2,443
S15 (MH "Headache") 13,498
S16 (MH "Musculoskeletal Pain") 366
S17 ((back or face or facial* or headache* or musculoskeletal* or neck or shoulder*) N3 pain*) 62,392
S18 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 16
S19 (MH "Chronic Pain") 21,648
S20 ((chronic* or complex or intractable or refractory) N3 pain*) 46,474
S21 (MH "Postoperative Pain") 18,691
S22 ((post operati* or postop* or post surg* or postsurg*) N3 pain*) 24,951
S23 (MH "Complex Regional Pain Syndromes") 1,286
S24 ((complex regional or locali#ed) N3 pain*) or crps or reflex* sympathetic* dystroph* or post-trauma* dystroph* or algodystroph* or algoneurodystroph* or neuroalgodystroph*) 16,598
S25 S19 OR S20 OR S21 OR S22 OR S23 OR S24 83,483
S26 S18 AND S25 30,382
S27 ((chronic* or complex or intractable or refractory) N3 neuropath* N3 pain*) 1,428
S28 (MH "Causalgia") 103
S29 (causalgia* or (("type II" or "type 2") N5 (regional pain* or crps))) 263
S30 (MH "Neuralgia") 4,620
S31 (neuralgia* or neuroma* or nerve* pain* or (neuropathic N3 pain*) or neurodynia* or (piriformis N2 syndrome*) or (pudendal N2 neuropath*) or (nerve* N2 entrapment) or impingement* or sciatic* or allodyni* or hyperalgesi*) 31,128
S32 S26 OR S27 OR S28 OR S29 OR S30 OR S31 58,248
S33 (MH "Electrodes, Implanted") 4,414
S34 (implant* N3 (lead or leads or electrode* or percutaneous*)) 7,534
S35 ((peripheral* N3 nerve* N3 stim*) or pn stim*) 625
S36 ((minimal* invasive* N3 (percutaneous* or PNS)) or (percutaneous N3 (PNS or nerve stim*)) 779
S37 (external* N5 pulse* N3 (generator* or transmitter*)) 23
S38 (stimrouter* or bioventus* or sprint* pns* or spr therapeutics* or stimq* or curonix* or stimwave* or nalu or ((pns or neurostimulat* or neuro-stimulat*) N3 (system* or device*))) 438
S39 S33 OR S34 OR S35 OR S36 OR S37 OR S38 9,187
S40 S32 AND S39 506
S41 (MH "Attitude to Health") 49,432
S42 (MH "Health Knowledge") 38,011
S43 (MH "Consumer Participation") 24,454
S44 (MH "Patient Preference") 2,821
S45 (MH "Attitude of Health Personnel") 55,228
S46 (MM "Professional-Patient Relations") 14,566
S47 (MM "Physician-Patient Relations") 17,464
S48 (MM "Nurse-Patient Relations") 14,759
S49 TI (choice or choices or value* or valuation* or knowledg*) 118,817
S50 (preference* or expectation* or attitude* or acceptab* or point of view) 565,418

S51 ((clinician* or doctor* or (health* N2 worker*) or nurse or nurses or (pain N3 (expert* or specialist*)) or patient or patients or personal or physician* or practitioner* or professional or professionals or provider* or user or users or women or men) N2 (knowledg* or misperception* or misunderstand* or participation or perceiv* or perception* or perspective* or understand* or value or values or view*)) 183,617
S52 health perception* 5,386
S53 (MH "Decision Making, Shared") 3,733
S54 (MH "Decision Making, Patient") 15,628
S55 (MH "Decision Making, Family") 4,238
S56 (MM "Decision Making") 26,077
S57 TI (clinician* or doctor* or (health* N2 worker*) or nurse or nurses or (pain N3 (expert* or specialist*)) or patient or patients or personal or physician* or practitioner* or professional or professionals or provider* or user or users or women or men) 1,419,831
S58 S56 AND S57 5,575
S59 TI (decision* and mak*) 22,015
S60 (decision mak* or decisions mak*) 183,393
S61 S59 OR S60 183,625
S62 (clinician* or doctor* or (health* N2 worker*) or nurse or nurses or (pain N3 (expert* or specialist*)) or patient or patients or personal or physician* or practitioner* or professional or professionals or provider* or user or users or women or men) 3,909,076
S63 S61 AND S62 131,071
S64 (discrete choice* or decision board* or decision analy* or decision support or decision tool* or decision aid* or latent class* or decision* conflict* or decision* regret*) 37,548
S65 (MH "Decision Support Techniques") 7,792
S66 TI (health and utilit*) 1,196
S67 (gamble* or prospect theory or health utilit* or utility value* or utility score* or utility estimate* or health state or feeling thermometer* or best worst scaling or time trade off or TTO or probability trade off) 21,258
S68 (preference based or preference score* or preference elicitation or multiattribute or multi attribute) 1,878
S69 S41 OR S42 OR S43 OR S44 OR S45 OR S46 OR S47 OR S48 OR S49 OR S50 OR S51 OR S52 OR S53 OR S54 OR S55 OR S58 OR S63 OR S64 OR S65 OR S66 OR S67 OR S68 939,691
S70 S40 AND S69 27
S71 Narrow by Language: english 27

Grey Literature Search

Performed on: November 6–13, 2023

Websites searched: Alberta Health Evidence Reviews, BC Health Technology Assessments, Canadian Agency for Drugs and Technologies in Health (CADTH), Institut national d'excellence en santé et en services sociaux (INESSS), Institute of Health Economics (IHE), University Of Calgary Health Technology Assessment Unit, Ontario Health Technology Assessment Committee (OHTAC), McGill University Health Centre Health Technology Assessment Unit, Centre Hospitalier de l'Universite de Quebec-Universite Laval, Contextualized Health Research Synthesis Program of Newfoundland (CHRSP), Health Canada Medical Device Database, International HTA Database (INAHTA), Agency for Healthcare Research and Quality (AHRQ) Evidence-based Practice Centers, Centers for Medicare & Medicaid Services Technology Assessments, Veterans Affairs Health Services Research and Development, Institute for Clinical and

Economic Review, Oregon Health Authority Health Evidence Review Commission, Washington State Health Care Authority Health Technology Reviews, National Institute for Health and Care Excellence (NICE), National Health Service England (NHS), Healthcare Improvement Scotland, Health Technology Wales, Ireland Health Information and Quality Authority Health Technology Assessments, Australian Government Medical Services Advisory Committee, Australian Safety and Efficacy Register of New Interventional Procedures -Surgical (ASERNIP-S), Italian National Agency for Regional Health Services, Belgian Health Care Knowledge Centre, Ludwig Boltzmann Institute for Health Technology Assessment, Swedish Agency for Health Technology Assessment and Assessment of Social Services, Ministry of Health Malaysia Health Technology Assessment Section, Tuft's Cost-Effectiveness Analysis Registry, PROSPERO, EUnetHTA, clinicaltrials.gov

Keywords used:
peripheral nerve, neuropathic, chronic pain, complex pain, intractable pain, refractory pain, neurodynia, nerve entrapment ,nerve impingement, neuralgia, causalgia, type II regional pain, type 2 regional pain, stimrouter, bioventus, sprint pns, spr therapeutics, stimq, curonix, stimwave, nalu

Clinical results (included in PRISMA): 48
Economic results (included in PRISMA): 48
Ongoing HTAs (PROSPERO/EUnetHTA/NICE/MSAC): 9
Ongoing clinical trials: 39

Appendix 2: Critical Appraisal of Clinical Evidence

Table A1: Risk of Bias[a] Among Randomized Controlled Trials (Cochrane Risk-of-Bias Tool)

Author, year Device (manufacturer)	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Incomplete outcome data	Selective reporting	Other bias
Deer et al, 2016[28] StimRouter (Bioventus Inc.)	Low	Unclear[b]	Unclear[c]	Low	Low	High[d]
Gilmore et al, 2019[33] SPRINT (SPR Therapeutics)	Low	Low	Low	High[e]	High[e]	High[f,g]
Gilmore et al, 2020[34] SPRINT (SPR Therapeutics)	Low	Low	Low	High[e]	High[e]	High[f,g]

[a] Possible risk-of-bias levels: low, high, and unclear.

[b] No information on allocation concealment.

[c] No information on blinding of outcome assessors.

[d] Of the 94 patients implanted, 15 did not participate in 6-month and 12-month follow-up, and 33 did not participate in 12-month follow-up, representing 51% attrition.

[e] Outcomes on percent change in hours of daily prosthetic usage and subject satisfaction were listed in the clinicaltrial.gov registration but were not reported.

[f] Loss to follow-up and withdrawal in the placebo control group was 50% at 6 months and 57% at 12 months.

[g] Partial crossover at 4 weeks, resulting in only 4 weeks of direct comparison between the intervention and placebo control groups. Findings may not capture the full treatment effect of the 60-day intervention.

Table A2: Risk of Bias[a] Among Nonrandomized Trials (ROBINS-I Tool)

Author, year[b] Device (manufacturer)	Pre-intervention		At intervention		Post-intervention		
	Confounding	Study participation selection	Classification of interventions	Deviations from intended intervention	Missing data	Measurement of outcomes	Selection of reported results
Oswald et al, 2019[11] StimRouter (Bioventus Inc.)	Serious[c,d]	Serious[e]	Low	Low	Serious[f]	Serious[g]	No information
Abd-Elsayed et al, 2023[29] Freedom (Curonix Inc.)	Serious[c,d]	Serious[h,i]	Low	Low	Serious[j]	Serious[g,k]	No information
Chahadeh et al, 2021[30] Freedom (Curonix Inc.)	Serious[c,d]	Serious[h]	Low	Low	No information	Serious[g]	No information
Fruh et al, 2023[31] Freedom (Curonix Inc.)	Serious[c]	Serious[h]	Low	Low	No information	Serious[g]	No information
Pollina et al, 2024[32] Freedom (Curonix Inc.)	Serious[c,d]	Serious[h]	Low	Low	Low[l]	Serious[g,k]	No information
Abd-Elsayed et al, 2023[35] SPRINT (SPR Therapeutics)	Serious[c,d]	Serious[h]	Low	Low	No information	Serious[g,k,m]	No information
Deer et al, 2021[36] SPRINT (SPR Therapeutics)	Serious[c]	Low	Low	Low	No information	Serious[g]	Low
Gilmore et al, 2021[38] SPRINT (SPR Therapeutics)	Serious[c]	Low	Low	Low	Moderate[n]	Serious[g]	Low
Gilmore et al, 2023[44] SPRINT (SPR Therapeutics)	Serious[c]	Low	Low	Low	Serious[o]	Serious[g]	Serious[p]
Hoffmann et al, 2021[39] SPRINT (SPR Therapeutics)	Serious[c]	Serious[h]	Low	Low	No information	Low	No information
Huntoon et al, 2023[40] SPRINT (SPR Therapeutics)	Serious[c]	Serious[h,i]	Low	Low	Low[q]	Serious[g,k]	No information
Pingree et al, 2022[41] SPRINT (SPR Therapeutics)	Serious[c,d,r]	Serious[h,i]	Low	Low	No information	Serious[g,s]	No information
Sudek et al, 2024[42] SPRINT (SPR Therapeutics)	Serious[c,d]	Serious[h]	Low	Low	No information	Serious[g,k]	No information

Author, year[b] Device (manufacturer)	Pre-intervention		At intervention		Post-intervention		
	Confounding	Study participation selection	Classification of interventions	Deviations from intended intervention	Missing data	Measurement of outcomes	Selection of reported results
Vangeison et al, 2023[43] SPRINT (SPR Therapeutics)	Serious[c,d]	Serious[h]	Low	Low	No information	Serious[g,k]	No information

Abbreviations: BDI-II, Beck Depression Inventory; PGIC, Patient Global Impression of Change; PNS, peripheral nerve stimulation; ROBINS-I, Risk of Bias in Non-randomized Studies – of Interventions.

[a] Possible risk-of-bias levels: low, moderate, serious, critical, and no information.

[b] Studies are grouped by device.

[c] Nonrandomized study at risk of confounding.

[d] No information about relevant demographics or clinical parameters to characterize study populations.

[e] Authors stated that "for unclear reasons, some locations contributed more to the dataset than others"; risk of sampling bias.

[f] Authors stated that "not all participants answered every question on the survey"; it was unclear if the participants who responded differed systematically from those who did not respond.

[g] Risk of reporting bias due to no separate control group, no blinding, participants' awareness of the intervention they received, and the nature of self-reported data.

[h] Retrospective study design at risk of selection bias.

[i] No information on inclusion or exclusion criteria used to select patients for PNS implantation.

[j] Substantial loss to follow up beyond 6 months; 64% loss to follow-up at 24 months.

[k] Study results obtained from electronic medical records were at risk of information bias from data-entry errors or measurement errors.

[l] Authors were able to call patients to obtain needed data that were missing from charts.

[m] The study reported outcomes before and after PNS implantation. The authors stated that they observed "the duration of improvement from 6 days post-implant and therapy initiation to nearly 2 years of relief"; it was unclear when the follow-ups were performed.

[n] 11% loss to follow-up at 6 months unaccounted for.

[o] 16% loss to follow-up at 12 months unaccounted for.

[p] 12-month follow-up data on patient global impression of change (PGIC), depression (BDI-II) and health-related quality of life (RAND-36) were not reported.

[q] The authors performed sensitivity analyses to assess the effects of missing data.

[r] Follow-up data were collected cross-sectionally, and duration of follow-up ranged from at least 1 month to greater than 2 years. Patients with a longer period of follow-up may have sought other interventions for pain management and confounded the outcomes.

[s] Follow-up data were collected via email and then matched with baseline data in the manufacturer's database. Data from baseline and 2 months after implantation were collected during active treatment. Baseline data were at risk of information bias from data-entry errors or measurement errors.

Table A3: GRADE Evidence Profile for the Comparison of Permanent PNS Versus Control for Pain Management in Adults With Chronic Neuropathic Pain

Number of studies (design)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Upgrade considerations	Quality
Proportion of patients with a positive response to PNS							
1 (RCT)	Serious limitations (−1)[a]	Not applicable[b]	No serious limitations	No serious limitations[c,d]	Undetected	None	⨁⨁⨁ Moderate
Pain scores							
1 (RCT)	Serious limitations (−1)[a]	Not applicable[b]	No serious limitations	No serious limitations[c,d]	Undetected	None	⨁⨁⨁ Moderate
Use of pain medications							
1 (RCT)	Serious limitations (−1)[a]	Not applicable[b]	No serious limitations	No serious limitations[c,d]	Undetected	None	⨁⨁⨁ Moderate
Functional outcomes							
1 (RCT)	Serious limitations (−1)[a]	Not applicable[b]	No serious limitations	No serious limitations[c,d]	Undetected	None	⨁⨁⨁ Moderate
Health-related quality of life							
1 (RCT)	Serious limitations (−1)[a]	Not applicable[b]	No serious limitations	No serious limitations[c,d]	Undetected	None	⨁⨁⨁ Moderate
Adverse events							
1 (RCT)	Serious limitations (−1)[a]	Not applicable[b]	No serious limitations	No serious limitations[c,d]	Undetected	None	⨁⨁⨁ Moderate

Abbreviations: GRADE, Grading of Recommendations Assessment, Development, and Evaluation; PNS, peripheral nerve stimulation; RCT, randomized controlled trial.

[a] No information about allocation concealment or blinding of outcome accessors; large attrition rate.

[b] Evidence from a single study.

[c] This RCT reported a power calculation to justify enrolment of a minimum of 90 patients, with at least 70 completing 3-month follow-up after at least 3 months of treatment with PNS (45 from the treatment group and 25 from the control group who crossed over to treatment and received PNS for 3 months). The actual sample size was 94 patients (49 in treatment group, 45 in control group). Among the 45 patients in the control group, 30 patients crossed over to treatment at the end of 3-month placebo period.

[d] Partial crossover from placebo to treatment occurred after a predefined 90-day treatment for primary outcomes.

Table A4: GRADE Evidence Profile for the Comparison of Pain Management With Versus Without Permanent PNS in Adults With Chronic Neuropathic Pain

Number of studies (design)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Upgrade considerations	Quality
Pain scores							
5 (nonrandomized studies)	Serious limitations (−1)[a]	No serious limitations	No serious limitations	Serious limitations (−1)[b]	Undetected	None	⨁⨁ Low
Use of pain medications							
4 (nonrandomized studies)	Serious limitations (−1)[a]	No serious limitations	No serious limitations	Serious limitations (−1)[b]	Undetected	None	⨁⨁ Low
Functional outcomes							
1 (nonrandomized study)	Serious limitations (−1)[a]	Not applicable[c]	No serious limitations	Serious limitations (−1)[b]	Undetected	None	⨁⨁ Low
Health-related quality of life							
3 (nonrandomized studies)	Serious limitations (−1)[a]	No serious limitations	No serious limitations	Serious limitations (−1)[b]	Undetected	None	⨁⨁ Low
Adverse events							
4 (nonrandomized studies)	Serious limitations (−1)[a]	No serious limitations	No serious limitations	Serious limitations (−1)[b]	Undetected	None	⨁⨁ Low

Abbreviations: GRADE, Grading of Recommendations Assessment, Development, and Evaluation; PNS, peripheral nerve stimulation.

[a] Inherent limitations of study designs: retrospective, no randomization, no blinding, no separate control groups, at risk of confounding, selection bias, reporting bias, and information bias.

[b] Sample sizes were small: 11 to 57 for outcomes on pain scores, use of pain medications, and adverse events; 39 for functional outcomes; and 11 to 25 for health-related quality of life.

Table A5: GRADE Evidence Profile for the Comparison of Temporary PNS Versus Control for Pain Management in Adults With Chronic Neuropathic Pain

Number of studies (design)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Upgrade considerations	Quality
Proportion of patients with a positive response to PNS							
1 (RCT)	Serious limitations (−1)[a]	Not applicable[b]	No serious limitations	Serious limitations (−1)[c]	Undetected	None	⨁⨁ Low
Pain scores							
1 (RCT)	Serious limitations (−1)[a]	Not applicable[b]	No serious limitations	Serious limitations (−1)[c]	Undetected	None	⨁⨁ Low
Use of pain medications							
1 (RCT)	Serious limitations (−1)[a]	Not applicable[b]	No serious limitations	Serious limitations (−1)[c]	Undetected	None	⨁⨁ Low
Functional outcomes							
1 (RCT)	Serious limitations (−1)[a]	Not applicable[b]	No serious limitations	Serious limitations (−1)[c]	Undetected	None	⨁⨁ Low
Health-related quality of life							
1 (RCT)	Serious limitations (−1)[a]	Not applicable[b]	No serious limitations	Serious limitations (−1)[c]	Undetected	None	⨁⨁ Low
Adverse events							
1 (RCT)	Serious limitations (−1)[a]	Not applicable[b]	No serious limitations	Serious limitations (−1)[c]	Undetected	None	⨁⨁ Low

Abbreviations: GRADE, Grading of Recommendations Assessment, Development, and Evaluation; PNS, peripheral nerve stimulation; RCT, randomized controlled trial.

[a] Selective reporting and attrition rate.

[b] Evidence from a single study.

[c] Sample size was based on funding availability instead of a power calculation.

Table A6: GRADE Evidence Profile for the Comparison of Pain Management With Versus Without Temporary PNS in Adults With Chronic Neuropathic Pain

Number of studies (design)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Upgrade considerations	Quality
Proportion of patients with a positive response to PNS							
5 (nonrandomized studies)	Serious limitations (−1)[a]	No serious limitations	No serious limitations	Serious limitations (−1)[b]	Undetected	None	⨁⨁ Low
Pain scores							
5 (nonrandomized studies)	Serious limitations (−1)[a]	No serious limitations	No serious limitations	Serious limitations (−1)[c]	Undetected	None	⨁⨁ Low
Use of pain medications							
3 (nonrandomized studies)	Serious limitations (−1)[a]	Serious limitations (−1)[d]	No serious limitations	No serious limitations	Undetected	None	⨁⨁ Low
Functional outcomes							
2 (nonrandomized studies)	Serious limitations (−1)[a]	No serious limitations	No serious limitations	Serious limitations (−1)[e]	Undetected	None	⨁⨁ Low
Health-related quality of life							
3 (nonrandomized studies)	Serious limitations (−1)[a]	Serious limitations (−1)[f]	No serious limitations	No serious limitations	Undetected	None	⨁⨁ Low
Adverse events							
5 (nonrandomized studies)	Serious limitations (−1)[a]	No serious limitations	No serious limitations	Serious limitations (−1)[e]	Undetected	None	⨁⨁ Low

Abbreviations: GRADE, Grading of Recommendations Assessment, Development, and Evaluation; PNS, peripheral nerve stimulation; RCT, randomized controlled trial.

[a] Inherent limitations of study designs: retrospective and no separate control groups in most studies, no randomization, no blinding, at risk of confounding, selection bias, reporting bias, and information bias.

[b] Sample sizes were generally small (ranging from 15 to 89), except for the studies that used manufacturer's databases, which had sample sizes of 252 to 6,160. Although most studies reported that 60% or more of patients responded to PNS and showed a clinically meaningful (≥ 30% to 50%) reduction in pain, it was uncertain how precise these estimates were, considering the large clinical heterogeneity (e.g., etiology, nerve targets, etc.) for this outcome.

[c] Sample sizes were generally small (ranging from 15 to 89), except the manufacturer's database review, which had a sample size of 6,160. The prospective study showed lower pain scores after PNS (this finding was statistically significant). Retrospective reviews of medical records and the manufacturer's database showed an average pain reduction of 35% to 70% without information about statistical significance, but the range was large (0% to 100%) when stratified by clinical factors.

[d] Results varied from no change, to reduced use, to complete cessation.

[e] Sample sizes were generally small, ranged from 74 to 89 for functional outcomes and from 15 to 89 for adverse events.

[f] Most patients who responded to PNS showed improvement in health-related quality of life; however, the extent of improvement varied between domains (e.g., physical or emotional) and biological factors (e.g., different causes of cancer pain).

Appendix 3: Selected Excluded Studies – Clinical Evidence

For transparency, we provide a list of studies that readers might have expected to see but that did not meet the inclusion criteria, along with the primary reason for exclusion.

Citation	Primary reason for exclusion
Baldeschi GC, Dario A, De Carolis G, et al. Peripheral nerve stimulation in the treatment of chronic pain syndromes from nerve injury: a multicenter-observational study. Neuromodulation 2017;20(4):369-74.	Devices not approved for use in North America
Busch C, Smith O, Weaver T, et al. Peripheral nerve stimulation for lower extremity pain. Biomedicines 2022;10(7):11.	Narrative review
Char S, Jin MY, Francio VT, et al. Implantable peripheral nerve stimulaiton for peripheral neruopathic pain: a systematic review of prospective studies. Biomedicines 2022;10(10):17.	Included early generations of PNS devices
Chmiela MA, Hendrickson M, Hale J, et al. Direct peripheral nerve stimulation for the treatment of complex regional pain syndrome: a 30-year review. Neuromodulation 2021;24(6):971-82.	Included early generations of PNS devices
Chow RM, Lee RY, Rajput K. Peripheral nerve stimulation for pain management: a review. Curr Pain Headache Rep 2023;27(9):321-7.	Narrative reivew
Cohen S, Gilmore C, Kapural L, et al. Peripheral peripheral stimulation for pain reduction and improvements in functional outcomes in chronic low back pain. Military Med 2019;184(Suppl 1):537-41.	Case series with n < 10 implanted
Cohen SP, Gilmore CA, Rauck RL, et al. Percutaneous peripheral nerve stimulation for the treatment of chronic pain following amputaiton. Military Med 2019;184(7-8):e267-74.	Narrative review
D'Souza RS, Her YF, Jin MY, et al. Neuromodulation therapy for chemotherapy-induced peripheral neuropathy: a systematic review. Biomedicines 2022;10(8):7.	Not the intervention of interest
D'Souza RS, Jin MY, Abd-Elsayed A. Peripheral nerve stimulation for low back pain: a systematic review. Curr Pain Headache Rep 2023;27(5):117-28.	Included early generations of PNS devices
Dalal S, Berger AA, Orhurhu V, et al. Peripheral nerve stimulation for the treatment of meralgia paresthetica. Orthop Rev 2021;13(2):24437.	Case report
De Carolis G, Paroli M, Dario A, et al. Peripheral nerve stimulation on the brachial plexus with ultrasound-guided percutaneous technique: a case series. Neuromodulation 2023;26(3):650-7.	Devices not approved for use in North America
Deer TR, Esposito MF, McRoberts WP, et al. A systematic literature review of peripheral nerve stimulation therapies for the treatment of pain. Pain Med 2020;21(8):1590-1603.	Included early generations of PNS devices
Erosa SC, Moheimani RS, Oswald JC, et al. Peripheral nerve stimulation for chronic pain and migraine: a review. Physical Med Rehabil Clin N Am 2022;33(2):379-407.	Narrative review
Ferreira-Silva N, Ferreira-Dos-Santos G, Gupta S, et al. Ultrasound-guided percutaneous peripheral nerve stimulation for chronic refractory neuropathic pain: a unique series. Pain Manage 2023;13(1):15-24.	Case series with n < 10 implanted
Frederico TN, da Silva Freitas T. Peripheral nerve stimulation of the brachial plexus for chronic refractory CRPS pain of the upper limb: description of a new technique and case series. Pain Med 2020;21(Suppl 1):S18-S26.	Not the intervention of interest
Freitas TDS, Fonoff ET, Marquez Neto OR, et al. Peripheral nerve stimulation for painful mononeuropathy secondary to leprosy: a 12-month follow-up study. Neuromodulation 2018;21(3):310-6.	Not the intervention of interest
Gilmore CA, Kapural L, McGee MJ, Boggs JW. Percutaneous peripheral nerve stimulation (PNS) for the treatment of chronic low back pain provides sustained relief. Neuromodulation 2019;22(5):615-20.	Case series with n < 10 implanted
Gilmore CA, Kapural L, McGee MJ, Boggs JW. Percutaneous peripheral nerve stimulation for chronic low back pain: prospective case series with 1 year of sustained relief following short-term implant. Pain Pract 2020;20(3):310-20.	Case series with n < 10 implanted
Gilmore CA, Patel J, Esebua LG, Burchell M. A review of peripheral nerve stimulation techniques targeting the medial branches of the lumbar dorsal rami in the treatment of chronic low back pain. Pain Med 2020;21(Suppl 1):S41-6.	Narrative review
Guentchev M, Preuss C, Rink R, et al. Long-term reduction of scaroiliac joint pain with peripheral nerve stimulation. J Oper Neurosurg 2017;13(5):634-9.	Not the intervention of interest

Citation	Primary reason for exclusion
Guentchev M, Preuss C, Rink R, et al. Technical note: treatment of sacroiliac joint pain with peripheral nerve stimulation. Neuromodulation 2015;18(5):392-6.	Not the intervention of interest
Helm S, Shirsat N, Calodney A, et al. Peripheral nerve stimulation for chronic pain: a systematic review of effectiveness and safety. Pain Ther 2021;10(2):985-1002.	Included early generations of PNS devices
Hoang Roberts L, Vollstedt A, Volin J, et al. Initial experience using a novel nerve stimulator for the mangement of pudendal neuralgia. Neurourol Urodyn 2021;40(6):1670-7.	Case series with n < 10 implanted
Ilfeld BM, Ball ST, Cohen SP, et al. Percutaneous peripheral nerve stimulation to control postoperative pain, decrease opiod use, and accelerate functional recovery following orthopedic trauma. Military Med 2019;184(Suppl 1):557-64.	Case series with n < 10 implanted
Kalia H, Pritzlaff S, Li A, et al. Application of the novel Nalu neurostimulation system for peripheral nerve stimulation. Pain Manage 2022;12(7):795-804.	Narrative review
Kaye AD, Ridgell S, Alpaugh ES, et al. Peripheral nerve stimlation: a review of techniques and clinical efficacy. Pain Ther 2021;10(2):961-72.	Narrative review
Li AH, Bhatia A, Gulati A, Ottestad E. Role of peripheral nerve stimulation in treating chronic neuropathic pain: an international focused survey of pain medicine experts. Reg Anesthes Pain Med 2023;48(6):312-8.	Not the outcomes of interest
Lin CP, Chang KV, Wu WT, Ozcakar L. Ultrasound-guided peripheral nerve stimulation for knee pain: a mini-review of the neruoanatomy and the evidence from clinical studies. Pain Med 2020;21(Suppl 1):S56-63.	Narrative review
Mainkar O, Singh H, Gargya A, et al. Ultrasound-guided peripheral nerve stimulation of cervical, thoracic and lumbar spinal nerves for dermatomal pain: a case series. Neuromodulation 2021;24(6):1059-66.	Not the indications of interest
Mainkar O, Solla CA, Chen G, Legler A, Gulati A. Pilot study in temporary peripheral nerve stimulation in oncologic pain. Neuromodulation 2020;23(6):819-26.	Case series with n < 10 implanted
Mazzola A, Spinner D. Ultrasound-guided peripheral nerve stimulation for shoulder pain: anatomic review and assessment of the current clinical evidence. Pain Physician 2020;23(5):E461-74.	Narrative review
Naidu R, Li S, Desai MJ, et al. 60-day PNS treatment may improve identiifcaiton of delayed respnonders and delayed non-responders to neruostimulation for pain relief. J Pain Res 2022;15:733-43.	Not the outcomes of interest
Nayak R, Banik RK. Current innovations in peripheral nerve stimulation. Pain Res Treat 2018:9091216.	Narrative review
Ni Y, Yang L, Han R, et al. Implantable peripheral nerve stimulation for trigeminal neuropathic pain: a systematic review and meta-analysis. Neuromodulation 2021;24(6):983-91.	Not the populations of interest
Rauck RL, Cohen SP, Gilmore CA, et al. Treatment of post-amputation pain with peripheral nerve stimulation. Neuromodulation 2014;17(2):188-97.	Included early generations of PNS devices
Regnier SM, Chen J, Gabriel RA, et al. A review of the StimRouter peripheral neuromodulation system for chronic pain management. Pain Manage 2021;11(3):227-36.	Narrative review
Reverberi C, Dario A, Barolat G, Zuccon G. Using peripheral nerve stimulation (PNS) to treat neuropathic pain: a clinical series. Neuromodulation 2014;17(8):777-83.	Devices not approved for use in North America
Schnack LL, Oexeman S, Rodriguez-Collazo ER. Implantable neuromodulation device in the lower limb: an adjunctive procedure in patients with continued chronic pain after failed revisional microneurosurgical procedure in a non-restructable zone of injury. Clin Podiatr Med Surg 2021;38(1S):e31-43.	Narrative review
Smith BJ, Twohey EE, Dean KP, D'Souza RS. Peripheral nerve stimulation for the treatment of postamputation pain: a systematic review. Am J Phys Med Rehab 2023;102(9):846-54.	Included early generations of PNS devices
Staats P, Deer T, Ottestad E, et al. Understanding the role of patient preferences in the treatment algorithm for chronic low back pain: results from a survey-based study. Pain Manage 2022;12(3):371-82.	Not the outcomes of interest
Strand N, D'Souza RS, Hagedorn JM, et al. Evidence-based clinical guidelines from the American Society of Pain and Neuroscience for the use of implantable peripheral nerve stimulation in the treatment of chronic pain. J Pain Res 2022;15:2483-504.	Included early generations of PNS devices
Vij N, Fabian I, Hansen C, et al. Outcomes after minimally invasive and surgical management of suprascapular nerve entrapment: a systematic review. Orthop Rev 2022;14(3):37157.	Not the intervention of interest

Citation	Primary reason for exclusion
Warner NS, Schaefer KK, Eldrige JS, et al. Peripheral nerve stimulation and clinical outcomes: a retrospective case series. Pain Pract 2021;21(4):411-8.	Included early generations of PNS devices
Wilson RD, Bennett ME, Nguyen VQC, et al. Fully implantable peripheral nerve stimulation for hemiplegic shoulder pain: a multi-site case series with two-year follow-up. Neuromodulation 2018;21(3):290-5.	Case series with n < 10 implanted
Wilson RD, Gunzler DD, Bennett ME, Chae J. Peripheral nerve stimulation compared with usual care for pain relief of hemiplegic shoulder pain: a randomized controlled trial. Am J Physical Med Rehabil 2014;93(1):17-28.	Included early generations of PNS devices
Wilson RD, Harris MA, Gunzler DD, Bennett ME, Chae J. Percutaneous peripheral nerve stimulation for chronic pain in subacromial impingement syndrome: a case series. Neuromodulation 2014;17(8):771-6.	Included early generations of PNS devices
Wilson RD, Knutson JS, Bennett ME, Chae J. The effect of peripheral nerve stimulation on shoulder biomechanics: a randomized controlled trial in comparison to physical therapy. Am J Physical Med Rehabil 2017;96(3):191-8.	Included early generations of PNS devices
Xu J, Sun Z, Wu J, et al. Peripheral nerve stimulation in pain management: a systematic review. Pain Physician 2021;24(2):E131-52.	Included early generations of PNS devices

Appendix 4: Selected Excluded Studies – Economic Evidence

For transparency, we provide a list of studies that readers might have expected to see but that did not meet the inclusion criteria, along with the primary reason for exclusion.

Citation	Primary reason for exclusion
Eldabe S, Kern M, Peul W, Green C, Winterfeldt K, Taylor RS. Assessing the effectiveness and cost effectiveness of subcutaneous nerve stimulation in patients with predominant back pain due to failed back surgery syndrome (SubQStim study): study protocol for a multicenter randomized controlled trial. Trials. 2013;14:189.	Study protocol; study terminated, findings not published, cost outcomes not reported on clinicaltrials.gov
Naidu R, Li S, Desai MJ, Sheth S, Crosby ND, Boggs JW. 60-Day PNS treatment may improve identification of delayed responders and delayed non-responders to neurostimulation for pain relief. J Pain Res. 2022;15:733-43.	Study outcomes
van Gorp E, Adang EMM, Gültuna I, Hamm-Faber TE, Bürger K, Kallewaard JW, et al. Cost-effectiveness analysis of peripheral nerve field stimulation as add-on therapy to spinal cord stimulation in the treatment of chronic low back pain in failed back surgery syndrome patients. Neuromodulation. 2020;23(5):639-45.	Not the intervention and comparator of interest

Appendix 5: Detailed Breakdown of Reference Case Analysis Results

Table A7: Reference Case Analysis Results

Findings	Standard care alone, mean (95% CI)	PNS in addition to standard care, mean (95% CI)	Difference, mean (95% CI)
Average total cost	$249.26	$21,312.46 (20,238.86–22,524.32)	$21,063.20 (19,989.60–22,275.06)
PNS costs	$0	$19,974.41 (18,908.05–21,185.55)	$19,974.41 (18,908.05–21,185.55)
Physician fees	$0	$1,088.79 (1,077.50–1,096.54)	$1,088.79 (1,077.50–1,096.54)
Opioid costs	$249.26	$249.26	$0
Average QALYs	0.97 (0.89–1.04)	1.21 (1.07–1.36)	0.24 (0.13 to 0.39)
ICER (cost per QALY gained)	–	–	$87,211

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; CI, credible interval.

Appendix 6: Letter of Information

Ontario Health is conducting a review of **Peripheral Nerve Stimulation for Chronic Neuropathic Pain.** The purpose is to better understand how this technique can be publicly funded in Ontario.

An important part of this review involves gathering perspectives of patients and care partners of those who have been diagnosed and/or managed with chronic neuropathic pain and who may or may not have used peripheral nerve stimulation.

What Do You Need From Me

- Willingness to share your story
- 30-40 minutes of your time for a phone interview
- Permission to audio- (not video-) record the interview

What Your Participation Involves

If you agree to share your experiences, you will be asked to have an interview with Ontario Health (OH) staff. Ontario Health staff will contact interested participants by collecting contact information (i.e., email address and/or phone number) to set up an interview. The interview will last about 30-40 minutes. It will be held over the telephone. With your permission, the interview will be audio-taped. The interviewer will ask you questions about your or your loved one's condition and your perspectives about your diagnosis and treatment options in Ontario. Participation is voluntary. You may refuse to participate, refuse to answer any questions, or withdraw before or at any point during your interview. Withdrawal will in no way affect the care you receive.

Confidentiality

All information you share will be kept confidential and your privacy will be protected except as required by law. The results of this review will be published, however no identifying information will be released or published. Any records containing information from your interview will be stored securely until project completion. After completion of the project, the records will be destroyed. If you are sending us personal information by email, please be aware that electronic communication is not always secure and can be vulnerable to interception.

Ontario Health is designated an "institution" by the *Freedom of Information and Protection of Privacy Act* (FIPPA) and is collecting your personal information pursuant to FIPPA and the *Connecting Care Act, 2019* to support the Health Technology Assessment Program. If you have any questions regarding Ontario Health's collection and use of personal information for the purposes of this program, please contact Team Lead, Jigna Mistry noted below.

Risks to Participation

There are no known physical risks to participating. Some participants may experience discomfort or anxiety after speaking about their experience.

If you are interested, please contact us.

Appendix 7: Interview Guide

Peripheral Nerve Stimulation Interview Guide

Impact of Living With Chronic Pain

- What is your experience living with chronic pain?
- What is the impact on your quality of life? (social, emotional, financial, mental health, work, family, other day-to-day)

Diagnosis/Care Journey

- Can you describe your journey to manage your pain?
- What treatment options have you explored? Costs? Side effects? Concerns?

Peripheral Nerve Stimulation (PNS)

- Awareness
- Cost
- Openness to PNS
- Experience (if applicable)
    - Cost
    - Pre-procedure
    - Implant procedure
    - Follow-up care
    - Maintenance
    - Impact of PNS: treatment, pain intensity

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About Us

We are an agency created by the Government of Ontario to connect, coordinate, and modernize our province's health care system. We work with partners, providers, and patients to make the health system more efficient so everyone in Ontario has an opportunity for better health and well-being.

Equity, Inclusion, Diversity and Anti-Racism

Ontario Health is committed to advancing equity, inclusion and diversity and addressing racism in the health care system. As part of this work, Ontario Health has developed an Equity, Inclusion, Diversity and Anti-Racism Framework, which builds on existing legislated commitments and relationships and recognizes the need for an intersectional approach.

Unlike the notion of equality, equity is not about sameness of treatment. It denotes fairness and justice in process and in results. Equitable outcomes often require differential treatment and resource redistribution to achieve a level playing field among all individuals and communities. This requires recognizing and addressing barriers to opportunities for all to thrive in our society.

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