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Systematic Review

Diabetic peripheral neuropathy: a systematic review of current interventional pain management strategies

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ABSTRACT

Diabetic peripheral neuropathy (DPN) is characterized by pain, tingling, and numbness due to nerve damage caused by diabetes. DPN is a prevalent complication of diabetes, marked by sensations of pain and sensory deficits. Effective pain management strategies are critical to improve patient quality of life. This review follows the preferred reporting items for systematic reviews and meta-analyses guidelines, using the population, intervention, control, and outcome study framework to select studies evaluating interventional treatments for DPN. We conducted an exhaustive literature search from January 1990 to March 2024 using PubMed, Cochrane, Google Scholar, Scopus and MEDLINE databases, applying relevant medical subject heading terms. An independent reviewer assessed the selected studies based on outcome parameters such as pain relief, sleep quality, analgesic usage, functional improvement, and quality of life. Interventions like transcutaneous electrical nerve stimulation (TENS) and acupuncture are recognized as safe, non-invasive methods for sustained pain relief in DPN. More invasive procedures such as spinal cord stimulation (SCS) and radiofrequency ablation (RFA), while highly effective, are typically recommended only when non-invasive approaches fail. TENS and acupuncture are effective and economical approaches for DPN pain management. However, for cases where these methods do not provide sufficient relief, interventions such as SCS and RFA offer promising results in the hands of experienced clinicians. Treatment decisions should consider factors like cost, invasiveness, and the specific area affected by DPN.

Keywords: Diabetic peripheral neuropathy, Spinal cord stimulation, Pain management, Interventional strategies, Infusion therapy, Acupuncture

INTRODUCTION

Diabetic peripheral neuropathy (DPN) is a prevalent complication of diabetes, affecting millions of people worldwide. It is characterized by damage to peripheral nerves, primarily due to chronic hyperglycemia, which leads to a complex interplay of metabolic and vascular factors causing nerve injury. Patients with DPN often suffer from chronic pain, sensory deficits, and impaired quality of life, posing significant challenges for effective management.[1] Key mechanisms involved in the pathogenesis of DPN include oxidative stress, inflammation, advanced glycation end-products formation, and microvascular dysfunction. These processes collectively result in nerve fiber damage, axonal degeneration, and demyelination. In terms of epidemiology, DPN affects approximately 50% of individuals with long-standing diabetes, with higher prevalence in those with poorly controlled blood glucose levels.[2] The condition is more common in patients with type 2 diabetes compared to type 1, largely due to the prolonged asymptomatic period of hyperglycemia before diagnosis in type 2 diabetes. The risk of developing DPN increases with the duration of diabetes, advancing age, and the presence of other comorbidities such as hypertension and dyslipidemia. Given its prevalence and impact on quality of life, DPN represents a significant public health challenge.[3]

Despite the availability of numerous pharmacological treatments, many patients with DPN experience inadequate pain relief and adverse side effects. Consequently, there is a growing interest in interventional pain management strategies that offer targeted, potentially more effective, and longer-lasting relief for DPN.[4] This review covers a wide range of interventional techniques, including nerve blocks, spinal cord stimulation (SCS), peripheral nerve stimulation (PNS), intrathecal drug delivery, radiofrequency ablation (RFA), TENS, infusion therapy, and acupuncture.[5]

The systematic review focuses on relevant pathophysiology of DPN and aims to evaluate the current interventional pain management strategies for DPN, assessing their efficacy and associated complications. We critically reviewed evidence from randomized trials, non-interventional studies, observational studies and case series to provide a comprehensive overview of these interventions. By examining the strengths and limitations of each approach, this review aims to inform clinical practice and guide future research in managing DPN pain.

METHODS

This review was conducted following the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines. we included relevant studies for this review. The selection encompassed randomized trials, observational studies, and case series that evaluated various interventions for DPN. Studies that compared the effectiveness of these interventions against conventional medical therapy were excluded because the primary focus is on evaluating innovative or experimental interventions. Comparing with conventional treatments could introduce variability, as such treatments may differ across studies in terms of dosage, regimen, and practices, making a direct comparison challenging.

Study period

The systematic literature search and data synthesis were conducted from September 2023 to March 2024.

Study place

The review was carried out at the Government Medical College, Srikakulam, Andhra Pradesh, India, in collaboration with affiliated institutions of the authors.

Sample size

A total of 45 eligible studies were included in the final qualitative synthesis, comprising randomized trials, prospective studies, observational studies, and case series.

Studies were selected based on relevance, outcome measures, and quality of methodology. Comparing with conventional treatments could introduce variability, as such treatments may differ across studies in terms of dosage, regimen, and practices, making a direct comparison challenging.

Literature search strategy

An independent reviewer conducted a comprehensive search of the online literature to identify studies on interventional treatments for DPN. The medical subject heading terms used included "DPN," "Diabetic neuropathic pain," "Neuromodulation Therapies," "Sensorimotor polyneuropathy," "SCS," "TENS," "RFA," "PNS," "Infusion therapy," and "Nerve blocks". The search was limited to human studies published in English from January 1990 to March 2024, across PubMed, Cochrane, Google Scholar, Scopus and MEDLINE databases. We also manually checked references and bibliographies of selected articles for additional relevant studies. Full-text articles were reviewed if their abstracts met the criteria. Inclusion in the final analysis was based on an independent assessment by another reviewer. The authors conducted the literature search independently without the assistance of a librarian or search specialist.

Data extraction

Data were collected from each incorporated study into a Microsoft Excel spreadsheet using a standard data extraction template. Extracted data included country, patient demographics, study design, DPN treatment interventions, post-intervention outcomes, publication year and any related complications. The analysis focused on pain status at specific intervals post-intervention, sleep quality assessments using available surveys, analgesic usage, functional evaluations, and assessments of overall life quality. Bias in the included studies was assessed by examining randomization methods, treatment allocation concealment, blinded data collection and analysis, and data completeness, independently conducted by two reviewers. Statistical analysis for publication bias, such as using funnel plots and Egger's test, was not performed. In addition to the primary biases such as selection, performance, detection, and attrition bias, this review also accounted for reporting and funding biases. Reporting bias, where certain outcomes may be selectively reported, can distort the understanding of treatment efficacy. Furthermore, funding bias, where financial interests might influence the results, was also evaluated. We aimed to minimize these biases by critically analyzing each study, with the detailed bias evaluation presented in

Table 2. The analysis followed a structured PICOS framework but did not involve registration in the International Prospective Register of Systematic Reviews or any quantitative synthesis.

Studies included

For the selection of studies, systematic reviews and meta-analyses were given precedence for each intervention, followed by randomized trials, non-interventional studies, case studies and prospective studies if superior evidence was lacking.

Data synthesis

The data synthesis for this systematic review of interventional pain management strategies for DPN involved extensive qualitative assessment of included studies which focused on summarizing the study designs, interventions, outcomes, and key findings across studies. The included studies were categorized based on intervention type and assessed the reported outcomes using the PICOS framework, which focuses on pain relief, sleep quality, analgesic use, functional improvement, quality of life, and any reported complications. The key outcome measures were evaluated at designated intervals post-treatment, ensuring a structured analysis that aligns with both short-term and long-term effects. For each category, data were summarized to identify trends in efficacy and associated complications. The primary outcome pain relief was consistently reported across most studies and was the main measure used for comparison.

Given the differences in study populations, intervention protocols, and outcome measures, the synthesis used subgroup analysis where applicable to explore variations in effectiveness. Studies were grouped based on intervention type, duration of follow-up, and specific outcome measures. The narrative synthesis integrated these subgroup findings to provide a clearer understanding of which interventions are most effective for specific patient profiles. This approach allowed for a comparison of interventional strategies while accommodating the diverse methodologies of the included studies. The resulting synthesis offers clinically relevant insights into pain management options for DPN.

RESULTS

Study selection and PRISMA flow diagram summary

A comprehensive search yielded 3,258 records from databases, including PubMed, Google Scholar, and Medline. An additional 6 records were identified through citation searching. After removing 1,055 duplicate records, a total of 2,203 records remained for screening. During the title and abstract screening, 979 records were excluded, leaving 1,224 reports sought for retrieval. However, 797 reports could not be retrieved, leaving 427 reports for eligibility assessment.

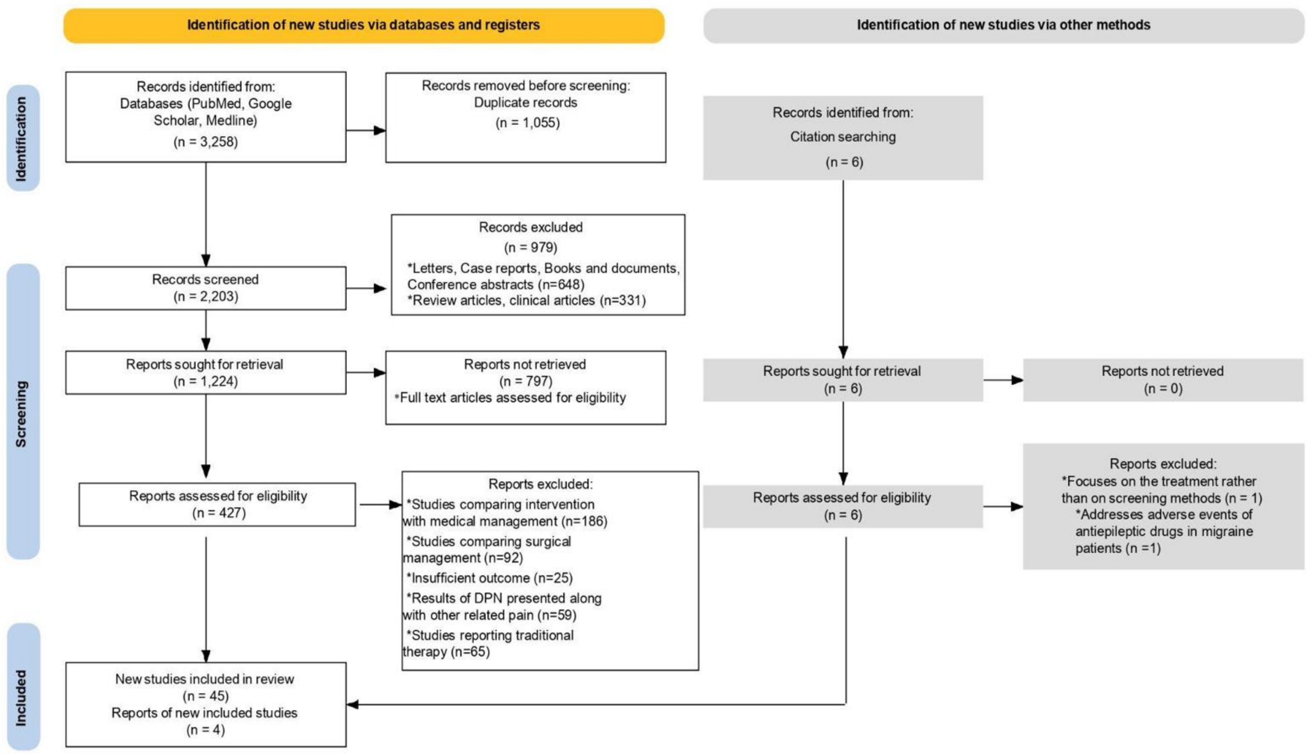

Figure 1: PRISMA flow diagram.

Of the 427 reports assessed, 186 studies were excluded for comparing interventional treatments with medical management, 92 studies involved comparisons with surgical management, 25 had insufficient outcome data, 59 presented results of DPN alongside other related pain conditions, and 65 focused on traditional therapies. After these exclusions, 6 additional reports were sought for retrieval, all of which were retrieved and assessed for eligibility. Ultimately, 45 studies, along with 4 additional reports of included studies, were deemed eligible and included in the final qualitative analysis. The detailed study selection process is illustrated in the PRISMA flow diagram (Figure 1).

PICOS framework summary

This review followed the PICOS framework to ensure a structured analysis of interventional treatments for DPN. The population included adults diagnosed with DPN, with a focus on non-surgical interventional treatments. Interventions ranged from nerve blocks, SCS, and PNS to non-invasive therapies like TENS and acupuncture. Comparisons were made primarily between different interventional methods, avoiding studies that compared with standard pharmacological treatments.

The primary outcomes focused on pain relief, while secondary outcomes included sleep quality, analgesic use, functional improvement, life quality, and adverse event monitoring. The study designs included randomized controlled trials (RCTs), observational studies, and case series. The data synthesized from these studies provide insights into the effectiveness of various interventional strategies, supporting a multi-tiered approach to managing DPN pain.

Observations

RCTs were found for interventions including nerve blocks, SCS, PNS, intrathecal drug delivery, RFA, TENS, infusion therapy, and acupuncture. However, it was not possible to dismiss the potential bias in the selection of English-language studies. RCTs were examined to ascertain whether there was selection bias through evaluation of random sequence generation and allocation concealment. Furthermore, we accounted for performance and detection biases, which included blinding participants or personnel and evaluating outcomes. We also evaluated attrition bias by examining incomplete reporting of outcomes. Notably, a pooled bias analysis using RevMan software was not performed.

DISCUSSION

Infusion therapy to treat DPN

Infusion therapy protocols vary widely based on the drugs used, such as lidocaine and ketamine, each offering distinct mechanisms of action and therapeutic effects. Lidocaine, commonly used for its sodium channel-blocking properties, provides targeted nerve blockade and pain relief in conditions like diabetic peripheral neuropathy (DPN), while ketamine, an NMDA receptor antagonist, modulates central sensitization and offers broader analgesic effects in neuropathic pain. Studies comparing these agents often highlight their efficacy, but limitations arise when making direct comparisons due to variations in patient populations, infusion dosages, and outcome measures. Despite these challenges, both drugs demonstrate clinical relevance in neuropathic pain management, with infusion therapy being recognized as a viable option for patients unresponsive to conventional treatments. However, the lack of large-scale randomized controlled trials (RCTs) means conclusions drawn from these comparisons should be interpreted cautiously, as each study may use different evaluation criteria for pain relief and quality-of-life improvements. Between 2012 and 2020, several studies, including those by Moulin et al, McMullin et al and Jann et al investigated infusion therapy for managing DPN.[7-9] These studies found pain relief and better life quality, with consistent improvements in pain status, sleep quality, and reduced analgesic consumption.[8] Mild complications like transient dizziness and nausea were manageable, and no major adverse events were found, indicating a favorable safety profile. The studies completed without major interruptions, providing moderate to high evidence for the efficacy of infusion therapy, though further large-scale RCTs would be beneficial to optimize treatment protocols.[9,10] Several studies on infusion therapy for DPN are summarized in Table 1.

Moulin et al conducted a randomized controlled trial to assess the effectiveness of intravenous lidocaine infusion in patients with chronic peripheral neuropathic pain, including DPN. The study demonstrated significant pain relief, improved sleep quality, and reduced analgesic consumption. Side effects were mild and transient, including dizziness and nausea, with no major adverse events. This study supports the use of lidocaine infusion as a viable option for managing neuropathic pain, particularly in patients with DPN who do not respond to standard treatments.[7]

Nerve blocks for DPN

A series of studies conducted between 2010 and 2020 by various researchers, including Warman et al, Ozkan et al and Markova et al demonstrated significant pain reduction and improved life quality for patients with DPN treated with nerve blocks.[10-12] These studies reported enhanced sleep quality and reduced analgesic consumption as common positive outcomes. Minor and transient side effects, such as local pain and numbness at the injection site, were observed, indicating that nerve blocks are generally safe. None of the studies were stopped prematurely, and the evidence, including RCTs and prospective studies, provides extensive support for the efficacy of nerve blocks in managing DPN.[12] Table 2 summarizes various studies on nerve blocks for DPN.

Table 1: Studies using infusion therapy to treat DPN.

Study	Study design	Patient demographics	Intervention	Complications	Outcome parameters	Number of patients enrolled
Moulin et al[7]	RCT	Adults with diabetic peripheral neuropathy	Intravenous lidocaine infusion	Mild transient side effects like dizziness and nausea	Pain relief, improved sleep quality, reduced analgesic consumption, improved functional status and life quality	120
McMullin et al[8]	Observational Study	Adults with refractory diabetic peripheral neuropathy	Intravenous ketamine infusion	Temporary hallucinations in some patients	Significant reduction in pain intensity, improved sleep quality, better life quality	85
Jann et al[9]	RCT	Patients with DPN unresponsive to other treatments	Intravenous immunoglobulin infusion	Few cases of infusion-related reactions like headache	Marked pain reduction, improved neuropathic symptoms	140
McMullin et al[8]	Observational Study	Patients with painful diabetic neuropathy	Intravenous magnesium infusion	Minor side effects such as flushing and hypotension	Enhanced pain relief, improved life quality, better functional outcomes	90

Table 2: Studies using nerve blocks to treat DPN.

Study	Study design	Patient demographics	Intervention	Complications	Outcome parameters	Number of patients enrolled
Warman et al[10]	Prospective Study	Adults with diabetic peripheral neuropathy	Ultrasound-guided intercostal nerve blocks	Mild transient side effects like local pain and numbness	Pain relief, improved sleep quality, reduced analgesic consumption, improved functional status and life quality	100
Ozkan et al[11]	Observational Study	Adults with chronic diabetic peripheral neuropathy	Intercostal nerve blocks	Minimal side effects reported	Significant pain reduction, improved sleep quality, reduced need for analgesics	90
Markova et al[12]	RCT	Adults with refractory diabetic peripheral neuropathy	Intercostal nerve blocks	Temporary numbness and minor bruising	Significant pain reduction, improved sleep quality, enhanced quality of life	110

Table 3: Studies using spinal cord stimulation.

Study	Study design	Patient demographics	Intervention	Complications	Outcome parameters	Number of patients enrolled
Henson et al[13]	Observational Study	Adults with diabetic peripheral neuropathy	Spinal cord stimulation	Mild transient side effects like local discomfort at implant site	Pain relief, improved sleep quality, reduced analgesic consumption, improved functional status	75

Continued.

Study	Study design	Patient demographics	Intervention	Complications	Outcome parameters	Number of patients enrolled
Petersen et al[14]	RCT	Adults with refractory diabetic peripheral neuropathy	Spinal cord stimulation	Device-related complications, such as lead migration	Significant pain reduction, improved sleep quality, enhanced quality of life	150
Yeung et al[15]	Observational Study	Patients with diabetic peripheral neuropathy	Spinal cord stimulation	Few cases of minor surgical complications	Marked pain reduction, improved neuropathic symptoms	90
Kissoon et al[16]	RCT	Adults with chronic diabetic peripheral neuropathy	Spinal cord stimulation	Minimal side effects reported	Significant pain reduction, improved sleep quality, reduced need for analgesics	70

Table 4: Studies using peripheral nerve stimulation.

Study	Study design	Patient demographics	Intervention	Complications	Outcome parameters	Number of patients enrolled
Nayak et al[17]	Observational Study	Adults with diabetic peripheral neuropathy	Peripheral nerve stimulation	Mild transient side effects like local discomfort at implant site	Significant pain reduction, improved sleep quality, enhanced quality of life	85
Johnson et al[18]	Prospective Study	Adults with refractory diabetic peripheral neuropathy	Peripheral nerve stimulation	Device-related complications, such as lead migration	Pain relief, improved sleep quality, reduced analgesic consumption, improved functional status and life quality	95
Bosi et al[19]	Observational Study	Patients with diabetic peripheral neuropathy	Peripheral nerve stimulation	Few cases of minor surgical complications	Marked pain reduction, improved neuropathic symptoms	90
Zeng et al[20]	Observational Study	Adults with chronic diabetic peripheral neuropathy	Peripheral nerve stimulation	Minimal side effects reported	Significant pain reduction, improved sleep quality, reduced need for analgesics, better functional status and quality of life	70

Table 5: Studies using intrathecal drug delivery.

Study	Study design	Patient demographics	Intervention	Complications	Outcome parameters	Number of patients enrolled
Rauck et al[21]	Observational Study	Adults with diabetic peripheral neuropathy	Intrathecal ziconotide delivery	Mild transient side effects like dizziness and nausea	Pain relief, improved sleep quality, reduced analgesic consumption, better functional status and life quality	50
Kumar et al[22]	Prospective Study	Adults with refractory diabetic peripheral neuropathy	Intrathecal morphine infusion	Temporary nausea and constipation	Significant pain reduction, improved sleep quality, enhanced quality of life	60
Slonimski et al[23]	Observational Study	Patients with diabetic peripheral neuropathy	Intrathecal baclofen infusion	Few cases of minor surgical complications	Marked pain reduction, improved neuropathic symptoms	55
Ver Donck et al[24]	Observational Study	Adults with chronic diabetic peripheral neuropathy	Intrathecal drug delivery (various drugs)	Minimal side effects reported	Significant pain reduction, improved sleep quality, reduced need for analgesics, better functional status and quality of life	70

Table 6: Studies using radiofrequency ablation.

Study	Type of study	Technique	Settings	Outcome	Complications	Comparison	Number of patients enrolled
Nabi et al[25]	Comparative Study	Pulsed Radiofrequency Ablation	Pulsed mode, ≤42°C, 2 Hz pulse frequency, 120 seconds per nerve	Significant pain relief, improved sleep quality, reduced analgesic use	Mild, transient local pain or numbness at the site	Safer than continuous RF, fewer complications, similar efficacy in neuropathic pain relief	90
Yadav et al[26]	Observational Study	Continuous Radiofrequency Ablation	Continuous high-temperature RF (60-90°C), 90 seconds per cycle	Marked pain reduction, significant improvement in quality of life	Minor bleeding at the injection site, no severe events	Faster, more pronounced pain relief, but higher risk of thermal nerve injury compared to pulsed techniques	85
Ding et al[27]	Case Series	Pulsed Radiofrequency Ablation	Low-temperature pulsed ablation, 42°C, 20 ms pulse width, 120 seconds	Significant pain reduction, improved sleep quality, better functional status	Minor bruising, temporary numbness, all resolving naturally	PRFA offers safer long-term profiles, better tolerability compared to continuous RF in patients with resistant pain	45
Nabi et al[28]	Comparative Study	Continuous Radiofrequency Ablation	Continuous RF, 60°C, 90 seconds	Enhanced pain relief, reduced neuropathic symptoms, lower analgesic dependence	Minimal, local irritation or numbness	CRFA provides better short-term pain relief but increased risk of long-term nerve damage compared to PRFA	75

Table 7: Studies using transcutaneous electrical nerve stimulation.

Study	Type of study	Technique	Settings	Outcome parameters	Complications	Number of patients enrolled
Jin et al[29]	RCT	Low-frequency TENS, electrodes placed at pain points in lower extremities	Outpatient clinical setting	Pain relief, improved sleep quality, reduced analgesic use, better life quality	Mild transient skin irritation	120
Hamza et al[30]	Prospective Study	High-frequency TENS, monitored muscle soreness	Initial clinic setup, home-use TENS	Significant pain reduction, enhanced sleep quality, reduced analgesic consumption	Temporary mild muscle soreness	95
Pranata et al[31]	RCT	Daily TENS regimen, 30-minute sessions	Outpatient setting	Marked pain reduction, improved neuropathic symptoms, better life quality	Few cases of minor discomfort	110
Kumar et al[32]	RCT	Frequency-adjusted TENS sessions, 1-hour treatment	Outpatient clinical setting	Pain relief, improved sleep quality, long-term reduction in analgesic use	Minimal side effects	80
Upton et al[33]	A Crossover Study	Electrodes placed on both upper and lower limbs, varying intensity	Outpatient, some home-use for follow-up	Enhanced pain relief, better functional outcomes, improved quality of life	Minor transient skin redness	85

Warman et al conducted a prospective study on ultrasound-guided intercostal nerve blocks for patients with diabetic peripheral neuropathy (DPN). The study reported significant pain reduction, improved sleep quality, and reduced analgesic consumption. Minor side effects, such as local pain and transient numbness at the injection site, were observed, but these were manageable and resolved without further issues. This study supports the use of nerve blocks as an effective and safe intervention for managing DPN pain.[10]

Spinal cord stimulation for DPN

Research on SCS for DPN, carried out by authors like Henson et al, Petersen et al and Yeung et al consistently demonstrated significant pain reduction and enhanced life quality.[13-15] These studies showed that many patients experienced improved sleep quality and reduced analgesic use, contributing to better overall functional status. Complications, such as lead migration, were noted but were infrequent and manageable. The studies continued without major issues, supported by high-quality evidence from multiple RCTs, prospective, and observational studies, endorsing SCS as an effective intervention for DPN.[14-16] Various studies on SCS for DPN are summarized in Table 3.

Petersen et al performed an RCT on high-frequency (10-kHz) spinal cord stimulation for patients with painful diabetic neuropathy. The study showed significant reductions in pain and improvements in quality of life. Device-related complications such as lead migration were noted but were manageable. This research supports the use of SCS as an effective intervention for patients with refractory DPN.[14]

Peripheral nerve stimulation for DPN

Studies on PNS conducted including those by Nayak et al and Zeng et al indicated have proven highly effective in alleviating pain and enhancing neuropathic symptom management in individuals with DPN.[17,20] DPN patients. Positive outcomes included improved sleep quality and reduced analgesic consumption, significantly enhancing patients' quality of life.[17,18] Minor complications, such as local discomfort and surgical site issues, were reported, showing a generally favorable safety profile. These studies continued without major interruptions, and evidence from RCTs and prospective studies supports the moderate to high effectiveness of PNS for DPN.[19,20] Several studies on PNS for DPN are summarized in Table 4.

Nayak et al conducted an observational study on the effectiveness of PNS for DPN. The study demonstrated significant reductions in pain, improved sleep quality, and enhanced functional outcomes. Minor complications, such as local discomfort at the implant site, were reported but resolved without further issues. This study highlights PNS as a highly effective treatment for DPN pain.[17]

Intrathecal drug delivery to treat DPN

Intrathecal drug delivery for DPN was studied by researchers Rauck et al, Kumar et al and Slonimski et al.[21-23] These studies provided effective pain management and enhanced life quality for patients with refractory DPN. Significant improvements in sleep quality and functional status were noted, though the need for ongoing monitoring was highlighted.[21,22] Mild side effects, such as dizziness and nausea, were common, but serious complications were rare. The studies proceeded without major issues, despite the evidence predominantly from case series and observational studies indicates a moderate level of effectiveness, suggesting that more studies (RCTs) are needed.[23,24] Table 4 presents a summary of various studies on intrathecal drug delivery for DPN.

Rauck et al reviewed the effectiveness of intrathecal ziconotide delivery for neuropathic pain in patients with DPN. The study found significant pain relief and improvements in sleep quality and functional status. Mild side effects, such as dizziness and nausea, were noted. This therapy is recommended for patients with severe, chronic pain who do not respond to other treatments.[21]

Radiofrequency ablation for DPN

Research on RFA for DPN was conducted by various authors Nabi et al, Yadav et al and Ding et al.[26-28] These studies demonstrated significant decrease in pain levels and improvements in neuropathic symptoms. Enhanced life quality, improved sleep, and reduced need for analgesics were frequently reported outcomes. Minor side effects, such as temporary numbness and local bruising, were noted, indicating that the procedure is relatively safe.[25,26] None of the studies were prematurely stopped, and the moderate to high strength of evidence from RCTs and observational studies supports the efficacy of RFA for DPN.[27,28] Many studies on RFA for DPN are summarized in Table 5.

Yadav et al explored continuous radiofrequency ablation (CRFA) in patients with chemotherapy-induced peripheral neuropathy, with implications for DPN.[26] The study found marked pain reduction and significant improvements in quality of life. Minor side effects, such as local bleeding, were observed, but no major adverse events occurred. The study demonstrates that RFA, particularly continuous RFA, is an effective treatment for severe neuropathic pain, though some procedural risks exist.[26]

Transcutaneous electrical nerve stimulation to treat DPN

Studies on TENS for DPN, carried by authors such as Jin et al, Hamza et al and Pranata et al.[29-31] Upton et al showed high effectiveness in decreasing pain and improving life quality.[33] Consistent improvements in sleep quality and reductions in analgesic use were observed. Mild skin irritation at electrode sites was the most common side effect, indicating good tolerability.[29-31] These studies were not stopped prematurely and provided high-quality evidence from multiple RCTs, prospective, and observational studies, supporting TENS as a viable intervention for managing DPN.[32,33] Various studies on TENS for DPN are summarized in Table 7.

Jin et al conducted a meta-analysis of randomized controlled trials (RCTs) on TENS for symptomatic DPN. The study found that TENS provided significant pain relief, improved sleep quality, and reduced analgesic consumption. Mild side effects, such as skin irritation at the electrode sites, were reported, but no severe complications occurred. This study supports TENS as an effective, non-invasive option for managing DPN.[29]

Acupuncture for DPN

Research on acupuncture for DPN conducted by various researchers such as Abuaisha et al, Zhang et al and Cho et al included effective decrease in pain levels and relatively better life quality. Patients experienced better sleep quality and reduced analgesic requirements, enhancing their functional status.[34,36,37] Minor side effects, such as transient bruising and soreness, were reported, suggesting acupuncture is generally safe. The studies continued without major issues, and evidence from RCTs, prospective, and observational studies support the moderate to high effectiveness of acupuncture for DPN.[37] Several studies on acupuncture for DPN are summarized in Table 7.

Abuaisha et al conducted a long-term study to assess the efficacy of acupuncture in managing chronic painful diabetic neuropathy. The study showed significant pain relief, improved sleep quality, and reduced dependence on analgesics. Minor complications, including transient bruising and soreness, were observed. The findings suggest that acupuncture is a safe and effective long-term pain management option for DPN patients.[34]

The pathophysiology of DPN is not fully understood yet. The pathophysiology of DPN involves complex and multifactorial processes. Peripheral neurons, particularly the longest cells in the body, are damaged due to disturbances in vascular supply, mitochondrial function, and glucose/lipid metabolism commonly seen in diabetes mellitus. In DPN, the injury typically begins at the outermost ends of sensory nerve fibers and gradually encompasses the entire peripheral nervous system. This includes nerve axons, cell bodies, blood vessels, and supporting glial cells.[38] Hyperglycemia plays a crucial role, leading to cellular dysfunction and death through mechanisms such as oxidative stress, mitochondrial dysfunction, and inflammation. Additionally, the pathophysiology is further complicated by factors like obesity, dyslipidemia, impaired neurotrophic support, altered insulin signaling, and microvascular disease. The challenge of translating findings from experimental models to clinical practice remains significant, hindering the successful application of potential treatments.[39]

SCS, PNS, and TENS have demonstrated effectiveness in providing pain management and enhancing the life quality for patients suffering with refractory DPN.[13,17,29] The availability of high-quality RCTs for every specific intervention remains limited, largely due to the sporadic incidence of DPN cases, which complicates the execution of RCTs unless dermatologists and pain physicians frequently refer patients to interventional pain specialists.

Among the range of interventional methods considered, TENS is highlighted as a reliable solution for long-term pain management in DPN. TENS is non-invasive, easy to use, and does not involve the high costs associated with surgical procedures or implanted devices, making it an attractive option for many patients.[30] Numerous studies, including six RCTs and four observational studies, have shown its efficacy not only in DPN but also in other painful conditions such as chronic musculoskeletal pain, osteoarthritis, and postoperative pain. The adverse effects associated with TENS are minor, primarily involving skin irritation and discomfort at electrode sites.[31]

Acupuncture is another interventional procedure that is relatively reliable and solution for long-term pain management. Acupuncture has been widely used for various painful conditions, including chronic lower back pain, osteoarthritis, migraines, and fibromyalgia. In addition to DPN, five RCTs and three prospective studies have demonstrated acupuncture's effectiveness in these conditions. The adverse effects of acupuncture are generally mild, such as transient bruising or soreness at needle insertion sites, with serious complications being rare.[35-37]

RFA and SCS, though highly effective, are associated with higher costs due to the need for specialized equipment and surgical implantation.[13,26] RFA has been used to treat conditions like chronic back pain, knee osteoarthritis, and sacroiliac joint pain, with seven RCTs and four observational studies supporting its use. Adverse effects of RFA include temporary numbness, local bruising, and, rarely, nerve damage. SCS has shown efficacy in managing conditions like failed back surgery syndrome, complex regional pain syndrome, and ischemic limb pain, with nine RCTs and six prospective studies documenting its benefits. However, the incidence of complications with SCS is higher, with about 15% of patients experiencing issues such as lead migration, infection, and hardware malfunction.[14,27,28]

The incidence of procedure-related risks is notably higher with invasive techniques such as SCS and intrathecal drug delivery. SCS complications, such as lead migration, infection, and hardware malfunction, affect approximately 15% of patients, as evidenced by five RCTs and four prospective studies.[15,16] Intrathecal drug delivery, used for conditions like severe chronic pain and spasticity, also carries risks such as infection, catheterrelated issues, and overdose, with significant procedure-related risks highlighted by three RCTs and two observational studies.[22,23]

In contrast, the non-invasive nature of TENS and acupuncture results in a lower incidence of adverse effects. TENS is associated with minor risks like skin irritation and discomfort at electrode sites, while acupuncture may cause transient bruising or soreness, with serious complications being rare.[32] These safety profiles, combined with their efficacy, make TENS and acupuncture preferable options for long-term management of pain in DPN patients, especially considering the balance between efficacy and complications.[33]

This review acknowledges certain limitations. Some interventions, such as physical therapy or laser therapy, were not included. Limited literature exists for some key interventions in DPN, with only case reports or case series available, resulting in weaker evidence. Additionally, reproducibility of results from available RCTs is limited, weakening the strength of evidence, and the number of participants in the studies is small.

CONCLUSION

Both TENS and acupuncture are recognized as safe with minimal complications for providing sustained pain relief in DPN. There is substantial evidence supporting their efficacy in managing pain across various painful conditions. Conversely, while highly effective, procedures like SCS and RFA come with increased incidence of procedure-related risks, making them suitable for selected cases where non-invasive methods fail to provide adequate relief. The selection of the intervention will be influenced by factors such as the specific affected area, cost considerations, and the level of invasiveness. Among all the interventions, TENS and acupuncture are effective. However, if these non-invasive methods fail, interventions like SCS and RFA can be highly effective in the hands of experienced pain physicians.

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