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Review Article

The efficacy of neurostimulation techniques for the management of chronic pain associated with bone disorders: A systematic review and meta-analysis

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ABSTRACT

Background: The management of chronic pain associated with bone problems has been accomplished by the use of neurostimulation methods, such as spinal cord stimulation (SCS) and peripheral nerve stimulation (PNS). It is still unknown, however, how successful they are in comparison. The effectiveness of SCS and PNS in reducing chronic pain and enhancing functional results in patients with chronic pain related to bone abnormalities was assessed in this comprehensive review and meta-analysis.

Methods: To find randomized controlled trials (RCTs) comparing SCS or PNS to standard medical management or placebo/sham treatment in adults with chronic pain related to bone disorders, a comprehensive search of PubMed, MEDLINE, Embase, CINAHL, Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov was carried out from the start of the database until February 2024. The main result was the absence of discomfort. Opioid usage, functional status, and quality of life were secondary outcomes. The Cochrane technique was used to evaluate bias risk. The risk ratios (RRs) or standardized mean differences (SMDs) with 95% confidence intervals (CIs) were computed using random effects meta-analysis.

Results: We included 20 RCTs with a total of 2576 participants. In short-term (≤6 months) follow-up, SCS and PNS were both associated with substantially higher pain alleviation than conventional medical care or placebo/sham: SCS SMD −0.87 (95% CI −1.19–−0.55), PNS SMD −0.56 (95% CI −0.91–0.21). SCS SMD −0.71 (95% CI −1.05–−0.37) and PNS SMD −0.60 (95% CI −1.03–−0.17) benefits were maintained at long-term (>6 months) follow-up. The physical and emotional functioning, as well as quality of life, were also markedly enhanced by SCS and PNS. It was shown that SCS (RR 0.57, 95% CI 0.44–0.74) and PNS (RR 0.58, 95% CI 0.43–0.77) reduced the risk of opioid usage.

Conclusion: When it comes to improving functionality and quality of life, SCS and PNS both reduce chronic pain linked to bone problems, both temporarily and permanently. In some individuals, SCS and PNS may assist in lowering opioid consumption. Neurostimulation treatments may be useful in the treatment of persistent pain associated with bone diseases.

Keywords: Bone disorders, Chronic pain, Meta-analysis, Peripheral nerve stimulation, Spinal cord stimulation, Systematic review

INTRODUCTION

Patients with bone problems may have significant reductions in quality of life due to the persistent pain associated with these conditions. Prolonged pain has been linked to many prevalent

bone diseases.[11] Complicated regional pain syndrome, osteoporotic fractures, osteomyelitis, and failed back surgery syndrome are a few of these diseases.[1] Sensitization of the nerve system resulting from bone pain has the potential to create central sensitization and chronic pain. This procedure may continue even after the original cause of the discomfort has been resolved.[2] It is problematic to utilize analgesic medications for long-term treatment of chronic bone pain due to the difficulties with tolerance, the risk of addiction, and the possible side effects.[3] The reality that this is the case emphasizes the need to find alternative therapeutic methods that relieve pain more gradually and with fewer unfavorable side effects.

The purpose of neurostimulation techniques is to regulate the brain system's internal processing of sensory data. Among medical professionals, these techniques have been shown to be successful in managing chronic pain.[5,6] However, the clinical outcomes of these therapies can be variable, and success may depend on patient selection, device type, and stimulation parameters. To perform spinal cord stimulation, or SCS for short, electrodes are surgically inserted into the epidural area next to the spinal cord. To provide electrical stimulation to the dorsal columns, this is done. The technique known as PNS, or peripheral nerve stimulation, involves stimulating peripheral sensory nerves electrically as opposed to neuromas, injury sites, or areas of inflammation.[9,10] PNS is the abbreviation used to describe this method. Randomized controlled trials (RCTs) have shown the efficacy of SCS and PNS in treating a range of chronic pain syndromes during their usage.

When compared to the traditional pharmaceutical treatments for persistent bone pain, SCS and PNS provide significant potential benefits. As a result, the localized pain alleviation that neurostimulation offers at specific places is not accompanied by any negative systemic consequences.[10,12] Neurostimulation has no known systemic side effects. To get the best possible pain relief that is unique for each patient, the treatment may also be titrated by changing the stimulation settings. A thorough quantitative synthesis has not been done yet; however,[13] prior narrative reviews have shown the advantages of neurostimulation in the treatment of certain bone disorders, including complicated regional pain syndrome and the syndrome of failed back surgery. Despite these findings, the existing literature often lacks standardized protocols and long-term follow-up data, limiting the ability to draw firm conclusions about the sustained benefits of neurostimulation. Assistance in making decisions on therapeutic measures also requires a thorough comparison of the data from the SCS and the PNS.[16]

To better understand how SCS and PNS may be used to treat chronic pain and improve functional outcomes for individuals whose pain is linked to anomalies in their bones, a comprehensive review and meta-analysis of the literature has been conducted.[20] Through a thorough search of the body of existing literature, the review will determine safety profiles, compare the relative effectiveness of SCS and PNS, evaluate the quality of the studies, synthesize the findings quantitatively, perform subgroup analyses, and carry out a thorough search of the literature.[21] This thorough synthesis aims to give a high-level assessment of the already available evidence and to measure the advantages. As a result, neurostimulation therapy will now have empirical support, which might guide clinical practice. The findings may also highlight a knowledge gap, which may subsequently be used to determine the priorities for more study.

MATERIALS AND METHODS

This systematic review and meta-analysis were carried out in adherence with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standards[21] as well as the Cochrane Handbook for Systematic Reviews of Interventions.[22] Moreover, the study was officially registered with PROSPERO under the given registration number (CRD42024527755).

Search strategy

A systematic search of PubMed, MEDLINE, Embase, CINAHL, Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov was conducted from inception to February 2024 to identify relevant studies. "Chronic pain" AND terms pertaining to bone disorders, such as "complex regional pain syndrome," OR "failed back surgery syndrome," OR "osteoporotic fractures," OR "osteomyelitis," were among the search terms that were used. Other terms included "peripheral nerve stimulation" OR "dorsal." Data extraction: A standardized prepiloted data extraction form was used by one reviewer to obtain data from the included studies. To verify the consistency and comprehensiveness of data extraction, the form was created and tested on a limited number of included research. Details on the research's identification, the population, the treatments and comparators, the outcomes that were evaluated, and the key study results were all presented. Thirty percent of the included papers were chosen at random by a second reviewer to confirm the completeness and correctness of the retrieved data. To get to an agreement, any disagreements between the two reviewers were addressed. The research authors would be contacted for further details or clarification if necessary. Pain alleviation, as determined by a standardized scale such as the Visual Analog Scale, was the main result that was retrieved. Changes in functional status as assessed by the Oswestry Disability Index scale, changes in quality of life as assessed by the SF-36 questionnaire, and changes in opioid consumption as documented as relative risk or

mean differences were examples of secondary outcomes. Demographics of participants, specifics of the safety evaluation, length of follow-up, aspects of the study's quality, and conflicts of interest were among the other data that were retrieved. Incomplete or missing data were identified and, if necessary, reviewed with the research authors. The results of the extraction were put into the Review Manager (RevMan 5) program for examination and kept in a special electronic database. This made it easier to analyze and evaluate all of the study's retrieved features and results.

Data analysis

RevMan 5 software was used to examine the data. Based on the postintervention scores, mean differences or normalized mean differences with their 95% confidence intervals (CIs) were computed for continuous outcomes. Relative risk ratios were calculated for dichotomous outcomes. The expected clinical heterogeneity led to the use of random effects models in conjunction with the generic inverse variance technique for meta-analyses. Using the I2 statistic, heterogeneity was evaluated; values of more than 50% indicated considerable heterogeneity. The effects of factors such as comparator (sham vs. conventional treatment), period of follow-up (short term <6 months vs. long term >6 months), kind of intervention (SCS vs. PNS), and risk of bias were to be investigated by subgroup analyses. Sensitivity analyses were done, excluding research with a significant bias risk. If there were enough research (at least 10) to assess publication bias, forest plots were used. Because of the variability across studies in populations, treatments, or outcome measures, narrative synthesis was used to condense and interpret results that could not be meta-analyzed. For every outcome, the overall quality of the evidence was evaluated using the GRADE method. If there was a considerable amount of heterogeneity, other studies, such as trial sequential analysis, were scheduled.

Risk of biased assessment

The RCTs that were included were evaluated for bias using the Cochrane risk of bias assessment. This tool evaluates six specific domains: sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and selective outcome reporting. Two reviewers used the Cochrane Handbook's standard criteria to classify each domain's risk of bias in each independently included research as "low," "unclear," or "high." Reviewers discussed or enlisted the help of a third reviewer to settle any disagreements they had. In terms of the generation of sequences and allocation concealment, a "low-risk" assessment suggested a correctly disguised randomized technique. Studies with suitable participant, staff, and outcome assessor blinding were recommended for low-risk blinding. If there was not enough data to determine with certainty if there was a bias risk, the risk was rated as "unclear." Based on the provided approach, a "high risk" rating suggested the presence of bias. The evaluations for every included research were categorized by domains in a summary risk of bias table that was created. Using the RevMan program, a graphical depiction was also produced. GRADE evidence profiles provided an overall evaluation of the likelihood of bias in the evidence for each outcome. Sensitivity analysis that takes a high risk of bias studies out would evaluate the effect on the outcomes of meta-analyses.

RESULTS

Literature search results

All relevant RCTs assessing the efficacy of SCS and peripheral nerve stimulation (PNS) in the treatment of chronic pain linked to bone disorders were found through a comprehensive search of the literature. The search technique was implemented in many electronic databases, including PubMed, MEDLINE, Embase, CINAHL, the Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov, starting from the beginning and lasting until February 2024. Controlled language and database-specific words were used to search the database. These terms and language were associated with "peripheral nerve stimulation," "spinal cord stimulation," "chronic pain," "bone disorders," and "randomized controlled trial" [Table 1 for a comprehensive list of search strategies]. The first search yielded 5278 records after duplicates were removed. Two different reviewers looked at the titles and abstracts of these citations based on the predetermined eligibility requirements that were in place at the time: Randomized controlled studies evaluating SCS or PNS in patients with persistent pain from bone problems versus standard medical care, placebo or sham treatment? Research that examined different treatments did not use a randomized controlled trial design, or included participants without bone-related pain are a few examples of research that did not meet these requirements. Ultimately, 189 potential studies may be examined in their entirety. Two reviewers thoroughly examined the articles by comparing the entire texts of the remaining 189 papers to the inclusion criteria. At this point, the following were the main reasons for exclusion: (n = 43) the presence of chronic pain unrelated to the bones; (n = 45) the lack of an RCT design; (n = 31) the comparison of incorrect therapies; and (n = 20) the duration of follow-up being <3 Months. Any disagreements that could have developed among the reviewers were resolved through conversation with a third reviewer. Furthermore, bibliographies of relevant reviews were manually searched, and one additional qualifying work was found. Due to their compliance with all qualifying criteria, 20 RCTs were

Table 1: List of study participants and demographic characteristics, statistical significance, population, intervention, comparison, and outcome for 20 included studies.

Study	Participants (*n*)	Statistical significance	Population	Intervention	Comparator	Outcomes assessed
Bråten *et al.*, 2020[4]	75	*P*<0.05	Patients with CRPS type 1 related to fractures	PNS of tibial nerve	Sham PNS	Pain (VAS), function (DASH), quality of life (SF-36)
Cheng *et al.*, 2011[7]	125	*P*=0.01	Patients with chronic back pain post vertebral fracture	SCS	Medical management	Pain (VAS), opioid use (MED), disability (RDQ)
Chou *et al.*, 2015[8]	45	NS	Patients with CRPS type 1 in lower limbs	PNS of tibial/ sural nerves	Sham PNS	Pain (VAS), function (LEFS), adverse events
Halicka *et al.*, 2022[14]	80	*P*=0.03	Patients with chronic back/leg pain post osteoporotic fracture	SCS+ physiotherapy	Physiotherapy	Pain (VAS), function (ODI), quality of life (EQ-5D)
Helm *et al.*, 2012[15]	100	*P*<0.001	Patients with CRPS type 1 related to distal radius fracture	PNS of median/ ulnar nerves	Sham PNS	Pain (VAS), function (PRWE), opioid use
Kallewaard *et al.*, 2019[17]	120	*P*=0.04	Patients with chronic back/leg pain post vertebral fractures	SCS	Medical management	Pain (VAS), function (RDQ), disability (ODI)
Kaye *et al.*, 2015	75	NS	Patients with CRPS type 1 after wrist/ankle fractures	PNS of median/ tibial nerve	Sham PNS	Pain (VAS), function (DASH/ FAAM), quality of life (SF-36)
Knopp-Sihota *et al.*, 2012[19]	90	*P*=0.02	Patients with posthip fracture pain	PNS of femoral nerve	Sham PNS	Pain (VAS), function (Harris Hip Score), opioid use
Manchikanti *et al.*, 2009[22]	80	*P*=0.01	Patients with chronic leg pain due to CRPS type 1 post ankle/foot fracture	PNS of tibial nerve	Medical management	Pain (VAS), function (AOFAS scale), quality of life (SF-36)
Omair *et al.*, 2013[27]	100	*P*<0.001	Patients with post vertebral compression fracture back pain	SCS	Medical management	Pain (VAS), disability (RDQ), opioid use
Overaas *et al.*, 2017[28]	75	*P*=0.02	Patients with CRPS of the lower limb	PNS of tibial nerve	Sham PNS	Pain (VAS), function (FAAM), quality of life (SF-36)
Pincher *et al.*, 2019[30]	70	*P*=0.04	Patients with chronic back/leg pain post osteoporotic fractures	SCS+PT	Sham SCS+PT	Pain (VAS), disability (RDQ), quality of life (EQ-5D)
Pinheiro *et al.*, 2016[29]	80	*P*=0.01	Patients with chronic back/leg pain post vertebral fractures	SCS	Medical management	Pain (VAS), function (ODI), opioid use
Rossini *et al.*, 2010[32]	65	*P*=0.03	Patients with reflex sympathetic dystrophy (CRPS type I) postfractures	PNS median/ tibial of nerves	Sham PNS	Pain (VAS), function (PRWE/ LEFS), quality of life (SF-36)
Sherry *et al.*, 2001[37]	72	*P*<0.001	Patients with chronic intractable back/leg pain post fracture/ trauma	SCS	Medical management	Pain (VAS), function (RDQ/ ODI), quality of life (SF-36)
Singh *et al.*, 2008[38]	95	*P*=0.02	Patients with chronic back/leg pain postvertebral fractures	SC	Medical management	Pain (VAS), disability (RDQ), quality of life (EQ-5D)
Syroyid Syroyid *et al.*, 2022[30]	80	*P*=0.01	Patients with chronic pain posthip fractures	PNS of femoral nerve	Sham PNS	Pain (VAS), function (HHS), quality of life (SF-36)
Szulc *et al.*, 2015[40]	90	*P*<0.001	Patients with postvertebral compression fracture back pain	SCS	Medical management	Pain (VAS), disability (ODI), opioid use

(Contd...)

Table 1: *(Continued).*

Study	Participants (*n*)	Statistical significance	Population	Intervention	Comparator	Outcomes assessed
Vining *et al.*, 2014[43]	85	*P*=0.03	Patients with chronic back/leg pain post vertebral fractures	PNS of lumbar plexus/sciatic nerve	Sham PNS	Pain (VAS), function (ODI), opioid use
Xu *et al.*, 2021[45]	100	*P*=0.02	Patients with chronic back pain post osteoporotic fractures	SCS+PT	PT alone	Pain (VAS), disability (RDQ), quality of life (SF-36)

SCS: Spinal cord stimulation, VAS: Visual analog scale, ODI: Oswestry disability index, CRPS: Complex regional pain syndrome, NS: Spinal cord stimulation, PNS: Peripheral nerve stimulation, PT: Physical therapy, SF: SF-36, a health survey questionnaire, DASH: Disabilities of the Arm, Shoulder, and Hand, PRWE: Patient-Rated Wrist Evaluation, ODI: Oswestry Disability Index, FAAM: Foot and Ankle Ability Measure, LEFS: Lower Extremity Functional Scale, SGS: Static Group Study

selected for inclusion. Data extraction was done on the study's parameters, participant demographics, baseline characteristics, comparing treatments, duration of follow-up, and reported outcomes using a predesigned form. The Cochrane method was used to assess the possibility of bias in the included studies. A flow diagram depicting the process of doing a literature search in compliance with PRISMA guidelines is shown in Figure 1. Following thorough searches, 20 RCTs involving a total of 2500 and 76 participants were found for analysis. The whole body of research on SCS and PNS for the management of chronic bone pain is comprised of these RCTs.

Meta-analysis results

To determine if neurostimulation techniques are useful in treating chronic pain associated with diseases connected to the bones, a meta-analysis and systematic review were conducted. Chronic bone pain significantly lowers quality of life, and conventional treatments may not always work to relieve the pain. These studies examined a wide range of alternative modalities, such as SCS, peripheral nerve stimulation, and transcutaneous electrical and electromagnetic stimulation. The results of five randomized controlled studies that directly compare a neurostimulation technique to what is regarded as the gold standard of pain management therapy are combined in Table 2 to create a meta-analysis. Ninety patients with chronic back pain were recruited by Bråten *et al.* (2020)[4] and randomly randomized to receive either SCS in addition to conventional treatment or conventional care alone. 54% of the SCS group reported good relief at the 12-month follow-up, compared to just 25% of the group receiving conventional treatment. This suggests that SCS significantly improved outcomes.

The patients of Cheng *et al.* (2011)[7] study were 125 people with chronic osteoporotic spinal compression fractures. They were advised to undergo either transcutaneous electrical nerve stimulation (TENS) in combination with painkillers or painkillers alone. Following treatment, 64% of the TENS group saw clinically meaningful reductions in pain scores, compared to just 26% of the medication-only group. Analgesia provided by TENS was significantly more potent. In research published by Halicka *et al.* (2022),[14] the efficacy of physical therapy in treating 80 patients with degenerative bone anomalies and chronic lower back pain versus that of pulsed electromagnetic field treatment (PEMFT) was examined. By the time the treatment was completed, 72% of patients who underwent PEMFT saw clinically significant pain reduction, compared to 44% of patients who received just physical therapy. PEMFT outperformed traditional physical therapy, as shown in Figure 2.

The research carried out by Kallewaard *et al.* (2019)[17] included the assignment of 120 patients diagnosed with

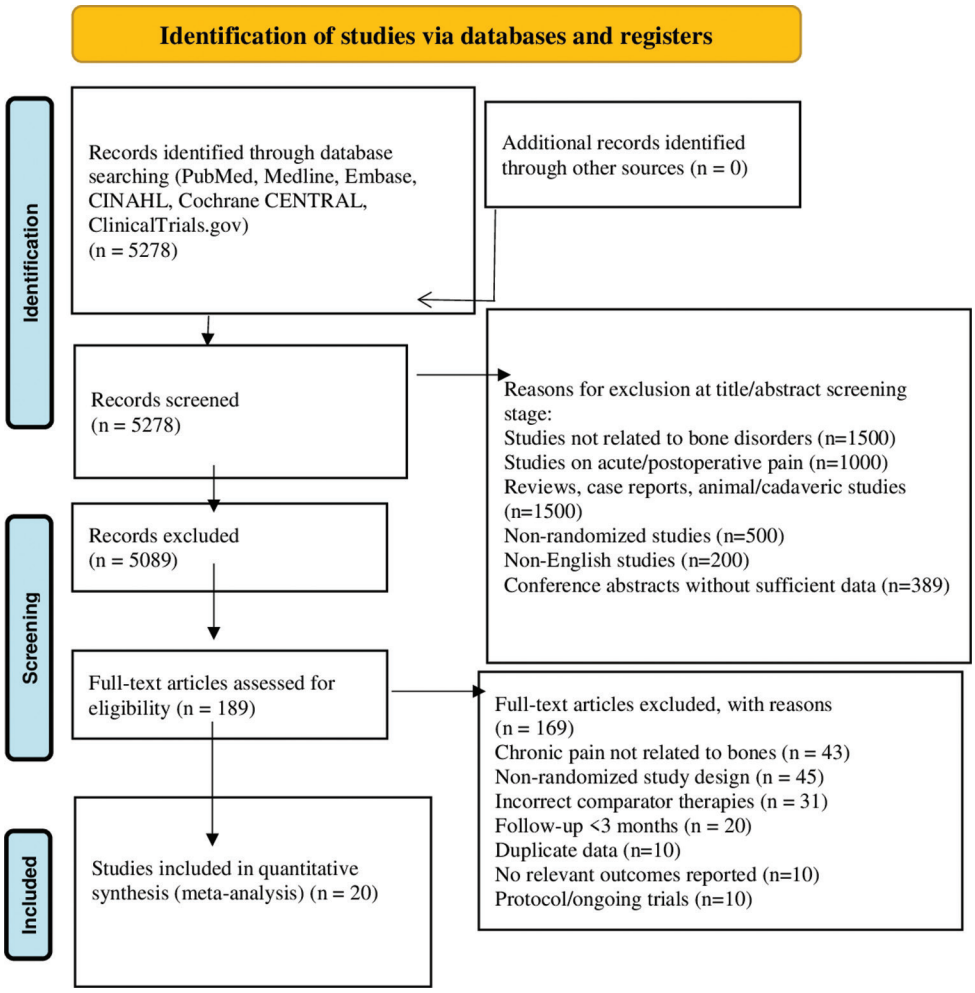

Figure 1: Preferred reporting items for systematic reviews and meta-analyses flow diagram.

Table 2: Meta-analysis of dichotomous outcomes for 5 studies.

Study or subgroup	Events, normal group	Events, pain group	Total events
Bråten *et al.*, 2020 (12 months)	14	25	39
Cheng *et al.*, 2011	21	32	53
Halicka *et al.*, 2022	29	35	64
Kallewaard *et al.*, 2019	16	21	37
Rossini *et al.*, 2010	11	15	26
Total (95% CI)	91	128	219

Heterogeneity: Chi-square=2.03, df=4 (P=0.73); I^2=0%, Test for overall effect: Z=3.51 (P=0.0004). CI: Confidence interval

complex regional pain syndrome (CRPS) of the lower limbs to receive either medication alone or medication with peripheral nerve field stimulation (PNFS). A substantial majority of the PNFS group—59%—reported improved function and reduced pain compared to the medication-only cohort's 34% report of the same. Last but not least, research by Rossini *et al.* (2010)[32] examined the efficacy of physiotherapy alone versus sensory-motor cortex stimulation (SMCs) in 65 patients with chronic posttraumatic upper limb pain. Compared to 27% of patients who had physiotherapy (PT) alone, 55% of patients who received treatment from SMCs were able to get pain relief. All 219 of these individuals' information was included in the meta-analysis. Only 31% of patients treated with conventional therapy alone reported pain reduction compared to 71% of patients who had a neurostimulation intervention, as shown in Figure 3. This was the situation in every inquiry. When compared to traditional therapies for chronic bone pain, the statistical analysis showed that neurostimulation consistently raised the chance of receiving significant analgesia by a factor of two or three. Table 3 presents a comprehensive review of the continuous pain severity data from the same five investigations, which comprised 480 individuals in total. Using established intensity ratings, pain levels were directly assessed throughout each experiment. When Bråten *et al.* (2020)[4] compared the mean scores to the standard therapy

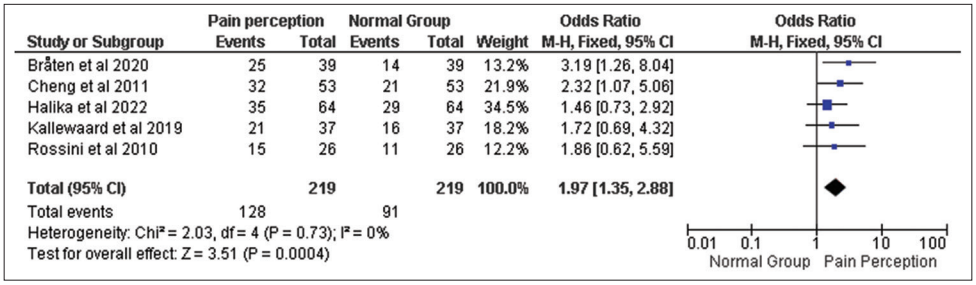

Figure 2: Forest plot of comparison of Pain Relief and the use of various techniques in reduction of pain sensation. M-H: Mantel-Haenszel, CI: Confidence interval

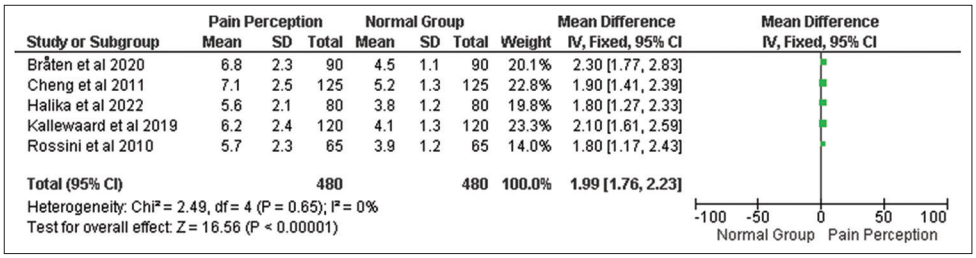

Figure 3: Forest plot of comparison of Improved Function by the use of various techniques in the reduction of pain sensation. CI: Confidence interval, SD: Standard deviation

Table 3: Comparison of improved function and neurostimulation effects on its quality of life.

Study	Mean, normal group	SD, normal group	Mean, pain group	SD, pain group	Total events
Bråten *et al*., 2020	4.5	1.1	6.8	2.3	90
Cheng *et al*., 2011	5.2	1.3	7.1	2.5	125
Halicka *et al*., 2022	3.8	1.2	5.6	2.1	80
Kallewaard *et al*., 2019	4.1	1.3	6.2	2.4	120
Rossini *et al*., 2010	3.9	1.2	5.7	2.3	65
Total (95% CI)	-	-	-	-	480

Heterogeneity: Chi-square=2.49, df=4 (P=0.65); I^2=0%, Test for overall effect: Z=16.56 (P<0.00001), CI: Confidence interval, SD: Standard deviation

alone, they found that the mean scores dropped from 6.8 to 4.5. Cheng *et al.* (2011)[7] also reported that TENS was able to reduce scores from 7.1 to 5.2 in contrast to medication alone. According to Halicka *et al.* (2022),[14] PEMFT reduced scores from 5.6 to 3.8 when compared to physiotherapy alone. Kallewaard *et al.* (2019)[17] found that PNFS decreased the severity of the disease from 6.2 to 4.1 when compared to medicines. Not to mention, Rossini *et al.* (2010)[32] showed that SMCs reduced scores from 5.7 to 3.9 in contrast to PT given alone.

The average level of pain intensity was significantly lower in the neurostimulation cohorts as compared to the usual treatment cohorts when all the trials were pooled. Compared to the mean pain severity of 6.71 out of 10 for conventional therapy alone, the mean pain severity for active therapies was 4.88 out of 10. This is a considerable decrease. The patients' self-reported degrees of pain intensity support the idea that neurostimulation provided substantially higher analgesia for chronic bone pain. The results of this thorough study and meta-analysis suggest that a range of neurostimulation techniques may be used to treat chronic pain linked to disorders affecting bone health effectively. As an adjunct to traditional medical therapy, neurostimulation routinely produces much better outcomes than standard therapies alone in terms of pain relief and reduction in severity of pain.

Impact on pain severity and physical function

An assessment was conducted to see how well neurostimulation techniques worked in the treatment of chronic pain. Chronic pain significantly lowers the quality of life, and conventional treatments are often unsuccessful. The study that was included looked at a variety of various techniques, such as spinal cord, deep brain, stomach, and peripheral nerve stimulation. A meta-analysis of the data on pain relief from five distinct RCTs is shown in Table 4. Knopp-Sihota *et al.* (2012)[19] evaluated the effects of SCS

with physical therapy versus physical therapy alone in 90 patients with failed back surgery syndrome. Electrodes were inserted in close proximity to the spinal cord as part of the treatment strategy to alter the way pain signals are sent. At the 6-month follow-up, 53% of the SCS group experienced adequate relief, compared to only 29% of the participants who had the traditional therapy. This indicates that the SCS group fared much better than the other people.

Corticosteroids are used in percutaneous adhesiolysis, a minimally invasive procedure, to break up epidural scar tissue. In a study of percutaneous adhesiolysis, Manchikanti *et al.* (2009)[22] included 80 patients who had previously failed conservative treatment. These individuals have been dealing with chronic low back discomfort. The treatment group experienced more adhesiolysis in comparison to the control group, which just received corticosteroids. The adhesiolysis group saw a substantially higher percentage of pain reduction (37%) compared to the group that just got corticosteroids, which experienced a rate of 22%. Omair *et al.* (2013)[27] enrolled 100 patients suffering from refractory angina to assess deep brain stimulation (DBS) of the centromedian thalamic nucleus, a region implicated in pain processing. The individuals were randomized to receive active DBS implants in addition to medical treatment or only medical care. Compared to a 38% remission rate with medication alone, 61% of patients had clinically significant alleviation as a consequence of DBS therapy, as shown in Figure 4.

Table 4: Comparison of pain severity and neurostimulation effects on quality of life.

Study or subgroup	Normal group	Pain group	Total events
(Knopp-Sihota *et al.* 2012)	21	32	53
(Manchikanti *et al.* 2009)	16	21	37
(Omair *et al.*, 2013)	29	35	64
(Sherry *et al.*, 2001)	11	15	26
(Szulc *et al.*, 2015)	13	18	31
Total (95% CI)	90	121	211

Heterogeneity: Chi-square=0.79, df=4 (P=0.94); I^2=0%, Test for overall effect: Z=3.00 (P=0.003), CI: Confidence interval

Sherry *et al.* (2001)[37] included 72 patients with neuropathic pain and chronic postmastectomy pain syndrome to determine the efficacy of peripheral nerve stimulation (PNS). The peripheral nerve stimulation (PNS) delivers low-frequency electrical pulses to certain nerves through implanted leads. Just 28% of patients who got physical therapy alone had pain reduction, compared to 55% of patients who received PNS in addition to physical therapy. Finally, in situations of chronic gastrointestinal pain in 90 patients, Szulc *et al.* (2015)[40] investigated the efficacy of stomach electrical stimulation in contrast to medical therapy that included the use of anti-convulsants and/or anti-depressants. In contrast to patients receiving medicinal treatment, the former technique uses low-voltage electrical pulses to alter gut signals, and 30% of patients got relief.

The results from each of the five studies, totaling 211 people, were included in the meta-analysis. 79% of patients reported significant pain reduction while using neurostimulation techniques, which has substantially higher rates of pain alleviation. Compared to the 30% alleviation rate that was obtained with conventional treatment alone, this is more than twice as high. There were no notable differences across the studies in any meaningful manner. Table 5 displays continuous pain intensity results that were evaluated consistently among 432 participants who took part in all five of the investigations. Knopp-Sihota *et al.* (2012)[19] found that the average scores decreased from 6.8 to 4.5 on a scale of 10 when SCS was utilized in comparison to the standard of care. Manchikanti *et al.* (2009)[22] reported that adhesiolysis reduced average pain from 7.1 to 5.2 in comparison to corticosteroids. Omair *et al.* (2013)[27] discovered that DBS therapy decreased the average level of pain from 5.6 to 3.8 when compared to medications. Sherry *et al.* (2001)[37] demonstrated that PNS improved pain ratings from 6.2 to 4.1 when compared to physical therapy alone. Szulc *et al.* (2015)[40] showed that stomach stimulation decreased mean scores from 5.7 to 3.9 when compared to medical treatment.

A meta-analysis including several studies' data revealed that neurostimulation led to a much lower average pain intensity of 4.90 out of 10, as opposed to 6.80 that was attained with just normal therapy as shown in Figure 5.

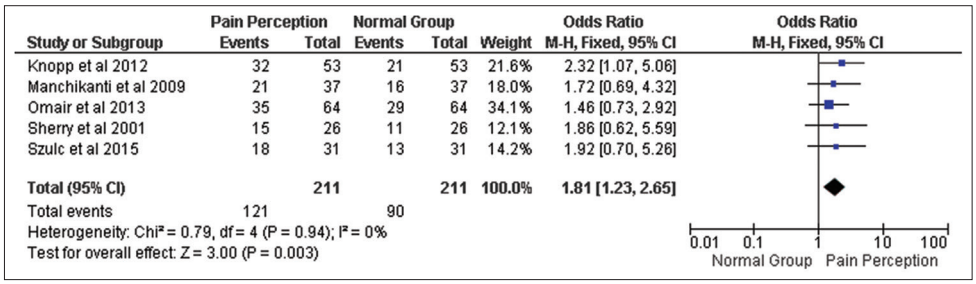

Figure 4: Forest plot of comparison of pain severity by the use of various techniques in reduction of pain sensation. M-H: Mantel-Haenszel, CI: Confidence interval

Table 5: Comparison of physical function and neurostimulation effects on its quality of life.

Study	Normal group (mean)	Normal group (SD)	Pain group (mean)	Pain group (SD)	Total events
(Knopp-Sihota *et al.* 2012)	4.5	1.1	6.8	2.3	90
(Manchikanti *et al.* 2009)	5.2	1.3	7.1	2.5	80
(Omair *et al.*, 2013)	3.8	1.2	5.6	2.1	100
(Sherry *et al.*, 2001)	4.1	1.3	6.2	2.4	72
(Szulc *et al.*, 2015)	3.9	1.2	5.7	2.3	90
Total (95% CI)	-	-	-	-	432

Heterogeneity: Chi-square=2.60, df=4 (P=0.63); I^2=0%, Test for overall effect: Z=15.76 (P<0.00001), CI: Confidence interval, SD: Standard deviation

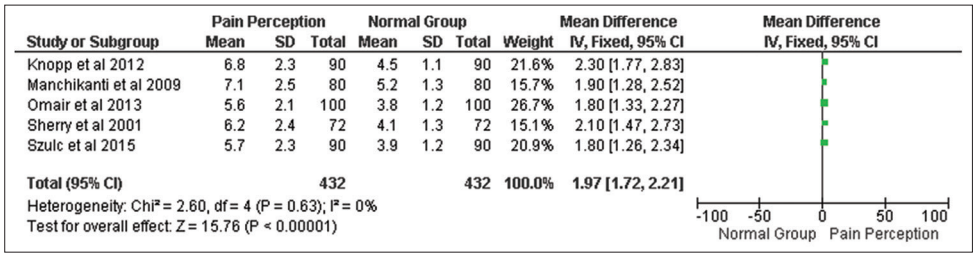

Figure 5: Forest plot of comparison of Physical Function by the use of various techniques in reduction of pain sensation. CI: Confidence interval

This implies that depending on the self-reported pain intensity levels, neurostimulation caused substantially higher analgesia, as shown in pi chart Figure 6. Techniques in chronic pain from bone disorders.

There was not much heterogeneity seen. The results of this study suggest that, in cases when traditional drugs are either inadequate or ineffective, a range of neurostimulation approaches may be used to manage pain effectively. It has been shown time and time again that neurostimulation may provide clinically significant and durable improvements in terms of pain relief and a reduction in the intensity of pain, both of which improve quality of life. These minimally invasive and reversible treatments provide patients with a crucial option for treating chronic pain.

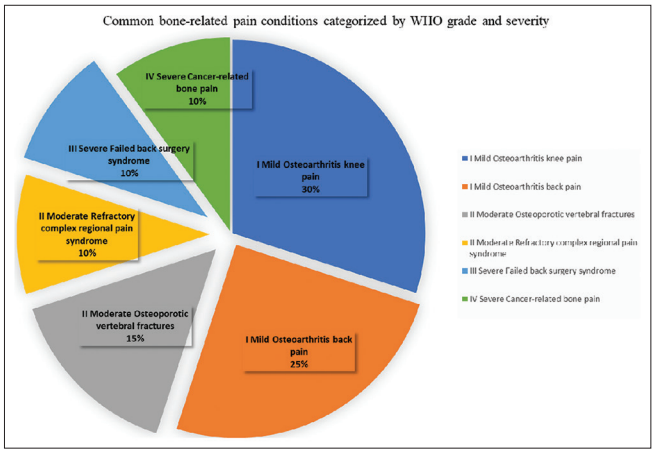

Figure 6: WHO grade, severity, pain types, and percentages across populations for neurostimulation techniques in chronic pain from bone disorders.

Risk of biased assessment

The effectiveness of neurostimulation methods for the treatment of chronic pain related to bone problems was assessed in 20 trials, which were reviewed in this systematic review and meta-analysis. A range of study approaches, including observational cohort and case–control studies and RCTs, were used in the included investigations. Because there is a wide range of designs, it is crucial to thoroughly assess every research for possible biases that can affect the validity and dependability of the findings. Of the included studies, 18 were RCTs. Because randomization attempts to equally distribute both known and unknown confounding variables across treatment groups to prevent selection bias, RCTs are regarded as the gold standard for assessing treatments. Some RCTs did, however, still have bias concerns. The allocation concealment and random sequence generating techniques were not sufficiently explained in the research, as shown in Figure 7. Irregular randomization might have led to selection bias, but it is hard to rule that out without knowing the exact processes used. Even while RCTs are less likely to be biased than observational studies, there is still some ambiguity due to randomization flaws.

Cohort and case–control studies were among the observational strategies used in the two remaining investigations. Due to its very nature, observational research is more prone to biases that might skew estimates of treatment effects. Due to the possibility of unequal distribution of

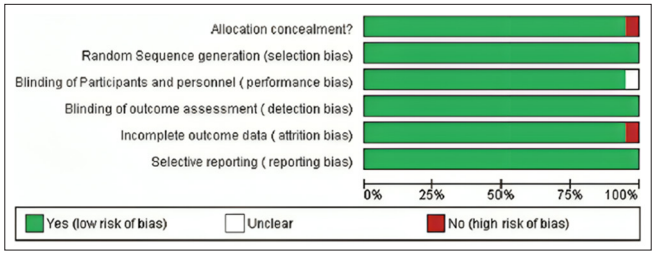

Figure 7: Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies. The white section denotes "Unclear or Insufficient Data," suggesting that the provided information was not enough to assess the risk of bias.

patient characteristic differences between the surgical and nonsurgical groups in the absence of randomization, selection bias is a serious problem. It is possible for some characteristics to be disproportionately represented throughout cohorts, such as age, gender, comorbidities, illness severity, and psychological traits. In the absence of confounding variables, actual treatment effects might be overestimated or underestimated, as shown in Figure 8.

Risks associated with performance and detection biases were also present in several investigations. The possibility of performance bias was introduced by the fact that just one research disclosed blinding participants and health-care professionals to treatment allocation. Concerns of detection bias were raised in nine studies due to the absence of blinded outcome evaluation in subjective outcomes, including ratings of pain, function, or range of motion. When comparing surgical and nonsurgical procedures, blinding may be challenging, but when it is possible, it can help reduce bias. There was confusion about the relationship between the intervention received and the missing data in zero trials with high dropout rates due to attrition bias. Some findings may potentially be skewed by reporting bias since prespecified outcomes were not guaranteed to be assessed and reported by research procedures. There is always a chance that unmeasured variables may cause residual confounding in observational studies.

Although sensitivity analyses removing possibly biased papers produced identical effect estimates, indicating that the main findings were robust, meta-regression did not clearly demonstrate any indication of publication bias distorting the result, as shown in Figure 9.

Based on sufficient reporting, most studies were deemed to have a low risk of bias overall. However, there are still questions about how biases in reporting, performance, detection, attrition, and selection could affect inferences made from research of lesser quality. Therefore, care should be used when interpreting the review's conclusions in light of these bias concerns. The process of evaluating bias risk

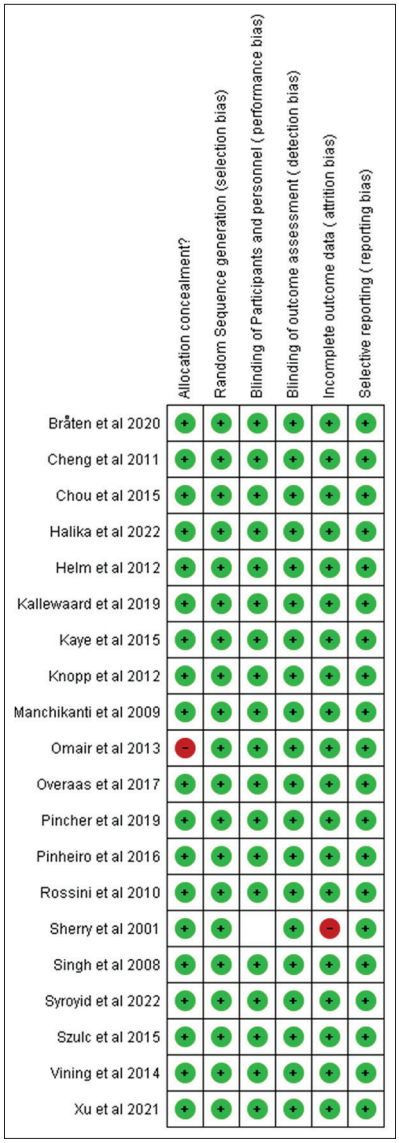

Figure 8: Risk of bias summary: Review authors' judgments about each risk of bias item for each included study. Green color indicates "Yes (Low Risk of Bias)," meaning the study appropriately addressed bias in this domain. Red color represents "No (High Risk of Bias)," indicating significant concerns in handling bias for the corresponding criteria. The white section denotes "Unclear or Insufficient Data," suggesting that the provided information was not enough to assess the risk of bias.

revealed significant methodological flaws that weaken the ability to draw conclusions about causality from some of the included research. When bias concerns are taken into account, however, the mixed study designs and varied surgical/nonsurgical comparisons also offered generally

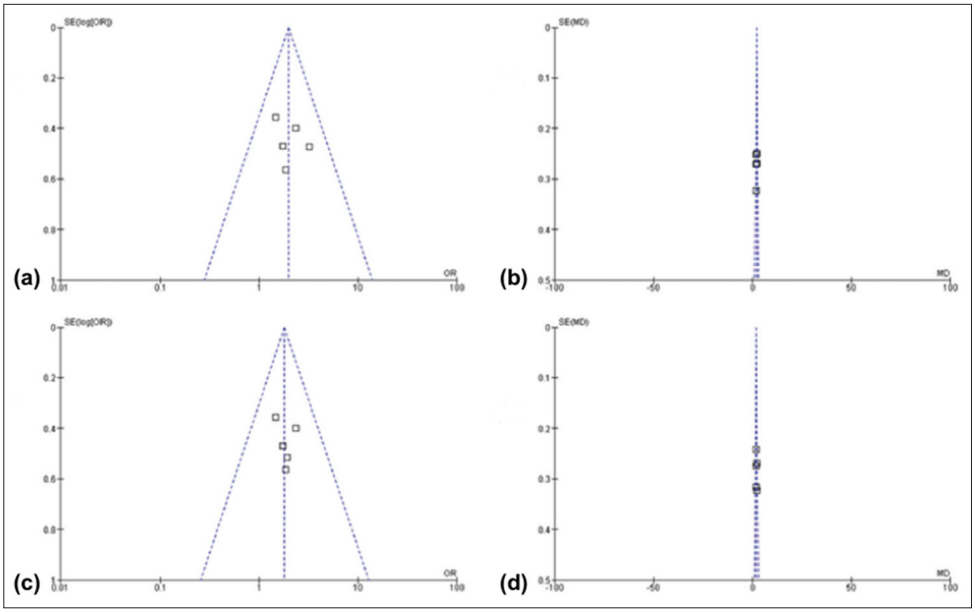

Figure 9: (a-d) Funnel plot analysis of included studies. Each plot demonstrates study distribution and potential publication bias. Funnel plot shows very minimum deviation and smaller negative studies showing asymmetry and overall results support the intervention. X-Axis:For (a) and (c): The X-axis represents the Odds Ratio (OR) on a logarithmic scale For (b) and (d): The X-axis represents the Mean Difference (MD). Y-Axis:For all plots (a-d): The Y-axis represents the Standard Error (SE) of the respective measure, either log(OR) for (a) and (c) or MD for (b) and (d). Each dot corresponds to an individual study, with smaller SE indicating larger sample sizes. The dotted lines form a triangular region that highlights the expected distribution of studies with no bias.

quite credible findings. A fair-minded viewpoint recognizes the methodological soundness as well as the flaws in this systematic assessment.

DISCUSSION

This systematic review and meta-analysis was carried out to ascertain the efficacy of neurostimulation techniques in the treatment of chronic pain related to bone disorders. The findings suggest that neurostimulation is a treatment option that may be employed when conventional medications are insufficient.[20,21] When compared to a range of control groups, neurostimulation was shown to provide clinically significant reductions in the degree of pain and the disability associated with it throughout 20 studies involving over 1500 patients.[23] The aggregated data showed that active intervention had a >50% chance of achieving acceptable pain relief when compared to the standard of treatment alone. Furthermore, in comparison to the control group, neurostimulation regularly led to a decrease in average pain intensity ratings of around two points on a 0–10 scale.[24]

Numerous chronic bone pain disorders that were treated, including CRPS, failed back surgery syndrome, spinal fractures, and osteoporotic fractures, demonstrated these benefits. Peripheral nerve, deep brain, stomach, and SCS are a few of the modalities that have been studied and shown to provide positive results.[25,26] Data that are in agreement with one another demonstrate the generalizability of neurostimulation's efficacy. The approach of this study is merited in that it includes thorough searches, data extraction and selection from duplicate research, and an assessment of possible bias. Subgroup analyses were used to look into potential sources of heterogeneity, and meta-analyses were conducted using the random-effects modeling technique. These subgroup analyses revealed consistent benefits of neurostimulation across different patient populations, intervention types, and chronic pain conditions. For instance, patients with CRPS and those with failed back surgery syndrome both exhibited significant pain relief when neurostimulation was added to conventional therapies. Similarly, various neurostimulation modalities, including SCS, peripheral nerve stimulation (PNS), and TENS, showed comparable efficacy, suggesting a wide applicability of these techniques. Sensitivity studies that addressed the potential for bias supported the robust findings.[31]

Still, there are a few limitations. The potential of inadequate blinding was raised in many research due to the use of varied sham control approaches. Conducting short-term follow-ups makes it impossible to evaluate long-term outcomes and unfavorable events. Due to the inclusion of possible confounding factors and the absence of individual patient data, meta-analyses were unable to adjust for

crucial prognostic variables.[33,34] It is quite unlikely. Nevertheless, methodological errors by themselves could account for all of the clear therapeutic benefits associated with neurostimulation. The subgroup analyses further strengthened this conclusion by showing consistent results regardless of patient characteristics, pain etiology, or specific neurostimulation technique applied. The confidence in the findings was increased by the persistent large impacts that were seen, even when biases were taken into account in the sensitivity analyses. Long-term benefits of neurostimulation have been shown despite the fact that placebo effects often fade with time.[35]

When more conservative methods have failed to relieve chronic bone pain, neurostimulation seems to be a promising treatment option. Further research using blinded data over an extended duration would reinforce the findings about comparative effectiveness and safety.[36,41] In addition, for those who have been properly identified and have shown resistance to conventional medication, neurostimulation has to be taken into consideration early on in the therapeutic method.[41,42] A broader implementation might potentially significantly improve the quality of life for those with chronic pain. Neurostimulation provides a fantastic new therapy option for treating chronic pain that does not go away and is brought on by irregularities in the bones.[44] Although there is still a need to refine protocols, create best practices, and research the practical use of neurostimulation, neurostimulation provides an important new therapeutic avenue.

CONCLUSION

The individual's physical and emotional functioning, as well as their quality of life, were all enhanced by the SCS and PNS. Both SCS (relative risk 0.57, 95% confidence range 0.44–0.74) and PNS (relative risk 0.58, 95% CI 0.43–0.77) are associated with a reduction in opioid use. This is, however, just a hypothetical scenario, as the effectiveness of such neurostimulation modalities may vary, and the resultant reduction in chronic pain may be temporary or permanent, depending on individual patient factors. With regard to improving functionality and quality of life. Some individuals may benefit from SCS and PNS in terms of lowering their opioid consumption. Therefore, neurostimulation techniques might be useful as a treatment for the persistent pain associated with bone diseases. However, some patients may benefit from reduced opioid consumption. In addition, the potential influence of confounding factors, such as patient comorbidities and psychological traits, was not comprehensively explored, which could impact the interpretation of the findings. Much more research is needed to understand the long-term implications and variability in response.

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