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Neurostimulation as a potential modality for transitioning patients with chronic refractory pain syndromes off opioid analgesics: A systematic review

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ABSTRACT

Opioid analgesics are mu-opioid agonists used in practice for pain management which pose significant health risks including, but not limited to, abuse, dependence, respiratory depression, overdose, and death. Medical devices such as spinal cord stimulators (SCS) – which fall under the category of neurostimulators – may offer an alternative method for pain management. Four searches were conducted on PubMed and the Cochrane Trials database to assess the effects neurostimulation has on opioid consumption. Sixty-two (62) unique results originally populated, and six studies out of the 62 results met inclusion criteria. One result was a neurophysiological study which found transcranial magnetic stimulation (TMS) decreased mu-opioid receptor availability ($P < 0.001$), thereby suggesting TMS may activate the release of endogenous opioids. Five results were clinical studies utilizing SCS for chronic pain. These five studies cumulatively enrolled 330 participants, 57 of which were withdrawn and 139 of which were using opioids at the time of enrollment. Following neurostimulation, 41% of participants discontinued opioid use altogether, 26.6% of participants decreased opioid use, 26.6% of participants remained on the same opioid dose, and 5.8% of participants increased opioid use. Overall opioid use decreased by an estimated 45.6% ± 13 following SCS. The median trial duration was 1 year, and the median sample size was 23 participants. Although the results unanimously showed effectiveness for pain control and opioid dose reductions, the studies in this review were small, and none were placebo-controlled. The statistical fallbacks of the five SCS studies make it difficult to draw concrete conclusions. More research is needed to ascertain the risk-benefit profiles of neurostimulators in chronic pain patients.

Keywords: Neurostimulation, Opioids, Spinal cord stimulation, Transcranial magnetic stimulation, Pain management, Chronic pain

INTRODUCTION

Opioid analgesics are drugs used in practice for pain management. These medications exert analgesia by agonizing mu-opioid receptors, therefore decreasing painful sensations. Common opioid analgesics utilized in medicine include oxycodone, hydrocodone, fentanyl, morphine, codeine, and hydromorphone. Opioids are reserved for arduous pain refractory to other pharmacological options because opioids can lead to abuse, dependence, respiratory depression, overdose, and death.[1] In 2021, there were a reported 80,816 opioid overdose deaths.[2] Opioids are often used illicitly outside practitioners' prescribing for self-treatment, euphoria, or both.[1]

Despite their effectiveness, opioids pose a substantial public health risk warranting a need to investigate alternative pain-management methods.

Neurostimulation refers to the use of electricity to stimulate nerves or brain regions implicated in painful sensations.[3,4] Electricity is transmitted to target regions through a medical device, and said medical device is either applied externally or surgically implanted.[3,5] External neurostimulators include a transcutaneous electrical nerve stimulator (TENS) unit – which applies electricity to painful areas[6] – or transcranial magnetic stimulation (TMS) – a device which applies magnetic energy to specific brain regions.[5] Surgically implanted neurostimulators include deep brain stimulation – which is a series of electrodes which stimulate target brain regions[7] – or spinal cord stimulators (SCS) – a device which stimulates components of the spinal cord.[3] Neurostimulators have demonstrated a promising niche in pain management, but their utility is limited.

Neurostimulators and opioids will intersect in this review because as the opioid epidemic continues in the United States (US), the need to transition eligible patients off opioids becomes greater. At present, there are a multitude of neurostimulators indicated for pain management available in the US, giving patients numerous avenues for pain management. As of August 18, 2022, more than 1400 neurostimulators for treating pain have been authorized by the Food and Drug Administration (FDA) according to the 510(k) Premarket Notification, *de novo*, and Premarket Approval databases.[7-11] The authorized neurostimulators were identified by pinpointing all relevant product codes and then searching each database under each product code. Product codes are used by the FDA to help identify a generic category of a medical device.[12,13] This repository of neurostimulators demonstrates a growing field of non-pharmacotherapeutic options for patients with acute or chronic pain. Not all neurostimulators are equal; each neurostimulator has its own unique attributes, effectiveness profile, and safety profile. As a result, some neurostimulators may have greater potential for helping patients than others, thereby creating the theoretical possibility that there is at least one effective neurostimulator for everyone somewhere on the market. If a neurostimulator is effective for a patient, it would hopefully provide pain relief to an extent such that opioid consumption is decreased or eliminated.

This review will henceforth serve as a literature review identifying clinical studies which address the effects neurostimulation has on opioid consumption. Collecting this information could suggest a role for neurostimulation in opioid cessation or opioid dose reduction. Transitioning from opioids to neurostimulation is a gap in care which requires more understanding. This review seeks to bridge that gap.

METHODS

Four searches were conducted on PubMed and the Cochrane trials database between August 18, 2022, and August 22, 2022, yielding 62 unique results. On PubMed, the searches were "neurostimulation and opioid consumption," "("Implantable Neurostimulations" [Mesh]) AND "Analgesics, Opioid"[Mesh]," and "("Neurostimulators") AND ("Opioids")." In Cochrane trials, the following search was conducted: "opioid in Title Abstract Keyword AND neurostimulator in Title Abstract Keyword – (Word variations have been searched)." Among the 62 results, 35 were relevant to neurostimulator-induced non-migraine pain control based on titles alone. These 35 entries were narrowed further by reading abstracts and/or full-body texts to eliminate articles which either did not meet inclusion criteria or met exclusion criteria. Each entry was evaluated for bias using the Cochrane Risk of Bias 2 tool. Articles were included if they were retrospective or prospective clinical studies, randomized controlled trials, or multi-case reports which assessed effects of neurostimulation on opioid consumption in humans. Articles were excluded (1) if neurostimulators were not being used for pain, (2) if they were commentaries or single case reports (one patient), (3) if they were protocols, or (4) if they were about neurostimulation used for acute pain (i.e., post-operative). After narrowing results based on inclusion-exclusion criteria, the remaining articles were reviewed and key points extracted for inclusion in the results.

RESULTS

Six search entries met all criteria for inclusion in the results. [Table 1] illustrates reasons why search entries were excluded from the final analysis. The six results consisted of three prospective clinical trials,[14-16] one retrospective study,[17] one study comprising three case reports,[18] and one prospective neurophysiological study which assessed mu-opioid receptor availability before and after TMS.[19] There were 273 participants included in final analyses with 139/273 (50.9%) using opioids before enrollment into their respective studies. Five studies analyzed opioid consumption as a primary or secondary outcome, and the neurophysiological study analyzed the effects neurostimulation has on opioid receptors.

Upon evaluating the study results, 57/139 (41%) participants discontinued opioid use altogether, 37/139 (26.6%) participants decreased opioid use, 8/139 (5.8%) participants increased opioid use, and 37/139 (26.6%) participants reported no change in opioid use. De Caridi *et al.* quantified "decreased" opioid consumption as a >50% reduction;[18] the remaining studies did not specify the amount by which participants decreased or increased their opioid doses. Assuming a decrease in opioid use translated to a reduction of 50% from baseline

Table 1: Distribution of excluded search results.

Reason for exclusion	Number of articles excluded
Review article, single case report, protocol, or commentary	16
Did not focus on neurostimulation	10
Did focus on neurostimulation	
Used for a pain indication	
No mention of effects on opioids	8
Used for acute pain	8
Used for migraine/headache	1
Not being used for pain	13
Total excluded	56 out of 62

(range 10–90%) and an increase in opioid use meant an increase of 50% (range 10–90%), overall opioid use among the 139 opioid users decreased by an estimated 45.6% ± 13 after neurostimulation. It is noteworthy that the aforementioned results reflect participants who successfully completed a trial. There were 330 participants before each study's completion. Forty-seven (47) participants withdrew before final analyses due to complications or lack of effectiveness, and 10 participants were lost at follow-up.[14,16] This translates to 17.3% (57/330) of participants failing to complete a study.

On average, 30% of participants per study lowered their opioid dose from baseline following neurostimulation (range 21–43.5%). Some participants remained on their original opioid dose; this was reported in three studies. The mean rate of participants remaining on the same opioid dose after neurostimulation was 17.9% per study (range 0–38%) and 29.8% per study among the three studies which reported the result. The two studies which did not report any participants continuing the same dose had sample sizes of three and 14.[15,18] Four studies reported some participants discontinued opioid use wholly after neurostimulation. On average, 46.4% of participants per study discontinued opioid use completely (range 0–71.4%), and 58% of participants per study among the four studies which reported the result discontinued opioid use altogether. McRoberts *et al*. did not report any participants who stopped taking opioids, and McRoberts *et al*. had a sample size of 23.[16] These results are summarized in [Table 2].

[Table 3] highlights details of the six results. Among the six studies, five utilized SCS technology, and one used TMS. Lamusuo *et al*. used TMS technology to determine effects TMS has on mu-opioid receptor availability; participants in this trial were otherwise young (age range 21–32 years) and healthy.[19] All five SCS studies reported statistically significant reductions in pain scores following SCS implantation. It is unclear what proportion of participants who reported substantial pain relief also decreased opioid use and to what extent. Various pain syndromes were treated across these studies including lower back pain due to multifidus dysfunction, cancer-related chest wall pain, phantom limb pain, failed back surgery syndrome, knee pain, and arm pain.[14-18] The median sample size was 23 participants (range 3–156).

Only Gilligan *et al*. and McRoberts *et al*. reported adverse events following SCS implantation.[14,16] Both trials reported infection, device migration, surgical revisions, and device removal due to complications or lack of effectiveness. McRoberts *et al*. published their study in 2013, and there were 45 adverse events reported with 32 participants (1.4 adverse events per participant).[16] Gilligan *et al*. published their study in 2021, and there were 56 adverse events reported with 204 participants (0.28 adverse events per participant).[14] The rate of adverse events per participant is 400% higher in McRoberts *et al*. than in Gilligan *et al*, therefore suggesting either an improvement in technology and/or technique over the past decade.

The median trial duration was 52 weeks (range 2–104 weeks). The mean age among the studies was 62.2 years (range 38–77 years). About 52.5% of all participants were female. Only McRoberts *et al*. identified race demographics of their trial population (all Caucasian, $n = 23$).[16] Two studies revealed the mean body mass index of their participants, and this was 28.1 kg/m^2 ± 4 between both studies.[14,17] In all studies, participants had failed to previously attain adequate pain relief from conventional modalities including, but not limited to medication therapy, intercostals/epidural steroid blocks, surgery, physical therapy, chiropractic medicine, TENS units, acupuncture, and massage. Two trials specified the mean duration of pain participants endured before receiving an implantable neurostimulator: 14 pain years ± 10.6[14] and 13.9 pain years ± 12.2.[16]

DISCUSSION

The results demonstrate that SCS has potential to reduce or stop opioid use among patients with chronic pain syndromes. Lamusuo *et al*. proposed that TMS at the M1/S1 cortex may invoke a release of endogenous opioids, but this theory was merely a suggestion for future research.[19] This theory along with the significant findings from the other five study results suggest neurostimulation may decrease or eliminate opioid use in pain patients by providing adequate pain relief and/or activating endorphins.[14-19] All studies found significant decreases in opioid use and significant reductions in pain scores, but the linearity of pain score versus opioid consumption is uncertain in all but two studies. The two studies in which complete linearity could be found ($n = 3$ and $n = 14$) were not reporting linearity as an outcome; rather, regression was found coincidentally through *post hoc* analysis.[15,18] Pain score changes and opioid consumption changes were assessed independently among the studies.

Table 2: Overview of effects SCS implantation has on opioid consumption.

Outcome	No. of participants (%)	No. of studies that reported result ("R")	Average rate per study [Σ(%)/5]	Adjusted average rate [Σ(%)/R]
Decreased dose	37/139 (26.6)	5	30%	30%
Stopped altogether	57/139 (41)	4	46.4%	58%
Increased dose	8/139 (5.8)	2	1.4%	3.4%
No change in dose	37/139 (26.6)	3	17.9%	29.8%

The average rate per study indicates the average percentage of participants who experienced a particular result in any of the studies. This was produced by calculating the rate of each particular outcome for each of the five studies, if present (ex: 25% of participants reduced their dose). These rates were summed and then divided by the listed denominator. If participants decreased their opioid dose by an average of 30% per study, this means that, on average, 30% of participants reported a decreased opioid dose in any given study. The studies are listed in [Table 3]. No.: Number; Σ: Sum

Table 3: Summary of the study designs, devices, outcome measures, and pertinent results.

Author (s)	Risk of bias	Trial design	Outcome measure (s)	Key results
Lamusuo *et al*. (2017)[19]	Low risk	Randomized, double-blind, sham-controlled crossover neurophysiological study *n*=10 healthy participants Duration of neurostimulation: 2 days Device: eXimia NBS navigation system and eXimia TMS stimulator utilizing (Nexstim) focal bipulse 8-coil to administer biphasic pulses	The purpose of the trial was to study effects of M1/S1 cortex TMS on dopamine D2 and mu-opioid receptor availabilities. Receptor availabilities were determined by injecting participants with [^{11}C] carfentanil after TMS or sham treatment. Participants underwent PET scans before and after TMS/sham treatment to determine if any changes in receptor availabilities	Mu-opioid receptor availability decreased by a mean of 7.2% and 8% in the right and left hemispheres, respectively, after TMS vs. sham (P<0.001). There were no differences in dopamine D2 receptor availabilities. The authors suggested this could indicate TMS stimulates release of endogenous opioids involved in pain relief. No adverse events reported
Gilligan *et al*. (2021)[14]	Unclear risk	Multicenter open-label clinical trial *n*=204 participants with chronic lower back pain Duration of neurostimulation: 2 years 156 participants completed 2-year follow-up Device: Reactive implantable neurostimulation system	Seven-day recall of average low back pain Percentage of pain relief Lower back pain resolution Medication usage Safety and adverse events	All outcomes were statistically significant (P<0.001). Lower back pain scores decreased by a mean of − 4.8cm on VAS vs. baseline. 72% of participants reported a ≥50% reduction in pain scores vs. baseline; the mean pain score reduction was 85%. 67% of participants had resolution of chronic lower back pain. 39% of participants using opioids discontinued opioid use. 21% of participants using opioids reduced their opioid dose; 2% of participants increased their opioid dose. Adverse events (≥1%): infection (2.9%), removal due to lack of effectiveness (8.8%), removal due to MRI (2.9%), and revision needed to replace or reposition device (7.4%)
Yakovlev *et al*.(2010)[15]	Unclear risk	Multicenter open-label clinical trial *n*=14 cancer survivors with cancer-related chest wall pain Duration of neurostimulation: 1 year Device: (Medtronic) 8-electrode epidural leads with RestorePRIME or RestoreULTRA generators	Pain reduction vs. baseline on the VAS Opioid use vs. baseline Safety and adverse events	All participants reported a ≥50% reduction in pain scores. Nine participants used the device around the clock; five participants used the device only during day hours. Four participants (28.6%) reduced their opioid dose vs. baseline. 10 participants (71.4%) discontinued opioid use altogether. One participant continued using pregabalin and lidocaine topical patches. No adverse events reported

(Contd...)

Table 3: *(Continued)*

Author (s)	Risk of bias	Trial design	Outcome measure (s)	Key results
De Caridi *et al.* (2016)[18]	Not applicable	Case reports Three patients who have failed "intensive' pharmacotherapy for phantom limb pain and critical limb ischemia Duration of neurostimulation: 3 months Device: (Nevro) SCS system	Reduction in pain scores on visual analog scale Increase in RPI vs. baseline Opioid use vs. baseline	All patients reported a >50% decrease in pain scores after implantation of the device to approximately 30/100 mm. All patients reported an increase in RPI (0.21–0.27–0.4–0.41). Two patients stopped opioids altogether; one patient reduced their opioid dose by > 50% vs. baseline.
McRoberts *et al.* (2013)[16]	Low risk	Randomized, crossover clinical trial *n*=32 participants with chronic intractable back pain Duration of neurostimulation: 1 year 23 participants completed the trial Device: (St. Jude Medical) Quattrode, Octrode, and/or Eon	Reduction in pain on the VAS vs baseline Quality of life assessed by the short form-36 Participant satisfaction Medication dosage and frequency Safety and adverse events	Pain scores decreased from a mean of 7.8–3.4–4.6 across four follow-up visits (p<0.001). 65.2% of participants reported a ≥30% reduction in pain score from baseline at 1 year. The mean baseline PCS score for quality of life was 16.9/60; this increased to 25.3–27.8 (P<0.001). At 1 year, 90.9% of participants were satisfied with the procedure and would undergo it again. Five participants increased their opioid dose from baseline. Ten participants decreased their opioid dose; eight participants remained on the same opioid dose. Adverse events: lead migration (15.6%), surgical site complications (13.3%), subcutaneous infection (4.4%), unintended stimulation effect (11.1%), diminished or loss of therapy (22.2%). 28.9% of adverse events required an additional surgery.
Barpujari and Erdek (2020)[17]	Low risk	Retrospective cohort analysis *n*=67 participants with either failed back surgery syndrome, back pain, knee pain, and/or arm pain Duration of neurostimulation: 14 days Device: various SCS devices	MED before and after intervention	There was no difference in MED dose reductions between participants who underwent a 7-day trial and participants who received a permanent implant. The mean MED before intervention was 40.32 ± 8.11. The mean MED after intervention was 15.84 ± 4.71. The adjusted change in MED was -23.87 (P<0.001).

N: Number of participants, NBS: Navigated brain stimulation, [^{11}C], radioisotope of carbon, M1: Primary motor cortex, S1: Primary somatosensory cortex, D2: Dopamine-2, PET: Positron emission tomography, p: Probability value, cm: Centimeter, VAS: Visual analog scale, MRI: Magnetic resonance imaging, RPI: Regional perfusion index, mm: Millimeter, PCS: Physical component summary, MED: Morphine equivalent dose, vs.: Versus

Seventy-two percent (72%) of participants from the trial published by Gilligan *et al.* (n = 156) reported 50% or greater reduction in pain, but only 60% decreased or stopped opioid use. In this case, 12% of participants who reported ≥ 50% pain reduction either continued their opioid dose or increased their opioid dose.[14] McRoberts *et al.* (n = 23) reported 65.2% of participants experienced ≥ 30% reduction in pain at 1 year, but only 43.5% lessened their opioid dose.[16] Barpujari and Erdek only assessed changes in morphine equivalent doses and not pain scores.[17] It is unclear (1) how many participants improved their pain but did not decrease their opioid dose or (2) how many participants neither alleviated their pain nor reduced their opioid dose. It is worth noting that opioids are only available by prescription in the US. For a patient to decrease or stop their dose, the practitioner and patient would need to come to a mutual agreement, or the prescription would have as-needed instructions on the label, or the participant would need to decrease their dose against prescription instructions. Opioids also have a potential for misuse and addiction, thereby posing as a challenge for dose tapering for some participants, especially those with addictive tendencies.[1,20]

It is difficult to draw conclusions from these results due to the varying ages and sample sizes of the studies. For instance,

sample sizes of 3, 14, and 23 will likely not produce the same statistical power as a sample size of 156. However, two studies – including Gilligan *et al*. who had the sample size of 156 – were deemed to have an unclear risk of bias, therefore making the significance of their results harder to determine. Statistical significance aside, SCS overall has uncertainty surrounding its effectiveness. Implantable SCS first became available in 1981, and technology has advanced since then.[21] Older technologies and techniques may not be as effective as more modern ones. Despite this, Ferraro *et al*. wrote in a 2022 review that safety and effectiveness of SCS remains largely uncertain. Ferraro *et al*. reviewed 15 randomized controlled clinical trials cumulatively enrolling 908 participants who received SCS for pain. Among these 15 trials analyzed by Ferraro *et al*., five were open-label – which the authors indicated had "inevitable limitations" – and 10 were blinded. The authors found six of the 10 blinded studies produced "small effects."[22]

The results of this review and reviews like that of Ferraro *et al*. reveal inconsistencies surrounding the safety and effectiveness of SCS. Garcia, Wray, and Kumar also acknowledged the information paucity surrounding SCS, writing "most of the studies that currently exist regarding SCS therapy are either small prospective studies or retrospective studies."[23] With a median sample size and duration of 23 and 1 year, respectively, results from this review may lack statistical power to ascertain solid long-term conclusions even though all five studies produced substantial results. In addition, this review sought to evaluate neurostimulation broadly but instead only reviewed SCS. Although all neurostimulators stimulate nerves with electricity,[3] it is impossible to assume all neurostimulators are equal without further comparison. The neurophysiological study by Lamusuo *et al*. shows promising potential of TMS in replacing opioids for pain, but more research is needed.[19] Finally, there were two open-label trials and one study presenting case reports, and these types of studies are not as powerful as randomized controlled trials.

Producing a randomized controlled clinical trial with implantable neurostimulators is burdensome but possible.[22] Implantable neurostimulators have inherent risks – such as lead failure, lead migration, absent effectiveness, infection, and the need for additional surgeries – as highlighted in [Table 3]. Surgically inserting a sham device may arguably have ethical considerations given the risks of surgery, the risks of complications, and the fact that participants with extensive unresolved pain are proceeding without treatment.[24-26] Notwithstanding the liabilities of placebo-controlled implantable neurostimulation trials, Duarte *et al*. found 12 sham-controlled SCS clinical trials between February 2018 and January 2019. The median sample size among the 12 trials was 24 participants (range 10–68), and the median placebo duration was 2 weeks (range 12 h–26 weeks). Duarte *et al*. emphasized validity and replicability concerns of the 12 trials attributed to small sample sizes and short durations as well as issues with reporting transparency.[27] Placebo-controlled non-invasive neurostimulator trials (like TMS or TENS units) could circumvent surgical and ethical problems of invasive neurostimulator trials.

Although not evaluated in this review, it is important to briefly highlight the safety and effectiveness of TMS and TENS units for completeness. Goudra *et al*. published a meta-analysis in 2017 which sought to assess the effectiveness of repetitive TMS from nine clinical trials. Across the nine trials, the mean reduction in pain score was −1.12 from TMS versus −0.28 from sham ($P < 0.001$). There were no significant adverse events reported. The duration and frequency of TMS was variable.[28] Yang and Chang further validated claims of effectiveness in a systematic review of 106 trials by finding TMS demonstrates widespread effectiveness with few adverse events, but long-term effectiveness (>3 months) and the extent of pain relief remain unclear.[29] Vance *et al*. wrote in a review that the data on TENS units' effectiveness are conflicting but promising, and, like TMS, there are fewer adverse events reported versus opioids.[30] The mechanism of action of TENS units is not fully elucidated, but anecdotal reports from patients suggest it can be effective.[31,32] There have been reports of "TENS tolerance" where overuse of TENS units results in diminished effects.[33]

Overall, neurostimulation has demonstrated at least some effectiveness for pain management and opioid dose reduction. All studies in this review produced statistically significant results favoring opioid dose reductions and/or pain management. There is a vast array of literature describing the effectiveness of invasive and non-invasive neurostimulators for pain, but many studies lack statistical power necessary to make sound suggestions for future use. This review did not investigate other neurostimulation devices outside of SCS which makes it difficult to produce any conclusions for any devices other than SCS (and minimally TMS). A deeper review utilizing more databases and less stringent inclusion-exclusion criteria may be necessary to identify more research. The dangers of implantable neurostimulators also identify the need to investigate noninvasive neurostimulators in more detail.

CONCLUSION

SCS successfully resulted in decreased opioid use across all the studies evaluated, and this reduction in opioid use can be attributed to better pain management. Despite the positive findings, the studies assessed in this review were mostly small in sample size, and several were either open-label or case reports. Due to the statistical limitations of the studies, it is difficult to draw a certain conclusion on the effectiveness

for SCS, TMS, and other neurostimulators for pain. With the current epidemic in opioid overdose deaths, the use of medical devices for pain management may become an option for some patients. Neurostimulators like SCS have promising potential for the future of pain management, but more randomized, controlled research is needed to evaluate the long-term safety and effectiveness profiles of these devices. In the future, hopefully, there will be more succinct approaches for addressing which patients would be the most suitable candidates for specific types of neurostimulation.

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Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

REFERENCES

1. Trescot AM, Datta S, Lee M, *et al*. Opioid pharmacology. *Pain Physician*. 2008;11:S133-S153.
2. Centers for Disease Control and Prevention. U.S. Overdose deaths in 2021 increased half as much as in 2020-but are still up 15%. CDC. Available from: https://www.cdc.gov/nchs/pressroom/nchs_press_releases/2022/202205.htm [Last accessed on 2022 Aug 22].
3. Provenzano DA, Heller JA, Hanes MC. Current perspectives on neurostimulation for the management of chronic low back pain: A narrative review. *J Pain Res*. 2021;14:463-479. doi:10.2147/JPR.S249580
4. Edwards CA, Kouzani A, Lee KH, *et al*. Neurostimulation devices for the treatment of neurologic disorders. *Mayo Clin Proc*. 2017;92:1427-1444. doi:10.1016/j.mayocp.2017.05.005
5. Hamid P, Malik BH, Hussain ML. Noninvasive transcranial magnetic stimulation (TMS) in chronic refractory pain: A systematic review. *Cureus*. 2019;11:e6019. doi:10.7759/cureus.6019
6. Teoli D, An J. Transcutaneous electrical nerve stimulation; 2022. Available from: https://pubmed.ncbi.nlm.nih.gov/30725873 [Last accessed on 2022 Aug 22].
7. Aum DJ, Tierney TS. Deep brain stimulation: Foundations and future trends. *Front Biosci* (*Landmark Ed*). 2018;23:162-182. doi:10.2741/4586
8. U.S. Food and Drug Administration. 510(k) premarket notification. Available from: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm [Last accessed on 2022 Aug 22].
9. U.S. Food and Drug Administration. Device classification under section 513(f)(2) (De Novo). Available from: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/denovo.cfm [Last accessed on 2022 Aug 22].
10. U.S. Food and Drug Administration. Premarket approval (PMA). Available from: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm [Last accessed on 2022 Aug 22].
11. U.S. Food and Drug Administration. Product classification. Available from: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpcd/classification.cfm [Last accessed on 2022 Aug 22].
12. U.S. Food and Drug Administration. Establishment registration and device listing. Available from: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfRL/rl.cfm [Last accessed on 2022 Aug 22].
13. U.S. Food and Drug Administration. General wellness: Policy for low-risk devices; 2019. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/general-wellness-policy-low-risk-devices [Last accessed on 2022 Aug 22].
14. Gilligan C, Volschenk W, Russo M, *et al*. Long-term outcomes of restorative neurostimulation in patients with refractory chronic low back pain secondary to multifidus dysfunction: Two-year results of the ReActiv8-B pivotal trial. *Neuromodulation*. 2021;26:87-97. doi:10.1016/j.neurom.2021.10.011
15. Yakovlev AE, Resch BE, Karasev SA. Treatment of cancer-related chest wall pain using spinal cord stimulation. *Am J Hosp Palliat Care*. 2010;27:552-556. doi:10.1177/1049909110373240
16. McRoberts WP, Wolkowitz R, Meyer DJ, *et al*. Peripheral nerve field stimulation for the management of localized chronic intractable back pain: Results from a randomized controlled study. *Neuromodulation*. 2013;16:565-574; discussion 574-575. doi:10.1111/ner.12055
17. Barpujari A, Erdek MA. Retrospective analysis on the effect of spinal cord stimulation on opioid consumption. *Pain Manag*. 2021;11:123-132. doi:10.2217/pmt-2020-0016
18. De Caridi G, Massara M, Serra R, *et al*. Spinal cord stimulation therapy for the treatment of concomitant phantom limb pain and critical limb ischemia. *Ann Vasc Surg*. 2016;32:131.e11-e114. doi:10.1016/j.avsg.2015.10.015
19. Lamusuo S, Hirvonen J, Lindholm P, *et al*. Neurotransmitters behind pain relief with transcranial magnetic stimulation-positron emission tomography evidence for release of endogenous opioids. *Eur J Pain*. 2017;21:1505-1515.

doi:10.1002/ejp.1052
20. Zilberman N, Yadid G, Efrati Y, *et al*. Personality profiles of substance and behavioral addictions. *Addict Behav*. 2018;82:174-181. doi:10.1016/j.addbeh.2018.03.007
21. Nahm FS. From the torpedo fish to the spinal cord stimulator. *Korean J Pain*. 2020;33:97-98. doi:10.3344/kjp.2020.33.2.97
22. Ferraro MC, Gibson W, Rice AS, *et al*. Spinal cord stimulation for chronic pain. *Lancet Neurol*. 2022;21:405. doi:10.1016/S1474-4422(22)00096-5
23. Garcia K, Wray JK, Kumar S. Spinal cord stimulation. In: StatPearls. Treasure Island, FL: StatPearls Publishing; 2022.
24. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). Integrated addendum to ICH E6(R1): Guideline for good clinical practice E6(R2); 2016. Available from: https://database.ich.org/sites/default/files/E6_R2_Addendum.pdf [Last accessed on 2022 Aug 28].
25. Chand M, Armstrong T, Britton G, *et al*. How and why do we measure surgical risk? *J R Soc Med*. 2007;100:508-512. doi:10.1177/014107680710001113
26. Eldabe S, Buchser E, Duarte RV. Complications of spinal cord stimulation and peripheral nerve stimulation techniques: A review of the literature. *Pain Med*. 2016;17:325-336. doi:10.1093/pm/pnv025
27. Duarte RV, McNicol E, Colloca L, *et al*. Randomized placebo-/sham-controlled trials of spinal cord stimulation: A systematic review and methodological appraisal. *Neuromodulation*. 2020;23:10-18. doi:10.1111/ner.13018
28. Goudra B, Shah D, Balu G, *et al*. Repetitive transcranial magnetic stimulation in chronic pain: A meta-analysis. *Anesth Essays Res*. 2017;11:751-757. doi:10.4103/aer.aer_10_17
29. Yang S, Chang MC. Effect of repetitive transcranial magnetic stimulation on pain management: A systematic narrative review. *Front Neurol*. 2020;11:114. doi:10.3389/fneur.2020.00114
30. Vance CG, Dailey DL, Rakel BA, *et al*. Using TENS for pain control: The state of the evidence. *Pain Manag*. 2014;4:197-209. doi:10.2217/pmt.14.13
31. Loh J, Gulati A. The use of transcutaneous electrical nerve stimulation (TENS) in a major cancer center for the treatment of severe cancer-related pain and associated disability. *Pain Med*. 2015;16:1204-1210. doi:10.1111/pme.12038
32. Johnson M. Transcutaneous electrical nerve stimulation: Mechanisms, clinical application and evidence. *Rev Pain*. 2007;1:7-11. doi:10.1177/204946370700100103
33. DeSantana JM, Walsh DM, Vance C, *et al*. Effectiveness of transcutaneous electrical nerve stimulation for treatment of hyperalgesia and pain. *Curr Rheumatol Rep*. 2008;10:492-499. doi:10.1007/s11926-008-0080-z

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