Chapter 7
Cervical Spinal Cord Stimulation in Headache

Matteo Costanzi and Giorgio Lambru

7.1 Introduction

Spinal cord stimulation (SCS) is a moderately invasive therapy employed for the treatment of chronic neuropathic pain for the past 40 years. Relevant body of literature has demonstrated improvement of efficacy and quality of life measures in difficult-to-treat neuropathic conditions [1, 2]. Neuromodulation therapies offer a treatment option that is generally well tolerated and that is relatively safe and potentially reversible. Traditionally, the objective of SCS therapy has been to replace the pain sensation with paraesthesia that requires mapping of stimulation to the region of pain. The anticipation is that the electrical current alters pain processing by masking the sensation of pain with a comfortable tingling or paraesthesia. The stimulation is provided either through electrodes that are placed percutaneously into the epidural space or through a surgical paddle lead that is delivered via a laminotomy. These devices are capable of delivering pulse frequencies in the range of 2–1200 Hz (typically 40–60 Hz). Patients typically undergo a trial of neuromodulation with an externalised power source, and if this trial proves to be positive and compelling, they subsequently have a subcutaneously implantable pulse generator (IPG) for the long-term therapy.

M. Costanzi (✉)
Pain Management and Neuromodulation Centre, Guy's and St Thomas' NHS Foundation Trust, London, UK

Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy

G. Lambru
Headache Centre, Guy's and St Thomas' NHS Foundation Trust, Pain Management and Neuromodulation Centre and Neurology Department, London, UK

Wolfson CARD, King's College London, London, UK

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Although this therapy is a well-established therapy in chronic pain, trials versus reliable sham have not been produced yet, hence limiting the level of evidence that could be produced with this technique.

Novel stimulating waives including high-frequency (10 kHz) stimulation (HF10) and burst stimulation have more recently been introduced in the field of neuromodulation. 10 kHz SCS is a form of tonic stimulation delivered at very high frequencies. Burst stimulation consists of intermittent trains of five high-frequency stimuli delivered at 500 Hz applied 40 times per second with a long pulse width of 1000 ms and 1000 ms interspike interval delivered in constant current mode. The monophasic pulses are charge balanced at the end of the burst, differentiating it from clustered high-frequency tonic stimulation [3]. Both stimulation modalities lack of any perceived paraesthesia by patients. Recent studies demonstrated the superiority of high-frequency paraesthesia-free stimulation compared to low-frequency stimulation for the treatment of chronic back and leg pain [4, 5], suggesting that paraesthesia in the painful areas may not be necessary for pain relief. This finding leads to speculation on mechanisms of action of these therapies and mostly offers the opportunity to create a reliable sham to finally design methodologically robust clinical trials in this field.

The application of neurostimulation approaches has also extended to more specific neurological diseases like headaches. Non-invasive neurostimulation therapies have shown to be potentially effective in patients with non-difficult-to-treat episodic and chronic migraine and cluster headache [6–9]. However, emerging evidence suggests that in the refractory population, non-invasive therapies may not constitute an effective treatment [10]. Invasive neurostimulation therapies targeting peripheral or central nervous system structures have been emerging as more appropriate treatments for this population. Occipital nerve stimulation (ONS) has the gold standard neurostimulation treatment for the management of various primary headache disorders, including CM, chronic CH (CCH), hemicrania continua (HC), short-lasting neuralgiform headache attacks with conjunctival injection and tearing (SUNCT) and short-lasting neuralgiform headache attacks with autonomic symptoms (SUNA), based upon the encouraging experience of open-label studies [11–15]. However, three large randomised controlled trials (RCTs), testing the efficacy of ONS for CM prevention, displayed modest efficacy, although the studies were criticised for poor methodological designs [16–18]. Furthermore, in view of the device producing paraesthesia, reliable sham is not possible, preventing robust evidence to be produced.

Cervical spinal cord stimulation using tonic low-frequency paraesthesia-inducing and high-frequency paraesthesia-free stimulations has gathered some initial open-label, promising evidence in patients with refractory chronic headache disorders. This chapter aims to summarise what has hitherto been published using this technique in the headache field.

7.2 Equipment and Procedure

The surgical procedure for an implant of an SCS system traditionally consists of a two-stage process, a trial phase followed by a permanent implant.

During the trial phase, the lead is positioned under fluoroscopy into the posterior epidural space through a percutaneous technique or a small laminectomy. The patient is awake or under temporary sedation so that the operator can maximise the paraesthesia evoked by the activated contact. As soon as the tingling sensation overlaps the painful area, the lead is connected, directly or through an extension, to an external battery. The length of a stimulation trial is still not standardised worldwide and varies between centres but normally lasts between 1 and 4 weeks. During this period, the patient is assessed and the therapeutic efficacy of the stimulation delivered is evaluated. Generally, if the improvement obtained is more than 50% compared to baseline, the trial is considered successful and the subject is considered for permanent IPG implant. Otherwise, the lead/s will be removed. The second phase consists of the implant of the definitive SCS, stimulating lead/s and a battery implanted into a subcutaneous pocket.

Location of the leads is the main difference between high-frequency and low-frequency stimulation implant procedure. For conventional low-frequency SCS, the level of stimulating contacts is guided by intraoperative paraesthesia mapping. Conversely, for HF10 or burst SCS, leads are positioned at a standardised level above the anatomical midline over the T9–T10 junction and do not need any feedback from the patient.

7.3 Spinal Cord Stimulation in Chronic Pain Conditions

Neuropathic back and leg pain, generally seen following back surgery (FBSS), is considered the primary indication for an implant of SCS. However, this indication is not supported by sufficiently robust trials. Similarly, initial evidence has suggested the possible effectiveness of low- and high-frequency SCS for other pain disorders, namely, neuropathic upper limb pain including CRPS, neck pain and axial pain without previous back surgery [19–21]. In a large multicentre randomised controlled trial, HF stimulation was compared to low-frequency paraesthesia-based stimulation for the treatment of back and leg pain at 12 and 24 months' follow-up [4, 5]. HF10 was superior to traditional SCS with a response rate (at least 50% in pain reduction) of 78.7% at 12-month follow-up compared to 51.3% in the low-frequency SCS group. Besides, patients with HF10 therapy achieved approximately a 67% reduction in pain score compared to 44% of those treated with conventional SCS. The superiority of HF10 SCS was maintained at 24 months' follow-up, suggesting the potential superiority of paraesthesia-free approaches to traditional SCS.

Bust stimulation was initially introduced in the neuromodulation field to treat tinnitus and subsequently applied in SCS for chronic pain treatment [22]. Some methodologically poor studies suggested the potential efficacy of these stimulation modalities for various pain conditions [23]. Furthermore, a recent multicentre, randomised, unblinded, crossover study in chronic pain of the trunk and/or limbs suggested the superiority up to 1-year time of burst stimulation compared to tonic stimulation [24].

The field of neuromodulation is in continuous development, and new stimulation waveforms such as high-frequency and burst stimulation may offer advantages over tonic stimulation for the treatment of patients with refractory chronic pain and ultimately also offer new potential treatment options in chronic headache disorders.

7.4 Clinical Evidence for SCS in Primary Headaches

One of the first studies of cervical SCS in primary headaches was a prospective feasibility study in a small group of intractable CCH patients. Seven subjects with a long history of CCH (median duration of 13 years) resistant to established medications received a permanent implant with a quadripolar or eight-contact leads inserted in the high cervical epidural space in order to generate a low-frequency (40–110 Hz) stimulation and evoke paraesthesia in the sensory territory of the second cervical nerve root (C2) and first trigeminal division. The study participants were followed up for a mean of 23 months and reported a reduction in the mean number of attacks per day from 6 to 1.4, a reduction in median attack duration from 50 to 23 min and mean reduction in headache intensity from 7.4 to 4.5 out of 10. Unfortunately, six of the seven subjects required a revision surgery due to hardware complications (lead migration, lead breakage, battery failure) or the need for an additional electrode for the development of contralateral headache [25]. This raised concern to whether cervical SCS should be preferred to ONS, given that the latter treatment modality is considered to be less invasive [26].

The first evidence of SCS in migraine management was a retrospective analysis of 17 CM without medication overuse subjects implanted with high cervical SCS [27]. The patients were diagnosed by a neurologist and considered refractory to pharmacotherapy for the duration of 2 years prior to the procedure. The procedure consisted of the insertion of a pair of four contact electrodes at the high cervical epidural space (C1–C2). Conventional low-frequency stimulation was used. The final position of electrodes was decided in such a way as to evoke a tingling sensation in the territory of greater occipital nerve, lesser occipital nerve and great auricular nerve but not the dermatomes of trigeminal division V3. Rechargeable and non-rechargeable IPGs were used. Out of 17 patients, 12 reported continuous pain pre-implant (71%). Post-implant, four patients continued reporting continuous pain (24%; Wilcoxon's two-sided $p = 0.0078$). Mean NRS pain intensity score before implant was 8.1 (SD ± 1.9, 95% CI 7.1 to 9.0) vs. 3.2 (±1.5, 95% CI 2.4 to 4.0) at the date the questionnaire was filled out, which corresponds to a significant relative reduction of pain intensity of 60% ($p < 0.0001$). Fourteen out of seventeen patients (82%) experienced a reduction in pain intensity of at least 30%, and 12 (71%) experienced a reduction of 50% or more. The mean number of days with migraine was 23.4 (median 28.0, range 12–28) pre-implant and 14.1 (median 9.0, range 0–28) post-implant (40% reduction, $p = 0.0313$).

The only major adverse events observed in this series were 3 out of 23 patients (13%) presenting with an intercurrent infection requiring device explanation. In

addition, electrode dislocation requiring repositioning occurred in 3 out of 17 patients (18%; one during the test phase and two within 3 months post-implant). No cases of lead fracture or battery loss were reported during the period of observation.

HF10 cervical SCS was tested for the first time in a small feasibility prospective open-label study of medically refractory CM (rCM) patients [28]. Patients were selected based upon the diagnosis and the lack of response to multiple medical and injectable treatments, including onabotulinumtoxin-A (Botox). Medication overuse headache was not an exclusion criterion. Stimulation of the dorsal columns was provided through one or two eight-contact cylindrical leads positioned in the posterior cervical epidural space in order to deliver the electrical pulses at the C2–C3 vertebral level (Senza System, Nevro Corp, Redwood City, CA). A 2–4 week-long stimulation trial was used to guide a permanent implant. However, the decision to proceed to the permanent implant of the system was left to the patients. Forty-seven subjects with a diagnosis of rCM were screened for the study and 17 of those underwent a trial of HF10 SCS.

Out of 20 participants, 17 underwent a trial of HF10 SCS and 15 decided to receive a permanent implant. None of the subjects reported any paraesthesia sensation while the device was providing HF10 SCS epidural stimulation. Six adverse events classified as severe occurred in five subjects. Four of them required surgical treatment (28.6%). At 6 months, the average reduction in headache days was 6.9 for the overall population and 12.9 among the responders. Five patients (36%) reported a reduction in headache days greater than 50% at 24 weeks. Eight subjects (57%) reverted to an episodic pattern of headache. All subjects were overusing medication prior to enrolment: 64% were using triptans. At 24 weeks follow-up, subjects overusing triptans or NSAIDs were, respectively, 36% and 14%; four subjects discontinued the use of triptans. At baseline, 100% of subjects were classified as severely disabled according to both scales, while at 24 weeks, the percentage severely disabled dropped to 69% (MIDAS) and 62% (HIT-6).

The preliminary results of a single-centre prospective open-label study testing the safety and efficacy of HF10 SCS have been recently presented at an international headache conference (European Headache Federation, Florence 2018) [29]. Twenty adults diagnosed with rCM without MOH and who failed to respond to or tolerate four preventive treatments including topiramate and botulinum toxin type A were included in this study. All subjects were implanted with HF10 SCS (Senza System, Nevro Corp, Redwood City, CA); no stimulation trial was performed. Stimulating leads were positioned in the epidural space with the distal tip at the C2 vertebral level (Fig. 7.1).

Baseline data were available for 19 subjects (43 ± 10 years; 84% female), who had failed an average of 11.7 ± 3.2 preventive treatments at the time of recruitment. The average number of headache days at baseline was 23.3 ± 5.2 days of which 21.6 ± 6.6 days were migraine days. The average migraine-specific quality of life (MSQ) score at baseline was 32.0 ± 15.7. Compared to baseline, the average reduction in headache days at 12 weeks was 3.9 days, which increased to 4.9 days at week 24. The average reduction in migraine days at 12 weeks was 6.2 days/month,

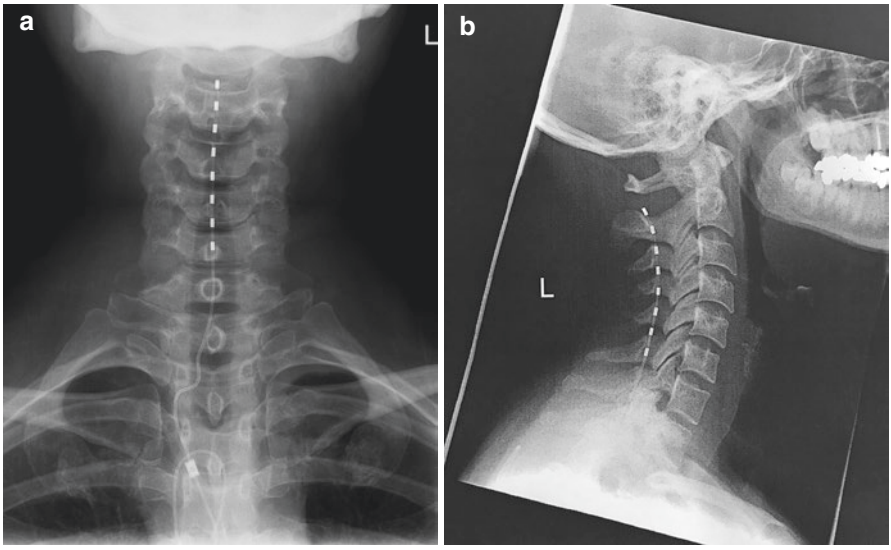

Fig. 7.1 Anteroposterior (**a**) and lateral (**b**) radiographic view of the cervical spine to demonstrate the final position of the implanted lead within the posterior epidural space in a chronic migraine patient

which increased to 7.2 days at weeks 24. Thirty-eight percent of the subjects at week 12 and 43% at week 24 obtained a 30% reduction in headache days; 44% of subjects at week 12 and 50% of subjects at week 24 reported a reduction of more than 30% in migraine days compared to baseline. In 50% of the subjects, the CM pattern reverted to an episodic pattern (<15 headache days/month) at week 24. We observed an improvement in the MSQ score of an average of 17.2 points at 24 weeks (50.8 ± 23.4). At week 24, five subjects reported pain at the site of implant, four reported musculoskeletal pain in the cervical and shoulder area and one experienced slight lead movement. No subjects required any further surgical procedure.

This preliminary evidence suggests that high cervical SCS, contrary to the first study in CCH, is a safe and well-tolerated treatment at least in experienced hands. In the only large-scale, prospective, controlled study evaluating ONS for CM with 1-year follow-up to date, the safety profile of the therapy was questioned by the authors themselves, as 183 device- or procedure-related AEs occurred, 8.6% of which required hospitalization and almost 41% required additional surgery [30]. In the first HF10 SCS study, four subjects (24%) required an additional surgical procedure, whereas none of the 20 patients implanted in the more recent trial required further surgery at 6 months f/u.

In terms of efficacy, these initial evidence may suggest that HF10 SCS is beneficial in rCM. One of the strengths of these studies is the fact that the migraine population included in these two trials was very refractory to medical treatments. Not many trials in ONS included a population who failed that many treatments and

Botox. The ONS RCT in CM included patients who failed at least two preventive treatments; however, it was unclear the mean numbers of treatments failed at enrolment. Furthermore, none of the patients tried Botox according to the PREEMPT trial in those trials. Botox is currently considered the standard of care for CM treatment [31, 32]; hence, its failure has been included in the most recent international guidelines for the definition of rCM [33]. A recent prospective open-label study, which studied the efficacy of a group of 35 rCM patients who failed an average of 9.36 (±2.61, range 4–19) preventative treatments, is somehow comparable to the HF10 SCS study populations, although there was no mention of the proportion of patients who failed Botox before implant [34]. At baseline, the patient group had a mean of 26.83 (±6.74) moderate to severe headache days. At a median f/u of 42 months, there was an average reduction of 5.8 headache days/month and 34.3% of rCM patients obtained >30% in monthly headache days. Although it is not appropriate to compare these trials, it is possible that HF10 SCS is as effective or even more effective than ONS in rCM. Similarly to chronic pain, paraesthesia may not be needed to obtain relief in headache conditions.

A retrospective analysis of seven patients with chronic refractory primary headache disorders followed up for a mean of 28 months also reported for the first time the long-term safety, tolerability and efficacy of HF10 cervical SCS not only in rCM but also in other primary headaches, namely CCH and SUNA (Fig. 7.2). Results demonstrated an improvement of at least 50% in headache frequency and/or intensity in all rCM subjects, improvement in attacks frequency and duration in one SUNA and headache freedom in the other SUNA patient. The CCH patient reported a reduction in attack duration but not frequency [35].

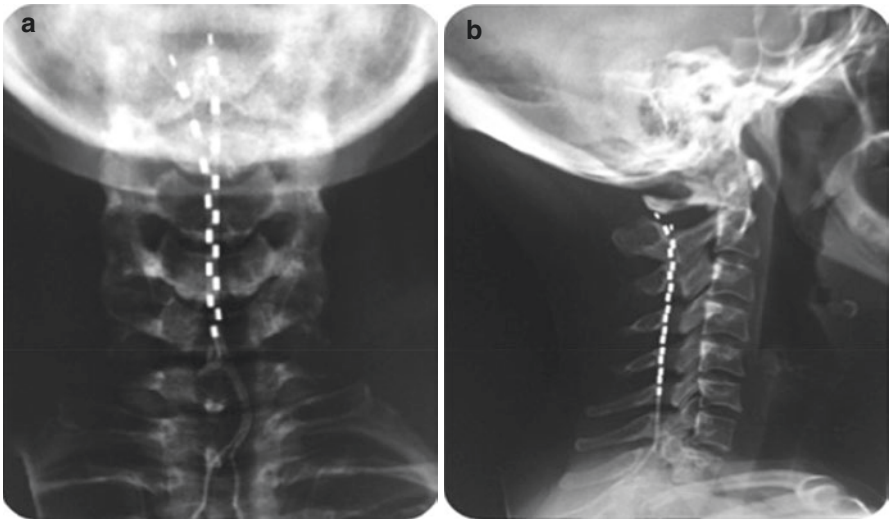

Fig. 7.2 Anteroposterior (**a**) and lateral (**b**) radiographic view of the cervical spine to demonstrate the final position of the implanted leads within the posterior epidural space (SUNA patient, 42 months follow-up)

7.5 Safety and Tolerability

SCS is considered a moderately invasive neuromodulation treatment, more invasive than ONS as far as headache disorders are concerned. Some of the complications may be severe, but they are extremely rare. These include spinal epidural haematoma, cerebrospinal leak and neurological deficit [36]. Common adverse events include hardware-related (e.g., lead migration, lead malfunction, connection malfunction and battery failure) and biological complications (e.g., infection, haematoma, seroma, dural puncture, nerve injury, IPG pocket pain). Most frequent AEs are infections and lead migrations with an average rate of 5% and 15% in the chronic pain literature [37]. In recent years, lead migration rate reported in clinical trials is decreasing arguably due to the better selection of patients, the improved device technology and more sophisticated technique of anchoring [38–40].

A panel of experts from the International Neuromodulation Society (INS) [41] has considered SCS of the cervical spine and of the thoracic spine similar in terms of adverse events [42]. The HF10 device (the Nevro Senza System) has received CE mark in 2010, TGA approval in 2011 and FDA approval in 2015 for treatment of failed back surgery syndrome, intractable low back pain and leg pain.

7.6 Spinal Cord Stimulation: Postulated Mechanisms of Action

SCS mechanisms of action are still not completely understood. Current hypotheses propose that a complex set of interactions at several levels of the nervous system mediate the effects of SCS. It has been postulated that SCS activates large A-beta fibres at the level of the dorsal horn and induces paraesthesia and simultaneously modulates the C-fibres transmission of pain signals [43, 44]. Animal studies have suggested a possible SCS target of stimulation at the wide dynamic range (WDR) neurons of the dorsal horn [45].

Later, several studies demonstrated a role of structures outside the dorsal horn and located in central and peripheral levels, such as supra-spinal circuits (demonstrated in fMRI studies) [46], and implication of descending inhibitory signals [47].

HF10 SCS has been shown to inhibit evoked afferent nociceptive inputs by modulating WDR neurons activity in the spinal cord of different animal models [48]. WDR neurons are spinal interneurons able to integrate C-fibres nociceptive inputs as well as multisynaptic inputs from myelinated A-type fibres signals before projecting to the brain. Significant modulation of WDR neuronal activity has been recorded in animal models of acute nociceptive and chronic neuropathic pain during SCS treatment [49].

Currently, no animal studies have tried to elucidate the mechanism of action of the high-frequency stimulation in headache disorders. Similarly to ONS, a modulation of the trigemino-cervical complex as well as a potential slow neuromodulatory effect at cortical levels may be postulated.

More research is needed to shed light upon the effect of paraesthesia-inducing and paraesthesia-free SCS and ONS neuromodulation modalities in headache models. Besides producing more scientifically robust basis to justify these therapies, such research may advance the understanding of the physiology of the trigeminocervical pathway, which is pivotal in headache medicine.

References

1. Mekhail N, Visnjevac O, Azer G, Mehanny DS, Agrawal P, Foorsov V. Spinal cord stimulation 50 years later: clinical outcomes of spinal cord stimulation based on randomized clinical trials—a systematic review. Reg Anesth Pain Med. 2018;43(4):391–406.
2. Sdrulla AD, Guan Y, Raja SN. Spinal cord stimulation: clinical efficacy and potential mechanisms. Pain Pract. 2018;18(8):1048–67.
3. Van Havenbergh T, Vancamp T, Van Looy P, Vanneste S, De Ridder D. Spinal cord stimulation for the treatment of chronic back pain patients: 500-Hz vs. 1000-Hz burst stimulation. Neuromodulation. 2015;18(1):9–12.
4. Kapural L, Yu C, Doust MW, et al. Novel 10-kHz high-frequency therapy (HF10 therapy) is superior to traditional low-frequency spinal cord stimulation for the treatment of chronic back and leg pain. Anesthesiology. 2015;123(4):851–60.
5. Kapural L, Yu C, Doust MW, et al. Comparison of 10-kHz high-frequency and traditional low-frequency spinal cord stimulation for the treatment of chronic back and leg pain: 24-month results from a multicenter, randomized, controlled pivotal trial. Neurosurgery. 2016;79(5):667–77.
6. Lan L, Zhang X, Li X, Rong X, Peng Y. The efficacy of transcranial magnetic stimulation on migraine: a meta-analysis of randomized controlled trails. J Headache Pain. 2017;18(1):86.
7. Schoenen J, Vandersmissen B, Jeangette S, et al. Migraine prevention with a supraorbital transcutaneous stimulator: a randomized controlled trial. Neurology. 2013;80(8):697–704.
8. Silberstein SD, Calhoun AH, Lipton RB, et al. Chronic migraine headache prevention with noninvasive vagus nerve stimulation: The EVENT study. Neurology. 2016;87(5):529–38.
9. Silberstein SD, Mechtler LL, Kudrow DB, et al. Non-invasive vagus nerve stimulation for the acute treatment of cluster headache: findings from the randomized, double-blind, sham-controlled ACT1 study. Headache. 2016;56(8):1317–32.
10. Trimboli M, Al-Kaisy A, Andreou AP, Murphy M, Lambru G. Non-invasive vagus nerve stimulation for the management of refractory primary chronic headaches: a real-world experience. Cephalalgia. 2018;38(7):1276–85.
11. Burns B, Watkins L, Goadsby PJ. Treatment of intractable chronic cluster headache by occipital nerve stimulation in 14 patients. Neurology. 2009;72(4):341–5.
12. Leone M, Proietti Cecchini A, Messina G, Franzini A. Long-term occipital nerve stimulation for drug-resistant chronic cluster headache. Cephalalgia. 2017;37(8):756–63.
13. Miller S, Watkins L, Matharu M. Treatment of intractable chronic cluster headache by occipital nerve stimulation: a cohort of 51 patients. Eur J Neurol. 2017;24(2):381–90.
14. Miller S, Watkins L, Matharu MS. Treatment of intractable hemicrania continua by occipital nerve stimulation. J Neurol Neurosurg Psychiatry. 2017;88(9):805–6.
15. Lambru G, Shanahan P, Watkins L, Matharu MS. Occipital nerve stimulation in the treatment of medically intractable SUNCT and SUNA. Pain Physician. 2014;17(1):29–41.
16. Lipton R, Goadsby PJ, Cady R, Aurora S, Grosberg B, Freitag F. PRISM study: occipital nerve stimulation for treatment-refractory migraine. Cephalalgia. 2009;29(S1):30.
17. Saper JR, Dodick DW, Silberstein SD, et al. Occipital nerve stimulation for the treatment of intractable chronic migraine headache: ONSTIM feasibility study. Cephalalgia. 2011;31(3):271–85.

18. Silberstein SD, Dodick DW, Saper J, et al. Safety and efficacy of peripheral nerve stimulation of the occipital nerves for the management of chronic migraine: results from a randomized, multicenter, double-blinded, controlled study. Cephalalgia. 2012;32(16):1165–79.
19. Al-Kaisy A, Palmisani S, Smith T, Harris S, Pang D. The use of 10-kilohertz spinal cord stimulation in a cohort of patients with chronic neuropathic limb pain refractory to medical management. Neuromodulation. 2015;18(1):18–23.
20. Russo M, Verrills P, Mitchell B, Salmon J, Barnard A, Santarelli D. High frequency spinal cord stimulation at 10 kHz for the treatment of chronic pain: 6-month Australian clinical experience. Pain Physician. 2016;19(4):267–80.
21. Al-Kaisy A, Palmisani S, Smith TE, et al. 10 kHz high-frequency spinal cord stimulation for chronic axial low back pain in patients with no history of spinal surgery: a preliminary, prospective, open label and proof-of-concept study. Neuromodulation. 2017;20(1):63–70.
22. De Ridder D, Plazier M, Kamerling N, Menovsky T, Vanneste S. Burst spinal cord stimulation for limb and back pain. World Neurosurg. 2013;80(5):642–649.e1.
23. Schu S, Slotty PJ, Bara G, Knop von M, Edgar D, Vesper J. A prospective, randomised, double-blind, placebo-controlled study to examine the effectiveness of burst spinal cord stimulation patterns for the treatment of failed back surgery syndrome. Neuromodulation. 2014;17(5):443–50.
24. Deer T, Slavin KV, Amirdelfan K, et al. Success using Neuromodulation with BURST (SUNBURST) study: results from a prospective, randomized controlled trial using a novel burst waveform. Neuromodulation. 2018;21(1):56–66.
25. Wolter T, Kiemen A, Kaube H. High cervical spinal cord stimulation for chronic cluster headache. Cephalalgia. 2011;31(11):1170–80.
26. Gaul C, Jürgens T, May A. Concerning high cervical spinal cord stimulation for chronic cluster headache. Cephalalgia. 2011;31(15):1588–9. authorreply1590–1
27. De Agostino R, Federspiel B, Cesnulis E, Sandor PS. High-cervical spinal cord stimulation for medically intractable chronic migraine. Neuromodulation. 2015;18(4):289–96.
28. Arcioni R, Palmisani S, Mercieri M, et al. Cervical 10 kHz spinal cord stimulation in the management of chronic, medically refractory migraine: a prospective, open-label, exploratory study. Eur J Pain. 2016;20(1):70–8.
29. Lambru G, Al-Kaisy A, Palmisani S, Carganillo R, Wesley S, Pang D. Safety and efficacy of cervical 10 kHz cervical spinal cord stimulation (SCS) for the management of refractory chronic migraine: a prospective, proof-of-concept open label study. J Headache Pain. 2016;19(Suppl 1):148.
30. Dodick DW, Silberstein SD, Reed KL, et al. Safety and efficacy of peripheral nerve stimulation of the occipital nerves for the management of chronic migraine: long-term results from a randomized, multicenter, double-blinded, controlled study. Cephalalgia. 2015;35(4):344–58.
31. Dodick DW, Turkel CC, DeGryse RE, et al. OnabotulinumtoxinA for treatment of chronic migraine: pooled results from the double-blind, randomized, placebo-controlled phases of the PREEMPT clinical program. Headache. 2010;50(6):921–36.
32. Andreou AP, Trimboli M, Al-Kaisy A, et al. Prospective real-world analysis of OnabotulinumtoxinA in chronic migraine post-National Institute for health and care excellence UK technology appraisal. Eur J Neurol. 2018;25(8):1069–83.
33. Martelletti P, Katsarava Z, Lampl C, et al. Refractory chronic migraine: a consensus statement on clinical definition from the European Headache Federation. J Headache Pain. 2014;15(1):47.
34. Miller S, Watkins L, Matharu M. Long-term outcomes of occipital nerve stimulation for chronic migraine: a cohort of 53 patients. J Headache Pain. 2016;17(1):68.
35. Lambru G, Trimboli M, Palmisani S, Smith T, Al-Kaisy A. Safety and efficacy of cervical 10 kHz spinal cord stimulation in chronic refractory primary headaches: a retrospective case series. J Headache Pain. 2016;17(1):66.
36. Bendersky D, Yampolsky C. Is spinal cord stimulation safe? A review of its complications. World Neurosurg. 2014;82(6):1359–68.

37. 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(2):325–36.
38. Kim DD, Vakharyia R, Kroll HR, Shuster A. Rates of lead migration and stimulation loss in spinal cord stimulation: a retrospective comparison of laminotomy versus percutaneous implantation. Pain Physician. 2011;14(6):513–24.
39. Justiz R, Bentley I. A case series review of spinal cord stimulation migration rates with a novel fixation device. Neuromodulation. 2014;17(1):37–40.
40. North RB, Recinos VR, Attenello FJ, Shipley J, Long DM. Prevention of percutaneous spinal cord stimulation electrode migration: a 15-year experience. Neuromodulation. 2014;17(7):670–6.
41. Deer TR, Mekhail N, Provenzano D, et al. The appropriate use of neurostimulation of the spinal cord and peripheral nervous system for the treatment of chronic pain and ischemic diseases: the Neuromodulation appropriateness consensus committee. Neuromodulation. 2014;17(6):515–50.
42. Deer TR, Skaribas IM, Haider N, et al. Effectiveness of cervical spinal cord stimulation for the management of chronic pain. Neuromodulation. 2014;17(3):265–71.
43. Shealy CN, Mortimer JT, Reswick JB. Electrical inhibition of pain by stimulation of the dorsal columns: preliminary clinical report. Anesth Analg. 1967;46(4):489–91.
44. Shealy CN, Taslitz N, Mortimer JT, Becker DP. Electrical inhibition of pain: experimental evaluation. Anesth Analg. 1967;46(3):299–305.
45. Yakhnitsa V, Linderoth B, Meyerson BA. Spinal cord stimulation attenuates dorsal horn neuronal hyperexcitability in a rat model of mononeuropathy. Pain. 1999;79(2–3):223–33.
46. Bentley LD, Duarte RV, Furlong PL, Ashford RL, Raphael JH. Brain activity modifications following spinal cord stimulation for chronic neuropathic pain: a systematic review. Eur J Pain. 2016;20(4):499–511.
47. Song Z, Meyerson BA, Linderoth B. Spinal 5-HT receptors that contribute to the pain-relieving effects of spinal cord stimulation in a rat model of neuropathy. Pain. 2011;152(7):1666–73.
48. Cuellar JM, Alataris K, Walker A, Yeomans DC, Antognini JF. Effect of high-frequency alternating current on spinal afferent nociceptive transmission. Neuromodulation. 2012;16(4):318–27.
49. Arle JE, Mei L, Carlson KW, Shils JL. High-frequency stimulation of dorsal column axons: potential underlying mechanism of paresthesia-free neuropathic pain relief. Neuromodulation. 2016;19(4):385–97.