Interv Pain Med Neuromod. 2021 December; 1(1):e117725. doi: 10.5812/ipmn.117725.

Published online 2021 August 15. **Editorial**

Spinal Cord Stimulation – New Technical Advancements

Georgios Matis [1,*]

[1]Department of Stereotactic and Functional Neurosurgery, Faculty of Medicine and University Hospital Cologne, Cologne, Germany

[*]*Corresponding author*: Department of Stereotactic and Functional Neurosurgery, Faculty of Medicine and University Hospital Cologne, Cologne, Germany. Email: georgios.matis@uk-koeln.de

Received 2021 July 09; **Accepted** 2021 July 27.

Keywords: Chronic Pain, Neuromodulation, Spinal Cord Stimulation, Technology

Spinal cord stimulation (SCS) is a 50-year-old neuromodulation therapy option for patients with chronic pain. It was in 1965 that Melzack and Wall published the famous "Gate theory" stating that the activation of the large fibers increases the inhibitory effect exerted by substantia gelatinosa on the afferent fiber terminals (1). Two years later, Wall and Sweet reported the first clinical results after stimulating peripheral nerves in patients with 'cutaneous pain'. The outcomes were found to be consistent with this theory (2). Some months later, the first clinical SCS lead implant was performed. The patient suffered from a diffuse pain in the right lower part of the chest and the upper part of the abdomen as a result of a bronchogenic carcinoma. On March 24, 1967, Shealy et al. undertook a thoracic laminectomy (T2-3) and approximated a Vitallium electrode to the dorsal columns by suturing it to dura (3). The stimulation began with a frequency of 10 - 50 Hz and a pulse width of 400 msec (0.8 - 1.2 Volts, 0.36 - 0.52 mA). The patient reported a significant pain relief but, sadly, 6 days later passed away from an undiagnosed endocarditis.

Since then, tonic stimulation (associated with a tingling sensation) has been the gold standard. Numerous studies have been published investigating the effect of tonic stimulation on patients with many conditions, including failed back surgery syndrome, complex regional pain syndrome, angina pectoris, peripheral vascular disease, etc. Over the last years, however, the neuromodulation field has witnessed a new trend towards subperception waveforms (stimulation without any tingling sensations). In 2010, De Ridder et al. implanted a spinal cord electrode (Lamitrode) in 12 patients via laminectomy (4 at the C2 level; 7 at the T8–T9 level; and 1 at T11 at another center) and tested a new stimulation paradigm (burst stimulation; 40 Hz burst with 5 spikes at 500 Hz per burst). The researchers showed that the new method could suppress neuropathic pain without the mandatory paresthesia (4). Five years later, a new paresthesia-free waveform (high frequency, HF) was presented. In a randomized trial by Kapural et al., the subjects received 30 μs pulses delivered at 10,000 Hz with amplitude adjusted to optimal analgesic response. The authors found that two-thirds of patients achieved remitter status, and over one-third decreased or eliminated opioid analgesic usage after 12 months (5).

The next step was to evaluate the effectiveness of combining different waveforms. Metzger et al. assessed the efficacy of a sequential or simultaneous delivery of neurostimulation (i.e., combination therapy) in 122 patients after 12 months and reported a 4.5-point pain decrease on Numeric Rating Scale (NRS), concluding that customizable SCS approaches may allow for highly effective pain relief (6). Andrade et al. showed that multiple combinations of SCS paradigms (tonic, burst, 1.2 KHz, Contour for dorsal horn stimulation) in the context of a rescue therapy was associated with significant pain relief in patients with failed conventional SCS (7).

Neuromodulation is an evolving field. New technologies and new waveforms are constantly under development, substantially helping patients with chronic pain to achieve a greater pain relief. An excellent example is the closed loop therapy (CLT). This therapy addresses the need to avoid any over- (while bending, twisting, walking, or coughing) or under-stimulation, which can be observed when using the classic tonic stimulation. CLT automatically adjusts the stimulation within a preferred range. This is possible because the SCS system provides an in vivo, real-time, and continuous objective measure of spinal cord activation in response to therapy via recorded evoked compound action potentials (ECAPs). In 2018, Russo et al. published some very encouraging results using this technology. At six months postimplant, 85.7% of patients with back pain and 82.6% of patients with leg pain reported a pain relief of 50% or greater (8); at 12 months, the corresponding proportions were 76.9% and 79.3%, respectively. More importantly, this prospective open-label

study (Avalon) showed that patients spent 84.9% (median) of their stimulation time in their therapeutic window, and 68.8% could eliminate or reduce their opioid intake (9). Another double-blind, randomized, controlled trial (Evoke) was carried out by Mekhail et al. The results were published last year (2020), highlighting the superiority of CLT over the open-loop SCS. In detail, at 12 months, 83.1% of the CLT patients reported a pain relief of at least 50% as compared to 61% of open-loop patients (10).

Two new SCS algorithms should also be mentioned. The first one uses multiple electrical pulsed signals (differential target multiplexed, DTM) modulating neuronal and glial gene expression back toward the non-pain state. The role of glial cells here is of utmost importance, since the glial cells outnumber the neurons in the spinal cord (12:1). It seems that DTM may impact the neuronal-glial interaction (11). Fishman et al. conducted a prospective multicenter feasibility study using DTM (12). The responder rate for low back pain relief was 80% at the end of the trial period. The patients could evaluate the standard programming, and 85% of them preferred the DTM approach. Of note, DTM patients did not feel any tingling.

The second algorithm is called Fast-acting subperception therapy (FAST). As the name implies, this waveform elicits a quick pain relief and is paresthesia-free. Moreover, it requires less energy than conventional subperception paradigms (13). The advantage of this paradigm is that it presents a fast analgesic "wash-in" in contrast to the other subperception waveforms that are currently available. In a recently published observational case-series, Metzger et al. employed physiological (paresthesia) mapping to guide subperception stimulation field targeting (symmetric biphasic waveform, frequency 90 Hz, pulse width of 210 $\pm$ 50 μs, amplitude 65% of perception threshold). At 6 months, 18 patients reported a significant reduction in pain scores (NRS: 1.7 $\pm$ 0.4; baseline: 8.4 $\pm$ 0.2 (n = 41)) (13). The rapid onset of analgesia (within 11.2 $\pm$ 1.9 minutes (n = 34)) could imply that alternative mechanisms of action are at play.

Although the pace of change has been exponentially speeding up, all those advances could begin to look trivial within a few years. At this point, most patients with neuropathic pain can achieve adequate pain relief using an SCS system. The next big goal will be the treatment of nociceptive pain or of mixed-pain syndromes, where the nociceptive component is the dominant one.

Footnotes

Authors' Contribution: Dr. Matis was responsible for the concept, design & drafting of the manuscript.

Conflict of Interests: It was not declared by the author.

Funding/Support: It was not declared by the author.

References

1. Melzack R, Wall PD. Pain mechanisms: A new theory. *Science*. 1965;**150**(3699):971–9. doi: 10.1126/science.150.3699.971. [PubMed: 5320816].
2. Wall PD, Sweet WH. Temporary abolition of pain in man. *Science*. 1967;**155**(3758):108–9. doi: 10.1126/science.155.3758.108. [PubMed: 6015561].
3. 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. [PubMed: 4952225].
4. De Ridder D, Vanneste S, Plazier M, van der Loo E, Menovsky T. Burst spinal cord stimulation: toward paresthesia-free pain suppression. *Neurosurgery*. 2010;**66**(5):986–90. doi: 10.1227/01.NEU.0000368153.44883.B3. [PubMed: 20404705].
5. Kapural L, Yu C, Doust MW, Gliner BE, Vallejo R, Sitzman BT, 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: The SENZA-RCT randomized controlled trial. *Anesthesiology*. 2015;**123**(4):851–60. doi: 10.1097/ALN.0000000000000774. [PubMed: 26218762].
6. Metzger CS, Hammond MB, Pyles ST, Washabaugh EP, Waghmarae R, Berg AP, et al. Pain relief outcomes using an SCS device capable of delivering combination therapy with advanced waveforms and field shapes. *Expert Rev Med Devices*. 2020;**17**(9):951–7. doi: 10.1080/17434440.2020.1812383. [PubMed: 32883126].
7. Andrade P, Heiden P, Visser-Vandewalle V, Matis G. 1.2 kHz high-frequency stimulation as a rescue therapy in patients with chronic pain refractory to conventional spinal cord stimulation. *Neuromodulation*. 2021;**24**(3):540–5. doi: 10.1111/ner.13278. [PubMed: 32929797].
8. Russo M, Cousins MJ, Brooker C, Taylor N, Boesel T, Sullivan R, et al. Effective relief of pain and associated symptoms with closed-loop spinal cord stimulation system: Preliminary results of the avalon study. *Neuromodulation*. 2018;**21**(1):38–47. doi: 10.1111/ner.12684. [PubMed: 28922517].
9. Russo M, Brooker C, Cousins MJ, Taylor N, Boesel T, Sullivan R, et al. Sustained long-term outcomes with closed-loop spinal cord stimulation: 12-month results of the prospective, multicenter, open-label avalon study. *Neurosurgery*. 2020;**87**(4):E485–95. doi: 10.1093/neuros/nyaa003. [PubMed: 32023344]. [PubMed Central: PMC8184296].
10. Mekhail N, Levy RM, Deer TR, Kapural L, Li S, Amirdelfan K, et al. Long-term safety and efficacy of closed-loop spinal cord stimulation to treat chronic back and leg pain (Evoke): a double-blind, randomised, controlled trial. *Lancet Neurol*. 2020;**19**(2):123–34. doi: 10.1016/S1474-4422(19)30414-4. [PubMed: 31870766].
11. Vallejo R, Tilley DM, Vogel L, Benyamin R. The role of glia and the immune system in the development and maintenance of neuropathic pain. *Pain Pract*. 2010;**10**(3):167–84. doi: 10.1111/j.1533-2500.2010.00367.x. [PubMed: 20384965].
12. Fishman MA, Calodney A, Kim P, Slezak J, Benyamin R, Rehman A, et al. Prospective, multicenter feasibility study to evaluate differential target multiplexed spinal cord stimulation programming in subjects with chronic intractable back pain with or without leg pain. *Pain Pract*. 2020;**20**(7):761–8. doi: 10.1111/papr.12908. [PubMed: 32462791].
13. Metzger CS, Hammond MB, Paz-Solis JF, Newton WJ, Thomson SJ, Pei Y, et al. A novel fast-acting sub-perception spinal cord stimulation therapy enables rapid onset of analgesia in patients with chronic pain. *Expert Rev Med Devices*. 2021;**18**(3):299–306. doi: 10.1080/17434440.2021.1890580. [PubMed: 33656411].