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Clinical utilization of fast-acting sub-perception therapy (FAST) in SCS-implanted patients for treatment of mixed pain

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ABSTRACT

Objectives: A significant proportion of patients with chronic pain exhibit mixed pain and thus do not display symptoms exclusively associated with either nociceptive or neuropathic pain syndromes. We aimed to explore whether Fast-Acting Sub-Perception Therapy, FAST – a new Spinal Cord Stimulation (SCS)-based approach capable of inducing a rapid-onset of analgesia using electrical neurostimulation applied below patient-perception threshold – could potentially be useful as a treatment for chronic mixed pain.

Methods: Fourteen consecutively-enrolled patients diagnosed with chronic mixed pain and implanted with an SCS device were enrolled in this single-center case-series. All patients completed a validated, self-administered painDETECT questionnaire prior to SCS-device implantation (baseline). The painDETECT questionnaire was used to characterize each patient's chronic pain as likely neuropathic only, uncertain (but potential for presence of a non-neuropathic component), or likely presence of a non-neuropathic component. Overall pain scores (Numeric Rating Scale, NRS), Oswestry Disability Index (ODI) and Quality-of-life (EQ-5D-5L) were collected (per standard-of-care) at baseline, 3-months, and 6-months post-implantation.

Results: The average age of those assessed in this study was 64.7 ± 11.5 (SD) years and 43% (6/14) were female. Fifty-percent (7/14) of patients were classified with non-neuropathic pain (painDETECT), while the remainder exhibited chronic pain that could not be characterized as either neuropathic or non-neuropathic (uncertain). Mean overall pain (NRS) among all patients was 8.3 ± 0.3 (SE) at baseline. At 6-months post-implant, a mean 6.9-points NRS score reduction was observed (1.4 ± 0.3 (SE); $p < 0.0001$). Notable improvements in disability (ODI) and Quality of Life (EQ-5D-5L) were also observed at 6-month follow-up.

Conclusions: The data from this observational case-series indicate that FAST-SCS can improve outcomes in patients reporting complex symptoms of mixed pain with a likely non-neuropathic component. These results suggest that neurostimulation modalities such as FAST may be a suitable treatment approach for non-neuropathic pain indications.

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1. Introduction

Spinal cord stimulation (SCS) involves the surgical implantation of a pulse generator interconnected to one or more leads containing stimulating electrodes that overlay the dorsal column within the epidural space of the spinal cord in order to electrically disrupt dysregulated pain signaling. Since its inception, SCS has been used as a therapeutic modality for pain, and the clinical indications that have been repeatedly demonstrated to be most effectively treated using SCS are Failed Back Surgery Syndrome (FBSS), now also termed as Persistent Spinal Pain Syndrome (PSPS) and Complex Regional Pain Syndrome (CRPS) [1]. Both of these pain syndromes are well-established as indications that are neuropathic in nature (i.e., pain resulting from a lesion or disease affecting the somatosensory system due to nerve injury) [2]. Hence, SCS has traditionally been used for these and other pain disorders that are known or at very least suspected to be etiologically neuropathic.

The mechanism thought to underlie the capability of SCS therapy to control pain is known as the “gate control theory”, which suggests that

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electrical stimulation of non-nociceptive Aβ fibers can block transmission of nociceptive pain signals via inhibitory interneurons in the spinal cord [3]. Simultaneously, stimulation of these Aβ fibers induces orthodromic action potentials that ultimately reach higher centers of the brain and may produce a tingling sensation, called paresthesia [4]. Thus, the presence of overlapping paresthesia (SCS-induced) at targeted pain areas has long-been associated with successful therapy and extensively used to guide SCS device "programming" (i.e., the application of variable stimulation field conformations, parameters, and/or waveforms). Interestingly, the purported mechanisms underpinning gate control theory indicate that SCS should in theory be capable of preventing the transmission of signals arising from acute nociceptive pain [5]. Nonetheless, traditional paresthesia-based SCS has been consistently shown to be ineffective in modulating the acute sensory perception of external stimuli (e.g., thermal, touch, pressure) as well as management of nociceptive-derived chronic pain (i.e., pain resulting from damage to non-neural tissue due to activation of nociceptors) [6,7]. Over the last decade however, new SCS-based techniques have been developed including the use of sub-perception-based (paresthesia-free) methods that do not require the production of paresthesia in order to provide analgesia to patients with chronic pain. Multiple observable aspects of sub-perception-based SCS including the absence for required paresthesia, longer time duration until analgesic onset, and lower applied stimulation amplitudes have led to various proposals regarding alternate mechanism(s) of action that might mediate this therapeutic approach (in contrast to traditional paresthesia-mediated SCS and/or gate control theory) [8–10].

Among the chronic pain patient population, those suffering from what is referred to now as "mixed pain" (defined as overlapping pain made up of different known pain types such as nociceptive, neuropathic, and/or nociplastic in any combination that can be experienced simultaneously and/or concurrently) are typically classified as challenging cases given the potentially heterogenous manifestation of their symptoms of chronic pain [11]. As SCS is a treatment option frequently employed as a last resort, SCS device-implanted patients are often observed to exhibit symptoms that are characteristic of mixed pain consisting of different pain components thought to be specifically neuropathic and/or nociceptive in origin [12]. In prior work, our group demonstrated that a sub-perception-based SCS methodology now termed Fast-Acting Sub--Perception Therapy (FAST) was effective for the treatment of chronic neuropathic pain using a biphasic-symmetric waveform precisely applied at 90 Hz (corresponding with a neural dose using optimized stimulation parameters [i.e., pulse-width and amplitude]) when combined with the use of paresthesia-guided stimulation field targeting [13].

Intriguingly, using the FAST approach we witnessed the induction of profound analgesia in patients implanted with an SCS device within seconds to minutes in contrast to much longer analgesic onset times observed using conventional sub-perception-based methods (e.g., 1–10 kHz) [14–16]. This observation suggested the potential involvement of a mechanism of action not previously associated with SCS given the unique clinical response phenomenology (i.e., rapid analgesia without paresthesia). As such, we thus considered whether the FAST-SCS methodological approach could help to improve pain relief outcomes in a population of SCS-implanted patients exhibiting symptoms of mixed pain consistent with the presence of different neuropathic and suspected non-neuropathic components.

2. Materials and methods

This observational case-series (Clinicaltrials.gov ID: NCT01550575) was carried out on the basis of retrospective chart review of 14 consecutive patients who were implanted with a permanent SCS system (Spectra WaveWriter/WaveWriter Alpha/Precision Montage, Boston Scientific, Valencia, CA) for treatment of chronic pain of the lower back and/or lower limbs. These systems are equipped with Multiple Independent Current Control (MICC) technology allowing for a specific current source per lead electrode as well as a model-based programming algorithm that can be adjusted rostrocaudally and mediolaterally simultaneously at high resolution (~300 μm increments) [17,18]. All patients were implanted and treated at University Hospital Cologne, Department of Stereotactic and Functional Neurosurgery, Cologne, Germany. Ethics Committee approval was obtained, and the study was conducted in accordance with Good Clinical Practices (ISO14155) guidelines and the Declaration of Helsinki. This study was sponsored by Boston Scientific Corporation.

All patients included in this study completed a validated, self-administered painDETECT questionnaire at baseline (i.e., prior to permanent device implantation) [19]. After completing the questionnaire, each patient was classified according to the following types of pain: likely neuropathic pain only (painDETECT score $\geq$19), uncertain (but still potential) for presence of non-neuropathic pain component (12 < painDETECT score <19), or likely presence of a non-neuropathic pain component (painDETECT score $\leq$12). FAST-based programming was applied using stimulation parameters as previously described [13]. As part of their routine clinic follow up, patient demographic information, medical history, and pain intensity data were collected. The following outcome measures were collected and assessed at 3- and 6-month after an initial, post operative FAST-SCS programming optimization visit: overall pain intensity (Numerical Rating Scale, NRS), quality of life (EQ-5D-5L), and disability (Oswestry Disability Index, ODI) [20]. All data collection was completed by site research personnel with no involvement by the study sponsor. Statistical analyses carried out in this evaluation included descriptive statistics (mean, standard deviation, or standard error). Paired *t*-test or Wilcoxon signed ranks test were used to assess differences, and p-values less than or equal to 0.05 were considered statistically significant. Prior to paired *t*-test assessments, the normality of the distribution was assessed based on plots and using the Kolmogorov-Smirnov test.

3. Results

Fourteen patients who completed the painDETECT questionnaire at baseline were included in this study. The characteristics of these patients at baseline are indicated in Table 1. The mean age was 64.7 ± 11.5 years (SD). The mean NRS pain score of this cohort at baseline was found to be 8.3 ± 0.3 (SE). At baseline, all included patients were determined to exhibit mixed pain as defined by the presence of a neuropathic pain component combined with either a "very likely" non-neuropathic pain component (i.e., painDETECT score $\leq$12) or a "potential" non-neuropathic component (i.e., 12 < painDETECT score <19) (Fig. 1). A majority of the assessed patients (13/14) were diagnosed with Persistent Spinal Pain Syndrome (PSPS) associated with at least one other pain ailment and/or syndrome (see Table 1).

Follow-up outcomes out to 6-months, demonstrated that mean overall pain intensity was reduced by a mean 6.9-points (versus mean baseline NRS score) to 1.4 ± 0.3 ($n = 14$, $p < 0.0001$) (Fig. 2a), and all patients

Table 1
Baseline demographic characteristics in analyzed patients.

Baseline Patient Demographics	
Age (mean years ± SD)	64.7 ± 11.5
Gender – Female % (n/N)	43% (6/14)
Baseline NRS Pain Score (Mean ± SE)	8.3 ± 0.3
Baseline Key Diagnosis (n)[a]	
Persistent Spinal Pain Syndrome (PSPS)	12
Kyphoplasty (T12 Fracture)	1
Lumbar Spinal Stenosis	1
Peripheral Vascular Diseases	1
Sacroiliac Joint Pain	2
Spinal Facet Join Pain	1
Follow-up Duration (Mean ± SD)	189.3 (6.3) days

[a] Patients may have multiple diagnoses.

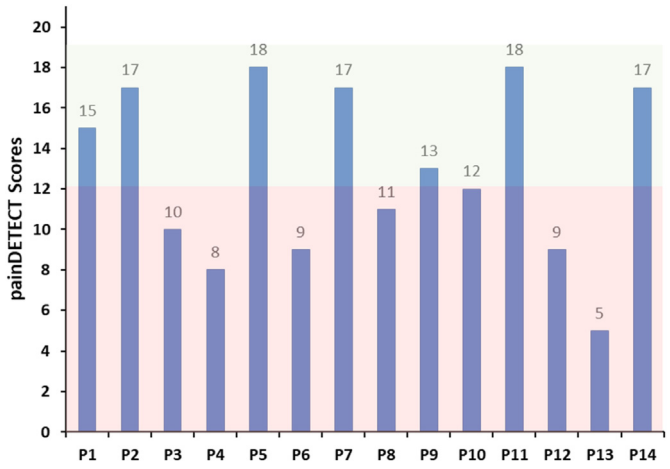

Fig. 1. PainDETECT Scores Across Patient at Baseline
The painDETECT questionnaire categories are defined according to the following: likely neuropathic pain only (painDETECT score ≥19), uncertain (but still potential) for presence of non-neuropathic pain component (12 < painDETECT score <19), or likely presence of a non-neuropathic pain component (painDETECT score ≤12).

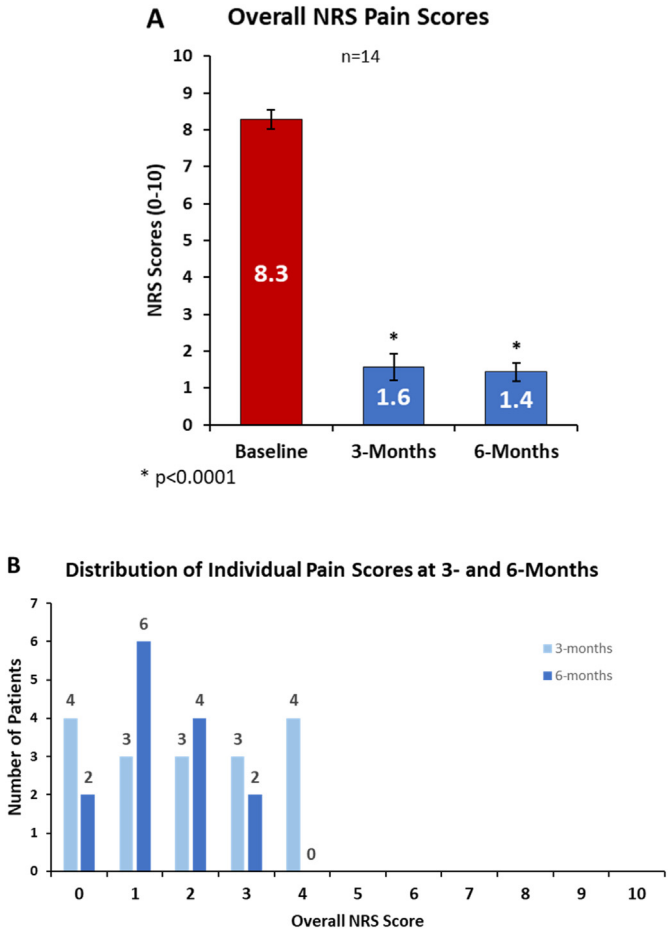

Fig. 2. Pain Reduction and Individual Pain Scores using FAST
(A) Mean overall pain scores: Pre-Implant Baseline (Red bars; n = 14): NRS before device implantation. Follow-Up visit (Blue bars; n = 14): NRS as measured at the 3- and 6-months. Error bars denote standard error. Significant difference ($p < 0.0001$) from Baseline is denoted by an asterisk (*).
(B) Distribution of individual pain scores using FAST at 3- and 6-months. . (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

reported an NRS pain score of 3 or less (Fig. 2b). Nearly identical results were observed at 3-month follow-up. When analyzing overall pain intensity at follow-up by stratified group according to painDETECT score, no statistically significant difference in the magnitude of pain relief was found between those patients with pain that was unlikely to have a neuropathic component versus those whose pain was uncertain. A notable improvement ($p < 0.001$) in patient quality of life was observed on the basis of a 53.1-point increase in EQ-5D-5L score at both 3-month (data not shown) and 6-month follow-up (Fig. 3). In addition, disability improvement ($p < 0.0001$) evaluated according to mean ODI score was reduced by 48.9-points at both 3-month (data not shown) and 6-month follow-up (note: the smallest change in ODI score perceived by patients as clinically beneficial is reported to be at least ~10-points) (Fig. 4) [20]. This degree of improvement thus represents a change in the categorical classification of patient disability from that of "crippling" (at baseline) to that of "minimal" disability (at follow-up) [21].

4. Discussion

This single-center, observational case-series provides initial evidence for the utilization of FAST-SCS methodology as a potentially effective treatment approach in patients reporting complex-symptom complaints characteristic of chronic mixed pain. Given the apparent lack of neuropathic-based pain in at least half (or possibly more) of those examined in this study, we hypothesize that the FAST-SCS technique could therefore represent a possible neuromodulatory approach for treatment of pain syndromes that are not thought or presently known to be neuropathic in origin. Traditional approaches of SCS, have been conventionally thought to be exclusively suited for the treatment of chronic neuropathic pain disorders [22–26]. Thus, the pain relief (and improvement in physical function and quality of life), as observed in this

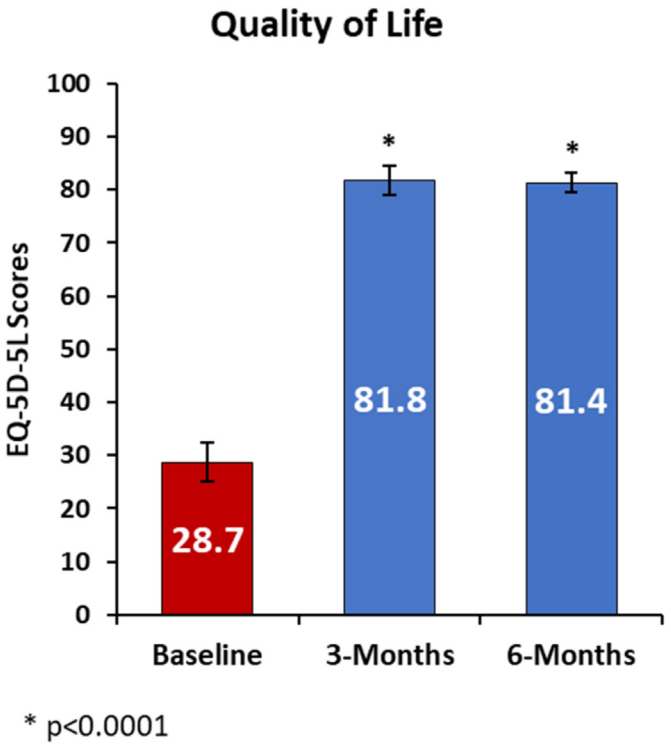

Fig. 3. Change in Quality of Life (EQ-5D-5L)
Pre-Implant Baseline (Red bars; n = 14): EQ-5D-5L before device implantation. Follow-Up visit (Blue bars; n = 14): EQ-5D-5L as measured at the 3- and 6-months. Error bars denote standard error. Significant difference ($p < 0.0001$) from Baseline is denoted by an asterisk (*). . (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

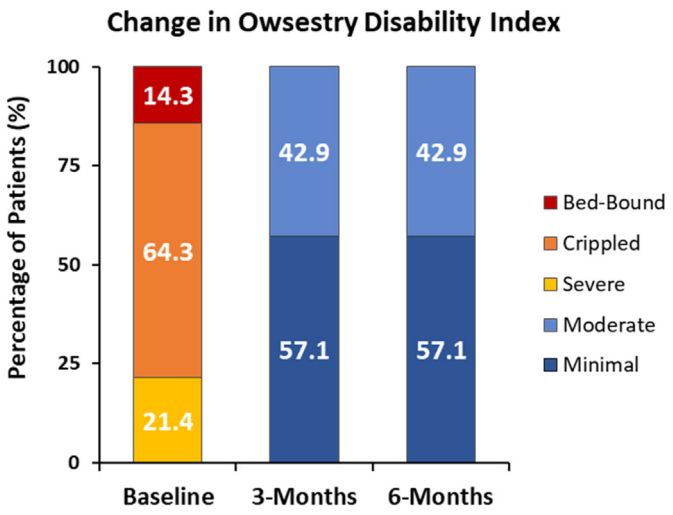

Fig. 4. Change in Oswestry Disability Index (ODI)
ODI score at Pre-Implant Baseline, 3- and 6-months. The scale is interpreted as: 0%–20% (minimal disability), 20%–40% (moderate disability), 41%–60% (severe disability), 61%–80% (crippled), 81%–100% (bed-bound or exaggerating symptoms).

pilot evaluation, offers initial evidence and support for the further study of FAST-SCS as a 'proof-of-concept' in patients who display symptoms of mixed pain.

Accurate diagnosis of neuropathic versus non-neuropathic pain is an essential aspect for the validation of any clinical approach as a potential treatment strategy for mixed pain and/or other pain disorders that typically are not treated using SCS. Yet, no validated screening tool specific for the diagnosis of mixed pain is currently available [27]. Therefore, for this preliminary study, we used painDETECT, a well-established, questionnaire-based tool designed to identify clinical symptoms of neuropathic pain [28]. To date, painDETECT has been reportedly used by hundreds of thousands of patients with chronic pain representing a range of different conditions and validated in subsequent studies conducted in several different countries [29–34]. The ability to effectively discriminate predominant neuropathic pain from predominant nociceptive pain in patients displaying mixed pain by relying on single metric (such as painDETECT) may have shortcomings [35]. However, we elected to utilize painDETECT given its prior validation as a screening tool, its long-established use as described in the published literature, and its readily available implementation per the preliminary nature of this evaluation of mixed pain-diagnosed patients.

Interest in uncovering the putative mechanism(s) mediating the clinical effects of FAST-SCS was first inspired by unexpected observations of rapid-onset of pain relief experienced by patients when treated according to optimized active recharge-driven stimulation parameters (i.e., biphasic, symmetric waveform at 90 Hz). These specific parameters were applied below the threshold of perception (sub-perception) while also utilizing patient-perceived paresthesia as a marker for stimulation field targeting (and not as a necessary constituent of actual therapy) [13]. In parallel, *In silico* analysis using realistic spatial and biophysical models demonstrated that application of low frequency, sub-threshold stimulation parameters consistent with those utilized when employing FAST-SCS to treat pain in humans (i.e., 90 Hz, 225 us, sub-threshold), induced a marked and prompt reduction in the response of wide dynamic range (WDR) neurons (an established proxy for pain), and this finding was corroborated in acute *in vivo* recordings [36,37]. These findings underscore the importance of precise waveform parameter selection and spatial targeting for suppression of neuronal activity and inhibition of pain signals from within the neural network of the dorsal horn. Intriguingly, from these reports, the strongest reductions by simulated FAST-SCS of *in silico* WDR and *in vivo* neuronal firing rate appeared to require the inclusive targeting of sensory fibers from laterally-situated receptive fields that were found adjacent to sites that were more centrally located within the overall field of stimulation, and the outcomes of these pre-clinical studies align significantly with the previously well-characterized neurophysiological mechanism known as surround inhibition [36–40]. Surround inhibition is hypothesized to play important roles in sensory processing and tuning from multiple systems [41–44], including pain [45–49], but its role in mediating SCS responses has only begun to be elucidated [50]. Our initial investigation as described in this report was therefore pursued, at least in part, on the premise that should FAST-SCS elicit pain relief via this (or any other) novel, putative SCS-enabling mechanism, this could in turn provide patients with mixed or other complex pain syndromes an opportunity to achieve improved clinical outcomes (versus that of using only traditionally-implemented SCS strategies).

As a "proof-of-concept" assessment conducted as a single-center, observational case-series, we acknowledge that conclusions regarding the use of FAST-SCS for mixed pain based on this current analysis are preliminary, and that this described clinical evaluation comes with expected limitations. Future studies will require larger cohorts incorporated by multicenter, prospective, and/or randomized controlled designs in order to establish more conclusive evidence for the ability of FAST-SCS to treat mixed pain. In addition, as noted above, sole use of painDETECT is not without risks for misdiagnosis, and had it been feasible to integrate other diagnostic tools as part of the practical implementation of this pilot study, a higher level of confidence regarding the neuropathic or non-neuropathic nature of the pain components displayed by the patients assessed in this study could have been achieved. Nonetheless, the aim of this current evaluation was to utilize readily available tools to preliminarily address whether FAST-SCS might display any capability as a treatment option for mixed pain and by extension presumably other chronic pain syndromes that are not exclusively neuropathic in origin. Given that most chronic pain in general is not neuropathic in nature and that a substantial proportion of SCS-implanted patents are thought to exhibit characteristics of mixed or complex pain, the opportunity to discover whether such patients in need may be successfully treated using FAST-SCS as a therapeutic treatment option is a question that we would contend is of considerable importance. Our study therefore provides for an indirect line of evidence for this possibility, and thus serves to support the rational pursuit of future investigations of FAST-SCS in the context of mixed pain.

5. Conclusion

As a 'proof-of-concept', pilot evaluation, data obtained from this single-center case-series indicate that FAST-SCS methodology may help improve clinical outcomes in patients reporting complex-symptom complaints characteristic of mixed pain. Thus, evaluation of FAST in future clinical studies of SCS-implanted patients with mixed pain as well as other non-neuropathic pain syndromes) is now warranted. Additional studies are also needed to evaluate the long-term impact of FAST-SCS in patients with mixed pain.

Authorship statements

Dr. Matis, Mr. Doan, and Mrs. Jain conceived and designed the study. Dr. Matis and their staff carried out the study including collecting patient data. Mr. Doan developed the FAST methodology and provided technical support. Statistical data analysis was performed by Ms. Chen and Mrs. Jain. and Mr. Doan helped prepare the manuscript. All authors critically reviewed and approved the submitted manuscript.

Data sharing

The data, analytic methods, and study materials for this clinical study will be made available to other researchers in accordance with the Boston Scientific Data Sharing Policy (https://www.bostonscientific.com/).

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Georgios Matis reports financial support, article publishing charges, statistical analysis, and writing assistance were provided by Boston Scientific Corp. Georgios Matis reports a relationship with University Hospital Cologne that includes: consulting or advisory. Que Doan reports a relationship with Boston Scientific Corp that includes: employment and equity or stocks. Roshini Jain reports a relationship with Boston Scientific Corp that includes: employment and equity or stocks. Lilly Chen reports a relationship with Boston Scientific Corp that includes: employment and equity or stocks.

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References

[1] Christelis N, Simpson B, Russo M, et al. Persistent spinal pain syndrome: a proposal for failed back Surgery syndrome and ICD-11. Pain Med 2021 Apr 20;22(4):807–18.
[2] IASP. https://www.iasp-pain.org/Advocacy/GYAP.aspx?ItemNumber=5054.
[3] Melzack R, Wall PD. Pain mechanisms: a new theory. Science Nov. 1965;150(3699):971–9.
[4] Joosten EA, Franken G. Spinal cord stimulation in chronic neuropathic pain: mechanisms of action, new locations, new paradigms. Pain 2020 Sep;161(Suppl 1):S104–13. 1.
[5] Dones I, Levi V. Spinal cord stimulation for neuropathic pain: current trends and future applications. Brain Sci 2018 Jul 24;8(8):138.
[6] Bordeleau M, Carrondo Cottin S, Meier K, Prud'Homme M. Effects of tonic spinal cord stimulation on sensory perception in chronic pain patients: a systematic review. Neuromodulation 2019 Feb;22(2):149–62.
[7] Vannemreddy P, Slavin KV. Spinal cord stimulation: current applications for treatment of chronic pain. Anesth Essays Res 2011 Jan-Jun;5(1):20–7.
[8] Lee KY, Bae C, Lee D, et al. Low-intensity, kilohertz frequency spinal cord stimulation differently affects excitatory and inhibitory neurons in the rodent superficial dorsal horn. Neuroscience 2020;428:132–139.11.
[9] Chakravarthy K, Richter H, Christo PJ, et al. Spinal cord stimulation for treating chronic pain: reviewing preclinical and clinical data on paresthesia-free high-frequency therapy. Neuromodulation 2018 Jan;21(1):10–8.
[10] Linderoth B, Foreman RD. Conventional and novel spinal stimulation algorithms: hypothetical mechanisms of action and comments on outcomes. Neuromodulation 2017;20(6):525–33. 13.
[11] Freynhagen R, Parada HA, Calderon-Ospina CA, et al. Current understanding of the mixed pain concept: a brief narrative review. Curr Med Res Opin 2019 Jun;35(6):1011–8.
[12] Maheshwari A, Pope JE, Deer TR, Falowski S. Advanced methods of spinal stimulation in the treatment of chronic pain: pulse trains, waveforms, frequencies, targets, and feedback loops. Expet Rev Med Dev 2019 Feb;16(2):95–106.
[13] Metzger CS, Hammond MB, Paz-Solis JF, et al. A novel fast-acting sub-perception spinal cord stimulation therapy enables rapid onset of analgesia in patients with chronic pain. Expet Rev Med Dev 2021 Mar;18(3):299–306.
[14] Shealy CN, Mortimer JT, Hagfors NR. Dorsal column electroanalgesia. J Neurosurg 1970;32(5):560–4.
[15] Al-Kaisy A, Palmisani S, Smith T, et al. 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.
[16] Thomson SJ, Tavakkolizadeh M, Love-Jones S, et al. Effects of rate on analgesia in kilohertz frequency spinal cord stimulation: results of the PROCO randomized controlled trial. Neuromodulation 2018;21(1):67–76.
[17] Veizi E, Hayek SM, North J, et al. Spinal cord stimulation (SCS) with anatomically guided (3D) neural targeting shows superior chronic axial low back pain relief compared to traditional SCS-LUMINA study. Pain Med 2017;18(8):1534–48.
[18] Bradley K. The technology: the anatomy of a spinal cord and nerve root stimulator: the lead and the power source. Pain Med 2006;7(s1):S27–34. 17.
[19] Freynhagen R, Baron R, Gockel U, Tölle TR. painDETECT: a new screening questionnaire to identify neuropathic components in patients with back pain. Curr Med Res Opin 2006 Oct;22(10):1911–20.
[20] Whynes DK, McCahon RA, Ravenscroft A, Hodgkinson V, Evley R, Hardman JG. Responsiveness of the EQ 5D health related quality of life instrument in assessing low back pain. Value Health 2013 Jan Feb;16(1):124–32.
[21] Fairbank JC, Pynsent PB. The Oswestry disability Index. Spine 2000 Nov 15;25(22):2940–52. ; discussion 2952.
[22] Lindblom U, Meyerson BA. Influence on touch, vibration and cutaneous pain of dorsal column stimulation in man. Pain 1975;1(3):257–70.
[23] Lee AW, Pilitsis JG. Spinal cord stimulation: indications and outcomes. Neurosurg Focus 2006 Dec 15;21(6):E3.
[24] Wolter T. Spinal cord stimulation for neuropathic pain: current perspectives. J Pain Res 2014 Nov 18;7:651–63.
[25] Fontaine D. Spinal cord stimulation for neuropathic pain. Rev Neurol (Paris) 2021 Sep;177(7):838–42.
[26] Dones I, Levi V. Spinal cord stimulation for neuropathic pain: current trends and future applications. Brain Sci 2018 Jul 24;8(8):138.
[27] Freynhagen R, Tölle TR, Gockel U, Baron R. The painDETECT project - far more than a screening tool on neuropathic pain. Curr Med Res Opin 2016 Jun;32(6):1033–57.
[28] Freynhagen R, Parada HA, Calderon-Ospina CA, Chen J, Rakhmawati Emril D, Fernández-Villacorta FJ, Franco H, Ho KY, Lara-Solares A, Li CC, Mimenza Alvarado A, Nimmaanrat S, Dolma Santos M, Ciampi de Andrade D. Current understanding of the mixed pain concept: a brief narrative review. Curr Med Res Opin 2019 Jun;35(6):1011–8.
[29] Alkan H, Ardic F, Erdogan C, et al. Turkish version of the painDETECT questionnaire in the assessment of neuropathic pain: a validity and reliability study. Pain Med 2013;14:1933–43.
[30] De Andres J, Perez-Cajaraville J, Lopez-Alarcon MD, et al. Cultural adaptation and validation of the painDETECT scale into Spanish. Clin J Pain 2012;28:243–53.
[31] Gudbergsen H, Bartels EM, Krusager P, et al. Test–retest of computerized health status questionnaires frequently used in the monitoring of knee osteoarthritis: a randomized crossover trial. BMC Muscoskel Disord 2011;12:190.
[32] Timmerman H, Wolff AP, Schreyer T, et al. Cross-cultural adaptation to the Dutch language of the PainDETECT-Questionnaire. Pain Pract 2013;13:206–14.
[33] Rienstra W, Blikman T, Mensink FB, et al. The modified painDETECT Questionnaire for patients with hip or knee osteoarthritis: translation into Dutch, cross-cultural adaptation and reliability assessment. PLoS One 2015;10:e0146117.
[34] Matsubayashi Y, Takeshita K, Sumitani M, et al. Validity and reliability of the Japanese version of the painDETECT questionnaire: a multicenter observational study. PLoS One 2013;8:e68013.
[35] Mulvey MR, Boland EG, Bouhassira D, et al. Neuropathic pain in cancer: systematic review, performance of screening tools and analysis of symptom profiles. Br J Anaesth 2017;119:765–74.
[36] Gilbert JE, Titus ND, Zhang TC, et al. Computational modeling predicts dorsal columns are involved in fast-acting sub-perception spinal cord stimulation (SCS)" [Abstract P166.01]. Society for Neuroscience Global Connectome: A Virtual Event; Jan .
[37] Gilbert JE, Titus N, Zhang T, Esteller R, Grill WM. Surround inhibition mediates pain relief by low amplitude spinal cord stimulation: modeling and measurement. ENEURO eNeuro 2022 Oct 5;9(5):0058. 22.2022.
[38] Grill WM. Surround inhibition contributes to SCS mechanisms. January Oral presentation at the Annual Meeting of the North American Neuromodulation Society 2022;14 [Orlando, FL USA].
[39] Jänig W, Spencer WA, Younkin SG. Spatial and temporal features of afferent inhibition of thalamocortical relay cells. J Neurophysiol 1979 Sep;42(5):1450–60.
[40] Angelucci A, Levitt JB, Lund JS. Anatomical origins of the classical receptive field and modulatory surround field of single neurons in macaque visual cortical area V1. Prog Brain Res 2002;136:373–88.
[41] Beck S, Hallett M. Surround inhibition in the motor system. Exp Brain Res 2011 Apr;210(2):165–72.
[42] Szikra T, Trenholm S, Drinnenberg A, Jüttner J, Raics Z, Farrow K, Biel M, Awatramani G, Clark DA, Sahel JA, da Silveira RA, Roska B. Rods in daylight act as relay cells for cone-driven horizontal cell-mediated surround inhibition. Nat Neurosci 2014 Dec;17(12):1728–35.
[43] Wehr M, Zador AM. Balanced inhibition underlies tuning and sharpens spike timing in auditory cortex. Nature 2003 Nov 27;426(6965):442–6.
[44] Aungst JL, Heyward PM, Puche AC, Karnup SV, Hayar A, Szabo G, Shipley MT. Centre-surround inhibition among olfactory bulb glomeruli. Nature 2003 Dec 11;426(6967):623–9.
[45] Lee KY, Ratté S, Prescott SA. Excitatory neurons are more disinhibited than inhibitory neurons by chloride dysregulation in the spinal dorsal horn. Elife 2019 Nov 19;8:e49753.
[46] Schlereth T, Magerl W, Treede R. Spatial discrimination thresholds for pain and touch in human hairy skin. Pain 2001;92(1–2):187–94.
[47] Quevedo AS, Mørch CD, Andersen OK, Coghill RC. Lateral inhibition during nociceptive processing. Pain 2017 Jun;158(6):1046–52.
[48] Price DD, McHaffie JG, Larson MA. Spatial summation of heat-induced pain: influence of stimulus area and spatial separation of stimuli on perceived pain sensation intensity and unpleasantness. J Neurophysiol 1989 Dec;62(6):1270–9.
[49] Coghill RC. The distributed nociceptive system: a framework for understanding pain. Trends Neurosci 2020 Oct;43(10):780–94.
[50] Brain Res 2014 Jun 20;1569:19–31. https://doi.org/10.1016/j.brainres.2014.04.039. Epub 2014 May 4. PMID: 24802658 Review.